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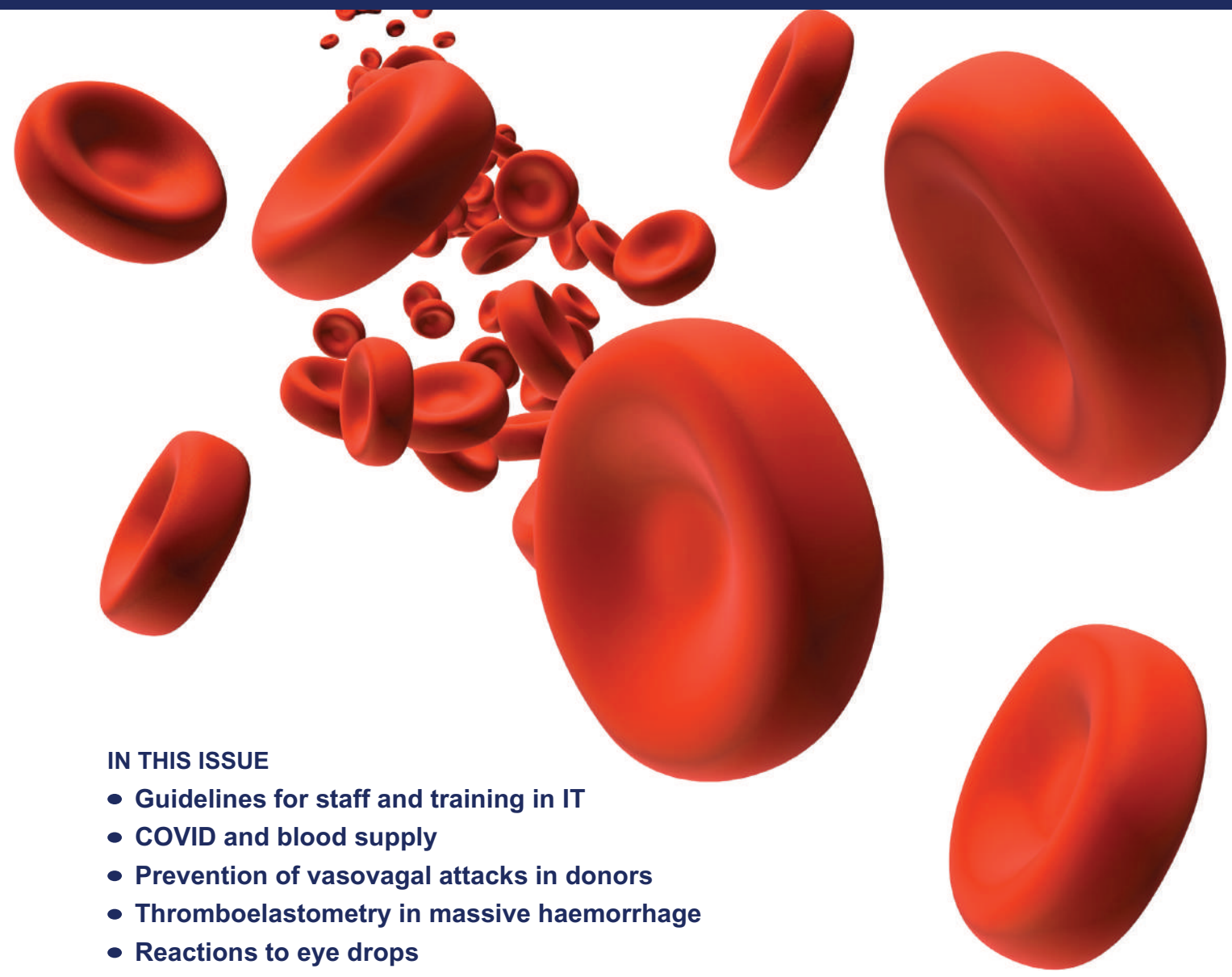

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Transfusion Medicine will publish articles on transfusion medicine in its widest context, including blood transfusion practice (blood procurement, pharmaceutical, clinical, scientific, computing and documentary aspects), immunohaematology, immunogenetics, histocompatibility, medico-legal applications, and related molecular biology and biotechnology.
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GUIDELINES

TRANSFUSION MEDICINE WILEY

SHOT UK Collaborative Reviewing and Reforming IT Processes in Transfusion (SCRIPT) survey: Laboratory information management systems: Are we ready for digital transformation?

Kerry Dowling [1,2] | **Jennifer Davies** [3] | **Shruthi Narayan** [4] | **Victoria Tuckley** [4,5] | **Chris Robbie** [6] | **Chris Ward** [7] | **Caroline Subramaniam** [8] | **Claire Whitham** [9] | **Tracey Tomlinson** [10] | **Georgia Stephens** [11] | **Anne Thomson** [12] | **Sinead Carty**[13] | **Anna Capps-Jenner** [14] | **Dan Willis** [15]

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1 | PURPOSE

Human T-cell leukaemia virus type 1 (HTLV-1) is a causative agent of human T-cell malignancy, adult T-cell leukaemia/lymphoma (ATL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP).1-3 The number of HTLV-1-infected individuals is estimated to be 10-20 million worldwide4 and over 1 million in Japan,5 and >95% of infected patients will remain asymptomatic throughout their lifetime. Therefore, asymptomatic HTLV-1 carriers could be at risk of becoming blood donors in Japan. Regarding the transfusion-transmission of HTLV-1.

2 | VISION

a serological test for all blood donors was mandated by the Japanese Red Cross Blood Centre (JRC) in 1986. At the same time, the JRC has permanently declined blood donation from HTLV-1-seropositive donors, and subse- quently, in 1999, a notification programme for

study and completed the questionnaire. The median age of the male and female respondents was 56.0 years (range 20-64 years) and 53.0 years (18-66 years), respectively (Table 1). Sixty (58.3%) of the 103 respondents accepted the notification of HTLV-1 infec- tion calmly and viewed the contents of the booklet favourably. Thirty-nine (37.9%) experienced anxiety and 5 (4.9%) experienced discomfort after being notified of their HTLV-1 infection status (Figure 1A). Forty donors answered that they had been aware of HTLV-1 before receiving the notification, and 17 (42.5%) of them had learned of HTLV-1 through maternity examinations and prena- tal (pre-mom) classes. Six (15.0%) had received the same notifica- tion at their previous blood donations. Two of the four responders who answered 'Other' revealed how they had learned about HTLV-1 (at school, n = 1; at their workplace, n = 1). Nine (22.5%) had received information on HTLV-1 from acquaintances and rela- tives, possibly reflecting the fact that this study was conducted in a highly endemic area (Figure 1B).

We obtained 154 answers from 80 donors about the information they needed. Forty-five (29.2%) requested knowledge about the transmission of the virus among family members and its prevention. Following that, 34 (22.1%) sought information about HTLV- 1-associated diseases, 33 (21.4%) sought information about available medical institutions and 19 (12.3%) and 12 (7.8%) sought information about the virus itself and experiences of other HTLV-1 carriers, respectively (Figure 1C). The most commonly used tools to obtain on-demand information were an Internet search engine (n = 33, 45.2%), followed by consulting an HTLV-1-specialised doctor at a medical institution (n = 20, 27.4%; Figure 1D).

In addition, we received 35 telephone inquiries, saying that the word 'HTLV-1' was unfamiliar and difficult to remember and pronounce for ordinary people or even the notification recipients. Therefore, when cre- ating a booklet, we chose 'HAD', as the easy-to-remember and easy-to- pronounce word; this was taken from JSHAD. Namely, 'HAD' is the abbreviation of 'HTLV-1 and associated diseases'.

We collected the latest information for the contents of the new information booklet to address the unmet needs of notification recipi- ents as follows: the virological and epidemiological aspects of HTLV-1 virus, the routes of infection, associated diseases, transmission and prevention of transmission in normal life among the family and in the workplace, and medical institutions to consult, along with comments from and experiences of other HTLV-1 carriers. A question-and-answer format that used easy-to-understand expressions was adopted, with technical terms eliminated when possible. The illustra- tions, which were drawn by an illustrator, an HTLV-1 carrier who had also learned about the infection after donating blood, were appropri- ately placed in order to promote understanding.

The new information booklet was reviewed by virologists, haematologists, neurologists, an ophthalmologist and a trans- fusionist, who were all authorities and experts in the field of HTLV-1. Considering the high rate of respondents who retrieved information using Internet search engines, we introduced the Ministry of Health, Labour and Welfare (MHLW) website, as well as a search map for medical institutions and attached a guide to con- sulting the HTLV-1-specialising medical institutions available in each prefecture in the Kyushu region.

As the most important issue for the improvement of the safety of blood products, we explicitly stated in the new information booklet that future blood donations from the notified recipients would be declined.The reviewed and revised information booklet (available at: https:// www.bs.jrc.or.jp/bc9/bbc/special/m6_05_04_index.html) has been distributed to the HTLV-1-seropositive donors since June 2019. A follow-up survey was conducted to assess the comprehension of the notification recipients and their status of HTLV-1 infection.For the follow-up survey, we distributed a questionnaire about the notification to 233 HTLV-1-seropositive blood donors, and 58 donors (male, n = 30; female, n = 28; 24.9%) replied. The median age of the male and female respondents was 56.0 years (range, 20-64 years) and 52.5 years (range, 24-64 years), respectively; and 19 (63.3%) of the male respondents and 16 (57.1%) of the female respondents were in their 50s (Table 2). Fifty-eight respondents reported 66 impressions of the new information booklet; 33 (50.0%) found it 'easy to understand', 11 (16.7%) found it 'useful' and 14 (21.2%) found it 'difficult to understand but still comprehensive', meaning that 87.9% of the respondents were able to gather the necessary information from the contents of the new information booklet (Figure 2). By attachment of the consultation guide for available medical institutions specialising in HTLV-1 con- sultation, seven of the nine introduced hospitals confirmed that they had outpatient visits from blood donors with an HTLV- 1-seropositive notification.

The first questionnaire survey revealed that 38.8% of respondents had been notified of their HTLV-1-seropositive status before their latest blood donation. After the distribution of the new information booklet, we investigated the change in the rate of repeating donors who had already received the notification of their HTLV-1-seropositive status at their previous donation.

To evaluate the utility of the new information booklet, we assessed the re-visiting rate of notified HTLV-1-seropositive donors from January 2017 to March 2021. Among 1383 HTLV-1- seropositive donors, 853 were identified before the distribution of the new information booklet. Among these 853 donors, 19 donations were made by 17 donors (1.99%) who had been noti- fied of their HTLV-1-seropositive status at their previous donation. Five recipients (0.59%) had re-visited for blood donation within 1 year after HTLV-1-seropositive notification. A total of 530 of 1383 received our new information booklet after the initiation of delivery in July 2019. Among these recipients, 310 were observed for more than 1 year, and none had re-visited for blood donation (Table 3).

3 | DUSCUSION

Japan is the only developed country where HTLV-1 is endemic.[4] In the Kyushu region, in particular, it was estimated that there were approximately 450 000 HTLV-1 carriers.[5]

The WHO reported that 37 countries conduct mandatory testing

of all blood donors for HTLV-1 and HTLV-2 and that seven countries conduct selective testing of new donors or donors who have not been previously tested.[6] It is a worldwide consensus in blood programmes that the notification and counselling of blood donors who show seropositive test results are important to blood safety; however, there are no fixed standards for either the regulatory requirements (legally prescribed criteria for notification) or the guidelines for notifying blood donors.[7,8] Notification of HTLV-positive blood donors was reported in Canada,[9] Australia[10] and the United States[11] in the 1990s. For example, in the UK,[12] notification recipients are asked to contact the blood service to arrange a discussion about their test results and onward clinical care. In Japan, this notification program started in 1999. The notification of healthy blood donors about seropositive test results can cause confusion, anxiety, and lack of understanding. In the recent report on health-related quality of life among blood donors who were notified viral infection, cases shown anxiety and depression had been 2.67-fold in HTLV carriers comparing to the control uninfected donors.[13] However, we have not adequately followed up the outcomes of notification.

In the present study, we defined the knowledge of HTLV-1 among notified blood donors and the unmet information needs according to the findings of a questionnaire. Taking the respondents' voice into consideration, we then created a new information booklet to provide the most necessary and up-to-date information in an easy-to-understand format. In the new information booklet, with the aim of improving health-related quality of life of the notification recipients, we included phrases to mitigate their anxiety, recommended early consultation to those with any symptoms, and listed the HTLV-1-specialised medical institutions for the consultation. In addition, we conducted a questionnaire survey to investigate the comprehension of recipients. In this survey, 90% of the respondents answered that the new information booklet was understandable, indicating that their knowledge had dramatically improved thanks to the contents, which coincided with the unmet needs of the notification recipients.

No HTLV-2-seropositive individuals have been confirmed among Japanese blood donors since the start of the notification program for HTLV-1-seropositive blood donors; thus, we did not mention HTLV-2 in the latest new information booklet. However, we might need to prepare an additional description about HTLV-2 in the future, as the first case of an HTLV-2-infected Japanese pregnant woman was recently reported.[14]

HTLV-1 antibody testing became mandatory in antenatal pregnancy screening throughout the nation in 2010. Simultaneously, the recommendation for mothers with positive results to refrain from breastfeeding was implemented for the prevention of mother-to-child transmission via breast milk. Following that, the MHLW of Japan collaborated in the production of the Japanese animation series, *Cells at Work!*, to conduct a public awareness campaign about HTLV-1 in 2018.[15] Enlightenment posters using popular comic book character have been distributed to health centres throughout Japan.

In our study, regarding the knowledge of HTLV-1, 17 recipients answered that they had learned about HTLV-1 in maternity examinations and prenatal (pre-mom) classes, suggesting that the education system for pregnant women had helped to spread knowledge about HTLV-1 in Japan; however, the efforts to disseminate knowledge regarding the ways to prevent horizontal transmission via transfusion remain insufficient.

Surprisingly, despite the receipt of a HTLV-1-seropositive notification following prior donations, 15% of respondents donated blood again. Five recipients had re-visited for blood donation within 1 year after seropositive notification, suggesting that we had not provided sufficiently useful information before the distribution of the new information booklet. Continuous blood donation by notified HTLV- 1-seropositive donors poses a risk to both the donor and patients, namely; a risk of an adverse effect of unnecessary blood collection for the donor and a risk of transfusion-transmission of the virus for patients. To reduce these risks, we clearly stated in the new information booklet that blood donation by those individuals would be refused. As a result, no repeated blood donations by recipients of the new information booklet were observed, indicating that appropriate presentation of information that addressed with the unmet needs of notified donors corrected their understanding of their HTLV-1 infection status and that blood donation would be declined.

In a study conducted among blood donors in India, donors were notified of their seropositive status in order to prevent transfusion-transmission of blood-borne infectious agents (TTIs).[16] A study in Thailand[17] showed that the behaviour of blood donors could be affected by providing a deeper knowledge about their HIV status, indicating that proper notification is necessary in order to prevent repeated blood donation. These investigations demonstrated thatm donor notification is an efficient method of curtailing TTIs, which is consistent with the results of our study.

