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COVID-19 Pandemic-to-Endemic Transition in Indonesia: What Does the Future Hold?

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Since first reported in December 2019, SARS-2 Coronavirus (SARS-CoV-2) infection has become a world-class pandemic, overwhelming every aspect of the global system. Globally, 526 billion confirmed cases with 6,3 billion death cases were reported by World Health Organization (WHO) by 31 May 2022. In that period, Indonesia has reported 6 billion confirmed cases with a case fatality rate reaching 2.58%.[1] The number of new weekly cases and new weekly death have continued the declining trend observed since its peak in January 2022, i.e. 3% decrease of new weekly cases and 11% decrease of new weekly death as compared to the previous week.[2] In response to the current epidemiology improvement, countries including Indonesia have relaxed some regulations on COVID-19 as the preparation for pandemic-to-endemic transition.

Endemic is not equal to harmless. Commonly, endemic is falsely interpreted as the end of COVID-19, bringing to a false complacency. Endemic "label" on an infectious disease, such as malaria[3], HIV infection[4], tuberculosis[5] in certain regions of the world, means the overall rates of infection are static — neither rising nor falling. Endemic "label" defines nothing about time duration to reach disease end or how many populations will still be susceptible to the disease.[6] Therefore, transition for pandemic-to-endemic of COVID-19 could not simply translated into the end of either public and health service awareness, or research on COVID-19. It then should add new emerging perspective on COVID-19 research as was mandated by WHO. One example of which is evidence-based strategies for infection prevention control and personal protective equipment for infection control de-escalation in relation to COVID-19 pandemic scaling back.[7]

In the spirit of nurturing research and publication in this transition for pandemic-to-endemic era, the Indonesian Journal of Internal Medicine published various COVID-19 associated-original articles, systematic review, and case series across various COVID-19 condition. Atici, et. al.[8] and Tunjungputri, et. al.[9] report articles on factors and treatment that is associated with higher COVID-19 survival. Corticosteroids, Interleukin-6 inhibitors and anticoagulant administered to the proper subset of COVID-19 population are several beneficial treatments among limited evidence-based proven treatment available today. These supportive treatments, whenever indicated at the proper time, should be considered in managing every COVID-19 patient.[10] In addition, high antibiotic use in COVID-19 patients despite low secondary bacterial infection has been widely reported.[11] Chen, et. al.[12] report a similar situation in Indonesia and should raise the awareness of antimicrobial resistance thread now and in the future. Together with proper diagnostic stewardship, the simple predictors

of secondary bacterial infection that have been concluded could potentially be used to reduce liberal antibiotic use while optimizing the use in indicated patients.[11,12] Prabowo, et al.[13] enriched our understanding on usage of telemedicine to monitor post COVID-19 condition in Indonesian populations.

High quality research has, and will again, save the livelihoods of people across the world. While future pandemics could not be completely prevented, the research infrastructures that have built during last 2 years could be used as a strong modality to be better prepared and coordinated in future outbreak/ pandemic response by detecting and preventing the emerging diseases at their very early stage.[7,14] Waste in COVID-19 research and multiple COVID-19 associated research article retractions should caution researchers -as evidence-producer- and clinicians -as evidence-user- in prioritizing the scientific inquiry and questioning individual conflict of interest. Insightful articles addressing the multitude aspects of the COVID-19 pandemic-to-endemic transition related topics are still needed in the future.

REFERENCES

1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. available from: https://covid19.who.int. Accessed 1 June 2022.
2. World Health Organization. COVID-19 Weekly Epidemiological Update 25 May 2022. Edition 93. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-may-2022. Accessed 1 June 2022.
3. Al-Awadhi M, Ahmad S, Iqbal J. Current status and the epidemiology of malaria in the Middle East Region and beyond. Microorganisms. 2021;9:338.
4. World Health Organization. HIV/AIDS: Framework for action in the WHO African Region, 2016-2020. Geneva: World Health Organization; 2017.
5. World Health Organization. WHO global lists of high burden countries for TB, multidrug/rifampicin-resistant TB (MDR/RR-TB) and TB/HIV, 2021–2025. Geneva: World Health Organization; 2021.
6. Katzourakis A. COVID-19: endemic does not mean harmless. Nature. 2022;601:485.
7. World Health Organization. How global research can end this pandemic and tackle future ones; Geneva: World Health Organization; 2022.
8. Atici A, Asoglu R, Barman HA, et al. Evaluation of COVID-19 patients according to the survival time. Acta Med Indones-Indones J Intern Med. 2022;54(2):176-89.
9. Tunjungputri RN, Tetrasiwi EN, Mulansari NA, Harimurti K, Nelwan EJ. Acta Med Indones-Indones J Intern Med. 2022;54(2):190-209.
10. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 1 June 2022.
11. Robert Sinto, Lie KC, Setiati S, et al. Blood culture utilization and epidemiology of antimicrobial-resistant bloodstream infections before and during the COVID-19 pandemic in the Indonesian national referral hospital. Antimicrobial Resistance & Infection Control. 2022;11:73.
12. Lie KC, Shakinah S, Pasaribu A, et al. Observational study on secondary bacterial infection and the use of antibiotics in COVID-19 patients treated in a tertiary referral hospital. Acta Med Indones-Indones J Intern Med. 2022;54(2):161-9.
13. Prabowo Y, Riza'i A, Habib H, et al. Post COVID-19 syndrome monitoring in confirmed COVID-19 patients with telemedicine at Cipto Mangunkusumo Hospital. Acta Med Indones-Indones J Intern Med. 2022;54(2):170-5.
14. Haldane V, Jung A-S, Neill R, Singh S, Wu S, Jamieson M. From response to transformation: how countries can strengthen national pandemic preparedness and response systems. BMJ. 2021;375:e067507.

Observational Study on Secondary Bacterial Infection and the Use of Antibiotics in COVID-19 Patients Treated in a Tertiary Referral Hospital

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ABSTRACT

***Background*:** *Data on secondary bacterial infection in patients with COVID-19 in Indonesia are still limited, while the use of empirical antibiotics continues to increase. This study aims to determine the secondary bacterial infection rate in hospitalized COVID-19 patients and factors related to secondary bacterial infection.* ***Methods*:** *This is a retrospective cohort study on hospitalized COVID-19 patients undergoing treatment at Cipto Mangunkusumo Hospital from March 2020 to September 2020. Secondary bacterial infection is defined as the identification of a bacterial pathogen from a microbiological examination.* ***Results*:** *From a total of 255 subjects, secondary infection was identified in 14.5%. Predictors of secondary infection were early symptoms of shortness of breath (OR 5.31, 95% CI 1.3 – 21.5), decreased consciousness (OR 4.81, 95% CI 1.77 – 13.0), length of stay > 12 days (OR 8.2, 95% CI 2.9 – 23.3), and central venous catheter placement (OR 3.0, 95% CI 1.1 – 8.0) The most common pathogen of secondary bacterial infection is Acinetobacter sp. (n=9; 28%). Empirical antibiotics were administered to 82.4% of subjects with predominant use of macrolides (n=141; 32.4%).* ***Conclusion*:** *The secondary bacterial infection rate in COVID-19 was 14.5% and is associated with dyspnea, decreased consciousness, length of stay >12 days, and central venous catheter placement. The use of antibiotics in COVID-19 reaches 82.4% and requires special attention to prevent the occurrence of antibiotic resistance.*

***Keywords**: COVID-19, secondary bacterial infection, antibiotics, antibiotic stewardship.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory infection with high morbidity and mortality worldwide. This disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has a wide spectrum of diseases from asymptomatic to severe pneumonia resulting in acute respiratory failure and death.[1,2] By 2022, there have been more than 300 million cases and 5 million cumulative deaths due to COVID-19 globally.[3]

Several studies have reported bacterial co-infection and secondary bacterial infection in patients with COVID-19. Langford et al[4] reported that 3.5% of COVID-19 patients had bacterial co-infection, and 14.3% had secondary bacterial infection. Another study on severe and critical COVID-19 also reported a high incidence of bacterial co-infection prevalence of up to 20% of total cases.[5] With the low prevalence of bacterial co-infection and secondary bacterial infection, however, studies showed that more than 70%

of COVID-19 patients who were hospitalized received antibiotics. This excessive use of antibiotics must be monitored closely because excessive and irrational use of antibiotics will affect the normal flora in the body and increase bacterial resistance.[4,6]

This study aims to provide an overview of the incidence of co-infection and secondary infection as well as the causative pathogen in COVID-19 patients. In addition, this study also assessed the predicting factors for the presence of secondary infection in COVID-19 patients undergoing treatment.

METHODS

Study Design and Participant

This retrospective cohort study collected data from medical records of COVID-19 patients who were hospitalized at Cipto Mangunkusumo Hospital. COVID-19 was confirmed by the reverse transcriptase-polymerase chain reaction (RT-PCR) method. Data on confirmed COVID-19 adult patients were collected consecutively from March to September 2020.

Ethics

This study was approved by the Ethical Committe of Faculty of Medicine Universitas Indonesia (Ref. Number: 1454/UN2.F1/ETIK/PPM.00.02/2020).

Study Definition

COVID-19 infection is defined as an RT-PCR confirmed positive COVID-19 from nasopharyngeal swab accompanied by signs and symptoms of COVID-19 and other laboratory examinations that support the diagnosis of COVID-19. Bacterial co-infection is defined as the presence of a pathogen other than SARS-CoV-2 in a COVID-19 patient within the first 48 hours of hospital admission. Secondary bacterial infection was defined as the presence of a pathogen other than SARS-CoV-2 in a COVID-19 patient after the first 48 hours of hospital admission. The microbiological examination was carried out in patients with suspected secondary bacterial co-infection according to the standard of care based on the instruction from the attending physicians.

The degree of COVID-19 is classified according to the World Health Organization (WHO) criteria. Corticosteroids and immunosuppressants, including anti-cytokine agents, calcineurin inhibitors, antimetabolites, and similar therapies were found in the medical records to be used for treating the comorbid prior to COVID-19 infection, as well as for treating the COVID-19 itself once a patient was infected. Procalcitonin (PCT) and c-reactive protein (CRP) values were obtained from laboratory tests performed at the admission. Sepsis and Sequential Organ Failure Assessment (SOFA) score were determined based on the diagnosis in the medical record or the worst SOFA score >2 was obtained during the hospitalization of the patients.

Sample Size and Data Collection

The sample estimate was calculated by considering the prevalence of COVID-19 infection when the study was designed, which was 21%, with a 95% confidence level, and 5% prediction error. Therefore, a sample size of 255 subjects was determined. Data were collected consecutively from the medical records of patients who were hospitalized in Cipto Mangunkusumo Hospital in the period from March 2020 until the required number of samples was achieved.

Outcome Measurement

The outcome measured in this study was the incidence of secondary bacterial infection in COVID-19 and its associated factors.

Statistical Analysis

Demographic and clinical characteristics of patients are presented in percentage, as shown in the table. Variables that are hypothesized to be related to the outcome (secondary bacterial infection) were analyzed univariately. The variables that meet the requirements for multivariate analysis using logistic regression were further analyzed to obtain the odds ratio (OR) value. The value of $p<0.05$ was considered as statistically significant. Data analysis was performed with SPSS version 25.0.

RESULTS

A total of 255 records of hospitalized COVID-19 patients were reviewed. It was found

that 98 subjects (36.5%) were diagnosed with sepsis, 27 subjects (10.6%) had bacterial co-infection, 37 subjects (14.5%) had secondary bacterial infection, and 45 subjects (17.6%) died during hospitalization. **Table 1** shows the demographic data and clinical characteristics.

Of all subjects, the average age was 46 years. The most frequently reported COVID-19 complaints are fatigue, cough, and fever. In the group with secondary bacterial infection, complaints of tachypnea, dyspnea, fatigue, anorexia, myalgia, nausea, vomiting, and decreased consciousness were more common than in the group without secondary bacterial infection. Compared to all subjects with COVID-19, the group with secondary bacterial infection had more comorbidities. The average length of stay for COVID-19 subjects was 11.9 days and the group with secondary bacterial infection has longer length of stay, *i.e.*, 22 days on average.

The group with secondary bacterial infection had a higher proportion of ventilator use, ICU care, corticosteroid and immunosuppressant therapy, sepsis, and in-hospital mortality than the group without secondary bacterial infection. The use of antibiotics in COVID-19 was 100% in the group with secondary bacterial infection and

Table 1. Characteristics of Study Subjects

Characteristics	Total Subject (n=255)	Secondary Bacterial Infection	
		With Secondary Bacterial Infection (n=37)	Without Secondary Bacterial Infection (n=218)
Gender			
Female, n (%)	122 (47.8)	25 (67.6)	101 (50.5)
Male, n (%)	133 (52.2)	12 (32.4)	108 (49.5)
Mean Age, (SD)	46 (16.2)	50 (15.9)	45 (16.2)
Clinical Manifestation			
Fever, n (%)	159 (62.4)	25 (67.6)	134 (61.5)
- Cough, n(%)	183 (71.8)	30 (81.1)	153 (70.2)
- Tachypnea, n (%)	122 (47.8)	30 (81.1)	92 (42.2)
- Dyspnea, n (%)	144 (56.5)	34 (91.9)	110 (50.5)
- Fatigue, n (%)	195 (76.5)	34 (91.9)	161 (73.9)
- Anorexia, n (%)	154 (60.4)	31 (83.8)	123 (56.4)
- Myalgia, n (%)	67 (26.3)	6 (16.2)	61 (28)
- Headache, n (%	34 (13.3)	1 (2.7)	33 (15.8)
- Diarrhea, n (%)	23 (9)	4 (10.8)	19 (8.7)
- Nausea, n (%)	71 (27.8)	17 (45.9)	52 (24.8)
- Vomiting, n (%	28 (11)	8 (21.6)	20 (9.2)
- Anosmia, n (%)	22 (8.6)	1 (2.7)	21 (9,6)
- Ageusia, n (%)	19 (7.5)	1 (2.7)	18 (8,3)
- Loss of consciousness, n (%)	45 (17.6)	21 (56.8)	24 (11)
Comorbidity (based on *Charlson Comorbidity Index*)			
- Without comorbid	106 (41.5)	7 (18.9)	99 (45.5)
- Mild	74 (29)	10 (27.1)	64 (29.4)
- Moderate	48 (18.8)	11 (29.7)	37 (17.0)
- Severe	27 (10.7)	9 (24.3)	18 (8.1)
COVID-19 Severity			
- Mild	138 (54.1)	6 (16.2)	132 (60.5)
- Moderate	22 (8.7)	1 (2.8)	21 (9.6)
- Severe/Critically ill	95 (37.2)	30 (81)	65 (29.9)
Length of stay, mean (SD)	11.9 (9)	22 (13.5)	10 (10)
ICU admission; n(%)	83 (32.5)	27 (73.0)	55 (25.2)
History of hospital admission within the previous 2 weeks; n (%)	101 (39.6)	18 (48.6)	83 (38.1)
History of long-term care, n (%)	59 (23.1)	15 (40.5)	44 (20.2)
CVC placement	43 (16.9)	21 (56.8)	22 (10.1)
History of mechanical ventilation, n (%)	35 (13.7)	18 (48.6)	17 (7.8)
History of corticosteroid consumption, n (%)	90 (35.3)	24 (64.9)	66 (30.3)

History of immunosuppressant consumption, n (%)	86 (33.7)	23 (62.2)	63 (28.9)
Antibiotics treatment, n (%)	210 (82.4)	37 (100)	173 (79.4)
Early antibiotics treatment*, n (%)	170 (81)	31 (83.8)	139 (63.8)
Combination of antibiotics treatment*, n (%)	124 (59)	30 (81.1)	94 (43.1)
Use of Broad-Spectrum Antibiotics*, n (%)	254 (99.5)	37 (100)	217 (99.5)
Organ dysfunction, n (%)	55 (21.6)	21 (56.8)	34 (15.6)
SOFA score, median (IQR)	2 (0-14)	6 (0-13)	0 (0-14)
Bacterial co-infection	27 (11.0)	11 (29.7)	16 (7.3)
Sepsis, n (%)	98 (36.5)	30 (81.1)	63 (28.9)
Mortality during hospitalization, n (%)	45 (17.6)	21 (56.8)	24 (11)

SD: standard deviation, COVID-19: coronavirus disease 2019, ICU: intensive care unit, CVC: central venous catheter
*from subjects receiving antibiotics

79.4% in the group without secondary bacterial infection. 59% of subjects with COVID-19 received combination of antibiotics, including 81% of subjects in the group with a secondary bacterial infection.

Table 2 describes the univariate and multivariate analysis of factors associated with secondary bacterial infection in COVID-19, including age, gender, clinical manifestations, length of stay, ICU care, use of mechanical ventilators, use of central venous catheters, corticosteroid therapy and/or immunosuppression, history of hospitalization in the previous two weeks, history of long-term care, bacterial co-infection, organ dysfunction, sepsis, comorbidities, CRP level, procalcitonin values, and SOFA scores. COVID-19 is classified into mild and moderate to critical groups. CRP level cut-off used in this study was 80 mg/L[7], procalcitonin levels cut-off point was 0.25 ng/ml[8], and SOFA score cut-off point was 2. Prolonged length of stay was determined with the cut-off of 12 days for the group with the length of stay associated with the risk of secondary infection.[9,10]

Table 2. Factors Associated with Secondary Bacterial Infection in COVID-19 Patients.

Variables	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age group (<60 y.o.)	1.1 (0.5 – 2.5)	0.68		
Gender	2.12 (1.0 – 4.4)	0.05	1.5 (0.58 – 4.9)	0.38
Fever	1.30 (0.62 – 2.7)	0.58		
Cough	1.82 (0.76 – 4.35)	0.236	1.0 (0.28 – 3.9)	0.92
Tachypnea	5.8 (2.4 – 13.9)	<0.001	1.4 (0.3 – 6.0)	0.61
Dyspnea	11.1 (3.3 – 37.3)	<0.001	5.31 (1.3 – 21.5)	0.02
Fatigue	4.0 (1.1 – 13.5)	0.02	1.21 (0.1 – 7.46)	0.834
Anorexia	3.99 (1.5 – 9.9)	0.002	1.3 (0.36 – 4.9)	0.657
Myalgia	0.49 (0.19 – 1.25)	0.16	1.82 (0.45 – 7.32)	0.39
Headache	0.1 (0.02 – 1.1)	0.037	0.12 (0.01 – 1.43)	0.095
Diarrhea	1.2 (0.40 – 3.9)	0.755		
Nausea	2.58 (1.2 – 5.2)	0.01	2.2 (0.8 – 5.7)	0.086
Vomiting	2.73 (1.1 – 6.7)	0.04	1.2 (0.24 – 5.7)	0.82
Anosmia	0.26 (0.03 – 1.99)	0.27		
Ageusia	0.309 (0.04 – 2.38)	0.32		
Loss of consciousness	10.6 (4.8 – 23.0)	<0.001	4.81 (1.77 – 13.0)	0.002
COVID-19 severity	7.93 (3.1 – 10.8)	<0.001	0.495 (0.045 – 5.38)	0.564
Length of stay	10.7 (4.5 – 25.8)	<0.001	8.2 (2.9 – 23.3)	<0.001
ICU admission	8.0 (3.6 -17.5)	<0.001	0.95 (0.24 – 3.7)	0.956
History of mechanical ventilation	11.2 (4.9 – 25.0)	<0.001	1.3 (0.28 – 6.1)	0.713
CVC placement	11.6 (5.3 -25.6)	<0.001	3.0 (1.1 – 8.0)	0.023

History of corticosteroid consumption	4.2 (2.0 – 8.8)	<0.001	1.33 (0.08 – 21.8)	0.84
History of immunosuppressant consumption	4.0 (1.9 – 8.3)	<0.001	0.75 (0.2 – 2.2)	0.61
History of hospital admission within the previous 2 weeks	1.54 (0.76 – 3.10)	0.27		
Long-term care	2.6 (1.2 – 5.6)	0.011	1.3 (0.43 – 3.9)	0.622
Organ dysfunction	7.1 (3.3 – 14.9)	<0.001	0.9 (0.1 – 5.5)	0.968
Sepsis	10.5 (4.4 – 25.2)	<0.001	2.3 (0.52 – 10.8)	0.258
Comorbidity	3.48 (1.7 – 7.12)	0.01	1.0 (0.3 – 3.4)	0.917
CRP level	2.7 (1.3 – 5.7)	0.006	1.3 (0.49 – 3.8)	0.537
Procalcitonin level	1.5 (0.74 – 3.0)	0.275		
SOFA score	8.37 (3.8 – 18.1)	<0.001	0.47 (0.11 – 2.0)	0.31
Bacterial co-infection	5.34 (2.2 – 12.7)	<0.001	1.8 (0.52 – 6.44)	0.34

OR: odds ratio, 95% CI: 95% confidence interval, COVID-19: coronavirus disease 2019, ICU: intensive care unit, CVC: central venous catheter, CRP: c-reactive protein, SOFA: sequential organ failure assessment

Based on multivariate analysis, several factors associated with secondary bacterial infection in COVID-19 were complaints of dyspnea (OR 5.31, 95% CI 1.3 – 21.5), decreased consciousness (OR 4.81, 95% CI 1.77 – 13.0), prolonged length of stay (OR 8.2, 95% CI 2.9 – 23.3), and central venous catheter placement (OR 3.0, 95% CI 1.1 – 8.0).

Etiologic Pathogens Cause Secondary Bacterial Infections in COVID-19

Secondary bacterial infection in COVID-19 was determined by the presence of microorganisms other than SARS-CoV-2 that grew from the culture sample after 48 hours of hospitalization. The prevalence of secondary bacterial infection in all study subjects was 14.5%. Of the 255 subjects, 46 subjects (18%) underwent microorganism culture examination.

There was a total of 66 samples used for microorganism culture examination, consisting of 22 blood samples, 32 sputum samples, two bronchoalveolar lavages (BAL) fluid samples, four urine samples, one pleural fluid sample, four wound tissue samples, and one cerebrospinal fluid sample. Of the total 66 samples, 49 samples were positive, and 17 were sterile

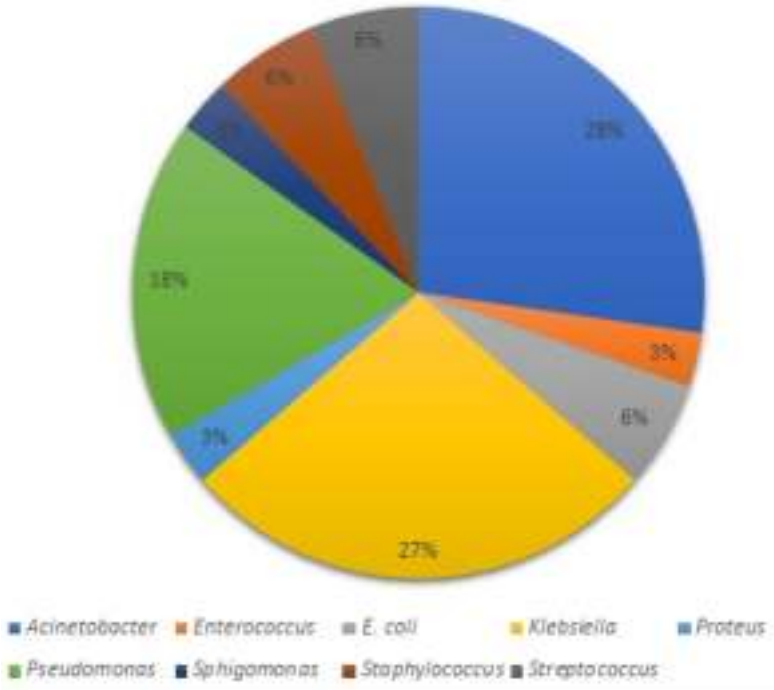

Figure 1. Etiologic Pathogen of Secondary Bacterial Infections in COVID-19

(14 blood culture samples, two urine culture samples, and one BAL fluid culture sample). The secondary bacterial infections found were hospital-acquired pneumonia (27 cases, 73%), catheter-related bloodstream infections (8 cases, 21.6%), and catheter-associated urinary tract infections (2 cases, 5.4%). Pathogenic etiology of secondary bacterial infection is dominated by gram-negative bacteria, *i.e.*, *Acinetobacter* sp. (28%), *Klebsiella* sp. (27%), and *Pseudomonas* sp. (18%). Fungal cultures were found positive in 5 sputum samples that showed the growth of *Candida* sp., and one blood sample showed the growth of *Candida albicans*.

Antibiotics Consumption in COVID-19

Antibiotics were used in 82.4% of subjects, including those without bacterial co-infection and secondary bacterial infection. 99.5% of the antibiotics administered in our subjects were broad-spectrum antibiotics, such as macrolides (33%), cephalosporins (25%), and quinolones (17%). The most frequently used antibiotics in this study was azithromycin from the macrolides, ceftriaxone, cefotaxime, and cefoperazone from the third generation of cephalosporins, and levofloxacin and moxifloxacin from the quinolones (**Figure 2**).

DISCUSSION

In this study, 14.5% of subjects with COVID-19 developed secondary bacterial infection during their hospitalization. Most of the subjects with secondary bacterial infection had severe/critical COVID-19. Approximately 50% of the subjects were admitted to the ICU, on ventilator, treated with corticosteroids and/or immunosuppressants, and diagnosed with sepsis. Mortality was observed in more than half of the subjects in the COVID-19 group with secondary bacterial infection (56.8%). This was much higher than the mortality in the group without secondary bacterial infection (11%).

The prevalence of secondary bacterial infection in COVID-19 in this study is in accordance with data in a systematic review conducted by Langford et al.[4] on 24 COVID-19 studies, where the prevalence of secondary bacterial in patients was 14.3%. A study in Surabaya, Indonesia, showed a prevalence of 19.7%.[11] These two studies also showed an increase in the duration of infection, use of ventilator, and ICU admission in the group with secondary bacterial infections.

COVID-19 infection leads to histological and functional respiratory damage. Histologically,

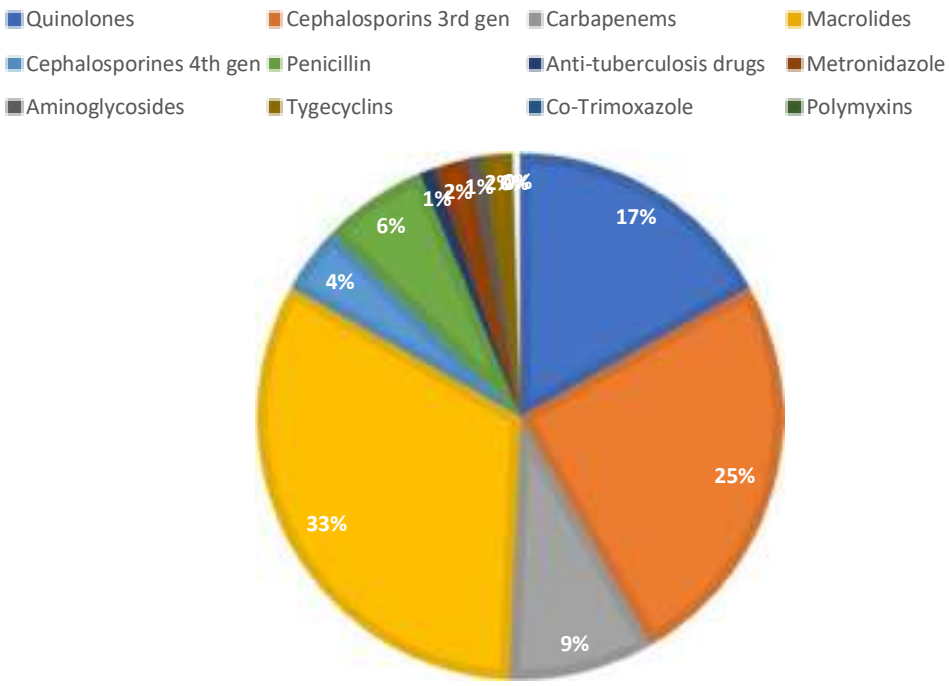

Figure 2. Antibiotic Consumption in COVID-19

cellular damage, goblet cell hyperplasia, increased mucus secretion, mucociliary disturbances, and discoordination may occur. In addition, the alveolar macrophage cells deplete and phagocytes' function is impaired, which cause a decrease in the ability of bacterial clearance by phagocytes and an increase in the rate of bacterial replication. In viral and bacterial co-infection, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are formed. These molecules bind to pattern recognition receptors (PRRs) and activate the formation of interferons (IFNs), cytokines, and chemokines that act as pro-inflammatory molecules, causing more extensive tissue damage.[12–14] The presence of immune dysregulation in both co-infection and secondary bacterial infection in COVID-19 leads to worse clinical manifestations in the COVID-19 group with secondary bacterial infection in this study.

Factors associated with secondary bacterial infection in COVID-19 are dyspnea on admission, decreased consciousness, prolonged hospital stay, and central venous catheter placement during treatment. In this study, dyspnea was experienced by almost all subjects with secondary bacterial infection. The association between the two could be due to complaints of dyspnea which were more common in severe/critical COVID-19 – the predominant grade in the secondary bacterial infection group. However, in multivariate analysis, it was found that the severity of COVID-19 was not associated with secondary bacterial infection, and therefore, the association between dyspnea and secondary bacterial infection appeared to be independent from the degree of COVID-19. Dyspnea was also found in other studies observing secondary bacterial infection in COVID-19, accompanied by fever and gastrointestinal symptoms.[15]

Impaired consciousness is a factor associated with secondary bacterial infection in COVID-19. COVID-19 patients with impaired consciousness have a higher risk of admission to ICU, intubation, need for mechanical ventilation, prolonged length of stay, prolonged need for ventilator, and mortality.[16] In addition, impaired consciousness also acts as an indicator of the severity of COVID-19, even before the respiratory disturbance appears.[17] Therefore, according to this study, impaired consciousness is associated with secondary bacterial infection in COVID-19.

Based on the analysis of this study, the prolonged length of stay for more than 12 days and central venous catheter placement in COVID-19 patients were associated with the risk of secondary bacterial infection. Prolonged treatment is associated with the risk of nosocomial infection, which is mainly related to medical devices and surgical procedures.[10,18–21] The results obtained from this study are in accordance with the results of other studies in COVID-19 patients with secondary bacterial infections. The most common infections reported in this study were pneumonia and catheter-associated bloodstream infections.[22,23] Central venous catheter placement is also associated with an increased risk of nosocomial infection.[24,25] In severe and critically ill COVID-19 patients, the risk of prolonged length of stay was increased, followed by an increase in the duration of use of a central venous catheter, the risk of entry of bacteria through the catheter (catheter as *port d'entrée*), and a decrease in the immune system of the patient, and hence, increased the risk of secondary catheter-related bacterial infection.[24]

All study subjects with secondary bacterial infection received broad-spectrum antibiotics therapy, and so did 80% of subjects without secondary bacterial infection. The same thing was found in another study, with the rate of antibiotics use in COVID-19 patients reached 90%.[4,26] This high number of antibiotics usage can be caused by the difficulties experienced by medical personnel in distinguishing clinical symptoms of bacterial and viral infections, since both have similar manifestations. In addition, at the beginning of the pandemic, administration of macrolide antibiotics, *i.e.*, azithromycin, was still recommended for COVID-19 with or without suspicion of co-infection or secondary bacterial infection, which led to extremely frequent use of it.[27] Cephalosporins and quinolones were also widely used in this study. These two groups were widely used because they are the recommended regimens in the management of community and nosocomial pneumonia in bacterial infections.[28,29]

The frequent use of antibiotics without bacterial infection increases the risk of antibiotic resistance and multi-drug resistant (MDR) bacteria.[30] This is also portrayed by identifying the pathogens causing secondary bacterial infections in this study, which were mostly gram-negative bacteria, *i.e.*, *Acinetobacter* sp., *Klebsiella* sp., and *Pseudomonas* sp. These data are consistent with the annual pattern of nosocomial bacteria and in line with other studies on secondary bacterial infection in COVID-19.[11,22,31,32]

Based on our result, we found that the intensification of proper implementation of antimicrobial stewardship is needed, mainly to prevent the irrational use of antibiotics in COVID-19. Guidelines for secondary bacterial infection in COVID-19, accurate and rapid laboratory investigations, and access to microbiological examinations are the keys in preventing antimicrobial resistance.[32,33]

The limitation of this study is that we used retrospective design with secondary data from medical records. Some of the required data, such as CRP and procalcitonin, were not always available, and only some subjects had the respective tests. In addition, the identification of patients with secondary bacterial infection was determined based on the results of microorganism cultures of patients who were suspected to have secondary bacterial infection. Secondary bacterial infection could not be appropriately identified in subjects without typical clinical characteristics.

CONCLUSION

Secondary bacterial infection was found in 14.5% of hospitalized COVID-19 patients. Factors associated with secondary bacterial infection were complaints of dyspnea on initial admission, decreased consciousness, length of stay of more than 12 days, and central venous catheter placement during treatment. The use of antibiotics in COVID-19 infection was found in 82.4% of subjects and was widely administered to subjects with and without secondary bacterial infection. The use of antibiotics in COVID-19 infection requires special attention to prevent the occurrence of antibiotic resistance.

REFERENCES

1. Coronavirus disease (COVID-19) – World Health Organization [Internet]. [cited 2022 Feb 14]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.
3. WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2022 Feb 3]. Available from: https://covid19.who.int/table
4. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26(12):1622–9.
5. Elabbadi A, Turpin M, Gerotziafas GT, et al. Bacterial coinfection in critically ill COVID-19 patients with severe pneumonia. Infection. 2021;49(3):559–62.
6. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal coinfection in individuals with Coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020;71(9):2459–68.
7. Elemraid MA, Rushton SP, Thomas MF, et al. Utility of inflammatory markers in predicting the aetiology of pneumonia in children. Diag Microbiol Infect Dis. 2014;79(4):458–62.
8. Cleland DA, Eranki AP. Procalcitonin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 Feb 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK539794/
9. Lambden S, Laterre PF, Levy MM, et al. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. Critical Care. 2019;23(1):374.
10. Wolkewitz M, Schumacher M, Rücker G, et al. Estimands to quantify prolonged hospital stay associated with nosocomial infections. BMC Med Res Methodol. 2019;19(1):111.
11. Asmarawati TP, Rosyid AN, Suryantoro SD, et al. The clinical impact of bacterial co-infection among moderate, severe and critically ill COVID-19 patients in the second referral hospital in Surabaya. F1000Res. 2021;10:113.
12. Manna S, Baindara P, Mandal SM. Molecular pathogenesis of secondary bacterial infection associated to viral infections including SARS-CoV-2. J Infect Publ Health. 2020;13(10):1397–404.
13. Mirzaei R, Goodarzi P, Asadi M, et al. Bacterial co-infections with SARS-CoV-2. IUBMB Life. 2020;72(10):2097–111.
14. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? EMBO Mol Med. 2020;12(7):e12560.
15. He S, Liu W, Jiang M, et al. Clinical characteristics of COVID-19 patients with clinically diagnosed bacterial co-infection: A multi-center study. PLOS

ONE. 2021;16(4):e0249668.
16. Attia AS, Hussein M, Aboueisha MA, et al. Altered mental status is a predictor of poor outcomes in COVID-19 patients: A cohort study. PLOS ONE. 2021;16(10):e0258095.
17. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus disease 2019 in Wuhan, China. JAMA Neurology. 2020;77(6):683–90.
18. Rees EM, Nightingale ES, Jafari Y, et al. COVID-19 length of hospital stay: a systematic review and data synthesis. BMC Medicine. 2020;18(1):270.
19. Vekaria B, Overton C, Wiśniowski A, et al. Hospital length of stay for COVID-19 patients: Data-driven methods for forward planning. BMC Infect Dis. 2021;21(1):700.
20. Zhou Q, Fan L, Lai X, et al. Estimating extra length of stay and risk factors of mortality attributable to healthcare-associated infection at a Chinese university hospital: a multi-state model. BMC Infect Dis. 2019;19(1):975.
21. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. N Engl J Med. 2010;362(19):1804–13.
22. Sharifipour E, Shams S, Esmkhani M, et al. Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. BMC Infect Dis. 2020;20(1):646.
23. Rothe K, Feihl S, Schneider J, et al. Rates of bacterial co-infections and antimicrobial use in COVID-19 patients: a retrospective cohort study in light of antibiotic stewardship. Eur J Clin Microbiol Infect Dis. 2021;40(4):859–69.
24. Fakih MG, Bufalino A, Sturm L, et al. Coronavirus disease 2019 (COVID-19) pandemic, central-line–associated bloodstream infection (CLABSI), and catheter-associated urinary tract infection (CAUTI): The urgent need to refocus on hardwiring prevention efforts. Infect Control Hosp Epidemiol;1–6.
25. Ong CCH, Farhanah S, Linn KZ, et al. Nosocomial infections among COVID-19 patients: an analysis of intensive care unit surveillance data. Antimicrobial Resistance & Infection Control. 2021;10(1):119.
26. Gaynes R, Edwards JR, National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis. 2005;41(6):848–54.
27. Burhan E, Susanto AD, Isbaniah F, et al. Pedoman Tatalaksana COVID-19. 3rd ed. Jakarta: PDPI, PERKI, PAPDI, PERDATIN, IDAI; 2020.
28. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–67.
29. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clinical Infectious Diseases. 2016;63(5):e61–111.
30. Feldman C, Anderson R. The role of co-infections and secondary infections in patients with COVID-19. Pneumonia. 2021;13(1):5.
31. O'Toole RF. The interface between COVID-19 and bacterial healthcare-associated infections. Clin Microbiol Infect. 2021;27(12):1772–6.
32. Abdela SG, Liesenborghs L, Tadese F, et al. Antibiotic Overuse for COVID-19: Are we adding insult to injury? The American Journal of Tropical Medicine and Hygiene. 2021;105(6):1519–20.
33. Founou RC, Blocker AJ, Noubom M, et al. The COVID-19 pandemic: a threat to antimicrobial resistance containment. Future Sci OA. 7(8):FSO736.

Post COVID-19 Syndrome Monitoring in Confirmed COVID-19 Patients with Telemedicine at Cipto Mangunkusumo Hospital

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ABSTRACT

Background: *The incidence of post-covid-19 syndrome is quite high and requires further monitoring after the patient is discharged from treatment. So we need a proper monitoring method and description of the Covid-19 syndrome in Indonesia.* ***Methods****: This retrospective cohort study with total sampling method uses data from medical records and telemedicine observations of confirmed COVID-19 patients who received treatment in the Kiara room at Cipto Mangunkusumo. The data were then analyzed using chi-squared and multinomial logistic regression techniques.* ***Results****: A total of 133 samples were used, including 44.4% male and 55.6% female, with an average age Standard Deviation (SD) of 40.36 (17.94). The severity levels of Covid-19 were mild (66.9%). The most common post-Covid-19 symptom manifestations was cough expressed at the first follow-up (first week after recovery) and second follow-up (the fourth week after recovery). Furthermore, the significant relationship between severity levels and post-Covid-19 symptomatic syndrome outcomes is the critical headache or vertigo symptoms with an RR of 8.70 (95% CI, 1.10-68.69,). In comparison, the telemedicine quality assessment was declared good, as shown by 98.7% of an examined sample.* ***Conclusion****: The most manifestation shown in the first and fourth week of follow-up is cough. Other symptoms tend to decrease in the second follow-up. The severity level associated with post-Covid-19 manifestations are severe-critical with headache or vertigo as a risk factor and mild with symptoms of headache or vertigo as a preventative. Meanwhile, the quality of telemedicine services was recognized as good by the majority of the sample.*

Keywords*: post-Covid-19 manifestations, Covid-19, Headache, Telemedicine, Indonesia.*

INTRODUCTION

Approximately 89.2% of post-treatment COVID-19 patients that have been declared cured experienced *sequelae* (residual symptoms), with 32.4% having a persistent impact. These include pulmonary fibrosis with symptoms of short breath aggravated by activities, dry cough, hypertension, heart rhythm disturbances, heart failure, depression, anxiety, and psychosis, consequently, these are known as post-COVID syndromes.[1,2] Indonesia one of countries affected by this COVID-19 Pandemic, has a fatality rate of 8.9% at the end of March, 2020.[3]

Telemonitoring is a process of exchanging

information related to symptoms and physiological data like vital signs and other health-related conditions through electronic, web-based, and telephone-based media,[4] and possibly applied to monitor post-COVID-19 patients. Advantages of using telemonitoring include providing early handling instructions for patient's worsening condition, reducing the number of patient admissions in the hospital, reducing the use of Personal Protective Equipment (PPE) as well as its efficiency in empowering human resources and disrupting the prevalence of the virus.[5]

Aims of this study are to make further observation of this phenomenon as there is still a paucity of studies or articles that discuss about the issue of *sequelae* in Indonesia and describe the quality of telemedicine, one of tools for monitoring patient which can be used to monitor COVID-19 patients, as it has an important role to reduce length of stay and prevent hospital overloading in this pandemic era.

METHODS

This study uses cohort retrospective method and the subject population is determined by using total sampling method which consists of 216 patients with 133 of them fulfiling all inclusion and exclusion criteria. Based on retrospective cohort formula for minimum sample, the minimum sample needed for this research is 76, so 133 patient data is enough for this research.

Inclusion criteria consists of: Patient agrees to be included in this research, Patients of all age categories, Post-treatment patients from Cipto Mangunkusumo Hospital (CMH) with Confirmed COVID-19 status based on clinical practice guidelines, Patients who are under the management of the hospital, while the exclusion criteria being: suspected and probable COVID-19 Patients, patients with ARI and/or pneumonia due to other than COVID-19, Patients with confirmed COVID-19 after hospitalization with death status[6,7]

Patients come from emergency room with confirmed COVID-19 status, then transfereed to CMH Kiara room for treatment where there are two type of isolastion rooms; relugar isolation room from mild to moderate status and intensive care unit isolation room from severe to critical status. Patient treated under COVID-19 protocol, between March 2021 and August 2021. After the symptoms subside, patient who are discharged can then be monitored using telemedicine as a stepdown mechanism to reduce length of stay. Treatment procedures use a team oriented approach method by COVID-19 board management, that consist of internist, pediatrician and anesthetist.

The patients are observed using telemedicine by general practicioner twice, guided by RSCM clinical practice guideline, in the first and fourth week after being declared free of COVID-19 based on a gold-standard laboratory test and reverse transcription-polymerase chain reaction (RT-PCR). Short contact period of observation is done to make data less biased. The patient's data taken include gender, age, the severity level of COVID-19, the manifestation of post-COVID-19 syndrome symptoms, and assessment of telemedicine.[8-10]

The data were then stored for COVID-19 monitoring, and this study was approved by the Ethical Committee of Faculty of Medicine, University of Indonesia, with reference number KET-404/ UN2.F1/ETIK/PPM.00.02/2021.

RESULTS

The study involved 133 post-treated patients with free or recovered status from COVID-19, including 59 males (44.4%) and 74 females (56.6%). The data also shows the average age SD being 40.36 with an approximate standard deviation of 17.94. The severity levels of COVID-19 for the samples are presented in **Table 1**.

Table 1. Demographic Data and Proportion of COVID-19 patient based on Severity (N=133).

Variables	Participants, n (%)	
Gender		
- Male	59	44.4 %
- Female	74	55.6 %
Age, mean (SD)	40.36 (17.94)	
Severity		
- Mild	89 (66.9)	
- Moderate	32 (24.1)	
- Severe	6 (4.5)	
- Critical	6 (4.5)	

In **Table 2**, the data on the proportion of post-COVID-19 symptom syndromes were summarized at the first follow-up and it was observed that the symptoms of the post-COVID-19 syndrome were mostly expressed in patients with mild symptoms including cough and excessive phlegm (19.1%) and sometimes fatigue and lethargy (13.5%).

In **Table 3**, there are data on the proportion of post-COVID-19 symptom syndromes in the second follow-up.

Table 4 contains the analysis carried out on the severity levels and its relationship to the manifestation of the post-COVID-19 symptomatic syndrome.

From **Table 4**, It is known that the relationship between severity and outcome of post-COVID-19 syndrome is significant, shown by the relative risk about 8.70 (95% CI, 1.10-68.69) of having Post COVID-19 symptom of headache or vertigo after severe-critical infection. Furthermore, at a mild level it was proven to be a protective factor against headache or vertigo with relative risk about 0.12 (95% CI, 0.02-0.91).

Table 2. Post COVID-19 Syndrome on First Follow Up.

Manifestation	Severity of COVID-19		
	Mild, n (%)	moderate, n (%)	severe-critical, n (%)
Fatigue	12 (13.5)	6 (18.8)	2 (16.7)
Dyspepsia	1 (1.1)	1 (3.1)	0
Chest pain	0	1 (3.1)	0
Anosmia	1 (1.1)	1 (3.1)	0
Diarrhea	1 (1.1)	0	0
Anorexia	2 (2.2)	1 (3.1)	0
Tinnitus	0	0	0
Intermittent fever	0	1 (3.1)	0
Myalgia	3 (3.4)	1 (3.1)	0
Cough	17 (19.1)	7 (21.9)	2 (16.7)
Dry mucous	0	0	0
Headache or vertigo	2 (2.2)	1 (3.1)	2 (16.7)
Dyspnea	1 (1.1)	4 (12.5)	0
Anxiety	0	1 (3.1)	0

Table 3. Post COVID-19 Syndrome on Second Follow Up.

Manifestation	Severity of COVID-19		
	Mild, n (%)	moderate, n (%)	severe-critical, n (%)
Fatigue	2 (2.3)	0	0
Dyspepsia	0	0	0
Chest pain	0	0	0
Anosmia	0	0	0
Diarrhea	0	0	0
Anorexia	0	0	0
Tinnitus	0	0	0
Intermittent fever	0	0	0
Myalgia	0	1 (3.1)	0
Cough	8 (9.0)	1 (3.1)	1 (16.7)
Dry mucous	0	0	0
Headache or vertigo	2 (2.2)	2 (6.3)	1 (16.7)
Dyspnea	3 (3.4)	3 (3.4)	1 (16.7)
Anxiety	1 (1.1)	1 (3.1)	2 (33.4)

Table 4. Correlation Between Severity of COVID-19 with the Manifestation of Post-COVID-19-Syndrome.

Manifestation	Severity of COVID-19					
	Mild (RR 95% CI)	p-value	Moderate (RR 95% CI)	p-value	Severe-critical, (RR 95% CI)	p-value
Fatigue	1.28 (0.25-6.59)	0.765	0.68 (0.23-1.98)	0.475	0.78 (0.15-3.99)	0.765
Dyspepsia	2.84 (0.17-46.77)	0.465	0.35 (0.02-5.80)	1.000	n/a	n/a
Chest pain	n/a	n/a	0.35 (0.02-5.80)	1.000	n/a	n/a
Anosmia	2.84 (0.17-46.77)	0.465	0.35 (0.02-5.80)	1.000	n/a	n/a
Diarrhea	2.84 (0.17-46.77)	0.465	n/a	n/a	n/a	n/a
Anorexia	0.12 (0.02-0.91)	0.540	0.35 (0.02-5.80)	1.000	n/a	n/a
Tinnitus	n/a	n/a	n/a	n/a	n/a	n/a
Intermittent fever	n/a	n/a	0.35 (0.02-5.80)	1.000	n/a	n/a
Myalgia	0.21 (0.01-0.33)	0.999	0.35 (0.02-5.80)	1.000	n/a	n/a
Cough	0.85 (0.17-4.23)	0.840	0.84 (0.31-2.27)	0.736	1.18 (0.24-5.89)	0.840
Dry mucous	n/a	n/a	n/a	n/a	n/a	n/a
Headache or vertigo	0.12 (0.02-0.91)	0.040	0.71 (0.06-8.14)	0.785	8.70 (1.10-68.69)	0.040
Dyspnea	2.84 (0.17-46.77)	0.465	0.103 (0.04-0.204)	0.999	n/a	n/a
Anxiety	n/a	n/a	0.35 (0.02-5.80)	1.000	n/a	n/a

Meanwhile, the quality of telemedicine was measured based on the five indicators contained in the questionnaire with eight questions.[11,12] The description of the results of the questionnaire itself is shown in **Table 5.**

Telemedicine quality measurement includes aspects of direct evidence, reliability, responsiveness, assurance and empathy.[12] It can

Table 5. An Overview of the Quality of Telemedicine in Terms of Convenience, Comfort and Safety as an Innovation in Monitoring Post-Treatment COVID-19 Patients at The CMH.

Variable of quality	Quality evaluation of telemedicine		
	Agree n(f/%)	Neutral n(f/%)	Disagree n(f/%)
Direct Evidence			
The monitoring method via telephone carried out by RSCM, for post-treatment patients is quite good	126 (94.7)	6 (4.5)	1 (0.8)
The monitoring team always introduces themselves as health workers, every time they make contact	130 (97.7)	2 (1.5)	1 (0.8)
Reliability			
RSCM Health Officers who carry out monitoring have a clear voice and articulation	132 (99.2)	1 (0.8)	0
Monitoring officers respond well to questions, complaints and suggestions	126 (94.7)	7 (5.3)	0
Responsiveness			
Questions, complaints or suggestions submitted by the patient are immediately responded to by the monitoring team	124 (93.2)	9 (6.8)	0

Assurance			
Patients feel safe with officers who provide information according to what patient needs	130 (97.7)	2 (1.5)	1 (0.8)
Empathy			
Monitoring officers understand what the problem is and can provide solutions to the problems raised	127 (95.5)	6 (4.5)	0
Patients feel cared for directly as individuals in this monitoring process	130 (97.7)	3 (2.3)	0

be seen that the quality of telemedicine in the 5 assessment indicators that have been determined, almost all patients stated that the quality of telemedicine was in the good category, based on the dimensions of direct evidence (94.7%) and (97.7%), reliability (99.2%) and (94.7%), responsiveness (93.2%), assurance (97.7%) and empathy (95.5%) and (97.7%).

The questionnaire has been validated by Pearson validity test and Cronbach alpha reliability test with the results of the significance value of each of the 8 question points being < 0.05, so it is considered valid and the Cronbach alpha value is 0.884 where if the Cronbach alpha value is above 0.6, then the study is considered reliable.

DISCUSSION

The data taken from 133 people used as the study sample shows that the post-COVID-19 symptoms are commonly at a mild level followed by moderate, severe, and critical. This finding is in line with Kamal et al,13 which reported that the most commonly found symptom severity is mild level with 80.2%, followed by moderate with 14.9%, and severe with 4.9%.

The post-covid-19 manifestations at the first follow-up indicate that the most common symptoms are cough and weakness/fatigue, this is different from other similar studies, such as the study conducted by Kamal *et al*,[13] which showed that the most common complaints were weakness/fatigue (72.8%). Furthermore, Huang *et al*[14] stated that the most comon post-COVID-19 symptoms were muscle weakness or fatigue (63%), difficulty in sleeping (26%), and hair loss (22%).

However, symptoms of the post-COVID-19 syndrome at the second follow-up presented in the fourth week showed almost similar results with Carfi *et al*[15] that observed a patient for two months after recovering from COVID-19 and concluded that the most prominent symptoms were fatigue (53.1%). This was further substantiated by Weerahandi *et al*[16] that observed between the 30th and 40th day after the patient was declared hospitalized with severe COVID-19 status reported that the most common post-COVID-19 symptoms were shortness of breath by 74% and worsening of the patient's mental and physical health. The difference in the proportion of symptoms is believed to be a manifestation of the incidence of severe primary infection accompanied by a systemic inflammatory response and usually followed by a counterbalancing compensatory anti-inflammatory response syndrome (CARS) . This leads to post-infection immunosuppression that varies in different patients.[1]

The relationship between severity levels and outcome of the post-COVID-19 symptomatic syndrome is related to Severe-critical COVID-19 symptom severity as a risk factor for post-COVID-19 headache or vertigo. This result is in line with Kamal *et al*,[13] which stated that there is a relationship between the severity level of COVID-19 infection and the level of manifestation, where the higher the severity level, the higher the prevalence of symptom. According to Del rio, [17] SARS-CoV-2 has the ability to penetrate the brain through blood vessels or affect the nerves, thereby leading to loss of smell, headache, or vertigo.

The quality of telemedicine in the five predetermined assessment indicators are good according to the patients. This result agrees with Silven *et al*,[5] which showed that telemonitoring conducted on 55 Covid-19 patients at home with mild to moderate symptoms levels demonstrated good service quality with no adverse effects

such as death or emergency care. However, this study is limited given that it used a population with non-homogeneous levels. Further studies are then expected to use a more homogeneous sample population in the context of the population per severity level. Also, it is recommended to analyze the relationship between the decrease in the incidence of manifestations at the second follow-up and the first one.

CONCLUSION

The manifestations shown in the first and fourth week of follow-up are the same, including cough and other symptoms that decreased in the second follow-up. The severity level associated with post-Covid-19 manifestations are severe-critical with headache or vertigo as a risk factor and mild with symptoms of headache or vertigo as a preventative. Meanwhile, the quality of telemedicine services was recognized as good by the majority of the sample.

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REFERENCES

1. Oronsky, B. *et al.* A Review of Persistent Post-COVID Syndrome (PPCS). *Clin. Rev. Allergy Immunol.* (2021) doi:10.1007/s12016-021-08848-3.
2. Al-Jahdhami, I., Al-Naamani, K. & Al-Mawali, A. The post-acute COVID-19 syndrome (Long COVID). *Oman Med. J.* **36**, 1–2 (2021).
3. Siti S, Muhammad K. A. COVID-19 and Indonesia. Acta Medica Indonesiana. 2020. Available from: http://www.actamedindones.org/index.php/ijim/article/view/1426/pdf
4. Telemonitoring - an overview | ScienceDirect Topics [Internet]. Sciencedirect.com. 2018 [cited 2020 Dec 1]. Available from: https://www.sciencedirect.com/topics/nursing-and-health-professions/telemonitoring.
5. Silven AV, Petrus AHJ, Villalobos-Quesada M, Dirikgil E, Oerlemans CR, Landstra CP, et al. Telemonitoring for Patients With COVID-19: Recommendations for Design and Implementation. Journal of Medical Internet Research [Internet]. 2020 Sep 2 [cited 2020 Nov 30];22(9):e20953. Available from: https://www.jmir.org/2020/9/e20953/pdf.
6. Respirology, S. O. & Indonesian. Diagnosis infeksi akut SARS-CoV-2 Pada Individu yang Dicurigai COVID-19 Dengan Hasil PCR Negatif. (2021).
7. CDC. Discontinuation of Transmission-Based Precautions and Disposition of Patients with SARS-CoV-2 Infection in Healthcare Settings. 2021. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html.
8. Nithyashri, J. & Kulanthaivel, G. Classification of human age based on Neural Network using FG-NET Aging database and Wavelets. *4th Int. Conf. Adv. Comput. ICoAC 2012* 12–16 (2012) doi:10.1109/ICoAC.2012.6416855.
9. Simamora Bilson. 2001. Remarketing For Business Recovery, Sebuah Pendekatan Riset. Jakarta: Gramedia Pustaka Utama.
10. Wanarto, G. B. 2013. Penilaian mutu pelayanan kesehatan oleh Pelanggan. Magetan : Forum Ilmiah Kesehatan (Forikes).
11. Mowen JC dan Minor M. 2002. Perilaku Konsumen Jilid 2. Edisi V. Penerjemah: Dwi Kartini Yahya. Jakarta: Erlangga.
12. Parasuraman A, Zeithaml VA, Berry LL. 1988. Servqual: A Multiple-Item Scale for Measuring Customer Perceptions of Service Quality . Journal of Retailing: Volume 64 Number 1 12-40.
13. Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. Int J Clin Pract. 2021 Mar;75(3):e13746. doi: 10.1111/ijcp.13746. Epub 2020 Nov 3. PMID: 32991035; PMCID: PMC7536922. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7536922/pdf/IJCP-9999-e13746.pdf.
14. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Li Y, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Wang Y, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021.
15. Carfi A, Bernabei R, Landi F, Gemelli Against Covid-Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020;324(6):603-605.
16. Weerahandi H, Hochman KA, Simon E, et al. Postdischarge health status and symptoms in patients with severe COVID-19. J Gen Intern Med 2021. DOI: 10.1007/s11606-020-06338-4.
17. Del Rio C, Collins LF, Malani P. Long-term Health Consequences of COVID-19. JAMA. 2020;324(17):1723–1724. doi:10.1001/jama.2020.19719.

Evaluation of COVID-19 Patients According to the Survival Time

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ABSTRACT

Background: *Coronavirus disease 2019 (COVID-19) was first detected as a form of atypical pneumonia. COVID-19 is a highly contagious virus, and some patients may experience acute respiratory distress syndrome (ARDS) and acute respiratory failure leading to death. We aim to evaluate the clinical, imaging, and laboratory parameters according to survival time to predict mortality in fatal COVID-19 patients.* ***Methods****: Fatal 350 and survived 150 COVID-19 patients were included in the study. Fatal patients were divided into three groups according to the median value of the survival days. Demographic characteristics and in-hospital complications were obtained from medical databases.* ***Results****: Of the non-survived patients, 30% (104) died within three days, 32% (110) died within 4-10 days, and 39% (136) died within over ten days. Pneumonia on computational tomography (CT), symptom duration before hospital admission (SDBHA), intensive care unit (ICU), hypertension (HT), C-reactive protein (CRP), D-dimer, multi-organ dysfunction syndrome (MODS), cardiac and acute kidney injury, left ventricular ejection fraction (LVEF), right ventricular fractional area change (RV-FAC), and Tocilizumab/Steroid therapy were independent predictors of mortality within three days compared to between 4-10 days and over ten days mortality. A combined diagnosis model was evaluated for the age, CT score, SDBHA, hs-TnI, and D-dimer. The combined model had a higher area under the ROC curve (0.913).* ***Conclusion****: This study showed that age, pneumonia on CT, SDBHA, ICU, HT, CRP, d-dimer, cardiac injury, MODS, acute kidney injury, LVEF, and RV-FAC were independently associated with short-term mortality in non-surviving COVID-19 patients in the Turkish population. Moreover, Tocilizumab/Steroid therapy was a protective and independent predictor of mortality within three days.*

Keywords*: COVID-19, mortality, acute respiratory distress syndrome, echocardiography.*

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus disease 2019 (COVID-19) was first detected as a form of atypical pneumonia in Wuhan, China, in December 2019.[1] COVID-19 was an unprecedented epidemic, and the World Health Organization (WHO) declared it a pandemic.[2] According to the WHO report, about 243 million people were diagnosed with COVID-19 in 219 countries by 24 October 2021. COVID-19 is a highly contagious virus and killed approximately 4.9 million people worldwide.[3]

Mild acute respiratory infection symptoms such as fever, dry cough, and tiredness are common in the early stages of COVID-19. Some COVID-19 patients may experience ARDS and acute respiratory failure leading to death. Although pulmonary complications were the leading cause of death, multiple organ dysfunction syndrome (MODS), myocardial, kidney, and liver injuries could lead to death in COVID-19 patients.[1,4-6] About two-thirds of severe COVID-19 patients have a fatal outcome.[7-9] Therefore, many clinical features and laboratory parameters were evaluated to predict mortality in COVID-19 patients. It was reported that age, gender, comorbidities, smoking history, and many biomarkers including d-dimer and troponin were a predictor of mortality.[10-13] Although there is no specific treatment for COVID-19 so far, corticosteroids and some anti-inflammatory agents have been shown to be effective in treatment.[14] In addition, supportive care and early detection are beneficial.[15,16] Therefore, the determination of simple and reliable predictors of survival in severe COVID-19 patients is necessary. Due to the limited number of intensive care unit beds and the financial burden of the COVID-19 disease in some countries, adequate supportive therapy and correct triage are essential in the survival period.

This study aimed to compare clinical, imaging, and laboratory parameters according to the day of death of patients who died from COVID-19 and determine independent predictors according to the day of death.

METHODS

The study was planned with a retrospective, cross-sectional, multicenter and observational design. Three hundred and fifty deceased and 150 surviving COVID-19 patients were included in the research for 28 March 2020 and 15 January 2021. The presence of SARS-CoV-2 RNA was detected by real-time reverse transcription-polymerase chain reaction (RT-PCR) in the Ministry of Health Public Health Microbiology Reference Laboratory after obtaining oropharyngeal and nasal specimens by using the same swab and placing the swab on the same transport medium. The guidelines for COVID-19, which the Ministry of Health prepared, were implemented, and the patients used the suggested medications. The anticoagulant, steroid, antibiotic therapy, antiviral therapy, invasive and non-invasive mechanical ventilation was performed according to these guidelines. COVID-19 RT-PCR (+), surviving COVID-19 patients, and deceased COVID-19 patients were included in the study. Patients with the following conditions were excluded from the study: age < 18 years, pregnancy, ST-elevation myocardial infarction, advanced malignancy, severe valvular heart disease, and negative PCR tests.

Demographic characteristics and in-hospital complications were obtained from medical databases. Patient age, gender, smoking status, hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), hyperlipidemia (HLD), malignancy, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) history were recorded. Also, laboratory parameters such as urea, creatinine, sodium, potassium, glucose, high-sensitivity troponin I (hs-TnI), d-dimer, hemoglobin, white blood cell (WBC), procalcitonin, and C-reactive protein (CRP) were obtained from hospital admission records. In all cases, a semi-quantitative computational tomography (CT) severity scoring proposed by Pan et al. was calculated for each of the five lobes considering the extent of anatomic involvement.[17] Deceased patients were divided into three groups according to the median value of the survival days. The study was conducted under the Helsinki

Declaration, and the study protocol was approved by the local ethics committee and the Ministry of Health (approval number: 2020/0623).

Definitions

Myocardial injury was defined as a troponin value exceeding the upper reference limit (URL, 99%) according to the Fourth Universal Definition of Myocardial Infarction (MI).[18] Acute kidney injury (AKI) was defined based on the kidney disease: Improving Global Outcomes (KDIGO) definition.[19] CAD was diagnosed in patients with a history of previous percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). MODS is defined as the concurrent dysfunction of two or more organs or systems, including hematological, gastrointestinal, cardiovascular, neurological, respiratory, hepatic, and renal.[9]

Transthoracic Two-dimensional Echocardiography

Two-dimensional echocardiography (2DE) studies were performed by a cardiologist using an X5 transducer (Philips Epiq7; Philips Healthcare, Inc., Andover, MA, USA) to evaluate the parasternal and apical images (2D, M-mode, Doppler echocardiography). The echocardiographic examination was performed within the first 24 hours after admission, and the data were recorded. In the echocardiographic examination, three cycles were recorded and analyzed during any phase of respiration. After the 2DE images were recorded, the analysis was performed by two independent, experienced cardiologists blinded by the clinical data of the patients. Echocardiographic images were obtained in all four standard views (long-axis parasternal, short-axis parasternal, two-chamber apical, and four-chamber apical) using the techniques recommended by the American Society of Echocardiography (ASE) guidelines.[20]

Electrocardiographic Evaluation

12-lead admission electrocardiography (ECG) was obtained from each patient on admission before any treatment was started. All standard 12-lead electrocardiograms were recorded on digitized 12-lead ECG recordings using the on-screen digital caliper software (Cardio Calipers version 3.3, Iconico, Inc., New York, NY). All ECGs (filter range 0.5-150 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV) were analyzed by two independent cardiologists blinded to the clinical data of the patients according to the modified Minnesota criteria, and the findings were recorded on sheets.[21] Corrected QT interval (QTc); the QT interval measured in either lead II or V5-6, QTc was calculated using Bazett's formula ($QTc = QT / (\sqrt{RR})$.[22] QRS fragmentation (fQRS) was defined as a notch in the R wave or S wave in two consecutive leads associated with the myocardial region, or multiple R' waves and QRS<120 ms.[23]

Statistical Analyses

All statistical tests were conducted using the Statistical Package for the Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze the normality of the data. Normally distributed variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median with interquartile range (IQR). The categorical variables are presented as percentages. A Chi-square test was used to assess differences in categorical variables between groups. The primary analysis used ANOVA to compare all reported data for parametric variables, whereas the Kruskal–Wallis test was used to compare nonparametric variables between the median value of the survival days. The univariate effects of type of age, gender, pneumonia on CT, symptom duration before hospital admission (SDBHA), intensive care unit (ICU), HT, CAD, CRP, d-dimer, cardiac injury, MODS, Acute kidney injury, LVEF, RV-FAC and Tocilizumab/ Steroid on death of patients was investigated using the log rank test. The possible factors identified with univariate analyses were further entered into the Cox regression analysis, with backward selection, to determine independent predictors of death. The proportional hazards assumption and model fit was assessed by means of residual (Schoenfeld and Martingale) analysis. Multinomial logistic regression analysis was used to identify independent predictors of mortality in three days. Receiver operating characteristic (ROC) curves were obtained, and the optimal values with the greatest total

sensitivity and specificity in the prediction of mortality in three days were selected. All the parameters in the ROC curve analysis were included in the binary logistic regression analysis. Combined model was created with the obtained probability value. A combined model, which was created with mortality predictors, was analyzed by ROC curves. Finally, 20 patients were assigned randomly to test the intra-observer and interobserver variability expressed as the intra-class correlation coefficient for the CT score, echocardiographic and electrocardiographic measurements, respectively. Significance was assumed at a 2-sided p <0.05.

RESULTS

Three hundred and fifty non-surviving patients were divided into three groups according to the day of the death. Of the non-surviving patients, 30% (104) died within three days, 32% (110) died within 4–10 days, and 39% (136) died after ten days. The patients' clinical and demographic characteristics are shown in **Table 1**. The patients who died within three days were older than the others (p<0.001). While the body mass index (BMI), gender, and smoking were similar between study groups (p>0.05), heart rate (HR), respiratory rate (RR), pneumonia on CT, CT score, and SDBHA were statistically different between the study groups (p <0.001). Moreover, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), ICU admission and body temperature values were different in study groups (p<0.001). In patients' past medical histories, DM, HLD, and malignancy were similar in the study population. Also, HT, CAD, COPD, and CKD were significantly higher in patients who died within three days (p<0.05). The hemoglobin, sodium, potassium, and glucose levels were similar among the three groups. WBC, creatinine, CRP, hs-TnI, d-dimer, procalcitonin, and oxygen saturation (sO2) levels were significantly different in patients who died three days compared to other groups (p<0.05). The previous medication was similar between the study groups (p>0.05). While the used drugs were compared between the groups during the disease, steroid and tocilizumab were significantly higher in the survival group than the non-survival group. Invasive mechanical ventilation (IMV), non-invasive mechanical ventilation (NIMV), high-flow oxygen (HFO), vasopressor, and renal replacement therapy (RTT) rates were higher in the non-surviving patients compared to surviving patients (p<0.05). MODS, cardiac, and kidney injury rates were significantly higher in patients who died three days than in other groups (p<0.05).

Table 1. The Demographic and Clinical Data of COVID-19 Patients.

	Survivor (n=150)	Non-survivor ≤3 days (n=104)	Non-survivor 4-10 days (n = 110)	Non-survivor >10 days (n = 136)	p
Clinical characteristics					
Age (years)	54.6±8.5$^{\#\&@}$	67.8±9.1$^{\#*a}$	64.0 ± 8.1$^{\&*}$	63.4 ± 7.7$^{@a}$	<0.001
Male, n (%)	93(62)	69(66)	74(67)	77(56)	0.187
BMI (kg/m^2)	23.9±3.3	23.4±2.3	24.2 ± 3.4	24.4 ±3.8	0.108
HR, beats/min	82.0±10.7$^{\#\&}$	91.3±12.3$^{\#*a}$	86.4±14.9$^{\&*e}$	81.3±12.0^{ae}	<0.001
RR, times/min	21.3±6.5$^{\#\&}$	28.0±8.5$^{\#*a}$	24.0±4.8$^{\&*e}$	21.7±4.2^{ae}	<0.001
SAP, mmHg	107.6±14.8$^{\#}$	98.514.4$^{\#*a}$	104.2±13.7*	106.9±15.0^{a}	<0.001
DAP, mmHg	66.1±11.1$^{\#}$	60.5±11.3$^{\#a}$	63.9±10.4	65.6±11.1^{a}	<0.001
Smoker, n (%)	65(43)	49(47)	54(49)	50(36)	0.125
Pneumonia on CT, n (%)	98(65)$^{\#\&}$	96(92)$^{\#*a}$	90(81)$^{\&*e}$	96(70)^{ae}	<0.001
CT score	2(0-4)$^{\#\&}$	6(3-11)$^{\#*a}$	2(2-7)$^{\&*e}$	2(1-5)^{ae}	<0.001
SDBHA (days)	4.1±2.0$^{\#\&@}$	7.23.1$^{\#*a}$	5.9±2.5$^{\&*e}$	4.9±2.1$^{@ae}$	<0.001
Hospital stay (days)	13(7-17)$^{\#\&}$	2(2-2)$^{\#*a}$	5(4-8)$^{\&*e}$	15(12-18)^{ae}	<0.001
ICU admission, n (%)	40(27)$^{\#\&}$	75(72)$^{\#*a}$	48(43)$^{\&*}$	43(31)^{a}	<0.001
Body Temperature (°C)	36.9±1.2$^{\#}$	37.71.9$^{\#*a}$	37.0±0.8*	36.9±0.6^{a}	<0.001
Chronic medical illness					
HT, n (%)	68(45)$^{\#}$	71(68)$^{\#*a}$	57(51)*	65(47)^{a}	0.012
DM, n (%)	36(24)	33(31)	25(22)	32(23)	0.301

CAD, n (%)	30(20)[#]	37(35)[#*a]	24(21)[*]	29(21)[a]	0.034
HLD, n (%)	38(25)	28(26)	31(28)	38(27)	0.875
Malignite, n (%)	9(6)	13(12)	9(8)	7(5)	0.203
COPD, n (%)	18(12)[#]	26(25)[#*a]	14(12)[*]	18(12)[a]	0.037
CKD, n (%)	15(10)[#]	24(23)[#*a]	14(12)[*]	16(11)[a]	0.039
Laboratory findings					
Haemoglobin(g/dl)	11.02.3	11.2±2.4	11.7 ± 1.8	11.5 ± 2.0	0.167
WBC (10^3 /µl)	8.0(5.0-14.0)[#]	9.3(7.0-19.7)[#*a]	8.3(5.1-13.1)[*]	8.3(5.9-13.0)[a]	0.009
Creatinine (mg/dl)	1.2(0.9-2.0)[#]	1.7(1.1-2.6)[#*a]	1.4(0.9-2.1)[*]	1.3(0.9-2.2)[a]	0.021
Sodium (mmol/L)	140.0±6.4	141.7±9.2	139.9 ± 9.3	141.4 ± 9.7	0.346
Potassium (mmol/L)	4.3±0.6	4.5±0.8	4.3 ± 0.8	4.3 ± 0.8	0.512
Glucose (mg/dL)	135(99-199)	141(105-205)	136(102-205)	149(112-237)	0.462
CRP (mg/dL)	110(80-165)[#]	131(111-185)[#*a]	114(89-171)[*]	113(70-172)[a]	<0.001
hs-TnI (NR<14pg/ml)	30(13-44)[#&@]	60(32-152)[#*a]	47(20-93)[&*e]	34(14-58)[@ae]	<0.001
D-dimer (ng/mL)	1460(757-2920)[#&@]	3490(1395-4080)[#*a]	2525(1120-4100)[&*e]	1465(925-3655)[@ae]	<0.001
Procalcitonin (ng/mL)	0.7(0.2-1.3)[#&]	1.8(0.4-11.7)[#a]	1.7(0.4-3.2)[&e]	0.9(0.3-2.7)[ae]	0.006
sO2	95.8±5.0[#&]	90.5±5.3[#*a]	92.9±5.1[&*e]	94.4±3.9[ae]	<0.001
Treatments					
ACEİ/ARB, n (%)	60(40)	50(48)	60(54)	58(42)	0.238
BB, n (%)	60(40)	51(49)	51(46)	52(38)	0.221
CCB, n (%)	38(25)	32(30)	35(31)	37(27)	0.665
ASA, n (%)	45(30)	37(35)	39(35)	38(27)	0.341
Statin, n (%)	38(25)	34(32)	32(29)	34(25)	0.421
OAD, n (%)	48(32)	36(34)	38(34)	41(30)	0.688
Steroid, n(%)	109(73)[#&@]	40(39)[#*a]	60(55)[&*]	78(58)[@a]	<0.001
Tocilizumab, n(%)	24(16)[#&@]	1(1)[#]	6(6)[&]	7(5)[@]	0.033
IMV, n(%)	33(22)[#&]	72(70)[#*a]	39(36)[&*]	38(28)[a]	0.004
NIMV, n(%)	21(14)[#&@]	28(27)[#*a]	58(53)[&*]	66(49)[@a]	<0.001
HFO, n(%)	37(25)[#&]	3(3)[#a]	12(11)[&e]	31(23)[ae]	0.007
Vasopressor, n(%)	24(16)[#&@]	70(68)[#*a]	35(32)[&*]	40(30)[@a]	<0.001
RRT, n(%)	0(0)[#&@]	27(26)[#]	20(19)[&]	28(21)[@]	0.031
Organ Injury					
Cardiac injury, n (%)	33(22)[#&@]	62(59)[#*a]	42(38)[&*]	44(32)[@a]	<0.001
MODS, n (%)	23(15)[#]	37(35)[#*a]	25(22)[*]	25(18)[a]	0.014
Acute kidney injury, n (%)	26(17)[#]	38(36)[#*a]	25(22)[*]	33(24)[a]	0.042

[#] *P*<0.05 Between surviver and ≤3 days groups, [&]*P*<0.05 Between surviver and 4-10 days groups, [@]*P*<0.05 Between surviver and >10 days groups, [*]*P*<0.05 Between ≤3 days and 4-10 days groups, [a]*P*<0.05 between 3 days and >10 days groups, [e]*P*<0.05 between 4-10 days and >10 days groups. **Abbreviations:** BMI, body mass index; HR, heart rate; RR, respiratory rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; CT, computed tomography; SDBHA, symptom duration before hospital admission; ICU, intensive care unit; HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HLD, hyperlipidemia; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; WBC, white blood cell, CRP, C-reactive protein; hs-TnI, high sensitive-Troponin I; NR, normal range; CK, creatinine kinase; sO2, oxygen saturation ; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; ASA, acetylsalicylic acid; OAD, oral antidiabetic; IMV, invasive mechanical ventilation; NIMV, non-invasive mechanical ventilation; HFO, high-flow oxygen; RRT, renal replacement therapy; MODS, multiple organ dysfunction syndrome.

The patients' echocardiography and ECG parameters are shown in **Table 2**. The LVEF and tricuspid annular plane systolic excursion (TAPSE) values were statistically different among the study groups (p<0.001). Left ventricular diastolic functions were lower in non-surviving patients than in patients who survived, and it was lowest in patients who died within the first three days. Left atrium (LA), right ventricular diameter, RV-FAC, systolic pulmonary artery pressure (sPAP), and pericardial effusion values were significantly higher in patients who died three days compared to other patients (p<0.001). While the left ventricular end-diastolic diameter (LVEDD) was similar between study groups, left ventricular end-systolic diameter (LVESD) was significantly higher in patients who died within three days. While there was no statistically significant difference between the groups in terms of the

Table 2. Comparison of Conventional Echocardiographic and Electrocardiographic Parameters of COVID-19 Patients.

Variables	Survive (n=150)	Non-survive 3 days (n=104)	Non-survive 4-10 days (n = 110)	Non-survive >10 days (n = 136)	p
Left heart findings					
LVEF (%)	59.9±7.1$^{\#\&}$	53.1±9.9$^{\#*a}$	57.3 ± 7.4$^{\&*e}$	59.6 ± 5.7^{ae}	<0.001
LVEDD (mm)	44.9±3.5	45.7±4.1	44.6±3.4	44.7±3.4	0.091
LVESD (mm)	28.8±3.7$^{\#}$	30.7±4.0$^{\#a}$	29.9 ± 3.9	28.9 ±3.3^{a}	0.013
LA (mm)	36.7±4.1$^{\#}$	42.3±4.5$^{\#*a}$	36.5±3.3*	37.3±5.1 ^{a}	<0.001
E/A ratio	1.2±0.4$^{\#\&@}$	0.7±0.2$^{\#*a}$	0.9±0.3$^{\&*}$	1.0±0.4$^{@a}$	<0.001
RV diamater(mm)	33.1±4.8$^{\#\&@}$	39.5±4.7$^{\#*a}$	36.5±4.1$^{\&*}$	36.1±4.4$^{@a}$	<0.001
RV-FAC (%)	45.5±5.5$^{\#\&}$	39.7±6.7$^{\#*a}$	42.9±5.3$^{\&*}$	43.9±4.8^{a}	<0.001
TAPSE (mm)	21.4±3.4$^{\#\&}$	18.2±3.2$^{\#*a}$	19.9±3.1$^{\&*e}$	21.5±3.0 ^{ae}	<0.001
sPAP, mmHg	30.1±5.1$^{\#}$	34.8±7.8$^{\#*a}$	31.6±8.0*	30.6±7.9^{a}	<0.001
ACP, n(%)	0(0)	7(7)	3(3)	3(2)	0.129
Pericardial effusion, n(%)	8(5)$^{\#\&@}$	31(30)$^{\#*a}$	16(17)$^{\&*}$	21(16)$^{@a}$	0.005
Sinus Rhythm, n (%)	139(93)$^{\#}$	82(78)$^{\#*a}$	97(88)*	125(91)^{a}	0.008
HR, beats/min	78.9±12.7$^{\#\&}$	91.3±12.3$^{\#*a}$	86.4±14.9$^{\&*e}$	81.3±12.0^{ae}	<0.001
RBBB, n(%)	12(8)	16(15)	10(9)	10(7)	0.182
LBBB, n(%)	9(6)	11(10)	7(6)	6(4)	0.328
ST depression,, n(%)	30(20)$^{\#}$	48(46)$^{\#*a}$	31(28)*	30(22)^{a}	<0.001
fQRS, n(%)	18(12)	15(14)	19(17)	19(14)	0.716
QTc	428.9±22.1	432.4±26.3	429.2±22.0	430.5±21.3	0.394

$^{\#}$ *P*<0.05 Between surviver and ≤3 days groups, $^{\&}$*P*<0.05 Between surviver and 4-10 days groups, $^{@}$*P*<0.05 Between surviver and >10 days groups, **P*<0.05 Between 3 days and 4-10 days groups, ^{a}*P*<0.05 between 3 days and >10 days groups, ^{e}*P*<0.05 between 4-10 days and >10 days groups. **Abbreviations:** LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESV, left ventricular end systolic diameter; LA, left atrial; RV-FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; sPAP, systolic pulmonary artery pressure; ACP, acute cor pulmonale; HR, heart rate; RBBB, right bundle branch block; LBBB, left bundle branch block; fQRS, fragmante QRS; QTc, corrected QT.

frequency of acute corrected QT values, it was highest in patients who died within the first three days. In the electrocardiographic analysis, right bundle branch block (RBBB), left bundle branch block (LBBB), fQRS, and QTc values were similar among the study groups. However, HR, ST-depression, and non-sinus rhythm ratios were higher in patients who died within three days compared to other patients.

