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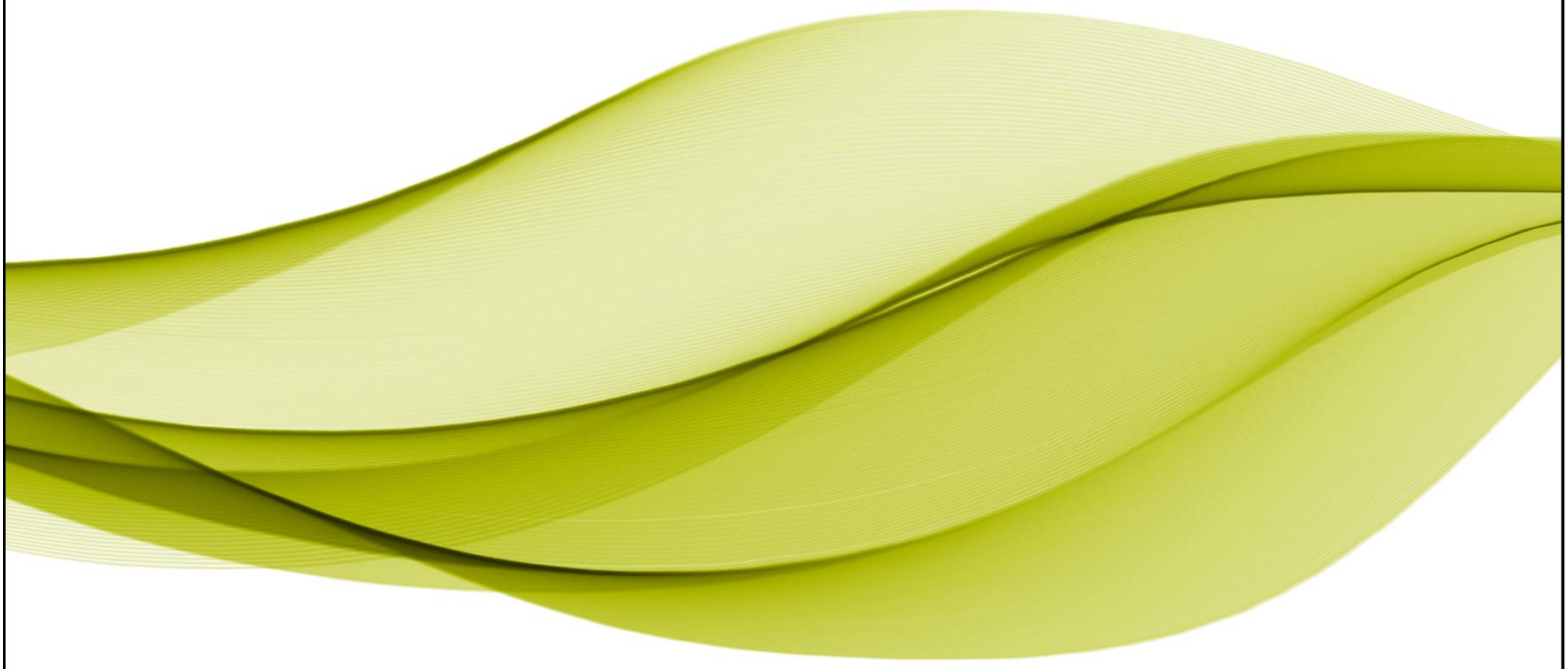

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Factors Influencing the Utilization of Antenatal Care, Institutional Delivery, and Postnatal Care Services Among Women in Bangladesh

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Abstract

Background: In Bangladesh, the utilization of maternal health services is low, which triggers pregnancy-related complications and maternal deaths. The current community-based cross-sectional study aims to evaluate the factors associated with antenatal care (ANC), institutional delivery, and postnatal care (PNC) service utilization among women in selected areas of Southwest Dhaka, Bangladesh.

Methods: The study was carried out among 391 mothers from rural and urban areas. Data were collected using a standard questionnaire. Univariate and multivariate analyses were performed to identify the significant determinants associated with maternity care service utilization.

Results: Result shows that approximately 65%, 71%, and 72% of women utilized the recommended ANC, institutional delivery, and PNC, respectively. The utilization of ANC was associated with residence type and women's education, whereas the utilization of institutional delivery and PNC was associated with residence type, women's education, husband's education and employment status, family size, monthly family income, and received ANC. The use of ANC and healthy delivery facilities is another important predictor of PNC service utilization.

Conclusions: Considering these findings, improved maternal health services, increased availability and affordability of services, counseling, and education during pregnancy are advocated throughout the country.

Keywords: antenatal care, Bangladesh, institutional delivery, maternal health, postnatal care

INTRODUCTION

Over the last two decades, maternal mortality is significantly reduced globally, although the ratio is still high in many low and middle-income countries (LMICs). In developing countries, approximately 5,500 women died because of maternal consequences in 2015 in Bangladesh.[1] In addition, Bangladesh's neonatal mortality rate reaches 23 deaths per 1,000 live births because of the lack of maternity care.[2] In Bangladesh, the utilization of maternal health services (MHS) is low, which triggers pregnancy-related complications and maternal deaths.[3] The government of Bangladesh sets a target to reduce maternal mortality by 176 to 105 per 10,000 live births by 2021 following Sustainable Development Goals (SDGs), which are focused on reducing maternal deaths by 70 per 10,000 deaths by 2030 globally.[4,5]

Antenatal care (ANC), delivery place, and postnatal care (PNC) are the important determinants of maternal and neonatal health, and ANC is an important predictor of the utilization of institutional delivery and PNC from medically provided trainers after delivery, which are important for the health of mothers and infants.[6] According to World Health Organization (WHO), at least four ANC visits should be taken to reduce pregnancy-related complications.[7] However, the utilization of ANC depends on the availability, affordability, quality of services, and cultural beliefs.[8,9] Given the lack of optimum ANC, several maternal complications, low birth, and preterm birth occur.[10] Maternity care defines taking care of mother health during pregnancy, child births, and postpartum period.[11] In Bangladesh, several studies have been conducted on the utilization of ANC and their associated factors.

Delivery place is another determinant that can reduce the maternal deaths and improve the health of mothers and infants. More than 70% of all births occurred at home were reported in a secondary analysis of 48 LMICs.[12] In Bangladesh, almost 71% of total births have occurred at home, and only one out of five women is attended by a medically trained provider.[13] The percentage of poor delivery care is high, as traditional/conventional birth attendants (TBAs) are easily available and affordable, although their services

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are not effective and safe.[14] Poverty, illiteracy, and type of residence are important factors for the utilization of poor MHS. Many studies reported that 62% of maternal deaths during the postpartum period were due to unhygienic delivery place and inappropriate utilization of PNC.[15] PNC is a service provided to mother and infants within six weeks of delivery, which is crucial for the survival of the mother and child.[16] Based on WHO recommendations, mothers and newborns should receive PNC care within the first 24 h of delivery, and a minimum of three additional PNC visits are recommended.[17] PNC care after delivery is necessary for monitoring danger signs of newborns, initial breastfeeding, and counseling of mothers about the necessity of exclusive breastfeeding, healthy nutrition and lifestyle practices, etc.[18]

In Bangladesh, the utilization of healthy delivery care and PNC for mothers and neonates is associated with residential type, educational, and occupational status of mothers and husband, previous experience of receiving healthy delivery care, PNC, and availability of mass media at the household level.[19,20] The utilization of proper ANC is a crucial predictor of using healthy delivery care and PNC.[21] However, knowledge regarding pregnancy-related complications among mothers is lacking, and existing knowledge is basically established from family traditions and culture related to the use of healthy maternal care services in this country.[19]

The utilization of health care services is a complex behavioral phenomenon, as it is related to availability, costs of services, social structure, and religious and personal beliefs. The availability and utilization of health care services are increasing in the selected areas after becoming a new part of South Dhaka City Corporation in 2016. To our best knowledge, no study has focused on this phenomenon in the southwest part of Dhaka City in Bangladesh. Thus, data about ANC, institutional delivery care, and PNC are lacking. Therefore, the present study aims to provide information about the factors associated with the use of health facilities during and after pregnancy, which includes ANC, institutional delivery, and PNC utilization in this part of the country.

METHODS

Ethical approval

This research is in accordance with the Helsinki Declaration, outlining the principles for research involving human subjects. The study was approved by the ethics board of Noakhali Science and Technology University. A consent form was taken, and the objectives, pros, and cons of the study were discussed with the participants.

Study design and sampling

The study was a community-based cross-sectional study carried out during April–July 2020, and it was primarily conducted in the southwest part of Dhaka City, Bangladesh. The study covered urban and rural people in the selected areas to compare the utilization of health facilities before, during, and after pregnancy.

Women who had children less than 59 months old were selected for the study. Women who refused to participate, had children aged >59 months, and physically ill were excluded from the study. A total of 391 data were collected conveniently from those who agreed to participate in this research. The sample size calculation was measured by using the Cochrane formulas: $n = Z^2PQ/d^2$,[22] where n is the smallest sample size to be achieved; p is the expected prevalence using at least ANC from a medically trained provider =0.82;[23] q is the proportion of not using ANC from a medical provider =0.18; d is the marginal error =0.05; Z is the statistic for a confidence level of 95% = 1.96.

Therefore, N = [(1.96)2*0.82*0.18/(0.05)2] = 227. Adding 10% non-response rate, the sample size reached 250. However, 391 data from different households were collected.

Data collection

Participants were interviewed face to face using a pre-tested and standard questionnaire. Data about antenatal visits, institutional delivery, and PNC services of last pregnancy were collected from the participants. The questionnaire also consisted of the demographic profile of respondents, pregnancy complications, follow-up of antenatal and PNC, and others. In this study, the independent variables included demographic variables, mode of delivery, follow-up of ANC, and PNC. The number of ANC and PNC visits and place of delivery were selected as dependent variables.

Data analysis

Data were cleaned, re-coded, and analyzed using Statistical Package for Social Sciences Version 23.0. Descriptive statistics of continuous variables were presented as means with standard deviation or frequency/percentage, depending on the distribution of variables. Categorical variables were presented as distribution (frequency and percentage). Binary logistic regression analysis was performed to determine independent association. Crude and adjusted odds ratios were calculated by using univariate and multivariate analyses to determine the strength of the association of the independent variables with the outcome variable at a 95% confidence interval.

RESULTS

This paper indicates associated factors of ANC, healthy delivery, and PNC. The mean age of respondents was 25.19 ± 4.79. The majority of women were Muslim (91.8%) and had finished college or higher education (70.8%), whereas only 27.4% of women engaged themselves in income-generating activities. Most women (97.4%) received ANC from health institutions, and among these women, two-third received four or more ANC visits. Only 28.6% of women had delivery at home environment and 35.8% of women delivered their child through cesarean section. Receiving PNC after delivery among women was quite satisfactory (71.6%), and 31.7% did not do their follow-up PNC (Table 1).

The type of living place, religion, and women's and husband's education had a significant effect on antennal, delivery, and PNC. The percentage of receiving ANC, delivery care at health facilities, and PNC were high among urban women. Women who finished primary education had lower percentage of receiving health facility delivery care and PNC in contrast to highly educated women, and the results were similar to the case of husband's education. The chance of receiving PNC and healthy delivery care increased if the family income was more than 20,000 Taka in Bangladeshi currency. Furthermore, antenatal care had a significant effect on delivery care and PNC (Table 2).

Based on the result, urban women had more than nine times the odds to receive ANC and more than three times the odds to receive PNC compared with rural women. Women living in urban areas utilized ANC, healthy delivery, and PNC more than those living in rural areas. Women having family income more than 20,000 Taka had two times (OR: 2.39, 95%CI: 0.818–7.042) more chance of receiving PNC. Women receiving ANC from health facilities had better chance of receiving PNC (OR: 6.215, 95%CI: 1.57–24.48), and those who selected health institution for delivery had almost two times (OR: 1.934, 95%CI: 1.21–3.09) more chance of receiving PNC (Table 3).

TABLE 1. Characteristics of respondents (N = 391)

Background characteristics	N (%)	Background characteristics	N (%)
Women age[a]	25.19 ± 4.79	**Women body mass index**[a]	25.03 ± 9.99
Residence		**Husband's education**	
Rural	194 (49.6)	Primary level	36 (9.2)
Urban	197 (50.4)	Secondary level	53 (13.6)
Religion		College or higher	302 (77.2)
Islam	359 (91.8)	**Husband's occupation**	
Hindus	31 (7.9)	Unemployment	50 (12.8)
Christian	1 (0.3)	Employment	341 (87.2)
Marital Status		**Family type**	
Married	389 (99.5)	Nuclear	87 (22.3)
Divorced	2 (0.5)	Extended	304 (77.7)
Women's education		**Family size**	
Primary level	53 (13.6)	4 or less	53 (13.6)
Secondary level	61 (15.6)	5 or more	338 (86.4)
College or higher	277 (70.8)	**Monthly income (BDT)**	
Women's occupation		<10,000	24 (6.1)
Unemployment	284 (72.6)	10,000–20,000	171 (43.7)
Employment	107 (27.4)	>20,000	196 (50.1)
Received antenatal care		**Mode of delivery**	
Yes	381 (97.4)	Normal/vaginal	251 (64.2)
No	10 (2.6)	Cesarean	140 (35.8)
No of antenatal visit		**Received postnatal care**	
Once	38 (9.7)	Yes	280 (71.6)
2–3 times	87 (22.3)	No	111(28.4)
≥4 times	256 (65.5)	**Follow-up of postnatal care**	
Delivery care		Yes	267 (68.3)
Home delivery	112 (28.6)	No	124 (31.7)
Health institution	279 (71.4)		

[a]Continuous variables are presented as mean ± SD.

TABLE 2. Relation of maternity care with background characteristics of women

Characteristics	Received antenatal care			Received delivery care			Received postnatal care		
	Yes	No	*p*	Home delivery	Institutional delivery	*p*	Yes	No	*p*
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Residence									
Rural	105 (27.5)	9 (90.0)	<0.05	107 (95.5)	7 (2.5)	<0.05	54 (22.5)	60 (39.7)	<0.05
Urban	276 (72.5)	1 (10.0)		5 (4.5)	272 (97.5)		186 (77.5)	91 (60.3)	
Religion									
Islam	351 (92.1)	8 (80.0)	NS	93 (83.0)	266 (95.3)	<0.05	263 (93.9)	96 (86.5)	<0.05
Hindus	29 (7.6)	2 (20.0)		18 (16.1)	13 (4.7)		17 (6.1)	14 (12.6)	
Christian	1 (0.3)	0 (0.0)		1 (0.9)	0 (0.0)		0 (0.0)	1 (0.9)	
Marital status									
Married	379 (99.5)	10 (100.0)	NS	112 (100.0)	277 (99.3)	NS	280 (100.0)	109 (98.2)	<0.05
Divorced	2 (0.5)	0 (0.0)		0 (0.0)	2 (0.7)		0 (0.0)	2 (1.8)	
Women education									
Primary level	49 (12.9)	4 (40.0)	<0.05	24 (21.4)	29 (10.4)	<0.05	33 (11.8)	20 (18.0)	<0.05
Secondary level	57 (15.0)	4 (40.0)		25 (22.3)	36 (12.9)		31 (11.1)	30 (27.0)	
College or higher	275 (72.1)	2 (20.0)		63 (56.3)	214 (76.7)		216 (77.1)	61 (55.0)	
Women occupation									
Unemployment	278 (73.0)	6 (60.0)	NS	74 (66.1)	210 (75.3)	NS	200 (71.4)	84 (75.7)	NS
Employment	103 (27.0)	4 (40.0)		38 (33.9)	69 (24.7)		80 (28.6)	27 (24.3)	
Husband education									
Primary level	33 (8.7)	3 (30.0)	NS	11 (9.8)	25 (9.0)	<0.05	12 (4.3)	24 (21.6)	<0.05
Secondary level	52 (13.6)	1 (10.0)		31 (27.7)	22 (7.9)		25 (8.9)	28 (25.2)	
College or higher	296 (77.7)	6 (60.0)		70 (62.5)	232 (83.2)		243 (86.8)	59 (53.2)	
Husband occupation									
Unemployment	48 (12.6)	2 (20.0)	NS	28 (25.0)	22 (7.9)	<0.05	29 (10.4)	21 (18.9)	<0.05
Employment	333 (87.4)	8 (80.0)		84 (75.0)	257 (92.1)		251 (89.6)	90 (81.1)	
Family size									
4 or less	52 (13.6)	1 (10.0)	NS	34 (30.4)	19 (6.8)	<0.05	33 (11.8)	20 (18.0)	NS
5 or more	329 (86.4)	9 (90.0)		78 (69.6)	260 (93.2)		247 (88.2)	91 (82.0)	
Monthly income (BDT)									
<10,000	24 (6.3)	0 (0.0)	NS	10 (8.9)	14 (5.0)	<0.05	11 (3.9)	13 (11.7)	<0.05
10,000–20,000	167 (43.8)	4 (40.0)		39 (34.8)	132 (47.3)		123 (43.9)	48 (43.3)	
>20,000	190 (49.9)	6 (60.0)		63 (56.3)	133 (47.7)		146 (52.1)	50 (45.0)	
Place of receiving ANC									
Health facilities				104 (92.9)	277 (99.3)	<0.05	277 (98.9)	104 (93.7)	<0.05
Not health facilities				8 (7.1)	2 (0.7)		3 (1.1)	7 (6.3)	
Delivery care									
Home delivery							69 (24.6)	43 (38.7)	<0.05
Health institution							211 (75.4)	68 (61.3)	

p-value derived from chi-square statistics at 5% level of significance ($p < 0.05$), NS; Not significant.

DISCUSSION

This paper demonstrates substantially lower utilization of health facilities delivery and PNC, although the utilization of ANC among women is increased. The study results reported that receiving ANC, healthy facility delivery care, and PNC are associated with the type of residence, women's education, husband's education and employment, family size, and monthly income of family. As health facility service and social environment are different in rural and urban areas, different proportions of ANC utilization, healthy delivery care, and PNC are expected.[24] In our study, a high proportion of less ANC utilization, healthy delivery care, and PNC among rural women were found, which may be due to low level of education, less availability of healthy facility service, and environment of society and communication. More than one-fourth of women in our study had no college or higher education, which may be due to poverty and early marriage. Women with higher education level may understand the necessity of receiving ANC, healthy delivery care, and PNC, which was consistent with our present study.[25,26]

Compared with national data, facilities available for deliveries were found at a better condition in this study. More than half of the women received PNC in this study, and the percentage was higher among those who received healthy delivery facilities, which corresponds to BDHS survey 2017–18.[23]

TABLE 3. Factors associated with maternity care and delivery care utilization

Characteristics	Received antenatal care		Received delivery care		Received postnatal care	
	Univariate OR (95%CI)	Multivariate OR (95%CI)	Univariate OR (95%CI)	Multivariate OR (95%CI)	Univariate OR (95%CI)	Multivariate OR (95%CI)
Residence						
Rural	1	1	1	1	1	1
Urban	9.5 (1.19–75.91)*	11.4 (1.21–107.08)*	5.96 (3.22–11.04)*	2.25 (1.10–4.60)*	3.73 (2.31–6.00)*	3.6 (1.86–6.94)*
Women education						
Primary level	1	1	1	1	1	1
Secondary level	11.2 (2.00–62.95)*	8.8 (1.29–60.24)*	3.5 (1.93–6.54)*	3.8 (1.57–9.15)*	2.14 (1.15–4.00)*	0.84 (0.36–1.94)
College or higher	9.6 (1.72–53.94)*	14.7 (2.20–97.97)*	4.2 (2.37–7.59)*	4.5 (1.95–10.65)	3.43 (1.92–6.10)*	2.78 (1.43–5.42)*
Husband education						
Primary level			1	1	1	1
Secondary level			2.1 (1.17–3.90)*	0.63 (0.27–1.44)	4.6 (2.51–8.48)*	3.85 (1.80–8.22)*
College or higher			6.8 (3.21–14.60)	3.49 (1.25–9.66)*	8.2 (3.89–17.42)*	8.27 (3.12–21.80)*
Husband occupation						
Unemployment			1	1	1	1
Employment			2.6 (1.39–4.70)*	1.10 (0.49–2.45)	2.02 (1.09–3.72)*	4.4 (1.90–9.80)*
Family size						
4 or less			1	1		
5 or more			5.96 (3.22–11.04)*	2.25 (1.10–4.60)*		
Monthly income (BDT)						
<10,000			1	1	1	1
10,000–20,000			1.60 (1.00–2.55)*	1.01 (0.54–1.89)	1.14 (0.71–1.81)	1.73 (1.00–2.97)*
>20.000			0.66 (0.27–1.57)	0.81 (0.24–2.62)	3.45 (1.45–8.19)*	2.39 (0.81–7.04)
Place of receiving ANC						
Not health facilities			1	1	1	1
Health facilities			1.9 (1.20–4.49)*	1.5 (0.97–2.93)	6.22 (1.57–24.48)*	3.71 (0.78–17.69)
Delivery care						
Home delivery					1	1
Health institution					1.93 (1.21–3.09)*	0.81 (0.42–1.55)

*p <0.05

In this study, a significant variation in the utilization of maternity care was observed between husband's education and occupation. Several studies indicated that partner's education and employment status were associated with the proper utilization of maternal health care.[26–28]

Logistic regression revealed that the type of residence is another important factor for receiving maternal health care services. In addition, family status, educational level, and economic condition were found to be the main determinants for less utilization of maternal care among rural women. Urban women received healthier facilities because of the availability and affordability of services compared with rural areas. Some studies also showed identical results between the two factors.[27,28]

The present study also revealed that ANC was not significantly associated with the income status of the family. This finding was inconsistent with that of Kamal *et al*.[26] However, the utilization of institutional delivery service and PNC showed significant correlation. Logistic regression analysis after adjusting for variables showed that only PNC service utilization was significantly associated with economic status, but these findings were contrary to the result of Kamal *et al*.[26] and Chowdhury *et al*.[29] where utilization of home delivery care from untrained TBA was significantly associated with the wealth index of family and utilization of medically facilitated place for delivery. Furthermore, PNC were associated with the wealth index.

There are great chances of receiving institutional delivery and PNC if women received ANC during pregnancy. These results were significantly associated with each other. Some studies showed similar results to this study.[27,30] Postnatal check-up was also associated with the place of delivery, which was similar to the result of Neupane *et al.*[28,30] This study highlighted the predictors associated with the utilization of healthy maternal services and indicated that more programs and research projects focusing on increasing the proper utilization of ANC, institutional delivery, and PNC services in rural and urban Bangladeshi women should be developed to meet SDGs.

This study has a number of limitations. The data were self-reported, and the study is cross-sectional, which does not conclude causal relationships.

CONCLUSIONS

The study revealed that the utilization of ANC, institutional delivery, and postnatal services increased in 2020 compared with the national data of 2018, whereas the risk of maternal and child mortality reduced. It also provided comprehensive understanding of the possible reasons for the utilization of healthy maternal care services and their associated factors. Therefore, increased availability and affordability of services as well as counseling and education during pregnancy were suggested throughout the country with the policy makers and government to achieve the WHO recommended number of ANC and PNC and the goals of SDG improvement of MHS.

CONFLICT OF INTEREST

None.

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A Cross-sectional Study of Nurses' Perception Toward Utilization and Barriers of Electronic Health Record

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Makara Journal of Health Research

A Cross-sectional Study of Nurses' Perception Toward Utilization and Barriers of Electronic Health Record

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Abstract

Background: The utilization of electronic health records (EHRs) is crucial. This study aimed to determine the perception of nurses on the utilization and barriers to the use of EHRs.

Methods: This descriptive cross-sectional study on 327 participants was conducted at the government hospitals of Hail City that use EHRs. Data collection was conducted between March and April 2022. The adapted questionnaire was used to collect the data.

Results: Nurses perceived EHRs as useful (5.76 ± 1.71), easy to use (4.74 ± 1.56), and intend to use (5.85 ± 1.81). Sex had no effect on perceived usefulness ($p > 0.671$), perceived ease of use ($p > 0.605$), or intention to use ($p > 0.880$). A significant difference was found in the perceived usefulness based on age ($p = 0.045$). On training, a significant difference was noted in perceived usefulness ($p = 0.039$) and intention to use ($p = 0.007$).

Conclusions: An EHR system is useful and easy to use, and nurses intended to use it. Sex had no effect on perceived usefulness, perceived ease of use, or intention to use. Age showed a significant difference in perceived usefulness. Moreover, training has a significant difference in perceived usefulness and intention to use. Policymakers can use these findings to create a program that targets the needs of nurses so that they can fully utilize EHRs.