Several limitations associated with the present study should be mentioned. First, the comprehension of recipients was evaluated by self-stated answers for the questionnaire, suggesting that the understanding might not have been sufficient. Second, recipients of the new information booklet could not be tracked for a long enough period to obtain an accurate evaluation of the re-visiting rate compared with before distribution. Third, there may have been some bias, as only 26.5% of recipients participated in this survey. Thus, recipients who did not send their answer sheet might have understood less than the participants. However, since no re-visiting donors were observed after the distribution of the new information booklet, the new infor- mation booklet might have improved their understanding of HTLV-1 infection.

We recently received an e-mail from a foreign student living in Kyushu, writing that his Japanese girlfriend had recently been notified that she was HTLV-1-seropositive and that he was strongly concerned about transmission through sexual intercourse. He was anxious to learn about infection routes and the frequency of HTLV-1 transmission, and he would like to visit a medical institution for consultation to HTLV-1-specialised doctors. A basic strategy for preventing TTIs is to notify and counsel infected blood donors. Although counselling of individuals infected with HTLV-1/2 has been recommended,[18] a nationwide consultation system has not yet been fully developed in Japan. The aforementioned international student wrote in his e-mail, 'Unfortunately I live in an HTLV-1 endemic area'. There is thus an urgent need to formulate nationally acceptable guide-

lines for the notification and follow-up of HTLV-1-seropositive individuals in health checks and to prevent the spread of HTLV-1, both domestically and abroad.

In this study, HTLV-1-seropositive blood donors expressed a strong wish for information about medical institutions capable of counselling HTLV-1 carriers. In response to our request, all nine certi- fied medical institutions in the Kyushu region accepted that the notifi- cation of HTLV-1 test results from the JRC would be regarded as a patient referral document and that recipients who visited the desig- nated medical institutions would be exempted from the additional fee for a first-time patient who presented no referral. Owing to the reduc- tion in the additional fee for consultation, the number of consultations for recipients of the new information booklet increased, and visits from those recipients were observed in seven of the nine designated medical institutions. In fact, visits from HTLV-1-seropositive donors increased 1.44-fold at the introduced medical institutions following the distribution of the new information booklets. The result indicated that the disclosure of available medical institutions and the reduction of medical expenses are effective measures for notified donors who are anxious about their status and who desire to visit appropriate medical institutions for consultation. The new information booklet was fruitful in two aspects: one was the facilitation of consultations of HTLV-1-seropositive notification recipients; the other was the deter- rent effect in relation to repeated donation by the recipients, leading to improvement of both the health-related quality of life of seroposi- tive blood donors and the safety of blood products.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

Hitomi Nakamura and Yasuko Sagara designed this study, analysed data, edited the information booklet and wrote this manuscript. Midori Yamamoto collected data. Atae Utsunomiya and Toshiki Watanabe reviewed the information booklet and supervised this manuscript. Masahiro Satake also reviewed the information booklet, supervised this study and supervised this manuscript. Kazuo Irita supervised this study.

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ORIGINAL ARTICLE

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Impact of the COVID-19 outbreak on blood supply in two large university hospitals

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Abstract

Objective: This study aimed to examine the relationship between the decrease in elective procedures and the need for blood donation during the novel coronavirus disease (COVID-19) pandemic at university hospitals.

Background: The COVID-19 pandemic has immensely impacted transfusion medicine. By cancelling elective surgery, the German government hoped to increase the available resources for patients infected with COVID-19, especially in intensive care units, and prevent the shortage of blood products.

Methods/Materials: Over 26 weeks, from the 3rd of February 2020 to the 2nd of August 2020, during the first phase of the pandemic, we assessed the number of crossmatches, blood group typing, use of donated blood, and case mix indices by retrospectively analysing data from two major university hospitals' information systems in Essen and Hamburg, Germany. Data were pooled, analysed, and compared with that of the same period in the previous year.

Results: Following the cessation of elective procedures, the number of requests for crossmatches and blood group typing significantly decreased in 2020 compared to that in 2019. However, the number of blood transfusions required was reduced to a lesser extent. The number of outpatient and inpatient cases significantly decreased, whereas the cases requiring transfusion decreased only.

Conclusion: During the initial phase of the pandemic, transfusion medicine, especially in large institutions, faced an almost unchanged high demand for donated blood. This should be considered regarding personnel and blood donation allocations. Therefore, we developed a monitoring system to display the availability of blood products in real-time. The quick and easy display of in-stock and expiring blood products can optimise the use of this valuable resource.

KEYWORDS
automated solutions, blood donors, COVID-19, laboratory testing, patient blood management

1 | INTRODUCTION

The coronavirus disease (COVID-19), first reported in December 2019 in Wuhan, Hubei province, China, is an virus caused disease leading to an acute respiratory pathology.[1,2] On January 7, 2020, the causative agent of this respiratory illness was identified as the novel severe acute respiratory syndrome COVID-19.[3] The first case in Germany was reported in Bavaria on January 27, 2020.[4] At that time, 4593 people had already been infected worldwide, and more than 100 had died from the viral infection.[5]

In Germany, the first two deaths were reported on March 8, 2020, and March 11, 2020, when the World Health Organisation (WHO) declared the disease a pandemic.[5,6] Twelve days later, the German government reacted to the increasing case numbers with drastic contact bans and severe restrictions on social gatherings. Infection numbers increased exponentially, and by this time, 18 610 people in Germany had been infected and 55 had died owing to COVID-19.[5]

The pathophysiology of COVID-19 manifests in a broad clinical spectrum, from an asymptomatic course to acute respiratory failure.[2] In 85%–90% of cases, contracting COVID-19 results in mild-to-moderate symptoms. In affected individuals, hospital treatment is usually not required; accordingly, anaemia or thrombocytopenia requiring transfusion is not expected. However, a severe clinical course from an acute respiratory distress syndrome (ARDS) to multi organ failure occurs in 10% of COVID-19 infected cases, and anaemia or thrombocytopenia requiring transfusion is more common.[7,8] As is common with other ribonucleic acid (RNA) viruses, the COVID 19 virus has adapted and evolved mutations. Over time, different variants of concern have been identified by the World Health Organisation.[9] The different variants have different characteristics in terms of transmissibility, clinical presentation and the effectiveness of detection methods and therapeutics. The first variant is Alpha variant. This variant was 43%–82% more transmissible than the previously existing variant. In addition, infection with this variant showed an increased case fatality rate.[10,11] In late 2020, a new variant, the beta variant, was reported. This also showed an increased risk of transmission and reduced neutralisation by monoclonal antibody therapy and convalescent plasma.[12]

As a result, some countries, such as Italy, quickly experienced high utilisation of intensive care beds and a large influx of patients requiring inpatient care.[13] This in turn led to a rapid overload of the healthcare system in several countries in early 2020. To prevent hospital overload, on March 13, 2020, the German Federal Ministry of Health urged hospitals to stop all elective procedures that were not medically urgent.[14] By taking this step, the Ministry of Health hoped to preserve resources for treating patients with COVID-19. It was feared that the pandemic could have a significant impact on blood donations and that there would be an increased need for donated blood for severely ill patients (e.g., cancer patients) and patients with COVID-19 infection.[15]

By drastically reducing elective surgeries at university hospitals, donated blood should have been needed less, thereby increasing its availability for patients with COVID-19. However, no studies have indicated that the measure at university hospitals actually led to the saving of blood products, and thus a potential drop in blood donations could be intercepted. The need for personnel in blood donation facilities and donated blood supply can be determined only with a better understanding of this relationship. Therefore, our study examined the relationship between the decrease in elective procedures and the need for blood donation during the COVID-19 pandemic at two exemplarily university hospitals.

2 | MATERIALS AND METHODS

2.1 | Study setting

This study was conducted at university hospitals in Essen and Hamburg, Germany. These are two maximum care hospitals that focus on the treatment of patients with haematological and cardiovascular pathologies.[16,17] At these hospitals, approximately 80% of platelet (PLT) transfusions occur in these two focus areas. The University Medical Centre Hamburg-Eppendorf treats approximately 497 000 patients annually and is the largest and most important healthcare provider in the northern region, with a population of approx. 2 million.[18,19] The University Hospital in Essen treats approximately 340 000 patients annually and plays an important role in healthcare provision in the Ruhr metropolitan area, which has a population of approx. 5 million.[20,21] In both hospitals, the Institute of Transfusion Medicine is responsible for blood products' planning, regulation, production, and delivery.

2.2 | Study design

The study was approved by the Institutional Ethics Committee of the Medical Faculty of the University Duisburg-Essen.

The data were collected at two department of transfusion medicine at Essen University Hospital and University Medical Centre Hamburg-Eppendorf which produce approximately 1% of all red blood cells (RBCs) and 4% of all PLT in Germany.[22]

This retrospective study investigated the number of packed RBC and PLT transfusions and requests for blood group typing and cross-matches during the first phase of the COVID-19 pandemic in Germany compared with the same period in 2019. Data acquisition started on February 3, 2020 (week 1), 1 week after the first confirmed case was reported in Germany. The study period lasted 26 weeks and ended on August 2, 2020 (week 26). At that time, the nationwide infection rate averaged fewer 1000 cases per day for 12 weeks. The following week, there was a significant increase in the number of cases, indicating the beginning of a new phase of the pandemic.[23]

The number of cross-match requests and blood group typing were determined using our laboratory information system. The total number of RBC and PLT transfusions was compiled from our laboratory information system. Additionally, a specific analysis was performed at the Clinic for Haematology and Stem Cell Transplantation,

Trauma Surgery, and Thoracic Surgery in Essen, as most blood products are transfused in these departments. In relation to the Essen site, 54.5% of all blood transfusions take place in the aforementioned departments of the university hospital.

The case mix index (CMI) for all clinical departments and institutes at the university hospitals were compiled from our hospital database. The CMI represents a comparative value and valuation value for the patient mix of a hospital and aims to represent the average severity of treated cases.[24,25]

Data of patients treated in hospitals were obtained from the central hospital database. The University Hospital Essen is a specialised centre for extracorporeal membrane oxygenation (ECMO) therapy in Metropole Ruhr. More than 42% of patients who were COVID-19-positive with ARDS were admitted from other hospitals for ECMO therapy.[26] Therefore, we analysed and compared ECMO cases in Essen between 2020 and 2019.

2.3 | Statistical analysis

The data were provided and analysed in Excel spreadsheets (Microsoft Office 2016, Microsoft Corp., Redmond). Statistical analyses and graphical representations were performed using the GraphPad Prism 8.4 (GraphPad Software, San Diego). Data were reported as the number of laboratory tests performed and blood products dispensed per week during the same study period in 2019 and 2020. For statistical comparisons between the periods an unpaired sample t-test was used. We calculated the CMI from the sum of all relative weights from the diagnosis-related groups (DRGs) and divided this result by the total number of treatment cases. The graphical representation was in the form of bar charts for 2019 and 2020. Data on the number of blood products administered during ECMO therapy were reported as the median with the associated confidence interval.

3 | RESULTS

The direction to stop elective procedures by the German government was adhered to by all institutes and departments of the investigated hospitals. Thus, from March 16, 2020 (the start of the seventh week of investigation), all non-urgent surgical procedures were postponed. This affected the overall operational caseload at both sites, particularly in March and April 2020. Table 1 shows the surgical case numbers of different specialties at University Hospital Essen. Only urgent medical procedures were performed at both sites. The reduction in elective cases led not only to a decrease in surgical cases at both hospitals but also to a significant decrease in the total number of outpatient and inpatient cases and bed utilisation (Table 2).

Due to the drop in caseload, we observed a dramatic year-on-year decline in crossmatch applications in our study in the following weeks, beginning in the seventh study week. However, the number of blood transfusions, especially of packed RBC and PLT, was reduced to a far lesser extent (Figure 1). Between weeks 7–10 of the study, we observed a significant decrease in crossmatch determination in both Essen (19%, $p < 0.0005$) and Hamburg (10%, $p < 0.05$) compared to the values in 2019. We observed an even greater decrease in both Essen (34%, $p < 0.0005$) and Hamburg (31%, $p < 0.0005$) in blood group determinations compared with the previous year. Despite the lower need for crossmatching and blood grouping, erythrocyte consumption at both hospitals did not decrease significantly (Essen, $p = 0.24$ and Hamburg, $p = 0.73$), and PLT consumption increased compared to the previous year during the study period (Figure 1). After 4 weeks, from April 13, 2020, scheduled procedures at the two clinics resumed after the number of COVID-19 infections in Germany showed a declining trend, and an overload on the healthcare system could be avoided. As the local incidence in Germany declined, elective procedures resumed from April 13, 2020 (start of study week 11), and there was a significant increase in case

TABLE 1 Operative case numbers at the Essen University Hospital in 2019 and 2020.

	General Surgery		Gynaecology		Neurosurgery		Cardiothoracic surgery		Trauma surgery[a]	
Month	2019	2020	2019	2020	2019	2020	2019	2020	2019	2020
January	546	412	680	579	398	340	288	217	589	572
February	361	388	378	328	260	304	213	203	417	478
March	390	336	392	267	324	251	207	164	425	428
April	425	291	634	392	305	225	209	141	490	413
May	394	267	385	301	327	261	215	160	501	464
June	367	351	321	303	258	295	181	192	458	508
July	444	378	643	594	358	308	195	203	576	451
August	370	387	386	342	315	314	216	162	533	471
September	356	371	269	300	326	333	197	195	490	504
October	376	326	439	582	317	329	179	202	512	467
November	364	324	360	322	304	224	195	159	482	421
December	277	258	263	237	264	220	146	151	451	395

[a]In trauma surgery, there was no change in the number of operative procedures in March and April 2020 compared with that in the same period in 2019.

TABLE 2 Inpatient and outpatient case numbers and bed utilisation in 2019 and 2020 in Essen.

	Inpatient case numbers Essen		Outpatient case numbers Essen		Bed utilisation rate Essen[a]	
Month	2019	2020	2019	2020	2019	2020
January	4469	4309	27 016	27 299	76.30	73.50
February	4345	4382	17 685	17 522	78.10	75.80
March	4585	3956	15 961	12 000	77.30	64.00
April	4361	3132	25 658	16 236	75.00	56.60
May	4655	3620	18 835	14 860	76.40	59.50
June	4324	3901	14 615	15 319	73.70	65.70
July	4865	4591	26 237	23 870	77.30	69.10
August	4769	4387	18 138	17 561	78.40	68.90
September	4482	4466	16 019	15 810	78.50	73.20
October	4659	4660	26 507	24 632	78.20	72.60
November	4511	4074	18 513	16 853	79.20	65.50
December	4305	3620	14 067	12 903	70.50	57.30

[a]The bed utilisation rate is shown as a percentage of all beds are occupied by patients.

