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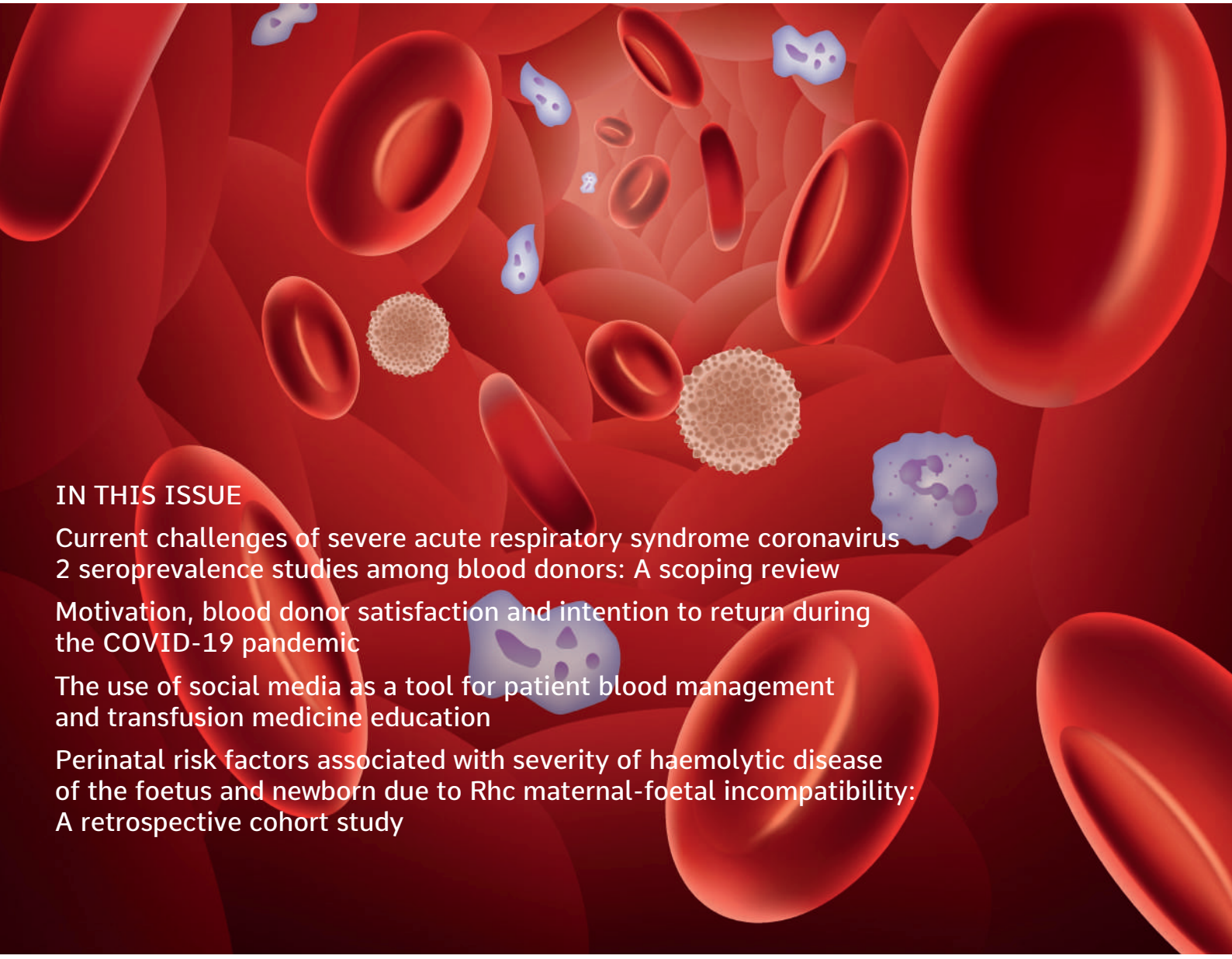

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ISBT International Society of Blood Transfusion

Vox Sanguinis

International Journal of Blood Transfusion

Official Journal of the International Society of Blood Transfusion

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Vox Sanguinis

International Journal of Blood Transfusion

Aims and Scope

Vox Sanguinis reports on all issues related to transfusion medicine, from donor vein to recipient vein, including cellular therapies. Comments, reviews, original articles, short reports and international fora are published, grouped into 10 main sections:

1. Blood Component Collection and Production: Blood collection methods and devices (including apheresis); blood component preparation; inventory management; collection and storage of tissues; quality management and good manufacturing practice; automation and information technology; plasma fractionation techniques and plasma derivatives;
2. Cellular Therapy: Cell-based therapies; CAR T-cell therapies; genetically modified cell therapies; cellular therapy (sources; products; processing and storage); stem cells; cell-based regenerative medicine; cellular immunotherapy; molecular therapy;
3. Donors and Donations: Donor recruitment and retention; donor selection; donor health
4. Haemovigliance: Adverse events in blood and blood component donors and transfusion recipients; corrective and preventive measures of complications; near-misses and errors in the transfusion chain; evaluation and outcomes of adverse events
5. Immunohaematology and Immunogenetics: autoimmunity in haematology; alloimmunity of blood; pre-transfusion testing; complement in immunohaematology; blood phenotyping and genotyping; genetic markers of blood cells and serum proteins: polymorphisms and function; parentage testing and forensic immunohaematology;
6. International Forum: Section in which topics related to any aspects of the transfusion chain (from technical to scientific, including socioeconomic and ethical facets) are discussed by invited participants and summarized by guest editors
7. Patient Blood Management: Bloodless surgery; preoperative anaemia; minimizing blood loss during surgery; alternatives to blood transfusion;
8. Review: Comprehensive reviews or short comments of any aspect related to transfusion medicine;
9. Transfusion Medicine: Transfusion indication, transfusion practice, thresholds and audits; transfusion efficacy assessment, clinical trials; therapeutic apheresis;
10. Transfusion-transmitted Disease and its Prevention: Identification and epidemiology of infectious pathogens transmissible by blood; donor testing for transfusion-transmissible infectious pathogens; bacterial contamination of blood components; pathogen inactivation;

This comprehensive coverage has made the journal essential reading for a wide range of specialists interested in the present state of transfusion research and practice.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

The use of social media as a tool for patient blood management and transfusion medicine education

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Abstract

Background and Objectives: Transfusion is one of the most performed medical procedures. Wrong indications are common and are probably related to the scarcity of transfusion teaching during medical education. The development of a new way to improve transfusion education is paramount. Social media has the potential to reach larger audiences for rapid communication of medical content. The use of social media for transfusion education in Brazil has not been published. The aim of this article is to describe a new tool to improve transfusion learning.

Materials and Methods: Evidence-based cards were created. Initially, these cards were sent by WhatsApp. Later, Instagram and Facebook pages were created. EducaSangue, as this e-learning project was called, is a tool for the spreading of transfusion knowledge that permits the exchange of experiences.

Results: By April 2021, Facebook and Instagram pages had 8300 and 5100 followers, respectively. Cards about single red blood cell (RBC) unit, alternatives to transfusion, transfusion reactions and pre-transfusion tests were published. Doctors and other health professionals follow EducaSangue. RBC transfusions reduced in Ceara and single-unit RBC increased by 28%, although not statistically significant. In Brazil, the minority of medical schools have transfusion as a discipline. The scarcity of transfusion education is related to the poorer care of the patient. Technological innovation has been used for educational changes and is an alternative to formal education.

Conclusion: Social media is an interesting tool to provide quality to medical services, since they can reach a broader public, especially where personal contact is difficult.

KEYWORDS
patient blood management, transfusion medicine, transfusion therapy

Highlights

- This is the first article that evaluates the use of social media in transfusion medicine education in Brazil.
- Social media is a powerful tool to improve transfusion safety and patient blood management.

INTRODUCTION

Transfusion is one of the most performed medical procedures in hospitalized patients worldwide [1]. In the United States during 2014, 5.7% hospitalized patients received a red blood cell (RBC) transfusion [2]. In Brazil, the National Agency of Sanitary Surveillance published that 3,432,210 units of blood components were transfused in 2019 from private and public blood banks [3].

The Hematology and Hemotherapy Center of Ceara (HEMOCE) is a public blood bank in Northeastern Brazil, responsible for transfusion assistance to 16,274 hospital beds and a population of almost 9,000,000 inhabitants. In 2020, 120,332 transfusions were provided by HEMOCE.

Some countries are reducing their transfusion rates based on the implementation of patient blood management (PBM) concepts in their hospitals and health system. PBM consists of an evidence-based approach, aimed to improve care of patients who need or might need transfusion. PBM can reduce the need for allogeneic blood transfusions with better patient outcome. It also reduces healthcare costs, while allowing blood to be available for those who actually need transfusion [4].

A paper published in 2014 evaluated the education and training of transfusion in developing countries [5]. Formal transfusion education in Brazil was evaluated in an article published in 2016. Only 3.9% had a discipline of transfusion medicine in the curricular grade. This result probably indicates a deficiency in the teaching of transfusion for medical graduates [1].

A test (BEST-TEST 2) was developed to measure the transfusion knowledge of medical professionals [6]. The result of the evaluation of transfusion knowledge in Brazil was poor. BEST-TEST 2 was translated to Portuguese and validated in a population of Ceara. The overall mean exam score was 61.6% (SD, 13.4%; range, 30%–100%) with no correlation in exam scores with the postgraduate year or previous transfusion medicine education in medical school or internal medicine residency (data not published).

Many transfusion requests made to our service are based only on a haemoglobin threshold, regardless of the patient's clinical state. Indeed, many are stable patients with iron deficiency anaemia that could be treated with iron supplementation and further management or investigation of the cause of anaemia. Such situations and many other misunderstandings about blood compounds raised concerns about the risks and the potential harm associated with blood transfusion, as it is often considered a simple and low-risk procedure with its risks being frequently neglected. This is likely related to the scarcity of transfusion education during medical training [7], emphasizing the importance of innovation in this teaching field. Due to these facts, EducaSangue was created by two haematologists from HEMOCE to provide transfusion medicine content in a light and dynamic way. Other medical professionals have been added to EducaSangue over the years. HEMOCE supported this initiative by using EducaSangue as its main education tool.

Social media networks (e.g., Facebook, Instagram) have the potential to reach larger audiences in a significantly shorter time span for rapid dissemination of medical content [8]. Over two-thirds of Americans reported using the Internet for health and fitness information [9]. Social media has become an impressive and strong tool used by physicians to disseminate knowledge to other health professionals and students and overall public. Some best practices have emerged despite the transient nature of the platforms. Many social media provide information and ideas about new research, evidence, or guidelines [10]. Additionally, numerous studies evaluate the use of social media as an open-learning resource in education [9, 11].

The use of social media for transfusion medical education in Brazil has not yet been reported to our knowledge. The aim of this article is to describe a new tool developed by a group of haematologists to reach a broader public, especially where personal contact is poor and difficult.

MATERIALS AND METHODS

Setting

Initially, a series of concise and attractive cards were created (Figures 1 and 2). All the information provided was selected from consolidated concepts regarding the most frequent wrong indications faced by the authors, such as packed RBC for stable patients with iron deficiency anaemia, RBC for stable patients to reach a target haemoglobin of 9 or 10 g/dl with no active haemorrhage after gastrointestinal bleeding, and platelet transfusion without a previously complete blood count. Another mistaken practice identified was the prescription of two units of packed RBCs without clinical and laboratory reassessment of the patient between transfusions, resulting in unnecessary transfusions and exposure of the patient to otherwise avoidable risks. The first cards created were aimed at these inappropriate prescriptions and all cards contained references to evidence-based transfusion literature with information selected from randomized trials, transfusion guidelines and other international publications for further knowledge.

Cards were created by two authors along with the agreement of another transfusion medicine specialist, in different moments, with new cards designed each year. Posts were organized into six categories: PBM, immunohaematology and compatibility, adverse transfusion events, good practices in transfusion procedure, blood components production and other subjects analysed according to scope and interactions. Table 1 describes the main characteristics of the platforms used by EducaSangue [12].

EducaSangue did not receive financial support from any institution. All authors donated their time to this project.

Intervention

Initially, these cards were sent through WhatsApp by the authors for different medical and student groups formed by health professionals and intra-hospital transfusion committees related to the

FIGURE 1 Card created about rational use of platelet unit. Platelets three times a day? Platelet is not antibiotic! Platelet transfusion should be based on the platelet count of the day. One dose is usually enough

FIGURE 2 Card created about iron deficiency anaemia and transfusion. Does your patient have anaemia? Low mean corpuscular value? It can be iron deficiency. Is it? Do not give blood, give iron

service. To reinforce this disclosure, the same cards were sent by institutional e-mail to all the medical members of the most important public hospitals in the capital of Ceara, Fortaleza. These hospitals are education-based and have professors and teaching doctors as part of their clinical staff.

The next step was the creation of both an Instagram account and a Facebook page. The e-learning project called EducaSangue aims to spread correct concepts related to transfusion prescription and related care in a quick and easy-to-read manner, disseminating accurate, evidence-based medical knowledge with distribution of cards that permit the exchange of experiences. All cards are published with complementary texts and links for freely available references. The timeline used with different tools for cards dissemination is provided in Table 2.

TABLE 1 Main characteristics of the platforms used to spread EducaSangue content

Social media	Characteristics	Active users in world
Facebook	Market leader, people of all ages and places use this to share information through text, photos and videos	2853 million [12]
Instagram	Mobile and desktop-accessible media sharing service that allows the sharing of images and videos	1386 million [12]
WhatsApp	Cross-platform instant messaging service for smartphones	2 million [12]

TABLE 2 Timeline with different tools used for cards dissemination

Tool	Year
WhatsApp	2016
E-mails	2016
Facebook	2017
Instagram	2017

TABLE 3 List of the videos' contents

Red blood cell transfusion in chronic kidney disease
Patient blood management and surgeries
Post-partum haemorrhage
Patient blood management and reduction of blood volume withdrawn for laboratory diagnostic purposes
Plasma transfusion
Iron deficiency anaemia and pregnancy
Use of tranexamic acid in trauma, surgeries and postpartum haemorrhage
Major haemorrhage in surgical patients
Transfusion reactions
Massive transfusion protocols

The authors also made some short videos with consolidated and well-respected physicians of several medical specialties, including internal medicine and liver transplant, obstetrics and neonatology. These videos cover aspects of PBM and transfusion reactions and have had their contents analysed and approved by transfusion medicine specialists. Their topics are described in Table 3.

As the project grew and reached more of the public, materials of various formats were created and posted on social media, such as cards, videos, infographics and presentations, among others. These were used in order to reinforce the information and concepts that were intended to be disseminated. Therefore, the material used in this project was created and publicized in different moments whenever new situations were identified or new evidence in transfusion medicine became available in specialized literature. It was observed that all of the posts were shared between users without the need of any boost, meaning that a wide public was reached with no sharing cost. This 'organic' sharing is an important way to evaluate the impact of the posts on EducaSangue followers.

TABLE 4 Questions used to evaluate the profile of EducaSangue followers on Facebook and its impact on transfusion practice

What is your graduation area?
How long have you been working in the healthcare field?
Are you involved in the education of students or other health professionals?
Did you change any aspect of your daily practice based on the content of EducaSangue?

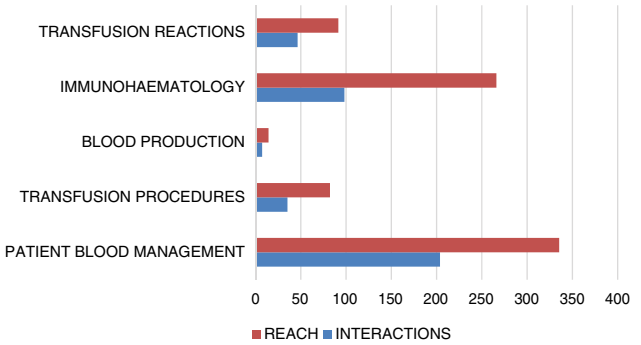

FIGURE 3 Reach and interactions in Facebook and Instagram according to the main topics (in thousands). Reach: the number of people who saw the content. Interactions: the number of interactions people have with your content (i.e., likes, comments, shares, etc.)

While there was no publicity campaign for the new Instagram and Facebook pages, EducaSangue social media was disseminated through presentations in local and national transfusion events. This expansion and project dissemination made voluntarily by the followers resulted in requests to address new topics related to transfusion and its dissemination by other institutions and health services. The authors allowed any person or institution who desired so to use them for educational purposes.

Evaluation of the impact

The impact of EducaSangue in transfusion medicine education was evaluated through a questionnaire and by the evolution of blood components transfused in Ceara since its beginning.

A four-question questionnaire was published to evaluate the number of health professionals that were reached and the impact on transfusion practice (Table 4). The impact of the EducaSangue was also evaluated by the change in transfusion practice in Ceara. The numbers of total transfusions and single RBC unit transfusion were studied from 2016 to 2020. The data on the total number of transfusions and the number of RBC units transfused in Brazil in the period 2016–2019, and in Ceara from 2012–2019 were analysed. These data

TABLE 5 Blood transfusions in Ceara and Brazil from 2016 to 2020

	2016	2017	2018	2019	2020
Total transfusions in Brazil	2,840,988	2,892,971	2,913,160	2,951,212	NA
Total transfusions in Ceara	128,652	128,894	118,055	122,940	120,332
RBC transfusions in Brazil	1,727,039	1,772,952	1,777,118	1,809,913	NA
RBC transfusions in Ceara	93,460	91,812	84,801	84,881	81,368
Percentage of transfusion episodes with single RBC unit transfusion in Ceara	53.17%	56.49%	61.81%	65.77%	68.58%

Abbreviations: NA, data not available; RBC, red blood cell.

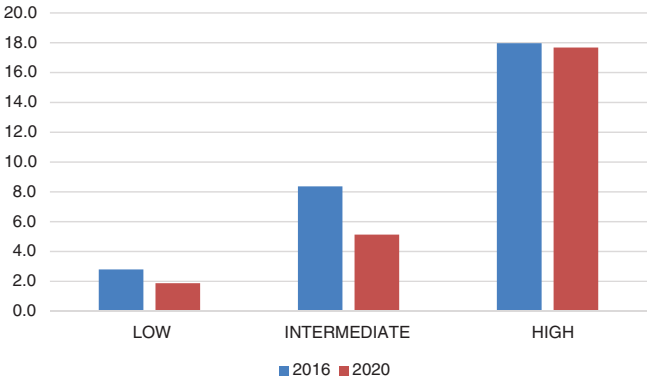

FIGURE 4 Reduction in transfusion rates per bed according to the hospital complexity between the years 2016 and 2020 in Ceara

were collected from the blood bank system of HEMOCE and Ministry of Health of Brazil [13]. All statistical analyses were performed using Jamovi version 2.0.

RESULTS

Up and until July 2021, 4 years after its creation, the Facebook and Instagram pages had 8408 and 5483 followers, respectively. Cards addressed to correct indications and alternatives to allogeneic blood transfusions, transfusion reactions and pre-transfusion tests were performed, however, the single-unit RBC transfusion policy was one of the most important concepts encouraged by the EducaSangue posts. All the cards had a reference to an evidence-based transfusion literature for further knowledge. Figure 3 shows topics distribution, reach and interactions. More than 500 cards and videos were posted.

A total of 365 followers answered the questionnaire posted on EducaSangue Facebook page. The followers are from every geographic region in Brazil, composed of biomedicine professionals (25.9%), nurses (19.8%), biologists (13.2%) and medical doctors (10.2%). About 13% of the followers described themselves as other health professionals and 1.3% were not healthcare professionals.

Half (49.6%) of the professional followers have been working in the healthcare field for more than 10 years. A total of 242 of the 358 healthcare professional followers (67.6%) responded that they are involved in the education of students or other health professionals, and 325 (90.8%) responded that they changed some aspect of their daily practice based on the content of EducaSangue.

At this moment, EducaSangue has followers in both Brazil and other Latin American countries, such as Argentina, Mexico, Panama, Ecuador and Peru. This is despite the fact that the posts are only in the Portuguese language. Additionally, there are also followers from Portugal.

All the comments on the posts were positive. Many followers commented about how easy the information was expressed and also about the need to spread transfusion knowledge among health professionals.

In the period 2012–2015, there was an increase of 11.4% in the total number of transfusions, and 11% RBC transfusions in Ceara. Between 2016 and 2019, it is possible to observe a 4.4% reduction in the number of total transfusions and a 9.2% reduction in RBC transfusions (Table 5). According to Ministry of Health data, in this same period, there was an increase in the total number of transfusions and RBC transfusions in Brazil, 3.9% and 4.8% respectively (Table 5) [13]. According to data published by the health department of the state of Ceara, there is a shortage of hospital beds in the state, with a bed occupation rate increase of 2% in 2019 compared to the previous year [14]. Therefore, this reduction in transfusion rates cannot be justified by a reduction in the number of patients seen in the health system. There is a greater impact on the reduction in total transfusion rates in patients seen in low and intermediate complexity units between the years 2016 and 2020, as shown in Figure 4. Furthermore, there was an increasing number of single-unit RBC transfusion over the years, reaching 28% reduction in 4 years in Ceara (Table 5). There was a trend for reduced RBC transfusion and for increased percentage of transfusion episodes with single RBC unit in Ceara over the years, but it was not statistically significant (Arima Model (0,1,0), $p > 0.05$).

DISCUSSION

Medical transfusion education has been more intensively studied in the past years. The results of an international forum of education in transfusion medicine were published in 2013. Almost all participants felt that the transfer of knowledge of transfusion medicine should be enhanced and that education in transfusion medicine should be increased for both students and residents [15].

The data from the questionnaire posted on the EducaSangue Facebook page show the importance of medicine transfusion education in social media. The role of followers as educators can potentialize the spread of knowledge and thus the impact of the posts. Also, the previously described change in the daily practice of these individuals is a surprising and inspiring result of EducaSangue. This work is continuous and new posts are needed.

It is possible that the use of these tools for transfusion education has already achieved good results in Ceara, as there has been a reduction in transfusion numbers (especially from 2017), although not statistically significant, with a greater impact on patients treated in low- and medium-complexity units, which due to their profile could have had a higher incidence of wrong indications for transfusion. This reduction has occurred after a period of constant increase in the number of transfusions and goes against the trend observed in Brazil. Although EducaSangue has a national public, almost 20% of the followers are from Fortaleza, the capital city of Ceara. This high frequency of Ceara followers must have contributed to the larger impact of this tool on transfusion practices in this state.

This study has certain important limitations. The most important limitation is that direct cause and effect of EducaSangue and reduction in transfusion rates cannot be proven. Ceara hospitals have different complexities, and the medical doctors have heterogeneous clinical approaches, all of which make it difficult to exclude biases that may also have contributed to the reduction of transfusions. Furthermore, we did not assess the real deficit in knowledge of the target population before the implementation of this initiative. Other limitations include absence of standardization for topics selection and the lack of control over the profile of followers.

The scarcity of transfusion medicine education is correlated to poorer treatment of patients, however, the usage of social media like Facebook, Instagram and WhatsApp, can spread transfusion knowledge to a larger public and it is most likely an interesting tool which can provide better quality to medical services and patient security. In the future, we need to evaluate more thoroughly the gathering of information, and how health professionals use EducaSangue for the care of their patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to Vox Sanguinis.

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Amifostine and rituximab in refractory immune thrombocytopaenia: A case series

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Abstract

Background and Objectives: Management of refractory immune thrombocytopaenia (ITP) can be challenging. Amifostine, a thiophosphate prodrug, induces megakaryocyte maturation. In 2010, Fan et al. published results for 21 Chinese splenectomized patients, aged 13–92, with steroid-refractory ITP. Nineteen patients (15 patients aged >18 years) achieved remission 2 months post-amifostine. This is the first publication utilizing amifostine and rituximab in refractory ITP.

Materials and Methods: At the Cairns Hospital in Australia, we identified five patients treated with amifostine and rituximab for refractory ITP. Amifostine IV 400 mg once daily was administered 5 days/week for 5 weeks as tolerated. Rituximab was administered concurrently with/preceding amifostine based on clinician preference. Data were obtained through medical records and follow-up serology up to 5 years post-amifostine was available.

Results: Three cases demonstrated durable responses up to 5 years' follow-up. One patient initially achieved remission but relapsed 1-year post-amifostine. One patient who did not have a splenectomy prior to amifostine did not respond.

Conclusion: Three out of five patients achieved durable responses with amifostine and rituximab. Although there is confounding by rituximab, given its established low durable response rate, it is likely that the excellent long-term responses achieved were a result of amifostine. Clinical trials with larger patient cohorts and further investigation are required to confirm the efficacy and mechanism of amifostine in ITP.

KEYWORDS
amifostine, immune thrombocytopenia, platelet, refractory ITP, rituximab

INTRODUCTION

Immune thrombocytopaenia (ITP) is an acquired autoimmune disorder resulting in platelet (PLT) destruction with a PLT count <100 × 10^9/L [1]. It has an incidence of 2–10 cases per 100,000 patient years [2] and 75% of adults are chronically affected [2]. ITP can be classified as primary or secondary. Primary ITP is idiopathic in aetiology and the pathogenesis is multi-modal: (1) Autoantibody generation against PLT surface glycoproteins and megakaryocytes [3]. (2) Dysregulated megakaryocyte function in the bone marrow [4]. (3) Inappropriate thrombopoietin levels relative to the degree of thrombocytopaenia [5]. (4) T cell dysregulation characterized by reduced levels of regulatory T cells and cytotoxic T cells directed against PLTs [6]. Secondary ITP is an immune mediated process attributable to a predisposing illness such as *Helicobacter pylori*, human immunodeficiency virus, autoimmune disorders or lymphoproliferative disease [7].

The goal of managing ITP is to maintain the PLT count at a level which is not associated with a significant bleeding risk whilst

minimizing therapy-related adverse effects. Corticosteroid therapy for 6–8 weeks constitutes first-line treatment but only 20%–25% of patients can maintain a safe PLT count post-cessation [8, 9]. Thrombopoietin receptor agonists have high response rates of ~75%. However, only 10%–30% maintain response post-cessation. Rituximab has a 20%–25% 5-year response rate [8, 9]. Deferral of splenectomy for 12–24 months after diagnosis is now recommended due to the possibility of spontaneous or therapy-induced remission. However, splenectomy has an excellent durable response rate of 50%–70% [8].

With updated guidelines recommending deferral of splenectomy, refractory ITP has been redefined to include those who are non-responsive to ≥2 lines of therapy, lack of response to any therapy, or bleeding associated with severe thrombocytopaenia [10]. In these cases, management can be challenging as alternative therapeutic options are associated with lower response rates, immunosuppressive complications, treatment-specific toxicities and poor durability of response [11].

AMIFOSTINE

Amifostine, a thiophosphate prodrug, was developed by the US Army Medical Research and Development Command to protect against nuclear radiation damage. It was subsequently employed as a cytoprotective agent to reduce toxicities from chemoradiotherapy [12]. In vitro experiments with Dami cells (human megakaryocytic cells) demonstrated induction of megakaryocytic differentiation by amifostine with resultant increased chromosomal ploidy and cellular diameter by increasing nuclear translocation of NF-E2 and GATA-1 [13]. Flow cytometry demonstrated maturation of the megakaryocyte immunophenotype with increased CD41a and decreased CD33 expression [13].

The 2010 Chinese study from Fan et al. involved 21 splenectomized Chinese patients, aged 13–92 years, with steroid-refractory ITP, whom received amifostine IV 400mg once daily, 5 days/week for 4–5 weeks [14]. Nineteen patients (15 patients aged >18 years) achieved remission defined as PLTs $>100 \times 10^9$/L at 2 months follow-up post-amifostine.

From 2006, amifostine was utilized as off-label therapy for refractory ITP at Cairns Hospital in Australia. With informed patient consent, amifostine was administered according to the Chinese protocol at $7984 AUD/cycle, funded by Cairns Hospital after review of individual patient applications by the institutional review board. Standard pre-medication with IV Dexamethasone 4–8 mg and a 5-HT3 receptor antagonist was prescribed 30 minutes prior to amifostine to minimize nausea and vomiting, common adverse effects [15]. Other adverse effects of amifostine include hypotension, severe skin reactions, hypocalcaemia, anaphylaxis and seizures [15]. Blood pressure and calcium levels should be monitored [15].

Rituximab was administered based on clinician preference and previous therapies received. It was not prescribed as standard adjunctive therapy to amifostine and hence, there was variation in the timing and number of cycles received. Most patients received four cycles of intravenous rituximab 375 mg/m^2 weekly. Over the last 14 years, we identified five patients with refractory ITP who received amifostine and rituximab with dramatic lasting responses in responders (Table 1).

CASE 1

Mr A, 71, was diagnosed with primary ITP in 2006. Prednisone, intravenous immunoglobulin (IVIG) and *H. pylori* eradication resulted in good initial response.

Unfortunately, with emotional lability on prednisone and relapse on rapid wean, splenectomy was performed without remission.

He received five cycles of amifostine and four cycles of rituximab with PLT count improving to 85×10^9/L after cycle 1. During amifostine infusion, he developed pulmonary oedema and atrial fibrillation necessitating diuretic administration with subsequent cycles.

After cycle 5, PLT count fell to 32×10^9/L but normalized 6 months post-amifostine and remained normal without further treatment until he passed away in 2019.

CASE 2

Mr B, 41, was diagnosed with primary ITP in 2001. He relapsed on steroid weaning and underwent splenectomy in 2003 without remission. Corticosteroid, cyclosporin, diltiazem and azathioprine were trialled without durable response.

In 2008, five cycles of amifostine and one cycle of rituximab were administered with PLT count incrementing from 10×10^9/L to 161×10^9/L after cycle 1. After cycle 5, PLT count was 135×10^9/L and 298×10^9/L after 6 months

One year post-amifostine, he relapsed and dexamethasone was re-initiated. Romiplostim 85μg subcutaneously, 3 weekly, was administered for 10 months with sustained PLT response. Unfortunately, he did not meet regulatory criteria to continue romiplostim and passed away from an ischaemic stroke complicated by haemorrhage when he was profoundly thrombocytopaenic.

CASE 3

Miss C, 18, was diagnosed in 1985 with primary ITP, treated with corticosteroid and azathioprine. In 1986, splenectomy was performed for multiple relapses without remission. Corticosteroid and azathioprine were subsequently continued.

In 2016, with PLTs of 26×10^9/L, amifostine and four cycles of rituximab were administered. After cycle 1, PLT count increased to 43×10^9/L and fluctuated between 32 and 49×10^9/L during weeks 2 and 3. Only three cycles of amifostine were administered due to infusion-related adverse effects: pruritus, fever, headache.

The day after amifostine cessation, PLTs fell to 5×10^9/L and one course of IVIG was administered resulting in PLT recovery to

TABLE 1 Patient characteristics, previous therapy and PLT response post-amifostine and rituximab therapy

Case	Age	Sex	Prior therapy	PLT count before amifostine ($\times 10^9$/L)	PLT count at 1 week[a] ($\times 10^9$/L)	PLT count at 5 weeks[a] ($\times 10^9$/L)	PLT count at 6 months[a] ($\times 10^9$/L)	PLT count at 1 year[a] ($\times 10^9$/L)	PLT count at 2 years[a] ($\times 10^9$/L)	PLT count at 5 years[a] ($\times 10^9$/L)	Adverse events
1	71	M	Steroid, IVIG, *Helicobacter pylori* eradication, splenectomy	21	85	32	278	312	312	Not available	Pulmonary oedema and atrial fibrillation
2	41	M	Steroid, splenectomy, cyclosporin, diltiazem, azathioprine	10	161	135	298	27	113	Not available	None
3	18	F	Steroid, azathioprine, splenectomy	27	43	108	258	168	293	380	Pruritus, fever, rigors, headache, agitation
4	70	F	Steroid	28	68	12	16	264	316	326	None
5	53	F	Steroid, IVIG, rituximab, splenectomy, cyclophosphamide, eltrombopag, romiplostim, *H. pylori* eradication	7	90	338	368	381	394	Not available	None

[a]Post-commencement of amifostine and rituximab therapy.

101 $\times$ 10^9/L. PLT count was 108 $\times$ 10^9/L 5 weeks post-amifostine and normalized at 6 months, 1, 2 and 4 years post-amifostine without further treatment.

CASE 4

Mrs D, 70, was incidentally diagnosed with ITP in 2005 during work-up of hemi-colectomy for colorectal cancer. She responded to prednisolone and proceeded to surgery.

Post-corticosteroid cessation, she experienced recurrent relapses and in 2007, five cycles of amifostine and four cycles of rituximab were administered with PLT count improving to 68 $\times$ 10^9/L after cycle 1. After cycle 5, PLT count fell to 12 $\times$ 10^9/L and 6 months post-amifostine, remained low at 16 $\times$ 10^9/L without bleeding complications.

Splenectomy and vincristine were discussed but due to her age and surgical risk, she opted for Vincristine. Only four cycles were administered, limited by nausea. PLT count improved to 44 $\times$ 10^9/L after cycle 4 but this was not sustained. Mrs D underwent splenectomy with good durable response.

CASE 5

Mrs E, 53, was diagnosed in 2017 with secondary Evans syndrome in the context of lupus during steroid tapering for autoimmune haemolytic anaemia. Haemoglobin dropped to 49 g/L and she developed severe thrombocytopaenia refractory to corticosteroid, IVIG and rituximab. Bone marrow biopsy was consistent with peripheral destruction. Splenectomy resulted in initial normalization of her counts.

Unfortunately, PLT count subsequently dropped to 1 $\times$ 10^9/L. Corticosteroid use was complicated by proximal myopathy, hyperglycaemia and osteopenia. Nuclear splenic scan confirmed no splenunculi. Repeat marrow confirmed normal trilineage haematopoiesis.

In 2019, despite cyclophosphamide, rituximab, eltrombopag, romiplostim and *H. pylori* eradication, she remained persistently thrombocytopaenic at 7 $\times$ 10^9/L. Five cycles of amifostine were administered with PLT count improving to 90 $\times$ 10^9/L after cycle 1, with normalization after cycle 5, at 6 months, 1 and 2 years post-amifostine without further treatment.

DISCUSSION

In this case series using amifostine and rituximab, three cases demonstrated good durability of response up to 14 years' follow-up. One patient achieved initial good response but relapsed after 1 year. One patient who did not have splenectomy prior to amifostine did not respond. Excellent results were seen at 2 months post-amifostine in 15 out of 17 splenectomized adult Chinese patients with steroid-refractory ITP in the 2010 study from Fan et al. Therefore, it appears that the best results from amifostine occur in splenectomized patients.

Apart from the differentiating effects of amifostine on megakaryocytes, amifostine may have a protective effect on haematopoietic cells given its pharmacological properties. Amifostine is dephosphorylated by alkaline phosphatase to the active thiol metabolite, WR-1065, which scavenges free radicals, protecting intracellular components. WR-1065 is oxidized to the disulphide metabolite WR-33,278, decreasing DNA damage by condensing DNA [16]. Protein expression for DNA repair and inhibition of apoptosis may be upregulated by amifostine through BCL-2 and hypoxia-inducible factor-1α [17]. Amifostine inhibits inflammatory cascades and modifies enzyme activity. Further studies are required to confirm whether these mechanisms contribute to PLT recovery in ITP patients in vivo.

Due to the co-administration of amifostine and rituximab in this case series, rituximab has a confounding effect on these results. There are no published data on the concurrent administration of amifostine and rituximab in ITP and we are not aware of a synergistic effect when used together. Rituximab is a CD20 monoclonal antibody resulting in B cell depletion and hypogammaglobulinaemia. B cells maintain T cell activation through CD40/CD40L ligation. In ITP, rituximab almost completely normalizes abnormalities in T cell function—elevations in Th1/Th2 cytokine ratios, CD4 associated Bcl-2/Bax mRNA levels and oligoclonal T cell expansion by 3 months [18].

In a systematic review of 313 patients with primary ITP [19], the median duration of response for rituximab was 10.5 months. In the study from Patel et al., only 21% of adults maintained response with 3–5 years follow-up [20]. This suggests that the long-term durable responses demonstrated in this case series are most likely attributable to amifostine as opposed to rituximab. Clinical trials with larger patient cohorts are required to confirm results seen in this case series.

In conclusion, in this case series, three out of five patients who received amifostine and rituximab achieved durable responses. Although there is confounding by rituximab, given its established low durable response rate, it is likely that the excellent long-term responses achieved were a result of amifostine. Amifostine is non-immunosuppressive with tolerable adverse effects and should be considered in patients who have failed splenectomy and/or are at significant risk of immunosuppressive complications. Clinical trials with larger patient cohorts are required to confirm the efficacy of amifostine and the optimal dosing schedule, as a potential curative therapy for refractory ITP. Further investigation is required to confirm the mechanism of amifostine in achieving PLT recovery in ITP.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REVIEW ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Ludwik Hirszfeld: A pioneer of transfusion and immunology during the world wars and beyond

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Abstract

Ludwik Hirszfeld (1884–1954) was a Polish physician, immunologist and microbiologist. Together with Emil von Dungern, he showed that blood groups are heritable traits and established the terminology of the ABO blood group system. He discovered A_1 and A_2 blood groups, and showed for the first time, in a large-scale population study, that blood group frequency differs between populations. During World War I, he volunteered as an army physician. In the interwar period, he helped to create the National Institute of Hygiene in Warsaw and was instrumental in developing transfusion centres in Poland. During World War II, which he barely survived, he co-organized secret medical courses in the Warsaw Ghetto and played a major role in containing the typhus epidemic that ran rampant there since 1941. After the war, he was the first in Poland to put the theory of serological conflict between mother and foetus into clinical practice, saving the lives of almost 200 children by introducing exchange transfusions.

KEYWORDS
blood groups, blood transfusion, Ludwik Hirszfeld

Highlights

- Ludwik Hirszfeld (1884–1954) was a Polish physician, immunologist and microbiologist.
- He made fundamental discoveries and contributions in immunogenetics and immunohematology, including blood group inheritance (together with Emil von Dungern), the nomenclature of the ABO blood group system, and blood group frequency differences between populations (with Hanna Hirszfeld).
- Hirszfeld's commitment to science and humanitarian ideas helped contain typhus and typhoid fever epidemics during the World Wars, and save dozens of children after WWII when he put the theory of foetomaternal serological conflict into clinical practice by introducing exchange transfusions.

THE EARLY YEARS

Ludwik Hirszfeld was born in Warsaw (then part of the Russian Empire) on September 5th, 1884, in a family of assimilated Polish Jews. When Karl Landsteiner described agglutination of human red blood cells by sera of other individuals [1, 2], Ludwik Hirszfeld was 17 years old, had just graduated from high school in Łódź, and left the town to study medicine in Germany. He graduated from the Friedrich

Wilhelm University in Berlin and defended his M.D. thesis (a part of Prussian medical education at the time), which described physical aspects of haemagglutination and was published in 1907 [3].

Hirszfeld's first position was as an assistant at the Cancer Research Institute in Heidelberg, Germany. He worked with the head of the Serology department, Dr. Emil von Dungern, and they found that dog sera could be used to identify blood groups, similar to those described by Landsteiner [4]. They also found that canines inherit blood groups, prompting them to hypothesize that human blood groups are heritable too. By examining 348 individuals from 72 families, they showed that blood groups A and B did not occur in the offspring unless they were present in at least one of the parents, fulfilling the Mendelian principles of inheritance [5]. They showed that A and B are dominant, while O is a recessive trait. In addition, they came up with the names A, B and O for these blood groups, which have been used since. Interestingly, they adopted Mendel's nomenclature ("A" for the dominant trait, "a" for the recessive trait), and used "A" for the blood group that occurred more often, and "B" for the less common blood group [4]. It seems that contrary to the popular belief, they never used the letter O as an abbreviation for the word "Ohne," meaning "without" in German [6]. Rather, they used the terminology "weder A, noch B," meaning "neither A, nor B" [7]. As Felix Milgrom recalls, initially Hirszfeld insisted on using the numeral 0 instead of the letter O and he would give his students lower grades in oral examinations if they spoke about blood group O [6, 8]. Before the advent of computers, the letter O and the digit 0 were used interchangeably, which confused transfusion practitioners. Finally, the "Commission Permanent de Standarisation" created by the Hygiene Committee of the League of Nations in April 1928 accepted the nomenclature "proposed by von Dungern and Hirszfeld" (i.e., A, B and O) [6], which is still recommended today [9].

One year later, von Dungern and Hirszfeld showed that agglutination of A red blood cells can be strong or weak, and proposed two subtypes, named A_1 and A_2 [7]. They hypothesized that inheritance of blood groups was under the control of two independent pairs of genes; A and non-A, and B and non-B, presumably located on different chromosomes. Thus, a blood type O individual should be non-A/non-A and non-B/non-B, while a type AB individual could be A/non-A B/non-B. The theory worked quite well except it allowed the possibility that a person with group AB could have an O group child, which was ruled out by later observations. In 1924, a German mathematician Felix Bernstein developed a correction to the theory, proposing three allelic genes: A, B and O, and this explanation holds up to this day [10].

The seminal discovery of von Dungern and Hirszfeld marked the beginning of human immunogenetics. When Karl Landsteiner received the Nobel Prize in Physiology and Medicine in 1930 "for his discovery of human blood groups," he stated in his Nobel lecture: "… in the studies of the hereditary transmission of the blood groups, the principal factual results in this field we owe to the work of von Dungern and Hirszfeld" [11, 12].

Four years spent in Heidelberg were considered by Hirszfeld as "the most creative period in my whole life" [4]. But when in 1912 his wife Hanna assumed her new position at a paediatric clinic in Zürich, Ludwik applied for a position at the university there. In 1914, he presented a dissertation summarizing his studies on blood clotting and the complement system and was awarded the title of *Privatdozent* from the University of Zürich, Hygiene Institute [4]. It was there that Hirszfeld started teaching, which became his passion for years to come (Figure 1).

FIGURE 1 Ludwik Hirszfeld during his stay in Switzerland, years 1912–1915 [69]

WAR, EPIDEMIC AND SCIENCE

When the war started in August 1914, Ludwik Hirszfeld volunteered to join the Serbian army and travelled to Valjevo, which was on the brink of an epidemiological disaster. Medical corps of the Serbian army all but collapsed and the hospitals were overwhelmed with injured and sick soldiers. Together with Hanna Hirszfeld and Serbian medical personnel, they tried to stop the advance of the typhoid fever epidemic by introducing means of mass disinfection (Figure 2). Eventually, they succeeded, but the death toll was devastating: some 300,000 Serbian civilians and 100,000 soldiers died [13]. Incredibly, amid these dire circumstances, Ludwik Hirszfeld made important findings: he isolated two new strains causing paratyphoid fever A and paratyphoid fever C; one of the strains was later named *Salmonella hirszfeldii* [14]. But the advance of Austro-Hungarian and Bulgarian armies forced the Serbian forces to retreat through the Dinaric Alps to Albania in the winter of 1916, and Hirszfelds joined the withdrawing army [4].

They returned to Zürich, but soon went to the Balkans again, this time as physicians in the "Armées Alliées d'Orient." The armies, sent there by the Allied forces and stationed in Thessaloniki, were supposed to be an armed branch of Entente in the Balkans and included soldiers of many ethnic backgrounds [4]. This encouraged Ludwik Hirszfeld to look at the frequency of blood groups among people from many different countries. Together with Hanna they tested over 8000 individuals from at least 16 different ethnic groups, and

FIGURE 2 Ludwik and Hanna Hirszfeld with colonels of Serbian army (Slatol and Nekić). Valjevo, 1914 [69]

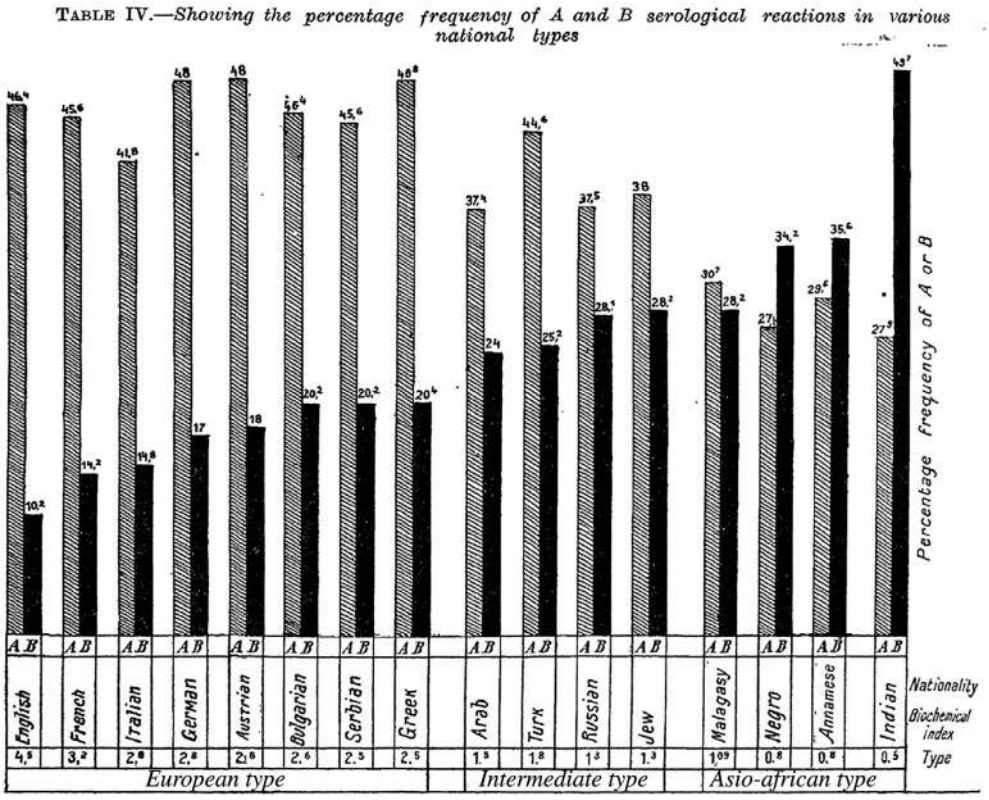

FIGURE 3 Frequency of A and B blood groups among individuals from different ethnic groups [15]. Reprinted with permission

found that the frequency of blood groups differed depending on the ethnic background; group A was more common among people from Western Europe (English 46% A, 10% B), while B was more common among Asians (Indian 27% A, 47% B). Their report was accepted by "The Lancet" and published in 1919, and it was the first paper showing that blood group frequencies differ between populations (Figure 3) [15]. Interestingly, in the same year, Frigyes Verzár and Oszkár Weszeczky from the University of Debrecen in Hungary performed a similar study among people living around Budapest [16]. Their study included 457 Hungarians, 81 "Gypsies" (now called Roma-Sinti) and 12 Germans. Despite the limited sample size, they obtained similar results: the most common blood group among

Germans was A, while B was predominant among Roma-Sinti. Their findings supported Hirszfeld's notion that the predominant blood group was A in Western Europe and B in Eastern Europe. Furthermore, the dominance of blood group B among Roma-Sinti, who arrived in Europe from the Indian subcontinent during the Middle Ages, suggested that blood groups may remain *racial traits* for hundreds of years, allowing to trace *racial origins* through blood analysis.

Ludwik and Hanna Hirszfeld's discovery introduced serological procedures into anthropology. They proposed that the A and B blood groups originated in geographically distinct locations: A in Europe and B in India. Notably, they used the term "race" when describing ethnic groups, and "blood" as a metaphor for heritage. At the time, these were widely used terms, devoid of any racist connotations that they have acquired later. However, the idea of different kinds of blood was corrupted by followers of the "völkisch" ideology in Germany, which emerged from the "blood and soil" mystic movements of the 18th century [17, 18]. The völkisch ideology started to gain traction in Germany when the Nazi party was rising into power after The Great Depression began in 1929. Studies by the German Society for Blood Group Science evaluated blood groups in several countries and found that blood group A predominated in Germany, while blood group B was more common in Poland (albeit by a small margin), which led them to the conclusion that "racially superior" people lived in Western Europe [19].

Admittedly, many beliefs about races as well as mental and physical differences between them that are currently controversial or have long been discarded were part of the zeitgeist in the 1930s. Thus, Hirszfeld's discovery found fertile ground and inadvertently made racial discrimination easier than other anthropological methods (such as craniometry), which had more obvious inconsistencies. So, it may be argued that Hirszfeld's theory of serological races buttressed the racial hierarchy, although it was not his intent to reinforce the idea of "superior" and "inferior" races [19]. In Nazi Germany, this misused theory led to biased research aiming at distinguishing "native Germans" from those who had mixed with other "inferior" races, such as Slavs or Jews. According to the völkisch theories, such mixing of blood between "superior" and "inferior" races would cause deterioration of the "Aryan" race [20]. As a result, fallacies of racial hygiene based on breeding a racial aristocracy from "uncorrupted peasant stock" became a staple among the community, and were endorsed by leading German scientists [19]. Ludwik Hirszfeld distanced himself from such pseudoscientific theories on many occasions, writing for example: "There are societies that would like to use blood groups for the goals that are not scientific, but solely political" [21].

In the landmark book "Les groupes sanguines" (1938), he said (translated from French by Rachel E. Boaz) [19]: "I would like to separate myself from those who link the blood types to the mystique of race. We have created the notion of the serological race analogous to the biological race. A biological race is made up of a group of individuals who share a unique characteristic. The notion of a serological race has nothing to do with that of an anthropological race. Furthermore, the actual distribution of blood types across the globe indicates the mixing of races and provides even more proof that mankind is a mosaic of races. The anthropological races, by contrast, are characterized by a mix of arbitrarily chosen traits" [19, 22].

Strangely enough, the bizarre connections linking Ludwik Hirszfeld with völkisch and racist theories have not died away after World War II, but persisted well into the 21st century. In 2013, a Swiss historian Myriam Spörri wrote in her book (which was also her PhD thesis at the University of Zürich) that "the fields of research Hirszfeld founded were "eugenically charged from the start," and the idea of "pure blood" first expressed by the Hirszfelds held on tenaciously and was never challenged, despite new findings" [23]. This recent reinterpretation of Hirszfeld's legacy shows how careless application of the contemporary worldview to historical analyses may pigeonhole historical figures and lead to absurd conclusions.

BUILDING A NEW WORLD IN INDEPENDENT POLAND

Poland regained independence in November 1918, and the Hirszfelds decided to come back to the newly formed country. Thanks to the support of Ludwik Rajchman who worked at the Ministry of Health, Ludwik Hirszfeld assumed responsibility to create the Institute of Serum Research, which later became the National Institute of Hygiene. He became deputy director, supervising the training of new generations of researchers in the fields of bacteriology, virology, immunology, cancer research and diagnostics [4].

The Institute grew from a small laboratory to a large institution employing several hundred people, keeping Hirszfeld busy with organizational matters, but he still managed to pursue his interest in blood groups. The research initiated by Ludwik Hirszfeld in the Balkans was continued at the National Institute of Hygiene by Jerzy Mokrzycki and Wanda Halber, who showed that the frequency of blood group A differed geographically across Poland, and varied from 32.2% in Lublin Voivodeship (province) to 46% in Kraków voivodeship, while group B frequency varied from 16.9% in Nowogródek Voivodeship (now Belarus) to 23.7% in Kraków Voivodeship [21]. In addition, Róża Amzel surveyed the distribution of the M blood group, which had been discovered at that time [24, 25]. Exploring links between blood groups and infectious diseases, Hirszfeld and his coworkers Amzel and Halber found that individuals with blood group O tested negative in the Wassermann reaction more often than people with other blood types [26].

In addition, he made important contributions to forensic science, which increasingly relied on blood group testing, and often testified as an expert witness in court [27]. Ludwik Hirszfeld also hypothesized on how blood groups may have evolved. He formulated the theory of pleiades, according to which the trait O is the precursor of A and B antigens [28]. Hirszfeld and Amzel showed that red blood cells from A or B individuals contain various amounts of "O substance," which today we would call the H antigen [29]. This led them to the hypothesis that the A and B antigens emerged from the O antigen by gradual mutations [29]. Today we know that this is indeed the case, as the H antigen is the precursor of A and B antigens, and both arise by sequential action of glycosyltransferases [30]. Later, the seminal studies by Morgan and Watkins supported that theory [31], which led

them to decipher the molecular background of the ABO blood group system [32]. At present, over 70 alleles of the ABO gene, which arose from recurrent mutations or intragenic recombination, are known, and their expression often leads to changes in phenotype [33]. It is tempting to speculate that Hirszfeld would have come to the same conclusions had the war never occurred. He summarized his views on the relationship between the ABO blood group antigens in the review written in occupied Poland in 1943 and published in the Journal of Immunology in 1947 [34].

Ludwik Hirszfeld was also interested in how ABO blood group incompatibility between mother and foetus may cause damage to the foetus or newborn [35]. It seems that he was the first to propose that serologic incompatibility between mother and foetus may lead to abortion or fetal or neonatal disease. The conclusive evidence for that idea came in the 1950s when it was demonstrated that the Rh blood antigen can cause hemolytic disease of the foetus and newborn [36].

As an internationally recognized blood group scientist, Ludwik Hirszfeld often participated in conferences and congresses. The international meeting of transfusion science, convened in Rome in 1935, was a particularly remarkable event. Ludwik Hirszfeld gave the opening address (translated from French by Hans Erik Heier [17]): "Our science expresses not only the intellectual progress, but also the moral values of a nation. To give blood to a fellow human being is an act of compassion, it is to imagine and suffer the suffering of the other. For this reason, the interest which a nation carries in the problem of organizing blood donors, allow to judge not only the culture and the spirit (of that nation), but its moral strength. It is in our area that a unique organization of anonymous donors was created, offering their blood to the unknown suffering one" [4, 17, 37]. The participants of the meeting decided to meet again in 1937 in Paris, where the International Society of Blood Transfusion (ISBT) was formed [17, 37]. Ludwik Hirszfeld participated in that conference too, as well as in several meetings of the Standardization Committee of the League of Nations.

MEDICINE IN THE WARSAW GHETTO

In September 1939, Ludwik Hirszfeld was supposed to attend the International Microbiology Congress in New York, but changed his mind and remained in Poland. Thus, the Hirszfelds were in Warsaw when the war started: Hanna organized a provisional hospital in the Saska Kępa (a prestigious Warsaw neighbourhood where they built a house), and Ludwik was busy organizing blood transfusions at the Ujazdowski Hospital because the Institute of Blood Transfusion, which was responsible for this task, had been destroyed in one of the first German air raids [4]. Warsaw surrendered on 28 September 1939, and the brutal German occupation began; meanwhile, the Eastern part of Poland was occupied by the Soviets. In one of the first decrees, Germans ordered that all Jews wear yellow armbands with the Star of David, but Hirszfeld ignored this order. However, he was powerless against the other German decree, which stated that the new director of the National Institute of Hygiene would be Dr. Robert von Kudicke, his former colleague from Heidelberg. In the autumn of 1940, Germans started forming a Ghetto in Warsaw, forcing over 300,000 people to live in the area of 2.9 km^2, but in the beginning, the Hirszfelds were able to remain in their home at Saska Kępa, where Ludwik wrote his book "General Immunology," which appeared after the war [38]. For some time, they were able to survive in the "Aryan" (i.e. not Jewish) part of Warsaw, but in February 1941 they were forced to move to the Ghetto. Hirszfeld recalled a meaningful episode: a German sentry at the entrance to the Ghetto inspected the suitcase and found a book written by Hirszfeld in German. Hirszfeld explained that he wrote that book as a scientist employed by the German government. The soldier said "but now you are just a Jew" [4].

In the Ghetto, they found shelter at the rectory of All Saints Church at Grzybowski Square. Ludwik Hirszfeld offered his services as a medical doctor, so the chairman of Jewish Community in the Ghetto, Adam Czerniaków, asked him to introduce measures against typhoid fever, which was the main cause of high mortality in the Ghetto in addition to hunger. He became the chairman of the Health Council and did his best to slow down the epidemic. Despite having very limited access to medications, diagnostic reagents and disinfectants, he managed to improve the health conditions. The great help in this work was provided by his former National Institute of Hygiene assistant, Róża Amzel (later murdered by Nazis), also forced to live in the Ghetto. They secretly vaccinated people against typhoid fever, using the vaccine invented by Prof. Rudolf Weigl and produced at the Weigl's Institute of Studies on Typhus and Viruses in Lwów (Lemberg), then under German occupation as well [39]. Later, the vaccine was produced according to Rudolf Weigl's protocol by Dr. Edmund Wojciechowski at the National Institute of Hygiene and smuggled to the Ghetto [40]. They also managed to design a simple test to detect typhoid fever bacteria in urine using precipitation by a patient's serum [41]. In addition, Ludwik Hirszfeld was teaching bacteriology and serology at secret courses of medicine. Over 500 students attended the courses, of whom fewer than 50 survived the war [40].

In 1941, at the beginning of his time in the Ghetto, Ludwik Hirszfeld and Róża Amzel came across an individual with Hodgkin's disease whose blood group was difficult to determine. The red blood cells did not agglutinate with any of the test sera and the patient's serum contained strong anti-O (anti-H in today's nomenclature) agglutinins. It seems that it was the rare Bombay phenotype, described by Bhende et al. 11 years later, and caused by the lack of H epitope, which is the precursor of A and B antigens. After the war, Ludwik Hirszfeld described his observation in a Polish journal [42]. When Bhende et al. published his results in *The Lancet* [43], Hirszfeld wrote a letter to the editor explaining that he had found a similar case during his time in the Ghetto [44]. It is tempting to speculate that the Bombay phenotype might have well been named Warsaw if history had taken a different turn.

Meanwhile, the situation in the Ghetto was on the verge of collapse. Overcrowding (the population density was over 140,000 people per km^2), inadequate food rations (less than 400 kcal per person per day) and an almost complete lack of healthcare were taking a crushing human toll. The monthly death rate was between 3000 and 5000. A

vivid account of living conditions in the Ghetto was provided by Hirszfeld in "The story of One Life" [4]. As the population of the Ghetto dwindled, the Germans shrank the borders, forcing people to move to an even smaller area. In line with this, the Germans ordered to close hospitals and laboratories. The last laboratory organized by Hirszfeld was located at Żelazna street, but it was never opened, as on July 22nd, 1942, Germans started "Grossaktion Warschau," which was the code name for deportation and mass murder of all Jews from the Warsaw Ghetto. The Jews were rounded up by Waffen SS forces, terrorized and brought to Umschlagplatz station square (today Stawki Street in the Wola neighbourhood), whence they were sent in overcrowded Holocaust trains to Treblinka extermination camp (about 100 km northeast from Warsaw). Before September 1942, over 300,000 Jews from the Warsaw Ghetto were deported to Treblinka. Over 800,000 Jews were murdered there, and fewer than 70 survived [45].