Keywords: electronic health records, hospitals, intention, nurses

INTRODUCTION

The implementation of electronic health records (EHRs) and other digital technologies in healthcare continues to lag, and hospitals continue to face professional resistance to their use.[1] The health industry has looked into several elements that influence healthcare professionals' acceptance of software programs. Unfortunately, because different investigations focus on various technology uses and occupational categories, conflicting findings have been reported.[2] As a result, more studies regarding the effects of contemporary technologies, such as electronic medical records, are being conducted.[3] Consequently, the use of electronic medical records has aided in minimizing patient waiting times, reducing prescription-ordering errors, directing healthcare processes, and simplifying the creation of obligatory reports to higher authorities.[4]

Several studies have suggested that EHR systems fail because of the lack of user participation and evaluation of system input.[5] It is normal to experience opposition from many users when a new system is introduced and made available over the counter for organizations and populations to use. This is especially true for conventional viewers who have got accustomed to utilizing a management and review system for years. Over time, this level of resistance may deteriorate, and the system may transform from being a resistant to a convenient user system. The high cost and lack of return on investment for small practices and safety net providers, undervaluation of organizational processes and change management required, failure to redesign the clinical process and workflow to incorporate communication components and processes that will become obsolete, and scarcity of skilled resources are just a few examples.[6] Although deploying an EHR system will improve clinical efficiency, research reveals the opposite.[7] User adaptation and simplicity of use influence the efficiency potential of data-intensive environments, enabling electronic patient and provider interactions.[8] According to Otto and Nevo, various mitigating factors such as political and economic constraints have limited the adoption of an EHR system in addition to safety issues.[9] Scholars such as Jamoom *et al*. provided a counterbalance to what little is known about nurses' perspectives on EHR adoption and use.[10]

The Ministry of Health launched a program in 2008 to increase and improve the use of EHRs in public healthcare facilities,[11] there has been a dearth of literature in Saudi Arabia,[12] and an ambitious goal still faces significant challenges, such as the unfavorable views of some healthcare professionals concerning the technology.[11]

Numerous studies have examined nurses' perspectives on EHR's perceived ease of use, attitudes toward use, and how EHRs affect care practices and patient outcomes.[13] While some nursing staff saw the benefits of EHRs, Higgins

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et al., McBride *et al*., and others were dissatisfied with their use, considered them difficult and time-consuming to use, and doubted EHRs' ability to improve patient care.[14–17] In a study of intensive care unit nurses, Carayon *et al.* discovered that the usability and utility of an her system influenced nurses' acceptance of it.[18] Lorenzi discovered that 50% of EHR implementations failed because of nurses' unwillingness to embrace and use the system.[19]

The utilization of EHR is critical and should not be overlooked, as it could affect the success or failure of its deployment. Assumingly, when the user recognizes the significance of high-quality patient data, their satisfaction with the system and its use is likely to rise. Nurses have access to everything they need to offer high-level care because the EHR includes all the vital information of a patient. Therefore, this study is of significance as it determines the usefulness, ease of use, and intention to use EHRs so that intervention and change should be made toward safe and quality care.

METHODS

This descriptive cross-sectional study was conducted to determine the usefulness, ease of use, and intention to use and barriers to EHR use so that intervention and change can be made.

Ethical approval

The Institutional Review Board of the University of Hail approved this study (H-2021-021). Completion of the questionnaires also indicated that the respondents provided written consent.

Setting/participants

This study was conducted at the government hospitals of Hail City that use EHRs, including the King Khalid Hospital, King Salman Specialist Hospital, and Hail General Hospital, and the sampling units were hospital staff nurses. As a result of convenience sampling, a total of 327 hospital staff nurses participated in this study, and they were readily available. Moreover, convenience sampling enables data collection with minimum advanced planning, making it valuable in time-sensitive research. The recommended samples according to the number of hospitals involved in this study were based on the RAOSOFT (http://www.raosoft.com/samplesize.html) online calculator, with a margin of error of 5%.

The inclusion criteria were as follows: (a) have been using EHRs for at least 3 months, (b) can write and understand English, and (c) provided informed consent.

Instrument

The questionnaire used in this study has two parts. The first part asked about the demographic profile of the participants such as sex, age, years of experience, and job title. The second part contains 28 items that measure perceived usefulness (PU), perceived ease of use, and additional three items to assess the likelihood of utilization (IU).[20] The items were scored on a five-point Likert scale, where 1 and 5 indicate strong disagreement and strong agreement, respectively. All of the subscale components were added to reach the overall score. On this basis, a mean score was calculated. As the mean score increased, the positive effects on PU and perceived ease of use were stronger; thus, the median point of the scale (1–5) was used to consider the cut-off point of the mean score. The tool was subjected for the validity test with three experts in the field and was pretested with 20 staff nurses, yielding to Cronbach's alpha of 0.89.

Data collection

The researcher explained to each hospital's nurse the purpose of the study, breadth of their participation, and researchers' expectations of them. The nurses then signed a consent form, confirming their willingness to participate. The survey took at least 10 min to complete. The nurses were instructed to submit their answered survey questionnaire to the person in charge in the unit. Data collection was conducted between March and April 2022.

Data analysis

IBM SPSS Statistics for Windows version 22 (IBM Corp., Armonk, NY, USA) was used. The Kolmogorov–Smirnov test was used to determine data distribution under the presumption that they were normally distributed. The Kolmogorov–Smirnov test result was higher, i.e., at 0.94 with a p-value of 0.05, showing that the data were normally distributed. Therefore, variations in the years of experience and PU, perceived ease of use, and intention to use were examined using analysis of variance (F-test). The t-test was employed to ascertain sex differences, age, number of trainings, and job title. Each statistical analysis was conducted with a significance threshold of 0.05. The frequency and percentage were used to determine the demographic profile of the nurses using EHRs and the barriers to EHR use. The weighted mean was used to determine the PU, perceived ease of use, and intention to use.

RESULTS

Of the 327 participants, female nurses dominate (61%) the nursing workforce and were 30 years old and below (59%) with 1–2 years of experience (35%). The participants mostly have had 1–5 trainings (52%), and the majority of them were staff nurses (54%) (Table 1).

Table 2 presents the PU, perceived ease of use, and intent to use. Accordingly, the nurses perceived EHRs as useful (5.76 ± 1.71) and easy to use (4.74 ± 1.56), and they intend to use it (5.85 ± 1.81).

TABLE 1. Demographic profiles of the nurses (N = 327)

Demographics	Frequency (N)	Percentage (%)
Sex		
Male	127	39
Female	200	61
Age		
30 and below	194	59
30 and above	133	41
Duration of experience		
1–2 years	115	35
3–4 years	100	31
5 years	112	34
Number of trainings		
1–5	171	52
≥5	156	48
Job title		
Staff nurse	178	54
Head nurse/supervisory	149	46

TABLE 2. Descriptive statistics on perceived usefulness, perceived ease of use, and intention to use

	Mean	SD
Perceived usefulness	5.76	1.717
Ease of use	4.74	1.561
Intention to use	5.85	1.817

Table 3 presents the differences between demographic profiles and PU, perceived ease of use, and intention to use. No significant sex difference in the PU ($p > 0.671$), perceived ease of use ($p > 0.605$), and intention to use ($p > 0.880$) was found.

Regarding age, a significant difference was found in the PU ($p = 0.045$) but not in the perceived ease of use ($p > 0.883$) and intention to use ($p > 0.223$). As regards trainings, a significant difference was noted in the number of trainings and PU ($p = 0.039$) and intention to use ($p = 0.007$), but no significant difference in the perceived ease of use ($p > 0.142$). Meanwhile, the duration of experience was not significant different in the PU ($p > 0.708$), perceived ease of use ($p > 0.577$), and intention to use ($p > 0.949$).

Table 4 presents the barriers to the utilization of EHRs among nurses. Accordingly, the lack of training was seen as the most frequent barriers (77.9%), followed by resistance to adopt EHRs (65.1%) and the lack of technical support (57.8%).

DISCUSSION

This study aimed to investigate nurses' perceptions on the usefulness, ease of use, and intention to use EHRs. In this study, nurses positively perceived the usefulness and intended to use EHRs. This might be because nurses understood that EHRs help improve the productivity of healthcare organizations with the increasing demand for digital information. According to Abdekhoda *et al*., the usefulness and intention to use EHRs were well worthwhile to both patients and healthcare professionals to obtain medical history, treatment results, and past diagnoses; thus, an increasing number of healthcare professionals have shifted to EHRs.[21] The results of the present study agree with those of Shaker *et al*. where more than half of their participants, independent of

TABLE 3. Differences between demographic profiles and PU, perceived ease of use, and intention to use

Variables	Perceived usefulness		Perceived ease of use		Intention to use	
	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p*
Sex						
Male	5.70 ± 1.74	0.671	3.68 ± 1.40	0.605	5.82 ± 1.87	0.880
Female	5.84 ± 1.69		3.81 ± 1.31		5.87 ± 1.76	
Age						
≤30	5.65 ± 1.79	0.045	3.73 ± 1.34	0.883	5.71 ± 1.90	0.223
≥30	6.01 ± 1.52		3.77 ± 1.41		6.14 ± 1.58	
Number of trainings						
1–5	4.94 ± 1.72	0.039	3.89 ± 1.17	0.007	5.10 ± 1.97	0.142
≥5	6.25 ± 1.13		3.68 ± 1.16		6.33 ± 1.07	
Duration of experience in using EHRs						
1–2 years	5.66 ± 1.76	0.708	3.64 ± 1.35	0.577	5.82 ± 1.81	0.949
3–4 years	5.70 ± 1.66		3.91 ± 1.34		5.81 ± 1.76	
≥5 years	5.97 ± 1.76		3.64 ± 1.41		5.93 ± 1.94	

TABLE 4. Barriers to the utilization of electronic health record (N = 327)

Barriers	Frequency (N)	Percentage (%)
Lack of training	255	77.9
Resistance to adopting the electronic health record	213	65.1
Lack of technical support	189	57.8
Difficult-to-use technology	164	50.2
Computer literacy	158	48.3

designation category, nationality, sex, age, or practice environment, have a favorable opinion of EHRs.[22] Such a result adds to the body of knowledge on topics linked to the adoption of technology to enhance safety and quality nursing care.

Meanwhile, the participants had the modest perception on the ease of use, which may be because of the complexities of navigating it. Further, the modest perception of the nurses could be due to problems in comprehending the values and benefits. In an earlier study, Nour El Din posited that the perceived ease of use of EHRs resulted in enthusiastic acceptance by physicians and nurses;[23] however, in Saudi Arabia's eastern province, the benefits of EHRs are not fully realized because of the underutilization of many of its core functions. As such, this can be improved through EHR training and improvement of its key identified aspects. During HER implementation, nurses must be continuously engaged. Nurse participation in all facets of EHR adoption is encouraged. In addition to streamlining nurses' workflow, gathering feedback from nurses regarding the system will help in efforts to provide patients with high-quality treatment.

In this study, no significant difference was found between sex, PU, perceived ease of use, and intention to use. This means that both male and female nurses perceived that they and healthcare organizations could all benefit from EHRs. The present study disagrees with that of Tubaishat, claiming that sex influences the PU, perceived ease of use, and intention of current healthcare professionals to use EHR.[24] Conversely, the findings of the present study agree with those of Shahbahrami *et al*., where no significant sex difference was found in PU, perceived ease of use, and intention to use.[25] Indeed, the value of diversity and fairness is being recognized in the context of sex.

As regards age, a significant difference was found in the PU, but no significant difference was found with perceived ease of use and intention to use. This suggests that older nurses compared with their younger counterparts have had problems with the PU of EHRs, which may be because they prefer traditional practice. As such, Laramee *et al*. mentioned that younger healthcare professionals were more tolerant of EHRs than older healthcare providers.[26] This is presumably associated with their experience with technology and computers. Managers must recognize the constraints in the perception of the healthcare providers of EHRs on the PU, perceived ease of use, and intention to use. Thus, managers should, for example, pay more attention to senior nurses, as this may be a contributing factor in the PU, perceived ease of use, and intention to use EHRs.

Meanwhile, the duration of the experience was not significantly different with PU, perceived ease of use, and intention to use. This implies that regardless of their exposure in their work using EHRs, nurses have perceived themselves to using EHRs, optimistically have the ease of use, and intention to use. The non-significant outcomes in this study can be attributed to the nurses' ongoing use of EHRs. As a result, these findings can be used to reassure and empower nurses that they can learn the usefulness, ease of use, and eventual usage of EHRs regardless of their duration of experiences. These considerations can help nurses become more enthusiastic about the usefulness, ease of use, and intention to use EHRs in their workplace. Thus, nurses learning regardless of experience can be facilitated, which is critical to the successful use of EHRs.[27] However, policymakers should understand the thoughts and sentiments of nurses who have limited experience in utilizing an EHR system and who have been reported to have problems with using the system.

A significant difference was found between the number of training and PU and intention to use, but no significant difference was noted in the perceived ease of use. Obviously, the significant difference between the number of training and PU and intention to use is due to the ongoing professional development. Indeed, the perceptions of EHRs alongside training are expected to make a significant influence on healthcare data quality, healthcare outcomes, and clinical practices.[28,29] In this context, nurses could develop a clear vision, build a credible team, engage staff, and sustain momentum through training. Thus, education and timely information are provided, supporting the change initiative to promote a positive self-image and confidence in EHRs.

The PU has no significant relationship with the perceived ease of use but with a significant relationship with the intention to use. This means that regardless of the complexity of use, nurses think that they certainly employ it. Moreover, while it is coupled by complexity, end users such as nurses have the willingness to use it. The results of the present study disagree with those of Mijin *et al*. who confirmed the positive relationships between perceived ease of use and PU.[30] In this context, healthcare practitioners must carefully create and manage work environments to promote confidence in the use of HER. To achieve a successful implementation of EHRs, a framework to change the management would be required, in addition to providing training, EHR acceptance, and quality improvement.

Accordingly, the lack of training was seen as the foremost barrier, followed by resistance to EHR use and the lack of technical support. This means that before system installation, employees' preparedness and training should be assessed, as they may not be willing to accept changes to a new system within their present work process. The lack of training as a barrier agrees with the result of the earlier study about clamors of the participants. According to Ajami and Bagheri-Tadi, participants were unhappy with their vendor's training and after-sales service.[31] Rather than a training schedule like that indicated in the

literature, the participants reported that their vendor only supplied one-half- to a full-day training session. Moreover, the focus of resistance is not on a specific information system but on the changes in the status quo that are brought about by information system modifications.[32] To this end, policymakers and administrators should search for a means to increase the self-efficacy of their nurses. Indeed, a user with high self-efficacy will optimistically accept a new information system without experiencing any worries and will be more interested in the information system's high value and proportional advantage.

To support nursing practice, policymakers should build systems that address the issues highlighted in this study. Nurses' involvement in tailoring their needs can make electronic records more user-friendly. Indeed, the findings of this study consider the needs of EHR users and must be interpreted from their perspective. Individual issues can be exacerbated by the lack of involvement of healthcare practitioners in the design, development, and use of EHRs.

This study has certain limitations to consider. The use of convenience sampling should be taken into account when generalizing the results. Furthermore, because the study was limited to a single location in Saudi Arabia, the conclusions cannot be applied to other situations. These drawbacks can be overcome by expanding the study and using probability sampling in a national survey.

CONCLUSIONS

Nurses perceived EHRs as useful and easy to use and something that they intended to use. Sex had no effect on PU, perceived ease of use, or intention to use. A significant difference was found in PU based on age. On training, a significant difference in PU and intention to use was noted. Policymakers can use the present findings to develop a program that tailor-fit the needs of nurses to fully use EHRs. A consistent positive learning environment from healthcare facility managers improves nurses' views on the use of health information technology, fosters acceptance, and raises awareness to improve high-quality patient care. More research addressing the challenges in the implementation of EHRs in different settings and with different groups of nurses is needed.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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Perceived Stress and Its Relationship to Moral Resilience Among Nurses in the Hail Region, Saudi Arabia

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Perceived Stress and Its Relationship to Moral Resilience Among Nurses in the Hail Region, Saudi Arabia

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Abstract

Background: This study aimed to determine the relationship between perceived stress and moral resilience among nurses.

Methods: The researcher used a quantitative–comparative correlational study design that utilized a self-administered questionnaire with 393 nurse participants in the Hail Region, Saudi Arabia. Adapted questionnaires were distributed through Google Form survey. Data collection was conducted between October and November 2021.

Results: The nurses were moderately stressed (21.69/30) but morally resilient (2.74/4). Perceived stress scale ($p < 0.033$) and moral resilience ($p < 0.25$) were found to be significantly associated with gender. The designated ward and age were not significantly associated with perceived stress and moral resilience. Conversely, the years of experience showed a significant association with perceived stress ($p < 0.038$) but not with moral resilience ($p > 0.255$). Finally, no relationship was observed between perceived stress and moral resilience ($p > 0.248$).

Conclusions: The nurses were perceived to be moderately stressed but morally resilient. Gender was found to have a significant association with perceived stress and moral resilience but not with designated ward and age. Conversely, the years of experience had a significant association with perceived stress but not with moral resilience. Meanwhile, perceived stress had no significant relationship with moral resilience. Therefore, being morally robust allows nurses to respond to challenging, frequently intractable ethical issues that arise in clinical practice and during pandemics, regardless of the underlying stress at work.

Keywords: correlational, moral resilience, nurses, perceived stress, Saudi Arabia

INTRODUCTION

Moral resilience refers to a person's ability to deal with morally challenging circumstances[1] and to maintain or restore his or her moral integrity in reaction to moral uncertainty and difficulties.[2] In its broadest sense, moral distress is a category of moral suffering that represents the sorrow felt in response to moral wrongs, failures, or injuries; it is frequently accompanied by the sensation that one's integrity has been compromised.[3] Simultaneously minimizing psychological distress, alongside the ongoing pandemic, frontline nurses have been challenged with moral distress because of on-the-job pressure. Moral distress has hovered above them because of the novel working conditions brought about by the COVID-19 pandemic.[4] The resulting circumstances have increased the difficulties involved in delivering vital services and added to the stress of frontline workers. Challenges such as inadequate supplies of personal protective equipment, shortages of lifesaving equipment, compromised standards of care, and professional duty colliding with personal health and safety concerns are faced by frontline healthcare professionals during the COVID-19 crisis.[5] Consequently, several nurses and other healthcare personnel are currently experiencing moral distress, which may worsen as the predicted spike in patients exacerbates the barriers to providing safe and effective care.[5]

Present and past pandemics and epidemics have all challenged the moral resilience of healthcare workers. For example, during the COVID-19 pandemic, studies indicated that healthcare workers were subjected to a variety of stressors that involved psychological consequences,[6] stigma,[7] and emotional distress.[8] During the MERS-COV outbreak in Saudi Arabia, healthcare workers experienced emotional distress, with the major stresses of that outbreak being their own safety and that of their families.[9] Based on the results from the SARS outbreak of 2003, the H1N1 outbreak of 2009, and numerous Ebola outbreaks, frontline healthcare workers may be at risk of suffering higher levels of stress.[10] Furthermore, 39.1% of the healthcare workers experienced clinically relevant psychological issues, particularly those based in Wuhan, who had experienced being quarantined and/or infecting a coworker or family member.[11] Such circumstances can be an appeal to an organization to examine the moral status of healthcare workers and to provide the conditions for the development of moral and ethical activity. Resilience is a significant characteristic that can help nurses manage their perceived stress when working in such critical situations and undergoing significant stress and fatigue.[12] When confronted with ethical challenges, nurses' knowledge, experience, risk-taking ability, bravery, and good problem-solving skills

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have been proven useful in motivating them to take positive action.[13]

Investigations that measure perceived stress and its relationship with the moral resilience of healthcare providers, particularly nurses, are limited. When one acknowledges one's moral responsibilities in a particular circumstance, one examines the possible courses of action and identifies the proper moral decision in accordance with one's own perspective. Regardless of the underlying systemic reasons, being morally resilient provides practitioners with the ability to respond to difficult, frequently intractable ethical concerns that occur in clinical practice and during a pandemic. Thus, this study aimed to determine the relationship between the perceived stress and moral resilience of nurses.

METHODS

Ethical approval

This study obtained clearance and approval from the Institutional Review Board of the University of Hail with IRB Number H-2021-003 dated September 1, 2021.

Study design and sampling

The researcher used a quantitative–comparative correlational study design to determine the relationship between the perceived stress and moral resilience of nurses. This study was conducted at four main hospitals of the Hail Region, Saudi Arabia: Hail General Hospital, King Khalid Hospital, King Salman Specialist Hospital, and Convalescent Hospital. This study used the RAOSOFT sample calculator with a 95% confidence level, resulting in a requirement of 393 participants. In selecting the 393 individuals, the researcher utilized a simple random selection technique and number generator. Based on the list of nurses under the Ministry of Health, each nurse was given a distinct sequential number. The numbers allotted to each eligible participant were obtained from a list of random numbers produced by an automatic random number generator program. The inclusion criteria included staff nurses working in a government hospital with a COVID area, who are able to write and understand English and are willing to participate. Nurses who had no direct contact with patients were excluded (*e.g.*, nurse administrators).

Data collection

Data collection commenced with the ethical clearance and approval from the directors of the participating hospitals. The researcher used a Google Form survey in this investigation. The link to the survey was given to the key person of each hospital. They shared the link to the WhatsApp number of the staff nurse, which was taken from the computer's random generator. The informed consent was on the first page of the Google Form survey. The nurses had to read and agree to that before they could proceed to the questionnaire proper. Data collection was conducted between October and November 2021.

Questionnaire

Two questionnaires were used in this investigation. The first questionnaire was the perceived stress scale (PSS) by Cohen, Kamarck, and Mermelstein.[14] It had 10 items in a five-point Likert scale (0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, and 4 = very often). The original developer of the PSS suggested that responses to items 4, 5, 7, and 8 could be reversed before summing their scores; the higher the score, the higher the level of perceived stress. Low stress would be a score between 0 and 13. Scores between 14 and 26 would be regarded as a moderate stress level, and scores between 27 and 40 would be regarded as a high perceived stress level. The second questionnaire was the Rushton Moral Resilience Scale.[15] It had 17 items answerable by a four-point Likert scale (1 = disagree, 2 = somewhat disagree, 3 = somewhat agree, and 4 = agree) and four subscales (response to moral adversity, personal integrity, relational integrity, and moral efficacy). Scores were obtained by summing items 1 through 17 and then dividing by 17; the higher the mean, the higher the level of moral resilience.

The questionnaires had undergone validation and testing for content and cultural sensitivity in one of the hospitals in the Hail Region. Four professionals in the field of nursing education and practice served as validators. The nursing education was composed of two people, one of whom serving as a psychometrician in their institutions, and nursing practice was composed of two nursing directors. According to these four experts, all objects were appropriate for the intended theme. Following content validation, the reliability of the instrument was evaluated with a pretest using 15 nurses. Alpha coefficient for the reliability test was 0.85 and 0.80 for PSS and Rushton Moral Resilience Scale, respectively.

Data analysis

SPSS version 25 was used to analyze the gathered data. Descriptive statistics were used to determine the frequency and percentage. Tests for difference (*t*-test and one-way ANOVA) were used to determine significant differences between various socio-demographic variables (*e.g.*, age, gender, years of experience, and designated ward), PSS, and moral resilience. Finally, correlation analysis was used to determine the relationship between PSS and moral resilience.

RESULTS

Of the 393 participants, the age range of 31–35 years dominated (34.8%), and more females (65.9%) than males (9.6%) were identified. Over 30% of the participants had at least 6–10 years of experience, and more nurses were assigned to the non-COVID ward (71%; Table 1). The level of perceived stress and moral resilience of the

nurses were 21.69 ± 2.04 and 2.74 ± 0.30 respectively. The nurses perceived that they were moderately stressed but morally resilient.

Table 2 shows the differences among the demographic characteristics, PSS, and moral resilience. Significant differences were observed between gender and PSS ($p < 0.033$) and moral resilience ($p < 0.025$), indicating that males perceived themselves to be moderately stressed and females to be more morally resilient. With regard to nurses' designated ward, no significant differences were found between being in the non-COVID or the COVID ward and the PSS ($p > 0.715$) or moral resilience ($p > 0.333$). Regarding the age of the nurses, no significant differences were found between age and perceived stress ($p > 0.530$) or moral resilience ($p > 0.709$). Conversely, years of experience showed a significant difference with perceived stress ($p < 0.038$) but not with moral resilience ($p > 0.255$). No significant relationship was found between perceived stress ($p > 0.248$) and moral resilience.