Parameters affecting mortality were evaluated by univariate and multivariate analyzes using Cox regression analysis. Age, Pneumonia on CT, SDBHA, ICU, HT, CRP, d-dimer, cardiac injury, MODS, acute kidney injury, LVEF, RV-FAC, and Tocilizumab/Steroid parameters, which were statistically significant in the univariate analysis, were included in the multivariate analysis. These parameters were determined as independent predictors of mortality (**Table 3**).

Table 4 shows the independent predictors of mortality within three days. First, a regression model was used to elicit mortality predictors in regression analyses. Age, gender, pneumonia on CT, SDBHA, ICU, HT, CAD, CRP, d-dimer, MODS, cardiac and acute kidney injury, LVEF, RV-FAC, and Tocilizumab/Steroid were included in the regression analyses. Gender and CAD were not independent predictors of mortality within three days. However, age, pneumonia on CT, SDBHA, ICU, HT, CRP, d-dimer, MODS, cardiac and acute kidney injury, LVEF, RV-FAC, and Tocilizumab/Steroid were independent predictors of mortality within three days compared to the 4–10 days and more than ten days mortality and the surviving patients.

ROC curve analysis was used to evaluate the values for age, CT score, SDBHA, hs-TnI, and d-dimer to predict mortality within three days (**Figure 1**). Areas under the curve (AUC) for Age, CT score, SDBHA, hs-TnI, and d-dimer were determined (0.755 / 0.734 / 0.766 / 0.639 / 0.620, respectively). **Table 5** shows the sensitivity, specificity, and cut-off values of age, CT score, SDBHA, hs-TnI, and d-dimer. The age, CT score, SDBHA, hs-TnI, and d-dimer were evaluated by binary logistic regression

Table 3. Cox Regression Analysis on the Risk Factors Associated With Mortality in PatientsWith COVID-19.

Variable	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Age	2.295	1.488-5.142	<0.001	1.110	1.033-1.254	0.001
Gender	1.601	0.771-4.976	0.450			
Pneumonia on CT	5.245	2.101-10.431	<0.001	6.513	2.266-12.765	<0.001
SDBHA	1.421	1.091-2.822	0.009	1.102	1.017-1.273	0.011
ICU	3.003	1.641-8.499	<0.001	4.653	1.989-9.762	<0.001
HT	1.932	1.081-4.989	0.002	2.010	1.256-5.665	0.008
CAD	1.210	0.991-1.909	0.231			
CRP	3.141	1.754-8.249	<0.001	1.975	1.168-4.052	0.005
D-dimer	1.215	1.084-1.413	<0.001	1.022	1.006-1.049	0.003
Cardiac injury	3.165	1.622-8.555	<0.001	1.952	1.075-3.405	0.010
MODS	3.972	1.255-7.973	<0.001	3.080	1.753-7.231	<0.001
Acute kidney injury	1.563	1.107-3.882	<0.001	1.217	1.029-3.918	0.014
LVEF	0.894	0.710-0.994	<0.001	0.924	0.886-0.981	<0.001
RV-FAC	0.855	0.612-0.949	<0.001	0.875	0.811-0.951	<0.001
Tocilizumab/Steroid	0.377	0.218-0.689	<0.001	0.410	0.261-0.732	0.001

Abbreviations: CT, computed tomography; SDBHA, symptom duration before hospital admission; ICU, intensive care unit; HT, hypertension; CAD, coronary artery disease; CRP, C-reactive protein; MODS, multiple organ dysfunction syndrome; LVEF, left ventricular ejection fraction; RV-FAC, right ventricular fractional area change.

analysis to determine the combined diagnosis model. Then the combined diagnosis model was analyzed by the ROC curve. In **Figure 2**, the red line represents the combined diagnosis model, and the AUC was 0.913.

Reproducibility

CT score, and echocardiography and electrocardiography values of 20 patients were randomly selected to assess intra-observer and interobserver reliability. The intra-observer and interobserver variabilities for CT score were 0.93 and 0.90, respectively. The intra-observer and interobserver variabilities for echocardiography were 0.91 and 0.88, respectively, and the intra-observer and interobserver variabilities for electrocardiography were 0.94 and 0.91, respectively.

DISCUSSION

This study has investigated short- and long-term mortality predictors in surviving and non-surviving COVID-19 patients. First, we showed that age, pneumonia on CT, SDBHA, ICU admission, HT, CRP, d-dimer, MODS, cardiac and acute kidney injury, LVEF, RV-FAC and Tocilizumab/Steroid therapy were independent predictors of mortality within three days. Second, the AUC values of the age, CT score, SDBHA, hs-TnI, and d-dimer were statistically significant in showing mortality within three days. Finally, the combined diagnosis model had a strong predictive value for mortality within three days in COVID-19 patients who died.

The rapid spread of COVID-19 infection worldwide has put the health systems in a difficult situation that has never been experienced before. The exact cause of patient death has not been fully elucidated against the hyperinflammatory reaction and hypercoagulopathy that is the primary pathophysiological mechanism of COVID-19.[24,25] Unlike classical ARDS, COVID-19 ARDS is characterized by early pulmonary endothelial damage using Ang 2 and ICAM-1 pathological pathways.[26] It is known that ICU patients have higher mortality rates than non-ICU patients (30–70%).[27]

Due to the high mortality rates in severe COVID-19 patients, many previous studies tried to find the best model for predicting mortality. As in our research, the data presented in the literature indicate that age was an independent predictor of mortality.[12,28,29] A recent study comparing patients according to age group showed that mortality increased with age.[30] Pulmonary infiltrates

Table 4. Multinomial Logistic Regression analysis on the risk factors associated with short-term mortality in patients with COVID-19.

Survive	OR	95% CI	p	Variable (4-10 days)	OR	OR	95% CI	p	Variable (>10 days)	OR	95% CI	p
Age	2.113	1.301-3.443	0.009	Age	1.654	1.654	1.064-2.741	0.017	Age	1.865	1.094-3.362	0.011
Gender	1.421	0.824-4.432	0.321	Gender	1.326	1.326	0.899-4.141	0.341	Gender	1.532	0.872-4.172	0.512
Pneumonia on CT	7.653	2.534-12.856	<0.001	Pneumonia on CT	3.031	3.031	1.754-6.10	0.001	Pneumonia on CT	6.012	2.210-13.978	<0.001
SDBHA	1.432	1.141-2.465	0.014	SDBHA	1.231	1.231	1.092-2.876	0.022	SDBHA	1.302	1.099-1.600	0.018
ICU	3.441	1.580-8.745	<0.001	ICU	3.352	3.352	1.243-8.683	<0.001	ICU	3.212	1.431-8.435	<0.001
HT	1.876	1.053-4.126	0.013	HT	1.142	1.142	1.020-2.637	0.020	HT	1.212	1.078-4.031	0.016
CAD	1.154	0.853-2.798	0.372	CAD	1.021	1.021	0.984-1.072	0.672	CAD	1.142	0.831-3.579	0.597
CRP	1.957	1.069-5.132	0.004	CRP	1.474	1.474	1.091-2.982	0.009	CRP	1.531	1.103-2.985	0.007
D-dimer	1.053	1.011-1.163	<0.001	D-dimer	1.012	1.012	1.003-1.028	0.003	D-dimer	1.021	1.006-1.039	0.001
Cardiac injury	4.765	1.949-11.423	<0.001	Cardiac injury	4.231	4.231	1.463-10.856	<0.001	Cardiac injury	4.972	1.342-9.187	<0.001
MODS	3.965	1.451-8.763	<0.001	MODS	3.442	3.442	1.474-7.345	<0.001	MODS	3.902	1.792-8.945	<0.001
Acute kidney injury	1.721	1.068-4.173	0.012	Acute kidney injury	1.451	1.451	1.143-3.373	0.026	Acute kidney injury	1.605	1.101-3.869	0.016
LVEF	0.821	0.713-0.951	<0.001	LVEF	0.912	0.912	0.887-0.972	0.005	LVEF	0.889	0.798-0.973	<0.001
RV-FAC	0.817	0.699-0.948	<0.001	RV-FAC	0.902	0.902	0.859-0.949	0.001	RV-FAC	0.873	0.727-0.956	<0.001
Tocilizumab/ Steroid	0.310	0.198-0.632	<0.001	Tocilizumab/ Steroid	0.409	0.409	0.238-0.825	<0.001	Tocilizumab/ Steroid	0.369	0.220-0.701	<0.001

Abbreviations: CT, computed tomography; SDBHA, symptom duration before hospital admission; ICU, intensive care unit; HT, hypertension; CAD, coronary artery disease; CRP, C-reactive protein; MODS, multiple organ dysfunction syndrome; LVEF, left ventricular ejection fraction; RV-FAC, right ventricular fractional area change.

Table 5. Parameter Values Predicting Early Mortality as a Result of ROC Analysis in Patients with Death due to COVID-19.

Variable	AUC	p	95%CI	Sensitivity	Specificity	Cut-off value
Age	0.755	<0.001	0.701-0.810	65	66	³ 64.5
CT score	0.734	<0.001	0.678-797	74	60	³ 3.5
SDBHA	0.766	<0.001	0.717-0.815	79	63	³ 5.5
hs-TnI	0.639	<0.001	0.576-0.701	59	57	40.5
D-dimer	0.620	<0.001	0.560-0.681	61	61	³ 2705
CDM	0.913	<0.001	0.883-0.942	84	80	³ 0.25

Abbreviation: CT, computed tomography; SDBHA, symptom duration before hospital admission hs-TnI, high sensitive-Troponin I; CDM, Combined diagnosis model

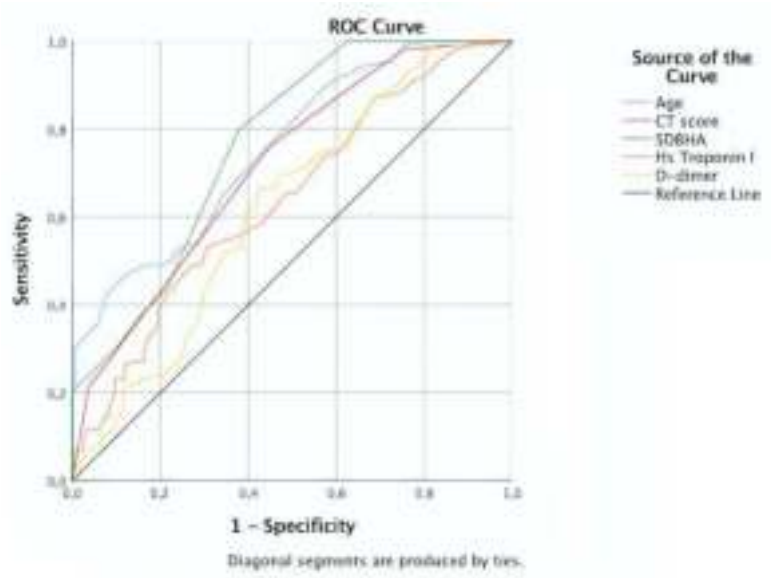

Figure 1. In ROC curve analyses, areas under the curve (AUC) for Age, computed tomography (CT) score, symptom duration before hospital admission (SDBHA), high sensitive-Troponin I (hs-TnI), and D-dimer were determined (0.755 / 0.734 / 0.766 / 0.639 / 0.620 respectively).

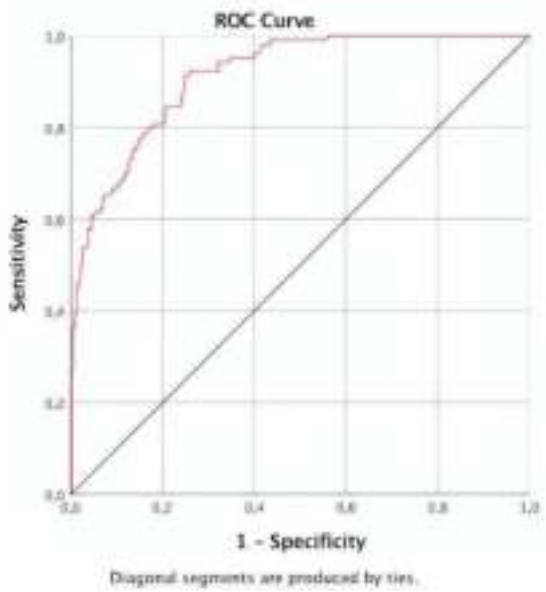

Figure 2. The combined diagnosis model of the age, computed tomography (CT) score, symptom duration before hospital admission (SDBHA), high sensitive-Troponin I (hs-TnI), and D-dimer was analyzed by the ROC curve. The red line represents the combined diagnosis model, and the area under the curve (AUC) was 0.913.

on CT are also an independent predictor of mortality over time. This study presented that COVID-19 patients with pulmonary infiltration have a poor prognosis, consistent with other literature reports.[30,31] Unlike previous studies,[11,32] we indicated SDBHA was an independent predictor of mortality. Possible mechanisms that affect SDBHA as an independent predictor were advanced disease due to delayed diagnosis and thrombotic complications. Given the importance of the early treatment of COVID-19, it seems logical that delayed hospital admissions are related to short-term mortality. The current study presented that ICU admission, HT, CRP, and d-dimer were short-term mortality predictors, which has been proven many times in previous studies.[33]

COVID-19 has adverse effects on the cardiovascular system, and the myocardial injury rate was 14%–19% in these patients.[1,34] High platelet activation has been shown to correlate with disease severity, myocardial damage, and mortality.[35] The current study showed that COVID-19 associated myocardial injury was an independent predictor of short-term mortality, consistent with the literature report.[29,36,37] Therefore, it seems logical that decreased LVEF and RV-FAC values were independent predictors of short-term mortality in COVID-19 patients with cardiac injury. Barman et al. demonstrated that decreased LVEF and RV-FAC were associated with disease severity in COVID-19 patients.[38] Similar to our study results, a previous investigation showed that decreased left and right ventricular function were related to mortality in COVID-19 patients.[39] It is known that myocardial injury is associated with worse prognosis in COVID-19 patients.[12,40] It seems that cardiac functions are affected by many mechanisms and mortality significantly increased in these patients. The mechanisms that affect cardiac functions, such as: (I) cytokine storm and multi-organ failure due to acute systemic inflammatory response, (II) an imbalance between myocardial oxygen supply and demand which secondary to severe hypoxia due to acute respiratory failure, (III) medications related to cardiotoxicity, (IIII) increased coronary thrombosis and embolic complications due to systemic inflammation, (V) the heart inflammation caused by COVID-19 can directly cause myocarditis. Considering these mechanisms, decreased left and right ventricular functions affect early mortality in COVID-19 patients. Moreover, in the regression analyses, we determined MODS was an independent predictor of short-term mortality. Our study results showed the COVID-19 adverse effect is not limited to lung injury but also renal insufficiency and cardiac injury.[41,42] Clinicians should be aware of and manage the potential systemic complications of COVID-19, such as MODS. COVID-19 associated mortality predictors provide potential clinical benefit to improve characterization and comprehensive evaluation of these patients who have an inadequate response to conventional therapy.

This study also determined that age, CT score, SDBHA, hs-TnI, and d-dimer were independently associated with short-term mortality in non-survived COVID-19 patients. Moreover, these parameters' diagnostic value was compatible with previous studies.[31,43-45] To determine the best-fitting model, we analyzed various variables in binary logistic regressions. Then we used a combined model to find the best predictor of short-term mortality in COVID-19 patients who died. The current study indicated the combined diagnosis model was a strong predictor of short-term mortality (AUC value 0.91 (95% CI, 0.88–0.94)). Because of the high mortality rate in critically ill COVID-19 patients (49%), it is crucial to identify patients with a bad prognosis in the early stages.[46] Therefore, we assumed the combined diagnosis model might help physicians predict the prognosis of COVID-19 patients earlier and guide their treatment methods. Thus, severe COVID-19 patients can be monitored closely for mortality and might be treated in the early stages of the disease.

Even though COVID-19 patients may have a good or poor clinical prognosis, the course of the disease is not entirely predictable. The current study was designed to partially fill this critical gap. Therefore, we have evaluated the effects of various clinical factors on mortality by days.

The current study is unique and has specific strengths compared to previous studies.

COVID-19 patients who died were categorized according to their survival time rather than other factors used in earlier reports. Another advantage of our study is that the combined diagnosis model was created by clinical, laboratory, and imaging parameters. The combined model was a predictor of short-term mortality in non-surviving COVID-19 patients, which is a strength of our study compared with literature data. Another essential difference in our study is that we tried to find a more accurate definition of patients who died within the first 72 hours. If we can identify the acute phase, and then we can raise awareness to diagnose these patients earlier.

On February 24, 2022, about 25 months since the first reported case of COVID-19 and after a global estimated 426 million cases and 5.8 million deaths was reported.[47] On 25 November 2021, the world health organization listed Omicron as a new variant of concern. Omicron has some deletions and more than 30 mutations.[48] Moreover, Omicron has 15 mutations in the receptor-binding domain of spike. These mutations are increased transmissibility, higher viral binding affinity, and higher antibody escape.[49,50] The Omicron variant is more infectious than the previous variants.[51] Also, an increased risk of reinfection related to Omicron.[52] Omicron variant is related to lower risk of COVID-19 hospitalization.[53] Vaccinated people have a much lower risk of severe disease from omicron infection. Cough, runny/stuffy nose, fatigue/lethargy, sore throat, headache, and fever were the most prevalent symptoms.[54] The current COVID-19 vaccines associated with lower immunity to the omicron variant. Moreover, a new booster dose will increase the efficacy against omicron infection.[55]

By March 2021, thirteen vaccines have been authorized for use in many countries. These vaccines have been demonstrated to be effective in preventing the infection of COVID-19 at varying efficacy. COVID-19 vaccines have essentially focused on prevention of infection and hospitalizations.[56,57] SARS-CoV-2 infection in vaccinated persons is expected to trigger memory antibody and cellular responses owing to prior vaccination; these immune responses could mitigate disease progression, possibly preventing life-threatening organ failure and death.[58,59] Tenforde et al. evaluated the association between vaccination and COVID-19 hospitalization and disease severity. They presented that COVID-19 hospitalization was strongly associated with lower likelihood of vaccination for previous variants. And vaccinated cases less commonly received invasive mechanical ventilation. Moreover, COVID-19 hospitalization was strongly related to a lower likelihood of vaccination. Among patients hospitalized with COVID-19, the outcome of death or invasive mechanical ventilation was associated with a lower likelihood of vaccination.[60] We have designed our research in March 2020 and January 2021. And our patients had not got omicron variant at that time. We know that patients with omicron have lower hospitality and mortality. Also, our patients were not vaccinated, so they have higher mortality rates than vaccinated patients.

This study has limitations, including the retrospective study design, and the number of patients was relatively low. Another limitation is that we did not include the complaints of the patients on admission. A subgroup analysis of MODS was not performed due to the limited number of patients. Also, the study's design did not allow the accurate retrieval of data to include underlying diseases, potentially up or down-scoring the net effect of each comorbidity. As criteria for hospitalization of COVID–19 patients are different across different institutions, an inclusion bias cannot be excluded. Finally, as this is an observational study, residual confounding may exist.

CONCLUSION

In conclusion, this study discovered that age, pneumonia on CT, SDBHA, ICU, HT, CRP, d-dimer, cardiac injury, MODS, acute kidney injury, LVEF, and RV-FAC were all independently associated with short-term mortality in COVID-19 patients in the Turkish population. Moreover, Tocilizumab/Steroid therapy was a protective and independent predictor of mortality within three days. The combined diagnosis model was a strong predictor of short-term mortality in non-

surviving COVID-19 patients. Because of the increased mortality risk in severe COVID-19 patients, it is essential to identify poor prognosis markers at an early stage. More prospective randomized studies are needed to confirm our findings.

COMPETING INTERESTS

All authors have no declarations of interest to report.

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AUTHORS' CONTRİBUTİONS

Atici A, Asoglu R, Barman HA and Aciksari G contributed to the conception and design of the study; Baycan OF, Tatlisu MA and Ozcan FB collected data; Atici A, and Yilmaz Y analysed the data; Atici A, and Caliskan M wrote and revised the manuscript.

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REFERENCES

1. Chaolin Huang, Yeming Wang, Xingwang Li, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497–506.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. 2020;
3. Coronavirus Disease (COVID-19) Situation Reports [Internet]. [cited 2021 Jan 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
4. Nanshan Chen, Min Zhou, Xuan Dong, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507–13.
5. Dawei Wang, Bo Hu, Chang Hu, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.
6. Yang F, Shi S, Zhu J, et al. Analysis of 92 deceased patients with COVID-19. J Med Virol. 2020; 10.1002/jmv.25891.
7. Matt Arentz, Eric Yim, Lindy Klaff, et al. Characteristics and outcomes of 21 critically Ill patients with COVID-19 in Washington State. JAMA. 2020;323(16):1612–4.
8. Chaomin Wu, Xiaoyan Chen, Yanping Cai, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7): 1–11.
9. Xiaobo Yang, Yuan Yu, Jiqian Xu, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;475-81.
10. Zhaohai Zheng, Fang Peng, Buyun Xu , et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;e16-e25.
11. Fei Zhou, Ting Yu, Ronghui Du, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet. 2020;395:1054–62.
12. Barman Hasan Ali, Atici Adem, Sahin Irfan, et al. Prognostic significance of cardiac injury in COVID-19 patients with and without coronary artery disease. Coron Artery Dis. 2020;10.1097.
13. Li Yan, Hai-Tao Zhang, Jorge Goncalves, et al. An interpretable mortality prediction model for COVID-19 patients. Nat Mach Intell. 2020;1–6.
14. Mikulska M, Nicolini LA, Signori A, et al. Tocilizumab and steroid treatment in patients with COVID-19. pneumonia. PLoS One. 2020;15(8):e0237831.
15. udadappanavar AM, Benni J. An evidence-based systematic review on emerging therapeutic and preventive strategies to treat novel coronavirus (SARS-CoV-2) during an outbreak scenario. J Basic Clin Physiol Pharmacol. 2020;2191-0286.
16. Lara Bull-Otterson, Elizabeth B Gray, Daniel S Budnitz, et al. Hydroxychloroquine and Chloroquine Prescribing Patterns by Provider Specialty Following Initial Reports of Potential Benefit for COVID-19 Treatment—United States. Morb Mortal Wkly Rep. 2020;69(35):1210.
17. Feng Pan, Tianhe Ye, Peng Sun, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020;295:715–21.
18. Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, et al. and The Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40(3):237–69.
19. John A. Kellum, Norbert Lameire, Peter Aspelin, et al.

Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1–138.
20. Roberto M. Lang, Luigi P. Badano, Victor Mor-Avi, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J-Cardiovasc Imaging. 2015;16(3):233–71.
21. Prineas RJ, Crow RS, Zhang Z-M. The Minnesota code manual of electrocardiographic findings. Springer Science & Business Media; 2009.
22. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. J Electrocardiol. 2004;37:81–90.
23. Das MK, Khan B, Jacob S, et al. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation. 2006;113(21):2495–501.
24. McGonagle D, Sharif K, O'Regan A, Bridgewood C. Interleukin-6 use in COVID-19 pneumonia related macrophage activation syndrome. Autoimmun Rev. 2020;102537.
25. Tang N, Bai H, Chen X, et al . Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094–9.
26. Spadaro S, Fogagnolo A, Campo G, et al. Markers of endothelial and epithelial pulmonary injury in mechanically ventilated COVID-19 ICU patients. Crit Care. 2021;25(1):74.
27. D. Thomas-Rüddel, J. Winning, P. Dickmann, et al. Coronavirus disease 2019 (COVID-19): update for anesthesiologists and intensivists March 2020. Anaesthesist. 2020;1–10.
28. Sufei Wang, Pei Ma, Shujing Zhang, et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. Diabetologia. 2020;63(10):2102–11.
29. Jiqian Xu, Xiaobo Yang, Luyu Yang, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. Crit Care. 2020;24(1):1–11.
30. Carrillo-Vega MF, Salinas-Escudero G, Garcia-Peña C, et al. Early estimation of the risk factors for hospitalisation and mortality by COVID-19 in Mexico. medRxiv. 2020; 20098145.
31. Celal Saticia Mustafa, Asim Demirkol, Elif Sargin, et al. Performance of pneumonia severity index and CURB-65 in predicting 30-day mortality in patients with COVID-19. Int J Infect Dis. 2020;98:84–9.
32. Martins-Filho PR, Tavares CSS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. Eur J Intern Med. 2020;76:97–9.
33. Wenjie Tian, Wanlin Jiang, Jie Yao, et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. J Med Virol. 2020; 92:1875–1883.
34. Shaobo Shi, Mu Qin, Bo Shen, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;802-10.
35. Campo G, Contoli M, Fogagnolo A, et al. Over time relationship between platelet reactivity, myocardial injury and mortality in patients with SARS-CoV-2-associated respiratory failure. Platelets. 2020:1-8.
36. Dominik Rath, Álvaro Petersen-Uribe, Alban Avdiu, et al. Impaired cardiac function is associated with mortality in patients with acute COVID-19 infection. Clin Res Cardiol. 2020;1–9.
37. Omer Faruk Baycan, Hasan Ali Barman, Adem Atici, et al. Evaluation of biventricular function in patients with COVID-19 using speckle tracking echocardiography. Int J Cardiovasc Imaging. 2020;1–10.
38. Barman HA, Atici A, Tekin EA, et al. Echocardiographic features of patients with COVID-19 infection: a cross-sectional study. Int J Cardiovasc Imaging. 2021;37(3):825-34.
39. Pimentel SLG, Nascimento BR, Franco J, et al. Bedside echocardiography to predict mortality of COVID-19 patients beyond clinical data: Data from the PROVAR-COVID study. Rev Soc Bras Med Trop. 2021;54:e03822021.
40. Frattini S, Maccagni G, Italia L, Metra M, Danzi GB. Coronavirus disease 2019 and cardiovascular implications. J Cardiovasc Med. 2020;21(10):725–32.
41. Hamming I, Timens W, Bulthuis M, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol J Pathol Soc G B Irel. 2004;203(2):631–7.
42. He Yan, Shanshan Lu, Liangpei Chen, et al. Multiple organ injury on admission predicts in-hospital mortality in patients with COVID-19. J Med Virol.2020;1–13.
43. Jing Zhou, Lili Huang, Jin Chen, et al. Clinical features predicting mortality risk in older patients with COVID-19. Curr Med Res Opin. 2020;0(ja):1–1.
44. Jiatian Cao, Yan Zheng, Zhe Luo, et al. Myocardial injury and COVID-19: Serum hs-cTnI level in risk stratification and the prediction of 30-day fatality in COVID-19 patients with no prior cardiovascular disease. Theranostics. 2020;10(21):9663.
45. Marco Francone, Franco Iafrate, Giorgio Maria Masci, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;1–10.
46. Lingxi Guo, Dong Wei, Xinxin Zhang, et al. Clinical features predicting mortality risk in patients with viral

pneumonia: the MuLBSTA score. Front Microbiol. 2019;10:2752.
47. WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2022 Feb 24]. Available from: https://covid19.who.int
48. GISAID - hCov19 Variants [Internet]. [cited 2022 Feb 24]. Available from: https://www.gisaid.org/hcov19-variants/
49. Greaney AJ, Starr TN, Gilchuk P, et al. Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition. Cell Host Microbe. 2021;29(1):44–57.
50. Harvey WT, Carabelli AM, Jackson B, et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol. 2021;19(7):409–24.
51. Karim SSA, Karim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. The Lancet. 2021;398(10317):2126–8.
52. Pulliam JR, van Schalkwyk C, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. MedRxiv. 2021.
53. Sheikh A, Kerr S, Woolhouse M, et al. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: National cohort with nested test negative design study in Scotland. 2021.
54. Brandal LT, MacDonald E, Veneti L, et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. Eurosurveillance. 2021;26(50):2101147.
55. Khoury DS, Steain M, Triccas J, et al. Analysis: A meta-analysis of early results to predict vaccine efficacy against Omicron. medRxiv. 2021.
56. Barda N, Dagan N, Balicer RD. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. Reply. N Engl J Med. 2021;384(20):1970.
57. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. The Lancet. 2021;397(10287):1819–29.
58. Cromer D, Juno JA, Khoury D, et al. Prospects for durable immune control of SARS-CoV-2 and prevention of reinfection. Nat Rev Immunol. 2021;21(6):395–404.
59. Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol. 2021;21(8):475–84.
60. Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA. 2021;326(20):2043–54.

Parenteral and Oral Anticoagulant Treatment for Hospitalized and Post-Discharge COVID-19 Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: *The use of anticoagulants has been endorsed by different hematological societies as coagulation abnormalities are key features of COVID-19 patients. This systematic review and meta-analysis aims to provide the most recent update on available evidence on the clinical benefits and risk of oral and parenteral anticoagulants, as well agents with anticoagulant properties, in hospitalized and post-discharge COVID-19 patients.* ***Methods:*** *This systematic review synthesizes data on the outcome of anticoagulation in hospitalized and post-discharge COVID-19 patients. Dichotomous variables from individual studies were pooled by risk ratio (RR) and their 95% confidence interval (95% CI) using the random-effects model. Meta-analyses were performed when feasible.* ***Results:*** *We included 32 studies from 2.815 unique citations, including 7 randomized clinical trials. A total of 33.494 patients were included. Outcomes measured include mortality and survival rates, the requirement for ICU care and mechanical ventilation. A pooled meta-analysis favors anticoagulant compared to no anticoagulant with reduced mortality in hospitalized patients (RR 0,55; 95%CI 0,43-0,66; p<0,001). Higher dose of anticoagulant also showed treatment benefit compared to standard prophylactic dose in selected populations (RR 0,68; 95%CI 0,40-0,96; p<0,001). Regular, pre-hospital anticoagulation prior to hospitalization yielded mixed result. There are currently no data on the benefit of anticoagulation on post-discharge COVID-19 patients.* ***Conclusion:*** *Determination of the presence of thrombosis in COVID-19 is important, as therapeutic dosage of anticoagulants, rather than prophylatic dose, would be indicated in such clinical situation. Anticoagulants were found to decrease the mortality of hospitalized COVID-19. The results from this study are important in the tailored treatment of COVID-19 patients. Further studies on the need for oral anticoagulation for outpatients or post-discharge is warranted. This study has been registered in PROSPERO database (CRD42020201418).*

Keywords**:** *COVID-19, anticoagulant, VTE, thromboprophylaxis.*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak in December 2019 developed into a pandemic of severe pneumonia, frequently with multiorgan involvement. Coagulation abnormalities in the direction of hypercoagulable state are present in a number of COVID-19 patients.[1] Additionally, acute illness and a hyperinflammatory state may predispose to thrombotic events in these patients.[2,3] The risk for venous thromboembolism (VTE) in COVID-19 patients is markedly increased, especially in intensive care unit (ICU) patients, with case series reporting a prevalence of between 20 to 43 percent among ICU patients, often despite prophylactic-dose anticoagulation.[4-8]

Data suggests that the COVID-19 associated coagulopathy is a combination of mild DIC with pulmonary thrombotic microangiopathy.[9] The pathogenesis of these abnormalities in patients with COVID-19 are still incompletely understood. The use of anticoagulants has been endorsed by different thrombosis and hematological societies based these observed findings. The guidance by the International Society of Thrombosis and Hemostasis (ISTH) states that a universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH in hospitalized non-ICU should be used after careful assessment of bleeding risk, with LMWH as the preferred agent in COVID-19 patients.[10-12] Furthermore, the American Society of Hematology (ASH) recommends the use of prophylactic dose when compared to high-intensity prophylaxis in the critically ill or acutely ill patients.[13] In the outpatient COVID-19 population, the ISTH guideline stated that it is reasonable to consider extended-duration thromboprophylaxis with LMWH or a DOAC for at least 2 weeks and up to 6 weeks post-hospital discharge in selected COVID-19 patients who are at low risk for bleeding and with key VTE risk factors.[10, 14] However, this recommendation was not specifically based on studies in COVID-19 patients.

Regardless of the recommendations above, evidence on the benefit and risk of both prophylactic or higher dose of anticoagulants in COVID-19 patients are lacking. Recently, agents with anticoagulation effects are also being studied as potential treatments for COVID-19 which could add to the repertoire of drugs used in the treatment of COVID-19.[15,16] This study aims to investigate the outcomes of parenteral and oral anticoagulants in the standard care of COVID-19 hospitalized inpatients and post-discharge outpatients. The population of interest are COVID-19 inpatients and post-discharge outpatients who tested positive with SARS-CoV-2 PCR. The interventions studied are parenteral anticoagulants, including the novel alternative anticoagulants and oral anticoagulants, with standard treatment as comparison. The main outcome includes mortality and survival rates, the requirement for ICU care and mechanical ventilation.

METHODS

This systematic review was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[17] The protocol of this systematic review has been registered in The International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020201418).

Eligibility Criteria

The inclusion criteria are human study, full-text, English, randomized control trial, and observational studies that investigate the use of anticoagulants in patients infected with 2019-novel coronavirus (COVID-19). Exclusion criteria include infection of unspecific coronaviruses or other respiratory viruses and studies on pediatric patients.

Search Strategy

A systematic review was performed on the literatures gathered between 22 September 2021 and 11 March 2022 using several databases: Cochrane, EBSCO, Pubmed, and EMBASE with keywords: ((Anticoagulant) AND ("COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19") AND ("admission" OR "hospital stay" OR "mortality" OR "morbidity" OR "outcome" OR "death" OR "survival"). The reporting of this study is based on the Preferred Reporting

Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[17]

Data Extraction

Data from included studies was extracted in standardized form, including characteristics of study design, setting, population description. Study citations included the name of the first author, year of publication, and title of the study. Therapies received, comorbidities, venous and arterial thrombosis, clinical severity, bleeding events and mortality are extracted from the included studies. Measures of associations extracted included odd's ratio (OR), hazard's ratio (HR) and relative risk (RR).

Quality and Risk of Bias Assessments

Two independent reviewers conducted the quality assessment of the studies on its validity, importance, applicability, and level of evidence (RNT and ENT). The quality of observational studies and risk of bias in the randomized clinical trials was assessed using the Newcastle Ottawa Quality Assessment Scale (NOS)[18] and Cochrane risk-of-bias tool for randomized trials (ROB2),[19] respectively. Any difference in assessments between reviewers were discussed until it reached a conclusion.

Statistical Analyses

Data for meta-analyses was synthesized based on minimum of three different high-quality studies with consistent findings. The obtained data was analyzed by taking into account the method of variable analysis used, study size, odds/hazard ratio, and confidence interval. Heterogeneity was evaluated using the I^2 statistic to assess the degree of inter-study variation. I^2 values of 0–24.9%, 25–49.9%, 50–74.9%, and 75–100% were considered as having no, mild, moderate, and significant thresholds for statistical heterogeneity, respectively.[20] A random-effects model was used. We intended to assess publication bias using funnel plot techniques, Begg's rank test and Egger's regression test, when the number of studies analyzed reached a minimum of 10.[21] Statistical analyses were made using Meta-Essentials (version 1.4, Rotterdam, The Netherlands).[22]

RESULTS

Study Selection

Literature searching was done from the study databases ProQuest, Pubmed, Medline and Cochrane. Out of 2.815 unique articles identified, we included a total of 32 studies. Of these studies, 7 were randomized clinical trials, 22 were observational studies and 3 were case series. Literature searching according to keywords listed in **Table 1** detailed the 32 studies eligible for review. The study flow is presented according to the PRISMA statement (**Figure 1**).

Table 1. Search Queries of This Systematic Review.

Database	Keywords	Hits
ProQuest	((anticoagulant* or anticoagulation*) AND ("COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19")) AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity OR outcome OR death OR survival)	103
Pubmed	(anticoagulant* or anticoagulation*) AND ("COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19") AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity OR outcome OR death OR survival)	37
Medline	(anticoagulant* or anticoagulation*) AND ("COVID-19" OR "SARS-CoV-2" OR "2019 novel coronavirus infection" OR "2019-nCoV" OR "coronavirus disease 2019" OR "coronavirus disease-19") AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity OR outcome OR death OR survival)	20
Cochrane	(anticoagulant* or anticoagulation*) AND (covid-19 OR coronavirus OR sars-cov-2) AND (hospitali?ation OR admission OR hospital stay OR mortality OR morbidity OR outcome or death or survival)	2
Handsearching	Anticoagulant and COVID-19	

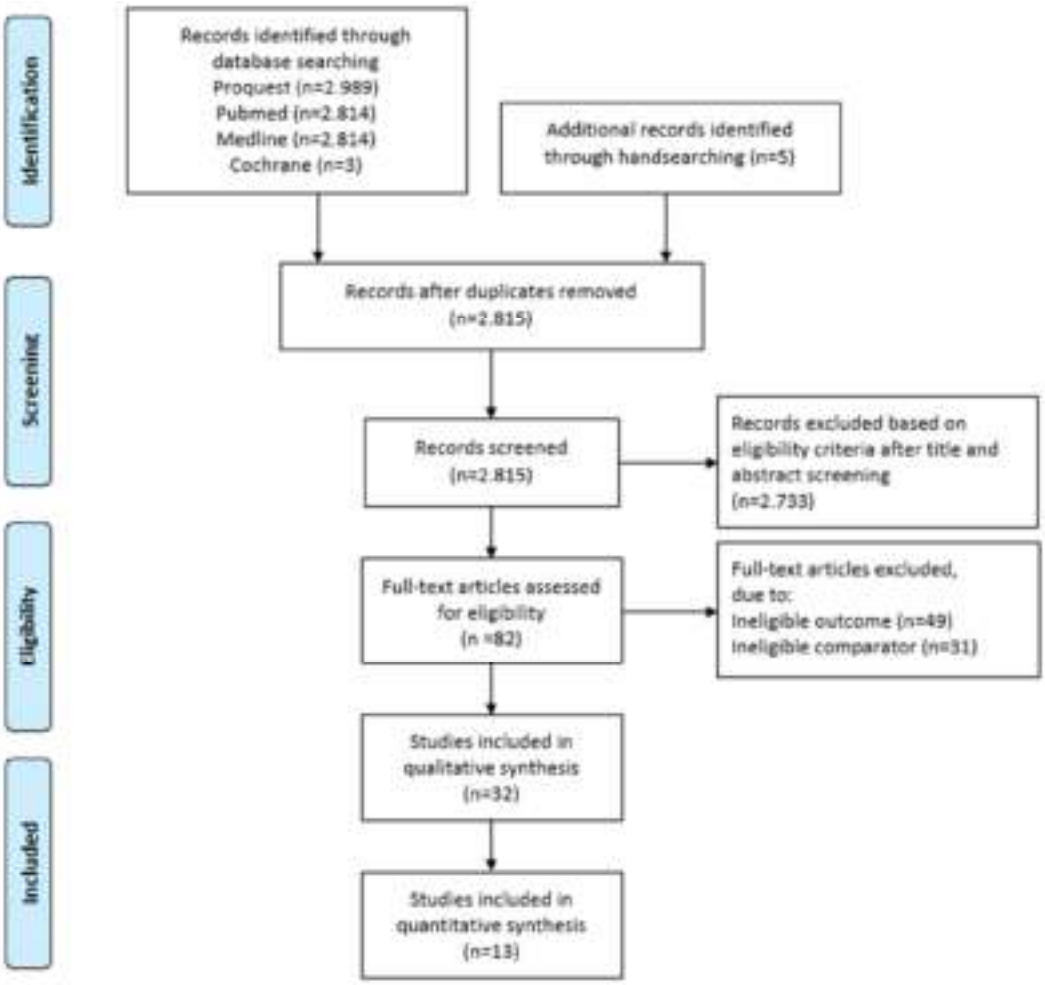

Figure 1. PRISMA flowchart of study selection.

Study Characteristics

This systematic review and meta-analysis include a total of 33,494 hospitalized COVID-19 patients from a total of 32 studies. Summary of the baseline study characteristics and results are listed in **Table 2**. We classified the studies into 3 groups, namely studies on in-hospital anticoagulant use (n=23), studies on pre-hospital anticoagulant use (n=6), and case series on the use of drugs with anticoagulant effects (n=3). Seven studies were conducted in the ICU setting, with one clinical trial involving patients categorized as requiring ICU care.[23] All observational studies used retrospective cohort design to assess the relationship between the use of anticoagulants and mortality or thromboembolism. During the course of the COVID-19 pandemic, the use of prophylactic anticoagulant was recommended by various hematological societies as standard care for hospitalized COVID-19 patients.[10,11,13] Therefore, the more recent studies compared the efficacies between standard prophylactic dose of anticoagulant vs. higher doses. Quantitative analyses were performed for 7 studies comparing anticoagulant vs. no anticoagulant use and for 6 studies comparing higher dose of anticoagulant vs. standard prophylactic dose.

Quality of Eligible Studies and Risk of Bias

The quality of each observational study was assessed using The Newcastle Ottawa Scale and all but one study was considered high quality (**Table 3**). All randomized clinical trials had low risk of bias except for one study with some concern of bias (**Figure 2**). There were inadequate numbers of included trials to properly assess a funnel plot or perform more advanced regression-based assessments

Table 2. Summary of Baseline Characteristics and Outcomes of the Included Studies.

Authors, location and date	Study design	Setting	Age	Sample size, M/F	Groups	Findings	Adverse events
Studies on in-hospital anticoagulant (AC) use							
Tang et. al.,[24] China, January-February 2020	Observational	Hospitalized patients	65,1±12	449, 268/181	Heparin at least 7 days (n=99) vs. no heparin or heparin less than 7 days (n=350). 99 patients (22%) received heparin for at least 7 days, in which 94 received LMWH (40-60 mg enoxaparin/d) and five received unfractionated heparin (10 000-15 000 U/d)	Heparin treatment was associated with lower 28-day mortality in patients with SIC score ≥ 4 (40.0% vs 64.2%, P =0.029), but not in those with SIC score < 4 (29.0% vs 22.6%, P =0.419). When D-dimer level was above 3.0 μg/mL (six-fold of upper limit of normal), there was significantly lower mortality in heparin users than nonusers (32.8% vs. 52.4%, P = 0.017).	Not stated.
Yin. et. al.,[25] China, January-February 2020	Observational	Hospitalized patients	65,1±12 in COVID group, 58,4±18 in non-COVID group	553, 340/213	Heparin at least 7 days (n=99 in COVID group, n=22 in non-COVID group) vs. no heparin or heparin less than 7 days (n=350 in COVID group, n=82 in non-COVID group). Ninety-nine (22.0%) patients of COVID group received heparin treatment for at 3least 7 days, in which 94 received LMWH (40–60 mg enoxaparin/day) and 5 received UFH (10,000–15,000 U/day); 22 (21.2%) patients of non-COVID group received heparin treatment, in which 20 received LMWH (40–60 mg enoxaparin/day) and 2 received UFH (10,000–15,000 U/ day).	When D-dimer level was above 3.0 μg/mL (six-fold of upper limit of normal), there was significantly lower mortality in heparin users than nonusers in COVID group (32.8% vs. 52.4%, P = 0.017). This difference between the heparin users and non-users was not found in the non-COVID group.	Not stated.
Paranjpe et. al.,[35] USA, March-May 2020	Observational	Hospitalized patients	Not stated.	2773, Not stated	Treatment-dose systemic AC (oral, subcutaneous or intravenous; n=786) vs. no AC (n=1.987)	In-hospital mortality for patients treated with AC was 22.5% with a median survival of 21 days, compared to 22.8% and median survival of 14 days in patients who did not receive AC. In patients who required mechanical ventilation in-hospital mortality was 29.1% with a median survival of 21 days for those treated with anticoagulants vs. 62.7% with a median survival of 9 days in patients who did not receive anticoagulants. In a multivariate proportional hazards model, longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89, p<0.001).	63% of the hospitalized patients with COVID-19 that were given systemic AC were found to have major bleeding.

Atallah et. al.,[36] Abu Dhabi, 2020	Observational	ICU	49 (40-61)	188, 154/34	Thrombotic events (n=21) vs. non-thrombotic events (n=188). Anticoagulation strategy in thrombotic events vs. non-thrombotic events were therapeutic AC with heparin or oral anticoagulant (19% vs. 12%), high-intensity prophylactic dose (29% vs. 41%), standard prophylactic dose of enoxaparin 40 mg daily (52% vs. 43%) or none (0 vs. 4%).	Overall thrombotic events were 12,2%. High-intensity thromboprophylaxis regimen, but not therapeutic dose, was associated with a lower-risk of thrombotic events compared with the regular prophylactic regimen (OR = 0.20; 95% confidence interval 0,008-1,86; p=0,01).	Thirty-one patients (16.5%) experienced haemorrhagic events during their ICU stay; 13 were classified as major bleeding. Out of the 24 patients who received therapeutic AC, five (21%) had major haemorrhagic events compared with 8 out of 164 patients (5%) who did not receive therapeutic AC (p = 0.014). Among the 75 patients who received high-intensity prophylactic regimen, only 2 (2.7%) experienced major bleeding.
Ayerbe et. al.,[40] Spain 2020	Observational	Hospitalized patients	67.57 (15.52)	2.075	Heparin (n=1734) vs. no heparin (n=285)	Heparin was associated with lower mortality when the model was adjusted for age and gender, with OR (95% CI) 0.55 (0.37–0.82), p=0.003. This association remains significant when saturation of oxygen <90%, and temperature >37°C were added to the model with OR 0.54 (0.36–0.82) p = 0.003, and when all the other drugs were included as covariates (OR 0.42, 0.26–0.66; p < 0.001).	Not stated.
Mouhat et. al.,[37] France, March-April 2020	Observational	ICU (n=48) and conventional ward (n=94)	65.57±13	349, 67.3% male	141 (87.0%, 95% CI 80.8–91.8%) out of 162 patients received AC initiated at admission, including 85.1% (95% CI 78.1–90.5%) with LMWH, 7.8% (95% CI 4.0–13.5%) with UFH and 7.1% (95% CI 3.5–12.7%) with oral AC.	D-dimer level and the lack of any anticoagulant therapy were significantly associated with the occurrence of CTPA-confirmed PE (OR 4.0 (95% CI 2.4–6.7) per additional quartile of D-dimer and OR of 4.5 (95% CI 1.1–7.4), respectively.	Not stated.
Boari et. al.,[43] Italy, February-April 2020	Observational	Hospitalized patients	71.0 ± 13.8	258, 173/	29 patients received ACs. In the beginning, prophylactic dose of 4000 Units sc once daily; then, higher doses were progressively used: 4000 Units twice daily, 6000 Units sc once daily or 100 Units/kg twice daily (anticoagulation dose), shifting after few days, when indicated, to one of the new oral AC (apixaban or edoxaban).	Enoxaparin at low, prophylactic dose (4000 Units sc once daily) was not associated with any effect on survival. On the other hand, higher doses (4000 Units twice daily, 6000 Units sc once daily or 100 Units/kg twice daily (anticoagulant dose), when considered together, significantly improved survival.	Not stated.

Ionescu et. al.,[38] USA, March-April 2020	Observational	Hospitalized patients.	74 years (±15)	127, 68	Therapeutic AC (n=67) vs. not on therapeutic AC (n=60). Among those not on therapeutic AC, 47 were on prophylactic dose.	Median time to death was longer with higher doses of AC (11 days for tAC, 8 days for pAC, and 4 days for no AC, p < 0.001). In multivariate analysis, AC was associated with longer time to death, both at prophylactic (hazard ratio [HR] = 0.29; 95% confidence interval [CI]: 0.15 to 0.58; p < 0.001) and therapeutic doses (HR = 0.15; 95% CI: 0.07 to 0.32; p < 0.001) compared with no AC.	Bleeding rates were similar among tAC and remaining patients (19 vs. 18%; p =0.877).
Iionescu et. al.,[39] USA, March-May 2020	Observational	Hospitalized patients. 18.5% (n = 642) in ICU.	64.5± 17.0	3480, 51.5% female	60.9% received pAC (n = 2121), 28.7% received ≥3 days of tAC (n = 998), and 10.4% (n = 361) received no AC.	Kaplan-Meier plot demonstrated different 25-day survival probability in the tAC and pAC groups (57.5% vs 50.7%). In a multivariate proportional hazards model, AC was associated with reduced risk of death at prophylactic (hazard ratio [HR] 0.35 [95% confidence interval CI 0.22-0.54]) and therapeutic doses (HR 0.14 [95% CI 0.05-0.23]) compared to no AC.	Major bleeding occurred more frequently in tAC patients (81 [8.1%]) compared to no AC (20 [5.5%]) or pAC (46 [2.2%]) subjects.
Musoke et. al.,[26] USA, March-May 2020	Observational	Hospitalized	66.21 ± 14.21	355, 181/174	Prophylactic dose for VTE n=216, subtherapeutic dose n= 23, therapeutic dose n=101, no anticoagulant n=15. Prophylactic doses of anticoagulation were based on institutional protocols (heparin 5000 units subcutaneously 2–3 times/day or low molecular weight heparin (LMWH) 30-40 mg daily. Therapeutic anticoagulation was based on indication with VTE (80 units/kg IV bolus followed by 18 units/kg/h infusion) while for atrial fibrillation/flutter or acute coronary syndrome (12 units/kg/h infusion). For therapeutic LMWH dose was 1 mg/kg q12 hours.	After multivariable logistic regression, only age OR 1.04 95% CI (1.01 to 1.07) p = 0.008, D-dimer≥ 1500 ng/mL OR 5.89 95% CI (2.84 to 12.20) p < 0.0001 and the use of therapeutic AC were independently associated with higher inpatient mortality OR 6.16 95% CI (2.96 to 12.83) p ≤ 0.0001	Therapeutic AC had a significantly higher rate of major bleeding compared to prophylactic doses (p = 0.04).
Tomasoni et. al.,[41] Italy, March-April 2020	Observational	Hospitalized	67.4 ± 13.2	692, 481/211	In-hospital heparin treatment (n=364) vs. no heparin treatment (n=328).	Heparin was associated with lower mortality at both univariate and multivariable analysis (HR 0.57; 95% CI 0.41–0.81; P <0.001; adjusted HR 0.41; 95% CI 0.25–0.67; P <0.001)	Not stated.
Yethindra et. al.,[46] Kyrgyzstan, until May 2020.	Observational	Hospitalized	58.54	110, 68/42	UFH vs. no AC.	AC with UFH was found to be correlated with lower mortality when the analysis was adjusted for age and gender (odds ratio (OR) [95% confidence interval]: 0.68 [0.48–0.94], *P* = 0.002). This correlation was significant for body temperature >37°C and SaO_2< 90% (OR: 0.67 [0.47–0.94], *P* = 0.002) as well as for other treatments added (OR: 0.54 [0.38–0.76], *P* < 0.001).	Not stated.

Yu et. al.,[42] China, December 2019 – April 2020	Observational	Hospitalized	61.86 ± 12.43	142, 81/61	AC vs. no AC	No anticoagulant was a risk factor for DVT (OR 3.0, 95% CI 1.1-7.8, p=0.025).	Not stated.
Lopes et. al., [32] ACTION trial Brazil, June 2020 – February 2021	Open-label, multicenter, randomized controlled trial	Hospitalized	56·6 years (SD 14·3	615, 368/247	Therapeutic (n=311) vs. prophylactic (n=304) AC. Therapeutic AC was in-hospital oral rivaroxaban (20 mg or 15 mg daily) for stable patients, or initial subcutaneous enoxaparin (1 mg/kg twice per day) or intravenous unfractionated heparin (to achieve a 0·3-0·7 IU/mL anti-Xa concentration) for clinically unstable patients, followed by rivaroxaban to day 30. Prophylactic AC was standard in-hospital enoxaparin or unfractionated heparin.	The primary efficacy outcome (win ratio of time to death, duration of hospitalization, duration of supplemental O2 to day 30) was not different between groups, with 34·8% wins in the therapeutic group and 41·3% in the prophylactic group (win ratio 0·86 [95% CI 0·59-1·22], p=0·40).	Bleeding was higher in the therapeautic AC group (relative risk 3·64 [95% CI 1·61-8·27], p=0·0010).
Goligher et. al.,[28] REMAP-CAP Trial US, Canada, UK, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain April – December 2020	Open-label, randomized clinical trial	Critically ill hospitalized patients	60.4±13.1	1.098, 772/326	Therapeutic-dose AC (n=534) and usual-care thromboprophylaxis (n=564)	The percentage of patients who survived to hospital discharge was similar in the two groups (62.7% and 64.5%, respectively; adjusted OR, 0.84; 95% credible interval, 0.64 to 1.11).	Major bleeding occurred in 3.8% in the therapeutic AC group and in 2.3% of thromboprophylaxis group.
Lawler et. al.,[27] ATTACC Trial US, Canada, UK, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain; April 2020 – January 2021	Open-label, randomized clinical trial	Non-critically ill hospitalized patients	59.0±14.1	2.219, 1.310/909	Therapeutic-dose AC (n=534) and usual-care thromboprophylaxis (n=564)	Therapeutic-dose anticoagulation increased organ support-free days as compared with usual-care thromboprophylaxis (adjusted OR, 1.27; 95% credible interval, 1.03 to 1.58)	Major bleeding occurred 1.9% in the therapeutic-dose AC group and in 0.9% of the thromboprophylaxis group
Di Castelnuovo et. al., [29] CORIST study Italy, February – June 2020	Observational	Hospitalized patients	NA	2.574	LMWH or UFH (n=1.827) vs. no AC (n=747)	40% lower risk of death in patients receiving heparin (HR=0.60; 95% confidence interval: 0.49-0.74.	Not stated.

Perepu et. al.,[44] US, April 2020 – January 2021	Multi-center, open-label, randomized controlled trial	Hospitalized patients in ICU (62%) or had evidence of coagulopathy	64 (24–86)	176, 99/77	Standard prophylactic dose enoxaparin (n=88) vs. intermediate weight-adjusted dose enoxaparin (n=88). The standard dose was 40 mg SC daily if the body mass index (BMI) was <30 kg/m2 and either 30 mg SC twice daily or 40 mg SC twice daily if the BMI was ≥30. The choice of 30 mg twice daily or 40 mg twice daily was determined by the treating physician according to the local institutional standard of practice. The intermediate dose was 1 mg/kg SC daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30.	All-cause mortality at 30 days was 15% for intermediate dose enoxaparin and 21% for standard prophylactic dose enoxaparin (OR 0.66; 95% confidence interval, 0.30-1.45; P = .31 by Chi-square test)	Major bleeding occurred in 2% of patients in each arm.
Sadeghipour et. al.,[45] INSPIRATION trial Iran, July 2020 – November 2020	Multicenter randomized trial	Hospitalized patients in ICU	62 (51-70.7)	600, 325/275	Intermediate-dose enoxaparin, 1 mg/kg daily (n = 276) vs standard prophylactic enoxaparin, 40 mg daily (n = 286)	The primary efficacy outcome was a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. The primary efficacy outcome occurred in 45.7% in the intermediate-dose group and 44.1% in the standard-dose prophylaxis group OR 1.06 [95% CI, 0.76-1.48]; P = 0.70).	Major bleeding occurred 2.5% in the intermediate-dose group and 1.4% in the standard-dose prophylaxis group OR 1.83 (1-sided 97.5% CI, 0.00-5.93)
Lemos et. al.,[30] HESACOVID trial Brazil, April – July 2020	Randomized, open-label, phase II clinical trial	Hospitalized patients requiring mechanical ventilation	58 ± 16	20, 16/4	Therapeutic enoxaparin vs. standard anticoagulant thromboprophylaxis.	Patients of the therapeutic group had a higher ratio of successful liberation from mechanical ventilation (HR: 4.0 [95% CI 1.035-15.053]), p = 0.031 and more ventilator-free days (15 days [interquartile range IQR 6-16] versus 0 days [IQR 0-11]), p = 0.028	There were no major bleeding events in both groups.
Rentsch et. al.,[31] US, March – July 2020	Observational	Hospitalized patients	69.0 (58.0-76.5)	4.297, 4.015/282	Prophylactic AC (LMWH and UFH) vs. no AC	Compared with patients who did not receive AC, those who had prophylactic AC had a 27% decreased risk for 30-day mortality (HR 0.73, 95% confidence interval 0.66 to 0.81).	Prophylactic AC compared to no AC was not associated with an increased risk of bleeding events that required transfusions (0.87, 0.71 to 1.05).

Hsu et. al.,[33] US, February – April 2020	Observational	Hospitalized patients	60 [49–73]	468, 257/211	Standard VTE prophylaxis vs. high-intensity prophylaxis vs. therapeutic AC vs. no AC. Standard VTE prophylaxis was defined as LMWH 40 mg once daily, unfractionated heparin subcutaneous (HSQ) 5000 units three times daily, or apixaban 2.5 mg twice daily. High-intensity prophylaxis was defined as LMWH 40 mg twice daily or HSQ 7500 units three times daily. Therapeutic AC was defined as intravenous heparin, LMWH 1 mg/kg twice daily, dose-adjusted warfarin with a target international normalized ratio (INR) of 2.0 to 3.0, apixaban 5 mg twice daily, or rivaroxaban 20 mg daily.	30-day mortality was significantly lower among all patients who received high-intensity thromboprophylaxis (adjusted RR vs. standard-intensity, 0.26; 95% confidence interval [CI], 0.07–0.97, p = 0.045).	No significant increased rate of bleeding (p = 0.11) in group with AC vs. no AC.
Nadkarni et. al.,[34] US, March – April 2020	Observational	Hospitalized patients	65	4.389, 2.457/1.931	Therapeutic AC vs. prophylactic AC vs. no AC. AC used includes UFH, LMWH and oral anticoagulants.	Compared with no AC (n = 1,530; 34.9%), therapeutic AC (n = 900; 20.5%) and prophylactic AC (n = 1,959; 44.6%) were associated with lower in-hospital mortality (adjusted HR [aHR]: 0.53; 95% confidence interval [CI]: 0.45 to 0.62 and aHR: 0.50; 95% CI: 0.45 to 0.57, respectively), and intubation (aHR: 0.69; 95% CI: 0.51 to 0.94 and aHR: 0.72; 95% CI: 0.58 to 0.89, respectively).	Major bleeding occurred in 3% on therapeutic, 1.7% on prophylactic, and 1.9% on no AC.
Spyropoulos et. al.[23] HEP-COVID trial US, May 2020 – May 2021	Multicenter randomized trial	Hospitalized high-risk patients in ICU (n=83) and non-ICU	65±13,9	253, 136/117	Therapeutic AC (n=129) vs. standard prophylactic dose (n=124). In the standard-dose group, patients received prophylactic doses of heparin (enoxaparin, ≤40 mg daily) or intermediate doses of heparin (enoxaparin, 30 mg twice daily, enoxaparin, 40 mg twice daily, enoxaparin, 0.5 mg/kg twice daily,	The primary efficacy outcome was venous thromboembolism (VTE), arterial thromboembolism (ATE), or death from any cause. It was met in 52 of 124 patients (41.9%) (28.2% VTE, 3.2% ATE, 25.0% death) with standard-dose heparins vs 37 of 129 patients (28.7%) (11.7% VTE, 3.2% ATE, 19.4% death) with therapeutic-dose LMWH (relative risk [RR], 0.68; 95% CI, 0.49-0.96; P = .03), including a reduction in thromboembolism (29.0% vs 10.9%; RR, 0.37; 95% CI, 0.21-0.66; P < .001). The primary efficacy outcome was reduced in non-ICU patients (36.1% vs 16.7%; RR, 0.46; 95% CI, 0.27-0.81; P = .004) but not ICU patients (55.3% vs 51.1%; RR, 0.92; 95% CI, 0.62-1.39; P = .71).	The incidence of major bleeding was 1.6% with standard-dose vs 4.7% with therapeutic-dose heparins (RR, 2.88; 95% CI, 0.59-14.02; P = .17).

Studies on regular, pre-hospital AC use							
Rivera-Caravaca et. al.,[48] USA	Observational	Hospitalized	81.5 (IQR 75-87)	1.002, 593/409	Patient on prior (n=892) vs. without prior AC (n=110)	Patients with prior OAC had higher mortality risk compared to patients without prior OAC (HR 1.53, 95% CI 1.08-2.16). Patients with prior AC had significantly higher all-cause mortality (p<0.001) and higher combined all-cause mortality or any thromboembolic event (p<0.001). Respiratory insufficiency during hospitalization (HR 6.02, 95% CI 2.18-16.62), systemic inflammatory response syndrome (SIRS) during hospitalization (HR 2.29, 95% CI 1.34-3.91) and the Short-Form CCI (HR 1.24, 95% CI 1.03-1.49) were the main risk factors for mortality in patients with prior OAC.	Bleeding was significantly higher in the group with prior AC (p<0.001).
Rossi et. al.,[49] Italy, February-April 2020	Observational	Hospitalized	79 (range: 70–92)	70, 35/35	Patients with prior DOAC (n=26) vs. without prior DOAC (n=44)	In a multivariate analysis, age [HR 1.39 (1.24 – 1.57), p<0.0001], absence of chronic DOAC intake [HR 0.38 (0.17 – 0.58), p<0.01] and male gender [HR 1.49 (1.11 - 1.63), p<0,02] was associated with increased mortality risk.	Not stated.
Khider et. al.,[47] France, March 2020	Observational	Hospitalized	66.0 [54.3-79.8]	96, 44/52	COVID-19 positive patients (n=66) with prior AC (n=12) vs. without prior AC (n=54)	COVID-19-positive patients had significantly more CECs at admission (P = .008) than COVID-19-negative ones. COVID-19-positive patients treated with curative AC prior to admission had fewer CECs (P = .02) than those without. Patients treated with curative AC and angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers had even fewer CECs (P = .007).	Not stated.
Russo et. al.,[50] Italy, February-April 2020	Observational	Hospitalized	67.7 (15.2)	192, 115/77	Patients with prior AC (n=26) vs. without prior AC (n=166)	Pre-admission AC was not associated with increased risk of ARDS at admission and in-hospital mortality in COVID-19 patients.	Not stated.
Menager et. al.,[51] France, March – June 2020	Observational	Hospitalized in geriatric acute unit	88.8 ± 4.5 years	82, 43/49	No regular use of VKA (n=73) vs. regular use of VKA (n=9)	HR for 7-day mortality in those regularly using VKA was 5.68 (95% CI: 1.17-27.53; p=0.031)	Not stated.
Tremblay et. al.[68] March – April 2020	Observational	Hospitalized	56.6 (18.2)	3.772, 1.533/2.239	Patients with prior AC (n=241) vs. without prior AC/antiplatelet (n=2.859)	No evidence for an effect of prediagnosis anticoagulation on mortality.	Major bleeding was significantly higher in group with prior AC (p=0,007).
Case series on drugs with AC effects							
Doi et. al.,[52] Japan, April 2020	Case series	ICU	68 (60–69)	11, 10/1	Nafamostat mesylate treatment in combination with favipiravir	(8 [73%]) who required MV requirement; however, the mortality rate was low (1 patient [9%])	Not stated.
Jang et. al.,[53] South-Korea, February-March 2020	Case series	Hospitalized	Over 65 years	3, 3/0	Nafamostat	administration of nafamostat was followed by improvement in clinical status, demonstrated by the decrease in CRP levels and WBC count.	Not stated

Rambaldi et. al.,[54] Italy, March 2020	Case series	ICU	56.5 (47–63)	6, 5/1	Narsoplimab	Following treatment, all patients improved clinically. Four patients (67 %) reduced ventilatory support from CPAP to non-rebreather or Venturi oxygen mask after a median of 3 narsoplimab doses (range 2–3). In three of these patients, oxygen support was weaned and then discontinued, and discharge followed a median of 6 (range 5–8) total narsoplimab doses.	No bleeding event.

Table 3. Quality Assessment of the Included Studies Using Newcastle Ottawa Scale.

Studies	Selection				Comparability	Outcome			Total score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of Interest Was Not Present at Start of Study	Comparability on the basis of the design or analysis	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of follow up cohorts	
Tang et. al.,[24]	*	*	*	*	*	*	*	*	8
Yin. et. al.,[25]	*	*	*	*	*	*	*	*	8
Paranjpe et. al.,[35]	*	-	*	*	**	*	*	*	8
Atallah et. al.,[36]	*	*	*	*	*	*	*	*	8
Ayerbe et. al.,[40]	*	*	*	*	**	*	*	*	9
Mouhat et. al.,[37]	*	-	*	*	*	*	*	*	7
Boari et. al.,[43]	*	-	*	*	*	*	*	*	7
Ionescu et. al.,[38]	*	-	*	*	*	*	*	*	7
Iionescu et. al.,[39]	*	*	*	*	**	*	*	*	9
Musoke et. al.,[26]	*	-	*	*	**	*	*	*	8
Tomasoni et. al.,[41]	*	*	*	*	**	*	*	*	9
Yethindra et. al.,[46]	*	-	-	*	*	*	*	*	6
Yu et. al.,[42]	-	-	*	*	*	*	*	*	6
Di Castelnuovo et. al.[29]	*	*	*	*	**	*	*	*	9
Rentsch et. al.,[31]	*	*	*	*	*	*	*	*	8
Hsu et. al.,[33]	*	*	-	*	**	*	*	*	8
Nadkarni et. al.,[34]	*	*	*	*	**	*	*	*	9
Rivera-Caravaca et. al.,[48]	*	*	*	*	**	*	*	*	9
Rossi et. al.,[49]	*	-	*	*	**	*	*	*	8
Khider et. al.,[47]	*	-	*	*	*	*	*	*	7
Russo et. al.,[50]	*	-	*	*	*	*	*	*	7
Menager et. al.,[51]	*	*	*	*	*	*	*	*	8
Tremblay et. al.[68]	*	-	*	*	**	*	*	*	8

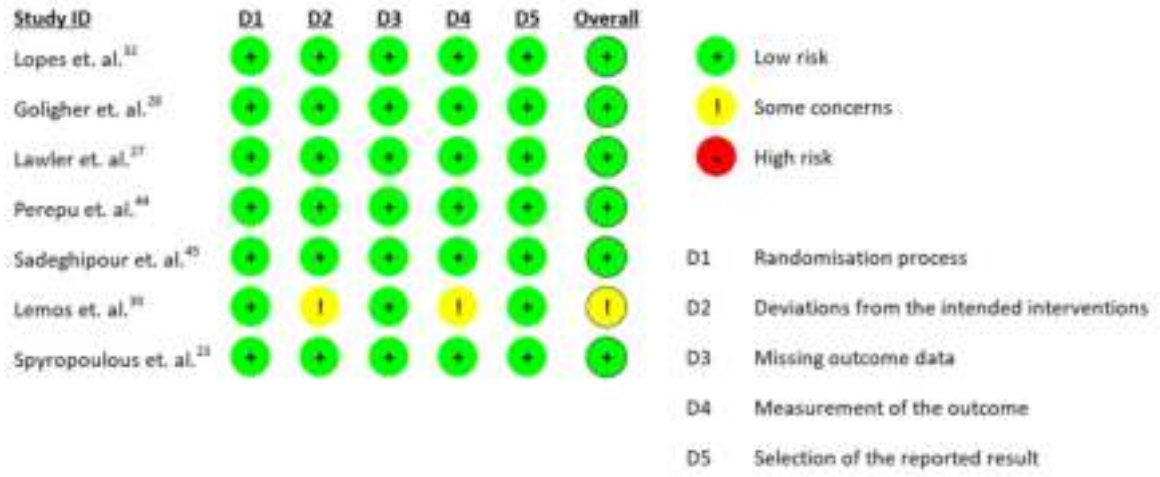

Figure 2. Risk of bias in the randomized clinical trials.

Meta-analysis of In-hospital Anticoagulants and Outcome of COVID-19 Patients

Diverse ACs were used in 23 studies on in-hospital anticoagulation. There were eight studies using UFH and LMWH;[24-34] eight using oral anticoagulants, UFH and LMWH;[35-39] three without specifying the type of AC used;[40-42] four with LMWH only[23, 43-45] and one with UFH only.[46] Eleven studies compare anticoagulant vs. no anticoagulant,[24, 25, 29, 31, 34, 35, 37, 40-42, 46] while the remaining studies involve comparisons between standard prophylactic dose vs higher doses of anticoagulant.[26-28, 32, 36, 38, 39, 43] The combined effect of anticoagulation on decreased mortality in 18.437 hospitalized patients is shown in **Figure 3** (RR 0.55; 95%CI 0.43-0.66; p<0.001).

In 3,210 patients from 6 studies we found that higher dose of anticoagulant, which ranged from high intensity prophylactic dose to therapeutic dose, showed treatment benefit when compared to the standard prophylactic dose (RR 0.69; 95%CI 0.31-1.07; **Figure 4**). The studies include the following populations: patients with D-dimer above the upper limit of normal,[32] the critically ill patients,[28, 45] ICU patients and/or patients who had laboratory evidence of coagulopathy,[44] unselected hospitalized patients,[33] and hospitalized adult patients with D-dimer levels more than 4 times the upper limit of normal or sepsis-induced coagulopathy score of 4 or greater.[23] Two studies out of the 6 studies showed clear survival benefit of higher dose of anticoagulant.[23, 33]

Regular, Pre-hospital Anticoagulation and Outcome of COVID-19 Patients

Five studies involving 1,442 subjects investigated the impact of regular, pre-hospital oral anticoagulation on mortality and other parameters with mixed, conflicting results.[47-51] Two studies involve patients with the use of both direct acting oral anticoagulant (DOAC) and vitamin K antagonist (VKA),[48,50] one with DOAC only,[49] one with VKA only,[51] and two without specifications on the type of anticoagulant used.[47] These studies generally consisted of older adults above 60 years old, and one study specifically was aimed to investigate the geriatric population in the acute care unit.[51]

Alternative Agents with Anticoagulant Properties

With regards to the use of alternative agents with anticoagulant properties, three case series reported the use of nafamostat mesylate and narsoplimab. Despite having low sample size, being used in conjunction with other drugs and lacking control groups, the patients showed improved outcome in all studies without any reported bleeding event.[52-54]

DISCUSSION

This systematic review and meta-analyses, which consists of 32 studies including 7 recently published randomized clinical trials, and a total

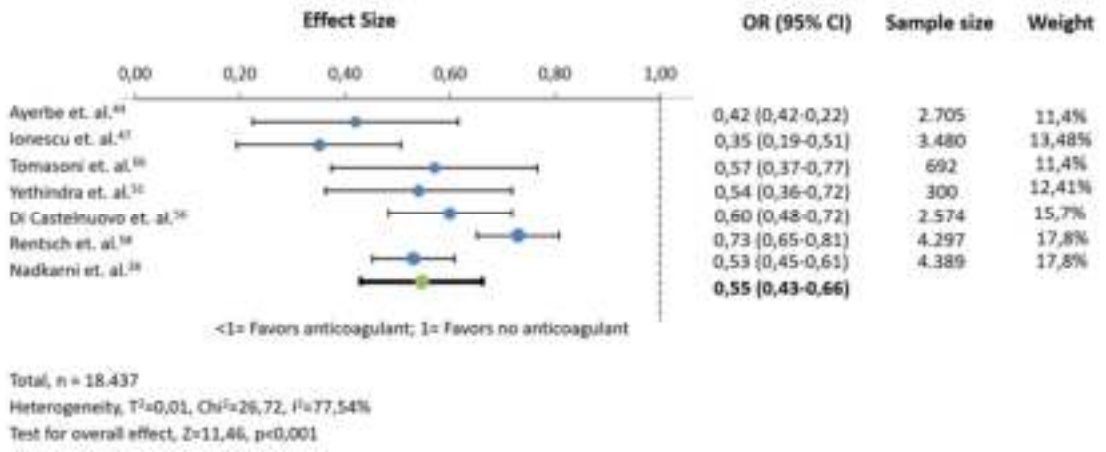

Figure 3. Forest plot for odds ratio for mortality in patients receiving anticoagulants.

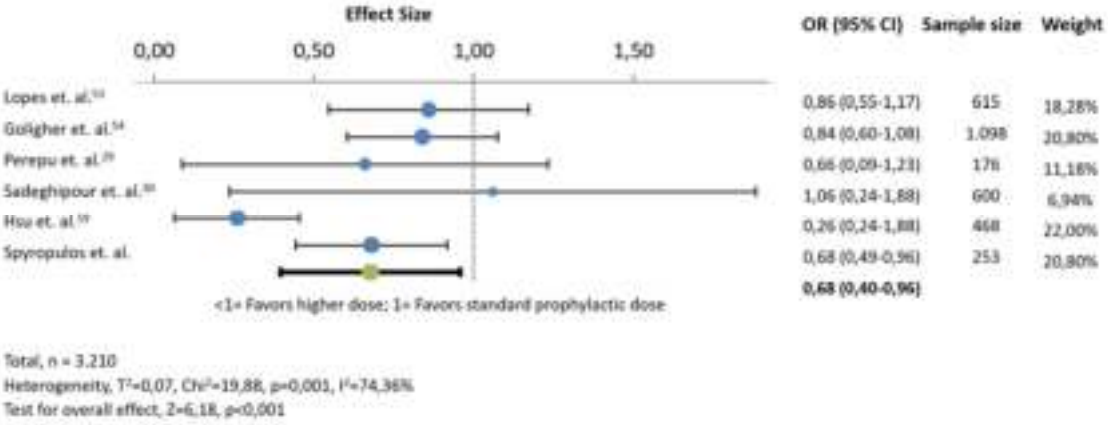

Figure 4. Forest plot for odds ratio for mortality in patients receiving anticoagulants with dose higher than standard prophylaxis.

of 33,494 patients show that anticoagulants reduce mortality and improve survival in COVID-19 patients when compared to no anticoagulation. The survival benefit was also found when comparing high-intensity and therapeutic dose anticoagulant with standard prophylactic dose. There are inconclusive, conflicting evidence on the effect of regular, pre-hospital anticoagulation on mortality as shown by this systematic review. These findings support the current recommendations of anticoagulant use in COVID-19 patients endorsed by ISTH and ASH.[10, 12-14] The use of standard prophylactic dose was endorsed in the critically ill and acutely ill population due to the lack of additional treatment benefit and the higher bleeding risk of higher-dose anticoagulation. However, in selected populations such as shown by the HEP-COVID trial, the use of therapeutic-dose LMWH reduced major thromboembolism and death compared with standard prophylactic heparin among inpatients with COVID-19 with very elevated D-dimer levels.[23] Indeed, understanding the risks and benefits of increased dose of anticoagulation in critically ill COVID-19 patients is especially challenging, with some conflicting evidence reported from different trials.[23, 27, 32, 44]

Critically ill patients are at increased risk of VTE due to the presence of patient factors such as age, pregnancy, obesity, immobilization, past history of VTE, cancer, sepsis, respiratory or heart failure, stroke, trauma or recent surgery) as well as ICU risk factors (sedation, vasopressors or central venous catheters).[55] Beyond ICU factors, increased VTE risk in COVID-19 patients may occur as a result of not

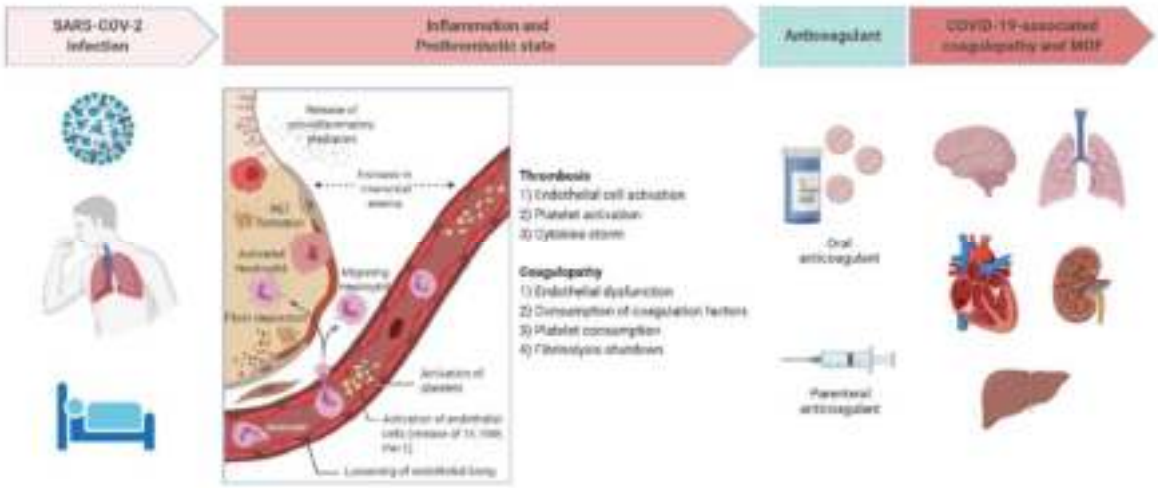

Figure 5. The potential pathophysiology of COVID-19-associated coagulopathy and the role of anticoagulants. The potential pathophysiological process underlying COVID-19-associated coagulopathy are the followings: infection, thromboinflammation, and coagulopathy with bleeding tendencies and multiple organ failure (MOF). Firstly, the SARS-CoV-2 is entering the respiratory tract through the angiotensin-converting enzyme 2 (ACE-2) in the epithelial cells in the trachea or lung tissues. Secondly, the viral proliferation and dissemination within the lung tissue lead to in situ endothelial cell, platelet and immune system activation. Activation of endothelium, neutrophils and platelets further induces neutrophil extracellular trap (NET) formation, contributing to the microthrombus with fibrin. This process is characterized by upregulation of inflammmatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), interferon (IFN), as well as molecules playing a role in thrombosis such as von-Willebrand factors (VWF), tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1). Oral and parenteral may play a role in preventing the development of prothrombotic state and its further consequences of coagulopathy and MOF. Thirdly, coagulopathy together with inflammation drive the progress of multiple organ failure (MOF), including in the major organs of brain, heart, lung, liver, and kidney.

only acute infection *per se*, but also the presence of respiratory failure and reduced mobility due to the need of oxygen supplementation and the isolation imposed by hospital restrictions.[56] However, given the diversity of the critically ill COVID-19 patients, the current body of evidence does not support routine empirical use of high-intensity or therapeutic dose anticoagulation in unselected patients with COVID-19 admitted to the ICU.