Ludwik and Hanna Hirszfeld managed to escape from the Ghetto between March and June 1942. The extremely risky and costly escape was organized by Konstanty Potocki, an apothecary who ran a pharmacy outside the Ghetto [40]. Their counterfeit documents were provided by Dr. Feliks Przesmycki, a former associate at the National Institute of Hygiene. At first, they were hiding in Warsaw, but soon moved to Kielce voivodeship, where they found shelter in the village Kamienna posing as fugitives from Warsaw. Their only daughter Maria died in the neighbouring village of Kocina and was buried at a small cemetery under the false name of Maria Halecka. After her passing, they moved to Tłuszcz in the Mazowsze region where they were hiding until the Germans withdrew [4].

PULLING THE MICROSCOPE OUT OF THE RUBBLE

When the Soviet army entered Poland, the Hirszfelds moved to Lublin, a city in Eastern Poland, where both helped to establish a new university (now Maria Curie-Skłodowska University). They did not want to return to Warsaw, which was razed to the ground, so they accepted the invitation to organize a new university in Wrocław, the former German city of Breslau, which after the Potsdam Conference was handed over to Poland. Ludwik Hirszfeld helped to organize the Faculty of Medicine at the University of Wrocław, and became its first dean. He gave the first lecture at the newly opened School of Medicine, and created the Department of Medical Microbiology. Thanks to the Rockefeller Foundation, he and Hanna travelled to the United States in 1946 and visited top American medical schools and laboratories. Hirszfeld was impressed with the progress of blood group research; he met Dr. Alexander Wiener and Dr. Philip Levine and discussed with them their studies on the haemolytic disease of the newborn caused by Rh incompatibility [46].

He returned to Poland realizing that science had advanced considerably, and the 6 years he lost to war was a time he could never reclaim. Nevertheless, he continued his research on blood groups. The Rh antigen, the main player in haemolytic disease of the foetus and newborn (HDFN), had already been discovered [47], but there was no prophylaxis, so Hirszfeld, together with obstetrician prof. Kazimierz Jabłoński, introduced exchange transfusion as a treatment for HDFN. This therapy saved the lives of almost 200 children [48, 49].

A large part of Ludwik Hirszfeld's interest in forensic medicine was paternity testing. Blood grouping has been used to that end since

FIGURE 4 Ludwik Hirszfeld with students. Wrocław, around 1950 [69]

the 1920s [50, 51], but the results were underwhelming because ABO was the only blood group system known at the time. The discovery of blood group systems MN in 1927, and Rh in 1940 significantly improved the reliability of testing. Ludwik Hirszfeld together with Prof. Hugo Steinhaus and Dr. Józef Łukaszewicz prepared a table of probability to guide paternity exclusion [52].

The post-war years were very busy for the Hirszfelds, but like after WWI, it was mainly with administrative efforts. While Hanna Hirszfeld organized a professional paediatric clinic in Wrocław, Ludwik and his coworkers at the Department of Medical Microbiology tried to improve the poor public health in the post-War Poland. Together with his close associate Felix Milgrom, he organized widely publicized diagnostics of sexually transmitted diseases, which ran rampant at the time. He was still an active teacher (Figure 4) [40]. In 1953, Hirszfeld founded the scientific journal *Archivum Immunologiae et Therapiae Experimentalis* and became its first editor-in-chief [53].

Meanwhile, the political situation in Poland was going from bad to worse, as the Communist party tightened the iron grip on the Polish people and the scientific community. The pseudoscientific follies of a Soviet biologist Trofim Lysenko, who argued that acquired traits could be inherited and genes do not exist, became the obligatory school of thought in biology [54]. "Followers of Mendelism-Morganism," as the scientists who refused to accept Łysenko theory were called, risked losing their jobs (and many of them did). Since most of Hirszfeld's works concerned genetics, he was often accused of "yielding to old superstitions" [40]. His studies on the frequency of ABO blood groups also sparked controversies with visiting Soviet scientists who considered it "an insult to the Russian nation" because the frequency of B blood group was quite high among Russians, similarly to people of Asian background [15, 55]. Both Hirszfelds resisted the pressure from the officials and never joined the Communist party, which was unusual at the time, especially among high-profile scientists, but that independence came at a cost. Ludwik Hirszfeld's efforts to transform the Department of Microbiology into an institute of the Polish Academy of Sciences had long been thwarted. Finally, a few months before his death, the Institute of Immunology and Experimental Therapy in Wrocław was created. He became its first director.

He died on March 7th, 1954 and was buried at the St. Laurentis cemetery in Wrocław. Several thousand people attended the funeral. The obituary appeared in The Lancet [56]. One of the auditoriums at the Medical University of Wrocław, as well as a major square in Wrocław, bear the name of Ludwik Hirszfeld. The Polish Post issued a stamp with Ludwik Hirszfeld in 2009 [57]. Ludwik Hirszfeld co-authored 395 papers, half of them devoted to blood group science and blood transfusion. He received honorary degrees from the University of Prague (1950) and Zürich (1951). He is considered one of the pioneers of blood group research [8, 57–59]; several books [40, 60, 61], as well as articles in scientific journals have been written about him [62, 63]. His students wrote articles devoted to him [64–67]. His closest associate and friend, Felix Milgrom, wrote two articles, one in the Vox Sanguinis series "Milestones in Blood Transfusion and Immunohematology" about his fundamental discoveries [68] and one in Hirszfeld-founded Archivum of Immunologiae and Therapiae Experimentalis, which tells about his interactions with Ludwik Hirszfeld [55]. Milgrom wrote in the former: "Hirszfeld belongs to the extinct group of scientists who created the fields of immunohematology and immunogenetics. He has had a profound influence on blood group science and transfusion medicine." Sadly, many of his associates involved in blood group science and immunology, including Felix Milgrom, Adam Bekierkunst and Władysław Mański were forced to leave the country after his death.

Ludwik Hirszfeld has been remembered by his students not only as a great scholar but also as a dedicated teacher. He epitomized his favourite aphorism "He who wants to ignite others must burn himself." Hirszfeld did burn with scientific passion and passed his enthusiasm along to his students.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

A comparison between liquid group A plasma and thawed group A plasma for massive transfusion activation in trauma patients

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Abstract

Background and Objectives: The use of group A thawed 24-h plasma when resuscitating haemorrhagic shock patients has become more common; however, limited data exist on the clinical use of liquid plasma (LP). Our aim is to determine whether LP is of clinical benefit to patients requiring massive transfusion.

Materials and Methods: The objective of this retrospective study was to detect any difference in 24-h survival between patients receiving liquid or thawed plasma (TP) during their massive transfusion activation. Other objectives were to report any difference in hospital length of stay (LOS), intensive care unit (ICU) LOS and in-hospital survival. Data collected included gender, age, mechanism of injury, Injury Severity Score, Revised Trauma Score and Trauma Injury Severity Score.

Results: A total of 178 patients received 1283 units of LP, median 4 and range (1–56), whereas 270 patients received 2031 units of TP, median 5 and range (1–87). The two study groups were comparable in terms of gender, age, mechanism of injury, whole blood, red blood cells, platelets and cryoprecipitate transfused. The use of LP during the massive transfusion activation in traumatically injured patients was not associated with increased 24-h survival compared to when using TP, $p = 0.553$.

Conclusion: Our study did not show a difference in 24-h or 30-day survival between the use of LP compared to TP in trauma patients. LP should be considered an alternative to TP in trauma patients requiring immediate plasma resuscitation.

KEYWORDS
massive transfusion, plasma, transfusion medicine, trauma

INTRODUCTION

Since haemorrhage remains a significant cause of preventable death in traumatic injury, early and balanced resuscitation beginning with plasma administration is associated with decreased mortality and has been demonstrated to improve survival in the severely injured [1–3]. In severe trauma or massive bleeding with coagulopathy, the importance of having plasma rapidly available is currently being recognised [4–6]. In the PAMPer study by Sperry et al. [7] of injured patients at risk for haemorrhagic shock, the administration of thawed plasma (TP) during prehospital air medical transport was safe and resulted in lower 30-day mortality and lower median prothrombin time ratio than

standard-care resuscitation. An alternative to TP is liquid plasma (LP), which may carry a longer shelf life for treatment of massively bleeding patients. Plasma frozen within 24 h and used as TP with a thaw time of approximately 25 min can delay administration to massively bleeding patients. The TP shelf life of 5 days limits the supply and may incur wastage. LP offers a good alternative given its immediate transfusion potential and extended shelf life. LP can be separated from whole blood at any time during storage and stored at 1–6°C for up to 5 days after the expiration date of the whole blood, which is 21 days when collected on citrate–phosphate–dextrose anticoagulant preservative [8]. Therefore, utilising LP enables more plasma to be readily available for immediate transfusion and improves early resuscitation during massive transfusion.

The objective of our study was to detect if there is any difference in 24-h survival between patients receiving group A LP or TP during massive transfusion resuscitation.

MATERIALS AND METHODS

The sources of the study data were trauma patients admitted to our trauma centre with Level 1 activation using both the blood bank database and the hospital electronic health records. All data were collected retrospectively and reviewed by the principal investigator. Group A LP units and TP units, received as plasma frozen within 24 h, were obtained from the American Red Cross blood services division. All plasma units were collected from only male donors to comply with the transfusion-related acute lung injury risk mitigation requirement [9]. All LP units were stored between 1 and 6°C for a maximum of 26 days. Isohaemagglutinin titres are not determined at our institution because the safety of using group A plasma in trauma resuscitation had been previously demonstrated in the STAT study [10]. LP is stored in the emergency department's monitored refrigerator and is available for immediate use before the recipient's ABO group is known as part of our massive transfusion protocol (MTP) or for emergency use [9]. LP units are not leukocyte reduced and are irradiated to mitigate against potential transfusion-associated graft-versus-host disease. All eligible adult male and female patients age 18 years and older receiving (≤6 h) emergency transfusion as Level 1 activation either for initial resuscitation or for MTP were included in the study. The exclusion criteria included patients who are 16 years old or younger, patients who did not receive at least one unit of either thawed or LP and patients who receive LP or TP after the initial 6-h period of their presentation. Sample size was determined based on an initial analysis at the time of protocol development

TABLE 1 Demographics, mechanism of injury, transfusion and study outcome data between groups

	Liquid ($N = 178$)	Thawed ($N = 270$)	*p* Value
Demographics			
Gender, *n* (%)			
Female	46 (25.8)	62 (23.0)	0.559
Male	132 (74.2)	208 (77.0)	
Age, mean (SD) years	43.2 (18.9)	42.5 (19.0)	0.670
ISS, mean (SD)	46.4 (16.6)	32.3 (18.0)	<0.001
RTS, mean (SD)	5.9 (2.3)	6.0 (2.0)	0.438
MOI, *n* (%)			
B	110 (61.8)	164 (60.7)	0.900
P	68 (38.2)	106 (39.3)	
TRISS prob of surv, mean (SD)	0.6 (0.3)	0.7 (0.3)	<0.001
Liquid (median, range)	4 (1–56)		
Thawed (median, range)		5 (1–87)	
WB or Cryo (median, range)[a]	1.5 (1–3)	2 (1–12)	0.851
RBC (median, range)[a]	3 (1–24)	4.5 (0–30)	0.752
Platelet (median, range)[a]	0.5 (0–6)	1 (0–7)	0.199
Total units (median, range)[a]	5 (0–69)	6 (0–106)	0.436
Outcome			
Survival >24 h *n* (%)	145 (81.5)	227 (84.1)	0.553
LOS, median (IQR) days	9.5 (15.3)	12.35 (15.5)	0.57
In-hospital survival, *n* (%)	122 (68.5)	263 (70.7)	0.695
ICU stay = yes, *n* (%)	101 (56.7)	170 (63.0)	0.223

Abbreviations: B, blunt; ICU, intensive care unit; IQR, interquartile range; ISS, Injury Severity Score; LOS, length of stay; MOI, mechanism of injury; P, penetrating; RBC, red blood cells; RTS, Revised Trauma Score; SD, standard deviation; TRISS, Trauma Injury Severity Score; WB, whole blood.
[a]During the first 6 h of admission.

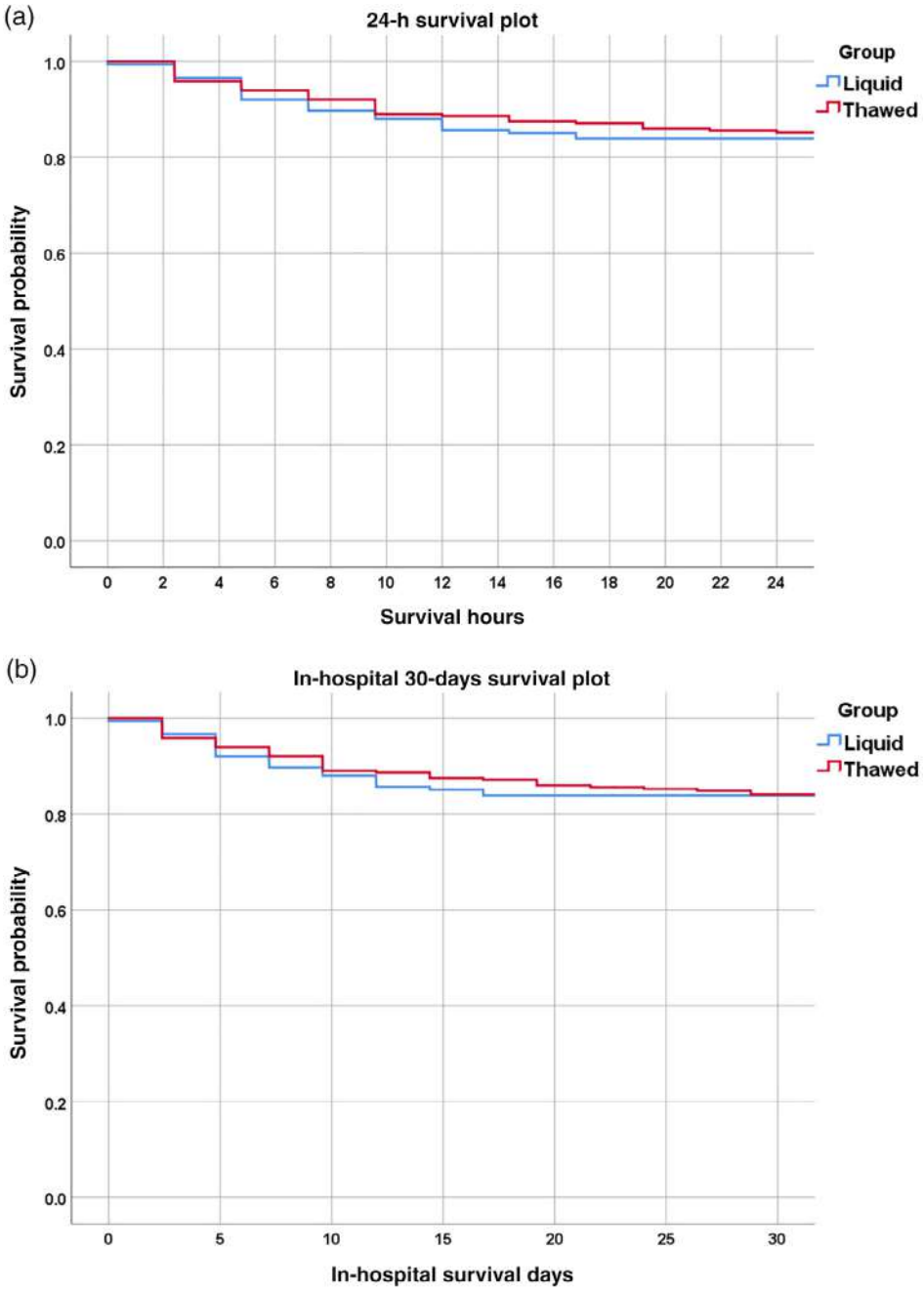

FIGURE 1 (a) 24-h survival plot. (b) In-hospital 30-day survival plot

indicating there might be at least 150 LP cases, of which 120 cases will have a greater than 24-h survival. Assuming 80% event rate for LP, a sample size of 172 for each group would provide an 80% power at the 0.05 significance level to detect a minimal odds ratio (OR) of 2.01 or larger using chi-squared analysis.

Level 1 activation includes any two of the following four criteria: penetrating injury, positive focused assessment with sonography in trauma, heart rate greater than 120 beats per minute and systolic blood pressure less than 90 mmHg [9]. TP was the standard of practice at our institution prior to October 2018, at which time the organisation transitioned to LP for the MTP. The study was conducted at a Level 1 academic trauma centre where the transfusion service utilises group O AS-1 or AS-3 red blood cell (RBC) units, group A LP or TP and one unit of single-donor platelet apheresis in a 4:4:1 ratio as component therapy for the MTP [9]. The total number of either TP or LP plasma units transfused to eligible recipients during the first 6 h of admission was collected from the blood bank's electronic database. This retrospective study collected transfusion and clinical data on a cohort of trauma patients receiving TP from January 2016 to September 2018 and LP from October 2018 to July 2020. Wake Forest University Health Sciences' Institutional Review Board approved this data collection protocol.

Statistical analysis

Results were analysed using descriptive statistics to compare transfusion of LP and TP groups by demographic and clinical characteristics, including age, sex, mechanism of injury, amount of units transfused, Injury Severity Score (ISS), Revised Trauma Score (RTS) and Trauma Injury Severity Score (TRISS) probability of survival. The primary outcome of this study was 24-h survival between LP and TP transfusions. Secondary outcomes included hospital length of stay (LOS), in-hospital survival and intensive care unit (ICU) stay during the transfusion episode. Comparison between TP and LP groups was done using chi-square tests for proportions and using student *t*-tests for continuous variables. Variables associated with the outcomes were included in a multivariable logistic regression model. Independent variables that were chosen as a priori for inclusion in the multivariable model were age, sex, mechanism of injury, ISS, RTS and TRISS and TP versus LP. Co-linearity within independent variables was assessed using variance inflation factor and condition index, with values greater than 10 indicating acceptability. We computed the ORs following multivariable logistic regression. All statistics were reported as point values with 95% confidence intervals (CIs). In addition, Kaplan–Meier survival analysis was performed to visualise difference in survival between the two groups.

Additionally, sensitivity analyses were performed to evaluate effect of heterogeneity of confounders on primary and secondary study outcomes using a 1:1 matching ratio. Variables used for propensity matching between LP and TP groups include age, gender, ISS, RTS and mode of injury. For each patient in trauma cohort, a propensity

TABLE 2 Primary outcome: 24-h survival following multivariable logistic regression

Primary outcome: 24-h survival				
		95% CI for odds ratio		
	Odds ratio	Lower	Upper	*p* Value
Age	0.982	0.965	0.999	0.042
Gender, female	1.025	0.5	2.103	0.946
ISS	0.963	0.946	0.98	0
RTS	1.911	1.639	2.227	0
MOI, blunt	2.482	1.245	4.95	0.01
Liquid versus thawed	1.533	0.796	2.954	0.201

Abbreviations: CI, confidence interval; ISS, Injury Severity Score; MOI, mechanism of injury; RTS, Revised Trauma Score.

TABLE 3 Secondary outcome analysis following multivariable logistic regression

			95% CI for odds ratio	
Covariates	*p* Value	Odds ratio	Lower	Upper
In-hospital survival				
Age	0.000	1.034	1.019	1.049
Gender, female	0.502	0.816	0.451	1.478
ISS	0.000	1.040	1.025	1.056
RTS	0.000	0.551	0.481	0.631
MOI, blunt	0.751	0.912	0.516	1.612
Liquid versus thawed	0.066	0.596	0.343	1.035
ICU stay during the transfusion encounter				
Age	0.256	1.006	0.995	1.018
Gender, female	0.066	0.651	0.412	1.028
ISS	0.418	1.005	0.993	1.017
RTS	0.003	1.158	1.051	1.277
MOI, blunt	0.064	1.499	0.977	2.300
Liquid versus thawed	0.154	0.734	0.479	1.123

Abbreviations: CI, confidence interval; ICU, intensive care unit; ISS, Injury Severity Score; MOI, mechanism of injury; RTS, Revised Trauma Score.

score (ranging from 0 to 1) was generated using logistic regression model. A random nearest-neighbour match, using a calliper width of 0.01, was performed to identify patients who were subsequently included in the sensitivity analysis.

In our study, a two-tailed p-value of <0.05 was considered statistically significant. Data were analysed using IBM SPSS Statistics version 26 (IBM Corporation, New York, NY).

RESULTS

A total of 448 patients and 3314 plasma transfusions were analysed. About 178 patients received 1283 of LP, whereas 270 patients received 2031 units of TP. The mechanism of injury for most patients was blunt trauma (motor vehicle accidents and falls) and penetrating trauma (gunshot wounds and stabbings). Table 1 shows the demographic and the transfusion data characteristics between the two groups. There were no statistically significant differences in patient age, sex or mechanism of injury. Similarly, there were no statistically significant differences in the amounts of transfused whole blood, RBC, platelets or cryoprecipitate units as part of the massive transfusion activation between the two groups. However, there was a statistical difference in TRISS indicating the LP group had a lower chance of survival than the TP group when assessing the type of injuries, LP TRISS versus TP TRISS mean (standard deviation) 0.6 (0.3) versus 0.7 (0.3) $p < 0.001$. Using chi-square analysis, there was no significant difference in the primary outcome of 24-h survival between the two groups. There were also no significant differences between the secondary outcomes of in-hospital LOS, in-hospital survival or ICU LOS between the two groups (Table 1). A logistic regression analysis was performed for 24-h survival, in-hospital survival and ICU LOS during the encounter as a linear combination of the following predictor variables: age, sex, mechanism of injury, ISS, RTS and LP versus TP.

In the univariate analysis, all examined variables, including the use of thawed versus LP were not significantly associated with primary outcome of 24-h survival and the secondary outcomes of in-hospital survival and ICU stay during the transfusion episode and did not show any statistical significance (Table S1). Likewise, in the univariate analysis of the amount of total blood products transfused during the 6-h encounter, all examined variables including use of whole blood or cryoprecipitate, RBC or platelet were not significantly associated with primary outcome of 24-h survival and the secondary outcomes of in-hospital survival and ICU stay did not show any statistical significance (Table S2).

There was no difference in the 24-h survival or the 30-day survival between the two groups (Figure 1a,b). The use of LP or TP was not identified as a significant predictor variable in any analysis (Tables 2 and 3).

After sensitivity analysis using propensity score matching, we were able to match 140 (81%) cases from the LP group with an equivalent number of controls from the TP group. Within the propensity-matched cohort, we determined that patients who received LP were 0.778 (95% CI 0.705–1.841, $p = 0.553$) times more likely to survive in 24 h compared to those who received TP. The odds for in-hospital survival was 0.414 (95% CI 0.334–1.196, $p = 0.227$) and for ICU stay was 0.614 (95% CI 0.532–1.692, $p = 0.466$) of the LP compared to TP within the propensity-matched cohort.

DISCUSSION

Plasma has been demonstrated in numerous studies to reverse coagulopathies associated with trauma and it can improve survival even in the absence of packed red blood cell transfusions [11–13]. The importance of having TP available for immediate resuscitation of trauma patients presenting to the emergency department with haemorrhagic shock is well recognised [14]. Therefore, when MTP is activated in trauma patients, the time necessary to thaw frozen plasma may delay the availability of this product. LP offers an attractive alternative given immediate transfusion potential since it is never-frozen plasma with an extended shelf life. Based on our findings, the use of LP during the massive transfusion activation in traumatically injured patients was not associated with increased 24-h survival compared to when using TP. Matijevic et al. [15] have demonstrated that initial haemostatic profiles of LP were better compared to TP. Their study indicates that LP has better coagulation properties in many aspects when compared with TP and retains enough of the initial factor and inhibitor activities during the approved storage time. By switching to LP, we noticed a slight decrease in total plasma wastage (0.07%) during the 4-year period. Even though the cost was minimal, the most significant difference was the decrease in turnaround time between the LP issued (≤3 min) compared to the TP issued (≤45 min).

An extended shelf life means decreased plasma wastage and improved turnaround time. Another study by Gosselin et al. [16] found that LP maintains at least 50% of factor activity and thrombin-generating capacity up to 15 days of storage at refrigerator temperature. Beattie et al. [1] recently reported on the use of LP as the primary plasma resuscitation product that can improve adherence to ratio of plasma to RBC transfusions used in MTP thereby avoiding delay of plasma transfusion. They also found in their study that patients who received LP demonstrated improved 28-day recovery and reduced odds of acute kidney Injury, suggesting an association between LP implementation and improved clinical outcomes. Another study by Cao et al. [17] found that LP stored up to 28 days, showed both a decrease in inflammation and TNF-α-induced endothelial cell permeability as effectively as TP. Recent findings by Meledeo et al. [18] demonstrated stable fibrinogen levels at day 40 of storage using thromboelastogram maximum amplitude. Another study by Taghavi et al. [19] found that TP may result in the decrease of several growth factors and/or procoagulants compared to LP. All of these findings demonstrate that LP, regardless of the duration of storage even up to 28 days, is comparable TP.

In a recently published study by Chehab et al. [20], the authors examine outcomes of trauma patients transfused with LP compared with TP using a propensity-matched analysis, which revealed no significant difference between the two groups post-matching in terms of mortality, major complications and hospital LOS. Likewise, in our study, they found no significant differences in 24-h mortality and in-hospital mortality.

Effective implementation of a MTP depends on 24 h a day and 7 days a week state of readiness in the blood bank for rapid delivery of components to the emergency department or to the operating room. However, in practice, it may be difficult to continuously maintain a desired ratio of transfused components during active bleeding and ongoing resuscitation when TP is in use. Since we instituted our LP programme for massive transfusion in trauma patients, we believed there has been improved emergent plasma availability for rapid delivery of components to the bedside. Likewise, Allen et al. [21] reported on the improvements in allocation of blood products with the use of LP by improving the early packed red blood cells: Plasma ratio transfused to patients requiring 'super MTP' (receiving >30 units of packed RBCs in 24 h) compared to when using TP.

There are limitations to our study. First, this study was performed at a Level 1 academic trauma centre and may not be generalisable to other trauma centres that may have different blood banking resources and practices [9]. Second, the lack of outcome differences between these two groups may be explained by the severity of injury and haemorrhage in both groups. Third, there could be limitations due to differences in clinical practices or patient management that could impact patient outcomes; however, we did not see any differences in patient outcomes due to the switch from TP to LP.

Whether LP use confers survival or morbidity advantages over TP remains to be determined, as this comparison will require a non-inferiority randomised controlled trials between LP and TP in trauma patients requiring massive transfusion.

In conclusion, our study did not show a difference between the use of LP compared to TP in trauma patients. Our study showed no significant difference in the 24-h or 30-day survival or the secondary outcomes of in-hospital survival, in-hospital LOS or ICU LOS. The survival analysis showed no statistically significant difference in survival outcomes between the two groups. LP should be considered an alternative to TP in trauma patients requiring immediate plasma resuscitation.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Association between leukoreduced red blood cell transfusions and hospital-acquired infections in critically ill children: A secondary analysis of the TRIPICU study

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Abstract

Background and Objectives: Hospital-acquired infections (HAIs) are an important problem in critically ill children. Studies show associations between the transfusion of non-leukoreduced red blood cell units (RBC) and increased HAI incidence rates (IRs). We hypothesize that transfusing pre-storage leukoreduced RBC is also associated with increased HAI IR. We aim to evaluate the associations between (1) a leukoreduced RBC restrictive transfusion strategy and HAI IR, (2) leukoreduced RBC transfusions and HAI IR, and (3) the number or volume of leukoreduced RBC transfusions and HAI IR in critically ill children.

Materials and Methods: This post hoc secondary analysis of the "Transfusion Requirement in Paediatric Intensive Care Units" (TRIPICU) randomized controlled trial (637 patients) used quasi-Poisson multivariable regression models to estimate HAI incidence rate ratios (IRRs) and 95% confidence intervals (CI).

Results: A restrictive transfusion strategy yielded an IRR of 0.88 (95% CI 0.67, 1.16). The association between transfusing leukoreduced RBCs (IRR 1.25; 95% CI 0.73, 2.13) and HAI IR was not statistically significant. However, we observed significant associations between patients who received >20 cc/kg volume of leukoreduced RBC transfusions (IRR 2.14; 95% CI 1.15, 3.99) and ≥3 leukoreduced RBC transfusions (IRR 2.40; 95% CI 1.15, 4.99) and HAI IR.

Conclusion: Exposing critically ill children to >20 cc/kg or ≥3 leukoreduced RBC transfusions were associated with higher HAI IR, suggesting dose–response patterns.

KEYWORDS
epidemiology, leukodepletion, transfusion medicine, transfusion strategy, transfusion-paediatrics

Highlights

- Critically ill children who receive >20 cc/kg or ≥3 leukoreduced RBC transfusions present higher incidence rates of hospital-acquired infections.
- Multiple leukoreduced RBC transfusions are associated with a higher incidence rate of hospital-acquired infections in critically ill children, even after controlling for disease severity.

- The observed association between the incidence rate of hospital-acquired infections associated with the number and volume of RBC transfusions suggests a dose-response pattern.

INTRODUCTION

Hospital-acquired infections (HAIs) are frequent adverse healthcare events. Rutledge-Taylor et al. estimated that the overall HAI prevalence in paediatric patients is 8%, increasing to 17.7% in Canadian paediatric intensive care units (PICUs) [1]. To help prevent HAIs, a greater knowledge of the biological mechanisms leading to infection risk is vital. One hypothesis is that despite the clinical benefits of red blood cell (RBC) transfusions, they may be associated with an increased risk of HAIs through transfusion-related immunomodulation (TRIM). The best well-described TRIM mechanisms suggest that the presence of white blood cells (WBCs) in transfused RBC units is associated with immunosuppression [2].

Proposed measures to prevent TRIM include pre-storage leukoreduction, which removes most WBCs from RBC units; however, it does not remove them entirely [3]. Thus, the few remaining WBCs may downregulate the transfusion recipient's immune system. Randomized controlled trials (RCTs) have evaluated the association between transfusing leukoreduced RBCs and HAIs compared to non-leukoreduced RBCs, but their results were controversial [4–7]. These studies suggest that transfusing leukoreduced blood is associated with fewer HAIs. Nevertheless, the question of if the transfusion of leukoreduced blood itself is associated with higher HAI incidence rates (IRs) remains.

To evaluate the existence of an association between the transfusion of leukoreduced RBCs and HAIs, we performed a post hoc secondary analysis of the Transfusion Requirements in Paediatric Intensive Care Units (TRIPICU) RCT, where transfused patients received pre-storage leukoreduced RBCs [8]. We primarily aimed to determine whether a leukoreduced RBC restrictive transfusion strategy compared with a liberal strategy was associated with reducing HAI IR. Furthermore, we investigated whether an association between any given transfusion of leukoreduced RBCs and HAI IR exists, including the existence of a dose–response (secondary aims).

TABLE 1 Clinical characteristics of the patients: restrictive-strategy versus liberal-strategy

Variable ($N = 637$) *n* (%)/median [IQR]	Restrictive-strategy ($N = 320$)	Liberal-strategy[a] ($N = 317$)	*p* value
Demographics			
Age (months)	14.0 [3.0–48.2]	12.0 [4.0–61.0]	0.64
Weight (kg)	10.0 [5.0–16.0]	9.0 [6.0–18.0]	0.53
Male sex	190 (59.4)	191 (60.3)	0.88
Previous blood transfusion in PICU	45 (14.1)	59 (18.6)	0.15
Length of stay in PICU before randomization (days)	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.97
Time between randomization and transfusion (days)	1.7	0.1	<0.001
Severity of illness (PRISM score) on day of randomization	4.0 [2.0–7.0]	4.0 [1.0–7.0]	0.93
Immunomodulatory drugs	76 (24.3)	78 (25.3)	0.87
Platelets	26 (8.1)	29 (9.1)	0.75
Fresh-frozen plasma	23 (7.2)	25 (7.9)	0.85
Comorbidities			
Inflammatory diseases	202 (63.7)	202 (63.1)	0.94
Haematological problems	54 (16.9)	53 (16.7)	1.00
Multiple trauma	19 (5.9)	21 (6.6)	0.85
Surgery			
Cardiac	63 (19.7)	62 (19.6)	1.00
Abdominal	15 (4.7)	16 (5.0)	0.98
Transplantation	3 (0.9)	5 (1.6)	0.71
Other surgery	51 (16.1)	54 (16.9)	0.87

Note: Percentages may not sum to 100 because of rounding.
Abbreviations: IQR, interquartile region; PICU, paediatric intensive care unit; PRISM, Paediatric Risk of Mortality.
[a]Reference group.

MATERIALS AND METHODS

Study design

TRIPICU was a noninferiority RCT in 19 PICUs across Canada, Belgium, the United Kingdom, and the United States from 2001 to 2005 [8]. For this secondary analysis, data were analysed either as a superiority RCT (primary aim) or an observational study (secondary aims).

Participants

Inclusion and exclusion criteria of the critically ill children included in TRIPICU were previously described [8]. When analysing our secondary aims, we further excluded patients who had had previous blood transfusions during their hospital stay and/or a protocol suspension. We aimed to ensure that our results would not be biased by the presence of residual effects from pre-trial transfusions and to avoid selection bias, given that protocol suspensions primarily occurred due to emergencies (e.g., worsened shock or increased bleeding) whose management could have increased the patient's HAI risk.

The primary aim analysed data from all 637 patients in the TRIPICU database. For secondary aim 1 (any given leukoreduced RBC transfusion) and 2 (the number of RBC transfusions), we included a subset of 498 patients who received no previous blood transfusions during their hospital stay and/or had had protocol suspensions. For secondary aim 3 (the volume of RBC transfusion), we further excluded two patients who did not have the volume of blood transfused recorded (496 patients).

Interventions

Our primary aim's intervention was the restrictive leukoreduced RBC transfusion strategy used in the TRIPICU RCT compared to a liberal strategy as stated in the original trial [8]. The secondary aims' exposures included (1) receiving at least one leukoreduced RBC transfusion, (2) the number of leukoreduced RBC transfusions and (3) volume (in cc/kg) of leukoreduced RBC transfusions. The control group for all secondary aims was non-transfused patients.

Outcomes

Our primary outcome was HAI IR. A list of HAIs recorded for the TRIPICU study can be found in Appendix S1 [9]. In TRIPICU, HAIs were defined according to the Centers for Disease Control and Prevention (CDC) [9]. However, to increase the specificity, central line-associated bloodstream infection and catheter-related urinary tract infection definitions were modified to only include cases that presented positive bacterial cultures [10]. HAIs were diagnosed by medical

TABLE 2 Adjusted and non-adjusted incidence rate ratios (IRRs) for each study aim

	Number of patients	Number of infections	Patient days (per 1000 person-days)	IR (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)[a]
Primary aim: leukoreduced RBC restrictive transfusion strategy and HAI IR						
Liberal	317	115	2615	43.98 (36.31, 52.79)	Ref.	Not applicable
Restrictive	320	95	2451	38.76 (31.36, 47.38)	0.88 (0.67, 1.16)	
Secondary aim 1: transfusion of leukoreduced RBC and HAI IR						
No transfusion	157	26	1033	25.17 (16.44, 36.88)	Ref.	Ref.
Transfused	341	95	2687	35.36 (28.60, 43.22)	1.40 (0.91, 2.17)	1.25 (0.73, 2.13)
Secondary aim 2: number of leukoreduced RBC transfusions and HAI IR						
No transfusion	157	26	1033	25.17 (16.44, 36.88)	Ref.	Ref.
1 transfusion	259	44	1699	25.90 (18.82, 34.77)	1.03 (0.60, 1.75)	1.10 (0.61, 2.01)
2 transfusions	62	29	627	46.25 (30.98, 66.43)	1.84 (1.03, 3.29)	1.91 (0.99, 3.69)
3+ transfusions	20	22	361	60.94 (38.19, 92.27)	2.42 (1.30, 4.52)	2.40 (1.15, 4.99)
Secondary aim 3: volume of leukoreduced RBC transfusions and HAI IR						
No transfusion	157	26	1033	25.17 (16.44, 36.88)	Ref.	Ref.
≤10 cc/kg	88	12	568	21.13 (10.92, 36.90)	0.84 (0.39, 1.79)	0.88 (0.42, 1.84)
10–20 cc/kg	182	41	1199	34.20 (24.54, 46.39)	1.36 (0.79, 2.34)	1.67 (0.89, 3.11)
>20 cc/kg	69	41	891	46.02 (33.02, 62.43)	1.83 (1.06, 3.14)	2.14 (1.15, 3.99)

Abbreviations: CI, confidence interval; HAIs, hospital-acquired infections; IR, incidence rate; IRR, incidence rate ratio; RBC, red blood cell.
[a]Secondary aim 1 adjusted for haematological problems, multiple trauma, cardiac surgery, use of cointerventions (i.e., immunomodulatory drugs, platelets and/or fresh-frozen plasma), PRISM score at randomization and TRIPICU RCT study group. Secondary aim 2 adjusted for patient age, presence of comorbidities (i.e., inflammatory diseases, haematological problems and/or multiple trauma), cardiac surgery, abdominal surgery, other surgery, PRISM score at randomization, use of cointerventions and TRIPICU RCT study group. Secondary aim 3 adjusted for presence of comorbidities, cardiac surgery, PRISM score at randomization, use of cointerventions and TRIPICU RCT study group.

and/or infection control teams and validated by TRIPICU site investigators and/or infection control teams. Events were defined as the number of infections diagnosed after randomization up until PICU discharge date, date of death during PICU stay, or 28 days after randomization, whichever came first. The denominator was the number of PICU patient days between randomization and those endpoints.

Statistical analysis

We used TRIPICU data for all variables included in this secondary analysis. Detailed definitions of the variables are found in Appendix S1. Using the TRIPICU study population (637 patients) and a superiority analytical approach, we estimated we could detect an HAI IR reduction of 22% between groups, using an alpha of 0.05% and 80% power [11]. We used descriptive statistics to summarize the group characteristics. Continuous data were expressed as medians (interquartile ranges [IQR]) and compared with the Wilcoxon rank-sum or the Kruskal–Wallis tests. Categorical variables were expressed as proportions and analysed using the chi-square or Fisher's exact tests.

We analysed the association between the restrictive transfusion strategy and HAI IR (primary aim) by calculating the incidence rate ratio (IRR) and its 95% confidence interval (CI). We used multivariable quasi-Poisson regression models with an offset of log(PICU patient days) to analyse our secondary outcomes as study data did not follow a Poisson distribution. Analyses were conducted using R version 4.0.0 [12].

RESULTS

Primary aim: Leukoreduced RBC restrictive transfusion strategy and HAI IR

Baseline demographics and clinical characteristics for all 637 TRIPICU participants are presented in Table 1. The HAI IR in the leukoreduced RBC restrictive transfusion strategy group was 38.76 per 1000 patient days (95% CI 31.36, 47.38) and 43.98 per 1000 patient days (95% CI 36.31, 52.79) for the liberal strategy group, corresponding to an IRR of 0.88 (95% CI 0.67, 1.16) (Table 2 and Figure 1).

Secondary aim 1: Transfusion of leukoreduced RBC and HAI IR

Table 3 shows the baseline characteristics of the 498 patients included. There were differences between study groups regarding haematological problems, multiple trauma, cardiac surgery, use of

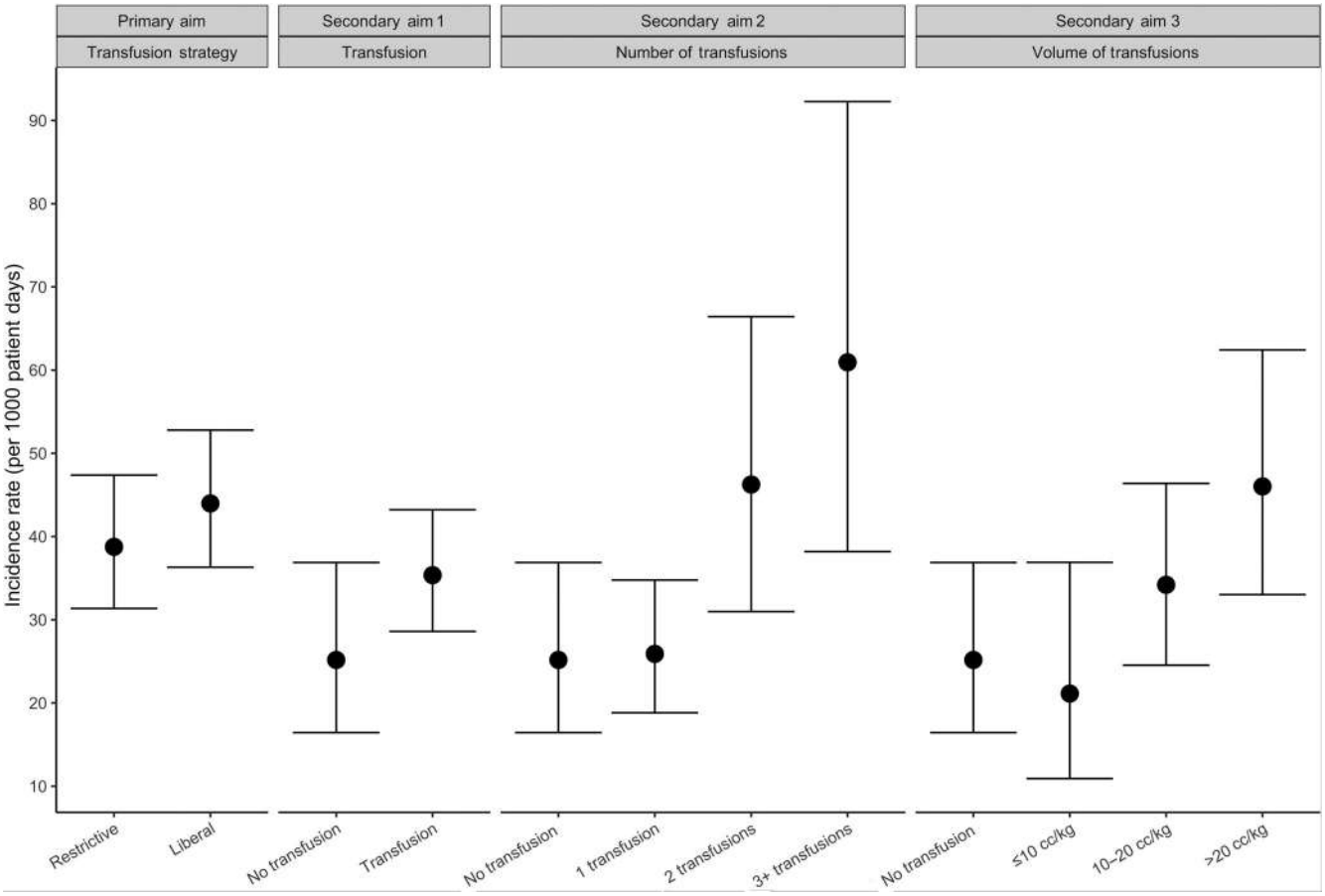

FIGURE 1 Incidence rates and 95% confidence intervals for the different interventions

TABLE 3 Clinical characteristics of the patients—secondary aims: (1) transfusion of leukoreduced RBC and HAI IR and (2) number of leukoreduced RBC transfusions and HAI IR

Variable ($N = 498$) *n* (%)/median [IQR]	No RBC transfusion[a] ($N = 157$)	RBC transfusion ($N = 341$)	*p* value	1 transfusion ($N = 259$)	2 transfusions ($N = 62$)	3+ transfusions ($N = 20$)	*p* value
Demographics							
Age (months)	15.0 [4.0–48.0]	11.0 [3.0–44.0]	0.30	10.0 [3.0–37.5]	13.5 [4.0–82.0]	15.0 [3.8–85.5]	0.32
Weight (kg)	10.0 [5.0–15.0]	9.0 [5.0–15.0]	0.41	9.0 [5.0–15.0]	9.5 [5.2–19.2]	10.0 [5.8–20.0]	0.43
Male sex	92 (58.6)	219 (64.2)	0.27	169 (65.3)	38 (61.3)	12 (60.0)	0.58
Length of stay in PICU before randomization (days)	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.69	2.0 [1.0–3.0]	2.0 [1.0–3.0]	2.0 [1.0–4.0]	0.81
Restrictive-strategy group[b]	150 (95.5)	98 (28.7)	<0.01	81 (31.3)	12 (19.4)	5 (25.0)	<0.01
Severity of illness (PRISM score) on day of randomization	3.0 [1.0–6.0]	4.0 [1.0–7.0]	0.06	4.0 [1.0–7.0]	4.0 [2.0–9.0]	5.5 [2.8–8.2]	0.08
Immunomodulatory drugs	29 (18.5)	75 (22.0)	0.44	54 (20.8)	14 (22.6)	7 (35.0)	0.38
Platelets	2 (1.3)	21 (6.2)	0.03	10 (3.9)	7 (11.3)	4 (20.0)	<0.01
Fresh-frozen plasma	3 (1.9)	25 (7.3)	0.03	14 (5.4)	6 (9.7)	5 (25.0)	<0.01
Comorbidities							
Inflammatory diseases	89 (56.7)	209 (61.3)	0.38	155 (59.8)	38 (61.3)	16 (80.0)	0.25
Haematological problems	11 (7.0)	49 (14.4)	0.03	31 (12.0)	11 (17.7)	7 (35.0)	<0.01
Multiple trauma	1 (0.6)	21 (6.2)	<0.01	16 (6.2)	5 (8.1)	0 (0.0)	0.01
Surgery							
Cardiac	36 (22.9)	61 (17.9)	0.23	47 (18.1)	11 (17.7)	3 (15.0)	0.64
Abdominal	4 (2.5)	21 (6.2)	0.12	14 (5.4)	3 (4.8)	4 (20.0)	0.02
Transplantation	3 (1.9)	3 (0.9)	0.39	2 (0.8)	1 (1.6)	0 (0.0)	0.54
Other surgery	20 (12.7)	57 (16.7)	0.31	42 (16.2)	9 (14.5)	6 (30.0)	0.23

Note: Percentages may not sum to 100 because of rounding.
Abbreviations: RBC, red blood cell; IQR, interquartile region; PICU, paediatric intensive care unit; PRISM, Paediatric Risk of Mortality.
[a]Reference group.
[b]In the restrictive-strategy group of the TRIPICU study, the haemoglobin threshold for transfusion was set at 7 g/dl, with a target range after transfusion of 8.5–9.5 g/dl.

immunomodulatory drugs, platelets transfusion, fresh-frozen plasma transfusion and Paediatric Risk of Mortality (PRISM) score at randomization. Study groups' IRs are shown in Figure 1. The adjusted association between leukoreduced RBC transfusion and HAI IR (Table 2), including the aforementioned variables and the original RCT assignment, was not statistically significant (adjusted IRR 1.25; 95% CI 0.73, 2.13).

Secondary aim 2: Number of leukoreduced RBC transfusions and HAI IR

Table 3 shows the baseline characteristics for the 498 participants analysed. Differences between the groups (no transfusion, 1, 2 and ≥3 transfusions) included patient age, inflammatory diseases, haematological problems, multiple trauma, cardiac surgery, abdominal surgery, other surgery, PRISM score at randomization, use of immunomodulatory drugs, platelets transfusion and fresh-frozen plasma transfusion. After adjusting for these variables and the original RCT group assignment (Table 2), we observed statistically significant associations between exposure to ≥3 leukoreduced RBC transfusions (adjusted IRR 2.40; 95% CI 1.15, 4.99) and HAI IR. Study groups' IRs are shown in Figure 1.

Secondary aim 3: Volume of leukoreduced RBC transfused and HAI IR

Table 4 presents the baseline characteristics of the 496 participants investigated. Significant differences between the groups (no transfusion, ≤10, 10–20, and >20 cc/kg transfusion) included inflammatory diseases, haematological problems, multiple trauma, cardiac surgery, PRISM score at randomization, use of immunomodulatory drugs, platelets transfusion and fresh-frozen plasma transfusion. Group HAI IRs are shown in Figure 1. Adjusting for the aforementioned variables and study group assignment in the original RCT showed a statistically significant association between

TABLE 4 Clinical characteristics of the patients—secondary aim 3: volume of leukoreduced RBC transfused and HAI IR

Variable ($N = 496$) *n* (%)/median [IQR]	No transfusion[a] ($N = 157$)	≤10 cc/kg transfusion ($N = 88$)	10–20 cc/kg transfusion ($N = 182$)	>20+ cc/kg transfusion ($N = 69$)	*p* value
Demographics					
Age (months)	15.0 [4.0–48.0]	11.0 [3.0–61.2]	11.0 [3.0–46.5]	9.0 [3.0–23.0]	0.40
Weight (kg)	10.0 [5.0–15.0]	9.0 [5.0–18.5]	9.0 [5.0–16.0]	8.0 [5.0–12.0]	0.33
Male sex	92 (58.6)	57 (64.8)	115 (63.2)	47 (68.1)	0.54
Length of stay in PICU (days)	2.0 [1.0–3.0]	2.0 [1.0–3.0]	2.0 [1.0–3.0]	1.0 [1.0–3.0]	0.89
Restrictive-strategy group[b]	150 (95.5)	45 (51.1)	41 (22.5)	11 (15.9)	<0.01
Severity of illness (PRISM score) on day of randomization	3.0 [1.0–6.0]	4.0 [2.0–7.0]	3.5 [0.2–7.0]	4.0 [2.0–9.0]	0.04
Immunomodulatory drugs	29 (18.5)	24 (27.3)	34 (18.7)	16 (23.2)	0.32
Platelets	2 (1.3)	5 (5.7)	7 (3.8)	9 (13.0)	<0.01
Fresh-frozen plasma	3 (1.9)	7 (8.0)	8 (4.4)	10 (14.5)	<0.01
Comorbidities					
Inflammatory diseases	89 (56.7)	55 (62.5)	109 (59.9)	44 (63.8)	0.72
Haematological problems	11 (7.0)	13 (14.8)	23 (12.6)	13 (18.8)	0.06
Multiple trauma	1 (0.6)	7 (8.0)	13 (7.1)	1 (1.4)	<0.01
Surgery					
Cardiac	36 (22.9)	13 (14.8)	33 (18.1)	15 (21.7)	0.41
Abdominal	4 (2.5)	3 (3.4)	13 (7.1)	5 (7.2)	0.17
Transplantation	3 (1.9)	0 (0.0)	2 (1.1)	1 (1.4)	0.71
Other surgery	20 (12.7)	16 (18.2)	28 (15.4)	13 (18.8)	0.58

Note: Percentages may not sum to 100 because of rounding.
Abbreviations: IQR, interquartile region; PICU, paediatric intensive care unit; PRISM, Paediatric Risk of Mortality.
[a]Reference group.
[b]In the restrictive-strategy group of the TRIPICU study, the haemoglobin threshold for transfusion was set at 7 g/dl, with a target range after transfusion of 8.5–9.5 g/dl.

transfusing >20 cc/kg of leukoreduced RBCs (adjusted IRR 2.14, 95% CI 1.15, 3.99) and HAI IR (Table 2).

DISCUSSION

Our post hoc secondary analysis of the TRIPICU study showed that a leukoreduced RBC restrictive transfusion strategy was not significantly associated with a reduction in HAI IR. Similarly, there was no association between receiving at least one leukoreduced RBC transfusion and an increase in HAI IR. However, when studying the association between the number and volume of leukoreduced RBC transfusions and HAI IR, we observed that exposure to ≥3 transfusions and to >20 cc/kg transfused volume were both significantly associated with an increase in HAI IR.

Studies have evaluated the effect of transfusing leukoreduced RBCs, compared to the transfusion of non-leukoreduced blood, on HAIs [4–7, 13, 14]. Despite evidence demonstrating a benefit of transfusing leukoreduced versus non-leukoreduced RBCs, the question about the former's effect on HAIs compared to no transfusion persists. In the TRIPICU study, Lacroix et al. found no statistically significant difference in the HAI risk between the two transfusion groups (absolute risk reduction 4.6; 95% CI −1.9, 11.1) [8]. When studying this question, we used HAI IR as our outcome, allowing us to account for patients with varying risks for developing HAI due to different PICU lengths of stay. However, similar to Lacroix's results, we could not detect a significant difference between groups. Based on our sample size calculation for this post hoc analysis, the TRIPICU study was underpowered to detect a 10% reduction in HAI IR associated with using a restrictive leukoreduced RBC transfusion strategy [11].

Our study observed that the HAI IR in patients who received at least one leukoreduced RBC transfusion was higher than in non-transfused patients. However, the result of our model regarding a possible association between leukoreduced RBCs and HAI IR was inconclusive. Nevertheless, our results showed that the HAI IR in stable, critically ill children who received ≥3 leukoreduced RBC transfusions was 2.40 times the HAI IR in children who had no transfusion. Furthermore, the HAI IR of patients who received one transfusion or two transfusions were higher than the HAI IR of non-transfused patients. We speculate that a dose–response associated with an increasing

number of leukoreduced RBC transfusions may exist. Horvath et al. demonstrated a similar dose-related association, with the HAI risk in adult patients increasing by an average of 29% per leukoreduced RBC unit transfused ($p < 0.001$) [15]. Similarly, Everhart et al. showed an association between HAI IR and the number of leukoreduced PRBC units transfused in patients undergoing shoulder arthroplasty (IRR 1.68 per PRBC unit; 95% CI 1.21, 2.35; $p = 0.002$) [16].

The dose–response may be related to patient factors. Rajasekaran et al. showed that critically ill children who received leukoreduced RBC transfusions had significantly higher severity of illness, a factor for which we have adjusted in our analysis [17]. More severely, ill patients present innate and adaptive immunological derangements putting them at a higher HAI risk [18]. Furthermore, critically ill patients with sepsis may present an exacerbation of both pro-inflammatory and anti-inflammatory responses, leading to excessive inflammation and immunosuppression, increasing the patient's susceptibility to secondary infections [19].

Alternatively, RBC transfusion dose-responses may be a result of TRIM. TRIM includes both pro-inflammatory and immunosuppressive effects due to residual WBCs in transfused RBC units and the release of biological substances by both WBCs and RBCs [20]. Thus, repeated transfusions could act as secondary insults to an already dysregulated immune system, further increasing the HAI risk [21, 22]. Furthermore, repeated transfusions of long-stored blood may also contribute to TRIM due to the release of bioactive substances resulting from physiological changes that occur during storage [23]. We previously observed that transfusing leukoreduced blood stored for ≥35 days was associated with increased HAI IR (IRR 3.66; 95% CI 1.22, 10.98) [24]. Finally, transfusion of stored RBC units has been shown to increase patients' serum iron levels due to RBC haemolysis that happens during the storage period [25]. This transfusion-related iron overload was correlated with increasing bacterial growth [25].

We also evaluated the existence of an association between blood transfusion volume and HAI IR. We found that children transfused with >20 cc/kg of leukoreduced blood had 2.14 times higher HAI risk than those receiving no transfusion. Similarly, Woods et al. reported an association between higher perioperative blood transfusion volume and postoperative infection in adult lumbar spine surgery patients (OR 2.87; 95% CI 1.63–5.06) [26]. Our study found that the HAI IR of patients who received one transfusion or a ≤10 cc/kg transfusion was slightly lower than the HAI IR of patients who received no transfusion. We speculate that these patients may not have received enough blood to trigger a negative immunologic effect. Furthermore, it has been shown that the magnitude of the physiologic insult dictates the patient's response to pathogens [27]. Thus, these patients may have presented only mild metabolic derangements that were improved by the RBC transfusion, allowing them to better cope with future infectious insults.

Our study has limitations. HAI diagnosis date was not recorded in the TRIPICU study. Nevertheless, all events happened after patient randomization and the time from randomization to transfusion was 0.1 and 1.7 days in the liberal and restrictive groups, respectively. Furthermore, the original study did not collect device days, except for mechanical ventilation, preventing us from calculating the IR for different HAIs. However, the overall HAI IR calculation was not impacted as it used PICU patient days as its denominator. The follow-up period for HAIs ended on the day of PICU discharge, making it impossible to capture HAIs infections occurring within 24 h after it, which would still be attributable to the PICU [28]. Additionally, data on antibiotic usage (type of antibiotic and dose) previous to the diagnosis of HAI were not recorded in the TRIPICU database. Therefore, we are unable to know the percentage of patients receiving antibiotics before a HAI was identified. Finally, there is the risk for unmeasured confounders as the database used, despite being extremely comprehensive, did not include data on all possible HAI risk factors. Therefore, given the nature of observational analyses of unbalanced groups, the results may be prone to residual confounding. To mitigate this limitation, we adjusted for all potential HAI confounders that were available in the database.

Nevertheless, our study has important strengths. The TRIPICU study had HAIs as a secondary outcome and recorded high-quality data on the most important HAI risk factors and blood transfusions. Furthermore, the HAI definitions used, modified to include the presence of positive bacterial cultures, align well with the current CDC HAI definitions [28]. All study HAIs were diagnosed based on such definitions. Despite the data being collected from 2002 to 2005, the decision to transfuse was based on a restrictive versus liberal transfusion strategy that is still used today. Additionally, supportive care provided to critically ill children (i.e., care other than transfusion practice), including the treatment of severe bacterial infections, has not significantly changed since TRIPICU, which ensures the clinical relevance of our findings.

In conclusion, our study showed that exposure to ≥3 leukoreduced RBC transfusions or >20 cc/kg of leukoreduced RBCs is associated with increased HAI IR in stable, critically ill children. Our results also suggest that children who receive multiple transfusions may be at a higher risk for HAI even after controlling for disease severity. We were underpowered to detect a possible association between using a restrictive transfusion strategy and HAI IR. Our results highlight important research questions that must be studied to inform the transfusion practices in the paediatric critical care setting, with the hope of reducing HAI IR.

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L.K.F. and P.S.F. developed the study protocol; L.K.F. analysed the data; P.S.F., D.A.F., T.D., J.L., J.P. critically analysed the results; L.K.F. wrote the manuscript; P.S.F., D.A.F., T.D., J.L., J.P. critically reviewed the manuscript; all authors read and approved the final manuscript as submitted.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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ORIGINAL ARTICLE

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Perinatal risk factors associated with severity of haemolytic disease of the foetus and newborn due to Rhc maternal-foetal incompatibility: A retrospective cohort study

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Abstract

Background and Objectives: Anti-c is the third red blood cell antibody responsible for haemolytic disease of the foetus and newborn (HDFN) requiring intrauterine transfusion. We aimed to identify risk factors associated with HDFN and severe HDFN due to Rhc maternal-foetal incompatibility.