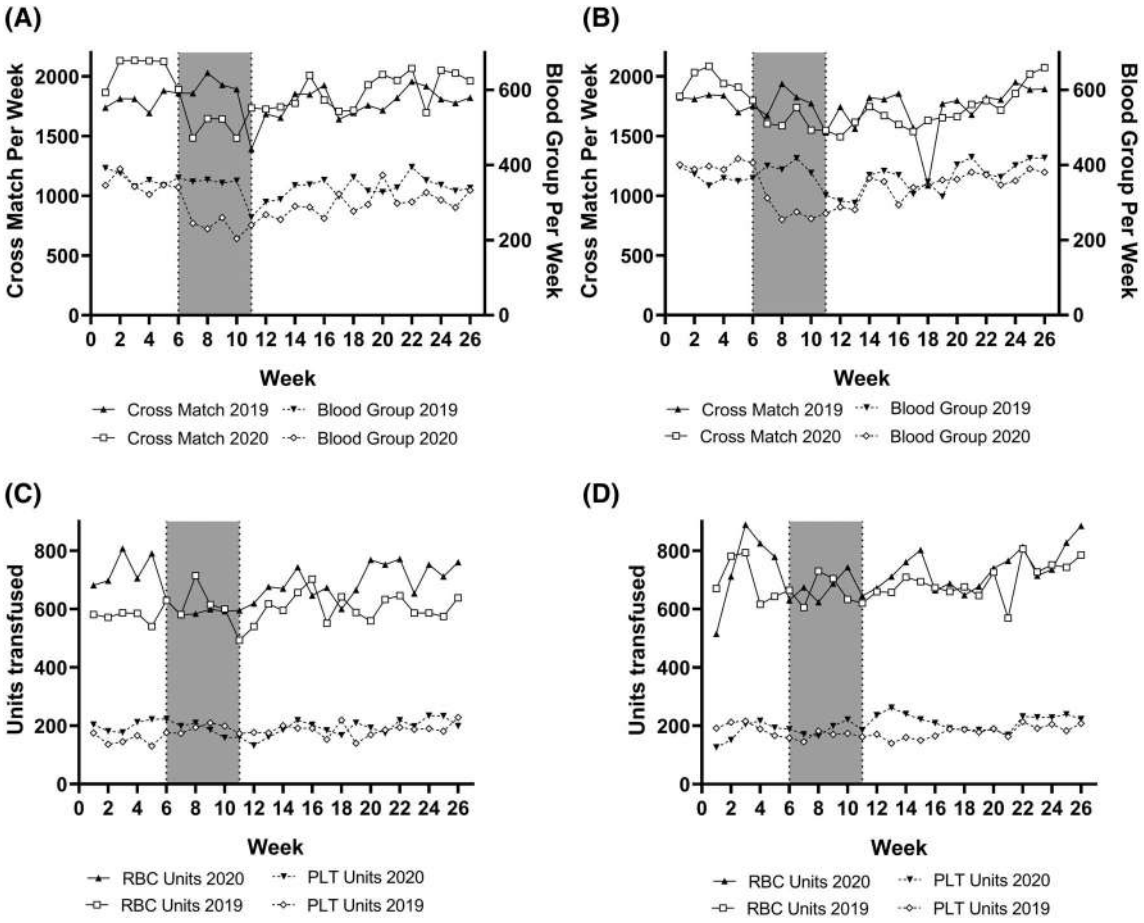

FIGURE 1 (A) Weekly crossmatch and blood group determinations over the period of 26 weeks at the Essen University Hospital and (B) at the University Medical Center Hamburg-Eppendorf. (C) Weekly transfused units of red blood cells (RBC) and platelets (PLT) at the Essen University Hospital and (D) at the University Medical Center Hamburg-Eppendorf. In the area highlighted in grey, the elective procedures were suspended and postponed.

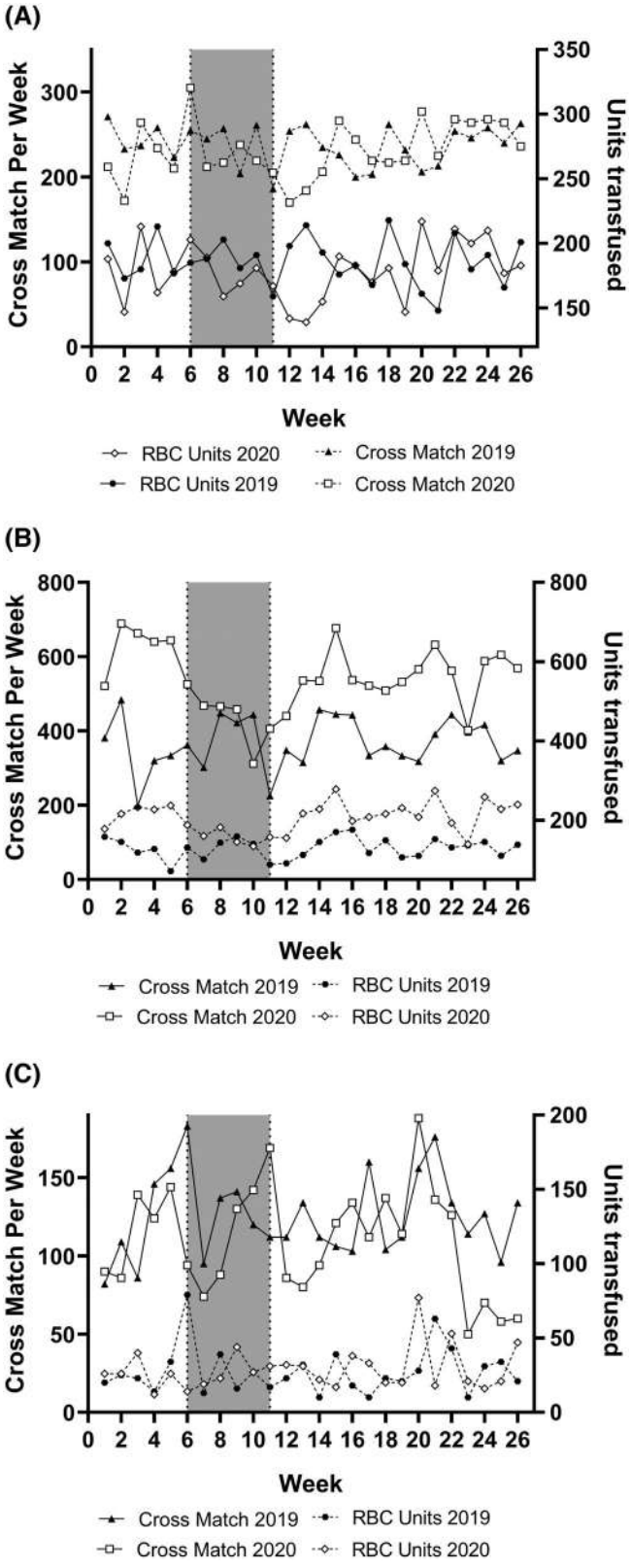

FIGURE 2 (A) Weekly crossmatch and blood group determinations over the period of 26 weeks in the Clinic for Haematology and stem cell transplantation at the Essen University Hospital, (B) in vascular surgery, and (C) in orthopaedic surgery. In the area highlighted in grey, the elective procedures were suspended and postponed.

numbers (Table 2). Weekly crossmatch determination was similar to that in the previous year. Moreover, there was an increase in the number of blood group determinations; however, this number was lower than that of the previous year. The number of transfused blood products was similar to that of before (study week 10), and RBC and PLT transfusions significantly increased compared to 2019.

To determine why blood product consumption hardly changed despite the cancellation of elective interventions, but the number of requests for crossmatch and blood grouping increased, a more detailed analysis was conducted in Essen for Haematology and Stem Cell Transplantation, thoracic surgery, and trauma surgery (Figure 2). Blood product consumption remained almost unchanged among the departments examined. The thoracic surgery department consumed more erythrocytes and PLT in the period under review than in the previous year.

To determine whether fewer severe and complex cases were treated at the two hospitals after the cessation of elective procedures compared to 2019, we examined the CMI of the two hospitals. In both Essen and Hamburg, the CMI increased in 2020 compared with 2019, even after elective procedures were stopped, despite lower numbers of inpatients, outpatients, and operative cases. (Table 3) During the study period, with the increasing number of COVID-19 cases in Germany, there was also an increased admission of patients with COVID-19 at both hospitals (data not shown). As Essen specialised as a centre for ECMO therapy for patients with ARDS and COVID-19 in the region, there was a significant increase in ECMO cases in 2020 compared to that in 2019 (Figure 3). In 2019, 75 patients required ECMO therapy. Of these, 71% were men and 29% were women and their average age was 54 years. In 2020, 295 patients underwent ECMO therapy. Of these, 67% were men and 33% were women. Their average age was 55 years. Blood products are highly consumed during ECMO.[27,28] In 2019, the median value of required units of RBCs for patients registered for ECMO treatment was 11 (0–170), for 2020 the median value was 12 (0–116). In 2019 the median value of required units of PLT was 1 (0–36) and for 2020 the median value was 0 (0–54; Figure 3). On average, there was no major difference in the number of blood products administered compared with that in the previous year; however, the consumption of blood products increased significantly owing to the increased number of ECMO cases. In summary, this study showed that the number of crossmatches and blood group determinations at both sites decreased significantly over a period of 4 weeks after the cessation of all elective procedures, but there was no significant difference in the consumption of blood products during the same period.

4 | DISCUSSION

Cessation of elective procedures at the hospitals in Germany led to a significant decrease in outpatients, inpatients, and surgical cases.[29,30] This was confirmed from our study (Table 2).

The COVID-19 pandemic had a major impact not only on the economic and social systems but also on the healthcare system, including

TABLE 3 Case Mix Index (CMI) and percentage change for the study period of 26 weeks at the University Hospitals of Essen and Hamburg for the years 2019 and 2020.

	CMI in Essen			CMI in Hamburg		
Examination weeks	2019	2020	Change [%]	2019	2020	Change [%]
1	1.297	1.434	9.55	1.613	1.599	−0.87
2	1.333	1.547	13.83	1.654	1.682	1.73
3	1.359	1.444	5.89	1.596	1.778	11.45
4	1.436	1.611	10.86	1.740	1.768	1.61
5	1.263	1.421	11.12	1.599	1.770	10.69
6	1.323	1.495	11.51	1.649	1.643	−0.36
7	1.298	1.690	23.20	1.652	1.729	4.65
8	1.346	1.457	7.62	1.792	2.111	17.83
9	1.390	1.612	13.77	1.779	2.057	15.61
10	1.321	1.639	19.40	1.719	1.785	3.84
11	1.303	1.830	28.80	1.552	1.992	28.33
12	1.237	1.514	18.30	1.908	2.034	6.60
13	1.374	1.479	7.10	1.478	2.004	35.57
14	1.430	1.664	14.06	1.776	2.075	16.86
15	1.200	1.506	20.32	1.533	1.698	10.77
16	1.324	1.429	7.35	1.737	1.859	7.05
17	1.331	1.371	2.92	1.584	1.797	13.46
18	1.355	1.440	5.90	1.565	1.789	14.35
19	1.361	1.421	4.22	1.696	1.906	12.38
20	1.446	1.207	−19.80	1.580	1.773	12.16
21	1.422	1.438	1.11	1.571	1.749	11.35
22	1.210	1.399	13.51	1.593	1.779	11.69
23	1.205	1.397	13.74	1.675	1.700	1.44
24	1.291	1.379	6.38	1.717	1.679	−2.21
25	1.284	1.261	−1.82	1.742	1.748	0.36
26	1.296	1.347	3.79	1.849	1.777	−3.88

on the supply of donated blood. Our study revealed a decrease in crossmatches and blood group requests during the first phase of the pandemic (Figure 1). However, at the same time, the consumption of packed RBCs and PLT did not change significantly. Compared with the previous year, there was only a slight decrease in the transfusion of RBCs and a modest increase in that of PLTs.

We observed this trend for 4 weeks after the elective procedures were stopped in hospitals. Table 1 shows that in the 4 weeks under review, the number of surgical cases decreased significantly. In January 2020, there was already a decrease in surgical cases compared to 2019. This was due to the fact that the first staff members fell ill with COVID-19 already in this month and thus some surgeries had to be cancelled. But also on the patient side, operations had to be cancelled because of the first COVID illnesses. However, the decrease in surgical cases was never more than 25% compared to the previous year. The effect of stopping elective surgeries is particularly evident in the months of March and April, where the decline was sometimes more than 50%. In the following months of May to June, the number of surgical cases still fell slightly, since, as is already known from the literature, many patients postponed operations or visited medical facilities less frequently for fear of contracting the virus. From July 2020 onwards, the number of cases increased slowly, as the first COVID-19 wave showed a decline and many patients resumed surgery appointments in the summer months. With the outbreak of the second COVID-19 wave at the end of 2020, the operative case numbers also decreased again from October 2020. Hardly any fluctuations can be seen in trauma surgery.

Reports from other hospitals tended to show a decrease in blood product use during the initial phase of the pandemic and after the suspension of elective procedures.[15,31–34] A study from Italy has reported that fewer blood products were needed during March to May 2020.[35] There was a restructuring of blood donation to ensure fewer preparations, and consequently, there was less wastage.

We assume that the continued increase in the proportion of transfused units during the study period correlated with the size of the hospital and its patient spectrum. Our study indicates that suspension of elective procedures at larger institutions had a limited impact on the use of donated blood (Figure 1). In our opinion, the continuous or even increased consumption of RBCs and PLT (Figure 2) reflects transfusion for patients in haematology, transplantation, and

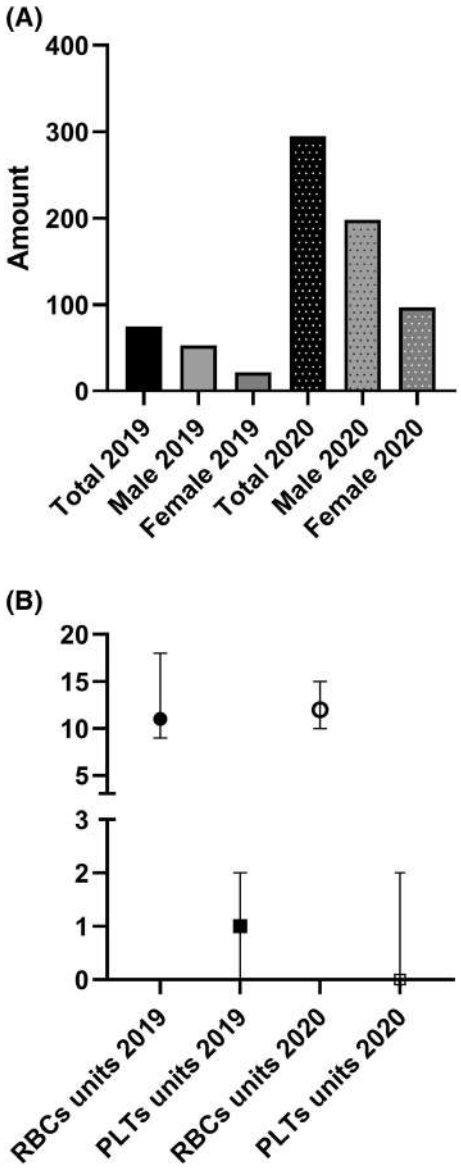

FIGURE 3 (A) Number of extracorporeal membrane oxygenation (ECMO) cases at Essen University Hospital in 2019 and 2020. (B) Plot of median value of red blood cell (RBC) and platelet (PLT) concentrate units required per ECMO case. In addition to the representation of the median value, a 95% confidence interval is also displayed.

cardiothoracic surgery; and for those who were severely ill with COVID-19 and in need of ECMO. In these scenarios, the ratio of transfusion-to-crossmatch was higher than that in elective surgery. We observe an increase in crossmatch requirements in Essen at the beginning of 2020 (Figure 1). There is a simple explanation for this. At the beginning of 2020, a new partner hospital with a large cardiothoracic surgery unit was added. This partner hospital was then also supplied by the blood donation centre of the university hospital from January 1, 2020. Consequently, the number of crossmatches has increased significantly with the new supply contract.