Infection with SARS-CoV-2 has been associated with a pattern of coagulopathy that is commonly characterized by elevations in plasma levels of fibrinogen (as an acute phase response) and D-dimer, and unlike the appearance of classic DIC in bacterial sepsis or trauma, prolongation of APTT and PT is minimal, with only modest thrombocytopenia.[57, 58] Occasionally, patients with severe COVID-19 and multiorgan failure may progress to overt DIC, reflected by more severe thrombocytopenia, prolonged PT and APTT, marked elevation of D-dimer and decreased fibrinogen. Taken together, data suggest that the COVID-19 associated coagulopathy is a combination of mild DIC with pulmonary thrombotic microangiopathy.[9] Coronavirus infections are also associated with an excessive activation of the fibrinolytic system tissue-type plasminogen activator (t-PA) compared to those with no infection. It is thought that inflammation-induced endothelial cell injury could result in the release of plasminogen activators, which could explain the high concentrations of D-dimer and fibrin degradation products in patients with severe COVID-19.[9, 59] Thrombotic microangiopathy is typically caused by pathological state of platelet-endothelial interaction due to ultra-large von Willebrand factor multimers that are cleaved by ADAMTS13.[60] In a hyperinflammatory state, secondary deficiency of ADAMTS13 due increased consumption have been reported.[61] There is currently no data on platelet-endothelial interaction and ADAMTS13 levels in patients COVID-19. Patients with VTE have been shown to have increased risk of in-hospital mortality.[62] A summary of the pathophysiology and potential role of anticoagulants is presented in **Figure 5**.

The proposed mechanism of the benefit of anticoagulation in COVID-19 patients is by

suppressing the pro-thrombotic coagulopathy and thereby preventing thrombosis in both the micro- and macro-vaculatures.[63] Considerations for the use of heparin in the setting of COVID-19 also include acknowledgement of its anti-inflammatory and anti-viral potential. Heparan sulfate may bind to SARS-CoV-2 spike protein and block viral attachment and entry and may attenuate inflammatory response by neutralization of proinflammatory proteins such as histone and HMGB1.[64] Selection of COVID-19 patients who are suitable for escalated dose of anticoagulant treatment using Padua or Geneva scores which predict the risk for VTE and pulmonary embolism, respectively, are reasonable but still lack validation as they may perform differently in patients with COVID-19 pneumonia.[65, 66]

Findings in this systematic review demonstrate the benefit of anticoagulation in hospitalized COVID-19 patients, especially in the setting of increased VTE in patients with severe disease. The ASH recommendation states that all unless patients are deemed to be at increased bleeding risk, patients with COVID-19 should receive thromboprophylaxis with LMWH or fondaparinux.[67] Furthermore, the Italian Society on Thrombosis and Haemostasis (SISET) suggested the administration of thromboprophylaxis at home for 7–14 days after hospital discharge or during the pre-hospital phase, especially in subjects with pre-existing or persisting VTE risk factors. Surprisingly, to date we found no published studies reporting the use of anticoagulants in COVID-19 patients post-discharge.

Newer drugs that have anticoagulant effects are currently under investigation. Nafamostat, a serine proteinase inhibitor, has been used in Japan to treat disseminated intravascular coagulation (DIC) and pancreatitis. Although nafamostat originally an antithrombin drug, it has a characteristically strong antiplasmin action and has recently been shown to block viral entry by inhibiting membrane fusion between SARS-CoV-2 and human cells.[15] Narsoplimab, a lectin inhibitor, down-modulates SARS-CoV-2-induced activation of the lectin pathway and endothelial cell damage and is thought to reduce the thrombotic risk of COVID-19 patients.[54]

The limitation of this study is the large heterogeneity observed. This may be due to the diverse populations, comparison groups, and types as well as doses of anticoagulant use. Although the use of prophylactic anticoagulant is a widespread practice, our study shows that therapeutic or high intensity anticoagulant should be used judiciously and only in selected population such as those with higher risk of thromboembolic events. We recommend that future clinical trials not only address the use of anticoagulant in COVID-19 patients but also their doses and indications, pre-existing comorbidities, risk of bleeding and the degree of severity, as well as regular, pre-hospital use of anticoagulation.

CONCLUSION

The administration of anticoagulant results in improved survival of hospitalized COVID-19 patients. Determination of thrombosis in COVID-19 is essential, as this would indicate therapeutic dose of anticoagulation. Selecting between standard vs. higher dose prophylaxis in nonthrombotic patients warrant judicious considerations of the risk benefit ratio and individual patient profile. The results from this study are important in the tailored treatment of COVID-19 patients, especially those at risk for increased complications, and in addressing the gap in knowledge from currently available evidence. Areas of uncertainties in the literature include the indications or risk stratifications and targeted populations for prophylactic or high-intensity prophylactic dose in COVID-19 patient, the need for supratherapeutic dose in selected patient population; and the need for oral anticoagulants for patients not admitted or after discharge from hospital. The use of anticoagulants is currently recommended by international hematological and thrombosis societies in selected COVID-19 population. However, precise parameters are still needed to identify those that may benefit the most from anticoagulants during admission and post-discharge.

REFERENCES

1. World Health Organization. HO Coronavirus Disease (COVID-19) Dashboard 2020 [Available from: http://covid19.who.int.
2. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research. 2020.
3. Gómez-Mesa JE, Galindo-Coral S, Montes MC, Martin AJMJC. Thrombosis and coagulopathy in COVID-19. 2020:100742.
4. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Medicine. 2020:1-10.
5. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thrombosis Research. 2020.
6. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thrombosis Haemostasis. 2020.
7. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thrombosis Haemostasis. 2020.
8. Poissy J, Goutay J, Caplan M, et al. Pulmonary embolism in COVID-19 patients: Awareness of an increased prevalence. Circulation. 2020.
9. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. The Lancet Haematology. 2020.
10. Thachil J, Tang N, Gando S. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. 2020;18(5):1023-6.
11. Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: A Comment. J Thrombosis Haemostasis. 2020.
12. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and standardization committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. 2020;18(8):1859-65.
13. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. 2021;5(3):872-88.
14. Spyropoulos AC, Ageno W, Barnathan ES. Hospital-based use of thromboprophylaxis in patients with COVID-19. Lancet. 2020;395(10234):e75.
15. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. J Thrombosis Thrombolysis. 2020;181(2):271-80.e8.
16. Yamamoto M, Kiso M, Sakai-Tagawa Y, et al. The anticoagulant nafamostat potently inhibits SARS-CoV-2 S protein-mediated fusion in a cell fusion assay system and viral infection in vitro in a cell-type-dependent manner. Viruses. 2020;12(6):629.
17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS med. 2009;6(7):e1000097.
18. Lo CK-L, Mertz D, Loeb MJBmrm. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. 2014;14(1):1-5.
19. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. 2019;366.
20. Higgins JP, Thompson SGJS. Quantifying heterogeneity in a meta-analysis. 2002;21(11):1539-58.
21. Macaskill P, Walter SD, Irwig LJSim. A comparison of methods to detect publication bias in meta-analysis. 2001;20(4):641-54.
22. Suurmond R, van Rhee H, Hak TJR. Introduction, comparison, and validation of Meta-Essentials: a free and simple tool for meta-analysis. 2017;8(4):537-53.
23. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: The HEP-COVID randomized clinical trial. JAMA Internal Medicine. 2021.
24. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thrombosis Haemostasis. 2020;18(5):1094-9.
25. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. 2020:1-4.
26. Musoke N, Lo KB, Albano J, et al. Anticoagulation and bleeding risk in patients with COVID-19. Thrombosis Research. 2020;196:227-30.
27. ATTACC A-a, Investigators R-C. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. New England J Med. 2021;385(9):790-802.
28. REMAP-CAP A-a, Investigators A. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. New Engl J Med. 2021;385(9):777-89.
29. Di Castelnuovo A, Costanzo S, Antinori A, et al. Heparin in COVID-19 patients is associated with reduced in-hospital mortality: The Multicenter Italian CORIST Study. 2021.
30. Lemos ACB, do Espírito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). 2020;196:359-66.

31. Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. 2021;372.
32. Lopes RD, Furtado RH, Macedo AVS, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. 2021.
33. Hsu A, Liu Y, Zayac AS, Olszewski AJ, Reagan JLJTr. Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia. 2020;196:375-8.
34. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. 2020;76(16):1815-26.
35. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020.
36. Atallah B, Mallah SI, AlMahmeed W. Anticoagulation in COVID-19. Eur Heart J Cardiovasc Pharmacother. 2020.
37. Mouhat B, Besutti M, Bouiller K, et al. Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. European Respiratory Journal. 2020;56(4).
38. Ionescu F, Grasso-Knight G, Castillo E, et al. Therapeutic anticoagulation delays death in COVID-19 patients: cross-sectional analysis of a prospective cohort. TH open: Companion Journal to Thrombosis and Haemostasis. 2020;4(3):e263.
39. Ionescu F, Jaiyesimi I, Petrescu I, et al. Association of anticoagulation dose and survival in hospitalized COVID-19 patients: A retrospective propensity score-weighted analysis. Eur J Haematol. 2020.
40. Ayerbe L, Risco C, Ayis S. The association between treatment with heparin and survival in patients with Covid-19. Journal of Thrombosis and Thrombolysis. 2020:1-4.
41. Tomasoni D, Inciardi RM, Lombardi CM, et al. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the Cardio-COVID-Italy multicentre study. European Journal of Heart Failure. 2020.
42. Yu Y, Tu J, Lei B, et al. Incidence and risk factors of deep vein thrombosis in hospitalized COVID-19 patients. Clinical and Applied Thrombosis/Hemostasis. 2020;26:1076029620953217.
43. Boari GEM, Chiarini G, Bonetti S, et al. Prognostic factors and predictors of outcome in patients with COVID-19 and related pneumonia: a retrospective cohort study. Bioscience Reports. 2020;40(12).
44. Perepu U, Chambers I, Wahab A, et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: a multi-center, open-label, randomised controlled trial. 2021.
45. Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. 2021;325(16):1620-30.
46. Yethindra V, Tagaev T. Decreased mortality among hospitalized coronavirus disease 2019 patients who underwent anticoagulant therapy with heparin. Indian Journal of Pharmacology. 2020;52(4):337.
47. Khider L, Gendron N, Goudot G, et al. Curative anticoagulation prevents endothelial lesion in COVID-19 patients. Journal of Thrombosis and Haemostasis. 2020;18(9):2391-9.
48. Rivera-Caravaca JM, Núñez-Gil IJ, Vivas D, et al. Clinical profile and prognosis in patients on oral anticoagulation before admission for COVID-19. European Journal of Clinical Investigation. 2020; 51(1):e13436.
49. Rossi R, Coppi F, Talarico M, Boriani G. Protective role of chronic treatment with direct oral anticoagulants in elderly patients affected by interstitial pneumonia in COVID-19 era. European Journal of Internal Medicine. 2020.
50. Russo V, Di Maio M, Attena E, et al. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. Pharmacological Research. 2020:104965.
51. Ménager P, Brière O, Gautier J, et al. Regular use of vka prior to covid-19 associated with lower 7-day survival in hospitalized frail elderly covid-19 patients: The geria-covid cohort study. 2021;13(1):39.
52. Doi K, Ikeda M, Hayase N, Moriya K, Morimura N. Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with COVID-19: a case series. Critical Care. 2020;24(1):1-4.
53. Jang S, Rhee J-Y. Three cases of treatment with Nafamostat in elderly patients with COVID-19 pneumonia who need oxygen therapy. International Journal of Infectious Diseases. 2020.
54. Rambaldi A, Gritti G, Micò MC, et al. Endothelial injury and thrombotic microangiopathy in COVID-19: Treatment with the lectin-pathway inhibitor narsoplimab. Immunobiology. 2020;225(6):152001.
55. Minet C, Potton L, Bonadona A, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Critical Care. 2015;19(1):287.
56. Porfidia A, Pola R. Correction to: Venous thromboembolism and heparin use in COVID-19 patients: juggling between pragmatic choices, suggestions of medical societies and the lack of guidelines. 2020:1.
57. Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. New Engl J Med.

2020;382(18):1708-20.
58. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.
59. Gralinski LE, Bankhead A, Jeng S, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. MBio. 2013;4(4):e00271-13.
60. Noone DG, Riedl M, Licht C. The role of von Willebrand factor in thrombotic microangiopathy. Pediatric Nephrology. 2018;33(8):1297-307.
61. Chen J, Chung DW. Inflammation, von Willebrand factor, and ADAMTS13. Blood. 2018;132(2):141-7.
62. Malato A, Dentali F, Siragusa S, et al. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. Blood Transfusion. 2015;13(4):559.
63. Chowdhury JF, Moores LK, Connors JMJNEJoM. Anticoagulation in hospitalized patients with COVID-19. 2020;383(17):1675-8.
64. Liu J, Li J, Arnold K, Pawlinski R, Key NS. Using heparin molecules to manage COVID-2019. Research and Practice in Thrombosis and Haemostasis. 2020.
65. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. The Lancet Haematology. 2020;7(5):e362-e3.
66. Porfidia A, Pola R. Venous thromboembolism and heparin use in COVID-19 patients: juggling between pragmatic choices, suggestions of medical societies and the lack of guidelines. 2020:1-4.
67. Baumann Kreuziger L LA, Garcia D, Cuker A, Cushman M, Connors JM. COVID-19 and VTE/Anticoagulation: Frequently Asked Questions 2020 [Available from: www.hematology.org/covid-19/covid-19-and-vte-anticoagulation.
68. Tremblay D, van Gerwen M, Alsen M, et al. Impact of anticoagulation prior to COVID-19 infection: a propensity score–matched cohort study. 2020;136(1):144-7.

Similar Blood Glucose Pattern with Highest Peak at Minute 45 on Oral Glucose Tolerance Test Despite Higher Fasting Insulin and Insulin Resistance in Healthy Obese than Non-Obese Subject

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ABSTRACT

Background*:** *Obesity increase the risk for type 2 diabetes through induction of insulin resistance. Diagnosis of diabetes were based on blood glucose level. However, insulin resistance may had happened far before diagnosis itself. This study aimed to compare fasting insulin level, insulin resistance, and blood glucose pattern during oral glucose load in healthy obese and non-obese subject.* ***Methods: *This semi-experimental study was conducted at Department of Internal Medicine, Sanglah Hospital, Denpasar. Sixteen subjects in each obese and non-obese group were matched by age and sex. Obesity was defined based on body mass index (BMI) of ≥25kg/m^2 and waist circumference (WC) ≥80cm (female) or ≥90cm (male). The non-obese group was defined by BMI of 18-25kg/m^2 and WC <80cm (female) or <90cm (male). Fasting insulin level and blood glucose was measured at minute 0, 15, 30, 45, 60, 75, 90, 120 after glucose load of 75 grams. Insulin resistance was calculated based on homeostasis model assessment of insulin resistance (HOMA-IR) with the following formula: HOMA-IR = (FPI×FPG)/22.5. Normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) subject was defined by American Diabetes Association (ADA) criteria.* ***Results*:** *Fasting insulin level in obese subjects was higher than non-obese subjects with median 12.75 (range 3.70 – 41.30) vs 3.80 (1.80 – 36.80) µU/mL, p=0.041. HOMA IR was also higher in obese subjects compared to non-obese subjects: 2.45 (0.70 – 8.00) vs 0.80 (0.40 – 8.50), p=0.001. Fasting insulin level was correlated with BMI (r=0.559, p=0.001) and WC (r=0.633, p<0.001). A significant correlation was also detected between HOMA IR with BMI (r=0.528, p=0.002) and WC (r=0.600, p<0.001). Blood glucose pattern in four groups: obese IGT, obese NGT, non-obese IGT, and non-obese NGT, were typically similar, in particular two peaks of blood glucose. The first peak was the highest blood glucose, shown in minute 45 in both obese and non-obese subjects. The second peak was lower than the first peak, found in minute 75 among NGT and minute 90 among IGT subject. Blood glucose level for each measurement point was consistently higher in obese than non-obese subjects.* ***Conclusion*:** *Fasting insulin level and HOMA-IR were higher in obese than in non-obese subjects. BMI and WC were significantly correlated with fasting insulin level and HOMA IR, so that high BMI and WC can be an earlier clinical sign of insulin resistance and prediabetes. Pattern of blood glucose level after oral glucose load were similar with two peaks, and blood glucose consistently higher in obese compared to non-obese subjects. The highest peak of blood glucose, shown in minute 45 in both obese and non-obese subjects.*

Keywords: *Blood glucose pattern, OGTT, fasting insulin, HOMA IR*

INTRODUCTION

Prevalence of diabetes is markedly increasing, along with increasing prevalence of obesity. According to the IDF Atlas 10th edition 2021, the number of people with diabetes in Indonesia is 19.6 million, placing at the 5th rank of Top 10 countries or territories for number of adults (20–79 years) with diabetes in 2021 and 2045, rising from 7th rank in 2019.[1,2] The increasing rank is predictable since Indonesia was at 3rd rank of top 10 countries or territories for the number of adults (20–79 years) with impaired glucose tolerance (IGT) in 2019.

In order to avoid burden of diabetes and its complications, preventing diabetes is important. Early detection and early management of prediabetes is the key strategy to prevent diabetes. Study on 3234 nondiabetic persons aged 25 or more with elevated fasting and post-load plasma glucose concentrations revealed that a lifestyle-modification program with the goals of at least a 7 percent weight loss and at least 150 minutes of physical activity per week in Diabetes Prevention Program, reduced the incidence of diabetes by 58 percent after followed for an average of 2.8 years.[3] Similar study on long term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study enrolled 577 adults with impaired glucose tolerance showed 51% lower incidence of diabetes during the active intervention period and a 43% lower incidence over the 20 year period.[4]

Obesity increased the risk for type 2 diabetes through induction of insulin resistance which is thought to precede the development of diabetes 10 to 15 years.[5-7] The development of insulin resistance typically results in a compensatory increase in endogenous insulin production, and at the time of compensatory insulin secretion, blood sugar may remain normal while hyperinsulinemia as a consequences of insulin resistance affect the metabolism known as metabolic syndrome.[8] Direct measurement of insulin resistance can be done by measuring insulin-mediated glucose disposal during insulin suppression test and the gold standard is the hyperinsulinemic-euglycemic glucose clamp technique. This test is a research technique with limited clinical applicability due to impractically and expensive. Some efforts have been tried to use both the fasting plasma glucose and insulin concentration to estimate of insulin-mediated glucose disposal in more practical way, and several indices have been proposed, including homeostasis model assessment insulin resistance (HOMA IR).[9]

In a study of 490−healthy nondiabetic volunteers, fasting plasma insulin concentration accounted for approximately one-third of the variability in insulin-mediated glucose disposal, and fasting plasma insulin concentration as well as HOMA IR was significantly correlated to the specific estimate of insulin action.[10] These two approaches, measuring fasting plasma insulin level and calculating HOMA IR, has almost universally been used in large population-based epidemiological studies, however in clinical practice still relatively expensive and not widely available. For a clinical purpose, we need to define more practical surrogate marker of insulin resistance.

There are some difficulties in early detection of diabetes and prediabetes since the symptoms may not be obvious. The available test in clinical practice as per guideline are fasting blood glucose and blood glucose two hours post oral glucose load during oral glucose tolerance test (OGTT), which may lead particular high risk patient detected as normal glucose tolerance since the peak blood glucose could not be captured. This study aims to compare the fasting insulin level, insulin resistance, and blood glucose pattern during oral glucose load in healthy subject without history of diabetes divided into obese and non-obese groups. This study defined glucose pattern in more detail during OGTT and confirmed the importance of simple measurement of obesity in clinical practice to recognize insulin resistance regardless blood sugar level.

METHODS

This semi-experimental study was conducted at Department of Internal Medicine, Sanglah Hospital, Denpasar. A total of 32 subjects without history of diabetes were recruited, grouped into obese and non-obese groups, matched by age and sex. Age of subjects was between 20-50

years (mean age 31.46 SD 4.81 years). Obesity was defined based on body mass index (BMI) of ≥25kg/m^2 and waist circumference (WC) ≥80cm (female) or ≥90cm (male). The non-obese group had BMI of 18-25kg/m^2 and WC <80cm (female) or <90cm (male).[11]

Subjects were instructed to fast for at least 8 and maximum 12 hours before performing the procedure. Blood sample for measurement of fasting plasma glucose level and fasting insulin level were drawn in fasting state (minute 0). Oral glucose load using 75 g anhydrous glucose dissolved in 250 ml water was done in no more than 5 minutes. During oral glucose tolerance test (OGTT), capillary blood glucose level were measured in several time points at minutes 0, 15, 30, 45, 60, 75, 90 and at 120 after glucose load. Another blood sample was drawn at minute 120 during OGTT for plasma glucose to confirm the normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes categorization.

Fasting insulin level was measured by solid phase enzyme-labeled chemiluminescent immunometric assay, using Immulite® 2000 Insulin analysis system, Cat. No. L2KIN2 (Siemens). Fasting plasma glucose (FPG) and 2 hours plasma glucose (2hPG) during oral glucose tolerance test (OGTT) were measured by enzymatic hexokinase method. Capillary blood glucose was measured using glucometer (Accucheck®, Roche) at minutes 0, 15, 30, 45, 60, 75, 90, and 120 after 75-gram glucose load.

Based on FPG and 2hPG during OGTT, subjects were categorized as normal, prediabetes, or diabetes. Prediabetes are defined by impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). IFG is defined as FPG levels between 100-125mg/dL, and IGT as 2-h PG levels between 140 and 199 mg/dL during 75-g OGTT. Diabetes is defined by FPG ≥126mg/dL or 2-h PG ≥200 mg/dL during OGTT.[12] Insulin resistance was calculated based on homeostasis model assessment of insulin resistance (HOMA-IR) with the following formula: HOMA-IR=(FPI×FPG)/22.5.[13]

Data were analyzed for normality by Shapiro-Wilk test, and expressed descriptively in mean ± SD for normally distributed data or in median with range for not normally distributed data. The difference of median fasting insulin and HOMA IR were calculated by non-parametric test. Correlation between fasting insulin and HOMA IR with BMI and WC were measured by Spearman's rho. Repeated measurement general linier model was applied to define the blood glucose pattern during OGTT. In all statistical analyses, values of $p<0.05$ were considered significant.

The study approved by the Ethical Committee of the Faculty of Medicine Udayana University and Sanglah Hospital (No. 2145/UN.14.2/KEEP/2017), and authorised by the Director of Sanglah Hospital (No. LB.02.01/IXIV.2.2.1/34463/2017). All subjects were given information regarding this study and signed the informed consent. This study was conducted by the Declaration of Helsinki.

RESULTS

Subject recruited in this study aged between 27-48 years old (mean 31.46 + 4.81), age and sex matched, each group consisted of 8 males and 8 females. Based on the FPG and 2-h PG during OGTT, 4 subjects in obese group and 1 subject in non-obese group were categorized IGT, none of the subjects were categorized IFG or diabetes. Distribution of fasting insulin level and HOMA-IR were not normally distributed. Thus, data for these variables was presented in median and range (**Table 1**).

Fasting insulin in obese subjects was higher than non-obese subjects, median 12.75 (range 3.70 – 41.30) vs 3.80 (1.80 – 36.80) μU/mL, p=0.041. HOMA IR was also higher in obese subjects than non-obese subjects: 2.45 (0.70 – 8.00) vs 0.80 (0.40 – 8.50), p=0.001 (Table 1). Fasting insulin level was correlated with BMI (r=0.559, p=0.001) and WC (r=0.633, p<0.001). A significant correlation was also detected between HOMA IR with BMI (r=0.528, p=0.002) and WC (r=0.600, p<0.001).

The pattern of increasing blood glucose level during OGTT was similar between obese and non-obese subjects. Pattern in both groups showed two peaks. The first peak blood glucose was at minute 45 (161.31 SD 25.24 mg/dL) follow by slightly lower at minute 60, and second

Table 1. Characteristics of the Subject.

Variable (unit)	Data distribution mean (SD) or median (range)		
	Obese N=16	Non obese N=16	Total N=32
Age (years)	31.56 (4.76)	31.37 (5.03)	31.46 (4.81)
Body height (cm)	164.40 (9.89)	163.25 (10.16)	163.82 (9.88)
Body weight (kg)	84.74 (15.94)	59.33 (10.77)	72 (18.59)
BMI (kg/m^2)	31.10 (2.91)	22.15 (2.31)	26.62 (5.23)
WC (cm)	97.31 (10.38)	77.62 (6.92)	87.46 (13.24)
Fasting insuln (µU/mL)	12.75 (3.70 – 41.30)	3.80 (1.80 – 36.80)	7.25 (1.80 – 41.30)
HOMA IR	2.45 (0.70 – 8.00)	0.80 (0.40 – 8.50)	2.50 (0.40 – 8.50)

peak was at minute 75 (155 SD 26.23 mg/dL) followed by lower level of blood glucose the minutes after (**Figure 1**). Blood glucose level for each point of measurement was consistently higher in obese than non-obese subjects. Test of sphericity for the blood glucose is significant (p=0.000) so the assumption of sphericity has not been met, then tests of between subject effects was conducted using the Greenhouse-Geisser row which was significant (p= 0.000).

Since not all subjects were categorized NGT based on the FPG and 2-h PG during OGTT (4 subjects in obese group and 1 subject in non-obese group were categorized IGT), the pattern of blood glucose during OGTT were further divided into four groups, obese IGT, obese NGT, non-obese IGT, and non-obese NGT. Generally, the blood glucose pattern in IGT were higher than NGT in all point minutes of examination, in both obese and non-obese groups. Blood glucose pattern in these 4 groups were typically similar, showing two peaks of blood glucose level. The first peak of blood sugar was in minute 45 in all groups, the second peak among NGT subjects was found at minute 75 meanwhile among IGT subjects was found delayed: at minute 90 (**Figure 2**).

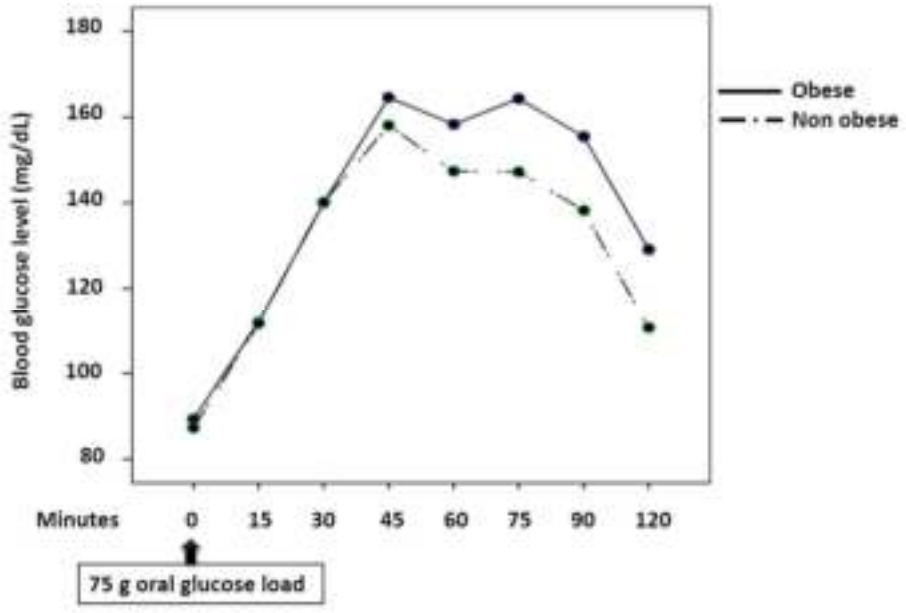

Figure 1. Blood glucose level for each minute point measurement during oral glucose tolerance test (OGTT) in obese and non-obese

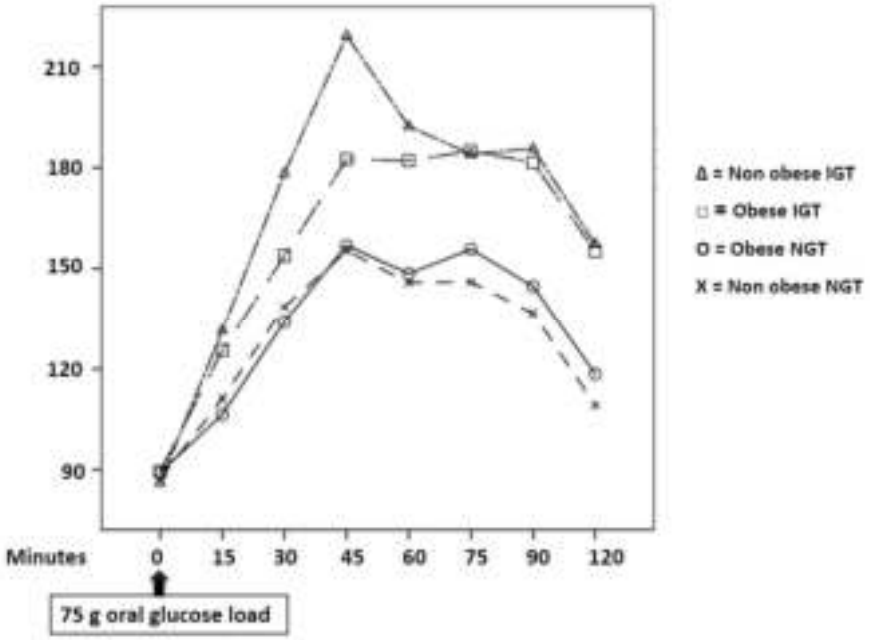

Figure 2. Blood glucose level for each minute point measurement during OGTT in 4 groups: obese IGT, obese NGT, non-obese IGT, and non-obese NGT
(OGTT = oral glucose tolerance test, NGT= normal glucose tolerance, IGT=impaired glucose tolerance)

Based on Kruskal-Wallis test, the distribution of fasting insulin across NGT or IGT and obese or non-obese categorizations were significantly different (p=0.005). The median of fasting insulin level across these categories were significantly different (p=0.41) (**Figure 3a**).

Similar finding was found for the distribution of HOMA IR between NGT or IGT categories in both obese and non-obese groups (p=0.004). The median of HOMA IR across these categories were significantly different (p=0.001) (**Table 2**). Since there was only 1 non-obese subject with IGT, the median data and range has been omitted. Fasting insulin level in this subject was 1.90 μU/mL and HOMA IR was 0.4. One non-obese subject with NGT has outlier fasting insulin level (36.80 μU/mL) and HOMA IR (8.5), as shown on the figure (**Figure 3a** and **3b**). Fasting insulin and HOMA IR were not correlated with blood glucose level at any of point measurement between minute 15 to 120.

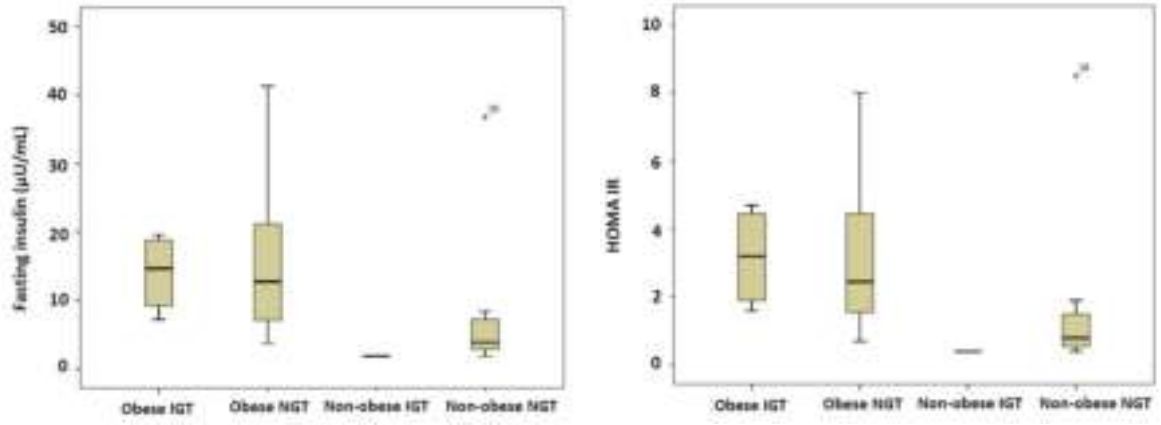

Figure 3. Median fasting insulin (a) and HOMA IR (b) in each group of obese IGT/NGT and non-obese IGT/NGT
(NGT= normal glucose tolerance, IGT=impaired glucose tolerance)

Tabel 2. Fasting Insulin and HOMA IR in Obese and Non-obese Subject.

Group		Fasting insulin ((µU/mL)		HOMA IR	
		Median	Range	Median	Range
Obese	IGT	14.65	7.20 – 19.60	3.20	1.60 – 4.70
	NGT	12.75	3.70 – 41.30	2.45	0.70 – 8.00
Non obese	NGT	3.90	1.80 – 36.80	0.80	0.40 – 8.50

DISCUSSION

Obesity is a rapidly growing nutritional disorder characterized by excessive accumulation of adipose tissue. Increased body weight is associated with insulin resistance and type 2 diabetes mellitus. In this study we found that obese subjects have higher fasting insulin level as well as HOMA IR, and both the fasting insulin level and HOMA IR were correlated significantly with the clinical obese parameters: BMI and WC. Higher fasting insulin level and HOMA IR, as well as positive correlation between BMI dan WC with HOMA IR confirmed the hypothesis that obese subjects were more likely to have insulin resistance compared with non-obese subjects.

In this study, one non-obese subject with NGT has high level of fasting insulin (36.80 µU/mL) and HOMA IR (8.5), as shown on the figure (**Figure 3a** and **3b**). Insulin resistance is present in the majority of patient with impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus (NIDDM) and in 25% of nonobese with normal oral glucose tolerance.[14]

Based on history, all subjects were considered to be healthy. However based on 2-hour plasma glucose during OGTT, 4 out of 16 subjects (25%) in obese group were identified as prediabetes (more specifically IGT), while in non-obese group only 1 subject was categorized as such (6.3%). This finding confirmed that obese subjects were more prone to be prediabetes. Blood glucose level for each point of measurement was consistently higher in obese than non-obese subjects. Pattern of increasing blood glucose level during OGTT were similar between obese and non-obese subjects in which they shown 2 peaks of blood glucose level regardless of their categorization as NGT or IGT. The first peak level of blood glucose level occurred in minute 45 during OGTT, followed by lower blood glucose. The second peak occurred in minute 75 among NGT subjects and a little delayed in minute 90 among IGT subjects. Since the number of IGT subjects was low, we need further study to evaluate the pattern of blood glucose in IGT subjects and evaluate the insulin response to explain this finding.

Fasting and 2-hour after 75 g glucose load on OGTT have been used to diagnose prediabetes and diabetes. However, evidence indicates that clinically relevant pathophysiological information can be obtained by adding intermediate time-points to a standard OGTT. A population-based study of 3666 Asian Indians underwent a three-point (fasting, minute 30 and 120) OGTT at baseline and then followed by another OGTT after 2 years follow up, found that elevated blood glucose at minute 30 after glucose load was associated with high risk of incident diabetes, even in individuals classified as NGT by a traditional OGTT.[15] Another cohort study of 5861 participants without diabetes at baseline from the Danish Inter99 study underwent similar three point (fasting, minute 30 and 120) OGTT identified four distinct glucose patterns during the OGTT, and the pattern with elevated glucose at minute 30 was associated with increased risk of diabetes and all-cause mortality rate independent of fasting and 2 hours glucose levels.[16] There is no data of minute 45 blood glucose in these particular studies. These findings alert us to define the highest peak of blood glucose during OGTT, so that we could choose the best time reflecting peak of blood glucose. In our study by doing frequent blood glucose measurement every 15 or 30 minutes (minute 0, 15, 30, 45, 60, 75, 90, 120) after glucose load on OGTT we found two peaks of the glucose pattern. Compare to these two studies, instead of minute 30, we found the first peak was at minute 45, the second peak was at minute 75 among NGT subject and at

minute 90 among IGT subjects. The first peak at minute 45 was the highest. Based on our finding, we conclude that considering only fasting and 2 hours glucose levels during an OGTT may not revealed the actual highest level of blood sugar. We suggest to check blood glucose at minute 45 during OGTT, in particular patient who are obese and high risk diabetes. Whether the 45 minute blood glucose provide a better prediction for future diabetes need further evaluation. We suggest to follow the obese subject group and reevaluate the blood glucose and fasting insulin level after a period of time. The data would be more comprehensive and important, if we could prescribe interventions to prevent more severe insulin resistance followed by longitudinal evaluation whether such intervention could prevent prediabetes and diabetes.

CONCLUSION

Fasting insulin level and HOMA-IR were higher in obese than in non-obese subjects. The BMI and WC were significantly correlated with fasting insulin level and HOMA IR. Since fasting insulin and HOMA IR were not correlated with blood glucose level during OGTT, these two simple markers of clinical obesity (high BMI and WC) should be taken as an earlier predictor of insulin resistance and prediabetes in clinical practice regardless blood glucose level.

Pattern of blood glucose level after oral glucose load were similar with two peaks despite higher fasting insulin and HOMA IR in obese than in non-obese subject. Even though fasting insulin and HOMA IR were not correlated with blood glucose level at any of point measurement during OGTT, blood glucose consistently higher in obese compared to non-obese subjects. The highest peak blood glucose, shown in minute 45 in both obese and non-obese subjects. Based on this finding, we suggest to check blood glucose at minute 45 during OGTT in particular for obese and high risk diabetes patient.

AUTHORS' CONTRIBUTION

MRS designed the study and performed data analysis, interpreted the data, and drafted the original manuscript. IBAN participated in informing subject and data collection. KS helped revised the final manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: https://www.diabetesatlas.org. Downloaded: 20 December 2021
2. IDF Diabetes Atlas. 9th Edition, 2019. https://www.diabetesatlas.org/upload/resources/2019/IDF_Atlas_9th_Edition_2019.pdf. Downloaded: 20 December 2021.
3. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403. doi: 10.1056/NEJMoa012512. PMID: 11832527; PMCID: PMC1370926.
4. Pendergrass M, Li G, Zhang P, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Diabetes Care. 2008;31:1921-2.
5. Blüher M. Adipose Tissue dysfunction in obesity. Exp Clin Endocrinol Diabetes. 2009;117(06):241-50. doi:10.1055/s-0029-1192044.
6. Ye J. Mechanisms of insulin resistance in obesity. Front Med. 2013;7(1):14-24. doi:10.1007/s11684-013-0262-6.
7. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000;106(4):473-81. doi:10.1172/JCI10842.
8. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinol Metab Clin N Am. 2004;33:283–303.

9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Tu rner RC. Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
10. Yeni-Komshian H, Carantoni M, Abbasi F, Reaven GM. Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy, nondiabetic volunteers. Diabetes Care. 2000;23:171–5.
11. World Health Organization. Regional Office for the Western Pacific. (2000). The Asia-Pacific perspective: redefining obesity and its treatment. Sydney : Health Communications Australia. https://apps.who.int/iris/handle/10665/206936.
12. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes – 2021. Diabetes Care. 2021;44(Suppl.1):S15-S33.
13. Diabetes trial units. HOMA calculator. The Oxford Centre for Diabetes, Endocrinology and Metabolisms, University of Oxford. Available from: http://www.dtu.ox.ac.uk/homacalculator/. Downloaded: 10 August 2020.
14. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-607. Doi:10.2337/diab.37.12.1595.
15. Hulman A, Gujral UP, Narayan KMV, Pradeepa R, Mohan D, Anjana RM, Mohan V, Færch K, Witte DR. Glucose patterns during the OGTT and risk of future diabetes in an urban Indian population: The CARRS study. Diabetes Res Clin Pract. 2017;126:192-197. doi: 10.1016/j.diabres.2017.01.009. Epub 2017 Feb 17. PMID: 28259008; PMCID: PMC5408861.
16. Hulman A, Vistisen D, Glümer C, Bergman M, Witte DR, Færch K. Glucose patterns during an oral glucose tolerance test and associations with future diabetes, cardiovascular disease and all-cause mortality rate. Diabetologia. 2018;61(1):101-107. doi: 10.1007/s00125-017-4468-z. Epub 2017 Oct 6. PMID: 28983719.

Supportive Psychotherapy for Healthcare Professionals in The Management of Acute Coronary Syndrome: The Use of Delphi Technique

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ABSTRACT

***Background**. Supportive psychotherapy (SP) may increase the benefit of acute coronary syndrome (ACS) management, but there is no structured SP as a guideline for healthcare professionals. This study aimed to develop structured SP as a guideline for implementing psychotherapy in the management of ACS patients in intensive cardiac care unit (ICCU).* ***Methods**. This qualitative study used Delphi technique as a modified Delphi method to reach a consensus among experts of structured SP for healthcare professionals in the management of ACS during hospitalized in ICCU. This was developed using self-reflection, observation, and interview of SP implementation in daily psychosomatic practice, gathering literature reviews, doing focus group discussion (FGD) and interview with ACS survivors. During the Delphi rounds, we interviewed 50 informants as source people using valid questionnaires, to proceed a draft of the SP framework and the structured sessions. The SP framework draft and the structured sessions were evaluated and corrected by experts anonymously until the consensus was reached. The validity of the consensus was tested, using Likert psychometric scale to reach an agreement. Cronbach alpha test was used to assess construct validity with SPSS 20.* ***Results**. All of preparations conducted before the Delphi rounds showed that ACS patients had psychosomatic disorders during in ICCU, that required support. SP is very helpful to reduce the negative impact of this disorders.Off 50 informants answered a valid and reliable questionnaire which supports the above statement. The draft was made based on the above process. The development of SP for healthcare*

professionals of ACS managements was reached in a consensus of expert panelists in the second round of the Delphi with Cronbach alpha of 0.9. ***Conclusion:*** *Supportive psychotherapy (SP) for healthcare professionals in the management of ACS in ICCU were developed and may be applied in clinical practice and research.*

Keywords*: Acute coronary syndrome, Delphi technique, Psychotherapy.*

INTRODUCTION

Acute coronary syndrome (ACS) causes disability, reduced productivity, which results in a global economic burden.[1] Acute coronary syndrome as part of coronary heart disease (CHD) is a syndrome with symptoms that include mainly chest pain due to atherosclerosis and/or acute thrombosis.

The role of psychological or stress factors in CHD and ACS has been widely researched. The INTERHEART study on 25,000 subjects from 52 countries found a relationship between chronic stressors and the incidence of myocardial infarction which could be prevented and improved.[2] Other studies also showed the negative impact of psychological injury in patients with CHD or ACS.[3,4]

This does not only occur during hospitalization, but also continues after hospitalization. This injury increases morbidity, mortality, and disabilities as well as decreases quality of life. [5-9] Advances in management of ACS have succeeded in reducing complications and mortality rates. Non-pharmacological therapeutic approaches such as psychotherapy should be an integral part of management to achieve optimal treatment. Psychotherapy can reduce the onset of psychological symptoms, accelerate healing, shorten the length of stay, reduce morbidity and mortality, and improve the patient quality of life.[10-12] A reviews and meta-analyses conducted in post-ACS patients or CHD patients also showed the benefit of psychotherapy.[13]

However, there are only several studies on supportive psychotherapy (SP) conducted in ACS patients during intensive care. Gruen[14] in 1975 began psychotherapy on the first or second day for 5 days a week in intensive cardiac care unit (ICCU), then continued in non-intensive ward. On the other hand, Roncella[15] started a combination of individual and group psychotherapy one week after primary cardiac intervention (PCI) for 3 months, and the outcome was assessed within one year. Yet, until now there has not been a structured SP for healthcare professionals in the management of ACS. Hence, this study aimed to develop a structured SP for healthcare professionals to manage ACS patients during hospitalized in ICCU

METHODS

This study is a part of randomized clinical trial (RCT) study using structured SP supplementing treatment ACS patients while in ICCU and assessing regulation of psycho-neuro-immuno-endocrine (PNIE).

This qualitative study which used Delphi technique as a modified Delphi method to reach a consensus from experts to develop structured SP for healthcare professionals to treat ACS patients during hospitalized in ICCU. Delphi method is an established method for reaching consensus among experts and practitioners and can be viewed as the standard method used in the health care and nursing sector.[16]

The study process occurred between January-April 2021, and the research was conducted at Integrated Cardiac Services, Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.

Most interviews and or communications used one or more internet-based media, such as zoom, email, WhatsApp, google form, related to global COVID-19 pandemic.

Ethics Statement

The studies were reviewed and approved by The Ethics Committee of the Faculty of Medicine of Universitas Indonesia. Written informed consent to participate in this study was provided by the participants. Nomor: KET-425/UN2F1/ETIK/PPM.00.02/2020.

Preparing the SP Draft

The steps for preparing the SP framework draft and the structured sessions were conducted before Delphi rounds, and those were including:

Self-reflection

Self-reflection of what had been done in the psychosomatic clinic related to the SP application.

Self-reflection is a process of looking back on the experiences that have been undertaken to be able to draw lessons learned for myself and followed by the preparation of an action plan to do better.[17]

Self-reflection can be part of a research method to give better results or even a single-method used in qualitative research.[18]

The Literature Study Aims to Explore Psychotherapy, CHD, ACS and PNIE

Literature search was done through keywords: superficial psychotherapy OR supportive psychotherapy AND acute coronary syndrome AND effect psychoneuroimmunoendocrine AND during hospitalize, through Cochrane, Emerald Insight, EBSCOhost, Google Scholar, JSTOR, Pubmed, and Scopus There were no specific articles found. Then, literature search conducted via Google regarding review material, and arranged according to the topic study on psychotherapy in ACS, PNIE and the relationship between psychotherapy and cerebral neuroplasticity, English language, without limited period of publications.

Observation of implementation of SP twelve times in a month and interview of SP implementation in psychosomatic clinic of internal medicine were done with open questions.

Interviews of "ICCU doctors and nurses "related to SP for healthcare professionals in the management of ACS, were done using open questions.

Focus group discussion (FGD) were done with ACS survivors via zoom. FGD were done to find out ACS patients about their feelings, emotional problems, psychosomatic disorders and also to find out what they need for SP during hospitalization in ICCU. Interview of survivors conducted during FGD using questionnaires.

Based on the above process, the questionnaire related to the topics and materials was created as an instrument to collect opinions from the Informant as a source person.

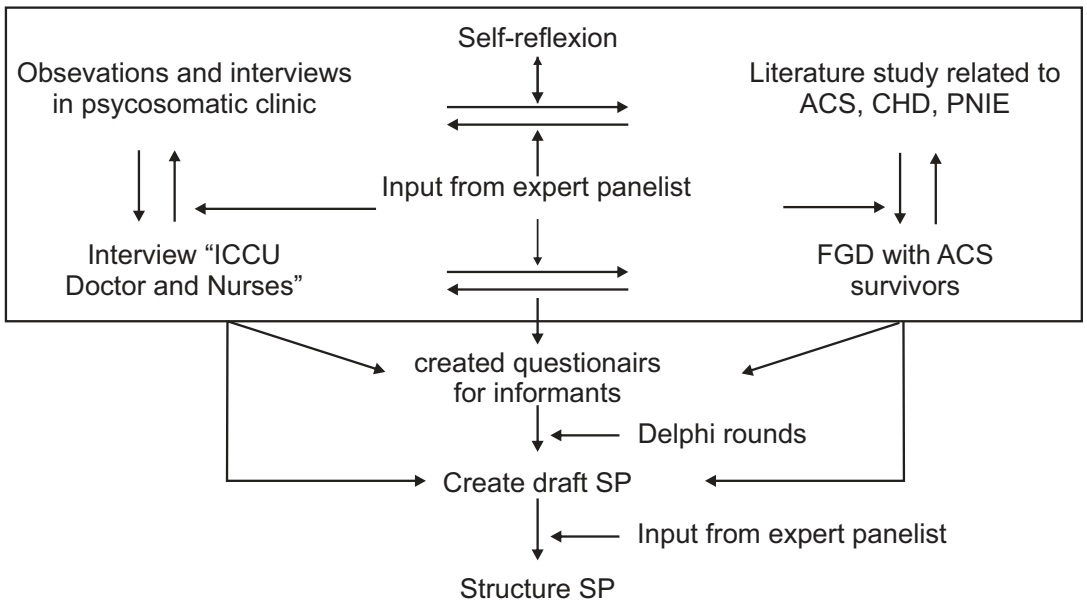

Figure 1. The conceptual framework flowchart.

The diagram below describes the flowchart conceptual framework. (**Figure 1**)

Delphi Methods

The First Round of Delphi

Collection of informants' opinions, with the questionnaires were done. The questionnaires were sent via *google form* to the informant as source person two times in the period of up to two weeks.

This study uses 50 informants, which consists of physicians or nurses who cared ACS patient and/ or SP services, each were competent in one or more the field of psychosomatic, cardiovascular, endocrine, immunology, psychiatry, clinical psychology, psychotherapist and internal medicine. Selection of informants were done by convenient sampling to those who are working or have worked in ICCU or understand problems related to ACS disease. Most informants work at Cipto Mangunkusumo Hospital as a tertiary hospital, and each one from Department of Community Medicine Faculty of Medicine Universitas Indonesia Jakarta, Faculty of Psychology Universitas Gadjah Mada, Jogjakarta, Psychosomatic Division Department of Internal Medicine Faculty of Medicine Universitas Syiah Kuala Banda Aceh, Indonesia.

Collected material was used for the draft of structured SP framework and SP sessions.

We recruited 10 expert panelists to assess SP framework draft and the structured sessions as an SP for professional healthcare in management of ACS. The expert panelists have more than 10 years of experience in some fields, such as internists- consultant of cardiovascular, internists-consultant of psychosomatic, psychiatrists-consultant, internists-consultant of endocrine, metabolism, and diabetes, internists- consultant of clinical immunology and allergy, internists-consultant-geriatric, psychiatric-consultant (psychotherapist), clinical psychologist-consultant and community medicine specialist-consultant.

SP framework draft and sessions were structured and sent to the expert panelists via *google form* to assess the eligibility, give input, and provide corrections to improve it until the SP framework and structured SP sessions were compiled.

The Second Round of Delphi

The second round of Delphi, the SP framework and structured sessions were sent via google form to the expert panelists to assess the eligibility using a Likert scale rating with score of 1-6 (1: unnecessary, 2: less necessary, 3: may be necessary, 4: almost necessary, 5: necessary, 6: very necessary) and to write comments for each component if necessary.

The agreement was reached if $\geq$ 80% of expert panelists gave the score of $\geq$ 4, the statement would be included for the SP framework and structured sessions, and if <80% of the expert panelists gave a score of $\leq$ 4 to a statement, the statement would be re-entered in the next Delphi round, accompanied by an attachment to the previous response as a basis for the expert panelists to reconsider the existing decision, until an agreement was reached.

Data Management and Statistical Analysis

Self-reflection, literature study, Observations and interview in psychosomatic clinic of internal medicine. Interview of the doctors and nurses in ICCU related to SP, Interview and FGD with ACS survivors would be report as a brief narrative.

Descriptive data is used to describe the demographic characteristics of the informants and expert panelists. Categorical data will be reported in the form of frequency (n) and proportion (%), and numerical data as a mean and SD. The face validity test for each statement of informant was tested using percent index and the reliability test using the Spearman-Brown coefficient. Data analysis was done using SPSS 20 version.

RESULTS

Self Reflection

Researcher has been working in the field of psychosomatic, internal medicine for more than 25 years. Self-reflection focus on psychotherapy gave the idea that SP is an

important aspect considering the psychosomatic therapy to all psychosomatic patients who were receiving holistic management. there was no structured SP that can be used as a guide for healthcare professionals, although SP is often discussed and used in daily practice in psychosomatic clinics. It has been encouraged to conduct research on SP related to psychosomatic patients to prove that SP is a therapy that can improve psychosomatic disorders scientifically. The SP can improve psychic and somatic functions related to psychophysiology and improving PNIE regulation. It would convince Healthcare professionals, doctors, especially those who work in the medical field (focusing more on the somatic aspect) in becoming more concerned about the psychological aspects and establishing better collaboration for the optimal benefit.

Study Literature of Psychotherapy in ACS Patients.

The results of the literature study could be concluded as follows:

ACS patients are patients with acute medical conditions that require immediate help. So far, medical assistance has focused more on somatic problems. Somatic medical treatment has succeeded in reducing the number of complications, morbidity and mortality in line with developments of cardiovascular drugs and technology. However, the results would be better, if it is combined and integrated with psychotherapy. It has been proven from many studies that psychotherapy works in synergy with pharmacological treatment, and may reduce complications, morbidity, mortality and also increase quality of life during and after hospitalization.

Stressors has been proven to have a role in the course of the disease and the incidence of ACS complications both during and after acute treatment at the ICCU.

SP during acute care at the ICCU has not been widely studied. Gruen (1975) has been conducted unstructured psychotherapy on the first day or the second day for 5 days a week to ACS patients at the ICCU, then continued in the ward. Another study by Roncella, where psychotherapy interventions were started on patients 1 week after PCI and were combined with individual psychotherapy, then followed by group psychotherapy for a long period of approximately 3 months, and the outcome was seen within one year. Both studies gave positive result.

Gruen's research is almost the same as the research that will be carried out in this study. Gruen started psychotherapy for ACS patients, but in Gruen's study, psychotherapy was carried out until the patient was discharged from the ICCU and continued in the regular ward until the patient went home between 11 and 22 days, which means the psychotherapy dose was different between patients. The outcome of psychotherapy interventions in Gruen's nor Roncella's studies involved PNIE. Currently, a structured SP has not been compiled as a guideline for healthcare professionals to manage ACS patients during hospitalization in ICCU.

Observation and Interview of SP Implementation in Psychosomatic Clinic of Internal Medicine Observations

Observations for 3 months gave the idea that SP is often given to psychosomatic patients such as ventilation, suggestion, guidance and reassurance as well as a spiritual approach, which involves cognitive function to improve emotional disturbance to reduce psychic and somatic symptoms. The results of SP administration were better when given together with oral medicine. However, SP, either separately or simultaneously with the use of medicine, has never been studied in psychosomatic patients or with certain medical conditions such as ACS. SP has also not been given in a structured manner, which is important to do research to assess its effectiveness consistently.

Interview

The concept of managing psychosomatic disorders is through a biopsychosocial-spiritual approach. One of the therapies that the researcher often does is supportive psychotherapy. Psychotherapy is one of the treatments that has an important role in patients with

psychosomatic disorders in addition to giving psychopharmacology. Psychotherapy is useful in improving and accelerating healing in patients with psychosomatic disorders. Encouraging patients to recognize themselves and their pain. Psychotherapy itself consists of ventilation, reassurance, support and others. Supportive psychotherapy can be carried out by all doctors, who have undergone training to suit the goals of supportive psychotherapy. In the psychosomatic polyclinic of Internal Medicine, SP is provided for all patients, while a small number of patients received deeper psychotherapy including cognitive behavioral therapy (CBT).

Interviews of "ICCU Doctors and Nurses "

Most ACS patients experience emotional disturbances, there are psychological and somatic problems, anxiety and depression. Anxiety or worry, fear of death related to the disease, related to the ICCU room and anxious about PCI and the condition of the disease. It needs explanation, psychological support, and needs SP either by a doctor or nurse.

FGD and Interview with ACS Survivor

There were 50 participants during FGD, and 30 of them were ACS survivors. Some of them are ACS survivors who took part in the post-ACS rehabilitation program organized by cardiac rehabilitation team of Integrated Cardiac Services, Cipto Mangunkusumo National Hospital, Jakarta, Indonesia**.**

The FGD clarified that during ACS treatment in ICCU, they need support from doctors, nurses, family and friends as early as possible. The need for a doctor related to psychological disorders is very necessary, may be a psychosomatic doctor, psychiatrist or psychologist, who can overcome the trauma that occurs during treatment. In fact, this condition persists after treatment and is helped by the group managed by PJT and the Medical Rehabilitation Team. Some patients feel traumatized, despairing over what happened to them for more than a year. Interview of

Table 1. Characteristics of the Informants.

Variables	N=50
Age (years)	
mean (SD)	41.74 (11.36)
Sex	
Male.	27
Female.	23
Education,	
Doctoral degree	9
Consultant	5
Master degree	9
Bachelor degree	23
Associate degree	4
Occupation	
Medical doctor	37
Clinical psychologist	1
Nurse	12
Types of occupation/profession	
Internist-consultant of psychosomatic	2
Internist-consultant of cardiovascular	4
Internist-consultant of endocrine metabolic, and diabetes	1
Internist-consultant of allergy and immunology	1
Internist-consultant of geriatric	1
Psychiatrist-consultant	3
Clinical psychologist-consultant	1
Community Medicine Specialist- Consultant.	1
Resident of internal medicine with subspeciality in cardiovascular	4
Resident of internal medicine with subspeciality in psychosomatic	3
Internist	2
Resident of internal medicine	15
ICCU nurse	6
ICCU ex-nurse	5
Ward nurse	1

ACS survivors conducted during FGD using questionnaires.

The Informants Characteristics and Opinions

The characteristics of the informants were as follows: a mean age of 41.74 (SD±11.36) years old, the male and female ratio almost equal, most participants with an education level of bachelor's degree, all health professionals, mostly doctors (**Table 1**).

All informants answered 19 statements in the questionnaire (Q) (**Table 2**). Face validity test for each question was between 88%-100% which means the items had good validity. Reliability test with test-retest reliability through the Spearman-Brown coefficient for each statement is above 0.90.

From 19 statements, almost all of them answered yes or agreed, except for Q7, 22% answered no. However, suggestions were given as needed. Some who agreed also gave the same advice. Q11, SP in ACS.

Table 2. Proportion of Statement Agreement of the Informants Questionnaire

No	Statement	Yes	%	No	%	Annotations/Comments
1.	Patient with heart attack such as acute coronary syndrome (ACS) will experience emotional disturbance, anxiety, restlessness, and fear mixed with sadness	50	100	0	0	
2.	Empathic accompaniment and support during intensive care are urgently needed by ACS patients	50	100	0	0	
3.	Supportive Psychotherapy (SP) as a form of psychological support is needed by ACS patients during intensive care.	50	100	0	0	
4.	SP is a non-pharmacological therapy that is needed by ACS patients during intensive care.	49	98	1	2	
5.	SP can be useful, synergistic, and complementary to the current existing standard therapy.	49	98	1	2	
6.	The core parts of SP needed for ACS patients are ventilation, suggestion, and reassurance SP.	48	96	2	4	
7.	The core parts of SP which are needed for ACS patients, should be given simultaneously at each SP session.	39	78	11	22	Types of SP given are according to the needs.
8.	Psychoeducation, which is given to ACS patients, complements SP for emotional improvement.	48	96	2	4	
9.	Spiritual support, namely greeting during the opening and prayer with the patient completes SP, which is given to ACS patients complement SP for emotional improvement	49	98	1	2	
10.	SP on ACS patients can be started on the first day of treatment after the patient is stable with the standard treatment given.	49	98	1	2	
11.	SP on ACS patients can be done every day for 5 consecutive days, with one session per day	39	78	11	22	Depend on patient's condition
12.	SP in ACS patients can be given within 30 minutes to 60 minutes in each session.	45	90	5	10	The suggestion 15-45 minutes or 20-40 minutes enough, and 30 minutes maximum. While the mean tries out .30 minutes
13.	SP will be useful in improving psychosomatic function.	49	98	1	2	
14.	SP will be useful in improving the dysregulatory function of psycho-neuro-immuno-endocrine (PNIE) function in ACS patients.	49	98	1	2	
15.	SP will be useful in improving the emotions of ACS patients.	50	100	0	0	
16.	SP will be useful in improving the symptoms of anxiety and depression in ACS patients.	50	100	0	0	
17.	SP will be useful in improving the autonomic nerves function of ACS patients	50	100	0	0	
18.	SP will be useful in improving the immune system function of ACS patients.	49	98	1	2	
19.	SP will be useful in improving the endocrine function of ACS patients.	48	96	2	4	

Patients can be given every day for 5 consecutive days, with the provision of one session per day. 78% agree that SP should be given for 5 consecutive days. Q12, SP in ACS patients can be given for the duration of 30 minutes to 60 minutes per session. Some informants suggest that the duration of SP should be around 20-40 minutes, 15-45 minutes or maximum 30 minutes, and the trial mean time was 30 minutes.

The characteristics of expert panelists were shown in **Table 3.**

All expert panelist level educations have doctoral or consultant of healthcare professionals related to research topic. The results of the statements SP framework by expert panelists. (**Table 4**). The expert panelists who agree with the statements related structured SP sessions. (**Table 5**)

Structured SP sessions consensus as a guideline for health care professional to manage ACS patients have been reached by expert panelists in the second round of Delphi could be seen in Attachment.

Table 3. The Expert Panelists Demographic Characteristic.

Variables	N=10
Age (years) mean (SD)	58.30 (7.30)
Sex	
Male	6
Female	4
Education,	
Doctoral degree	7
Consultant	3
Occupation/profession	
Internist-consultant of psychosomatic	1
Internist-consultant of cardiovascular	1
Internist-consultant of endocrine metabolic, and diabetes	1
Internist-consultant of allergy and immunology	1
Internist-consultant of geriatric	1
Psychiatrist-consultant	3
Clinical psychologist-consultant	1
Community medicine specialist- consultant	1

Table 4. Proportion of Panelist Agreement of Framework SP Statements Base on Lickert Score.

No	Statements	LS 6	LS 5	LS 4	LS 3	LS 2	LS 1	Agreement ≥ 4, N (%)
1	Greet in a friendly manner, introduce yourself to the patient	9	1	0	0	0	0	10 (100)
2	Ensuring matters relating to the identity of the patient	8	2	0	0	0	0	10 (100)
3	Explain the aim and purpose of the meeting	8	2	0	0	0	0	10 (100)
4	Asking about problems and, asking the patient to express his feelings today	6	4	0	0	0	0	10 (100)
5	Provide support according to patient needs	6	4	0	0	0	0	10 (100)
6	The doctor analyzes the functioning ability of the patient's ego	3	5	0	2	0	0	8 (80)
7	Convince the patient of his ability to deal with problems that arise	5	5	0	0	0	0	10 (100)
8	Ask family members, friends who care about the patient's problems	3	6	1	0	0	0	10 (100)

9	Provide education and understanding regarding patient problems both psychologically or somatically	6	4	0	0	0	0	10 (100)
10	Ask about comfort, conditions, and constraints that exist.	4	5	1	0	0	0	10 (100)
11	Provide support to the patient in dealing with current and future problems.	5	5	0	0	0	0	10 (100)
12	Ask if there is still anything to say regarding the patient's problem	5	4	1	0	0	0	10 (100)
13	Provide support in accordance with the problems described by the patient.	5	5	0	0	0	0	10 (100)
14	Summarize the meeting's results	6	4	0	0	0	0	10 (100)
15.	Pray for each other's health, and end the meeting	5	4	0	0	0	1	10 (100)

LS: Lickert Score. (1: unnecessary, 2: less necessary, 3: may be necessary, 4: almost necessary, 5: necessary, 6: very necessary). N: number of expert panelist

Table 5. The Expert Panelists Who Agree of The Statements of SP Sessions.

SP session	Total Statement	100% Agree N 10	90% Agree N 10	80% Agree N 10	<80% Agree N 10
SP. Session1	15	6	8	1	0
SP. Session2	15	10	4	1	0
SP. Session3	15	15	0	0	0
SP. Session4	11	11	0	0	0
SP. Session5	15	14	1	0	0

It could be seen that the results of the assessment of 10 expert panelists in the second round had reached an agreement.

DISCUSSION

All prepared resources related to SP structure for healthcare professionals in the management of ACS patients were supported this study.

Delphi method has often been used in extensive health-related studies and can produce an adequate level of evidence-based medicine,[19] that is a reliable and creative method for exploring ideas to reach a consensus among experts.[20-22] The expert panel did not interact directly with each other to avoid social interaction bias, but they are made aware of the group responses and change their views, leading the expert panel towards group consensus.[20,26]

This study uses Delphi technique as a modified Delphi method that is generally accepted to collect information in the first of Delphi using informant questionnaires based on literature reviews and other necessary source.[23-25] to prepare the draft SP framework and structured Sessions and to reach a consensus of "expert" opinion.[26-28]

Informants who meet the representatives of the expertise group according to the topic will increase the validity of the results.[29-32]

The number of informants depends on the topic as well as the time and resources available with varying amounts.[31-33] There are 50 informants, including 10 expert panelists, and more than 30 informants are considered to be a large and adequate number.[33] Even though online survey response rate is usually lower than paper-based surveys[30], this study response rate was 100%. This may indicate a representative sample target population and reduced non-responder bias.[34-35]

From 19 statements, almost all of the informants agreed. It means that the statement may be taken as a representative material that includes structured SP sessions as the aim of

this study. Patients with ACS will experience anxiety and worry accompanied by sadness and emotional disturbances, and these were evidenced by several other studies,[36-40]which require adaptation.[41]

This condition can have a negative impact or short-term or long-term complications through various pathophysiological mechanisms[42-54] that require empathic accompaniment and require SP to quicken adaptation, strengthen coping mechanisms, facilitate healing and reduce complications.[55-60]

Q7 is related to the type and strategy of SP intervention, and is based on the goals, socio-cultural and clinical background of the patient. The type and technique used to provide SP can also vary, from the length (duration), the time interval for the next meeting, to the assessment of the outcomes that occur.[61-63]

SP is a non-pharmacological therapy, synergizing and in-line with and complementing the standard.

ACS treatment. Types of SP include venting, suggestion, reassurance, encouragement, praise persuasion, rationalizing and reframing, also with education and spiritual support to complement SP in correcting existing psychological or emotional disorders, in a way that is compatible to the patient.[14,64]

Q11 and Q12 are both related to SP durations and sessions, and it can be brief and intensive psychotherapy, which is related to the fact that short and intensive psychotherapy can give good results. Patients are more tolerant, and it is easier to get insurance coverage, especially in primary services.[65-67]

The meaning of short psychotherapy is relative and varies, but in simple terms, short psychotherapy can mean doing psychotherapy in a short time, as it can only be 15 minutes [57/60] or with as few sessions as possible which can already overcome the patient's condition, and it does not exceed the need even if it is only one session.[68]

There is also a definition that brief psychotherapy is generally carried out in fewer than 8 sessions, which is different from standard psychotherapy which is usually carried out between 8 and 12 sessions in depressed patients. In critical studies and meta-analyses, depressed patients require 6- 8 sessions of psychotherapy to obtain good results.[69]

Some even do psychotherapy with a combination of exposure, participant modelling, cognitive challenges, and reinforcement with a maximum duration of 3 hours in patients with specific phobias, such as social phobia, with just one session to obtain effective results. [70]

One-session psychotherapy is also effective in patients with multiple specific phobias accompanied by other anxieties.[71]

Intensive psychotherapy can mean giving psychotherapy every day,[72,73] and it can also mean providing deep psychotherapy by exploring various things that are the patient's problems both new and old to improve the patient's emotions, this meaning gives a contrasting impression with the meaning of SP which focuses only on patients and current problem solutions.[74,75]Therefore, it is very possible to use SP every day in a short duration in acute conditions such as in ACS patients. Ehler et al.[76] reported that daily cognitive psychotherapy for 7 consecutive days in PTSD was as effective as 3 months of weekly psychotherapy toreduce symptoms of anxiety and depression as well as improve quality of life.

Based on the explanation above, SP can be given in 5 consecutive sessions with the duration of each session ranging from 15 to 45 minutes for the implementation of a structured SP in ACS patients while still observing the patient condition.

SP can improve patient's psychosomatic function, emotional conditions, and reduce anxiety and depression symptoms through PNIE regulation.

The physiological mechanism of the brain and body relationship illustrates that there is a strong relationship between the magnitudes of disturbances in the brain, in this case emotions and thoughts, and their effects on the body. They will communicate with each other and send signals that produce biological changes (somatic) and physiological processes, which can improve a person health status, and PNIE clarifies its psycho-physio-pathological mechanisms.[77-81] Buchheim et. al.[82] in a study

of psychotherapy in depressed patients found an improvement in the limbic system, the left anterior hippocampus (amygdala), subgenual cingulate, and medial prefrontal cortex which initially experienced activation, followed by the activation subsiding along with a reduction in depressive symptoms. This is an important study that shows psychotherapy improvements in the limbic system pathway or circuit which is an important emotional pathway that is then related to the HPA pathway.[83] From a clinical study conducted by Holzel et. al.[83], it was found that there was a change in the gray matter density of the brain region that is involved in emotion regulation, causing changes in neuroplasticity and immuno-endocrine returned to physiological capacity.[84] Imaging clinical studies in major depression have shown that the administration of CBT affects the clinical recovery of the limbic and cortical areas including the frontal, cingulate and hippocampus areas as well as the use of antidepressants.[43] There is also evidence that psychotherapy can improve the uptake and metabolism of neurotransmitters, especially serotonin[85,86] Research by Joffe et. al.[87] found an increase in T4 in depressed patients who responded to cognitive and behavioral psychotherapy, while those who did not respond had a decrease in T4. This proves that psychotherapy, besides being able to improve psychosomatic symptoms, can also affect the hormonal axis such as the hypothalamic pituitary thyroid (HPT) axis, as well as another hormonal axis such as the hypothalamic pituitary adrenal (HPA) axis.[88]

The studies mentioned above prove that psychotherapy provides improvements in not only the psychological function but also improve the somatic function related to the organ at the cellular or even molecular level, through the limbic system as an emotional center, through the psycho- neuro-immuno- endocrine (PNIE) pathway; however, it needs further integrative studies.

Psychotherapy is provided of course based on the goals, socio-cultural and clinical background of the patient. The type and technique used to provide SP can also vary, from the length (duration), the time interval for the next meeting, as well as the assessment of the outcomes,[61-63] as planned in this developed SP for professionals healthcare.[89-90]

The second round of Delphi, the expert panelists assessed the feasibility of SP framework and structured sessions for ACS patient with a Likert scale of one to six which could already describe the level of agreement of the expert panelists.[91-92]

The characteristics of the expert panelists related to education and profession show adequate qualifications, at least according to their respective fields that support the topic and material in this study. Expert panelists who have at least 10 years of experience in the field will add to the validity of this study. It can be seen in the result of the second round Delphi method that an agreement was reached according to the specified conditions (>80%). According to Hasson et. al.[93], consensus does not have to be agreed upon by all expert panelists, and this study determined that a minimum of 80% of participants' consent was needed to reach a consensus. The number of samples, research objectives, and available resources were taken into account in determining consensus, and this may increase validity.

The strength of the study we use many resources and many experts related to the topic and study material while the limitations of the study conducted during a global pandemic that may limit communication with both psychotherapists and patients. It was done only in one country, Indonesia.

CONCLUSION

All resources related to SP for professionals healthcare of ACS patients' management support this study Valid and reliable self-reported questionnaire was created to collect informant opinions uses Delphi technique as a modified Delphi method. The first round of Delphi, a draft was compiled which received input and improvements from expert panelists. The second round of Delphi, an assessment was carried out by expert panelists on a Likert scale and a consensus was reached. The SP framework and structured sessions for professionals healthcare of ACS patients' management was developed. This SP may be

applied in clinical practice and research for professional healthcare in the management of ACS with attention to socio-cultural.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

HS contributing author, designing, analyzing, writing the results, and discussion. IA, RI, KW, contributing the analyzing and the review process. HQ, KH. contributing designing and results analyzing. IA, PS, IR, SS contributing the review process. RP, VA. results analyzing, writing discussion. PR, SD contributing the analyzing and the review process. All author contributed equally for this paper.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors.