Materials and Methods: A retrospective cohort study was conducted in Paris and the surrounding area (France), between 2013 and 2015. We included mothers and their children managed by the National Reference Centre in Perinatal Hemobiology for alloimmunization and maternal-foetal incompatibility for the Rhc antigen ($N = 121$). We conducted bivariate analyses to assess a relationship between perinatal factors (e.g., titre and concentration of anti-c antibodies, direct antiglobulin test) and HDFN, its severity and duration.

Results: The incidence of HDFN was 30% ($n = 36$), including 11% of severe HDFN ($n = 13$). Seven percent ($n = 9$) of neonates received at least one transfusion during the first week and 21% ($n = 26$) after this period until 3 weeks of life. During pregnancy, a concentration ≥7.5 IU/ml and a titre ≥4 and above were associated with HDFN and severe HDFN ($p < 0.05$). At birth, the high intensity of the quantitative direct antiglobulin test was associated with HDFN and severe HDFN ($p < 0.05$). A concentration ≥15 IU/ml is the best factor (area under curve [AUC] = 0.78) in predicting HDFN, followed by a titre ≥8 (AUC = 0.76).

Conclusion: Anti-c alloimmunization causes neonatal anaemia, which is often belated. Paediatricians have to be aware of these risk factors and organize prolonged monitoring of neonates.

KEYWORDS
anti-c alloimmunization, foetal and neonatal anaemia, haemolytic disease, neonatal jaundice, neonatal transfusion

Highlights

- Among fetuses and neonates with isolated anti-c maternal-fetal incompatibility and a positive DAT at birth, HDFN occurred in 30% of cases and severe HDFN requiring fetal or

neonatal transfusion, exchange transfusion or intravenous immunoglobulin in the first 7 days of life occurred in 11% of cases.

- In case of isolated anti-c maternal-fetal incompatibility, a titre ≥ 4 and/or a concentration of anti-c anibodies ≥ 7.5 IU/mL during pregnancy were both significantly associated with HDFN.
- In case of isolated anti-c maternal-fetal incompatibility, neonatal anemia can be belated with 21% of the neonates requiring blood transfusion after the first week of age. This result emphasizes the need for a prolonged follow-up of neonates after hospital discharge.

INTRODUCTION

With the introduction of Rh immune globulin in the majority of developed countries, the incidence of alloimmunization caused by anti-D (RH1) has decreased. In consequence, the proportion of alloimmunization caused by other antibodies, such as anti-Kell (KEL), anti-c (RH4) and anti-E (RH3), has relatively increased representing up to 78% of the alloimmunized pregnancies [1–5]. The prenatal management of these other alloimmunizations has been derived from the more largely described management of anti-D (RH1) immunization. However, these other alloimmunizations present differences that may have a significant impact on the expression and severity of the associated haemolytic disease of the foetus and newborn (HDFN) [4, 6]. Moreover, the natural history of anti-c alloimmunization in neonates may differ from what is observed in cases with anti-D alloimmunization [7, 8].

We studied a consecutive series of 121 cases of pregnancies with anti-c alloimmunization and maternal-foetal incompatibility with the primary objective to identify perinatal factors associated with HDFN. Our secondary objective was to identify perinatal factors associated with severe HDFN, and with neonatal transfusion after the first week of life.

MATERIALS AND METHODS

Patients and data collection

A retrospective study was conducted in the French National Reference Centre in Perinatal Hemobiology (CNRHP). The CNRHP is organized around two functional units working in close collaboration in Paris to monitor and manage immunized women and their children: a biological unit expert in perinatal immuno-haematology, and an obstetric-paediatric clinical unit. As part of its mission defined by the French Ministry of Health, the CNRHP collects all prenatal and neonatal data [9].

We extracted from our database the records of children born between 1 January 2013 and 31 December 2015, in Paris and the surrounding area, with a mother diagnosed with anti-c alloimmunization. We included all children presenting isolated Rhc maternal-foetal incompatibility proven by Rh-Kell blood phenotyping. We excluded children with the compatible phenotype (Rhc negative) or with elution test positive to another associated antibody.

The data collection was carried out by an obstetrician and the clinical paediatrician referent from the CNRHP. We first collected the biological samples including maternal screening for red blood cells antibodies and all available sera during pregnancy, direct antiglobulin test (DAT) and elution tests of the newborn. Medical files were reviewed to collect maternal characteristics, ultrasound follow-up and perinatal management of the cases. We also collected data from the delivery and the neonatal characteristics (haemoglobin and bilirubin, treatment of HDFN).

Prenatal monitoring

Rhc foetal genotyping was not performed in our center during the study period since it was implemented in 2015 [10]. Thus, if the fathers were cc homozygous, Rhc maternal-foetal incompatibility was certain; in case of Cc heterozygous fathers, pregnancies were followed as if they were incompatible, until otherwise proven at birth.

Anti-c antibody levels were quantified using two techniques: titration and concentration. The antibody concentration is an automated, continuous flow hemagglutination technique that is more accurate and demonstrates reactivation of alloimmunization more rapidly than titration [11]. In our center, the threshold for risk of foetal anaemia related to the anti-c antibody is defined by a concentration greater than 500 UCHP/ml (*units of the CNRHP*) [12]. This threshold of 500 UCHP/ml is comparable to the critical threshold of 7.5 IU/ml found in the UK Guidelines [13, 14]. It was considered that beyond 1000 UCHP/ml (i.e., approximately 15 IU/ml), the risk of HDFN was major. The threshold value used for the titration was 4 using the indirect antiglobulin test with the tube method (saline medium). Reactivation of the immunization was considered if the concentration increased more than 30% compared to the previous value or if the titration increased by more than two dilutions compared to the previous value [11].

The titration and the concentration were performed every 2–4 weeks from 18 weeks of gestation (WG) and every 2 weeks from 28 WG [14].

Ultrasonography and Doppler assessment of the Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) measurements were

performed for women having an anti-c concentration over 7.5 IU/ml, once a week until delivery. In case of MCA-PSV value increasing above 1.5 Multiples of Median (MoM), associated or not with indirect signs of foetal anaemia, a cordocentesis was performed to confirm anaemia, and perform an intrauterine transfusion (IUT) if necessary [15].

Severely anaemic foetuses were transfused with group O adult donor packed red cells, cross-matched with the mother, irradiated, fresh (<5 days) and with haematocrit at 70%–80%; Rhc negative (RH: 2,−4) and if possible, with respecting the extensive mother's phenotype (D, C, E, K, Jk, MNS, Fy).

For all patients with anti-c concentration ≥7.5 IU/ml, delivery at 37 weeks was recommended.

Postnatal monitoring

At birth, haemoglobin (Hb) level and bilirubin levels were measured on cord blood. An immunological diagnosis of incompatibility was performed including Rh-K blood phenotyping and quantitative DAT to test for the presence of anti-red blood cells bound antibodies (DAT performed on Bio-Rad Diaclon ABO/Rh for Newborns gels cards and

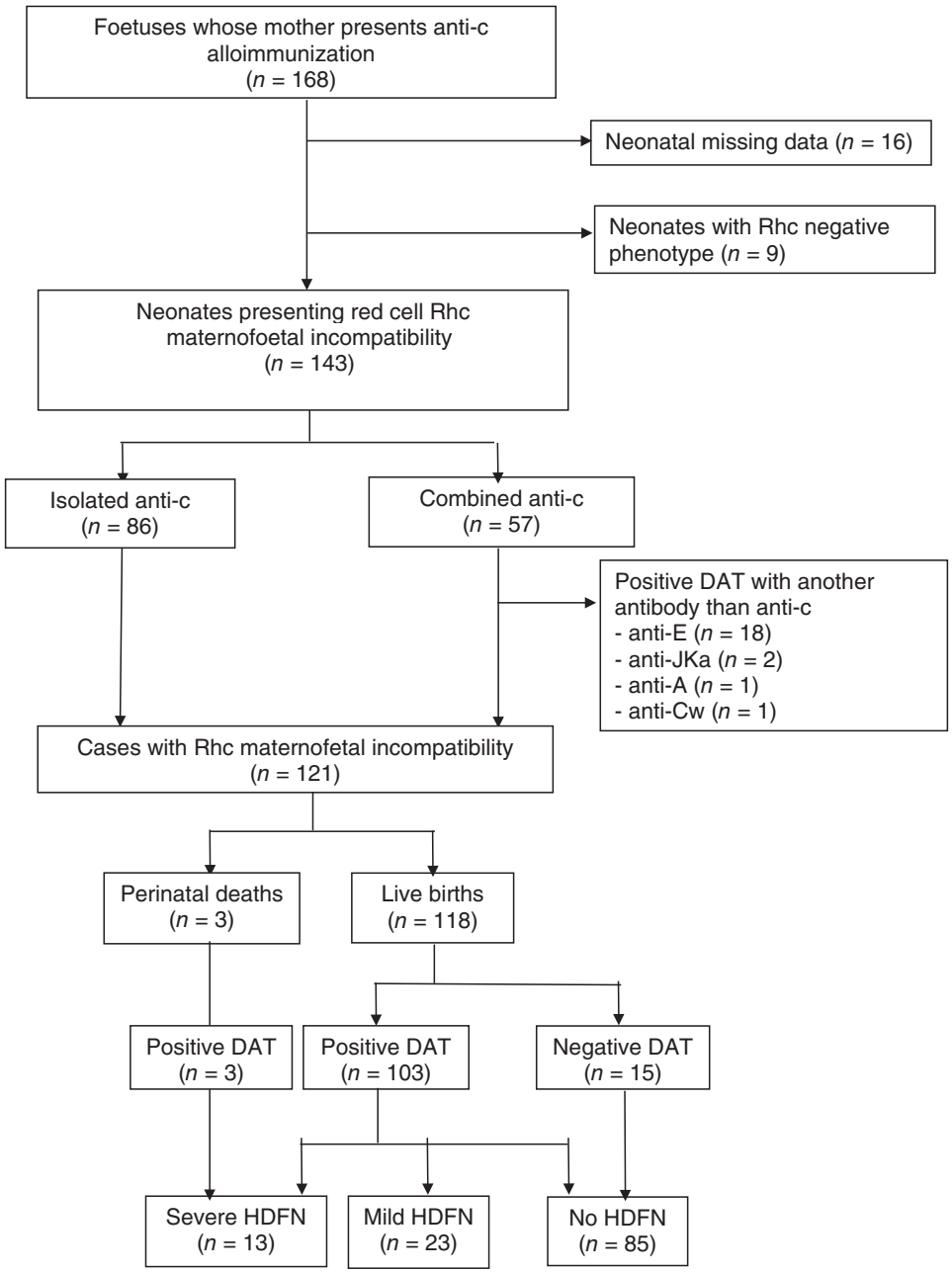


FIGURE 1 Flow-chart. DAT, direct antiglobulin test; HDFN, haemolytic disease of the foetus and newborn, defined as a neonatal anaemia with Hb less than 14 g/dl in the first hour of life and/or newborn pathologic icterus with adequate phototherapy based on bilirubinemia according to the clinical practice guidelines of the American academy of Pediatrics; severe HDFN, foetal or neonatal transfusion, exchange transfusion or intravenous immunoglobulin within the first 7 days of life

TABLE 1 Maternal and neonatal characteristics of the population ($n = 121$)

Maternal characteristics	
Maternal age (years)[a]	34 [30–37]
Gestity[a]	3 [2–4]
Parity[a]	2 [1–3]
History of HDFN[b]	
None	100 (83%)
Mild HDFN	10 (8%)
Severe HDFN	11 (9%)
Immunohaematologic characteristics	
Date of immunization[b]	
Before pregnancy	52 (43%)
First trimester	16 (13%)
Second trimester	17 (14%)
Third trimester	34 (28%)
Missing data	2 (2%)
Titre at delivery[b]	
<4	58 (47%)
4	9 (7%)
8	9 (7%)
>16	16 (13%)
Missing data	29 (27%)
Concentration at delivery (IU/ml)[a]	
<7.5	67 (55%)
≥7.5	28 (23%)
Missing data	26 (22%)
Reactivation of alloimmunization[b]	36/70 (51%)
Obstetrical characteristics	
Foetal transfusion[b]	2 (1%)
Gestational age at delivery[a]	38 [37–39]
Neonatal characteristics	
Birth weight (g)[a]	3150 [2892–3448]
Perinatal death[b]	3 (2%)
Direct antiglobulin test[b]	
0	15 (12%)
1+	24 (20%)
2+	19 (16%)
3+	24 (20%)
4+	39 (32%)
Haemoglobin at day 0 (g/dl)	15.3 [14.4–17.0]
Total bilirubin at day 0 (μmol/L)	38 [31–59]
Intensive phototherapy[b]	24 (20)
Blood transfusion <72 h	8 (7)
Exchange transfusion <72 h	3 (2)
Blood transfusion <7 days	9 (7)
Intravenous immunoglobulins	4 (3)
After 7 days	
Blood transfusion >7 days[a]	26 (21)
Age of the last transfusion (weeks)	3 [3–4.75]
Haemoglobin nadir (g/dl)	8.6 [7.6–10.2]

Abbreviation: HDFN, haemolytic disease of the foetus and newborn.
[a]Data are expressed in median [interquartile range].
[b]Data are *n* (%). Direct antiglobulin test was also measured on foetal blood sampling for the two cases with intrauterine transfusion.

on Bio-Rad DC Screening II gel cards using a 4-crosses scale to rate the intensity of hemagglutination). In case of DAT positivity, an elution test was realized to confirm the anti-c specificity of the antibodies. Iterative blood tests were repeated at 6 h and every 12 h during the first 72 h. HDFN was defined by neonatal anaemia with Hb less than 14 g/dl in the first hours of life and/or newborn hyperbilirubinemia requiring intensive phototherapy according to the clinical practice guidelines of the American Academy of Pediatrics [16]. Severe HDFN was defined by the need for foetal or neonatal transfusion, exchange transfusion or intravenous immunoglobulin within the first 7 days of life. Blood transfusions performed after the 7th day of life were also recorded.

Neonatal management of jaundice relied on intensive phototherapy and exchange transfusion when indicated in accordance with the American Academy of Pediatrics guidelines [16]. Intensive phototherapy was prescribed to maintain bilirubin levels below 340 μmol/L and prevent kernicterus as long as needed. Postnatal transfusion was recommended for Hb less than 8 g/dl and according to clinical tolerance [17]. The transfused blood was 25–30 ml/kg of group O packed red cells cross-matched with the newborn sera, irradiated (if previous foetal transfusions had been performed). A polyvalent immunoglobulin infusion was used to inhibit hemolysis if the bilirubin level increased from 8 to 10 μmol/h under intensive phototherapy. Some children were eligible for a combination of several treatments.

Clinical examination and blood tests (Hb level and reticulocyte count) were repeated within the first 2 months of life.

Ethics

Subjects have given their informed consent and the study protocol has been approved by the national committee in obstetrics and gynaecology research (CEROG 2020-OBS-0407).

Statistical analysis

We conducted bivariate analyses to assess a possible relationship between perinatal factors and HDFN, its severity and duration. Significant effects were based on the Chi-square (χ^2) test to compare categorical variables and Fisher's exact test was used when the assumptions of the χ^2 test were violated. Continuous variables were compared with the

TABLE 2 Risk factors of HDFN: Bivariate analysis

	No HDFN ($n = 85$), n (%)	HDFN ($n = 36$), n (%)	OR [95% CI]	p
History of HDFN	11 (13)	10 (28)	2.56 [0.87–7.56]	0.07
History of severe HDFN	6 (7)	5 (14)	2.11 [0.47–9.0]	0.30
Titre at first trimester				
≥4	3 (5)	7 (37)	9.69 [1.88–66.80]	0.002
≥8	2 (4)	7 (37)	14.7 [2.41–161.8]	<0.001
≥16	1 (2)	6 (32)	23.5 [2.54–1158]	<0.001
Titre during pregnancy				
≥4	14 (16)	21 (58)	7.1 [2.68–15.8]	<0.001
≥8	10 (12)	21 (58)	10.5 [4.12–26.8]	<0.001
≥16	5 (6)	14 (38)	10.2 [3.3–31.3]	<0.001
Concentration at first trimester				
≥7.5 IU/ml	6 (10)	8 (33)	4.33 [1.31–14.3]	0.04
≥15 IU/ml	4 (7)	4 (17)	2.66 [0.45–15.8]	0.22
Concentration during second or third trimester				
≥7.5 IU/ml	21 (25)	28 (78)	10.7 [4.2–27.0]	<0.001
≥15 IU/ml	6 (7)	19 (53)	14.7 [5.1–42.3]	<0.001
Date of immunization				
Second or third trimester	17 (31)	4 (23)	0.69 [0.14–2.69]	0.76
Discovery at the time of delivery	15 (18)	4 (11)	0.49 [0.08–1.92]	0.57
Reactivation at third trimester	23 (44)	13 (72)	3.3 [1.0–10.5]	0.05
Direct antiglobulin test				
0	15 (18)	0 (0)		
1+	21 (25)	3 (8)		
2+	17 (20)	2 (5)		<0.001
3+	15 (18)	9 (25)		
4+	17 (20)	22 (61)		

Abbreviations: CI, confidence interval; HDFN, haemolytic disease of the foetus and newborn; OR, odds ratio.

Wilcoxon rank-sum test. The odds ratios and the corresponding 95% confidence intervals were derived using bivariate analysis. Receiver operating characteristic (ROC) curves were performed to assess the performance of prediction of HDFN according to different thresholds of titration and concentration of anti-c antibodies during pregnancy. Statistical analyses were performed with R software version 3.5.1. *p Values* were used to estimate the strength of association with each parameter and statistical significance was set at $p < 0.05$.

RESULTS

Population

During the study period, we identified 168 pregnancies with anti-c alloimmunization referred to the CNRHP from 74 maternity hospitals. Among these pregnancies, 25 cases were excluded due to missing neonatal data in 16 cases or exclusion of maternal-foetal Rhc incompatibility (newborn with an Rhc negative phenotype) in 9 cases.

In our population of 143 pregnancies with anti-c alloimmunization and maternal-foetal incompatibility, 57 women had multiple red blood cell antibodies (40%). Among these cases of multiple immunizations, 22 were subsequently excluded because of a positive elution test to another antibody than anti-c at birth (Figure 1).

A total of 121 pregnancies fulfilled the inclusion criteria with neonates presenting isolated maternal-foetal incompatibility related exclusively to anti-c alloimmunization (Table 1).

Prenatal outcomes

Severe foetal anaemia occurred in three cases. In the first case, an IUT was performed at 21 WG for MCA-PSV over 1.5 MoM without hydrops (maternal titre was 512 and foetal Hb was 5.0 g/dl). Intrauterine foetal death (IUFD) was diagnosed the next day, due to a hematoma of the umbilical cord.

In the second case, IUFD occurred at 37 WG in a woman with an anti-c alloimmunization without prior appropriate follow-up. When a

TABLE 3 Risk factors of severe HDFN: Bivariate analysis

	No HDFN or not severe ($n = 108$), *n* (%)	Severe HDFN ($n = 13$), *n* (%)	OR [95% CI]	*p*
History of HDFN	17 (16)	4 (31)	2.36 [0.48–9.73]	0.24
History of severe HDFN	8 (6)	3 (18)	3.7 [0.54–18.9]	0.10
Titre at first trimester				
≥4	6 (10)	4 (36)	5.25 [0.87–29.55]	0.04
≥8	5 (8)	4 (36)	6.4 [1.0–38.5]	0.02
≥16	3 (5)	4 (36)	10.8 [1.5–90.0]	0.008
Titre during pregnancy				
≥4	27 (25)	8 (62)	4.80 [1.45–15.92]	0.01
≥8	20 (18)	11 (85)	24.2 [5.0–118]	<0.001
≥16	12 (11)	7 (54)	9.3 [2.7–32.4]	<0.001
Concentration at first trimester				
≥7.5 IU/ml	10 (14)	4 (40)	4.0 [0.71–20.9]	0.06
≥15 IU/ml	5 (7)	3 (30)	5.5 [0.71–36.7]	0.14
Concentration during pregnancy				
≥7.5 IU/ml	37 (34)	12 (92)	23.0 [2.9–184]	0.003
≥15 IU/ml	13 (12)	12 (92)	87.7 [10.5–731]	<0.001
Date of immunization				
Second or third trimester	19 (30)	2 (18)	0.52 [0.05–2.86]	0.72
Discovery at the time of delivery	17 (16)	2 (15)	0.95 [0.1–5.0]	1
Reactivation at third trimester	31 (49)	5 (71)	2.6 [0.46–14.3]	0.47
Direct antiglobulin test				
0	15 (14)	0 (0)		
1+	23 (21)	1 (8)		
2+	19 (18)	0 (0)		0.01
3+	22 (20)	2 (15)		
4+	29 (27)	10 (77)		

Abbreviations: CI, confidence interval; HDFN, haemolytic disease of the foetus and newborn; OR, odds ratio.

blood sample was performed at 35 WG for maternal purposes, the titre was 8 and the concentration was 38.1 IU/ml. Unfortunately, the ultrasound examination led to the diagnosis of an IUFD associated with foetal hydrops.

In the third case, a first IUT was indicated at 25 WG (maternal titre at 128, foetal haemoglobin raised from 5.2 to 11.2 g/L). A second IUT was planned 13 days later but secured cordonal access was impossible to achieve (maternal body mass index = 50 kg/m^2) and only a foetal blood sample was available with Hb level at 5.8 g/dl. The mother had a caesarean section 1 h later for a sinusoidal foetal heart rate at 26 WG. Palliative care was decided at 3 weeks of life because of a grade IV intraventricular haemorrhage and ischemic involvement of the basal ganglia leading to death at day 50.

Neonatal outcomes

Among the 118 live neonates, 103 (87%) had a positive DAT with anti-c at elution. A negative DAT was observed at birth in 15 neonates (absence of placental transfer of the anti-c antibodies to the newborns incompatible with their mother).

Twenty-four neonates (20%) required intensive phototherapy and four (3%) were treated with intravenous immunoglobulins. An exchange transfusion was required in three neonates (3%) with a high bilirubin level (358, 255 and 445 μmol/L, respectively) and a low haemoglobin level (6, 8.8 and 8.3 g/dl, respectively). A top-up transfusion was required in 29 neonates (24%), with a median of 2 transfusions (range: 1–3 transfusions) and the last transfusion at 3 weeks of age (range: 2–11 weeks). Nine neonates received at least one transfusion during the first week of age and 26 neonates (21%) required blood transfusion after this period. Among those, it was the first transfusion for 20 (17%) of them (Table 1).

Risk factors for HDFN

The incidence of HDFN was 30% ($n = 36$), including 11% of severe HDFN ($n = 13$). A titre ≥4 and above, a concentration ≥7.5 IU/ml during

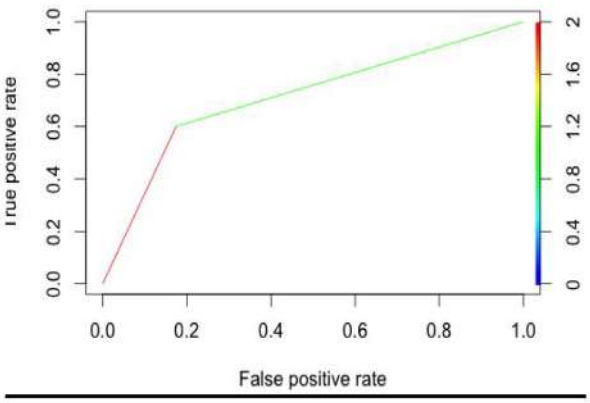
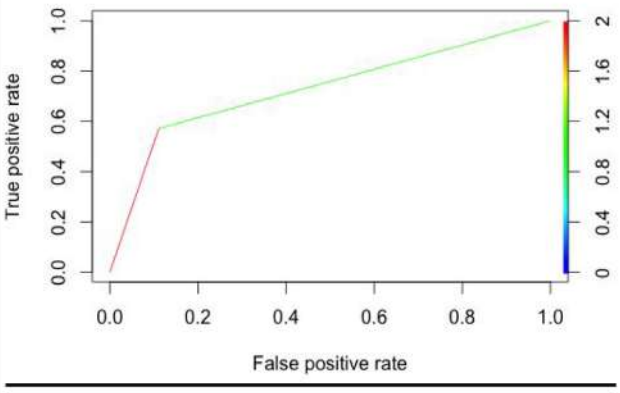
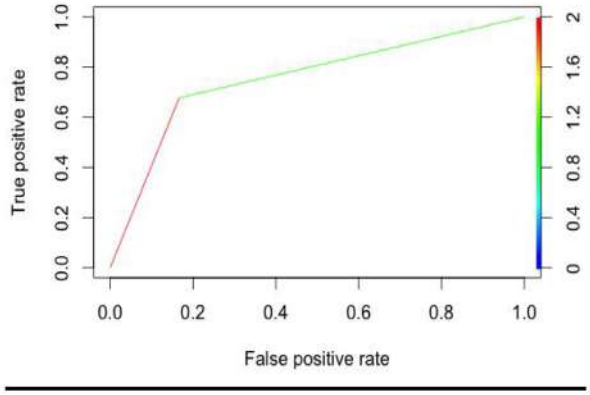
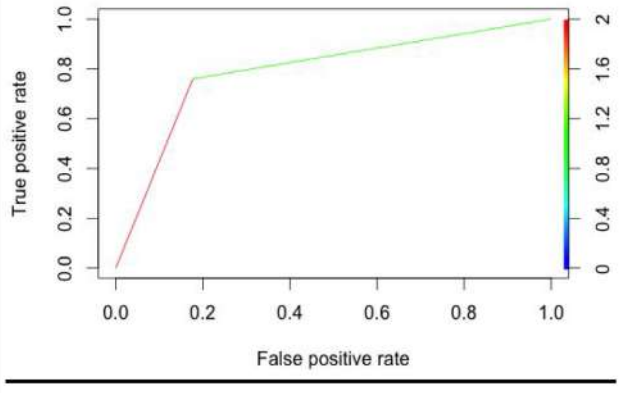
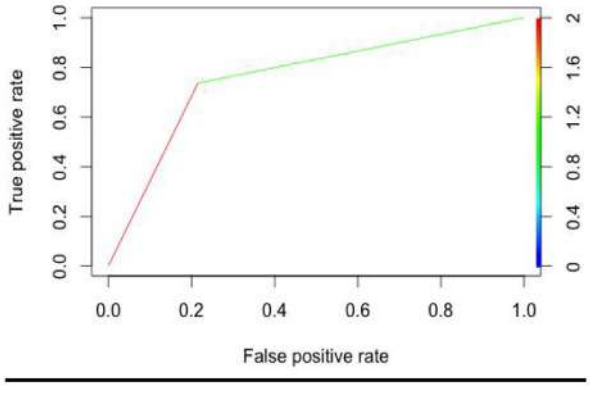
Concentration (IU/ml)	Titration
	≥4: area under curve = 0.71
	
≥7.5 IU/ml: area under curve = 0.73	≥8: area under curve = 0.76
	
≥15 IU/ml: area under curve = 0.78	≥16: area under curve = 0.76
	

FIGURE 2 Receiver operating characteristic curves for the performance of prediction of haemolytic disease of the foetus and newborn according to different thresholds of titration and concentration of anti-c antibodies during pregnancy

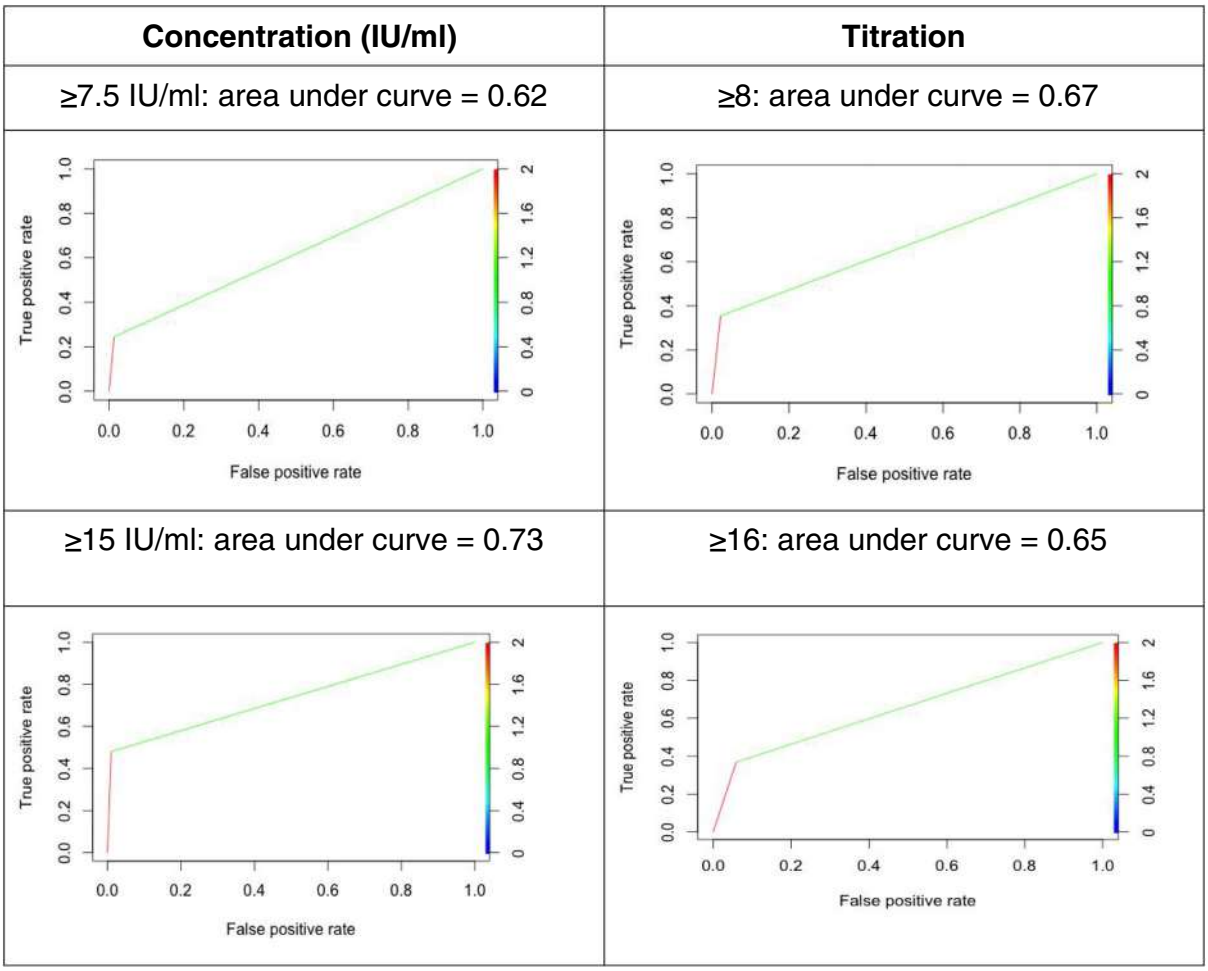


FIGURE 3 Receiver operating characteristic curves for the performance of prediction of severe haemolytic disease of the foetus and newborn according to different thresholds of titration and concentration during pregnancy

pregnancy and high intensity of the DAT were significantly associated with HDFN (Table 2). No association was found with a history of severe HDFN in a previous pregnancy, a concentration ≥15 IU/ml during the first trimester, the timing of immunization, and reactivation at third trimester. A titre of anti-c antibodies ≥8, a concentration ≥7.5 IU/ml throughout pregnancy and the strength of the DAT were significantly associated with severe HDFN (Table 3). The same criteria and medical history of severe HDFN were associated with a higher risk for the need of a postnatal transfusion at more than 7 days of life (Table S1). Using ROC curves, the concentration threshold of 15 IU/ml had the best performance (area under curve [AUC] = 0.78) in predicting HDFN, followed by a titre threshold of 8 or 16 (AUC = 0.76 for both) (Figure 2). Similarly, these three thresholds predicted severe HDFN with respective AUC of 0.73, 0.67 and 0.65 (Figure 3).

DISCUSSION

Among 121 foetuses and neonates with isolated anti-c maternal-foetal incompatibility, 106 (88%) had a positive DAT at birth. Among these 106 foetuses and neonates, HDFN occurred in 30% of cases and severe HDFN requiring foetal or neonatal transfusion, exchange transfusion or intravenous immunoglobulin in the first 7 days of life occurred in 11% of cases.

To the best of our knowledge, this is the largest series of pregnancies with anti-c alloimmunization for which perinatal care followed the most recent standard of care and current practice guidelines [12, 16–18]. Moreover, the strength of these results relies on the short inclusion period restricted to 2 years and the homogenous management of cases supervised by a single expert centre for perinatal haemobiology. The limits of our study are its retrospective design which leads to missing data and the limited number of severe cases. Data collection was exhaustive for the vast majority of criteria. Unfortunately, we did not present some criteria such as reticulocyte values due to missing data while they could have been of great interest.

Although several studies have shown that maternal anti-D titre is a good indicator of the severity of haemolytic disease, this had not been established in anti-c immunization due to the restricted number of cases in the previous series. This series allowed to determine thresholds helpful for all practitioners involved in the perinatal management of these

cases. Thus, a titre ≥4 and/or a concentration ≥7.5 IU/ml during pregnancy were both significantly associated with HDFN.

Considering our experience with anti-c quantitation, we found that a quantitative approach allows an earlier diagnosis of immune activation during pregnancy considering a longitudinal follow-up strategy of each case [11]. We thus observed that 500 UCHP/ml (CNRHP unit) could be brought back to 7.5 IU/ml in international unit and was more accurate than titration in the detection of reactivation (unpublished data).

The results of our study confirm our current policy of performing weekly MCA-PSV only if anti-c concentrations are ≥7.5 IU/ml. However, we must be careful with this result regarding foetal disease due to the use of a composite criterion including prenatal and postnatal outcomes, and the limited number of severe foetal cases.

Recently, Koelewijn et al. [19] used monocyte-driven antibody-dependent cellular cytotoxicity (ADCC) tests as a supplement to antibody concentration or titre to detect all cases at risk for severe HDFN. Repeated testing may add a more accurate risk estimation in cases with a titre ≥16. With an ADCC test ≥30%, a positive predictive value of 38% was obtained to detect severe HDFN.

Regarding the overall perinatal outcomes, we observed that anti-c immunization seems at low foetal risk. In this study, there were only 3 cases of severe foetal anaemia. The severe adverse outcomes we observed may be explained by initial very severe clinical cases or difficult technical conditions. These results are not representative of survival rates reported by our department and the other expert centers in the literature [20, 21]. In the majority of cases, in utero haemolytic risk is low, probably due to the low affinity of anti-c antibodies for foetal red blood cells or to other biochemical characteristics like the IgG-Fc glycosylation pattern of these antibodies [22]. Unlike our study, Rath et al. [6] report 41% of foetal transfusions in a small series of 22 foetuses with severe anti-c immunization. It is difficult to compare these results since in the Netherlands, only the most severe cases of anti-c immunizations with titres >16 are referred to the national reference center. Older series are not comparable since they included a majority of cases managed before implementation of non-invasive monitoring of MCA-PSV [23–25].

Like others, we have demonstrated that the neonatal risk of HDFN is high. The highest rate of top-up transfusion has been reported by Rath et al. close to 60% in a population of severe alloimmunization [6]. Unlike previous authors, our series allows to discriminate neonates at higher risk of HDFN and to offer appropriate postnatal management. At birth, quantitative DAT on cord blood appears as a very significant marker of the severity of HDFN. This very accessible test should be performed systematically as a postnatal marker to anticipate the risk of severe HDFN and organize appropriate follow-up. Thus, newborns with a negative DAT or a negative Rhc phenotype at birth do not have to be followed up for anti-c related HDFN. For others, follow-up can be weighted according to the strength of the DAT.

The history of HDFN in previous pregnancy does not appear to be associated with HDFN or severe HDFN. It can be explained by the low rate of patients with a history of HDFN (17%) in this population. We observed that 14% of the children of these patients had a transfusion or exchange transfusion in the first 72 h and half of them had a transfusion after 7 days regardless of the degree of history of HDFN. Paediatricians should be aware of this specific risk factor.

Finally, we observed a high rate of late top-up transfusions performed more than 7 days after birth (21%). This result emphasizes the need for a prolonged follow-up of neonates after hospital discharge.

Our national referral center currently uses Rhc foetal genotyping. For Rhc negative foetuses, the pregnancy continues to term doing antiglobulin testing monthly. For Rhc positive foetuses, we recommend inducing the delivery at 37 weeks if the alloimmunization is severe (concentration ≥ 7.5 IU/ml) and 39 weeks for moderate alloimmunization (concentration < 7.5 IU/ml). We also recommend performing the following cord blood samplings at birth: bilirubinemia, complete blood count including reticulocytes, ABO Group and Rhc antigen typing, DAT and elution. A paediatrician should examine the neonate looking for haemolytic disease. Bilirubin control at H6/H8, Rh Kell phenotype group determination and DAT must be performed on a peripheral blood sampling regardless of clinical manifestations. Treatment should be discussed according to biological results and evolution within the first 24 h. Monitoring of Hb level and reticulocyte count should be organized over the first 2 months of life if the DAT is positive regardless of the neonatal clinical picture [26].

In conclusion, perinatal factors predictive of HDFN in anti-c immunization comprise a titre ≥4 and a concentration ≥7.5 IU/ml during pregnancy and the strength of DAT positivity. The same criteria and a history of severe HDFN were associated with a higher risk of late postnatal transfusion beyond 7 days of life. Clinicians should be aware of these criteria to organize appropriate management of pregnancies complicated by anti-c immunization and need for referral in specialized tertiary centers.

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L.F., E.M. and J-M.J. conceptualized and designed the study and drafted the manuscript. C.T.N., S.H-J. and A.M. designed the data collection instruments, carried out the initial analyses and critically reviewed the manuscript. S.F. and P.M. carried out the final analyses and reviewed the manuscript. A.C. conceptualized and designed the study, supervised data collection and critically reviewed the manuscript.

CONFLICT OF INTEREST

The authors do not have any financial relationships and any conflicts of interest relevant to this article to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

COVID-19 convalescent plasma: Evolving strategies for serological screening in France

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Abstract

Quantitation of anti-SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) neutralizing antibodies (Nabs) is a key parameter in determining the effective dose for treatment with COVID-19 convalescent plasma (CCP). Interpretation of results from clinical trials conducted worldwide requires comparison of Nabs titres obtained from different methods. As virus neutralization tests (VNTs) are not standardized scalable or commercially available, strategies based on intensity of ELISA (Enzyme Linked Immunosorbent Assay) or chemiluminescent binding serological tests were implemented to allow comparisons and establish criteria for determining 'high-titres' of anti-SARS-CoV-2 antibodies (Abs). To this end, the FDA (Food and Drug Administration) has proposed criteria to define high-titre plasmas using different serological assays, including the one used in France for the CCP SARS-CoV-2 Abs screening (Euroimmun anti-S1 IgG). A retrospective study revealed that when using the FDA criteria (ELISA signal-to-cut-off [S/C ratio] ≥3.5), 91% of CCP had Nabs titres ≥40 as assessed with an in-house VNT. French strategy to ensure sufficient stocks of CCP of increasing titre has evolved over time. Recently, we improved our strategy by collecting only plasma from vaccinated convalescent donors as we confirmed that the mean IgG antibody level (ELISA S/C ratio) was significantly higher in plasma from vaccinated convalescent donors compared to donations from unvaccinated convalescent donors: 9.31 (CI 95%: 8.46–10.16) versus 3.22 (CI 95%: 3.05–3.39) ($p < 0.001$).

KEYWORDS
anti-spike, convalescent plasma, neutralizing antibodies, SARS-CoV-2, vaccination

INTRODUCTION

As the COVID-19 pandemic strikes worldwide, effective treatment of this viral pneumonia remains elusive. In this context, passive immunotherapy, that is, passive antibody administration has been heralded as a potential effective treatment. Such immunotherapy comprises polyclonal antibodies (Abs) contained in plasma donations from COVID-19 convalescent patients and anti-SARS-CoV-2 monoclonal Abs. The expected beneficial effect of COVID-19 convalescent plasma (CCP) relies primarily on the neutralizing power of anti-SARS-CoV-2 Abs to limit viral replication and promote viral clearance [1, 2]. The rapid availability of screening ELISA assays for anti-SARS-CoV-2 Abs and methods to quantify neutralizing antibodies (Nabs) have been key factors in selecting CCP with high Abs content for use in clinical trials.

INITIATING CCP COLLECTION AND SCREENING IN FRANCE

In France, the ELISA assay selected in March 2020 for CCP screening was the Euroimmun Anti-SARS-CoV-2 IgG test, Euroimmun, which targets the S1 subunit of the SARS-CoV-2 spike protein including the receptor-binding domain (RBD) region. The neutralizing activity of anti-spike or anti-RBD Abs has been shown to block virus entry into cells [3]. Titration of Nabs was performed by a cell culture virus neutralization test (VNT) [4]. In April 2020, CCP collection was implemented in donors reporting a history of COVID-19 illness with at least 14 days since symptom resolution. SARS-CoV-2 serological testing included both IgG ELISA and Nabs titration by VNT. A threshold Nabs titre of ≥40 was required to retain the CCP for therapeutic use. Results from plasma samples collected during the first 2 weeks ($n = 256$) were analysed. All samples with a negative ELISA ratio (R) ($R < 0.7$; $n = 46$) had a Nabs titre <40 and were disqualified for COVID-19 treatment. Among the ELISA positive samples ($n = 210$), the predictive value for having Nabs titre ≥40 was estimated to be 98% for those with $R \geq 5.7$ and 95% for Nabs titre ≥80 if $R > 8$. Consequently, CCP samples collected after 1 May 2020 and found to be with an $R > 5.7$ were no longer tested by VNT and were directly characterized as CCP. As evidence favouring a strong Abs dose-dependent effect emerged [5, 6], the cut-off Nabs titre value for use as CCP was increased to ≥80 in October 2020 as a criterion for 'high-titre' CCP selection, and the cut-off ELISA ratio raised accordingly ($R > 8$). Samples with positive ELISA ratio but lower than these new cut-off values were tested by VNT and among these, only those with a titre ≥80 were characterized as CCP (Table 1).

THE DIFFICULTY OF COMPARING CCP Ab CONTENT

Comparing the Abs titration result in CCP collected by different teams internationally quickly became a challenge. Indeed, many anti-SARS-CoV-2 serological tests were rapidly available, which allowed the detection of Abs isotypes or total Abs targeting different viral antigens: spike protein (all or part: S1, S2 sub-units, RBD region) or the nucleocapsid antigen. Similarly, comparing results regarding Nabs titres was complex because the techniques are not standardized. The main differences concern the methodology used (wild-type virus, pseudo-virus) and parameters used in the protocols (viral strain, infectious dose, duration of cell culture, etc.). Accordingly, a 100-fold difference in raw titres was observed when comparing the performance of CCP Nabs titration methods across 12 European laboratories [7]. In addition, poor agreement between commercial serological assays and virus neutralization assays was frequently reported [8–10].

A RATIONALE FOR 'HIGH-TITRE' PLASMA SELECTION

As briefly mentioned earlier, several studies highlighted a dose-dependent relationship between Nabs and therapeutic benefit of CCP [5, 6, 11–15]. The Mayo Clinic team observed a gradient of mortality in relation to IgG Abs levels in the transfused plasma [5, 11]. In these studies, Abs levels were estimated using the Ortho-Clinical-Diagnostics VITROS Anti-SARS-CoV-2 IgG qualitative immunoassay based on a recombinant form of the SARS-CoV-2 spike subunit 1 protein. Signal-to-cut-off ratios for anti-SARS-CoV-2 IgG antibody levels were established as low (<4.62), medium (4.62–18.45) or high (>18.45) [11]. The upper threshold was selected to provide 90% specificity for the detection of a dilution of the sample of ≥1:2560 when tested by a semi-quantitative assay developed at the Mayo Clinic that measured the capacity to neutralize a pseudo-virus bearing the SARS-CoV-2 spike protein [5]. In addition, Libster et al. reported that infusion of high-titre CCP reduced the progression of COVID-19 to severe illness [6]. In this study, high levels of antibody were defined as a sample harbouring an IgG titre greater than 1:1000 against SARS-CoV-2 spike protein when tested by the ELISA assay COVIDAR IgG (Instituto Leloir, Argentina). Correlation between ELISA titration and virus-neutralizing activity was determined by using SARS-CoV-2 pseudotyped VSV (Vesicular Stomatitis Virus) particles (CoV2pp) [16]. The

TABLE 1 Adjustments of convalescent plasma (CCP) selection strategy in France

	April 2020	1 May to 29 October 2020	29 October 2020 to 22 March 2021	22 March to 1 June 2021	>1 June 2021
ELISA ratio (R)	$R \geq 1.1$	$R \geq 1.1$	$R \geq 1.7$	$R \geq 2$	$R \geq 3.5$
Condition for Nabs titration	None, titration was systematic	$1.1 < R < 5.7$	$1.7 < R < 8$	$2 < R < 6$[a]	$3.5 < R < 6$
Criteria for COVID-19 therapeutic use	Titre ≥40	$R \geq 5.7$ or titre ≥40	$R \geq 8$ or titre ≥80	$R \geq 6$ or titre ≥80	$R \geq 6$ or titre ≥80
Minimal titre for COVID-19 therapeutic use	40	40	80	80	80
Additional criteria	None	None	None	None	Vaccination history

Note: Voluntary convalescent donors for plasma donation were all selected by evidence of clinical and/or biological COVID-19 diagnosis and tested for the presence of IgG anti-SARS-CoV-2 Abs (Euroimmun). Criteria having been modified or added are presented over time.

[a]The predictive value of a ratio ≥6 for a Nabs titre ≥80 was found to be 100%.

significant differences between protocols presented above illustrate the current difficulty when comparing findings from clinical trials using CCP.

SIGNAL INTENSITY AS A PROXY FOR 'HIGH-TITRE' PLASMA SELECTION

Since estimating the amount of Nabs is a key element in the comparison of CCP clinical trials, a pragmatic approach has been chosen to establish correlations between the signal intensity of serological tests and the amount of Nabs. This allowed the determination of cut-off values for different serological tests with a high predictive value for selecting plasmas with high NAbs titres. As previously reported [5, 6], the first published criterion for defining plasmas with high levels of Nabs (≥18.45) was based on the results of the Ortho VITROS SARS-CoV-2 IgG technique and the signal-to-cut-off value was revised in December 2020 to ≥12 [17] and more recently to ≥9.5 [18] in updates that defined cut-off values for 10 other qualitative or quantitative serological methods. These included the anti-SARS-CoV-2 IgG test (Euroimmun) used in France for CCP screening and for which the criterion for 'high-titre' CCP proposed by the FDA was a ratio ≥3.5 [18], corresponding to ~140 binding antibody units/ml (using the standardized unit recommended by the World Health Organization referring to the international standard NIBSC code 20/136). As a large proportion of the CCP collected in France has been titrated by VNT in addition to ELISA, this FDA definition of 'high-titre', based on thresholds for serological assays, provided the opportunity to estimate the NAbs titre meeting this threshold as measured by our VNT method. For this purpose, we selected a panel of 174 samples on the basis of NAbs titres (VNT) irrespective of the result of the Euroimmun ELISA assay. Based on VNT titre, we identified five subgroups (Figure 1), and we calculated for each the percentage of samples with (i) negative ELISA results ($R < 1.1$); (ii) positive 'low titre' ELISA ratio results ($1.1 \leq R < 3.5$) and (iii) positive 'high-titre' ELISA ratio results ($R \geq 3.5$). We observed that samples with a negative ELISA had VNT titres of 10 (negative) or 20 (cut-off value). The proportion of samples with $R \geq 3.5$ ('high-titres') increased with titre value from 9% to 85% for CCP with VNT titre of 20 and 160, respectively. In our study, 91% of plasma with an ELISA ratio ≥3.5 had Nabs titres ≥40 (64% ≥80) when tested by VNT. The implementation of a CCP VNT titre threshold of ≥40 seems to have been appropriate at the early phase of CCP collection, as it ensured the presence of Nabs in CCP while avoiding the disqualification of too many Nabs-positive donations, making it possible to reconcile the supply needs that can be critical during epidemic peaks.

The strategy based on the correlation between the ELISA screening assay and the VNT titration technique appears to be the most

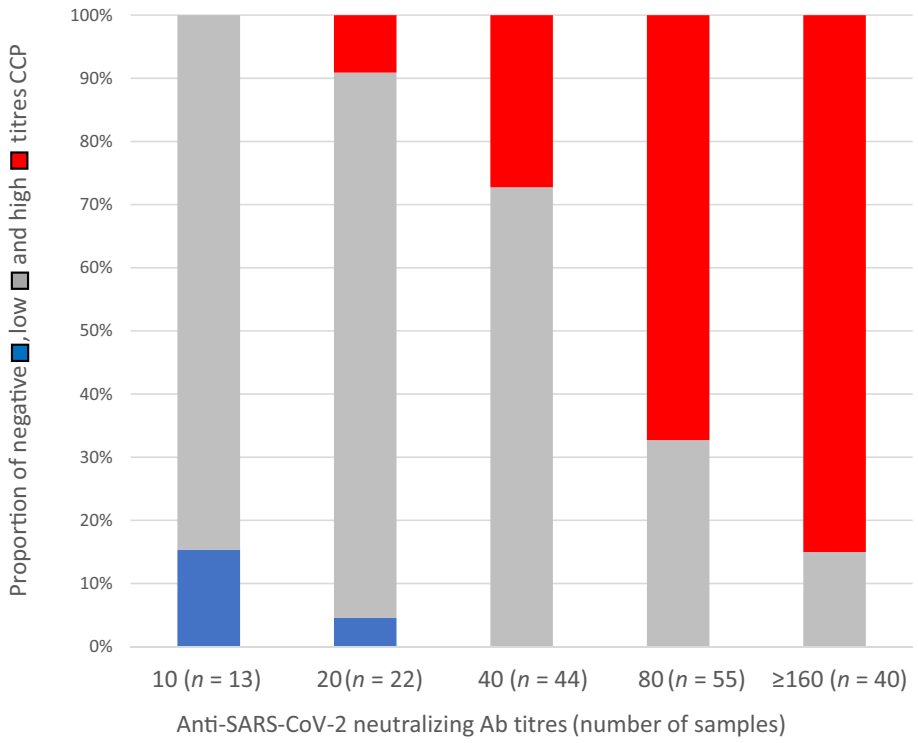

FIGURE 1 Distribution of low and high-level convalescent plasma (CCP) according to neutralizing antibody (Nab) titres. In each subpopulation with the same Nabs titre, samples were classified into three categories: negative, low and high titre based on ELISA ratio and according to the specification of the FDA when using the anti-SARS-CoV-2 IgG (Euroimmun) assay. Nabs titres were measured by a virus neutralization test (VNT) method (specificity previously estimated 100% for anti-SARS-CoV-2 Nabs titres ≥40 [4])

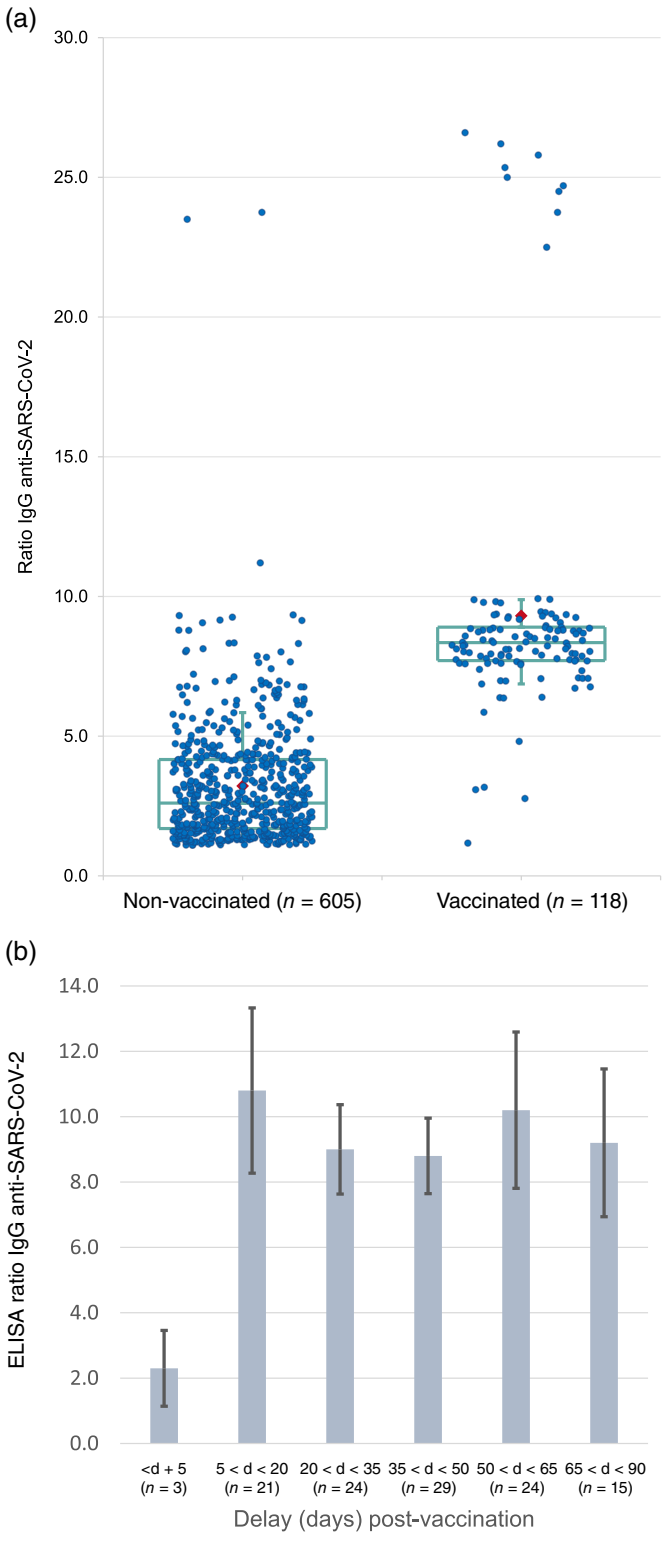

FIGURE 2 Impact of vaccination on ELISA ratio of convalescent plasma (CCP) donations. (a) Distribution of anti-SARS-CoV-2 IgG ELISA ratio (Euroimmun) in donations (collected between 27 October 2020 and 16 April 2021) tested positive ($R > 1.1$) according to the vaccine status. (b) Distribution of anti-SARS-CoV-2 IgG ELISA ratio according to time between date of vaccination and date of serological testing

suitable to allow limitation of titration by VNT for samples with ELISA ratio comprised in a grey zone above the ELISA cut-off signal in order to guarantee that the minimum threshold for COVID-19 therapeutic use is respected. However, referring to ratio values of a serological test as a proxy for Nabs levels has some limitations. Farnsworth et al. reported that, when using thresholds proposed by the FDA, samples may have discordant 'high-titre' status depending on the assays used [19]. In addition, these cut-off thresholds are likely to evolve according to the findings in clinical trials using CCP and/or as a result of collaborative efforts to calibrate and ensure comparability between the different assays used internationally [7]. The neutralizing activity of Abs can be altered when new antigenic variants circulate. The use of ELISA intensity as a proxy for true neutralization, therefore, requires periodic monitoring of neutralizing activity and, if needed, adaptation of CCP donor selection to recruit convalescent vaccinated donors and/or donors who have been infected with the variants of interest.

MOVING TO VACCINATED CONVALESCENT DONORS

With the implementation of large-scale vaccination in January 2021, the serological strategy for selection of 'high-titre' CCP was improved by selecting CP donors with a history of vaccination. Indeed, it has been described that individuals who were infected and vaccinated had higher Abs levels in addition to increased cross-reactive Nabs to SARS-CoV-2 variants of concern [20]. In order to investigate this opportunity, we studied a population of 1298 CCP donations from donors having reported vaccination history ($n = 118$) or not ($n = 605$). We observed that the mean Euroimmun ELISA ratio was around three times higher in plasma from vaccinated convalescent donors compared to unvaccinated convalescent donors: mean ELISA ratio 9.31 (CI 95%: 8.46–10.16) versus 3.22 (CI 95%: 3.05–3.39), $p < 0.001$; using an analysis of variance (Figure 2a). Mean ELISA ratios of donations from convalescent vaccinated donors is >8 as early as the second-week post-vaccination (Figure 2b). As a result, it was decided in France as of 1 June 2021 to prioritize the collection of CCP from convalescent donors with a history of vaccination (Table 1). Between June and October 2021, such CCP has been transfused to 275 COVID-19 immunosuppressed patients included in a monitored access programme issued by the French Competent Authority (ANSM). Safety and efficacy assessments are currently underway.

CONCLUSION

Our experience highlights the need to continuously adapt the criteria for selecting CCP according to the availability and accuracy of screening tests, evolving knowledge regarding COVID-19 disease and the epidemiological dynamics, including vaccine rollout. The experience acquired during the COVID-19 pandemic will make it possible to

better anticipate future challenges when considering passive immunotherapy as a treatment for a novel emerging pathogen.

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CONFLICT OF INTEREST

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ORIGINAL ARTICLE

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The continued decline of plasma transfusions in Taiwan: An 11-year population-based study

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Abstract

Background and Objectives: In Taiwan, plasma use per capita ranks among the highest in the world. We aimed to describe the trends in usage after the introduction of new hospital accreditation standards that evaluate compliance with institutional plasma transfusion guidelines.

Materials and Methods: We identified hospitalizations receiving plasma between 2007 and 2017 from the national health insurance database. We estimated plasma transfusions per thousand capita. The risk ratio of transfusion rates among hospitalizations in 2017 compared to 2007 was estimated using logistic regression.

Results: The total number of plasma transfusions declined from 964,408 in 2007 to 659,828 in 2017, yielding a rate of 28.00 per thousand capita. The proportion of hospitalizations receiving plasma declined by 38%, from 3.89% (95% confidence interval: 3.86%–3.91%) to 2.62% (2.61%–2.64%). Gastroenterology (16.4%) and general surgery (15.3%) accounted for the largest proportions of plasma usage. Within these two services, liver diseases were the top diagnoses needing plasma use. For hospitalized patients with liver diseases, approximately 40% of plasma units were administered to patients with neither noticeable bleeding nor red blood cells transfusions. Among these patients, almost 50% received plasma with an international normalized ratio trigger of less than 1.50. The use of potential alternative therapies or anticoagulants remained quite low during this period.