TABLE 1. Demographic characteristics of the participants (N = 393)

Characteristics	Frequency (N)	Percentage (%)
Age		
≤25 years old	44	11.2
26–30 years old	114	29.0
31–35 years old	137	34.9
≥36	98	24.9
Gender		
Male	50	12.7
Female	343	87.3
Years of experience		
≤5 years	127	32.3
6–10 years old	135	34.4
11–15 years	76	19.3
≥16 years	55	14.0
Designated ward		
Non-COVID ward	279	71.0
COVID ward	114	29.0

TABLE 2. Differences among demographic characteristics, perceived stress scale, and moral resilience

Variables	Perceived stress scale		Moral resilience	
	Mean ± SD	*p*	Mean ± SD	*p*
Gender				
Male	22.00 ± 2.28	0.033*	2.70 ± 0.24	0.025*
Female	21.60 ± 2.01		3.20 ± 0.31	
Designated ward				
Non-COVID ward	21.60 ± 2.04	0.715	2.73 ± 0.31	0.333
COVID ward	21.70 ± 2.05		2.76 ± 0.27	
Age				
≤25 years old	21.70 ± 1.79	0.530	2.68 ± 0.32	0.709
26–30 years old	21.40 ± 2.01		2.74 ± 0.30	
31–35 years old	21.70 ± 2.00		2.73 ± 0.28	
≥36	21.80 ± 2.23		2.76 ± 0.31	
Years of experience				
≤5 years	21.30 ± 1.76	0.038*	2.69 ± 0.32	0.255
6–10 years old	21.70 ± 2.03		2.75 ± 0.27	
11–15 years	22.00 ± 2.28		2.70 ± 0.29	
≥16 years	21.90 ± 2.21		2.77 ± 0.32	

DISCUSSION

The COVID-19 pandemic appears to be expanding its reach through new mutations, putting strain on healthcare systems. Thus, this study aimed to evaluate the association between the perceived stress and moral resiliency among nurses battling the COVID-19 pandemic. Nurses are unavoidably subjected to stressors because of their multiple roles. The present study found that nurses are morally resilient, although they are being moderately stressed. Being morally resilient despite stressful experiences can be attributed to their self-awareness and dedication to the profession. Accepting situational limitations and recognizing situations that are outside an individual's control[2] indicates true resilience. This finding is in concurrence with earlier studies that reported nurses having moderate-to-high stress[16,17] and being moderately resilient.[18]

In context, nurses who are resilient can cope with stress better.[19] These findings contribute to the need for nurses to continue their individual or institutional initiatives in maintaining or restoring their moral integrity to manage their stress. The support of colleagues and families and clear communication of orders and preventative measures from their higher authorities are all imperative to manage stress under these circumstances.

A significant difference between gender and perceived stress was noted, indicating that male nurses were more stressed than their female counterparts probably because males have fewer strategies to express their

stress, as compared with females. In a longitudinal analysis on gender, appraisal, and coping by Ptacek and colleagues,[20] they claimed that women utilized more problem-focused coping techniques. However, Puspitasari *et al*.[21] found that male and female nurses who are exposed to a stressful situation in a hospital have the same stress level. Moreover, findings from an earlier study suggested that female health professionals were more stressed than their male counterparts.[22] By contrast, female nurses had greater moral resilience than their male counterparts in this study. This finding could be attributed to the fact that females are more expressive; thus, they receive more support, leading to their higher scores in this study. In addition, females might have established greater regulation of their feelings,[23] which could strategically increase their moral resilience. Afshari *et al*.[24] reported that women had less resilience than men. Therefore, determining suitable strategies to support male nurses in managing their stress and to promote moral resilience among female nurses is important. Addressing such challenges can help nurses to work in accordance with the quality of care they provide.

Whether the nurses were placed in a COVID or a non-COVID ward, this present study found no significant difference with perceived stress and moral resilience. Therefore, nurses could adapt and pull through the effect of the COVID-19 situation. Nevertheless, previous research reported that hospital staff had experienced several psychological struggles[25,26] that could affect integrity to their commitment. This finding suggests that the hospital management must conduct a consistent evaluation of the holistic status of hospital staff and plan strategically to reconcile staff crises with regard to disaster situations. Moreover, no significant difference in perceived stress and moral resilience was found when the age of the nurses and ward assignment were considered. This result might imply that nurses are committed and dedicated their work probably because they can develop their coping skills or abilities to stressful situations as they grow older.[24] Although nurses play an essential role in healthcare organizations, ensuring their commitment and dedication is crucial. Thus, nurses must be given the tools they need to handle tough situations with moral fortitude.

The years of experience of nurses were found to have a significant difference in their perceived stress, indicating that those who have more years of experience perceived more stress. People with more work experience were given more workloads because their abilities had been tested at work, which causes them more stress. Pasay-an[17] explained that nurses who have more work experience in the field have been recognized to have more competencies; thus, they are considered to be critical during the pandemic. This finding is consistent with the study conducted in China among frontline nurses during the COVID-19 pandemic; it revealed that male and female nurses with few years of hospital experience and those who just graduated had a high level of emotional stress when the pandemic emerged.[27] By contrast, the present study found no significant difference between years of experience and moral resilience. This result indicates that nurses could develop their abilities to bounce back during stressful situations regardless of the years of experience. The current finding is inconsistent with those of Afshari *et al*.,[24] who reported that resilience differed with years of experience.

The current study found no significant relationship between perceived stress and moral resilience, which indicates that perceived stress does not affect moral resilience. Therefore, perceived stress in nurses does not always affect their moral resilience. The present finding is inconsistent with the previous report, that is, perceived stress had a significant relationship with resilience,[18,28] and the finding of Garcia-Leon *et al*.,[29] that is, resilience plays a role in stress perception. In this study, which was conducted during a time when boosting the need to manage stress and boosting resilience were of critical importance, support from colleagues, family, and managers could instill a sense of belongingness and may decrease stress and boost moral resilience. Furthermore, the present finding shows that the designs of policy makers should include distinct training courses explicitly for managing stress and boosting the moral resiliency of nurses.

This study had some limitations that future scholars may consider undertaking. For example, it was conducted in only one region, which underrepresents the nurses in Saudi Arabia. Therefore, a national or international study targeting nurses globally is recommended. In addition, the non-inclusion of nurses who were in private hospitals and clinics may have a different perception, as compared with those who are in government hospitals.

A balance must be achieved between the obligation to care and the protection of healthcare staff; thus, policy makers must consider the protection of nurses. Nurses must have access to up-to-date information, and clear counseling must be provided in a timely manner. Moreover, nurses should be given top priority in resource distribution, particularly in situations where the availability of healthcare personnel is paramount.

CONCLUSIONS

Nurses were perceived to be moderately stressed but morally resilient. Gender was found to have a significant association with perceived stress and moral resilience. However, designated ward and age were found to have no significant correlation with perceived stress and moral resilience. Conversely, the years of experience had a significant correlation with perceived stress but not

with moral resilience. Meanwhile, perceived stress had no significant relationship with moral resilience. Therefore, being morally robust allows nurses to respond to challenging, frequently intractable ethical issues that arise in clinical practice and during a pandemic, regardless of the underlying stress at work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Daily Living Assistance Provided by Residents to Other Residents in Residential Aged Care Homes: Knowledge, Attitudes, and Practices

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Daily Living Assistance Provided by Residents to Other Residents in Residential Aged Care Homes: Knowledge, Attitudes, and Practices

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Abstract

Background: The rise of the aged population in Malaysia has resulted in the increased need for services, especially in terms of healthcare. Hence, continuous support is crucial to managing the daily living activities of this group. This study aimed to identify the knowledge, attitudes, and practices of older adults residing in Malaysian aged care homes concerning daily living activities and their provision of assistance to other residents with more significant disabilities.

Methods: Semi-structured interviews were conducted on ten older adults and six staff members of two selected residential aged care homes. The interview session concerned the knowledge, attitudes, and practices of older people related to the basic activities of daily living (BADL) and instrumental activities of daily living (IADL). We also applied a qualitative content analysis method.

Results: Three themes emerged after the interviews: (1) knowledge of older adults on BADL and IADL (highest response); (2) attitudes toward the assistance given to other residents; (3) types of assistance given to other residents and the staff.

Conclusions: The knowledge, attitude, and practices related to the assistance in activities of daily living by older adults may contribute to the development of a program or module that can fulfill the needs of other residents with more significant disabilities, especially in aged care homes.

Keywords: activities of daily living, interview, older adults, qualitative, residential facilities

INTRODUCTION

The Malaysian society incorporates a range of ethnicities with different beliefs, culture, and languages; however, the members of this group all agree that people of all ages should be encouraged to be active participants in their communities.[1] The government changed the retirement age from 56 years to 60 years in 2009, indicating the expansion of employment opportunities for older adults. Similarly, in developed countries, such as Sweden and Australia, older adults are still active in employment sectors although their age exceeds the cut-off for their aged population.[2] This notion of adults remaining as employees is accepted because their experience and skills are highly valued. In Australia, for example, the new Age Discrimination Act 2004 is used to protect against ageism and unlawful discrimination in the workplace; hence, this policy will enable older adults to remain active and work beyond the official retirement age.[3]

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Malaysia, similar to many countries in the world, has an increased population of older adults. The percentage of the population aged 65 years and over is expected to increase by almost three-fold over the next 20 years from 5.0% in 2010 to 14.5% in 2040.[4] With an estimated increase in total dependency rate of older adults from 12.1% in 2010 to 16.5% in 2020,[5] the burden and obligation of the care of older adults may fall more heavily onto family members[6] and may negatively impact their economic status.[7,8] The increased burden and obligation of care may also likely to affect older adults residing in residential aged care homes.

Issues pertaining to limited social engagement can influence the well-being of elderly adults.[9] Wilcock and Townsend stated that the amount of time spent by older adults on meaningful activities can be affected by their mental and physical health.[10] Deterioration in health conditions may also affect one's mobility.[11] Hence, these conditions may eventually result in the inactivity of older adults in their daily life.

The rise of the aged population in Malaysia has resulted in the increased need for healthcare services for this population; however, the facilities provided in residential

aged care homes are inadequate, and shortage has been observed in the number of staff or carers needed to accommodate the increasing number of residents.[12] The shortage of staff or care in such facilities often prompts capable residents to help out in managing self-care activities of other residents with more significant disabilities; often without proper guidance, this condition can result in injury to both parties. Residents with more significant disabilities comprise those who need help in managing their self-care activities. This study was undertaken to obtain information about the knowledge of basic activities of daily living (BADL) and instrumental activities of daily living (IADL), attitudes, and practices, including the help that older individuals give to other residents in aged care homes. To date, no research has been conducted to identify these aspects within the Malaysian context. This study acts as preliminary research to obtain the information needed to develop a buddy-program module that will be used in the next phase of the research.

BADL can be identified as activities oriented toward taking care of one's own body.[13] These activities include personal hygiene, bathing, toileting, climbing stairs, dressing, feeding, bowel and bladder control, transfer, and mobility. Meanwhile, IADL involve more complex interactions that support daily life within the home and community[14] and can be divided into cognitive IADL (CIADL) and physical IADL (PIADL).[14,15] Refer to Table 1 for the items under CIADL and PIADL.

TABLE 1. IADL adapted from the work of Holm and Rogers (2014)

IADL items
Cognitive instrumental activities of daily living (CIADL)
Money management: Shopping
Money management: Bill paying by check
Money management: Checkbook balancing
Money management: Mailing bills
Telephone use
Medication management
Obtaining critical information from the media: Auditory
Obtaining critical information from the media: Visual
Home maintenance: Flashlight repair
Home safety
Playing bingo
Meal preparation: Oven use
Meal preparation: Stovetop use
Meal preparation: Use of Sharp Utensils
Physical instrumental activities of daily living (PIADL)
Heavy housework: Taking out garbage; Key use
Heavy housework: Changing bed linens
Home maintenance: Sweeping
Light housework: Clean-up after meal preparation

METHODS

Ethical approval

Ethical approval to conduct this study was granted by the Medical Research and Innovation Secretariat, Universiti Kebangsaan Malaysia (project number: NN-2017-163) and Department of Social Welfare Malaysia (JKMM 100/12/5/2: 2017/331).

Study design and sampling methods

This study consisted of qualitative semi-structured interviews. Knowledge is defined as understanding of[16] or information about BADL and IADL that a person gains by experience; attitudes are feelings or opinions[17] concerning the assistance given in BADL and IADL to other residents with more significant disabilities; practices are the physical action[18] of providing assistance in BADL and IADL to residents with more significant disabilities. In Malaysia, ten residential aged care homes known as "*Rumah Seri Kenangan*" (RSK) are publicly funded by the Ministry of Women, Family and Community Development of Malaysia. Two of the residential aged care homes, namely, RSK Johor Bahru and RSK Cheras, were selected for the study because they represent different geographical areas, with one home being close to the city of Johor and the other being located in the city of Kajang, Selangor. Notably, all government residential aged care homes have the same schedule of daily activities.

Participants

Ten older adults and six staff were recruited. The sampling size of the participants was based on data saturation. The inclusion criteria in the study were aged 60 years and above, ability to speak and understand the Malay language, and residency of more than six months in the selected residential aged care homes.

Information about the study, including its title, inclusion and exclusion criteria, and ways of contacting the researchers if anyone were interested in taking part in the study, were posted on the notice board at the residential aged care homes. Those who agreed to participate in the study were provided with informed consent forms for them to sign and return to the researchers. The participants were informed about the objective of the study, that is, to gain understanding regarding the knowledge, attitudes, and practices of their daily living assistance, and notified that the researcher herself is an occupational therapist. They were interviewed using a 13-item questionnaire between 15 and 35 min, depending on the amount of information that they were willing to share. The 13 items on the questionnaires were based on BADL and IADL, and questions related to the assistance given by residents to other residents were also included. A set of questions was prepared to steer the interview process. The questions were constructed by the primary researcher and discussed with the other researchers involved in the study. The validity of the questionnaire was evaluated using face

validity and content validity among four researchers, who were academicians and with occupational therapy background, to evaluate the structure and content of the questionnaire. The researchers were asked for any inconsistencies with the clarity, phrasing, sentence structure, and meaning and to provide feedback for improvement of the questionnaire.

All interviews were performed in a quiet room, audio recorded, and conducted by the researcher (first author) in the Malay language. The other residents and staff on duty were closely available if help was needed during the interview session. The interview was conducted by a researcher who is competent to perform the session based on her previous research experience during her master's study. In addition, the researcher's interest lies in the provision of healthcare services for older adults. The participants were encouraged to answer all questions in their own words to establish a full perspective of the information given. Additional questions relating to the participants' responses were posed to gather more information. Field notes were made by the researcher during the interview sessions to record additional information, such as the date, time, and participants' reactions or gestures that had been observed.

After the first point of contact with the participants through the notice board advertisement for the study, a snowball sampling effect was performed. After the first interview session, the respondents were asked to suggest another resident who met the inclusion criteria and who may be potentially interested in participating in the study. The recruitment and interview process continued until no new information was discovered, and data saturation was achieved until the fifth respondent for the first residential aged care. The recruitment for the second residential aged care was continued until the tenth respondent to identify any new information. However, no new emerging theme was found.

Data analysis

The interviews were transcribed verbatim by the first author. A qualitative content analysis (QCA) approach[19] was used to analyze the data from the Malay language version of the original transcript. The older adults' interview transcripts were triangulated with the information gathered from the interview session using a 3-item questionnaire with the staff in the residential aged care homes to support the findings and the development of a theme. The 3-item questionnaires sought information regarding the main problems or difficulty faced by residents in residential aged care homes, the presence of healthy residents helping other residents with more significant disabilities in physical or/and cognitive function, and any suggestions or recommendations to overcome the current situation (i.e., guidelines or module). Six staff were purposely selected and interviewed individually: an occupational therapist, an office attendant, a staff nurse from the first residential aged care home, and three staff nurses who were in charge of the participants, including those who are bed-ridden from the second home. Member checking, peer review, and audit trailing were conducted to ensure the credibility and trustworthiness of the findings. Member checking was performed at the end of the interview session with the participants to clarify the summary of the information they provided. Peer review was conducted with an academician and an occupational therapist who was not directly involved in the study to review the transcript and themes developed. Concurrently, an academician who was external to the study was recruited to ascertain that data analysis was conducted in a logical measure.[20]

RESULTS

Participants' demographic information

Ten older adults and six staff who agreed to participate in this study were recruited from both residential aged care homes. Table 2 presents the participant demographics. The older adults were equally distributed by gender, whereas for the staff, female participation was higher (83.3%) than that of males (16.7%). Malays account for the highest percentage of the population for older adults and staff, followed by Indians (older adults).

Within the marital status categories, most of the older adult participants were widow/widower (40%), and the highest level of education reported was primary school (50%). For the staff, most participants were married (66.7%), and the highest level of education reported was secondary school (66.7%).

Themes, categories, and sub-categories

The researcher transcribed the audio recorded into a full transcript of all interviews. Codes were manually developed using highlighters. In the first step, questions from the interview were used to create an initial set of concept-based categories (literature reviews, discussion, experience, and peer discussion), followed by data-based sub-categories and the remaining categories. A coding frame was generated using a combination of deductive (concept-based) and inductive (data-based) strategies.[19] Analysis of interview data derived 6 categories and 31 sub-categories, which were grouped within the three specified main themes, namely, knowledge in BADL and IADL, attitudes toward the help given related to BADL and IADL, and types of assistance that is given (Table 3).

Theme 1: Knowledge of BADL and IADL

Two categories with 15 sub-categories were identified for knowledge in BADL and IADL. For BADL, most of the participants reported their engagement in religious activities, such as praying, reciting the Al-Quran, and zikr, in their daily lives. For Muslims, prayer is one of the five pillars of Islam, and the Muslim participants prayed five times a day (Fajr, Dhur, Asr, Maghrib, and Isha).

TABLE 2. Demographic data of older adults and staff

Variables	Older adult (N = 10)		Staff (N = 6)	
	Male	Female	Male	Female
	N (%)	N (%)	N (%)	N (%)
Gender	5 (50)	5 (50)	1 (16.7)	5 (83.3)
Age (years)				
20–29				2 (33.3)
30–39			1 (16.7)	3 (50.0)
60–69	2 (20)	3 (30)		
70 and above	3 (30)	2 (20)		
Ethnicity				
Malay	4 (40)	4 (40)	1 (16.7)	5 (83.3)
Indian	1 (10)	1 (10)		
Marital status				
Single	3 (30)			2 (33.3)
Married	2 (20)	1 (10)	1 (16.7)	3 (50.0)
Widow/Widower		4 (40)		
Level of education				
No schooling		1 (10)		
Primary school	1 (10)	4 (40)		
Secondary school	4 (40)		1 (16.7)	3 (50.0)
University/College				2 (33.3)

The majority of the participants mentioned prayer as an obligation that they must perform as long as they can do so without any restriction. In addition, other activities included personal hygiene, bathing, dressing, and feeding.

For IADL, the majority of the participants stated engage in home management, such as sweeping, cleaning, and mopping the floor, dorm area, and the toilet, in the residential aged care homes. Some participants reported the importance of keeping the clusters clean and tidy. Moreover, most of the participants volunteer to wash the floor without any complaint when another resident accidentally passes urine outside the toilet area. Other IADL activities included telephone use, gardening, meal preparation, and shopping.

Theme 2: Attitude toward the assistance given related to BADL and IADL

A positive attitude was exhibited in response to the question about the participants' attitude toward the assistance that they give related to BADL and IADL. Two categories with six sub-categories were identified for this theme. The participants showed a positive attitude when they were helping other residents in the residential aged care homes together with the staff. One of the participants, Mr. A., mentioned that, *"Sometimes when he passed urine I would just help to clean, together with the staff in charge, not just myself."* Similarly, most of the participants help the staff with other residents in the residential aged care homes, especially those who are staying in the same cluster. Mr. M., another participant, stated that, *"one day, someone fell and I assisted him when he wanted to go to the toilet….sent him to the clinic… we live here (residential aged care homes) and are growing old together, so I just helped him."* Another attitude was the participants' sense of responsibility toward the assistance that they extend in daily living function activities.

The majority of the participants reported their sense of obligation to help other residents who have health problems, especially during the night. In the residential aged care homes, no staff is on duty to take charge of independent clusters out of office hours. Therefore, if any of the residents fell sick and needs immediate treatment, the participants will send the ill resident to the main office or ask the staff to come and check if they personally cannot move the resident. One of the participants who used to be the cluster leader mentioned that, *"I would contact the nurses in charge straight away. They would come and know what should be done. I kept all of the staff numbers so that it would be easier for me to call if something happened."*

Theme 3: Types of assistance

The residents stated that they help other residents in the residential aged care homes in their daily life activities, including BADL and IADL. For this theme, two categories with 10 sub-categories were identified. The type of assistance given by the residents in terms of BADL included helping the residents in bathing. One of the participants, Mrs. N., mentioned that, *"She called me into the bathroom and asked me to help her to put the foam on both her legs because she has limited movement."* Other participants help in pushing residents in wheelchair in in and out of the toilet. Some of the participants also reported that they are more likely to help residents voluntarily in regard to their personal hygiene, such as cutting fingernails. Moreover, some of them aid bed-ridden residents in feeding activities.

For assistance in IADL, the majority of the participants support other residents in their respective dorms by sweeping and mopping the floor. Most of them stated that if they notice that the floor is dirty, then they will take the initiative and clean the entire dorm. Some participants help other residents in money management. Some residents cannot keep their own money, and, if they need to buy something, they will ask the abled resident to buy the item using their money. Some healthy participants stated that they help the dining hall attendants. They push the trolley containing plates and cups in an out of the dining area to be washed, help prepare the food by cutting onions and other vegetables, and aid other residents in washing the dishes.

TABLE 3. Themes, categories, and sub-categories identified in the study

Theme and categories	Sub-categories
Knowledge in BADL and IADL	
BADL	Religious activity
	Personal hygiene
	Bathing
	Feeding
	Dressing
	Bowel and bladder management
	Morning exercise/jogging
	Socialization
	Rest and sleep
IADL	Home management
	Telephone use
	Gardening
	Food preparation
	Community management
	Craft activity
Attitude towards the help given related to BADL and IADL	
Positive attitude	Helping residents together with staff
	Helping residents with the other residents
	Give moral support to the residents (wait patiently until the staff arrive to help)
	Give motivation to the other residents in remembering of God to reduce the feeling of pain
Responsibilities	Inform to the staff on duty if any residents having health problems
	Try to solve the problem on their own if they could, before asking help from the staff
Types of assistance that was given	
Assistance in BADL	Helping the residents in bathing
	Helping the residents to cut fingernails
	Helping to feed the residents who were bedridden
	Helping to push the residents get in and out of the toilet by using wheelchair
	Helping the residents to get the food from the café
	Helping the residents to buy food from outside of the elderly care homes
Assistance in IADL	Helping the residents by sweeping and mopping the floor
	Helping residents to keep their money
	Helping the residents in gardening (planting, watering, washing the drain)
	Helping the attendant at the dining hall (e.g. pushing the trolley with plates and cups in and out of the dining hall; helping to prepare the food by cutting the onion and vegetables; helping the other residents to wash the cups and plates)

The interviews conducted on the staff supported the results of interviews conducted on the residents of the residential aged care homes. Some of the residents were healthy and can assist other residents who have more significant disabilities in their daily life resulting from problems either in cognitive or physical functions. One staff who is also an occupational therapist stated that, *"Anyone who has a cognitive problem or is bed-ridden is indeed they have a problem… most of the healthy residents will help them*." Another staff working as a nurse also indicated that, *"There are those who are willing to help…. even if they do not have enough strength, they will help what ever that they could for example, change clothes and diapers."* The attendant also said that, *"We don't deny that he (the resident) will be the first to help the staff in the residential aged care homes to clean the residential area."* Based on the themes, categories and sub-categories that emerged, and supporting evidence from the staff in the residential aged care homes, some of the healthy residents can and are willing to help other residents with more significant disabilities.

DISCUSSION

The most frequent activity reported by the residents in the residential aged care homes was religious activity for knowledge in BADL, followed by personal hygiene and bathing. In Malaysia, Malays represent the highest population among other ethnics[21], and they are all Muslims. For Muslim residents, their religious practices include the five daily prayers, fasting, reciting of the Qur'an, and remembrance of Allah (zikr). Most of the residents stated their sense of obligation to perform such religious practices in their daily lives. This point is important because it shows that performing these religious activities provides a purpose in life as the residents strive to become a better person in the world and the hereafter. Similarly, a study conducted by Baharuddin and Ismail[22] among residents at the

government and non-government residential aged care homes indicated a significant positive relationship between the spiritual intelligence of the residential aged study subjects and their religious practices. Furthermore, participation and engagement in different associations among older adults in religious groups and community activities can help them remain active in their daily living.

However, in most Western countries, religious activity is regarded as an activity in IADL, which means that it is aimed at supporting daily life within homes and communities and requires more complex interactions than BADL. The Occupational Therapy Practice Framework: Domain and Process-Fourth Edition[23] categorized religious and spiritual expression under one of the IADL activities, supporting the daily life within individual homes and communities. In the context of this study, the Muslim residents mentioned their obligation to perform spiritual activities, such as praying five times daily, as one of the important aspects in caring for their mental and emotional well-being.

A previous study stated that the prevalence of functional disability among older adults in the ASEAN region reaches 22% and 47% for ADL and IADL problem, respectively.[24] The difficulties encountered related to BADL and IADL activities are more prevalent among older adults who are women, live alone, have low income, do not engage in physical activity, have poor social relationships, and live in a restricted environment.[25] Therefore, older adults may require assistance and become dependent on the help of the staff to cater for their daily needs, especially older adults in residential aged care homes. The findings of this study showed that the help provided by resident participants to other residents included BADL and IADL activities, such as bathing, cutting nails, feeding, money management, meal preparation, and gardening, indicating that some residents have difficulty performing their daily activities. Furthermore, Razaob *et al*. indicated that home-dwelling older adults are more independent in self-care activities compared with the institutionalized group in terms of oral hygiene, trimming toenails, house mobility, and shower mobility.[26]

Some residents have their own responsibilities for other residents, especially those who are having health problems. They inform the staff on duty or take the person to the main office using a wheelchair, depending on the situation. This action is considered an important factor because the residents saw an obligation to help other residents who are in need. Some of the residents stated that they like helping other residents because it makes them stay connected to the people around them. Amran *et al*. stated that to overcome the feeling of loneliness and improve social relationships among older adults, residents prefer to perform activities with other residents, such as watching television, having conversation, and taking a walk around the residential aged care homes.[27] Thus, to overcome the feeling of loneliness and improve social relationships among the older adults, residents will engage in daily living activities that they love to do, which include the aforementioned activities. Furthermore, social networks and active social involvement of older adults can reduce the process of memory decline.[28]

The residents who participated in this study conversed freely, and most were very happy to relate their experiences in assisting other residents at their residential aged care homes. Some of them help the staff at the residential aged care homes in their daily activities, especially when a heavy person needs to be transferred from their bed to a wheelchair. This finding is supported by the interview conducted on the staff at the same aged care homes. Most of the residents showed a positive attitude in assisting other residents who are more passively receiving care, along with other residents who are relatively able to perform physical and mental functions.