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REFERENCES

1. Kolansky DM, Acute coronary syndromes: morbidity, mortality, and Pharmacoeconomic Burden, Am J Manag Care. 2009;15: S36-41.
2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifi able risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364:937-52.
3. Gidron Y, Armon T, Gilutz H, Huleihel M, Psychological factors correlate meaningfully with percent-monocytes among acute coronary syndrome patients, Brain, Behavior, and Immunity. 2003;(17):310-5. Doi:10.1016/S0889-1591(03)00061-8.
4. Kenyon LW, Ketterer MW. Psychological factors related to prehospital delay during acute myocardial infarction. Circulation. 1991;84:5-9.
5. Fresure-smith N, Lesperance F, Talajic M. Depression and 18 month prognosis after myocardial infarction. Circulation. 1995;91:999-1005.
6. Barefoot JC, Helms MS, Mark DB. Depression and long-term mortality risk in patients with coronary artery disease. Am J Cardiol. 1996;78:613-7.
7. Shatri H, Harun S, Nurhay A, Sutrisna B. The influence of stress on acute myocardial infarction during intensive care. 16th World Congress of Psychosomatic medicine. Sweden 2001.
8. Bonaguidi B, Cini E, Rovai D. Psycho-emotional impact of acute coronary syndromes' Ital Cardiol (Rome). 2011;12(9):606- 10. doi: 10.1714/926.10175.
9. JLichtman JH, Froelicher ES, Blumenthal JA, et.al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: Systematic review and recommendations. Circulation. 2014;129 (12):1350-69. https://doi.org/10.1161/CIR.0000000000000019
10. Anderson L, Brown JP, Clark AM, Dalal H, Rossau HK, Bridges C, Taylor RS. Patient education in the management of coronary heart disease patient education in the management of coronaryheart disease. [Cochrane Database Syst Rev. 2011].
11. Whalley B, Rees K, Davies P, et.al. Psychological interventions for coronary heart disease. Cochrane Database Syst Rev. 2011;10 (8):CD002902. Doi: 10.1002/14651858.CD002902.pub3.
12. Richards SH, Anderson L, Jenkinson CE, et al. Psychological interventions for coronary heart disease. Cochrane database of systematic reviews. Eur J Prev Cardiol. 2018;25(3):247–59. 165.
13. Whalley B, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. Int J Behav Med. 2014;21(1):109-21. Doi: 10.1007/s12529-012-9282-x.
14. Gruen W, Effects of brief psychotherapy during the hospitalization period on the recovery process in heart attacks. Journal of Consulting and Clinical Psychology. 1975:43 (2):223-32.
15. Roncella A, Giornettia A, Cianfroccaa C, et al. One year results of the randomized, controlled, short-term psychotherapy in acute myocardial infarction (STEP-IN-AMI)-trial. Intl J of Cardiol. 2013;170:132-9.
16. Niederberger M, Köberich S. Coming to consensus: the Delphi technique. Eur J Cardiovasc Nurs. 2021; 20 (7): 692- 5, https://doi.org/10.1093/eurjcn/zvab059).
17. Stynes M, Murphy T, McNamara G, O'Hara Dublin J. Reflection-on-action in qualitative research: A critical self-appraisal rubric for deconstructing research. Issues in Educational Research, 2018;28(1):153-67.
18. Ezealah, Ikenna Q. The role of self-reflection in the spiritual quest to make meaning of experiences (2019). All Dissertations. 2514. https://tigerprints.clemson.edu/all_dissertations/2514.
19. Jorm AF.Using the Delphi expert consensus method in mental health research. Australian & New Zealand Journal of Psychiatry. 2015;49(10):887–97. DOI: 10.1177/0004867415600891
20. Ziglio E. The Delphi method and its contribution to decision-making; Gazing into the Oracle: The Delphi method and its application to social policy and public health. Jessica Kingsley Publishers; ISBN 1-85302-

104-0; 2002; 1(1): 3–33.
21. Langlands RL, Jorm AF, Kelly CM, Kichener BA. First aid for depression: A Delphi consensus study with consumers careers and clinicians. Journal of Affective Disorder. 2008; 105:157–65.
22. Revez A, Dunphy N, Harris C, Mullally G, Lennon B, Gaffney C. Forecasting: Using a modified Delphi method to build upon participatory action research in developing principles for a just and inclusive energy transition. International Journal of Qualitative Methods. 2020;19:1-12. on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage). DOI: 10.1177/1609406920903218 journals. sagepub.com/home/ijq.
23. Hsu C-C, Sandford BA. The Delphi technique: Making sense of consensus. Practical Assessment Research & Evaluation. 2007;12(10).
24. Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLoS One. 2011;6(6): e20476. https://doi. org/10.1371/journal.pone.0020476 PMID: 21694759
25. Stewart D, Gibson-Smith K, MacLure K, et al. A modified Delphi study to determine the level of consensus across the European Union on the structures, processes and desired outcomes of the management of polypharmacy in older people. PLoS One. 2017; 12(11): e0188348. https://doi.org/10.1371/journal.pone.0188348 PMID: 29155870
26. Dalkey N, Helmer O. An experimental application of the Delphi method to the use of expert; United States Air Force under Project RAND; 1962; 1–17.
27. Solovieva N. A mixed method Delphi study to determine professional consensus on the key elements of outpatient Psychodynamic Group Psychotherapy (PGP) for psychosis; A thesis submitted for the degree of Professional Doctorate in Counselling Psychology; Department of Health and Human Science University of Essex; 2015.
28. Scheibe M, Skutsch M, Schofer J. Experiments in Delphi methodology. The Delphi method: Techniques and applications. In: Murray Turoff and Harold A, eds. Linstone; ISBN 0-201-04294-0; 2002; IV.C. p. 257–81.
29. Morrison AP, Barrat S. What are the Components of CBT for psychosis? A Delphi study; Schizophrenia Bulletin. 2009;36(1):136–42.
30. Linstone HA, Turoff M. Computers and the future of Delphi: Introduction; The Delphi method : Techniques and applications. In: Murray Turoff and Harold A, eds. Linstone; ISBN 0-201-04294-0; 2002; VIIA. p. 483–9.
31. Levy PS, Lemeshow S. Sampling populations; methods and aplications. 4th ed. John Wiley & Sons Inc; 2008.
32. Giannarou L. Zervas E. Using Delphi technique to build consensus in practice. Int. Journal of Business Science and Applied Management. 2014; 9(2):65-82.
33. Nult DD. The adequacy of response rates to online and paper surveys: what can be done? Assessment & Evaluation in Higher Education. 2008; 33 (3): 301–14.
34. Fincham JE. Response rates and responsiveness for surveys, standards. The Journal American Journal of Pharmaceutical Education. 2008;72 (2) :43.
35. Draugalis JR, Plaza CM. Best practices for survey research reports revisited: Implications of target population, probability sampling, and response rate. American Journal of Pharmaceutical Education. 2009; 73 (8):142.
36. Cassem NH, Hacket TP. Psychiatric consultation in coronary care unit. Ann's intern Med.1971;75: 9-14.
37. Cay E, Vetter N, Phillip A, et al. Psychological status during recovery from an acute heart attack. J Psychosom Res.1972; 16:425- 9.
38. Wishnie H, Hacket TP, Cassem NH. Psychological hazard of convalescence following myocardial infarction. JAMA; Cassem EH. Depression and Anxiety secondary to medical illness. Psychiatry Clin Nort Am. 1990; 13:597-611.
39. Eliot RS. Morales-Ballejo HM. The heart, emotional stress, and psychiatric disorders. In: Schlant RC, Alexander, editors. 8th ed. Hurst's the heart. New York: McGraw-Hill;1994. p. 2087-97.
40. Schwartz BG, French, WJ, Mayeda GS, et al. Emotional stressors trigger cardiovascular events. Int J Clin Pract. 2012;66 (7): 631-9.
41. 38Stern MJ, Pascale L, Nekerma A. Life adjustment post myocardial infarction. Arch Intern Med. 1977; 137: 1680-5.
42. Brachett CP, Powell LH. Psychosocial and psychological predictors of sudden cardiac death after healing of acute myocardial infarction. Am J Cardiol.1988;61:979-83.
43. Fresure Smith N, In hospital symptoms of psychological stress as predictors of long-term outcome after acute myocardial infarction in man. Am J Cardiol.1991; 67:1217.
44. Case RB, Mess AJ, Case N, Mc Dermott M, Eberly S. Living alone after myocardial infarction: impact on prognosis. JAMA. 1992;267: 515-9.
45. Fresure-Smith N, Lesperence F, Talajic M. Depression Following myocardial infarction. Impact on 6 month survival. JAMA SEA. 1994:13-9.
46. Fresure-smith N, Lesperance F, Talajic M. Depression and 18 month prognosis after myocardial infarction. Circulation. 1995; 91: 999-1005.
47. Barefoot JC, Helms MS, Mark DB. Depression and long-term mortality risk in patients with coronary artery disease. Am J Cardiol.1996;78:613-7.
48. Meneghetti CC, Guidolin BL, Zimmermann PL Sfoggia A. Screening for symptoms of anxiety and depression in patients admitted to a university hospital with acute coronary syndrome. Trends Psychiatry Psychother. 2017;39 (1). https://doi.org/10.1590/2237- 6089-2016-0004.
49. Weiner H. Stressed Experience and cardio respiratory disorders. Circulation. 1991;83 (S II):II2-8.
50. Varrier RL, Hagested EL, Lown B. Delayed myocardial

ischemia by anger. Circulation. 1987;75: 249-54.
51. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implication for therapy. Circulation. 1999; 99:2192-217.
52. Nah DY, Rhee MY, The inflammatory response and cardiac repair after myocardial infarction, http://creativecommons.org/licenses/by-nc/3.0, DOI 10.4070/kcj.2009.39.10.393.
53. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Effect of hyperventilation and mental stress on coronary blood flow in syndrome X. Br Heart J. 1993;69:516–24.
54. de Morree HM1, Szabó BM, Rutten GJ, Kop WJ. Central nervous system involvement in the autonomic responses to psychological distress. Neth Heart J. 2013;21(2):64-9. doi: 10.1007/s12471- 012-0351-1.
55. Cassem NH, Hacket TP. Psychiatric consultation in coronary care unit. Ann intern Med.1971:75:9-14
56. Meltzer LE. Anxiety in cardiovascular disease in Rees WL editor, Anxiety factors in comprehensive patient care. Excerpta Medica. Netherland. 1973:47-57.
57. Wishna H, Hacked TP, Kassem NH. Psychological hazard of convalescence following myocardial infarction. JAMA. 1971:1292- 6.
58. Kassem EH. Depression and anxiety secondary to medical illness. Psychiatry Clin North Am. 1990; 13:597-611.
59. Eliot RS. Morales-Vallejo HM. The heart, emotional stress, and psychiatric disorders in Schlundt RC, Alexander's editors. Hurst's the heart. McGraw-Hill, 8th ed.1994.2087-97.
60. Schwartz BG, French, WJ, Mayeda GS, et al. Emotional stressors trigger cardiovascular events. Int J Clin Pract, 2012;66 (7):631–9.
61. Appelbaum. AH Supportive Psychotherapy. Focus 2005;3:438-49.
62. Arnold W, Rosenthal RN, Pinsker H. Introduction to supportive psychotherapy. Washington, D.C: American Psychiatric Publishing; 2004.
63. Hoffman RS, Practical psychotherapy: Working with a patient's defense in supportive psychotherapy psychiatry serv. 2002;53:141-2.
64. Grover S, Avasthi A, Jagiwala M. Clinical practice guidelines for practice of supportive psychotherapy. Indian J Psychiatry. 2020;62:S173-82.
65. Davanloo H. Intensive Short-Term Dynamic Psychotherapy. In: Kaplan H, Sadock B, eds, Comprehensive textbook of psychiatry. 8th ed. 2nd Chapter 30.9. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 2628-52.
66. Suszek H, Holas P, Wyrzykowski T, Lorentzen S, Kokoszka A. Short-termintensivepsychodynamic group therapy versus cognitive- behavioral group therapy in day treatment of anxiety disorders and comorbid depressive or personality disorders: study protocol for a randomized controlled trial. BioMed Central, Open Access. 2015; 16:319 DOI 10.1186/s13063-015-0827-6
67. Nicoletti B. Intensive behavioural counselling for cardiovascular disease, HCPCS Codes, Medicare Rules, Preventive Medicine Services Primary Care. United Healthcare. Intensive Behavioural Therapy for Cardiovascular Disease (NCD 210.11).2019. United Health Care Services, Inc. Preventive Primary
68. de Shazer S. Keys to solutions in brief therapy, W.W. Norton and Company London; 1985.
69. Nieuwsma JA, Ranak B, Trivedi RB, et al. Brief psychotherapy for depression: A systematic review and meta-analysis. Int J Psychiatry Med. 2012;43(2): 129-51.
70. Ollendick TH, Thompson E DavisTE. One-session treatment for specific phobias: a review of Öst's single-session exposure with children and adolescents. Cogn Behav Ther. 2013; 42(4): 275-83.\
71. Zlomke K, Davis TE. One-session treatment of specific phobias: a detailed description and review of treatment efficacy Behav Ther. 2008; 39(3):207-23.
72. Nicoletti B. Intensive behavioural counselling for cardiovascular disease, HCPCS Codes, Medicare Rules, Preventive Medicine Services Primary Care.
73. Wade Thompson W, Lorna Adcock L. Intensive day treatment programs for mental health treatment: a review of clinical effectiveness, cost effectiveness, and guidelines Ottawa: CADTH; 2017. (CADTH rapid response report: summary with critical appraisal). Acknowledgments: ISSN: 1922- 8147 (online).
74. Chessick RD, what is intensive psychotherapy? Am J Psychother. 1981;35(4):489-501.
75. Medical Dictionary by Farlex. TheFreeDictionary. com – FarlexMedical.
76. Ehlers A, Hackmann A, Grey N, et al. A randomized controlled trial of 7-day intensive and standard weekly cognitive therapy for PTSD and emotion-focused supportive therapy. Am J Psychiatry. 2014;171:294–304.
77. Nakatani E, Nakagawa A, Ohara Y, et al. Effect of behavior therapy on regional cerebral blood flow in obsessive-compulsive disorder. Psych Res. 2003;124:113 - 20.
78. Olff M, De Vries GJ, Güzelcan Y, Assies J, Gersons BPR. Changes in cortisol and DHEA plasma levels after psychotherapy for PTSD.PNI. 2007; (32): 619-26.
79. Dichter GS, Felder JN, Petty C, Bizzell J, Ernst M, Smoski MJ. The effects of psychotherapy on neural responses to rewards in major depression. Biol psychiatry.2009;66(9):886-97.
80. Chang S, Salamon N, Brody AL, Schwartz JM and London, ED. Rapid effects of brief intensive cognitive-behavioral therapy on brain glucose metabolism in obsessive-compulsive disorder. Molecular Psychiatry. 2009;14:197–205.
81. Karlsson, H. How psychotherapy changes the brain. Psychiatric Times. 2011.
82. Buchheim A, Viviani R, Kessler H, et al. Changes in

prefrontal-limbic function in major depression after 15 months of long-term psychotherapy. PLoS ONE. 2012; 7(3): e33745. doi:10.1371/ journal pone 00337453.
83. Hölzel BK, Carmody J. Vangel M, et al. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res. Neuroimaging. 2011; 191:36–43.
84. Goldapple K, Segal Z, Garson C, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry. 2004;61:34-41.
85. Viinamaki H, Kuikka J, Tiihonnen J, Lehtonen J. Changes in monoamine transport density related to clinical treatment: a Case controlled study. Nordic J Psychiatry. 1998; 55:39–44.
86. Etkin A, Pittenger C, Polan HJ, Kandel ER. Toward a neurobiology of psychotherapy: Basic science and clinical applications. J Neuropsychiatry Clin Neurosci. 2005; 17:145-58.
87. Joffe R, Segal Z, Singer W. Change in thyroid hormone levels following response to cognitive therapy for major depression. Am J Psychiatry. 1996;153:411–3.
88. Schlosser N, Wolf OT, Wingenfeld K. Cognitive correlates of hypothalamic–pituitary–adrenal axis in major depression Expert Rev. Endocrinol. Metab. 2011;6(1): 109-26.
89. Gabbard GO. Theory of supportive psychotherapy, Chapter 14. Textbook of psychotherapy treatments, Chapter 14. American Psychiatric Publishing, Inc; 2009. p. 239-46.
90. Kennedy GA, Macnab FA, Ross JJ. The effectiveness of spiritual/religious interventions in psychotherapy and counselling: a review of the recent literature. Melbourne: PACFA. gerard.kennedy@cairnmillar. edu.au. 2015.
91. Likert R. A technique for the measurement of attitude. Archives of Psychology. 1932;140:5–55.
92. Krabbe PFM. Constructs and scales: Likert scaling. The measurement of health status. Elsevier Inc.; 2017. 5:79–83.
93. Hasson F, Keeney S, and McKenna H. Research guidelines for the Delphi survey technique. Journal of Advanced Nursing; 2000;32(4): 1008–15.

ATTACHMENT

Structured SP Session's Model for professionals healthcare in the management of ACS.

First Session: aims to develop a good relationship and cooperation between doctors and their patients, **build therapeutic alliances**, provide opportunities for patients to express themselves (according to the patient's ability) and doctors to become better listeners.

First Session

No	Question/Statement	10 Expert panelist Agree %
1.	D: Assalamu'alaikum,wr,wb. / Good morning, (smile in a friendly manner), what is your name? P : …….	100
2.	D: This is our first meeting. I am dr.…… from the psychosomatic division. Is there anything I can help you with? P: ……. If the patient doesn't response, see if SP is needed or proceed to point 3.	100
3.	D: Please tell me how you feel today. P: …….. (Next question/statement depends on the patient's response) . If needed, give SP related to point 2	100
4.	D. Please tell me about the complaints you're feeling today. (Current symptoms or complaints: chest pain/shortness of breath/nausea/vomiting/tingling/numbness/fatigue/dizziness? etc.). P: ……. (If P states one or more complaintsthat he/she feels , then D proceeds to point 5)	100
5.	D: What are you concerned about at the moment (current symptoms or complaints: chest pain/ shortness of breath/ nausea/vomiting/tingling/numbness/fatigue/dizziness? Etc.) P: ……. (The questions/statements asked by D to P are related to the patient's response regarding symptoms or complaints)	100
6.	D: These are your concerns → (Point 6 is D's response towards patient's response or the doctor sums up the patient's concerns	80
7.	D: Other than those complaints, do you have any other complaints?? P: ……. (Point 7 as a continuation to P's response in point 5)	100
8.	D: After knowing that you have this condition, (corresponding to point 7), what efforts have you made to remedy this condition? P:	100
9.	D: Alright, that's what you experienced and how you tried to solve it. If P hasn't made any efforts . D's Response: nod to show understanding. If P makes an effort and tells the results of his efforts and the efforts are not dangerous and according to D are good, D: nod to show understanding. If necessary, support these positive efforts	100
10.	D: Yes, hopefully we can deal with this condition well. P: ……. D: SP if needed, the type of SP used is according to the needs.	100
11.	D: Tell me about the treatment that you have had P: …….	100
12	Please tell me your opinion about the treatment that will be undertaken/ what do you think about the treatment that you will get? P: ……. D: Explain and use SP when needed	100
13	D: Is there anything else you would like to tell or ask me?	100
14	D: Thank you for sharing your current condition with me. We will discuss it further tomorrow, insha'Allah. Let us pray together so that you will get well soon and be healthy again. Aamiin P: ……. Pray silently with the patient.	100
15	D: 1st meeting session is ended with greetings: Assalamu'alaikum / Good Morning / Afternoon / Evening. P: …… D: See you tomorrow	100

D: doctor; P: patient

The Second Session: aims to help patients relate to the problems/conditions being faced, **increase self- confidence (esteem-building) and patient's coping mechanism**.
(Note: The **second session** and **third session** may precede each other according to the patient's needs).

Second Session

No	Question/Statement	10 Expert panelist Agree %
1.	D: Assalamu'alaikum Wr. Wb./Good morning/afternoon/evening Sir/Ma'am P: …….	100
2.	D: This is our second meeting… In this meeting, we will discuss the conditions that you explained yesterday. P:	100
3.	D: Please tell me about the complaint (chest pain / shortness of breath / nausea / vomiting / tingling / numbness / fatigue / dizziness, etc.) you told me about previously) P: ……. (the next process depends on the patient's response), D: explain and use SP when needed	100
4.	D: What efforts have you made? (related to chest pain/shortness of breath/tiredness or others). P: ……. D: SP strengthens patient's positive efforts.	100
5.	D: So far you have understood the treatment and the continuation of the treatment, hopefully you will be able to implement it P: ……..	100
6.	D: Doyou already know or remember the rules for taking your medication or the treatment plan? P: …….. D:(Educate and do SP related to the rules for taking medication or treatment plan as needed)	100
7.	D: Please tell me your expectation from this treatment? P: …….. Observe the patient's emotions. Give reassurance if the patient is worried about the outcome of the treatment.	100
8.	D: What physical activities can you already do? P:…….	80
9.	D: Alright, Sir/Ma'am. So far, are you comfortable? P: ……..	90
10.	D: Yes, that is our hope that you will get well soon and be healthy again P:…….	100
11.	D: (According to the patient's response) I will try to support you. The feelings that you have and the activities that you have achieved could happen to anyone who faces similar conditions. Keep up the spirit to be stronger. P:	90
12.	D: (According to the patient's response) Try to imagine positive things in your life; remember that everything is in His power. Hopefully it will get better gradually, P:…….	90
13.	D: May Allah ease any hardship you are going through, Amiin	90
14.	Is there anything else you would like to tell me? P:……	100
15.	D: Alright, Sir/Ma'am, I think this concludes our meeting today, tomorrow we'll meet again, Assalamu'alaikum / Good morning/afternoon/evening	100

D: doctor; P: patient

Third Session: aims to help reducing **the tension**, related to problems/illness faced by patient.

Third Session

No	Question/Statement	10 Expert panelist Agree %
1.	D: Assalamu'alaikum Wr. Wb./Good morning/afternoon/evening Sir/Ma'am. We meet again for the third time. P:	100
2.	D: This is our third meeting, we will discuss the conditions that concern you or make you anxious/sad the most (according to session 1 point 8) P: ……. Explain and use SP when needed	100
3.	D: Please tell me about the condition of your disease ? (pay attention to anything that makes the patient anxious, sad, emotional, etc.) P: ……. D: Explain and use SP when needed	100
4.	D: Please describe the efforts that you have done in dealing with the worrisome condition (disease)? P: ……. (Support it if the effort is positive and avoid it when the patient's efforts are not profitable)	100
5.	D: What have you been thinking about so far? (Explore all the things that concern the patient or make the patient anxious; for example: the future, how to live a life with coronary heart disease, guilt towards family, friends at work, family support, undergoing a series of examinations and therapies that must be endured, side effects of therapy, costs treatment, life companion) P: ……. D: Explain and use SP when needed	100
6.	D: What do you know or think about the examination and treatment that you are currently undergoing or will undergo? (related to medication/side effects/medication fee/intervention procedure,etc) P:……. D: Explain and use SP when needed	100
7.	D: What do you think about point 6 related to your current disease/condition? P:……. D: Explain and use SP when needed	100
8.	D: In your opinion, what efforts need to be made to go through this kind of condition? P: ……. (D: SP if needed to support the patient's positive efforts, etc)	100
9.	D: How is your family's attention to your current condition?/ How much attention does your family pay to your current condition? P: …… D: Explain and use SP when needed	100
10.	D: How is your family's support for the treatment that you will have to undergo? P: ……. D: Explain and use SP when needed	100
11.	D: How is the support from your friends for the treatment that you will have to undergo? P: ……. D: Explain and use SP when needed	100
12.	D: What are your future views regarding this condition? P: ……. Pay attention to the patient's response. The doctor can discuss anxiety, depression that often occurs in ACS	100
13.	D: Do you have feelings of anxiety, sadness, anger, etc.? P:…… Doctor can discuss anxiety, depression. If the patient looks worried, sad, emotional, SP; sooth and reassure him/her and say that everything will get better..	100
14.	Is there anything else you would like to tell or ask me? P: ……. D: Explain and use SP when needed	100
15.	D: Alright, let's meet again tomorrow. Thank you, Sir/Ma'am. Assalamu'alaikum/ Good Morning/ Afternoon/Evening. P:…….	100

D: doctor; P: patient

Fourth Session: aims to help in **decision-making** and in educating the patient about the current concerns/disease he/she is facing.

Fourth Session

No	Question/Statement	10 Expert panelist Agree %
1.	D: Assalamu'alaikum/Good morning/afternoon/evening, Sir/Ma'am. We meet again for the fourth time. P: …….	100
2.	D: In this meeting, we will discuss the medication/treatment that you will undergo. P: ……	100
3.	D: Explain if needed D: How are you feeling today? P: …….	100
4.	D: Explain and use SP when needed D: What do you know about the treatment/procedure that you're going to undergo? P: ……	100
5.	D: Explain and use SP when needed D: What do you think about the medication/treatment that you will get?P: …….	100
6.	D: Explain and use SP when needed D: Do you know about the next treatment? P: ……	100
7.	D: Explain and use SP when needed D: Do you know the rules for taking medicine/ getting treatment? P: ……	100
8.	D: Explain and use SP when needed D: What can support your treatment? P : …….	100
9.	D: Explain and use SP when needed D: What kind of results do you expect from the treatment? P: …….	100
10.	(D: Reassurance SP is given if the patient is anxious, worried, pessimistic,etc) D: Is there anything else you would like to tell or ask me? P:…….	100
11.	D: Explain and use SP when needed D: Alright, let's meet again tomorrow. Thank you, Sir/Ma'am. Assalamu'alaikum/ Good Morning/Afternoon/Evening. P:…….	100

D: doctor; P: patient

Fifth Session (termination): aims to explain the results of the meeting and assess what is necessary to help the patient deal with the disease and its treatment

Fifth Session.

No	Question/Statement	10 Expert panelist Agree %
1.	D: Assalamu'alaikum/Good morning/afternoon/evening, Sir/Ma'am We meet again for the fifth time, our last day of meetings. P: …….	100
2.	D: In this meeting, we will discuss what we have talked about in previous meetings P: …….	100
3.	D: How are you feeling today? P: …….	100
	SP to strengthen the patient's psychological state	
4.	D: How do you currently feel about your complaints? (chest pain, dizziness, nausea, vomiting, numbness / tingling, shortness of breath, etc.). according to the previous meetings. P: ……	100
	D: Explain and use SP when needed	
5.	D: Please tell me about your efforts in developing your ability to deal with the symptoms / complaints that arise? (chest pain, dizziness, nausea, vomiting, numbness / tingling, shortness of breath, etc. (According to the 4 previous meetings) P: …….	100
	D: Explain and use SP when needed	
6.	D: Do you still have any complaints, worries, sadness or feelings of helplessness, etc. ? Can you tell me about the improvement you have experienced? P: ……	100
	(Reflection with the patient)	
7.	D: What do you think about your ability in overcoming the problem in point 6 session 5? (Reflection with the patient) P: …….	100
	D: If needed, strengthen/help the patient with SP as needed	
8.	D: How do you feel about being allowed to be discharged? P: …….	100
	D: Stregthen the positive parts	
9.	D: Is there anything you would like to sayregarding the things that we have discussed so far? P:…….	100
	D: Explain and use SP when needed	
10.	D: Is there anything else you want to talk about besides the issues we discussed? P:…….	100
11.	D: After we undergoing these five sessions, I can conclude that P: …….	100
12.	D: It seems that ... you are quite able to accept this condition. (or vice versa, do you still need support to accept the conditions that you are currently experiencing? D: Explain and use SP when needed, consider when to refer to a Psychiatrist / Clinical Psychology P: …….	100
13.	D: You are able to make the decisions about the treatment that you will have (or are there still things that you want to consider in making decisions about the treatment you will undergo) (depending on the patient's response, if necessary, give SP, according to the circumstances and needs) P: …….	100
14.	D: Do you feel well, comfortable and safe? P:…… Look at the patient's response. If the patient says yes, advise him/her to consult the Psychosomatic Polyclinic or to the Psychiatry Clinic or a clinical psychologist. If needed, SP can be continued for a while to make the patient feel safe and comfortable.	100
15	D: I'll end our fifth session meeting. May you get well soon. Wassalamua'alaikum/ Good morning/afternoon/evening. P :	

D: doctor; P: patient

Growth Differentiation Factor-15 (GDF-15) as a Predictor of Major Adverse Cardiac Event in Acute Myocardial Infarction Patients

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ABSTRACT

***Background*:** *Growth Differentiation Factor-15 (GDF-15) has emerged as a biomarker that capable to predicting cardiovascular events. Recent studies suggest that GDF-15 is elevated in patients with acute myocardial infarction (AMI), but the prognostic remains incompletely defined. This study aimed to investigate the role of GDF-15 levels with major cardiac adverse events (MACE) on three months follow up in patients with AMI.* ***Methods*:** *This cohort study was conducted from November 2020 until May 2021 at Dr. Moewardi Hospital. GDF-15 was measured at admission, clinical data was collected and 3 months follow up events was registered. Prognostic value of GDF-15 and hazard ratio between high and low GDF-15 level were analyzed.* ***Results*:** *A total of 64 AMI patients were included in this study. MACE at three months follow-up occurred in 26.5% of patients. In multivariate analysis, GDF-15 was independently associated with risk of MACE at 3 months follow up (OR 1.501; p = 0.003). The cut-off point value of GDF-15 was analyzed with the ROC curve, obtained 2256 pg/mL which has a sensitivity of 94.1% and a specificity of 73.8% (area under the curve (AUC) 86.2%; 95% CI 0.768-0.956). Risk model with Kapplan Meier showed significant association between high GDF-15 levels (≥ 2256 pg/mL) and the incidence of MACE at 3 months follow up (HR 12.029; 95% CI 3.429- 42.197; p <0.001)* ***Conclusion*:** *In patients with AMI, high level of GDF-15 was significantly associated with the risk of MACE at 3 months of observation.*

***Keywords*:** *acute myocardial infarction, growth differentiation factor-15, major adverse cardiac event.*

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, have brought heavy burden to social healthcare and individuals. Seven million people die every year, accounting for 12.8% of all deaths. Data from the World Health Organization (WHO) in 2012 showed that 17.5 million people died from cardiovascular disease, or 31% of the 56.5 million deaths worldwide. This number was estimated to continue to increase to 23.6 million deaths in 2030.[1] In this case, data from Dr. Moewardi General Hospital, Surakarta, Indonesia, revealed that the death rate from acute coronary syndrome (ACS) from 2014-2018 reached 15.9%.[2]

More specifically, concerning myocardial infarction, tissue necrosis following myocardial infarction is often followed by a later incidence of

heart failure, myocardial rupture, or arrhythmias. In this regard, early management of ischemia to prevent myocardial necrosis with medications, such as fibrinolytic, percutaneous coronary intervention, and coronary artery bypass surgery, has improved the clinical outcome of patients with ACS. Biomarkers have an essential role in establishing the diagnosis and prognostication to predicting future cardiovascular risk. Various emerging biomarkers have been known to have a vital role in the pathophysiology of ACS.[3]

Growth Differentiation Factor-15 (GDF-15) has emerged as a promising biomarker for predicting cardiovascular events in later life. GDF-15 is a superfamily of transforming growth factors (TGF-β). It is synthesized as a 40 kDa propeptide with an N-terminal propeptide and a mature C-terminal domain of GDF-15.[4] Under physiological conditions, GDF-15 is slightly expressed by endothelial cells and macrophages. GDF-15 increases during the inflammatory process and is associated with cardiometabolic risk.[5] In previous studies, GDF-15 levels link to the adverse cardiovascular events across a spectrum of CVD conditions including heart failure (HF), chest pain, acute coronary syndromes (ACS), stable ischemic heart disease, stroke and atrial fibrilation.[6,7] The potential role of GDF-15 may attribute to the earlier diagnosis, risk stratification and prognosis assessment. However, limited research have analyzed the association between GDF-15 levels and all-cause mortality or heart failure on the long-term follow-up. Hence, this study aimed to analyzed relationship between GDF-15 levels with survival and major cardiovascular events (MACE) in patients with post acute myocardial infarction (AMI).

METHODS

Research Subjects

The research subjects were AMI patients who underwent treatment at the Intensive Cardiovascular Care Unit (ICVCU) Dr. Moewardi General Hospital, Surakarta, Central Java from November 2020 to April 2021. The researchers excluded patients with severe comorbidities, such as malignancy, chronic renal failure, stroke, and severe sepsis.

Research Design

This cohort analytic study applied a prospective design. Data were acquired from the intensive cardiovascular care unit (ICVCU) and cardiology ward at RSUD Dr. Moewardi, Surakarta, Central Java. The Ethics Committee of Dr. Moewardi General Hospital approved this study's protocol with ethical approval No. 1.287/XII/HREC/2020 issued on 17th November 2020.

Acute myocardial infarction (AMI) is defined as presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia of at least one value above the 99th percentile of the upper reference limit, accompanied by at least one of the following: 1) Presence of a complaint of acute myocardial ischemia; 2) ECG changes as evidence of new ischemia; 3) Pathological Q wave formation; 4) Imaging evidence of loss of myocardial viability or the presence of new regional myocardial wall motion abnormalities consistent with the etiology of ischemia.[8] Meanwhile, major adverse cardiac event/MACE is defined as the presence of death, reinfarction, and nonfatal heart failure events requiring rehospitalization.[9,10]

In this study, GDF-15 was obtained from venous blood samples of patients with AMI at the time of admission and measured using the enzyme-linked immunosorbent assay (ELISA) with pg/mL units. Cut-off points for GDF-15 were determined utilizing receiver operating characteristic (ROC) analysis. MACE was followed up to 90 days after admission by reviewing medical records and communicating directly with patients.

Statistical Analysis

Statistical analysis was performed utilizing the Statistical Package for the Social Sciences (SPSS) 22 (IBM, Chicago, USA). A Chi-square test was used to compare two categorical variables, while an independent t-test or Mann-Whitney test was employed to compare data with categorical and numerical variables. Significant variables were included in multivariate logistic regression analysis. The cut-point value of the optimal GDF-15 level to predict MACE occurrence was analyzed by the receiver operating characteristic (ROC) curve. Survival

analysis was carried out using the log-rank test on the Kaplan-Meier curve. The p-value <0.05 were considered to be statistically significant.

RESULTS

In total there were 70 patients with acute myocardial infarction who were the subjects of the study obtained by consecutive sampling that met the inclusion criteria. There were 3 patients with chronic renal failure, 2 patients with severe sepsis, and 1 patient with stroke who were excluded in this study. Demographically, the patient's age who were the subjects of this study ranged from 38 years to 86 years, with a mean value of 58.5 SD 9.5 years. A total of 48 people were male, or 66.66%, while the remaining 16 people, or 33.33%, were female. The majority of subjects had a body mass index (BMI) of *normoweight* or normal (16.35-33.20).

Hypertension was the most dominant risk factor in this study population. A total of 41 (64%) people were stated to have a history of hypertension. In the subjects of this study, 48 patients (75%) were diagnosed with STEMI, and 16 patients (25%) were diagnosed with NSTEMI.

MACE on Research Subjects

MACE was followed up to 90 days after hospital admission and was recorded in 17 subjects (26.5%), with the proportions of death, the incidence of acute heart failure leading to rehospitalization, and reinfarction of 14.1%, 9.3%, and 3.1%, respectively (**Figure 1**). Characteristics of research subjects based on the occurrence of MACE during hospitalization and MACE in 3-month observation are presented in **Table 1**.

Patients with MACE at 3-months follow up had a higher mean GDF-15 level than patients without MACE (3736 SD 1857 vs. 2348 SD 1500). When the bivariate analysis was performed, the parameters that were significant for the incidence of MACE were GRACE score (p=0.033), estimated glomerular filtration rate (eGFR) (p=0.037), urea (p=0.037), GDF-15 (p<0.001), percutaneous coronary intervention (PCI) (p=0.041), and the medication of ß-Blockers (p=0.039) **(Table 2).**

Table 1. Subject's Characteristic Based on MACE.

Variables	MACE in 3 months follow up	
	MACE (+) (n=17)	MACE (-) (n=47)
Male	10 (58.8%)	38 (80.9%)
Age (years)	61.41 SD 15.28	59.68 SD 11.28
Onset (hours)	15 (1-124)	24 (1.5-168)
BMI (kg/m^2)	24.27 SD 3.62	23.44 SD 2.97
SBP (mmHg)	128 (78-179)	126 (90-215)
DBP (mmHg)	80 (42-124)	79 (50-130)
Heart Rate (x/m)	68 (40-124)	77 (52-130)
Resppiratory rate (x/m)	20 (16-32)	20 (0-30)
TIMI score	5 (2-9)	3 (1-10)
GRACE score	128.7 SD 36.79	105.66 SD 37.62
Kilip > I	8 (47.1%)	18 (38.3%)
Previous medical history		
Hypertension	10 (58.8%)	31 (66.0%)
DM	3 (17.6%)	15 (31.9%)
Stroke	0 (0.0%)	2 (4.3%)
Smoking	7 (41.2%)	23 (48.9%)
Dyslipidemia	1 (5.9%)	2 (4.3%)
Previous CAD	6 (35.3%)	8 (17.0%)
Hb (g/dL)	13.20 (8.5-15.6)	13.8 (9.8 -17.2)
Leucocyte (1000/uL)	14.5 (6.59-41)	11.6 (4.8-19.5)
Thrombocyte (1000/uL)	200 (41.5-346)	239 (2.5-427)
Glucose (mg/dL)	122 (86-388)	116 (69-388)
Urea (mg/dL)	53 (10-85)	32 (1.1 -162)
Creatinine (mg/dL)	1.2 (0.6-10)	1 (0.3-18)
eGFF (ml/min/1.73 m^2)	13.19 SD 2.45	43.56 SD 2.74
Na (mmol/L)	133.94 SD 4.84	134.36 SD 4.19
K (mmol/L)	3.6 (3-5.1)	3.8 (2.9-6.3)
hs-Trop I (ng/L)	15464 (25-40000)	18803 (7-40000)
Total Cholesterol	152 (75-188)	160 (89-307)
LDL (mg/dL)	100 (40-180)	126 (59-327)
HDL (mg/dL)	35.19 SD 16.19	35.72 SD 12.20
GDF-15 (pg/nL)	6000 (1738-6000)	2256 (720-6000)
LVEF (%)	38.71 SD 10.73	43.60 SD 9.26
Treatment		
PCI	5 (29.4%)	37 (78.7%)
Fibrinolitic	3 (17.6%)	12 (25.5%)
Anticoagulant	17 (100.0%)	47 (100.0%)
DAPT	17 (100.0%)	47 (100.0%)
Statin	17 (100.0%)	47 (100.0%)
ß-Blocker	10 (58.8%)	40 (85.1%)
ACE inhibitor	14 (82.4%)	40 (85.1%)

Table 2. Bivariate Analysis of MACE at 3-months Follow Up.

Variables	MACE in 3 months follow up		*p*
	MACE (+) (n=17)	MACE (-) (n=47)	
Male	10 (58.8%)	38 (80.9%)	0.103
Age (years)	61.41 SD 15.28	59.68 SD 11.28	0.625
Onset (hours)	15 (1-124)	24 (1.5-168)	0.144
BMI (kg/m2)	24.27 SD 3.62	23.44 SD 2.97	0.358
SBP (mmHg)	128 (78-179)	126 (90-215)	0.681
DBP (mmHg)	80 (42-124)	79 (50-130)	0.951
Heart Rate (x/m)	68 (40-124)	77 (52-130)	0.245
Resppiratory rate (x/m)	20 (16-32)	20 (0-30)	0.418
TIMI score	5 (2-9)	3 (1-10)	0.063
GRACE score	128.7 SD 36.79	105.66 SD 37.62	0.033*
Kilip > I	8 (47.1%)	18 (38.3%)	0.529
Previous medical history			
Hypertension	10 (58.8%)	31 (66.0%)	0.599
DM	3 (17.6%)	15 (31.9%)	0.353
Stroke	0 (0.0%)	2 (4.3%)	1.000
Smoking	7 (41.2%)	23 (48.9%)	0.583
Dyslipidemia	1 (5.9%)	2 (4.3%)	1.000
Previous CAD	6 (35.3%)	8 (17.0%)	0.170
Hb (g/dL)	13.20 (8.5-15.6)	13.8 (9.8 -17.2)	0.178
Leucocyte (1000/uL)	14.5 (6.59-41)	11.6 (4.8-19.5)	0.215
Thrombocyte (1000/uL)	200 (41.5-346)	239 (2.5-427)	0.082
Glucose (mg/dL)	122 (86-388)	116 (69-388)	0.390
Urea (mg/dL)	53 (10-85)	32 (1.1 -162)	0.037*
Creatinine (mg/dL)	1.2 (0.6-10)	1 (0.3-18)	0.072
eGFF (ml/min/1.73 m^2)	13.19 SD 2.45	43.56 SD 2.74	0.026*
Na (mmol/L)	133.94 SD 4.84	134.36 SD 4.19	0.735
K (mmol/L)	3.6 (3-5.1)	3.8 (2.9-6.3)	0.988
hs-Trop I (ng/L)	15464 (25-40000)	18803 (7-40000)	0.888
Total Cholesterol	152 (75-188)	160 (89-307)	0.085
LDL (mg/dL)	100 (40-180)	126 (59-327)	0.065
HDL (mg/dL)	35.19 SD 16.19	35.72 SD 12.20	0.888
GDF-15 (pg/nL)	6000 (1738-6000)	2256 (720-6000)	<0.001*
LVEF (%)	38.71 SD 10.73	43.60 SD 9.26	0.079
Treatment			
PCI	5 (29.4%)	37 (78.7%)	0.041*
Fibrinolitic	3 (17.6%)	12 (25.5%)	0.740
Anticoagulant	17 (100.0%)	47 (100.0%)	-
DAPT	17 (100.0%)	47 (100.0%)	-
Statin	17 (100.0%)	47 (100.0%)	-
ß-Blocker	10 (58.8%)	40 (85.1%)	0.039*
ACE inhibitor	14 (82.4%)	40 (85.1%)	1.000

Multivariate analysis was performed by logistic regression, showed only eGFR (OR 1.011; p=0.049; 95% CI 1.000-1.022) and GDF-15 (OR 1.501; p=0.001; 95% CI 1.000-1.602) were independent predictors of the occurrence of MACE within the 3-months follow-up in AMI patients (**Table 3**).

Table 3. Multivariate Analysis of MACE Predictors in 3-month Observation.

Variables	OR	95%CI	p-value
GRACE score	0.999	0.978-1.021	0.956
GFR	1.011	1.000-1.022	0.049*
Urea	0.983	0.954-1.013	0.263
GDF-15	1.501	1.000-1.602	0.003*
PCI	0.102	0.016 -1.032	0.054
ß-Blocker	0.621	0.083 -4.644	0.642

Note: *p<0.005

On the ROC curve, GDF-15 levels had an AUC of 0.862 (p<0.001; 95% CI 0.768-0.956) in predicting MACE at 3-months follow-up (**Figure 1**). From this ROC curve, it was found that the cut-off point for GDF-15 was 2655 at a sensitivity of 91.7% and a specificity of 73.8%. This cut-off value had a positive predictive value (NDP) of 59.3% and a negative predictive value (NDN) of 93.7%.

Furthermore, patients were divided into two groups based on GDF-15 levels. GDF-15 levels were categorized as high if more than 2655 pg/mL, and GDF-15 levels were categorized as low if <2655 pg/mL. In all study subjects, there were 32 patients with high GDF-15 levels and 32 patients with low GDF-15 levels.

The analysis to determine the difference in MACE in the group with high and low GDF-15 levels is described in **Table 4**. In this table, it appears that there was a significant difference in MACE in the three months follow-up between groups of patients with high and low GDF-15 levels (48.3% vs 7.5%, p< 0.001) (**Table 4**).

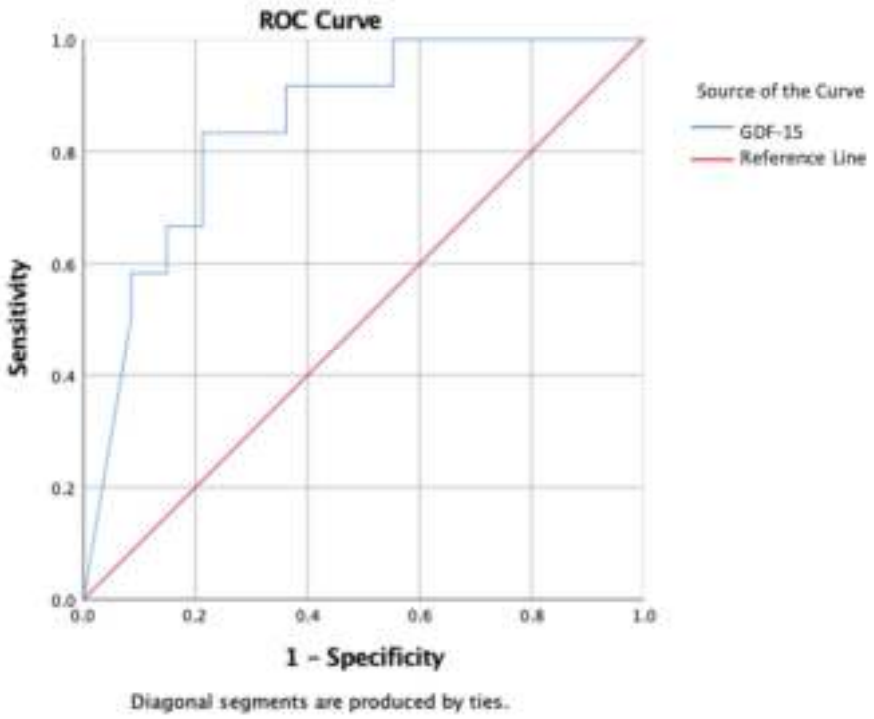

Figure 1. ROC Curve of GDF-15 to MACE at 3 Months Follow-up.

Table 4. Association Between MACE with High and Low Levels of GDF-15.

Variables	GDF-15 High ≥2655 (n=32)	GDF-15 Low <2655 (n=32)	p-value
MACE in three months	19 (58.3%)	2 (7.5%)	<0.001*
All Cause mortality	12 (37.5%)	0 (0.0%)	<0.001*
Acute heart failure	5 (16.7%)	2 (5.0%)	0.121
Reinfarction	2 (8.3%)	0 (0.0%)	0.064

Note: *p<0.005

Kaplan-Meier curve analysis was performed, to determine the difference in survival between patients with high (≥2655 pg/mL) and low (<2655 pg/mL) GDF-15 levels. At three months follow-up, more frequent MACE events were found in the group with high levels of GDF-15 with a hazard ratio (HR) of 12,029 (95% CI 3,429-42.197; p<0.001). It means that high levels of GDF-15 had a 12-fold risk of causing MACE within three months post-AMI (**Figure 2**).

DISCUSSION

In this study, the researchers analyzed the role of GDF-15 as a predictor of MACE occurrence in patients with acute myocardial infarction at 3-months follow-up. The researchers reported three main findings. First, this study's data indicated a difference between high and low levels of GDF-15 in MACE occurrence. A higher GDF-15 value was associated with an increased risk of developing MACE after a 3-month observation. In line with research studies Eitel et al, Bonaca et al, and Hagstrom et al.[11-13] GDF-15 has been associated with an increased risk of all-cause mortality, reinfarction, heart failure, and major hemorrhage in post-AMI.[9]

Second, this study revealed that GDF-15 was a strong predictor of MACE occurrence in AMI patients on 3-month follow-up, along with other clinical factors, namely GFR. Furthermore, Peiro and colleges has found that the addition of the variable GDF-15 level to the clinical variables, such as age, GRACE score, and LVEF <40%, had additional prognostic value with a corresponding and significant increase in the ROC curve. Furthermore, GDF-15 provides better prognostic information than peak cardiac troponin I (cTnI).[9]

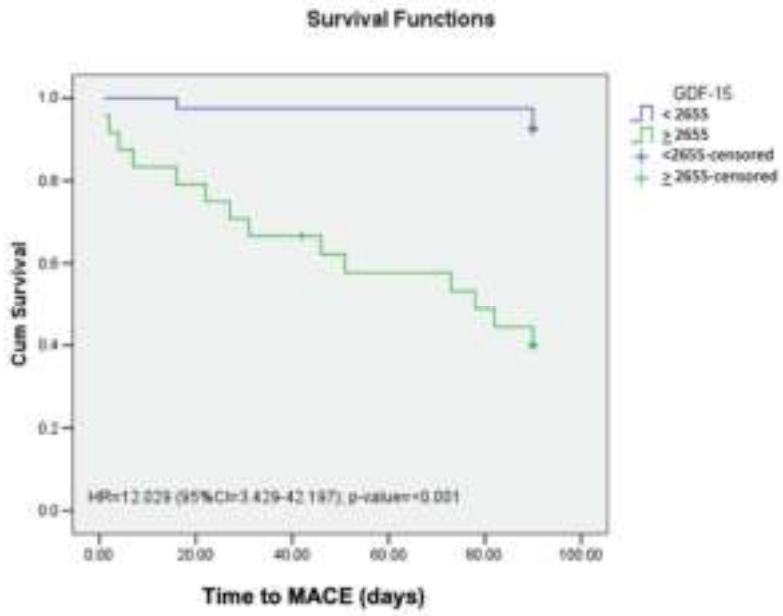

Figure 2. Kapplan-Meier curve showing the survival between patients with high and low levels of GDF-15 to MACE at 3 months follow-up

The researchers also found that the GDF-15 cut-off value for MACE risk was 2655 pg/mL with the ROC curve. This figure is quite different from previously reported, where, in previous studies, the majority used a cut-off point of 1800 pg/mL.[7,10,14] Study by Walter and collegues tried to find the cut-off point with the ROC curve, obtained a value of 1560 ng/L.[15] It might be because, in this study, the population included in the study was patients with the suspected acute coronary syndrome, with or without acute myocardial infarction. Meanwhile, in the current study, only patients with acute myocardial infarction were included. Besides, it might also be due to racial and ethnic differences. With this research, it is hoped that it will find the appropriate cut-off point for the Indonesian population.

The cut-off value of 2655 in current study had a sensitivity of 94.1% and a specificity of 73.8%. Slightly different from the study by Peiro and collegues, the cut-off value in patients with AMI was 1759 ng/L with 100% sensitivity for predicting death within 6.5 years. This study also explained that the advantage of GDF-15 in predicting mortality compared to hs-Trop I was statistically significant.[9]

Third, the researchers reported that GDF-15 was one factor in assessing the survival of patients with AMI. In the current analysis, high levels of GDF-15 (≥2655 pg/mL) tended to develop MACE at 3-month follow-up with a hazard ratio (HR) of 12,029 (95% CI 3,429-42.197; p<0.001). These results align with previous studies, which revealed that high levels of GDF-15 (>1800 ng/L) had a tenfold risk of death and a fourfold MACE at 6.5 years post-AMI.[9] The same results were obtained in a previous study by Khan and collegues, that GDF-15 was an independent predictor of MACE occurrence within one year in patients with AMI.[10]

Several factors explain the increase of GDF-15 concentration in post-AMI patients. The first is the tissue response to inflammation, which appears to be responsible for most of the discharge observed in the acute phase and will include local reactions to myocardial ischemia, volume and pressure overload, and systemic responses to myocardial injury and other organ disturbances (**Figure 3**).[4]

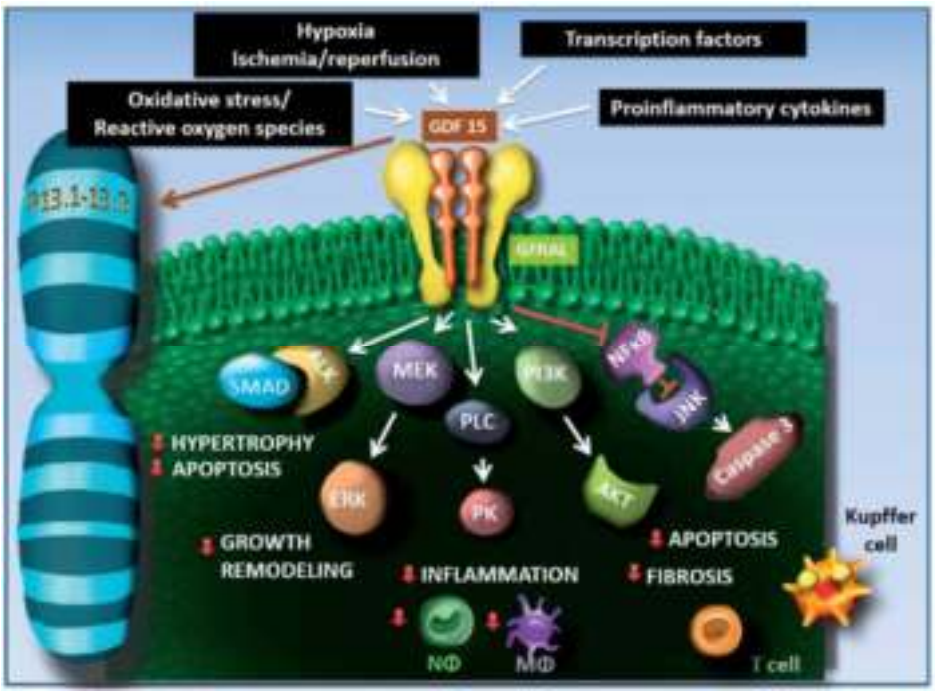

Figure 3. GDF-15 expression is increased in several responses to signals as diverse as oxygen deprivation (eg oxidative stress, hypoxia, and anoxia); inflammation and acute tissue injury [proinflammatory cytokines such as TNF-, IL-1β, IL-6, macrophage colony stimulating factor (M-CSF), and NF-κB]. Although its exact mechanism of action has not been clarified, GDF-15 can function as an autocrine, anti-inflammatory, and cell repair factor that is secreted in proportionate amounts in acute and chronic tissue injury. [4]

These factors explain the strength of GDF-15 as a short-term predictor of MACE. On the other hand, a lower but persistent increase in circulating GDF-15 may appear to reflect the chronic inflammatory background. In a cohort study of community-dwelling individuals, in patients with stable coronary heart disease[12] and heart failure patients[17], an increase in GDF-15 concentrations was a predictor of long-term cardiovascular events and all-cause mortality.

GDF-15 under physiological conditions is only expressed in small amounts, which is increased in the presence of ischemia or reperfusion as endogenous protection against ischemia and reperfusion with a cardiomyopathic apoptotic effect. Thus, GDF-15 can also be conceptualized as a marker of biological age and chronic heart disease burden[18], which may be a key determinant for long-term outcome. In this regard, according to some clinicians, GDF-15 could identify ACS patients who would benefit most from invasive strategies[18], more intense P2Y12 inhibitors[19], or high-dose statin therapy.[20] In addition, reflecting the connection between ischemic risk and bleeding, GDF-15 levels at admission have been identified as an equally strong and independent predictor of major bleeding and ischemic complications during the 12-month observation in ACS patients from the PLATO study.[13]

CONCLUSION

In this study, we found differences in major cardiovascular events (MACE) between patients with high GDF-15 levels and low GDF-15 levels at the 3-month follow-up in acute myocardial infarction patients. Thus, high levels of GDF-15 could be a predictor of the occurrence MACE at 3-month follow-up in acute myocardial infarction patients.

Further studies with bigger sample, multicenter, serial measurements, and longer observation times are needed to add strength to the study and establish the role of GDF-15 as a predictor of MACE in patients with myocardial infarction.

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REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018;137(12):e67-e492.
2. Wasyanto T, Tridamayanti A. Blood urea nitrogen as a predictor of in-hospital mortality in acute coronary syndrome patients. Indones J Med. 20194(3): 241-51.
3. Tzikas S, Palapies L, Bakogiannis C, et al. GDF-15 predicts cardiovascular events in acute chest pain patients. PLoS One. 2017;12(8):e0182314.
4. Li JJ, Liu J, Lupino K, Liu X, Zhang L, Pei L. Growth differentiation factor 15 maturation requires proteolytic cleavage by PCSK3, -5, and -6. Mol Cell Biol. 2018;38(21):e00249-18.
5. Wang X, Chen LL, Zhang Q. Increased serum level of growth differentiation factor 15 (GDF-15) is associated with coronary artery disease. Cardiovasc Ther. 2016;34(3):138-43.
6. Eggers KM, Kempf T, Lagerqvist B, et al. Growth-differentiation factor-15 for long-term risk prediction in patients stabilized after an episode of non-ST-segment-elevation acute coronary syndrome. Circ Cardiovasc Genet. 2010;3(1):88-96.
7. Kempf T, von Haehling S, Peter T, et al. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. J Am Coll Cardiol. 2007;50:1054-60.
8. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. J Am Coll Cardiol. 2018;72(18):2231-64.
9. Peiró ÓM, García-Osuna Á, Ordóñez-Llanos J, et al. Long-term prognostic value of growth differentiation factor-15 in acute coronary syndromes. Clin Biochem. 2019;73:62-9.
10. Khan SQ, Ng K, Dhillon O, et al. Growth differentiation factor-15 as a prognostic marker in patients with acute myocardial infarction. Eur Heart J. 2009;30(9):1057-65.
11. Eitel I, Blase P, Adams V, et al. Growth-differentiation factor 15 as predictor of mortality in acute reperfused ST-elevation myocardial infarction: insights from cardiovascular magnetic resonance. Heart.

2011;97(8):632-40.
12. Bonaca MP, Morrow DA, Braunwald E, et al. Growth differentiation factor-15 and risk of recurrent events in patients stabilized after acute coronary syndrome: observations from PROVE IT-TIMI 22. Arterioscler Thromb Vasc Biol. 2011;31(1):203-10.
13. Hagström E, James SK, Bertilsson M, et al. Growth differentiation factor-15 level predicts major bleeding and cardiovascular events in patients with acute coronary syndromes: results from the PLATO study. Eur Heart J. 2016;37(16):1325-33.
14. Wollert KC, Kempf T, Peter T, et al. Prognostic value of growth-differentiation factor-15 in patients with non-ST-elevation acute coronary syndrome. Circulation. 2007;115(8):962-71.
15. Walter J, Nestelberger T, Boeddinghaus J, et al. Growth differentiation factor-15 and all-cause mortality in patients with suspected myocardial infarction. Int J Cardiol. 2019;292:241-5.
16. Wallentin L, Lindhagen L, Ärnström E, et al. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. Lancet. 2016;388(10054):1903-11.
17. Cotter G, Voors AA, Prescott MF, et al. Growth differentiation factor 15 (GDF-15) in patients admitted for acute heart failure: results from the RELAX-AHF study. Eur J Heart Fail. 2015;17(11):1133-43.
18. Wollert KC, Kempf T, Lagerqvist B, et al. Growth differentiation factor 15 for risk stratification and selection of an invasive treatment strategy in non ST-elevation acute coronary syndrome. Circulation. 2007;116(14):1540-8.
19. Wallentin L, Lindholm D, Siegbahn A, et al. Biomarkers in relation to the effects of ticagrelor in comparison with clopidogrel in non-ST-elevation acute coronary syndrome patients managed with or without in-hospital revascularization: a substudy from the Prospective Randomized Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2014;129(3):293-303.
20. Tentzeris I, Farhan S, Freynhofer MK, et al. Usefulness of elevated levels of growth differentiation factor-15 to classify patients with acute coronary syndrome having percutaneous coronary intervention who would benefit from high-dose statin therapy. Am J Cardiol. 2017;120(5):747-52.

Empirical Antibiotic for Diabetic Foot Infection in Indonesian Tertiary Hospital, Is It Time to Rethink the Options?

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ABSTRACT

Background: *The choice of empiric antibiotics in Diabetic Foot Infection (DFI) is a key to successful therapy. Meanwhile, the management of DFI in Indonesia is based on guideline originating from western countries which have different bacteriological patterns. Therefore, this study aimed to describe the bacterial and antibiotic susceptibility pattern on DFI which potentially contribute to better antibiotics selection guidelines.* ***Methods:*** *This was a cross-sectional descriptive study conducted using consecutive sampling with DFI patients admitted in the emergency room and wards of Hasan Sadikin Hospital between February and July 2020. Tissue samples were obtained from all wounds, while antibiotic susceptibility tests were carried out on the culture results.* ***Results:*** *A total of 65 bacterial growths were obtained from 45 enrolled patients. Gram-negative bacteria dominated with 54 growths (83.07%) including Klebsiela pneumonia 13 (20%) as the most common. Furthermore, antibiotics with good susceptible (> 80%) against Gram-negative bacteria are the carbapenemes (meropenem and ertapenem) and amikacin. The multi drug resistant bacteria were found in 18 growths (27.7%), which include ESBL, Carbapenemase producing bacteria, and MRSA. However, there were no susceptibility pattern differences between patients with ulcer duration above or below 2 months, higher grade wound (Wagner 4 and 5) and lower, as well as patients with previous or no antibiotic history.* ***Conclusion:*** *The growth of Gram-negative bacteria dominated DFI with limited susceptibility to the empirical first-line antibiotics in the known international guidelines. Therefore, there is a need to reconsider the algorithm for selecting empirical antibiotics and management of DFI which is appropriate in our current condition.*

Keywords*: diabetic foot infection, antibiotic susceptibility, bacterial pattern.*

INTRODUCTION

The main problem in the management of diabetic foot infection (DFI) is chronic ulcers which are often difficult to heal. This is mostly caused by impaired wound healing due to immunopathy and peripheral arterial disease. Besides, inappropriate use of antibiotics also interferes with the wound healing process due to unresolved infection. Consequently, the choice of empirical therapy is important because antibiotiçs need to be given immediately before culture results are available.[1]

Currently, Indonesia does not have a personal guideline for the management of DFI. The country still uses the international guidelines issued by the Infectious Disease Society of America (IDSA) and the International Working Group of Diabetic Foot (IWGDF) for the choices of empiric antibiotic therapy. Meanwhile, the guidelines were developed based on bacterial patterns different from the types found in Asia. This indicates there is a need to study the bacterial type and local susceptibility pattern in Indonesia.[2-4]

The bacterial pattern and antibiotic susceptibility continuously change over time due to a long-term history of antibiotic use and hospitalization, duration, as well as wound grade.[2, 5] Therefore, this study aims to determine the pattern of bacteria and antibiotic susceptibility test on DFI in Hasan Sadikin General Hospital Bandung, a tertiary referral hospital in Indonesia. The results are expected to help clinicians with rational empiric antibiotic use and determining the factors that guide the selection.

METHODS

The subject of this study is patients with diabetes mellitus aged >18 years with diabetic foot infection, namely wounds under the malleolus with more than 2 signs of inflammation: redness, pus secretions, warmth, and swelling, were admitted to the ER and wards of Hasan Sadikin General Hospital Bandung from February to July 2020. Baseline data collection and scraping samples were conducted immediately in the ER or in the ward, with the following procedure: the ulcers were cleaned by Nacl 0,9% using a sterile syringe with a minimum pressure of 15 Psi, samples were taken aseptically from the base or edge of the ulcer by the curettage method with a scalpel. The sample was placed into Amies transport medium/sterile tube and immediately sent to the Microbiology and Clinical Pathology Laboratory. Furthermore, inoculation to culture media was carried out less than 30 minutes from the time of sample collection into blood agar and Mc.Conkey agar, then incubated for 24 hours at 35.6 ° C. The initial identification of the isolates on the growing medium was carried out by the analyst, then, further analysis was carried out for identification of bacteria and automatic bacterial susceptibility test by the Vitek2 Compact tool. The susceptibility test results were obtained in the form of Minimum Inhibitory Concentration (MIC) and divided into 3 categories namely resistant, intermediate, and sensitive.[6]

Ethical Approval

This study has approved by the Ethical Committee of Hasan Sadikin Hospital on February 3, 2020 (Reference number LB.02.01/X.6.5/27/2020).

RESULTS

The 45 subjects consist of 19 patients (42.2%) with polymicrobial bacterial growth, hence, a total of 65 bacterial growth were obtained. The grade of ulcer found was Wagner 2 (8.9%), 3 (42.2%), 4 (26.7%), and 5 (22.2%), while the predominant bacteria are Gram-negative with a total of 54 growths (83.07%). Furthermore, patients with Gram-negative growth had history of antibiotic use (30.6%) compared to others with Gram-positive growth (22.2%). The subjects had normal ABI values (0.9-1.3) on average, but 66.7% (2/3) of patients with combined Gram-positive and negative bacterial growths had values above 1.3 which indicate arterial calcification. Additionally, polymicrobial growth was found in 18 patients (50%) with Gram-negative bacteria cultures, while 3 cultures showed the growth of both Gram-positive and negative bacteria (**Table 1**).

The direct Gram staining examination results were compared with the growth of bacteria on the culture. The Gram-negative reading detected 10/20 (50.0%) of Gram-negative bacterial

growth, then combined with the mix result, a total of 17/27 Gram-negative growth with a sensitivity of 63.0% were detected. Gram negative result shows Gram-negative bacterial growth in 10/11 giving a specificity of 87.5%. Meanwhile, Gram-positive microscopy reading was sensitive at 7/8 (87.5%) with a specificity of 10/20 (50.0%) without the mix reading and 17/27 (63.0%) with the mix Gram-positive/negative findings. All the reading of mix Gram-positive and negative shows growth of Gram-negative bacterial group (**Table 1**).

Based on the results, a total of 15 bacterial species were found in the culture, the 5 most commonly found were *Klebsiella pneumonia* (20%), *Acinetobacter baumanii* (12.3%), *Escherichia coli* (10.8%), *Pseudomonas aeruginosa* (9.2%) and *Staphylococcus aureus* (9,2%) as shown in **Table 2**. Antibiotics with a good susceptibility (>80%) to all bacterial growth were carbapenems (meropenem and ertapenem) and amikacin. The results also showed that the antibiotics with good susceptibility against all Gram-negative bacteria was amikacin (96.2%), while meropenem and ertapenem have good susceptibility to almost all Gram-negatives except for *A. baumanii*. Moreover, cefepime is the only cephalosporin with good susceptibility

Table 1. Characteristics of Research Subjects.

Variables	Bacteri classification		
	Gram (-) N=34	Gram (+) N=8	Mixed Gram (+) and (-) N=3
Age (year)			
Median (IQR)	58 (12.2)	57.5 (10.5)	43.0 (-)
Sex			
Female	18 (52.9)	3 (37.5)	1 (33.3)
Male	16 (47.1)	5 (62.5)	2 (66.7)
ABI			
0.60 – 0.89	11 (32,4)	2 (25.0)	1 (33.0)
0.90 – 1.30	22 (64.7)	6 (75.0)	-
>1.30	1 (0.02)	0 (0)	2 (66.7)
Laboratorium			
RPG, Median (range)	231 (80 – 589)	219 (96 – 469)	259 (244 – 275)
FPG, Median (range)*	211 (107 – 492)	264 (148 – 567)	310 (286 – 334)
2hPG, Median (range)	225 (94 – 341)	344 (162 – 704)	338 (316 – 361)
Bacteria, n (%)*			
>1	15 (44.1)	-	3 (100)
1	19 (55.9)	8 (100)	-
Initial test	(N=27)		
Gram (-)	10 (37.0)	1 (12.5)	1 (50.0)
Gram (+)	10 (37.0)	7 (87.5)	1 (50.0)
Mixed Gram (+) and (-)	7 (25.9)	-	-
MDR, n (%)			
Yes	21 (61.8)	7 (87.5)	2 (66.7)
No	13 (38.2)	1 (12.5)	1 (33.3)
Wagner classification			
2 and 3	18 (52.9)	4 (50.0)	1 (33.3)
4 and 5	16 (47.1)	4 (50.0)	2 (66.7)
Wound duration			
<2 months	22 (64,7)	3 (37,5)	3 (100)
≥2 months	12 (35,3)	5 (62,5)	0 (0.0)

Notes : ABI : Ankle Brachial Index, RPG : Random plasma glucose, FPG : Fasting plasma glucose, 2hPG : 2 hour post prandial plasma glucose, MDR : Multi Drug Resistance.

*P value ≤ 0,05

Table 2. Types of Bacterial Growth

Pathogen	Gram	n=65	
		Total	%
Gram-Negative			
Klebsiella pneumonia	Negative	13	20,0
Acinetobacter baumanii	Negative	8	12,3
Escherichia coli	Negative	7	10,8
Pseudomonas aeruginosa	Negative	6	9,2
Proteus mirabilis	Negative	5	7,7
Morganella morganii	Negative	5	7,7
Citrobacter freundii	Negative	4	6,2
Enterobacter cloacae	Negative	2	3,1
Pantoea agglomerans	Negative	1	1,5
Proteus hauseri	Negative	1	1,5
Serratia marcescens	Negative	1	1,5
Gram-Positive			
Staphylococcus aureus	Positive	6	9,2
Enterococcus faecalis	Positive	2	3,1
Staphylococcus haemolyticus	Positive	2	3,1
Staphylococcus hominis	Positive	1	1,5

Table 3. Frequency Distribution of Antibiotic Susceptibility Based on Gram Classification.

Antibiotic	Total test	Susceptible result n, (%)	Gram			
			Gram Negative (N=54)		Gram Positive (N=11)	
			Total test	Susceptible result, n (%)	Total test	Susceptible result, n (%)
Cephalosporin						
Ceftriaxone	56	26 (46.4)	47	21 (44.7)	9	5 (55.6)
Cefotaxime	47	25 (53.2)	38	20 (52.6)	9	5 (55.6)
Ceftazidime	62	30 (48.4)	53	25 (47.2)	9	5 (55.6)
Cefepime	63	41 (65.1)	54	33 (66.7)	9	5 (55.6)
Cefeporazone	9	5 (55.6)	-	-	9	5 (55.6)
Penicilin						
Ampicillin sulbactam	57	21 (36.8)	46	14 (30.4)	11	7 (63.6)
Amoxicillin clavulanat	12	7 (58.3)	1	0 (0)	11	7 (63.6)
Piperacilin tazobactam	64	39 (60.9)	53	32 (60.4)	11	7 (63.6)
Ampicillin*	41	6 (14.6)	39	4 (10.3)	2	2 (100)
Florokuinolon						
Ciprofloxacin	63	28 (44.4)	54	23 (42.6)	9	5 (55.6)
Levofloxacin	11	6 (54.5)	1	0 (0)	10	6 (60.0)
Moxifloxacin	8	4 (50.0)	0	0 (0)	8	4 (50.0)
Karbapenem						
Meropenem	58	52 (89.7)	53	47 (88.7)	5	5 (100)
Ertapenem	44	40 (90.9)	39	35 (89.7)	5	5 (100)
Aminoglikosida						
Amikacin	53	51 (96.2)	53	51 (96.2)	-	-
Gentamycin*	65	38 (58.5)	54	30 (55.6)	11	10 (90.9)
Others						
Tigecycline*	63	43 (68.3)	53	33 (62.3)	10	10 (100)
Vancomycin	12	11 (91.7)	1	0 (0)	11	11 (100)
Aztreonam	46	24 (52.2)	46	24 (52.2)	-	-
Clindamycin	9	5 (55.6)	1	0 (0)	8	5 (62.5)
Cotrimoxazol	55	33 (60.0)	47	27 (57.4)	8	6 (75.0)

Note : *P value ≤ 0,05

Table 4. Frequency Distribution of Antibiotic Susceptibility in Most Bacteria.

	Gram (-)														Gram (+)	
	AB		CF		EC		KP		MM		PA		PM		SA	
	n=8		n=4		n=7		n=13		n=5		n=6		n=5		n=6	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AN	6	75	4	100	7	100	13	100	5	100	5	83	5	100	-	-
SAM	3	37,5	0	0	0	0	6	46,2	0	0	-	-	4	80	5	83,3
AM	-	-	0	0	0	0	0	0	0	0	-	-	4	80		
ATM	-	-	2	50	2	28,6	6	46,2	4	80	4	67	4	80		
CZ	0	0	0	0	0	0	-	-	0	0	0	0	-	-	5	83,3
FEP	1	12,5	4	100	5	71,4	11	84,6	5	100	3	50	5	100	5	83,3
CTX	-	-	2	50	2	28,6	6	46,2	4	80	-	-	4	80	5	83,3
CAZ	1	12,5	2	50	3	42,9	6	46,2	3	60	3	50	5	100	5	83,3
CRO	1	12,5	2	50	2	28,6	6	46,2	4	80	-	-	4	80	5	83,3
CIP	1	12,5	2	50	1	14,3	6	46,2	4	80	3	50	4	80	4	66,7
SXT	5	62,5	2	50	2	28,6	6	46,2	4	100	-	-	4	80	5	100
ETP	-	-	4	100	7	100	13	100	5	100	-	-	4	80	5	100
GM	2	25	3	75	2	28,6	7	53,8	5	100	4	67	4	80	5	83,3
MEM	3	37,5	4	100	7	100	13	100	5	100	5	83	5	100	5	100
TZP	1	12,5	2	50	6	85,7	10	76,9	4	80	3	60	4	80	5	83,3
TGC	7	87,5	4	100	7	100	12	92,3	0	0	0	0	-	-	6	100
VA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	100
AMC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	83,3
MXF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	66,7
LFX	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	66,7
E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	80
CC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	80

Note: AB *: Acinetobacter baumanii,* CF *: Citrobacter freundii,* Ecl *: Enterobacter cloacae,* EC *: Escherichia coli,* KP *: Klebsiella pneumonia,* MM *: Morganella morganii,* PA *: Pantoea agglomerans*, PM *: Proteus mirabiis*, SA : Staphylococcus aureus, AN : Amikacin, AMC : amoxicillin clavulanat, SAM : ampicilin sulbactam, AM: ampicilin, ATM : aztreonam, PEN : benzylpenicillin , CZ : cefazolin, CC : clindamycin, CF : cephalotin, CXM : cefuroxime, CFP : cefoperazone, CFR : cefadroxil, E : erythromycin, FEP : cefepime, CTX : cefotaxime, CAZ : ceftazidime, CRO : ceftriaxone, CIP : ciprofloxacin, SXT : cotrimoxazol, ETP : ertapenem, GM: gentamycin, LFX : levofloxacin, LNZ : linezolide, MEM: meropenem, TZP: piperacillin tazobactam, TGC: tigecycline, MXF : moxifloxacin, STR : streptomycin, TE : tetracycline, VA : vancomycin.

against Gram-negative bacteria except for *A. baumanii* and *P. aeruginosa* (**Table 3**).

Staphylococcus aureus, the most common Gram-positive bacteria has good susceptibility to many of the antibiotics tested, which are penicillin with beta-lactamase inhibitors, the cephalosporin group namely ceftriaxone, ceftazidime, cefotaxime and cefepime, as well as other antibiotics such as cotrimoxazole, erythromycin, gentamycin and the carbapenem group (**Table 4**). The growth of MDR bacteria was found in approximately 18 growths (27.7%), including 11 ESBL-producing Enterobacteriaceae, and 6 carbapenemase-producing bacteria with 5 growths of *A. baumanii* and 1 growth of *P. aeruginosa*, as well as 1 growth of *Methicillin*

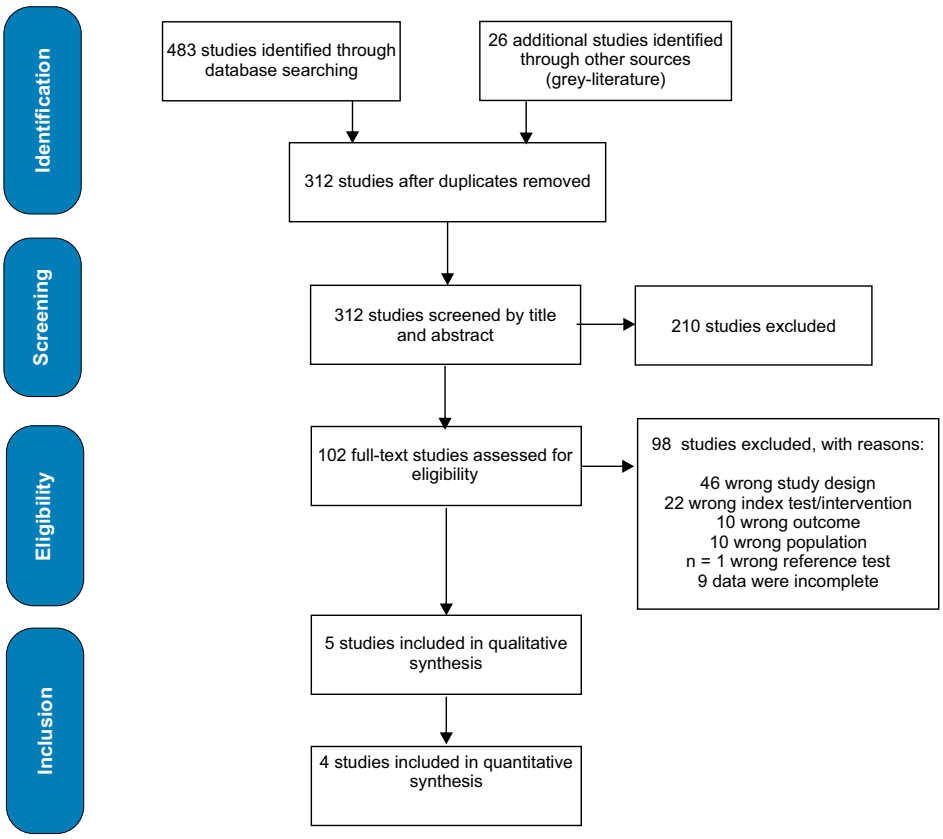

Figure 1.

Resistance Staphylococcus aureus (MRSA).

Several antibiotics have better susceptibility in patients without a history of previous hospitalization, including amoxicillin clavulanate, piperacilin tazobactam, levofloxacin, moxifloxacin, and clindamycin with susceptibility of 40%, 46.4%, 20%, 25% and 40% and higher susceptibility in patients without history, which were 71.4%, 72.2%, 83.3%, 75% and 75%, respectively, but among these antibiotics only ampicillin and piperacillin tazobactam have a p-value of ≤0.05 (**Figure 1**). There were no significant differences in the susceptibility pattern among patients with or without a previous history of antibiotics, and in the group of patients with moderate (Wagner 2-3) or severe ulcer grade (Wagner 4-5).

DISCUSSION

Based on the results, Gram-negative bacteria were the most dominant in bacterial growth. This is consistent with previous studies which stated that the growth of Gram-negative bacteria dominates diabetic foot infections in Asia. [7,8] In contrast, Gram-positive bacteria are more often found in western countries. The cause of this difference is still not clearly known, but several reports suggest differences in environmental factors, use of footwear, personal hygiene, and history of antibiotics.[7-10]

The direct Gram examination results did not correctly correlate with the characterization of bacteria based on isolation. The gram-negative in microscopy show modest sensitivity to detect true culture result but with good specificity (87.5%). However, when the microscopic finding is Gram-positive, the sensitivity was 87.5%, but the specificity was low. Therefore, when the microscopy smear finding is gram-negative, it indicates the presence of gram-negative bacteria. Previous studies found that Gram and culture results were inconsistent.[11, 12]

Based on the results, the antibiotics with good susceptibility (above 80%) for Gram-negative bacteria were the carbapenems (meropenem and ertapenem) and amikacin.

This pattern has changed compared to previous study by Astawa (1996) conducted at the same hospital which reported that ciprofloxacin was the best antibiotic for Gram negative bacteria.[13] Antibiotics for Gram-negative bacteria recommended by international guidelines are ceftriaxone, ampicillin sulbactam, ciprofloxacin and tigecycline.[4] However, these antibiotics have poor susceptibility to Gram-negative bacteria in this study.

Antibiotics with good susceptibility for Gram-positive bacteria in this study were carbapenems, gentamicin, tigecycline and vancomycin. This is in line with Wu (2018) which stated that tigecycline and vancomycin were the best antibiotics for Gram-positive bacteria. Antibiotics recommended for moderate-to-severe DFI by Gram-positive bacteria include quinolones, cephalosporins and beta-lactam antibiotics,[4, 14, 15] but, these antibiotics have poor susceptibility in this study.

Furthermore, multidrug resistance (MDR) bacteria were found in this study including ESBL, Carbapenem Resistance *A. baumanii* and *P. aeruginosa,* as well as MRSA. The prevalence of MDR bacteria and ESBL bacteria is increasing worldwide. MDR bacterial infection is commonly found in severe and chronic ulcers, as well as patients with a history of antibiotics and previous hospitalization.[5, 8] In this study, MDR bacteria were more commonly found in patients with a history of previous hospitalization.

Several studies reported that certain antibiotics had better susceptibility in a group of patients without previous hospitalization history and low grade Wagner group.[5] In this study, only ampicillin and piperacillin tazobactam had a higher susceptibility level in the patient without previous hospitalization history. However, the susceptibility difference between the moderate (Wagner 2 and 3) and the severe ulcer group (Wagner 4 and 5) was not statistically significant.[5]

This study has several limitations, first, the sample size was small, hence, an association analysis was not performed. Second, the culture facility in the laboratory did not accommodate the isolation of anaerobic bacteria. Meanwhile, anaerobic bacteria species might also participate in the pathology of DFI. [8]

CONCLUSION

The growth of Gram-negative bacteria dominates diabetic foot infection in RSHS Hospital Indonesia. Some antibiotics had a lower susceptibility level compared to previous studies conducted in the same setting. This indicates that the choice of antibiotics with good susceptibility toward Gram-positive and negative bacteria is limited. Therefore, international guidelines used for antibiotics selection are no longer applicable because the recommended antibiotics have poor susceptibility in this study.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests concerning the publication of this paper.