Conclusion: Plasma utilization rates during hospitalizations continuously declined over 11 years. However, inappropriate plasma use remained high, while the use of alternative therapies remained low in services such as gastroenterology. To improve the appropriateness of plasma transfusions, patient blood management should be implemented in the near future.

KEYWORDS
hospital accreditation standards, international normalized ratio, liver diseases, national health insurance, plasma

Highlights

- After the introduction of new standards to evaluate the appropriateness of plasma used for hospital accreditation, a 38% reduction in plasma transfusion rates was observed from 2007 to 2017.
- Liver diseases were the predominant diagnoses in gastroenterology and general surgery, which are the top two services of plasma use.
- For liver diseases, approximately 40% of plasma was administered to patients with neither bleeding nor red blood cells transfusions. Inappropriate plasma use remained high.

INTRODUCTION

Plasma transfusion is used for several medical conditions, including prophylactic bleeding prevention, therapeutic haemostasis or plasma exchange [1]. Based on the recommendations of the American Association of Blood Banks (AABB), indications for plasma transfusion include: (i) patients who are deficient in one or multiple clotting factors and no factor-specific concentrate is available; (ii) patients who are undergoing massive transfusions because of life-threatening trauma/haemorrhages and (iii) patients who have clinically significant coagulation deficiencies [2]. Other indications include plasma exchange for patients with thrombotic thrombocytopenic purpura. Despite its many indications, evidence supporting the beneficial effects of prophylactic plasma use remains limited. For example, the use of fresh frozen plasma (FFP) prior to invasive procedures in non-bleeding patients with abnormal coagulation tests (prothrombin time [PT], partial thromboplastin time or international normalized ratio [INR]) is debatable, because these tests are poor predictors of bleeding risk [3, 4].

Plasma transfusion is an important medical therapy and benefits patients in a wide spectrum of clinical settings. However, this product is commonly overused, and a high rate of inappropriate use was reported in several previous studies [5–13]. Overuse of plasma may cause negative consequences, as transfusion therapy is susceptible to adverse effects such as acute allergic and anaphylactic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulation overloads (TACO) or transfusion-transmitted diseases [14]. In recent years, the utilization of plasma has been declining across the United States, Canada and New Zealand [15–17]. Patient blood management (PBM) is an evidence-based model involving the early diagnosis and management of anaemia, perioperative bleeding control and the minimization of unnecessary transfusions. The implementation of PBM may explain the reduction in plasma use in the above-mentioned countries. Declining plasma use may also be due to the increasing use of plasma alternatives such as prothrombin complex concentrate (PCC) or intravenous vitamin K [15]. In this study, our primary aim was to describe trends in plasma transfusions and to identify clinical and hospital characteristics that may account for differences in plasma utilization. Our secondary aim was to determine the proportion of inappropriate plasma transfusions among admission services with high plasma usage.

STUDY DESIGN AND METHODS

Taiwan National Health Insurance programme

Taiwan has had a National Health Insurance (NHI) programme in place since 1995. By the end of 1999, the NHI programme's coverage rate for Taiwan's 23 million citizens reached 96.1% and rose to 99.0% and 99.9% by the end of 2006 and 2015, respectively [18]. All medical centres (>500 beds), regional hospitals (>300 beds), district hospitals and more than 90% of clinics are NHI-contracted medical institutions. The NHI database includes complete outpatient visits, emergency visits and hospital admissions. It also includes comprehensive healthcare information such as diagnoses, prescriptions, surgical procedures, hospital stays, payments for treatment, as well as demographic characteristics of patients. The system covers most forms of treatment, including surgeries, examinations, laboratory tests, prescription medications and all blood components.

New hospital accreditation standards relevant to blood usage

In Taiwan, all medical centres, regional hospitals and district hospitals need to be regularly accredited. Starting in 1999, hospital accreditations have been performed by a non-governmental organization called the Taiwan Joint Commission on Hospital Accreditation, and new standards relevant to blood usage and management were developed in the mid-2000s. According to the new standards, the following aspects regarding blood usage are evaluated: the implementation of an institutional transfusion advisory committee; the development of an institutional guideline for blood transfusions, with particular emphasis on plasma; the performance of coagulation tests such as PT or INR and examination of compliance with institutional guidelines as well as the proportion of inappropriate plasma use (Table S1) [19]. In Taiwan, there are no standardized transfusion guidelines that apply to all hospitals, and institutional guidelines for plasma use vary between hospitals. Institutional guidelines may be based on previous experiences or expert opinions, and the definition of inappropriate plasma use may also vary between hospitals.

Clinical profiles of blood component transfusions

Using the NHI database, we identified all hospitalizations receiving plasma (both FFP and frozen plasma [FP], which is plasma frozen

beyond 8 h after phlebotomy) for the years between 2007 and 2017. We also retrieved each plasma recipient's healthcare information, such as primary diagnoses and prescription medications, including anti-fibrinolytic drugs such as tranexamic acid (TXA) and aminocaproic acid, as well as PCC, cryoprecipitate, coagulation factors VII, VIII, IX, recombinant factor VIIa, anti-coagulant factors such as low-molecular-weight heparin, heparin, vitamin K antagonist, direct-acting anticoagulant factor Xa and thrombin inhibitors. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to define diseases. We retrieved all INR measurements during the entire hospitalization from NHI laboratory test results, and identified the first, highest and last INR.

Statistical analysis

Plasma use per capita was estimated as the total units of plasma transfused divided by the population of Taiwan, which was obtained from the Taiwan Census Bureau, Department of Household Registration, Ministry of the Interior. The proportion of hospitalizations receiving plasma (also expressed as the 'transfusion rate') was also estimated. The mean number of plasma units was estimated by dividing the total units of plasma transfused by the number of hospitalizations receiving plasma. A breakdown analysis of plasma use according to service types was then performed. We examined the changes in transfusion rates for hospitalizations by estimating a risk ratio (RR) and 95% confidence interval (CI) using logistic regression. We also examined the transfusion rates among the top services and top diagnoses according to various clinical conditions: group I—'excessive bleeding or received a transfusion of >3 units of red blood cells (RBCs)'; group II—'no documented bleeding but received a transfusion of ≤3 units of RBCs'; group III—'received invasive procedure, no documented bleeding or RBC transfusion' and group IV—'none of the above conditions'. We used the highest INR during the entire hospital stay as a plasma transfusion trigger. We also examined the distribution of trigger INRs and the correlation between trigger INRs and a decrease in INR per transfusion unit.

All analyses were performed using SAS statistical software (version 9.1.2, SAS Institute Inc., Cary, NC). This study was approved by the Institutional Review Board of the Taiwan Blood Services Foundation. All NHI data were anonymized, and no identifiable patient information was included in this study.

RESULTS

The total number of plasma transfusions (including transfusions during hospitalizations and outpatient visits) in 2007 was 964,408 units, yielding a population rate of 42.01 units per 1000 capita. By 2017, the number of transfusions decreased by 31.58% to 659,828 units, for a population rate of 28.00 units per 1000 capita. Figure 1 shows temporal trends in plasma transfusions from 2007 until 2017 among hospitalizations, as well as the mean number of units transfused per

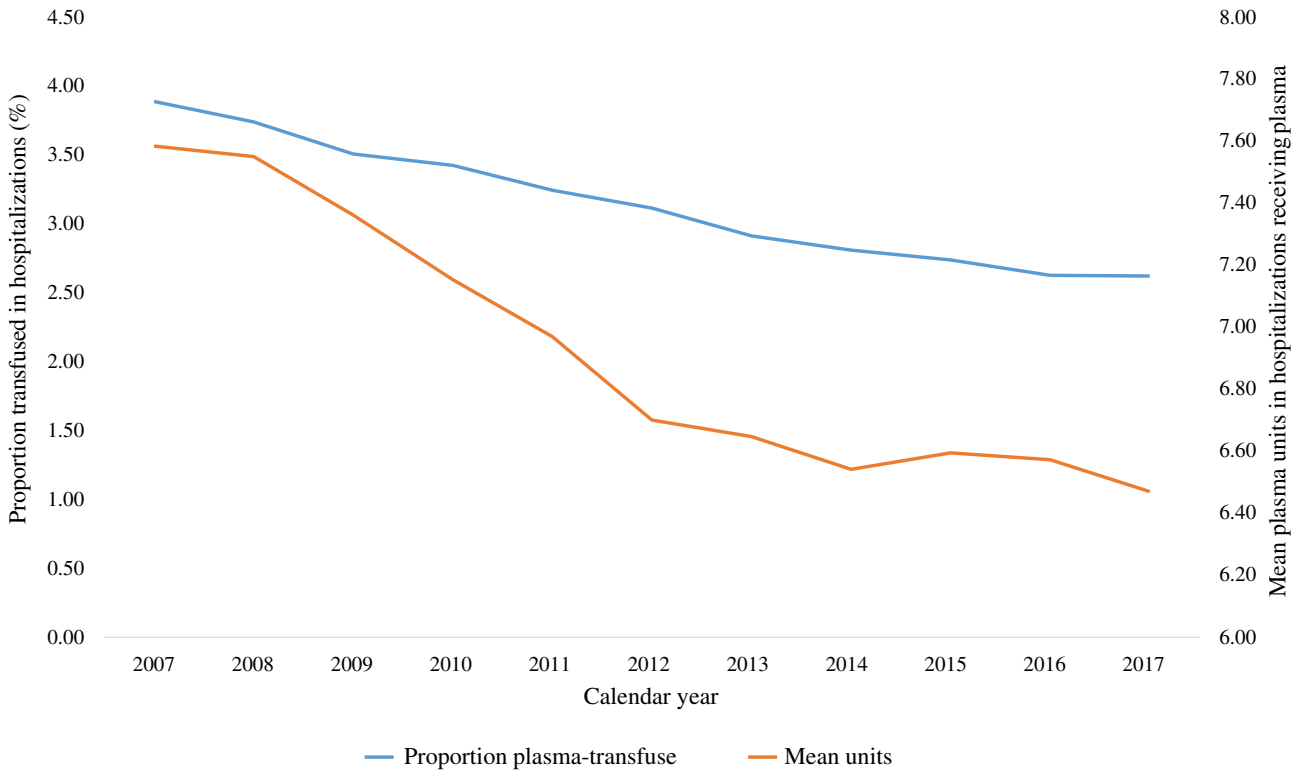

FIGURE 1 Temporal trends in plasma transfusions among hospitalizations and mean plasma units transfused in hospitalizations over the study period, 2007–2017

hospitalization receiving plasma among 19 medical centres, 76 regional hospitals, 234 district hospitals and 26 clinics. The proportion of hospitalizations receiving plasma steadily declined from 3.89% in 2007 to 2.62% in 2017 ($p_{trend} < 0.0001$). Similarly, the mean units also decreased from 7.58 (SD: 10.68) to 6.47 (SD: 11.74).

Table 1 presents the total number of hospitalizations receiving plasma as well as the changes in total transfused units between 2007 and 2017 according to various admitting services. Overall, approximately 40% of plasma transfusions were to support surgical procedures, while 48% were for internal medicine. Both in 2007 and 2017, gastroenterology (19.7% [2007], 16.4% [2017]) and general surgery (14.2% [2007], 15.3% [2017]) accounted for the two largest proportions of plasma usage, followed by thoracic medicine (12.6% [2007], 10.6% [2017]), haematology and oncology (5.6% [2007], 8.2% [2017]) and cardiac surgery (5.1% [2007], 8.2% [2017]). Compared to 2007, we observed a noticeable reduction in gastroenterology (−80,049), general internal medicine (−52,836) and thoracic medicine (−50,989). Reduced plasma use was observed in most service types except for cardiac surgery, neurology, paediatrics and gynaecology/obstetrics.

Table 2 presents the changes in transfusion rates between 2007 and 2017 stratified by admitting services. During this time, there was a 28%–57% decrease in the proportion of individuals receiving plasma for medical services, and a 20%–40% decrease for surgical services. We observed a 39% (95% CI: 37%–40%) and 30% (29%–33%) decrease in transfusion rates within gastroenterology and general surgery, respectively. On the other hand, we observed a slight increase within gynaecology/obstetrics (+9%).

Table 3 presents changes in plasma transfusions among hospitalizations for various clinical conditions among services with high plasma use, including gastroenterology, thoracic medicine and haematology/oncology. We found that approximately 30%, 20% and 30% of plasma units were administered to patients with neither noticeable bleeding nor RBC transfusions within gastroenterology, thoracic medicine and haematology/oncology, respectively, both in 2007 and 2017. Plasma transfusion rates decreased across all clinical conditions within these services over the study period. However, among hospitalized patients who received an invasive procedure and had neither bleeding nor RBC transfusions, plasma transfusion rates were still 4.55% in gastroenterology, 1.59% in thoracic medicine and 1.17% in haematology/oncology at the end of the study.

Table 4 presents changes in plasma transfusions among hospitalizations for clinical conditions related to liver diseases (including chronic hepatitis, liver cirrhosis and liver abscess) and liver malignancy. Among gastroenterology and general surgery, which were the top two services for plasma use, liver diseases and malignancy

TABLE 1 The number of hospitalizations receiving plasma and total transfused units in 2007 and 2017, stratified by admitting services

	2007		2017		
	No. hospitalizations (%)[a]	Units (%)[b]	No. hospitalizations (%)[a]	Units (%)[b]	Change in units 2007–2017
Overall	115,365	933,416	91,606	633,069	−300,347
Paediatrics	2066 (1.8)	7271 (0.8)	2343 (2.6)	8684 (1.4)	+1413
General internal medicine	11,918 (10.3)	84,139 (9.0)	4856 (5.3)	31,303 (4.9)	−52,836
Thoracic medicine	14,511 (12.6)	118,022 (12.6)	9866 (10.8)	67,033 (10.6)	−50,989
Cardiology	3634 (3.2)	24,706 (2.7)	3086 (3.4)	16,304 (2.6)	−8402
Gastroenterology	20,764 (18.0)	183,778 (19.7)	13,973 (15.3)	103,729 (16.4)	−80,049
Neurology	1785 (1.6)	19,739 (2.1)	992 (1.1)	20,152 (3.2)	+413
Nephrology	4423 (3.8)	32,677 (3.5)	3950 (4.3)	28,820 (4.6)	−3857
Critical care service	1326 (1.2)	11,878 (1.3)	1414 (1.5)	10,214 (1.6)	−1664
Haematology and oncology	5968 (5.2)	52,237 (5.6)	5713 (6.2)	52,190 (8.2)	−47
Rheumatology	518 (0.5)	9212 (1.0)	353 (0.4)	6485 (1.0)	−2727
General surgery	12,760 (11.1)	132,938 (14.2)	10,840 (11.8)	96,674 (15.3)	−36,264
Thoracic surgery	1545 (1.3)	16,099 (1.7)	1647 (1.8)	11,646 (1.8)	−4453
Cardiac surgery	6098 (5.3)	47,602 (5.1)	7046 (7.7)	52,182 (8.2)	+4580
Intestinal surgery	1839 (1.6)	21,157 (2.3)	1477 (1.6)	18,562 (2.9)	−2595
Neurological surgery	7035 (6.1)	44,694 (4.8)	6683 (7.3)	26,073 (4.1)	−18,621
Rectal surgery	2784 (2.4)	24,294 (2.6)	2682 (2.9)	18,945 (3.0)	−5349
Urology	1879 (1.6)	11,223 (1.2)	1618 (1.8)	7143 (1.1)	−4080
Orthopaedics	5567 (4.8)	25,008 (2.7)	4952 (5.4)	14,529 (2.3)	−10,479
Gynaecology/obstetrics	1908 (1.7)	9435 (1.0)	2631 (2.9)	10,249 (1.6)	+814
Others	7037 (6.1)	57,309 (6.1)	5484 (6.0)	32,152 (5.1)	−25,157

[a]Percentage of total hospitalizations receiving plasma.
[b]Percentage of total plasma use.

TABLE 2 Changes in plasma transfusions during hospitalizations from 2007 to 2017, stratified by admitting services

	Total hospitalizations		Proportion of hospitalizations receiving plasma			
	2007	2017	2007 (%)	2017 (%)	adjRR	(95% CI)
Overall	2,968,834	3,498,752	3.89	2.62	0.62	0.61–0.62
Paediatrics	323,420	307,160	0.64	0.76	0.96	0.91–1.02
General internal medicine	228,821	172,070	5.21	2.82	0.51	0.49–0.53
Thoracic medicine	207,065	283,354	7.01	3.48	0.49	0.48–0.51
Cardiology	131,040	172,979	2.77	1.78	0.64	0.61–0.67
Gastroenterology	178,836	193,852	11.61	7.21	0.61	0.60–0.63
Neurology	87,975	102,845	2.03	0.96	0.47	0.43–0.51
Nephrology	77,074	116,026	5.74	3.40	0.57	0.54–0.59
Critical care service	5282	7387	25.10	19.14	0.72	0.66–0.77
Haematology and oncology	103,694	174,721	5.76	3.27	0.56	0.54–0.58
Rheumatology	14,325	23,772	3.62	1.48	0.43	0.38–0.49
General surgery	231,680	259,382	5.51	4.18	0.70	0.67–0.71
Thoracic surgery	17,317	31,552	8.92	5.22	0.57	0.53–0.61
Cardiac surgery	22,656	33,887	26.92	20.79	0.78	0.76–0.81
Intestinal surgery	19,381	24,283	9.49	6.08	0.61	0.57–0.65
Neurological surgery	89,118	119,863	7.89	5.58	0.68	0.65–0.70
Rectal surgery	55,791	85,348	4.99	3.14	0.62	0.59–0.66
Urology	115,744	152,692	1.62	1.06	0.60	0.56–0.64
Orthopaedics	254,408	294,018	2.19	1.68	0.77	0.74–0.80
Gynaecology/obstetrics	298,451	304,370	0.64	0.86	1.09	1.03–1.16
Others	506,756	639,191	1.39	0.86	0.60	0.56–0.61

Abbreviations: adjRR, risk ratio adjusted for age, sex and hospital characteristics; CI, confidence interval.

TABLE 3 Plasma transfusions among hospitalizations according to various clinical conditions in gastroenterology, thoracic medicine and haematology/oncology

	2007			2017		
Clinical conditions	Total hospitalizations	Hospitalizations with plasma transfusions	Transfusion rate	Total hospitalizations	Hospitalizations with plasma transfusions	Transfusion rate
Gastroenterology						
Excessive bleeding or RBC transfusions >3 units	52,264	10,008 (48.20%)	19.15%	52,011	6669 (47.76%)	12.82%
No documented bleeding and RBC transfusions ≤3 units	14,641	4121 (19.85%)	28.15%	14,028	2776 (19.81%)	19.79%
Invasive procedure	71,934	5272 (25.39%)	7.33%	73,260	3333 (23.87%)	4.55%
None of above	39,997	1363 (6.56%)	3.41%	54,553	1195 (8.56%)	2.19%
Thoracic medicine						
Excessive bleeding RBC transfusions >3 units	20,639	6760 (46.59%)	32.75%	18,477	4228 (42.85%)	22.88%
No documented bleeding and RBC transfusions ≤3 units	26,096	4687 (32.30%)	17.96%	31,560	3443 (34.90%)	10.91%
Invasive procedure	94,545	2808 (19.35%)	2.97%	120,479	1910 (19.36%)	1.59%
None of above	65,705	256 (1.76%)	0.39%	112,838	285 (2.89%)	0.25%
Haematology/oncology						
Excessive bleeding RBC transfusions >3 units	8084	2444 (40.95%)	30.23%	11,054	2212 (38.72%)	20.01%
No documented bleeding and RBC transfusions ≤3 units	13,559	1745 (29.24%)	12.87%	22,512	1722 (30.14%)	7.65%
Invasive procedure	71,497	1536 (25.74%)	2.15%	118,972	1387 (24.28%)	1.17%
None of above	10,554	243 (4.07%)	2.30%	22,183	392 (6.86%)	1.77%

Abbreviation: RBC, red blood cell.

TABLE 4 Plasma transfusions among hospitalizations according to various clinical conditions for liver diseases

Year (total hospitalizations)	2007 (79,647)				2017 (83,245)			
Clinical conditions	Total hospitalizations	Hospitalizations with plasma transfusions (percentage of total use)	Transfusion rate	Mean units (±SD)	Total hospitalizations	Hospitalizations with plasma transfusions (percentage of total use)	Transfusion rate	Mean units (±SD)
Liver diseases (chronic hepatitis, liver cirrhosis, liver abscess and liver malignancy)								
Overall	79,647	17,849	22.41%	10.38 ± 15.58	83,245	12,051	14.48%	9.48 ± 18.31
Clinical subgroups								
I: Excessive bleeding or RBC transfusions >3 units	16,552	7810 (43.75%)	47.18%	12.78 ± 19.88	12,740	4851 (40.25%)	38.08%	11.78 ± 19.69
II: No documented bleeding and RBC transfusions ≤3 units	8523	3648 (20.44%)	42.80%	10.05 ± 13.12	8216	2767 (22.96%)	33.68%	9.03 ± 24.14
III: Invasive procedure	39,696	5133 (28.76%)	12.93%	7.78 ± 9.43	44,385	3385 (28.09%)	7.63%	7.07 ± 10.27
IV: None of above	14,876	1258 (7.05%)	8.46%	7.23 ± 7.58	17,904	1048 (8.70%)	5.85%	7.47 ± 8.00

Note: Mean unit: subtotal plasma units divided by the hospitalizations with plasma use.
Abbreviations: ICD-9, the International Classification of Diseases, 9th revision; RBC, red blood cell.

TABLE 5 Selected treatments among hospitalizations for liver diseases in 2007 and 2017

Year (total hospitalizations)	2007 (79,647)		2017 (83,245)	
Liver diseases (chronic hepatitis, liver cirrhosis, liver abscess and liver malignancy)	Hospitalizations with treatment	Transfusion rate	Hospitalizations with treatment	Transfusion rate
Red blood cells	20,544	25.79%	16,673	20.03%
Plasma	17,849	22.41%	12,051	14.48%
Platelets	8570	10.76%	8313	9.99%
Cryoprecipitate	343	0.43%	673	0.81%
Prothrombin complex concentrate	0	0%	0	0%
Coagulant factors	4	0.01%	9	0.01%
Aminocaproic acid	381	0.48%	199	0.24%
Tranexamic acid	9197	11.55%	9241	11.10%
Albumin	8908	11.18%	8523	10.27%
Any anti-coagulant[a]	3802	4.67%	6166	7.30%

Abbreviation: ICD-9, the International Classification of Diseases, 9th revision.
[a]Any coagulants include heparin, low molecular weight heparin, direct factor Xa inhibitor, thrombin inhibitor, vitamin K antagonist.

were the top diagnoses, accounting for 66.36% and 32.84% of total plasma use within these services, respectively. For patients hospitalized due to liver diseases, plasma transfusion rates declined from 22.4% in 2007 to 14.5% in 2017 (35% reduction). The mean (SD) number of units transfused declined from 10.38 (15.58) to 9.48 (18.31), while the median number of units declined from 6.67 to 5.00. Among patients hospitalized for liver diseases who were given plasma, almost 38% of plasma units in both 2007 and 2017 were administered to patients with neither noticeable bleeding nor RBC transfusions. The plasma transfusion rates declined from 12.93% to 7.63% for patients with liver diseases receiving invasive procedures, and from 8.46% to 5.85% for patients with no invasive treatments.

Table 5 presents the use of blood components, procoagulant therapies, anticoagulant therapies, anti-fibrinolytic drugs and albumin among hospitalizations for liver diseases in 2007 and 2017. The RBC transfusion rate significantly decreased (25.79% in 2007 and 20.03% in 2017), while the platelet transfusion rate remained unchanged (10.76% in 2007 and 9.99% in 2017). The use of procoagulant therapies (prothrombin/cryoprecipitate/specific

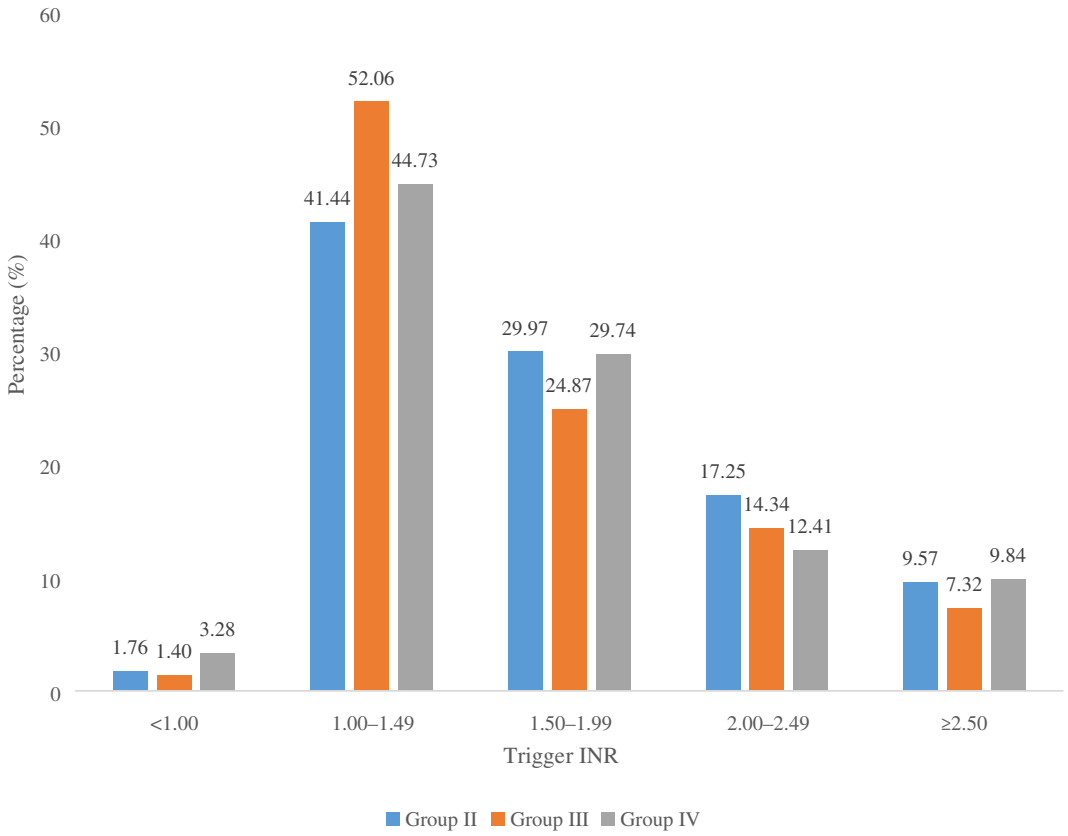

FIGURE 2 Distribution of trigger international normalized ratios among patients hospitalized for liver diseases without noticeable bleeding but who received a plasma transfusion. group II—'no documented bleeding but receiving ≤ 3 RBC transfusions'; group III—'received invasive procedure, no documented bleeding or RBC transfusions' and group IV—'none of the above conditions'. INR, international normalized ratio; RBC, red blood cell

coagulation factors) remained quite low (0.44% in 2007; 0.82% in 2017). The use of anti-fibrinolytic drugs (TXA or aminocaproic acid) as well as albumin remained steady during the study period (10%). The use of anticoagulants increased from 4.67% in 2007 to 7.30% in 2017.

Figure 2 illustrates the distribution of trigger INRs among patients hospitalized for liver diseases without noticeable bleeding but receiving plasma transfusions (group II, III and IV). We observed that 43%–53% of these patients received plasma transfusions with a trigger INR <1.50 and 25%–30% with a trigger INR between 1.50 and 1.99. In other words, approximately 75% of the patients in these three groups received plasma administration with a trigger INR <2.00.

Figure S1 illustrates the correlation between trigger INR and <24-h decreases in INR per unit of plasma among patients hospitalized for liver diseases without noticeable bleeding and who did not receive >3 units of RBCs transfused (group II, III and IV), stratified by trigger INR levels. Only 455 data points were available for this analysis. The median number of plasma units was 4.4 for a trigger INR ≥1.5 and 2.2 for a trigger INR <1.5, respectively. The change in INR per unit was highly correlated with trigger INR among trigger INR ≥1.5 (correlation coefficient 0.65, $p < 0.0001$). On the other hand, the correlation was attenuated among trigger INR <1.5 (correlation coefficient: 0.15, $p > 0.05$).

DISCUSSION

This is the first comprehensive population-based assessment to examine real-world plasma use after the introduction of a new standard for the evaluation of appropriateness of plasma use in hospital accreditations. We observed an overall reduction of 304,580 units (a 32% decrease) from 2007 to 2017, and our results show a steady decrease in the proportion of hospitalizations receiving plasma, as well as in the mean plasma units used per hospitalization. After considering recipient and hospital characteristics, we estimated an approximate 38% decrease in the proportion over 11 years. Although plasma transfusions have been declining for more than 10 years, plasma usage remained as high as 28.00 per 1000 capita in 2017, which is still disproportionately higher than rates in other developed countries [20, 21]. The top two services with the most plasma use were gastroenterology and general surgery, accounting for 16% and 15% of total plasma use, respectively. The top diagnoses were liver diseases and liver cancers, accounting for 66.36% and 32.84% of the plasma use within gastroenterology and general surgery, respectively.

In Taiwan, endemic hepatitis B and C infection contribute to a high incidence and prevalence of liver cirrhosis and liver cancers. Liver cirrhosis and liver cancers are very common indications for blood components transfusions. In liver disease patients, there are multiple

defects in pathways critical to coagulation, with deficiency of both pro- and anti-coagulant factors [22, 23]. In this study, gastroenterology was the service with the most plasma use, and liver cirrhosis was the predominant diagnosis. Furthermore, in general surgery, liver cancer was the predominant diagnosis with the most plasma use. A previous study performed from 2003 to 2004 in a tertiary-care teaching medical centre in southwestern Taiwan indicated that plasma was frequently misused for volume expansion, nutritional supplementation or the enhancement of wound healing in gastroenterology [9]. In our present study, we observed that after the introduction of new hospital accreditation standards relevant to plasma use in the mid-2000s, plasma transfusion rates among patients hospitalized for liver diseases decreased from 22.41% to 14.48% during 2007–2017. However, at the end of this study, 30% of plasma units were still administered to patients without bleeding or red blood cell transfusions, but who received an invasive procedure, while another 8% were administered to patients without any procedures. For these cases, plasma may have been administered for prophylaxis due to a perceived bleeding risk or presumably as a reaction to abnormal coagulation test results. However, these were potential cases of inappropriate use because current guidelines do not recommend plasma transfusions for patients with an increased INR with no evidence of bleeding [12, 24].

Previous studies suggested that plasma transfusion could decrease INR more effectively for patients with moderate-to-severe INR prolongation than for patients with mild prolongation. Our data were consistent with these observations and showed no significant correlation between decreases in INR and trigger INR while the trigger INR was <1.5. However, we found that almost 50% of liver disease patients without noticeable bleeding or RBC transfusions were administered with plasma with trigger INR values ranging between 1.0 and 1.5. According to The Cardiovascular and Interventional Radiological Society of Europe (CIRSE) guideline recommendations, low-risk procedures are safe with an INR <2.0 and moderate or high-risk procedures are safe with an INR <1.5 [25]. Thus, for these patients, the indication for plasma use was not compliant with clinical guidelines. In this situation, other possible indications for plasma administration may be hypoalbuminaemia. In Taiwan, institutional guidelines for plasma use vary between hospitals because there are no standardized transfusion guidelines that apply to all hospitals. The guidelines for each institution may be based on previous experiences or expert opinions, and inappropriate indications for plasma use, such as FP for hypoalbuminaemia with severe ascites or oedema, may have existed in some hospitals since the early 2000s [9]. Plasma may be used instead of albumin, but this is ineffective due to the low concentration of albumin in plasma, in comparison to albumin itself. Furthermore, liberal transfusion of blood components, including plasma may lead to harmful effects such as fluid overload and worsening portal hypertension for patients with cirrhosis [26, 27]. Administering albumin to severe liver cirrhosis patients for severe hypoalbuminaemia and the improvement of circulatory and kidney function is recommended by at least two guidelines [28, 29]. We believe that inappropriate indications can be modified after the introduction of new accreditation standards relevant to plasma use in medical centres and teaching hospitals. However, we cannot rule out the possibility that inappropriate indications remained at some hospitals at the end of this study. Furthermore, according to the NHI Administration, the NHI reimbursement for albumin use in liver disease patients with hypoalbuminaemia was restricted to persons with an albumin level lower than 2.3 g/dl. Such restrictive criteria may be one of the explanations for high plasma use in patients without bleeding or abnormal coagulation test results. To further improve the appropriateness of plasma transfusions, restrictive NHI reimbursement for some conservative replacement therapies needs to be further reviewed and modified.

Plasma transfusions are frequently used to correct coagulopathy in bleeding patients. However, very limited data are available regarding the effectiveness of FFP in correcting coagulative abnormalities or in reducing bleeding risk in acute or chronic liver diseases [30]. The American Gastroenterology Association's clinical practice guidelines recommend that FFP should be used sparingly in patients with liver cirrhosis because it can increase portal pressure from volume expansion and carries a risk of bacterial contamination and severe transfusion reactions such as TACO or TRALI [31]. Potential alternatives for the correction of coagulopathy in bleeding patients include PCC, cryoprecipitate or specific coagulant factors [32]. However, the approach to coagulation derangements in liver diseases has changed that thrombosis is more common and a higher risk than bleeding [33, 34]. Chronic liver disease is not only associated with impaired synthesis of most coagulant factors but is also associated with partial deficiency of anticoagulant proteins. Patients with compensated liver cirrhosis have normal coagulative balance. However, if a disturbance of this balance occurs through worsening liver function, bleeding or acute kidney insufficiency, patients with cirrhosis are now considered to be at higher risk for thrombotic events than for bleeding [34]. Thrombotic complications include portal vein thrombosis, which is the most common of thrombotic events, intrahepatic microthrombosis and peripheral deep vein thrombosis. Thus, choosing appropriate blood products, procoagulants or anticoagulants for therapy or prophylaxis in cirrhotic patients is challenging. We found that the use of procoagulant therapies such as PCC, cryoprecipitate or specific coagulation factors remained low, only slightly increasing from 0.44% to 0.82% over the study period. The use of TXA, aminocaproic acid or albumin remained quite steady. The use of anticoagulants slightly increased from 4.67% in 2007 to 7.30% in 2017. Thus, the decline in blood component transfusions among these patients could not to be explained by an increased use of these therapies. We believe that the decline in plasma use over the study period can be mainly attributed to the growing implementation of institutional transfusion advisory committees, periodic evaluations of compliance with institutional guidelines and periodic educational trainings that highlight hospital accreditation standards.

Although a markedly decline in plasma transfusion rate was observed within thoracic medicine and haematology/oncology over the study period, we still found 20% and 30% of plasma was administered to hospitalized patients with neither bleeding nor RBC transfusions, respectively, at the end of the study. Within thoracic medicine,

most of these patients were ventilator-dependent and approximately 45% patients were administered with plasma with trigger INR value ranging between 1.0 and 1.5 (unpublished NHI data). Within haematology/oncology, 25.90% of these patients received an insertion of central vein catheter, and 18.32% received abdominal drainage. Only 2.58% received high-risk procedures under CIRSE guidelines [25]. Most of these patients received procedures with low to moderate bleeding risk and approximately 55% patients were administered with plasma with trigger INR value ranging between 1.0 and 1.5 (unpublished NHI data). Plasma use during ventilation or the treatment of procedures with low to moderate bleeding risk may be inappropriate, especially for the situation with normal range INR. These were potential cases of inappropriate plasma use and further audits of these situations are needed.

The strength of this study is the use of the NHI database to provide long-term, comprehensive estimates of plasma utilization in our country. Except for a small number of self-pay private clinics, more than 90% of healthcare facilities contract with the NHI, including all medical centres, regional and district hospitals. Several validation studies have demonstrated the high accuracy of the diagnoses in the NHI database for several major diseases, including circulatory, thoracic and neoplasms [35–40]. The NHI database includes detailed clinical information related to both outpatient visits and hospitalizations. Details of transfusions, including type and amount of blood components, diagnoses, procedures, prescriptions, expenditures and recipient characteristics can be retrieved from the claims data. Furthermore, the records of routine blood testing for hospitalized patients were directly retrieved from automated clinical chemistry analysers. There is no question of the quality and completeness of the records. Thus, this big-data analysis was adequately robust for describing the real-world utilization of blood components in Taiwan, with no selection bias.

Nevertheless, there were several limitations that should be noted. First, is the retrospective nature of the study. Detailed documentation is not complete in this database. We determined patients' bleeding status based on ICD-9 codes, and the accuracy of the diagnosis codes for bleeding has not yet been evaluated, which may also lead to some underestimation. Furthermore, the NHI database was primarily created for administrative purposes. Complete clinical data such as surgery or transfusion time was not available. We had the date and times of each INR measurement but not for FFP transfusions. We had no further information to define the latest INR measurement prior to plasma transfusion. Therefore, we designated the highest INR as the trigger for plasma transfusion. If an INR of 2.0 was chosen as a cutoff point for the safety of a low-risk procedure, the misclassification of a trigger INR >2.0 or INR <2.0 may exist. However, we performed sensitivity analyses among hospitalized patients with only one INR measurement during a hospital stay, which we assumed was the latest INR prior to plasma transfusion. An approximately 5%–8% higher proportion of INR <2.0 was observed in the sensitivity analysis. Thus, we conclude that using the highest INR as the trigger for plasma transfusion resulted in a less than 10% underestimation of the proportion of INR <2.0. Furthermore, complete laboratory test results were only available for a portion of admissions. Therefore, the exact indications for plasma use as well as the appropriateness of plasma use cannot be reliably determined throughout the country. Further efforts to comprehensively audit the appropriateness of plasma use are warranted. Lastly, the use of self-pay healthcare and out-of-pocket payments, such as self-paid albumin, was not available in this study. Thus, the use of albumin may be underestimated.

In conclusion, in Taiwan, plasma use steadily declined after the introduction of new standards to evaluate the appropriateness of plasma use for hospital accreditations. We observed a 38% reduction in transfusion rates over 11 years. Gastroenterology and general surgery were the two services with the highest plasma use, and liver diseases were the predominant diagnoses in these services. Although we observed an almost 35% reduction in transfusion rates for liver diseases, 40% of plasma was still administered to patients with neither bleeding nor RBC transfusions. Among these patients, almost 75% of patients received plasma transfusions with a trigger INR <2.0. The use of procoagulant therapies remained low. Future efforts to promote alternative therapies as well as to comprehensively audit the use of plasma are warranted.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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ORIGINAL ARTICLE

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Development and evaluation of a community of practice to improve stem cell donor recruitment in Canada

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Abstract

Background and Objectives: Communities of practice (CoPs) represent effective models to achieve quality outcomes in health care. We report the development and evaluation of a CoP to improve stem cell donor recruitment in Canada.

Materials and Methods: In September 2017, we invited national stakeholders in stem cell donor recruitment to participate in a Facebook group and regular e-meetings. E-meetings involved speakers and roundtable discussion on topics related to donor recruitment. The Facebook group facilitated sharing of resources. We evaluated stakeholder perspective of the CoP and the impact on recruitment outcomes.

Results: As of December 2020, the CoP included 382 members who published 243 posts to the Facebook group about patient/donor stories (40%), resources (27%), updates/questions (21%) and recruitment outcomes (12%). In January 2020, we surveyed 44 CoP participants; the majority felt that the Facebook group (86%) and e-meetings (59%) supported the community, and that the CoP fostered collaboration (82%), improved their donor recruitment knowledge (75%) and practice (77%) and improved their ability to recruit needed donors (64%). The launch of the CoP

correlated with improved donor recruitment outcomes. In 2016–2017, CoP participants recruited 2918 registrants (46% male; 55.9% non-Caucasian) compared to 4531 registrants in 2018–2019 (52.9% male; 62.7% non-Caucasian). Members of the CoP developed innovative resources to support recruitment efforts and led national campaigns securing coverage in major media outlets.

Conclusion: We describe the first CoP in stem cell donor recruitment to be formally evaluated. The CoP model may be adopted by donor recruitment organisations, registries and blood banks worldwide to improve recruitment outcomes.

KEYWORDS
blood donation, bone marrow, community of practice, donor recruitment, donors, stem cell transplantation

Highlights

- A community of practice (CoP) in stem cell donor recruitment was valued by participants and supported efforts to improve recruitment outcomes.
- The CoP model may be adopted by donor recruitment organizations, donor registries, and blood banks worldwide to improve recruitment outcomes.

INTRODUCTION

Many patients in need of an allogeneic haematopoietic stem cell transplantation do not have a suitable human leukocyte antigen (HLA)-matched donor in their family and require an alternative donor to proceed with treatment. HLA-matched unrelated donors represent the most common and preferred alternative donor choice, with data from the Centre for International Blood and Marrow Transplant Research showing increasing numbers of unrelated donor transplantations performed each year since 2016 [1, 2]. However, despite over 38 million potential unrelated stem cell donors on registries in 54 countries worldwide, many patients, and particularly those of non-European ancestry, do not have an HLA-matched unrelated donor available to them [3–5].

Unrelated donors may be recruited either online or at stem cell drives [6], where recruiters secure informed consent and guide registrants to provide a tissue sample for HLA typing. Donor recruitment organisations, however, face several challenges. First, they need to preferentially recruit individuals from needed demographic groups: young-adult males [7–9] and individuals from diverse ancestral groups [4, 10]. Donor recruitment organisations should develop approaches that target recruitment of needed demographic groups within their jurisdictions, and that address specific barriers to donation among these groups [10–12]. Additionally, they need to work to reduce donor attrition, which is considerably higher among racial/ethnic minorities [11–13]. Finally, implementation of strategies that address challenges in donor recruitment requires buy-in and support from stakeholders in donor recruitment, which is difficult to achieve in the absence of structures supporting community collaboration.

The establishment of communities of practice (CoPs) represents a strategy to collaboratively improve quality outcomes in health care. A CoP represents "a group of people who share a concern or a passion for something they do, and learn how to do it better as they interact regularly" [14]. CoPs provide a means through which knowledge can be generated, shared and managed so that members can draw upon, promote and develop innovations in a field of practice [14]. CoPs have been increasingly used in the health care sector to improve interprofessional collaboration, connect practitioners within a field, and improve engagement between academics and practitioners [15–17]. CoPs have further been successfully applied to achieve quality outcomes important in cancer care [18–20]. However, there have been no efforts to date evaluating the impact of a CoP in the context of donor recruitment.

We report the development and evaluation of a CoP to improve stem cell donor recruitment in Canada. The CoP was spearheaded by recruiters from the Canadian donor recruitment organisation Stem Cell Club, a non-profit organisation that works to improve the quality and quantity of stem cell donors on the Canadian Blood Services Stem Cell Registry [21]. In this report, we evaluate (1) participation in the CoP, (2) participants' perceptions of the CoP's value, and (3) the impact of the CoP on resource development and donor recruitment outcomes.

METHODS

CoP framework

We developed the CoP to have a learning focus based on the United States Institute of Medicine's learning networks model [22]. CoPs comprise three elements: a domain of knowledge, a community of people and a shared practice [14]. The domain is the area of shared inquiry: the key issue, problem, or goal that members share. The community is the group of people who interact regularly in relation to

their domain. The practice is the knowledge that the community develops, shares, and maintains. In our CoP, the domain of knowledge was the information and skills necessary for the recruitment of committed unrelated donors from needed demographic groups. The community consisted of stakeholders involved in stem cell donor recruitment, including donor recruiters, donor registry staff, patients, and donors. The shared practice involved the recruitment of unrelated stem cell donors.

We adapted considerations for the development of an oncology care CoP [23] and applied them to the CoP in stem cell donor recruitment: (1) to involve key stakeholders; (2) to include roundtable discussions at CoP meetings; (3) to encourage CoP participants to identify resources that address practice gaps, support knowledge exchange, and reduce barriers to donor recruitment; (4) to consider the development of online resources to support the CoP; and (5) to host regular meetings to continue to build the CoP. We implemented participatory, community-based approaches by Averling et al. for quality improvement through clinical communities [24].

CoP development

We set out to develop a CoP that had an online hub on Facebook with regular e-meetings. In September 2017, we sent an email invitation to donor recruiters across Canada, donor registry staff, stem cell donors, and transplant recipients and their caregivers to join a Facebook group (https://www.facebook.com/groups/stemcellclub) and attend regular e-meetings. E-meetings consisted of speakers and roundtable discussion on topics related to donor recruitment. We invited participants to share resources and discuss problems in between e-meetings using the Facebook group. Members of the CoP formed subcommittees to develop resources that would support the recruitment of unrelated stem cell donors.

CoP evaluation

We evaluated participation in the CoP by the number of members in the Facebook group, attendance across e-meetings, and the number of posts in the CoP Facebook group. Two researchers (E.K. and W.F.) reviewed and assigned all Facebook posts to a category. Reviewers resolved disagreements by discussion and, when necessary, by adjudication with a third member (G.J.). In January 2020, we emailed a survey to 59 senior leaders in Stem Cell Club across Canada, 4 donor registry staff, and 14 donors/patients to evaluate their perspective of the CoP and whether its objectives had been met. Survey questions employed 5-point Likert scales (see Table S1 for a copy of the survey questions). This work was conducted as a quality improvement project according to the Western University Research Ethics Board [25].

Since most donor recruiters from the Stem Cell Club are members of the CoP, we evaluated the impact of the CoP by comparing Stem Cell Club's annual donor recruitment outcomes across Canada before and after the launch of the CoP. Recruiters ran stem cell drives as previously described [6]. Following each drive, recruiters logged total, male and non-Caucasian male registrants. We similarly evaluated the impact of the CoP on donor recruitment outcomes at the registry level by comparing outcomes on the Canadian Blood Services Stem Cell Registry before and after the launch of the CoP. We also assessed the number of national donor recruitment campaigns, the media coverage secured, and the resources developed by the CoP.

RESULTS

Characteristics of the CoP

As of December 2020, the CoP included 382 stakeholders in stem cell donor recruitment (350 donor recruiters, 16 donor registry staff, and 16 patients/donors). One hundred and twenty unique attendees participated in eight e-meetings, 30 of whom attended two or more e-meetings. The community set objectives at the first e-meeting, and subsequent e-meetings discussed a range of topics relevant to donor recruitment (Table 1). Following related e-meetings, the community expanded its objectives to include reducing donor attrition, transitioning to virtual donor recruitment during the COVID-19 pandemic and running donor recruitment campaigns targeting needed demographic groups (Table 1).

Members of the CoP published 243 posts to the Facebook group about patient/donor stories (40%), resources in stem cell donation (27%), stem cell drive outcomes (12%), updates related to stem cell donor recruitment (18%) and questions (4%) (Figure 1).

Resources developed by the CoP

Subcommittees of the CoP developed high-quality resources to support the recruitment of unrelated stem cell donors, including a

TABLE 1 Objectives of the CoP in stem cell donor recruitment

Initial objectives (September 2017)

- Foster teamwork and collaboration
- Improve knowledge and practice related to donor recruitment
- Improve recruitment of the most-needed donors
- Improve donor recruiters' ability to run high-quality stem cell drivesAdded objectives
- Reduce donor attrition (February 2020)
- Transition to virtual donor recruitment during the COVID-19 pandemic (April 2020)
- Run campaigns targeting needed demographic groups (April 2020)

Meeting topics

1. Conducting larger stem cell drives
2. Recruiting male stem cell donors
3. Recruiting ethnically diverse stem cell donors
4. Redirecting non-optimal donors to help in other ways
5. Reviewing drive outcomes and identifying strategies to improve
6. Using patient stories to support donor recruitment
7. Reducing donor attrition
8. Leveraging social media to support online donor recruitment

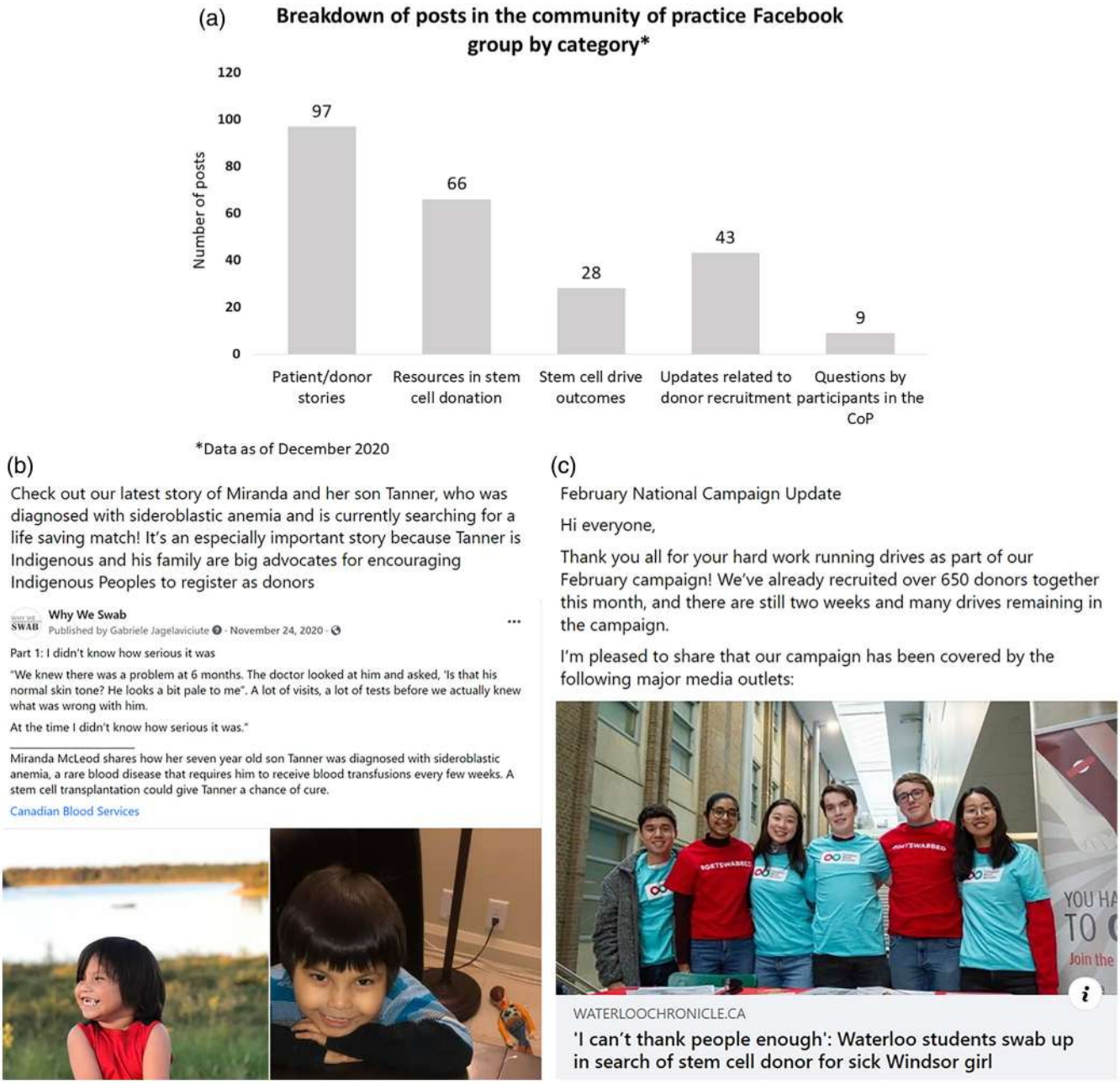

FIGURE 1 Posts shared in the CoP Facebook group. (a) Frequency of posts shared in the CoP Facebook group as of December 2020. Example posts include (b) a patient/donor story and (c) a stem cell drive outcome

whiteboard video series, a library of Canadian stories in stem cell donation, infographics, and TikTok videos (Figure 2). Many of these resources have been evaluated for their utility and impact on donor recruitment outcomes (Table S2). Recently, the CoP developed resources to engage needed demographics as potential stem cell donors (i.e., Black Canadians, Figure 2e).

Donor recruitment campaigns led by the CoP

Members of the CoP collaborated on four in-person national donor recruitment campaigns that recruited substantial donor registrants, of whom a considerable proportion came from needed demographics (Table 2). Several of these campaigns secured media coverage in national and local news outlets. Since the onset of the COVID-19 pandemic, members of the CoP have collaborated on virtual campaigns to engage needed donor demographics. These campaigns have been featured in print and broadcast media across Canada [26–30].

Impact of the CoP on donor recruitment outcomes

The launch of the CoP correlated with an increase in the number of recruited donor registrants and the proportion representing needed

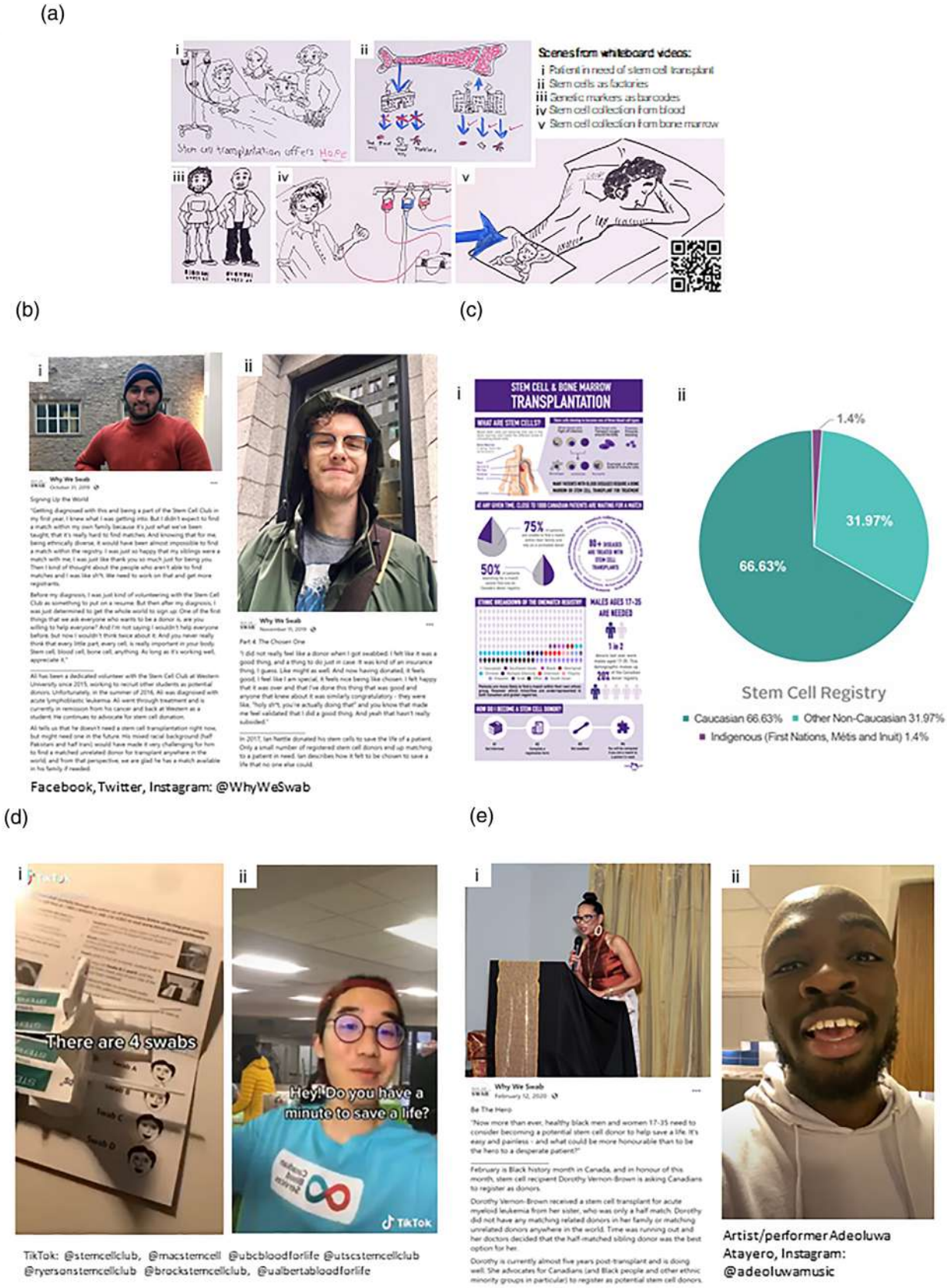

FIGURE 2 Resources developed by subcommittees of the CoP in stem cell donor recruitment. (a) A whiteboard video series to support the education and recruitment of unrelated stem cell donors (youtube.com/playlist?list=PL9prrDkqE0rR7cSRLsTGmdrr7VP6miulL). (b) Why W e Swab, a library of Canadian stories in stem cell donation (Facebook, Instagram and Twitter; @WhyWeSwab). (c) Infographics to support the education and recruitment of unrelated stem cell donors (stemcellclub.ca). (d) TikTok videos to support the virtual recruitment of unrelated stem cell donors (TikTok: @stemcellclub, @macstemcell @ubcbloodforlife @utscstemcellclub @ryersonstemcellclub @brockstemcellclub, @ualbertabloodforlife). (e) Resources related to a virtual campaign of the CoP to recruit Black stem cell donors

TABLE 2 National campaigns since the launch of a CoP in stem cell donor recruitment

Campaign	Date	Drives	Provinces	Total donor registrants recruited	Male donor registrants recruited (% of total)	Non-Caucasian male donor registrants recruited (% of males)	Media coverage
World Marrow Donor Day	September 2018	7	6	350	228 (65%)	160 (70%)	Toronto Star, Global News, Toronto Sun, CTV News Winnipeg, CTV News Edmonton, Global News Regina, London Free Press, Windsor Star, Sudbury Star, Waterloo Chronicle, Victoria News, Castanet News
Pride Stem Cell Drive	Summer 2018/2019	7	3	354	142 (40%)	60 (42%)	
Get Swabbed	November 2019	22	5	900	486 (54%)	321 (66%)	
Why We Swab	February 2020	30	6	1134	624 (55%)	349 (56%)	
Virtual Donor Drive	November 2020–ongoing	30	7			Ongoing	

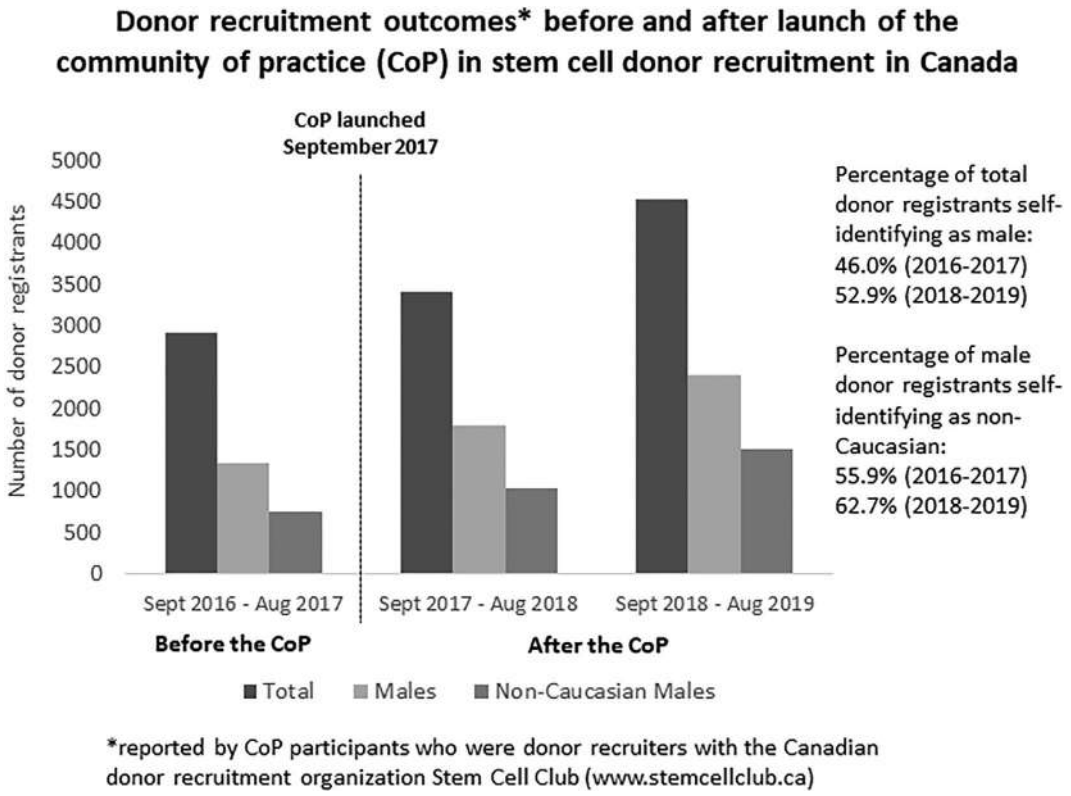

FIGURE 3 Donor recruitment outcomes before and after the launch of the CoP. Results show the donor recruitment outcomes of the Canadian donor recruitment organisation Stem Cell Club, before (2016–2017) and after (2017–2018 and 2018–2019) the launch of the CoP in September 2017

demographics (Figure 3). In 2018–2019, CoP members from the Stem Cell Club recruited 4531 registrants (52.9% male, of whom 62.7% were non-Caucasian) compared to 2918 registrants (46% male, of whom 55.9% were non-Caucasian) in the year prior to the start of the CoP (2016–2017). Data from the Canadian Blood Services Stem Cell Registry demonstrated a similar correlation: 458,253 registrants (44.1% male, of whom 22.3% were non-Caucasian) were listed in January 2020, compared to 401,996 registrants (42.5% male, of whom 18.9% were non-Caucasian) in December 2016, 9 months prior to the start of the CoP.