The Malaysian Government has launched the new National Policy for Older Persons and Plan of Action for Older Persons 2011 to ensure that older adults experience a healthy, active, and productive aging, which may lead to an improved well-being.[14,29] This step is crucial because the policy ensures that the people who deal with older adults provide appropriate services and a supportive environment for them. However, the recruitment of appropriate staff for residential aged care homes should be addressed to overcome the expected increased number of older adults. The current study showed that the assistance in BADL and IADL by the residents themselves may reduce the burden or shortage of staff/attendants in residential aged care homes.

Most of the resident participants help other residents in BADL, such as bathing, cutting fingernails, feeding, and transfer. As for IADL, they help other residents by sweeping and mopping the floor and helping in money management and aid the attendants at the dining hall by cleaning the dishes and preparing meals. The residents who are relatively well organized and mentally capable assist other residents and staff/attendants by assuming some of their daily living activities. However, limited knowledge and experience in how to conduct activities properly have been noted. Exposure to a specialized module or manual will enhance the knowledge of residents to provide appropriate care to other residents in residential aged care homes. The module may include the buddy-program given its appropriateness for aged care homes involving healthy older adults to assist the other older adults with more significant disabilities in physical or cognitive function. Furthermore, modules that are available in our Malaysian context do not focus on the steps of BADL and IADL.[30–32] Another important aspect that needs to be considered in the development of this

module is the emotional and social support to the user of the module because dealing with older adults without the necessary support may lead to depression.[33]

The limitations of this study must be acknowledged. For the QCA, limitations in the triangulation process were noted, and any future study should include information, such as a daily activity diary or checklist, to further strengthen the findings. The semi-structured interview can be changed to an in-depth interview to gain more details regarding the issues in residential aged care homes. Being a qualitative study, the transferability of the findings of this research is limited to other similar residential aged care facilities in Malaysia.

CONCLUSIONS

The findings of the study indicated the knowledge, attitudes, and practices of residents at residential aged care homes concerning the provision of assistance in daily living activities to other residents with more significant disabilities. These findings are important in highlighting the needs of older adults, focusing on their BADL and IADL, including their participation and assistance to other residents with more significant disabilities. Hence, the findings of this study may contribute to the development of a buddy-program training module for residents in the residential aged care homes and older adults in the community.

CONFLICT OF INTEREST

None declared.

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Caregivers of Elderly with Moderate to Total Dependence in Activities of Daily Living in Yogyakarta Indonesia: Correlation of Burden and Quality of Life

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Caregivers of Elderly with Moderate to Total Dependence in Activities of Daily Living in Yogyakarta Indonesia: Correlation of Burden and Quality of Life

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Abstract

Background: Aging is accompanied by a functional decline leading to the loss of independence in conducting activities of daily living. The dependence of the elderly can cause burden that affects the quality of life of caregivers. This study aimed to assess the correlation between the burden and quality of life of caregivers looking after moderately to totally dependent elderly.

Methods: This research is a cross-sectional study that used Zarit Burden Interview to assess caregiver burden and World Health Organization Quality of Life to measure the quality of life of people caring for elderly with moderate to total dependence based on the scores in Activities of Daily Living and Instrumental Activities of Daily Living questionnaires. The data were analyzed using Spearman's rank correlation test.

Results: A total of 30 caregivers participated in this study. Significant negative correlations were observed between the burden and quality of life of caregivers of elderly with moderate to total dependence in all four domains: physical (p = 0.001), psychological (p < 0.001), social relationships (p = 0.028), and environmental (p < 0.001).

Conclusions: The findings imply that the burden of caring for the elderly with moderate to total dependence may affect the caregivers' burden and quality of life in all domains.

Keywords: burden, caregiver, elderly, quality of life

INTRODUCTION

Aging is accompanied by many organ and system changes associated with functional decline. These changes vary individually. Some elderlies exhibit a slow decline and remain independent until the end of life, and others experience a more advanced decline that leads to the loss of independence in daily activities. The latter ones will be dependent on caregivers.[1–3] Indonesia has societal norms that require family members to take care of the elderly.[4] In addition, the lack of alternatives due to inadequate health services prompts families to assume the main responsibility of elderly care.[4]

Caregiver is a general term referring to anyone who provides care for a dependent person to help their daily life activities.[5] As the elderly age, their dependence increases, causing an increase in the caregivers' burden. Caregiver burden is defined as a multidimensional negative response observed whilst undertaking the role of primary caregiver.[6] It affects the caregivers' quality of life.[7–10]

A number of research have been conducted on the correlation between the burden and quality of life of caregivers taking care of elderly.[11–14] However, the number of studies on the burden and quality of life of caregivers of elderly with moderate to total dependence is still limited.[15] The study aimed to analyze the correlation between the burden and quality of life of caregivers who care for the elderly with moderate to total dependence in Yogyakarta, Indonesia. The research on the relationship between family caregivers' burden and quality of life was previously conducted in India in 2016.[12] Samples in the study were obtained by purposive sampling by selecting caregivers who care for the elderly diagnosed with Alzheimer's dementia; the caregiver specifically must have cared for and lived with the elderly for more than 1 year and must not have suffered from a chronic disease in the last 1 year.[12]

Naing *et al*. conducted similar research on caregiver burden from caring for the dependent elderly in Myanmar; the participants involved were caregivers aged 18–59 years old and who cared for dependent elderly in the least 6 months.[15] Meanwhile, in this research, the caregivers were not required to be <60 years. Thus, old

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caregivers were not excluded. This study aimed to assess the correlation between the burden and quality of life of caregivers looking after moderately to totally dependent elderly. Data were collected from the caregivers of elderly living in Yogyakarta Special Province because this location has the highest percentage of elderly population (14.5%) in Indonesia compared with other provinces.[16] The growing population of elderly will increase the demand for caregivers, especially family as informal caregivers. This condition may lead to the increased burden borne by productive people.[16] Observing the data, the caregivers' quality of life must be considered as an important issue in Indonesia. A part of the result of this study was presented at the International Conference on Public Health in 2020.[17] This study will provide data for policy makers to develop programs to support caregivers.

METHODS

Ethical approval

This research was approved by the Research Ethics Committee of the Faculty of Medicine, Duta Wacana Christian University.

Study design

This cross-sectional research was an analytic observational study and conducted from December 2019 to January 2020. Data were collected by home visits to the respondents. The study participants were informal caregivers of elderly with moderate to total dependence based on the Activities of Daily Living (ADL) score for more than six months. No age limit was applied for the caregivers. However, caregivers aged 60 years or over were screened for unimpaired cognitive function as indicated by their Mini-Mental State Exam (MMSE) score (>23). The interview of the caregivers was conducted in private to avoid bias if the elderly they took care of was present during the data collection.

Study procedure

Data were collected in two phases. In the first phase, a screening was conducted to identify elderly (aged ≥ 60 years old) with moderate to total dependence. The data of elderly were collected from health volunteers in Kampung Pakuncen, Yogyakarta Municipality, who also provided information of the elderly whom they considered as dependent. The researchers paid home visits to the elderly to assess their level of independence, which was measured using Instrumental Activities of Daily Living (IADL) and ADL questionnaires. ADL assesses the independence in daily activities, including personal hygiene or dressing, toileting, grooming, eating or transferring, and ambulating. The ADL scores range from 0 to 20. A score of 0–4 is classified as total dependency, 5–8 as severe dependency, 9–11 as moderate dependency, 12–19 as mild dependency, and 20 as independent. The inclusion criterion for this study was a score < 12. The independence in more complex activities in daily life was measured using the IADL.[18] IADL covers eight domains, namely, the capability to use the telephone, do housework, wash clothes, shop, prepare food, use transportation, manage finances, and prepare and take medication. The IADL score ranges from 0 to 16. A score of 9–16 is considered as independent, 1–8 as dependent, and 0 as totally dependent. The inclusion criterion for this study was a score < 9. The IADL is more sensitive to assessing the presence of early cognitive decline, and the ADL is more sensitive to determining a person's physical function.[19]

In the second phase, data were collected from the caregivers of the elderly identified in the first phase. In this phase, the caregivers had to meet the inclusion criteria, such as being able to communicate well. If the caregiver(s) were aged ≥ 60 years old, they had to undergo MMSE assessment as a cognitive screening tool. The Zarit Burden Interview (ZBI) was used to measure the caregiver burden in caring for the elderly. It is a 22-item questionnaire using a 5-point Likert scale, where 0 means "never," and 4 means "almost always."[20] ZBI measures the impact of care on the social, physical, emotional, and financial well-being of individuals.[20] The items are added up with a total score ranging from 0 to 88, and a high score implies a high burden experienced by a caregiver. The validity and reliability tests of the Indonesian version of ZBI were implemented by Rahmat LAE in 2009, resulting in 75.7% sensibility and 83.6% spesifity.[21]

The World Health Organization Quality of Life (WHOQOL-BREF) was used to assess the caregivers' quality of life; it consists of 26 items and has 4 domains consisting of physical health, psychological, social relationships, and environmental domains.[22] This Indonesian version instrument has good discriminant, content, and retest validity.[22] The domain scores were scaled in the positive direction (high scores indicate high quality of life). The scores were transformed on a scale from 0 to 100.[22]

Sampling method

Participants were selected by consecutive sampling. Based on previous research, the percentage of the elderly in Yogyakarta City with moderate to severe dependence is 2.4%.[23] Calculating 2.4% from the 1,332 total elderly in Kampung Pakuncen, Yogyakarta Municipality, 32 samples were generated; however, in the end, only 30 people were selected due to the inclusion and exclusion criteria of the study.[24]

Data analysis

The correlation between caregiver burden (ZBI) and quality of life (WHOQOL-BREF) was analyzed using Spearman's rank correlation test. Confounding factors were included in the test and comprised the age of dependent elderly, age of caregivers, education of caregivers (two groups: no schooling to primary school,

high school, and university), marital status of caregivers (two groups: married and not married), relationship between elderly and caregivers (four groups: spouse/siblings, children or children-in-law, grandchildren, and neighbor), duration of caregiving, and the number of hours of caregiving per day. The results were significant if $p < 0.05$.[25]

RESULTS

Initially, 45 elderlies were referred by the health volunteers. After the assessment, 30 elderlies met the inclusion criteria of having moderate to total dependence. The elderlies were aged between 60–90 years old, with ADL scores in the range of 0–11 and IADL scores of 0–8. Then, the data of caregivers of the 30 elderlies were collected. Table 1 shows the demographic data of the caregivers. Table 2 shows the age, the correlation analysis between the burden, which was measured using ZBI, and the quality of life of the caregivers, which was assessed using WHOQOL-BREF, in this study was carried out with the Spearman's rank correlation test. Table 3 presents the results of the statistical analysis.

All seven confounding factors (age of dependent elderly, age of caregivers, education of caregivers with two groups (no schooling to primary school, high school, and university), marital status of caregivers (married and not married), relationship between elderly and caregivers (spouse/siblings, children or children-in-law, grandchildren, and neighbors), duration of caregiving, and the number of hours of caregiving per day) were included in the statistical analysis and showed significant correlations between the caregivers' burden and all four domains of the quality of life: physical ($p = 0.001$), psychological ($p < 0.001$), social relationships ($p = 0.028$), and environmental ($p < 0.001$).

DISCUSSION

Thirty caregivers of elderly with moderate to total dependence were assessed for their burden and quality of life. Studies have reported varied ZBI scores, implying the wide range of caregiver burden. The burden of the caregivers in this study was lower or higher than those in reported other research.[11,12,26,27] These variations may be related to the caregivers' age, education, financial situation, and relation to the person being cared for.[28]

The quality of life of caregivers also varies. The mean quality of life of caregivers of elderly with moderate to total dependence in this study was higher in one or some domains and lower in other domains compared with the values reported by other researchers.[2,5,27,29] The quality of life is affected by many factors, including culture.[30–32] A study that investigated the quality of life of 1,056 Indonesians aged 17–75 years using WHOQOL-BREF reported values that were higher in all four domains than

TABLE 1. Demographic data of caregivers (N = 30)

Variable	N (%)
Gender	
Female	24 (80.0)
Male	6 (20.0)
Educational status	
Uneducated	2 (6.7)
Primary school	4 (13.3)
Senior high school	19 (63.3)
Diploma (Associate degree)	1 (3.3)
University (Bachelor's degree)	4 (13.3)
Occupational status	
Unemployed	13 (43.3)
Entrepreneur	10 (33.3)
Private employee	2 (6.7)
Laborer	1 (3.3)
Other occupations	4 (13.3)
Marital status	
Married	21 (60.0)
Not married (single/widowed/divorced)	9 (40.0)
Relation to care recipient	
First generation (wife/husband/sibling)	10 (33.3)
Second generation (children/adopted children/son in law/daughter in law)	16 (53.3)
Third generation (granddaughter/ grandson)	2 (6.7)
Neighbor	2 (6.7)
Duration of Caregiving	
6 months to 3 years	11 (36.7)
4–6 years	13 (43.3)
7–9 years	3 (10.0)
10–12 years	2 (6.7)
16–18 years	1 (3.3)
Time frequency of caregiving	
≤ 6 hours	4 (13.3)
7–12 hours	3 (10.0)
13–18 hours	1 (3.3)
19–24 hours	22 (73.3)

TABLE 2. Age, burden, and quality of life of caregivers

Variable	Mean ± SD
Age	49.00 ± 12.28
ZBI Scores	34.27 ± 18.94
WHOQOL-BREF	
Physical Health Domain	63.30 ± 12.83
Psychological Domain	58.17 ± 12.31
Social Relationships Domain	59.77 ± 9.03
Environmental Domain	51.90 ± 9.99

TABLE 3. Correlation between the ZBI and WHOQOL-BREF Caregiver

WHOQOL-BREF	r	*p*
Physical	−0.659	0.001**
Psychological	−0.730	<0.001**
Social relationships	−0.459	0.028*
Environmental	−0.680	<0.001**

*indicates $p < 0.05$; ** indicates $p < 0.01$

those found in this study.[33] Thus, the quality of life of the caregivers of elderly with moderate to total dependence was lower than that of average Indonesians in all four domains: physical, psychological, social, and environmental. This study revealed a negative correlation between the burden and all four domains of the quality of life of moderately to totally dependent elderly caregivers. The higher the burden of caregivers, the lower the quality of life, and vice versa. The caregiver burden has subjective and objective dimensions. Caregivers experience stress and anxiety as a result of their own situation and the feeling of being manipulated by the care recipient. On the other hand, objective distress refers to the interference and changes in the caregiver's life habits and household caused by care work.[34]

A significant correlation was observed between the burden and physical domain of caregivers. The burden experienced by caregivers triggers stress.[35] When the body experiences stress, the body activates the hypothalamic–pituitary–adrenal axis and the sympathetic adrenergic nervous system. The exposure to stressful stimuli stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH triggers the adrenal cortex to release glucocorticoids (cortisol). The simultaneous release of epinephrine (adrenaline) from the adrenal medulla and norepinephrine from the sympathetic nerves activates the sympathetic nervous system. The release of molecules during a stress response affects profoundly the function of most cells and organs throughout the body, including the brain, respiratory system, heart, liver, digestive tract, muscles, skin, and immune system, which deteriorates the caregiver's physical condition.[29] The caregiver burden with physical tension while caring for a dependent individual (low ADL score), such as bathing, nursing, and other personal care activities, will increase the occurrence risk of physical health problems. Caregiver burden leads to the increased search for health care.[35]

A strong correlation was also observed between the caregivers' burden and the quality of life psychological domain. Caregivers are prone to developing depression and anxiety.[36,37] A study revealed the positive correlation of care burden with anxiety and depression.[37] This study revealed a significant correlation between burden and social relationship in the quality of life of caregivers. A total of 22 caregivers spent 19–24 hours per day to care for dependent elderly, leaving very limited time for themselves. The long duration of for caring adversely affects the caregivers' social life, and this change in social interaction aggravates over time.[38] Most caregivers in this study were female, which probably explained the lower quality of life in the psychological domain, as reported by Mathias *et al.*, who showed that women typically had greater burden than men in regard to caregiving and consistently described more somatic symptoms linked to caregiving.[39] Previous studies indicated that although both genders are strongly expected to support their elderly parent, task divisions tend to be gender based. Women are more likely to provide direct daily care, as opposed to sons who are more likely to play indirect organizational roles, including monetary support. Nevertheless, changes have been observed in the attitudes of male children, who have started to think that caregiving is also integral to the process of redefinition of gender roles. Similar to breadwinning, they saw that family caregiving should be considered to be a less gendered task. However, this willingness is difficult to change. A study on transnational families reported that men who either migrated or stayed behind in their home country acted as reluctant caregivers, and women remained feeling obliged to undertake care work.[40]

A negative correlation was observed between caregivers' burden and their quality of life in the environmental domain. Caro *et al*. showed that the level of burden can be influenced by factors not related to care due to the burden resulting from the interrelationships between individuals and their environment.[41] Therefore, environmental mental factors may mediate the relationship between caregiver burden and quality of life, indicating the need for future research to identify their role.[41]

This study found correlations between the caregiver burden and quality of life in all four domains. Other studies investigating caregivers of elderly with some degree of dependence found a correlation between the burden and quality of life in some domains but not all.[12,41] The findings of this study indicated that taking care of elderly with more severe level of dependence may have a large impact on the quality of life of caregivers, affecting all domains of their quality of life. A study mentioned that elderly care is family focused, whereby family members are the only persons deserving to provide care for their elderly parents. This cultural habit led to an opinion that involving non-family members in care was perceived as a violation of filial values; it was often considered to be something shameful and to be avoided. This caregiving norm can be found in some cultures, particularly those with a collectivistic orientation as in Indonesia.[40] This finding was in line with that of the present study, that is, more than 90% of the caregivers were family members (first generation: 33.3%, second generation: 53.3%, and third generation: 6.7%). This factor can be assumed to be a worsening factor of caregiver burden.

The results of this study showed that caregiving for moderately to totally dependent elderly affects the quality of life of caregivers. Support must be provided for caregivers to prevent burnout and risks of abuse of the elderly. The support can be given in several forms. A systematic review has shown that trainings on how to provide care can reduce the burden of caregivers.[42]

Regular meetings, either offline or online, can be a means to provide peer support to caregivers.[43] Not only the support from their peers but also professional help and psychotherapy can be given to strengthen their coping mechanisms, which will ultimately have an impact on the quality of life of caregivers.[12] The utilization of respite care services held by several health facilities in Indonesia can be socialized actively to increase the number of caregivers that use this service when they have other commitments within a certain period. As respite care services are not covered by the national health insurance, their advocacy can be an issue. Support from the central government or local government in the form of caregiver allowance can help solve the financial problems faced by caregivers.[44]

This study encountered some limitations, including the small number of participants and the cross-sectional research method used. This study also did not control for confounding variables, such as chronic illness that the caregiver experienced, which can directly or indirectly affect their quality of life. Therefore, further research should focus on the in-depth exploration of the correlation between the burden and quality of life of caregivers who care for the dependent elderly in Indonesia by controlling these confounding factors.

CONCLUSIONS

Significant negative correlations were observed between the burden and quality of life (physical, psychological, social, and environmental domains) of caregivers of elderly with moderate to total dependence. The higher the burden experienced by the caregivers, the lower their quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Evaluation of Internalized Stigma and Quality of Life of Patients with Psoriasis

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Evaluation of Internalized Stigma and Quality of Life of Patients with Psoriasis

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Abstract

Background: Internalized stigma is defined as individuals' acceptance of negative stereotypes created by society and then their alienation from society. Psoriasis is a dermatological disease that affects the quality of life. The study evaluated the internalized stigma and quality of life of patients diagnosed with psoriasis.

Methods: This cross sectional study enrolled 222 patients. Data were collected using the internalized stigma scale and the dermatology life quality index questionnaires. Data were analyzed using the Cronbach's alpha.

Results: The internalized stigma score of the patients was 78.41 ± 23.14, and the quality of life score was 12.30 ± 5.67. Stigmatization and quality of life were affected by patients' physical, psychological, and social lives ($p < 0.05$).

Conclusions: Patients' internalized stigma level was high, their quality of life was low, and their quality of life decreased as the internalized stigma level increased. Furthermore, the internalized stigma level of the patients who suffered more from psoriasis was higher, but their quality of life was lower than those who suffered less.

Keywords: patient, psoriasis, quality of life, stigma

INTRODUCTION

Psoriasis is a dermatological disease where stigmatization is common.[1,2] The World Health Organization (WHO) prepared a global report to reduce the disease burden in patients with psoriasis, enable them to combat stigma and exclusion, and increase their healthcare and social participation. In 2014, the WHO declared psoriasis a noncommunicable disease to increase awareness of its stigma.[3] Internalized stigma is the feeling of stigma experienced by the individual despite not being stigmatized by the society.[4] Internalized stigma is defined as individuals' acceptance of negative stereotypes created by society and subsequent withdrawal from society, with feelings such as worthlessness and shame.[1,5,6] Psoriasis, which is a visible disease, leads to feeling shy and embarrassed, thinking one has a defect, and having a negative body image, fear, loneliness, stress, and loss of self-confidence.[7,8] Patients experience hopelessness about the symptoms and treatment. Psoriasis is a stigmatizing disease and causes higher levels of stigmatization than other dermatological diseases.[9]

Researchers have stated that psoriatic lesions may be an important determinant of psychosocial functioning and that the lesions may cause stigma and decrease the quality of life of patients.[2] Even a small plaque lesion in psoriasis may be enough for patients to feel stigmatized. Researchers have also explained that the quality of life of patients with psoriasis is as important as those with other chronic diseases because they experience high levels of stigma. Moreover, a study reported that quality of life and stigma interact with each other in patients with psoriasis; thus, they should be considered together.[1]

Lesions, itching, and flaking seen in patients with psoriasis decrease their quality of life.[10] Although psoriasis is benign, it is a lifelong skin disease. Experience of relapses decreases the quality of life of patients with psoriasis.[11] Psoriasis affects the physiological and psychological life of the patients, causing a decrease in social functionality and deterioration of interpersonal relationships.[12,13]

No studies have discussed the internalized stigma and quality of life of patients with psoriasis living in a city located in the east of Turkey. This study investigated the internalized stigma, quality of life, and affecting factors in patients with psoriasis.

METHODS

The research was conducted in accordance with the principles of the Declaration of Helsinki. The patients were informed about the study, and their consent was obtained. The study was approved by the ethics committees of the Ataturk University Faculty of Health Sciences (No. 2018-2/6) and of the hospital where the study was conducted (No. 42190979-000-E.1800130824).

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This descriptive and cross-sectional study was enrolled patients with psoriasis who were admitted to Ataturk University Research and Application Hospital Dermatology Outpatient Clinic between March 2018 and February 2019. Between these dates, 240 patients were interviewed. Of these patients, 18 were excluded because they did not agree to participate in the study; finally, the study enrolled 222 patients. Psoriasis patients aged ≥18 years, those who had adequate communication, and those who agreed to participate were included in the study. In the power analysis, the statistical power of the research was 0.99 at 95% confidence interval and 0.05 significance level, showing that the sample size was sufficient.[14] Study data were collected using the internalized stigma scale and dermatology life quality index questionnaires.

The researcher-prepared questionnaire was in line with the literature.[12,15] Before starting the study, a pilot study was conducted with 10 patients. The final questionnaire contained 21 questions, including sociodemographic characteristics of patients with psoriasis such as age, sex, education, and employment status and disease-related variables such as the duration of the illness and effect of the disease on psychological status, family, work, and social life.

The internalized stigma scale was developed by Ritsher *et al*. to measure the subjective stigma experience of individuals.[16] The scale can be used for psoriasis and mental illness. The Turkish validity and reliability study of the scale for patients with psoriasis was performed by Alpsoy *et al*.[17] The scale consists of 29 questions. Responses to the items in the internalized stigma scale are given according to a 4-point Likert-type scale, including "strongly disagree" (1 point), "disagree" (2 points), "strongly agree" (3 points), and "strongly disagree" (4 points). The total scale score ranges from 29 to 116. High scale scores indicate that more severe internalized stigma. The Cronbach's alpha value in the reliability study of the scale conducted with patients with psoriasis was 0.89.[17] In the present study, the Cronbach's alpha value of the scale was 0.98.