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REFERENCES

1. Uckay I, Gariani K, Pataky Z, Lipsky BA. Diabetic foot infections: state-of-the-art. Diabetes, Obesity & Metabolism. 2014;16(4):305-16.
2. Ramakant P, Verma AK, Misra R, et al. Changing microbiological profile of pathogenic bacteria in diabetic foot infections: time for a rethink on which empirical therapy to choose? Diabetologia. 2011;54(1):58-64.
3. Lipsky BA, Aragon-Sanchez J, Diggle M, et al. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes/metabolism research and reviews. 2016;32 (Suppl 1):45-74.
4. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(12):e132-73.
5. Xie X, Bao Y, Ni L, et al. Bacterial profile and antibiotic resistance in patients with diabetic foot ulcer in Guangzhou, Southern China: Focus on the differences among different Wagner's grades, IDSA/IWGDF grades, and ulcer types. International Journal of Endocrinology. 2017;2017:8694903.
6. Weinstein MP, Lewis JS, 2nd. The clinical and laboratory standards institute subcommittee on antimicrobial susceptibility testing: Background,

organization, functions, and processes. Journal of Clinical Microbiology. 2020;58(3).
7. Kow RY, Low CL, Ruben JK, Zaharul Azri WMZ, Mor Japar Khan ESK. Microbiology of diabetic foot infections in three district hospital in Malaysia and comparison with South East Asian Countries. The Medical Journal of Malaysia. 2019;74(5):394-9.
8. Hatipoglu M, Mutluoglu M, Uzun G, Karabacak E, Turhan V, Lipsky BA. The microbiologic profile of diabetic foot infections in Turkey: a 20-year systematic review: diabetic foot infections in Turkey. European Journal of Clinical Microbiology & Infectious Diseases. 2014;33(6):871-8.
9. Nurwahidah YS, Tahir T. Identifikasi jenis bakteri pada luka kaki diabetik berdasarkan penyebab luka di Rumah Perawatan Luka dan Poliklinik luka di kota Makasar. Jurnal Kesehatan Manarang. 2018;4:97-103.
10. Rinaldo C FN. Hubungan antara pola kuman dengan infeksi kaki diabetik berdasarkan derajat PEDIS di RSUP Dr. Kariadi. JKD. 2017;6:385-401.
11. Samuel LP, Balada-Llasat JM, Harrington A, Cavagnolo R. Multicenter assessment of Gram stain error rates. Journal of Clinical Microbiology. 2016;54(6):1442-7.
12. Shaigany S, Steuer A, Seminara N, Brinster N, Femia A. Comparison between organismal staining on histology and tissue culture in the diagnosis of cutaneous infection: A retrospective study. J Am Acad Dermatol. 2020;82(6):1400-8.
13. Astawa IM Pola dan hasil uji kepekaan kuman pada kaki diabetes terinfeksi penderita rawat inap. 1996:32-69.
14. Wu M, Pan H, Leng W, Lei X, Chen L, Liang Z. Distribution of microbes and drug susceptibility in patients with diabetic foot infections in Southwest China. J Diabetes Res. 2018;2018:9817308.
15. Sanchez-Sanchez M, Cruz-Pulido WL, Bladinieres-Camara E, Alcala-Duran R, Rivera-Sanchez G, Bocanegra-Garcia V. Bacterial prevalence and antibiotic resistance in clinical isolates of diabetic foot ulcers in the Northeast of Tamaulipas, Mexico. The International Journal of Lower Extremity Wounds. 2017;16(2):129-34.

Comparisons of Characteristics and Nutritional Inadequacies in Indonesian Older Adults Consuming or Refraining from Dairy Products

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ABSTRACT

***Background*:** *Milk consumption in the Indonesian elderly population is among the lowest in the world, and two-thirds of the population are lactose intolerant. This might have an impact on energy and nutrient intakes. However, data on the prevalence of nutrient intake inadequacies in dairy users versus non-dairy users, as well as population characteristics, are lacking. Therefore we obtained data comparing nutritional inadequacies and characteristics of Indonesian older adults consuming or refraining from dairy products.* ***Methods*:** *A cross-sectional study was conducted in 2021 as a part of the INA LACTASE study, involving 194 community-dwelling older adults in the outpatient geriatric clinic at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. We collected data on demographic and clinical characteristics as part of a routinely performed comprehensive geriatric assessment. A structured questionnaire was developed to categorize participants as dairy-or non-dairy users based on habitual dairy intake. Food records were collected to assess nutrient intakes. The prevalence of inadequacies of energy, macronutrients, and a selection of micronutrients (calcium, vitamin D, and vitamin B12) was calculated by comparing the reported mean intakes to the recommended dietary intakes of the Indonesian population (Indonesian RDA). Prevalence ratios were calculated to measure the association between dairy product consumption and the prevalence of nutrient inadequacies.* ***Results*:** *We recruited 194 eligible participants. This study found that dairy users had a higher proportion of women, a higher monthly income, but a lower proportion of hypertension, diabetes mellitus, and dyslipidaemia in older adults consuming dairy products. We observed wide variability in energy and nutrient intakes, as well as a high prevalence of inadequacies for all*

dietary intake parameters, particularly micronutrients. Dairy users had a lower prevalence of micronutrient inadequacies than non-dairy users. The prevalence of vitamin D inadequacies in dairy users versus non-dairy users was 91.6% vs. 99.3% in men and 71.9% vs. 98.0% in women, respectively. Inadequate vitamin B12 intake was found in 60.6% of dairy users vs. 89.4% of non-dairy users in men and 65.5% vs.. 68.4% of women, respectively. The most pronounced difference was found in the prevalence of calcium intake inadequacies in dairy users vs. non-dairy users, which was 64.8% vs. 99.5% in men and 89.9% vs. 99.8% in women. We found statistically significant differences in the prevalence of calcium, vitamin D, and vitamin B inadequacies between dairy and non-dairy users. ***Conclusion*****:** *This study identified that dairy users had a higher monthly income and had a lower proportion of hypertension, diabetes mellitus, and dyslipidemia. In addition, we discovered a high prevalence of nutrient intakes inadequacies in Indonesian older adults, particularly among non-dairy users. Micronutrient inadequacies are major sources of concern, with statistically significant difference in calcium, vitamin D, and vitamin B12 prevalence of inadequacies.*

Keywords**:** *characteristics, nutrient intakes, the prevalence of inadequacies, older adults, Indonesia*

INTRODUCTION

Indonesia has an aging population.[1] Over the last four decades, the proportion of older adults (age 60 year or older) has increased, accounting for 9.5 percent of Indonesian population. This increase is due to improved health services, which have increased life expectancy and lower mortality rates. On the other hand, the aging population increases the demand for healthcare services, healthcare spending, and the need for socio-economic support.[1,2]

Nutrition is essential for older adults to improve their health status,[3] and nutritional status is an independent risk factor for frailty in older adults.[4] Inadequate nutrient intakes result in malnutrition, putting older adults at a high risk of developing frailty.[5] According to Setiati et al.., 25.2% of the older adults in Indonesia were frail, 61.6% were pre-frail and only 13.2% were robust.[6] Recently, some systematic reviews found that dairy products consumption lowers the risk of frailty and sarcopenia, as well as improves muscle mass. [7,8] As a result, incorporating dairy products into the daily diets of older adults could be a relevant strategy to improve health status.[7,8] Milk consumption in the Indonesian older adults, on the other hand, is among the lowest in the world,[9] and 66% of the population is lactose intolerant.[10]

Studies investigating dairy products consumption and nutrient intake inadequacies in Indonesian older adults are scarce. This study analyzed data from the Indonesian Lactose Intolerance and Dairy Products Study in the Elderly (INA LACTASE), which included data on dairy products consumption in Indonesian community-dwelling older adults. To be more specific, this study took a closer look at the characteristics and prevalence of nutrient inadequacies in dairy users versus non-dairy users. In addition with our previous publication,[10] this study presented the characteristics in a larger sample size, and used the data set to perform additional calculation analysis to determine the prevalence of nutrient intakes inadequacies. The aims of this study were to gain insight into the characteristics of Indonesian older adults consuming or refraining from dairy products and into their nutritional inadequacies**.**

METHODS

A cross-sectional study was conducted in January until August 2021 among community-dwelling older adults in the outpatient geriatric clinic, Dr. Cipto Mangunkusumo Hospital, Jakarta. The recruitment period of participants was between April to October 2019, using a consecutive sampling method. The inclusion criteria were older adults aged 60 years or older who lived in their own houses (community-dwelling). Exclusion criteria were suffering from cognitive impairment and unwillingness to participate in the study. To avoid potential bias, we used validated measures, objective data sources, and standardized interviewer's interaction with subjects.

Subjects Characteristics

Data on demographical and clinical characteristics, nutritional status, dietary intake, habitual dairy intake, were collected from all participants by trained physicians and a dietitian. A structured questionnaire was used to collect data on age, gender, level of education, monthly income, and living situation from the participants or their primary caregivers. Monthly income was classified based on the cutoff level of mean income for Indonesian older adults.[11] We assessed the functional status of participants by using the Barthel Index for Activities of Daily Living (ADL). The mini-mental state examination (MMSE) was used to assess cognitive function, and the geriatric depression scale (GDS) was used to assess psychological status as a routine assessment in the geriatric outpatient clinic. Recent cognitive function was assessed by using the Indonesian abbreviated mental test (AMT) for screening of study participants. All of the above-mentioned instruments are routinely used to conduct the comprehensive geriatric assessment by the Indonesian Ministry of Health.[12]

Nutritional Status

Weight, height, arm circumference, and calf circumference were measured to obtain anthropometric data. Body weight was measured using calibrated digital scales with a 0.1 kg accuracy. Knee height was measured in a supine position with a knee height caliper to calculate body height using the Chumlea formula validated for Indonesia.[13] Body mass index (BMI) was calculated by dividing the weight by the height squared. We also measured middle upper arm circumference (MUAC) and calf circumference (CC) as nutritional status indices based on the protocol that was utilized by Wijnhoven, et al..[14] The Indonesian version of the mini nutritional status assessment (MNA) full form was used to classify participants as well-nourished, at risk of malnutrition, or malnourished.[12]

Assessment of Dietary Intake

Current dietary intake was assessed using 3-day food records (2 weekdays and one weekend day). Nutrient intakes were calculated using Nutrisurvey software developed according to the Indonesian food composition table. The portion size was confirmed using a food model kit.[15]

Classification of Older Adults Consuming or Refraining from Dairy Products

We classified participants as consuming or refraining from dairy products based on their habitual dairy intake. Habitual dairy intake was derived from a structured questionnaire that described the amounts of milk and dairy products consumed by a person on a daily basis. Based on reported dairy product consumption, subjects were classified as dairy users or non-dairy users. Criteria for "dairy user" were: consuming at least 15 grams of milk powder (similar to 100 ml of water-dissolved milk); 100 grams of (ultra-high temperature) UHT/flavored/cultured milk or drink yoghurt; 50 grams of yoghurt; 10 grams of condensed milk or ice cream; or 5 grams of cheese on a daily basis. If the consumption of each dairy product was less than these standards, but the total consumption of all dairy products was more than 100 grams, a subject was also classified as a "dairy user".[16]

Prevalence of Nutrient Intake Inadequacies

The prevalence of inadequacies of energy and nutrient intakes were calculated based on the Indonesian RDA for the age group 60–85-year-old,[17] from which we derived 2/3 RDA as a proxy of the estimated average requirement (EAR).[18] We calculated the prevalence of inadequacy by using the following calculation: $z = (x - \mu)/SD$, with x as the dietary reference intake (2/3RDA), μ the mean nutrient intake, and SD the standard deviation of the nutrient intake. Then we calculated the percentage below the dietary reference intake based on its corresponding value in the Z-scores table.[19,20]

Sample Size

To compare the characteristics of Indonesian older adults who consume or refrain from dairy products, we included all eligible participants in the dataset, for a total data on 194 subjects. We calculated the minimum sample size required to compare the prevalence of nutritional inadequacies between two groups, using the formula to calculate differences in proportions between two independent groups. The sample

size was estimated using a level of significance of 5%, a power of 80%, a 2-sided p-value of 0.05, and a proportion difference of 30%.[21] As a result, a subset data of 103 subjects would be sufficient to achieve the desired power of this study to calculate differences of proportion in nutrient inadequacies between dairy users and non-dairy users.

Statistical Analyses

We carried out descriptive analyses for baseline characteristics (age, sex, level of education, monthly income, living situation, functional status, mental status, height, weight, BMI, MNA score, and comorbidities). We used the Kolmogorov-Smirnov test to check the normality distributions of all variables. We depicted data from normally distributed distributions as mean and standard deviation (SD), whereas data from non-normally distributed distributions was presented as median and interquartile range (IQR). Categorical data was presented as numbers and percentages. As the measure of association, we calculated the prevalence ratio of macronutrient and micronutrient inadequacies in dairy users compared with non-dairy users. Prevalence ratios (PRs) with a 95% CI not including 1.0 were considered statistically significant. Data analyses were carried out using SPSS® version 26.0.0 (IBM Corporation, Chicago, IL, USA).

Ethical Approval

This study has been approved by the Ethical Committee of the Faculty of Medicine Universitas Indonesia, with approval number KET.385/UN2.F1/ETIK/PPM.00.02/2019. Informed consents were obtained from all study participants.

RESULTS

We gathered information from 194 eligible subjects. Seventy-six of them were classified as dairy users, and 118 of them as non-dairy users. The majority of subjects had independent functional status (as measured by ADL Barthel index scores) and had current normal cognitive function (as screened by the AMT). **Table 1** presents the comparison of characteristics between dairy users and non-dairy users. According to **Table 1**, dairy users are mostly women Dairy users also had better socio-economic status, better functional status, a lower proportion of being malnourished or at risk of malnutrition, as well as lower proportions of comorbidities particularly hypertension, diabetes mellitus, and dyslipidemia.

For 103 subjects, a 3-day food intake was recorded. **Table 2** shows their mean intakes of energy, macronutrients, and selected micronutrients. While the mean daily intakes of energy, carbohydrate, and fat in dairy users compared with non-dairy users were not different, the mean daily protein intakes in dairy users compared with non-dairy users' groups were clinically different, with intakes of 67.6 (SD 15.6) g vs. 57.0 (SD 12.2) g in men and 58.4 (SD 13.7) g vs. 49.7(SD 14.3) g in women, respectively. Dairy users had higher mean calcium, vitamin D, and vitamin B12 intakes than non-dairy users. The mean daily intakes of calcium in dairy users compared with non-dairy users' groups were 603.5 (SD 283.5) mg vs. 301.1 (SD 194.8) mg in men and 476.2 mg (SD 336.1) vs. 264.8 (SD 181.2) mg in women, respectively. The mean daily intake of vitamin D in dairy users vs. non-dairy users were 6.6 µg (SD 4.7) vs. 2.5 (SD 4.3) in men and 8.3 (SD 6.5) µg vs. 1.9 (SD 5.4) µg in women, respectively. For vitamin B12, mean daily intakes in dairy users vs. non-dairy users were 2.6 (SD 6.5) µg and 1.5 (SD 1.2) µg in men and 2.9 (SD 2.7) µg vs. 1.9 (SD 2.3) µg in women, respectively.

When compared to the EAR estimates, we found wide variability in energy and nutrient intake, as well as a high prevalence of inadequacies for all dietary intake parameters. Prevalence on inadequacies for protein, calcium, vitamin D, and vitamin B12 were higher in non-dairy users than in dairy users. Prevalence of protein intake inadequacies in dairy users compared with non-dairy users were 5.7% vs. 12.5% in men and 7.8% vs. 22.4% in women, respectively. Prevalence of micronutrient inadequacies in non-dairy users was more profound compared with dairy users. Prevalence of vitamin D intake inadequacies in dairy users compared with non-dairy users groups were

Table 1. Characteristics of Dairy Users compared with Non-dairy Users in Indonesian Older Adults.

Characteristics	Total (n= 194)	Dairy Users N = 76	Non-dairy Users N = 118
Age (years), n (SD)	71.9 (5.7)	72.1 (5.3)	71.7 (5.9)
Sex			
Men, n (%)	86	29 (33.7)	57 (66.3)
Women, n (%)	108	47 (43.5)	61 (56.5)
Level of education, n (%)			
Primary school	16	5(31.3)	11(68.7)
Junior high school	13	4(30.8)	9(69.2)
Senior high school	50	22(44.0)	28(56.0)
College or higher	115	45(39.1)	70(60.9)
Monthly income, n (%)			
< IDR 1.800.000	49	14 (28.6)	35 (71.4)
≥IDR 1.800.000	145	62 (42.8)	83 (57.2)
Living situation, n (%)			
Living alone	24	13(54.2)	11(45.8)
Living with spouse	105	40(38.1)	65(61.0)
Living with children	58	21(36.2)	37(63.8)
Others	7	2(28.6)	5(71.4)
Functional status, n (%)			
Independent	138	83 (60.1)	55 (39.9)
Mild dependent	56	35 (62.5)	21 (37.5)
Mental status, n (%)			
Normal	158	62 (39.2)	96 (60.8)
Risk of depression	36	14 (38.9)	22 (61.1))
Height, cm (SD)	155.9	155.4 (6.0)	156.1 (6.3)
Weight, kg (SD)	61.7	61.1 (11.5)	62.1 (11.9)
BMI, kg/m^{2,} (SD)	25.3	25.3 (4.2)	25.4 (4.3)
MUAC, cm (SD)	28.0	28.0 (4.9)	28.0 (4.3)
MNA Score, n (%)			
Normal	175	71 (40.6)	104 (59.4)
At risk of malnutrition or malnourished	19	5 (26.3)	14 (73.7)
Comorbidities, n (%)			
Hypertension	153	55 (35.9)	98 (64.1)
Diabetes Mellitus	108	31 (28.7)	77 (71.3))
Dyslipidemia	69	25 (36.2)	44 (63.8)
Osteoarthritis	60	23 (38.3)	37 (61.7)
Neuropathy	53	18 (33.9)	35 (66.1)
Others	51	23 (45.1)	28 (54.9)

Note:
BMI= Body Mass Index, MNA= Mini Nutritional Assessment, UAC= Upper Arm Circumference

91.3% vs. 99.3% in men and 76.4% vs. 98.0% in women, respectively. Prevalence of vitamin B12 intake inadequacies in dairy users vs. non-dairy users were 43.3 % vs. 89.4% in men and 48.4% vs. 68.4% in women, respectively. The most pronounced difference was found in prevalence of calcium intake inadequacies in dairy users compared with non-dairy user's groups were 75.5% vs. 99.5% in men and 83.1% vs. 99.8% in women, respectively. In both genders, we found statistically significant prevalence ratios of micronutrients for calcium, vitamin D, and vitamin B12.

DISCUSSION

This study revealed comparisons of characteristics and nutritional inadequacies in Indonesian older adults consuming or refraining from dairy products. Dairy users included a larger proportion of women and subjects with higher monthly incomes. They were at lower risk of malnutrition and had fewer comorbidities, particularly hypertension, diabetes mellitus, and dyslipidemia. Furthermore, dairy products consumption came with lower proportions of inadequacies for protein, calcium, vitamin D, and vitamin B-12 in dairy users compared with

Table 2. The Comparison of Mean Energy-Nutrient Intakes, and Prevalence of Inadequacies between Dairy Users and non-Dairy Users in Indonesian Older Adults.

Dietary Intake	Dairy users n= 39		Non-dairy users n= 64		Prevalence ratios of Nutrient Inadequacies (95% CI)
	Intake	% Below 2/3 RDA	Intake	% Below 2/3 RDA	
Total energy (kcal), mean (SD)					
Men, n= 56	1779 (372)	5.8	1643 (288)	6.2	0.75 (0.18 - 3.19)
Women, n= 47	1478 (277)	5.5	1421 (262)	6.9	0.67 (0.12 - 3.81)
Carbohydrate (g), mean (SD)					
Men, n= 56	236.9 (64.8)	20.3	231.9 (49.0)	16.1	1.22 (0.55 - 2.72)
Women, n= 47	200.8 (39.1)	11.1	188.3 (46.3)	22.4	0.45 (0.17 - 1.21)
Protein (g), mean (SD)					
Men, n= 56	67.6 (15.6)	5.7	57.0 (12.2)	12.5	0.43 (0.12 - 1.57)
Women, n= 47	58.4 (13.7)	7.8	49.7 (14.3)	22.4	0.36 (0.12 - 1.06)
Fat (g), mean (SD)					
Men, n= 56	60.2 (23.6)	12.5	55.3 (18.3)	11.1	1.17 (0.42 - 3.25)
Women, n= 47	52.5 (14.2)	10.1	54.9 (16.9)	7.1	1.67 (0.42 - 6.64)
Calcium (mg)					
Men, n= 56	603.5 (283.2)	75.5	301.1 (194.8)	99.5	0.76 (0.65 - 0.89) *
Women, n= 47	476.2 (336.1)	83.1	264.8 (181.2)	99.8	0.85 (0.74 - 0.97) *
Vitamin D (mg)					
Men, n= 56	6.6 (4.7)	91.3	2.5 (4.3)	99.3	0.92 (0.84 - 0.99) *
Women, n= 47	8.3 (6.5)	76.4	1.9 (5.4)	98.0	0.78 (0.66 - 0.92) *
Vitamin B12(mg)					
Men, n= 56	4.1 (6.5)	43.3	1.5 (1.2)	89.4	0.48 (0.35 - 0.66) *
Women, n= 47	2.9 (2.7)	48.4	1.9 (2.3)	68.4	0.69 (0.48 - 0.99) *

*= statistically significant. EAR= estimated average requirement. Proxy of EAR based on two-thirds of the Indonesian Recommended Dietary Allowance (RDA) for age group 65-80 years old, for men and women respectively, are as follows: Energy: 1200 kcal & 1034 kcal. Carbohydrate: 183 g & 153 g. Protein: 43 g & 39 g. Fat: 33g & 30 g. Calcium: both men and women are 800 mg. Vitamin D: both men and women are 13mg. Vitamin B12: both men and women are 3 μg. The colors indicate the level of severity of inadequacies: green indicates mild inadequacies, yellow indicates moderate inadequacies, and red indicates severe inadequacies.

non-dairy users. The differences in inadequacies were more pronounced for micronutrients (calcium, vitamin D, and vitamin B12), and they were statistically significant for both genders. In addition to our previous publication from INA-LACTASE project, this study also provides a closer look at the characteristics and prevalence of nutrient inadequacies in dairy users versus non-dairy users.[10]

We classified the older adults into two groups: those who consume dairy products (dairy users) and those who refrain from dairy products (non-dairy users). It was challenging to define the "dairy user" criteria in older adults, particularly in the Asian population. We found two previous studies that quantified the amount of dairy products consumed on a regular basis. The first one is a study by Ribiero et al., who as 240 g for milk or equivalent, with an average dairy product intake of 2.6 servings/day in the adult population.[22] However, Ribiero et al. did not explicitly define dairy user criteria, and many Indonesian older adults do not meet the above-mentioned average intake of dairy products.[21] Therefore, we referred to the criteria used by Nguyen Bao et. al., in a survey on dairy products consumption and its association with nutritional status among children in the Southeast Asian countries, which is more relevant for Indonesian older adults. Because the dairy product categories were similar to the Indonesian diet, these criteria accommodate a wide range of dairy products consumed by the subjects.[16] Furthermore, we assessed the current dietary intake of the subjects using a three-day 24-hour food record, with an additional structured questionnaire to describe

the amounts of dairy products consumed by a person on a daily basis. We used 2/3*RDA as a proxy for the EAR to estimate prevalence of nutrient intakes inadequacies. This approach is considered to be more informative than RDA, which may overestimate the prevalence of inadequacies.[18,19] Almost all of Asian countries derived their recommended daily intakes or allowances (RDI or RDA) from national nutrition surveys, small scale surveys, and/or household food consumption findings, following the framework established by the Institute of Medicine's Food and Nutrition Board, which aimed to meet the requirements of 97.5 percent of healthy individuals by life stage and gender. In general, the reported mean intake values were compared to the RNI/RDA. The reported values did not include any proportions lower than the estimated average recommendation (EAR), which is now used globally. Most of the countries agreed that these recommendations should be updated. Several countries are in the process of updating their reference values.[23]

In this study, we found that dairy users included a larger proportion of women and subjects with higher monthly incomes. Historical and cultural factors heavily influence food preferences for milk and dairy products consumption. In a qualitative study, Best et al. (2013) investigated the factors associated with high-protein food consumption in older adults. Taste, texture, and odor, for example, may become more important as people age due to chemosensory losses and eating difficulties associated with tooth loss and denture use. Cost, medical constraints, and a variety of health conditions are also factors to consider.[24] Gender differences are discussed from various scientific perspectives, as well as the impact of gender on consumer behaviour. There was a distinction between men's and women's preferences. A study conducted by Ubreiová et al. in Russia and Slovakia discovered that women buy dairy products more frequently and are more concerned about the health benefits of dairy products consumption.[25] However, a qualitative study of differences in dairy products consumption, particularly between genders, is needed to be explored in the Indonesian population. A study by Lugito et al. found dairy products consumption was associated with high socio-economic status in Indonesia.[26] As a result, uthe affordability of dairy products in Indonesia has become a concern. In terms of the prevalence of nutrient intakes inadequacies, this study found that dairy users had a lower prevalence of inadequacies in protein, calcium, vitamin D, and vitamin B12 intakes. This finding is consistent with the pronounced inadequacies of nutrient intakes in general Indonesian elderly population as reported by a multicenter study by Setiati et al..[21]

We calculated the prevalence of inadequacies and found that vitamin D had the highest prevalence, followed by calcium, vitamin B12, and protein; particularly in non-dairy users. This situation may increase the risk of clinical problems associated with nutrient inadequacies in older adults, such as sarcopenia and frailty (low protein intakes),[27] osteoporosis and pathological fractures (low vitamin D and calcium intakes), cognitive impairment (low B-vitamin intakes), as well as chronic degenerative diseases (low calcium and vitamin D intakes).[28] Protein intake reference values for older adults are a topic of constant debate. Protein requirements may increase with age due to conditions such as muscle mass loss and anabolic resistance. Therefore a higher intake of protein is recommended for older adults.[29] Special attention is paid to inadequate intake of calcium and vitamin D. These nutrient deficiencies affect bone loss and can increase the risk of osteoporotic fracture. A literature review was conducted to determine the problem of calcium intake inadequacy in older adults. Data from the literature shows that calcium intake is reduced for both the elderly and people with osteoporotic fractures when global reference values are taken into account. Asians have the lowest intake of this element among the elderly. As a result, calcium supplementation should be considered in populations that are particularly vulnerable to deficiency.[30] The high prevalence of vitamin D inadequacy has been a global concern. Since dietary sources of vitamin D are limited (such as oily fish, egg yolks, and dairy products), a large proportion of the population has inadequate intakes. Most of the vitamin D source comes from skin synthesis and/or dietary

supplements.[31] Despite the fact that Indonesia is a tropical country with high sun exposure all year, genetic BsmI polymorphisms in the vitamin D receptor gene exist in the Indonesian–Malay race, which may contribute to the high prevalence of vitamin D deficiency.[32] Regarding the inadequacy of vitamin B12 intake in our population, it may be due to dietary patterns. Animal-derived foods such as meat, milk, fish, and shellfish, which are infrequently consumed in our population, are dietary sources of vitamin B12. To prevent Vitamin B12 deficiency in a high-risk population, it is necessary to identify plant-derived food sources that naturally contain a high amount of Vitamin B12.[33]

Despite these low intakes, most of our subjects were well-nourished based on MNA assessment, as the total calorie, carbohydrate and fat intake was not different between dairy users and non-dairy users group. Notwithstanding the aforementioned finding, the proportion of subjects who were at risk of malnutrition was higher in non-dairy users. Therefore, incorporating dairy products into the diets of older adults is both beneficial and well-tolerated,[10] without worrying of excessive total calorie, carbohydrate, and fat intake.

We also identified that dairy users had lower proportions of hypertension, diabetes mellitus, and dyslipidemia. These findings are consistent with a systematic review conducted by Godos et.al, who found convincing and probable evidence of reduced risks of hypertension, type-2 diabetes mellitus, metabolic syndrome and cardiovascular disease.[34] Moreover, a systematic review and meta-analysis conducted by Schwingshackl et.al found that each additional daily 200 g of dairy products was inversely associated with diabetes risk, as shown in Asian studies and subjects aged 50-years and older.[35] Aside from genetic and environmental factors, unhealthy diet and lifestyle are central to the development of CVD and a key modifiable risk factor for its prevention. Several meta-analyses conclude that, despite having a high SFA content, dairy products have a positive or neutral effect on human cardiovascular health. Recent research and meta-analyses have shown that full-fat dairy consumption has health benefits due to higher bioavailability of high-value nutrients and anti-inflammatory properties. Furthermore, full-fat dairy products contribute to higher intakes of important nutrients.[36] Besides the fat, the synergistic effects of monounsaturated fatty acids, protein components (including bioactive peptides), calcium, and antioxidant vitamins may be responsible for a number of mechanisms that benefit cardiometabolic health and reduce arterial stiffness.[37] As a result, the negative image of milk fat is fading after years of debate. As a result, consumers can continue to consume full-fat dairy products in moderation as part of a healthy and balanced lifestyle, but fermented dairy products would be preferential for optimum nutrient intake and potential cardiovascular health benefits. Thus, dairy products may be good choices of nutrient-dense food that improve nutrient intakes in older adults without increasing the risk of cardiovascular diseases due to excess total calorie, carbohydrate and fat intake.[30,31]

In addition to data on mean daily nutrient intakes, this study provides information on a lack of data reporting on the prevalence of nutrient intake deficiencies in Indonesian older adults, with a focus on dairy products consumption.[10] Our findings showed benefits of dairy products consumption in Indonesian older adults' population, particularly on micronutrients. This finding is consistent with the findings of Staveren et al., who found that dairy products contain significant amounts of protein as well as a variety of minerals and vitamins important for healthy aging. Furthermore, replacing dairy products with other foods will be difficult for the frail older adults.[38]

Moreover, the dairy user category was validated using a structured questionnaire. Thus, the dietary intake data should be reliable since it was assessed using two different instruments based on their indications. The limitation of this study was that data of food records was only available in a subset data of 103 participants. As a result, the prevalence of energy and nutrient inadequacies could only be analyzed in the subset data. However, we found that most of the characteristics of the subset data of 103 subjects were comparable to those of the 194-subject total data. The proportion of dairy users in the subset

data was almost similar to that of the participants in the total data, 38% vs. 39% respectively. As a result, the comparability of total data and subset data in our study is sufficient, and the results of the sub-group analysis might represent the total subjects.[39]

Despite the fact that our study was conducted at a single center site, we believe that our findings can be extrapolated to the general population of apparently healthy older Indonesians, taking into account comparable characteristics to a national multicenter study conducted by Setiati et al.[21] The findings of nutrient inadequacies might also be extrapolated to other populations with similar characteristics. However, our findings must be replicated under different socio-cultural conditions and/or in other countries.

Our findings show that dairy products consumption is important in supporting better intakes of protein, calcium, vitamin D, and vitamin B12 in Indonesian older adults. Dairy products might be good nutrient-dense food choices for older adults to improve nutrient intake without worrying about excess total calorie, carbohydrate, and fat intake leading to an increased risk of cardiovascular diseases. However, the affordability of dairy products might be a socioeconomic barrier. Therefore, strategies to promote affordable dairy products or other alternative nutrient- dense foods in the diets of Indonesian older adults are required.

CONCLUSION

This study identified that dairy users have higher monthly income and have lower proportions of hypertension, diabetes mellitus, and dyslipidemia; compared with non-dairy users. We also found a high prevalence of nutrient intake inadequacies in Indonesian older adults, particularly among non-dairy users. Micronutrient inadequacies are major sources of concern, with statistically significant difference in the prevalence of inadequacies for calcium, vitamin D, and vitamin B12.

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CONFLICTS OF INTEREST

None declared.

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REFERENCES

1. Pusat Data dan Informasi Kementerian Kesehatan RI. Situasi dan analisis lanjut usia [Internet]. Jakarta: Kementerian Kesehatan RI; 2014 [cited 17 Nov 2020]. Available from: https://www.kemkes.go.id/article/view/14010200005/situasi-dan-analisis-lanjut-usia
2. Badan Pusat Statistik. Statistik penduduk lanjut usia 2019 [Internet]. Jakarta: Badan Pusat Statistik; 2019 [citied 17 Nov 2020]. Available from: https://www.bps.go.id/publication/2019/12/20/ab17e75dbe630e05110ae53b/statistik-penduduk-lanjut-usia-2019.html
3. Marshall TA, Stumbo PJ, Warren JJ, Xie XJ. Inadequate nutrient intakes are common and are associated with low diet variety in rural, community-dwelling elderly. J Nutr. 2001;131(8):2192–6.
4. Hong X, Yan J, Xu L, Shen S, Zeng X, Chen L. Relationship between nutritional status and frailty in hospitalized older patients. Clin Interv Aging. 2019; 14:105–11.
5. Dodds R, Sayer AA. Sarcopenia and frailty: new challenges for clinical practice. Clin Med. 2016;16(5):455–8.
6. Setiati S, Laksmi PW, Aryana IGPS, et al. Frailty state among Indonesian elderly: prevalence, associated factors, and frailty state transition. BMC Geriatr. 2019;19(1):182.
7. Yang Du, Chorong Oh, Jaekyung No. Advantage of dairy for improving aging muscle. J Obes Metabol Syndr. 2019;28:167-74.
8. Cuesta-Triana F, Verdejo-Bravo C, Fernández-Pérez C, Martín-Sánchez FJ. Effect of milk and other dairy products on the risk of frailty, sarcopenia, and cognitive performance decline in the elderly: A systematic review. Adv Nutr. 2019;10 (suppl_2):S105–19.

9. Singh GM, Micha R, Khatibzadeh S, et al. Global, regional, and national consumption of sugar-sweetened beverages, fruit juices, and milk: a systematic assessment of beverage intake in 187 countries. PLoS One. 2015;10(8):e0124845.
10. Dewiasty E, Setiati S, Agustina R, Roosheroe AG, Abdullah M, Istanti R, de Groot LC. Prevalence of lactose intolerance and nutrients intake in an older population regarded as lactase non-persistent. Clin Nutr ESPEN. 2021; 43:317-21.
11. Ada YR, Musfiroh M, Priyo D, Wiyono VH. [Gambaran kemandirian ekonomi pada lansia. Placentum Jurnal Ilmu Kesehatan dan Aplikasinya]. 2019:7(2):16-23.
12. Kementerian Kesehatan RI. [Juknis Instrumen pengkajian paripurna pasien geriatri (P3G)]. Jakarta: Kementerian Kesehatan Republik Indonesia (The Indonesian Ministry of Health); 2017.
13. Fatmah F. Diagnostic test of predicted height model in Indonesian elderly: a study in an urban area. Med J Indones. 2010;19(3):199e204.
14. Wijnhoven HAH, van Bokhorst-de van der Schueren MAE, Heymans MW, et al. Low mid-upper arm circumference,calf circumference, and body mass index and mortality in older persons. J Gerontol Ser A. 2010;65A (10):1107e14.
15. Charrondiere UR, Stadlmayr B, Haytowitz D, Oseredczuk M, Ireland J, Wolmarans P, Rittenschober D, Selley B, Puwastien P, Reykdal Ó. FAO/INFOODS guidelines for checking food composition data prior to the publication of a user table/database version 1.0. Rome: Food and Agriculture Organization of the United Nations; 2012.
16. Nguyen Bao KL, Sandjaja S, Poh BK, et al. The consumption of dairy and its association with nutritional status in the south east Asian nutrition surveys (SEANUTS). Nutrients. 2018;13;10(6):759.
17. [Angka Kecukupan Gizi yang Dianjurkan untuk Masyarakat Indonesia. Permenkes Nomor 28 Tahun 2019]. The Indonesian Ministry of Health Regulation no.28, 2019.
18. Slater B, Fisberg DLMR. Estimating prevalence of inadequate nutrient Intake. Rev Saude Publica. 2003;38(4):1-6.
19. Roman Viñas B, Ribas Barba L, Ngo J, Gurinovic M, Novakovic R, Cavelaars A, de Groot LC, van't Veer P, Matthys C, Serra Majem L. Projected prevalence of inadequate nutrient intakes in Europe. Ann Nutr Metab. 2011;59:84–95.
20. Institute of Medicine. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington DC: The National Academies Press; 1998.
21. Setiati S, Harimurti K, Dewiasty E, et al. Profile of food and nutrient intake among Indonesian elderly population and factors associated with energy intake: a multi-centre study. Acta Medica Indones. 2013;45(4):265–74.
22. Ribeiro AG, Mill JG, Cade NV, Velasquez-Melendez G, Matos SMA, Molina MDCB. Associations of dairy intake with arterial stiffness in Brazilian adults: the Brazilian longitudinal study of adult health (ELSA-Brasil). Nutrients. 2018;10(6):701.
23. Ong S, Woo J, Parikh P, et al. Addressing nutritional requirements of ageing consumers in Asia-recommendations from an expert workshop. Asia Pac J Clin Nutr. 2019;28(2):204-13.
24. Best RL, Appleton KM. The consumption of protein-rich foods in older adults: an exploratory focus group study. J Nutr Educ Behav. 2013;45:751-5.
25. Ubrežiová I, Urbánová M, Kozáková J, Kráľová T. Gender differences in consumer preferences when buying dairy products in Slovakia and Russia. Potr S J F Sci. 2019;1(13):720-29. https://doi.org/10.5219/
26. Lukito W, Malik SG, Surono IS, Wahlqvist ML. From "lactose intolerance" to "lactose nutrition." Asia Pac J Clin Nutr. 2015;24 Suppl 1: S1-8.
27. Wolfe RR. Update on protein intake: importance of milk proteins for health status of the elderly. Nutr Rev. 2015;73(1):41–7.
28. ter Borg S, Verlaan S, Hemsworth J, et al. Micronutrient intakes and potential inadequacies of community-dwelling older adults: a systematic review. Br J Nutr. 2015;113(8):1195–206.
29. Volkert D, Beck AM, Cederholm T, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr. 2019;38(1):10-47.
30. Warzecha M, Czerwinski E. Calcium consumption in diet of elderly patients- literature review. Post N Med. 2016; 29(10):777-80.
31. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. Nutr J. 2010;8(9):65.
32. Nugroho P, Lydia A, Suhardjono S, Harimurti K. Association of BsmI polymorphisms in the vitamin D receptor gene among Indonesian population with diabetic kidney disease. Acta Med Indones. 2021;53(2):149-55.
33. Watanabe F, Yabuta Y, Bito T, Teng F. Vitamin B12-containing plant food sources for vegetarians. Nutrients. 2014;6(5):1861–73.
34. Godos J, Tieri M, Ghelfi F, et al. Dairy foods and health: an umbrella review of observational studies. Int J Food Sci Nutr. 2020;71(2):138-51.
35. Schwingshackl L, Hoffmann G, Lampousi AM, et al. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. Eur J Epidemiol. 2017;32(5):363-75.
36. Lordan R, Tsoupras A, Mitra B, Zabetakis I. Dairy fats and cardiovascular disease: do we really need to be concerned? Foods. 2018;7(3):29.
37. Grosso G. Dairy in human health and disease across the lifespan. Philadelphia: Elsevier Inc; 2017. p. 385-93.
38. van Staveren WA, Steijns JM, de Groot LC. Dairy products as essential contributors of (micro-) nutrients in reference food patterns: an outline for elderly people.

J Am Coll Nutr. 2008;27(6):747S-54S.
39. Hoes AW, Grobbee DE. Clinical epidemiology: principles, methods, and applications for clinical research. Sudbury: Jones and Bartlett Publishers; 2009.

Accuracy of Bedside Lung Ultrasound in Emergency (BLUE) Protocol to Diagnose the Cause of Acute Respiratory Distress Syndrome (ARDS): A Meta-Analysis

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ABSTRACT

Background**:** *There is a stigma that ultrasound cannot be used to see abnormalities in the air-filled organs makes ultrasound rarely used to identify lung abnormalities. This study purpose comparing diagnostic accuracy of BLUE protocol with gold standard for each diagnosis causing acute respiratory failure.* ***Methods*****:** *Systematic search was done in 6 databases (Pubmed/MEDLINE, Embase, Cochrane Central, Scopus, Ebscohost/CINAHL dan Proquest) and multiple grey-literature sources for cross-sectional studies. We manually extracted the data from eligible studies and calculated pooled sensitivity, pooled specificity, likelihood ratio (LR) and diagnostic odds ratio (DOR). We follow PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline throughout these processes.* ***Results*****:** *Four studies has been picked from total 509 studies involved. The results yield parameters indicating BLUE protocol as a reliable modality to diagnose pneumonia with pooled sensitivity 84% (95% CI, 76-89%), pooled specificity 98% (95% CI, 93-99%), LR+ 42 (95% CI, 12-147), LR- 0.12 (95% CI, 0.07-0.2) and DOR 252 (95% CI, 81-788), respectively. It also considerably applicable to diagnose pulmonary oedema with pooled sensitivity 89% (95% CI, 81-93%), pooled specificity 94% (95% CI, 89-96%), LR+ 14 (95% CI, 8-25), LR- 0.165 (95% CI, 0.11-0.24), and DOR 116 (95% CI, 42-320), respectively.* ***Conclusion*****:** *BLUE protocol has good diagnostic accuracy to diagnose pneumonia and pulmonary oedema. We recommend implementing BLUE protocol as a tool in evaluating cause of ARF.*

Keywords**:** *Ultrasonography, BLUE protocol, Accuracy, Respiratory Failure, Meta-analysis*

INTRODUCTION

Dyspnea is a common symptom and is an important sign of acute respiratory failure (ARF). This condition is a life-threatening situation and it is not uncommon for patients with ARF to require intensive oxygen therapy such as a mechanical ventilator. The case of ARF continues to increase every year with a mortality rate reaching 37%. Determining the cause of respiratory failure is an important step in the management of ARF.[1-3]

The BLUE (Bedside Lung Ultrasound in Emergency) protocol is an ultrasound examination algorithm of the lung to assist in searching for the diagnosis of various lung disorders by combining various artefacts.[4-9] The accuracy of the BLUE protocol reaches 90.5% with a duration of approximately 3 minutes, so this Protocol very suitable for use in patients with ARF. However, the stigma that ultrasound cannot be used to see abnormalities in the air-filled organs makes ultrasound rarely used to identify lung abnormalities.[9-10]

Through this meta-analysis, the authors are going to assess several previous studies regarding the accuracy of the BLUE Protocol in diagnosing pulmonary disorders. With prompt and precise diagnosis, appropriate management for the patient can also be achieved. This study aims to determine the accuracy of the BLUE protocol in diagnosing the causes of ARF.

METHODS

Search Strategy

A comprehensive search was carried out from six online databases namely Pubmed/ MEDLINE, Embase, Cochrane Central, Scopus, Ebscohost/CINAHL, and Proquest on 6-13 September 2020 . The search is performed with a combination of keywords based on MESH and text word combined with the Boolean operator. The keywords used come from the Population and Index Test components of the research questions that have been formulated. The keyword used from the Population component is Acute Respiratory Failure with its synonym and examples of the diagnosis of the cause of respiratory failure. The keyword used in the Index Test component is the BLUE protocol or Bedside Lung Ultrasound in Emergency. A manual search for grey-literature was carried out at various sources on September 7, 2020. The search was carried out on several portals, namely the GARUDA portal (Indonesia Ministry of Research and Technology Portal), Proquest (focus on thesis results, dissertations, scientific posters, or proceeding books), abstracts from the scientific book Jakarta International Chest and Critical Care Internal Medicine (JICCIM) in the last 5 years, snowballing method, the repository of the Library of the University of Indonesia and the National Library as well as the Global Index Medicus (GIM).

Study Selection

Inclusion criteria are diagnostic studies with a cross-sectional design, study subject age > 18 years, and comparing the diagnostic ability of the BLUE protocol with the gold standard. No language or year limits were applied. Exclusion criteria were studies that didn't include data to calculate overall accuracy. The assessment of risk of bias and study quality was carried out by APA dan CWP. If there are differences of opinion regarding the selection criteria of an article, it will be resolved through consensus and reviewed by KH. The authors use the Covidence® software to assist in the selection stages of articles in this meta-analysis.

Ethics Approval and Consent to Participate

PROSPERO Systematic Review Registry number: CRD42020203208.

BLUE Protocol Method

Bedside lung ultrasound examination was introduced by Dr. Lichtenstein in 1989 to monitor critically ill patients in ICU setting. It has been widely used for detecting many lung disorders such as pleural effusion, pulmonary oedema, pneumothorax, pneumonia, and pulmonary embolism. He formulized the lung ultrasound findings into one framework called BLUE Protocol and become one of the most important parts of Point of Care Ultrasound (POCUS). In BLUE Protocol, patients were positioned in semi recumbent or supine position. Scans were done longitudinally and evaluated based on artefacts finding on some certain anatomical landmarks. The normal

lung is characterized by normal A or B Line with lung sliding. BLUE Protocol also evaluate the presence of alveolar consolidation and/or pleural effusion.[10] Details of the BLUE protocol's component is shown in **Figure 1**.

Data Extraction and Quality Assessment

Data extraction was carried out independently by two researchers. Basic characteristics data such as name of the principal investigator, type of study, place/country, year of publication, basic demographic characteristics of study subjects, population eligibility, eligibility of the gold standard used, sample size, characteristics of the ultrasound device, The characteristics of the ultrasound operator, duration of lung ultrasound, blinding, and comparison of outcomes from selected studies will be displayed in the form of a descriptive table. The output is written in a 2x2 table form and is displayed in terms of sensitivity and specificity. The performance of the BLUE protocol is displayed in the form of a receiver operating characteristic (ROC) curve. Assessment of the quality and risk of bias of selected studies was carried out using the Quality Assessment of Diagnostic Accuracy Study - 2 (QUADAS - 2).

Data Synthesis and Statistical Analysis

Statistical analysis on this meta-analysis was performed using RevMan software version 5.4 (Cochrane Collaboration, the Nordic Cochrane Center, Copenhagen) and STATA 14. The results of data analysis are presented in the form of a forrest plot if meta-analysis can be done. Heterogeneity assessed using I^2 or X^2 test with result of I^2 <25%, 26-50%, and >50% reflecting low or insignificant, moderate, and significant heterogeneity, respectively. Fixed-effect model was chosen for insignificant heterogeneity, otherwise random-effect model was used. The expected results are in the form of accuracy, sensitivity, and specificity along with the confidence interval, likelihood ratio, diagnostic odds ratio, and the area under the ROC curve. The analysis was carried out in the form of an accumulation of all diagnoses and then continued with the analysis of each diagnosis.

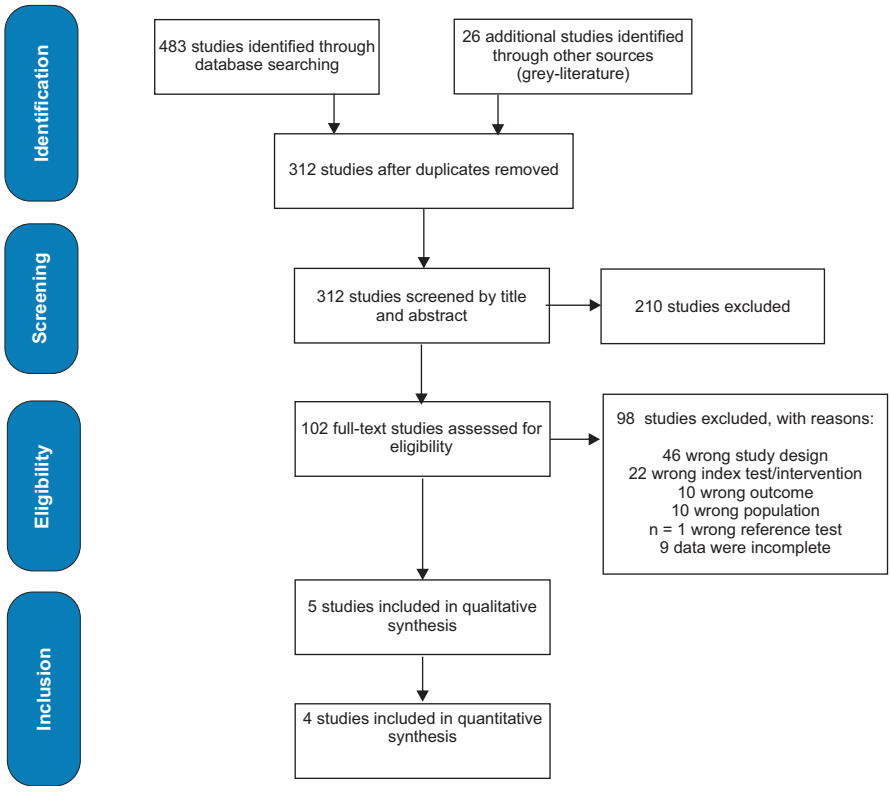


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram for Study Selection

RESULTS

Literature search

Based on the systematic search carried out, a total of 509 articles were obtained and after adjusting for the eligibility criteria only 4 studies could be continued for the meta-analysis process (**Figure 1**).

Study Characteristics

In general, these studies classified as homogenous because most of the important characteristics were almost the same such as population eligibility, the unit site of the study, BLUE protocol implementation, ultrasound device/specification, gold standard used, and the presented output (**Table 1** and **2**). The unit/site used for Lichtenstein, Neto, and Danish study is the ICU whereas Patel and Bekgoz study takes place at the ER. The ICU and ER has almost the same characteristics, both taking care patient with breathing problem which life-threatening cases and require immediate care. From the origin of the country of the study, the findings from this meta-analysis could represent various types of major populations in the world.[11-14]

The population eligibility used by the five studies is almost the same which is patients with breathing problem and admitted into the criteria of breathing failure with indication intensive care. Patel's research used population age above 12 years which is different from the other four studies which used adult population. The author had sent email correspondence on requisition for research data by Patel et al. however, to the date of this report is finished, the author had not received any reply therefore the author excluded Patel et al. research in both qualitative and quantitative synthesis. However, the author tried to include Patel et al research in sensitivity analysis to see if its exclusion from this research would produce significant output relative to the findings of this meta-analysis. The total samples used in the 4 studies is 770 patients.

There is a difference in the ultrasound operator which performs the BLUE protocol. In the Lichtenstein, Bekgoz, and Danish studies, they used certified ultrasound operators with 2 years minimum experience on lung ultrasound. Neto et al used ultrasound operators who had received 5 hours theoretical training and performed 10 times lung ultrasound under supervision. The probes used in the five studies have similar characteristics, they are the probes with low frequency (curvilinear and microconvex) which frequency range 2-6 MHz. Low-frequency probes is the best option for lung ultrasound because it has broader and deeper exploration area than high-frequency probes.[11-14].

Assessment of Risk of Bias

Two reviewers (O.D.A and A.P.A) evaluate the methodological quality of included studies according to Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) criteria. The assessment shown in **Figure 2**. Any discrepancies found would be resolved by consultation with the third expert reviewer (K.H).

Data synthesis and analysis

The results of t he included studies can be seen in **Table 3**. From all of the studies, it was found that the sensitivity of the BLUE protocol in diagnosing pneumonia was in the range of 83% to 97% with the combined sensitivity calculation being 84% (95% CI 76-89%). Whereas the specificity of the BLUE protocol in diagnosing pneumonia was in the range of 86% to 100% with the combined specificity calculation was 98% (95% CI 93-99%). Forest plot for pneumonia can be seen in **Figure 3** and summary receiving operating characteristic (SROC) curve can be seen in **Figure 4**. The combined result of LR + is 42 (95% CI 12-147) and and LR- 0.12 (95% CI 0.07–0.2) respectively with DOR of 252 (95% CI 81–788).

In diagnosing pulmonary edema, the sensitivity of the BLUE protocol was found to be in the range of 76% to 94% with a combined sensitivity calculation of 89% (95% CI, 81-93%). Meanwhile, the specificity of the BLUE protocol in diagnosing pneumonia is in the range of 90% to 100% with the calculation of the combined sensitivity is 94% (95% CI, 89-96%). The combined results for LR+ were 14 (95% CI, 8-25) and LR- 0.165 (95% CI, 0.11-0.24), respectively, with a DOR number of 116 (95% CI, 42-320). Forest plot for pulmonary edema can be seen in **Figure 5** and summary receiving operating characteristic (SROC) curve can be seen in **Figure 6**.

Table 1. Study Characteristics.

Study	Year	Country	Unit	Study Design	Number of Patients	Inclusion Criteria	Mean Age	Ultrasound Operator	Ultrasound Device	Number of Area	Blinded
Lichtenstein et al[11]	2008	France	ICU	Cross sectional	260	adult patients with acute respiratory failure	68	Investigators (several years of experience)	Microconvex probe 5-MHz (Hitachi-405; Hitachi Medical; Tokyo, Japan)	6 points	No, investigators were not blinded to the patient's clinical presentation
Neto et al[12]	2015	Brazil	ICU	Cross sectional	37	age ≥ 18 years and admission to the ICU for ARF, defined by one of the following: a respiratory rate ≥ 30 breaths/ min; a PaO2 ≤ 60 mmHg; an oxygen saturation on room air ≤ 90%, as measured by pulse oximetry; or a carbon dioxide tension (PCO2) ≥ 45 mmHg with an arterial pH ≤ 7.35	73.2	Newly trained operators (attending 5 hours of theoretical training and performing 10 supervised LUS examinations)	Curvilinier Probe 3-5 MHz (Toshiba Tosbee; Toshiba, Tokyo, Japan)	6 points	Yes
Patel et al[15]	2018	India	ER	Cross sectional	50	Patients having age >12 years, Patients and/or relatives giving informed consent, Patients of acute respiratory distress requiring ICU admission were included.	59.64	Ultrasound was performed in emergency department by same emergency physician	Curvilinier (2-5 MHz) and Linear probe (5-10 MHz), Micromax ultrasound system, Sonosite	6 points	No
Bekgoz et al[13]	2019	Turkey	ER	Cross sectional	383	All consecutive patients aged >18 years admitted to the ED with a primary complaint of acute dyspnea and who consented to paricipate	65.5	LUS was conducted by 5 ED physicians who had been previously certified by basic and advanced US education and had at least 2 years of ED and US experience. These ED physicians were also informed by 2 h of theoretical lectures regarding LUS and the BLUE protocol. They also performed 10 supervised LUS examinations according to the BLUE protocol	Microconvex probe 2-6 MHz (Fujifilm Fazone CB, Japan)	4 points	Yes
Danish et al[14]	2019	India	ICU	Cross sectional	90	Adult patients admitted to medical-surgi- cal ICU who had evidence of lung pathology as demonstrated by an acute lung injury (ALI) score of ≥1	47.66	The intensivist performing LUS had >2 years of experience in performing LUS	Curvilinier Probe (2-5 MHz) SonoSite M-turbo (Fujifilm SonoSite Inc., Bothell, WA, USA)	3 points	Yes

Table 2. Gold Standards Used in Included Studies.

	Lichtenstein et al[11]	Neto et al[12]	Patel et al[15]	Bekgoz et al[13]	Danish et al[14]
Pneumonia	Infectious profile, radiologic asymmetry, microorganism isolated (blood, invasive tests), recovery with antibiotics. Included were infectious, aspiration, community, or hospital-acquired pneumonia. Pneumonia complicating chronic respiratory disease was classified as pneumonia	Not stated	Infectious profile, radiologic asymmetry, microorganism isolated (blood), recovery with antibiotics	infection findings, chest X-rays, microorganism isolation (if possible), CT (if necessary)	Not stated
Pulmonary Edema	Evaluation of cardiac function using echocardiography, functional tests, and American Heart Association recommendations	Not stated	Chest radiography, evaluation of cardiac function using echocardiography, responding to diuretics	electrocardiography, cardiac biomarkers echocardiography (by a cardiologist)	Not stated
Pneumothorax	Radiography (CT if necessary)	-	Chest radiography (CT if necessary)	Chest X-rays and CT (if necessary)	Not stated
Pulmonary Embolism	Helical CT	-	Helical CT	Thorax CT angiography	-
Asthma/COPD	Asthma (History, responds to bronchodilator treatment) COPD (Condition defined as exacerbation of chronic respiratory disease without pneumonia, pneumothorax, pulmonary edema, pleurisy, or pulmonary embolism. COPD was confirmed by functional tests.)	Not stated	History, responds to bronchodilator treatment, chest radiography, and COPD was confirmed by functional tests	History, respiratory functional tests, and responses to bronchodilator treatment	-
For all patients	History, clinical examination, radiography read by radiologists, CT when available, favorable clinical progression under treatment	The final diagnosis of the episode of ARF made by the ICU team before patients were discharged from the ICU was considered the gold standard	For all patients: History, clinical examination, basic blood tests and specific blood investigations (arterial blood gas analysis, D-dimer), electrocardiography, radiography reporting by radiologists, CT as needed, favorable clinical progression under treatment was followed along with	The final clinical diagnosis was made by attending emergency physicians (for 215 ED patients before discharge from the ED), attending consultant physicians (for 126 hospitalized patients before discharge from the hospital), and an ICU team (for 46 ICU patients before discharge from the ICU)	Thorax CT scan

Table 3. Results of Included Studies

	Lichtenstein et.al[11]		Neto et.al[12]		Patel et.al[15]		Bekgoz et.al[13]		Danish et.al[14]	
	Sn (%)	Sp (%)	Sn (%)	Sp (%)	Sn (%)	Sp (%)	Sn (%)	**Sp (%)**	**Sn (%)**	**Sp (%)**
Pneumonia	89	94	88	90	94.11	93.93	82	98	75.9	100
Pulmonary Edema	97	95	85	87	92.3	100	87	97	83.3	88.5
Pneumothorax	88	100	-	-	80	100	85	100	88.9	100
Pulmonary Embolism	81	100	-	-	100	100	46.2	100	-	-
Asthma/ COPD	89	97	67	100	85.17	88.88	96	75	-	-

Table 4. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) of Each Outcome[16]

GRADE Recommendations for BLUE Protocol Accuracy by Each Outcomes					
GRADE Domain	**Pneumonia (4 cross-sectional studies)**	**Pulmonary Edema (4 cross-sectional studies)**	**Pneumothorax (3 cross-sectional studies)**	**Pulmonary Emboly (2 cross-sectional studies)**	**Asthma/COPD (3 cross-sectional studies)**
Risk of Bias	None	None	None	None	None
Inconsistency	None	None	None	Serious (-1)	Serious (-1)
Indirectness	None	None	None	None	None
Imprecision	None	None	Serious (-1)	Serious (-1)	Serious (-1)
Publication Bias	None	None	Serious (-1)	Serious (-1)	Serious (-1)
Certainty of Evidence	⊕⊕⊕⊕	⊕⊕⊕⊕	⊕⊕◯◯	⊕◯◯◯	⊕◯◯◯
Results					
Sensitivity	84%	89%	71-89%	46-81%	50-98%
Specificity	98%	94%	100%	99-100%	69-100%

⊕⊕⊕⊕	High certainty (we are very confident that the true effect lies close to that of the estimate of the effect)
⊕⊕⊕◯	Moderate certainty (we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)
⊕⊕◯◯	Low certainty (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect)
⊕◯◯◯	Very low certainty (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

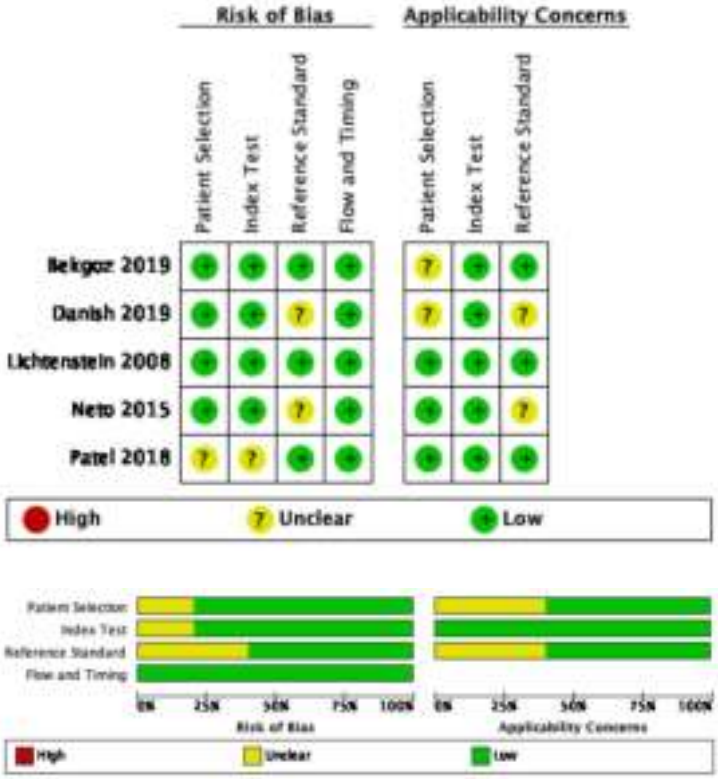
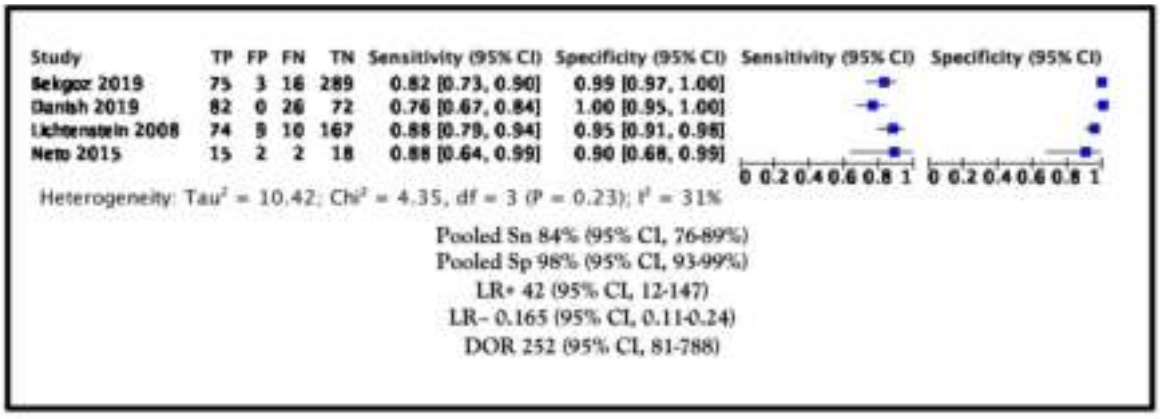


Figure 2. Quality of Assessment of Included Studies by QUADAS-2 Tool.



CI = *confidence interval*; DOR = *diagnostic odds ratio*; FN = *false negative*; FP = *false positive*; LR+ = *Positive likelihood ratio*; LR- = *Negative likelihood ratio*; Sn = *Sensitivity*; Sp = *Specificity*; TN = *true negative*; TP = *true positive*

Figure 3. Forest Plot and Diagnostic Accuracy of BLUE Protocol for Pneumonia.

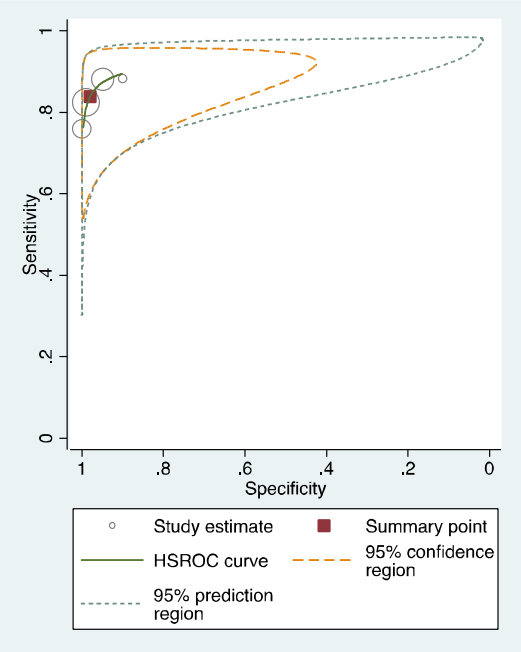
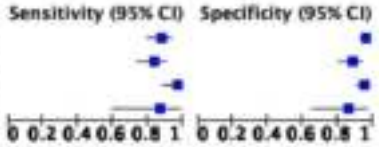


Figure 4. Summary Receiving Operating Characteristic Curve of BLUE Protocol for Pneumonia

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bekgoz 2019	85	11	12	275	0.88 [0.79, 0.93]	0.96 [0.93, 0.98]
Danish 2019	70	11	14	85	0.83 [0.74, 0.91]	0.89 [0.80, 0.94]
Lichtenstein 2008	62	9	2	187	0.97 [0.89, 1.00]	0.95 [0.91, 0.98]
Neto 2015	13	3	2	19	0.87 [0.60, 0.98]	0.86 [0.65, 0.97]



Heterogeneity: Chi^2 = 5.65, df = 3 (P = 0.13); I^2 = 47%

Pooled Sn 89% (95% CI, 81-93%)
Pooled Sp 94% (95% CI, 89-96%)
LR+ 14 (95% CI, 8-25)
LR- 0.12 (95% CI, 0.07-0.2)
DOR 116 (95% CI, 42-320)

CI = *confidence interval*; DOR = *diagnostic odds ratio*; FN = *false negative*; FP = *false positive*; LR+ = *Positive likelihood ratio*; LR- = *Negative likelihood ratio*; Sn = *Sensitivity*; Sp = *Specificity*; TN = *true negative*; TP = *true positive*

Figure 5. Forest Plot and Diagnostic Accuracy of BLUE Protocol for Pulmonary Edema

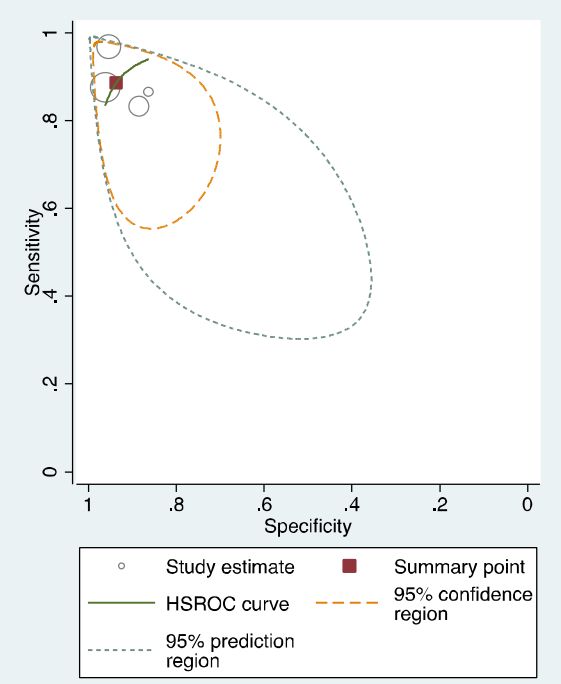
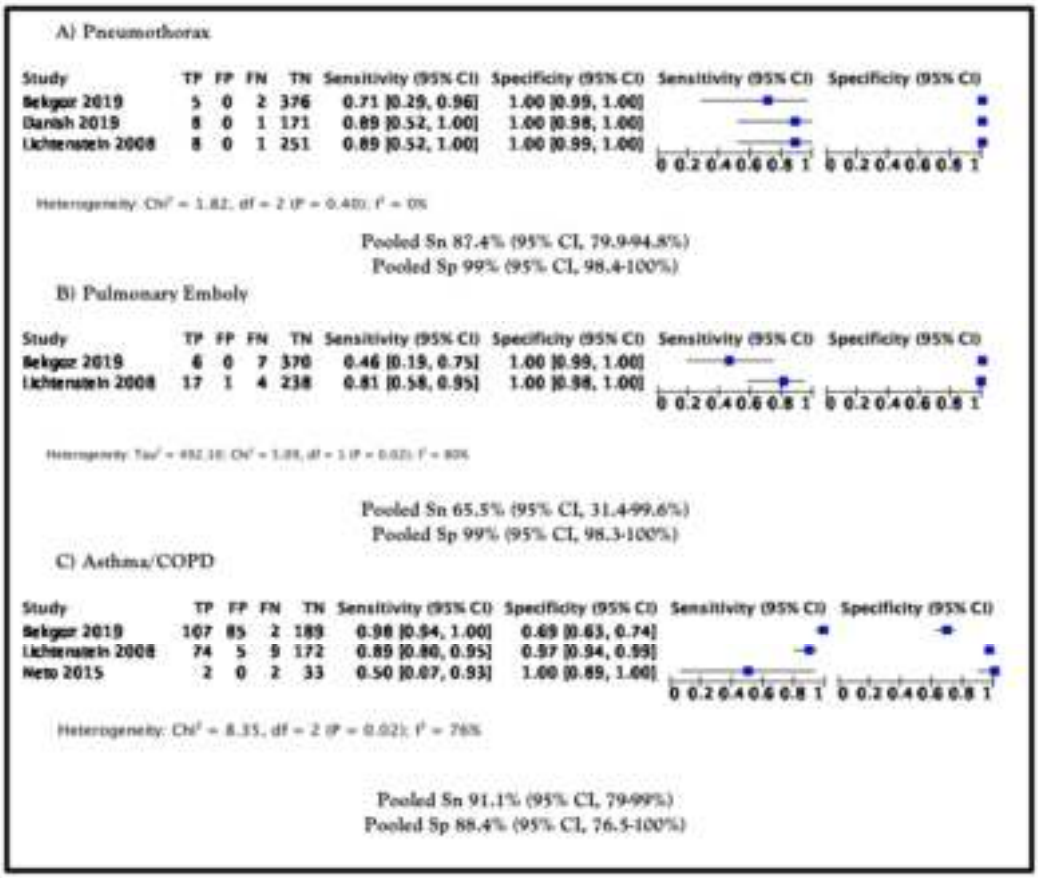


Figure 6. Summary Receiving Operating Characteristic Curve of BLUE Protocol for Pulmonary Edema



CI = *confidence interval*; FN = *false negative*; FP = *false positive*; Sn = *Sensitivity*; Sp = *Specificity*; TN = *true negative*; TP = *true positive*

Figure 7. Forest Plot and Diagnostic Accuracy of BLUE Protocol for Pneumothorax, Pulmonary Emboly, Asthma/COPD

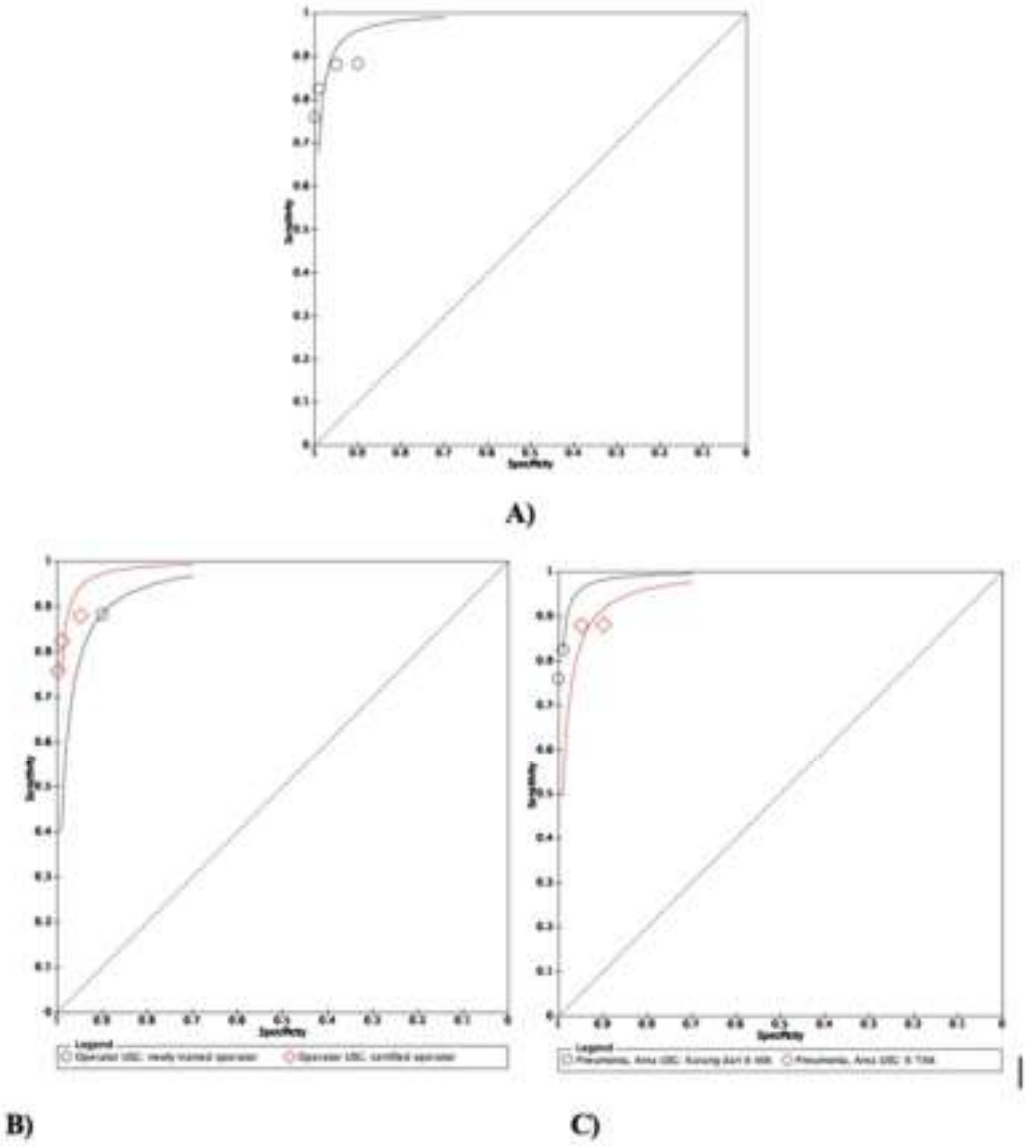


Figure 8. Area Under Curve (AUC) BLUE Protocol for A) Pneumonia B). Subgroup Analysis: Ultrasound Operator C) Subgroup Analysis: Number of Ultrasound Zone.

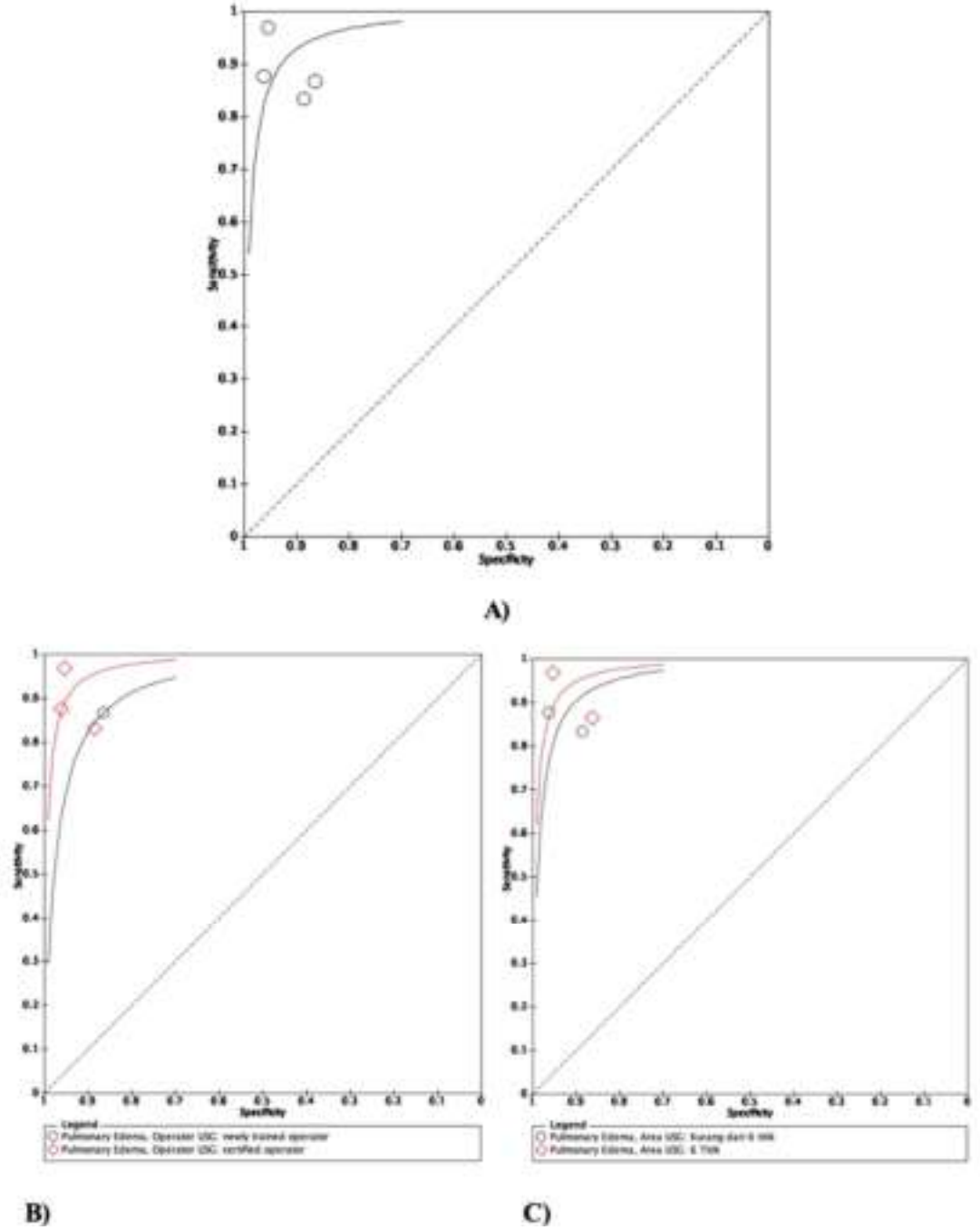


Figure 9. Area Under Curve (AUC) BLUE Protocol for A) Pulmonary Edema B) Subgrup Analysis: Ultrasound Operator C) Subgroup Analysis: Number of Ultrasound Zone.