Development of a tool to evaluate donor attrition

Members of the CoP collaborated with the Canadian Blood Services to develop a tool that tracks the retention of donors recruited by

teams in the CoP. The CoP now has the ability to follow-up on registrants recruited at specific drives, by individual teams, and during particular campaigns to evaluate differences in donor attrition. This tool became operational in February 2020 and will be used to prospectively characterise and evaluate strategies aimed at improving donor attrition.

Stakeholder perspectives on the CoP

In January 2020, 44 CoP participants (40 donor recruiters and 4 donor registry staff, response rate: 70%), with a median of 3 years (range: 1–5 years) of experience in donor recruitment and from 6 provinces across Canada, completed an evaluation survey. The majority agreed or strongly agreed that the Facebook group (86%) and e-meetings (59%) supported the community, and that the CoP fostered collaboration (82%), improved their knowledge (75%) and practice (77%) in donor recruitment, and improved their ability to run drives (64%) and recruit the most-needed donors (64%) (Figure 4). Four donors and three patients (response rate: 50%) completed a separate evaluation survey regarding the use and sharing of stories within the CoP. The majority agreed or strongly agreed that sharing their story provided a positive experience (100%), and that these stories help to raise awareness (86%), educate others about donation (86%) and support recruitment of unrelated stem cell donors (100%).

DISCUSSION

We describe and evaluate the first CoP in stem cell donor recruitment. The virtual CoP (1) proved feasible and valuable to participants; (2) supported national recruitment campaigns that secured media coverage; (3) correlated with improved donor recruitment outcomes at the CoP and registry level; and (4) generated high-quality resources to support recruitment efforts.

We assessed achievement of the CoP using intermediate outcomes proposed by Fung-Kee-Fung et al., including knowledge transfer, social capital, innovation and organisational memory [19, 20]. The survey results demonstrate that the CoP improved knowledge transfer from the perspective of CoP participants, and that the CoP generated social capital through improved collaboration and organisational structure with the e-meetings and Facebook group. The CoP fostered innovation through collaborative national donor recruitment campaigns that secured coverage in major media outlets across Canada. These campaigns also recruited substantial donor registrants, of whom the majority were from needed demographics. Evidence of innovation includes the development of high-quality resources across different mediums to support the recruitment of committed and diverse donors. The establishment of subcommittees within the CoP provided an opportunity to build organisational memory. Subcommittees were empowered to develop resources to meet identified needs, and were positioned to work alongside stakeholders and donor registry administration to advance issues important to the community.

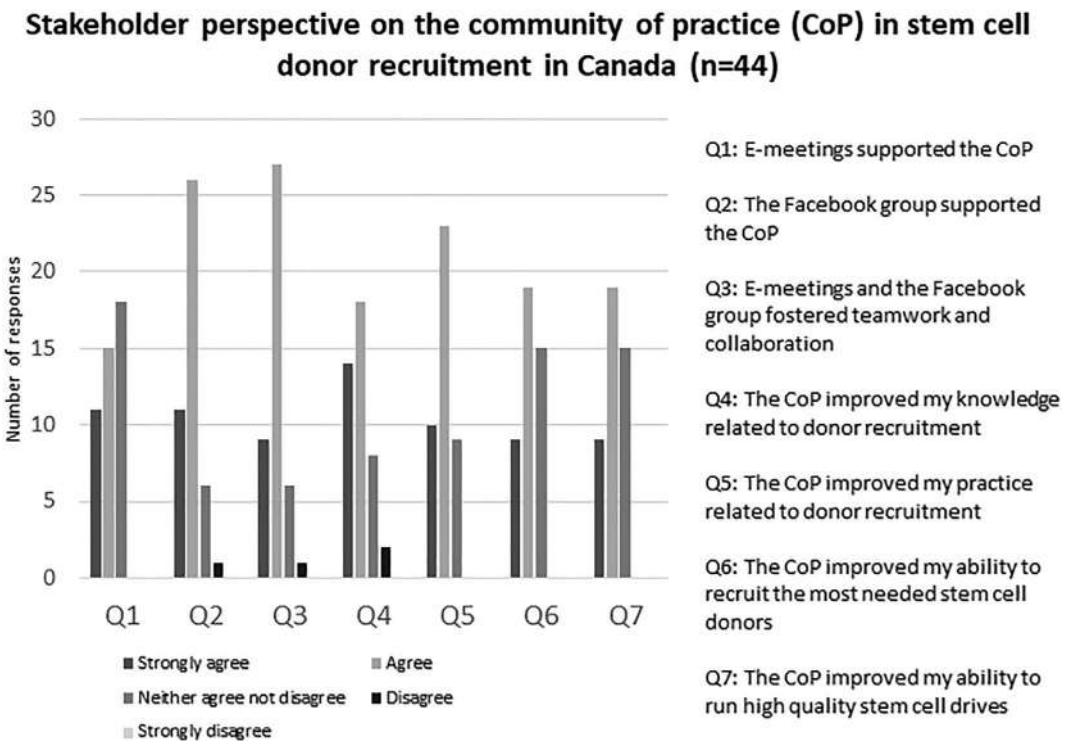

FIGURE 4 Stakeholder perspective on the CoP in stem cell donor recruitment. Results of a survey conducted in January 2020 to evaluate CoP participants' perspectives on the value of the CoP

The COVID-19 pandemic has led to the suspension of in-person donor recruitment drives in Canada and in many countries worldwide [31, 32]. Emphasis has since been placed on increasing virtual donor recruitment during the pandemic. The virtual format of the CoP has supported the shift to online donor recruitment by facilitating a campaign of online events across Canada to register stem cell donors. Furthermore, subcommittees of the CoP are developing online multimedia (i.e., TikTok videos, Why We Swab stories [33, 34], infographics [35], and whiteboard videos [36, 37]) to support the virtual recruitment of donors. CoP members are currently working in partnership with the Canadian Blood Services to develop a tool that tracks the impact of their virtual donor recruitment efforts. Data from this tool will inform on who is being recruited virtually by the CoP and the effectiveness of online recruitment strategies. Although the CoP was designed to meet recruitment needs in a Canadian context, multiple resources developed by this CoP have already been shared by organisations worldwide, including World Marrow Donor Association, American Association of Blood Banks, Be The Match, and DKMS. This underscores that the resources developed and the work that CoP committees perform can be adapted to support global recruitment efforts.

An ongoing objective of the CoP is to address donor attrition, which remains a problem for Canadian and global registries. From 2015 to 2018, 32%–40% of potential donors on the Canadian Blood Services Stem Cell Registry who were identified as potential matches for patients did not proceed with donation [36]. This donor attrition was multifactorial, including lost interest of the donor and inability of the registry to contact or locate the potential donor. Anthony Nolan in the United Kingdom and the National Marrow Donor Program of the United States report similar rates of attrition, with attrition considerably higher among racial/ethnic minorities [11–13]. In addition to the potential harm this attrition can incur for patients, including false hope and delayed procurement of a suitable donor, registries must also bear financial and reputational impacts of having individuals typed and listed as donors who will never become available for donation [13]. To address this, our CoP developed a tool to track the retention of donors recruited at specific drives and by individual teams. Future data from this tool will inform strategies to mitigate registrant and recruitment-related factors associated with donor attrition. Furthermore, the CoP will continue to develop, deploy, and evaluate resources to support recruitment efforts. Several studies have shown that ambivalence at or following registration is associated with attrition at multiple stages in the donation process, and that registrants who are less informed or who have unanswered questions at the time of recruitment are more likely to be ambivalent toward donating [12, 38, 39]. Future resources developed by the CoP will address concerns and knowledge gaps that present barriers to donation for specific demographics [11, 12, 40, 41]. Additionally, donor ambivalence and less interaction with the registry are associated with greater donor attrition, especially among ethnic minority registrants [11]. These findings support continued education and engagement with registrants beyond the point of recruitment to optimise donor availability [11]. Members of the CoP will collaborate with the Canadian Blood Services Stem Cell Registry to incorporate our multimedia into donor retention programmes of the registry (including regular e-blasts and newsletters).

The CoP model may be relevant for related fields, including blood donor recruitment. Challenges in blood donor recruitment include meeting an increasing demand for donors, ensuring a constant supply of safe blood products and addressing a decline of young donors [42, 43]. One strategy to address these challenges is to develop CoPs that connect multiple recruitment organisations and stakeholders, leading to the generation, sharing, and implementation of strategies and resources. For example, there is an ongoing need for racially/ethnically diverse blood donors to support phenotype matching to reduce the risk of alloimmunisation in patients who require chronic blood transfusions [44]. In our CoP, we have demonstrated substantial recruitment of diverse stem cell donors, and a similar model could be employed to support recruitment of diverse blood donors. Development of CoPs in other areas should be adapted to the context, objectives, geography, and needs of participating organisations and stakeholders.

Limitations of our study include that the survey data may be subject to selection bias that overrepresents those who have stronger opinions about the CoP. The durability of the survey results is also unclear, as participant perspectives could change over time. We plan to address this issue by performing needs assessment surveys of CoP participants at regular intervals to clarify participant perspectives on whether the CoP is achieving its goals, and how it can be improved. The analysis of the impact of the CoP on donor recruitment outcomes is limited by possible confounding variables, such as the growth of Stem Cell Club and the Canadian Blood Services Stem Cell Registry. Nevertheless, we observed a concomitant increase in the proportion of the most-needed donor registrants recruited at both the CoP and registry level, and in the number and scope of national donor recruitment campaigns, suggesting that the CoP had a positive impact on recruitment outcomes. Finally, the CoP had a virtual format with a goal to improve stem cell donor recruitment in Canada. Two limitations with the virtual format include that there may be technological hindrances to collaboration and access to subject matter experts, and that our results may not be generalisable to CoPs with different structures and geographical locations. Further research should address optimal structures for CoPs when applied for different objectives and geographical locations. Donor recruitment organisations seeking to adopt the CoP model should also consider practical challenges in establishing a CoP, including initial investment of effort and time, and necessary buy-in and collaboration from donor registries to achieve objectives.

In conclusion, we demonstrate that a CoP in stem cell donor recruitment was valued by participants and supported efforts to improve stem cell donor recruitment in Canada. The CoP will continue to address knowledge and practice gaps identified during e-meetings and on the Facebook group, develop and deploy resources to meet identified needs, and work with stakeholders and donor registries to recruit donors nationally. Our work may be of interest to donor registries, donor recruitment organisations, and blood banks that can adopt the CoP model to support recruitment efforts.

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W.F. designed the study. E.K. and W.F. collected, analysed, and interpreted the data, and wrote the manuscript. All authors were leaders in the CoP, critically reviewed and edited the manuscript, and approved the final manuscript.

CONFLICT OF INTEREST

The authors disclose no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Active seeking of post-donation information to minimize a potential threat to transfusion safety: A pilot programme in the context of the COVID-19 pandemic

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Abstract

Background and Objectives: Early in the pandemic, the transmissibility of coronavirus disease-19 (COVID-19) by transfusion was unknown. We piloted a systematic, post-donation outreach programme to contact blood donors and inquired about symptoms post-donation.

Materials and Methods: Persons who donated on on May 1 and 2, 2020 were contacted 3 days post-donation, by phone to assess COVID-19-related symptoms. Half of the donors were administered a short questionnaire, consisting of only three questions. Others were questioned using a longer, more specific questionnaire. If symptoms were reported, products were quarantined until donors were contacted again by a trained nurse who more thoroughly assessed the likelihood of COVID-19. Blood products were withdrawn if symptoms indicative of COVID-19 were identified.

Results: Of 654 donors, 609 (93.1%) were successfully contacted. Of 310 donors who answered the short questionnaire and 299 who answered the long questionnaire, 19 (6.1%) and 8 (2.7%) had one or more symptoms, respectively. Based on the nurses' assessment, two donations (0.3%) had to be withdrawn.

Conclusion: These results suggest that actively seeking post-donation information might be feasible to mitigate emerging, unqualified transfusion risks.

KEYWORDS
blood safety, donor health, hemovigilance, quality control, quality management, tranfusion-transmissible infection

Highlights

- Active of post-donation information is feasible to mitigate potential threat to transfusion safety.
- With climate change and a growing world population, new or emerging pathogens poised to become more frequent.
- Our approach may help preserve the safety of the blood supply while awaiting the introduction of more sensitive and specific measures, such as systematic testing of all donations.

INTRODUCTION

New or emerging pathogens can pose a significant threat for the safety of the blood supply, particularly when reliable diagnostic tests are not yet available or widely implemented. While existing evidence suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unlikely to be transmitted through blood transfusions [1, 2], such data were not available at the beginning

of the pandemic. For blood operators, this lack of evidence significantly complicated risk assessment and management. Given the uncertain risk associated with SARS-CoV-2-positive donations early in the pandemic, our institution implemented a pilot programme to proactively inquire about donors' health status within 72 h post-donation and withdraw donations made in the early, pre-symptomatic phase of coronavirus disease-19 (COVID-19) infection. In this report, we share our experience on the feasibility of this outreach approach, which may prove useful in the event of a new or emerging pathogen.

MATERIALS AND METHODS

Study population and setting

We evaluated the proportion of donations that would be withdrawn after a proactive post-donation, evaluation of individuals who donated whole blood or apheresis-separated products at one of our centres in Québec, Canada. Donors of plasma for fractionation were excluded since these donations are treated using pathogen inactivation, which should significantly reduce the risk of SARS-CoV-2 transmission. We estimated that up to 3% of donations could be withdrawn without any significant impact on supply. Therefore, the target sample size needed was 280 donors with a precision of 2% and a type I error of 5%. This estimate was doubled (i.e., 560 donors) given that two versions of a screening questionnaire were tested (see below). All individuals who donated on May 1 and 2, 2020 participated in the pilot programme.

Questionnaires

Participating donors were administered a phone-based screening questionnaire (developed in collaboration with medical experts) to assess COVID-19-related symptoms. The questionnaire was administered ~72 h post-donation since viremia might be significant in the first few days pre-symptom onset [3, 4]. Up to four attempts were made to contact donors by phone.

The screening questionnaire was administered by non-medical staff and was designed to be highly sensitive (albeit likely unspecific) to capture as many suspected cases of COVID-19 as possible. Donors were administered one of two versions of this screening questionnaire in a 1:1 ratio: (1) a short version (3 questions) with more general questions, and (2) a long version (7 questions) with more specific questions (see Supplementary Materials for full questionnaires). Per protocol, samples from donors who positively answered ≥1 question on the screening questionnaire were quarantined until results of the follow-up assessment were available.

Donors of quarantined products were subsequently contacted by trained nurses to more thoroughly assess their symptoms using a follow-up questionnaire, which included 13 questions and was designed to be more specific (see Supplementary Materials for full questionnaire). Per decisional algorithm, the presence of one or more symptoms deemed more specific (e.g., respiratory distress, sudden loss of smell), ≥2 symptoms deemed less specific (e.g., major fatigue, generalized myalgia), or a diagnosis or suspicion of COVID-19 triggered product withdrawal. Donors whose products were withdrawn were informed that their symptoms were consistent with COVID-19 but not that their donation would be withdrawn. These donors were also deferred from giving blood for 14 days post-symptom onset.

More details on the algorithm are available in Supplementary Materials. This project was not subject to ethical review owing to its operational and urgent nature.

TABLE 1 Responses to the screening questionnaire ($N = 609$)

Reported symptom(s) or condition	*N* (%)
Short version	
Any	19 (6.1)
Unusual discomfort	19 (6.1)
New health problem	2 (0.6)
COVID-19 diagnosis or suspicion	0 (0.0)
Long version	
Any	8 (2.7)
Fever	0 (0.0)
Fatigue	5 (1.7)
Cough	0 (0.0)
Dyspnoea	1 (0.3)
Loss of sense of smell	0 (0.0)
Other	2 (0.7)
COVID-19 diagnosis or suspicion[a]	1 (0.3)

Abbreviation: COVID-19, coronavirus disease 2019.
[a]Convalescent plasma donor who donated because he was diagnosed with COVID-19.

RESULTS

A total of 654 donors donated whole blood or an eligible apheresis-separated product during the study period. Six hundred and nine out of 654 eligible donors (93.1%) were successfully contacted by phone within 72 h post-donation, with the vast majority reached with one (68.3%) or two attempts (18.1%). Patients who could not be reached by phone (i.e., non-respondents) tended to be younger than those who could be reached (i.e., respondents) after four attempts (i.e., mean age: 41.1 vs. 46.2 years). However, the proportion of female donors appeared similar between respondents (45.9%) and non-respondents (48.9%).

In total, 310 donors received the short version of the screening questionnaire, and 299 received the long version. Nineteen donors (6.1%) who received the short version positively answered ≥1 question, and eight donors (2.7%) who received the long version positively answered ≥1 question (Table 1, Figure 1), for a total of 27 donors (4.4%). Of these, four (14.8%) positively answered ≥1 question on the

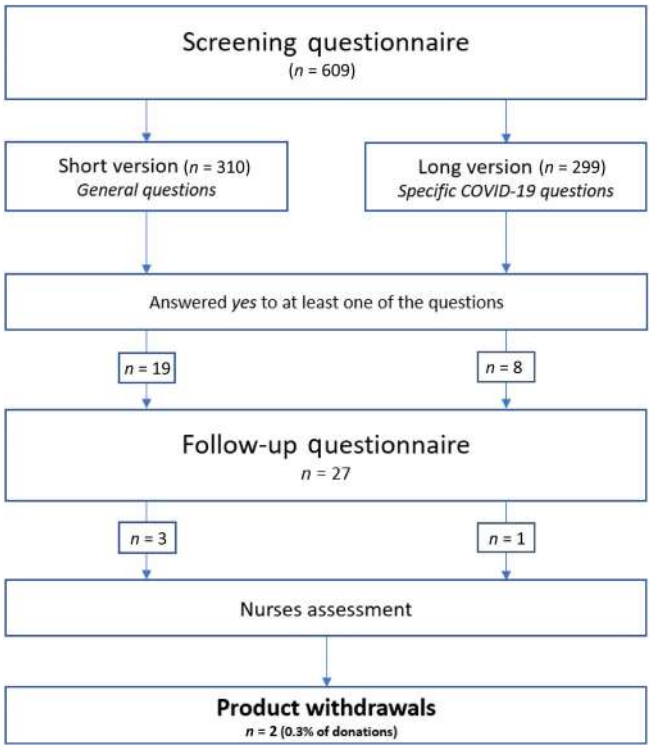

FIGURE 1 Screening and follow-up questionnaires flow chart with number of participants for each step

TABLE 2 Responses to the follow-up questionnaire ($N = 27$)

Reported symptom(s) or condition	*N* (%)
Any	4 (14.8)
Fever	0 (0.0)
Fatigue	1 (3.7)
Cough	0 (0.0)
Muscle aches and pain	1 (3.7)
Dyspnoea	0 (0.0)
Loss of sense of smell	0 (0.0)
Sore throat	1 (3.7)
Diarrhoea	1 (3.7)
Nausea/vomiting	2 (7.4)
Headache	1 (3.7)
Dizziness	1 (3.7)
Abdominal pain	0 (0.0)
COVID-19 diagnosis or suspicion	0 (0.0)

Abbreviation: COVID-19, coronavirus disease 2019.

follow-up questionnaire given by the nurse (Table 2), including three initially evaluated with the short version of the screening questionnaire and one with the long version (Figure 1). Based on nurses' assessment, two of these donors reported signs and symptoms that were consistent with mild post-donation fatigue or delayed vasovagal reaction; thus, their donations were not destroyed. One reported having a sore throat and fatigue within 48 h post-donation, and another reported diarrhoea within 48 h post-donation. Per decisional algorithm, these two donations (0.3% of contacted donors) were recalled and withdrawn. We could not confirm whether these donors were subsequently diagnosed with COVID-19 infection.

DISCUSSION

Prior to the pandemic, donors were instructed to report symptoms that may be indicative of a contagious illness (e.g., diarrhoea, vomiting, chills, muscle aches) within 1–2 weeks post-donation, and any diagnosis of hepatitis or human immunodeficiency virus (HIV) within 12 months post-donation. However, this passive approach may not capture all significant events.

Our results support the feasibility of a proactive, donor outreach approach to identify post-donation symptoms and possibly mitigate these risks associated with emerging pathogens. Only a small fraction of products (0.3%) were withdrawn. An assessment by a medically trained person reduced the number of product disqualifications by almost 10 times and was thus essential. However, rates of product withdrawal are likely sensitive to the incidence of COVID-19 in a given population, so that pilot studies in other epidemiological contexts may be warranted. Furthermore, the rate of post-donation health events (short version: 2.7%, long version: 6.1%) was higher than that observed at our institution in 2019 (1.3%), when donors were instructed to self-report health events. Therefore, the present outreach approach might have improved post-donation reporting, although other factors may be at play (e.g., greater awareness amid a pandemic, seasonal or temporal effects). Despite its apparent effectiveness, this approach was not implemented in our routine operations because concerns over transfusion-transmitted COVID-19 illness have substantially alleviated since the start of this pilot study [2].

Our approach did not withdraw donations from non-responding donors, which was deemed appropriate given the context of restricted supply and the risks that this situation entailed. The additional withdrawal of all donations from non-responding donors, would have resulted in an overall 6.6% withdrawal rate. Thus, doing so would have had a significant impact on supply, but this alternative strategy may be sustainable during times of reduced demand, as was the case in the initial phase of the pandemic. Also, one could argue that in times of restricted supply, it could be justified, from a risk/benefit perspective, to qualify donations from donors who cannot be reached by this process. In that situation, our experience shows that only a very small fraction of products would be discarded (0.3%), while the majority of donations would be subjected to questionnaire screening. However, those numbers could vary depending on incidence of the disease in the population.

As expected, the short version of the screening questionnaire appeared to be less specific than the long version. This caveat translated into a larger number of quarantined products and the administration of more follow-up questionnaires, thereby increasing costs and

(potentially) wasting health care resources. The short questionnaire detected more possibilities for withdrawals than the more specific long questionnaire. Nonetheless, our study was not adequately powered to identify COVID-19-positive donors and draw conclusions on the sensitivity of both versions. It remains unclear whether the short version may offer benefits in terms of sensitivity that could outweigh its lower specificity.

Non-respondents tended to be younger than respondents, suggesting phone calls may be suboptimal to reach younger donors, in which case other means (e.g., e-mails, SMS) might be considered. Notifying donors during the donation that they would be called within 72 hours likely facilitated telephone follow-up. A hybrid contact method by telephone and e-mail or SMS could also be considered to increase the contact rate. Regardless, a proactive outreach approach is likely warranted as some individuals may experience shame after contracting COVID-19 [5], and such feelings are associated with lower compliance with public health safety measures [6]. Proactively contacting donors thus likely improves the rate of reporting as feelings of shame may interfere with self-reporting. Regardless, contact rate was excellent in our study, likely in part because of the application of lockdown rules during the early phase of the pandemic.

A limitation of our approach is the inability of the screening questionnaires to identify asymptomatic cases of COVID-19. Nonetheless, historical precedents with other pathogens, such as HIV and West-Nile virus (WNV) [7, 8], suggest asymptomatic donors are less likely to transmit a given disease, which should mitigate the risks associated with this limitation.

At around the same time that we concluded this pilot study, there were already some strong and reassuring indications that COVID-19 did not pose a significant threat to transfusion safety. This is why we did not implement this active post-donation information programme in our routine operations. Although the current consensus is that transfusion-associated transmission of SARS-CoV-2 is unlikely, future new or emerging pathogens may not behave similarly. For example, WNV and Zika virus are relatively recent emerging pathogens that proved relevant for blood safety. With climate change and a growing world population, these events are poised to become increasingly frequent. When such pathogens emerge, the outreach approach outlined in this study may help preserve the safety of the blood supply (at least partially and temporarily) while awaiting the introduction of more sensitive and specific measures, such as systematic testing of all donations.

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CONFLICT OF INTEREST

The authors have nothing to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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LETTER TO THE EDITOR

Vox Sanguinis ISBT International Society of Blood Transfusion

Evaluation of prophylactic polyclonal anti-D antibodies: Differences in Fc-glycosylation in commercial products

We are writing to share our efforts to help patients in preventing RhD Disease, an alloimmune condition also known as Haemolytic Disease of the Foetus and the Newborn (HDFN) [1]. To prevent a pathogenic immune reaction, an RhD negative mother carrying an RhD positive foetus should receive hyperimmune polyclonal RhD-specific IgG antibodies [1]. Monoclonal anti-D IgG have been produced by a variety of methods that give rise to differences in anti-D Immunoglobulin activity and some of these differences can be attributed to the glycans linked to the Fc region of IgG anti-D [2]. Glycomics is a rapidly developing discipline with the aim of identifying a relationship between glycan structures and protein functionality. In particular, the glycosylation of immunoglobulins is extensively studied due to the important role these proteins play in the immune response [3]. Previously published work [4, 5] has shown that anti-D products with low fucose (low fucosylation) and high galactose (high galactosylation) content may be more potent and protective for prophylaxis in HDFN. We decided to investigate the glycosylation pattern of two prophylactic anti-D immunoglobulin products,

TABLE 1 % Fucosylation, sialylation and galactosylation content of IMMUNORHO®, RhoGam® and IgVena®

	IMMUNORHO			RhoGam			IgVena		
Glycan structure	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**
Fucosylation (%)	83.31	81.55	79.43	81.19	79.74	77.00	95.04	95.41	95.36
Mean (%)		81.43			79.31			95.27	
CV (%)		2.38			2.68			0.21	
Sialylation (%)	24.96	25.70	25.53	26.03	27.22	21.26	17.77	18.90	20.93
Mean (%)		25.40			24.84			19.20	
CV (%)		1.53			12.68			8.33	
Galactosylation (%)	87.11	89.31	91.20	89.78	91.32	89.05	74.09	74.04	74.52
Mean (%)		89.21			90.05			74.22	
CV (%)		2.29			1.28			0.35	

TABLE 2 Breakdown of galactosyl content of IMMUNORHO®, RhoGam® and IgVena®

	IMMUNORHO			RhoGam			IgVena		
Glycan structure	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 1**	**Batch 2**	**Batch 3**
Agalactosyl (G0) (%)	12.90	10.67	8.79	10.22	8.69	10.95	25.91	25.96	25.47
Mean (%)		10.79			9.95			25.78	
CV (%)		19.08			11.55			1.05	
Monogalactosyl (G1) (%)	34.02	33.03	33.98	32.59	31.53	36.59	41.33	40.53	39.49
Mean (%)		33.68			33.57			40.45	
CV (%)		1.66			7.96			2.28	
Digalactosyl (G2) (%)	53.08	56.29	57.23	57.20	59.77	52.46	32.77	33.51	35.04
Mean (%)		55.54			56.48			33.77	
CV (%)		3.92			6.57			3.44	

IMMUNORHO® and RhoGam®, along with the intravenous immunoglobulin (IVIG) product IgVena®.

European Pharmacopoeia (Ph Eur) methods 2.7.13 B and C were used to determine anti-D potency for three lots of each anti-D product. For glycan analysis, anti-D products were affinity purified on group O, R_2 R_2 cells and further purified on immobilised protein G prior to preparing all samples (six lots of anti-D and three lots of IVIG) for Mass Spectrometry analysis using a GlycoWorks RapiFluor MS kit (Waters, UK). Glycan separation was carried out on an Acquity UPLC H-class Bio system (Waters, UK) with a BEH Glycan Amide column (Waters, UK) using in-house methodology. Data were acquired and processed manually using Empower 3.1 software. Peaks were assigned to glycan structures and each glycan structure was expressed as a percentage relative peak area of the total percentage area of assigned peaks.

All six batches of prophylactic anti-D complied with the Ph Eur specification for potency. There are clear differences in the mixture and abundance of glycan structures for anti-D and IVIG. In IVIG, fucosylated structures are typically the most abundant glycan forms (Table 1). Digalactosyl structures are in greater abundance in the anti-D products (Table 2) and in addition to low fucosylation [4, 5] important for enhanced ADCC activity. As reported for Rhophylac® [4, 5] and RhoGam [5] our results show that higher levels of sialylation and galactosylation and lower levels of fucosylation are present in IMMUNORHO and RhoGam products compared to IVIG. Further work is required to elucidate the link between glycosylation and anti-D immunoglobulin function. We intend to collect additional data to contribute to the better understanding of the properties of anti-D immunoglobulins in relation to the variation in IgG-Fc glycosylation profiles.

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CONFLICT OF INTEREST

F.M., A.S., E.A. and R.D. work full time for Kedrion Biopharma Inc. B.F. works full time for NIBSC.

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DATA AVAILABILITY STATEMENT

Data will be stored at Kedrion S.p.A. in the Global Medical Affairs Department.

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Influenza-associated thrombotic thrombocytopenic purpura: A report of two cases and a brief review of the literature

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Abstract

Background and Objectives: Thrombotic thrombocytopenic purpura (TTP) is often preceded by a recent history of an acute infection and influenza is the most implicated virus.

Materials and Methods: We identified two cases of TTP, which were preceded by influenza between 2010 and 2021. In one patient, we epitope mapped the binding specificity of antibodies using an overlapping peptide approach of the stalk protein of Influenza B and the cysteine-rich spacer domain (CRSD) of ADAMTS13. A literature search was performed for reports of influenza-associated TTP over the period 1980–2021.

Results: Two patients were identified in which TTP was preceded by influenza, one Influenza A and the other Influenza B. Epitope mapping of the latter's plasma identified target epitopes in both the stalk protein of Influenza B and CRSD of ADAMTS13. The literature review revealed only seven case reports, all but one from Europe or Asia and associated with Influenza A. Severe ADAMTS13 deficiency was demonstrated in only four cases.

Conclusion: We report the first small case series of influenza-associated TTP. Moreover, it is the first case implicating Influenza B and a mechanism favouring polyclonal B-cell proliferation rather than molecular mimicry as the stimulus to form anti-ADAMTS13 auto-antibodies is suggested.

KEYWORDS
ADAMTS13, influenza, thrombotic thrombocytopenic purpura

Highlights

- Thrombotic thrombocytopenic purpura (TTP) is often preceded by a viral infection, but the implicating virus is rarely identified.
- We describe two cases of TTP following influenza infection.
- This is the first case series of Influenza associated TTP and also the first case of TTP following Influenza B infection.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening condition characterized by severe thrombocytopenia, haemolytic anaemia and the presence of fragmented red cells in the peripheral blood smear [1]. TTP is now known to be caused by either a congenital or acquired deficiency of a von Willebrand factor (vWF) cleaving protease, ADAMTS13, which cleaves a Tyr1605–Met1606 site on the vWF-A2 domain [2]. This transforms the unusually large vWF multimers into lower molecular weight multimers [3]. Inhibitory auto-

antibodies to ADAMTS13 are found in acquired TTP. Patients presenting with acquired TTP sometimes have a history consistent with a recent acute infection [4]. Rare single-case reports have documented an association between influenza and TTP (IA-TTP) [5]. Although the first of such association was described in the United States in 1981 [6], all subsequent reported cases have been in Europe or Asia. The purpose of this report is to describe two new cases of IA-TTP, one of which was triggered by Influenza B infection, and also to provide a brief review of previously reported cases.

MATERIALS AND METHODS

Two known cases of IA-TTP in our institution were reviewed for relevant clinical and laboratory data. For the more recent case of IA-TTP, a plasma sample was sent for analysis using PEPperMAP® Epitope Mapping (PEPperPRINT, Heidelberg, Germany). This plasma was tested against the haemagglutinin protein of Influenza B and a 245 amino acid region of interest in hADAMTS13, which includes the cysteine-rich/spacer domain (CRSD), a region that serves as a major epitope for ADAMTS13 auto-antibodies [7]. The sequences of the stalk domain of the haemagglutinin B protein and hADAMTS13 (245 aa region of interest) were linked and elongated with neutral GSGSGSG linkers. The reason we chose the haemagglutinin stalk domain was because it is common to both Influenza A and B. The linked and elongated antigen sequences were translated into linear 15 amino acid peptides with a peptide–peptide overlap of 14 amino acids. The resulting peptide microarrays contained 830 different peptides printed in duplicate and were framed by additional V5 and polio as control peptides. The peptide microarrays were incubated with the plasma sample at dilutions of 1:1000, 1:100 and 1:10 followed by staining with secondary and control antibodies and a read-out with a LI-COR Odyssey Imaging System. Quantification of spot intensities and peptide annotation were performed with PepSlide® Analyser.

Using 'TTP' and 'influenza' as keywords, PubMed and Google Scholar were used to find reported cases of IA-TTP for the time period 1980–2021.

RESULTS

Case 1

In February 2011, a 22-year-old male was referred to our tertiary care hospital with symptoms of fever, dark urine and jaundice. The patient had been taking oseltamivir for 3–5 days for a diagnosis of influenza based on a positive reverse transcription - polymerase chain reaction (RT-PCR) test for Influenza A. Physical examination revealed scleral icterus and oral cavity purpura. Peripheral blood smear showed numerous schistocytes with occasional spherocytes. The pertinent laboratory studies upon admission are shown in Table 1. Treatment was initiated with intravenous prednisone and daily therapeutic plasma exchange (TPE) using cryo-poor plasma as the exchange fluid, equivalent to one plasma volume. On day 6, the patient experienced a TRALI reaction but stabilized the next day and he was discharged home 2 days later with a steroid taper. Subsequently, an ADAMTS13 activity of <5% and ADAMTS13 inhibitor level of 3.2 Bethesda units/ml were resulted from a reference laboratory on a sample collected prior to the initiation of TPE. On the day of discharge, the platelet count was 184×10^9/L and ADAMTS13 activity was 105%. There has not been any recurrence of TTP.

Case 2

In February 2020, a 63-year-old male was referred to our hospital for management of suspected TTP. The patient had a previous history of TTP in 2013, managed with TPE from July to September, 2013. On presentation, the patient reported dyspnoea on exertion and a dry cough for 10 days. Peripheral blood smear showed numerous schistocytes. Influenza B infection was confirmed with RT-PCR. Oseltamivir was not given due to the late diagnosis of influenza. The pertinent laboratory studies upon admission are shown in Table 1. The diagnosis of TTP was confirmed with an on-site ADAMTS13 fluorescence resonance energy transfer assay of 8% (normal: 80%–140%) and an ADAMTS13 inhibitor ELISA assay of 40 U/ml (normal: <15 U/ml). TPE was initiated with cryo-poor plasma, equivalent to one plasma volume together with intravenous steroids at 1 mg/kg body weight. Cryo-poor plasma was used as exchange fluid until day

TABLE 1 Pertinent laboratory findings of the two cases at the time of admission (day 0)

	Case 1	Case 2
Haematology		
White cell count (3.5–11 × 10^9/L)	6.0	9.4
Haemoglobin (13.5–16 g/dl)	11.5	7.4
Platelets (150–400 × 10^9/L)	10	29
ABO and rhesus type	O, Rh positive	B, Rh negative
Blood chemistries		
Creatinine (0.64–1.27 mg/dl)	1.66	0.96
Lactate dehydrogenase (100–220 IU/L)	1612	977
Total bilirubin (0.2–1.3 mg/dl)	3.1	1.3
Haptoglobin (40–268 mg/dl)	N/A	<8
Coagulation		
Prothrombin time (10–13 s)	12.8	12.6
Fibrinogen (150–400 mg/d)	241	572
Direct antiglobulin test	Negative	Negative
RT-PCR for influenza	Positive, Influenza A	Positive, Influenza B

Abbreviations: N/A, not available; RT-PCR, reverse transcription - polymerase chain reaction.

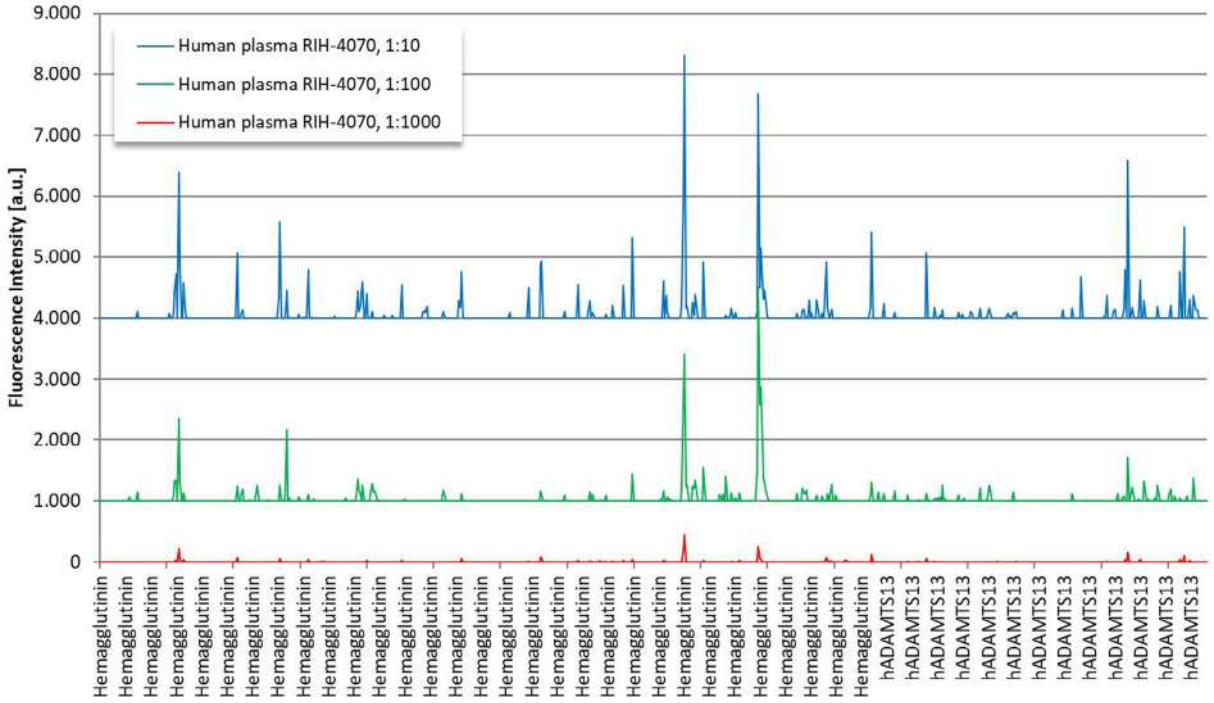

FIGURE 1 The PEPperPRINT intensity plot for case 2, showing a moderate antibody response against epitope-like spot patterns formed by adjacent peptides with the consensus motifs SHFANLKGTKT, EVPYICTEGED, MDELHNEILELDEK, VEIGNGCFE (all haemagglutinin) and PDITFTYFQPKP (hADAMTS13)

3, when a severe allergic reaction occurred during TPE causing the procedure to be discontinued. TPE was later restarted with 25 units of solvent-detergent plasma. He received one dose of rituximab (375 mg/m^2) on day 4. The patient continued to improve and was discharged home on day 6 with a steroid taper regimen. Prior to discharge, the platelet count was 196 $\times$ 10^9/L, ADAMTS13 activity was 64% and the ADAMTS13 inhibitor level was 7 U/ml.

Incubation of peptide microarray copies with this patient's plasma resulted in antibody responses against epitope-like spot patterns formed by adjacent peptides with the consensus motifs SHFANLKGTKT, EVPYICTEGED, MDELHNEILELDEK, VEIGNGCFE on the haemagglutinin stalk protein and PDITFTYFQPKP on the CRSD of hADAMTS13 at moderate signal-to-noise ratios. This confirmed the Influenza B infection and the diagnosis of TTP, but there were no overlapping sequences to support molecular mimicry as a mechanism of the aetiology of IA-TTP. The PEPperPRINT display is shown in Figure 1.

Brief literature review

The first case of suspected IA-TTP was described by Wasserstein et al. in the United States [6]. The patient was a 50-year-old man who presented with sudden onset aphasia during the influenza epidemic of 1977. The patient had features of chronic glomerular disease, which led to a renal biopsy and a diagnosis of TTP. Despite therapy with prednisone, plasmapheresis, whole blood exchange transfusion and ultimately splenectomy, the patient died of respiratory failure 6 weeks after the hospitalization. Although it was the first report to suggest an association between TTP and influenza, the data supporting the diagnosis of TTP is not conclusive.

Since 1981, there have been six additional cases of IA-TTP reported either in Europe or Asia and all within the past 10 years. All were associated with Influenza A infection. Some relevant demographic, laboratory and clinical data are shown in Table 2. The diagnosis of TTP was made on clinical grounds in three cases [6, 7, 9], and reduced ADAMTS13 activity and the presence of ADAMTS13 inhibitors were documented in only four of the seven cases [8, 10–12]. One of the six non-US cases died, receiving only three TPE procedures [8].

DISCUSSION

TTP is a rare disease with an incidence rate of about 5 per 10^6 per year, and some cases have a history consistent with a viral infection 1–2 weeks preceding their presentation with implications of causality. However, the infectious agent is rarely identified [4]. Seven previously reported cases of TTP suggest Influenza A virus as the causative agent. However, in three of these cases, the diagnosis of TTP was not established using current accepted criteria [13]. In that respect, our two cases differ in that the diagnosis of TTP was firmly established and the recent influenza infection was confirmed by RT-PCR. The case of Influenza B virus-associated TTP was also supported by PEPperMAP® Epitope Mapping study showing antibodies to Influenza

TABLE 2 Comparison of our two cases with the previously reported cases of influenza-associated thrombotic thrombocytopenia purpura

Report [reference]	Year	Patient's age, gender and country	Influenza sub-type	ADAMTS13 activity[a]	ADAMTS13 inhibitor[b]	No. of TPE procedures	Adjunctive therapy	Patient outcome
Wasserstein et al. [6]	1981	50 years, M, United States	A2	—	—	N/A	Systemic corticosteroids, whole blood exchange transfusion, splenectomy	Death
Kosugi et al. [8]	2010	68 years, F, Japan	A	<0.5	6 BU	3	Systemic corticosteroids	Death
Mammas et al. [7]	2011	12 years, M, Greece	A/H1N1	—	—	30	—	Complete recovery
Koh et al. [9]	2011	27 years, M, Korea	A/H1/N1	—	—	17	Systemic corticosteroids	Complete recovery
Jonsson et al. [10]	2015	35 years, F, Norway	A	<0.04	>2 BU	10	Systemic corticosteroids	Complete recovery
Joseph et al. [11]	2016	47 years, F, France	A	<5	70 U/L	12	Systemic corticosteroids, rituximab, 6 sessions of renal replacement therapy	Complete recovery
Ning et al. [12]	2020	2 years, F, China	A	0	Present	15	Systemic corticosteroids, rituximab, 4 sessions of renal replacement therapy	Complete recovery
Case 1	2011	22 years, M, United States	A	<5	3.2 BU	5	Systemic corticosteroids	Complete recovery
Case 2	2020	63 years, M, United States	B	8	40 U/L	7	Systemic corticosteroids, rituximab	Complete recovery

Abbreviation: TPE, therapeutic plasma exchange.

[a]Enzyme activity measured in case 1 and case 2 using fluorescence resonance energy transfer assay.

[b]ADAMTS13 inhibitor level measured in case 1 using a functional Bethesda assay (normal value: <0.5 BU/ml), and in case 2 using an enzyme immunoassay (normal value: <15 U/L).

B haemagglutinin stalk protein and confirmatory antibodies to the CRSD region of ADAMTS13.

Viral diseases are known to precipitate both haematologic and neurologic illness, and of the implicated viral illnesses, influenza is likely the best known [5]. Two popular potential pathogenesis theories are molecular mimicry [14] and polyclonal B cell proliferation [15]. With regard to the former, the development of inhibitory antibodies to ADAMTS13 has been linked to certain regions of ADAMTS13, which are critical for substrate recognition and VWF cleavage [16]. A detailed epitope mapping study by Klaus et al. [17] revealed that a major epitope for ADAMTS13 auto-antibodies resides within the CRSD of ADAMTS13. Kanduc [14] hypothesizes that immune responses following influenza infection may cross-react with epitopes on the ADAMTS13 protein and lead to the generation of anti-ADAMTS13 auto-antibodies. This is based on the presence of pentapeptide sharing sequences between the Influenza A and B viruses and the ADAMTS13 protein. An alternative explanation of IA-TTP is polyclonal B cell activation in which microbes can directly induce proliferation and differentiation of antibody secreting cells from naive B cells, regardless of their antigen specificity [15]. Influenza haemagglutinin is one such microbial molecule [18]. The antibodies secreted by B cells stimulated by polyclonal activators are non-specific and they recognize heterologous as well as homologous antigens. This could lead to anti-ADAMTS13 response explaining the acquired TTP in patients with influenza. In our two cases, the symptoms of influenza were noticed at least 5 days prior to the development of TTP, which would be sufficient to mount an IgG antibody response. In our study, the PEPperMAP® Epitope Mapping of the human plasma from patient with Influenza B was not able to demonstrate any overlapping amino acid sequences and was more consistent with the latter hypothesis of polyclonal B cell proliferation. We confirm that there was no homology observed between the sequences of the stalk domain of haemagglutinin B protein and the CSRD region of ADAMTS13 protein, which serves as a major epitope for anti-ADAMTS13 antibodies. The limitation is that the entire protein of ADAMTS13 was not analysed for homology with the haemagglutinin B protein.

Both TTP and influenza show seasonal variation in incidence [19, 20], with TTP reported as more common between June and August [19], while influenza mostly occurs between December and February [20]. Our institutional data with 31 cases of TTP over the previous 8 years show a preponderance in the fall (13/31) versus the

winter season (6/31). Thus, TTP presenting in the winter may reflect antecedent influenza infection and suggest that such cases be tested for influenza with RT-PCR.

In summary, we present the first small case series of IA-TTP and the first case implicating Influenza B in which both the documentation of recent influenza infection and the diagnosis of TTP are complete and adds to the list of the rare and intriguing association between influenza and TTP.

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Y.O.M. performed literature search, reviewed the institutional case studies and wrote the manuscript. J.D.S. supervised the study, reviewed and edited the manuscript.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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ORIGINAL ARTICLE

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Short-term high-dose intravenous iron reduced peri-operative transfusion after staggered bilateral total knee arthroplasty: A retrospective cohort study

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Abstract

Background and Objectives: Staggered bilateral total knee arthroplasty, two procedures performed 4–7 days apart during a single hospitalization, has an increased risk of blood transfusion. This observational study aimed to evaluate whether immediate post-operative single, high-dose intravenous iron supplementation could reduce transfusion requirements and facilitate anaemia recovery in patients.

Materials and Methods: We retrospectively analysed 131 patients who underwent staggered bilateral total knee arthroplasty. The ferric carboxymaltose (FCM) group received 1000 mg of FCM after the first operation. The non-FCM group did not receive intravenous iron. The transfusion rate and post-operative complications were compared between the groups. The anaemia rate was evaluated pre-operatively, during hospitalization, and 5 weeks after the second total knee arthroplasty.

Results: The FCM group comprised 78 patients (59.5%). The rate (21.8% vs. 47.2%, $p = 0.004$) and amount of transfusion (0 [0–2] vs. 0 [0–0], $p = 0.001$) was significantly lower in the FCM group than in the non-FCM group. Although both groups' pre-operative haemoglobin concentrations were not significantly different, the FCM group demonstrated higher haemoglobin values 5 weeks post surgery (12.25 ± 0.83 mg/dl vs. 11.48 ± 1.36 mg/dl, $p < 0.001$). More non-FCM patients developed moderate to severe anaemia at 5 weeks post surgery ($p < 0.001$). The mortality and complication rates were not significantly different.

Conclusions: Immediate post-operative, high-dose, intravenous iron treatment may contribute to reduced transfusion rates, facilitate haemoglobin recovery after staggered bilateral total knee arthroplasty, and minimize the development of moderate to severe anaemia.

KEYWORDS
anaemia, bilateral staggered, ferric carboxymaltose, intravenous iron, total knee arthroplasty, transfusion

Highlights

- Staggered bilateral total knee arthroplasty causes moderate to severe anaemia in patients during hospitalization.

- Intravenous (IV) iron administration can facilitate erythropoiesis in surgical patients with iron deficiency.
- Administration of a single high-dose IV iron in the short-term peri-operative period (up to 7 days before and/or after surgery) could contribute to haemoglobin improvement.

INTRODUCTION

The use of total knee arthroplasty (TKA) has increased over the past decade because of its effectiveness in patients with end-stage knee osteoarthritis [1]. Unilateral TKA usually generates blood loss with a decrease of 1.0–3.0 g/dl of haemoglobin (Hb) from the baseline [2]. Furthermore, pre-operative anaemia is prevalent in elderly patients who receive major orthopaedic surgery, and thus it often requires peri-operative allogeneic blood transfusion [3]. The transfusion rate varies from 10% to 64% in TKA [4–6].

Staggered bilateral TKA refers to two procedures performed 4–7 days apart during a single hospitalization [7]. Patients indicated for staggered bilateral TKA sequentially receive a second operation, which may cause further blood loss without sufficient Hb recovery time after the first TKA [8]. It may lead to an increase in the rate and severity of anaemia and the requirement of blood transfusion in such patients.

Patient blood management (PBM) recommends the early detection of pre-operative and post-operative anaemia and its treatment before major surgery using iron preparations and/or erythropoiesis-stimulating agents (ESAs) [9, 10]. However, there are time frame limitations for pre-operative application. Therefore, clinicians resort to a short-term intravenous (IV) iron administration. As iron deficiency is a common cause of anaemia, short-term (up to 7 days before and/or after surgery) IV iron administration in major surgery could help increase Hb incrementally [11, 12]. When IV iron replacement is achieved between the two procedures of bilateral staggered TKA patients, it is expected to positively affect erythropoiesis in patients with acute post-operative anaemia. However, a previous retrospective study, which assessed patients who received IV iron 300 mg after each TKA, did not show significantly reduced transfusion rates in bilateral staggered TKA patients [13] .

Therefore, we retrospectively evaluated the effect of post-operative, single, high-dose IV iron (1000 mg) on the peri-operative transfusion rate and Hb change in patients undergoing staggered bilateral TKA. In addition, we hypothesized that patients with high-dose IV iron supplementation would have a more mitigated severity of anaemia than those without IV iron supplementation.

MATERIALS AND METHODS

Patient population

This retrospective observational study was approved by the institutional review board of the study centre (No. 2020-1436). We collected the data of patients who had undergone elective staggered bilateral TKA between January 2016 and August 2020 at a single tertiary teaching hospital. The requirement for informed consent was waived, as the data were obtained through a retrospective review of electronic medical records. Staggered bilateral TKA refers to two arthroplasties performed on different days, within 7 days between the first and second operation, during a single hospitalization [7]. We included cases wherein there were 8 days between the procedures because of holidays or unexpected schedule alterations. The exclusion criteria were patients with haematological and renal disorders (serum creatinine level > 1.5 mg/dl) and/or patients on pre-operative iron preparations or transfusion treatment.

Data collection

We reviewed the patients' electronic medical records and collected the following data: age, sex, height, weight, body mass index, pre-operative comorbidities, and American Society of Anesthesiologists physical status. Intra-operative variables included the use of tranexamic acid, type of anaesthesia (general or spinal), and duration of the operation. The following data were also abstracted from the records: post-operative clinical complications, and mortality in 30 days and 1 year, as well as overall mortality. The red blood cell (RBC) transfusion rates after the first TKA, after the second procedure, and overall were also investigated accordingly. The length of hospital stay was calculated from the day of the second TKA until hospital discharge. We also collected data on the adverse events associated with IV iron infusion from the electronic medical records. Each patient's Hb levels during the peri-operative period and fifth post-operative week were also collected. The Hb results from the fifth post-operative week included Hb results between post-operative days (PODs) 25 and 46.

Peri-operative PBM and iron preparation administration strategy

After the application of standard monitoring, the patients received either spinal anaesthesia with IV sedation or general anaesthesia using a supraglottic airway device with inhaled anaesthetics and medical air. During the operation, an intra-operative tourniquet was applied for all the patients before the skin incision, and it was released at the end of surgery after the application of the surgical wound dressing. Since the end of 2016, tranexamic acid 10 mg/kg is being administered intra-operatively before tourniquet placement for all the patients except for those who are allergic to tranexamic acid and those who had a history or any risks of ischaemic disease, deep vein thrombosis, and/or other thromboembolic conditions.

Our orthopaedic department had started using IV iron from early 2016. The IV iron group received 1000 mg IV ferric carboxymaltose (FCM group; Ferinject®, Vifor Int., St. Gallen, Switzerland). The patients who had provided informed consent for the use of IV iron received it on the day of the first TKA, within 1–2 h after returning to the general ward from the post-anaesthesia care unit. IV iron was administered in these patients for 15–30 min. During this period, the nurses providing care closely monitored each patient and checked for any possible side effects relating to FCM administration. If the side effect was severe or life-threatening, it was recorded as a serious adverse event [14].

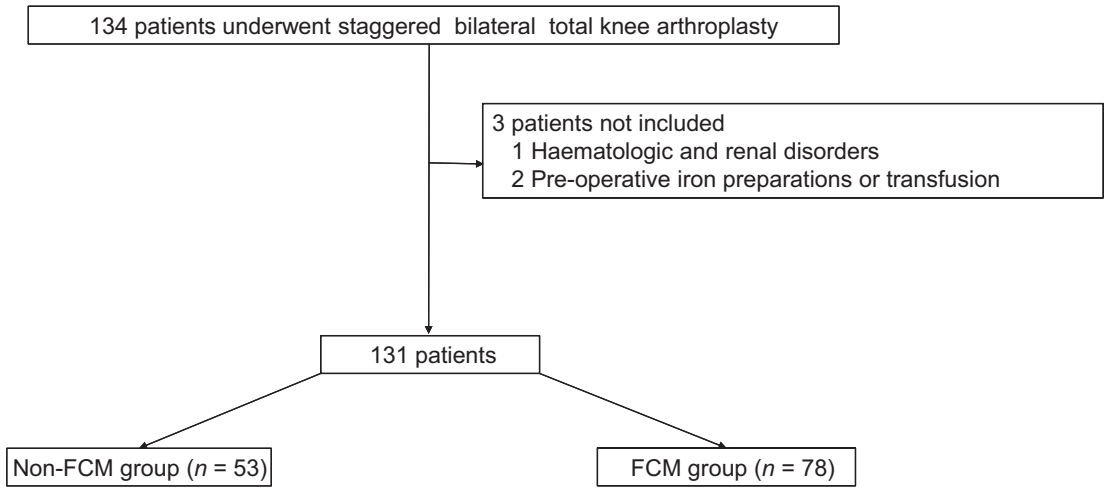

FIGURE 1 Flow diagram of the study. FCM, ferric carboxymaltose

TABLE 1 Patient baseline characteristics, pre-operative comorbidities, and operative variables

	Non-FCM group ($n = 53$)	FCM group ($n = 78$)	*p*-Value
Age	71.2 ± 8.9	70.3 ± 4.9	0.500
Sex (female)	51 (96.2%)	76 (97.4%)	1.000
Height (cm)	151.7 ± 5.3	152.7 ± 5.8	0.296
Weight (kg)	62.1 ± 9.6	62.9 ± 8.6	0.613
Body mass index (kg/m^2)	26.9 ± 3.8	27.0 ± 2.9	0.954
Comorbidities			
Diabetes mellitus	12 (22.6%)	17 (21.8%)	1.000
Hypertension	34 (64.2%)	48 (61.5%)	0.905
Cardiac disease	4 (7.5%)	5 (6.4%)	0.761
Cerebrovascular disease	3 (5.7%)	5 (6.4%)	1.000
Pulmonary disease	2 (3.8%)	2 (2.6%)	1.000
ASA			0.470
1 or 2	50 (94.3%)	73 (93.6%)	
3	3 (5.7%)	5 (6.4%)	
Hb (g/dl)	12.33 ± 1.22	12.67 ± 0.86	0.084
ANS type (spinal)			
First operation	48 (90.6%)	69 (88.5%)	0.925
Second operation	50 (94.3%)	65 (83.3%)	0.106
Operation time (min)			
First TKA	115.0 [104.0–127.0]	127.5 [119.0–136.0]	<0.001
Second TKA	115.5 [101.0–130.0]	126.5 [120.0–132.0]	<0.001
Tranexamic acid[a]	37 (69.8%)	63 (80.8%)	0.215

Note: Data are expressed as number of patients (%), mean ± SD or median [interquartile range].
Abbreviations: ANS, anaesthesia; ASA, American Society of Anesthesiologists physical status; FCM, ferric carboxymaltose.
[a]Tranexamic acid was used at the same rate in the first and the second operations.