The dermatology life quality index, a self-administered questionnaire widely used in dermatological diseases, consists of 10 questions addressing the issues most complained about related to the quality of life over the last week. The questions cover the following topics: symptoms and emotions (questions 1 and 2), daily activities (questions 3 and 4), hobbies (questions 5 and 6), work and school (question 7), personal relationships (questions 8 and 9), and treatment (question 10). In the scale, nine questions are answered according to a Likert-type scale (0, not at all; 1, a little; 2, a lot; and 3, very much). Question 7 is answered "yes" or "no." In question 7, if the answer is "yes," it is scored as 3; however, if the answer is "no," it is scored as 0. The total scale score is the sum of the scores of each question. The maximum and minimum scores of the scale are 30 and 0, respectively. As the score increases, the quality of life decreases. Öztürkcan *et al*. performed the Turkish validity and reliability study of the scale, and Cronbach's alpha was 0.87 in the validity and reliability study.[18] In the present study, the Cronbach's alpha value of the scale was 0.87.

Data were analyzed using SPSS Statistics for Windows, version 17 (SPSS Inc., Chicago, IL, USA). Numbers, percentages, mean, and standard deviation were used in the data analysis. Skewness and kurtosis were used to examine whether the data were normally distributed. Independent samples t-test, one-way analysis of variance, least significant difference, Pearson's and Spearman's correlation test were used for data analysis.

RESULTS

Table 1 shows age, disease period, life quality, and internalized stigma of the patients. The mean internalized stigmatization score and quality of life score of the patients were 78.41 ± 23.14 and 12.30 ± 5.67, respectively (Table 1). The majority of the participants were women (51.8%), married (60.4%), higher education graduates (54.1%), unemployed (55.4%), and living in the city center (55%). Of the patients, 28.3% visited the hospital for treatment and 52.3% for their symptoms, 40.5% did not receive treatment regularly, 20.7% had another disease, 15.8% had psoriatic arthritis, and 35.6% had a family member with psoriasis. Of the patients, 46.8% were smokers, and patients reported that their psychological (80.2%), physical (91.9%), and sexual health (14.4%), family (23.4%), work (17.6%), and social life (69.8%) were affected (Table 2).

The internalized stigma and quality of life scores were significantly higher in patients who visited the hospital for treatment and symptoms, did not receive treatment regularly, had other illnesses and psoriatic arthritis, had a family member with psoriasis, were smokers, and reported that psychological, physical and sexual health, family, work, and social life were affected ($p < 0.05$) (Table 3).

A significant difference was found between the reasons for the patients visit to the hospital for treatment and the internalized stigma and quality of life scores ($p < 0.05$). Further analysis showed that the mean internalized stigma and quality of life scores for those who visited the hospital for treatment and symptoms were higher than for those visiting for follow-up (Table 3).

A significant moderate positive relationship was found between the internalized stigma and quality of life scores ($p < 0.05$) (Table 4). The mean patient age and disease duration were 36.95 ± 12.42 and 11.77 ± 10.86, respectively. A significant positive correlation was found between age and disease duration and internalized stigma and mean quality of life scores ($p < 0.05$).

The internalized stigma scores of those who were female, married, unemployed, and lived in villages were higher

than those of their counterparts, but the difference was not significant. As the education level of the patients decreased, the mean internalized stigma score increased, but the difference was not significant. No significant association was found between sex, place of residence, and marital, educational, and employment statuses with the mean quality of life scores ($p > 0.05$).

TABLE 1. Age, disease period, life quality, and internalized stigma of the patients

Variables	Mean ± SD
Age, years (min–max, 18–68)	36.95 ± 12.42
Disease period, years (min–max, 1–50)	11.77 ± 10.86
Life quality (min–max, 0–26)	12.30 ± 5.67
Internalized stigma (min–max, 29–109)	78.41 ± 23.14

TABLE 2. Patients' characteristics (N = 222)

Variables	Frequency (N)	Percentage (%)
Sex		
Female	115	51.8
Male	107	48.2
Marital status		
Married	134	60.4
Single	88	39.6
Educational status		
Literate	10	4.5
Primary school	20	9.0
Secondary school	24	10.8
High school	120	54.1
University	48	21.6
Employment status		
Employed	99	44.6
Unemployed	123	55.4
Place of residence		
Village	21	9.4
District	79	35.6
City	122	55
Reason for visiting hospital		
Symptoms	116	52.3
Follow-up	43	19.4
Treatment	63	28.3
Receiving regular treatment		
Yes	132	59.5
No	90	40.5
Psoriatic arthritis		
Yes	35	15.8
No	187	84.2
Smoking		
No	118	53.2
Yes	104	46.8
Another disease		
No	176	79.3
Yes	46	20.7
Family member with psoriasis		
Yes	79	35.6
No	143	64.4
Psychological health		
Affected	178	80.2
Not affected	44	19.8
Family life		
Affected	52	23.4
Not affected	170	76.6
Business life		
Affected	39	17.6
Not affected	183	82.4
Social life		
Affected	155	69.8
Not affected	18	8.1
Physical health		
Affected	204	91.9
Not affected	18	8.1
Sexual health		
Affected	32	14.4
Not affected	190	85.6

TABLE 3. Comparison of patients' characteristics, internalized stigma, and life quality scores (N = 222)

Variables	Internalized stigma Mean ± SD	*p*	Life quality Mean ± SD	*p*
Sex				
Female	80.23 ± 22.89	0.223[a]	12.20 ± 5.44	0.575[a]
Male	76.44 ± 23.35		12.52 ± 5.91	
Marital status				
Married	78.69 ± 22.81	0.819[a]	12.48 ± 5.61	0.569[a]
Single	77.97 ± 23.76		12.03 ± 5.76	
Educational status				
Literate	86.70 ± 22.72		15.00 ± 7.06	
Primary school	83.65 ± 19.30	0.609[b]	13.60 ± 5.73	0.434[b]
Secondary School	78.25 ± 22.70		12.25 ± 6.10	
High school	77.51 ± 23.48		11.99 ± 5.24	
University	76.81 ± 24.28		12.00 ± 6.14	
Employment status				
Employed	77.64 ± 23.57	0.658[a]	12.09 ± 5.49	0.620[a]
Unemployed	79.02 ± 22.87		12.74 ± 5.82	

TABLE 3. Continued

Variables	Internalized stigma Mean ± SD	*p*	Life quality Mean ± SD	*p*
Place of residence				
Village	82.10 ± 23.05	0.473[b]	13.52 ± 5.72	0.566[b]
District	79.96 ± 22.21		12.30 ± 5.24	
City	76.76 ± 23.78		12.09 ± 5.93	
Reason for visiting hospital				
Symptoms	81.72 ± 21.80	**<0.001**[b]	12.88 ± 5.50	**<0.001**[b]
Follow-up	64.51 ± 24.06		8.51 ± 4.65	
Treatment	81.79 ± 21.65		13.83 ± 5.53	
Receiving regular treatment				
Yes	75.17 ± 24.29	**0.009**[a]	11.65 ± 5.75	**0.038**[a]
No	83.14 ± 20.57		13.26 ± 5.43	
Psoriatic arthritis				
Yes	87.49 ± 21.29	**0.009**[a]	15.63 ± 5.45	**<0.001**[a]
No	76.71 ± 23.13		11.68 ± 5.50	
Smoking				
No	74.09 ± 23.55	**0.003**[a]	11.31 ± 5.69	**0.005**[a]
Yes	83.30 ± 21.76		13.42 ± 5.45	
Another disease				
No	75.22 ± 24.06	**<0.001**[a]	11.55 ± 5.60	**<0.001**[a]
Yes	90.61 ± 13.70		15.17 ± 4.98	
Family member with psoriasis				
Yes	82.67 ± 20.24	**0.041**[a]	13.37 ± 4.68	**0.037**[a]
No	76.05 ± 24.35		11.71 ± 6.08	
Psychological health				
Affected	85.79 ± 18.63	**<0.001**[a]	13.82 ± 4.98	**<0.001**[a]
Not affected	48.55 ± 13.36		6.16 ± 3.85	
Family life				
Affected	94.94 ± 6.33	**<0.001**[a]	17.81 ± 3.93	**<0.001**[a]
Not affected	73.35 ± 24.05		10.62 ± 5.01	
Business life				
Affected	93.36 ± 9.78	**<0.001**[a]	19.05 ± 4.21	**<0.001**[a]
Not affected	75.22 ± 23.92		10.86 ± 4.84	
Social life				
Affected	85.39 ± 14.53	**<0.001**[a]	14.67 ± 4.54	**<0.001**[a]
Not affected	52.99 ± 19.01		5.44 ± 5.04	
Physical health				
Affected	81.06 ± 21.48	**<0.001**[a]	12.91 ± 5.32	**<0.001**[a]
Not affected	48.33 ± 20.27		5.44 ± 5.04	
Sexual health				
Affected	91.66 ± 13.66	**<0.001**[a]	16.78±4.67	**<0.001**[a]
Not affected	76.17 ± 23.68		11.55±5.47	

Bold values: Results are significant if $p < 0.05$.
[a]Independent sample t-test; [b]One-way analysis of variance (ANOVA).

TABLE 4. Correlation of patients' characteristics, internalized stigma, and life quality scores

Variables	r	*p*	r	*p*
Age, years (min–max, 18–68)	0.181	**0.007**[a]	0.155	**0.021**[a]
Disease Period, years (min–max, 1–50)	0.167	**0.013**[b]	0.137	**0.041**[b]
Life quality (min–max, 0–26)	0.745	**<0.001**[a]		
Internalized stigma (min–max, 29–109)			0.745	**<0.001**[a]

Bold values: Results are significant if $p < 0.05$.
[a]Pearson's correlation analysis; [b]Spearman's correlation analysis.

DISCUSSION

In this study, patients with psoriasis were to have high levels of internalized stigmatization and low quality of life. In addition, as the internalized stigma increased, the quality of life decreased. Internalized stigmatization is the feeling of stigmatization experienced by an individual, despite not being stigmatized by society.[4] Internalized

stigma is defined as individuals' acceptance of negative stereotypes created by society and subsequent withdrawal from society, with feelings such as worthlessness and shame.[1,5,6,19] Internalized stigmatization causes a decrease in self-esteem and life satisfaction, an increase in depression and tendency to commit suicide, and difficulty in coping with the disease.[15]

This study determined that patients with psoriasis have high levels of internalized stigma and low quality of life. In addition, as the internalized stigma increased, the quality of life decreased. Studies conducted with patients with psoriasis in various regions of Turkey, except the present study, have high levels of internalized stigma but a low quality of life. Similarly, the quality of life decreased as the internalized stigma increased.[15,17] Intense emotional and psychosocial effects in patients with psoriasis cause stigmatization.[12] Patients with psoriasis who have lesions in visible areas such as the face, nails, and scalp experience high levels of stigma.[17] Patients with psoriasis have higher levels of stigma than patients with acne vulgaris, atopic dermatitis, sun-damaged skin, eczema, or fungal and viral skin infections. The same study also found a relationship between the stigma subscale of the internalized stigma and poor quality of life.[9] The quality of life is low in patients with psoriasis who hide their skin symptoms and retreat from social environments and people.[2,5,20] Psoriasis causes a decrease in the quality of life because of its physical, psychological, and social effects.[2] In line with these results, healthcare professionals should provide necessary training and support for patients with psoriasis to reduce internalized stigma levels and improve their quality of life.

The physical health of a majority of the patients was affected, and their internalized stigma level was high, and their quality of life was low. In this study, 15.8% of the patients had psoriatic arthritis and had similarly high internalized stigma levels and low quality of life. The physical health of patients who have pain, movement limitation, skin involvement, and psoriatic arthritis was negatively affected, and their quality of life was low.[10] A study of patients with psoriasis found that 2.9% had psoriatic arthritis and those with psoriatic arthritis had higher levels of internalized stigma.[15] Another study comparing the effects of skin and joint symptoms in psoriasis found that the feelings of depression, shame, and guilt and the perception that others thought that the disease was contagious were significantly higher in those with skin symptoms.[21,22] Health professionals can contribute to improving the quality of life of patients by reducing the physiological and psychological effects of psoriasis.[23]

In this study, the psychological state of the majority of the patients was affected, and their internalized stigma levels were high, and their quality of life was low. However, others report fewer psychological effects. A study reported that 33% of their patients had depressive symptoms and experienced guilt, rejection, and stigma[4], whereas another reported that 58% of their patients with psoriasis felt ashamed of their appearance and 24% experienced depression.[24] In another study, 58.1% of the patients with psoriasis had depression and higher internalized stigma levels than those who suffered from depression. Stigma leads to a feeling of humiliation, defective thinking, having a negative body image, and low self-esteem.[7] Patients with psoriasis whose psychological status is affected had low quality of life.[25] Skin diseases affecting appearance also influence interpersonal relationships.[26] A study suggested that health professionals should provide the necessary training and psychological and social support for patients with psoriasis.[27]

Skin diseases affect social life and induced patients to feel separate from society.[9] In this study, the social life of the majority of the patients was affected, their internalized stigma level was high, and their quality of life was low. Patients with psoriasis whose social life is affected, hide their lesions, and avoid doing activities where their lesions would appear have higher levels of stigma.[28] A study conducted with Polish patients with psoriasis reported that the disease limited their social life and induced patients to feel a higher level of internalized stigma.[5] Psoriasis limits relationships in the family and among friends, group activities, going to public places, and participating in social activities. Patients with psoriasis who limit their social activities in public areas such as swimming, sunbathing, and going to the beach also have a low quality of life.[29] Patients with psoriasis feel hopelessness and social withdrawal, which negatively affects their quality of life.[30]

In this study, 23.4% of patients' family life and 14.4% of patients' sexual life were affected, and these patients had high levels of internalized stigma and low quality of life. Moreover, the level of internalized stigma was high in married and female participants, but the difference was not significant. A study reported that married patients with psoriasis experienced higher levels of internalized stigma but sex did not affect internalized stigma.[17] Stigma, negative self-esteem, depression, ideas of suicide, anxiety, and sexual dysfunction negatively affect the family and friendship relations of patients with psoriasis.[22,29] Of the patients with psoriasis, 63% had at least one genital involvement in their lifetime, and these patients' psychological condition deteriorated and their quality of life decreased.[31]

In the present study, 17.6% of the patients' business life was affected, and their internalized stigma level was high, and their quality of life was low, but this difference was not significant. Psoriasis negatively affects the ability to work and decreases productivity and quality of life.[5] A study reported that 12% of their patients with psoriasis

were unemployed, and 92% of them could not work because of psoriasis symptoms and psoriatic arthritis.[9] In another study, 60% of the patients with psoriasis quit their jobs because of the illness, requested excessive sick leave from their workplaces, and had low quality of life.[25]

In the present study, 35.6% of the patients had a family member with psoriasis, and these people experienced higher levels of stigma and lower quality of life. Another study found that 32.8% of the participants had a family member with psoriasis and their internalized stigma levels were higher than those without an affected family member.[15] A study of Polish patients with psoriasis determined that those who had a family member with psoriasis understood psoriasis better and received more support from their family members; thus, they coped with the disease better.[5]

In the present study, 20.7% of the patients had another disease. The internalized stigma level of these patients was high, and their quality of life was low. Mental illnesses such as depression and anxiety in patients with psoriasis cause higher levels of stigmatization.[7] Comorbidities such as Crohn's disease, cardiovascular, metabolic, and chronic intestinal diseases, and psychological disorders in patients with psoriasis create additional disease burden and decrease the quality of life.[3,32] Contrary to the present study, a study reported that the presence of another disease in patients with psoriasis did not affect internalized stigma.[15]

In the present study, 40.5% of the patients did not receive treatment regularly. These patients and those who visited the hospital for their treatment and symptoms had high levels of internalized stigma and low quality of life. In psoriasis, compliance with the treatment is low, and the internalized stigma level is high.[15] Patients with psoriasis are incompatible with treatment, unable to cope with symptoms, have a negative body image, and withdraw socially. In addition, patients who have no hope of recovery, cannot cope with the symptoms, and do not follow the treatment have a lower quality of life.[30]

Psychological problems are also common in patients with psoriasis, and these problems increase cigaret and alcohol consumption.[30] In the present study, 46.8% of the patients smoked, their internalized stigma level was higher, and their quality of life was lower than those who did not. Similarly, a study found that 43.2% of patients with psoriasis smoked, their internalized stigma level was high, and their quality of life was low.[15] Another study found a relationship between increased smoking and antidepressant use and low quality of life in patients with psoriasis.[33]

In the present study, as patients' age and disease duration increased, their internalized stigma levels increased, and their quality of life decreased. In patients with psoriasis, their internalized stigma level increases with an increasing duration of illness.[17] In contrast to this study, Alpsoy *et al*.[15] did not find a relationship between age and internalized stigmatization in patients with psoriasis. Patients with psoriasis at a young age, where physical appearance is important, experience higher levels of stigma than older patients.[5] The quality of life of young patients with psoriasis is lower, but as they get older, they become more experienced in managing the symptoms and more successful in dealing with these symptoms.[21] A study reported that as a recurrent disease, psoriasis causes patients to feel despair, fail to plan for the future, and a have decreased quality of life.[11] Healthcare professionals should provide necessary training and support for patients with psoriasis, which should focus on older patients with psoriasis and patients with chronic disease.

The most important limitation of the study is the absence of a control group. Data collection tools are limited to patients' self-reports. This study was limited to 222 patients with a diagnosis of psoriasis from a single center. Thus, the results may not be generalizable to the entire population with psoriasis.

CONCLUSIONS

Internalized stigmatization level was found to be high, and the quality of life was low in patients with psoriasis. In addition, as the internalized stigma level increased, the quality of life decreased. Moreover, sociodemographic characteristics, psychological, physical, and sexual health, and family, work, and social life affect the internalized stigma and quality of life of patients with psoriasis. Health professionals should provide significant support to patients by decreasing stigma and increasing the quality of life. Health professionals play an important role in preventing stigmatization by supporting patients with psoriasis psychologically and socially and informing society about psoriasis. Health professionals must make significant contributions to preventing psoriasis to worsen, ensuring that the individual is being active and functional, decreasing the psychological effects of the disease, and increasing the quality of life.

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CONFLICT OF INTEREST

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Association of Smoking with Total Oxidant and Antioxidant Levels in Breast Milk

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Association of Smoking with Total Oxidant and Antioxidant Levels in Breast Milk

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Abstract

Background: Breast milk is a natural food that contains all the fluids, energy, and nutrients necessary for the optimum growth and development of newborns. Smoking is a public health problem that has harmful effects on the mother and baby. This study aimed to examine the association of exposure to smoking with total oxidant status (TOS) and total antioxidant status (TAS) in breast milk.
Methods: Healthy mothers without any health problems during their pregnancy and lactation periods were selected as subjects. Eighty-eight milk samples (44 in the smoking group and 44 in the nonsmoking group) were examined. TOS and TAS were analyzed using Rel Assay commercial kits.
Results: TAS level was significantly lower in the smoking group than in the nonsmoking group ($p < 0.05$). TOS level was higher in the smoking group than in the nonsmoking group, although the difference was not statistically significant ($p > 0.05$). Oxidative stress index (OSI) was significantly higher in the smoking group than in the nonsmoking group ($p < 0.05$).
Conclusions: Exposure to smoking was associated with low TAS and high OSI in breast milk.

Keywords: cigarette smoke, human breast milk, oxidative stress, total antioxidant level, total oxidant level

INTRODUCTION

Owing to its excellent composition (such as carbohydrate, fat, protein, vitamins, and minerals), breast milk is the best food for newborns and babies. Breast milk volume is highly variable, and its content is affected by the mother's diet or stored nutrients.[1] Breast milk plays an important role in transferring the antibodies that the baby needs from the mother to the baby.[2] Colostrum is valuable for newborns because of its immune molecules and is abundant in proteins, immunoglobulins, cytokines, and leukocytes.[3] After a few weeks, the content of colostrum changes and it transitions to mature milk containing numerous bioactive components, such as essential nutrients, hormones, growth factors, and enzymes.[2,4] The quality of breast milk is directly related to the mother's health. Essential nutrients passing from the mother into the milk are affected by maternal nutrition and lifestyle.[1]

Cigarettes have various oxidants, particularly nitric oxide (NO) and nitrogen dioxide (NO_2) in the gas phase. Particles in the gas phase are short lived. In the tar phase, water-soluble radicals are produced by the hydroquinone–quinone cycle.[5] These oxidants derived from tobacco smoke can damage biomolecules such as proteins, lipids, and DNA, which are the basic structural and functional molecules of the cell.[6] Certain substances in cigarettes and smoke have various harmful effects on an organism, including mutagenic/carcinogenic effects, irritation, and tumor acceleration.[7] These effects also cause many diseases, such as cardiovascular diseases,[8] periodontal diseases,[9] inflammatory diseases,[10] neurodegenerative diseases,[11] inflammatory bowel disease,[12] chronic obstructive pulmonary disease,[13] and lung cancer.[14] Exposure to cigarettes alters the total oxidant status (TOS), total antioxidant status (TAS), and vitamin C and E levels.[15] Overproduction of oxidant molecules can suppress the protective effect of breast milk. Smoking reduces the protective properties of milk by causing negative changes in milk composition and negatively affecting the health of the baby. Nicotine levels in breast milk are three times higher than those in the plasma of women who smoke.[16] Therefore, this study aimed to show how smoking exposure affects TAS and TOS in breast milk.

METHODS

Ethical approval

Ethics committee approval was obtained (2017/77 e.c. approval code) from Recep Tayyip Erdoğan University in Turkey Non-Interventional Clinical Research Ethics Committee. Breast milk samples were collected from puerperant women from the patient portfolio of the Family Health Centers of Erzurum Provincial Health Directorate. This study was carried out in two phases, namely, questionnaire assessment and biochemical analysis.

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Participants

G* Power 3.1.9.2 program was used to calculate the number of samples. Power analysis revealed effect size: 0.80, margin of error (α): 0.05, and 95% power. On the basis of these results, the minimum number of samples to be collected was set as 35 for each of the experimental and control groups. Eighty-eight mothers participated in this study. According to their responses, two groups were established, namely, exposed to smoking (N = 44) and not exposed to smoking (N = 44). Individuals excluded from the study were those with hypertension, gestational diabetes, constipation, chronic kidney failure, severe anemia, and malignity.

Questionnaire application

Informed consent was obtained from the volunteer mothers between 1st and 6th months of lactation. Responses to the questions in the Interview Questionnaire Form (information on maternal health, pregnancy and baby, and smoking status) were recorded.

Biochemical analysis

No preservatives were used while collecting the breast milk samples. Approximately 10 mL of milk samples were collected from each mother and placed in falcon tubes. The milk samples were stored at −20 °C in the dark. TAS and TOS in milk samples were measured in one single batch using Abbott C16000 autoanalyzer at Recep Tayyip Erdoğan University Training and Research Hospital Biochemistry Laboratory, Turkey.

Measurement of total antioxidant status (TAS)

TAS in breast milk samples was measured by an autoanalyzer using the automated colorimetric method. The hydroxyl radical ($OH^{\cdot}$) produced by the Fenton reaction reacts with the colorless substrate O-dianisidine to produce the yellowish brown dianisyl radical. After the plasma sample is added, the oxidative reactions initiated by the hydroxyl radicals are suppressed by the antioxidant components of the plasma. Discoloration is prevented by antioxidants. In this way, the total antioxidant capacity of the plasma is measured. Trolox, a water-soluble analog of vitamin E, was used as the calibrator standard. The results were expressed as mmol Trolox equivalent/L.[17]

Measurement of total oxidant status (TOS)

TOS in milk samples was measured using the method of Erel (2005). İn the first step, oxidants in the sample oxidize the Fe^{+2}-o-dianisidine complex to Fe^{+3}. This oxidation is enhanced by glycerol molecules in the reaction medium. Ferric ion is generated as a result of the reaction and forms a colored complex with xylenol orange in an acidic environment. Color intensity was measured spectrophotometrically, and the total oxidant molecule level was determined. Calibration was conducted with hydrogen peroxide (H_2O_2). The results were expressed as micromolar H_2O_2 equivalent per liter (μmol H_2O_2 equivalent/L).[18]

Calculation of Oxidative Stress Index (OSI)

OSI is an indicator of oxidative stress. For the calculation of OSI in the samples, the units of TAS and TOS were equalized and expressed as the ratio of TOS to TAS in terms of percentage.[19] The results were expressed as arbitrary unit (AU).

$$OSI = \frac{TOS, \mu mol\ H2O2\ Equivalent/L}{TAS, \mu mol\ Trolox\ Equivalent/L} \times 100$$

Statistical analysis

Statistical analysis was conducted using the SPSS for Windows Version 17.0 package program. Nonparametric Mann–Whitney U test was used to evaluate the difference between groups. $p < 0.05$ was considered significant.

RESULTS

The demographic characteristics of the participating mothers in both groups showed similarities ($p > 0.05$) in terms of the mean age, weight, weight before pregnancy, total number of births, first gestational age, and gestational age of the mother and the mean birth weight of the baby (Table 1).

In Table 2, TAS levels are expressed in millimoles, TOS levels in micromoles, and OSI levels in arbitrary units. While the mean of TAS level was 0.678 (±0.534) in the group exposed to cigarettes, the mean of TAS level was found to be 1.404 (±1.472) in the group not exposed to cigarettes. The mean of TAS level is approximately two times higher in non-exposed to smoking. While the mean of TOS level was 3.686 (±1.749) in the group exposed to cigarettes, the mean of TOS level was found to be 3.387 (±1.314) in the group not exposed to cigarettes. The average of TOS levels is relatively higher in smokers. While the mean of OSI value was 1.178 (±1.258) in the group exposed to cigarettes, the mean of OSI value was found to be 0.761 (±1.187) in the group not exposed to smoking. The reason why the OSI index was lower in the non-smoker group is that TAS levels were higher in this group.