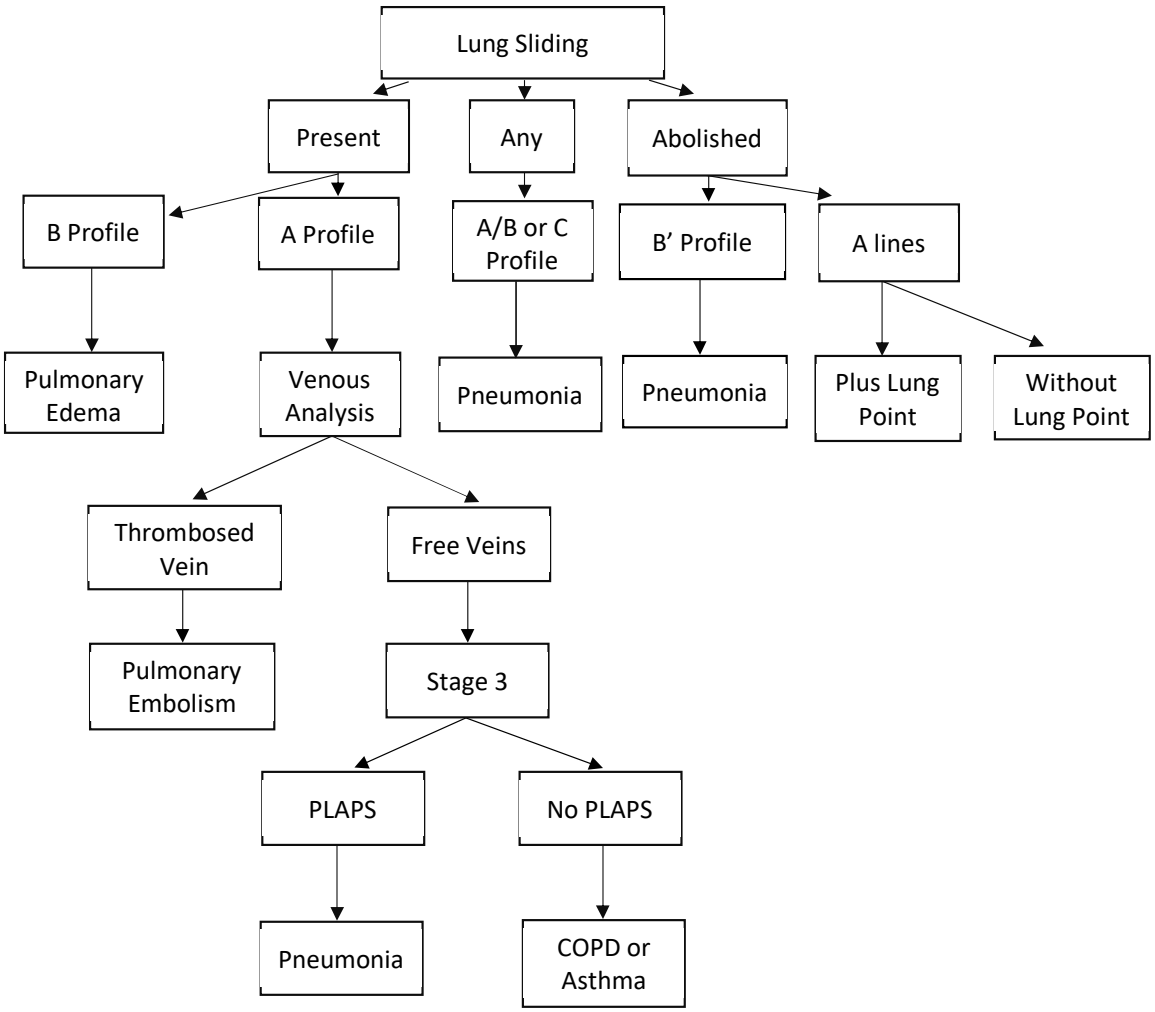


Figure 10. BLUE Protocol Alghoritm

Not all studies have examined every diagnosis used by Lichtenstein as the original author of the BLUE protocol. The sensitivity and specificity ranges of the BLUE protocol in pneumothorax are 71-89% and 50-98%, in pulmonary emboli it ranges from 46-81% and 100%, and in asthma/COPD ranges from 50-98% and 69-100%, respectively. Forest plot for pneumothorax, pulmonary emboli, and asthma/COPD can be seen in **Figure 7**.

DISCUSSION

Several meta-analyses on the roles of lung ultrasound for diagnosing lung abnormalities had been conducted by previous researchers. The author recorded that there are at least 4 meta-analysis with lung ultrasound topics in diagnosing pneumonia. The main difference of this meta-analysis with previous study is in the population. This study enrolled all patients with breathing problems whereas the previous 4 meta-analysis studies specifically enrolled population suspected with pneumonia. During the search process, the authors found 14 original studies that discussed the accuracy of BLUE protocol but among them, there were 9 studies in the form of gray-literature that could not be included in the analysis because there was no complete text. Another limitation is that there are studies that did not include findings of pleural effusions. The discovery of a pleural effusion may guide the diagnosis of pulmonary disorders.[32-35] In addition, the intervention/index test used by those meta-analysis studies were not standardized, whereas this study specified the assessment on the accuracy of the BLUE Protocol. However, the

accuracy of this 4 meta-analyses are nearly even with current study. The range of sensitivity and specificity of the lung ultrasound in pneumonia diagnosis by meta-analysis conducted by Chavez et al. is 80-95%, Ye et al., Long et.al, Llamas-Alvarez et al. is 70-96%, consecutively.[7, 15-17]

Three of five studies analyzed by this study included the operator who didn't know the patient's clinical and still produce good accuracy because the ultrasound output is objective. Ultrasound accuracy might be better if it is adjusted with patient's clinical examination data. History taking and physical examination is mandatory and irreplaceable. Lung ultrasound is complimentary of history taking and physical examination to enhance the physician's diagnosis probability. A study in Italy by Peris et al. shows that lung ultrasound could reduce the need for thorax X-Ray imaging by 26% and thorax CT scan by 47%.[1, 28-31]. We use GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to summarize our recommendations. Summary of this approach for this meta-analysis is shown in **Table 4**.[36]

In sensitivity analysis calculation, the author included Patel et al. study and compared it to the analysis results without Patel et al. The author analyzed the accuracy of pneumonia diagnosis using the 5 studies in total and obtained the aggregate sensitivity 85% (95%CI 78-90%), specificity 97% (95%CI 93-99%), LR positive 34 (95%CI 12-94%), LR negative 0.15 (95%CI 0.1-0.23%) and the DOR 222 (95%CI 89-554%). These findings is not much different with the findings of the 4 studies which qualified the inclusion criteria presented in this paper.[14]

The sensitivity of the BLUE Protocol for pulmonary emboli and asthma/COPD has varied range from 46% to 98%. This inconsistent result might be caused by the BLUE Protocol algorithm to diagnose lung emboli and asthma/COPD which is based on exclusion criteria and it needs to be confirmed with emboli findings in extremity's vein. Performing ultrasound on the extremity's vein requires a skilled operator and longer ultrasound procedure. From the date, the author did not recommend lung ultrasound to screen asthma/COPD or lung emboli, but if emboli was found in the vein extremities and no lung image abnormality in any case this might lead to emboli diagnosis. This is also found in pneumothorax cases which image shows the loss of lung sliding and the presence of lung point and barcode sign which is specifically found in pneumothorax.[18-20] The ultrasound area used in the five studies is almost the same except in the study by Danish et al. and Bekgoz et al. Lichtenstein et al., Neto et al., and Patel et al., in performing lung ultrasound at 6 points of each hemithorax, therefore, resulted 12 examined points in total. Danish et al. performed lung ultrasound at 3 points of each hemithorax and the total is 6 points and Bekgoz et al. performed it at 4 points and the total is 8 points of all lung areas. This variability might explain the lower sensitivity value of pneumonia and lung edema in the research by Danish et al. and Bekgoz et al. when compared to other researches. Lung edema yield better AUC value in 6 points examination of each hemithorax (**Figure 8** and **9**). This is slightly different on pneumonia which shows that the lung ultrasound at 6 locations did not any better than 3 or 4 locations.[11-15]

The four studies also show that the lung ultrasound can be performed within the first 20 minutes when the patient is admitted to the intensive unit or emergency unit without any necessary interruption to the standard procedure because the duration of the examination is brief and performed beside the patient's bed. Lichtenstein et al. and Bekgoz et al. only need less than 3-5 minutes, sequentially to complete the BLUE protocol. The lung ultrasound can be performed while other medic or paramedic doing other procedures. For any patient who needs advanced breathing support, lung ultrasound can also be performed right after the procedure without having to remove the patient to radiology unit.[21-23]

Operator bias tends to be found in ultrasound examination. Subgroup analysis with operator competence as a variable showed an experienced and certified operator yield better accuracy than newly trained operators, in both groups. However, the accuracy level of newly trained operators is considerably good in both groups. The operator in Neto et al. research is a rookie doctor in lung ultrasound who received 5 hours BLUE

protocol theoretical training and performed 10 lung ultrasounds under supervision. The research shows sensitivity 85-88% and specificity 87-90% to detect lung edema and pneumonia. Certain shows that the BLUE protocol can be learned in relatively short time by any doctor who possesses basic knowledge of ultrasound. It is feasible for any on-duty doctor in intensive or emergency unit to be trained with BLUE protocol to help them manage patients with acute breathing problem (**Figure 8** and **9**). The study to assess the time needed training duration could be the subject for future research.[24-27]

CONCLUSION

In conclusion, the BLUE protocol has high sensitivity and specificity in diagnosing pneumonia and pulmonary edema. These high diagnostic accuracy values came from a good quality study based on the GRADE approach. The BLUE protocol has high specificity in diagnose pneumothorax and pulmonary embolism but with varying sensitivity. This accuracy assessment comes from a poor-quality study based on the GRADE approach.

ABBREVIATION

BLUE	Bedside Lung Ultrasound in Emergency
ARF	Acute Respiratory Failure
LR	Likelihood Ratio
DOR	Diagnostic Odds Ratio
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
JICCIM	Jakarta International Chest and Critical Care Internal Medicine
GIM	Global Index Medicus
ROC	Receiver Operating Characteristic
QUADAS - 2	Quality Assessment of Diagnostic Accuracy Study - 2
ICU	Intensive Care Unit
ER	Emergency Room
SROC	Summary Receiving Operating Characteristic
COPD	Chronic Obstructive Pulmonary Disease
AUC	Area Under Curve
GRADE	Grading of Recommendations, Assessment, Development and Evaluations

COMPETING INTERESTS

The authors declare that there is no competing interest.

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AUTHORS' CONTRIBUTIONS

ODA is the chief principle of the study and also the coordinator of the Study. ODA, CWP, VW conceived the Idea and developed the theory and design of the study. KH help to finalize the study conception and design, verified the analytical method and supervised the analytical calculation ODA and APA carried out the data collection and analyze the result. CWP and VW review the data collection and gave revision regarding interpretation of the data. ODA, APA and KH made draft manuscript preparation.All authors reviewed the results and approved the final version of the manuscript.

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REFERENCES

1. Peris A, Tutino L, Zagli G, et al. The use of point-of-care bedside lung ultrasound significantly reduces the number of radiographs and computed tomography scans in critically ill patients. Anesth Analg 2010;111.
2. Zanobetti M, Scorpiniti M, Gigli C, et al. Point-of-care ultrasonography for evaluation of acute dyspnea in the ED. Chest. 2017;151.
3. Cochi SE, Kempker JA, Annangi S, et al. Mortality trends of acute respiratory distress syndrome in the United States from 1999 to 2013. Ann Am Thorac Soc. 2016;13.

4. Lichtenstein DA. Lung ultrasound in critically ill. Ann Intensive Care. 2014;30.
5. Leidi A, Rouyer F, Marti C, et al. Point of care ultrasonography from the emergency department to the internal medicine ward: current trends and perspectives. Intern Emerg Med. 2020;15.
6. Silva S, Biendel C, Ruiz J, et al. Usefulness of cardiothoracic chest ultrasound in the management of acute respiratory failure in critical care practice. Chest. 2013;144.
7. Chavez MA, Shams N, Ellington LE, et al. Lung ultrasound for the diagnosis of pneumonia in adults: A systematic review and meta-analysis. Respir Res. 2014;15.
8. Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med. 2012;38.
9. Vignon P, Repessé X, Vieillard-Baron A, et al. Critical care ultrasonography in acute respiratory failure. Crit Care. 2016;20.
10. Lichtenstein D. Lung ultrasound in acute respiratory failure an introduction to the BLUE-protocol. Minerva Anestesiol. 2009;75.
11. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure the BLUE protocol. Chest. 2008;134.
12. Dexheimer Neto FL, Andrade JMS de, Raupp ACT, et al. Diagnostic accuracy of the Bedside Lung Ultrasound in Emergency protocol for the diagnosis of acute respiratory failure in spontaneously breathing patients. J Bras Pneumol. 2015;41.
13. Bekgoz B, Kilicaslan I, Bildik F, et al. BLUE protocol ultrasonography in Emergency Department patients presenting with acute dyspnea. Am J Emerg Med. 2019;37.
14. Danish M, Agarwal A, Goyal P, et al. Diagnostic performance of 6-point lung ultrasound in ICU patients: A comparison with chest X-ray and CT thorax. Turkish J Anaesthesiol Reanim. 2019;47.
15. Patel CJ, Bhatt HB, Parikh SN, et al. Bedside lung ultrasound in emergency protocol as a diagnostic tool in patients of acute respiratory distress presenting to emergency department. J Emergencies Trauma Shock. 2018;11.
16. Ye X, Xiao H, Chen B, et al. Accuracy of lung ultrasonography versus chest radiography for the diagnosis of adult community-acquired pneumonia: Review of the literature and meta-analysis. PLoS One. 2015;10.
17. Long L, Zhao H-T, Zhang Z-Y, et al. Lung ultrasound for the diagnosis of pneumonia in adults. Med. 2017;96.
18. Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Accuracy of lung ultrasonography in the diagnosis of pneumonia in adults: Systematic review and meta-analysis. Chest. 2017;151.
19. Cibinel GA, Casoli G, Elia F, et al. Diagnostic accuracy and reproducibility of pleural and lung ultrasound in discriminating cardiogenic causes of acute dyspnea in the Emergency Department. Intern Emerg Med. 2012;7.
20. Lichtenstein D. Novel approaches to ultrasonography of the lung and pleural space: Where are we now?. Breathe. 2017;13.
21. Narendra DK, Hess DR, Sessler CN, et al. Update in management of severe hypoxemic respiratory failure. Chest. 2017;152.
22. Xirouchaki N, Kondili E, Prinianakis G, et al. Impact of lung ultrasound on clinical decision making in critically ill patients. Intensive Care Med. 2014;40.
23. Seyedhosseini J, Bashizadeh-fakhar G, Farzaneh S, et al. The impact of the BLUE protocol ultrasonography on the time taken to treat acute respiratory distress in the ED. Am J Emerg Med. 2017;35.
24. Seif D, Perera P, Mailhot T, et al. Bedside ultrasound in resuscitation and the rapid ultrasound in shock protocol. Crit Care Res Pract. 2012;2012.
25. Lichtenstein DA. BLUE-Protocol and FALLS-Protocol: Two applications of lung ultrasound in the critically ill. Chest. 2015;147.
26. Staub LJ, Mazzali Biscaro RR, Kaszubowski E, et al. Lung ultrasound for the emergency diagnosis of pneumonia, acute heart failure, and exacerbations of chronic obstructive pulmonary disease/asthma in adults: A systematic review and meta-analysis. J Emerg Med. 2019;56.
27. Wooten WM, Shaffer LET, Hamilton LA. Bedside ultrasound versus chest radiography for detection of pulmonary edema: A prospective cohort study. J Ultrasound Med. 2019;38.
28. Al Deeb M, Barbic S, Featherstone R, et al. Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: A systematic review and meta-analysis. Acad Emerg Med. 2014;21.
29. Abdalla W, Elgendy M, Abdelaziz AA, et al. Lung ultrasound versus chest radiography for the diagnosis of pneumothorax in critically ill patients: A prospective, single-blind study. Saudi J Anaesth. 2016;10.
30. Lichtenstein DA, Mezière GA, Lagoueyte JF, et al. A-lines and B-lines: Lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. Chest. 2009;136.
31. Huang D, Ma H, Xiao Z, et al. Diagnostic value of cardiopulmonary ultrasound in elderly patients with acute respiratory distress syndrome. BMC Pulm Med. 2018;18.
32. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA - J Am Med Assoc. 2012;307.
33. Soldati G, Demi M, Demi L. Ultrasound patterns of pulmonary edema. Ann Transl Med. 2019;7.
34. Saraogi A. Lung ultrasound: present and future. Lung

India. 2015;32.
35. Prosen G, Klemen P, Strnad M, et al. Combination of lung ultrasound (a comet-tail sign) and N-terminal pro-brain natriuretic peptide in differentiating acute heart failure from chronic obstructive pulmonary disease and asthma as cause of acute dyspnea in prehospital emergency setting. Crit Care. 2011;15.
36. Schünemann HJ, Mustafa R, Brozek J, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. J Clin Epidemiol. 2016;76.

Secondary Choledocholithiasis in Obstructive Jaundice Patient due to Choledochoduodenal-fistula Stricture

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ABSTRACT

Choledochoduodenal fistula (CDF) is a rare condition marked by an abnormal connection between the biliary duct and duodenum. The common etiology of secondary CDF are cholecystolithiasis, tumor, and duodenal ulcer. CDF may also caused by prior inflammatory condition or as a complication of radiation therapy. Management for this case is based on the patient condition. Herein we aimed to present a case of secondary choledocholithiasis due to stricture in the CDF which presented with cholangitis treated by self-expanding metal stent (SEMS) for biliary drainage. Patient admitted with jaundice, fever, right upper quadrant pain, and history of cholecystectomy. Diagnosis of CDF was determined by endoscopic retrograde cholangiopancreatography (ERCP) and followed by putting biliary stent for urgent biliary drainage. The follow up result after stent removal was excellent.

Keywords**:** *choledochoduodenal fistula, CDF, cholangitis, choledocolithiasis.*

INTRODUCTION

Choledochoduodenal fistula (CDF) is a rare condition in which an abnormal connection forms between the biliary duct and duodenum.[1–3] They account for 5–25% of all internal biliary fistulas.[1] Biliary-enteric fistula was first described by Bartholin in 1654.[4] First case report of CDF was described in 1840, however there are only a few cases reported in the world.[1–4] Virtually 90% of CDF, the particular type of biliary-enteric fistulas, are caused by cholecystolithiasis.[4,5] Other causes are pancreatobiliary tumor, and less commonly by duodenal ulcer.[5,6] CDF may ensue following inflammatory causes or as a consequence of radiation therapy. In few cases, it may serve as an alternative pathway of biliary drainage while the main biliary duct is obstructed.[3] This is a case report of secondary choledocholithiasis due to stricture in the CDF which presented with cholangitis.

CASE ILLUSTRATION

A 43 years old female presented with jaundice in the last 10 days. She had fever for 7 days, with right upper quadrant abdominal pain. Patient undergone cholecystectomy 3 years ago. On clinical examination, she was hemodynamically stable with tachycardia and fever (38.1°C). Her sclerae was icteric and abdominal pain at the right upper quadrant. The rest of the physical examination was normal. Laboratory investigations showed raised WBC count (16,550/mm^3), ureum (52 mg/dl), creatinine (2,1 mg/dl), total bilirubin (9.27 mg/dl), direct bilirubin (7.54 mg/dl), mildly raised liver enzymes (AST 70 U/L, ALT 135 U/L),

increased alkaline phosphatase (247 U/L), Gamma-GT (337 U/L), while amylase and lipase were within normal limits.

Ultrasonography revealed biliary stone with dilatation of intra and extra hepatic biliary ducts. Patient was diagnosed with severe cholangitis based on Tokyo Guidelines for cholangitis, consequently required urgent biliary drainage. Endoscopic retrograde cholangiopancreatography (ERCP) was performed, however cannulation at ampulla of Vater was unsuccessful. We discovered a fistula adjacent to the ampulla of Vater, proceeded with fistula cannulation. Medium contrast was injected showing a fistula between bile duct and duodenum with stricture at distal part toward the duodenum, multiple biliary stones in the bile duct, and total obstruction at ampulla of Vater (**Figure 1**). The stricture at distal fistula made secondary-choledocholithiasis which lead to severe cholangitis. A Pigtail Plastic Stent 10F was inserted for urgent temporary bile-drainage (**Figure 2**). Subsequently patient's condition improved clinically. Second ERCP was done and the plastic stent was replaced by fully-covered self-expanding metal stent (SEMS) 3 days afterwards (**Figure 3**). Six weeks later, third ERCP was done and SEMS was removed. Follow up cholangiography showed no stones in the bile duct, this result indicated the biliary stones passed spontaneously through the fistula while SEMS was still in placed (**Figure 4**).

DISCUSSION

CDF was one of the rare conditions reported. A study presents 81 biliary fistula cases from 1948-1998 and choledochoduodenal fistula was only found in 7 cases (8.6%).[7] The most common cause of CDF was cholecystolithiasis.[1,6] Some reported CDF was caused by duodenal ulcer, tumors, and tuberculosis.[6,8] In a study reviewed in the period between 1976 and 1989, 14 (0.7%) patients who underwent ERCP because of biliary disease were found to be having CDF.[9] Another

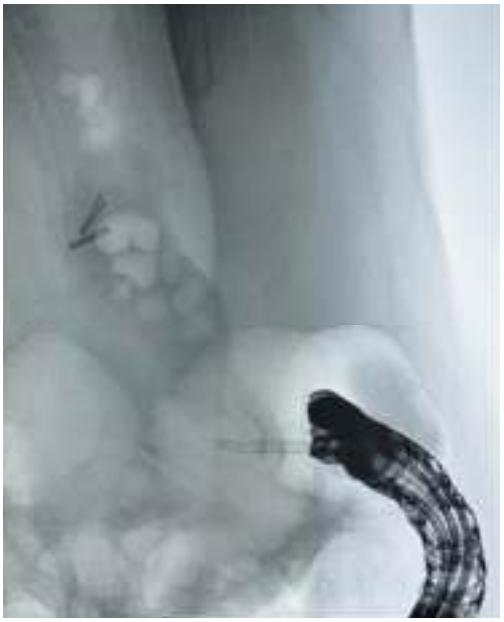

Figure 1. CBD Cannulated via CDF with Multiple Biliary Stones.

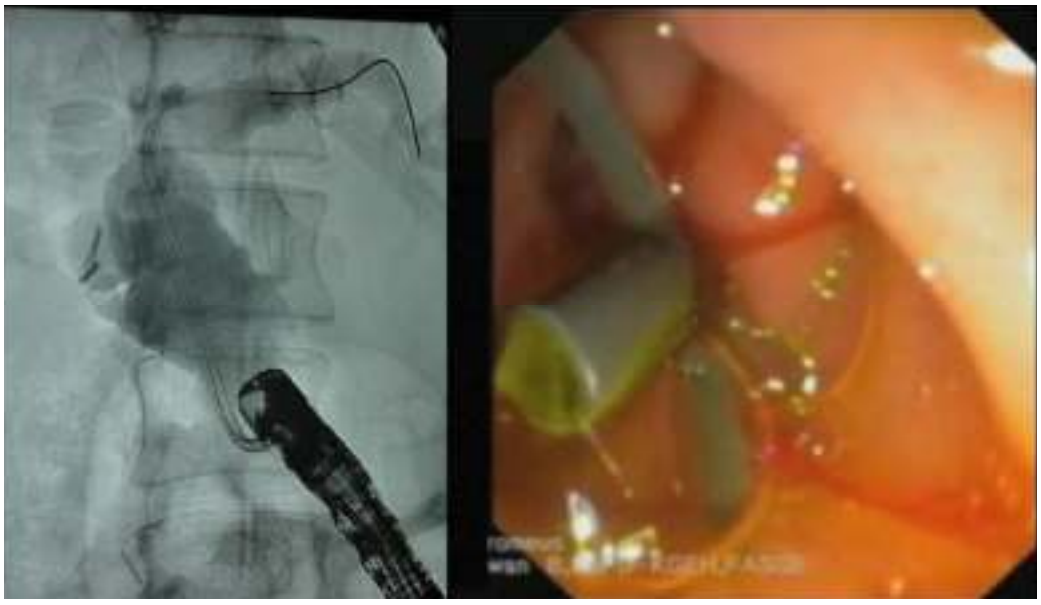

Figure 2. CBD Plastic stent

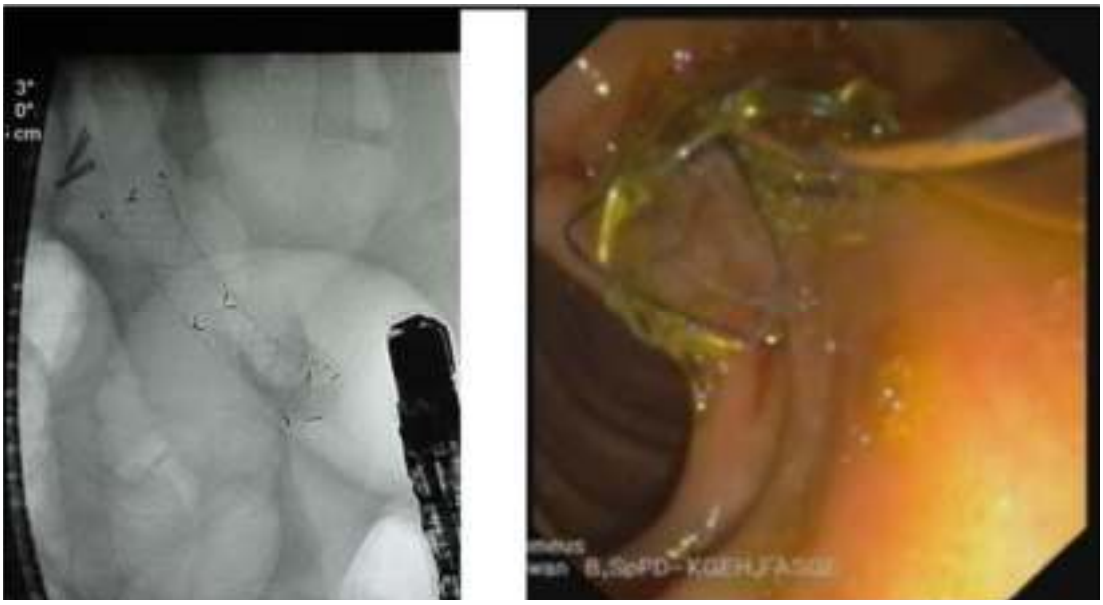

Figure 3. SEMS.

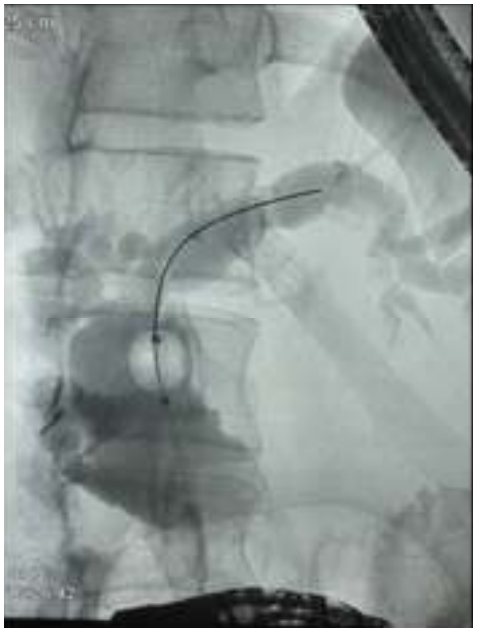

Figure 4. Post SEMS removal.

study in China found 50 cases of CDF from 1200 patient with biliary disease who underwent ERCP.[10] The incidence of CDF in an endemic area of cholelithiasis documented as high as 2.53%.[11] The exact pathophysiology of CDF formation is not well known. One hypothesis sugests that it is caused by recurrent gallstone or cholangitis resulting in increased proximal ductal pressure leading to the formation of the fistula. The clinical presentation of CDF is usually unclear. Most of the patients with CDF presented with symptoms of cholangitis with right upper quadrant pain, jaundice, and fever.[4] Infection occurred due to the ascending bacteria from duodenum to the biliary tract.[1,10,11] In our case, she was admitted with severe cholangitis, noticed by symptoms, ultrasound findings, and sign of organ failure which was acute kidney injury.

Although CDF is difficult to diagnose, recent advances in imaging and endoscopic techniques are developed to increase detection of CDF. Fistulography and cholangiography are commonly used to acquire an accurate diagnosis for all fistula in all cases. The study demonstrated that imaging did not show the fistula in any various imaging modalities.[12] However, some studies reported patients with CDF presenting with pneumobilia on their imaging workups (X-Ray and/or CT).[1,13–15]

In 1975, Ikeda classified CDF into two types of fistulas based on the location. Type I was located on the longitudinal fold of the papilla, while type II was on the posterior wall of the duodenal bulb.[4,16] This patient was considered type II Ikeda classification, owing to the fact that the location of the fistula was posterior from papilla fold or minor papilla. The ampulla of Vater orifice was completely obstructed since unsuccessful attempt of the cannulation. Even so, cannulation resulted in biliary drainage success

in duodenal bulb where the fistula presented.

The option of CDF treatment was based on the etiology, type of the fistula, and severity of the disease. The management of CDF was surgery in general, however, in conditions where surgery remains a relative contraindication, endoscopic biliary drainage is the alternative option.[1,3] The biliary drainage is aimed to reduce the intraluminal pressure to allow bile to flow. The stent will usually be left in place for four to six weeks and removed after excellent follow up result.[17] Previous study describes larger fistula orifices > 1 cm recommended to have surgical therapy since they have higher recurrence rate of cholangitis. However, for fistula orifices less than 1 cm, a biliary drainage can be considered as treatment.[10]

Chintanaboina et al. demonstrated biliary stenting in alternative to surgery for CDF patient with several comorbidities.[3] Study from France shows successful treatment in CDF patient with biliary obstruction by placing endoprostheses for biliary drainage and have good clinical result in follow up.[18] Other studies demonstrated that using SEMS on endoscopic procedure are found to be effective and reliable for patient with bilioduodenal obstruction and the clinical outcome was excellent.[19,20] We decided to insert 10F pigtail plastic stent, which was subsequently replaced with self-expandable metal stent (SEMS) to optimize drainage since it had a larger diameter. Compared to plastic stents, the use of SEMS in malignant biliary obstruction results in higher rate of patient survival and lower risk of future complication.[21] The follow up result was excellent, patient's condition improved and laboratory parameters returned to normal. The benefit of using large diameter stent also allowed biliary stones to migrate spontaneously, which has never been reported yet.

CONCLUSION

This case demonstrated a secondary choledocholithiasis with severe cholangitis due to the choledochoduodenal fistula stricture. Inserting self-expandable stent in the fistula allows both bile and even biliary stone to pass spontaneously. Fully covered SEMS insertion may serve as an alternative practice to avoid surgery procedures on biliary drainage and removing biliary stones, in choledochoduodenal fistula cases.

REFERENCES

1. B S B, Kar A, Dutta M, et al. A case of choledochoduodenal fistula - an unusual case report. Clin case reports. Wiley-Blackwell. 2017;5(9):1462–4.
2. Aguilar-Espinosa F, Maza-Sánchez R, Vargas-Solís F, et al. Cholecystoduodenal fistula, an infrequent complication of cholelithiasis: Our experience in its surgical management. Rev Gastroenterol México. 2017;82(4):287–95.
3. Chintanaboina J, Mathew A, Moyer MT. Taking an alternate route home: Stenting of choledochoduodenal fistula. ACG Case Reports J. 2015;2(2):104–6.
4. Wu M-B, Zhang W-F, Zhang Y-L, et al. Choledochoduodenal fistula in mainland China: a review of epidemiology, etiology, diagnosis and management. Ann Surg Treat Res. 2015;89(5):240.
5. Mallikarjunappa B, S. R. A. Choledochoduodenal fistula: a rare case report with review of literature. JIMSA. 2013;26(4):226.
6. Chansaenroj P, Wood S, Rogers SJ. Selective management for gastrointestinal hemorrhage caused by choledochoduodenal fistula. Siriraj Med J. 2017;67:97–101.
7. Stagnitti F, Mongardini M, Schillaci F, et al. Spontaneous biliodigestive fistulae. The clinical considerations, surgical treatment and complications. G Chir. 2000;21(3):110–7.
8. Yamamoto T, Yamamoto T, Abe K, et al. Choledochoduodenal fistula associated with recurrent peptic ulcer. J Med Cases. 2012;3(4):243–6.
9. Jorge A, Diaz M, Lorenzo J, et al. Choledochoduodenal fistulas. Endoscopy. 1991;23(02):76–8.
10. Li Z-H, Ding J, Ye Y, et al. New strategy to prevent ascending cholangitis in larger choledochoduodenal fistula. ANZ J Surg. 2006;76(9):796–800.
11. Sheu BS, Shin JS, Lin XZ, et al. Clinical analysis of choledochoduodenal fistula with cholelithiasis in Taiwan: assessment by endoscopic retrograde cholangiopancreatography. Am J Gastroenterol. 1996;91(1):122–6.
12. Oikarinen H, Päivänsalo M, Tikkakoski T, et al. Acta radiologica findings in biliary fistula and gallstone ileus. Acta radiol. 1996;37(6):917–22.
13. Antony A. Pneumobilia resulting from choledochoduodenal fistula secondary to metastatic colon adenocarcinoma. ACG Case Reports J. 2016;3(2):112–4.
14. Tonolini M. Spontaneous pneumobilia revealing choledocho-duodenal fistula: A rare complication of peptic ulcer disease. J Emerg Trauma Shock. Wolters Kluwer -- Medknow Publications. 2013;6(2):146–7.
15. Dadzan E, Akhondi H. Choledochoduodenal fistula

presenting with pneumobilia in a patient with gallbladder cancer: a case report. J Med Case Rep. 2012;6(1):61.

16. Ikeda S, Okada Y. Classification of choledochoduodenal fistula diagnosed by duodenal fiberscopy and its etiological significance. Gastroenterology. 1975;69(1):130–7.
17. Crespi M, Montecamozzo G, Foschi D. Diagnosis and treatment of biliary fistulas in the laparoscopic era. Gastroenterol Res Pract. 2016;2016:6293538.
18. Ponchon T, Gallez J-F, Valette P-J, et al. Endoscopic treatment of biliary tract fistulas. Gastrointest Endosc. 1989;35(6):490–8.
19. Hori Y, Naitoh I, Hayashi K, et al. Covered duodenal self-expandable metal stents prolong biliary stent patency in double stenting: The largest series of bilioduodenal obstruction. J Gastroenterol Hepatol. 2018;33(3):696–703.
20. Lu L, Tang X, Jin H, et al. Endoscopic ultrasound-guided biliary drainage using self-expandable metal stent for malignant biliary obstruction. Gastroenterol Res Pract. 2017;2017:6284094.
21. Dumonceau J-M, Tringali A, Papanikolaou I, et al. Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline – Updated October 2017. Endoscopy. 2018;50(09):910–30.

Pontine Infarct as Initial Presentation of Catastrophic Antiphospholipid Syndrome in Systemic Lupus Erythematous

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ABSTRACT

Antiphospholipid syndrome (APLS) is an autoimmune condition which commonly manifests as an arterial or venous thrombosis affecting medium to large vessels, with the presence of antiphospholipid antibodies. APLS can be a primary disease by itself, or secondary to other autoimmune diseases, such as Systemic Lupus Erythematosus (SLE). Catastrophic APLS is a rare but a fatal sequelae of APLS, affecting up to three or more organs, and progresses rapidly with a high mortality rate. We report a case of catastrophic APLS in a young woman with underlying SLE who presented to us with multiple cranial nerve palsies due to bilateral pontine infarct, and eventually developed deep vein thrombosis and pulmonary embolism during the course of the illness. She was treated with high dose corticosteroids and intravenous cyclophosphamide with biochemical improvement. In this case report, we would like to highlight the fact that our patient had bilateral pontine infarcts as the initial presentation, with no inciting events and antiphospholipid antibodies were negative during the acute illness.

Keywords: *Antiphospholipid Syndrome, Catastrophic APLS, Infarct, Thrombosis, Cyclophosphamide*

INTRODUCTION

Antiphospholipid syndrome (APLS) was first described in 1983 by Graham Hughes, in which there will be a single arterial or venous thrombosis as a result of an occlusion of the medium to large vessels with the presence of antiphospholipid antibodies.[1] APLS is a hypercoaguable state that predominantly affects females with a mean age of 37 years.[2] It can either stand on its own as primary APLS, or associated with other autoimmune conditions, primarily SLE. Anticardiolipin antibodies (aCL) and Lupus anticoagulant antibodies (LA) are seen in a significant amount in patients with SLE, which then contributes to the formation of APLS.

Catastrophic APLS is a life threatening, rare variant of APLS seen in less than 1% of APLS.[3] It progresses rapidly to cause diffuse small vessel ischemia due to the presence of micro-thromboses, in contrary to APLS. The four most commonly affected organs are renal (71% - 89%), followed by cerebral (62%), lungs (45% - 64%) and cardiac (45% - 51%).[4,5] Diagnosing catastrophic APLS is rather challenging and often be blinded by other differential diagnoses, especially disseminated intravascular coagulopathy (DIVC) and thrombotic thrombocytopenic purpura (TTP). The diagnostic criteria include a history of APLS or persistent positive antibodies in two occasions six weeks apart, with three or more organs affected, symptoms onset within a week and biopsy proven micro-thrombosis. A definite catastrophic APLS requires all four criteria to be

fulfilled, whereas a probable catastrophic APLS requires three out of four criteria.[6]

Many reviews have reported catastrophic APLS to have a mortality rate as high as 44%, and patients usually succumb due to cerebral involvement, cardiac cause and infection. A combination of anticoagulant, corticosteroids and plasma exchange was thought improve outcomes, while the use of intravenous cyclophosphamide was not proven to be beneficial.[3]

CASE ILLUSTRATION

We report a case of a 28-year-old lady, single, nulliparous, who was diagnosed to have SLE with musculoskeletal and hematological involvement at a private hospital in 2017 where she presented with anaemic symptoms and fever. She first presented to our institution in 2018 with relapsed SLE and lupus nephritis (LN). Renal biopsy showed diffuse proliferative lupus nephritis (ISN/RPS LN Class IV). She was then treated with intravenous Methylprednisolone and subsequently induced with Mycophenolate Mofetil (MMF) and Cyclosporin A (CSA). However, she never achieved complete remission (normal renal function and albumin, but persistent proteinuria of 3g/day). Renal biopsy was repeated in June 2019 and showed the presence of focal proliferative lupus nephritis (ISN/RPS LN Class III). She was once again treated with intravenous Methylprednisolone and scheduled for intravenous Cyclophosphamide. Two weeks later, she presented with complaints of left eye ptosis, preceded with three days of fever and cough which had resolved. She denied having any constitutional symptoms, recent trauma or surgery.

Upon examination, she was comfortable, orientated and not septic looking. She was neither hypertensive nor febrile with BP being 140/83. Both pupils were equal and reactive. She had a partial ptosis over the left eye. There was limited adduction of the left eye, whereas on the right eye, the adduction and abduction were both limited. She also had right facial lower motor neuron weakness. Other examinations were unremarkable.

Her full blood count showed normochromic normocytic anaemia, with thrombocytopenia (Hb 9.3 g/dL; Platelet 106 x 10^9/L). Peripheral blood film showed no evidence of haemolysis. The coagulation profile was normal. There were no biochemical or radiological evidence of infection (WBC 4.4 X 10^9/L; CRP 0.95 mg/L; Blood C&S showed no growth; Chest X-ray clear lung fields). Her renal function was normal throughout admission, but had a heavy proteinuria of 6g/day. Serum albumin was 26. Urine full examination and microscopic examination (UFEME) showed protein of 4+ and blood 5+. Her antinuclear antibody (ANA IF) was positive, 1:640 homogenous. But, her antiphospholipid antibodies were tested to be negative (We do not have a prior antiphospholipid antibody tests done). Her serum complement C3 and C4 levels were low. Patient was subjected for contrast enhanced computerized tomography (CT) scan and MRI/MRA brain. Both were suggestive of bilateral pontine infarct, with no meningeal enhancement or dural venous thrombosis.

She was empirically started on intravenous antibiotics. She was also given intravenous Methylprednisolone 250mg once daily for three days, followed by oral prednisolone. We decided to continue the second cycle of intravenous cyclophosphamide during this period for her active lupus nephritis.

During the 5th day of admission, she complained of shortness of breath. Further workup showed the presence of extensive left lower limb deep vein thrombosis and bilateral acute pulmonary embolism. With regards to her rapidly progressing thrombotic symptoms involving three major organs (brain, renal and lungs), she was deemed to have probable catastrophic APLS. Patient was started with low molecular weight heparin (LMWH) in ward and switched to warfarin upon discharge.

During her clinic follow up for further Cyclophosphamide doses, we did see a significant biochemical improvement (proteinuria), but remained to have residual neurological symptoms.

DISCUSSION

The hallmark of catastrophic APLS includes the presence of antiphospholipid antibodies, thrombocytopenia, anaemia, and prolonged

clotting time as opposed to the absence of haemolytic picture in the blood film. Thrombotic storm, is an alternative diagnosis that presents in a similar manner, whereby the thrombotic events occur rapidly without a triggering factor diagnosed based on clinical grounds.[7] Both conditions keep physicians on the ball in events of patient progressing into definite catastrophic APLS, requiring aggressive treatment with corticosteroid and immunosuppressants.

The nervous system is the second most commonly affected organ in catastrophic APLS after the renal system. The dual pathology of thrombotic damage and antibodies induced oxidative stress contributes to the formation of infarction. They vary in terms of distribution of lesion (central or peripheral) and phenotype due to genetic predisposition or individual susceptibility. With middle cerebral artery territory being the most common affected site, pontine infarcts are said to be the least commonly affected area involving less than 10% of individuals.[8] Catastrophic APLS can also present with non-thrombotic features such as headache, seizures, neuropsychiatric symptoms and movement disorders.

Asherson et al,[4] reported that almost half of the patients with catastrophic APLS will have a preceding event mainly infection, followed by trauma, surgery, malignancy or obstetric condition, none of which were seen in our case. Epstein Bar virus (EBV) and Cytomegalovirus (CMV) infections are closely linked to catastrophic APLS. Catastrophic APLS leads to immune activation, then systemic inflammatory response syndrome and small vessel thrombosis.

The presence of antiphospholipid antibodies with thrombosis is needed to define APLS and catastrophic APLS, portraying the importance of these antibodies in the pathogenesis of the disease. The most commonly seen antibodies are aCL IgG and LA, 83% and 82% respectively. But, there have been cases reported where the antibodies were only positive two months later. [9,10] It can be explained by the fact that the antibodies can be falsely negative due to the antibody consumption by a larger thrombus size during the acute period and become positive shortly after. It is also postulated that these antibodies are occasionally directed to some other antigens and creating a complex that cannot be tested using the conventional method. Therefore, it is wise to repeat the test later on.[10,11] It is not known to when is the best time to repeat the test.

As mentioned above, catastrophic APLS mostly affects the kidney causing a rise in serum creatinine, proteinuria of more than 6g/day and severe hypertension. Be it definite or probable catastrophic APLS, the standard treatment regime includes anticoagulant plus corticosteroids plus plasma exchange with or without intravenous immunoglobulin.[12] This is to treat the precipitating factor and thrombotic event, thus further suppressing the cytokines released during the acute period. Few reports have suggested that the use of cyclophosphamide during the acute period does not confer a better prognosis.[12] But for some physicians, high dose corticosteroids together with cyclophosphamide had been the preferred initial choice of treatment. On the other hand, Rituximab, an anti-CD20 monoclonal antibody used in hematological malignancies, has been widely studied in catastrophic APLS. Catastrophic APLS and hematological malignancies often have the same blood picture, which is anaemia, thrombocytopenia or thrombotic micro-angiopathies. Hence, the use of Rituximab in catastrophic APLS with haematological involvement has shown to be equally effective. Rituximab has also been proven to be beneficial in patients with renal and cardiac involvement.[13]

Besides being a poor prognostic factor for catastrophic APLS, the co-existence of active SLE and APLS with both pulmonary and renal involvement confers a higher rate of relapse. Age of more than 36 years and the presence of antinuclear antibodies and lupus anticoagulant also have an added value to cause relapse.[14]

With regards to our patient, a normal clotting time and fibrinogen level excludes DIVC, whereas the absence of haemolysis with a background of thrombocytopenia excludes TTP. The onset of symptoms was within days and progressed to involve three major organs (renal,

cerebral and lungs) but the antiphospholipid antibodies were tested to be negative. We regarded her as having probable catastrophic APLS, as any further delay in aggressive treatment could cause a detrimental effect. The decision to continue the cyclophosphamide instead of plasma exchange or giving intravenous immunoglobulin was made as she was having active lupus nephritis which did not respond to MMF. And, as to whether Rituximab can lead to neurological improvement, it is still unknown as there is lack of trials in this aspect. It is imperative for us to follow her up closely to repeat her antiphospholipid antibodies and be watchful for relapse.

CONCLUSION

Catastrophic APLS can have various clinical and biochemical presentations. The diagnosis criteria is a useful guide, but high index of suspicion and early initiation of treatment is needed to prevent any unwanted complications.

REFERENCES

1. Koike T. Antiphospholipid syndrome: 30 years and our contribution. Int J Rheum Dis. 2015;18(2):233-41.
2. Nayer A, Ortega LM. Catastrophic antiphospholipid syndrome: a clinical review. J Nephropathol. 2014;3(1):9.
3. Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M, Font J, Asherson RA. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis & Rheumatism. 2006;54(8):2568-76.
4. Asherson RA. Multiorgan failure and antiphospholipid antibodies: the catastrophic antiphospholipid (Asherson's) syndrome. Immunobiology. 2005;210(10):727-33.
5. Asherson RA, Cervera R, De Groot PG, Erkan D, Boffa MC, Piette JC, Khamashta MA, Shoenfeld Y. Catastrophic Antiphospholipid Syndrome Registry Project Group. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus. 2003;12(7):530-4.
6. Aguiar CL, Erkan D. Catastrophic antiphospholipid syndrome: how to diagnose a rare but highly fatal disease. Therapeutic advances in musculoskeletal disease. 2013;5(6):305-14.
7. Ortel TL, Kitchens CS, Erkan D, et al. Clinical causes and treatment of the thrombotic storm. Expert Review of Hematology. 2012;5(6):653-9.
8. Fleetwood T, Cantello R, Comi C. Antiphospholipid syndrome and the neurologist: from pathogenesis to therapy. Frontiers Neurol. 2018;9.
9. Mull ES, Aranez V, Pierce D, Rothman I, Abdul-Aziz R. Newly diagnosed systemic lupus erythematosus: atypical presentation with focal seizures and long-standing lymphadenopathy. JCR: Journal of Clinical Rheumatology. 2019;25(7):e109-13.
10. Miret C, Cervera R, Reverter JC, et al. Antiphospholipid syndrome without antiphospholipid antibodies at the time of the thrombotic event: transient'seronegative'a ntiphospholipid syndrome?. Clinical and Experimental Rheumatology. 1997;15(5):541-4.
11. Drenkard C, Sanchez-Guerrero J, Alarcon-Segovia D. Fall in antiphospholipid antibody at time of thromboocclusive episodes in systemic lupus erythematosus. Journal Rheumatol. 1989;16(5):614-7.
12. Cervera R, Rodríguez-Pintó I, Colafrancesco S, et al. 14th international congress on antiphospholipid antibodies task force report on catastrophic antiphospholipid syndrome. Autoimmunity Rev. 2014;13(7):699-707.
13. Elagib EM, Eltahir NI, Adam ME, Mahmoud ZI, Yousif HH. Catastrophic antiphospholipid syndrome in combination with SLE treated by Rituximab: A case report and literature review. Lupus: Open Access. 2019;4:137.
14. Bucciarelli S, Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: treatment, prognosis, and the risk of relapse. Clinical Reviews Allergy & Immunology. 2009;36(2-3):80-4.

COVID-19 Associated Pulmonary Aspergillosis: A Case Series

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has been a worldwide pandemic with several problems, one of which is the lack of definitive treatment. COVID-19-associated pulmonary aspergillosis (CAPA), the presence of invasive pulmonary aspergillosis (IPA) in COVID-19 patients, is one of the concerning secondary infections associated with higher mortality and worse clinical outcomes. Diagnosing CAPA may be challenging due to the possible absence of classic host factors and clinical symptoms or obscured radiological findings. We described two CAPA cases, which were suspected due to persistent respiratory failure despite standard treatment of COVID-19 with additional therapies and antimicrobial agents for secondary infections, eventually diagnosed with serum galactomannan testing. Clinical conditions of both patients improved significantly after the administration of voriconazole. This case series emphasizes the importance of being aware of clinical suspicions indicating CAPA followed by galactomannan testing as a relatively fast, noninvasive test for its diagnosis, which leads to appropriate antifungal treatment.

Keywords: *Aspergillosis, Aspergillus, COVID-19, COVID-19-associated pulmonary aspergillosis (CAPA), invasive pulmonary aspergillosis (IPA).*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been a pandemic with several issues, including the lack of definitive treatment. Secondary infection in patients with COVID-19 has been a serious concern. One concerning pathogen among these is *Aspergillus,* which can cause invasive pulmonary aspergillosis (IPA). IPA in patients with COVID-19 is referred to as COVID-19-associated pulmonary aspergillosis (CAPA). A systematic review found that the overall CAPA incidence was 13.5%, with the majority requiring invasive mechanical ventilation. CAPA was also found to have a mortality rate as high as 48.4% with prolonged mechanical ventilation use and hospitalization.[1] Patients with CAPA may not present with the classic clinical criteria or radiological findings of IPA. Difficulties in differentiating IPA from other secondary infections in COVID-19 have caused delayed or missed diagnosis of CAPA.[1,2] We describe two cases of CAPA diagnosed with clinical suspicion in COVID-19 patients with respiratory failure and persistently high oxygen supplementation needs despite standard medical therapy, including anti-inflammatory, immunomodulating, and antimicrobial agents for secondary infection.

CASE ILLUSTRATION

Case 1

A 70-year-old woman was admitted with a fever three days before hospital admission. The fever was unmeasured at home but was felt to be not high. The patient also complained of productive cough with difficult expectoration. The patient denied nasal discharge or blockage, shortness of breath, loss of smell or taste, nausea, vomiting, or changes in the stool. The patient had a history of diabetes mellitus and was routinely consuming pioglitazone. There was no past medical history of hypertension, cardiovascular diseases, tuberculosis, stroke, kidney or liver diseases, asthma, and allergies. The patient was in close contact with her son, who was confirmed to have COVID-19. The patient had already received two doses of Coronavac vaccination.

On initial physical examination, the patient was alert, blood pressure 138/78 mmHg, heart rate 87 bpm, axillary temperature 36.8°C with tachypnea of 22 breaths per minute and SpO_2 91% on room air which improves to the respiratory rate of 18 breaths per minute and SpO_2 98% with 4 LPM of oxygen via nasal cannula. Minimal crackles were heard on both lungs, while other general exams revealed normal results.

Two days before admission, the patient had already undergone a chest x-ray which showed bilateral interstitial pneumonia and a positive SARS-CoV-2 naso-oropharyngeal RT-PCR swab test. On the day of admission (D1), additional lab exams were done (**Table 1**). The patient was assessed with severe COVID-19 and type 2 diabetes mellitus. Initial treatment consisted of IV remdesivir 200 mg (loading dose) followed by 100 mg qd, dexamethasone 6 mg IV qd, ranitidine 50 mg IV bid, paracetamol 500 mg PO tid, N-acetylcysteine 200 mg tid, zinc 20 mg bid, vitamin D3 1000 U bid, subcutaneous heparin 5000 IU qd, and basal-bolus insulin regiment to regulate blood glucose.

On the night of D5 of hospitalization, the patient had a rapid desaturation until she only maintained SpO_2 91% with 15 LPM of oxygen via a non-rebreathing mask (NRM). On the following day (D6), the high-flow nasal cannula (HFNC) was used, and SpO_2 of 96% could be maintained with FiO_2 80% and 40 LPM flow. A repeat chest x-ray showed heterogeneous opacities on both lungs' middle to lower section, indicating bilateral pneumonia (**Figure 1**). The antimicrobial levofloxacin 750 mg IV qd was started, and dexamethasone was also increased to 5 mg bid. On D7, the blood interleukin-6 (IL-6) level was measured at 5.79 pg/mL. The patient's required amount of oxygen supplementation gradually increased, and dyspnea remained unresolved. On the D12, the patient was administered two doses of convalescent plasma therapy of 200 mL.

There was no significant improvement in the patient's clinical condition after convalescent plasma therapy, ten days of dexamethasone, and levofloxacin (**Table 2**). In addition, procalcitonin level was not high (0.14 nG/mL). Therefore, a secondary infection caused by aspergillosis or cytomegalovirus was suspected. The patient was tested for galactomannan, anti-cytomegalovirus (anti-CMV) antibodies, and CD4 count on D17. Anti-CMV IgM was nonreactive while IgG was

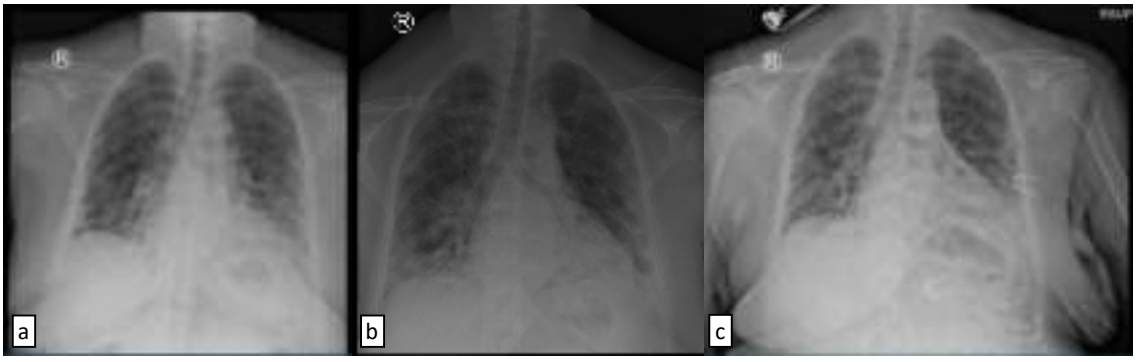


Figure 1. Serial Chest X-ray on: (a) Day 6; (b) Day 16; and (c) Day 26 of Hospitalization of Patient 1.

Table 1. Clinical condition and laboratory results of patient 1.

Days of hospitalization	D1	D5	D6	D12	D17	D22	D27
Temp. (^{0}C)	36.2	37	36.2	36.9	36.8	36.7	36.6
RR (times/min)	18	24	26	23	17	22	27
SpO_2 (%)	98	91	96	97	97	96	97
O_2 therapy device	NC	NRM	HFNC	HFNC	HFNC	HFNC	NRM
Flow (LPM)	4	15	40	60	60	45	15
FiO_2			80	85	90	50	
ROX index			4.62	4.96	6.34	8.73	
Leukocyte (/uL)	5920	11060	10260	12580		12610	12610
Neutrophil (/uL)	4458	9890	9410	11290		10520	9880
Lymphocyte (/uL)	959	680	650	660		1070	1380
Neu/Lym ratio (NLR)	4.65	14.54	14.48	17.11		9.83	7.16
ALT (U/L)	68			80		35	27
AST (U/L)	39			71		27	34
Procalcitonin (nG/mL)	0.07	0.09	0.15	0.14	0.16	0.05	
CRP (mg/L)		114.6	191.7	33.7	45.7	20.5	
aPTT (s)				28.4 (31.5)	52.6 (32.3)	48.6 (32.0)	26.3 (33.3)
Fibrinogen	725.4						
D-dimer (ug/mL)	990		1890	1130	1060	800	

Table 2. Notable therapies of Patient 1.

Days of hospitalization	D1	D5	D6	D12	D17	D22	D27
Antiviral	Remdesivir IV						
Corticosteroid	Dexamethasone IV					Methylprednisolone PO	
Antimicrobial	Levofloxacin IV (14 days)						
Colchicine	Colchicine PO						
Convalescent Plasma (CP)	CP						
Antifungal	Voriconazole IV						

reactive 341.7 U/mL, CD4 was 38% with an absolute count of 489 /uL. On D20, the patient underwent a second SARS-CoV-2 RT-PCR, which had a negative result. Dexamethasone was reduced to 5 mg qd. The Galactomannan test revealed a positive result (2.04) on D21, and the patient was assessed with invasive pulmonary aspergillosis (IPA). Voriconazole was started on D22 with the dose of 6 mg/kgBW IV q12h (loading dose) followed by 4 mg/kgBW IV q12h from the second to the fourteenth day. She was transferred to the medical non-COVID-19 high-care unit (HCU) after the third negative SARS-CoV-2 RT-PCR result. On D27, oxygen supplementation was stepped down from HFNC to 15 LPM via NRM. After that, the patient's clinical condition improved, and three days later, the patient could maintain SpO2 of 95% with 3 LPM of oxygen via nasal cannula.

Case 2

A 51-year-old man was admitted with shortness of breath four days prior to hospitalization. The patient initially had a fever, headache, muscle pain, and occasional dry cough in the past week before hospitalization. He initially did not have breathing problems and denied complaints of nasal discharge or blockage, loss of smell or taste, or any other complaints. Two days later, he underwent a SARS-CoV-2 antigen test, and the results came out positive. He then started self-isolation and developed shortness of breath four days before hospitalization. The patient had a history of diabetes mellitus and routinely consumed glimepiride 2 mg qd and metformin 500 mg tid.

He also had a 4-year history of hypertension treated with irbesartan. There was no past medical history of cardiovascular diseases, kidney or liver diseases, asthma, and allergies. The patient was not vaccinated for COVID-19.

On initial physical examination, the patient was alert, blood pressure 133/81 mmHg, heart rate 87 bpm, axillary temperature 36.5°C with tachypnea of 30 breaths per minute, and SpO_2 93% with 3 LPM of oxygen via nasal cannula. Slight rales were heard on both lungs, while other general exams were normal. Initial laboratory and chest x-ray were done (**Figure 2**). The patient's D-dimer was elevated, and the circulating IL-6 level was high (**Table 3**). Chest x-ray showed bilateral alveolar opacities in the perihilar and paracardial area consistent with bilateral pneumonia. The patient was assessed with severe confirmed COVID-19, type 2 diabetes mellitus, and hypertension. Initial treatment consisted of IV remdesivir 200 mg (Loading dose) followed by 100 mg qd (D2-D14), dexamethasone 6 mg IV qd, paracetamol 1000 mg IV qd, vitamin C 1000 mg IV bid, vitamin D3 5000 mg PO qd, Zinc 20 mg PO bid, heparin 10.000 U/24h (2 mL/h), and basal-bolus insulin to regulate blood sugar.

Nasopharyngeal swab for SARS-CoV-2 RT-PCR was obtained and the result was positive (ORF1b Cq = 27.20, RdRP Cq = 30.24). On D4, 5 LPM of oxygen via nasal cannula was needed to maintain SpO2 of 96%, and levofloxacin 750 mg IV qd was started for secondary infection. The patient's oxygen desaturation worsened that he needed 15 LPM of oxygen via NRM on D5. The deterioration continued as the patient fell into acute respiratory distress syndrome (ARDS) on D6. He was transferred to the HCU, and HFNC was initiated in addition to increasing the dose of dexamethasone to 5 mg bid, the addition of colchicine 0.5 mg tid for five days, and treatment with tocilizumab was planned. On the night of D6, the D-dimer result was extremely high at 30.990 ug/mL, warranting escalation of the anticoagulant. Heparin was switched to enoxaparin 0.6 cc bid, and antioxidant therapy with N-acetylcysteine 5000 mg IV qd was started. Tocilizumab 400 mg IV was administered on D9, followed by 200 mg IV 12 hours after. On D13, the meropenem 3 gr IV qd was added.

On D14, due to the need for supplementary oxygen still being high and ROX index had not reached safe levels after standard therapy including antiviral remdesivir, corticosteroid, tocilizumab, and adequate antibiotics (**Table 4**), fungal infection was suspected, and serum sample for Galactomannan test was taken. SARS-CoV-2 RT-PCR was reassessed the next day (D15), and it was still positive but with a higher CT value (ORF1b Cq = 38.04 dan RdRP Cq = 38.77).

On D16, the result of the serum galactomannan test came out positive (2.03), hence invasive pulmonary aspergillosis (IPA) was assessed, and voriconazole 6 mg/kgBW q12h IV loading dose followed by 4 mg/kgBW IV q12h for fourteen days was administered. Anti-CMV was also checked, but only IgG was reactive of 107.4 U/mL. Three days later (D20), oxygen supplementation could be deescalated to 15 LPM via NRM, and RT-PCR was shown to be negative, so the patient was considered to be moved to a non-isolation HCU. Repeat chest x-ray on D21 showed reduced lung opacities with signs of pulmonary fibrosis. The patient's clinical condition improved gradually after that, and he was discharged from the hospital a few days later.

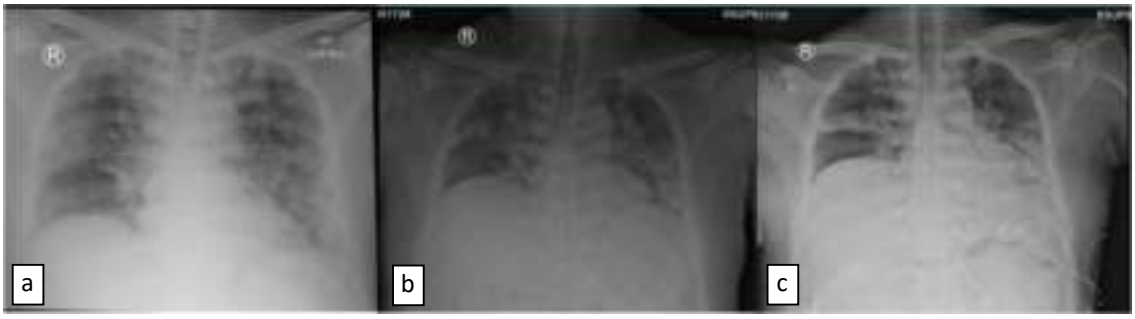
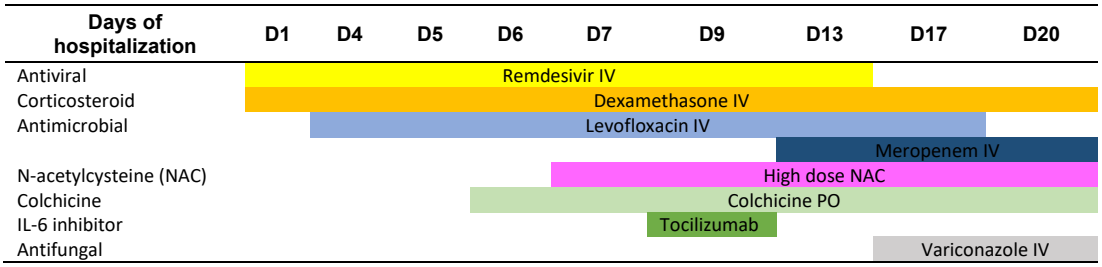


Figure 2. Serial Chest X-ray on: (a) Day 1; (b) Day 6; and (c) Day 21 of Hospitalization of Patient 2.

Table 3. Clinical condition and laboratory results of Patient 2.

Days of hospitalization	D1	D4	D5	D6	D7	D9	D13	D17	D20
Temp. (^{0}C)	36.5	36.4	36.9	35.6	36.5	36	36.8	36.1	36.
RR (times/min)	30	24	32	28	38	26	22	22	24
SpO_2 (%)	93	96	97	97	95	95	97	98	95
O2 therapy device	NC	NC	NRM	HFNC	HNC	HFNC	HFNC	HFNC	NRM
Flow (LPM)	3	5	15	60	65	70	60	80	15
FiO_2			100	80	97	95	70	95	
ROX index				4.33	2.58	3.85	6.30	4.69	
Leukocyte (/uL)	8460	12660		14940					
Neutrophil (/uL)	6240	10840		13460					
Lymphocyte (/uL)	1610	1030		990					
Neu/Lym ratio (NLR)	3.88	10.52		13.60					
ALT (U/L)	45			43					
AST (U/L)	52			26					
Procalcitonin (nG/mL)	0.68			0.11					
CRP (mg/L)	55			72.9					
aPTT (s)					31.2 (31.7)	32.6 (30.9)			
D-dimer (ug/mL)	960			30990			4110		
IL-6	75.18								

Table 4. Notable therapies of Patient 2.



DISCUSSION

COVID-19-associated pulmonary aspergillosis (CAPA) is defined as invasive pulmonary aspergillosis (IPA) occurring in coronavirus disease 19 (COVID-19) patients.[1] Patients with CAPA often do not have classic host factors for invasive fungal infections. Extensive pulmonary epithelial damage, dysregulation of the immune response, lymphopenia, or treatment factors such as widespread broad-spectrum antibiotic use in intensive care units, corticosteroid therapy, and anti-interleukin 6 (IL-6) treatment are some of the several mechanisms are thought to predispose COVID-19 patients to IPA.[3,4] The varied time to CAPA diagnosis from illness onset of about 8 to 16 days might be caused by difficulty differentiating IPA from COVID-19 pneumonia with other causes of secondary infections[1]. According to various studies, the diagnostic criteria for CAPA were based on the same criteria for IPA mentioned before, mostly using the AspICU criteria.[1,3] The diffuse bilateral lung infiltrates in COVID-19 patients might obscure important radiologic clues for IPA.[5] An awareness of clues suggesting CAPA followed by prompt diagnostic testing for *Aspergillus* is crucial in preventing the delay of diagnosing and treating CAPA.

The European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) stated that the diagnosis of invasive fungal diseases needs to fulfill certain host factors, clinical features (certain radiologic findings for IPA), and mycological evidence. A high index of suspicion may arise

from host factors such as immunocompromise, neutropenia, hematologic malignancies, prolonged corticosteroids use, treatment with T-cell or B-cell immunosuppressants, and other factors.[2] Severe COVID-19 with ARDS might also be considered as a host criterion (acquired immunodeficiency).[8] The clinical criteria for IPA from the AspICU are also often used. Fulfilling the criteria requires one of the following signs and symptoms: refractory fever despite three or more days of antibiotic therapy; recrudescent fever lasting 48 hours or more despite antibiotic therapy; pleuritic chest pain/rub, dyspnea; hemoptysis; or worsening respiratory failure despite antibiotic therapy and ventilatory support.[9] Diagnostic investigation for CAPA is triggered in COVID-19 patients with refractory respiratory failure for more than five to fourteen days despite having already received all support recommended for patients with COVID-19 who are critically ill.[3] Both patients have in common a persistent respiratory failure lasting more than fourteen days after COVID-19 symptom onset, showed by the intractably high oxygen supplementation need to maintain a stable SpO_2 despite receiving the antiviral remdesivir, dexamethasone, adequate antimicrobial agents, and even additional therapies such as convalescent plasma (case 1) and the IL-6 inhibitor tocilizumab (case 2). This raised the clinical suspicion of IPA, which is called CAPA, in COVID-19 patients.

Thoracic high-resolution computed tomography scan (HRCT scan) is the preferred radiologic modality for IPA. HRCT scan might show either: dense, well-circumscribed lesions with or without a halo sign; air crescent sign; pleural-based cavitation; or wedge-shaped and segmental or lobar consolidation. The halo sign is a localized ground-glass appearance representing hemorrhagic infarction surrounding a nodule or consolidation.[6,7]

The definitive diagnosis of invasive aspergillosis requires either a positive culture of samples from an ordinarily sterile site (e.g., a brain abscess) or positive results of both histologic testing and culture of a sample from the affected organ. The fast progression of the disease and other factors that might make invasive procedures not feasible makes it challenging to diagnose the patient before further clinical deterioration or even death. These reasons cause up to 40% of invasive aspergillosis to be missed clinically and are only diagnosed postmortem.[6] Therefore, using faster, noninvasive modalities, such as serum biomarkers (galactomannan and beta-D-glucan assays) and/or with microscopic examination and culture of sputum samples, is preferred as a first step to diagnose IPA.

The antigen test for *Aspergillus* typically relies on the detection of galactomannan, which is a polysaccharide constituent of *Aspergillus* cell walls released during growth. Galactomannan can be detected in serum, plasma, BAL fluid, sputum, or other body fluids.[6,10] Galactomannan test of serum was done on the two patients. Both patients had a positive result of 2.04 (patient 1) and 2.03 (patient 2), exceeding the high cut-off of 1.0-1.5, with a positive predictive value (PPV) for IPA as high as 100%.[11,12] The presence of clinical suspicion supported by a positive galactomannan test is usually enough evidence of diagnosis aspergillosis and to start preemptive antifungal therapy.

The recommended treatment of invasive aspergillosis is initial intravenous (IV) antifungal therapy. Voriconazole and isavuconazole are the preferred first-line agents, while caspofungin, posaconazole, micafungin, and lipid Amphotericin B are second-line agents.[6] Both patients received voriconazole IV and showed clinical improvements after administration of the drug.

CONCLUSION

COVID-19-associated pulmonary aspergillosis (CAPA) is a concerning secondary infection in patients with COVID-19. Aside from being associated with higher mortality and poorer clinical outcomes, CAPA might not present with the classic host factor, clinical criteria, or radiological findings of invasive pulmonary aspergillosis (IPA). Awareness of patients with suspicion of CAPA is crucial, particularly concerning the worsening of persistence of respiratory failure in COVID-19 patients in whom clinical conditions do not improve despite anti-inflammatory, immunomodulating agents

and appropriate antimicrobial therapy in addition to standard therapy, especially after two weeks of symptom onset. The Galactomannan test is a useful, relatively quick, noninvasive test for diagnosing IPA, including CAPA. The use of antifungals in these patients is essential and may significantly improve their outcomes.

DECLARATION OF CONFLICTING INTERESTS

The Authors declare that there is no conflict of interest.

REFERENCES

1. Chong WH, Neu KP. Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. J Hosp Infect. 2021;113:115–29.
2. Mitaka H, Kuno T, Takagi H, Patrawalla P. Incidence and mortality of COVID-19-associated pulmonary aspergillosis: A systematic review and meta-analysis. Mycoses. 2021;1–9. doi: 10.1111/myc.13292.
3. Koehler P, Bassetti M, Chakrabarti A, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis. 2021;21:e149–62. doi: 10.1016/S1473-3099(20)30847-1.
4. Arastehfar A, Carvalho A, van de Veerdonk FL, et al. COVID-19 associated pulmonary aspergillosis (CAPA)—from immunology to treatment. J Fungi. 2020;6:1–17. doi: 10.3390/jof6020091
5. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol. 2020;30:4381–9. doi: 10.1007/s00330-020-06801-0
6. Denning D. Aspergillosis. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's principles of internal medicine. 20th ed. New York: McGraw-Hill; 2018. p. 1352–6.
7. Peter Donnelly J, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71:1367–76. doi: 10.1093/cid/ciz1008
8. Koehler P, Cornely OA, Böttiger BW, et al. COVID-19 associated pulmonary aspergillosis. Mycoses. 2020;63:528–34. doi: 10.1111/myc.13096
9. Blot SI, Taccone FS, Van Den Abeele AM, et al. A Clinical algorithm to diagnose invasive pulmonary Aspergillosis in critically ill patients. Am J Respir Crit Care Med. 2012;186:56–64. doi: 10.1164/rccm.201111-1978OC.
10. Karapinar D. A review of a diagnostic tool: Galactomannan. J Immunol Sci. 2018;2:38–42. doi: 10.29245/2578-3009/2018/5.1137
11. Maertens J, Theunissen K, Verbeken E, et al. Prospective clinical evaluation of lower cut-offs for galactomannan detection in adult neutropenic cancer patients and haematological stem cell transplant recipients. Br J Haematol. 2004;126:852–60. doi: 10.1111/j.1365-2141.2004.05140.x
12. Marr KA, Balajee SA, McLaughlin L, Tabouret M, Bentsen C, Walsh TJ. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: Variables that affect performance. J Infect Dis. 2004;190:641–9. doi: 10.1086/422009.

Confirmed Delta Variant COVID-19 Infection at A Single Centre Tertiary Hospital: A Case Series

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ABSTRACT

SARS-CoV-2 continues to mutate with the emergence of new variants. Variant B.1.617.2 (Delta) is a variant of concern with evidence of increased transmission, more severe disease, decreased effectiveness of treatment or vaccines, or failure of diagnostic detection. In this article, we report on the clinical and biological picture of the first confirmed delta variant COVID-19 infection in Indonesia. From May 31 to June 17, we identified ten cases with confirmed delta variant COVID-19 infection admitted to a tertiary academic hospital in Jakarta. All subjects that have been vaccinated presented with mild-moderate disease. Most patients present with initial respiratory complaints, without radiological abnormalities on chest x-ray examination, and an increase in C-reactive protein. Seven out of ten patients have been vaccinated; the three patients who had not been vaccinated experienced severe COVID-19 symptoms, two of whom died. Due to the increased transmission of this variant, we recommend vaccination, wearing a mask, and social distancing to reduce the impact of infection with delta variant B.1,617.2.

Keywords**:** *COVID-19, delta variant, vaccination status, variant of concern.*

INTRODUCTION

Since the initial detection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more than 281 million cases of Covid-19 have been confirmed worldwide.[1] The evolution of SARS-CoV-2 is characterized by the emergence of new genetic lines and several mutations that affect the infectivity and antigenicity of the virus.[2] SARS-CoV-2 continues to mutate with the emergence of new variants.[3] The United Stated SARS-CoV-2 Interagency Group (SIG) has established a classification system including the Variant Being Monitored, Variant of Interest, Variant of Concern, and Variant of High Consequence.

Variant B.1.617.2 (Delta) is a variant of concern, that is, a variant with evidence of increased transmission, more severe disease, decreased effectiveness of treatment or vaccines, or failure of diagnostic detection.[4] Centers for Disease Control and Prevention (CDC) has stated that the variant Delta is estimated to be around 60% more infectious than Alpha variants, the basic reproduction rate of between 5 and 8.[3] In Indonesia, the Delta variant is also thought to have spread rapidly, in part because of low initial vaccination coverage.

Concerns have also been raised about the vaccine's effectiveness against SARS-CoV-2, in particular the Delta variant. Cases of infection in vaccinated individuals (breakthrough infection) are reported in this variant of interest; however,

patients with vaccine breakthrough infection were more likely to be asymptomatic or have milder symptoms, with a milder course of the disease. The effect of delta variant infection on the severity of the clinical manifestations of COVID-19 in susceptible populations, including the elderly and pregnant persons; and populations with comorbid or chronic conditions is unclear.[5]

In this article, we report on the clinical and biological picture of the first confirmed delta variant COVID-19 infection in Indonesia, which occurred in a tertiary hospital, and its dynamics related to clinical manifestations, disease course, and vaccination status of study subjects.

CASE ILLUSTRATION

From May 31 to June 17, we identified ten cases with confirmed delta variant COVID-19 infection admitted to a tertiary academic hospital in Jakarta. Subjects included three patients with moderate-to-severe disease resulting in immediate care in the cardiac intensive care unit (ICCU) and seven patients with mild disease diagnosed early in the course of infection. None of the subjects had a history of traveling to other countries with known delta variant transmission, however, seven subjects had contact with someone known to be infected with COVID-19. The most common symptoms were fever and cough in 9 subjects. Seven subjects with mild disease were fully vaccinated with the CoronaVac vaccine, covering two doses given over two to four weeks.

Table 1 shows the laboratory and radiological findings at the initial hospital visit. At the initial visit, an increase in C-reactive protein was typical, with a mean count of 8.9. Severe uremia, elevated D-dimer and leukocyte levels, and elevated troponin concentrations were found in patients admitted to the ICCU. All ICCU patients had complaints of cardiac involvement and underwent echocardiography and coronary angiography. One patient was diagnosed with a left atrial mass on echocardiography with normal coronary angiography results. One patient was diagnosed with coronary artery disease of three coronary vessels. One patient underwent single stent placement during percutaneous coronary intervention.

Table 1. Clinical Characteristics of Subjects.