It is well known that in elective procedures, the amount of donated blood requested often exceeds the actual number of units transfused.[36–38] Thus, we interpret the decrease in crossmatches and blood group determination as a result of the suspension of elective surgeries.

Certainly, the consumption of blood products is impacted not only the patients who are chronically and acutely ill and treated at major hospitals during the pandemic, but also those who have COVID-19 infection and require ECMO therapy. ECMO treatment is sometimes necessary for patients who are critically ill with the COVID-19 infection and is associated with a higher bleeding tendency and an increased need for packed RBCs and PLT.[27,28] In our study, we were able to demonstrate that ECMO therapy is associated with a significantly increased need for erythrocyte and PLT preparations, independent of the COVID-19 infection (Figure 3). Consequently, the increase in the number of ECMO cases has increased the demand for blood products.

The CMI confirmed the assumption that large hospitals continued to treat critically ill and medically complex cases during the pandemic. This suggests that significantly more severe cases were treated in 2020 than in 2019, as the CMI indicates case severity and the high technical effort of treatments.[39] Especially in the 4 weeks after the stop of elective procedures, a significant increase of the CMI was shown in Essen as well as in Hamburg (Table 3). Therefore, a decrease in the number of laboratory tests cannot be explained by case severity.

Other countries had also ceased elective surgeries and medical procedures, with an associated decrease in blood transfusions.[15,33,40] We were unable to determine whether the decrease in elective procedures was associated with a significant decrease in the use of donated blood. However, we observed a significant decrease in the requests for blood group determination and cross-matches. This indicates that, even during the pandemic, seriously ill and medically complex cases were treated at large institutions. Thus, we conclude that during the COVID-19 pandemic, transfusion medicine, especially at large institutions, faces an unchanged demand for donated blood, which should be considered during personnel and blood donation allocations.

The cessation of elective procedures led to a reduction in laboratory requirements, and thus relief in the daily work of the staff, which was important in this period considering the increased sick leave among the staff due to contracting the COVID-19 infection. Considering the demographic changes and the relative shortage of blood donors leading to the shortage of stored blood products, in the future, even without a pandemic, the requirements of cross-matching should be handled in a more restrained manner, especially for scheduled surgeries.[41,42] This is because the lower rate of crossed RBC preparation implies that fewer products need to be stocked, and therefore potential discards can be reduced. In contrast to other studies, there was a continued high consumption of blood products at both sites. As a consequence, we developed an automated monitor, that allows real-time monitoring of stored blood products with a latency of less than 1 min. A simple graphical representation provides an overview of the available and patient-specific products. Quick and easy viewing of in-stock and expiring blood products can help optimise the management of this valuable resource. Further studies are required to determine the

extent to which this new automated technology can reduce blood product deterioration. This would be interesting from economic, medical, and ethical points of view, considering the possible shortage of blood products in the near future.[41,42]

This study had a few limitations. It was conducted in only two large maximum care hospitals. As previous reports from small hospitals tended to show a decrease in consumption, additional research should be conducted in larger hospitals to confirm our assumptions. Consumption and number of laboratory requests were similar at both sites. However, significantly more erythrocyte concentrates were produced at the Hamburg site than at Essen, which implies that the impact of new automated techniques, such as the one we developed, could differ between the sites. This influence was not investigated in our study and should be evaluated in future studies.

5 | CONCLUSIONS

By stopping elective admissions and interventions, the German government aimed to ease the burden on its healthcare system. This study shows that this has a limited impact on large hospitals that treat complex and critical cases regarding transfusion medicine. Although it was possible to reduce the number of laboratory requirements and thus, create some relief, the consumption of blood products in large institutions remained largely unchanged and presented the institutes of transfusion medicine with a major challenge regarding both the personnel and organisation during this period. These challenges will become even greater in the future owing to demographic changes and shortage of blood products, and the use of modern and automated techniques can be of great help in solving this problem.

AUTHOR CONTRIBUTIONS

Brieske CM, Temme C, Hiller J, and Goebel M contributed to the acquisition, analysis, and interpretation of the data. Peine S and Horn PA conceived and designed the study. All authors contributed to drafting the manuscript and critically revised it for intellectual content. All authors provided final approval for the version to be published.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

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Prevention strategies for vasovagal reaction in whole blood donors: A quadri-armed randomised control trial

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Abstract

Introduction

Vasovagal reaction (VVR) is a frequently encountered generalised donor adverse reaction, associated with donor deterrence towards future donation. Several mitigation strategies for prevention of VVR were tried but still not standardised. This quadri-armed randomised study evaluated the utility of water ingestion, applied muscle tension (AMT) and combination of both in preventing the VVR among blood donors.

Methods

A quadri-armed randomised controlled trial was performed on 4320 whole blood donors. Blood donors of 18-65 years of age were randomised into four groups based on the interventions performed i.e., control with no intervention (Group 1, n = 1081), water ingestion (Group 2, n = 1082), AMT (Group 3, n = 1070) and combined intervention (Group 4, n = 1087). VVR during and immediately after blood donation were observed along with assessment of risk factors in blood donors and the effectiveness of interventions were analysed.

Results

The incidence of VVR observed 1.6% in our study, with the highest occurrence in the control group (2.5%) and the lowest in the combined intervention group (0.9%). Multivariable logistic regression revealed that the control group donors faced a 1.38-fold greater risk of VVR compared to those receiving interventions (OR: 1.38, 95% CI: 1.10-1.75). Other risk factors included younger age (OR: 1.5, 95% CI: 1.05-2.17), first-time donation (OR: 5.7, 95% CI: 1.66-5.74), prior history of VVR (OR: 2.5, 95% CI: 10.4-101.52).

Discussion/Conclusion

The combined approach of water ingestion and AMT proved significantly more effective in VVR prevention compared to individual interventions.

KEYWORDS
Haemovigilance, blood, medicine, transfusion

1 | INTRODUCTION

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

Convalescent plasma (CP) is typically collected from donors with confirmed diagnosis of infection at least 2 weeks after recovery.[7] CP contains neutralising antibodies specific to the infectious agent but may also contain other immune modulators and clotting factors that can be fractionated out to produce hyperimmune-immunoglobulin (hIVIG).[8]

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918–1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | OBJECTIVE

To evaluate the evidence for the safety and effectiveness of using convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) to treat severe respiratory disease caused by coronaviruses or influenza.

3 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

3.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Science). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

3.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

3.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarification from trial authors where necessary.

3.4 | Risk of bias assessment

Two review authors (CK, AL, LJG, JS) independently assessed all eligible studies for risk of bias (ROB), using the Cochrane ROB tools. ROB1 for RCTs[14] and ROBINS-I for observational studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Reviewers who had worked on a trial (AL, LE) did not participate in ROB assessments for those studies.

Observational studies assessed as having "critical" ROB were not included in quantitative analyses.

3.5 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel-Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean difference (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

3.5.1 | Subgroup and sensitivity analysis

We subgrouped included trials by the type of respiratory infection.

We also subgrouped COVID-19 studies by their use of high titre or low titre/unselected plasma (see Appendix A3 in Data S1) in response to emerging research that highlighted the wide variability in CP titres used in practice.

We intended to undertake sensitivity analyses based on selection bias to examine evidence from 'low risk' studies only. However, this was not necessary for the RCTs as all included RCTs were assessed as low (or unclear) risk for mortality endpoints within this domain.

3.5.2 | *Post hoc* analysis of seropositivity

We performed a *post hoc* analysis of trials where there were sufficient data to assess the impact of SARS-CoV-2 antibody status at baseline due to emerging evidence of greater effectiveness of passive antibody therapy (monoclonal antibodies) for patients who are antibody negative at baseline.[21] Meta-regression for *post hoc* analysis of seropositivity was performed using the metafor[18] package in R.

4 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

4.1 | Study Characteristics

We identified 110 completed studies (Figure 1), including 30 RCTs (four for influenza, n = 578; and 26 for COVID-19 SARS-CoV-2, *n* = 18 204).[3,7,22-49] There were no RCTs or non-randomised controlled trials identified for MERS or SARS (SARS-CoV-1) (Appendix A Supplementary Table A1 in Data S1). We included 76 non-randomised studies (Appendix B in Data S1). Of these, eleven were controlled studies, of which only two were at less than "critical" ROB[50,51] (Appendix A Supplementary Table A2 in Data S1) We included 67 uncontrolled studies: 12 assessing influenza A; two on MERS-CoV; four on SARS-CoV, and 49 on COVID-19 (SARS-CoV-2).

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (*n* = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (*n* = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (*n* = 36/12575 pregnant women). Eight RCTs[22,24,30-33,36,44] did not report whether they included pregnant women.

4.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22-25,27-31,33-36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40-43,45] and one compared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

The comparators and baseline characteristics of participants in each of the thirty RCTs and two non-RCTs (retrospective observational studies)[50,51] within meta-analyses are summarised in Appendix A Table A1 in Data S1.

4.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3-A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which pre- vents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died
up to day 90 being assigned —1, people who were on MV at randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

Duration of viral detection was expressed as time (median IQR) to first negative test (2 RCTs).[23,36] One study,[25] reported the number of patients who had had two consecutive negative tests by day 30. See table A5 for viral detection data and table A6 for details of changes in viral loads.

4.4 | ROB in included studies

4.4.1 | RCTs (using Cochrane ROB1)

Nineteen RCTs were open-label, comparing CP to SoC, and were therefore assessed as having a high ROB for all outcomes except mortality, as knowledge of treatment allocation may have affected clinical decision-making. A summary of ROB judgements is available in Table A7 and Figure A1 in Data S1.

4.4.2 | Non-RCTs (using ROBINS-I)

Two non-RCTs[50,51] were assessed at serious RoB for selection bias and confounding at baseline. The remaining 9 studies[53-61] were at critical ROB due to baseline confounding or selection bias and were therefore not meta-analysed.

4.5 | Certainty of the evidence (GRADE)

Certainty of the evidence was GRADEd as very-low to high; primary reasons for downgrading were ROB and imprecision (wide confidence intervals and small sample size) (Tables A8-A11 in Data S1). We assessed publication bias through the generation of a funnel plot (Figure A2 in Data S1) for 30-day mortality in comparison 1, which suggests that some small studies have not been published. However, this was not significant enough to downgrade the certainty of the evidence because the analysis is dominated by two large, high-quality, and RCTs.

4.6 | Effect of the Intervention

See Table 1 for an overview of meta-analysed results.

4.6.1 | Comparison 1: CP versus SoC or biologically inactive placebo

Twenty RCTs and two retrospective studies assessed CP compared with SoC or a biologically inactive placebo.

All-cause mortality

30-day mortality data were available from 15 RCTs (30 days, 5 RCTs; 28 days, 9 RCTs; 21 days, 1 RCT) (Figure 2a); 90-day mortality data were available from 6 RCTs (56 days, 1 RCT; 60 days, 3 RCTs; 90 days, 2 RCTs) (Figure 2b).

Overall, CP did not reduce 30-day mortality (15 RCTs, n = 17 266; moderate-to-high certainty of evidence [Table A8 and footnotes in Data S1]) and there may be no effect on 90-day mortality (6 RCTs n = 3210; low certainty of evidence [Table A8]).

Two non-RCTs reported in-hospital mortality, and showed results consistent with the randomised evidence (2 studies, n = 436; very-low certainty evidence) (Figure A3A Table A8 in Data S1).

Improvement of clinical symptoms

Duration of NIV was reported in 4 studies (2 RCTs),[3,24,50,51] and duration of MV was reported by 11 studies (9 RCTs).[3,24,25,28-30,35,38,39,50,51] Two RCTs[27,31] reported any ventilatory support, but did not differentiate between MV, NIV, and passive oxygen support. One RCT[29] reported any ventilation, but also reported separately a composite outcome of patients who progressed to MV or death. Most studies reported the data as duration of support, either median (IQR) or mean (SD) (Table A4 in Data S1).

These outcomes were very variably reported, and many did not fully account for competing events, or report methods of analysis in

sufficient detail. Based on what was reported, there was no apparent difference in duration of MV, NIV or ECMO support between the two groups.

Length of stay (LOS): hospital and ICU

Length of hospital stay was reported by 16 RCTs[7,23,25-28,30,31,38,39,42-47] and 1 non-RCT,[51] and length of ICU stay was reported by 9 RCTs[23,26,28,29,33,39,43,45,47] (Table A3 in Data S1). There was no evidence of an effect in length of hospital stay or length of ICU stay (Table A3 in Data S1).

Duration of viral detection from admission up to 30 days (viraemia, nasopharyngeal swabs, bronchoalveolar lavage, stool)

The 3 RCTs which reported time to negative test do not suggest any evidence of an effect (Table A5 in Data S1).

Adverse events

AEs due to transfusion were reported in 15 RCTs[3,7,22-39] (Table S10 in Data S1).

Seven RCTs reported no Grade 3 or 4 AEs due to transfusion.[22,24,26,27,31,35,39] Both non-RCTs reported AEs due to transfusion. All but one RCT[26] had SoC comparators, and therefore no transfusion-related SAEs are reported for the control group. Group comparison was not possible; results are summarised in Table A12 of in Data S1.

There was no evidence of an effect on reported SAEs[3,23-31,35,36,39] (13 RCTs, n = 16 730, very-low certainty of evidence) (Figure A3B). Data were not available on SAEs in seven RCTs.[7,22,32-34,37,38]

See forest plots Figure A3 in Data S1 and GRADE profile Table A8 in Data S1 for further detail.

4.6.2 | Comparison 2: CP versus biologically active control (FFP or IVIG)

RCTS assessed CP compared to FFP[40-43,45] or IVIG[44]

All-cause mortality

There was insufficient evidence to say whether or not there is a difference between groups in all-cause mortality at up to 30 days (5 RCTs n = 700; very-low certainty evidence, Figure A4A in Data S1), or at up to 90 days (2 RCTs, n = 264; very-low certainty evidence Figure A4B in Data S1). See forest plots Figures A4A and A4B in Data S1 and GRADE profile Table A9 in Data S1 for further detail.

Adverse events

Six RCTs reported transfusion-related Grade 3 or 4 AEs.[40-45] Events were rare (~2%) with no clear evidence of a difference (6 RCTs, n = 716; very-low certainty evidence. [Figure A4C in Data S1]). Four RCTs[40-42,45] reported SAEs up to 30 days, showing no evidence of an effect, although the rate of SAEs seems very low, given the severity of disease in hospitalised individuals (4 RCTs, n = 523; low certainty evidence, Figure A4D in Data S1). See forest plots Figure A4 and GRADE profile Table A9 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV[40,43,45] and any ventilatory support[41] were reported as median (IQR) or mean (SD). Given the difficulties of dealing with competing events, and the small number of patients involved, it is very unclear if CP therapy had any effect on the duration of MV, NIV or ECMO support between the two groups. We have presented the data in Table A4 in Data S1 as reported by the individual studies.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.3 | Comparison 3: hyperimmune immunoglobulin versus control

Three assessed hIVIG compared with SoC or a biologically inactive placebo.