As shown in Table 3, TAS was higher in women not exposed to smoking than in those exposed to smoking ($p < 0.05$). No significant difference in TOS was observed between the two groups ($p > 0.05$). OSI was statistically significantly higher in the mothers exposed to smoking than in those not exposed to smoking ($p < 0.05$).

TABLE 1. Demographic characteristics of the participants

Variables	Exposed to smoking			Not exposed to smoking			*p*
	Range	Median	IQR	Range	Median	IQR	
Maternal age (year)	19–41	31.50	8	21–43	29.50	7	0.815
Maternal weight (kg)	47–100	65	15	52–105	69	17	0.732
Weight before pregnancy (kg)	46–100	64.50	19	48–92	64.50	16	0.764
Total births	1–9	3	2	1–6	2	2	0.079
First pregnancy age (year)	17–38	23	6	15–35	25	6	0.089
Gestational age (weeks)	33–41	39	2	32–42	38	2	0.105
Birth weight (g)	2,100–5,000	3,100	750	1,360–4,500	3,000	575	0.296

IQR: Interquartile range

TABLE 2. TAS, TOS, and OSI in the groups exposed and not exposed to smoking (N =44)

Group	Range	Mean	SD	Median	IQR
Exposed To Smoking					
TAS (mmol)	0.045–1.777	0.678	0.534	0.522	0.700
TOS (μmol)	1.530–9.400	3.686	1.749	3.199	2.350
OSI (AU)	0.100–5.770	1.178	1.258	0.619	1.400
Not exposed to smoking					
TAS (mmol)	0.074–5.689	1.404	1.472	0.923	1.349
TOS (μmol)	0.640–5.980	3.387	1.314	3.323	1.360
OSI (AU)	0.030–7.320	0.761	1.187	0.384	0.830

Values are presented as mean, standard deviation (SD), and IQR: Interquartile range.

TABLE 3. Comparison of TAS, TOS, and OSI between the two groups (Mann–Whitney U test) (N = 44)

Group	Median	IQR	*p*
TAS			
Exposed To Smoking	0.522	0.700	0.010
Not exposed to smoking	0.923	1.349	
TOS			
Exposed To Smoking	3.199	2.350	0.924
Not exposed to smoking	3.323	1.360	
OSI			
Exposed To Smoking	0.619	1.400	0.013
Not exposed to smoking	0.384	0.830	

IQR: Interquartile range

DISCUSSION

In this study, we aimed to reveal the relationship between exposure to smoking and breast milk TAS and TOS. Results showed that TAS of the milk from mothers exposed to smoking was lower than the other group. Plasma total antioxidant level decreases substantially in individuals who smoke.[15] Some studies revealed a similar result for breast milk. In one research testing the colostrum and mature milk samples of 30 women exposed to smoking at least five times a day during pregnancy and lactation and 29 women not exposed, the colostrum TAS was found to be significantly lower in the smoking group than in the other group.[20]

One study on the effects of maternal smoking exposure during pregnancy and lactation on colostrum found that breast milk TAS was significantly lower in smokers than in nonsmokers. Smoking during pregnancy and lactation decreases the antioxidant properties of colostrum.[21] Comparison was conducted on the breast milk samples of smoking and nonsmoking women in terms of vitamin E concentration in the third trimester of pregnancy and tocopherol concentration in the postpartum period, and the results showed that serum vitamin E concentration did not differ between the groups but vitamin E concentration in mature milk was significantly lower in smokers than in nonsmokers.[22] In another study, beta carotene concentrations in maternal blood and umbilical cord were found to be significantly higher in smoking mothers than in nonsmoking mothers.[23] Venous blood samples were collected from smokers and nonsmokers on the day they gave birth, and β-carotene, retinol, α-tocopherol, and cotinine levels were measured in milk and infant urine samples on the 7th day after birth. The results showed lower α-tocopherol levels in the milk of smoking mothers compared with that of nonsmokers. Maternal smoking may decrease vitamin E levels in milk because

the antioxidants are utilized to limit lipid peroxidation.[24] In a study measuring nesfatin-1, irisin, malondialdehyde (MDA) levels, and superoxide dismutase (SOD) activity in the milk of smoking and nonsmoking mothers, nesfatin-1 and MDA levels of the mothers who smoked were found to be higher than those of the nonsmoker group. In the same study, the breast milk SOD activity of smoking mothers was found to be lower than that of the control group.[25]

Karademirci *et al*. investigated the effects of long-term smoking on oxidative stress on 78 smokers and 82 individuals with no risk factors and found that serum TAS was significantly low in chronic smokers.[15] In another study on 20 smokers and 20 nonsmokers, the mean TAS was found to be low in the smoker group due to the numerous toxic substances in cigarettes and the severity of oxidative stress.[26] An investigation of the effect of smoking cessation on oxidative stress-related plasma components and enzyme activities among 1255 smokers and 524 healthy nonsmokers found that erythrocyte superoxide dismutase, catalase, and glutathione peroxidase enzyme activities were significantly low in smokers.[27] Our TAS results conformed with the previous studies. Smoking and exposure to smoking negatively affect and eventually reduce the level of antioxidant systems in tissues and breast milk.

In our study, TOS did not differ between the two groups. However, a significant difference in OSI (TOS/TAS ratio) was determined between the two groups. OSI was significantly higher in the breast milk of women with smoking exposure compared with that in the other group. Therefore, exposure to smoking increases oxidative stress in breast milk. In a previous work, many nonsmoking women exposed to second-hand tobacco smoke during lactation showed increased plasma oxidative stress and decreased antioxidant level.[28] Karademirci *et al*. evaluated the relationship of smoking with TAS, TOS, and OSI and reported that chronic smoking caused a significant increase in serum TOS level.[15] As a result, oxidative stress was high in the smoking group. Ermiş *et al*. investigated MDA level and SOD and glutathione peroxidase (GPx) activities in the serum and breast milk samples of 15 active-smoker, 22 passive-smoker, and 23 nonsmoker women.[29] Serum MDA and SOD displayed no difference, but GPx activities were significantly different between the groups. Among the milk samples of the three groups, the difference in MDA level and SOD activity was significant but that in GPx activity was not significant. They interpreted this result as human milk (even for passive smokers) is more vulnerable to oxidative stress and lipid peroxidation than serum samples. Another research revealed an increase in peripheral blood leukocytes and oxidant release among passive smokers.[30] Mahmood *et al*. found increased oxidant levels in individuals with exposure to smoking. Tobacco and certain ingredients in cigarettes deteriorate oxidative balance, increase oxidative stress, and eventually cause cell damage.[26]

Among patients with breast cancer, an increased plasma oxidative stress and decreased antioxidant level were found to be associated with exposure to smoking.[31] Another investigation found no difference in on TAS, TOS, OSI, and paraoxonase activity between smokers and nonsmokers.[32] Our results revealed significantly higher OSI in the group with smoking exposure compared with the control group; however, the difference for TOS was not statistically significant. This result was affected by the low TAS and/or the high ratio of TOS/TAS and indicated the increased levels of oxidants in the milk of mothers exposed to smoking.

CONCLUSIONS

In concordance with literature, this study shows that exposure to smoking adversely affects biochemical processes in breast milk and human tissues, resulting in reduced levels of antioxidants and increased levels of oxidants. As the essential nutrient for newborns, the content of breast milk is affected by maternal smoking exposure, which is an important risk factor for newborn health.

CONFLICT OF INTEREST

None declared.

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Ratio of Vascular Pedicle Width and Thoracic Diameter to Differentiate Cardiogenic and Non-Cardiogenic Pulmonary Edema

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Ratio of Vascular Pedicle Width and Thoracic Diameter to Differentiate Cardiogenic and Non-Cardiogenic Pulmonary Edema

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Abstract

Background: Excess intravascular volume evaluation is essential in the intensive care unit (ICU); however, clinical information to differentiate cardiogenic and non-cardiogenic pulmonary edema has been proven ineffective. Thus, this study aimed to distinguish cardiogenic from non-cardiogenic pulmonary edema using the ratio of vascular pedicle width (VPW) to thoracic diameter (VPTR).

Methods: This cross-sectional study was conducted based on secondary data from chest radiographs of 100 patients with clinical symptoms of pulmonary edema in the ICU from January 2013 to December 2015. Cardiogenic and non-cardiogenic pulmonary edema were distinguished using VPW and cardiothoracic ratio measurements (CTR). VPTR was measured to differentiate between the two types of pulmonary edema, and the cut-off value was obtained using a receiver operating characteristic curve.

Results: This study revealed a prevalence of 21% and 79% for cardiogenic and non-cardiogenic pulmonary edema, respectively. A VPTR cut-off value of 25.1% with a sensitivity of 90% and specificity of 86%, may distinguish cardiogenic from non-cardiogenic pulmonary edema.

Conclusions: VPTR is an alternative method to differentiate between cardiogenic and non-cardiogenic pulmonary edema, and this ratio measurement is useful in cases where radiograph films are not standardized.

Keywords: blood vessels, critical illness, diagnostic imaging, intensive care units, pulmonary edema, radiography

INTRODUCTION

Failure to promptly determine excess intravascular volume in the intensive care unit (ICU) has been associated with increased mortality, in-hospital stay duration, and multi-system organ dysfunction.[1,2] Accurate intravascular volume status measurement in patients with critical illness remained one of the most challenging tasks in the ICU, and forecasting patients' hemodynamic condition solely based on clinical information was not proven very successful.[3] Lung edema is one of the most often encountered excess intravascular volume manifestations in the ICU.

Lung edema is classified into two categories according to its etiology: cardiogenic and non-cardiogenic. Differentiating between the various types of pulmonary edema is important because their management varies and cardiogenic edema requires ICU management. More rapid detection of each form of pulmonary edema would aid in treating patients with critical illness in the emergency unit because of the limited capacity of the hospital's ICU, thereby reducing the ICU admission requirements for patients. A decreased death rate has been related to more targeted hemodynamic therapy for the specific kind of pulmonary edema.[4] Excess intravascular volume is usually caused by acute kidney injury (AKI) in the ICU. In Indonesia, the incidence of AKI is approximately 41–43% and mortality rates are approximately 58–77%.[5,6] Delayed diagnoses and treatment of hypervolemia can result in complications, including multiple organ system failure, longer hospitalization, length of ICU stays, and even death.[7]

Predicting intravascular volume status in patients clinically suspected of pulmonary edema has several approaches, including non-invasive procedures, such as brain-type natriuretic peptide, echocardiography, and lung ultrasound, and invasive procedures, such as transpulmonary thermodilution and pulmonary artery occlusion pressure (PAOP) catheterization.[8,9] Numerous studies have cited PAOP catheterization as the gold standard for measuring intravascular volume status due

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to its excellent accuracy. The North American-European Consensus Committee criterion of PAOP of <18 cm H_2O to detect non-cardiogenic pulmonary edema has an 82% sensitivity and 76% specificity.[10] However, the test is intrusive, operator-dependent, costly, and must be performed in specialized places, such as the ICU. Additionally, numerous risks related to the procedure include insertion site hematoma, pneumothorax, arrhythmia, and infection.[1]

Measuring vascular pedicle width (VPW) in conventional chest radiographs could be used as an alternative to differentiate between cardiogenic and non-cardiogenic pulmonary edema due to excess intravascular volume. Not only does this reduce costs and hazards, but it can also be performed outside of the ICU and is relatively fast. However, not every hospital is equipped to digitally measure VPW. VPW measurement discrepancies could arise due to the unstandardized magnification utilized in each film. Therefore, the vascular pedicle-thoracic ratio (VPTR) could be the solution to the unstandardized magnification of films in hospitals not equipped with digital radiography. This study aimed to investigate the cut-off value of VPTR on conventional chest radiographs to differentiate cardiogenic and non-cardiogenic pulmonary edema.

METHODS

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia. The study did not include any patient identities or personal information.

This cross-sectional study was conducted based on secondary data from adult patients with critical illness in the ICU of Dr. Cipto Mangunkusumo National Central General Hospital. Secondary data were gathered from February 2012 to December 2015. Random sampling was conducted regardless of sex from December 2015 and backward. All chest x-ray measurements were conducted using secondary data obtained from Picture archiving and communication system (PACS) Infinitt Healthcare software (Seoul, South Korea). All x-ray machines during the study period have passed a routine standard calibration following the hospital's accreditation standard. The sample size in this study was calculated based on a previous study by Kwok *et al*., wherein the prevalence of cardiogenic pulmonary edema in a Hong Kong emergency department is at 40.7% in 2004–2005.[11]

This study included 100 participants. The inclusion criteria for the participants were: adult patients (aged ≥18 years), clinically diagnosed with pulmonary edema, anteroposterior (AP) chest films that met standard reading criteria (e.g., adequate inspiration), and native Indonesians. Standard reading criteria were referred to the hospital's standard operating procedure.[12] Participants with signs of mediastinum pathology (aortic dissection, tumors, lymphadenopathy, or pneumothorax), a history of mediastinum, heart, or lung surgery or radiotherapy, a massive pleural effusion covering the left or right heart borders, normal chest radiographs, or a rotation of >15° on chest x-ray film were excluded from this study.

Clinical signs of pulmonary edema of participants were checked by the anesthesiologist and written in the electronic medical record. AP chest radiographs were obtained in the ICU with portable chest x-rays, with patients in the supine position. Cardiogenic and non-cardiogenic pulmonary edema was differentiated and confirmed in the hospital based on specific chest radiographic features VPW of >70 mm and cardiothoracic ratio (CTR) of >0.55, or VPW of >70 mm for cardiogenic pulmonary edema while non-cardiogenic pulmonary edema was categorized based on VPW of <70 mm alone.

VPW, CTR, and VPTR measurement methods were obtained in reference to the previous studies.[3,13] The VPW value was visually measured in millimeters from a point closest to the left subclavian artery's left border to the right superior vena cava's outermost side, where it crosses with the main right bronchus. The measurement was performed by drawing a vertical line on both sites and measuring the horizontal distance between the two vertical lines using the tools included in the PACS. The CTR value was determined by tracing the longest horizontal line on the heart boundaries and chest cavity using digital measurement tools from the PACS software. VPTR was manually calculated by dividing VPW by the chest cavity's largest diameter. Additionally, expert radiologists remeasured the data to produce a more reliable result by taking the average of the two readings. The techniques for calculating VPW, CTR, and VPTR from AP chest radiographs are detailed in Figure 1. Figures 2, 3, and 4 exhibit examples of measurements obtained during this study.

Data analysis

The data were statistically analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 17.0 software (Armonk, NY, USA). The Kolmogorov-Smirnov tests were used to determine the normality of data distributions for samples of >50. Next, the mean and standard deviation of quantitative data with a normal distribution were determined. Conversely, the median and range were recorded for data without a normal distribution. Finally, the cut-off value for the VPTR was determined using the receiver operating characteristic (ROC) curve, which allows for simultaneous sensitivity and specificity measurements.

VPW, thoracic diameter, and VPTR in this study were remeasured by two raters. The Intra-class correlation coefficient (ICC) between the two raters for VPW, thoracic diameter, and VPTR was analyzed using IBM SPSS version 25.0 software (Armonk, NY, USA) and calculated using a two-way mixed model and absolute agreement type. Rater

1 was a cardiothoracic radiologist consultant with >10-year experience, and Rater 2 was a senior radiology resident with prior training in VPTR measurement. ICC was calculated using measurement data from all 100 participants (males and females). ICC was tested to determine the need for additional training to standardize measurement if utilized by someone else, as well as the accuracy of manual measurement between two raters.

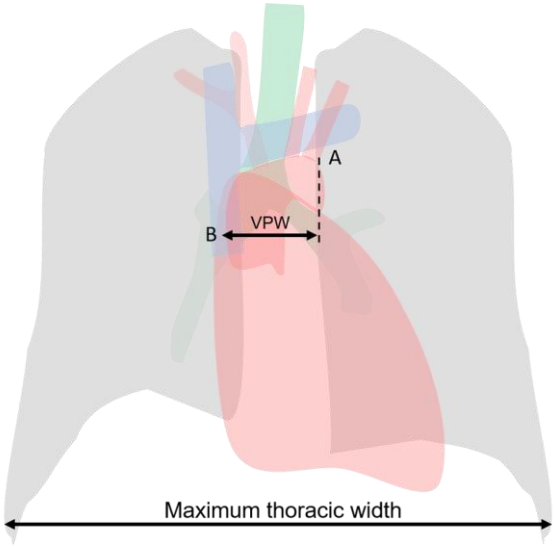

FIGURE 1. The landmarks for measuring VPW on a standard chest radiograph are illustrated. The term "Point A" refers to the location of the left subclavian artery's origin in the aortic arch. The superior vena cava and the right main bronchus intersect at point B. VPTR can be calculated by dividing VPW by the maximum thoracic width.

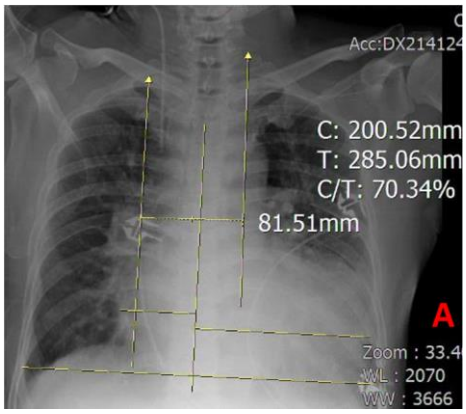

FIGURE 2. Example of VPW, CTR, and VPTR measurements in conventional AP supine chest radiographs of patients with clinical symptoms of lung edema. (A) A 63-year-old male patient. VPW measurement is 81.51 mm, the cardiac diameter is 200.52 mm, and the thoracic diameter is 285.06 mm, hence CTR is 70.34%, this case is a cardiogenic lung edema, with VPTR of 28.6%.

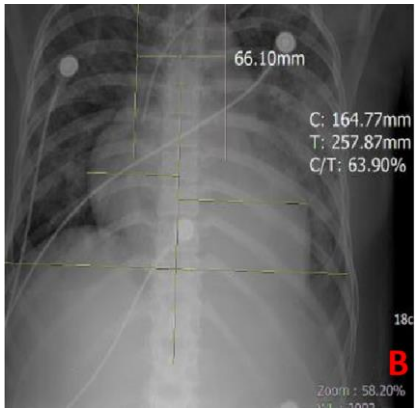

FIGURE 3. (B) A 30-year-old female patient. VPW measurement is 66.1 mm, the cardiac diameter is 167.77 mm, and thoracic diameter is 257.87 mm, hence CTR is 63.90%, this case is a non-cardiogenic lung edema, with VPTR of 25.6%.

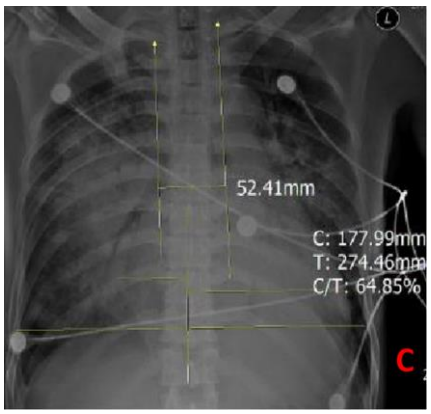

FIGURE 4. (C) A 37-year-old male patient. VPW measurement is 52.41 mm, the cardiac diameter is 177.99 mm, and the thoracic diameter is 274.46 mm, hence CTR is 64.85%, this case is a non-cardiogenic lung edema, with VPTR of 19.1%.

RESULTS

The study includes 100 out of 106 people after excluding participants based on the exclusion criteria. Six patients were excluded from the study because they were under the age of 18 (2), had a history of cardiac surgery (3), or demonstrated symptoms of a mediastinum tumor (1). All 100 participants who meet the inclusion criteria would undergo VPW, CTR, and VPTR measurement. Of the participants, 42% are males and 58% are females. The participants were not normally distributed in age and had a median age of 50.5 years (19–83). Table 1 summarizes the participant characteristics.

The diameters of the thorax or chest cavity, CTR, and VPTR on AP conventional chest x-rays were normally distributed in this study using the Kolmogorov-Smirnov test. In comparison, the VPW value did not follow a normal distribution. The median VPW value is 62.5 mm (46.8–89.4 mm), whereas the mean thorax diameter is 267.3 ± 21.5 mm; the mean CTR value is 59.9% ± 6.3%, while the mean

VPTR value is 23.7% ± 3.2%. The characteristics (VPW, thorax diameter, CTR, and VPTR) were further summarized in Table 2. Cardiogenic and non-cardiogenic pulmonary edema affected 21% and 79% of patients, respectively.

The VPTR cut-off value of 25.1% was determined using the ROC curve and boxplot (>25.1% for cardiogenic lung edema and ≤25.1% for non-cardiogenic lung edema). The sensitivity was 90.5% and the specificity was 86.1%. Table 3 contains a two-by-two matrix summarizing the VPTR cut-off value to distinguish cardiogenic and non-cardiogenic pulmonary edema.

TABLE 1. The distribution of participant characteristics

Characteristics	Frequency (N)	Percentage (%)
Sex		
Males	42	42
Females	58	58
Lung edema		
Cardiogenic	21	21
Non-cardiogenic	79	79

Data normality was calculated using the Kolmogorov-Smirnov test. Participants included are native Indonesian adults (aged ≥18 years), clinically diagnosed with pulmonary edema with AP chest films that met the standard reading criteria.

TABLE 2. Values of parameters (VPW, diameter of the thorax, CTR, and VPTR) in the AP conventional chest radiograph

Parameter	Mean ± SD	Median	Min–Max
VPW (mm)	63.1 ± 8.7	62.5	46.8–89.4
Diameter of the thorax (mm)	267.3 ± 21.5	265.2	224.0–318.1
CTR (%)	59.9 ± 6.3	58.9	44.3–80.4
VPTR (%)	23.7 ± 3.2	23.4	17.7–31.6

SD = standard deviation; min= minimum; max= maximum.

TABLE 3. Sensitivity and specificity of VPTR to differentiate cardiogenic and non-cardiogenic pulmonary edema

VPTR cutoff value	Pulmonary Edema		Total
	Cardiogenic	Non-cardiogenic	
Positive (>25.1)	19	11	30
Negative (≤25.1)	2	68	70
Total	21	79	100

VPTR cut-off value of >25.1% for cardiogenic pulmonary edema and ≤25.1 for non-cardiogenic pulmonary edema. Sensitivity: 90.5%; Specificity: 86.1%.

TABLE 4. Interobserver reliability and agreement

Parameter	ICC (95% CI)	*p*
VPW	0.73 (0.07–0.89)	<**0.001**
Thoracic diameter	0.82 (0.74–0.88)	<**0.001**
VPTR	0.36 (0.06–0.56)	**0.012**

The ICC for VPW, thoracic diameter, and VPTR are 0.73 ($p < 0.05$), 0.82 ($p < 0.05$), and 0.36 ($p < 0.05$), respectively (Table 4). Each rater separately assessed the quantitative aspects of the chest radiograph. The VPTR cut-off value is >25.1 mm in the case of cardiogenic lung edema and ≤25.1 mm in the case of non-cardiogenic lung edema.

DISCUSSION

This study used the AP chest radiograph to measure the VPTR to evaluate the cut-off point and sensitivity and specificity to distinguish cardiogenic and non-cardiogenic pulmonary edema. VPTR would be useful in a resource-limited setting where digital radiography is not available and plain radiograph magnification varies, not allowing for accurate VPW measurements. Studies examining the link between VPW and pulmonary edema remained uncommon, and to the author's knowledge, no studies have examined the association between VPTR and pulmonary edema.

No correlation was found between sex and the occurrence of pulmonary edema; hence, the fact that females are more than males in the current study is controversial. The median VPW and mean VPTR are larger compared to normal healthy participants in reference to the study conducted by Zunera *et al*.[13] The incidence of non-cardiogenic pulmonary edema in the center was also higher within the study period. The low ICC for VPTR measurement may be caused by the combined differences in VPW and thoracic diameter measurements, as well as differences in experience between raters in measuring VPW and thoracic diameter. Additional training should be conducted to familiarize radiologists with the VPTR measurement technique if it is practiced in the future.