TABLE 2 Post-operative outcome variables including transfusion and anaemia rate

	Non-FCM group ($n = 53$)	FCM group ($n = 78$)	p-Value
Transfusion			
No. of patients transfused	25 (47.2%)	17 (21.8%)	0.004
First TKA	15 (28.9%)	12 (15.6%)	0.111
Second TKA	19 (36.5%)	10 (13.0%)	0.003
Transfusion amount (units)	0 [0–2]	0 [0–0]	0.001
No. of units transfused			
1	3 (12.0%)	7 (41.2%)	
2	10 (40.0%)	5 (29.4%)	
3	4 (16.0%)	3 (17.6%)	
≥4	8 (32.0%)	2 (11.8%)	
Length of hospital stay[a]	7.0 [6.0–11.0]	8.0 [7.0–11.0]	0.015
Mortality			
30 days	0	0	
1 year	1 (1.9%)	0	0.845
Overall	2 (3.8%)	0	0.316
Complication rate			
Nephrotic	0	0	
Cardiac	0	1 (1.3%)	1.000
Pulmonary	1 (1.9%)	1 (1.3%)	1.000
Vascular	1 (1.9%)	1 (1.3%)	1.000
Psychiatric	0	2 (2.6%)	0.654
Neurological	0	1 (1.3%)	1.000
Infection	2 (3.8%)	1 (1.3%)	0.729
Urology	0	4 (5.2%)	0.249

Note: Data are expressed as number of patients (%), mean ± SD or median [interquartile range].
Abbreviations: FCM, ferric carboxymaltose; TKA, total knee arthroplasty.
[a]Length of hospital stay, duration between second operation and discharge day.

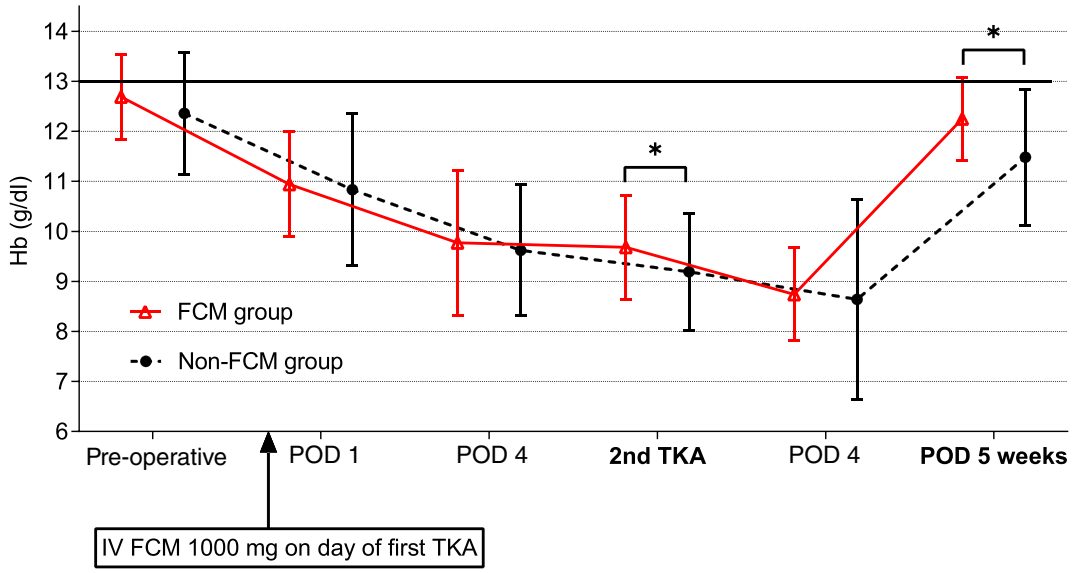

FIGURE 2 Alteration of mean haemoglobin during the peri-operative period. FCM, ferric carboxymaltose; Hb, haemoglobin; POD, post-operative day; TKA, total knee arthroplasty. *$p < 0.05$ vs. Non-FCM group

TABLE 3 Incidence of anaemia during the peri-operative period

	Non-FCM group ($n = 53$)	FCM group ($n = 78$)	p-Value
Rate of anaemia			
Pre-operative	38 (71.7%)	52 (66.7%)	0.676
First POD 1	46 (86.8%)	76 (97.4%)	0.044
First POD 4	53 (100%)	78 (98.7%)	
Second OP day	53 (100%)	78 (100%)	
Second POD 4	53 (100%)	78 (100%)	
POD-5 weeks	44 (83.0%)	59 (75.6%)	0.376
Moderate-to-severe anaemia			
Pre-operative	8 (15.1%)	3 (3.8%)	0.050
First POD 1	30 (56.6%)	38 (48.7%)	0.479
First POD 4	46 (86.8%)	69 (88.5%)	0.988
Second OP day	45 (84.9%)	70 (89.7%)	0.577
Second POD 4	51 (96.2%)	76 (97.4%)	1.000
POD-5 weeks	19 (35.8%)	6 (7.7%)	<0.001

Note: Anaemia, Hb < 13.0 g/dl; moderate to severe anaemia, Hb ≤ 11.0 g/dl.
Abbreviations: FCM, ferric carboxymaltose; Hb, haemoglobin; OP, operation; POD, post-operative days.

Outcome variables

The primary clinical outcome was the transfusion requirements and its volume during the peri-operative period. This institute follows the standard care practice of restrictive transfusion triggers strategy for TKA of Hb < 8.0 g/dl throughout the peri-operative period. If the patient presented with symptoms of significant haemodynamic instability despite adequate fluid administration, and the use of vasopressor was essential, allogeneic transfusion of packed RBCs was permitted even with Hb ≥ 8.0 g/dl.

The value of Hb and the rate of anaemia in each time point during the peri-operative period and fifth post-operative week was evaluated accordingly. We defined anaemia as a sub-optimal Hb concentration (<13.0 g/dl) in both females and males according to consensus guideline [15, 16]. We further categorized the severity of anaemia into moderate-to-severe (Hb < 11.0 g/dl) based on the World Health Organization guideline [17].

Statistical analysis

Continuous variables are reported as mean with SD or median with interquartile range. Student's t-test or the Mann–Whitney test was used to compare continuous variables. Categorical variables are presented as frequencies and percentages (%) and were analysed using the Chi-square test or Fisher's exact test, as appropriate. p-Values <0.05 were regarded as statistically significant. The statistical analyses were performed using R software, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Data of 134 patients who underwent primary staggered bilateral TKA from January 2016 to August 2020 were included in this study. Of these patients, the following were excluded: (1) patients with haematological and renal disorders (serum creatinine level > 1.5 mg/dl) ($n = 1$), and (2) patients who received pre-operative iron preparations or transfusion ($n = 2$). Finally, 53 patients were classified into the non-FCM group and 78 into the FCM group (Figure 1). The baseline characteristics, pre-operative comorbidities, and operative variables are shown in Table 1.

The peri-operative transfusion rate of each group is presented in Table 2. A total of 42 (32.1%) patients required RBC transfusion. The non-FCM group had a significantly higher requirement and received a larger volume of overall RBC transfusion than did the FCM group. With respect to transfusion timing, the non-FCM group required significantly more transfusion after the second TKA operation than the FCM group (Table 2). The duration of hospital stay was significantly longer in the FCM group. There were no differences in mortality or complication rates between both groups.

The changes in Hb at each time point are shown in Figure 2. Nadir Hb was similar at POD 4 (8.96 ± 1.0 for non-FCM group vs. 8.73 ± 0.93 g/dl for FCM group, $p = 0.168$) after the second operation prior to discharge from the hospital in both groups. At the fifth post-operative week, the FCM group showed significantly higher Hb levels compared to those of the non-FCM group (12.25 ± 0.83 vs. 11.48 ± 1.36 g/dl, $p < 0.001$, Figure 2).

The prevalence of pre-operative anaemia was 71.7% and 66.7% in non-FCM and FCM group, respectively (Table 3). Of them, more patients in the non-FCM group had moderate anaemia. Most patients underwent the second operation with an anaemic state of Hb < 13.0 g/dl in both groups, and every patient in each group presented with anaemia at POD 4 after the second operation. However, the number of patients presenting moderate to severe anaemia was significantly higher in the non-FCM group than in the FCM group at the fifth post-operative week (19 [35.8%] vs. 6 [7.7%], $p < 0.001$).

DISCUSSION

In this study, we assessed the effect of peri-operative, short-term, single high-dose IV iron supplementation on transfusion requirements and anaemia recovery in patients undergoing staggered bilateral TKA. The IV FCM-treated group presented a reduction of peri-operative transfusion with higher Hb increments at the fifth post-operative week compared with the non-FCM group.

Staggered bilateral TKA is a surgical strategy wherein two procedures are performed on two different operative days within a 4–7-day interval. This strategy has advantages over staged bilateral TKA, wherein two unilateral knee replacement arthroplasties are performed within 1 year at different hospitalization schedules [7]; that is, the surgery of both knees can be accomplished during a single hospitalization, thereby decreasing the overall recovery time and hospitalization for replacement of both knees [18]. However, a previous study showed that staggered bilateral TKA results in more acute post-operative anaemia (11% vs. 3%) and blood transfusions (93% vs. 54%) compared with staged bilateral TKA [18]. The causes of post-operative anaemia can be the presence of pre-existing anaemia, surgical blood loss, and surgery-related inflammation, which may blunt erythropoiesis for recovery. Thus, during the hospitalization period between two sequential TKAs, IV iron administration may hasten the recovery of anaemia following the first operation. It is well known that the administration of parenteral iron can replenish depleted body iron stores more rapidly than oral iron, as it can improve the erythropoiesis response to blood-loss anaemia in healthy persons by five-fold [19].

Pre-operative anaemia and a sub-optimal Hb (<13.0 g/dl for both sexes) is an independent predictor of peri-operative transfusion [20]. Elderly patients who are scheduled for elective major orthopaedic surgery have a high prevalence of anaemia (Hb < 13.0 g/dl) of up to 19.4%–26%, with iron deficiency present in 30% of patients [16, 21]. The prevalence of pre-operative anaemia in our data was over 66%, which worsened further after surgery. The FCM group in our study received short-term peri-operative IV iron supplementation immediately after the first operation to hasten post-operative anaemia recovery. Short-term peri-operative IV iron treatment in iron-deficient patients has been known to improve Hb recovery [12, 22] and iron storage profiles during the first 4 weeks after major elective and cardiac surgery [11, 23], gastrectomy, and postpartum haemorrhage [24, 25]. Although the current study did not evaluate iron metabolism profiles, it could be expected that patients with post-operative anaemia had iron deficiency or low iron stores. Thus, it appeared that the iron deficiency in the FCM group was rapidly corrected with high-dose IV iron supplements, considering the faster incremental increase in Hb during the post-operative 5 weeks. Furthermore, a second-dose IV iron treatment, rather than a single-dose treatment, may facilitate the improvement of anaemia as well. However, this assumption needs further research for the validation of a second dose of IV iron in surgical patients during the peri-operative period.

The optimal dose of IV iron has not yet been determined in the literature. A previous study for staggered bilateral TKA used a total post-operative dose of 600 mg iron, unlike the 1000 mg of iron in the current study [13]. The authors did not find any improvement of Hb recovery at 6 weeks and 3 months post surgery, and the need for transfusion was not significantly different. According to the adopted Ganzoni formula [26], the iron deficit in a patient with 62 kg and 10.0 g/dl of Hb was 968 mg. In the same previous study, the amount of iron may not have been adequate, which led to negative results of incremental Hb increases and transfusion requirements [13]. Other previous studies administered relatively low doses of iron (<600 mg/patient) during a short-term peri-operative period. This did not lead to any significant improvement of anaemia recovery or a reduction in transfusion, hospital stay, and infection rates [27–29]. Favourable results for increasing Hb were shown in recent randomized controlled trials and two large pair-matched observational studies that administered IV iron doses >600 mg in a short period [11, 23, 30, 31]. Hence, 1000 mg of FCM administered in the current study was sufficient for the replacement of the calculated iron deficit in most patients. Therefore, this resulted in increased erythropoiesis in staggered TKA patients.

This study had some limitations. First, it was retrospectively conducted and employed a limited intervention. Prospective design and adequate sample size calculations are needed to focus on specific points, such as transfusion, anaemia recovery, or length of hospital stay. Second, staggered bilateral TKA is not a mainstream surgical procedure; thus, the clinical impact may not be high. However, we believe that the current study has value in that it presents the results of immediate post-operative IV iron administration in a population with relatively rare data pertaining to an elective major orthopaedic surgery. Third, the patients in our study had a high prevalence of pre-operative anaemia and there was an imbalance in the pre-operative moderate anaemia rate; most patients were discharged in a moderate to severe anaemic state. According to the PBM, early detection and management of pre-operative anaemia is encouraged to optimize erythropoiesis and, therefore, improve the Hb level [9]. The iron metabolism test, which indicates the iron storage state and the cause of anaemia, is important because it further allows the effective treatment of peri-operative anaemia with reference to the outcome of the iron response. If clinicians do not have pre-operative iron study results on time, performing the iron metabolism test 24 h after surgery is recommended before the ferritin increase in response to surgery-related inflammation [32]. However, owing to the retrospective nature of the current study, we could not evaluate the early management of pre-operative anaemia and its impact on the transfusion rate. Further, we could not include iron studies and thus did not clarify the reason underlying the anaemia; however, we confirmed the effect of IV iron treatment. Fourth, the effect of IV iron might have been underestimated because of RBC transfusion. However, the number and amount of transfusion requirements were significantly lower in the FCM group. Therefore, it could overcome the bias associated with transfusion. Lastly, the use of short-acting ESAs in addition to iron treatment in patients with Hb < 13.0 g/dl prior to major orthopaedic surgery is recommended [9]. However, since the use of ESAs for surgical patients in our country is limited, it was not used in our study.

In conclusion, short-term post-operative treatment with high-dose IV FCM alone reduced the requirement for allogeneic RBC transfusion in staggered bilateral TKA patients in this retrospective cohort study. Furthermore, there was a significant increase in the Hb levels at the fifth post-operative week. Despite the prevalence of anaemia being similar during hospitalization, higher rates of patient recovery from anaemia was noticed at discharge after 5 weeks. The study results hence support the peri-operative use of high-dose IV iron in this group of patients.

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H.-S.P. performed the research and wrote the first and final draft of the manuscript. S.-I.B. designed study and performed the research. H.-J.K. and J.K. analysed the data. T.-Y.K. designed study. H.K. and Y.R. revised the manuscript. W.U.K. supervised the conduct of the study. All authors read and revised the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest associated with this study.

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REVIEW ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Current challenges of severe acute respiratory syndrome coronavirus 2 seroprevalence studies among blood donors: A scoping review

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Abstract

Background and Objectives: Blood donors are increasingly being recognized as an informative resource for surveillance. We aimed to review severe acute respiratory syndrome coronavirus 2 seroprevalence studies conducted among blood donors to investigate methodological biases and provide guidance for future research.

Materials and Methods: We conducted a scoping review of peer-reviewed and preprint publications between January 2020 and January 2021. Two reviewers used standardized forms to extract seroprevalence estimates and data on methodology pertaining to population sampling, periodicity, assay characteristics, and antibody kinetics. National data on cumulative incidence and social distancing policies were extracted from publicly available sources and summarized.

Results: Thirty-three studies representing 1,323,307 blood donations from 20 countries worldwide were included (sample sizes ranged from 22 to 953,926 donations). The majority of the studies (79%) reported seroprevalence rates <10% (ranging from 0% to 76% [after adjusting for waning antibodies]). Overall, less than 1 in 5 studies reported standardized seroprevalence rates to reflect the demographics of the general population. Stratification by age and sex were most common (64% of studies), followed by region (48%). A total of 52% of studies reported seroprevalence at a single time point. Overall, 27 unique assay combinations were identified, 55% of studies used a single assay and only 39% adjusted seroprevalence rates for imperfect test characteristics. Among the nationally representative studies, case detection was most underrepresented in Kenya (1:1264).

Conclusion: By the end of 2020, seroprevalence rates were far from reaching herd immunity. In addition to differences in community transmission and diverse public health policies, study designs and methodology were likely contributing factors to seroprevalence heterogeneity.

KEYWORDS
blood donors, COVID-19, immunoassays, SARS-CoV-2, scoping review, seroprevalence

Highlights

- Thirty-three blood donor SARS-CoV-2 seroprevaelnce studies world-wide between January 2020 and January 2021 were identified.
- The pre-vaccine reported seroprevalence was generally less than 10%.
- It is difficult to distinguish true variability in seroprevalence from variability due to study designs and methodology.

INTRODUCTION

As health authorities contend with the unrelenting coronavirus disease 2019 (COVID-19) pandemic, resources continue to be invested in tracking population-level exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Case detection can be used to monitor infection rates but may underestimate prevalence by limited testing capacity; the restricted time period SARS-CoV-2 is detectable by diagnostic tests; and a significant proportion of mild and asymptomatic cases that do not seek testing. In contrast, serological tests that identify SARS-CoV-2-specific antibodies are commonly used for surveillance studies, overcoming the limitations of relying on case detection alone.

Given the unprecedented urgency to evaluate the burden of COVID-19, SARS-CoV-2 seroprevalence studies were mobilized quickly. While in theory, random sampling from the general population (e.g., population-based seroprevalence studies) should yield the most generalizable results, this approach is both time-consuming and expensive. Additionally, time-varying response rate may lead to a complex selection bias. In contrast, populations of blood donors have increasingly been recognized as an informative and cost-effective strategy to monitor epidemics [1]. Blood services have the operational capacity to sample and test large proportions of the healthy population for surveillance purposes [2–4]. The Surveillance Risk Assessment and Policy sub-group of the Transfusion Transmitted Infectious Diseases Working Party (TTIDW) of the International Society of Blood Transfusion (ISBT) recently published that 73% (32/48) of blood operators surveyed worldwide were undertaking or planning to conduct seroprevalence studies to inform public health [5].

Methodological challenges have emerged unique to this pandemic. The validity, interpretability, and ability to pool seroprevalence studies are limited by study designs, sampling strategies, study timing, the variability in assay characteristics, and antibody kinetics. Seroprevalence studies, including those among blood donors, are compiled by on-line dashboards such as SeroTracker (https://serotracker.com) [6], and editorials and perspective articles have been published on limitations of seroprevalence studies in general [1, 7, 8], but to our knowledge there has not been an attempt to systematically bridge these two elements together to provide epidemiological guidance for future research. In this scoping review, we summarized studies conducted specifically among blood donors to characterize SARS-CoV-2 seroprevalence studies, evaluate how well subpopulations and geographic areas have been represented, and determine the diversity of methodology used to address limitations associated with these studies.

MATERIALS AND METHODS

This scoping review was conducted and supplemented with publicly available data on cumulative COVID-19 cases and social distancing policies nationally. Additionally, members of the ISBT TTIDWP (representing blood collectors from Canada, United States, Denmark, the Netherlands, and Australia) provided expert opinions. Findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews [9].

Two reviewers (S.S. and S.U.) independently searched articles using the search engines PubMed and medRxiv for SARS-CoV-2 seroprevalence studies in English among blood donor populations from 1 January 2020 to 19 January 2021. Search terms were [SARS-CoV-2] AND/OR [COVID-19] AND [seroprevalence] AND [donor] OR [blood donor]. A seroprevalence survey was defined as the serological testing of residual blood from blood donations over a restricted time period, to estimate the prevalence of SARS-CoV-2 antibodies in a specified population. Therefore, only studies that reported the sample size, sampling dates, and prevalence estimates (or the number of reactive samples) were included in this review. They excluded studies that used residual blood from convalescent plasma donors or as negative controls to evaluate assay performance. Seroprevalence estimates from the grey literature were not included in this review since methods are not routinely reported.

Articles were screened on titles and abstracts by the same two authors. The full-text assessment and data extraction were performed by one reviewer per article and subsequently checked for accuracy by a second reviewer. Consensus was reached between the authors when discrepancies arose. Data were entered into Microsoft Excel using a standardized form, which included: The full reference, region, data of sample collection, data necessary to calculate unadjusted SARS-CoV-2 seroprevalence (the number of samples tested and reactivity). When available, the adjusted seroprevalence estimate(s) and 95% confidence intervals or a range of estimates were extracted. The authors a priori identified specific challenges of seroprevalence studies (graphically represented as Figure 1):

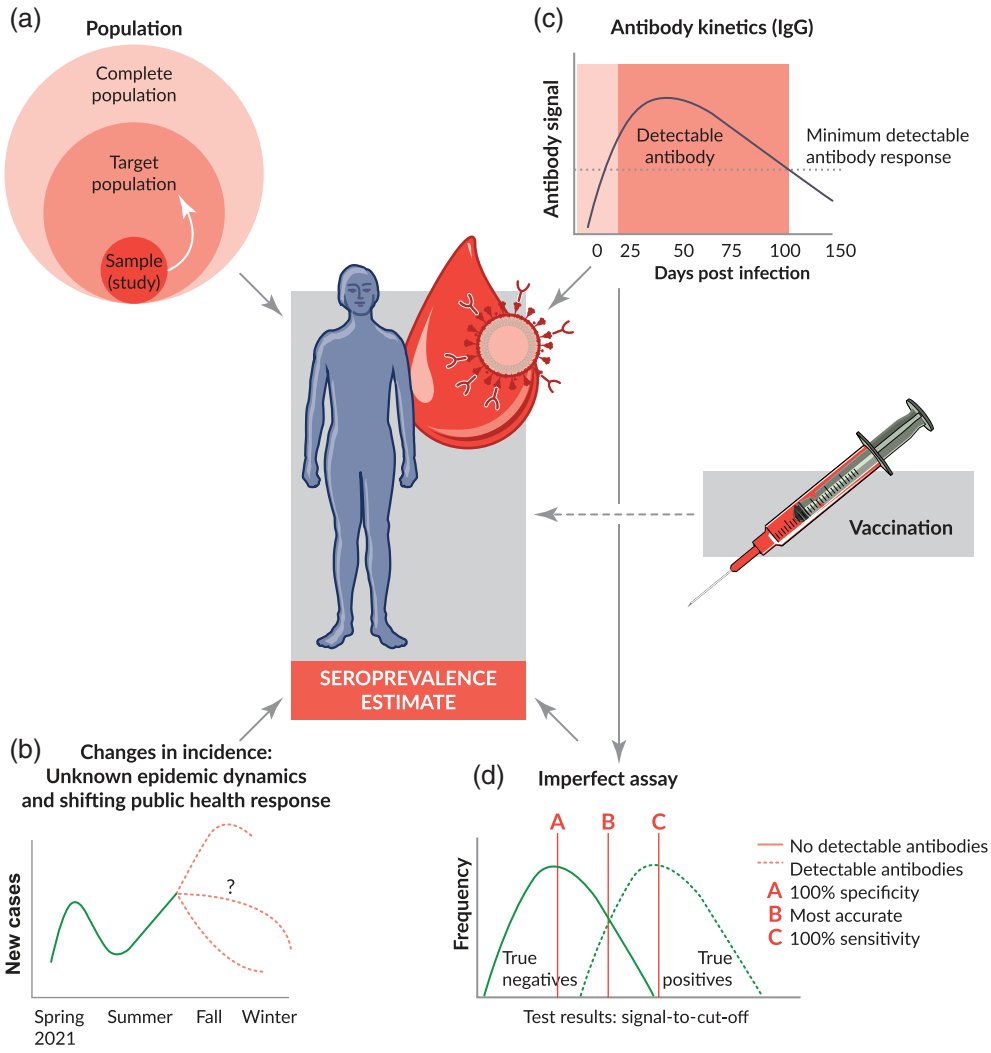

FIGURE 1 Overlapping determinants of estimating population-level seroprevalence. (a) Population: The WHO endorses seroprevalence studies of blood donors because they can represent a convenient sample of a healthy adult population, but care should be taken when generalizing the results beyond the target population. Summarizing prevalence rates may miss significant differences since infection rates are likely differential by geographic regions, socioeconomic status, age and racialized populations within a country. There may also be a potential for selection bias as donors are a self-selected group of individuals. (b) Shifting public policy: Seroprevalence rates can be influenced by changing population-level trends, defined as surges of new cases followed by a downturn (epidemic waves). (c) Antibody kinetics: From the time of infection, on average, it takes 10–28 days to develop specific immunoglobulin G (IgG) antibodies to severe acute respiratory syndrome coronavirus 2. And by approximately 100 days, the level of these antibodies detectable in the blood begins to decrease (wane). If sampling occurs outside this window of detection, people both early and later in their infection will be missed. (d) Accuracy of tests: Assay performance is measured by the proportion of test results that accurately identified those having antibodies 'sensitivity' and not having antibodies 'specificity', at a given threshold (signal-to-cut-off ratio). Vaccines: Distinguishing between natural infections and vaccine-induced immunity is an additional challenge when estimating seroprevalence rates

1. Population sampling: What was the scope of the study, national or regional? Were blood donor populations characterized? Were seroprevalence rates stratified by age, sex, socioeconomic status (SES) or by specific regions? Was the seroprevalence estimate standardized to population-level characteristics?
2. Dynamic epidemic: What was the type of study design (single or serial cross-sectional) to evaluate temporal trends?
3. Assay characteristics: Was the assay reported? Was the assay commercial or an in-house assay? Were the seroprevalence estimates adjusted for imperfect assay characteristics? And how?
4. Antibody kinetics: Were estimates adjusted for waning antibody titres?

We extracted cumulative case counts from the World Health Organization Coronavirus Disease (COVID-19 Dashboard; https://covid19.who.int/). We estimated the ratio of reported to expected infections. Since seroprevalence data reflects infections that occurred prior to the date of measurement, case detection was extracted 2 weeks from the end of the donation collection/study period for each study [10].

Public health policies were summarized using the Government Stringency Index as the average of the daily index 2 weeks before the beginning and end of the study period [11]. This composite measure was based on nine response indicators including school closures, workplace closures and travel bans, rescaled to a value from 0 to 100 (100 = strictest). If policies varied at the subnational level, the index is shown as the response level of the strictest subregion.

We evaluated the correlation between seroprevalence and cumulative incidence by linear regression.

RESULTS

From 157 articles (32 peer-reviewed and 125 preprints), 33 studies (22 peer-reviewed and 11 preprints) were included in this review (Figure 2). The 33 studies represented 20 countries, the majority from Europe ($n = 8$) followed by North America ($n = 4$), Asia ($n = 4$), Africa ($n = 2$), South America ($n = 1$) and Australia ($n = 1$) (Figure 3). Seroprevalence studies from low- and middle-income countries were limited.

Table 1 characterizes the data extracted from each of the 33 studies included in this review [12–44]. Of the published studies, the vast majority (91%; 20/22) were published in clinical or public health journals, two were specifically published in transfusion medicine journals. The median sample size was 1996 donations but ranged from as many as 953,926 in the United States [28] to as few as 22 in Libya [41]. The time frames for studies ranged from beginning 1 January 2020 to ending 11 December 2020. Nine (27%) studies began between January and 29 February 2020; one study began in September 2020.

Seroprevalence rates ranging from as low as 0% in Saudi Arabia to as high as 34%–37% in Pakistan (Figure 4). A study from Brazil reported unadjusted seroprevalence rates of 25.8% but after adjusting for waning antibodies, seroprevalence rates were as high as 76% [43]. Among studies that were nationally representative or had regional cumulative incidence data publicly available we found case detection was most underreported in Kenya (ratio of reported cases to expected 0.001 = 1:1264) (Table 1). We found no linear association between seroprevalence rates and cumulative incidence.

There was significant heterogeneity by methodological factors that influence seroprevalence estimates (Figure 5). Characterization of the blood donor populations varied; five studies did not report the age of donors sampled [16, 23, 38, 39, 41]. The scope of studies varied; the majority (76%; 25/33) provided regional estimates within countries. Approximately half of the studies (52%; 17/33) provided a single seroprevalence estimate [13–17, 19, 21, 26, 29, 31–33, 35, 38, 39, 41, 44]. Stratification by age and sex were most common (64%; 21/33), followed by region (48%; 16/33). While age stratification was common, there was no standardized age grouping. Very few studies stratified by a broad definition of SES (15%; 5/33) (definition of SES varied: i.e., income, occupation, or neighbourhood-level social and material deprivation) [24, 25, 29, 34, 42]. Overall, less than 1 in 5 studies adjusted seroprevalence rates to reflect the demographics of the general population.

There were almost as many unique assay combinations ($n = 27$) as studies included in the review (Table S1). A single assay was used most often (55%; 18/33), 15 studies used two or more assays to determine seroprevalence estimates. Of the 18 studies that used a single assay, we found 15 were unique. Of the 15 studies that used two or more assays, 12 different assay combinations were used. At least one in-house assay was used by a third of studies. Overall, 39% of studies adjusted seroprevalence estimates by imperfect test characteristics; (38%; 5/13) of the studies used the Rogan–Gladen [12–14, 24, 43] equation to adjust for imperfect sensitivity and specificity and (54%; 7/13) used Bayesian methods [18, 22, 23, 31, 32, 40, 44] and one study did not state the method for adjustment [42]. Only two studies (Sweden and Brazil), adjusted their seroprevalence estimates for waning antibodies [23, 43].

DISCUSSION

In this scoping review, we summarized results from 33 SARS-CoV-2 seroprevalence studies among blood donors, representing 1,323,307 donations worldwide. As of 11 December 2020, 79% of studies reported seroprevalence rates <10%; thresholds far from reaching herd immunity. In addition to variations in community transmission and the diverse public health response to the COVID-19 pandemic, we found study designs and methodology were contributing factors to seroprevalence heterogeneity. As health officials turn to seroprevalence studies to bridge the gap left by diagnostic testing, we provide epidemiological guidance to improve seroprevalence reporting specifically among blood donor populations.

Blood donors are a selected population of a target population (Figure 1). To evaluate the generalizability of seroprevalence studies, demographic characteristics of both the study and target populations are necessary. We found, only one in five studies adjusted their donor population to reflect the demographics of the general population [45–47]; a straightforward adjustment that can be accommodated by most statistical software. Furthermore, it is important to note there can be significant variations of an individual's willingness to donate blood, recruitment strategies and eligibility criteria across blood operators. For example, according to the WHO, donating blood is more common in high-income compared to lower-income countries [48]. Additionally, many low- and middle-income countries rely on family replacement donors to donate on behalf of patients rather than altruistic volunteers. In 2016, it was estimated that nearly 30% of blood donations worldwide, occurred in Europe, which only accounts for 10% of the world's population. As a larger and more representative proportion of the general population donates blood, the generalizability of the results from blood donor studies improves. Indeed, a recent study comparing seroprevalence estimates from European blood donors to household surveys targeting the general population found seroprevalence rates to be very similar [49].

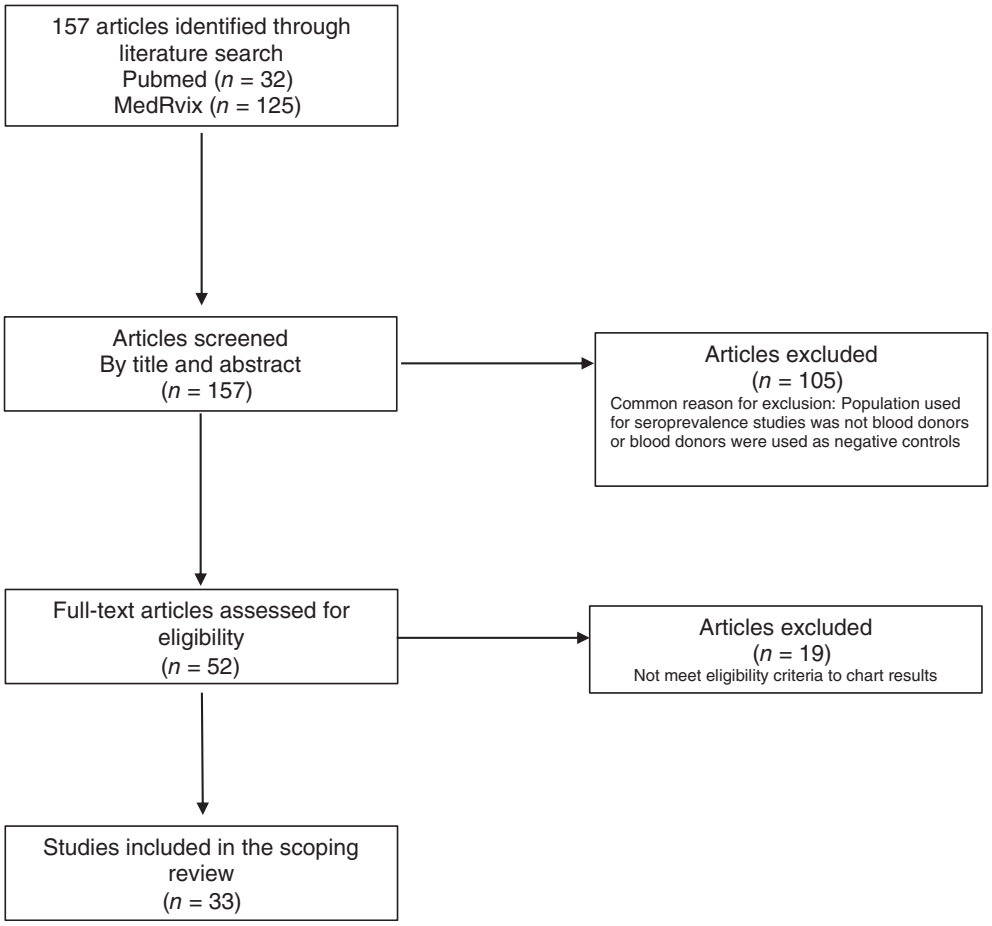

FIGURE 2 Inclusion of studies in review

FIGURE 3 Worldwide coverage of seroprevalence studies among blood donor populations. Shaded countries are represented in this review

TABLE 1 Summary of studies included in this review

First author [ref]	Type of publication	Location	National versus regional	Sample size	Date of sample	Type of study	Age	Seroprevalence estimate % (95% CI)	Comparison of reported and seroprevalence-derived expected number of infections						
									Population	Policy index[a]	Infections 14 days prior to end of the study (cumulative cases)	Seroprevalence-derived expected number of infections	Seroprevalence-derived expected number of infections (lower range)	Seroprevalence-derived expected number of infections (upper range)	Ratio of reported infections to seroprevalence-derived number of infections
Europe															
Erikstrup [12]	Clinical	Denmark	National	20,640	6 April to 3 May 2020	Serial CS	17–69	1.90 (0.80, 2.30)	5,792,202	71.45	7384	110,052	46,338	133,221	0.067
Iversen [13]	Clinical	Denmark	Regional	4672	15 April and 23 April 2020	Single CS	18–64	3.04 (2.58, 3.57)	5,792,202	NA	5819[b]	176,083	149,439	206,782	0.033[b]
Pedersen [14]	Clinical	Denmark	National	1201	2 June to 19 June 2020	Single CS	70+	1.40 (0.30, 2.50)	5,792,202	59.37	11,771	81,091	17,377	144,805	0.145
Gallian [15]	Clinical	France	Regional	998	March to April 2020	Single CS	19–64	2.70	65,273,511	NA	102,534[b]	1,762,385	0	0	0.058[b]
Fischer [16]	Public health	Germany	Regional	3186	9 March to 3 June 2020	Single CS	NA	0.91 (0.58, 1.24)	83,783,942	NA	175,210[b]	762,434	485,947	1,038,921	0.230[b]
Percivalle [17]	Public health	Italy	Regional	390	18 March to 6 April 2020	Single CS	19–70	23.00	60,461,826	NA	53,578[b]	13,906,220	0	0	0.004[b]
Valenti [18]	medRxiv	Italy	Regional	789	24 February to 8 April 2020	Serial CS	18–70	5.20 (2.40, 9.00)	60,461,826	NA	74,386[b]	3,144,015	1,451,084	5,441,564	0.024[b]
Fiore [19]	Clinical	Italy	Regional	904	1 May to 31 May 2020	Single CS	18–65	0.99	60,461,826	NA	225,886[b]	598,572	0	0	0.377[b]
Slot [20]	Clinical	The Netherlands	National	7361	1 April to 20 May 2020	Serial CS	18–72	2.70 (1.60, 5.40)	17,134,872	77.65	40,841	462,642	274,158	925,283	0.088
Olariu [21]	Clinical	Romania	Regional	2115	8 July to 1 September 2020	Single CS	18–65	1.51 (1.07, 2.13)	19,237,691	NA	71,194[b]	2,904,891	205,843	409,763	0.025[b]
Thompson [22]	Public health	Scotland	National	3500	17 March to 18 May 2020	Serial CS	Median 47	3.00 (0.00, 14.00)	5,460,000	60.65	12,226	163,800	0	764,400	0.075
Dopico [23]	medRxiv	Sweden	Regional	2100	14 March to 11 December 2020	Serial CS	NA	14.80 (12.20, 18.00)	10,099,265	NA	231,554[b]	1,494,691	1,232,110	1,817,868	0.155[b]
North America															
Saeed [24]	Transfusion	Canada[c]	National	74,642	9 May to 21 July 2020	Serial CS	18–65+	0.70 (0.63, 0.76)	29,247,654	70.82	50,169	204,734	184,260	222,282	0.245
Martinez-Acuña [25]	medRxiv	Mexico	Regional	1968	1 January to 30 August 2020	Serial CS	18–65	3.99	128,932,753	NA	505,751[b]	5,144,417	0	0	0.098[b]
Villarreal [26]	medRxiv	Panama	Regional	255	30 April to 7 July 2020	Single CS	20–79	11.72 (8.30, 16.30)	4,314,767	NA	24,274[b]	505,691	358,126	703,307	0.048[b]
Basavaraju [27]	Clinical	United States	Regional	5477	30 December 2019 to 17 January 2020	Serial CS	16–95	0.86	82,375,418	NA	0	708,429	0	0	0

(Continues)

TABLE 1 (Continued)

First author [ref]	Type of publication	Location	National versus regional	Sample size	Date of sample	Type of study	Age	Seroprevalence estimate % (95% CI)	Comparison of reported and seroprevalence-derived expected number of infections						
									Population	Policy index[a]	Infections 14 days prior to end of the study (cumulative cases)	Seroprevalence-derived expected number of infections	Seroprevalence-derived expected number of infections (lower range)	Seroprevalence-derived expected number of infections (upper range)	Ratio of reported infections to seroprevalence-derived number of infections
Dodd [28]	Clinical	United States	National	953,926	15 June to 23 August 2020	Serial CS	16–55+	1.82 (1.79, 1.84)	331,002,651	69.11	4,999,815	6,024,248	5,924,947	6,090,449	0.830
Vassallo [29]	medRxiv	United States	National	189,656	1 June to 31 July 2020	Single CS	16–85+	1.55	331,002,651	70.71	3,405,494	5,130,541	0	0	0.664
Kamath [30]	medRxiv	United States-New York	Regional	1559	March to July 2020	Serial CS	17–80	11.60 (6.00, 21.20)	20,201,249	NA	428,477	2,343,345	1,212,075	4,282,665	0.183
Jin [31]	medRxiv	United States-New York City	Regional	1000	16 June to 15 July 2020	Single CS	16–78	10.00 (9.10, 14.27)	8,230,290	NA	212,072	823,029	748,956	1,174,462	0.258
Nesbitt [32]	medRxiv	United States-Rhode Island	Regional	1996	27 April to 11 May 2020	Single CS	Median 56	0.60 (0.20, 1.10)	1,097,379	NA	7997	6584	2195	12,071	1215
Ng [33]	Clinical	United States-San Francisco	Regional	1000	March 2020	Single CS	19–89	0.40 (0.01, 0.79)	883,255	NA	51	3533	88	6978	0.014
Asia															
Chang [34]	medRxiv	China-Wuhan, Shenzhen, Shijiazhuang	Regional	17,794	January to April 2020	Serial CS	18+	2.29 (2.08, 2.52)	1,439,323,776	NA	83,071[b]	32,960,514	29,937,935	36,270,959	0.003[b]
Xu [35]	Clinical	China-Guangzhou	Regional	2199	23 March to 2 April 2020	Single CS	18–59	0.09	1,439,323,776	NA	81,178[b]	1,295,391	0	0	0.063[b]
Sughayer [36]	medRxiv	Jordan	Regional	746	January to June 2020	Serial CS	18–63	0.00	10,203,134	NA	921[b]	0	0	0	0[b]
Younas [37]	Transfusion	Pakistan	Regional	380	June to July 2020	Serial CS	Mean 31	34.00	220,892,340	NA	257,914[b]	75,103,396	0	0	0.003[b]
Rezwan [38]	Clinical	Pakistan	Regional	505	1 September to 14 September 2020	Single CS	NA	37.80	220,892,340	NA	295,849[b]	83,497,305	0	0	0.004[b]
Alandijany [39]	Public health	Saudi Arabia	Regional	956	1 January to 31 May 2020	Single CS	NA	0.00	34,813,871	NA	59,854[b]	0	0	0	0[b]
Africa															
Uyoga [40]	Clinical	Kenya	National	3098	30 April to 16 June 2020	Serial CS	15–64	5.20 (3.70, 7.10)	53,771,296	88.89	2216	2,796,107	1,989,538	3,817,762	0.001
Kammon [41]	medRxiv	Libya	Regional	22	February to May 2020	Single CS	NA	0.00	6,871,292	NA	64[b]	0	0	0	0[b]
South America															

(Continues)

TABLE 1 (Continued)

First author [ref]	Type of publication	Location	National versus regional	Sample size	Date of sample	Type of study	Age	Seroprevalence estimate % (95% CI)	Comparison of reported and seroprevalence-derived expected number of infections					
									Population	Policy index[a]	Infections 14 days prior to end of the study (cumulative cases)	Seroprevalence-derived expected number of infections	Seroprevalence-derived expected number of infections (lower range)	Seroprevalence-derived expected number of infections (upper range)	Ratio of reported infections to seroprevalence-derived number of infections
Filho [42]	Public health	Brazil	Regional	2857	14 April to 27 April: three time points	Serial CS	18–69	3.30 (2.60, 4.10)	212,559,417	NA	19,638[b]	7,014,461	5,526,545	8,714,936	0.003[b]
Buss [43]	Clinical	Brazil	Regional	12,867	February to October 2020	Serial CS	16–17	25.80 (20.9, 31.3)	212,559,417	NA	5,103,408[b]	54,840,330	44,424,918	66,531,098	0.093[b]
Oceania															
Gidding [44]	Clinical	Australia	Regional	1548	20 April to 2 June 2020	Single CS	20–69	0.29 (0.04, 0.75)	25,499,884	NA	7068[b]	73,950	10,200	191,249	0.096[b]

Abbreviations: CI, confidence interval; CS, cross-sectional.

[a]Policy stringency only available for nationally representative studies.

[b]Seroprevalence rates are regional, however infection rates are based on national summaries, ratio of expected to reported infections are an extrapolation.

[c]The study does not include the province of Quebec.

Differential characteristics between study and target populations not only affect the generalizability of the estimates but a selection bias known as the 'healthy donor effect' when evaluating predictors of seroprevalence that can bias the results in either direction. Donor's self-selection and eligibility criteria skew blood donors to be younger and healthier than the general population [50]. If unhealthy donors self-defer or are deferred at the time of collection, this will leave a group of healthier and health-conscious donors. It is possible this group of people may be more adherent to non-pharmaceutical interventions making them less likely to have been exposed to SARS-CoV-2. In contrast, it is possible some blood donors may have been incentivized to donate by disclosure of SARS-CoV-2 antibody results. This may distort the sample towards people who may have reason to believe they were previously infected and are seeking confirmation. This was more likely when testing capacity was limited and is unlikely to pose a significant incentive to donate as immunoassays are more readily available. Addressing selection bias is more complicated and requires additional information that may not be readily available to researchers, such as the data on variables influencing selection and the outcome among non-donors. When these data are available, methods such as inverse probability of selection weighting can correct for this bias [51].

There is strong evidence to support differential SARS-CoV-2 infection rates by calendar time, geographic region, age groups, and SES [52, 53]. Therefore, providing a single seroprevalence estimate may miss significant disparities. While most studies did provide stratified rates by age, there was no standardized age grouping making comparison between regions/countries difficult. Furthermore, very few studies stratified by a broad definition of SES and the definition for SES varied considerably. Stratifying seroprevalence estimates by socioeconomic demographics can provide public health officials critical data to implement targeted interventions. Additionally, the granular data can be used to produce more precise estimations of case identification fractions and infection fatality rates by subgroups [54, 55]. Careful consideration should be made when designing studies with sufficient sample sizes to accurately estimate these sub-group analyses. Furthermore, we recommend seroprevalence studies to state their target population and the cumulative incidence reported by case detection to provide readers insight on the magnitude of testing capacity.

The accuracy of the assay, antibody kinetics and population-level epidemic changes are overlapping challenges that affect the validity of seroprevalence estimate (Figure 1). No assay is 100% sensitive and specific yet only a third of the studies we reviewed adjusted the seroprevalence estimates for this imperfection. When the sensitivity and specificity are known, seroprevalence estimates can be adjusted using either the Rogen-Gladen equation or using Bayesian methods [56, 57]. Orthogonal testing may also increase accuracy of estimates when multiple assays are available. We found the majority of the studies used a single assay to identify seropositivity. In the absence of a gold standard multiple methods can be applied to correct for this measurement error ranging from deterministic predefined rules to more advanced latent class models [58, 59].

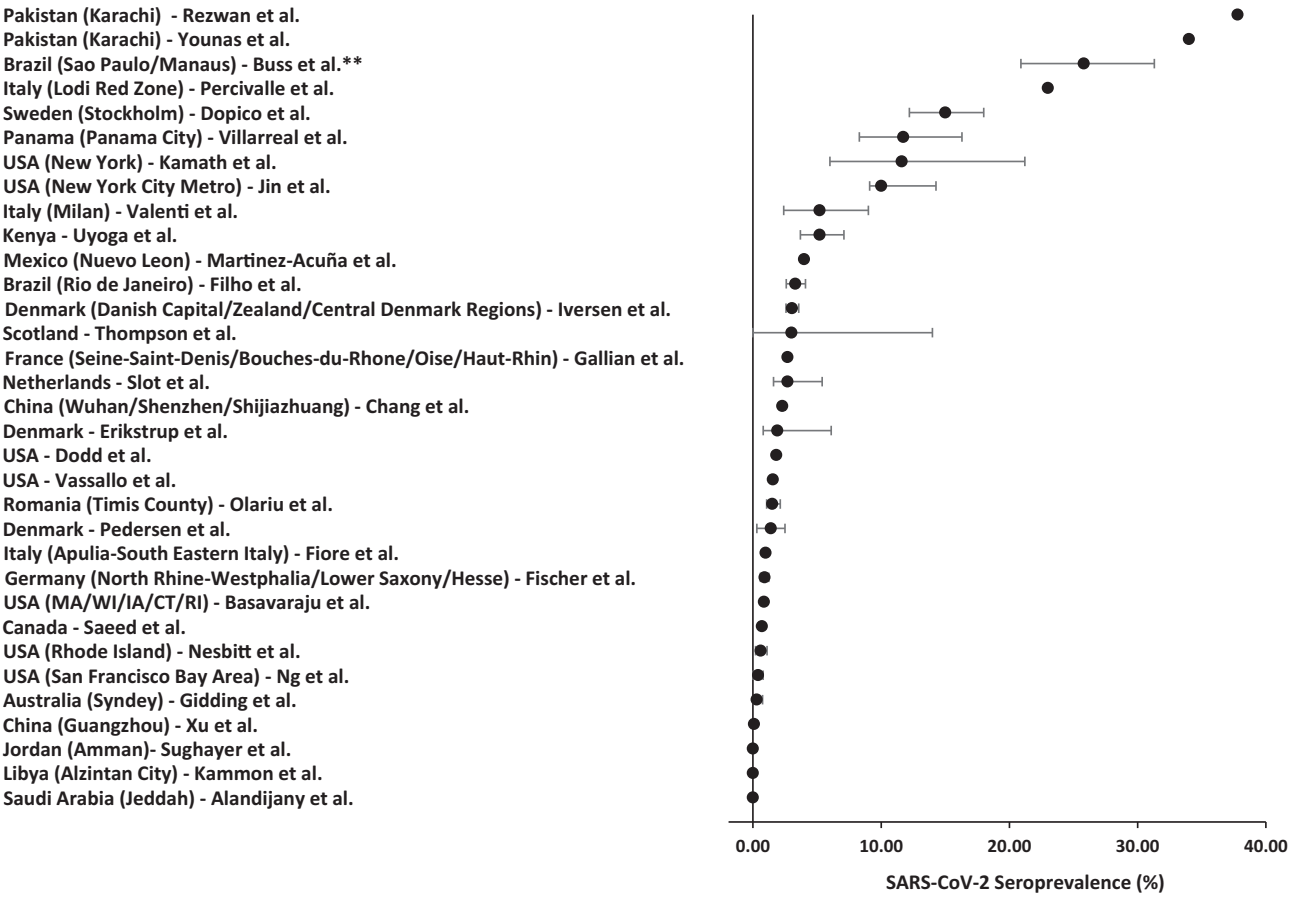

FIGURE 4 Forest plot of seroprevalence estimates. Seroprevalence estimates from each study is ranked from highest to lowest. Regional estimates within countries are specified in brackets. Bars around the estimates represent 95% confidence intervals (when available) or estimate ranges (Scotland). **Seroprevalence unadjusted for waning antibodies (76% if adjusted)

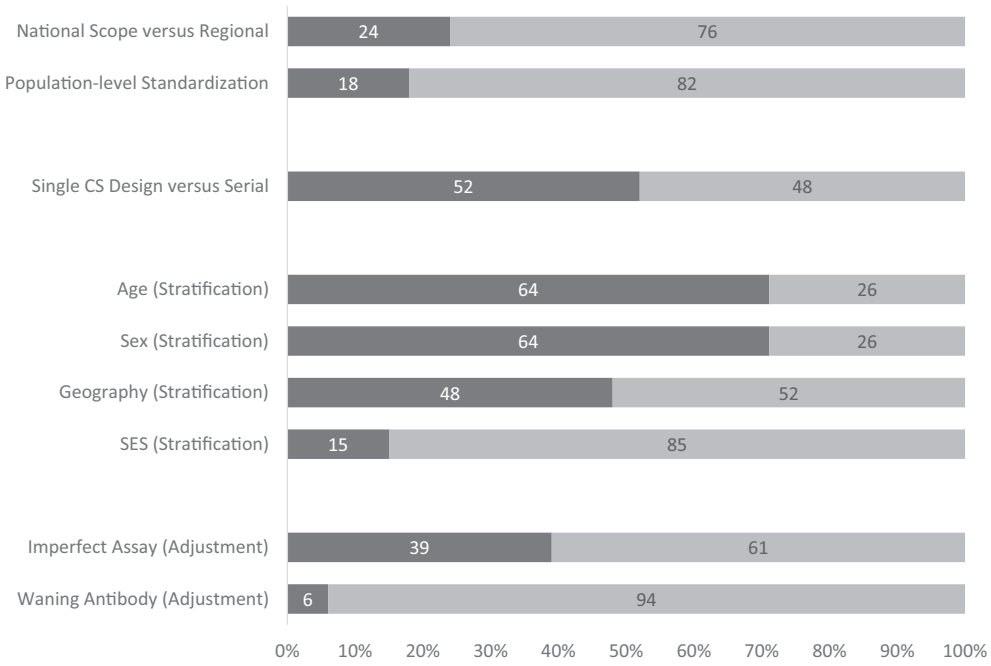

FIGURE 5 Summary of analytical considerations. CS, cross-sectional; SES, socioeconomic status

Further consideration when comparing and interpreting seroprevalence studies using different assays include different antibody isotypes and that target various SARS-CoV-2 proteins. For example, the type of antibody isotypes (IgA, IgM or IgG) reflects various stages of an infection. IgG is detectable 10–21 days post infection and remains detectable longer than IgA and IgM. Even though SARS-CoV-2 is likely not transmissible by transfusion [60, 61], it was common for blood operators to defer donations for 2–4 weeks following resolution of symptoms (after confirmed diagnosis of COVID-19) or were exposed to SARS-CoV-2 through travel or contact [62]. Given this deferral period, the early period of undetectable IgG levels is less likely to be an issue among blood donors, although some early-stage asymptomatic donors may not be detected. Assays vary by detecting specific SARS-CoV-2 proteins (surface or spike glycoprotein, spike protein receptor binding domain and nucleocapsid) and currently there is no consensus on which antigen is most frequently expressed and for how long. While underlying disease prevalence does not affect the sensitivity and specificity of serological assays, the positive and negative predictive values of assays are affected. In this review, we found the majority of studies included were low-prevalence settings (<10%) meaning minor fluctuations from perfect specificity would cause inflation of false positive results affecting seroprevalence estimates.

Typically, seroprevalence studies are cross-sectional and occur either at a single time point or serially. Based on consultation of ISBT members conducting ongoing seroprevalence surveys, there was no consensus on how often seroprevalence studies should be conducted. However, given the dynamic nature of the pandemic multiple estimates over time would provide more informative results for public health authorities. Single cross-sectional studies are appropriate for chronic infections when the antibodies remain present for extended periods of time. However, there is mounting evidence that by approximately 100 days post infection, anti-SARS-CoV-2 IgG antibodies begin to wane and can fall below levels of detectability [43, 63]. Therefore, depending on the timing of the study, seroprevalence estimates will include a varying proportion of 'recent' infections which will mirror epidemiology curves by case detection and 'past' infections which may or may not be detectable given a specific threshold. Blood donor seroprevalence studies are used as a proxy of the general population who may not have known they were infected with SARS-CoV-2. Without a known date of infection waning, antibody signals make it difficult to quantify what proportion had previous infections that are no longer detectable. While the studies that focused on the first wave of the pandemic are likely to capture most infections (past and recent), it will become more difficult for future studies to capture cumulative seroprevalence without serial designs adjusting for waning antibodies. Various methods are being explored to adjust for waning antibody signals including increasing sensitivity by lowering sample to cut-off ratio thresholds and by using population-level incidence and mortality data to model approximate infection dates [43, 64]. Given the goal of seroprevalence studies is to determine population-level immunity, more research is needed to identify the correlates of immunity through evaluating waning antibody signals, antibody titres versus neutralizing capacity and the role of cell-mediated immunity [65]. This will require pairing modelling approaches with confirmatory neutralization assays or a surrogate immunoassay, once confirmed as a correlate [66]. Additionally, longitudinal studies will be required to evaluate the rate of antibody and signal decline. One advantage of conducting seroprevalence studies within blood donor populations is donors tend to donate multiple times a year therefore creating a pseudo-longitudinal cohort that can be used to monitor antibody kinetics.

This review has limitations. It is possible seroprevalence estimates from blood donors were conducted but have yet to be published or possibly never intended to be published as research articles instead reported directly to public health authorities. For example, in Denmark, the Netherlands and England weekly seroprevalence reports were generated from blood operators to inform COVID-19 modelling. Therefore, it is possible our sample is biased towards blood operators and countries who had sufficient resources to prepare findings in the form of a manuscript. We report the stringency policy index to provide readers with context on the extent non-pharmaceutical interventions were applicable for each country. However, this index does not take into consideration the heterogeneity within each country therefore associations should be made cautiously.

Overall, the results from these studies indicate that worldwide seroprevalence rates vary considerably but by the end of 2020, the majority of the countries were far from reaching thresholds to achieve herd immunity. Despite all studies being conducted in blood donors, caution should be exercised when comparing seroprevalence estimates given the significant variability in study designs and methodology as we highlight in this article. Public health authorities mobilized resources quickly and new partnerships were accelerated such as those with blood operators. Despite the limitations we highlight, individual studies have been extremely informative in informing public health authorities and blood donors will continue to play a vital role in facilitating seroprevalence studies to assess and monitor the burden of COVID-19.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

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LETTER TO THE EDITOR

Vox Sanguinis ISBT International Society of Blood Transfusion

Changes in Parvovirus B19 positivity rates in plasma units for fractionation: An unexpected effect of non-pharmaceutical interventions against COVID-19?

Parvovirus B19 (B19) is a small non-enveloped DNA virus, discovered in 1975 by Yvonne Cossart in the blood of a healthy blood donor. Although B19 infection is usually mild in children and adults, some subjects can develop severe arthropathy and transient aplastic crisis that, in immunodeficient patients, can evolve to persistent red cell aplasia requiring transfusion. Respiratory droplets spread B19, and it is highly infectious [1]. B19 DNA copy-number is often higher than 10^{10} copies/ml, and transmission through blood components and plasma-derived medicinal products has also been documented [2]. The European Pharmacopoeia stipulates that B19 concentration in manufacturing plasma pools should not exceed a concentration of 10^4 IU/ml [3].