All-cause mortality

There was insufficient evidence to say whether or not there is an effect on mortality compared to control at up to 30 days (3 RCTs n = 392; very-low certainty evidence) (Table 1, Figure A5A, Table A10 in Data S1). There were no data for 90-day mortality.

Adverse events

Two RCTs reported transfusion-related AEs; neither reported any AEs due to transfusion in either group (2 RCTs, n = 84; very-low certainty evidence, Figure A5B in Data S1). Two RCTs reported SAES (2 RCTs n = 342; very-low certainty evidence. [Figure A5C in Data S1]). See forest plots Figure A5 and GRADE profile Table A10 in Data S1 for further detail.

Improvement of clinical symptoms

One RCT in influenza[48] reported on duration of MV and NIV. However, the data were presented using an ordinal scale that was not mappable to our outcomes or other trial results, and we were unable to extract the data.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.4 | Comparison 4: early CP versus deferred CP

One RCT assessed early CP compared to deferred CP.

All-cause mortality

There was insufficient evidence to say whether there is a difference in 30-day mortality between early CP and deferred CP (1 RCT n = 58; very-low certainty of evidence) (Figure A6 in Data S1). There were no data for 90-day mortality. See forest plots Figure A6 and GRADE profile Table A11 in Data S1 for further detail.

Adverse events

There were three Grade 3 or 4 transfusion-related AEs within 24 h, all in the early CP group: (1 RCT $n = 58$, very-low certainty evidence) (Table A12 in Data S1). SAEs were not reported. See forest plots and GRADE profile Table A11 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV and NIV was reported as median (IQR). We have presented the data in Table A4 in Data S1 as reported by the RCT. Both groups had similar duration of ventilatory support. It is unclear if the authors accounted for competing events.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.7 | Results from uncontrolled studies (for safety only)

We identified 73 non-randomised or uncontrolled studies [49 case reports or case series] that assessed the use of CP or hIVIG in respiratory viral infection and reported AEs: 12 in influenza A, 2 in MERS-CoV, and 4 in SARS-CoV-1, and 67 in SARS-CoV-2 (COVID-19). Of the influenza studies, 10 were from the 1918 to 1920 pandemic. Fifty-one studies reported that no AEs were observed (37/49 case reports or case series). Eighteen studies reported transfusion-related AEs, and four studies reported other SAEs. These data are presented in Appendix B in Data S1.

4.8 | Post hoc subgroup analysis: seropositivity at baseline

Three RCTs,[3,30,62] including the two largest, reported 30-day mortality for subgroups defined by seropositivity at baseline. These results are shown in Figure 3.

FIGURE 3 Subgrouped by seropositivity at baseline: RCTs reporting 30-day mortality for comparison 1 (CP compared to SoC or a biologically inactive placebo)

With almost all the information coming from the two large, high-quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a p-value of 0.20 with very little heterogeneity either within or between groups.

We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1).

5 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG.

5.1 | Main findings

We were able to meta-analyse 32 studies for our primary outcome of 30-day mortality (30 RCTs and 2 non-RCTs). We found little evidence of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre subgroup in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

Adverse events were variably reported. No RCTs reported a high number of transfusion-related AEs (proportion 0% to 5.67%[22-24,26,27,31,35,38,39,43,44,46,47]) (very-low to low certainty evidence). There was no evidence of an increase in harms com- pared with standard plasma.

5.2 | Quality (certainty) of the evidence

Where meta-analysis was possible, we used GRADE to assess our certainty in the result (Table 1). Certainty in the evidence was assessed as very-low to low certainty for all outcomes apart from mortality data in the comparison CP versus standard care.

Evidence was downgraded for serious ROB (lack of blinding, baseline imbalance, randomisation processes, missing data and unclear reporting of outcomes) and imprecision (wide confidence intervals around the effect estimate, and small sample sizes for the outcome of interest). Some of the sources of potential bias (such as patient and personnel blinding) would be hard to overcome in future trials due to the issues in finding an ethical control infusion: even saline is problematic, with the risk of volume overload, and ease with which it can be differentiated from plasma.

SAEs were also downgraded for inconsistency as the heterogeneity was significant between studies, this is likely to be due to the variation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

5.3 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evidence base, which are discussed more fully in the next section.

5.4 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough according to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA reference method. Since we conducted our first search, several variants of SARS-CoV-2 have arisen worldwide and may require much higher antibody titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

Similarly, between trials, there was heterogeneity of patient groups and severity of illness on admission to hospital (Table 1). The RCTs in COVID may not have used the same criteria to categorise trial participants at enrolment and trials designed to treat different patient groups based on comorbidities and immune states were absent. Several COVID-19 studies reported clinical improvement using the WHO ordinal scale. However, the scale was revised several times over the course of 2020-2021, going from an 8-point scale[70] to a 10-point scale at its latest revision[71] which have made comparisons between trials difficult.

The results of our post hoc subgroup analysis by seropositivity at baseline are very similar to the results reported by RECOVERY alone. We have not found stronger evidence of this potential interaction than that reported by RECOVERY (with a similar trend also reported by REMAP-CAP, especially for organ support-free days) but similarly, we have not found any reason to discount the possibility that there is a small but important interaction, with immunocompromised individuals potentially benefitting more. This hypothesis is consistent with the REGN-COV2 RECOVERY trial,[21] which has shown no benefit of monoclonal antibodies for seropositive patients who either have advanced disease or who are immunocompetent. The very high baseline risk of immunocompromised individuals might translate very small relative risks into substantial absolute risk differences. REMAP-CAP has recently reopened for immunocompromised people to test this hypothesis.[72]

5.5 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recipient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and report immunocompromised patients separately, to establish whether

certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40-43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

6 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

AUTHOR CONTRIBUTIONS

Catherine Kimber: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Abigail A. Lamikanra: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Louise J. Geneen: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Josie Sandercock: data extraction, risk of bias assessment, and undertook all metaregression analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Carolyn Doree: developed and performed all search strategies and de-duplication, retrieved full text publications, contributed to the development of the manuscript. Sarah J. Valk: screening and full text assessment, retrieved full text publications, contributed to the development of the manuscript. Lise J. Estcourt: developed the initial idea of the review, developed, wrote, and registered the protocol, interpreted the results, and contributed to the development of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Support- ing Information section at the end of this article.

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ORIGINAL ARTICLES

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Validation of the Sysmex XN analyser and Blood Bank mode for the quality and safety of donor blood and transfusion products

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Abstract

Objectives

Our objective was to compare the measurement of residual white blood cell (rWBC) and residual red blood cell (rRBC) counts in blood products using the XN Blood Bank mode and the laboratory standard operating procedures for manual counts. In addition, to compare the whole blood complete blood count (CBC) values of blood donors and the quality of blood products using the Sysmex XN analyser versus the XS-1000i analyser.

Materials and Methods

For blood donors, 190 samples from blood or apheresis donors were analysed on both the the red blood cell count (RBC), haemoglobin (HGB), haematocrit (HCT), the mean corpuscular volume (MCV), the platelet count (PLT). For blood products, 164 samples were collected: 13 Plasma products – whole blood, 9 Plasma products – apheresis, 36 RBC concentrates – whole blood, 30 PLT concentrates – buffy coats, 36 PLT concentrates – buffy coats – pooled and 55 PLT concentrates – apheresis.

Results

All CBC parameters of the blood donors tested showed similar performance, with excellent correlation coefficients (r) ranging from 0.821 to 0.995. meaning the number of rWBC and rRBC, if present, was below the limit of quantitation (LoQ) of the different methods. rWBC were detected by Blood Bank mode in Plasma products – whole blood with a mean rWBC of 0.012 × 109/L and in PLT concentrates – buffy coats with a mean rWBC of 0.19 × 109/L. The correlation coefficient in both analysers for all three parameters (HGB, HCT, RBC) in RBC concentrates – whole blood was excellent, ranging from 0.95 to 0.99. For platelet count, r ranged from 0.98 to 0.99.

Conclusion

The XN-Series analyser, equipped with a Blood Bank mode, demonstrated reliable performance when used for blood donor evaluation, rWBC

KEYWORDS

RBC; HGB; HCT; MCV; PLT; blood, medicine, transfusion

1 | INTRODUCTION

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

Convalescent plasma (CP) is typically collected from donors with confirmed diagnosis of infection at least 2 weeks after recovery.[7] CP contains neutralising antibodies specific to the infectious agent but may also contain other immune modulators and clotting factors that can be fractionated out to produce hyperimmune-immunoglobulin (hIVIG).[8]

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918–1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

2.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing stud- ies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Sci- ence). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

2.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

2.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these `publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarification from trial authors where necessary.

2.4 | Risk of bias assessment

Two review authors (CK, AL, LJG, JS) independently assessed all eligible studies for risk of bias (ROB), using the Cochrane ROB tools. ROB1 for RCTs[14] and ROBINS-I for observational studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Reviewers who had worked on a trial (AL, LE) did not participate in ROB assessments for those studies.

Observational studies assessed as having "critical" ROB were not included in quantitative analyses.

2.5 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel-Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean difference (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

2.5.1 | Subgroup and sensitivity analysis

We subgrouped included trials by the type of respiratory infection.

We also subgrouped COVID-19 studies by their use of high titre or low titre/unselected plasma (see Appendix A3 in Data S1) in response to emerging research that highlighted the wide variability in CP titres used in practice.

We intended to undertake sensitivity analyses based on selection bias to examine evidence from 'low risk' studies only. However, this was not necessary for the RCTs as all included RCTs were assessed as low (or unclear) risk for mortality endpoints within this domain.

2.5.2 | *Post hoc* analysis of seropositivity

We performed a *post hoc* analysis of trials where there were sufficient data to assess the impact of SARS-CoV-2 antibody status at baseline due to emerging evidence of greater effectiveness of passive antibody therapy (monoclonal antibodies) for patients who are antibody negative at baseline.[21] Meta-regression for *post hoc* analysis of sero- positivity was performed using the metafor[18] package in R.

3 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

3.1 | Study Characteristics

We identified 110 completed studies (Figure 1), including 30 RCTs (four for influenza, n = 578; and 26 for COVID-19 SARS-CoV-2, *n* = 18 204).[3,7,22-49] There were no RCTs or non-randomised controlled trials identified for MERS or SARS (SARS-CoV-1) (Appendix A Supplementary Table A1 in Data S1). We included 76 non-randomised studies (Appendix B in Data S1). Of these, eleven were controlled studies, of which only two were at less than "critical" ROB[50,51] (Appendix A Supplementary Table A2 in Data S1) We included 67 uncontrolled studies: 12 assessing influenza A; two on MERS-CoV; four on SARS-CoV, and 49 on COVID-19 (SARS-CoV-2).

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (*n* = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (*n* = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (*n* = 36/12575 pregnant women). Eight RCTs[22,24,30-33,36,44] did not report whether they included pregnant women.

3.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22-25,27-31,33-36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40-43,45] and one compared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

The comparators and baseline characteristics of participants in each of the thirty RCTs and two non-RCTs (retrospective observational studies)[50,51] within meta-analyses are summarised in Appendix A Table A1 in Data S1.

3.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality

and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3-A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which pre- vents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned —1, people who were on MV at randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

Duration of viral detection was expressed as time (median IQR) to first negative test (2 RCTs).[23,36] One study,[25] reported the number of patients who had had two consecutive negative tests by day 30. See table A5 for viral detection data and table A6 for details of changes in viral loads.

3.4 | ROB in included studies

3.4.1 | RCTs (using Cochrane ROB1)

Nineteen RCTs were open-label, comparing CP to SoC, and were therefore assessed as having a high ROB for all outcomes except mortality, as knowledge of treatment allocation may have affected clinical decision-making. A summary of ROB judgements is available in Table A7 and Figure A1 in Data S1.

3.4.2 | Non-RCTs (using ROBINS-I)

Two non-RCTs[50,51] were assessed at serious RoB for selection bias and confounding at baseline. The remaining 9 studies[53-61] were at critical ROB due to baseline confounding or selection bias and were therefore not meta-analysed.

3.5 | Certainty of the evidence (GRADE)

Certainty of the evidence was GRADEd as very-low to high; primary reasons for downgrading were ROB and imprecision (wide confidence intervals and small sample size) (Tables A8-A11 in Data S1). We assessed publication bias through the generation of a funnel plot (Figure A2 in Data S1) for 30-day mortality in comparison 1, which suggests that some small studies have not been published. However, this was not significant enough to downgrade the certainty of the evidence because the analysis is dominated by two large, high-quality, and RCTs.

3.6 | Effect of the Intervention

3.6.1 | Comparison 1: CP versus SoC or biologically inactive placebo

Twenty RCTs and two retrospective studies assessed CP compared with SoC or a biologically inactive placebo.

All-cause mortality

30-day mortality data were available from 15 RCTs (30 days, 5 RCTs; 28 days, 9 RCTs; 21 days, 1 RCT) (Figure 2a); 90-day mortality data were available from 6 RCTs (56 days, 1 RCT; 60 days, 3 RCTs; 90 days, 2 RCTs) (Figure 2b).

Overall, CP did not reduce 30-day mortality (15 RCTs, n = 17 266; moderate-to-high certainty of evidence [Table A8 and footnotes in Data S1]) and there may be no effect on 90-day mortality (6 RCTs $n = 3210$; low certainty of evidence [Table A8]).

Two non-RCTs reported in-hospital mortality, and showed results consistent with the randomised evidence (2 studies, $n = 436$; very-low certainty evidence) (Figure A3A Table A8 in Data S1).

Improvement of clinical symptoms

Duration of NIV was reported in 4 studies (2 RCTs),[3,24,50,51] and duration of MV was reported by 11 studies (9 RCTs).[3,24,25,28-30,35,38,39,50,51] Two RCTs[27,31] reported any ventilatory support, but did not differentiate between MV, NIV, and passive oxygen support. One RCT[29] reported any ventilation, but also reported separately a composite outcome of patients who progressed to MV or death. Most studies reported the data as duration of support, either median (IQR) or mean (SD) (Table A4 in Data S1).

These outcomes were very variably reported, and many did not fully account for competing events, or report methods of analysis in sufficient detail. Based on what was reported, there was no apparent difference in duration of MV, NIV or ECMO support between the two groups.

Length of stay (LOS): hospital and ICU

Length of hospital stay was reported by 16 RCTs[7,23,25-28,30,31,38,39,42-47] and 1 non-RCT,[51] and length of ICU stay was reported by 9 RCTs[23,26,28,29,33,39,43,45,47] (Table A3 in Data S1). There was no evidence of an effect in length of hospital stay or length of ICU stay (Table A3 in Data S1).

Duration of viral detection from admission up to 30 days (viraemia, nasopharyngeal swabs, bronchoalveolar lavage, stool)

The 3 RCTs which reported time to negative test do not suggest any evidence of an effect (Table A5 in Data S1).

Adverse events

AEs due to transfusion were reported in 15 RCTs[3,7,22-39] (Table S10 in Data S1).

Seven RCTs reported no Grade 3 or 4 AEs due to transfu-

sion.[22,24,26,27,31,35,39] Both non-RCTs reported AEs due to transfusion. All but one RCT[26] had SoC comparators, and therefore no transfusion-related SAEs are reported for the control group. Group comparison was not possible; results are summarised in Table A12 of in Data S1.