Based on the ROC curve, manual calculations using a 2 × 2 table provided a relative sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 90.5%, 86.1%, 63.3%, 97.1%, and 87%, respectively, for differentiating cardiogenic and non-cardiogenic pulmonary edema with a VPTR cut-off point of 25.1%. This investigation did not significantly differ from those of Wichansawakul *et al*. in terms of the sensitivity and specificity of the VPW value.[14] However, Wichansawakul *et al*. conducted prospective cohort research on patients in the ICU in Thailand, and their findings slightly differed from Farshidpanah *et al*. and Thomason *et al*., probably due to variances in the participants' ethnicity.[3,15]

Milne *et al*. published a study in 1984 on the quantitative estimation of intravascular volume status using VPW.[16] The VPW is comprised of the mediastinal silhouette of major vessels, such as the superior vena cava, azygos vein, thoracic aorta, and left subclavian artery, on conventional chest radiographs. Understanding that the VPW's left

border is comprised of veins while the right border is made up of arteries is fundamental. This is because any changes in VPW size caused by increased intravascular volume are primarily attributable to greater venous compliance rather than the arteries.[16]

The magnification parameters of the cardiac silhouette may affect the accuracy of the VPW reading. The VPTR is measured similarly to the CTR on a chest radiograph. The ratio of VPW to thoracic diameter was developed to eliminate the magnification problem in chest radiographs when film sizes and magnifications are inconsistent. Measuring the relative size of an organ to another variable in a chest radiograph has been documented to be useful since 1919 by Danzer *et al*., who pioneered the use of the CTR measurement technique.[17] This technique is advantageous because the relative ratio is not reliant on the magnification scale of the silhouette of the other organs, as both organs have a linear proportion in magnification, thereby eliminating any magnification disparities. VPTR is designed to assist radiologists at facilities lacking a digital system in predicting the kind of pulmonary edema based solely on conventional chest radiographs.

Several variables could negatively affect the study outcomes. A rotational or asymmetrical image and insufficient inspiration of the chest radiograph are two examples. Patients whose chest radiographs are taken while their chest is tilted to the right or left may have increased VPW values, and patients with insufficient inspiration may have an increased heart diameter on an AP chest radiograph. Milne *et al*.[16] reported on both of these aspects, stating that participants tilting to the left or right every 15° could increase the VPW score by as much as 6% and insufficient inspiration has minimal effect on VPW measurement.[16]

Obtaining the ratio of size between two objects has been previously used, such as calculating CTR. Since 1919, CTR was developed to easily determine cardiac enlargement.[18] CTR remained widely used today despite having a weak correlation to true chamber size obtained from cardiac MRI. This may be because CTR measurement is relatively affordable and practical, and conventional chest radiography is widely available.[19] However, a CTR value of >0.55 suggests a true heart chamber enlargement and has an excellent interobserver agreement between raters.[19]

Zunera *et al*. first mentioned VPTR. According to the study, the normal VPW in an erect chest PA radiograph is 48 ± 5.5 mm, and the VPTR is 17.2% ± 17%. Additionally, it indicated that the average VPW and VPTR readings were 10% higher in an AP projection compared to an erect PA projection.[13] This difference in magnification due to positioning could affect the physician's VPW measurement to distinguish cardiogenic from non-cardiogenic edema.

Several studies have been conducted to determine the VPW value in patients with critical illness in the ICU. For example, Farshidpanah *et al*.[3] found no significant difference in VPW measurement between a radiologist and a non-radiologist with prior training in diagnosing lung edema. The study enrolled 80 patients in the ICU and used a reference value of VPW of >70 mm as the cut-off for cardiogenic and non-cardiogenic pulmonary edema, respectively. This cut-off point has sensitivity, specificity, PPV, NPV, and accuracy of 55%, 88%, 81%, 69%, and 73%, respectively, for diagnosing cardiogenic lung edema.[3]

This study is comparable to that of Ely *et al*., who assessed the intravascular volume status of 100 patients in the ICU with and without pulmonary edema.[20] Ely *et al*. then determined that a VPW value of >70 mm and a CTR value of >55% was the most significant discriminator for predicting a PAOP of >18 mmHg.[20] Additionally, the study uses a prospective cohort and 100 samples (similar to our study). Based on chest x-ray alone, these parameters could result in a likelihood ratio greater than three, thereby increasing the diagnostic accuracy of cardiogenic lung edema to 70%.[21] Measuring both a VPW of >70 mm and CTR of >0.55 results in a sensitivity, specificity, PPV, and NPV of 46%, 85%, 65%, and 70%, respectively.[20,21] Numerous other investigations have indicated that a VPW of >68 mm is associated with hydrostatic or cardiogenic pulmonary edema.[15,22–24] Additionally, Thomason *et al*. used both CTR of >0.52 and VPW of >63 mm to indicate cardiogenic pulmonary edema, finding that combining the two criteria improves diagnosis accuracy by up to 73% than VPW or CTR alone.[15]

This study has various limitations that should be highlighted. First, this study could not validate the diagnosis of pulmonary edema with PAOP, which is the gold standard for distinguishing cardiogenic from non-cardiogenic lung edema. This is because PAOP assessment is not a standard operation in the hospital's ICU due to its high cost.

CONCLUSIONS

VPTR can distinguish between cardiogenic and non-cardiogenic causes of pulmonary edema. Additional research showed a cut-off value of 25.1% (sensitivity: 90.5%; specificity: 86.1%) to differentiate between the two etiologies. VPTR can be beneficial in healthcare facilities that continue to employ analog radiography techniques, which are usually unable to accurately determine absolute values due to magnification problems. Further studies are needed to validate the diagnostic performance of VPTR with PAOP to differentiate cardiogenic and non-cardiogenic pulmonary edema.

CONFLICT OF INTEREST

The author(s) declare no competing interests.

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Apoptotic Effect of Bortezomib on Pancreatic Islet Cells in STZ-induced Diabetic Rats

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Apoptotic Effect of Bortezomib on Pancreatic Islet Cells in STZ-induced Diabetic Rats

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Abstract

Background: This study aimed to investigate the possible apoptotic role of bortezomib (BMZ) on pancreatic islets of streptozotocin (STZ)-induced diabetic rats.

Methods: Sprague-Dawley rats were divided into groups that were administered BMZ alone or in combination with STZ. To evaluate the effect of BMZ on the development of diabetes, blood glucose levels were measured regularly in the animals. Islet cell viability was determined by staining the islets with fluorescein diacetate and propidium iodide. Expression of the Bcl-2 and bax genes was determined in islet cells by quantitative real-time polymerase chain reaction.

Results: Administering STZ-induced hyperglycemia in the rats reduced the viability of islet cells and the bcl-2/bax ratio. In the group administered BMZ alone, the bcl-2/bax gene expression rate in islets increased significantly compared to the control group. BMZ co-administered with STZ significantly increased islet cell viability and the bcl-2/bax ratio compared to the diabetic group.

Conclusions: This study demonstrates that BMZ may protect pancreatic islet cells from apoptosis by increasing islet viability and upregulating the bcl-2/bax gene expression ratio, even though it failed to protect against the destructive effect of STZ.

Keywords: apoptosis, bortezomib, pancreatic islets, rats, type 1 diabetes

INTRODUCTION

Type 1 diabetes is an autoimmune disease characterized by selective and progressive destruction of insulin-secreting beta cells of the pancreas.[1] The nuclear factor kappa B (NF-κB) signaling pathway plays a role in the development of diabetes.[2,3] NF-κB is a transcriptional factor that transcriptionally activates the genes required for important biological processes, such as cell proliferation, apoptosis, survival, and inflammation.[4,5]

Most studies that have shown the role of NF-κB activation in pancreatic beta cell death indicate that NF-κB has a predominant pro-apoptotic function.[2,6] However, activation of NF-κB is generally considered to be anti-apoptotic and pro-oncogenic in many tumor types. Therefore, blocking NF-κB activation is a successful target therapy for cancer treatment.[4,5] Blocking NF-κB activation directly with chemical inhibitors or transgenic animal models results in resistance to STZ-induced development of diabetes, decreased inflammation, and increased survival of islet grafts in transplantation experiments.[6,7]

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Bortezomib (BMZ) is a proteasome inhibitor approved by the Food and Drug Administration for use in the treatment of multiple myeloma and mantle cell lymphoma. BMZ is a potent inhibitor of the NF-κB pathway.[8] It inhibits the activation of NF-κB by blocking the proteasomal degradation of IκB and inducing apoptosis in many tumor cell types in preclinical studies.[8,9] However, the exact mechanism of how BMZ affects pancreatic islet cell apoptosis remains unclear. A recent study showed that BMZ regulates the immune system in autoimmune diabetes and reported that administering BMZ to pre-diabetic non-obese mice prevents the development of diabetes in 80% of the mice, while it did not show any therapeutic effect when administered alone to overtly diabetic mice.[10] In addition, BMZ reduced islet rejection in another study where BMZ was systemically administered to STZ-induced diabetic mice before islet transplantation.[6] In both studies, it was suggested that BMZ prevented the development of diabetes due to its anti-inflammatory properties, but the apoptotic process in the islets has not been investigated. Other proteasome inhibitors induce apoptosis in mouse and rat beta insulinoma cell lines,[11,12] but the proteasome inhibitors containing MG-132, celastrol and epoxomicin, lactacystin, and N-Acetyl-Leu-Leu-Nle-CHO (ALLN) have quite contradictory results such as reducing, increasing, or no effect on rat islet viability.[11,13,14] The purpose of this study was to investigate the apoptotic

effects of BMZ on rat pancreatic islet cells in STZ-induced diabetes using *in vivo* and *in vitro* experiments.

METHODS

Ethical approval

All procedures were conducted following the accepted principles for the care and use of laboratory animals and were approved by the Local Ethical Committee of Laboratory Animals at Diskapi YB Education and Research Hospital, Ankara, Turkey (Protocol no: 2016/05).

Animals

Female Sprague-Dawley rats (average weight, 200–250 g; age, 4–6 months old) were used to investigate the effect of BMZ on the development of type 1 diabetes. All animals were housed in a special pathogen-free and temperature-controlled room (21 ± 2 °C) with a 12 h light/12 h dark cycle. The rats were fed a standard pelleted diet and water *ad libitum*. All animal experiments were performed following the Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80–23) and approved (2016/05) by the Ethical Committee of Laboratory Animals at YB Teaching and Research Hospital, Ankara, Turkey.

STZ-induced diabetic rat model

The STZ-induced diabetes rat model was used to determine the apoptotic effect of BZM on pancreatic islets. The rats were randomly selected and divided into four groups: 1) Control, 2) STZ group, 3) BZM group, and 4) STZ + BZM group (n = 10). Diabetes was induced in the rats by a single intraperitoneal injection of STZ (Sigma-Aldrich, St. Louis, MO, USA) at a dose of 45 mg/kg in freshly prepared citrate buffer (50 mM sodium citrate, pH 4.5).[15] The control group was administered citrate buffer alone. BMZ (0.2 mg/kg, Milenium Pharmaceutical, Cambridge, MA, USA) was injected intraperitoneally 3 times (days 1, 4, and 8) in all related groups as described previously.[16] The first BMZ dose was administered to the STZ+BZM group 2 h before the STZ injection (day 1). Then, the other two BMZ doses were injected as in the BZM group (days 4 and 8). All rats were anesthetized by intraperitoneal injection of a mixture of ketamine and xylazine on day 10, and the pancreas was removed.

Blood glucose levels and body weight were measured before the drugs were administered and every other day after the injections. Blood glucose levels were detected in the tail vein blood of all rats using the Accu-check blood glucose meter (Bayer Corp., Whippany, NJ, USA). Rats with blood glucose levels > 250 mg/dL were defined as diabetic.

Isolation and purity of the islets

The islets were isolated as described previously.[17] Briefly, the pancreas was inflated by injecting 7 ml of cold collagenase type V solution (1 mg/ml) into the bile ducts of the rats. The pancreas was removed, and the islets were separated by Ficoll density centrifugation. After isolation, the islets were hand-picked under a stereomicroscope. The number and purity of the islets were determined by counting after diphenylthionarbazon (DTZ; Sigma-Aldrich) staining in which islets were dyed scarlet at 37 °C for 10 min. After adding 50 mM BMZ to the culture medium of the BZM and STZ + BZM groups, all islets were cultured at 37 °C in humidified air and 5% CO_2 in RPMI-1649 medium supplemented with 1% L-glutamine, 10% heat-inactivated fetal bovine serum (Sigma-Aldrich), and a 1% antibiotic mixture (100 units/mL of penicillin and 100 μg/mL of streptomycin; GIBCO, Grand Island, NY, USA) overnight in 25 cm^2 flasks.

Islet viability

The viability of 3–5 islets collected from each rat was analyzed by dual fluorescent staining consisting of fluorescein diacetate (FDA) and propidium iodide (PI) (Sigma-Aldrich).[18] The percentage of viable islets was obtained from the ratio of living cells stained green with FDA to dead cells stained red with PI. Stained islet cells were visualized with a fluorescent microscope (Olympus CX-41: Tokyo, Japan), and the mean viability values were determined using the MatLab color analysis program (MathWorks Inc., Natick, MA, USA).

Real-time quantitative polymerase chain reaction (RT-PCR)

Total RNA was isolated from the cultured islets of each rat using the PureLink RNA Mini kit (Ambion Corp. Naugatuck, CT USA), following the manufacturer's instructions. RNA concentration and purity were determined with the Thermo NanoDrop2000 (Thermo-Fisher Scientific, Waltham, MA, USA), and sample integrity was assessed by gel electrophoresis. A 1 µg portion of total RNA was reverse-transcribed using the Applied Biosystems High-Capacity cDNA Kit (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's instructions. The cDNA was diluted 1:10 in RNase-free water. The real-time PCR reaction was performed using the cDNA samples and the TaqMan Gene expression assay kit (Applied Biosystems). The assay ID numbers for the primer pairs and probes were bcl-2 (Rn 99999125_m1), bax (Rn 01480161-g1), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH; Rn 99999916-s1). Each assay was run in triplicate on the ABI-7500 Fast RT-PCT system. The GAPDH gene was used as the endogenous control. Relative quantification of gene expression was determined by the $2^{-\Delta\Delta Ct}$ method.[19]

Data analysis

Results are presented as mean ± SD or SE per group. Differences between two groups were compared by the independent Student's *t*-test and differences between several groups were detected using one-way variance analysis followed by Tukey's method for multiple

comparisons (SPSS version 20.0; SPSS Inc., Chicago, IL, USA). A $p < 0.05$ was considered significant.

RESULTS

The effect of BMZ on weight and blood glucose in the STZ-induced diabetic rats

To investigate the role of BMZ in the development of STZ-induced diabetes, we generated four different experimental groups of non-obese rats. Their body weights were measured before each injection. All of the animals had similar initial body weights. As shown in Table 1, no significant changes in body weight were observed during the experimental period.

Diabetes was induced by a single STZ injection. The rats were diabetic 3 days following the STZ injection, as indicated by an elevated blood glucose level (349.0 ± 24.8 mg glucose/dL, 10 days), compared with the control group (96.2 ± 2.52) ($p < 0.05$). Blood glucose levels did not change significantly in the BMZ group compared with the control group (98.2 ± 7.1), and they were almost identical to the control. As shown in Figure 1, blood glucose levels increased significantly in the STZ+BZM group (407.6 ± 11.0) compared to the control and BZM groups ($p < 0.05$).

TABLE 1. Body weight changes

Group	First body weight (g)	Final body weight (g)
Control	212.00 ± 5.85	219.00 ± 9.20
STZ group	214.60 ± 12.97	205.60 ± 10.62
BZM group	215.40 ± 19.24	220.40 ± 13.11
STZ+BZM group	209.80 ± 13.06	192.20 ± 4.42

Data are mean ± SE of 10 rats per group. No significant difference was observed between the first and final body weights of the animals.

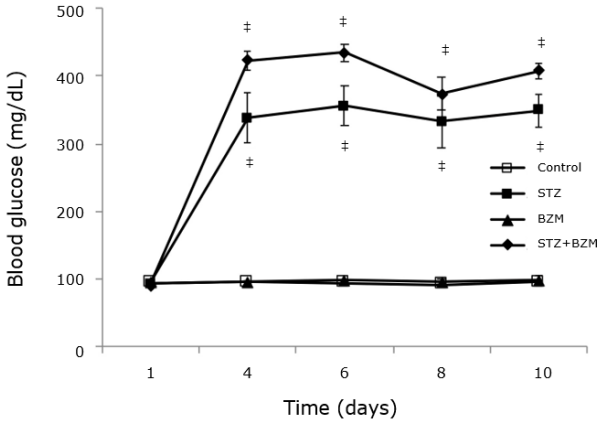

FIGURE 1. Blood glucose levels on different days. Values are mean ± SE of 10 rats per group. The increases in the blood glucose levels of the STZ and STZ+BZM groups were all significant compared with the control and BZM groups after day 4.

The effect of BMZ on islet cell viability

The islets were isolated to investigate the effect of BMZ on islet cell viability. The purity of the islets was determined by DTZ staining. Islet viability was determined by a MatLab analysis following FDA/PI staining.

Average islet viability in the STZ group (63.55 ± 3.90%) was significantly lower than that in the control and BZM groups, respectively (83.13 ± 7.12%; 80.21± 5.60%) ($p < 0.05$) (Figure 2 and Figure 3). BZM alone was not cytotoxic to the islets. In contrast, BZM protected the islets from apoptosis by STZ when STZ and BZM were co-administered to the rats (77.94 ± 10.99%) ($p < 0.05$).

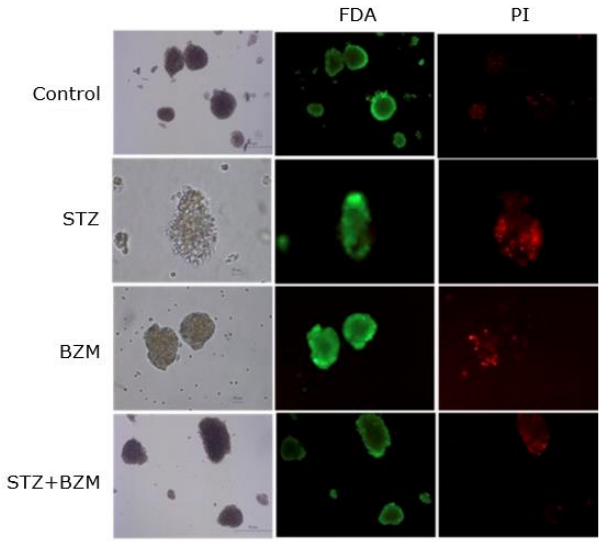

FIGURE 2. Fluorescent microscopic images of living islet cells stained green with fluorescein diacetate (FDA) and dead islet cells stained red with propidium iodide (PI). Images were analyzed with the MatLab program to determine the percentage of cell viability. At least 3 islet samples were used for each rat.

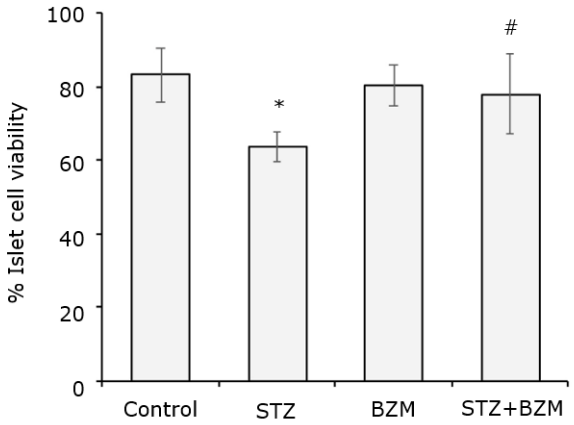

FIGURE 3. Islet cell viability values are expressed according to the results of the MatLab analysis after FDA/PI staining of the islets. The percentages of viable

cells in the control, BZM, and STZ+BZM groups were significantly higher than that in the STZ group ($p < 0.05$). Data are mean ± SD. * $p < 0.05$ vs. control, BZM and STZ+BZM groups; # $p < 0.05$ vs. STZ group.

The effect of BMZ on bax and bcl-2 gene expression levels

The effects of BMZ on bax and bcl-2 gene expression levels in pancreatic islet cells were determined by RT-PCR. As shown in Figure 4a, expression of the pro-apoptotic bax gene increased significantly in STZ-induced diabetic rats, as expected ($p < 0.05$). A decrease in the bax expression level was detected in the STZ + BZM group, compared to the STZ group, indicating that BZM protected the cells from apoptosis by STZ. Furthermore, the expression level of the anti-apoptotic bcl-2 gene was highest in the STZ+BZM group. This increase was significant vs. the control and the STZ and BZM groups ($p < 0.05$). Because apoptosis is mediated by the balance between the bcl-2 and bax gene expression levels, the bcl-2/bax ratio determines cell survival or death. Figure 4b shows that the mitochondrial bcl-2/bax gene expression ratio increased significantly in the BZM group compared to the control group ($p < 0.05$), indicating that BZM promoted an anti-apoptotic effect in the islets. The ability of BMZ to increase the bcl-2/bax ratio in the STZ+BZM group compared to the STZ group ($p < 0.05$) indicates that it protected the islets from apoptosis by STZ.

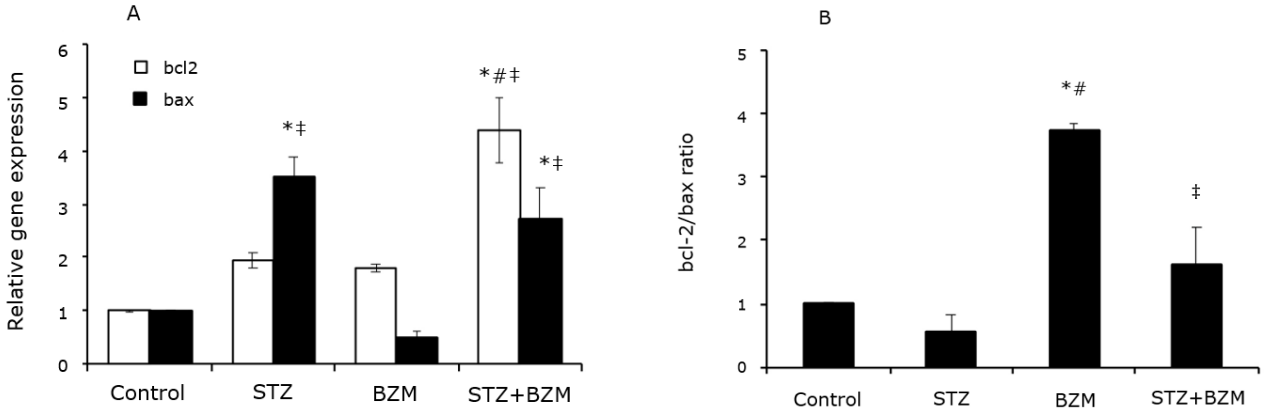

FIGURE 4. Gene expression levels. Bax and bcl-2 gene expression levels in the pancreatic islets were determined by qRT-PCR (A). The bcl-2/bax gene expression ratio (B). Data are mean ± SD. of three separate experiments. * $p < 0.05$ vs. control group; # $p < 0.05$ vs. STZ group; ‡ $p < 0.05$ vs. BZM group.

DISCUSSION

BMZ is a reversible proteasome inhibitor that selectively inhibits the chymotrypsin-like activity of the proteasome and is currently clinically used to treat multiple myeloma and mantle cell lymphoma.[9,20] One of the BMZ anticancer mechanisms is suppression of the NF-κB signaling pathway.[8] Many studies have shown that activation of NF-κB plays a key role in beta cell destruction and progression to diabetes,[2,3] in contrast to the anti-apoptotic function in cancer cells.[4,5] This study was conducted to examine the apoptotic role of BMZ in pancreatic islets from STZ-induced diabetic rats.

STZ is a toxic glucose and N-acetyl glucosamine analog that selectively destroys pancreatic beta cells. Thus, it is widely used to induce type 1 diabetes in experimental animals.[15,21,22] STZ is transported to the pancreatic beta cells via the low-affinity GLUT 2 glucose transporter, which preferentially facilitates the uptake of STZ, and causes DNA alkylation and eventual death of beta cells.[21,22] STZ (single high dose; 35–65 mg/kg rat) administration depletes the pancreatic beta cells, resulting in elevated fasting blood glucose levels within 72 h after administration.[21–23] In this study, we observed a significant increase in blood glucose levels in diabetic rats compared with the control rats 3 days after STZ administration. Moreover, we determined a significant decrease in viability in isolated islets 10 days after administering the STZ. These data confirm that STZ destroyed the pancreatic beta cells by increasing blood glucose levels and decreasing islet cell viability.