Parameters	(N=10)
Mean age (median)	34.5
Gender, n (%)	
Male	2 (20.0)
Female	8 (80.0)
Clinical degree of disease, n (%)	
Mild-moderate	7 (70.0)
Severe-critical	3 (30.0)
Comorbid conditions, n (%)	
Hypertension	3 (30.0)
Asthma	1 (10.0)
Chronic kidney disease	1 (10.0)
Diabetes mellitus	1 (10.0)
Heart failure	1 (10.0)
Coronary artery disease	1 (10.0)
Without comorbidity	3 (30.0)
Symptoms, n (%)	
Fever	7 (70.0)
Shortness of breath	2 (20.0)
Cough	8 (80.0)
Sore throat	4 (40.0)
Headache	2 (20.0)
Diarrhea	1 (10.0)
Nasal congestion	6 (60.0)
Muscle pain	2 (20.0)
Chest pain	2 (20.0)
Length of stay in hospital, mean (SD)	11.1 (5.8)
Vaccination status, n (%)	
Vaccinated	7 (70.0)
Unvaccinated	3 (30.0)
Laboratory results	
Lymphocyte counts, 10^3 cells/uL, mean (SD)	1.23 (0.69)
Hemoglobin, g/L, mean (SD)	11.72 (1.52)
Thrombocytes, 10^3 cells/L (median)	267
C-reactive protein, mg/L (median)	8.9
d-Dimer, ug/L (median)	505
Thoracal x-ray findings, n (%)	
Unilateral lung opacity	1 (10.0)
Bilateral lung opacity	1 (10.0)
Bilateral pleural effusion	1 (10.0)
Inhomogeneous consolidation and bronchiectasis	1 (10.0)
No radiological abnormalities	6 (10.0)
Intensive unit care (ICCU), n (%)	3 (30.0)
Outcome, n (%)	
Mechanical ventilation	1 (10.0)
Death	2 (20.0)
Recovery	8 (80.0)

Chest radiographs were obtained for each subject. All patients admitted to the ICCU showed bilateral lung opacities. Unless indicated, we do not routinely examine markers of infection with influenza, respiratory viruses, or other respiratory viral panels. Blood samples from 3 patients were sent for bacterial culture, and one sample was positive for Staphylococcus aureus bacteria growth. Clinical samples for Covid-19 diagnostic tests were obtained following WHO

guidelines, taken from nasopharyngeal swabs.[6] As part of active genomic surveillance, whole-genome sequencing was performed for all samples with confirmed SARS-CoV-2 detected by RT-PCR. Lineage B.1.617.2 was determined as the SARS-CoV-2 variant for these ten cases.

One patient required invasive mechanical ventilation, with the Pao2:Fio2 ratio consistent with severe ARDS. Tracheostomy was not performed. Two patients received remdesivir as antiviral therapy. None of the subjects received therapy with hydroxychloroquine, lopinavir-ritonavir, systemic glucocorticoids, ivermectin, or tocilizumab. In subjects not admitted to the ICCU, favipiravir was prescribed for eight days.

All subjects were monitored for a minimum of 14 days of follow-up. Two patients died, one patient was discharged from the ICCU but was re-hospitalized for another diagnosis in a different treatment episode, and seven patients were discharged from inpatient/isolation. The mean duration of isolation among living patients was eight days (standard deviation 1.8), and the mean length of stay for ICCU patients was 17 days (standard deviation 7). The duration of mechanical ventilation was six days in the only patient receiving mechanical ventilation.

DISCUSSION

The subjects in this report primarily complained of respiratory symptoms. The duration of symptoms before treatment varied, between 1 day and one week. The most common symptoms were fever, cough, and nasal congestion, consistent with symptoms reported in the initial cohort in China.[7] Lymphocytopenia is common, as noted by several reviews and meta-analyses regarding lymphocyte counts and cytokine storm in patients with COVID-19.[8]

Three out of ten subjects were admitted to the ICCU. Two of the three patients admitted to the ICCU had chronic disease prior to infection, consistent with a poorer outcome in patients with underlying comorbidities.[9] Lower respiratory tract bacterial coinfection was only identified in blood cultures of one of the ICCU patients, similar to a study by Langford et al., stating that only a small proportion of COVID-19 patients had concomitant bacterial infections. Coinfection with bacteria is common in critically ill patients.[10]

Like other RNA viruses, the SARS-CoV-2 virus frequently undergoes mutations during the replication process due to the absence of a mismatch repair mechanism in the virus. Mutations, in essence, make the virus more infectious and more challenging to identify and isolate properly.[2] The delta variant or variant B.1,617.2 has spike mutations G142D, T19R, F157del, E156G, R158del, L452R, D614G, P681R, T478K, and D950 N relative to Wuhan-1 D614G 118.[11] Our genome sequencing results indicate that the delta variant has reached the stage of community transmission in Indonesia.

Our study involved seven vaccinated subjects, suggesting that vaccination does not protect against all infections, particularly against variants of concern. However, vaccinated subjects had better outcomes compared to non-vaccinated subjects; none of the patients admitted to the ICCU had been vaccinated. Vaccinated subjects received an inactivated CoronaVac vaccination, which showed a lower degree of neutralization against the SARS-CoV-2 virus.[12] Studies have estimated the Oxford–AstraZeneca, Pfizer–BioNTech, and Moderna COVID-19 vaccines to effectively reduce the risk of SARS-CoV-2 infection and hospitalization in persons infected with the Delta variant.[13,14]

CONCLUSION

In our study of cases of delta variant COVID-19 infection in an Indonesian tertiary academic hospital, we found that all samples that have been vaccinated presented with mild-moderate disease. Most patients present with initial respiratory complaints, without radiological abnormalities on chest x-ray examination, and an increase in C-reactive protein. Seven out of ten patients have been vaccinated; the three patients who had not been vaccinated experienced severe COVID-19 symptoms, two of whom died. Due to the increased transmission of this variant, we recommend vaccination, wearing a mask, and social distancing to reduce the impact of infection with delta variant B.1,617.2.

STATEMENT OF ETHICS

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

FUNDING SOURCES

No external funding sources were provided in this study.

REFERENCES

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard 2021 [Available from: https://covid19.who.int/.
2. Harvey WT, Carabelli AM, Jackson B, et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol. 2021;19(7):409-24.
3. Del Rio C, Malani PN, Omer SB. Confronting the Delta Variant of SARS-CoV-2, Summer 2021. JAMA. 2021.
4. Centers for Disease Control and Prevention. SARS-CoV-2 Variant Classifications and Definitions 2021 [Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html.
5. Chia PY, Ong SWX, Chiew CJ, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. MedRXiV. 2021.
6. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3):2000045.
7. Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of Coronavirus disease 2019 in China. 2020;382(18):1708-20.
8. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int. 2020;44(9):1792-7.
9. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069-76.
10. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26(12):1622-9.
11. Mlcochova P, Kemp S, Dhar MS, et al. SARS-CoV-2 B.1.617.2 Delta variant emergence, replication and sensitivity to neutralising antibodies. Nature. 2021:2021.05.08.443253.
12. Vacharathit V, Aiewsakun P, Manopwisedjaroen S, et al. CoronaVac induces lower neutralising activity against variants of concern than natural infection. Lancet Infect Dis. 2021;21(10):1352-4.
13. Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021;397(10293):2461-2.
14. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. NEJM. 2021;384(15):1412-23.

Symptomatic Bradycardia Due to Alectinib in a Patient with Advanced Stage of NSCLC

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ABSTRACT

Alectinib is one of the targeted therapies commonly given to patients with advanced non-small cell lung cancer (NSCLC) with mutations in the ALK gene. The most common adverse effects of alectinib are fatigue, constipation, edema, myalgia and anemia. Meanwhile, bradycardia was reported as a very common adverse effect, but generally asymptomatic, unlike the reported patient in this case report. This case report's purpose is to increase awareness of the possibility of adverse effects due to alectinib administration that require immediate intervention in order to improve the quality of life and patient survival, especially in patients with advanced NSCLC.

Keywords**:** *alectinib, bradycardia, NSCLC.*

INTRODUCTION

Lung cancer is the second most common type of cancer in both genders with a 5-year relative survival of 15.7% in the US[1] which are classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[2] Lung adenocarcinoma is one of the NSCLC types.[1] Non-small cell lung cancer with alterations in the ALK gene (ALK positive [ALK+]) is very sensitive to ALK inhibitors, such as alectinib.[3] The administration of alectinib can cause several adverse effects, one of them being bradycardia.[4] Alectinib-related bradycardia is mainly presented as asymptomatic sinus bradycardia,[5] whereas in this case report we elaborate a case of symptomatic bradycardia in ALK+ NSCLC patient treated with alectinib.

CASE ILLUSTRATION

A 57-year-old female patient presented with shortness of breath that had worsened since 10 days prior to the hospital admission in November 2020. The complaint had been getting worse over the past few months, accompanied by dizziness that suddenly occurred and chest heaviness that didn't go away with rest. The patient was diagnosed with ALK+ left lung adenocarcinoma with vertebral metastases in May 2020. The patient has been receiving chemotherapy with alectinib using the reduced dose of 2x300 mg orally (PO) due to recurrent bradycardia in higher doses. The patient's condition was clinically stable for months until bradycardia recurred in November 2020. The patient also took zoledronic acid monthly, mesalazine for Crohn's disease and ursodeoxycholic acid for cholelithiasis which

were both diagnosed several months after the lung cancer. There was diastolic dysfunction from the patient's latest echocardiography in early November 2020.

The patient's vital signs were normal except for a pulse rate of 55 beats per minute (bpm). Physical and laboratory examinations were within normal limits with no signs of peripheral congestion. Chest X-ray examination revealed an image associated with a left lung mass. Initially, the cause of the patient's conditions was thought to be diastolic heart failure. The patient received oxygen supplementation of 3 litres per minute (lpm), anticoagulant and other supportive treatments. Drugs that were routinely consumed were also continued. However, at the first 48 hours of observation, shortness of breath didn't resolve completely. Bradycardia was still ongoing by 45-55 bpm. Re-echocardiography was performed and found grade I diastolic dysfunction with an ejection fraction of 61%.

The patient was diagnosed with symptomatic bradycardia due to alectinib therapy for advanced left lung adenocarcinoma and diastolic heart failure. Alectinib was discontinued. Thereafter, the patient's breath was gradually getting better significantly compared to the admission. The patient's heart rate was also improved, about 55-65 beats per minute. The patient was then discharged after being treated for 6 days.

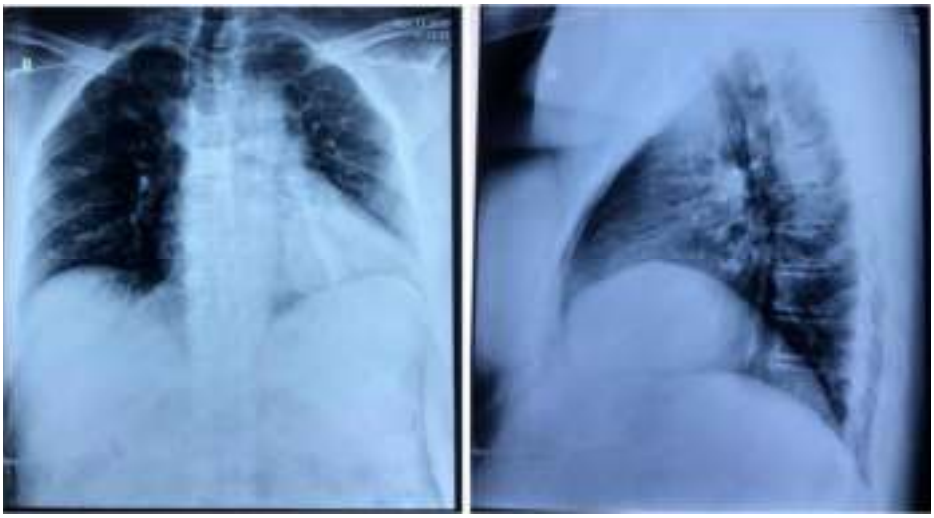

Figure 1. X-ray Imaging of the Patient's Chest.

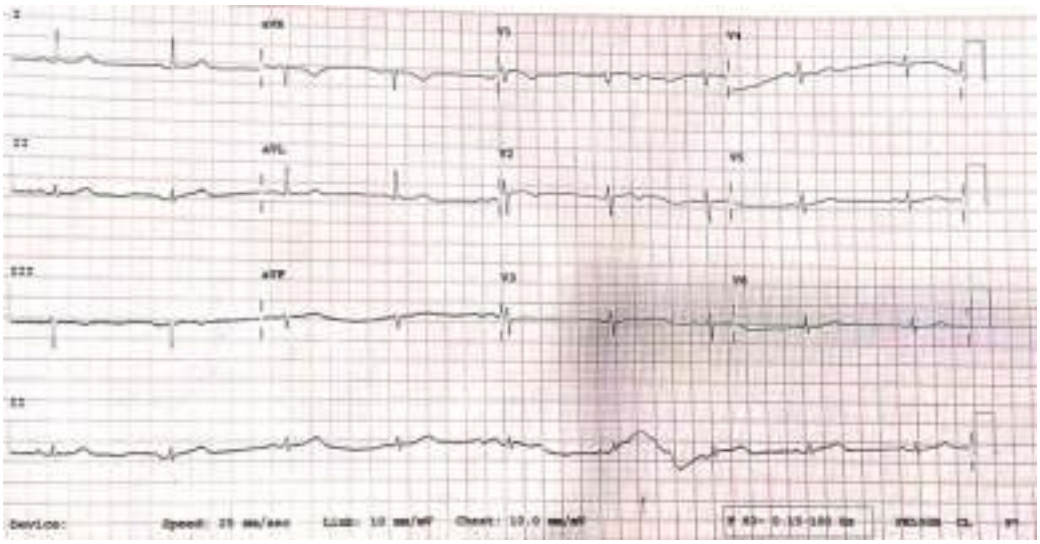

Figure 2. The Patient's ECG on Day 1 of Care.

DISCUSSION

Non-small cell lung cancer patients with distant metastases such as in the brain or bone are generally treated with chemotherapy, targeted therapy, or a combination of both.[1] Alectinib is a targeted therapy for advanced NSCLC with ALK+.[3] The recommended dose of alectinib is 2x600 mg PO. The dose can be reduced to 2x450 mg PO then 2x300 mg PO according to the patient's tolerance and liver function. Alectinib should be discontinued if the patient cannot tolerate the lowest recommended dose.[4]

The most common adverse reactions of alectinib (incidence ≥20%) were fatigue, constipation, edema, myalgia and anemia.[6] Bradycardia was categorized as a very common adverse drug reaction which may occur in ≥1 person out of 10 people.[4] Bradycardia was described as the effect of alectinib on cardiac physiology by a decrease in heart rate of 11-13 beats per minute which is generally asymptomatic, reversible, and majorly presented as sinus bradycardia.[5] Bradycardia occurred in 11% of a total of 405 patients across 3 clinical trials where 18% of patients had heart rates below 50 beats per minute after alectinib administration. There were no cases of symptomatic bradycardia reported.[4] However, according to European Medicines Agency (EMA) and US Food and Drug Administration (FDA), alectinib should be temporarily discontinued if symptomatic bradycardia occurs until the patient's condition improves to asymptomatic bradycardia or until the heart rate is ≥60 beats per minute. Simultaneously, contributing concomitant medication such as anti-hypertensive drugs should be discontinued or have its dose adjusted. Subsequently, alectinib may be resumed at the reduced dose. If life-threatening bradycardia occurs, alectinib should be permanently discontinued if there is no contributing concomitant medications.[4,6] Alectinib can be substituted into drugs of the same class such as ceritinib or brigatinib.[7,8]

In this case report, the patient presented with shortness of breath with sinus bradycardia of 55 bpm with the history of taking the lowest dose of alectinib for about 6 months. There was no significant clinical improvement after the first 48 hours of observation and therapy. Bradycardia was still ongoing. The patient didn't take any medication for diastolic heart failure nor any known drugs that may cause bradycardia, except mesalazine. Out of 4 available case reports, mesalazine-related bradycardia was reported to occur within 24-48 hours after administration of mesalazine either by PO or intravenously (IV).[9-12] The patient didn't have any prior history of bradycardia right after taking mesalazine since September 2020 thus the possibility was disregarded. Another possible cause of bradycardia in this patient is sinoatrial node dysfunction or atrioventricular block which is common in patients with heart failure.[13] However, Holter examination confirmed the sinus bradycardia. Thus, bradycardia was suspected due to alectinib consumption. Alectinib was stopped. Thereafter, the patient's conditions gradually improved.

CONCLUSION

Alectinib is a targeted therapy for NSCLC. One of its adverse effects is bradycardia. Bradycardia is very common and occured in about 11% patients. Although reported cases of bradycardia are mainly asymptomatic, EMA and FDA still warn about the possibilities of symptomatic bradycardia that needs to be treated or even requires immediate treatment during alectinib administration. Rapid identification of adverse effects and appropriate decision making regarding alectinib treatment in patients with advanced NSCLC needs to be encouraged to improve patient's quality of life and survival.

REFERENCES

1. PDQ Adult Treatment Editorial Board. Non-Small Cell Lung Cancer Treatment (PDQ®): Health Professional Version. 2020 Nov 19. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65865/
2. Cersosimo RJ. Lung cancer: a review. Am J Health Syst Pharm. 2002;59(7):611-42. doi: 10.1093/ajhp/59.7.611. PMID: 11944603.
3. Elliott J, Bai Z, Hsieh SC, et al. ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis. PLoS One. 2020;15(2):e0229179. Published 2020 Feb 19. doi:10.1371/journal.pone.0229179
4. European Medicines Agency. Alecensa, INN-alectinib

– European Medicines Agency [Internet]. 2018 Jul 05 [cited 2021 Jan 13]. Available from: https://www.ema.europa.eu/en/documents/product- information/alecensa-epar-product-information_en.pdf
5. Morcos PN, Bogman K, Hubeaux S, et al. Effect of alectinib on cardiac electrophysiology: results from intensive electrocardiogram monitoring from the pivotal phase II NP28761 and NP28673 studies. Cancer Chemother Pharmacol. 2017;79(3):559-68. doi: 10.1007/s00280-017-3253-5. Epub 2017 Feb 27. PMID: 28243683.
6. Food and Drug Administration. Alecensa (alectinib) – FDA) [Internet]. 2018 Jun [cited 2021 Jan 13]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208434s004lbl.pdf
7. Bryson E, Ramalingam S, Beardslee T. Switching to an alternative ALK-inhibitor after alectinib- induced pneumonitis resulted in resolution of this adverse event. Current Problems in Cancer: Case Reports. 2020;2:100023. doi:10.1016/j.cpccr.2020.100023
8. Deng L, Sharma J, Ravera E, Halmos B, Cheng H. Hypersensitivity in ALK-positive lung cancers exposed to ALK inhibitors: a case of successful switch to an alternative ALK inhibitor and systematic review of the literature. Lung Cancer (Auckl). 2018;9:73-77. doi: 10.2147/LCTT.S173948. PMID: 30233266; PMCID: PMC6134951.
9. Odofin A, Wanogho J, Elsadany M, Kostela J, Mattana J. Mesalamine-associated sinus bradycardia. Am J Ther. 2019;26(6):e763-e764. doi: 10.1097/MJT.0000000000000932. PMID: 30883396.
10. Krzyzak M, Gupta A, Antonov E, et al. Mesalamine associated bradycardia. Cureus. 2018;10:e2425.
11. Asirvatham S, Sebastian C, Thadani U. Severe symptomatic sinus bradycardia associated with mesalamine use. Am J Gastroenterol. 1998;93:470–471.
12. Barquero-Romero J, Arrobas-Vacas J, López-Santamaría JL, et al. Sinus bradycardia associated with mesalazine. Med Clin (Barc). 2006;126:639.
13. Masarone D, Limongelli G, Rubino M, et al. Management of Arrhythmias in Heart Failure. J Cardiovasc Dev Dis. 2017;4(1):3. Published 2017 Feb 28. doi:10.3390/jcdd4010003

Quality of Life in Patients with Renal Failure Undergoing Hemodialysis

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ABSTRACT

A good quality of life is one of the many indicators that determine the success of hemodialysis (HD) therapy. Factors that significantly affect the quality of life of patients with renal failure who undergo HD include sociodemographic condition, mental state (depression), severity of kidney disease, accompanying disorders, HD duration, non-adherence towards prescribed medication and nutritional problems. Among said factors, the metabolic and nutritional disorder commonly known as protein energy wasting (PEW), plays an important role in the clinical course of renal failure patients. The aim of nutrition management in patients with renal failure is to slow down the progression of kidney disease, improve quality of life, and reduce cardiovascular morbidity and mortality.

Keywords**:** *Quality of Life, Renal Failure, Hemodialysis.*

INTRODUCTION

The rising prevalence of chronic kidney disease (CKD) has led to an increase in the number of patients requiring hemodialysis (HD). The Global Burden of Disease data in 2010 reported that CKD rose from the 27th leading cause of death globally in the year 1990 to become the 18th in 2010.[1] Renal failure is a clinical condition characterized by an irreversible reduction of renal function, resulting in the inability to maintain biochemical homeostasis and accumulation of body fluids and waste products if one only relies on the help of conservative treatments. Hence, this condition requires renal replacement therapy (RRT) in the form of either dialysis or kidney transplantation.[2] Based on the 2016 Indonesian Renal Registry (IRR), 98% of renal failure patients undergo HD therapy and 2% undergo Peritoneal Dialysis (PD) therapy.[1]

Hemodialysis can be defined as a process of exchanging the composition of blood solutes using a solution of dialysate (dialysis fluid). It can also be described as a process of separating, filtering, or cleaning of blood through a semipermeable membrane which is performed on patients with both acute and chronic impaired renal function.[2] The frequency of HD varies depending on the remaining kidney function, although on average a patient undergoes HD three times a week, with a duration of three to four hours per treatment. Besides the time intensive nature, HD also poses physiological, psychological, and socioeconomic issues that

impacts not only the patient but also the caregiver and society in general. Collectively, these effects will impacts the quality of life of renal failure patients undergoing HD.[2,3]

THE CONCEPT OF QUALITY OF LIFE

Definition

The quality of life of an individual cannot be determined for certain due to its subjectivity, and only the person in question will be able to assess it.[4] The World Health Organization Quality of Life (WHOQOL) group states that quality of life is an individual's perception of their position in life, in the cultural context and value system in which the individual lives, and in correlation with personal goals, expectations, standards and desires. This is a concept, which coalesces with the various ways one can reach adequate levels of physical and psychological state, functional independence, social relations, and bond with the surrounding environment.[4,5]

There are two basic components of quality of life, namely subjectivity and multidimensionality. Subjectivity means that the quality of life can only be determined from the point of view of the individual, and hence can only be known by direct query towards said individual. Meanwhile, the multidimensionality of quality of life refers to the way that it is viewed from multiple aspects within an individual's life, including biological/ physical, social, and environmental. Polinsky (2000) concluded that a person's quality of life is measured by considering the physical, psychological, social and the disease state or condition.[4]

The scope of quality of life

Based on a questionnaire developed by the WHO, there are five general areas of assessment used in the measurement of quality of life, which includes physical health, psychological health, degree of independence, social relationships and the individual's relationship with the environment. These five quality of life indicators are described in detail below.[4]

1. Physical health: general health, protein energy malnutrition (PEM), pain, energy and vitality, sexual activity, sleep and rest.
2. Psychological health: ways of thinking, learning, memory and concentration.
3. Level of independence: mobility, daily activities, communication, work ability.
4. Social relationship: social relations, social support.
5. Environment: security, home environment, job satisfaction.

RENAL FAILURE PATIENTS RESPONSE TO HEMODIALYSIS

Chronic kidney disease (CKD) negatively affects the physical and biopsychosocial aspects of the lives of individuals with the disease, thereby affecting the quality of life (QOL) of patients and their families.[6]

Since chronic diseases have an impact on health-related quality of life (HRQOL), this has become a key outcome measure in disease management. Patients with end stage renal disease (ESRD) require RRT in the form of dialysis or a kidney transplant. Kidney transplantation may offer a nearly normal life and is considered the optimum treatment for eligible patients. Alternative dialysis modalities are HD and PD.[7] The initial response towards HD is generally favorable because the patient deems the intervention as something that can help overcome disease. However, varying response was reported among patients with acute kidney disease who received HD as part of emergency care.[8]

When the onset of renal failure is in the adaptive phase, several studies reported that there are 3 stages of adaptation to dialysis, which includes: [8]

1. The Honeymoon period.

This phase is the initial response towards HD, starting from for the first few weeks until the next 6 months. Usually during this phase, improvement in physical and psychological conditions appear followed by the emergence of hope and confidence to achieve recovery. During the honeymoon period, patients tend to respond positively to the healthcare providers involved.

2. Disenchantment and discouragement period

This period is marked by a decrease in self-confidence and hope for recovery. This

period lasts for 3 - 12 months. This phase arises due to boredom from the the inability to carry out everyday activities and the necessity to periodically undergo HD. During this time, the patient will experience prolonged sadness and hopelessness.

3. Long-term adaptation period

During this period, patients become more accepting of their own limitations as well as the complications they experience while undergoing HD. Although patients may still experience occasional depressive episodes, they are eventually able to adapt especially with support from their surrounding environment.

In reality, not all patients will experience these three phases, and it is common for each individual to go through different experiences. Other psychological issues that may arise among patients undergoing HD include depression, dementia or delirium, anxiety, sexual function disorders and socioeconomic problems.[9]

FACTORS THAT INFLUENCE THE QUALITY OF LIFE OF PATIENTS WITH RENAL FAILURE WHO UNDERGO HEMODIALYSIS

Sociodemographic Factors

Several studies have shown that social demographic factors such as age, gender, ethnicity, economic status, marital status, and employment status are related to a person's quality of life. In general, the physical domain of quality of life will deteriorate as the patient gets older. Differences in treatment outcome expectations and the ability to accept or adapt towards deteriorating health status can also explain the differences in quality of life between older and younger patients. Older patients tend to be more accepting of their health condition and consider it a consequence of aging.[10]

Race also affects the quality of life of patients who undergo HD. Some studies report that European patient groups report better physical and mental health compared to Asian patients. African-American patients who undergo HD report better quality of life compared to Caucasian, Hispanic and Asian patients.[10]

Several studies have reported that lower socioeconomic and education status are associated with lower quality of life among HD patients, wherein employed patients have been shown to have a better quality of life.[11,12]

Female patients with renal failure who undergo HD have a lower quality of life. Likewise, married patients report higher quality of life compared to patients those who are not married. [11,12]

Clinical Factors

Several studies on HD patients have identified clinical and biochemical markers related to the quality of life of patients, particularly towards the physical dimension. [10,11]

1. Hemoglobin: as a marker of anemia that often accompanies renal disease, hemoglobin level is strongly related to the physical function and well-being of the patient. Increased hemoglobin levels after treatment and erythropoietin therapy have been known to improve energy, stamina and patient participation in everyday activities.
2. Protein Energy Malnutrition (PEM): the prevalence of renal failure patients receiving HD therapy is increasing. Various attempts have been made to inhibit the progression of CKD. One of the factors that can hinder CKD progression is to implement a therapeutic diet during the pre-dialysis stage. On the other hand, CKD patients often suffer from nutritional disorders, which are a common comorbidity in renal disease. Among the multiple risk factors found in CKD, metabolic and nutritional disorders commonly known as PEM plays an important role in the course of CKD patients. The pathogenesis of PEM in CKD is multifactorial.
3. Comorbidity of HD patients: increase in the number of comorbid conditions (e.g., cardiovascular disease, peripheral vascular disease, hypertension and diabetes) exerts a negative influence on the physical quality of life domain of and may also affect the emotional domain of quality of life.

Psychosocial Factors

Psychological factors are related to the quality of life and mortality rates of HD patients, most notable among which are depression, the patient's perception of their disease, and the

amount of social support that they receive. Anxiety disorders have also been found to be associated with lower quality of life. Assessment of depression in patients undergoing HD is quite difficult because of the similarities between somatic depression symptoms with symptoms of kidney failure and the side effects of kidney replacement therapy. Several studies have proven a decrease in quality of life and increased mortality rates among HD patients with depression.[10,11]

Social support, either from the patient's family or healthcare providers, plays an important role in improving the quality of life. Patients who received adequate social support from both their family and healthcare provider have reported a better quality of life.[10,11]

Coping strategies hold an important role in determining the quality of life of HD patients. Kidney disease and HD are traumatic experiences that cause stress to patients and their families thereby reducing quality of life. Inability to adapt or cope with the situation will reduce the quality of life for HD patients. [10,13]

EFFORTS TO IMPROVE THE QUALITY OF LIFE OF PATIENTS WITH RENAL FAILURE WHO UNDERGO HEMODIALYSIS

Resolving Anemia

Extensive studies and articles that investigate anemia among renal failure patients have come to similar conclusions. A systematic study by Leaf and Goldfarb concluded that erythropoietin therapy in a study using SF-36, showed a dramatic improvement in physical symptoms, vitality, energy, and performance. It also found a small improvement in social functioning and mental health, and an improvement in emotional health. Optimal improvement was found when hemoglobin levels ranges around 10-12 g/dl.[10,14,15]

Resolving Malnutrition

Nutritional status assessment, monitoring, and intervention are components that play a crucial role in the management of patients with CKD. Adequate nutritional therapy is very important in the long-term management of CKD patients. The increasing prevalence of renal failure has led to improved awareness throughout the world to further enhance strategies to inhibit the progression of CKD. The approach of nutritional therapy in pre-dialysis CKD is one of the strategies that aim to inhibit CKD progression. The approach generally focuses on the intake of protein, salt, potassium, calcium, phosphorus, alkaline derivates, oxalate, citrate, uric acid and water.[16]

The goal of nutrition management in cases of protein-energy wasting (PEW) is to fulfill optimal nutrient intake (carbohydrates, protein fats and micronutrients) which are expected to improve the nutritional status of patients. For decades, protein restriction has been the basic regime for CKD in the pre-dialysis stage. This restriction allows an intake of <0.6-0.8 gram/kg/day in which 50% of the protein source is expected to come from proteins with high biological value. This protein restriction must be accompanied by adequate calorie intake of 30-35 kcal/kg/day. The dietary regime is expected to prevent the occurrence of PEW in the pre-dialysis stage. When the patient has undergone dialysis, the amount of protein intake must be modified from <0.6-0.8 gram/kg/day to 1.2-1.5 grams/kg/day, depending on the patient's dialysis modality.[17]

Besides meeting the needs of protein and calories, fulfillment of other nutrients must also be considered using the following recommendations: 1) Adequate fat intake, especially unsaturated fats; 2) Recommended sodium intake is 2-3 grams/day; 3) Recommended potassium intake is 2-4 grams/day; 4) Fluid requirements must be regulated individually referring to the daily mandatory requirements of 1,000 mL/day (+ urine volume); 5) The need for micronutrients in the form of folic acid (1 mg/day), vitamin B6 (10-20 mg/day), vitamin C (30-60 mg/day), vitamin B1 (0.5-1.5 mg/day), and vitamin E 800 IU.[17]

Resolving Depression

Various treatment regimens have been reported to treat depression in patients with chronic kidney disease. Anti-depressant medications have been used and the results have been reported to significantly improve symptoms

of depression. However, overcoming depression pharmacologically is often contradictory for various reasons.[10]

Assessing Sexual Function

Studies have reported the correlation between sexual dysfunction and other quality of life parameters, such as various mental and physical components. Recent studies have shown that in men with mild to moderate depression, improvement of erectile dysfunction is associated with significant improvement of depression symptoms and quality of life.[10]

Resolving Stress

Stress in patients with kidney disease may become a burden. There are various stressors that affect the lives of HD patients. These stressors may include the impact of the disease on the overall body function, nutritional problems, unemployment, financial difficulties, time constraints, mood fluctuations, functional limitations, and fear of physical disability and death.[10]

Providing Social Support

Social support has been shown to correlate with a variety of domains including symptoms of depression, the patient's perception of disease, life satisfaction, and overall quality of life of patients. Marital and family problems are generally observed in patients with end stage renal disease and may have a negative impact on the individual. Active support from the community also includes spiritual involvement.[10]

CLINICAL APPLICATION OF QUALITY OF LIFE IN PATIENTS WITH RENAL FAILURE WHO UNDERGO HEMODIALYSIS

Assessing quality of life in patients who undergo hemodialysis

Assessing quality of life, in addition to more objective clinical indicators, is now increasingly applied given the numerous questions on its effectiveness and suitability. The Centers for Disease Control and Prevention (CDC) in USA recommends measuring quality of life to help determine the burden of preventable disease, based on its correlation with risk factors. Measuring quality of life will help monitor the progress towards achieving health goals.[18]

In nephrology, evaluating the quality of life involves determining the efficiency and effectivity of various forms of kidney replacement therapy (e.g., HD and peritoneal dialysis), in addition to evaluating the efficiency and effectiveness of various treatments that are applied to patients with renal failure (e.g., recombinant human erythropoietin therapy). Various disease-specific and domain-specific assessment tools have been used to assess quality of life in patients undergoing hemodialysis. Disease-specific assessment tools include Quality of Life Index-D (QLI-D), Kidney Disease Quality of Life Short Form (KDQOL-SF), Kidney Disease Questionnaire (KDQ), Renal Quality of Life Profile (RQLP), CHOICE Health Experience Questionnaire (CHEQ) and Renal Dependent Individualized Quality of Life Questionnaire. Domain-specific assessment tools include Barthel Index of Disability (BI) and McGill Pain Questionnaire (MPQ).[18]

Jesus NM et al (2018) who measured the QOL of individuals with CKD and compare the QOL scores of patients with CKD to the scores of disease-free individuals to find factors associated with better QOL. The WHOQOL-BREF scores of patients with CKD on hemodialysis were lower than the scores observed in the control group. Only the scores in the physical and psychological domains were statistically different between the case and control groups. The variables that more significantly affected the QOL of individuals with CKD on hemodialysis were having a spouse, the number of comorbidities, undergoing hemodialysis at a public clinic, more years of schooling, older age, living with more persons in the household, and longer hemodialysis sessions.[6]

Pratiwi DT et al (2019) at their study who determined the determinants quality of life among 200 hemodialysis patients in the HD Unit Dr. Hardjono Hospital, Ponorogo, East Java, in April 2019 using the Kidney Disease Quality of Life (KDQoL) SF-36 questionnaire showed age, gender, education, type of financing, family income, stress, frequency of hemo-dialysis, level of physical dependence, comorbidity, and social group affect the quality of life of HD patients.[19]

Assist in Decision-making on Patient Management

There are some studies compare the HRQOL of HD and CAPD patients. Surendra NK et al (2019) who measured the health utilities and identified socio-demographic and clinical factors associated with HRQOL for HD and continuous ambulatory peritoneal dialysis (CAPD) of 141 patients (77 HD and 64 CAPD) in Malaysia, showed that CAPD patients had a higher utility index score than HD patients but this was not statistically significant.[7] Jung HY et al (2019) who compared HRQOL over time in 989 patients starting HD or PD showed both patients on HD and PD experienced significant decreases in different HRQOL domains over two years and the degree of changes in HRQOL over time was not different between dialysis modality. However, the scores of three (effects of kidney disease, burden of kidney disease, and dialysis staff encouragement, all $P < 0.05$) and two (sexual function and dialysis staff encouragement, all $P < 0.05$) ESRD domains were still higher in patients on PD compared with patients on HD at one and two years after initiation of dialysis, respectively. PD shows better HRQOL during the initial period after dialysis even after adjusting for clinical and socioeconomic characteristics, and the effect lasts up to two years.[20]

The largest impact that quality of life poses on clinical practice is towards decision-making processes regarding administration of HD. Patients with renal failure are faced with various treatment options which must be decided on, such as when to start HD, acceptable HD modalities, the decision on kidney transplantation, and etc. If no medical contraindications are present, these decisions are made based on personal preference while considering the patient and family condition, and the patient's quality of life to treatment options.[2117]

CONCLUSION

A good quality of life is one of the several indicators of HD therapy success. The factors that affect the quality of life among renal failure patients who undergo HD include sociodemographic factors, mental factors (depression), severity of kidney disease, accompanying disorders, HD duration, non-adherence to prescribed medications and nutritional problems. All are important comorbidities in kidney disease.

Among said risk factors, the metabolic and nutritional disorder commonly known as protein energy wasting (PEW) plays a crucial role in the course of renal failure patients. Nutrition management in patients with renal failure aims to not only slow down the progression of kidney disease, but to also improve quality of life and reduce cardiovascular morbidity and mortality.

REFERENCES

1. Kemenkes RI. Cegah dan kendalikan Penyakit Ginjal dengan Cerdik dan Patuh [online]. (updated on 7 March 2018). www.depkes.go.id/article/view/18030700007/cegah-dan-kendalikan-penyakit-ginjal-dengan-cerdik-dan-patuh.html [accessed on 5 September 2018].
2. Suhardjono. Hemodialisis; Prinsip dasar dan pemakaian kliniknya. Buku ajar ilmu penyakit dalam. 6th ed. Jakarta: Interna Publishing; 2014. p. 2194.
3. NKF-KDIGO. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. ISN. 2013; 3(1):1–163.
4. Gerasimoula K, Lefkothea L, Maria L, et al. Quality of life in hemodialisis patients. Materia socio-medica. 2015;27(5):305.
5. Mollaoglu M. Quality of life in patients undergoing hemodialysis. In Hemodialysis 2013. InTech.
6. Jesus NM, de Souza GF, Mendes-RodrigueS C, de Almeida Neto OP, Rodrigues DDM, Cunha CM. Quality of life of individuals with chronic kidney disease on dialysis. Braz. J. Nephrol. 2019;41(3):364-74.
7. Surendra NK , Abdul Manaf MR, Hooi LS, et al. Health related quality of life of dialysis patients in Malaysia: Haemodialysis versus continuous ambulatory peritoneal dialysis. BMC Nephrology. 2019;20(151):1-10.
8. Theofilou P. Outcomes assessment in end-stage kidney disease—Measurements and applications in clinical practice. Bentham Science Publishers. 2014.
9. Finkelstein FO, Wuerth D, Finkelstein SH. Health related quality of life and the CKD patient: challenges for the nephrology community. Kidney International. 2009;76(9):946-52.
10. Kallenbach JZ. Review of hemodialysis for nurses and dialysis personnel. Elsevier Health Sciences; 2015.
11. Desnauli E, Nursalam N, Efendi F. Indikator kualitas hidup pasien gagal ginjal kronis yang menjalani hemodialisa berdasarkan strategi koping. Jurnal Ners. 2017;6(2):187-91.
12. Soponaru C, Bojian A, Iorga M. Stress, coping mechanisms and quality of life in hemodialysis patients. Archives of Medical Science-Civilization

Diseases. 2016;1(1):16-23.
13. Jaar BG, Chang A, Plantinga L. Can we improve quality of life of patients on dialysis? Clinical Journal of the American Society of Nephrology. 2013;8(1):1-4.
14. Chen SS, Al Mawed S, Unruh M. Health-related quality of life in end-stage renal disease patients: how often should we ask and what do we do with the answer?. Blood Purification. 2016;41(1-3):218-24.
15. Maglakelidze N, Pantsulaia T, Tchokhonelidze I, et al. A. Assessment of health-related quality of life in renal transplant recipients and dialysis patients. Transplantation Proceed. 2011;43(1):376-9.
16. Rasyid H. Pengaturan nutrisi pada pasien penyakit ginjal kronik: Fokus diet rendah protein. National congress XII and annual scientific meeting 2014 Indonesia society of nephrology. 2014;221-7.
17. Rasyid H. Manajemen protein energy wasting pada gagal ginjal; Tantangan dalam menurunkan angka morbiditas dan mortalitas pasien dialisis. Disampaikan pada pidato penerimaan jabatan profesor dalam bidang ilmu penyakit dalam fakultas kedokteran Universitas Hasanuddin. 2017. p. 7-14.
18. Mollaoglu M. Quality of life in patients undergoing hemodialysis. Cumhuriyet University, Health Sciences Faculty, Turkey. 2013:829-33.
19. Pratiwi DT, Tamtomo DG, Suryono A. Determinants of the quality of life for hemodialysis patients. Indonesian Journal of Medicine. 2019;4(2):145-54.
20. Jung HY, Jeon Y, Park Y, et al. Better quality of life of peritoneal dialysis compared to hemodialysis over a two-year period after dialysis initiation. Available at: www.nature.com/scientificreports. 2019.
21. Spiegel BM, Melmed G, Robbins S, et al. Biomarkers and health-related quality of life in end-stage renal disease: a systematic review. Clinical Journal of the American Society of Nephrology. 2008;3(6):1759-68.

Extrapulmonary Manifestations COVID-19

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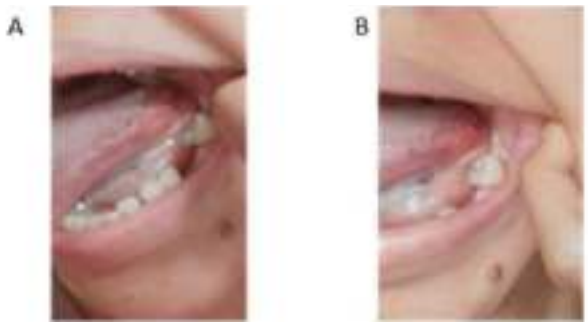
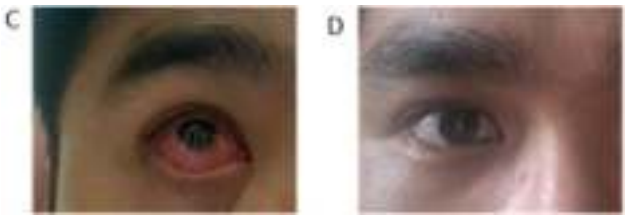
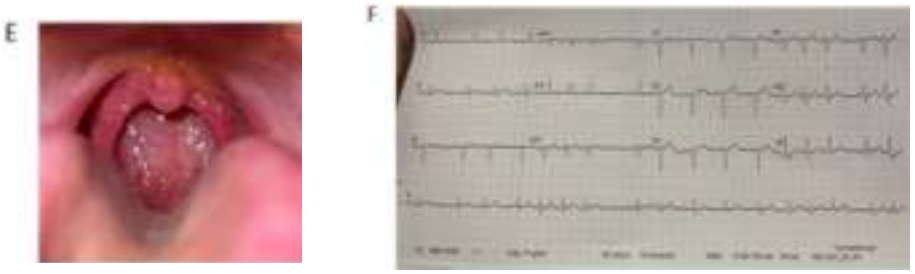


(A). A 44 year-old-female patient with COVID-19 stomatitis and (B) after recovery.



(C) A 37-year-old male with COVID-19 conjunctivitis and (D) after recovery.



(E) A 44-year-old female with COVID-19 pharyngitis.

(F) A 30-year-old female with COVID-19-associated atrial fibrillation.

Figure 1.

After being declared as a pandemic on March 11, 2020 by the World Health Organization, COVID-19 has affected 497 million people worldwide as of 9 April 2022.[1] COVID-19 is a disease with a plethora of clinical manifestations, which extends to those beyond pulmonary signs and symptoms. Studies that report on the clinical presentation of COVID-19 rarely report specifically on cases with only extrapulmonary manifestations of COVID-19.[2,3] Extrapulmonary clinical presentations of COVID-19 without pulmonary signs and symptoms is rare, and in such cases, COVID-19 is rarely suspected.[4]

We herewith describe four patients with extrapulmonary manifestations of COVID-19, with positive SARS-COV-2 PCR when the test was performed for initial patient screening. The first patient is a 44-year-old female who developed painful ulcer (**Figure 1A**) with burning sensation at the lateral side of the tongue along with low grade fever. This symptom appeared after the initial complaints of coughing and nasal congestion subsided. She received steroid-containing mouthwash and aloclair topical. She had no complaint after 14 days. However, the tongue lesion had not recovered completely (**Figure 1B**). The second patient is a 37-year-old male, who complained of red eyes (**Figure 1C**) with itchiness and increased tear production for 3 days before seeing an ophthalmologist. He received anti-inflammatory topical eyedrop 6 times daily. He developed coughing and burning sensation of the throat. On day 10, due to the persistence of symptoms, PCR SARS-COV-2 was performed and came back positive. The eye redness eventually subsided after 12 days of symptom onset (**Figure 1D**). The third patient is a 44-year-old female who developed burning sensation and soreness on her throat (**Figure 1E**) upon swallowing with fever and chills. These symptoms appear consecutively without any respiratory complaint. She received symptomatic medications, and symptoms last for a total of 7 days. Her complaints were resolved after 14 days. The fourth patient is a previously healthy, 30-year-old female, with a normal weight and BMI, and without any comorbidity, cardiovascular risk and neither personal nor family history of cardiovascular disease. Due to complaints of fever, she underwent SARS-COV-2 PCR which came back positive. On day 7, she complained of sudden lightheadedness, exertional dyspnea, anxiety and palpitations and went to the emergency department. ECG was performed, showing non-rapid ventricular response atrial fibrillation (**Figure 1F**). Upon further examinations, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), CRP, Troponin I, and echocardiography were found to be normal. She was admitted for observation, and was started oral bisoprolol. ECG was evaluated the following morning and normal sinus rhythm was found. In these 4 patients, COVID-19 stomatitis, conjunctivitis, pharyngitis and COVID-19-associated atrial fibrillation was subsequently diagnosed, respectively.

In the pandemic stage of COVID-19, COVID-19 screening has often been routinely performed due to the high risk of transmission.[5] However, the decrease in the number of COVID-19 cases may prompt physicians to perform SARS-COV-2 testing based on clinical suspicion. It is imperative to consider the likelihood of COVID-19 and perform SARS-COV-2 PCR in patients with extrapulmonary complaints that have persisting complaints despite treatment.

REFERENCES

1. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus pandemic (COVID-19). 2020.
2. Elrobaa IH, New KJ. COVID-19: Pulmonary and extra pulmonary manifestations. Frontiers in Public Health. 2021;9.
3. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nature Medicine. 2020;26(7):1017-32.
4. Abobaker A, Raba AA, Alzwi A. Extrapulmonary and atypical clinical presentations of COVID-19. J Medical Virology. 2020;92(11):2458-64.
5. Chin ET, Huynh BQ, Chapman LAC, Murrill M, Basu S, Lo NC. Frequency of routine testing for coronavirus disease 2019 (COVID-19) in high-risk healthcare environments to reduce outbreaks. Clinical Infectious Diseases. 2021;73(9):e3127-e9.

Effectiveness of Bendamustine-Rituximab Compared to R-CHOP/R-CVP as a First-Line Treatment of Indolent Non-Hodgkin's Lymphoma or Mantle-Cell Lymphoma

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ABSTRACT

Background: *R-CHOP/R-CVP is the only recommended first-line treatment for Non-Hodgkin's Lymphoma (NHL). Limited treatment alternatives often lead to relapse and refractory NHL, which increases disease progressivity and worsens prognosis. Bendamustine-rituximab is being studied for its potential as a superior first-line therapy for indolent NHL and mantle-cell NHL (MCL); however, it is not in the national guidelines. Evidence-based research is needed to demonstrate the effectivity of bendamustine-rituximab compared to R-CHOP/R-CVP for a complete response of indolent NHL and MCL.* ***Methods:*** *A literature search was conducted using PubMed, Scopus, EBSCOHost, and Cochrane. Studies consistent with clinical question and eligibility criteria were included and critically appraised using the Oxford Centre for Evidence-Based Medicine (CEBM) tool.* ***Results:*** *Two randomized controlled trials (RCTs) were included in this study, both concluding that bendamustine-rituximab is superior to R-CHOP/R-CVP with a complete response, with RR values of 0.90 (95% CI 0.80 – 1.01) and 0.86 (95% CI 0.76 – 0.98).* ***Conclusion:*** *Bendamustine-rituximab is more effective than R-CHOP/R-CVP as a first-line treatment of indolent NHL or MCL.*

Keywords**:** *bendamustine-rituximab, R-CHOP/R-CVP, complete response, indolent non-Hodgkin's lymphoma, mantle-cell, NHL, MCL.*

INTRODUCTION

Non-Hodgkin's Lymphoma (NHL) is the most prevalent hematological cancer, comprising 2.8% of cancer incidence worldwide with 509,590 new cases and mortality rates almost half of the number of new cases (248,724 deaths).[1] In 2018, in Indonesia, NHL was ranked seventh on the list of the most prevalent of all types of cancer, affecting 14,164 citizens, and causing 7,565 mortalities. NHL has been well-known for its increased incidence in the last few decades, which cannot be clearly explained by theorems of etiology, risk factor, and pathogenesis.[3] Even though NHL survival rates top some cancer types, its mortality rate is almost half of its new cases.[1-3] NHL is classified into indolent (slowly-progressing) and aggressive (rapidly-progressing). Indolent NHL subtypes include follicular lymphoma, small lymphocytic lymphoma, chronic lymphocytic lymphoma, marginal zone lymphoma, and lymphoplasmacytic lymphoma. NHL can be

classified, using the Ann Arbor classification system, into four stages based on lymph node involvement. The stages of involvement are: one lymph node is stage I, two or more lymph node regions in one hemidiaphragm is stage II, at least one lymph node in two hemidiaphragms is stage III, and one or more extra lymphatic organs is stage IV.[4]

Referring to the national guidelines *Panduan Nasional Penatalaksanaan Kanker Limfoma Non-Hodgkin's (PNPK LNH)* published by Indonesia's Ministry of Health in 2015; the first-line chemotherapy used to treat stage I and stage II NHL is cyclophosphamide, hydroxydaunorubicin, oncovin/vincristine, prednisone/prednisolone combined with rituximab (R-CHOP) and stages II, III, and IV are treated by cyclophosphamide, vincristine, and prednisone/prednisolone combined with rituximab (R-CVP). If rituximab is contraindicated for stages II, III, or IV indolent NHL patients; then CHOP, COP, and procarbazine (COPP), or fludarabine (FND) can be considered as first-line chemotherapy regimens.[4] A limited number of chemotherapy regimens in Indonesia is a challenge for generating successful outcomes, especially in stages III and IV indolent NHL.[5] Even with a complete response to initial treatment there is still a high chance of relapse and treatment failure (non-complete response or a false complete response) when NHL becomes refractory and progresses faster into more advanced stages.[5] R-CHOP and R-CVP can no longer be used in patients with NHL resistant or refractory cancers.[5] This challenge could be overcome by alternative first-line chemotherapy agents that generate a greater complete response rate, in order to prevent refractory and relapse in patients who fail first-line chemotherapy.[5]

Bendamustine is an alternative chemotherapy regimen widely used in Europe as the first-line treatment of NHL. Based on the European Society for Medical Oncology (ESMO) guidelines, the bendamustine-rituximab combination is the first-line chemotherapy regimen for high-stage follicular lymphoma (Ann Arbor III-IV)[6] and follow-up chemotherapy for relapsed MCL.[7] However, the bendamustine-rituximab treatment efficacy compared to standard R-CHOP and R-CVP regimen is still being extensively researched. Bendamustine is considered to be superior to R-CHOP and R-CVP in its chemotherapy side effects (alopecia, neuropathy, infection, hematological toxicity, stomatitis, etc.), even though it increases the incidences of vomiting, drug hypersensitivity, and secondary malignancy.[8-10] Currently, bendamustine is currently self-produced in Indonesia and is covered by the national health insurance (*BPJS*) as stated in the National Drug Formularium 2018. This development supports bendamustine to be an accessible and applicable chemotherapy choice in Indonesia.[11,12] Therefore, an evidence-based review needs to be conducted to systematically assess bendamustine-rituximab efficacy compared to the current standards for first-line chemotherapy of indolent NHL and MCL.

CASE ILLUSTRATION

A male patient, 43 years old, was admitted to the hospital with a primary complaint of abdominal fullness for three months before admission. Physical examination showed hepatomegaly into the pelvic cavity and general lymph node swelling. Peripheral blood count results showed 12,600/µl leukocytes that consisted of 34% atypical lymphocytes.

Lymph node biopsy confirmed NHL, subtyped as small-cell follicular NHL. Flow cytometry showed 19.1% CD-1, 38.1% CD-10, 84.6% CD-19, and 80.5% CD-20. Test results were negative for Hepatitis B (HB) antigens and antibodies, hepatitis C virus (HCV), and human T- cell leukemia virus type 1 (HTLV-1). Early immunoglobulin (Ig) G antigen tests for Epstein Barr anti-virus and virus capsid IgM showed negative results, viral capsid antigen (VCA) IgG, and Epstein-Barr nuclear antigen (EBNA) showed positive results. Serum immunoglobulin demonstrated 674 mg/dL IgG, 85 mg/dL IgA, and 9 mg/dL IgM. The soluble interleukin (IL)-2 receptor value was 12.800u/mL. Lymphoma chromosomal analysis showed (A) 46XY, t(14:18) (q32;q21) in 1/10 metaphase, and (B) 46 (q32) in 9/10 metaphase. There were no changes in the Bcl-2 and chimeric IgH genes. Mutation tests for p53 genes and EB virus DNA were not conducted.

Table 1. Clinical Question.

Patient/Problem (P)	Intervention (I)	Comparison (C)	Outcome (O)
Patients with indolent NHL or MCL	Bendamustine-rituximab chemotherapy regimen	R-CHOP/R-CVP chemotherapy regimen	Complete Response
Type of Clinical Question	Therapeutic		
Study Design	A meta-analysis, systematic review, randomized controlled trial (RCT)		

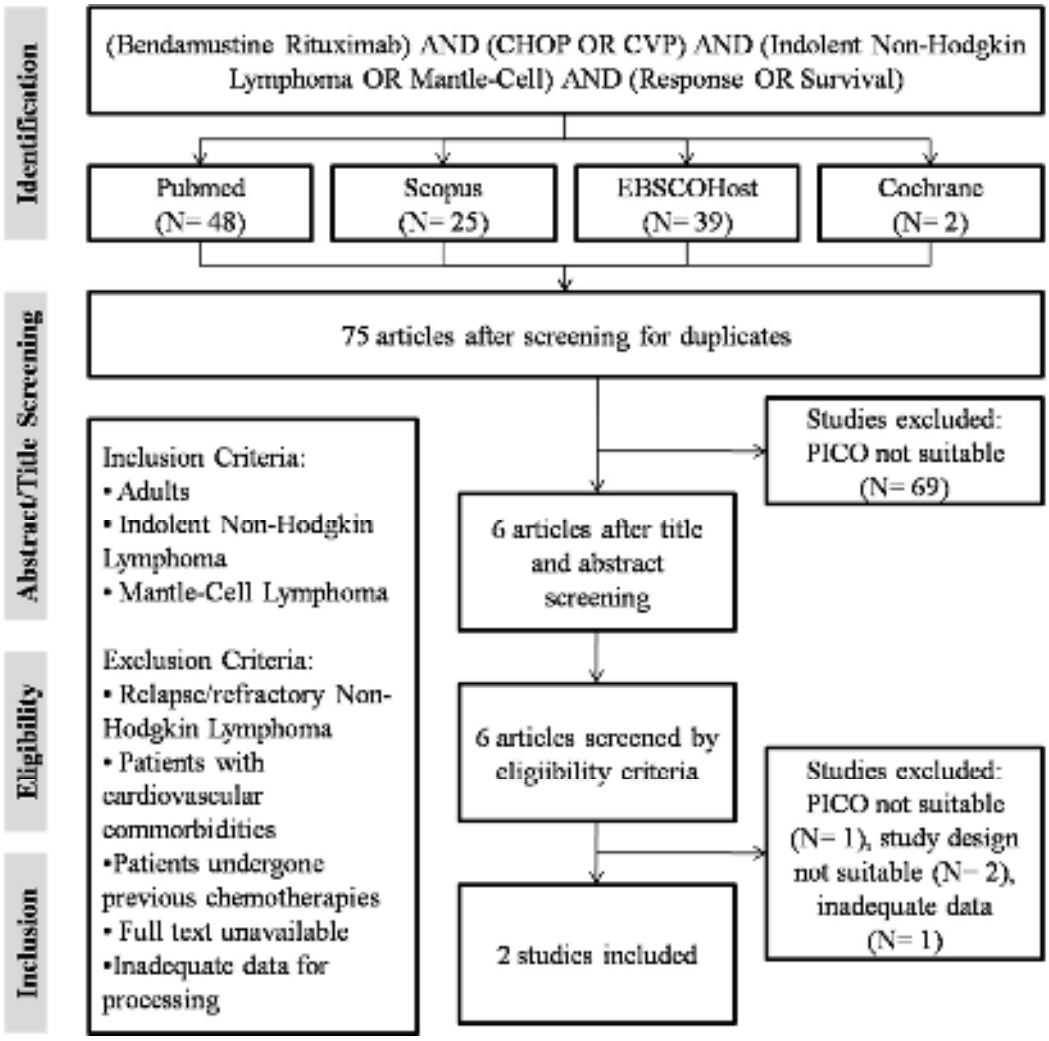

Figure 1. Article Selection Process.

After being told about his diagnosis, the patient stated that his cousin also had a severe case of NHL that progressed quickly. His cousin used an imported drug named bendamustine, which was effective in treating his cancer. The patient had heard that bendamustine was produced in Indonesia and asked if bendamustine was an option for him too.

(Case illustration was modified from a case report in reference.[13])

Clinical Question

"Is bendamustine-rituximab, compared to R-CHOP/R-CVP, more effective in increasing the complete response of indolent NHL or MCL?"

METHODS

A literature search for relevant studies was conducted on March 27-28, 2020, in four electronic databases: PubMed, Scopus, EBSCOHost, and Cochrane. The keywords and Boolean operators typed into the database search engine were "(Bendamustine Rituximab) AND (CHOP OR CVP) AND (Indolent Non-Hodgkin Lymphoma OR Mantle-Cell) AND (Response OR Survival)".

The keyword search in the four databases generated 114 results or 75 studies after duplicates were filtered out. After screening for title and abstract, the author deemed six studies relevant to the clinical question. Based on the eligibility criteria (**Figure 1**), two RCTs by Flinn, et al. and Rummel J, et al. were included. Included studies were critically appraised by the Oxford Center of Evidence-Based Medicine (CEBM) tool.

RESULTS

Two studies selected from the literature search by Flinn IW, et al. and Rummel J, et al. both had a 1b level of evidence, with study characteristics shown in **Table 1**.

A study by Flinn IW, et al. was a randomized clinical trial comparing the effectivity of bendamustine-rituximab to R-CHOP or R-CVP as the first-line therapy of NHL or MCL. Individuals who were eligible based on the study criteria (n=447) were assigned to receive either R-CHOP or R-CVP based on their clinical conditions. They were then stratified randomly to bendamustine-rituximab (n=224) or R-CHOP/R-CVP (n=223) intervention groups. Chemotherapy was given in six cycles, 28 days per cycle for bendamustine-rituximab, and 21 days per cycle for R-CHOP and R-CVP. The regimens used were as follows: Rituximab IV 375mg/m^2, bendamustine IV 90mg/m^2, cyclophosphamide IV 750 mg/m^2 (or 1000mg/m^{2}in R-CVP), vincristine 1.4 mg/m^2 (maximum dose of 2g), oral prednisone 100 mg/day, doxorubicin IV 50mg/m^{2}in the R-CHOP regimen. The primary outcome of this study was a complete response to therapy, meanwhile, the secondary outcome of this study was the overall response and the safety comparison between two regimens. This study is the initial review of the five-year follow-up study, researching the *progression-free survival* and quality-of-life between the two groups.[9]

A study by Rummel J, et al. was a multicenter randomized-controlled trial assessing the effectivity of bendamustine-rituximab compared to R-CHOP as the first-line therapy for indolent NHL and MCL. There were 549 patients randomized based on histological subtypes to either the bendamustine-rituximab intervention group (n=274) or the R-CHOP control group

Table 2. Characteristics of Selected Articles.

Author (Year)	Title	Study Design	samples	Results	Level of Evidence
Flinn IW, et al. (2014)[9]	Randomized Trial of Bendamustine-rituximab or R-CHOP/R-CVP in First-Line Treatment of Indolent NHL or MCL: The BRIGHT Study	RCT	447	CR BR, CR R-CHOP/R-CVP: 31% (95% CI 25.3, 28.2), 25% (95% CI 19.5, 31.7) *p-value for NI test* = 0.0225 (0.88 margin) OR BR, OR R-CHOP/R-CVP: 97%, 91% (p= 0.0102)	1b
Rummel J, et al. (2013)[10]	Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial	RCT	514	CR BR, CR R-CHOP/R-CVP: 40%, 30% (p = 0.021) Median PFS BR, R-CHOP/R-CVP: 69.5 months (26.1-not yet reached), 31.2 months (15.2–65.7) HR: 0.58 (95% CI 0.44–0.74; p<0,0001)	1b

*CR: Complete response, OR: Overall response, PFS: Progression-free survival, HR: Hazard ratio, BR: Bendamustine-rituximab

(n=275). Chemotherapy was prescribed in a maximum of six cycles, 28 days per cycle for bendamustine-rituximab, and 21 days for R-CHOP. The chemotherapy regimens used were as follows: Rituximab IV 375mg/m^2, bendamustine IV 90mg/m^2, cyclophosphamide IV 750mg/m^2, vincristine 1.4mg/m^2 (maximum dose of 2g), oral prednisone 100mg/day, doxorubicin IV 50mg/m^2. Baseline characteristics between the intervention and control groups are presented in **Table 2**. The primary outcome of this study was progression-free survival, meanwhile, its secondary outcomes were complete response, overall response, and comparison of safety.[10]

Both studies showed the complete response of bendamustine-rituximab was superior to R-CHOP/R-CVP, with a significant p-value.[9,10]

Critical Appraisal

Validity

Table 3. Validity Appraisal of Flinn IW, et al.[9]

Parameter		Flinn IW, et al.		Rummel J, et al.
Was the allocation to the intervention group randomized?	Yes	Patients who were already eligible to receive R-CHOP/R-CVP therapy were randomized into intervention and control groups. The method of randomization was not mentioned.	Yes	Randomization was conducted by the center of the study by a 1:1 method to allocate patients to either the bendamustine-rituximab or R-CHOP groups.
Were the initial characteristics of the participants in both groups similar?	Yes	Participants of both groups were similar in baseline characteristics of age, gender, histologic classification, ECOG performance status, Ann Arbor stage, FLIPI risk group, IPI risk group, and clinical manifestations.	Yes	Participants in both groups were similar in age, Ann Arbor stage, histological classification, clinical manifestations, bone marrow, and extra-nodal involvements, LDH levels, median B-2 microglobulin, IPI prognostic group, and FLIPI prognostic group.
Was the follow-up of patients complete?	Yes	The follow-up duration was adequate to judge the complete response, even though the authors did not distinguish between true complete response or relapse. The number of analyzed and excluded patients and reasons for exclusion was presented in the article.	Yes	*A follow-up* of 45 months was adequate to evaluate the complete response of therapies. All patients completed follow-up, though not all were analyzed (reasons elaborated in the study)
Were all patients accounted for in the analysis, according to the randomization groups?	No	Not all patients were accounted for in the analysis, eight out of 221 patients in the bendamustine-rituximab group were excluded, nine out of 215 patients in the R-CHOP/R-CVP group were excluded. However, the patients were analyzed according to their randomization groups.	No	Not all patients were accounted for in the analysis, 13 out of 274 patients in the bendamustine-rituximab group were excluded, 22 out of 225 patients in the R-CHOP/R-CVP group were excluded. The analysis of patients was according to their respective groups.
Were the interventions blinded?	Yes	Evaluation of response was evaluated using the patient's radiology and pathology results, and was conducted by clinicians and workers blinded to the diagnosis.	No	Clinicians, response evaluators, and participants knew the diagnosis and intervention given.
Besides the intervention given, did both groups receive the same treatment?	No	Supportive therapies (antipyretics, antiemetics, or antibiotics) were prescribed based on clinicians' clinical judgment, patients' condition, and health facility protocols.	Yes	All patients received prophylactic antiemetics and did not receive prophylactic antibiotics. G-CSF was given according to the American Society of Clinical Oncology guidelines.

Importance

Table 4. Importance Analysis of Flinn IW, et al.[9]andRummel J, et al.[10]

Parameter	Flinn IW, et al.	Rummel J, et al.
RR	RR = 0.90 (95% CI = 0.80 – 1.01)	RR = 0.86 (95% CI = 0.76 – 0.98)
CER	CER = 75.9%	CER =70.0%
EER	EER = 68.5%	EER = 60.2%
RRR	RRR =9.7%	RRR = 14.0%
ARR	ARR = 7.4% (95% CI =1.05– 15.85)	ARR = 9.8% (95% CI =1.60 – 17.99)
NNT	NNT = 13.51 (95% CI = 6.31 – 95.24)	NNT = 10.2 (95% CI = 5.56 – 62.5)

Applicability

Table 5. Applicability Appraisal of Flinn IW, et al. and Rummel J, et al.

Parameter	Flinn IW, et al.	Rummel J, et al.
Suitability of patient characteristics to study participants	Yes Data on NHL epidemiology in Indonesia was still limited. The average participant age was 60 years old which was in line with the age distribution of NHL patients in Southeast Asia. As appropriate to the characteristics of participants, patients in need of alternative first-line NHL therapy were patients with a high cancer stage, poor prognosis, and poor disease progression.[14]	Yes Study participants were primarily 60-70 years old. This is in line with the characteristics of patients with NHL in Southeast Asia. Patients in need of alternative therapies had higher stage cancers and poor prognostic risk.[14]
The capability of implementing intervention based on available resources	Yes Bendamustine is self-produced in Indonesia and is in the 2018 list of National Drugs Formularium. Bendamustine is available as 25mg and 100mg of injection powder and 100mg, accessible in third level healthcare facilities.[12]	Yes Bendamustine is self-produced in Indonesia and is in the list of National Drugs Formularium 2018. Bendamustine is available as 25mg and 100mg of injection powder and 100mg, accessible in third level healthcare facilities.[12]
Risk and benefit evaluation of intervention	Yes Bendamustine had a superior complete response compared to standard regimens(31.4% to 24.1%) and was proven to decrease incidences of alopecia and neuropathy. Bendamustine was given twice every 28-days cycle, was more cost-effective than CHOP – cyclophosphamide was given every three weeks and vincristine every five days.[12] However, bendamustine increased the incidence of vomiting and increased drug hypersensitivity reactions.	Yes Bendamustine had a superior complete response compared to standard regimens(39.8% to 30%) and was proven to decrease incidences of alopecia, hematological toxicity, neuropathy, infection, and stomatitis. Bendamustine was given twice every 28-days cycle, was more cost-effective than CHOP – cyclophosphamide was given every three weeks and vincristine every five days.[12] However, bendamustine increased the incidence of vomiting and increased drug hypersensitivity reactions.

DISCUSSION

Analysis of Literature Search Results

Alternative therapies to the standard R-CHOP/R-CVP regimen are needed for first-line therapy of indolent NHL and MCL to help solve poor therapy response, minimize relapse, limit complications, and avoid secondary diseases. Bendamustine-rituximab is a combination chemotherapy frequently researched for its potential as a more effective and prognosis-increasing first-line therapy of NHL and MCL.

Both studies reviewed after an evidence-based literature search demonstrated that the combination of bendamustine-rituximab

had a statistically significant (p 0.0225[9], p 0.021[10]) greater complete response compared to R-CHOP/R-CVP (31% to 25%[9], 40% to 30%[10]). Its relative risks were 0.90 (95% CI = 0.80 – 1.01) in Flinn IW, et al. and 0.86 (95% CI = 0.76 – 0.98) in Rummel J, et al. Both results indicated bendamustine-rituximab as a first-line therapy had greater success in eliminating cancer cells compared to the standard regimen of R-CHOP/R-CVP. Even so, the confidence interval of relative risk in Flinn IW spanned through 1.0, while the confidence interval of absolute risk reduction (ARR) and number needed to treat (NNT) in both studies were wide in range.

Besides greater complete response, according to Rummel J, et al., bendamustine-rituximab also had longer progression-free survival compared to R-CHOP (69.5 months to 31.2 months).[10] The results of the Flinn et al. five-year follow-up study also showed better five-year progression-free survival in the bendamustine-rituximab group compared to the R-CHOP group (65.5% to 55.8%).[8] Both results were consistent with a retrospective study by Mondello P, et al. which reported that long-term progression-free survival of 3A follicular lymphoma treated with bendamustine-rituximab was 15 years, while those treated with R-CHOP/R-CVP only had long term progression-free survival of 11.7 years (p 0.03).[15] This suggested that besides being more effective in eradicating cancer cells on initial therapies, bendamustine-rituximab was also better in preventing relapse and cancer progression in the long run.

As for its safety, bendamustine-rituximab decreased incidences of alopecia, hematological toxicity, neuropathy, infection, and stomatitis.[9,10] However, it is also important to consider the fact that bendamustine increased incidences of secondary malignancy,[11] vomiting,[9,] and hypersensitivity reactions[10].

Bendamustine-rituximab is also feasible in implementation, as it is already available in third level healthcare with R-CHOP and R-CVP. Bendamustine-rituximab is also considered more cost-effective, as it has only two types of drugs consumed more infrequently compared to R-CHOP/R-CVP.[12]

Strengths and Limitations of the Study

The strength of this evidence-based case report is being able to analyze the short and long-term effectivity of the regimens and compare their safety profiles. Studies included in this report had met the review's very specific eligibility criteria, resulting in values almost representative of the genuine effect of an intervention on the outcome.

However, this evidence-based case report is limited since it could not confirm the direct effects of bendamustine-rituximab on the indolent NHL subset nor other subsets. This study was also unable to identify the controls as R-CHOP and R-CVP separately. This is caused by the limited amount of studies available.

CONCLUSION

A combination of bendamustine-rituximab is more effective than R-CHOP/R-CVP in generating a complete response against indolent NHL or MCL.

Bendamustine-rituximab should be considered as an alternative to R-CHOP/R-CVP as a first-line therapy for indolent NHL and MCL. More researches comparing bendamustine-rituximab to R-CHOP and R-CVP as different control subgroups, and in each lymphoma subsets, are needed to provide a more accurate representation of their efficacy and safety.

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REFERENCES

1. GLOBOCAN 2018. Worldwide Cancer Incidence. Geneva: IARC WHO; 2019.
2. GLOBOCAN 2018. Indonesia Cancer Incidence. Geneva: IARC WHO; 2019.
3. Chiu BCH, Weisenburger DD. An update of the epidemiology of non-hodgkin's lymphoma. Clin Lymphoma. 2003;4(3):161-8.
4. Komite Nasional Penanggulangan Kanker. Panduan Penatalaksanaan Limfoma Non-Hodgkin. Jakarta: Kementerian Kesehatan Republik Indonesia; 2015.
5. Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma R-CHOP failure-what to do? Hematology Am Soc Hematol Educ Program. 2016;2016(1):366-78.

6. Dreyling M, Ghielmini M, Rule S, Salles G, Vitolo U, Ladetto M. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical practice guidelines. Ann Oncol. 2016; 27(suppl5): v83-v90.
7. Dreyling M, Campo E, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO clinical practice guidelines. Ann Oncol. 2017; 28(suppl 4): iv62-iv71.
8. Flinn IW, Jagt R, Kahl BS, et al. First-line treatment of patients with indolent non-hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: Results of the BRIGHT 5-year follow-up study. J Clin Oncol. 2019; 37(12):984-91.
9. Flinn IW, Jagt R, Kahl BS, et al. Randomized trial of Bendamustine-Rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: The BRIGHT study. Blood. 2014;123(19):2944-52.
10. Rummel J, Nierdele N, Maschmeyer G, Banat GA, Grunhagen U, Losem C, et al.
11. Anna LK. Obat kanker limfoma diproduksi di dalam negeri, harga lebih terjangkau [Internet]. Jakarta: KOMPAS; 2018 [cited 2020 Mar 31]. Available from: https://sains.kompas.com/read/2018/01/29/090000923/obat-kanker-limfoma-diproduksi-di-dalam-negeri-harga-lebih-terjangkau.
12. Keputusan Menteri Kesehatan Republik Indonesia nomor HK. 01.07/MENKES/707/2018. Tentang Perubahan Atas Keputusan Menteri Kesehatan nomor HK.01.07/MENKES/659/2017. Tentang Formularium Nasional. Menteri Kesehatan Repulik Indonesia; 2018.
13. Ota I, Shinohara K, Muraki K, et al. Two cases of non-Hodgkin's lymphoma in first degree relatives. Japanese Journal of Clinical Oncology. 2000;30(12):571-3.
14. GLOBOCAN 2018. Non-Hodgkin Lymphoma. Geneva: IARC WHO; 2019.
15. Mondello P, Steiner N, Willenbacher W, et al. Bendamustine plus Rituximab versus R-CHOP as first-line treatment for patients with follicular lymphoma grade 3A: Evidence from a multicenter, retrospective study. Oncologist. 23(4):454-60.

National Consensus on Portal Hypertension Management in Indonesia

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ABSTRACT

Portal hypertension is a clinical syndrome that consists of hypersplenism, ascites, gastroesophageal varices, and encephalopathy. This condition is marked by increased portal pressure gradient and may occur with or without liver cirrhosis. To date, portal hypertension remains as the leading cause of severe complications and death of a patient with chronic liver disease, especially liver cirrhosis. Therefore, thorough understanding about management of portal hypertension is strongly required, especially considering that many complications of portal hypertension require early diagnosis and treatment to improve the prognosis of the patients. Additionally, although hepatic venous pressure gradient (HVPG) measurement has become a gold standard procedure for measuring portal pressure in the last twenty years, utilization of this method in Indonesia has been hindered by reluctance of the patients due to its invasiveness, high cost, and limited availability. This consensus is developed with evidence-based medicine principles to provide a guideline for portal hypertension management for general practitioners, specialists, and consultants, to achieve better clinical outcomes of portal hypertension in Indonesia.

Keywords: *portal hypertension, liver cirrhosis, chronic liver disease*

INTRODUCTION

Portal hypertension is a clinical syndrome that consists of hypersplenism, ascites, gastroesophageal varices, and encephalopathy. This condition is marked by increased portal pressure gradient in different levels of the portal vein system. Portal hypertension can occur with or without liver cirrhosis. In liver cirrhosis, structural changes in liver sinusoids, such as liver fibrosis and production of regenerative nodules, can increase intrahepatic resistance; thus, increasing the portal pressure. Increased production of nitric oxide (NO) in splanchnic circulation can also induce splanchnic vasodilatation. Eventually, splanchnic vasodilatation will increase portal blood flow,

causing worsened portal hypertension. As a result, there will be abnormal circulation in the form of hyperdynamic circulation, leading to other complications.[1,2]

To date, portal hypertension remains as the leading cause of severe complications and death in a patient with liver cirrhosis. Additionally, although in the last twenty years hepatic venous pressure gradient (HVPG) measurement has become a gold standard procedure for measuring portal pressure, utilization of this method has been hindered by its invasiveness and limited availability, especially in less specialized medical centers. Therefore, this consensus is developed to provide a guideline for portal hypertension management for general practitioners, specialists, and consultants, to achieve better clinical outcomes of portal hypertension in Indonesia.

EPIDEMIOLOGY

Chronic liver disease has affected approximately 300 million people around the world. Globally, the incidence and prevalence of liver cirrhosis are still increasing every year. In Indonesia, ten healthcare centers reported that more than 1,500 patients were diagnosed with liver cirrhosis in 2020. Unfortunately, gastrointestinal endoscopic examination was performed only in a small portion of the patients (35.5% patients with liver cirrhosis) (**Figure 1**).[3] Liver cirrhosis is also the fourth most common cause of death due to non-communicable diseases. The death rate caused by liver cirrhosis has increased up to 65% in the last 17 years.[4] A cumulative data in Cipto Mangunkusumo National General Hospital showed that patients with liver cirrhosis are dominated by male gender (77%) and Child-Pugh A category (51%). Other reports demonstrated an increase in death caused by liver cirrhosis and hepatocellular carcinoma, which is estimated to be 50 million deaths annually in the last two decades.[3,5]

CLASSIFICATION

As mentioned above, HVPG measurement is currently the gold standard to evaluate portal pressure, as well as the best indirect method to assess portal vein pressure. HVPG is defined as the pressure gradient between portal vein and inferior vena cava. The normal range of HVPG is 3-5 mmHg. Diagnosis of portal hypertension can be determined if HVPG is higher than 5 mmHg.[1,2]

Mild Portal Hypertension

In general, patients with compensated liver cirrhosis usually do not show any symptoms.

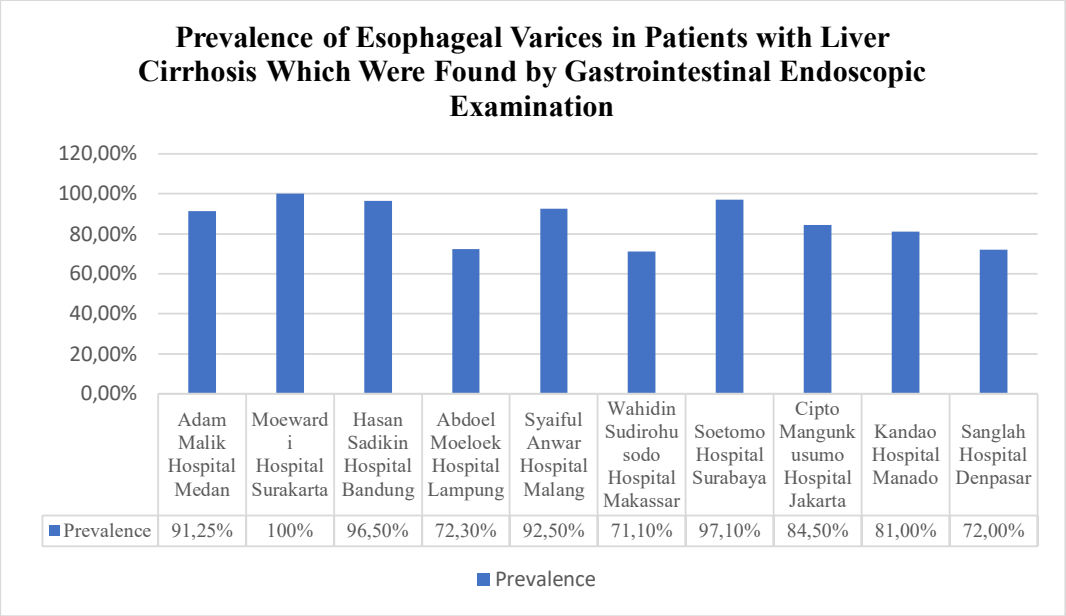

Figure 1. Prevalence of esophageal varices (%) in patients with liver cirrhosis diagnosed with gastrointestinal endoscopic examination in Indonesia (2020).