There was no evidence of an effect on reported SAEs[3,23-31,35,36,39] (13 RCTs, n = 16 730, very-low certainty of evidence) (Figure A3B). Data were not available on SAEs in seven RCTs.[7,22,32-34,37,38]

See forest plots Figure A3 in Data S1 and GRADE profile Table A8 in Data S1 for further detail.

3.6.2 | Comparison 2: CP versus biologically active control (FFP or IVIG)

RCTS assessed CP compared to FFP[40-43,45] or IVIG[44]

All-cause mortality

There was insufficient evidence to say whether or not there is a difference between groups in all-cause mortality at up to 30 days (5 RCTs n = 700; very-low certainty evidence, Figure A4A in Data S1), or at up to 90 days (2 RCTs, n = 264; very-low certainty evidence Figure A4B in Data S1). See forest plots Figures A4A and A4B in Data S1 and GRADE profile Table A9 in Data S1 for further detail.

Adverse events

Six RCTs reported transfusion-related Grade 3 or 4 AEs.[40-45] Events were rare (~2%) with no clear evidence of a difference (6 RCTs, n = 716; very-low certainty evidence. [Figure A4C in Data S1]). Four RCTs[40-42,45] reported SAEs up to 30 days, showing no evidence of an effect, although the rate of SAEs seems very low, given the severity of disease in hospitalised individuals (4 RCTs, n = 523; low certainty evidence, Figure A4D in Data S1). See forest plots Figure A4 and GRADE profile Table A9 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV[40,43,45] and any ventilatory support[41] were reported as median (IQR) or mean (SD). Given the difficulties of dealing with competing events, and the small number of patients involved, it is very unclear if CP therapy had any effect on the duration of MV, NIV or ECMO support between the two groups. We have presented the data in Table A4 in Data S1 as reported by the individual studies.

Data were not available for LOS (hospital or ICU), and duration of viral load.

3.6.3 | Comparison 3: hyperimmune immunoglobulin versus control

Three assessed hIVIG compared with SoC or a biologically inactive placebo.

All-cause mortality

There was insufficient evidence to say whether or not there is an effect on mortality compared to control at up to 30 days (3 RCTs n = 392; very-low certainty evidence) (Table 1, Figure A5A, Table A10 in Data S1). There were no data for 90-day mortality.

Adverse events

Two RCTs reported transfusion-related AEs; neither reported any AEs due to transfusion in either group (2 RCTs, n = 84; very-low certainty evidence, Figure A5B in Data S1). Two RCTs reported SAES (2 RCTs n = 342; very-low certainty evidence. [Figure A5C in Data S1]). See forest plots Figure A5 and GRADE profile Table A10 in Data S1 for further detail.

Improvement of clinical symptoms

One RCT in influenza[48] reported on duration of MV and NIV. However, the data were presented using an ordinal scale that was not mappable to our outcomes or other trial results, and we were unable to extract the data.

Data were not available for LOS (hospital or ICU), and duration of viral load.

3.6.4 | Comparison 4: early CP versus deferred CP

One RCT assessed early CP compared to deferred CP.

All-cause mortality

There was insufficient evidence to say whether there is a difference in 30-day mortality between early CP and deferred CP (1 RCT n = 58; very-low certainty of evidence) (Figure A6 in Data S1). There were no data for 90-day mortality. See forest plots Figure A6 and GRADE profile Table A11 in Data S1 for further detail.

Adverse events

There were three Grade 3 or 4 transfusion-related AEs within 24 h, all in the early CP group: (1 RCT n = 58, very-low certainty evidence) (Table A12 in Data S1). SAEs were not reported. See forest plots and GRADE profile Table A11 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV and NIV was reported as median (IQR). We have presented the data in Table A4 in Data S1 as reported by the RCT. Both groups had similar duration of ventilatory support. It is unclear if the authors accounted for competing events.

Data were not available for LOS (hospital or ICU), and duration of viral load.

3.7 | Results from uncontrolled studies (for safety only)

We identified 73 non-randomised or uncontrolled studies [49 case reports or case series] that assessed the use of CP or hIVIG in respiratory viral infection and reported AEs: 12 in influenza A, 2 in MERS-CoV, and 4 in SARS-CoV-1, and 67 in SARS-CoV-2 (COVID-19). Of the influenza studies, 10 were from the 1918 to 1920 pandemic. Fifty-one studies

reported that no AEs were observed (37/49 case reports or case series). Eighteen studies reported transfusion-related AEs, and four studies reported other SAEs. These data are presented in Appendix B in Data S1.

4 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG.

4.1 | Main findings

We were able to meta-analyse 32 studies for our primary outcome of 30-day mortality (30 RCTs and 2 non-RCTs). We found little evidence of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre sub- group in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

Adverse events were variably reported. No RCTs reported a high number of transfusion-related AEs (proportion 0% to 5.67%[22-24,26,27,31,35,38,39,43,44,46,47]) (very-low to low certainty evidence). There was no evidence of an increase in harms compared with standard plasma.

4.2 | Quality (certainty) of the evidence

Where meta-analysis was possible, we used GRADE to assess our cer- tainty in the result (Table 1). Certainty in the evidence was assessed as very-low to low certainty for all outcomes apart from mortality data in the comparison CP versus standard care.

Evidence was downgraded for serious ROB (lack of blinding, baseline imbalance, randomisation processes, missing data and unclear reporting of outcomes) and imprecision (wide confidence intervals around the effect estimate, and small sample sizes for the outcome of interest). Some of the sources of potential bias (such as patient and personnel blinding) would be hard to overcome in future trials due to the issues in finding an ethical control infusion: even saline is problem- atic, with the risk of volume overload, and ease with which it can be differentiated from plasma.

SAEs were also downgraded for inconsistency as the heterogene- ity was significant between studies, this is likely to be due to the vari- ation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

4.3 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evidence base, which are discussed more fully in the next section.

4.4 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many

ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough accord- ing to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA ref- erence method. Since we conducted our first search, several variants of SARS-CoV-2 have arisen worldwide and may require much higher anti- body titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

Similarly, between trials, there was heterogeneity of patient groups and severity of illness on admission to hospital (Table 1). The RCTs in COVID may not have used the same criteria to categorise trial partici- pants at enrolment and trials designed to treat different patient groups based on comorbidities and immune states were absent. Several COVID-19 studies reported clinical improvement using the WHO ordi- nal scale. However, the scale was revised several times over the course of 2020-2021, going from an 8-point scale[70] to a 10-point scale at its latest revision[71] which have made comparisons between trials difficult.

The results of our post hoc subgroup analysis by seropositivity at baseline are very similar to the results reported by RECOVERY alone. We have not found stronger evidence of this potential interaction than that reported by RECOVERY (with a similar trend also reported by REMAP-CAP, especially for organ support-free days) but similarly, we have not found any reason to discount the possibility that there is a small but important interaction, with immunocompromised individ- uals potentially benefitting more. This hypothesis is consistent with the REGN-COV2 RECOVERY trial,[21] which has shown no benefit of monoclonal antibodies for seropositive patients who either have advanced disease or who are immunocompetent. The very high base- line risk of immunocompromised individuals might translate very small relative risks into substantial absolute risk differences. REMAP-CAP has recently reopened for immunocompromised people to test this hypothesis.[72]

4.5 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recip- ient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40-43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

5 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

AUTHOR CONTRIBUTIONS

Catherine Kimber: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Abigail A. Lamikanra: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Louise J. Geneen: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Josie Sandercock: data

extraction, risk of bias assessment, and undertook all metaregression analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Carolyn Doree: developed and performed all search strategies and de-duplication, retrieved full text publications, contributed to the development of the manuscript. Sarah J. Valk: screening and full text assessment, retrieved full text publications, contributed to the development of the manuscript. Lise J. Estcourt: developed the initial idea of the review, developed, wrote, and registered the protocol, interpreted the results, and contributed to the development of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Support- ing Information section at the end of this article.

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SHORT COMMUNICATION

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Utility of rotational thromboelastometry in the management of massive haemorrhage at a regional Australian hospital

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Abstract

Background: Rotational thromboelastometry (ROTEM) allows targeted and individualised blood product replacement.

Objectives: The study aimed to determine the impact of ROTEM-guided transfusion on the clinical course of patients with acute massive haemorrhage in a regional Australian hospital.

Methods/Materials: A retrospective review of all patients with acute massive haemorrhage that compared the characteristics, blood product use, and clinical outcomes of patients with massive haemorrhage before and after the introduction of ROTEM-guided transfusion.

Results: In per-protocol analysis, the 31/97 (32%) with ROTEM-guided transfusion used less packed red blood cells (median [interquartile range]: 6 [6–8] vs. 8 [6–12] units, $p = 0.03$) than patients whose transfusion was not ROTEM-guided. They were also less likely to receive fresh frozen plasma (2/31 [6%] vs. 45/66 [68%], $p < 0.0001$) or platelets (2/31 [6%] vs. 31/66 [47%], $p < 0.0001$); they were, however, more likely to receive fibrinogen products (26/31 [84%] vs. 38/66 [58%], $p = 0.01$). Patients receiving ROTEM-guided transfusion had lower in-hospital mortality (6/31 [19%] vs. 20/66 [30%], odds ratio 0.55 [95% confidence interval]: 0.20–1.55, $p = 0.26$) although this did not achieve statistical significance in this small cohort.

Conclusion: ROTEM-guided massive transfusion of patients with acute haemorrhage in this regional Australian hospital led to a reduction in packed red blood cell, fresh frozen plasma, and platelet utilisation and may also have reduced mortality.

KEYWORDS
blood products, massive haemorrhage, massive transfusion, obstetrics, regional hospital, rotational thromboelastometry, surgery, trauma, viscoelastic haemostatic assays

1 | INTRODUCTION

Massive haemorrhage has a significant attributable morbidity and mortality and requires urgent blood product transfusion.[1,2] The decision to transfuse individual blood components is often guided by clinical judgement and traditional laboratory tests, however, both have limitations in emergent situations.[3] Transfusion protocols based on estimated blood loss in massive haemorrhage are not individualised

and therefore do not reliably correct coagulopathy.[4] Traditional coagulation tests such as platelet count, international normalised ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen level are unable to assess haemostasis as a whole and therefore may not be able to guide urgent clinical decisions.[5,6] In contrast, viscoelastic testing such as rotational thromboelastometry (ROTEM Sigma, Werfen, Spain) provides prompt, quantitative data on functional coagulopathy, allowing for targeted blood product replacement. In addition, treating clinicians can perform the ROTEM testing, reducing laboratory workloads and generating results in real-time that can guide transfusion of different blood products promptly.

A recent Cochrane review found transfusion guided by viscoelastic tests reduced mortality, morbidity, and blood product utilisation.[7] However, most of the data included in this meta-analysis came from elective cardiac surgery patients at referral centres; indeed, there are few studies that compare ROTEM and non-ROTEM-guided transfusion in massive haemorrhage outside of this patient population. Those that have examined patients from large metropolitan centres whose massive haemorrhage had a single, specific aetiology, such as trauma, post-partum haemorrhage, or chronic liver disease; these studies have had inconsistent results.[8–11] This study was therefore performed to determine if ROTEM-guided massive transfusion at a regional hospital reduced blood product utilisation and improved outcomes for patients presenting emergently with massive haemorrhage, whatever its aetiology.

2 | METHODS

The Far North Queensland Human Research Ethics Committee provided ethical approval for the retrospective study (EX/2022/QCH/90519) which was conducted at Cairns Hospital, a 676-bed hospital located in the state of Queensland in tropical Australia. The hospital is the main referral centre for a population of approximately 290 000 people who live across an area of 380 000 km^2. It has a 16-bed intensive care unit (ICU) and offers all major health specialties (medicine, surgery, women's health, paediatrics and mental health), but the hospital does not provide cardiac surgery, neurosurgery, or transplant surgery. The hospital has one ROTEM sigma machine which is located in the ICU, but all staff have access to real-time remote viewing of ROTEM results using any hospital computer.

We reviewed all cases of massive haemorrhage at the hospital from 1st July 2015 to 30th June 2017 (pre-ROTEM period) and 1st July 2019 to 30th June 2021 (post-ROTEM period). A 12-month period after the introduction of ROTEM service in December 2017 was excluded to ensure adequate hospital-wide education about ROTEM. Patients aged ≥18 years who received ≥10 units of packed red blood cells (PRBC) within 24 h or ≥four units of PRBC within 4 h for any cause of massive haemorrhage were eligible for inclusion.[8] Transfusion of blood products other than PRBC prior to hospital arrival or recurrent episodes of massive transfusion during a single hospital admission were exclusion criteria.

The patients' medical records were reviewed. Data on the patients' demographics, concurrent medication use, clinical presentation, baseline laboratory findings, therapeutic interventions, and clinical course were collected.

The massive transfusion protocol (MTP) was initiated at the discretion of treating clinician. Four units of PRBC were provided in the first pack of the MTP and clinicians were encouraged to utilise ROTEM to guide transfusion. Non-ROTEM-guided transfusion was performed due to ROTEM unavailability or clinician preference. It is local policy to administer 1 g tranexamic acid (TXA) intravenously over 10 min for obstetric patients or trauma patients within 3 h of injury, followed by continuous infusion of TXA 1 g over 8 h.[12]

For ROTEM-guided transfusion, the initial ROTEM was performed at MTP initiation, although transfusion was at the clinician's discretion at all times. All ROTEM tests were performed by the on-call ICU medical officer who then interpreted the results in a stepwise manner following an algorithm which was used widely in Queensland public hospitals, based on evidence collected in trauma and obstetrics patient (Appendix A).[13,14] The ICU medical officer informed the treating clinicians of the ROTEM interpretation results, and the treating clinicians were responsible for communicating with the blood bank to request the recommended blood products. Transfusion of all non-PRBC blood products transfusion was solely guided by the algorithm, with blood bank scientists only preparing the blood products when requested by the clinicians. The ROTEM test was repeated 10 min after transfusion of recommended blood products, after every four units of PRBC, or if there was ongoing bleeding.

For transfusion that was not ROTEM-guided, each subsequent pack included four units of PRBC and four units of FFP; One unit of pooled platelets was provided in every second pack starting from pack number two; 20 units of cryoprecipitate was available at the clinician's request from pack number two.

The study's primary outcome was the quantity of blood products used. Secondary outcomes included the total cost of blood products, duration of mechanical ventilation, ICU length of stay (LOS), hospital LOS, and in-hospital death. All patients with ROTEM performed were included in the intention-to-treat ROTEM-guided transfusion group. If the ROTEM algorithm was followed at all times, they were included in the per-protocol ROTEM-guided transfusion group.

3 | STATISTICS

Data were entered into a spreadsheet (Microsoft Excel) and analysed using statistical software (Stata 14.2). As many continuous variables had a non-parametric distribution they are presented as median with interquartile range (IQR). Groups were analysed using the Chi-square, Fisher's exact, or Kruskal–Wallis tests or logistic regression where appropriate. Outcomes were assessed using intention-to-treat and per-protocol analyses.

4 | RESULTS

There were 105 episodes of massive transfusion which satisfied the study's inclusion criteria, eight were excluded: in six (6%) non-PRBC

TABLE 1 Characteristics, admission physiology, and baseline therapy, by statistical analyses.