In our Regional Blood Bank in Catalonia (Spain), plasma units obtained from whole blood donations and plasma apheresis are sent to the fractionation industry, where units are tested for B19 DNA. B19 infections follow a seasonal pattern in plasma donors, most positive plasma units corresponding to donations obtained between March and July [1]. From 2014 to 2019, we have been informed of 256 plasma units positive for B19 (Figure 1). However, between January 2020 and July 2021, the plasma fractionator has reported only three plasma units positive for B19, from three whole blood donors, one male and two females that donated on 18 January, and 17 and 28 February 2020. In the following 16 months, no more B19 infections have been reported among the 314,898 plasma units sent for fractionation. There are significant differences when comparing B19 yearly positivity rates between 2014–2019 and 2020–2021 (Figure 1). The plasma fractionator confirms that there have not been any changes in the B19 screening policy.

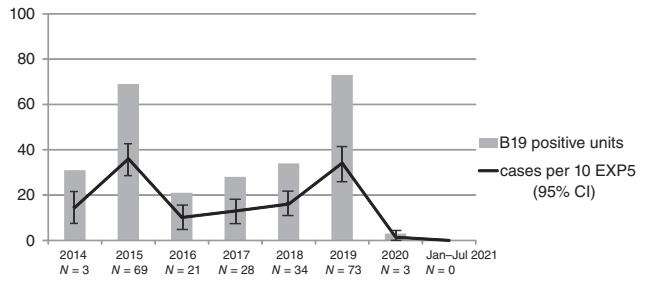

FIGURE 1 Annual trends of B19 positivity rates in plasma units. Bars represent the number of B19 positive units, and the line represents B19 positive units per 100,000 plasma units sent for fractionation. 95% confidence intervals (CIs) of B19 positivity per 100,000 plasma units are: 9.91–20.71 in 2014, 28.06–45.64 in 2015, 6.27–15.48 in 2016, 8.66–18.78 in 2017, 11.13–22.46 in 2018, 24.79–42.97 in 2019, 0.29–4.05 in 2020 and 0.00–0.00 in 2021 (Clopper–Pearson 95% CI)

On 11 March 2020, the World Health Organization declared COVID-19 a pandemic, and a few days later, the lockdown was implemented in Spain until the end of May 2020. Non-pharmaceutical interventions (NPI), such as social distance and mandatory facemask outdoors and indoors have been maintained until very recently. Facemask wearing is still mandatory indoors of public buildings, including schools, public transportation and outdoors when physical distance is not possible. Although plasma donors with low viral load might have been missed by B19 screening, the continuous absence of high viral load infections in plasma donors for more than one year supports an association to the use of NPI. In Europe, seasonal influenza activity in 2020 was very low, also probably due to the extended use of NPI [4].

In conclusion, we describe here an unexpected but not surprising effect of strict and sustained NPI in decreasing B19 infection among plasma donors in Catalonia. B19 is unusual inasmuch as it is transmitted both by droplets and by transfusion, therefore, this finding may reinforce the usefulness of NPI if a future pandemic agent emerges.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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INTERNATIONAL FORUM

Vox Sanguinis ISBT International Society of Blood Transfusion

International Forum on Home-Based Blood Transfusion: Responses

Briony Shaw | Erica Wood | Zoe McQuilten | Jeannie Callum | Iñigo Romon | Pedro Sanroma | Dora Garcia | Philip Crispin | Lilian Castilho | Jose Mauro Kutner | Ana Paula Hitomi Yokoyama | Amalia Bravo | Emmanuel Fernandez Sanchez | Karla Maldonado Silva | Satyam Arora | Nita Radhakrishnan | Seema Dua | Alyssa Ziman | Agneta Wikman | Norbert Lubenow | Linda Bodecker Zingmark | Vernon Louw | Perry Loebenberg | Davinder Sidhu | Tara Redfern | Susan Nahirniak | Nancy Dunbar

SPAIN

Iñigo Romon, Pedro Sanroma & Dora Garcia

Question 1

Ours is a tertiary university Hospital, with 650 active beds, capable of expanding to 1000. The Hospital at Home Service (HaH) attends up to 72 patients. The Medical and Surgical Day Hospitals receive about 200 patients a day each.

The Hospital maintains busy transplant programmes for solid organ (kidney, lung, liver, pancreas) and haematopoietic stem cells (autologous, related and non-related), acting as reference centre for a population of up to seven million people, depending on the organ. We also act as reference centre for complex cardiovascular surgery and critical cardiac (extracorporeal membrane oxygenation [ECMO], portable devices, etc.) and nephrological (hypersensitised patient, ABO incompatible live donor) conditions.

Patients using our reference services can come from 600 km away.

Cantabria is a small coastal region in Northern Spain with a population a little over half a million people. The region's size is about 5000 km^2. Population is concentrated in urban and coastal areas although remote mountain sites also exist.

The Regional Health Service comprises a network of several dozens of community health centres and country practices and four hospitals, three of them small community hospitals and one tertiary centre, ours. We are the main provider of advanced healthcare in the region, and serve as reference centres to other regions for specific conditions, as mentioned above.

The HaH Service attends patient inside a radius of 25 km (or half an hour by car) from the Hospital [1, 2].

Question 2

Yes, we offer home-based transfusions.

Question 3a

Our home transfusion activity is part of integral healthcare for whatever the patient's condition may be.

We transfuse all kind of adult patients, with all clinical conditions [3].

Question 3b

Our service offers all kind of blood products, but we usually transfuse only red cells and platelets.

Question 4a

There are several exclusion criteria:

1. Actively bleeding patients.
2. Patients with acute lung or cardiac failure.

3. Patients with previous severe, unexplained severe transfusion reactions or with unidentified irregular antibodies.

Question 4b

This is a recommendation, not a strict requirement.

Question 4c

The patients' home must comply with basic hygienic and living standards, assessed before being admitted to HaH care. All patients admitted to HaH must have a working telephone line or mobile phone.

A caregiver must be present during the transfusion.

Patients who live alone cannot take part in the programme, as caregivers play a key role in HaH.

Question 4d

Our HaH Service is an acute care hospital service. Home transfusion is an integral part of hospital at home, and will be given to any patients who need them [3].

Question 4e

Patients with red cell antibodies are not excluded from home transfusion. Irregular antibodies are a cause of exclusion, only if they cannot be identified and there's a strong concern that they could be potentially haemolytic.

Question 4f

Vascular access is managed as with other ordinary in-hospital patients. Central venous catheters (CVCs) are placed only as required by the patients' clinical process, but not due to their admittance to HaH. However, patients on active chemotherapy treatment usually have a CVC placed.

Question 5a

All cellular blood products are leukoreduced, as recommended by the Spanish Transfusion Safety Council, a consultive organ of the Spanish Health Ministry. Blood products are supplied by the Regional Blood Centre, which performs leukoreduction before issuing the products to hospitals.

Question 5b

Premedication is not used unless the patient has had more than one transfusion reaction. Patients who need premedication are not excluded from the programme, unless the reaction was severe or life-threatening.

Question 5c

Compatibility testing can be done on the same day the transfusion is prescribed and given. Pretransfusion samples can be taken at the patient's home, and are considered valid for 72 h if the patient is transfused, and up to a week if not. We use electronic crossmatch instead of serologic crossmatch, unless irregular antibodies are present.

Question 5d

HaH staff will bring the blood order and the pretransfusion samples to the blood bank.

When the compatibility tests are ready (the information can be seen on the patients' electronic record), the HaH staff (usually a nurse) will collect the blood components at the blood bank and carry them to the patient's home.

The home care team will bring the required containers to the patients' home so that the blood bags and related equipment are correctly disposed of. There is a predefined home transfusion kit with the needed materials that is deployed at the patients' homes when transfusion is needed. Waste from transfusion (or other clinical waste) are usually taken home by the nursing staff at the end of their round, or kept at the patient's home if needed (for example, during weekends).

Question 5e

The bags or coffers used to carry blood products to the patients' homes are validated by the blood bank before being put into use. They should maintain an adequate temperature for at least an hour.

Question 6a

HaH is carried out by a team of specialists in internal medicine, geriatrics or family medicine. This is also applied to Palliative Care Service.

Before admitting a patient to be hospitalised at home, they analyse the case with the patient's hospital physician.

Home transfusion is supervised by the blood bank haematologist, and is discussed before the patient is treated at home.

Question 6b

The patient's physician in charge will decide whether the patient needs to be transfused during the daily rounds, and also the product needed and the dose to be given.

Due to logistic limitations, that is usually restricted to 1 unit of red cells and 1 platelet unit or 2 red cells each day.

Question 6c

The decision is based on the Hospital transfusion guide. The decision must be based on the patient's status and comorbidities, and coupled with the haemoglobin level. Usually, the haemoglobin level is to be maintained between 7 and 10 g/dL.

Platelets are indicated if their blood count falls below 10,000/μl or below 20,000 if fever, severe hypertension or other pro-haemorrhagic conditions are present.

Question 6d

The decision is based on the Hospital transfusion guide. The decision must be based on the patient's status and comorbidities, and coupled with the haemoglobin level, as mentioned above. For example, patients with ischaemic heart disease are kept with a higher haemoglobin level.

Question 7a

During the red cell transfusion, the nurse is present during the initial 15 min, and returns at the end of her round to assess the patient's living signs and collect waste.

The patient or carer can contact the nurse at a mobile phone number when the transfusion is finishing and always when an adverse event appears.

Question 7b

Yes, a caregiver must be present at the patient's home at all times.

Question 7c

When a patient is to be transfused, the nurse leaves a kit with corticoids, anti-histaminics, diuretics at the patient's home. This is part of the transfusion kit that is left at the patients' homes.

Caregivers are trained to give medication (including intravenous) as part of their role in home hospitalisation, but giving treatment for an adverse reaction should be done only if told by the nurse or physician on call.

Question 7d

All patients treated at home must live within half an hour drive from the hospital.

There is always a physician and a nurse on call.

If needed, the healthcare team on call will co-ordinate the emergency response, call an ambulance, etc.

Question 7e

1. Stop the transfusion and check the patient's status.
2. Call the nurse on call, who will alert the physician on call.
3. Check the patient's identity against the product, to rule out an administrative error.
4. Give drugs according to the symptoms (corticoid for fever, anti-histaminics for allergic and cutaneous reactions, diuretics for transfusion-associated circulatory overload [TACO]).

Question 7f

Yes, the patient or caregivers are given the telephone numbers of the physician and nurse on call.

Question 7g

When an adverse reaction is detected, take the adequate samples (usually a mauve and a brick tube for blood samples) from the patient.

The physician in charge must fill the transfusion reaction report.

The blood bank haematologist will investigate the reaction and act according to the results: start a corrective action, recommend premedication to be used before transfusions.

Once the reaction is researched, the haematologist must record the adverse reaction on the hospital transfusion management system and on the national haemovigilance system web.

The Regional Blood Bank will acknowledge the report and explore the links to the donor, processing, etc.

Question 7h

Never in the 30+ years the programme has been operating.

Question 8a

Our home transfusion programme has been operating since 1987 without cancellations.

Question 8b

Geographical dispersion.

Lack of effective, simple monitoring devices.

Lack of simple and effective electronic record systems, accessible from the patients' homes.

Question 8c

Yes, family nurses can take pretransfusion samples and send them to hospital with the blood transfusion order we give the patient. The physician in charge (usually a haematologist) will review the blood count, interview the patient and order the transfusion needed.

The main problem is the lack of a clear sample circuit, the difficulty of working with paper orders and records.

Sometimes the healthcare centre staff refuse to cooperate because they do not feel competent or understand the circuit.

Question 8d

When patients are attended by the Palliative Care Service, their physicians in charge are responsible of the indication of transfusion, and work with the same protocols and procedures as other patients being transfused at home.

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AUSTRALIA

Philip Crispin

Question 1

Canberra Hospital is a tertiary level teaching hospital with greater than 650 inpatient beds located in a regional capital. There are over 50 outpatient haematology, oncology and day infusion chairs. It has a geographically large surrounding rural catchment, which accounts for around 25% of inpatient bed occupancy.

The hospital is located in a regional capital of around 350,000 and provides tertiary services for a region including over 550,000 people and 9 smaller metropolitan and rural hospitals.

Question 2

No, we do not offer home-based transfusions.

Question 8a

No, we have never had a home transfusion programme.

Question 8b

The primary issue is having staff dedicated to monitoring in the home during transfusions. We have a limited home chemotherapy service, usually for subcutaneous or short intravenous infusions, so there is potential infrastructure. However, the additional staff time to perform double independent checks in the home and remain throughout a transfusion has been considered the major logistical barrier as these staff would be more efficiently used in the clinic setting where several patients can be observed at once and additional staff are available for checking and should the need arise.

The lack of medical staff support has been discussed as a barrier. Although this has been raised, solutions have not been explored in any detail.

Blood transport is another issue that has been considered, primarily over concerns of keeping blood within stable temperatures to allow it to be returned to laboratory stocks should transfusions not proceed. There is a model from our aeroretrieval service, so this would simply require purchasing additional shippers.

Question 8c

Community collections are available. For patients without indwelling venous access devices, these are performed by our pathology department, through community collection centres or domiciliary visits. The pathology collectors are not able to access central venous catheters so these patients either come to the clinic or have haematology and oncology outreach nurses to come to their homes.

Question 8d

The use of transfusions for home-based palliative care is made on a case-by-case basis. Frequently, haematology patients have ongoing care via haematology outpatient clinics with transfusion and specialty malignancy nurse care coordinators monitoring patients and organising

transfusions in haematology outpatient clinics. Similar arrangements apply to some patients with advanced solid organ malignancies.

For patients known only to palliative care, transfusions are organised through the hospice or occasionally through other services, such as emergency departments, if the hospice is not able to accommodate them in a timely way.

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BRAZIL

Lilian Castilho, Jose Mauro Kutner & Ana Paula Hitomi Yokoyama

Question 1

We are a tertiary care hospital located in Brazil. We provide adult and paediatric services, including haematology/oncology, solid organ and bone marrow transplantation, surgical specialties (cardiology, neurosurgery, gastrointestinal, orthopaedic, gynaecologic, ophthalmologic) and maternity care. We have 684 inpatient beds and 28 outpatient beds.

Our service is located in São Paulo, Brazil. We provide services for one smaller community-based hospital, also located in São Paulo.

Question 2

No, we do not offer home-based transfusions.

Question 8a

No, we never had a home transfusion programme.

Question 8b

The logistical barriers to implementation of a home transfusion programme are:

1. Limited staff available, since in Brazil it is mandatory that at least one physician [1] and one nurse must be available full time;
2. High cost;
3. Patient safety [2], since we would have limited access to hospital or urgent care facility for management of severe adverse reactions. Traffic issues in the city we are located are to be considered in case of life-threatening transfusion reactions.

Question 8c

Yes, we are able to collect samples for pretransfusion testing in the community when a routine transfusion is scheduled.

Question 8d

We do not perform home transfusions. However, in our institution, transfusions are considered as part of end-of-life for inpatient palliative care. Decisions for transfusion are made on a case-by-case basis, considering life expectancy, especially if presumed survival exceeds 1 month; and benefits on fatigue and dyspnoea relief.

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MEXICO

Amalia Bravo, Emmanuel Fernandez Sanchez & Karla Maldonado Silva

Question 1

Our evaluation was for two hospitals in the Mexico City with attention to haematology-oncology patients one for adults and other for children.

1. Instituto Nacional de Cancerología (National Institute of Oncology) is a national reference tertiary hospital that offers 24 postgraduate training programmes having around 150 new national and international subspecialists per year. It has 120 inpatient beds and around 30 outpatient beds, attends more than 200,000 consultations per year and hospitalises more than 7000 patients per year [1, 2].
2. Instituto Nacional de Pediatría (National Institute of Paediatrics) is a national reference tertiary teaching hospital that has attending patients between 0 and 18 years; about 40% of them have onco-haematology pathologies. It has 251 inpatient beds and 30 outpatient beds, attends 183,563 ambulatory patients and had 6039 hospitalised patients in 2019 [3].

The Instituto Nacional de Cancerología and Instituto Nacional de Pediatría are reference hospitals for haemato-oncologic patients in Mexico City, and receive patient from all around the country, mainly within the central region.

Question 2

No, we do not offer home-based transfusions.

Question 8a

No, both hospitals have never had a home transfusion programme.

Question 8b

1. Some patients do not live in Mexico City and live in cities that may be 3–5 h away, so the programme must involve regional hospitals from other cities, within Mexico City and its metropolitan area, there are places that may be 2 or 3 h away.
2. The shortage of personnel could be a barrier because to reach a broad number of patients, a lot of personnel would be necessary.
3. Official Mexican Standard [4] in Mexico does not recommend home transfusion only in emergency situations or any other cause that prevents the transfer of the patients to the health care facility, the blood bank or the transfusion service.

Question 8c

No, we are not able to collect pretransfusion samples in the community. I reckon that the obstacles for doing so would be the same as for implementing a home transfusion programme.

Question 8d

Transfusion is considered in palliative care, but not within a home-based programme. Home palliative visits are short because of the lack of personnel and the accessibility difficulties. Many patients in palliative care are transfused in ambulatory beds in the hospital, at finish return to home.

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INDIA

Satyam Arora, Nita Radhakrishnan & Seema Dua

Question 1

The institute that we work in is a tertiary care teaching paediatric hospital in Uttar Pradesh, in North India. The centre caters to patients from the states of Uttar Pradesh, New Delhi and many other neighbouring states. The institute is a referral centre for children needing super speciality care such as blood diseases, cancers, cardiac surgeries, abdominal and other congenital surgeries as well as neonatal care etc. The inpatient service has around 250 beds and the institute caters to around 1000 paediatric outpatients per month. The area caters geographically to Western Uttar Pradesh, New Delhi, Punjab, Haryana, Uttarakhand and Bihar.
It is located in the city of Noida. It however caters to the entire West UP region and patients from remote areas are referred here for treatment of blood diseases (thalassaemia and haemophilia) and cancer. The network of district hospitals and regional medical colleges are linked to this facility for timely referrals.

Question 2

No, we do not offer home-based transfusions.

Question 8a

We do not provide home transfusion for blood products but we do provide home infusion for clotting factor concentrates in patients with haemophilia and other bleeding disorders. This is being done regularly. The centre caters to >250 patients with haemophilia and allied disorders and many are on prophylaxis regimens. Clotting factor concentrate is

issued to the patient and empty vials are collected upon next visit. We also teach self-infusion to our patients who are above 10 years old.

Question 8b

Major barrier is the absence of regulatory approval for the home transfusion policy. Next would be lack of appropriate parental understanding and education, which may be the biggest barrier. Another barrier is management of any transfusion associate adverse reaction during a home transfusion.

Question 8c

Samples can be collected by the family either directly or through a laboratory, and can be provided to us in the hospital but this policy is not followed as the blood is made available on most of the visits to the hospital.

Question 8d

Yes. Transfusions are a part of end-of-life care. This is currently only provided in hospital or hospice settings and is not offered at home.

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UNITED STATES

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Question 1

UCLA Health comprises four hospitals and over 200 clinics. UCLA Health hospitals (Ronald Reagan UCLA Medical Centre; UCLA Mattel Children's Hospital; Stewart and Lynda Resnick Neuropsychiatric Hospital at UCLA; and UCLA Santa Monica Medical Centre) have a total of 801 inpatient beds, and offer patients of all ages comprehensive care, from routine to highly specialised medical and surgical treatment. Ronald Reagan UCLA Medical Centre is a tertiary and quaternary referral centre that includes a Level 1 trauma centre, multiple transplantation programmes, a paediatric intensive care unit and a Level 4 neonatal intensive care unit. UCLA Santa Monica Medical Centre is a teaching community hospital and includes a paediatric emergency department, as well as adult, paediatric and neonatal ICU units. The wide-reaching health system also includes more than 200 primary care and specialty-care clinics across Southern California.

None of the other University of California's academic medical centres (UC San Francisco, UC Davis, UC Irvine or UC San Diego) offer home transfusion programmes.

UCLA Health Medical Centres are located in Los Angeles, and the clinics provide services to the greater Los Angeles country and throughout Southern California.

Question 2

No, we do not offer home-based transfusions.

Question 8a

UCLA has not offered routine home for the past 18 years.

Question 8b

The logistical barriers to implementing a home transfusion programme include training and competency regarding proper patient identification, specimen collection and blood administration; monitoring for transfusion reactions; clinical and regulatory responsibility from the physician and laboratory perspectives; reimbursement and identification of contracted home health providers.

Question 8c

UCLA Health allows for collection of specimens at UCLA Health clinics; however, we will not accept a specimen that is collected by a non-UCLA provider over concerns about proper patient identification and adherence to collection protocols.

Question 8d

There is a longstanding concern that patients enrolled in hospice should be able to receive blood products while on hospice. However, transfusions are not part of end-of-life home palliative care as there are patient safety, logistical and reimbursement challenges. If transfusion is necessary, it occurs in an infusion centre (or inpatient) setting.

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SWEDEN

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Question 1

Home-based transfusions are offered in almost all regions in Sweden and follow similar recommendations. In the Stockholm region covering a population of around 2 million people there are six hospitals with a blood bank in each hospital. There are many home-based teams, both public and private teams responsible of the home care. They have an office where documentation and transfusions are recorded. Pretransfusion samples are left at the blood bank and blood units are collected after approved pretransfusion tests.

The main health service is located in a city, with smaller hospital with a blood bank outside the city. Many visits at home are made in remote areas by nurses.

Question 2

Yes, we offer home-based transfusions.

Question 3a

Home-based transfusions are open to all patients who need it. The majority of patients have an oncology or haematology diagnosis.

Question 3b

Red cells and platelets are given.

Question 4a

There are no specific exclusion criteria for home-based transfusions.

Question 4b

Prior transfusions are not required to be enrolled.

Question 4c

A nurse is always present during the whole transfusion. Patients who live alone can be enrolled.

Question 4d

Home-based transfusions are offered to all patients who need it. If the patient needs transfusions several times a week and the distance is too long, the request can be denied, due to logistics and lack of resources.

Question 4e

No patients are excluded due to immunohaematological findings. If it is "difficult crossmatches" pretransfusion samples are requested well in advance.

Question 4f

Most patients have central venous access, but peripheral access is also used.

Question 5a

Universal leukoreduction is standard for all transfusions in Sweden.

Question 5b

Premedication is used only to those with previous transfusion reactions.

Question 5c

Normally, the pretransfusion tests are taken the day before the planned transfusion. The pretransfusion tests and crossmatches are valid for 5 days including the day of sample collection.

Question 5d

The blood units are normally collected at the blood bank by the nurses on their way to the patient. The blood units are transported in approved blood boxes. Usually no external couriers are involved, but if the care giving team are based in a geriatric hospital, the

blood units can be transported there by the hospital transport service. The empty blood bags are brought back to the office and disposed there.

Question 5e

Approved blood boxes are used for the transport, no routine temperature monitoring is done.

Question 6a

There are no specific requirements of the responsible physician. Often oncologists or haematologists are responsible but it can also be the physician in the palliative team.

Question 6b

The physician responsible for the patient makes the decision to transfuse.

Question 6c

Most often the decision to transfuse is based on the haemoglobin value or the platelet count.

Question 6d

Most often the decision to transfuse is based on the pretransfusion value, but symptoms and quality of life can be considered.

Question 7a

A nurse is present during the whole blood transfusion.

Question 7b

A nurse has to be present during the whole blood transfusion.

Question 7c

The nurses have an emergency box with acute medication and procedures and prescriptions of what to do if a reaction occurs.

Question 7d

The nurses are available 24/7 and they have telephone access to a consultant.

Question 7e

In a life-threatening reaction, the emergency service—ambulance or rescue helicopter—is called.

Question 7f

A 24-h telephone contact is always available.

Question 7g

The process of reporting adverse events is the same as in hospital. In acute situations, a telephone contact is done, in controlled, stable situations samples and a report are sent to the blood bank.

Question 7h

No severe reaction is reported from the home-based transfusions for the last 12 months.

Question 8a

Not applicable, most regions in Sweden have a home transfusion programme.

Question 8b

Most regions in Sweden offer home transfusions. In the northern part of Sweden, it is less frequent, probably due to long distances and lack of time for the home care team.

Question 8c

The logistics with pretransfusion testing are planned of the nurses in the home care team.

Question 8d

Most often, transfusions are part of the end-of-life care. Discontinuation of transfusions may be decided by the physician.

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SOUTH AFRICA

Vernon Louw & Perry Loebenberg

Question 1

Groote Schuur Hospital is a government-funded, tertiary level, teaching hospital affiliated with the University of Cape Town. It has 893 inpatient beds, 53,000 inpatient admissions per year with 91% bed occupancy. About 27,000 surgical procedures are performed per year, more than 3000 deliveries and 529,000 patients visit the outpatient clinics every year.

The hospital is located in Cape Town and services a network of smaller hospitals in the region.

Question 2

No, we do not offer home-based transfusions.

Question 8a

No, never.

Question 8b

Staff shortages and logistical difficulties related to the environments where many of our patients reside. As an example, the patient numbers managed, as mentioned above, is done by 515 doctors, 1449 nurses and 260 allied health professionals. Cold chain management is also a potential problem as many patients live in very poor circumstances and/or long distances away. A further problem is the lack of adequate number of trained nurses who can manage implanted venous access devices or indwelling venous catheters.

Question 8c

No, again, we work under incredible resource constraints, with very few doctors, nurses and laboratory staff, and the regional blood services are not able to do this on the hospital's behalf.

Question 8d

Patients on home palliative care can still come to our haematology clinic or go to their local secondary level hospital to receive a blood transfusion as part of that care. Unfortunately, the resource constraints as mentioned, do not allow for more than that at this stage.

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CANADA

Davinder Sidhu, Tara Redfern & Susan Nahirniak

Question 1

Alberta Precision Laboratories provides the transfusion support to urban, regional and remote facilities for the two provincial health authorities, Alberta Health Services and Covenant Health, which combined serve a total population of 4.4 million. The home transfusion programmes are coordinated out of the two major regional teaching hospital hubs based in Calgary and Edmonton. The most robust programme for home transfusion utilises community paramedics (aka CPP) and currently based in the city of Calgary (population 1.58 million) but is planning expansion throughout the remainder of the province over the next 5 years. In other areas of the province, home transfusion is approached on an individual case-by-case approval basis with specific criteria that must be met to ensure compliance with Canadian Standards.

The hospital is based in a city of 1.58 million people but serves a region of 4 million people.

Question 2

Yes.

Question 3a

Both programmes will accept any chronic transfusion recipient for consideration.

Question 3b

Red cells are the predominant components transfused but platelets, plasma and albumin have been provided via these services.

Question 4a

The criteria for the Community Paramedic Programme are provided below:

Your patient must have received previous transfusion(s) without serious complications;

1. The patient must have received at least two (2) transfusions within the previous 120 days without serious complications; or
2. More than four (4) transfusions within the previous year without serious complications; or
3. At the discretion of transfusion medicine physician lead.

Your patient must be able to tolerate infusion rates between 90 and 120 min per unit of RBC.

If the referral is for albumin, the patient must be able to tolerate all doses within a 4 h time period.

The order must not exceed 2 units of RBCs and 1 dose of platelets.

The referral must be received at least 48 h prior to the requested transfusion date.

CBC and type & screen, if applicable must be completed and interpreted within 72 h of the requested transfusion date.

For the case-by-case assessments, there must be a request submitted for review by the transfusion service medical director for chronic transfusion recipients. To be approved for the home transfusion, the patient must have had at least two administration episodes within a hospital facility to ensure acceptable tolerability and no evidence of severe or anaphylactic reaction. The home environment must have electricity and a working telephone. There must be at least one health care professional approved by the health professions act to provide intravenous medications and blood transfusion who can be trained and available for all transfusions and up to 15 min postinfusion in the home environment. Those performing the administration must participate in a training/competency programme that must include access, aseptic technique, handling of and administration as well as appropriate discard of equipment and recognition/management of adverse events.

Question 4b

Yes, the patient must have received at least two prior uncomplicated transfusions.

Question 4c

The home environment must have electricity and a working telephone. While patients who live alone are not explicitly excluded, there must be a competent adult available to stay with the individual for at least an hour following the transfusion but there is not a requirement that they be a permanent member of the same household.

Question 4d

A request can be submitted for any patient who is a chronic transfusion recipient. Due to logistics and capacity, those who have challenges with coming to a hospital facility for transfusion are preferentially enrolled.

Question 4e

The blood group and antibody screen results are part of the assessment of eligibility for enrolment in the programmes but this is more to determine the timing of the type and screen collection and number of units that could feasibly be available for each transfusion episode than to exclude patients with red cell antibodies.

Question 4f

Patients must be capable of having an intravenous catheter started. There is no requirement for a central venous access device but some patients have had one placed due to challenges with difficult venous access.

Question 5a

The blood supplier for Alberta, Canadian Blood Services, has been utilising prestorage leukoreduction since the late 1990s.

Question 5b

Premedication requirements are determined as part of the patient assessment and enrolment process but are not mandatory nor is their use explicit criteria for exclusion, unless they were being used for management of moderate to severe recurrent reactions.

Question 5c

Serologic testing is required for cellular components but the requirement for an "in date" type and screen/crossmatch specimen is only mandated for red cell concentrates. Although our current policy has a 96 h expiry from the time of collection, in general it is preferred to have testing collected at least 24 h in advance for patients needing red cell concentrates to allow for appropriate allocation and packing of the component. Specific to the CPP process, the requirement is that the specimen must be collected within 72 h for collection.

Question 5d

Since the Community paramedic programme has prebooked transfusions as part of the referral, the blood bank only requires a dispense notification submission 90 min prior to pick up. The community paramedic picks up from the nearest transfusion service to the patients' home and returns empty cooler and any documentation to same site.

For the case-by-case programme, the initial orders and registration in the programme require the orders to include the patient demographics, the product and dose requested, the preferred site of pickup and identification of any individual who would be designated as a "pick up" person for the components or plasma protein products. These individuals must be aware that they need to provide identification of themselves and a copy of the "order/prescription" for what they are picking up. The designated "pick up" person must have training regarding transport and handling of the product. There is a review of tolerability monthly for the first 3 months, enrolment in the programme must be re-evaluated on an annual basis. Any changes to the patient transfusion dosing or interval must be communicated as soon as they are aware. Any adverse reactions and/or product wastage must be reported to the transfusion service.

Question 5e

The transport boxes and packing configurations used for the home transfusion programme are the same as those used for inter- and intrafacility transport. As such they undergo quarterly confirmation of validation of the temperature preservation.

Question 6a

There is always a transfusion medicine physician involved in reviewing the request to participate in home transfusion and to evaluate any reported adverse reactions but the ability to enrol a patient is not restricted to any other medical specialty. The majority of medical practitioners that enrol patients are haematology/oncology or palliative care practitioners but family medicine physicians and paediatricians have also used the programmes available.

For the Community Paramedic Programme, the first formal referral is from the physician to the community paramedic who then refer them to the transfusion medicine physician. The goal of the programme is to have the patient booked within 24–48 h of the referral but due to the current increased demand the booking is 7–10 days. The CP programme requires a new referral by the treating physician/ANP for each appointment to ensure that follow-up is done appropriately but not every follow-up requires re-review by the transfusion service.

Question 6b

The transfusion therapy plan is designed prior to initiation of any home transfusion by the treating physician or advanced nurse practitioner, the patient and the transfusion medicine physician reviewing the application. It details the clinical situations/symptoms that can trigger a transfusion booking, the laboratory thresholds for transfusion (if applicable) and the number of units/vials to administer for each individual patient.

Question 6c

This is dependent on the patient and the product but in many of the patients the haemoglobin or platelet transfusion thresholds are part of the decision to transfuse and the number of units required for each episode.

Question 6d

This is dependent on the patient and the product but in many of the patients the symptoms are predetermined, along with any prerequisite lab parameters that can trigger a transfusion episode.

Question 7a

The Community Paramedic Programme has one Paramedic present for the entire transfusion. A second one is present for "bedside" checks virtually. One competent adult is required to stay with the patient post transfusion for 60 min.

For patients receiving component transfusion as part of the case-by-case programme, there is the requirement that the transfusion be performed by a trained health professional. For plasma protein recipients, the individual administering the product can be a trained caregiver approved by the programme intake.

For both programmes, there does not have to be a medical practitioner available on site during the transfusion but they must be available by phone. A competent adult must be available to stay with the recipient for at least 1 h following the transfusion.

For both programmes, the vital signs are recorded following the same criteria as any in hospital transfusion. This includes heart rate, blood pressure, temperature, respiratory rate and oxygen saturations—prior to initiation, within 15 min of initiation, and at the completion of transfusion. There must be a competent adult that will stay with the recipient for 60 min following the transfusion.

Question 7b

For both programmes, there does not have to be a medical practitioner available on site during the transfusion but they must be available by phone. A competent adult must be available to stay with the recipient for at least 1 h following the transfusion.

Question 7c

Epinephrine, diphenhydramine, furosemide and dexamethasone are recommended as emergency medications to be available for management of reactions in the home environment.

Question 7d

In the case of a mild–moderate reaction, there is first contact with the medical practitioner responsible for the patient or their off shift designate who will advise on acute management and whether or not to contact emergency medical services.

Question 7e

The CP programme employs an anaphylaxis protocol as needed per their scope of practice and can arrange for transport if the patient's goals of care support. For participants in the case-by-case programme, in the situation of a life-threatening reaction, the instructions are to contact emergency medical services immediately then contact the most responsible medical practitioner or their off shift designate for management while awaiting EMS arrival. There is also a mandatory requirement to report all transfusion reactions to the transfusion service that provided the component/product.

Question 7f

The medical practitioner responsible for the patient is required to have a process to manage patients on a 24 h basis through an on-call coverage system. The coordinating transfusion service also has a 24/7 on call transfusion medicine physician for support.

Question 7g

Both programmes provide training on the recognition, management and reporting of adverse events are part of the approval process for the patient and caregivers. The health professional providing the transfusion, the patients and their caregivers are provided with a standardised form, online links to more resources and contact information to use for advice or to provide notification.

Question 7h

Reactions as part of the programmes are rare. The CP programme had a 1.4% reaction rate with 1 EMS transport recorded between October 2015 and 28 February 2019.

Question 8a

Not applicable.

Question 8b

Not applicable.

Question 8c

Yes, we have mobile lab collection programme that can schedule for a home collection. If the patient on home transfusion does not qualify for that programme and they are registered with the Community Paramedic Programme, then the CP will co-ordinate with the most responsible health care provider to get orders so that they can perform the collection.

Question 8d

Palliative patients are considered as part of the home transfusion programme but each patient's cessation of transfusion criteria is

discussed and determined as part of the application to the programme.

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INTERNATIONAL FORUM

Vox Sanguinis ISBT International Society of Blood Transfusion

International Forum on Home-Based Blood Transfusion: Summary

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INTRODUCTION

Home-based transfusion has been used in a number of settings around the world since the 1970s [1], in patients with haemophilia [2], haematological and oncological malignancies and chronic medical conditions [3–11]. During the coronavirus disease of 2019 pandemic, due to the higher mortality rates in patients with haematological malignancies [12], many institutions have taken steps to reduce the contact vulnerable patients have with medical facilities and the general public. This is on a background of increased use of 'hospital in the home' services for antibiotic administration, chemotherapy, wound care and other services [13–16]. In addition, with the increase in therapeutic options for older patients with life-limiting malignant conditions, patients are living longer with significant anaemia, thrombocytopenia and transfusion requirements [17, 18].

The practice of home-based transfusion varies around the world, particularly with respect to safety considerations such as logistics and medical oversight [3, 5, 9, 10], as well as barriers to implementation of this service [11]. There are also many different funding sources for inpatient and outpatient transfusion programmes, which could affect the likelihood of establishment of a home administration service [11]. This forum is referring to 'home' transfusion of blood components and products within the patient's private domestic residence. It is not designed to include the administration of subcutaneous immunoglobulin or recombinant factor concentrates within the home.

QUESTION 1

Respondent demographics

Responses to the survey were received from nine institutions, representing a wide geographical distribution over six continents, including Australia, Brazil, Canada, India, Mexico, South Africa, Spain, Sweden and the United States. All respondents were from large academic or tertiary centres, the majority representing adult hospitals, with two primarily paediatric hospitals (Mexico and India) included.

There was variation in the population served by the institution, and therefore, the potential home transfusion programme. The majority of the respondents represented a central hospital, which receives referrals from a larger region or serves a network of smaller hospitals. The Spanish hospital, which does have a home transfusion programme, serves a region of 5000 square kilometres; however, their 'Hospital at Home' program only offers their service to patients within 25 km of the main hospital or a half-hour drive. The Swedish respondent does have the capacity for nurses to make home visits in more remote areas.

QUESTION 2

Does your healthcare service, region or country offer home-based transfusions?

Three respondents do currently have a home transfusion service (Spain, Sweden and Canada) and the following five questions were

directed only towards these respondents. Seven respondents do not currently have a home transfusion programme and were requested to skip to question 8, where obstacles to providing a home transfusion program are described.

QUESTION 3

Programme demographics

a. Is your home-based transfusion service designed to be utilized by a specific disease-based cohort of patients (i.e., myeloid malignancy, myeloma, solid organ malignancy and/or non-malignant) or open to a wide patient cohort?
b. Does your home-based service offer blood products other than red cells, such as platelets, plasma or albumin?

All participants responded positively, including patients with all clinical diagnoses who require chronic transfusion. The Swedish respondent stated the majority of patients have an oncology or haematology diagnosis. The Spanish respondent indicated their service can transfuse multiple different types of blood products but most commonly administers red cells or platelets. The Swedish service performs transfusion of red cells and platelets. The Canadian respondent transfuses predominantly red cells but also offers platelets, plasma and albumin at home.

QUESTION 4

Criteria for home transfusion

a. Do you have eligibility criteria for home transfusion that exclude patients with medical conditions, which could result in medical instability during transfusion?
b. Do you require the patient to have had a certain number of uncomplicated transfusions in the hospital prior to enrolment?
c. Are there stipulations in regard to an appropriate home environment? Is it mandatory to have a responsible caregiver present during the transfusion? Can patients who live alone be enrolled in the programme?
d. Is home-based transfusion only offered to a select group of patients? For example, only those with a poorer performance status or those with difficulty with transport to the hospital?
e. Are patients with red cell antibodies excluded from home transfusion? Are those with a 'difficult crossmatch' excluded, and how is this defined?
f. What are the vascular access requirements in your home transfused patients? Is a central venous access (CVC) device required in all patients? Is a CVC used in those with 'difficult access' only?

All respondents indicated that home transfusion is open to any patient who would benefit, not just limited to those with poor mobility, poor performance status or transport difficulties. The Swedish respondent indicated that barriers to enrolment or continuation in the programme could include a high transfusion burden (several times per week) and/or geographical distance, due to issues with logistics or lack of resources. The Canadian programme preferentially enrols those with mobility or transport difficulties but will enrol all patients if capacity and logistics allow.

The role of the caregiver varied significantly between the home transfusion programmes. This is reflected in the Spanish response, stating that having a caregiver who is present during the transfusion is mandatory, and the caregivers play a key role in their hospital at home programme. In contrast, the Swedish respondent indicated that given the nurse is present throughout the transfusion, those who live alone can be enrolled in the programme. In the Canadian programme, the caregiver must be available to stay with the patient during the transfusion and for 60 min afterward, but there is no requirement that this caregiver lives with the patient, therefore, allowing those who live alone but have family or friends available for this role to be enrolled in the programme. Both the Spanish and Canadian respondents indicated that having a working telephone or mobile phone is mandatory in their programme.

The respondent from Sweden indicated there are no specific exclusion criteria in their programme. The respondent from Spain stated the following exclusion criteria:

- Actively bleeding patients
- Acute lung or cardiac failure
- Previous severe, unexplained severe transfusion reactions or with unidentified irregular antibodies

The Canadian respondent indicated that the recipient must have had:

- At least two transfusions within the previous 120 days without serious complications, or
- More than four transfusions within the previous year without serious complications, or
- Enrolment at the discretion of the transfusion medicine physician lead and
- Can tolerate infusion rates between 90 and 120 min per unit of red cells

The Canadian respondent mandates prior uncomplicated transfusions as part of their eligibility criteria or at the discretion of the transfusion medicine lead. The Swedish and Spanish respondents indicated that prior transfusions within the hospital or outpatient centre are not a requirement before enrolment on a home transfusion programme. None of the respondents indicated that having red cell antibodies is an exclusion criteria. However, the Spanish respondent stated that unidentifiable and potentially haemolytic antibodies may be an exclusion criteria. The Swedish programme allows 'difficult crossmatches' but stated the pre-transfusion samples would be requested in advance of the usual timeframe. None of the programmes mandate patients

have indwelling vascular access while enrolled on the home transfusion programme, however, all respondents indicated that a proportion of patients will already have CVC prior to enrolment.

QUESTION 5

Programme logistics

a. Does your institution or blood supplier mandate universal leukoreduction for all red cell products provided? If not, is leukoreduction mandatory for home-based transfusion products?
b. In your service, is any routine pre-medication given prior to home transfusion? Is this used in select patients with previous transfusion reactions, or would patients requiring pre-medication be excluded from enrolment in the program?
c. In regard to pre-transfusion testing: can the crossmatch be facilitated on the same day of transfusion, or is it required to be taken prior? Can this be facilitated at home? For chronically transfused patients, for how long does your laboratory allow a crossmatch to be valid?
d. Please briefly outline the logistical steps in regard to delivery of the product from the blood bank to the residence of the patient: Who brings the product and how is it stored prior to transfusion? Is an external courier service used? How are the blood product bags and equipment disposed of after the transfusion?
e. What quality measures are in place for cold chain management during the transport process?

All three respondents with home transfusion services had different methods regarding logistics, in respect to transfusion testing, collection of the blood product and staff member involvement.

For pre-transfusion testing, the Spanish programme indicated that in some patients, compatibility testing can be performed the same day as the transfusion. The samples can be taken at home, and are usually valid for 72 h. In Sweden, the crossmatch is valid for 5 days. In their programme, the pre-transfusion sample is usually taken the day prior to the transfusion. In the Canadian programme, the red cell crossmatch is valid for 72–96 h and red cells are generally not able to be supplied the same day due to logistical requirements. However, some platelets and albumin products may be available the same day as the request if available in the inventory as a pre-transfusion sample was not required. The pre-transfusion samples in Canada are able to be taken at home by a mobile laboratory testing team.

In most cases, the blood product is collected by the programme staff (usually a nurse) on the way to visit the patient. No external couriers are used in the Swedish or Spanish programmes. However, the Swedish respondent stated that in some cases the blood product can be transported by the hospital transport service. The Canadian respondent has two separate logistical methods for home transfusion. In the 'community paramedic' programme, paramedics are used to transport and transfuse the blood product. They are pre-booked, and pick up the product after a dispensing notification from the nearest blood centre, facilitated by the entire province under one laboratory program. The Canadian respondent has an additional 'case by case' programme in which a dedicated 'pick up' person is nominated to collect the blood product. This individual must have appropriate identification and training in transport and storage of the product. All respondents indicated that approved or validated blood transport containers are used in the programme. The Spanish respondent estimated that adequate temperature should be maintained for an hour in the container. No routine temperature monitoring is undertaken in the Swedish programme. The Canadian programme uses the transport boxes that are standard for movement of blood products within and to other facilities, which undergo routine validation for temperature preservation.

All respondents indicated clinical waste is usually brought back to the programme for disposal. However, the Spanish programme sometimes (e.g., on weekends) stores waste at the patient's home in appropriate containers.

The respondents all indicated universal leukoreduction is standard for all red cell products in Canada, Spain and Sweden. Currently, pre-medication is not mandatory or routine standard of care in any of the home transfusion programmes. It is used only if there is a concern in regard to previous transfusion reactions. The Spanish and Canadian respondents indicated that the use of pre-medication (due to previous reactions) is considered, but is not a cause for exclusion from the programme unless the patient has had prior serious reactions.

QUESTION 6

Medical oversight

a. Is the medical practitioner providing oversight to the transfusion, a palliative care physician, transfusion program physician/haematologist, family medicine physician or are there no specific requirements?
b. Who is making the decision whether to transfuse individual patients each appointment, and how many units of product they require? That is, a physician, a nurse coordinator or the patient/carer?
c. Is the decision to transfuse based on standard haemoglobin and platelet parameters, aiming for a specific pre-transfusion threshold or post-transfusion target?
d. Is the decision to transfuse based on symptoms and quality of life or the pre-transfusion haemoglobin?

All respondents indicated that a variety of specialists are involved in their home transfusion programme, with the medical oversight the responsibility of internal medicine specialists, palliative care physicians, geriatricians, oncologists or haematologists. In the Canadian programme, there is always a transfusion medicine physician involved, and there is the additional involvement of the community paramedic who will assist with the programme.

The physician or advanced nurse practitioner responsible for the patient is the decision-maker in regard to whether to transfuse the individual each time. In the Spanish programme, there is usually only capacity to transfuse a maximum of two product units per day: two units of red cells or one unit of red cells and one unit of platelets. In the Canadian programme, a detailed plan is created upon enrolment. There is a maximum of two red cells and one platelet unit per day, and if albumin is transfused it must be transfused within 4 h.

The Spanish respondent indicated that a Hospital Transfusion Guide is utilized to assist with decision-making in regard to transfusion parameters. This is based on the patient's clinical status and comorbidities, aiming to maintain the haemoglobin level between 7 g/dl and 10 g/dl. Platelet transfusions are usually given if the count is <10,000/μl or <20,000/μl in those with fever, severe hypertension or pro-haemorrhagic conditions. The Swedish programme uses haemoglobin value and platelet count as transfusion parameters more commonly than symptoms or quality of life considerations. In the Canadian programme, the decision to transfuse varies between the patient and the product, but in many cases, this is based on transfusion thresholds.

QUESTION 7

Medical supervision

a. During the transfusion, is a nurse and/or medical practitioner present? For the entire transfusion or only at certain timepoints? If not, how are they contacted should the need arise?
b. Is it mandatory for a caregiver to be present?
c. What emergency medications are 'on-hand' during or after the transfusion, and who is trained to administer these (i.e., caregivers or only staff)?
d. In case of a mild-moderate reaction, is there timely access to hospital medical staff, or are ambulance or emergency services used?
e. What is the procedure for a life-threatening reaction?
f. Do you have a 24-h phone contact for emergencies after the transfusion?
g. Please describe the process of adverse event reporting in your home transfusion service.
h. In the last 12 months have you had a severe transfusion reaction requiring transfer to hospital and what was(were) the cause(s)?

The respondents described very different processes for supervision during the transfusion. In the Spanish programme, the nurse is present during the initial 15 min. After this time, the caregiver is responsible for monitoring the patient and must be present at all times. A phone number for the nurse is available for any adverse events, and to notify when the transfusion is finishing. The nurse returns after the transfusion to assess vital signs and dispose of the waste. In the Swedish programme, the nurse is present throughout the entire transfusion, so a caregiver is not mandatory or expected. In the Canadian 'community paramedic' programme, the paramedic remains with the patient for the duration of the transfusion. They utilize a second paramedic 'virtually' to complete the pre-transfusion bedside check. In the 'case by case' programme, a 'trained health professional' transfuses the product and remains with the patient. However, some plasma protein products can be infused with a trained caregiver rather than a professional present. In both of these programmes, a competent caregiver must be present during and for at least 60 min after the transfusion.

The Spanish respondent described the transfusion kit, which is left at the patient's home during the transfusion, containing corticosteroids, anti-histamines and diuretics. The caregiver is trained to give emergency medication (including intravenous) as part of inclusion in the programme, if instructed by a nurse or physician. In the Swedish programme, the nurse has an emergency box with medications and procedures to respond to an adverse reaction. The Canadian programme stipulates the following be available: epinephrine, diphenhydramine, furosemide and dexamethasone.

The Spanish respondent indicated that the patient must live within a half-hour drive from the hospital in case of emergency. All programmes have a 24-h contact, with nurses available 24/7 with access to a physician. All programmes have telephone access to a medical practitioner for transfusion reactions.

Given the caregiver is responsible for the majority of the monitoring during the transfusion in the Spanish programme, there is a documented procedure for life-threatening reactions, which includes:

- Stop the transfusion and check the patient's status.
- Call the nurse on call, who will alert the physician on call.
- Check the patient's identity against the product, to rule out an administrative error.
- Give drugs according to the symptoms (corticosteroid for fever, anti-histamines for allergic and cutaneous reactions and diuretics for transfusion-associated circulatory overload).

The Swedish programme has a nurse monitoring the patient during the transfusion, so if required the procedure for a life-threatening reaction is to call the emergency service.

In the Canadian 'community paramedic' programme, the anaphylaxis and other appropriate protocols are directly utilized if needed, and can arrange transport to a medical facility. In the 'case by case' programme, the emergency medical services and the responsible medical practitioner should be contacted while awaiting the emergency services.

The Spanish respondent indicated adverse reaction reporting involves the following:

- When an adverse reaction is detected, take the appropriate samples from the patient.
- The physician in charge must fill in the transfusion reaction report.
- The blood bank haematologist will investigate the reaction and act according to the results, start corrective action and may recommend pre-medication to be used before transfusions.

- Once the reaction is investigated, the haematologist must record the adverse reaction on the hospital transfusion management system and report through to the national haemovigilance system web.
- The Regional Blood Bank will acknowledge the report and explore the links to the donor, processing, etc.

The Swedish respondent indicated that the adverse event reporting follows the same guidelines as a transfusion in the hospital. The Canadian programmes provide training on the recognition, management and reporting of adverse events, which is part of the approval process for the patient and caregivers. There is a standardized form, and electronic links to resources for reporting and notification.

All respondents indicated that there has been no severe transfusion reaction in their patients transfused at home within the last 12 months. The Spanish respondent indicated there has been no severe transfusion reaction reported in more than 30 years of operating the programme. The Canadian programme had one emergency medical transport incident from 2015–2019; the nature of this incident was not further elaborated.

QUESTION 8

Barriers to programme implementation

a. Did your region ever have a home transfusion program, and if yes, why was it cancelled?
b. What are the top three logistical barriers to the implementation of a home transfusion program in your jurisdiction?
c. For patients on a hospital/clinic-based chronic transfusion program, are you able to collect samples for pre-transfusion testing in the community to reduce the number of visits for transfusion? If not, what are the obstacles you have encountered collecting samples in the community?
d. For patients on home palliative care, are transfusions considered part of end-of-life care and if yes, how are these coordinated? If not, what is the justification for the discontinuation of transfusions at the end of life?

The respondents from Australia, Brazil, Mexico, United States and South Africa indicated their institution or region has never had a home transfusion programme. In contrast, the respondent from Sweden stated that most regions in Sweden have a home transfusion programme. The Spanish respondent reiterated that their home transfusion programme has been running continuously since 1987. The Indian respondent indicated their institution does not have a home transfusion programme, however, does provide home infusion of clotting factor concentration for patients with bleeding disorders.

The most frequent logistical barrier identified was related to staff availability, education and training, cited by six respondents (Table 1). The concerns included the length of time a staff member is required to be present with the patient compared with a day unit, and availability of nursing staff with appropriate training. Geographical dispersion was a logistical barrier for four respondents, including the two respondents that currently do have a home transfusion programme. This is likely closely linked to staff availability, but also related to concerns in accessing appropriate medical care in the event of an adverse transfusion reaction. The ability to manage an adverse reaction in the home

TABLE 1 Logistical barriers for home transfusion programme implementation

Country	What are the top three logistical barriers to the implementation of a home transfusion programme in your jurisdiction?

Australia	• Major issue: Staff availability
	  ○ Nursing staff to monitor the patient during the transfusion
	  ○ Medical staff support
	• Blood transport concerns: Keeping blood at a stable temperature
	• Wastage of blood if it is not transfused due to storage concerns

Brazil	• Staff availability • High cost • Patient safety: Access to hospital or urgent care facility to manage severe adverse reactions ○ Additional concern in regard to traffic congestion causing delays in the treatment of life-threatening reactions
Canada	Not applicable
India	• Absence of regulatory approval • Lack of parental understanding and education (paediatric institution) • Management of adverse events
Mexico	• Geographical dispersion: Patients living up to 3–5 h away • Staff availability
South Africa	• Staff availability • Logistical difficulties in regard to patient's home environments • Cold chain management: Geographical dispersion and home environment • Inadequate nursing staff training in regard to venous access
Spain	• Geographical dispersion • Lack of effective, simple monitoring devices • Lack of simple and effective electronic records systems, accessible from the patients' homes
Sweden	• Geographical dispersion • Staff availability

United States	• Training and competency in regard to
	  ○ Patient identification
	  ○ Specimen collection
	  ○ Blood administration
	• Monitoring for transfusion reactions
	• Clinical and regulatory responsibility—physician and laboratory
	• Reimbursement and identification of contracted home health providers

TABLE 2 Community sample collection

Country	Are you able to collect samples for pre-transfusion testing in the community to reduce the number of visits for transfusion?—description of pre-transfusion testing in the community	If no, what are the obstacles you have encountered to collecting samples in the community?
Australia	Yes—for patients without indwelling venous access devices, these are performed by our Pathology department, through community collection centres or domiciliary visits.	The pathology collectors are not able to access central venous catheters so these patients either come to the clinic or have haematology and oncology outreach nurses come to their homes.
Brazil	Yes—no information provided.	No information provided.
Canada	Yes—there is a mobile lab collection programme that can be scheduled for a home collection. If the patient on home transfusion does not qualify for that programme and they are registered with the Community Paramedic Programme, then the Community Paramedic will co-ordinate with the most responsible health care provider to get orders so that they can perform the collection.	Not applicable.
India	Yes—samples can be collected by the family either directly or through a laboratory and provided to us in the hospital.	Not applicable.
Mexico	No—not applicable.	The obstacles for doing so would be the same as for implementing a home transfusion programme.
South Africa	No—not applicable.	We work under incredible resource constraints, with very few doctors, nurses and laboratory staff, and the regional blood services are not able to do this on the hospital's behalf.
Spain	Yes—the family nurse can take pre-transfusion samples and send them to the hospital with the blood transfusion order. The physician in charge (usually a haematologist) will review the blood count, interview the patient and order the transfusion needed.	The main problem is the lack of a clear sample circuit, the difficulty of working with paper orders and records. Sometimes the healthcare centre staff refuse to cooperate because they do not feel competent or understand the circuit.
Sweden	Yes—no information provided.	No information provided.
United States	No—not applicable.	University of California Los Angeles (UCLA) Health allows for collection of specimens at UCLA Health clinics, however, we will not accept a specimen that is collected by a non-UCLA provider over concerns about proper patient identification and adherence to collection protocols.

was a concern for three respondents. In Brazil, this was partly due to concerns over traffic congestion inhibiting transport to urgent medical care. Storage and transport of the blood products were identified as a major logistical barrier by two respondents. Only one respondent (United States) specifically cited reimbursement as a major logistical barrier to implementation of a home transfusion programme.

Six respondents indicated that collection of pre-transfusion samples in the community is possible within their health service (Table 2). Three respondents indicated this is not possible, with major barriers cited being staff availability and geography. The Australian respondent stated that a barrier to sample collection is the presence of central venous catheters and the ability of pathology collectors to access these devices. The United States respondent indicated that their institution will not accept pre-transfusion samples from external providers, which can be a barrier to sample collection in the community. Both respondents with a current home transfusion programme described a

TABLE 3 End-of-life transfusions

Country	Are transfusions considered part of end-of-life care? How are these coordinated?
Australia	Yes (on a case-by-case basis). Frequently, haematology patients have ongoing care via haematology outpatient clinics with transfusion and specialty malignancy nurse care coordinators monitoring patients and organizing transfusions in haematology outpatient clinics. For patients known only to palliative care, transfusions are organized through the hospice or occasionally through other services, such as emergency departments, if the hospice is not able to accommodate them in a timely way.
Brazil	Decisions for transfusion are made on a case-by-case basis, considering life expectancy, especially if presumed survival exceeds 1 month; and benefit on fatigue and dyspnoea relief. No information provided.
Canada	Yes, but each patient's transfusion criteria are discussed and determined as part of the application to the programme. Palliative patients are considered part of the home transfusion programme and can be enrolled.
India	Yes. This is currently only provided in hospital or hospice settings and is not offered at home.
Mexico	Yes. Many patients in palliative care are transfused in ambulatory beds in the hospital, at finish return to home.
South Africa	Yes. Patients on home palliative care can still come to our Haematology clinic or go to their local secondary level hospital to receive a blood transfusion as part of that care.
Spain	Yes. When patients are attended by the Palliative Care Service, their physicians in charge are responsible for the indication of transfusion, and work with the same protocols and procedures as other patients being transfused at home.
Sweden	Yes. Most often, transfusions are part of the end of life care. Discontinuation of transfusions may be decided by the physician. No information provided.
United States	Yes, and there is a longstanding concern that patients enrolled in hospice should be able to receive blood products while on hospice. Transfusions are not part of end-of-life home palliative care, as there are patient safety, logistical and reimbursement challenges. If transfusion is necessary, it occurs in an infusion centre (or inpatient) setting.

system in which a nurse can take pre-transfusion samples in the community and coordinate with the physician in the programme to prescribe the blood product.

All respondents indicated that transfusions are considered part of end-of-life-care in their institution or region (Table 3). Of the six respondents without a home transfusion programme, patients are transferred to a hospital, emergency department, ambulatory care centre or infusion centre for transfusions.

CONCLUSION

Among the nine survey respondents, a home transfusion programme was uncommon; however, the three programmes were described as effective and safe over the long-term. Programme administration was variable, particularly with respect to the staff and monitoring involved, suggesting multiple models of care have the potential to be successful.

Despite safety concerns as a commonly reported barrier to the establishment of a home transfusion programme [19, 20], among the respondents with a home transfusion programme only one adverse event requiring transport to acute medical facilities was reported. The programmes described did not mandate particularly strict enrolment criteria to assist with risk mitigation.

Cost does not appear to be a significant logistical barrier; however, may be linked to other concerns about regulations, complexity of the process, and lack of people/staff availability. Given that three countries are reporting long-standing successful programmes without safety concerns, other jurisdictions may wish to consider addressing identified obstacles to implementation to provide this patient-centred service to more patients, with a view to improving quality of life, especially for chronically transfused patients, and to reduce the burden on hospitals.

Future research could be directed towards patient and clinician interest in these programmes, evaluation of safety and cost-effectiveness and patient quality of life. Development of a home transfusion toolkit with policies, procedures and guidelines could be helpful to assist with implementation and assessment of home transfusion programmes in other jurisdictions.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Utility of reticulocyte haemoglobin content and immature reticulocyte fraction in early diagnosis of latent iron deficiency in whole blood donors

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Abstract

Background and Objectives: The present study was planned to assess the clinical utility of reticulocyte haemoglobin content (CHr) and immature reticulocyte fraction (IRF) in the early detection of latent iron deficiency in blood donors.