Compensated liver cirrhosis itself can be differentiated into mild portal hypertension and clinically significant portal hypertension (CSPH).[1,6] Mild portal hypertension is diagnosed when HVPG is within the range of 6-9 mmHg. The therapeutic goal is to prevent the progressivity into CSPH.[6,7]

Clinically Significant Portal Hypertension (CSPH)

CSPH is diagnosed when HVPG is ≥ 10 mmHg. Increase of portal pressure by more than 10 mmHg will contribute to the progression of liver cirrhosis into more advanced stages. Patients with CSPH can be present with or without complications. The therapeutic goal in patients with or without complications is to prevent any decompensation events, especially gastroesophageal variceal bleeding.[6,7]

Clinical Stages of Portal Hypertension

Clinical stages and manifestation of portal hypertension depend on the presence of decompensation, as well as the presence of esophageal varices and other complications of portal hypertension in liver cirrhotic condition. Therefore, the therapeutic goal needs to be adjusted with the clinical stages (**Table 1**).[6,7] A study conducted by Procopet, et al.[8] also highlighted the association between HVPG measurement and clinical outcomes in patients with portal hypertension (**Table 2**).

Table 1. Stages, clinical manifestation, and therapeutic goal of portal hypertension in patients with compensated and decompensated liver cirrhosis.[6,7]

Stages	Compensated Liver Cirrhosis			Decompensated Liver Cirrhosis		
HVPG (mmHg)	< 10	> 10		> 12		
Varices	No	No	Yes	Yes		
Portal Hypertension Complications	No	No	No	Acute variceal bleeding	History of variceal bleeding without other complications	History of variceal bleeding with other complications
Therapeutic Goal	Prevent the CSPH	Prevent the decompensated condition	Prevent the decompensated condition (the first episode of bleeding)	Bleeding control, early prevention of bleeding recurrence and mortality	Prevent the progressivity of decompensated condition (the continuous bleeding) and other complications	Prevent the progressivity of decompensated condition and mortality or other complications

Table 2. Association between portal pressure measurement and clinical outcomes in patients with portal hypertension.[8]

HPVG (mmHg)	Clinical Outcomes
< 5	Normal
6-9	Mild portal hypertension
>6	Progressivity of chronic viral hepatitis, high risk of recurrence after liver transplantation
10	Clinically significant portal hypertension (CSPH)
>10	Progression into esophageal varices, ascites, decompensation, advanced hepatocyte abnormalities, decompensation after liver resection
>12	Esophageal varices bleeding
>16	High mortality
> 20	Failure to bleeding control
> 22	High mortality in severe alcoholic hepatitis

PATHOGENESIS

As time goes by, production and accumulation of extracellular fibrosis in the liver, which were caused by chronic liver injury, can also induce septal fibrosis progressively. Consequently, septal fibrosis will inhibit oxygenation and blood diffusion in the liver parenchyma. The final stage of liver destruction is marked by the significant distortion of the anatomical structure of the liver, such as diminished normal hepatocytes, microvascular and macrovascular changes, neovascularization, formation of nodules, and portosystemic shunt.[1] Another main characteristic of chronic liver disease is a long asymptomatic period. In the first phase (compensated cirrhosis), the patient may show no sign or only minimal symptoms. In that period, portal hypertension occurs minimally in line with decreased liver function. Portal hypertension is a critical process of the transition from compensated cirrhosis into the decompensated state, which is also marked by clinical complications, such as ascites, acute variceal bleeding, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), and hepatic encephalopathy.[3,5]

Portal pressure is mainly influenced by vascular resistance and portal venous system blood flow (**Figure 2**).[9] Increased portal pressure is caused by increased intrahepatic resistance and portal blood flow.[10] The increase of intrahepatic resistance is caused by mechanical (structural distortion of liver parenchyma) and functional (an increase of intrahepatic vascular tone caused by the reduced vasodilatation and imbalance between vasoconstrictor and vasodilator) factors. There are two different mechanisms associated with NO production which may cause increased portal blood flow. The increase of NO production will induce splanchnic vasodilatation, leading to increased portal blood flow. Higher concentration of NO can also induce vasodilatation in systemic circulation, causing arteriole hypotension and relative renal hypoperfusion. Both conditions can stimulate the activation of the renin-angiotensin-aldosterone system (RAAS), promote fluid and sodium retention, cause blood augmentation, and increase cardiac output. As a result, blood flow into the portal system will be increased, and portal pressure will also increase.[11]

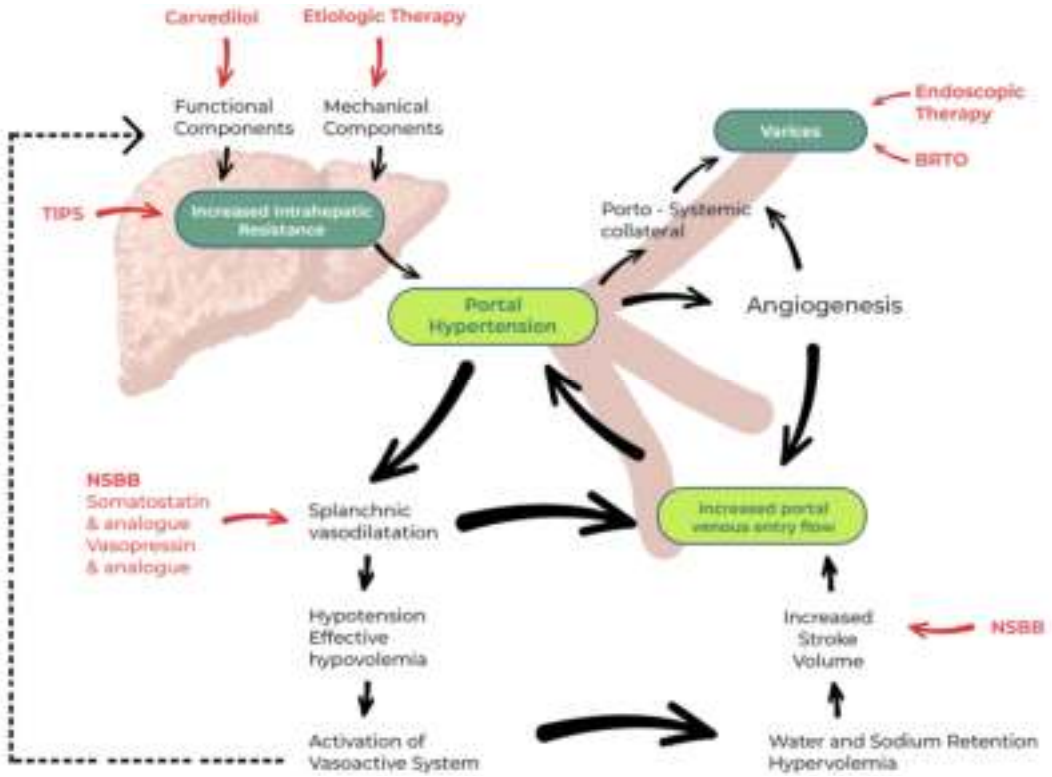

Figure 2. Pathophysiology of portal hypertension (Adapted from [10]).

Increased portal pressure will signal the splanchnic system to induce vasodilatation, and thus, leading to increased blood flow into the portal system. A factor associated with this condition is production of local vasoactive substances by vascular endothelium (NO, prostacyclin, carbon monoxide). The angiogenesis mechanism is stimulated by vascular endothelial growth factors (VEGF) and platelet-derived growth factors (PDGF). NO also plays an important role to induce the splanchnic vasodilatation and angiogenesis process. The concentration of NO in hepatic circulation will be decreased, but it will be increased in the splanchnic area.[10,11]

Portal hypertension also stimulates the production of portosystemic collateral vascular as a response to the increase of portal pressure. Changes of portal pressure is detected by intestinal microvascular cushion and artery from splanchnic circulation. The microvascular cushion will then produce several angiogenic factors, such as VEGF and placental growth factors (PlGF), which will stimulate the formation of portosystemic collateral vessels. The formation of collateral vessel or angiogenesis is an important process to form esophageal varices and ascites.[10,12] Portal hypertension also induces hyperdynamic circulation through the β-adrenergic system as a response towards systemic hypotension.[10] This condition is marked by reduced mean arterial pressure (MAP), reduced systemic vascular resistance (SVR), and elevated cardiac index (CI).[12,13]

DIAGNOSIS

There are several methods to measure portal vein pressure, and currently, hepatic vein catheterization is considered as the best method. The difference between wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) is called HVPG. Therefore, HVPG describes a pressure gradient between portal vein and inferior vena cava.[6,7,14] A study reported that HVPG > 10 mmHg is an independent indicator for varices,[14] decompensation (variceal bleeding, ascites, encephalopathy),[15] increased hepatocellular carcinoma incidences (up to 6-folds increase), and worsened conditions after liver resection.[16] In compensated CSPH, the value of HVPG > 16 mmHg is a prognostic factor for clinical decompensation.[17] In acute variceal bleeding, the value of HVPG > 20 mmHg is also a prognostic factor of recurrent bleeding, therapeutic failure, and higher mortality.[18]

Non-Invasive Examination

Clinical Examination

Clinical examination of portal hypertension consists of physical examination, laboratory examination, imaging studies, liver stiffness measurement, and spleen stiffness measurement. Spider nevi or abdominal portosystemic collateral signs can be found in patients with portal hypertension through physical examination. Other common clinical findings are splenomegaly and ascites.[6]

Biomarker Examination

One of the most common laboratory findings in portal hypertension is thrombocytopenia. Thrombocytopenia is associated with HVPG and gastroesophageal varices, but it is not accurate in diagnosing and excluding portal hypertension or gastroesophageal varices.[18]

Several biomarkers have been evaluated for diagnosing CSPH or severe portal hypertension (**Table 3**). However, most studies were conducted with small sample size, with history of alcohol consumption as the most common etiology of chronic liver disease. In addition, not all serum biomarker examinations are available widely. In conclusion, further validation studies are still needed before these biomarkers can be applied in daily clinical practices.

Other examinations to measure portal hypertension with non-invasive methods are AST to Platelet Ratio Index (APRI) score and Fibrosis-4 (FIB-4) index. APRI can be used as a value or index of reference to predict severe esophageal varices. The measurement of APRI and FIB-4 are recommended by World Health Organization (WHO) to assess the degree of liver fibrosis.[27]

Table 3. Summary of studies which evaluated serum biomarkers for portal hypertension examination in liver cirrhotic patients.

No.	Authors	Biomarkers	Etiology	Results
1.	Busk, et al. (2014)[19]	Tissue inhibitor metalloproteinase -1 (TIMP-1)	n = 84 (dominantly caused by alcohol consumption)	TIMP-1 is significantly correlated with HVPG (r = 0.40; p < 0,0001) For HVPG ≥ 12 mmHg Threshold value: 173.9 ng/mL with sensitivity 99%, specificity 49%, NPV 86%, PPV 88% Cut-off: 33.6 ng/mL, sensitivity 57%, specificity 93%, NPV 33%, PPV 98%
2.	Sandahl, et al. (2015)[20]	CD163-fibrosis portal hypertension score -0.05xsCD163 (mg/L) + 0.03xP3NP (mg/L) + 0.021x HA (mg/L) + 0.001xTIMP-1 (mg/L)	Estimation cohort = 80 Alcohol = 31 Viral = 41 Others = 8 Validation Cohort = 80 Alcohol = 63 Others = 14	For CSPH detection (HVPG > 10 mmHg): Cohort estimation Threshold value: 1.4; sensitivity 100%, specificity 25%, PPV 93%, NPV 100% Threshold value: 3.6; sensitivity 70%, specificity 88%, PPV 99%, NPV 27% Validation cohort Threshold value: 1.4; sensitivity 98%, specificity 50%, PPV 89%, NPV 94% Threshold value: 3.5; sensitivity 92%, specificity 69%, PPV 93%, NPV 73%
3.	Leeming, et al. (2015)[21]	Type IV Collagen (Pro C5)	n = 94 Alcohol consumption	Correlation coefficient between Pro-C5 and HVPG: r = 0.33, p < 0.01 For CSPH Detection: Threshold value: 330 ng/mL; sensitivity 79.7%, specificity 64%, PLR+: 2.2; NLR: 0.32; AUC: 0.73 For detection of HVPG > 16 mmHg vs 10-16 mmHg: Threshold value: 346 ng/mL; sensitivity 80.5%; specificity 48.3%; PLR 1.6; NLR 0.4; AUC: 0.68
4.	Hametner, et al (2016)[22]	VITRO Score (Von Willebrand Factor Antigen/ Thrombocyte Ratio)	n=236 Alcoholism = 93 Hepatitis C = 67 NASH = 29 Others = 19 Unknown = 28	For CSPH detection: Threshold value > 1.58; AUC: 0.86 (95% CI 0.81-0.91); sensitivity 80%, specificity 70%, PPV 93.2%, NPV 40.1%
5.	Bruha, et al. (2016)[23]	Osteopontin	n =154 Alcoholism = 112 Viral = 112 Others included NASH = 20	Correlation between osteopontin and HVPG, p = 0.002, r = 0.25 For detection of HVPG > 10 mmHg: Threshold value: 80 ng/mL; sensitivity 75%, specificity 63%, PPV 92%, NPV 31%; AUC 0.763 For detection HVPG > 12 mmHg: Threshold value 90 ng/mL; sensitivity 71%, specificity 62%, AUC 0.725
6.	Lim, et al. (2016)[24]	Serum Apelin	n = 215 Alcoholism = 155 HBV = 36 HCV = 3 Alcoholism and HBV infection = 12 Alcoholism and HCV infection = 2 Cryptogenic = 7	Association between s-apelin and HVPG (R^2 = 0.356, p < 0.001) AUC for prediction of CSPH: 0.962 Mean of s-apelin concentration in CSPH vs non-CSPH: 946.3±155.0 pg/mL vs 550.9±126.6 pg/mL, p < 0.001

7.	Kirnake, et al. (2018)[25]	APRI	n= 277	Correlation between APRI and HVPG (Spearman's rho = 0.450, p < 0.001)
			Alcoholism=135	For detecting HVPG > 12 mmHg.
			Cryptogenic/NASH = 104	Threshold value: 0.876; sensitivity 71% (95% CI 65-77%), specificity 78% (95% CI 65-89%), PPV 94% (95% CI 90-96%), NPV 38% (95% CI 32-44%), AUC 73% (95% CI 67-78%)
			Hepatitis B = 8	
			Hepatitis C = 23	
			Hepatitis B and C = 3	
8.	Zou, et al. (2019)[26]	von Willebrand Factor (vWF)	Meta-analysis from six studies (n=994)	
			Alcohol (282), viral (260), others etiologic (N/A)	For HVPG > 10 mmHg: pooled sensitivity 82% (95% CI 78-86%); specificity 76% (95% CI 68-83%); PLR: 3.11 (95% CI 1.99-4.86); NLR: 0.21 (95% CI 2.49-4.72); NLR: 0.21 (95% CI 0.11-0.40); AUC: 0.87 (95% CI 0.80-0.94)
				For HVPG > 12 mmHg: pooled sensitivity 86% (95% CI 80-90%); specificity 75% (95% CI 66-83%); PLR: 3.43 (95% CI 2.49-4.72); NLR: 0.19 (95% CI 0.14-0.27)

Equation (1):

$$\text{APRI} = \frac{\text{AST (upper limit normal)}}{\text{Thrombocyte Count}} \text{ x } 100 \text{ x } 10^9 \text{ L}$$

Equation (2):

$$\text{FIB} - 4 = \frac{\text{Age (Year)}}{\text{Thrombocyte Count x } \sqrt{ALT}} \text{ x AST}$$

A study by Kirnake V, et al. on 277 patients with liver cirrhosis shows a significant correlation between APRI and HVPG. The cut-off of APRI is 0.876, and this cut-off has a tremendous positive predictive value (PPV) as high as 94% to predict HVPG > 12 mmHg with moderate accuracy (73%). APRI can be used as a predictor for severe esophageal varices. The value of APRI > 1.4 demonstrated sensitivity of 93.9% and specificity of 60% as a reference of index value for early intervention in patients with severe esophageal varices.[25] Cho EJ, et al. reported the accuracy of several biomarkers for assessing CSPH and esophageal varices in patients with liver cirrhosis caused by alcohol consumption. In their study, FIB-4 with cut-off 4.1 to detect CSPH had sensitivity of 70%, specificity of 42.3%, PPV of 13.5%, and NPV 59.2% with area under the curve (AUC): 0.65 (95% CI: 0.5-0.8).[28] This study showed that FIB-4 had low accuracy for assessing CSPH or even esophageal varices. The limitation of APRI and FIB-4 is the value of these diagnostic modalities is dominantly influenced by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) by the degree of inflammation, such as in acute hepatitis or acute on chronic liver failure (ACLF).[27] Due to its low sensitivity, specificity, and positive predictive value compared to endoscopic examination, APRI is not recommended as an alternative examination for esophageal varices screening.[29]

Imaging Modalities

Several imaging modalities can be used to diagnose and evaluate portal hypertension, such as abdominal ultrasonography (Abdominal US), magnetic resonance imaging (MRI), computed tomography (CT-scan), and transient elastography.[30]

- **Abdominal US**
  Abdominal US is a non-invasive examination for patients with chronic liver disease and liver cirrhosis. Abdominal US is considered as a more cost-effective method with less adverse events in comparison to CT-scan and abdominal MRI to assess portal hypertension and liver fibrosis. Abnormal

findings that support the diagnosis of CSPH are the signs of liver cirrhosis, splenomegaly, ascites, portal vein dilatation, splenic vein or mesenteric vein dilatation, portosystemic collateral (recanalization of the paraumbilical vein, spontaneous splenorenal circulation, and the dilatation of gastric vein), venous return of portal vein, and reduced velocity of hepatofugal portal venous blood flow.[29] Abdominal US can also be used for blood flow identification in hepatic artery, hepatic vein, and portal vein. An example of abdominal US image with M-mode in the spleen of patients with portal hypertension is attached below. The figure also shows prominent varices at the posterior side of the spleen (**Figure 3**).[31] Hepatic vein blood flow wave can be used as a predictor to assess the severity of portal hypertension because of its clinical association with HVPG. Nevertheless, abdominal US also has several limitations, such as operator-dependent, variability between intra- or even interobserver, influence of inspiration and expiration towards the results, as well as the presence of gas, ascites, and obese condition which may also influence the validity of the results.[29]

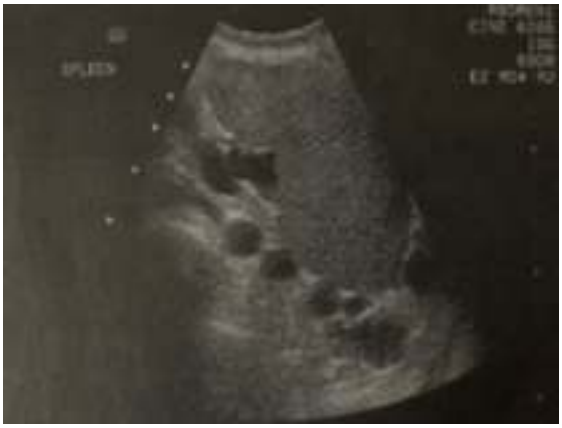

Figure 3. Abdominal ultrasound image of a patient with portal hypertension.[31]

Several parameters of Doppler US that are used as diagnostic parameters are blood flow velocity, flow direction, damping index, intraparenchymal splenic artery resistance index (SA-RI), superior mesenteric artery-pulsatility index (SMA-PI), and right interlobar renal artery resistive index (RRA-RI)[31] (**Table 4**).

- MRI and CT-scan
  These modalities can be used as a standard method for diagnosing hepatocellular carcinoma in patients with liver disease,

Table 4. Summary of studies which evaluated diagnostic performance of Doppler parameters in portal hypertension.

Study	Number of Subjects	Etiology	Parameters	Cut-Off	Diagnosis	Se/Sp/PPV/NPV	AUROC
Kondo, et al.[32]	236	Mixed	Blood flow velocity	12.8 cm/s	Decompensation	68/75/68/75	0.73895
			Flow direction	Hepato-fugal	Prognosis	21.8/99.3/70.6/60.6	-
Kim, et al.[33]	76	Mixed	Damping index	0.6	Severe portal hypertension (HVPG > 12 mmHg)	75.9/81.8/91.1/58.1	0.860
Vizzutti, et al.[34]	66	Hepatitis C Viral	SA-RI	0.6	Severe Portal Hypertension	84.6/70.4/80/76	0.82
			SMA-PI	2.7	Severe Portal Hypertension	85.7/65.2/79/75	0.78
			RRA-RI	0.65	Severe Portal Hypertension	79.5/59.3/74/66	0.78

including liver cirrhosis. However, the accuracy of CT-scan and MRI in diagnosing early stages of liver cirrhosis are limited. However, MRI and CT-scan can still be used if complications, such as ascites and portal vein dilatation, occur. MRI and CT-scan are also considered as the best diagnostic modalities to find morphological changes in hepatic and adjacent tissues. Both modalities can also detect hemodynamic changes. With multidetector CT, the scanning process can achieve submillimeter size, and thus, enabling the device to assess portosystemic collateral condition. The sensitivity and specificity of both modalities are 93% and 80%, respectively, for detecting esophageal varices. Another application of CT-scan is esophagography CT multidetector. Esophagography needs air insufflation into the esophagus via an oral tube and patient is requested to ingest a capsule. Hitherto, these supporting examinations are still considered as safe and reliable. Therefore, these methods can be used as alternative examinations, especially for patients with contraindications to esophagogastroduodenoscopy.[35]

- **Magnetic Resonance Elastography (MRE)**
  MRE is a method to assess liver elasticity quantitatively. MRE can distinguish different body tissues with higher accuracy compared to other modalities, such as abdominal US, CT-scan, and conventional MRI. Another advantage in using this modality is lack of influence of body composition, lack of influence of the ability of operator, and the ability to assess liver function more thoroughly. Nonetheless, MRE is still considered as an expensive modality, and thus, making it less available for routine diagnostic modality.[29]
- **Transient Elastography**
  According to recent studies, progressivity of liver fibrosis is associated with increased liver stiffness. Transient elastography (Fibroscan) is the most common method for assessing liver stiffness.[30] Liver stiffness showed good correlation with HVPG (r= 0.55-0.86; $p < 0.04$), and hence, making it also possible to detect CSPH. The Baveno VI consensus recommended cut-off value of > 21 kPa to suspect CSPH in patients with compensated advanced liver disease caused by viral infection.[30,35] In line with progression of portal hypertension, there will also be a progressive increase in spleen size due to venous return to the spleen, hyperplasia, angiogenesis, and fibrogenesis.[30] In another study, spleen stiffness also showed good correlation with the findings of transient elastography and HVPG (r=0.78; $p < 0.05$). A study in patients with liver cirrhosis caused by hepatitis C infection demonstrated threshold value of liver stiffness < 40 kPa to exclude the probability of CSPH. This value had sensitivity as high as 98%. Moreover, threshold value of ≥ 53 kPa to suspect CSPH had specificity of 97%.[36] However, measurement of spleen stiffness with transient elastography also showed failure rate as high as 15-20%.[1]

Invasive Examination

HVPG Measurement

Measurement of HPVG is considered as the gold standard examination for portal hypertension. HVPG is the difference between WHVP and FHVP (**Table 5**). WHVP is measured by occluding hepatic vein until blood flow stopped and stasis occurred. Hepatic vein occlusion can be performed through distention of hepatic veins with a balloon catheter, while non distended balloon catheter can be used for measuring free hepatic venous pressure (non-occlusion). In patients with liver cirrhosis, HVPG is also a predictor of survival and risk of decompensation. Meanwhile, in decompensated patients, HVPG can be used to assess the risk of mortality. Furthermore, HVPG measurement can also be used as an indicator of prognosis and therapeutic efficacy in patients with portal hypertension, for instance, in the usage of propranolol.[24]

Continuous monitoring of HVPG changes should be performed due to its association with

clinical outcomes of the patients. Previous studies indicated that if HVPG value could drop for more than 20% from baseline value or decrease until it reaches < 12 mmHg, then the risk of rebleeding, ascites, encephalopathy, and death will also decrease significantly. In compensated liver cirrhosis, > 10% decrease in HVPG from baseline reduces the risk of esophageal varices, variceal bleeding, and death.[37] However, to date, non-invasive examination with decent accuracy in diagnosing changes of HVPG is still not available yet. A retrospective study by Choi SY, et al. in 23 liver cirrhosis patients with serial HVPG measurement showed that changes in liver stiffness level measured with shear-wave elastography correlated with HVPG changes. However, further studies with larger sample size are still necessary to validate the benefit of monitoring HVPG with liver elastography.[38] More data are also required to support the validity and applicability of HVPG monitoring in patients who receive primary prophylaxis.[39]

Esophagogastroduodenoscopy (EGD)

EGD is a standard procedure to diagnose gastroesophageal varices. EGD has also been demonstrated to be useful in predicting bleeding risk. Location, size, and characteristics of esophageal varices can be assessed with EGD (**Table 5**). However, there are still several concerns on the use of EGD due to its invasiveness, high cost, and complications, such as infection, bleeding and perforation.[6,36]

EGD screening is recommended for all liver cirrhotic patients at the time when diagnosis of cirrhosis has been established. After endoscopic screening, patients with moderate or large varicose veins should be treated to prevent bleeding episodes, while other patients, who do not have any history of prior esophageal varices and who have not received any therapy for the etiology of their liver cirrhosis, have to undergo periodical surveillance endoscopic examinations every two years. Meanwhile, patients, who have received therapy for the etiology of their liver cirrhosis, are recommended to have the surveillance every three years. If the initial screening reveals small esophageal varices, it is recommended to repeat the endoscopy one year afterwards if no etiologic therapy has been given or after two years if etiologic therapy has been given. If the patient shows any clinical signs of decompensation, it is advisable to perform EGD examination again.[6]

Liver Biopsy

Liver biopsy is a gold standard examination for diagnosing liver cirrhosis. Liver biopsy is usually followed by evaluation with scoring system to determine the degree and stages of chronic liver disease. However, this examination is invasive, thus the usage is limited. The risk of error in tissue sampling may also affect the results of examination (**Table 5**).[35]

Table 5. Summary of non-invasive and invasive diagnostic modalities for patients with portal hypertension in liver cirrhosis.[40]

Diagnostic Methods	Findings
Non-Invasive	
Ultrasonography (USG)	
Liver	Irregular surface, inhomogeneous, focal lesion in liver
Portal Vein	Dilatation, thrombosis +/-
Spleen	Splenomegaly
Portosystemic Collaterals, ascites	+
CEUS (Contrast-Enhanced Ultrasound) Examination	Slow enhancement of periportal/heterogeneous/ homogenous
Cross-sectional imaging	Better characterization of liver focal lesion
Elastography	
Liver Stiffness	↑
Spleen Stiffness	↑
Invasive	
Liver Biopsy	Fibrosis and changes in liver architecture
Liver Hemodynamic	Normal FHVP, WHVP↑, HVPG↑, hyperdynamic circulation
Endoscopy	Esophageal varices and hypertensive gastropathy are more commonly observed, whereas gastric varices are less common to be found

MANAGEMENT

Effective reduction of portal pressure can reduce the incidence of complications and improve survival in patients with cirrhosis. Therapeutic efficacy on portal pressure can be assessed indirectly through clinical outcomes, such as the incidence of variceal bleeding, or directly through HVPG assessment. Achieving a pressure gradient of less than 12 mmHg or a 20% decrease from baseline is associated with decreased incidence of significant complications.[11]

Ascites

The presence of ascites is one of the poor prognostic markers in cirrhotic patients, with a reduction in 5-year survival from 80% in compensated cirrhotic patients to 30% in decompensated cirrhotic patients with ascites. The main pathophysiology of ascites is sodium retention by the kidneys due to activation of the sodium retention system, such as RAAS and sympathetic nervous system. Decreased effective volume due to vasodilation of splanchnic arteries can lead to a positive fluid balance, causing an increase in extracellular fluid volume.[5] Ascites is classified according to the amount of fluid in the abdominal cavity (**Table 6**).[1,41] Diagnostic paracentesis is indicated in all patients with episodes of first, second, or third grade of ascites, as well as in all patients who require treatment for complications of cirrhosis. Assessment of neutrophil levels, total protein, albumin concentration, and fluid cultures should be performed. Cultures with at least 10 mL of ascites fluid were performed to exclude the possibility of bacterial peritonitis. In cases where the cause of ascites is unclear, serum ascites albumin gradient (SAAG) calculation can be helpful where SAAG > 1.1 g/dL indicates the involvement of portal hypertension in ascites formation.[5]

Ascites without Complications

Ascites without complications is defined as ascites without infection or refractory episodes or HRS. Generally, the management of ascites consists of sodium restriction, administration of diuretics, and therapeutic paracentesis. Sodium intake is maintained between 80-120 mmol/day, which is equivalent to 4.6-6.9 grams of salt/day. A diet with very low sodium intake (<40 mmol/day) should be avoided because it can cause complications when administered together with diuretics and interfere with the nutritional status of the patient. Fluid restriction is only recommended in hypervolemic hyponatremic patients with sodium levels <130 mEq/L with ascites and/or edema.[5,42]

Meanwhile, the goal of diuretic administration is to achieve a negative fluid balance, which can be shown from the weight loss. The effectiveness of diuretic administration in controlling ascites is about 90% in patients without renal impairment.[42] Ideally, weight loss must not exceed 500 mg/day in patients without peripheral edema and must not exceed 1000 mg/day in patients with peripheral edema to avoid contractions in plasma volume, which may lead to renal failure or hyponatremia.[43] In cirrhotic patients, secondary hyperaldosteronism plays a major role in sodium retention. Hence, drugs that work as anti-mineralocorticoids become drugs of choice for ascites. The maximum recommended dose is 400 mg/day. Related with delayed anti-mineralocorticoid effects, the dose of these drugs should not be increased in less than 72 hours.[5] On the other hand, in patients with long-standing ascites, sodium reabsorption in the proximal

Table 6. Management of ascites according to the severity grading.[5]

Classification	Definition	Management
1st Grade (mild ascites)	Ascites is only detected through ultrasonography examination.	No special treatment is required.
2nd Grade (moderate ascites)	Ascites appears as symmetric abdominal distension.	Sodium restriction and diuretic administration.
3rd Grade (severe ascites)	Ascites appears as a significant abdominal distention.	Large volume paracentesis and administration of albumin (8 gram/L of ascitic fluid that is removed through paracentesis) followed by sodium restriction and diuretic administration

tubule may occur. Therefore, in this group of patients, strong diuretics (loop diuretics) can be given. Furosemide can be administered as an adjunctive therapy by increasing the dose gradually (starting at 40 mg/day up to 160 mg/day – increased by 40 mg). In patients with good compliance, but ascites is still not controlled, the dosage of diuretic can be increased by doubling the dose (1:1 ratio) until it achieves the maximum dose of spironolactone (400 mg/day) and furosemide (160 mg/day). Once ascites mobilization is achieved, the dose of diuretic should be reduced gradually to the lowest dose needed to control ascites in order to minimize side effects.[42] The side effects that need to be noticed are fluid and electrolyte imbalances, such as hyponatremia, dehydration, renal impairment, hyperkalemia or hypokalemia, and subsequently, hepatic encephalopathy. Spironolactone also tends to cause gynecomastia and muscle cramps in some patients. [5,42]

In patients with large or grade 3 ascites, the first line of treatment is large-volume paracentesis (LVP) (more than 5 liters) performed in a single session. It is recommended to perform LVP with ultrasound guidance to reduce the possibility of side effects. Taking ascites fluid in large volume can potentially cause post-paracentesis circulatory dysfunction (PPCD). The clinical manifestations can be renal failure, dilutional hyponatremia, and hepatic encephalopathy. For this reason, plasma volume expansion at the end of the paracentesis is necessary. Administration of plasma expanders, such as dextran-70 (8 g/L of ascitic fluid taken), polygeline (150 ml/L), and saline (170 ml/L), has demonstrated similar efficacy to 20% albumin (8 g/L) if the fluid taken is less than five liters.[42]

Refractory Ascites

Refractory ascites is defined as ascites which cannot be mobilized or recurrent in a short duration after LVP or without any adequate response towards pharmacological treatment (**Table 7**). Refractory ascites is also one of the bad prognostic markers in cirrhotic patients, indicated by approximately 6-months of mean survival duration. Another term, i.e., recurrent ascites, is defined as the presence of recurrent ascites episodes for at least three times in one year.[5,42] Therapeutic LVP is considered as a safe and effective option for refractory ascites. It is recommended to stop diuretic administration when diagnosis of refractory ascites has been determined. Diuretic administration can be considered again if it can be tolerated by the patient with renal sodium excretion > 30 mmol/day.[42]

Aside from LVP, several other therapeutic options can be considered in managing refractory ascites. The first option is by creating Transjugular Intrahepatic Portosystemic Shunt (TIPS), where intrahepatic stent will be placed between hepatic vein and portal vein for portal decompression and for stimulating peripheral artery vasodilatation in short time.[42] The most common complication of TIPS is hepatic encephalopathy, especially with the use of bare stent graft.[44,45] The rate of complications decreased by 18% with the use of polytetrafluoroethylene-covered stent.[46] In general, TIPS is not recommended in the presence of serum bilirubin level higher than 3 mg/dL, platelet counts < 75,000, hepatic encephalopathy grade ≥ 2 or chronic, active infection, progressive renal dysfunction, severe systolic or diastolic dysfunction, or pulmonal hypertension.[5] The use of continuous drainage catheter can be considered if TIPS cannot be performed. Peritoneal catheter can be placed percutaneously by using tunnel or non-tunnel technique, depends on the types of catheters. It is important to remember that the use of catheter for more than 12 weeks has been associated with significantly higher risk of infection.[47,48] Hitherto, additional administration of alpha-adrenergic agonists, such as midodrine or clonidine, has not been recommended as a therapeutic option for refractory ascites.[5,42]

Hepatic Hydrothorax

Hepatic hydrothorax is defined as accumulation of transudate fluid inside the pleural cavity (usually more than 500 mL) in decompensated cirrhotic patients without any other cardiopulmonary comorbidities or pleural abnormalities.[49,50] The presence of intrathoracic negative pressure and intraabdominal positive pressure may lead to ascitic fluid movement through diaphragm minor openings. These openings are usually located on the tendinous

Table 7. Definition and diagnostic criteria of refractory ascites.[5]

Definition	
Diuretic-resistant ascites	Ascites which cannot be mobilized or recurrent ascites in short duration and cannot be prevented due to inadequate responses with sodium restriction and diuretic administration.
Diuretic-intractable ascites	Ascites which cannot be mobilized or recurrent ascites in short duration and cannot be prevented to avoid diuretic complications, and thus, leading to inability to achieve the most effective dose of diuretic.
Diagnostic Criteria	
Duration of therapy	When the patient has already been in intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least one week and sodium restriction (< 90 mmol/day).
Inadequate response	Mean weight loss < 800 gram after four days and lower urinary sodium excretion compared to sodium intake.
Early recurrence	Re-appearance of grade 2 or 3 ascites within 4 weeks after early mobilization.
Diuretic complications	- Hepatic encephalopathy caused by diuretics (excluding other possible causes). - Renal dysfunction caused by diuretics: increased serum creatinine for > 100% until > 2 mg/dL (177 umol/L). - Hyponatremia caused by diuretics: decreased serum sodium level > 10 mEq/L until < 125 mEq/L. - Hypo- or hyperkalemia caused by diuretics: changes of serum potassium level until < 3 mEq/L (hypokalemia) or > 6 mEq/L (hyperkalemia). - Unexplained muscle cramps.

part of diaphragm, which is usually covered with pleuroperitoneum. Hepatic hydrothorax is also considered as a marker of bad prognosis with approximately 8-12 months of mean duration of survival.[51,52] In hepatic hydrothorax, pleural effusion is usually found in the right pleura with transudate characteristic. Other common laboratory findings from pleural fluid analysis include < 250/mm^3 polymorphonuclear leukocytes (PMN) count, protein < 2.5 gram/dL, ratio between protein in the pleural fluid/serum protein < 0.5 with the gradient of serum albumin-pleural fluid > 1.1 gram/dL, and ratio between LDH in pleural fluid/serum LDH < 2:3. In the presence of spontaneous bacterial empyema, diagnosis can be established when positive result is obtained from pleural fluid culture accompanied with increased neutrophil count by > 250/mm^3 or negative result from pleural fluid culture accompanied with increased neutrophil count by > 500/mm^3.[5,50]

The first line management in hepatic hydrothorax is treating ascites by administering diuretics and/or LVP. Therapeutic thoracocentesis is indicated in refractory hepatic hydrothorax. To prevent the risk of re-expansion pulmonary edema, it is recommended to perform thoracocentesis without exceeding 2 liters of fluid in one session.[50] Nevertheless, due to the increased risk of pneumothorax, pleural and/or soft tissue infection, and bleeding, liver transplantation remains as the best therapeutic option for refractory hepatic hydrothorax. TIPS insertion has a role as a bridging therapy prior to liver transplantation. In conditions where liver transplantation or TIPS cannot be conducted, pleurodesis can be considered with success rate as high as 72%.[53] In cirrhotic patients with normal renal function and well-localized diaphragmatic defect, thoracoscopic procedure using mersilene mesh can also be considered.[54]

Hyponatremia

Hyponatremia is defined as serum sodium level < 130 mEq/L, which can be found in approximately 22% of cirrhotic patients. In liver cirrhosis, most hyponatremia events are caused by dilutional hypervolemia due to increased extracellular fluid volume. Vasodilatation of splanchnic artery in cirrhosis also contributes to decreased effective blood volume. Consequently, RAAS will be activated, leading to excessive release of antidiuretic hormone and, ultimately, reduced fluid excretion.[55] In patients without ascites and edema, usually hyponatremia hypovolemia is observed.[5] Hyponatremia has also been associated with worse prognosis, shown by its role in Model for End-Stage

Liver Disease-Natrium (MELD-Na) scoring. Utilization of MELD-Na scoring system is correlated with reduced mortality rate by up to 7% during waiting period for liver transplantation, in comparison to conventional MELD scoring system.[56]

Hyponatremia needs to be treated when serum sodium level reaches less than 130 mEq/L. Plasma volume expansion with saline solution is necessary in hyponatremia hypovolemia condition. On the contrary, the goal of therapy for hyponatremia hypervolemic is negative fluid balance, for instance through non-osmotic fluid restriction. Administration of hypertonic sodium chloride solution can improve hyponatremia in decompensated cirrhotic patients with special precautions in fluid overload condition. It is recommended to avoid administration of hypertonic sodium chloride solution exceeding 8 mEq/L in 24 hours to reduce the risk of osmotic demyelination syndrome. Liver transplantation remains as the definitive treatment for chronic liver disease with hyponatremia. Meanwhile, the use of intravenous albumin or selective antagonist of arginine-vasopressin V2 receptor in collecting duct still needs further studies.[5,57,58]

Spontaneous Bacterial Peritonitis (SBP)

SBP is defined as bacterial infection in ascitic fluid without any clear source of intraabdominal infection. Bacterial translocation from the gut, modified systemic defense mechanism, as well as deficiency of antimicrobial activity in ascitic fluid are the key factors in the pathogenesis of SBP. In liver cirrhosis, bacterial translocation often occurs due to bacterial overgrowth caused by disturbed transition inside the colon. Portal hypertension causes increased colon permeability through hypoxic mucous, oxidative stress, splanchnic vascular stasis, and congestion of the mucous layer of the colon. Disturbance in phagocytic activities of reticuloendothelial system represents the changes in systemic immunity. Moreover, low C3 level and low opsonization activity in ascitic fluid also contribute to low antimicrobial activity.[50] Diagnosis of SBP is established if increased absolute PMN count $\geq$ 250 cells/mm^3 is obtained from ascitic fluid analysis. This condition is known as neutrocytic ascites if there is no evidence of intraabdominal infection. If this result is accompanied with positive culture of ascitic fluid, then the condition is known as culture-positive neutrocytic ascites. In neutrocytic ascites with negative culture of ascitic fluid, the condition is called culture-negative neutrocytic ascites. If positive culture of ascitic fluid is obtained without neutrocytic ascites, then the condition is called bacterascites.[59] The most common etiologic bacteria are *Eschericia coli, Klebsiella pneumoniae*, and *Streptococcus pneumoniae*.[42]

Prognosis of patients with SBP is very atrocious with in-hospital mortality rate as high as 20%-40%. Therefore, early diagnosis and adequate treatment are highly compulsory for improving the prognosis. Empirical antibiotic therapy should be administered as soon as the diagnosis has been established, adjusted according to the possible etiologic microorganisms, severity of infection, and local antibiotic resistance profiles. In polymicrobial bacterascites, the third generation of cephalosporin can be given with additional anti-anaerobic therapy, such as metronidazole.[60] Administration of the third generation of cephalosporin demonstrated resolution of infection in 77%-98% of the patients.[61] As an alternative, amoxicillin/clavulanate also showed comparable resolution of infection and mortality rate with administration of cefotaxime, although higher number of drug-induced hepatitis was also observed.[62,63] Piperacillin/tazobactam or carbapenem also becomes drug of choice in nosocomial SBP or in regions where high level of resistance towards the third generation of cephalosporin is found.[42] Tigecycline or combination of tigecycline and carbapenem can be administered when *carbapenemase-producing* and *carbapenem-resistant non-carbapenemase-producing Enterobacteria* are suspected as the etiologic agent. In severe infection due to carbapenem-resistant and quinolone-resistant *Pseudomonas aeruginosa*, combination of amikacin and tobramycin or colistin-carbapenem/ceftazidime can be an option. If vancomycin-resistant *Enterococci* is suspected as the etiologic agent, administration of linezolid, daptomycin, and tigecycline can be conducted. It is also critical to perform

antibiotic de-escalation based on the results of microorganism culture to minimize the risk of antibiotic resistance.[64,65] It is recommended to evaluate the effect of antibiotic as early as 48 hours after the initial administration. Failure of the first-line antibiotic must be suspected when there is no improvement of clinical symptoms, or the absence of decreased white blood cells count by at least 25% in 48 hours.[5]

Aside from treatment, antibiotics also have a prominent role as prophylaxis of SBP. There are three populations who are deemed to have high risk of SBP, i.e., patients with acute gastrointestinal bleeding, patients with low protein level (< 1 gram/dL) in ascitic fluid without any history of prior SBP, and patients with history of prior SBP. Patients with history of prior SBP demonstrated cumulative recurrence rate in one year as high as 70%. Long-term oral administration of norfloxacin (400 mg/day) showed significant decrease of recurrence rate by 48%.[5] When norfloxacin is not available, 500 mg ciprofloxacin daily can be given as primary or secondary prophylaxis. Other alternative antibiotics are 960 mg trimethoprim-sulfamethoxazole daily per oral, 250 mg levofloxacin daily per oral, or intravenous 1 gram ceftriaxone daily.[66-68] Primary and secondary prophylaxis are recommended to be administered until ascites is resolved or liver transplantation can be performed or death.[68]

Renal Dysfunction

Acute Kidney Injury (AKI)

In liver cirrhotic patients, renal dysfunction is defined as a condition where serum creatinine level is at least 1.5 mg/dL or increased serum creatinine level by > 50% from the baseline with glomerular filtration rate (GFR) index ≤ 40 ml/min/1.73 m^2. Renal dysfunction can be found in the form of AKI or chronic kidney disease (CKD). In liver cirrhotic patients, AKI can be caused by diuretics, beta-blockers, vasodilator agents, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and other nephrotoxic drugs. In the condition of infection-induced AKI or AKI stage > 1A and the cause of AKI cannot be determined clearly, the intravenous administration of 20% albumin is recommended (1 gram/kgBW/day, maximum dose: 100 gram) for two consecutive days. For patients with AKI and grade 3 ascites, therapeutic paracentesis can be performed, and then followed by intravenous albumin administration. Other therapeutic options include renal replacement therapy (RRT) or kidney transplantation (**Figure 4**).[69,70]

Hepatorenal Syndrome (HRS)

HRS can be present with (HRS-AKI) or without AKI (HRS-NAKI).[69,71] HRS is mainly caused by renal hypoperfusion due to

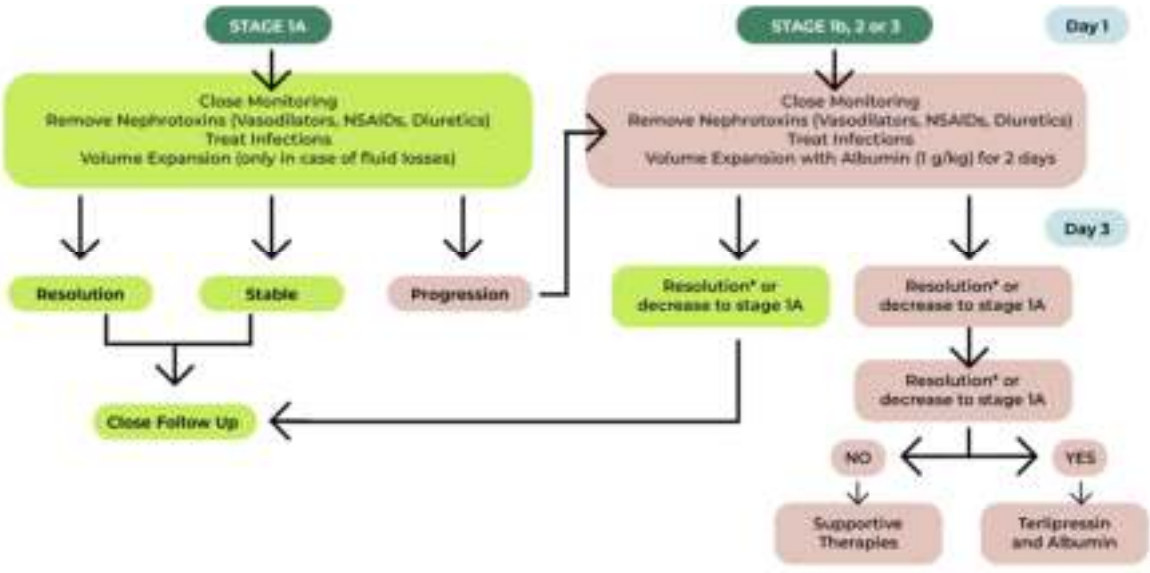

Figure 4. Management of renal dysfunction in cirrhosis (Adapted from [70]).

synergistic work between inflammation and microvascular disturbances in end-stage chronic liver disease. Both factors may amplify signals elicited by Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) on epithelial cells of proximal tubules. This process will lead to metabolic down-regulation mediated by mitochondria. Additionally, signal transduction will also change the priority of cell functions into prioritizing cell viability. RAAS activation and decrease of GFR also happen because of increased sodium chloride in macula densa. If the patient also has cholestasis, renal dysfunction will also be worsened since bile salts may trigger inflammation, disrupt circulation, and damage renal tubules.[72]

The first line of pharmacological management in HRS is vasoconstrictor and albumin (**Figure 4**).[70] An example of vasoconstrictor is terlipressin as a vasopressin analogue. Terlipressin also plays a role in decreasing stroke volume of patients with HRS. On the other hand, albumin has antioxidant and anti-inflammatory traits with recommended dose of 20-40 gram/day (adjusted according to the central venous pressure (CVP) measurement). Albumin administration is maintained until complete resolution (serum creatinine level < 1.5 mg/dL) for maximum duration of 14 days or partial resolution (decrease of serum creatinine level by ≥ 50%) or if no clinical changes are observed. It is also recommended to administer 1.5 gram/kgBW of albumin on the first day within 6 hours after diagnosis of SBP is confirmed and 1 gram/kgBW of albumin on the third day, in order to prevent AKI in patients with SBP.[5] Other choices of vasoconstrictors include noradrenaline, midodrine, and octreotide (**Table 8**).[73,74] TIPS placement can be considered in both HRS-AKI and HRS-NAKI, although its use is still limited and contraindicated in patients with severe liver failure.[75] RRT must be considered in patients with AKI, especially if there is acid-base imbalance or severe and/or refractory electrolyte imbalance. Continuous RRT has also demonstrated better contribution towards stability of heart and blood vessels compared to hemodialysis.[71] Nonetheless, the best definitive therapy for HRS is liver transplantation. Simultaneous Liver-Kidney Transplantation (SLK) is indicated in patients with liver cirrhosis and CKD with the following conditions:[5]

- Estimated GFR (with Modification of Diet in Renal Disease equation) ≤ 40 mL/min/1.73 m^2 or GFR measured by

Table 8. Recommended doses of vasoconstrictors in the management of HRS.[5,73,74]

	Terlipressin	Noradrenaline	Midodrine	Octreotide
Recommended dose	Initial dose for intravenous bolus: 0.5-1 mg every 4-6 hours. OR Continuous infusion dose 2 mg/day. After 2 days, the dose can be increased into maximum dose of 12 mg/day. OR Fixed dose (1 mg every 8-12 hours), increased by 2 mg every 4 hours.	Continuous infusion dose: 0.5 – 3 mg/hour. OR Initial dose: 0.5 mg/hour, increased by 0.5 mg/hour every 4 hours until maximum dose of 3 mg/hour (only if at least one of these targets are not achieved: increase of MAP by minimum 10 mmHg or increase urinary output > 200 mL/4 hours).	Initial dose: 7.5 mg/8 hours. Maximum dose: 15 gram/8 hours.	Subcutaneous dose: 50 ug/hour. Continuous infusion dose: 100-200 ug/8 hours.
Duration	Administered until serum creatinine level ≤ 1.5 mg/dL or maximum duration of 14 days.	Administered until serum creatinine level ≤ 1.5 mg/dL or maximum duration of 14 days.	Administered until serum creatinine level ≤ 1.5 mg/dL or maximum duration of 14 days.	Administered until serum creatinine level ≤ 1.5 mg/dL or maximum duration of 14 days.

iothalamate clearance ≤ 30 ml/min/1.73 m^2.
- Proteinuria ≥ 2 gram/daily.
- Histopathological findings of the kidney: more than 30% glomerulosclerosis or more than 30% interstitial fibrosis.
- Hereditary metabolic disorders.

SLK is also indicated for patients with liver cirrhosis and AKI without any improvement (e.g., HRS-AKI which does not show any improvement after pharmacological management) with the following conditions:[5]
- AKI on RRT for ≥ 4 weeks, or
- Estimated GFR ≤ 35 mL/min/1.73 m^2 or measured GFR ≤ 25 mL/min/1.73 m^2 for at least 4 weeks.

Acute Variceal Bleeding

Acute variceal hemorrhage (AVH) is defined as variceal bleeding in patients with confirmed or suspected portal hypertension, with the presence of hematemesis and/or ongoing melena within 24 hours upon admission. Generally, the timeframe of AVH episode is 48 hours. The main principle of AVH treatment is preventing recurrent bleeding episode and death (**Figure 5**).[35] Fluid replacement therapy must be initiated as soon as possible to return hemodynamic stability. The recommended fluids are crystalloid or colloid. To date, starch is not recommended as an option for fluid replacement therapy. Administration of restrictive blood transfusion can be done if the patient had low hemoglobin level (< 7 gram/dL) with target of hemoglobin level post-transfusion: 7-9 gram/dL.[5,73]

Currently, non-selective beta-blocker (NSBB) has a role as primary prophylaxis, while Endoscopic Band Ligation (EBL) plays a role as secondary prophylaxis (**Table 9**)[76] to prevent variceal bleeding in high-risk cirrhotic patients. Propranolol and nadolol manage portal hypertension by decreasing stroke volume and splanchnic blood flow. Simultaneously, the effect of alpha-1 adrenergic receptor also triggers splanchnic vasoconstriction, and thus,

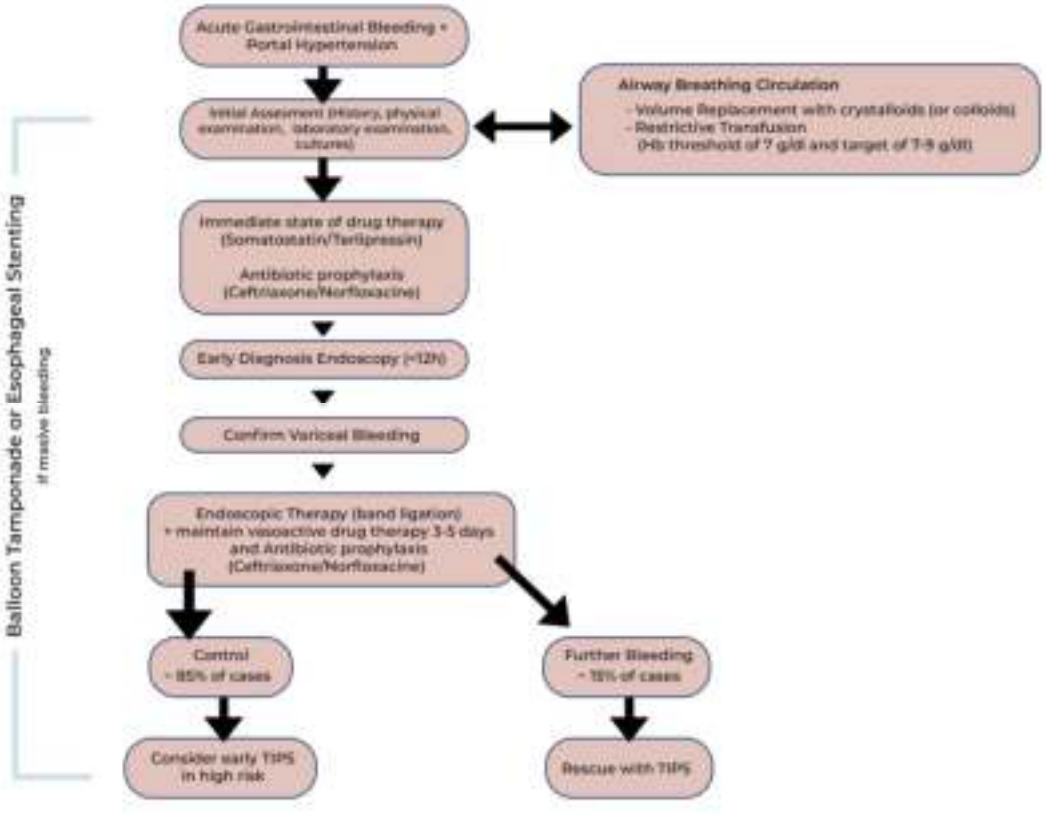

Figure 5. Treatment algorithm of acute gastrointestinal bleeding in liver cirrhosis (Adapted from [5]).

Table 9. Prophylaxis for preventing recurrent variceal bleeding.[5-6,76]

Therapy	Recommended Doses	Therapeutic Goals	Maintenance Therapy
Propranolol	20-40 mg (twice daily) → adjust the dose in 2-3 days. Maximum daily dose: 320 mg/day in patients without ascites or 160 mg/day in patients with ascites.	Resting heart rate: 55-60 beats/minute. Systolic blood pressure should not be lower than 90 mmHg.	Continue therapy for maintenance.
Nadolol	20-40 mg once daily. Dose adjustment: 160 mg/day in patients without ascites or 80 mg/day in patients with ascites.	Resting heart rate: 55-60 beats/minute. Systolic blood pressure should not be lower than 90 mmHg.	Continue therapy for maintenance.
Carvedilol	Initial dose: 6.25 mg once daily. After 3 days, the dose can be increased to 6.25 mg (twice daily). Maximum dose: 12.5 mg/day (in patients with persistent arterial hypertension, the dose can be increased until 12.5 mg twice daily or 25 mg/day).	Systolic blood pressure should not be lower than 90 mmHg. Decreased heart rate should not be a reference for dose titration.	Continue therapy for maintenance.
EBL	Every 2-8 weeks until varices can be eradicated.	Until varices can be eradicated	The first EGD should be performed within 3-6 months after varices has been eradicated and every 6-12 months afterwards.

decreasing portal pressure. Carvedilol can also be an alternative to lower intrahepatic resistance and porto-collateral blood flow.[5,6] NSBB must be halted when severe hyponatremia occurs (serum sodium level < 130 mEq/L), or if the mean of MAP is low (< 65 mmHg), or if the stroke volume is low with systolic blood pressure < 90 mmHg, or if serum creatinine level is increased by > 1.5 mg/dL. Carvedilol or high-dose NSBB is also recommended to be avoided in severe or refractory ascites. In the condition of intolerance towards NSBB, EBL can be performed. Combination of NSBB and EBL can also be an option for secondary prophylaxis with higher therapeutic efficacy in comparison to monotherapy. The therapeutic efficacy of this combination is also comparable with TIPS in preventing bleeding episode.[5,73]

Aside from fluid replacement, vasoactive agents and antibiotics also need to be administered as early as possible to control active bleeding and increase the possibility of survival. Recommended vasoactive agents include terlipressin, somatostatin, and octreotide (**Table 10**).[5] Bolus of intravenous somatostatin or octreotide can still be administered if bleeding episode still occurs. When AVH diagnosis has been confirmed, vasoactive agents can be continued for 5 days to prevent early recurrent bleeding (**Table 11**).[77] Shorter duration of vasoactive administration (48-72 hours) is contemplated when the bleeding episode is not too severe. Endoscopic examination is recommended to be conducted as soon as blood volume resuscitation and hemodynamic stability have been achieved (within 12 hours after hospital admission).[78] Combination between endoscopic therapy and vasoactive agent has more efficacy compared to monotherapy due to local hemostatic effect from endoscopic therapy and portal pressure lowering effect from vasoactive agents.[79] Cyanoacrylate injection is currently recommended as an endoscopic therapy for patients with gastric varices (cardio-fundal varices).[80] In addition, fluoroscopy-guided coil insertion and/or cyanoacrylate injection can also be done to treat fundal varices (**Table 12**).[5,77,81]

It is also important to remember that variceal bleeding can lead to several morbid complications, such as bacterial infections, hepatic encephalopathy, and renal dysfunction. Antibiotic prophylaxis is recommended to lower the incidence of secondary infection, control

Table 10. Recommended doses of vasoactive agents for acute variceal hemorrhage management.[5]

Therapy	Recommended Doses	Duration of Therapy
Octreotide	Initial IV bolus 50 ug (can be repeated within the first one hour if bleeding persists). Continuous infusion: 50 ug/hour.	2-5 days.
Somatostatin	Initial IV bolus 250 ug (can be repeated within the first one hour if bleeding persists). Continuous infusion: 250-500 ug/hour.	2-5 days.
Terlipressin	Within the first 48 hours: 2 mg intravenous until bleeding can be controlled. Maintenance dose: 1 mg intravenous every 4 hours to prevent recurrent bleeding.	2-5 days.

Table 11. Clinical definitions of acute and recurrent variceal bleeding.[77]

Clinical Conditions	Timeframe from T_0	Subtypes	Timeframe from T_0
Acute variceal bleeding	48 hours	Active (based on endoscopic examination)	48 hours
Recurrent bleeding	After 48 hours	Inactive (based on endoscopic examination)	48 hours
		Very early recurrent bleeding	48-120 hours
		Early recurrent bleeding	6-42 days
		Late recurrent bleeding	After 42 days

Table 12. Classification, prevalence, and bleeding risk of gastric varices.[77]

Types	Definition	Relative Frequency	Risk of Bleeding Without Therapy
GOV1	Esophageal varices extended until lower cardia towards minor curvature.	70%	28%
GOV2	Gastroesophageal varices extended until lower cardia towards fundus.	21%	55%
IGV1	Isolated varices on fundus.	7%	78%
IGV2	Isolated varices in locations other than gaster.	2%	9%

the bleeding, and increase life expectancy.[6] The first line antibiotic for patients with advanced cirrhosis, who are consuming quinolone as a prophylaxis with history of hospitalization in a healthcare center with high prevalence of quinolone resistance, is intravenous ceftriaxone (1 gram/day) for 7 days. Oral quinolone can be given if the patient cannot tolerate ceftriaxone (**Table 13**).[66] In 10-15% cases, where AVH still persists or becomes recurrent despite the administration of vasoactive agents and antibiotic prophylaxis combined with EBS, TIPS should be considered as a salvage therapy.[6] If TIPS cannot be performed, endoscopic therapy can be conducted for the second time with optimalization of vasoactive drugs and 2-fold increase of somatostatin dose and/or replacement with terlipressin. Balloon tamponade or self-expanding esophageal stents can also be placed as an alternative bridging therapy.[82]

Table 13. Recommended doses of antibiotic prophylaxis in acute variceal bleeding.[5,66,78]

Therapy	Recommended Doses	Duration of Therapy
Ciprofloxacin	500 mg per oral twice daily OR 400 mg intravenous twice daily,	3-7 days
Ceftriaxone	1 gram daily.	7 days

Others

Coagulopathy

Vitamin K deficiency is commonly found in decompensated cirrhotic patients, which is affected by a complex mechanism involving bile salt deficiency, failure in bile salt secretion, and the use of broad-spectrum antibiotics. Nowadays, vitamin K injection 10 mg daily for 3 days is recommended as an adequate option to treat vitamin K deficiency in decompensated cirrhotic patients. Prophylactic correction of prothrombin time with Fresh Frozen Plasma (FFP) remains controversial due to a significant number of adverse events, e.g., fluid overload, exacerbation of portal hypertension, increased risk of infection, or acute liver injury related to transfusion. Platelet transfusion can be considered when platelet count is lower than 50,000/mm^3 with platelet count target > 70,000/mm^3. Maintaining low CVP and reducing portal pressure can also be helpful during surgical management. Other options for bleeding control are topical hemostatic agents, aprotinin, tranexamic acid, and epsilon caproic amino acid, which may have a role in controlling local bleeding. These agents, however, still need further trials due to higher thrombotic risk.[83]

Portal Hypertension Gastropathy (PHG)

PHG is commonly found in decompensated cirrhotic patients. The presence of esophageal varices and Child-Pugh B or C category can also predict the incidence of PHG.[84] Diagnosis of PHG can be confirmed by endoscopic examination, from which mild subtype of PHG usually appears with mosaic pattern or may overlap with red signs (severe subtype of PHG). PHG is usually located on the proximal part of gaster (fundus and corpus).[85,86] In the progression of chronic liver disease, PHG plays a critical role since it may cause occult bleeding, which ultimately leads to chronic iron deficiency anemia. PHG can also be an incidental asymptomatic finding in the absence of gastric or esophageal varices.[35] The first line therapy for chronic bleeding with PHG is NSBB. Iron supplementation and/or blood transfusion can also be given according to the clinical indications.[5] In patients with refractory PHG and compensated cirrhosis, TIPS placement can improve endoscopic findings, as well as lower the requirements for blood transfusion. Additionally, similar to AVH, antibiotic prophylaxis can also be administered to patients with acute PHG bleeding.[87] An electrosurgical technique, called Argon Plasma Coagulation (APC), has emerged as an option to manage bleeding episodes and devitalization of abnormal tissues. Previous evidence indicated higher hemoglobin level and lower blood transfusion requirement after APC.[88,89] Although further validations are still required, rebamipide has been proposed as a potential therapeutic agent for PHG due to its antioxidant effect (free radicals scavenging), ability to decrease nitration process of tyrosine residues from Extracellular Signal-Regulated Kinases (ERK), and mucosal healing capability.[90]

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REFERENCES

1. Turco L, Garcia-tsao G. Portal hypertension: pathogenesis and management. Clin Liver Dis. 2019;23(4):573–87.
2. Koh C, Heller T. Approach to the diagnosis of portal hypertension. Clin Liver Dis. 2012;1(5):133–5.
3. Berzigotti A. Advances and challenges in cirrhosis and portal hypertension. BMC Med. 2017; 15: 200.
4. Tapper E, Parikh N. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ. 2018;362:k2817.
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69:406–60.
6. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2017;65(1):310–35.
7. Garcia-Tsao G, Bosch J, Haven N, et al. Varices and variceal hemorrhage in cirrhosis. A new view of an old problem. Clin Gastroenterol Hepatol. 2016;13(12):2109–17.
8. Procopet B, Berzigotti A. Diagnosis of cirrhosis and portal hypertension: imaging, non-invasive markers

of fibrosis and hepar biopsy. Gastroenterol Rep. 2017;5(2):78–89.
9. Berzigotti A, Bosch J, Escorsell A. Pathophysiology of variceal bleeding in cirrhotics. Ann Gastroenterol. 2001;14:150–7.
10. Simonetto DA, Liu M, Kamath PS. Portal hypertension and related complications: Diagnosis and management. Mayo Clin Proc. 2019;94(4):714–26.
11. García-Pagán J, Groszmann R, Bosch J. Portal Hypertension. In: Hawkey C, Bosch J, Richter J, Garcia-Tsao G, Chan F, editors. Textbook of clinical gastroenterology and hepatology. 2nd. Sussex: Wiley-Blackwell; 2012.
12. Iwakiri Y. Pathophysiology of portal hyperthension. Clin Liver Dis. 2014;18(2):281–91.
13. Gulamhusein A, Kamath P. The epidemiology and pathogenesis of gastrointestinal varices. Tech Gastrointest Endosc. 2017;19(2):62–8.
14. Atterbury C, Glickman M, Garcia-Tsao G, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology. 1985;5(3):419–24.
15. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 2007;133(2):481–8.
16. Ripoll C, Groszmann R, Garcia-tsao G, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol. 2009;50(5):923–8.
17. Turco L, Garcia-Tsao G, Magnani I, et al. Cardiopulmonary hemodynamics and C-reactive protein as prognostic indicators in compensated and decompensated cirrhosis. J Hepatol. 2018;68(5):949–58.
18. Abraldes J, Villanueva C, Bañares R, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol. 2008;48(2):229–36.
19. Busk T, Bendtsen F, Nielsen H, et al. TIMP-1 in patients with cirrhosis: relation to liver dysfunction, portal hypertension, and hemodynamic changes. Scand J Gastroenterol. 2014;49(9):1103–10.
20. Sandahl T, McGrail R, Møller H, et al. The macrophage activation marker sCD163 combined with markers of the Enhanced Liver Fibrosis (ELF) score predicts clinically significant portal hypertension in patients with cirrhosis. Aliment Pharmacol Ther. 2016;43:1222–31.
21. Leeming D, Veidal S, Karsdal M, et al. Pro-C5, a marker of true type V collagen formation and fibrillation, correlates with portal hypertension in patients with alcoholic cirrhosis. Scand J Gastroenterol. 2015;50(5):584–92.
22. Hametner S, Ferlitsch A, Ferlitsch M, et al. The VITRO score (Von Willebrand factor antigen/thrombocyte ratio) as a new marker for clinically significant portal hypertension in comparison to other non-invasive parameters of fibrosis including ELF test. PLoS One. 2016;11(2):e0149230.
23. Bruha R, Jachymova M, Petrtyl J, et al. Osteopontin: A non-invasive parameter of portal hypertension and prognostic marker of cirrhosis. World J Gastroenterol. 2016;22(12):3441–50.
24. Lim Y, Choi E, Jang Y, et al. Clinical implications of the serum apelin level on portal hypertension and prognosis of liver cirrhosis. Gut Liver. 2016;10(1):109–16.
25. Kirnake V, Arora A, Sharma P, et al. Non-invasive aspartate aminotransferase to platelet ratio index correlates well with invasive hepatic venous pressure gradient in cirrhosis. Indian J Gastroenterol. 2018; 37(4):335-341.
26. Zou Z, Yan X, Li C, et al. von Willebrand factor as a biomarker of clinically significant portal hypertension and severe portal hypertension: a systematic review and meta-analysis. BMJ Open. 2019;9:e025656.
27. Yen Y, Kuo F, Kee K, et al. APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. PLoS One. 2018;1–16.
28. Cho EJ, Kim MY, Lee JH, et al. Diagnostic and prognostic values of noninvasive predictors of portal hypertension in patients with alcoholic cirrhosis. PLoS ONE. 2015;10(7):e0133935. DOI: 10.1371/journal.pone. 0133935.
29. Leung JC, Loong TC, Pang J, et al. Invasive and non-invasive assessment of portal hypertension. Hepatol Int. 2017;30–2.
30. Ferraioli G, Wong V, Castera L, et al. Liver ultrasound elastography: An update to the World Federation for ultrasound in medicine and biology guidelines and recommendations. Ultrasound Med Biol. 2018;44(12):2419–40.
31. Owen C, Meyers P. Sonographic evaluation of the portal and hepatic systems. Journal of Diagnostic Medical Sonography. 2006;22(5):317-328. DOI: 10.1177/8756479306293101.
32. Kondo T, Maruyama H, Sekimoto T, et al. Impact of portal hemodynamics on Doppler ultrasonography for predicting decompensation and long-term outcomes in patients with cirrhosis. Scand J Gastroenterol. 2016;51(2):236-244. DOI: 10.3109/00365521.2015.1081275.
33. Kim MY, Baik SK, Park DH, et al. Damping index of Doppler hepatic vein waveform to assess the severity of portal hypertension and response to propranolol in liver cirrhosis: A prospective nonrandomized study. Liver International. 2007;27(8):1103-10. DOI: 10.1111/j.1478-3231.2007.01526.x.
34. Vizzutti F, Arena U, Rega L, et al. Performance of Doppler ultrasound in the prediction of severe portal hypertension in hepatitis C virus-related chronic liver disease. Liver International. 2007; 27(10): 1379-1388. DOI: 10.1111/j.1478-3231.2007.01563.x.
35. Franchis R De, Vi B. Position paper expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and

individualizing care for portal hypertension. J Hepatol. 2015;63(3):743–52.
36. Colecchia A, Montrone L, Scaioli E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology. 2012;143(3):646–54.
37. Sharma BC, Sarin SK. Hepatic venous pressure gradient in cirrhosis: Role in variceal bleeding, non-bleeding complications and outcome. Asian Journal of Surgery. 2006; 29(3): 113-119.
38. Choi SY, Jeong WK, Kim Y, et al. Shear-wave elastography: A noninvasive tool for monitoring changing hepatic venous pressure gradients in patients with cirrhosis. Radiology. 2014;273(3): 917-26.
39. Thalheimer U, Mela M, Patch D, et al. Monitoring target reduction in hepatic venous pressure gradient during pharmacological therapy of portal hypertension: A close look at the evidence. Gut. 2004;53(1):143–8.
40. Nicoară-farcău O, Stefănescu H, Tanţău M, et al. Diagnostic challenges in non-cirrhotic portal hypertension - porto sinusoidal vascular disease. World J Gastroenterol. 2020;26(22):3000–11.
41. Runyon B. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013;57(4):1651–3.
42. Huelin P, Fortea JI, Crespo J, et al. Ascites: treatment, complications, and prognosis. In: Rodrigo L, editor. Ascites - physiopathology, treatment, complications and prognosis. Intech Open; 2017.
43. Pockros P, Reynolds T. Rapid diuresis in patients with ascites from chronic liver disease: the importance of peripheral edema. Gastroenterology. 1986;90:1827–33.
44. Casado M, Bosch J, Garcia-Pagan J, et al. Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings. Gastroenterology. 1998;114:1296–303.
45. Riggio O, Angeloni S, Salvatori F, et al. Incidence, natural history, and risk factors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt with polyetrafluoroethylene-covered stent grafts. Am J Gastroenterol. 2008;103:2738–46.
46. Sauerbruch T, Mengel M, Dollinger M, et al. Prevention of rebleeding from esophageal varices in patients with cirrhosis receiving small-diameter stents vs hemodynamically controlled medical therapy. Gastroenterology. 2015;149:660–8.
47. Caldwell J, Edriss H, Nugent K. Chronic peritoneal indwelling catheters for the management of malignant and nonmalignant ascites. Proc (Bayl Univ Med Cent). 2018;31(3):297–302.
48. Reinglas J, Amjadi K, Petrcich BP, et al. The palliative management of refractory cirrhotic ascites using the PleurX (©) catheter. Can J Gastroenterol Hepatol. 2016;4680543.
49. Rossle M, Gerbes AL. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. Gut. 2010;59:988–1000.
50. Kashani A, Landaverde C, Medici V, et al. Fluid retention in cirrhosis: pathophysiology and management. Q J Med. 2008;101:71–85.
51. Garbuzenko D, Arefyev N. Hepatic hydrothorax: an update and review of the literature. World J Hepatol. 2017;1197–204.
52. Badillo R, Rockey D. Hepatic hydrothorax: clinical features, management, and outcomes in 77 patients and review of the literature. Medicine (Baltimore). 2014;93:135–42.
53. Hou F, Qi X, Guo X. Effectiveness and safety of pleurodesis for hepatic hydrothorax: A systematic review and meta-analysis. Dig Dis Sci. 2016;61:3321–34.
54. Huang P, Kuo S, Chen J, et al. Thoracoscopic mesh repair of diaphragmatic defects in hepatic hydrothorax: results of a survey. Ann Thorac Surg. 2016;101:1921–7.
55. Attar B. Approach to hyponatremia in cirrhosis. Clin Liver Dis. 2019;13:98–101.
56. Kim W, Biggins S, Kremers W, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359:1018–26.
57. Cárdenas A, Ginès P, Marotta P, et al. Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. J Hepatol. 2012;56:571–8.
58. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367:2407–18.
59. Evans L, Kim W, Poterucha J, et al. Spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhotic ascites. Hepatology. 2003;37:897–901.
60. Feldman M, Friedman L, Brandt J. Sleisenger and Fordtran's gastrointestinal and liver disease. 8th ed. Saunders. Philadelphia; 2006. p. 1935–64.
61. Rimola A, Salmeron J, Clemente G, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. Hepatology. 1995;21:674–9.
62. Ricart E, Soriano G, Novella M, et al. Amoxicillin-clavulanic acid vs cefotaxime in the therapy of bacterial infections in cirrhotic patients. J Hepatol. 2000;32:596–602.
63. DeLemos A, Ghabril M, Rockey D, et al. Drug-induced liver injury network (DILIN). Amoxicillin-clavulanate-induced liver injury. Dig Dis Sci. 2016;61:2406–16.
64. Fernandez J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology. 2012;55:1551–61.
65. Magiorakos A, Srinivasan A, Carey R, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for

interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268–81.
66. Fernández J, Ruiz L, Arbol DEL, et al. Norfloxacin vs Ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology. 2006;131(4):1049–56.
67. Singh N, Gayowski T, Yu V, et al. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. Ann Intern Med. 1995;122(8):595–8.
68. Garcia-Tsao G. Bacterial infections in cirrhosis: treatment and prophylaxis. J Hepatol. 2005;42(Supple(1)):S85-92.
69. Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. J Hepatol. 2015;62(4):968–74.
70. Allegretti AS, Sola E, Gines P. Clinical application of kidney biomarkers in cirrhosis. Am J Kidney Dis. 2020; 76(5): 710-719. DOI: 10.1053/j.ajkd.2020.03.016.
71. Wong F, Nadim MK, Kellum JA, et al. Working party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut. 2011;60(5):702–9.
72. Erly B, Carey WD, Kapoor B, et al. Hepatorenal syndrome: A review of pathophysiology and current treatment options. Semin Intervent Radiol. 2015; 32(4): 445-454. DOI: 10.1055/s-0035-1564794.
73. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, evaluation, and management of ascites and hepatorenal syndrome. Hepatology. 2021. DOI: 10.1002/hep.31884.
74. Esrailian E, Pantangco ER, Kyulo NL, et al. Octreotide/midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. Dig Dis Sci. 2007;52(3):742–8.
75. Guevara M, Ginès P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: Effects on renal function and vasoactive systems. Hepatology. 1998;28(2):416–22.
76. Rodrigues SG, Mendoza YP, Bosch J. Beta-blockers in cirrhosis: Evidence-based indications and limitations. JHEP Reports. 2020;2(1):100063.
77. Sarin SK, Kumar A, Angus PW, et al. Diagnosis and management of acute variceal bleeding: Asian Pacific Association for study of the liver recommendations. Hepatol Int. 2011;5(2):607–24.
78. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46(3):922–38.
79. Salcedo M, Alonso S, Rincón D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: A meta-analysis. Hepatology. 2002;35(3):609–15.
80. Ríos Castellanos E, Seron P, Gisbert JP, et al. Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in people with portal hypertension. Cochrane Database Syst Rev. 2015;2015(5).
81. Villanueva C, Escorsell À. Optimizing general management of acute variceal bleeding in cirrhosis. Curr Hepat Rep. 2014;13(3):198–207.
82. Escorsell À, Pavel O, Cárdenas A, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology. 2016;63(6):1957–67.
83. Amarapurkar PD, Amarapurkar DN. Management of coagulopathy in patients with decompensated liver cirrhosis. Int J Hepatol. 2011;2011:1–5.
84. Yoshikawa I, Murata I, Nakano S, et al. Effects of endoscopic variceal ligation on portal hypertensive gastropathy and gastric mucosal blood flow. Am J Gastroenterol. 1998;93(1):71–4.
85. Nakamura K, Honda K, Akahoshi K, et al. Suitability of the expanded indication criteria for the treatment of early gastric cancer by endoscopic submucosal dissection: Japanese multicenter large-scale retrospective analysis of short- and long-term outcomes. Scand J Gastroenterol. 2015;50(4):413–22.
86. Nguyen H, Le C, Ngyuyen H. Gastric antral vascular ectasia (watermelon stomach) – An enigmatic and often overlooked cause of gastrointestinal bleeding in the elderly. The Permanente Journal. 2009;13(4):46-9.
87. Kamath PS, Lacerda M, Ahlquist DA, et al. Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. Gastroenterology. 2000;118(5):905–11.
88. Zenker M. Argon plasma coagulation. GMS Krankenhaushygiene Interdisziplinar. 2008;3(1).
89. Hanafy A, El Hawary A. Efficacy of argon plasma coagulation in the management of portal hypertensive gastropathy. Endosc Int Open. 2016;04(10):E1057–62.
90. Gjeorgjievski M, Cappell MS. Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history, and therapy. World J Hepatol. 2016;8(4):231-262. DOI: 10.4254/wjh.v8.i4.231.