Apoptotic cell death is a fundamental mechanism involved in the loss of pancreatic beta cells.[1] The biochemical properties of apoptotic cell death include internucleosomal cleavage of DNA, phosphatidylserine externalization, and proteolytic cleavage of several intracellular substrates. Apoptosis is a tightly regulated process, and the fate of cells depends on the balance between pro-apoptotic and anti-apoptotic proteins. The Bcl-2 family of proteins is a critical regulator of apoptotic cell death. Pro-apoptotic bax gene expression promotes cell death, whereas anti-apoptotic bcl-2 results in cell survival. The Bcl-2/bax ratio determines cell death or survival. Low levels of Bcl-2 and/or high levels of Bax permeabilize the mitochondria after the apoptotic

stimulus. Caspase 3 becomes active with the release of cytochrome *c* from the intermembrane space into the cytoplasm followed by the formation of the apoptosome. Caspase 3 activates the DNase/DNA fragmentation factor to breakdown nuclear DNA, resulting in DNA fragmentation and cell death.[24] In this study, increased expression of bax and bcl-2 was observed in the diabetic rats administered STZ alone. However, because the increase in bax expression was higher than bcl-2 expression and significantly increased compared to the control, the decrease in the bcl-2/bax ratio promoted apoptotic cell death in the rats. This result is compatible with previous studies showing overexpression of the pro-apoptotic bax gene and low expression of the anti-apoptotic bcl-2 gene in pancreatic beta cells exposed to STZ.[25,26]

The main objective of this study was to examine the apoptotic effect of BMZ on pancreatic islets in STZ-induced diabetic rats. BMZ administration alone did not change the fasting blood glucose level or islet viability, compared to the control group. In our study, BMZ was used at a dose of 0.2 mg/kg, which is well tolerated[10,16,27] without any apparent toxicity. Previous studies have reported that many of the side effects of BMZ, such as gastrointestinal toxicity, neuropathy, and anemia, are mild and manageable. BMZ has not been reported to affect blood glucose, except for the indication that it should be used with caution in diabetic patients. The unchanged blood glucose levels observed in the BMZ-administered rats were compatible with the fact that BMZ has no effect on blood glucose in non-diabetic patients.[27] BMZ induces apoptosis in many tumor cells by decreasing cell viability; thus, it is currently used to treat multiple myeloma.[8] However, the effect of BMZ on the viability of pancreatic islet cells is not well known. We observed that BMZ did not change the viability of pancreatic islet cells. This result is consistent with a study showing that BMZ does not change the viability of the MIN6 beta cell line even at a high concentration.[28] Previous studies have reported that other proteasome inhibitors induce severe apoptosis in mouse and rat beta insulinoma cell lines.[11,12] However, the effect of proteasome inhibitors on rat islet viability has been contradictory, as a decrease in viability was observed in rat islets cultured with MG-132,[13] and an increase in viability was observed with non-toxic concentrations of celastrol and epoxomicin,[14] but lactacystin and ALLN exerted no visible adverse effects on rat islet cell viability[11,13] and even partially protected against the toxic effect of pro-inflammatory cytokines such as interleukin-1 and interferon.[11] Interestingly, we observed that administering BMZ alone upregulated bcl-2 and downregulated bax, although the differences were not significant when compared with the control. However, these changes in gene expression led to a significant increase in the bcl-2/bax ratio, indicating that BMZ administration alone may be anti-apoptotic in pancreatic islets, even if it is not reflected in total islet viability. This result seems contrary to the ability of BMZ to induce apoptosis, which is widely used in cancer therapy. However, many studies have shown that BMZ is more selective in tumor cells than normal cells[29,30] and more effective in hematological cancers than solid tumors[29] indicating that BMZ may cause different effects depending on the tissue and cell types and the stress conditions.

In this study, we observed that BMZ co-administered with STZ significantly increased the bcl-2/bax gene expression ratio and islet viability compared to those in the control rats, but the same antiapoptotic effect was not reflected in the blood glucose levels. These results indicate that BMZ does not completely protect beta cells from the selective destructive effect of STZ, and possibly provides partial protection by causing an antiapoptotic effect in islet cells. A recent study has directly shown that BMZ prevents the development of diabetes when administered to pre-diabetic NOD mice.[10] NOD mice are a model of autoimmune diabetes in which no toxin is administered. Therefore, administering BMZ to NOD mice in that study prevented hyperglycemia unlike in our study. In addition, another study demonstrated that systemic BMZ administration of STZ-induced diabetic mice delays the rejection of allogeneic islet grafts, suggesting that BMZ prevents the development of diabetes by delaying beta cell loss.[6] These results may contribute to the protective effect of BMZ, which we observed at the total islet viability and gene expression levels. However, this antiapoptotic protective effect did not prevent the loss of beta cells enough to block the development of diabetes. Blood glucose levels are only affected by beta cell loss, whereas islet viability is the total viability value of all cell types including alpha and delta cells in the pancreatic islets. For example, it has been reported that even STZ administration, which selectively destroys beta cells, increases the survival percentage of alpha and delta cells in pancreatic islets.[23] The finding that BMZ causes a similar proliferative effect by increasing total islet cell viability and bcl-2/bax gene expression rates may explain why we did not see an improvement in blood glucose levels. This condition can also be considered one of several reasons to explain the conflicting results of other proteasome inhibitors on rat islet viability.[11–14] Therefore, it would be more accurate to determine individual cell viability for each cell type rather than total islet cell viability in future diabetes research.

CONCLUSIONS

In conclusion, this study provides evidence that BMZ induced an antiapoptotic effect by increasing islet cell viability and the bcl-2/bax ratio in rat pancreatic islets, although it was inadequate to prevent the loss of beta cells and the development of STZ-induced diabetes. The antiapoptotic mechanism of BMZ on pancreatic islet cells

needs to be further elucidated for each cell type in the pancreas.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Potential Antihyperlipidemia Effect of Lactoferrin in Hyperlipidemia-Induced Male Sprague–Dawley Rats

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Potential Antihyperlipidemia Effect of Lactoferrin in Hyperlipidemia-Induced Male Sprague–Dawley Rats

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Abstract

Background: Hyperlipidemia is a condition that is characterized as an increase in total cholesterol and triglyceride levels in the blood. Lactoferrin is a protein that can serve as an antioxidant. This study aims to determine whether lactoferrin can reduce total cholesterol and triglyceride levels.

Methods: This study used 24 Sprague–Dawley rat strains, which were divided into six groups: normal group; negative control; positive control; and dose groups 1, 2, and 3. The normal group was given standard feed, whereas the other group was given high cholesterol and fat. The positive control group and dose groups 1, 2, and 3 were given 1.5 mg/kg BW of simvastatin and 100, 200, and 400 mg/kg of BW lactoferrin, respectively. After 6 weeks, total cholesterol and triglyceride levels were measured.

Results: This study showed that lactoferrin doses of 100, 200, and 400 mg/kg BW could significantly reduce total cholesterol and triglyceride levels ($p < 0.05$). Lactoferrin could also significantly reduce activated Kupffer cell and steatosis area in the liver ($p < 0.05$).

Conclusions: Lactoferrin can reduce total cholesterol and triglyceride levels. Thus, further research is needed to address the existing bias and confirm that lactoferrin can reduce cholesterol and triglyceride levels.

Keywords: cholesterol, hyperlipidemia, lactoferrin, sprague–Dawley, triglyceride

INTRODUCTION

Hyperlipidemia is a common cause of atherosclerotic plaque formation in coronary arteries.[1] An increase in total cholesterol and triglyceride levels shows hyperlipidemia.[2,3] Hyperlipidemia, also known as dyslipidemia, is a common condition, which is associated with cardiovascular diseases, with elevated plasma low-density lipoprotein (LDL) cholesterol being the 8th leading risk factor of death in 2019.[4] Approximately 4.4 million deaths and 98.62 million disabilities were related to high-plasma LDL-cholesterol. Based on data from Indonesia Basic Health Research 2018, 35.9% of people in Indonesia aged 15 years and above have abnormal lipid profiles, of which 5.9% have a high level of LDL, 22.9% have a low level of high-density lipoprotein, and 11.9% have a high level of triglyceride.[5]

Hyperlipidemia could be divided into primary hyperlipidemia and secondary hyperlipidemia. Primary hyperlipidemia is due to heredity, whereas secondary hyperlipidemia is due to low physical activity, smoking, diabetes mellitus, nephritic syndrome, hypothyroidism, and drug use. Complications from hyperlipidemia condition include atherosclerosis, coronary artery disease, myocardial infarct, and ischemic stroke.[6] At present, statin is a common medication for treating hyperlipidemia; however, this medication still has side effects such as myalgia.[7,8] Many types of research are conducted on the basis of this condition, such as lactoferrin research in reducing lipid profile levels.[9]

Lactoferrin is an iron-binding glycoprotein in the body. Mammals such as cows, horses, dogs, and humans can produce lactoferrin.[10] Lactoferrin plays an important role in the physiological function of the human body, such as antimicrobial, antiviral, immune system enhancement, and antioxidants.[10] Antioxidants from lactoferrin can reduce total cholesterol and triglyceride levels in the blood as well as the steatosis area in the liver. The high affinity for the binding of lactoferrin to iron in the body can prevent the production of free radicals during the Fenton reaction, thereby inhibiting the oxidation of lipoproteins in the body.[11] A study conducted by Nozari *et al.* showed that bovine lactoferrin reduces total cholesterol and triglyceride levels in male rats fed with high-cholesterol diet.[12] However, no *in vivo* studies in Indonesia had been conducted to assess the potential

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application of lactoferrin in reducing total cholesterol and triglyceride levels in hyperlipidemia-induced male rats. Thus, this paper aims to examine the potential application of lactoferrin as antihyperlipidemia in hyperlipidemia-induced male Sprague–Dawley male rats.[12]

METHODS

All experiments performed in this study were approved by the ethical review committee of School Medicine and Health Sciences—the Atma Jaya Catholic University of Indonesia on January 20, 2021 (protocol number 01/01/KEP-FKIKUAJ/2021), and all procedures were in accordance with international standards for animal experimentation. This experimental study was conducted from April 2021 until June 2021 at Pharmacology Laboratory and Animal House School of Medicine Atma Jaya Catholic University of Indonesia, Jakarta. Bovine lactoferrin was purchased from Xi'an Ruisaen Biotechnology Co., Ltd., China, as water-soluble pinkish-white crystals with purity of 99% (RSN201119).

Male Sprague–Dawley rat strains (N = 30) aged 5 weeks, with 150–200 g body weight, were obtained from the Indonesian Food Drug Administration Laboratory Service (certificate no. 02/LHP/SKKH/IV/2021). Subjects were calculated on the basis of the degree of freedom or resource equation method formula. The minimum sample size of at least four Sprague–Dawley rats was obtained for each group based on the formula. This study used a sample of four rats per study group. The total number of samples in each study group was added by 10% to five rats to overcome the dropout. Subjects were randomly divided into six experimental groups. The first group was the normal group fed a normal diet. The second group was composed of hypercholesterolemic rats fed a high-cholesterol diet (HCD) containing 15% sucrose, 5% cow's fat, 80% quail egg yolk, and 0.01% propylthiouracil (PTU). The third group was given orally HCD and 1.5 gr/150 g BW simvastatin therapy. The fourth, fifth, and sixth groups were given HCD and lactoferrin doses of 100, 200, and 400 mg/kg BW, respectively. All groups were fed HCD for 3 weeks except for the normal group, and then the third group was given simvastatin. The fourth, fifth, and sixth groups were given lactoferrin for 3 weeks. After induction of hyperlipidemia, all groups except for the normal group were still given HCD for another 3 weeks.

After 6 weeks of research, all rats were necropsied. Two milliliters of rat blood were drawn through the rat's heart and placed into the Eppendorf tube. We kept the sample for around 45 min until the blood clotted, and then the sample was centrifuged for around 30 min with 1500 g of power on 400C. Next, we collected 10 µL of serum and placed into the plastic cuvette. Afterward, 1000 µL of reagent kit was mixed with 10 µL of the sample in the plastic cuvette, and then the mixture was incubated for 10 min at 20 °C–25 °C or for 5 min at 37 °C. Absorbance was read within 60 min against reagent blank at a wavelength range of 500–546 nm. Total cholesterol levels were measured by cholesterol FS (10') reagent (manufactured by *DiaSys Diagnostic Systems GmbH*, Germany). However, triglyceride levels were measured by triglyceride FS (10') reagent (manufactured by *DiaSys Diagnostic Systems GmbH*, Germany).

The total cholesterol level was measured as follows:
Cholesterol (mg/dL) = $\frac{Abs\ Sample}{Abs\ Standard}$ × Cholesterol Standard (mg/dL)

The triglycerides level was measured as follows:
Triglyceride (mg/dL) = $\frac{Abs\ Sample}{Abs\ Standard}$ × Triglyceride Standard (mg/dL)

All livers were fixed using formaldehyde and collected to the anatomic pathology laboratory to slice the tissue samples and stain with hematoxylin and eosin. Steatosis in the liver was scored on the basis of the method of Kleiner *et al.* This method determined steatosis based on the following percentage: grade 0, <5% steatosis; grade 1, 5–33% steatosis; grade 2, 33–66% steatosis; grade 3, >66% steatosis.[13] The activated Kupffer cell was scored in accordance with the method of the Arsad *et al*. This method was used to measure activated Kupffer cells in sinusoid, which were graded as follows: grade 0, 0% activated Kupffer cell; grade 1, <30% activated Kupffer cell; grade 2, 30–50% activated Kupffer cell; grade 3, >50% activated Kupffer cell.[14] Three microscopic fields of view were selected for each slide, and histopathological changes were analyzed under a light microscope with 400× magnification.

SPSS for MacOs (SPSS, Chicago, IL, USA) version 28 was used for statistical analyses. Data were shown as means ± SD. One-way ANOVA was used to test established variance analysis. Tukey post hoc test was used to assess the significance of differences among groups (if the homogeneity of variables and normality distribution was assumed). $P < 0.05$ was considered statistically significant. Data for activated Kupffer cell and steatosis were analyzed by Kruskal–Wallis test followed by Mann–Whitney test to compare group differences.

RESULTS

All data were analyzed by one-way ANOVA and then Tukey post hoc test. The result of one-way ANOVA showed a significant difference among all groups ($p < 0.05$). The effect of bovine lactoferrin treatment on total cholesterol and triglyceride alteration in experimental animals is shown in Table 1. The total cholesterol and triglyceride levels were significantly higher in the HCD group than in the normal group ($p < 0.05$). Total cholesterol and triglyceride levels were significantly lower in bovine lactoferrin treatment in all dose groups than in the HCD group ($p < 0.05$). In addition, no significant changes were

observed between the normal group and all bovine lactoferrin dose groups. No significant difference was also found between all bovine lactoferrin dose groups and the positive control group. Similarly, no significant difference was observed among dose groups 1, 2, and 3. Dose group 2 had the lowest total cholesterol level and triglyceride level compared with the other dose groups; however, dose group 3 had the highest total cholesterol level and triglyceride level compared with the other dose groups.

All lobes (right lobe, left lobe, quadrate lobe, and caudate lobe) from the liver were examined in this study. Histopathological analysis showed that rats from the HCD group had fatty livers. However, lipid accumulation reduces in groups administered with lactoferrin. This condition was supported by a higher steatosis score in the HCD group compared with the normal group (Table 2; $p < 0.05$). The lactoferrin treatment group had significantly lower histopathological steatosis scores than the control group (Table 2; $p < 0.05$) Lipid accumulation can increase oxidative stress, characterized by the activation of Kupffer cells in the liver. The activated Kupffer cell score was significantly higher in the HCD group than in the normal and lactoferrin treatment groups (Table 2; $p < 0.001$). No significant difference in activated Kupffer cell score was found among the normal group, positive control group, and groups administered with lactoferrin (Figure 1). Many activated Kupffer cells were found in negative control rats (Figure 1A) compared with the normal group (Figure 1B). Activated Kupffer cells were also shown to be minimal in the positive control group (Figure 1C), dose 1 group (Figure 1D), dose 2 group (Figure 1E), and dose 3 group (Figure 1F). As shown in the picture, lactoferrin dose 2 group has least activated Kupffer cells compared with the other lactoferrin dose groups.

TABLE 1. Effects of bovine lactoferrin on total cholesterol and triglyceride in male rats

Parameter	Normal	HCD	HCD + 1,5 mg/150 g BW Simvastatin	HCD + 100 mg/kg BW bLf	HCD + 200 mg/kg BW bLf	HCD + 400 mg/kg BW bLf
Total Cholesterol (mg/dL)	84,440 ± 36,641[a]	157,514 ± 40,010[b]	76,435 ± 2,470[a]	73,043 ± 28,765[a]	71,604 ± 23,572[a]	78,781 ± 23,093[a]
Triglyceride (mg/dL)	39,741 ± 16,380[a]	70,818 ± 14,385[b]	36,044 ± 8,819[a]	35,669 ± 10,983[a]	31,747 ± 7,140[a]	39,927 ± 17,381[a]

HCD: high-cholesterol diet; bLF: bovine lactoferrin.
Different letters in the same row indicate a significant difference ($p < 0.05$).

TABLE 2. Effects of bovine lactoferrin on activated Kupffer cells and steatosis score in the liver

Parameter	Normal	HCD	HCD + 1,5 mg/150 g BW Simvastatin	HCD + 100 mg/kg BW bLf	HCD + 200 mg/kg BW bLf	HCD + 400 mg/kg BW bLf
Activated Kupffer Cell Score	0.83 ± 0.389[a]	2.42 ± 0.515[b]	1.08 ± 0.515[a]	0.75 ± 0.452[a]	0.42 ± 0.515[a]	1.17 ± 0.577[a]
Steatosis Score	0.00 ± 0.000[a]	2.58 ± 0.515[b]	1.58 ± 0.669[c]	1.33 ± 0.888[c]	1.00 ± 0.739[c]	2.00 ± 0.739[c]

HCD: high-cholesterol diet; bLF: bovine lactoferrin.
Different letters in the same row indicate a significant difference ($p < 0.05$).

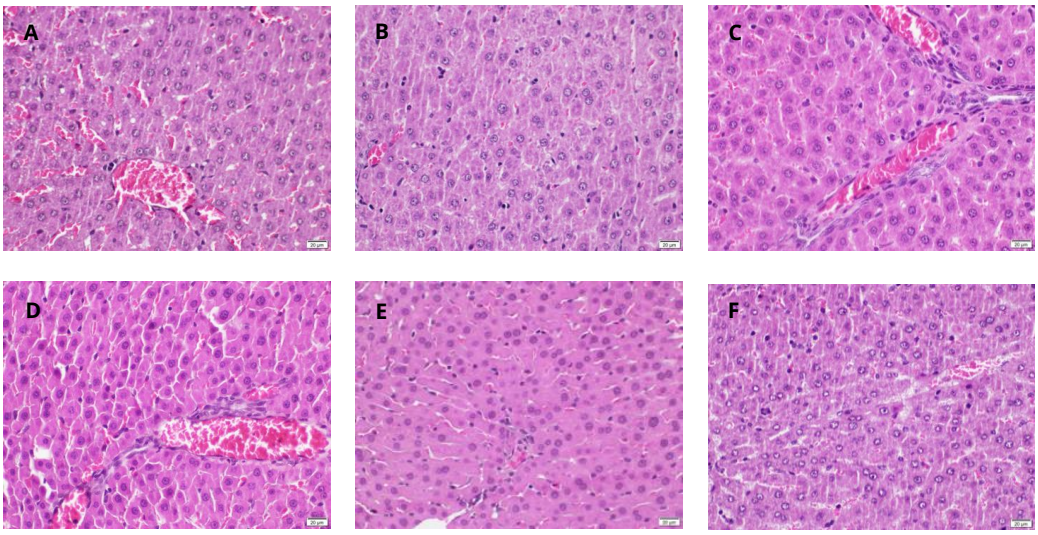

FIGURE 1. Histopathologic examination of rat liver. (A) negative control shows several activated Kupffer cells, (B) normal control (C), positive control, (D) dose 1 (E) dose 2, and (F) dose 3 shows minimal activated Kupffer cells.

DISCUSSION

This study analyzes antihyperlipidemia from lactoferrin by measuring blood total cholesterol and triglyceride levels and performing microscopic liver analyses. Histopathological analyses measured the amount of activated Kupffer cells and steatosis score in rat liver. The results show that bovine lactoferrin treatment could decrease total cholesterol and triglyceride levels in male Sprague–Dawley rats, commonly at risk of cardiovascular diseases.

High-sucrose consumption can increase lipid profile levels such as total cholesterol, triglycerides, VLDL, NASH, NAFLD, and insulin resistance. Insulin resistance is a condition where insulin's ability to suppress glucose and VLDL production is impaired; thus, TG will be released to the bloodstream through VLDL lipoproteins, leading to dyslipidemia.[15] Another food that can induce hyperlipidemia is cow's fat because 100 g of cow's fat contains 126 mg of cholesterol.[16] PTU can also induce hyperlipidemia by inhibiting the thyroid hormone. Thyroid hormones will activate the LDL receptor-related protein 1 (LRP1). LRP1 is a receptor that binds lipid-conjugated apolipoprotein E (ApoE) and internalizes triglyceride-rich lipoproteins containing ApoE, such as chylomicron remnants and LDL remnant, thereby contributing to the clearance of chylomicron. The consumption of PTU will reduce the expression of LRP1 receptors, thereby increasing the LDL levels in the bloodstream.[17]

Lactoferrin promotes lipid absorption through the stimulation of bile acid synthesis. The lactoferrin pathway inhibits the production of TNF-α.[18] TNF-α is a proinflammatory cytokine that inhibits the expression of HNF4A.[19] HNF4A is a gene that activates the CYP7A1 enzyme.[20] The HNF4A gene makes instructions for making a protein, namely, hepatocyte nuclear factor-4 alpha.[21] This protein contributes to the development of the liver, kidney, and intestine; however, CYP7A1 is a catalyzed enzyme for converting cholesterol to bile acids.[22] By phosphorylating AMP-activated protein kinase (AMPK), lactoferrin serves as an agonist of AMPK, which is a protein that regulates energy homeostasis and coordinates metabolic pathways, thereby balancing nutrient supply with energy demand. Two enzymes (FAS and ACC) and genes (SERBP1) are controlled by AMPK.[23] SERBP1 is a mediator of hepatic lipogenesis, which is over-induced in obese animals; however, FAS and ACC are the key enzymes for lipid synthesis, and ATGL is the main enzyme for triglyceride degradation.[24–26] The supplementation of LF can decrease the expression of SERBP1, inhibit the protein expression of FAS and ACC, and elevate the protein expression of ATGL. Therefore, lactoferrin decreases lipid synthesis and increases the degradation of lipid in the liver.[23,27] These research results are consistent with a study conducted by Faridvand *et al.*, who stated that bovine lactoferrin can reduce lipid profiles such as total cholesterol and triglyceride levels in rats induced with a HCD. This lipid profile–lowering effect follows the role of lactoferrin as an antioxidant in inhibiting lipid synthesis in the body.[28] Nakamura *et al.* reported that lactoferrin could significantly reduce hepatic cholesterol levels in rats by increasing cholesterol excretion through interaction with bile acids.[9]

Our data showed that the decrease in total cholesterol and triglyceride levels was not consistent with the increase in lactoferrin dose. 200 mg/kg BW of lactoferrin had the lowest total cholesterol and triglyceride levels; thus, this dose was considered as optimal for decreasing total cholesterol and triglyceride levels. Nozari *et al.* also showed that 200 mg/kg BW of lactoferrin could reduce total cholesterol and triglyceride levels.[12] Hence, further research is recommended to ensure that 200 mg/kg BW is the optimal dose for lactoferrin in lowering total cholesterol and triglyceride levels. In addition, 400 mg/kg BW of lactoferrin had higher total cholesterol and triglyceride levels than the other doses. A high dose of lactoferrin can reduce cell proliferation by inhibiting the activation of extracellular signal-regulated kinase, releasing IL-8 cytokines, increasing NF-Kβ, and activating hypoxia-inducible factor-1α (HIF-1α).[29] Therefore, excessively high lactoferrin dose can increase the inflammatory effect, thereby promoting cholesterol synthesis.

A similar effect was found in microscopic analysis of the liver, where the steatosis area score was significantly lower in the group administered with lactoferrin compared with the HCD group. That is, lactoferrin could be a potential drug to prevent fatty liver. Lactoferrin also has an antioxidant effect, thereby preventing lipid accumulation in the liver. This condition indicates that activated Kupffer cells were significantly higher in the HCD group than in the lactoferrin treatment group. Activated Kupffer cell is a physiological response of the liver to injury or infection. High-fat diets can increase gut permeability and trigger the accumulation of lipopolysaccharides. The binding of LPS to their receptors on Kupffer cell surface promotes the production and secretion of cytokines that recruit T and B lymphocytes and other leukocytes; therefore, activated Kupffer cells can indicate dyslipidemia.[30] Recent studies have also shown that lactoferrin could treat fatty liver and serve as an antioxidant.[31]

Statin is a common class of drugs that reduce cholesterol levels in the blood. Their mechanism of action is primarily via the inhibition of HMG-CoA (hydroxymethylglutaryl-coenzyme-A) reductase, which is the enzyme responsible for the cholesterol biosynthetic pathway. Statin could lower LDL-c and reduce cardiovascular morbidity and mortality, in primary and secondary prevention; however, statin has some serious side effects. Statin toxicity or intolerance is commonly presented as statin-associated

muscle symptoms). Another side effects of statin therapy, which can be more serious, include new-onset type 2 diabetes mellitus, neurological and neurocognitive effects, hepatotoxicity, renal toxicity, and other conditions. Mechanistically, statin toxicity can arise because of HMG-CoA reductase inhibition effects, direct cellular and subcellular effects, or a combination of both. Other possible causes include genetic factors, drug–drug interactions, vitamin D status, and other metabolic or immune effects.[32]

This research still had some limitations from various aspects during the research process. Differences in the amount of normal feeding to rats were found among the groups, and not all food given using a probe could be swallowed completely by rats. The researchers could not assess the average total cholesterol and triglyceride levels before and after the intervention with lactoferrin. Therefore, further research is necessary to measure total cholesterol and triglyceride levels before and after intervention with lactoferrin.

CONCLUSIONS

Bovine lactoferrin could be used in treating patients with hyperlipidemia. In addition, 100, 200, and 400 mg/kg BW of lactoferrin could reduce total cholesterol and triglyceride levels to normal levels.

CONFLICT OF INTEREST

The author stated there is no conflict of interest.

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