Variable	Intention to treat			Per protocol		
	Non ROTEM-guided $n = 42$	ROTEM-guided $n = 55$	p value	Non ROTEM-guided $n = 66$	ROTEM-guided $n = 31$	p value
Median age (IQR)	59 (36–73)	58 (40–68)	0.43	59 (39–69)	57 (35–67)	0.39
Male sex—no. (%)	31/42 (74%)	35/55 (64%)	0.29	42/66 (64%)	24/31 (77%)	0.18
Prior anti-coagulant use—no. (%)	4/42 (10%)	4/55 (7%)	0.72	6/66 (9%)	2/31 (6%)	1.0
Prior anti-platelet use—no. (%)	9/42 (21%)	14/55 (25%)	0.64	13/66 (20%)	10/31 (32%)	0.18
Admission characteristics						
Trauma patients—no. (%)	16/42 (38%)	17/55 (31%)	0.46	23/66 (35%)	10/31 (32%)	0.80
Vascular patients—no. (%)	12/42 (29%)	14/55 (25%)	0.73	17/66 (26%)	9/31 (29%)	0.73
GI bleed patients—no. (%)	12/42 (29%)	12/55 (22%)	0.45	19/66 (29%)	5/31 (16%)	0.21
ICU admission—no. (%)	32/42 (76%)	50/55 (91%)	0.047	52/66 (79%)	30/31 (97%)	0.03
Intubated and ventilated—no. (%)	25/32 (78%)	43/50 (86%)	0.36	44/52 (85%)	24/30 (80%)	0.59
Admission physiology						
Median APACHE III score (IQR)[a]	63 (45–74)	57 (41–86)	0.83	64 (44–86)	55 (38–77)	0.14
Median injury severity score (IQR)[b]	34 (16–43)	43 (25–57)	0.19	38 (16–50)	37 (25–52)	0.83
Median Hb (IQR)—g/L	109 (69–126)	99 (78–129)	0.86	99 (69–122)	104 (87–131)	0.19
Median INR (IQR)	1.3 (1.2–1.6)	1.2 (1.1–1.6)	0.59	1.3 (1.2–1.6)	1.2 (1.1–1.5)	0.33
Median aPTT (IQR)—sec	32 (28–42)	31 (27–37)	0.53	32 (28–39)	31 (26–38)	0.46
Median fibrinogen level (IQR)—g/L	2.4 (1.8–3.6)	2.2 (1.7–3.6)	0.48	2.4 (1.8–3.6)	2.2 (1.8–3.4)	0.76
ROTEM parameters[c]						
Median initial FIBTEM A5 (IQR)—mm	-	8 (5–13)	-	9 (4–14)	8 (5–13)	0.65
Median initial EXTEM A5 (IQR)—mm	-	43 (35–52)	-	40 (29–51)	45 (37–52)	0.14
Median initial EXTEM CT (IQR)—seconds	-	70 (61–83)	-	69 (59–92)	70 (62–80)	0.89
Baseline therapy						
Received prothrombin complex concentrate—no. (%)	3/42 (7%)	1/55 (2%)	0.31	4/66 (6%)	0/31 (0%)	0.30
Received tranexamic acid—no. (%)	24/42 (57%)	43/55 (78%)	0.03	46/66 (70%)	21/31 (68%)	0.85
Intervention within 24 h—no. (%)	36/42 (86%)	48/55 (87%)	0.82	58/66 (88%)	26/31 (84%)	0.75
Surgical intervention within 24 h—no. (%)	29/42 (69%)	40/55 (73%)	0.69	45/66 (68%)	24/31 (77%)	0.35

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; aPTT, activated partial thromboplastin time; GI, gastrointestinal; Hb, haemoglobin concentration; INR, international standardised ratio; IQR, interquartile range.

[a]APACHE III score calculated for ICU patients only.

[b]Injury severity score calculated for trauma patients only.

[c]There were 55 patients who had ROTEM analysis performed; 31 had all their blood product replacement guided by the ROTEM algorithm.

blood products were received prior to hospital arrival and two (2%) were a patient's second episode of massive transfusion within the same hospital admission. This left 97 in the final analysis, 36 from the pre-ROTEM and 61 patients from the post-ROTEM period. Six episodes of massive transfusion in the post-ROTEM period had non ROTEM-guided transfusion. In all six of these cases (three ruptured aortic aneurysms and three massive upper gastrointestinal haemorrhages) the attending clinicians felt that—as the patients were exsanguinating—there was insufficient time to wait for ROTEM results before commencing transfusion.

Of the 97, 33 (34%) were trauma patients, 25 (76%) of whom had blunt trauma. There were 26 (27%) vascular surgery patients, 22 (85%) of whom had emergency surgery. There were 24 (25%) patients with gastrointestinal bleeding: seven (29%) had oesophageal variceal bleeds and six (25%) had peptic ulcer disease. There were six (6%) obstetric patients, five (83%) were post-partum haemorrhages. There were eight massive haemorrhage episodes related to miscellaneous medical and surgical conditions. Primary and secondary outcome data were available for all patients.

4.1 | Intention-to-treat analysis

The baseline characteristics of two groups were similar, although there was a greater use of TXA and a higher ICU admission rate - although a similar rate of mechanical ventilation - in the ROTEM-

TABLE 2 Primary and secondary outcomes (intention-to-treat analysis).

	Not ROTEM-guided $n = 42$	ROTEM-guided $n = 55$	p value
Primary outcomes			
Median PRBC transfused at 24 h (IQR)—unit	7 (6–12)	7 (6–10)	0.67
Received platelets—no. (%)	19/42 (45%)	14/55 (25%)	0.04
Median platelets transfused at 24 h (IQR)—unit	0 (0–1)	0 (0–1)	0.04
Received FFP—no. (%)	34/42 (81%)	13/55 (24%)	<0.0001
Median FFP transfused at 24 h (IQR)—unit	4 (2–7)	0 (0–0)	0.0001
Received fibrinogen products—no. (%)[a]	17/42 (40%)	47/55 (85%)	<0.0001
Median cryoprecipitate transfused at 24 h (IQR)—unit	0 (0–10)	20 (10–20)	0.0001
Median equivalent dose of fibrinogen transfused at 24 h (IQR)—gram	0 (0–4)	9 (8–12)	0.0001
Secondary outcomes			
Median cost of total blood product used (IQR)—AUD	4321 (2935–9283)	6327 (5200–9754)	0.02
Mortality in hospital—no. (%)	11/42 (26%)	15/55 (27%)	0.91
Median ICU LOS in survivors (IQR)—days	2.5 (1.3–5.5)	1.6 (0.7–7.8)	0.53
Median hospital LOS in survivors (IQR)—days	11.9 (6.7–29.0)	9.3 (5.5–19.0)	0.48
Median ventilator duration in survivors (IQR)—hours	39 (13–87)	23 (12–158)	0.89

Abbreviations: FFP, fresh frozen plasma; IQR, interquartile range; LOS, length of stay; PRBC, packed red blood cell.
[a]Fibrinogen products include RiaSTAP (human fibrinogen concentrate) and cryoprecipitate.

TABLE 3 Primary and secondary outcomes (per protocol analysis).

	Not ROTEM-guided $n = 66$	ROTEM-guided $n = 31$	p value
Primary outcomes			
Median PRBC transfused at 24 h (IQR)—unit	8 (6–12)	6 (6–8)	0.03
Received platelets—no. (%)	31/66 (47%)	2/31 (6%)	<0.0001
Median platelets transfused at 24 h (IQR)—unit	0 (0–1)	0 (0–0)	0.0001
Received FFP—no. (%)	45/66 (68%)	2/31 (6%)	<0.0001
Median FFP transfused at 24 h (IQR)—unit	4 (0–6)	0 (0–0)	0.0001
Received fibrinogen products—no. (%)[a]	38/66 (58%)	26/31 (84%)	0.01
Median cryoprecipitate transfused at 24 h (IQR)—unit	10 (0–20)	20 (10–20)	0.048
Median equivalent dose of fibrinogen transfused at 24 h (IQR)—gram	4 (0–9)	9 (6–9)	0.02
Secondary outcomes			
Median cost of total blood product used (IQR)—AUD	6165 (3116–11 634)	5500 (5200–7436)	0.65
Mortality in hospital—no. (%)	20/66 (30%)	6/31 (19%)	0.33
Median ICU LOS in survivors (IQR)—days	2.7 (1.1–6.7)	1.5 (0.6–8.4)	0.29
Median hospital LOS in survivors (IQR)—days	10.1 (6.7–23.7)	8.9 (5.6–19.9)	0.77
Median ventilator duration in survivors (IQR)—hours	44 (15–98)	15 (10–165)	0.44

Abbreviations: FFP, fresh frozen plasma; IQR, interquartile range; LOS, length of stay; PRBC, packed red blood cell.
[a]Fibrinogen products include RiaSTAP (human fibrinogen concentrate) and cryoprecipitate.

guided transfusion group (Table 1). The ROTEM-guided group were less likely to receive platelets and FFP but were more likely to receive fibrinogen products. The median units of PRBC transfused within 24 h was similar (Table 2).

4.2 | Per-protocol analysis

The baseline characteristics of two groups were similar. There was a higher ICU admission rate, however the rate of TXA use was similar (Table 1). The ROTEM-guided group received less PRBC, platelets, and FFP, but more fibrinogen products (Table 3).

Patients receiving ROTEM-guided transfusion had lower in-hospital mortality (6/31 [19%] vs. 20/66 [30%], odds ratio 0.55 [95% confidence interval]: 0.20–1.55, $p = 0.26$). Patients receiving ROTEM-guided transfusion had shorter ICU and hospital LOS, a shorter duration of mechanical ventilation, and a lower total cost of transfused blood products than patients in the non-ROTEM-guided group, however these differences did not reach statistical significance in this small sample (Table 3).

5 | DISCUSSION

Meta-analyses suggest that transfusion guided by viscoelastic tests significantly reduces mortality, morbidity, and blood product use,[7] however these studies have been performed predominantly in patients having elective cardiac surgery in referral centres. There is an urgent need for studies that evaluate ROTEM-guided transfusion in other patient populations. Our study—performed in a diverse population of patients presenting acutely with massive haemorrhage to a regional Australian hospital—demonstrated that ROTEM-guided massive transfusion was associated with a significant reduction in PRBC, FFP, and platelet utilisation. Patients receiving ROTEM-guided massive transfusion also had a lower mortality rate than those receiving non-ROTEM-guided transfusion. Although not statistically significant in this small sample, the reduction in mortality was similar to that reported in meta-analysis (odds ratio 0.55 in this cohort vs. 0.52 in the meta-analysis) suggesting that there may also be clinical benefit of ROTEM-guided transfusion beyond blood product conservation in this patient population.

There are significant benefits to blood product conservation in regional settings. The short shelf life of certain blood products (particularly platelets), poses a significant challenge to blood inventory management outside of tertiary settings.[15] This is particularly germane in countries like Australia, where there are frequently vast distances between central and regional laboratories. There is no other source for blood products within a 400 km radius of Cairns Hospital, the setting for this study, and the delivery time for blood products ranges between 12 and 24 h. In addition, Cairns Hospital laboratory has a maximum of five pooled platelets at any time.

Although there was a significant difference in blood product utilisation, the total financial cost of blood products used were similar, as relatively expensive fibrinogen products were used more in ROTEM-guided transfusion, a function of the algorithm that is presently used in Queensland hospitals. The ROTEM algorithm that is currently employed in Cairns Hospital was devised in 2017, however, since 2018 the fibrinogen content of apheresis cryoprecipitate has increased from approximately 800 to 1012 mg/unit, an increase which is explained by the increase in the average volume of plasma collected for cryoprecipitate manufacture from 697 to 870 mL (personal communication, Dr James Daly, Australian Red Cross Lifeblood). In step 2 of the algorithm—the fibrinogen assessment—patients can receive either cryoprecipitate or fibrinogen concentrate (Appendix A). Therefore after 2018, the patients receiving apheresis derived cryoprecipitate in our cohort would have received more fibrinogen. Furthermore, the cost per gram of fibrinogen is likely to have been lower in patients receiving apheresis derived cryoprecipitate than those receiving whole blood derived cryoprecipitate or concentrated fibrinogen from commercial products (Appendix B). It is likely that future iterations of the ROTEM algorithm used in Queensland hospitals will take the increase in fibrinogen content of apheresis derived cryoprecipitate into consideration, and this may further reduce the costs of ROTEM-guided transfusion.

This is only the second study, to our knowledge, to examine the utility of ROTEM-guided transfusion for acute massive haemorrhage in a regional setting. Our findings were similar to those of an Indian series, which compared ROTEM-guided transfusion for acute massive haemorrhage due to trauma, surgery, postpartum haemorrhage and snake bite with standard care.[16] There were 122 patients in this Indian study, 61 in each arm. Patients having ROTEM-guided transfusion had a significant reduction in PRBC, FFP, and platelet utilisation and a shorter hospital stay. The investigators reported that there was no statistical difference in mortality between the two arms, although the raw mortality data were not presented and their study, like ours, may have been underpowered to detect a difference.

Indeed, the small sample size is a significant limitation of this study as it increases the risk of type two statistical errors which may underestimate the benefit of ROTEM-guided transfusion. In this context it is notable that the scale of the salutary effects on mortality and length of stay observed in our series were similar to those reported in a large meta-analysis.[7] Another limitation is the fact that ROTEM was introduced to the hospital in December 2017, later in the study period, during a time of evolving ICU capacity and growing understanding of general critical care and transfusion strategies and this may have influenced our findings. Future larger studies might examine how ROTEM, and evolution of patient management algorithms, can further refine transfusion strategies to reduce blood product use and unnecessary costs while also improving patient outcomes. It is likely that the ROTEM algorithm will evolve with greater understanding of the pathophysiology of massive haemorrhage, its response to therapeutic interventions and changes in blood product management and storage.

In conclusion, ROTEM-guided transfusion of patients presenting emergently with massive haemorrhage in this regional Australian

hospital reduced the utilisation of PRBCs, FFP and platelets. These patients also had a lower overall mortality. ROTEM-guided transfusion may have particular utility in rural and remote locations where access to blood products may be limited. It also appears likely that, as in elective cardiac surgery patients, ROTEM-guided transfusion has beneficial effects on the clinical course of patients with acute haemorrhage due to other causes.

AUTHOR CONTRIBUTIONS

Conceptualization: Y-H.L., A.M., H.L.L, J.S, C.T. Methodology: Y-H.L., A.M., C.T., J.H. Formal analysis: J.H. Investigation: Y-H.L., J.S, A.M., K.S, H.L.L, C.T., J.H. Data curation: Y-H.L., J.S, A.M., K.S, H.L.L, C.T., J.H. Writing–original draft preparation: Y-H.L. Writing–review and editing: Y-H.L, A.M., C.T., J.H. Visualization: Y-H.L, A.M., C.T., J.H. Supervision: A.M., C.T., J.H. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

PATIENT CONSENT

As the study was retrospective and the patient data were de-identified the Ethics Committee waived the requirement for informed consent from the patients.

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APPENDIX A: ROTEM RESULT INTERPRETATION ALGORITHM*

Step one—Hyperfibrinolysis assessment

- Early diagnosis: If FIBTEM clotting time (CT) > 600 s and EXTEM A5 < 35 mm, then administer tranexamic acid (TXA) 1 g and fibrinogen concentrate (RiaSTAP) 4 g.
- Late diagnosis: If FIBTEM maximum lysis (ML) > 5% or EXTEM ML > 5%, then administer TXA 1 g.

*The ROTEM result interpretation algorithm was initially published in 2016 by Winearls et al. and utilised in the Gold Coast University Hospital. The algorithm is now used widely in public hospitals in Queensland to interpret ROTEM results.

Step two—Fibrinogen assessment

- If FIBTEM A5 ≤ 8 mm (or ≤10 mm in obstetric patients), then administer 20 units of cryoprecipitate or fibrinogen concentrate 1 g per 25 kg of total body weight at clinician's discretion.
- If FIBTEM A5 ≤ 10 mm (or ≤12 mm in obstetric patients), then administer 20 units of cryoprecipitate.

Step three—Platelet assessment

- If FIBTEM A5 > 10 mm and EXTEM A5 < 35 mm, then administer one pooled platelet.

Step four—Clotting factors assessment

- If FIBTEM A5 > 10 mm and EXTEM CT > 90 s, then administer four units of fresh frozen plasma or prothrombin complex concentrate 12.5 units per kg of total body weight at clinician's discretion.

APPENDIX B

In step 2 of the algorithm—the fibrinogen assessment—patients can receive either cryoprecipitate or fibrinogen concentrate. After 2018, the amount of fibrinogen in apheresis derived cryoprecipitate increased meaning that after this date patients would have received more fibrinogen. Furthermore, the cost per gram of fibrinogen would have been lower than the other options as the following example shows:

We have chosen 2021, as this was the end of the study and allows us to determine the mean fibrinogen concentration in each of the replacement options and their cost that year.

If a hypothetical 100 kg patient received fibrinogen replacement as per the ROTEM algorithm in 2021 (Appendix A), he/she would receive 1 of 3 fibrinogen replacement options:

1. 20 U of whole blood derived cryoprecipitate with a mean—in 2021—of 396 mg fibrinogen and a cost—in 2021—of $167.33/unit.

   In this case the patient would receive 7.9 g of Fibrinogen at a total cost of $3347.
   Cost per gram of fibrinogen: $424.

2. 10 U of apheresis derived cryoprecipitate with a mean—in 2021—of 1185 mg fibrinogen and a cost—in 2021—of $328.55/unit.

   In this case the patient would receive 12 g of Fibrinogen at a total cost of $3286.
   Cost per gram of fibrinogen: $274.

3. 1 g/25 kg of fibrinogen concentrate, with a cost—in 2021—of $925.05/unit.

   In this case the patient would receive 4 g of Fibrinogen at a total cost of $3700.
   Cost per gram of fibrinogen: $925.

(Note: whole blood derived cryoprecipitate and apheresis derived cryoprecipitate were delivered as a fixed dose in Cairns Hospital during the study period, while the Fibrinogen concentrate was delivered as 1 g per 25 kg body weight. The cost per gram of fibrinogen would clearly vary with the weight of the patient).

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CASE STUDY

TRANSFUSION MEDICINE WILEY

Validation of the Sysmex XN analyser and Blood Bank mode for the quality and safety of donor blood and transfusion products

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Abstract

Background

Rh is one of the most important blood group systems in transfusion medicine. The two homologous genes RHD and RHCE are located on chromosome 1p36.11 and encode for RhD and RhCE proteins, respectively. Complex genetic polymorphisms result in a variety of antigenic expression of D, C, E, c, and e. Here, we describe a case of a young female with D−− who developed anti-Rh17 secondary to blood transfusion and had signs of haemolytic disease of the fetus and fetal death in five consecutive pregnancies.

Case Description

EDTA-whole blood samples were collected from the patient, husband and eight siblings for blood grouping, phenotyping, and red cell antibody screening. Extracted DNA was genotyped by SNP-microarray and massively parallel sequencing (MPS) with targeted blood group exome sequencing. Copy number variation analysis was performed to identify structural variants in the RHD and RHCE. Routine phenotyping showed all family members were D+. The patient's red blood cells were C−E−c−e−, Rh17− and Rh46− and had anti-Rh17 and anti-e antibodies. MPS showed the patient carried a wildtype RHD sequence and homozygous for RHCE (1)-D (2-9)-CE (10) hybrid gene predicted to express a D−− phenotype.

Conclusions

Our patient had a rare D−− phenotype and confirmed to have RHCE/RHD hybrid gene with replacement of 2-9 exons of RHCE by RHD sequences. Unfortunately, our patient developed anti-Rh17 and anti-e antibodies due to blood transfusion and suffered fetal demise in her very first pregnancy. The adverse outcomes could have been prevented by active prenatal management.

KEYWORDS
RBC; HGB; HCT; MCV; PLT; blood, medicine, transfusion

1 | INTRODUCTION

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918-1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

2.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing stud- ies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Sci- ence). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

2.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

2.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these `publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarification from trial authors where necessary.

2.4 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel-Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean differ-

ence (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

3 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

3.1 | Study Characteristics

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (n = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (n = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (n = 36/12575 pregnant women). Eight RCTs[22,24,30-33,36,44] did not report whether they included pregnant women.

3.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22-25,27-31,33-36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40-43,45] and one com- pared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

The comparators and baseline characteristics of participants in each of the thirty RCTs and two non-RCTs (retrospective observational studies)[50,51] within meta-analyses are summarised in Appendix A Table A1 in Data S1.

3.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3-A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which prevents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned —1, people who were on MV at randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

Duration of viral detection was expressed as time (median IQR) to first negative test (2 RCTs).[23,36] One study,[25] reported the number of patients who had had two consecutive negative tests by day 30. See table A5 for viral detection data and table A6 for details of changes in viral loads.

4 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG. of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre sub- group in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

SAEs were also downgraded for inconsistency as the heterogeneity was significant between studies, this is likely to be due to the variation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

4.1 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evidence base, which are discussed more fully in the next section.

4.2 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough according to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA reference method. Since we conducted our first search, several variants of SARS-CoV-2 have arisen worldwide and may require much higher antibody titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

4.3 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recipient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40-43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

5 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A

minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

AUTHOR CONTRIBUTIONS

Catherine Kimber: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Abigail A. Lamikanra: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Louise J. Geneen: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Josie Sandercock: data extraction, risk of bias assessment, and undertook all metaregression analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. Carolyn Doree: developed and performed all search strategies and de-duplication, retrieved full text publications, contributed to the development of the manuscript. Sarah J. Valk: screening and full text assessment, retrieved full text publications, contributed to the development of the manuscript. Lise J. Estcourt: developed the initial idea of the review, developed, wrote, and registered the protocol, interpreted the results, and contributed to the development of the manuscript.

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TRANSFUSION MEDICINE WILEY

LETTER TO THE EDITOR

Apparent changes in RhD status during pregnancy: A case study of weak D variant due to RHD*DAU-2

Dear Editor,

A 33-year-old Caucasian woman was referred at 32^{+5} weeks of gestation after the finding of severe fetal intracranial haemorrhage (ICH) at routine ultrasound. The woman had two previous uneventful pregnancies (singleton and twins). Fetal ultrasound and magnetic resonance imaging confirmed multiple ICHs especially located in the left hemisphere, wide areas of periventricular leukomalacia, obstructive hydrocephalus and macrocrania. Fetal-neonatal alloimmune thrombocytopenia (FNAIT) was investigated. Maternal blood group was A RhD positive, paternal O RhD positive. The maternal sample was screened for platelet-reactive antibodies using solid phase technology for the detection of IgG anti-HLA class I and anti-HPA antibodies (SPRCA Capture P Ready Screen, Immucor, Italy) with and without chloroquine treatment to remove HLA antigen interference. The results were positive and negative respectively. No antibodies attached to maternal platelets were found (Capture-P, Immucor, Italy). ELISA and Luminex based platforms were used to identify the specificity of the detected antibodies (Pak-Lx Luminex and ELISA Pak plus, Immucor, Italy and Luminex MoAb, Lagitre, Italy). The assays only recognised the presence of anti-HLA A02 and anti-HLA B51 at high titre, greater than 8000 and 20 000 MFI (average fluorescence intensity) respectively, in association with different cross-reactions. Cross-match testing (Capture-P, Immucor, Italy) using maternal serum against paternal platelets tested reactive with both chloroquine-untreated and treated platelets. Additional cross-match testing was performed using platelets. Additional cross-match testing was performed using maternal serum against 14 random donor platelet samples. Eight donors were compatible and six were not. Two non-compatible donors were HLA class I A*02 and A*02 B*51 respectively. The remaining four non-compatible donors were not typed for HLA I antigen. All compatible donors were typed for the main HPA antigens but comparison of the typings did not allow to quickly exclude HPA 4b, 6b, 7b, 8b, 9b, and 11b antigen immunisation. A male newborn was delivered by caesarean section at 36 weeks of gestation after spontaneous onset of labour. At birth, platelet count was $4x10^3/\mu l$ with normal white and red blood cell count. An urgent transfusion with a platelet blood component not tested with maternal serum increased platelets to $116 \times 10^3/\mu l$; intravenous immunoglobulins were also infused. Another two transfusions were administered on days 4 and 13 due to a drop in the number of platelets ($28 \times 10^3/\mu l$ and $48 \times 10^3/\mu l$ respectively): the platelet pools were obtained from cross-match between maternal serum and sample platelets of random donors. Normal values were reached on day 17.

The newborn blood group was 0 Rh D positive. Capture-P Ready Screen aimed to detect anti-platelet antibodies was non-reactive. Cross-match testing using newborn blood was performed twice. At birth, the neonatal sample was cross-matched against paternal and maternal platelet samples: results were positive and negative, respectively. After 14 days, cross-matching against paternal platelets was repeated with and without chloroquine treatment; both resulted non-reactive.

Results of parental and neonatal HLA I and HPA genotyping performed using polymerase chain reaction (PCR) with sequence-specific oligonucleotides (PCR-SSO) and HPA BeadChip (Immucor, Italy), are shown in Table 1. The mismatches identified prompted further testing in the mother. Cross-match testing against 6 HPA-9b antigen negative donors resulted in two non-compatible and four compatible donors. The same two non-compatible donors were all compatible when The same two non-compatible donors were all compatible when cross-matching was performed with chloroquine. Cross-match testing against two donors expressing the HPA9b antigen was reactive with and without chloroquine. Cross-match testing against paternal and neonatal platelets with and without chloroquine was equally reactive. Cross-match testing was performed between maternal serum and 107 different donors in order to have available and compatible blood components available for any neonatal transfusions.

TABLE 1 Trio HLA and platelet genotyping. Newborn genes not present in the mother are in bold

	Mother	Father	Newborn
HLA class I genotype	A*01*69 B*35*37 C*06*12	**A*02** **B*35*51** C*04*16	A*01***02** B*37***51**
HPA genotype	1a/a, 2a/a, 3a/**b**, 4a/a, 5a/a, 6a/a, 7a/a, 8a/a, **9a/a**, 11a/a, 15a/b	1a/a, 2a/a, 3b/b, 4a/a, 5a/a, 6a/a, 7a/a, 8a/a, **9a/b**, 11a/a, 15a/b	1a/a, 2a/a, 3a/b, 4a/a, 5a/a, 6a/a, 7a/a, 8a/a, **9a/b**, 11a/a, 15b/**b**

Abbreviations: HLA, human leukocyte antigen; HPA, human platelet antigen.

FNAIT is a cause of severe thrombocytopenia and ICH in both the fetus and newborn.[1] FNAIT-related ICH is estimated to occur in at least 10:100 000 neonates. It mainly occurs in the third trimester of pregnancy and is associated with severe neurological sequelae and mortality. In most cases, FNAIT is caused by an alloimmune response against human platelet antigens (HPAs). In the Caucasian population HPA-1a antigen accounts for up to 80% cases,[2] followed by HPA-5b (8–15% of cases) and to a lesser extent HPA-3a/5a/15b.[3] More rarely, FNAIT is associated with low-frequency human platelet antigens (LFHPAs) or to HLA class I antigens, especially when related to locus A and B and with a highly expressed titre.[4] Among LFHPAs, HPA-9b is emerging as a significative trigger for FNAIT.[5] Almost two-thirds of apparent cases of FNAIT are not resolved by laboratory confirmation of maternal immunisation against HPA antigens. When other causes of thrombocytopenia are not identified, a possible explanation may be involvement of HLA antibodies or limitations of laboratory studies.

In the current case, parental ABO compatibility excluded ABO-mediated thrombocytopenia. The detection of maternal HLA class I antibodies, identified as HLA A02 and HLA B51 antibodies, and paternal HLA I genotype (HLA A*02; B*35*51), were consistent with the clinical suspicion of FNAIT. However, an additional factor was likely to be involved, presumably related to the HPA system: genotyping showed a parental mismatch in the HPA 9 locus (mother HPA- 9a/a, father HPA 9a/b) and neonatal inheritance of the HPA-9b antigen from the father. Search for HPA antibodies (Pak-Lx Luminex and ELISA Pak plus) was inconclusive because no reactivity was detected against the glycoproteins GPIIb/IIIa, GPIa/IIa, GPIb/IX and GPIV. This can be explained by the limitations of the GP assay used which was not able to recognise the rare specificity HPA-9b. Moreover, it was not possible to find readily available source platelets from local donors carrying the target antigen because only a limited number of them had been typed for HPA and the expected frequency of HPA 4b, 6b, 7b, 8b, 9b, 11b in the population is extremely low (<1%).[3] Cross-match testing between maternal serum and both paternal and neonatal platelets was reactive after chloroquine treatment. This finding was supported by cross-match performed against HPA9b positive donors. This allowed to attribute the FNAIT to the presence of the paternally inherited HPA9b antigen on the son's platelets. It was not possible to identify any antibody specificity in neonatal serum (Capture—P Ready Screening method) presumably due to the extremely low platelet count as a result of the adhesion of the maternal alloantibodies to the neonatal platelets with consequent uptake and elimination.

Since the first report of a HPA-9b related FNAIT in 1995,[6] a total of 15 cases have been reported[5,7,8] and increasing evidence suggests that its prevalence in the population and among fathers of unresolved cases of FNAIT might be greater than previously reported.[6,9] The severity of thrombocytopenia and clinical presentation in our case is consistent with the argument that HPA-9b might be more immunogenic than others HPAs.[5] Our case supports the need to investigate alloimmunisation to HPA-9b and other rare specificities when routine screening for the most common antigens is negative or inconsistent with the laboratory and clinical findings.[3,5] We experienced diagnostic limitations mainly due to the fact that the Ag panel used (Pak-Lx Luminex Immunocor and Elisa Pak Plus Immunocor) does not identify HPA-9b. Difficulties with the detection of antibodies against HPA-9b antibodies have been described by some authors who urged further studies to fully understand the issue.[5,7] Nonetheless, even if FNAIT was strongly suspected both on clinical grounds and after the finding of anti-HLA I antibodies, the mother could not be offered intrauterine therapy of proven efficacy to begin at that gestational age.[1,9]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not openly available due to sensitivity reasons and are available from the corresponding author upon reasonable request.

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