Materials and Methods: The prospective longitudinal observational study was conducted using the purposive sampling method. Written informed consent was obtained and donors were allocated into the first-time (FTD) and regular donor (RD) group. The enrolled blood donors ($n = 205$ in each group) were followed up for two subsequent whole blood donations. Haemoglobin (Hb), CHr, IRF and serum ferritin values were recorded at enrolment and two follow-ups.

Results: The sensitivity of CHr in detecting iron-deficient erythropoiesis (serum ferritin values ≤ 26 μg/dl) was 45% and 56.7%, specificity 96.7%, positive predictive value (PPV) 85.6% and 90.8% and negative predictive value (NPV) 80.1% and 78.7%, respectively in FTD and RD cohorts. The sensitivity of IRF was 45.1% and 44.8%, specificity 93.4% and 97.1%, PPV 74.8% and 90.4% and NPV 79.6% and 74.5%, respectively in both the cohorts.

The sensitivity of CHr in detecting absent iron stores (serum ferritin values ≤ 15 μg/dl) was 66.2% and 74.4%, specificity 92% and 90.6%, PPV 56.7% and 68.7% and NPV 94.5% and 92.8% among FTD and RD cohort, respectively. The sensitivity of IRF was 72.7% and 65.3%, specificity 90.3% and 94.3%, PPV 54.4% and 76% and NPV 95.4% and 90.8%, respectively in both the cohorts.

Conclusion: Reticulocyte hemoglobin content and IRF can be used along with complete blood count for early detection of iron deficiency in blood donors using the same blood sample at no extra cost.

KEYWORDS
immature reticulocyte fraction, latent iron deficiency, reticulocyte haemoglobin content

Highlights

- Reticulocyte hemoglobin content and immature reticulocyte fraction were found to have a high positive predictive value and negative predictive value in detecting iron deficiency in whole blood donors at an early stage.

- It is feasible to perform these tests on the same automated hematology analyzer used to run a complete blood count at no extra cost.
- These tests can be used in regular blood donors for early detection of iron deficiency.

INTRODUCTION

Red blood cells contain about two-thirds of total body iron in the form of haemoglobin (Hb). With each whole blood donation of 500 ml, approximately 200–250 mg of iron is lost from the body. However, only a limited amount of 1–2 mg/day iron can be absorbed under normal circumstances [1]. Replenishment of lost iron may take place gradually over months thereby leading to a negative iron balance with the increasing number of donations.

Diagnosis of iron deficiency at an early stage is a challenging task as there is no single simple test with immediate results approved in clinical practice. A major limitation of using Hb alone as a screening method is that the decrease in Hb levels occurs only when there is complete consumption of iron stores [2]. Serum ferritin is a reliable marker of bone marrow iron stores with high sensitivity and specificity making it the first-line diagnostic tool for iron deficiency anaemia [3, 4]. Though unusual in healthy blood donors, the serum ferritin levels may be falsely raised in inflammatory conditions as it is an acute phase reactant. Furthermore, serum ferritin requires a longer turnaround time [4] as serum ferritin assay is usually ELISA or electrochemiluminescence based and results may not be available on the same day. Reticulocytes are immature non-nucleated red blood cells (RBCs) that are released into the peripheral circulation where they mature into erythrocytes in 1–2 days [5]. Nowadays, reticulocyte indices namely reticulocyte haemoglobin content (CHr) and immature reticulocyte fraction (IRF) can be easily measured along with complete blood count using automated haematology analysers and their role is being explored in assessing iron stores and bone marrow erythropoietic activity.

CHr is the product of the cellular volume and the cellular haemoglobin concentration [6]. CHr is an early biomarker for impaired haemoglobinization as it provides an indirect measure of functional iron available for RBCs production over the previous 3–4 days [7]. In one of the studies, no effect of inflammation was observed on the diagnostic efficacy of CHr in comparison to serum ferritin [8]. IRF is a sum of the fractional percentage of reticulocytes containing both medium and high content of RNA [9]. IRF is a sensitive indicator for knowing a person's erythropoietic status [10]. As the anaemia develops, IRF also starts increasing [11]. IRF was found to have a strong correlation with Hb and the correlation was stronger in patients with acute anaemia than with chronic anaemia [10]. Iron depletion can lead to cognitive impairment, pica and restless leg syndrome [12], thereby; prevention of significant iron depletion at an early stage in blood donors is of utmost importance. Therefore, the present study was planned to assess the clinical utility of CHr and IRF as a screening tool in the early detection of latent iron deficiency in whole blood donors with a hypothesis that CHr and IRF testing in blood donors might help to improve donor's health by revealing iron deficiency at an early stage. The study also determined the effect of whole blood donation on haematological parameters in both first-time and regular whole blood donors.

MATERIALS AND METHODS

The prospective longitudinal observational study was conducted in a tertiary care hospital from April 2019 to August 2020 after approval by the Institutional Ethics Committee. Whole blood donors presenting to the department either in-house or in-station outdoor blood donation camps on weekdays (Monday to Friday) and residing within a span of 12 miles of our blood center were enrolled using the purposive sampling method. Enrolment was done on weekdays and in-station outdoor blood donation camps as blood samples had to be processed within 4 h of collection on the automated haematology analyser. Nearby residing blood donors were preferred as the study involved follow-ups for two subsequent whole blood donations.

Whole blood donors were screened as per criteria laid by the national regulatory authority [13]. Pre-donation Hb estimation was done in all the eligible blood donors using quality-checked copper sulfate solution as per the departmental standard operating procedure (SOP). If pre-donation Hb was found to be ≥12.5 g/dl, the donor was explained about the study. Blood donors taking iron supplements in the last 3 months and regular blood donors who had not donated in the last preceding year were excluded from the study. Written informed consent was obtained from all the eligible donors willing to participate and the donors were further allocated into two groups depending upon the donation status.

Group I: ($n = 205$) First-time blood donor (FTD): Who had never donated earlier and was donating whole blood for the first time. The first-time donors once enrolled remained classified as first-time for the entire study period.
Group II: ($n = 205$) Regular blood donor (RD): Those donors who had donated whole blood twice or more in their lifetime and at least once in the last preceding year [14].

Once the required numbers of blood donors were enrolled, the enrolment process was stopped. Each whole blood donor of groups I and II were followed up for subsequent two whole blood donations. The minimum interval between the two whole blood donations was kept as 90 days for males and 120 days for females. The donors were asked to report within 15 days of the stipulated time of subsequent whole blood donation and those not reporting were considered as dropouts. Whole blood (350 ml) was collected from all the enrolled participants as per the SOP of the department.

Collection, storage, handling and processing of blood samples

Before each whole blood donation, 4 ml of blood sample was drawn from each donor and dispensed into 2 ml ethylene diamine tetraacetic acid (EDTA) and 2 ml plain vacutainers and labelled with the donor identification number.

From the EDTA sample, Hb, CHr and IRF were performed within 4 h of collection on the automated haematology analyser Sysmex XN 1000 (Sysmex Corporation, Kobe, Japan).

Serum was separated by centrifugation of plain vacutainer sample using a table-top centrifuge (3000 r.p.m. for 3 min, REMI India) and stored in the cryovials in minus 40°C deep freezer (REVCO, Thermo Fisher Scientific, Waltham, MA) for the serum ferritin analysis.

Reticulocyte analysis

The Sysmex XN 1000 device performs haematology analyses according to the Hydro-Dynamic Focusing, flow cytometry method and SLS-Hb method. Reticulocyte (RET) analysis is done by the flow cytometry method. The CHr is derived using the reticulocyte scattered light signals and a proprietary Sysmex calculation equation. For IRF, a two-dimensional scattergram is plotted using a semiconductor laser with the *x*-axis representing the intensity of the side fluorescent light and the *y*-axis representing the intensity of the forward scattered light. This scattergram displays groups of reticulocytes (Figure 1). The scattergram is divided into three RET zones based on the intensity of the fluorescent light and the ratio of the reticulocytes in each zone to the total number of reticulocytes is calculated (Figure 2).

High fluorescence ratio:

$$\text{High fluorescence ratio (HFR)} = \frac{\text{particle count in HFR zone}}{\text{particle count in reticulocyte zone}} \times 100.$$

Middle fluorescence ratio:

$$\text{Middle fluorescence ratio (MFR)} = \frac{\text{particle count in MFR zone}}{\text{particle count in reticulocyte zone}} \times 100.$$

Low fluorescence ratio:

$$\text{Low fluorescence ratio (LFR)} = 100 - \text{HFR} - \text{MFR}.$$

Immature reticulocyte fraction:

$$\text{Immature reticulocyte fraction (IRF)} = \text{MFR} + \text{HFR}.$$

For serum ferritin analysis, cryovials were thawed and brought to room temperature before processing. Serum ferritin was then estimated using an ELISA kit (ORGENTEC Diagnostika GmbH, ORG 5FE Ferritin) as per kit inserts.

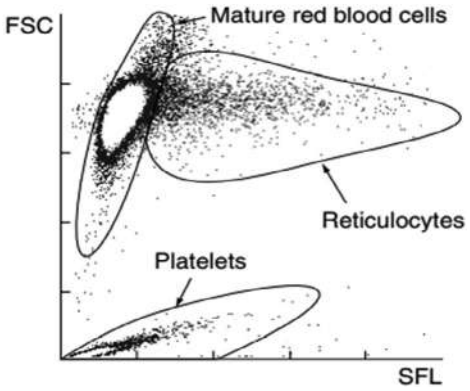

FIGURE 1 2D-Scatter diagram. FSC, forward scattered light; SFL, side fluorescent light

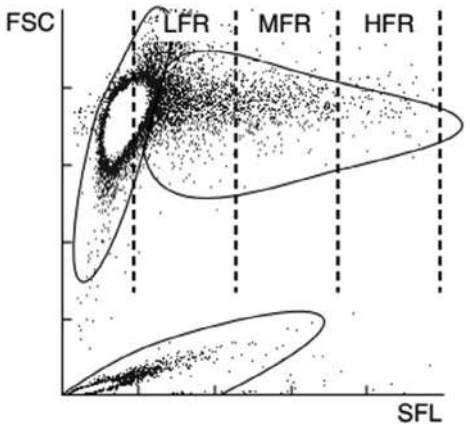

FIGURE 2 Scatter diagram showing reticulocyte zones. FSC, forward scattered light; HFR, high fluorescence ratio; LFR, low fluorescence ratio; MFR, middle fluorescence ratio; SFL, side fluorescent light

Iron-deficient erythropoiesis was referred to as serum ferritin levels ≤26 μg/dl and absent iron stores as serum ferritin levels ≤15 μg/dl with pre-donation Hb ≥12.5 g/dl (Table 1). Values of haematological parameters were recorded at the time of enrolment, first and second follow-up.

Statistical analysis

The optimum sample size was calculated based on 40% latent iron deficiency among the regular whole blood donors. Among the first-time donors, there was no figure available in the existing literature. We anticipated a 10% less iron deficiency rate among first-time donors. Based on this assumption, the odds ratio came out to be 1.56 assuming 95% confidence levels and with 20% relative precision the optimal sample size came to be 168. To adjust for the loss to follow up, the sample size was elevated further by 20%, and accordingly, a

TABLE 1 Normal values of haematological parameters

Name of investigation	Normal values
Haemoglobin	≥12.5 g/dl
Serum ferritin	27–250 μg/dl ≤26 μg/dl suggestive of (s/o) iron-deficient erythropoiesis ≤15 μg/dl s/o absent iron stores
CHr	32.1–38.8 pg <32.1 pg s/o iron deficiency
IRF	1.6%–10.5%

Abbreviations: CHr, reticulocyte haemoglobin content; IRF, immature reticulocyte fraction.

minimal sample size of 205 was recruited in each group using the purposive sampling method.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CHr and IRF were calculated taking serum ferritin as a gold standard in both the first-time and regular donor cohort. Correlation between CHr, IRF and serum ferritin in first-time and regular donors at enrolment and second follow-up were calculated using Spearman's rho correlation coefficient. Hb, serum ferritin, CHr and IRF values were described as median with interquartile range because of the skewed data. Levels of Hb, serum ferritin, CHr and IRF among the first-time and regular donors were compared using the Mann–Whitney test at enrolment and second follow-up. *p*-value <0.05 was considered significant.

RESULTS

The whole blood donors were enrolled over 8 months, that is, from April 2019 to November 2019 using the purposive sampling method. The enrolled blood donors ($n = 205$ in each group) were then followed up for two subsequent whole blood donations. At the first follow-up, 15 FTD and 21 RD were lost to follow up. In all, 190 FTD and 184 RD completed the first follow-up. At the second follow-up, 22 FTD and 14 RD were lost to follow up. In all, 168 FTD and 170 RD completed the second follow-up. A total of 72 blood donors, that is, 37 FTD and 35 RD were lost to follow up accounting for a 17.56% drop-out rate.

The mean age of the whole blood donors was 27.6 ± 9.2 years (range 18–57 years). The majority of our donors were males ($n = 399$, 97.3%).

Latent iron deficiency among first-time and regular blood donors and correlation with CHr and IRF

First-time donors

Iron-deficient erythropoiesis with serum ferritin values ≤26 μg/dl and normal pre-donation Hb values (≥12.5 g/dl) was found in

TABLE 2 Diagnostic value of reticulocyte haemoglobin content in first-time and regular blood donors to detect iron-deficient erythropoiesis

Donations	Normal iron status, S. Ferritin > 26 μg/dl	Latent iron deficiency, S. Ferritin ≤ 26 μg/dl	CHr ≥ 32.1 pg	CHr < 32.1 pg	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)
FTD								
Enrolment ($n = 205$)	180	25	173	32	88 (68.8–97.5)	94.4 (90–97.3)	68.8 (54.2–80.3)	98.3 (95.1–99.4)
First follow up ($n = 190$)	134	56	163	27	44.6 (31.3–58.5)	98.5 (94.7–99.8)	92.6 (75.4–98.1)	81 (77.1–84.4)
Second follow up ($n = 168$)	78	90	137	31	33.3 (23.7–44.1)	98.7 (93.1–99.97)	96.8 (80.7–99.5)	56.2 (52.5–59.8)
Total samples processed ($n = 563$)	392	171	473	90	45 (37.4–52.8)	96.7 (94.4–98.2)	85.6 (77.2–91.2)	80.1 (77.9–82.2)
RD								
Enrolment ($n = 205$)	158	47	162	43	78.7 (64.3–89.3)	96.2 (91.9–98.6)	86.1 (73.5–93.2)	93.8 (89.8–96.4)
First follow up ($n = 184$)	118	66	145	39	44.6 (31.3–58.5)	98.5 (94.7–99.8)	92.6 (75.4–98.1)	81 (77.1–84.4)
Second follow up ($n = 170$)	73	97	121	49	49.5 (39.2–59.8)	98.6 (92.6–99.97)	98 (87.2–99.7)	59.5 (54.6–64.2)
Total samples processed ($n = 559$)	349	210	428	131	56.7 (49.7–63.5)	96.7 (94.1–98.2)	90.8 (84.9–94.6)	78.7 (76–81.2)

Abbreviations: CHr, reticulocyte haemoglobin content; CI, confidence interval; FTD, first-time donor; NPV, negative predictive value; PPV, positive predictive value; RD, regular donor.

TABLE 3 Diagnostic value of immature reticulocyte fraction in first-time and regular blood donors to detect iron-deficient erythropoiesis

Donations	Normal iron status, S. Ferritin > 26 μg/dl	Latent iron deficiency, S. Ferritin ≤ 26 μg/dl	IRF ≤ 10.5%	IRF > 10.5%	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)
FTD								
Enrolment ($n = 205$)	180	25	173	32	68 (46.5–85.1)	91.7 (86.6–95.3)	53.1 (39.4–66.4)	95.4 (92.1–97.3)
First follow up ($n = 190$)	134	56	156	34	50 (36.3–63.4)	95.5 (90.5–98.3)	82.4 (67.2–91.4)	82.1 (77.8-85.6)
Second follow up ($n = 168$)	78	90	131	37	35.6 (25.7–46.4)	93.6 (85.7–97.9)	86.5 (72.4–94)	55.7 (51.7–59.7)
Total samples processed ($n = 563$)	392	171	460	103	45.1 (37.4–52.8)	93.4 (90.4–95.6)	74.8 (66.4–81.6)	79.6 (77.2–81.7)
RD								
Enrolment ($n = 205$)	158	47	175	30	53.2 (38.1–67.9)	98.6 (92.8–99)	83.3 (67–92.5)	87.4 (83.7–90.4)
First follow up ($n = 184$)	118	66	152	32	44 (31.7–56.7)	97.5 (92.8–99.5)	90.6 (75.4–96.8)	75.7 (71.8–79.4)
Second follow up ($n = 170$)	73	97	128	42	41.2 (31.3–51.7)	97.3 (90.5–99.7)	95.2 (83.3–98.8)	55.5 (51.2–59.7)
Total samples processed ($n = 559$)	349	210	455	104	44.8 (37.9–51.8)	97.1 (94.8–98.6)	90.4 (83.4–94.6)	74.5 (72.1–76.8)

Abbreviations: CI, confidence interval; FTD, first-time donor; IRF, immature reticulocyte fraction; NPV, negative predictive value; PPV, positive predictive value; RD, regular donor.

TABLE 4 Diagnostic value of reticulocyte haemoglobin content in first-time and regular blood donors to detect absent iron stores

Donations	Normal iron status, S. Ferritin > 15 μg/dl	Latent iron deficiency, S. Ferritin ≤ 15 μg/dl	CHr ≥ 32.1 pg	CHr < 32.1 pg	Sensitivity% (95% CI)	Specificity % (95% CI)	PPV%	NPV%
FTD								
Enrolment ($n = 205$)	192	13	173	32	92.3 (63.4–99.8)	89.6 (84.4–93.5)	37.5 (27.8–48.3)	99.4 (96.3–99.9)
First follow up ($n = 190$)	165	25	163	27	68 (46.5–85.1)	93.9 (89.1–97.1)	63 (46.8–76.7)	95.1 (91.6–97.2)
Second follow up ($n = 168$)	129	39	137	31	56.4 (39.6–72.2)	93 (87.2–96.8)	71 (55.1–82.9)	87.6 (68.8–97.5)
Total samples processed ($n = 563$)	486	77	473	90	66.2 (54.6–76.6)	92 (89.2–94.2)	56.7 (48.2–64.8)	94.5 (92.6–95.9)
RD								
Enrolment ($n = 205$)	183	22	162	43	100 (84.6–100)	88.5 (83–92.8)	51.2 (41.2–61)	100
First follow up ($n = 184$)	142	42	145	39	61.9 (45.6–76.4)	90.9 (84.9–95.1)	66.7 (53.1–78)	89 (84.5–92.3)
Second follow up ($n = 170$)	113	57	121	49	73.7 (60.3–84.5)	93.8 (87.7–97.5)	85.7 (74.2–92.6)	87.6 (82–91.6)
Total samples processed ($n = 559$)	438	121	428	131	74.4 (65.7–81.9)	90.6 (87.5–93.2)	68.7 (61.7–75)	92.8 (90.4–94.6)

Abbreviations: CHr, reticulocyte haemoglobin content; CI, confidence interval; FTD, first-time donor; NPV, negative predictive value; PPV, positive predictive value; RD, regular donor.

TABLE 5 Diagnostic value of immature reticulocyte fraction in first-time and regular blood donors to detect absent iron stores

Donations	Normal iron status, S. Ferritin > 15 μg/dl	Latent iron deficiency, S. Ferritin ≤ 15 μg/dl	IRF ≤ 10.5%	IRF > 10.5%	Sensitivity% (95% CI)	Specificity % (95% CI)	PPV% (95% CI)	NPV% (95% CI)
FTD								
Enrolment ($n = 205$)	192	13	173	32	76.9 (46.2–95)	88.5 (83.2–92.7)	31.3 (21.7–42.7)	98.3 (95.5–99.4)
First follow up ($n = 190$)	165	25	156	34	80 (59.3–93.2)	91.5 (86.2–95.3)	58.8 (45.5–71)	96.8 (93.2–98.5)
Second follow up ($n = 168$)	129	39	131	37	66.7 (49.8–80.9)	91.5 (85.3–95.7)	70.3 (56.3–81.3)	90.1 (85.3–93.4)
Total samples processed ($n = 563$)	486	77	460	103	72.7 (61.4–82.3)	90.3 (87.4–92.8)	54.4 (46.8–61.8)	95.4 (93.6–96.8)
RD								
Enrolment ($n = 205$)	183	22	175	30	77.3 (54.6–92.2)	92.9 (88.2–96.2)	56.7 (42.3–69.8)	97.1 (94–98.7)
First follow up ($n = 184$)	142	42	152	32	59.5 (43.3–74.4)	95.1 (90.1–98)	78.1 (62.5–88.5)	88.8 (84.6–92)
Second follow up ($n = 170$)	113	57	128	42	64.9 (51.1–77.1)	95.6 (90–98.6)	88.1 (75.5–94.7)	84.4 (79.1–88.5)
Total samples processed ($n = 559$)	438	121	455	104	65.3 (56.1–73.7)	94.3 (91.7–96.3)	76 (67.9–82.5)	90.8 (88.5–92.6)

Abbreviations: CI, confidence interval; FTD, first-time donor; IRF, immature reticulocyte fraction; NPV, negative predictive value; PPV, positive predictive value; RD, regular donor.

25/205 (12.2%) FTD at enrolment which increased to 56/190 (29.5%) at first follow-up and 90/168 (53.6%) at second follow up. CHr values were observed to be below the normal range (<32.1 pg) in 22/25 (88%) iron-deficient donors at enrolment, 25/56 (44.6%) at first follow-up and 30/90 (33.3%) at second follow-up (Table 2). IRF values were found to be >10.5% in 17/25 (68%) iron-deficient donors at enrolment, 28/56 (50%) at first and 37/90 (41.1%) at second follow-up (Table 3).

Absent iron stores with serum ferritin values ≤15 μg/dl and normal pre-donation Hb values (≥12.5 g/dl) was found in 13/205 (6.3%) FTD at enrolment which increased to 25/190 (13.2%) at first follow-up and 39/168 (23.2%) at second follow up. CHr values were observed to be below the normal range (<32.1 pg) in 12/13 (92.3%) iron-deficient donors at enrolment, 17/25 (68%) at first follow-up and 22/39 (56.4%) at second follow-up (Table 4). IRF values were found to be >10.5% in 10/13 (76.9%) iron-deficient donors at enrolment, 20/25 (80%) at first follow-up and 26/39 (66.7%) at second follow-up (Table 5).

Regular donors

Among RD, iron-deficient erythropoiesis was found in 47/205 (22.9%) donors at enrolment which increased to 66/184 (35.9%) at first follow-up and 97/170 (57.1%) at the second follow-up. Among iron-deficient regular donors, CHr values were <32.1 pg in 43/47 (91.5%) at enrolment, 39/66 (59.1%) at first follow-up, and 49/97 (50.5%) at second follow-up (Table 2). IRF values were >10.5% in 30/47 (63.8%) at enrolment, 32/66 (48.5%) at first follow-up, and 42/97 (43.3%) at second follow-up (Table 3).

Among RD, absent iron stores were found in 22/205 (10.7%) blood donors at enrolment which increased to 42/184 (22.8%) at first follow-up and 57/170 (33.5%) at the second follow-up. Among iron-deficient regular donors, CHr values were <32.1 pg in all the 22 (100%) iron-deficient regular donors at enrolment, 26/42 (61.9%) at first and 42/57 (73.7%) at second follow-up (Table 4). IRF values were >10.5% in 17/22 (77.3%) at enrolment, 25/42 (59.5%) at first and 37/57 (64.9%) at second follow-up (Table 5).

Diagnostic value of reticulocyte Hb content in comparison with serum ferritin in first-time and regular blood donors

The overall sensitivity of CHr in detecting iron-deficient erythropoiesis among the FTD cohort was found to be 45%, specificity 96.7%, PPV 85.6% and NPV 80.1%. In the RD cohort, the sensitivity was found to be 56.7%, specificity 96.7%, PPV 90.8% and NPV 78.7% (Table 2).

The overall sensitivity of CHr in detecting absent iron stores among the FTD cohort was 66.2%, specificity 92%, PPV 56.7% and NPV 94.5%. In the RD cohort, the overall sensitivity was 74.4%, specificity 90.6%, PPV 68.7% and NPV 92.8% (Table 4).

TABLE 6 Correlation of reticulocyte haemoglobin content, immature reticulocyte fraction and serum ferritin in first-time and regular donors at enrolment and second follow-up

At enrolment							
		Group I (FTD, $n = 205$)			Group II (RD, $n = 205$)		
Haematological parameters		CHr	IRF	Serum ferritin	CHr	IRF	Serum ferritin
CHr	Correlation coefficient	1.000	−0.531	0.756	1.000	−0.535	0.707
IRF	Correlation coefficient	−0.531	1.000	−0.563	−0.535	1.000	−0.576
At second follow-up							
		Group I (FTD, $n = 168$)			Group II (RD, $n = 170$)		
Haematological parameters		CHr	IRF	Serum ferritin	CHr	IRF	Serum ferritin
CHr	Correlation coefficient	1.000	−0.516	0.754	1.000	−0.566	0.684
IRF	Correlation coefficient	−0.516	1.000	−0.540	−0.566	1.000	−0.528

Note: Correlation calculated using Spearman's rho correlation coefficient.
Abbreviations: CHr, reticulocyte haemoglobin content; FTD, first-time donor; IRF, immature reticulocyte fraction; RD, regular donor.

TABLE 7 Haematological parameters among first time and regular blood donors at enrolment and second follow-up

	At enrolment			At second follow up		
Haematological parameters	Group I (FTD), $n = 205$, median (IQR)	Group II (RD), $n = 205$, median (IQR)	p value[a]	Group I (FTD), $n = 168$, median (IQR)	Group II (RD), $n = 170$, median (IQR)	p value[a]
Hb	15.1 (14.3-15.8)	14.7 (13.9–15.5)	0.014	14.2 (13.4–14.8)	13.8 (13.2–14.6)	0.046
Serum ferritin	59.2 (35.4–96.9)	54.0 (28.1–98.5)	<0.001	22.5 (15.3–48.5)	21.9 (11.4–40.2)	<0.001
CHr	33.5 (32.8–34.4)	33.5 (32.6–34.4)	0.628	32.4 (32.1–32.8)	32.3 (31.5–32.7)	0.145
IRF	7.8 (5.9–9.6)	8.0 (6.4–9.4)	0.534	9.3 (8.2–10.4)	9.8 (8.6–10.5)	0.063

Abbreviations: CHr, reticulocyte haemoglobin content; FTD, first-time donor; Hb, haemoglobin; IQR, interquartile range; IRF, immature reticulocyte fraction; RD, regular donor.
[a]p-value calculated using Mann–Whitney test.

Diagnostic value of IRF in comparison with serum ferritin in first-time and regular blood donors

The overall sensitivity of IRF in detecting iron-deficient erythropoiesis among the first-time donor cohort was 45.1%, specificity 93.4%, PPV 74.8% and NPV 79.6%. In RD cohort, the sensitivity was 44.8%, specificity 97.1%, PPV 90.4% and NPV 74.5% (Table 3).

The sensitivity of IRF in detecting absent iron stores among the FTD cohort was 72.7%, specificity 90.3%, PPV 54.4% and NPV 95.4%. In RD cohort, the sensitivity was 65.3%, specificity 94.3%, PPV 76% and NPV 90.8% (Table 5).

Correlation of reticulocyte Hb content, IRF and serum ferritin in first-time and regular blood donors at enrolment and second follow-up

A strong positive correlation was observed between CHr and serum ferritin at enrolment and second follow-up. Moderate negative correlations were observed between IRF and CHr and serum ferritin using Spearman's rho correlation coefficient at enrolment and second follow-up (Table 6).

Haematological parameters among the first-time and regular donors at enrolment and after two subsequent whole blood donations (second follow-up)

Group I (FTD) versus group II (RD)

Regular donors were found to have lower median Hb, median serum ferritin and median CHr values as compared to the FTD both at enrolment and second follow-up. Median IRF values were also found higher in RD in comparison to FTD both at enrolment and second follow-up. A significant difference was observed in median Hb and serum ferritin values between the FT and RD both at enrolment and second follow-up. However, the difference was not found to be significant in median CHr and IRF values (Table 7).

DISCUSSION

Blood donors play a pivotal role in maintaining the inventory of blood centres. However, blood donors tend to develop iron deficiency with repeated donations, hence, there is a need to develop tests for its timely detection.

In our study, blood donors were young with a mean age of 27.6 ± 9.2 years which is in corroboration with the data by the World Health Organization stating that the majority of the donors belong to the younger age group in low- and middle-income countries [15]. Females constituted only 2.7% of the study population. In the Indian scenario, females in the reproductive age group are not able to donate blood because of the increased prevalence of iron deficiency anaemia due to poor nutrition, pregnancy and menstruation [14].

Currently, a donor having pre-donation Hb ≥12.5 g/dl is eligible to donate blood [13]. However, Hb levels remain normal till overt iron deficiency anaemia ensues [14]. In our study, it was observed that 318 blood donor samples (159 each FT and RD samples) with serum ferritin ≤26 μg/dl and 198 blood donor samples (77 FT and 121 RD samples) with serum ferritin ≤15 μg/dl had pre-donation Hb levels within the normal range. Therefore, pre-donation Hb estimation alone as a screening tool is insufficient to detect latent iron deficiency.

Latent iron deficiency in blood donors was found to increase with the increasing frequency of whole blood donations. Iron deficient erythropoiesis was present in 12.2% of FTD at enrolment which increased to 53.6% at the second follow-up while for RD, it increased from 22.9% at enrolment to 57.1% at the second follow-up. Absent iron stores were present in 6.3% of FTD at enrolment which increased to 23.2% at the second follow-up and among RD, increased from 10.7% at enrolment to 33.5% at the second follow-up. The primary reason for the decrease in serum ferritin with increasing donation frequency is that the body demand for iron increases with repeated blood donations at shorter intervals. Though the rate of iron absorption is increased among blood donors still the amount of lost iron cannot be recovered fully by diet alone and therefore iron deficiency ensues with an increased donation frequency of 4–5 blood units annually [16]. Our data mimic the results in the RISE study where the authors found previous donation intensity and shorter intervals between whole blood donations as important predictors of absent iron stores and iron-deficient erythropoiesis at enrolment and subsequent visits [12].

Reticulocytes are a more sensitive indicator of erythropoiesis due to the rapid turnover of 1–2 days in the peripheral circulation [17]. In this study, we assessed whether routine CHr and IRF measurement could reliably detect latent iron deficiency in blood donors which would help in timely blood donor management.

Reticulocyte Hb content has been found as a good screening tool for detecting reduced iron stores at an early stage in donors before overt anaemia develops [17]. As iron stores are depleted, more reticulocytes with reduced Hb content are produced leading to a decrease in CHr [17]. Tiwari et al. observed a high PPV of 93.1% and NPV of 96.3% of CHr for diagnosing latent iron deficiency in 501 blood donors [14]. In another study conducted on blood donors, authors found CHr to be 69% sensitive, 93% specific with 42% PPV and 96% NPV in assessing iron deficiency [18]. In a study by Semmelrock et al., the sensitivity of CHr to detect absent iron stores in frequent male donors was found to have PPV 57.7% and NPV 93.7% while among frequent female donors, the PPV was 82.9% and NPV was 86.2% [7]. Similarly in our study also, the CHr was found to have a high PPV (85.6% in FTD and 90.8% in RD; 56.7% in FTD and 68.7% in RD) and NPV (80.1% in FTD and 78.7% in RD; 94.5% in FTD and 92.8% in RD) in detecting iron-deficient erythropoiesis and absent iron stores respectively in both the cohorts. Thus, CHr was observed to be a useful and practical screening tool for the early diagnosis of latent iron deficiency in blood donors.

CHr was found to have a strong positive correlation with serum ferritin values in both the first-time ($r = 0.756$) and regular ($r = 0.707$) donors making it a reliable parameter for screening. Low levels of CHr were found to have a good correlation ($p = 0.001$, $r = 0.3$) with low serum ferritin values in iron deficiency anaemia in a study conducted on haemodialysis patients [19]. A significant positive correlation was also found between CHr and serum ferritin ($r = 0.786$; $p < 0.0001$) in another study [17]. However, in contrary in a study on patients with solid tumours or haematological malignancies on chemotherapy or radiotherapy, the authors found an inverse relationship between CHr and serum ferritin. The main reason for discordance could be the presence of inflammation, chronicity and/or tumour-derived ferritin in cancer patients leading to spurious high ferritin values as against our healthy blood donor population [20].

IRF constitutes the young population of immature reticulocytes with medium and high RNA content [11, 21]. The presence of immature reticulocytes in peripheral circulation indicates increased stress erythropoiesis [21]. Watanabe et al. in their study on patients with haematological disorders and healthy controls observed a significant increase in immature reticulocytes despite a normal or reduced number of reticulocytes in circulation ($p < 0.001$) [21]. A significant increase of 0.23%–0.58% in immature reticulocytes 5 h post blood donation ($p < 0.001$) was observed by Tanke et al. in their study on 30 healthy blood donors as a control group and patients with various haematological disorders [22]. Wells et al. in their study showed an increase in mean fluorescence of reticulocytes to 85.6 ± 4.6 in patients with iron deficiency anaemia ($p < 0.001$) and to 81.1 ± 8.4 in patients with depleted iron stores as compared to normal healthy individuals (69.7 ± 2.6) [23].

In our study, IRF was found as a good screening tool with a high PPV (74.8% in FTD and 90.4% in RD; 54.4% in FTD and 95.4% in RD) and NPV (79.6% in FTD and 74.5% in RD; 95.4% in FTD and 90.8% in RD) in detecting iron-deficient erythropoiesis and absent iron stores respectively in both the cohorts. However, there is a paucity of data in the literature about the use of IRF as a screening method among blood donors.

In our study, a moderate negative correlation ($r = -0.563$ among FTD and $r = -0.576$ among RD) was found between IRF and serum ferritin. Reticulocyte immaturity has been found to have a correlation with serum ferritin concentration in patients with iron deficiency anaemia ($p < 0.001$) [21]. A significant correlation between mean fluorescence of reticulocytes and serum ferritin ($p < 0.001$, $r = 0.40$) was observed suggesting an increase in mean channel fluorescence in iron deficiency [23]. Another study revealed a strong correlation between IRF and Hb in detecting iron deficiency anaemia. The authors found IRF to have a negative relationship with Hb values in patients with acute anaemia ($r = -0.239$, $p < 0.001$) [10].

The majority of our study population consisted of males and young donors; hence, the results cannot be directly extrapolated to the female and older population of blood donors.

In conclusion, reticulocyte Hb content and IRF were found to have a high PPV and NPV in detecting iron deficiency in whole blood donors at an early stage. These tests can be used in regular blood donors for early detection of iron deficiency as it is feasible to perform these tests on the same automated haematology analyser used to run complete blood count using the same blood sample at no extra cost. However, these are not point of care tests as they cannot be used in outdoor blood donation camps and thus, cannot replace Hb estimation. Nonetheless, more studies are required to demonstrate the effectiveness of these tests.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

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Viscoelastometric versus standard coagulation tests to guide periprocedural transfusion in adults with cirrhosis: A meta-analysis of randomized controlled trials

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Abstract

Background and Objectives: Due to rebalanced haemostasis in cirrhosis, viscoelastometric testing (VET) is more accurate than standard coagulation tests (SCTs) in preprocedural haemostatic evaluation, resulting in decreased unnecessary transfusion. We aimed to determine the impact of VET-guided strategy on postprocedural bleeding, periprocedural transfusion rates and quantities, transfusion-related adverse events (TRAEs), lengths of stay (LOS) and mortality from randomized controlled trials (RCTs) of cirrhotic patients.

Methods: PubMed and EMBASE were searched for RCTs comparing VET-guided with SCT-guided transfusion in cirrhotic adults undergoing esophagogastroduodenoscopy, liver transplantation or other invasive interventions. Using random-effects models, the pooled risk ratios (RRs) and/or mean differences (MDs) of postprocedural bleeding-free events and the other outcomes were estimated alongside 95% confidence intervals (CIs).

Results: Of seven included RCTs ($n = 421$; 72.2% men; mean age 49.1 years), VET-guided transfusion did not change postprocedural bleeding-free statuses (RR 1.05; 95% CI 0.94–1.17). However, VET-based algorithms decreased the rates of fresh frozen plasma (FFP; RR 0.52; 95% CI 0.35–0.77) and platelet transfusions (RR 0.34; 95% CI 0.16–0.73), the quantities of transfused FFP (MD −1.39 units; 95% CI −2.18 to −0.60), platelets (MD −1.06 units; 95% CI −2.01 to −0.12) and cryoprecipitate (MD −7.13 units; 95% CI −14.20 to −0.07) and the risk of TRAEs (RR 0.42; 95% CI 0.27–0.65). The overall mortality rates and LOS were not significantly different between two groups.

Conclusion: Compared with conventional SCT-guided, VET-guided strategy decreases periprocedural plasma and platelet transfusions and TRAEs, without increasing haemorrhagic complications, LOS or mortality in cirrhosis.

KEYWORDS
blood coagulation tests, blood transfusion, liver cirrhosis, post-operative haemorrhage, thromboelastography

Highlights

- Compared with standard coagulation tests, VET-guided periprocedural transfusion can reduce plasma and platelet uses in adults with cirrhosis.
- Post-procedural bleeding, mortality and lengths of hospital stay are not increased by the VET-guided strategy.
- Transfusion-related adverse events are less frequent in the VET-guided group, but RBC transfusion is not reduced.

INTRODUCTION

Patients with cirrhosis frequently require invasive interventions [1, 2] and, therefore, need special evaluation and care during the periprocedural period [3]. The major concerns are bleeding risks from multiple haemostatic disturbances. Thrombocytopenia, deficiencies of multiple coagulation factors and elevated tissue plasminogen activator levels all promote anticoagulation. On contrary, reduced synthesis of natural anticoagulants and plasminogen, but increased levels of von Willebrand factor, factor VIII and plasminogen activator inhibitor synergistically drive toward procoagulation. Consequently, a sum of these alterations results in a new haemostatic balance [4, 5]. Acquired medical conditions, for example, variceal ruptures and infections, can disrupt this fragile equilibrium, precipitating bleeding and thrombosis [4]. The standard coagulation tests (SCTs) comprising platelet counts, prothrombin time (PT) and activated partial thromboplastin time are unable to accurately assess the whole haemostatic complexity. Hence, using SCTs may result in excessive plasma and/or platelet transfusions to correct laboratory abnormalities [5].

Whole blood-based viscoelastometric testing (VET), for example, thromboelastography (TEG) and rotational thromboelastometry (ROTEM) may overcome the limitations of SCTs, since VET can depict the in vivo haemostasis by comprehensively evaluating all blood components and representing the measurable clot kinetics and strength [6]. A recent meta-analysis of 21 studies, two of which included cirrhotic patients [7, 8], showed that uses of preprocedural VET were associated with lower postprocedural mortality, as well as platelet and fresh frozen plasma (FFP) transfusions, compared with those of SCTs [9]. Although observational studies revealed benefits of VET in cirrhotic patients undergoing invasive procedures, the clinical significances have to be confirmed by randomized controlled trials (RCTs) [10]. However, each RCT contained a relatively small sample size. We, therefore, performed a meta-analysis of all the published RCTs to determine the pooled efficacy of VET-guided transfusion strategy in this particular population.

METHODS

We prespecified a research protocol before the initiation of the literature search. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11], eligible RCTs were qualitatively appraised in a systematic review, followed by a quantitative data synthesis in a meta-analysis. Participants in the VET-guided transfusion group were compared with those in the SCT-guided transfusion group to determine effects on the prespecified outcomes of interest. The primary outcome was the postprocedural bleeding-free event. The rates and quantities of periprocedural transfusions (FFP, platelets, cryoprecipitate and red blood cells [RBCs]), transfusion-related adverse events (TRAEs), lengths of stay (LOS), as well as postprocedural mortality were the secondary outcomes.

Eligibility criteria

RCTs published in any formats or languages were eligible for inclusion into the systematic review. The inclusion criteria comprised (1) RCTs, which enrolled adults (≥18 years) with cirrhosis from any causes; (2) compared preprocedural TEG, ROTEM or new-generation VET (ClotPro, TEG 6S or Quantra systems) with SCTs for transfusion guidance during the periprocedural period of any invasive interventions and (3) reported at least one outcome of interest. Any trials recruiting fewer than 10 participants in each comparative arm, non-original articles and duplicated studies were excluded.

Data sources and search strategy

Online databases, including PubMed and EMBASE, were systematically searched between the inception date of each database and 10 July 2021. The reference lists of retrieved articles and recent meta-analyses were also reviewed. The search strings are available in Table S1. Duplicated search results from two databases were excluded before screening for eligibility. Two researchers (NT and CM) separately performed the literature search, screened titles and abstracts and read full-texts to identify eligible RCTs. A consensus with a third author (PR) was necessary in case of a disagreement. The PRISMA flow diagram depicts the search results and study selection (Figure 1).

Data extraction

Two authors (NT and CM) independently extracted data from the included RCTs after thoroughly reviewing. In a discordance of data, a third author (PR) was consulted for the final decision. Predefined variables consisted of baseline characteristics (age, gender, Child-Pugh and Model for End-Stage Liver Disease scores), types of invasive procedures, VET types and parameters, SCT parameters (platelet counts,

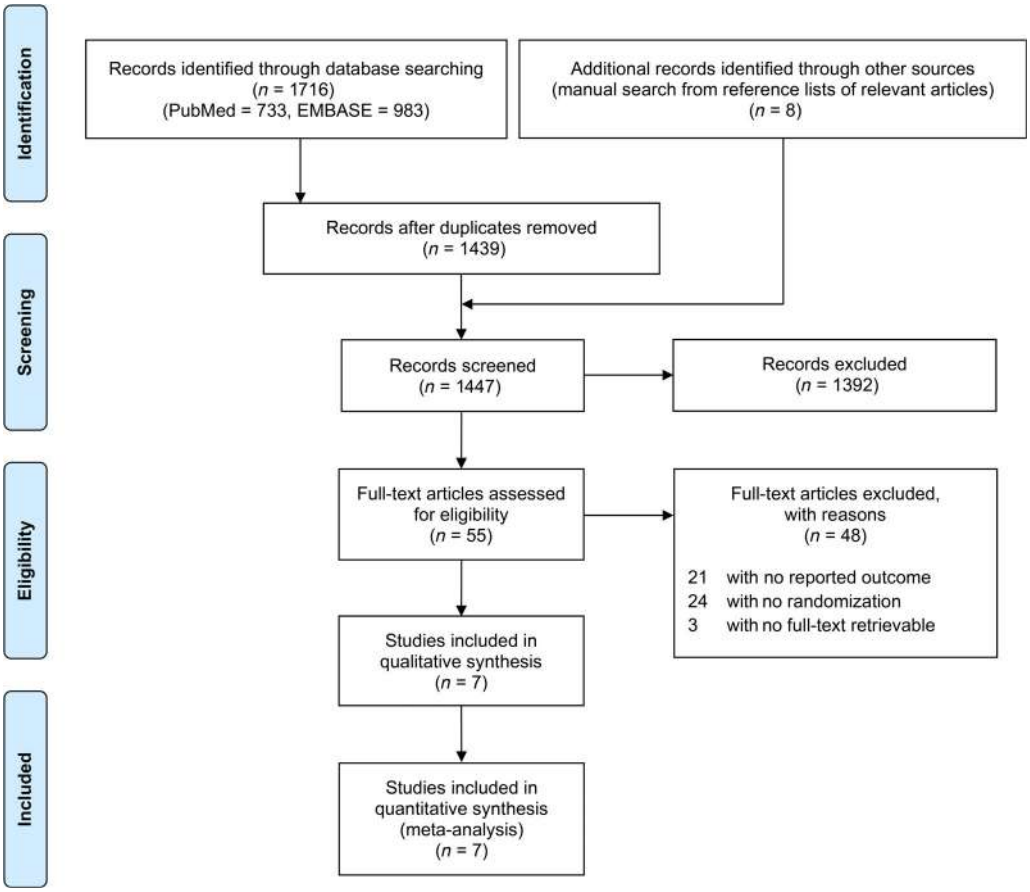

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection

PT or international normalized ratio [INR] and fibrinogen levels) and outcomes of interest.

For a study using TEG, a prolonged reaction time (r time), a short maximum amplitude (MA) and a small alpha angle indicated transfusion of FFP, platelets and cryoprecipitate, respectively. For a study using ROTEM, a prolonged clotting time (CT) in extrinsically tissue factor-activated assay (EXTEM), a short clot amplitude at 10 min (A10) or a decreased maximum clot firmness (MCF) in EXTEM and a short A10 in fibrin-based EXTEM with platelet inhibitor cytochalasin D (FIBTEM) were applied for FFP, platelet and cryoprecipitate transfusions, respectively (Table S2).

Regarding the outcome variables, the postprocedural bleeding-free event was the number of patients who did not develop major bleeding after esophagogastroduodenoscopy (EGD), orthotopic liver transplantation (OLT) or any other invasive interventions [12]. The rate of periprocedural transfusion was calculated from the number of patients receiving blood or plasma products during the preprocedural, intraprocedural or postprocedural periods. Meanwhile, the quantity of transfusion was the number of transfused blood or plasma units as defined by the authors in each study. If only transfused volumes of FFP were reported, 250-ml FFP would be estimated as one unit [13]. A platelet unit refers to an apheresis unit or a pool of six platelet concentrates [14]. The TRAEs comprised haemolytic and nonhaemolytic reactions, including transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO). Any continuous variables reported in medians were converted into means before the quantitative data synthesis [15].

Risk-of-bias assessment

The modified Cochrane Collaboration tool [16] was applied independently by two authors (NT and CM) to assess methodological quality and risk of bias (RoB) of the included RCTs. A summary of responses to all seven items assigns an RCT into high, low or unclear RoB. A joint reassessment (NT, CM and PR) was required for a discrepancy. A publication bias would be estimated by a funnel plot and Egger's regression if at least 10 RCTs were accumulated in the meta-analysis.

Quantitative data synthesis and statistical methods

All analyses were performed using Review Manager version 5.4 (Cochrane Collaboration, London, UK) and Comprehensive Meta-Analysis version 3.0 (Biostat Inc, Englewood, NJ). The primary analyses compared VET-guided with SCT-guided transfusion in cirrhotic subjects for the prespecified primary and secondary outcomes, using the DerSimonian and Laird method with random-effects models. The

pooled event rates and risk ratios (RRs) with 95% confidence intervals (CIs) were computed for postprocedural bleeding-free events, periprocedural transfusions, TRAEs and mortality. Meanwhile, the pooled means and mean differences (MDs) with 95% CIs were calculated for quantities of transfusions and LOS.

For the secondary analyses, subgroup analyses (patients with or without active gastrointestinal [GI] bleeding; patients undergoing EGD due to active GI bleeding, OLT or the other invasive procedures; in-hospital or intensive care unit [ICU] LOS and 30-day postprocedural mortality) were performed as appropriate. The influence of VET-specific thresholds on the RRs of transfusions was subsequently determined by meta-regression analyses based upon restricted maximum likelihood estimation [17]. Inter-study heterogeneity was assessed by the I^2 statistic as insignificant (0%–25%), low (26%–50%), moderate (51%–75%) or high (>75%) heterogeneity [18].

RESULTS

From a total of 1724 records identified, 1447 unique abstracts were screened for eligibility. Fifty-five studies were included for the full-text evaluation due to fulfilment of at least one inclusion criterion. Of those, 48 studies were excluded due to no reported outcomes of interest, non-randomized methodology or no retrievable full-texts. Seven RCTs involving 421 patients with cirrhosis remained for the qualitative and quantitative syntheses (Figure 1).

Two RCTs [19, 20] ($n = 156$; 37.1%) were conducted in patients with active GI bleeding undergoing EGD, whereas the others were among those receiving OLT [7, 21] (two studies; $n = 109$; 25.9%), central venous catheterization [22] (one study; $n = 38$; 9.0%) or various types of invasive procedures [8, 23] (two studies; $n = 118$; 28.0%). In VET arms, TEG was applied in five RCTs [7, 8, 19, 20, 23] while ROTEM was used in the other two [21, 22]. None of the studies employed ClotPro, TEG 6S or Quantra systems. Between RCTs, TEG-/ROTEM-specific thresholds were heterogeneous but SCT-driven cut-offs were comparable (Table S2).

The majority of study participants were male ($n = 304$; 72.2%): 67.8% in VET, and 76.7% in SCT groups ($p = 0.12$). The mean age was 49.1 years (95% CI 47.9–50.2; $I^2 = 94\%$). Sixty-two per cent of patients (95% CI 41.0–80.3; $I^2 = 90\%$) were categorized into Child-Pugh classes B and C. Baseline characteristics were similar between two comparative arms (Table S3).

Four RCTs were published in 2020 [19, 20, 22, 23], whereas the others were issued in the 2010s [7, 8, 21]. None of the studies were at high RoB; however, five [7, 8, 20, 21, 23] carried concerns regarding the blinding processes (Table S4). The publication bias was not evaluated since fewer than 10 studies were aggregated.

Postprocedural bleeding-free events

Postprocedural bleeding was reported in five RCTs ($n = 312$) [8, 19, 20, 22, 23]. None of OLT studies described this outcome. In active GI bleeding conditions [19, 20], the post-EGD bleeding-free rates in VET (78.5%; 95% CI 68.0–86.2; $I^2 = 0\%$) and SCT groups (62.7%; 95% CI 45.3–77.3; $I^2 = 55\%$) were not statistically different (RR 1.24; 95% CI 0.92–1.67; $I^2 = 45\%$). The bleeding-free rates following the other invasive procedures [8, 22, 23] in VET (98.1%; 95% CI 91.2–99.6; $I^2 = 0\%$) and SCT groups (97.4%; 95% CI 90.2–99.3; $I^2 = 0\%$) were also similar (RR 1.01; 95% CI 0.96–1.06; $I^2 = 0\%$; Figure 2). Overall, the pooled postprocedural bleeding-free rates in VET and SCT groups were 89.5% (95% CI 74.9–96.0; $I^2 = 58\%$) and 85.7% (95% CI 63.1–95.4; $I^2 = 79\%$), respectively.

FFP transfusion

Six RCTs ($n = 393$) reported the numbers of patients receiving FFP perioperatively [8, 19–23]. The pooled rate of FFP transfusion was 48% significantly lower in VET group (RR 0.52; 95% CI 0.35–0.77; $p = 0.001$; $I^2 = 56\%$; Figure 3a). The pooled rates of FFP transfusion in VET and SCT groups were 28.1% and 60.5%, respectively. When guided by SCTs, FFP was often transfused in active GI bleeding and OLT subgroups (Table S5 and Figure S4a).

Concerning the quantities of transfusion, the weighted mean of transfused FFP units (four RCTs; $n = 265$) [7, 8, 19, 21] was also decreased in VET (3.60 units; 95% CI 1.74–5.47; $I^2 = 95\%$) compared with SCT groups (4.12 units; 95% CI 2.60–5.63; $I^2 = 94\%$). The pooled MD of transfused FFP was 1.39 units lower in VET group (95% CI −2.18 to −0.60; $p < 0.001$; $I^2 = 49\%$; Figure 3b).

Platelet transfusion

The rates of periprocedural platelet transfusion were described in six RCTs ($n = 393$) [8, 19–23]. Using VET-guided strategy was associated with a 66% reduction of platelet transfusion (RR 0.34; 95% CI 0.16–0.73; $p = 0.006$; $I^2 = 79\%$; Figure 4a). This significant efficacy was observed in a subgroup of the other invasive procedures. However, the pooled rates of platelet transfusion in VET and SCT groups were not significantly different in subgroups of active GI bleeding and OLT (Table S5 and Figure S5a).

Similar to the pooled transfusion rates, the pooled mean of transfused platelet units (four RCTs; $n = 265$) [7, 8, 19, 21] in VET group (1.28 units; 95% CI 0.51–2.06; $I^2 = 95\%$) was significantly lower than that in SCT group (2.34 units; 95% CI 1.40–3.27; $I^2 = 95\%$). The pooled MD of transfused platelets was 1.06 units lower in VET group (95% CI −2.01 to −0.12; $p = 0.03$; $I^2 = 92\%$; Figure 4b).

Cryoprecipitate transfusion

The pooled rate of cryoprecipitate transfusion (two RCTs; $n = 134$) [19, 22] in VET group (57.8%; 95% CI 42.7–71.5; $I^2 = 29\%$) was numerically lower than that in SCT group (84.9%; 95% CI 3.0–99.9; $I^2 = 92\%$) but did not reach statistical significance (Figure S1a). One study using fibrinogen concentrate [21] was not primarily included. A post hoc analysis based upon three studies [19, 21, 22] consistently

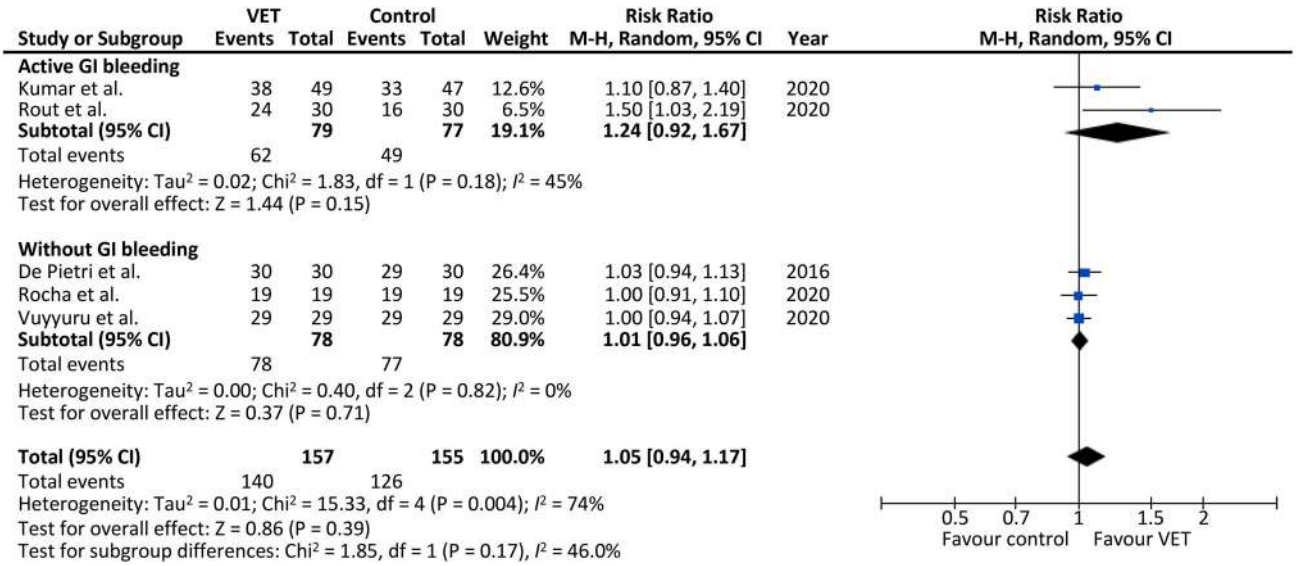

FIGURE 2 Pooled risk ratios of postprocedural bleeding-free events among cirrhotic patients receiving transfusion guided by viscoelastometric testing compared with standard coagulation tests (control). CI, confidence interval; df, degree of freedom; GI, gastrointestinal; VET, viscoelastometric testing

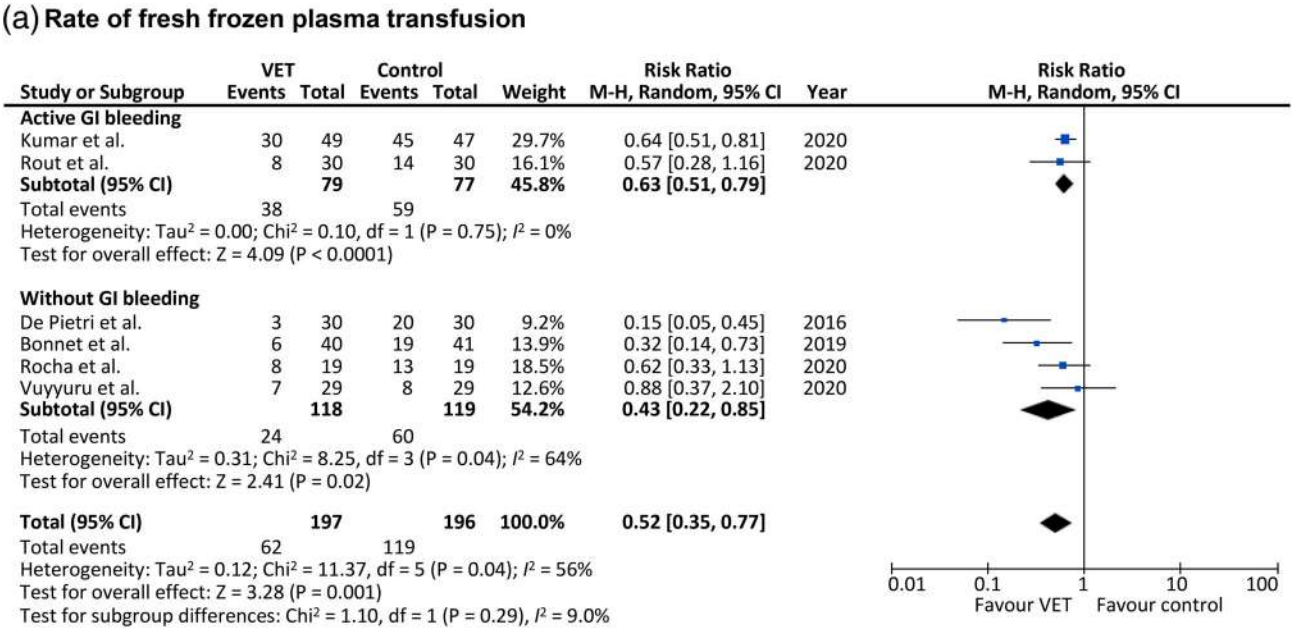

FIGURE 3 Pooled (a) risk ratios of fresh frozen plasma (FFP) transfusion and (b) differences in mean quantities of transfused FFP units among cirrhotic patients using viscoelastometric test-guided strategy compared with standard coagulation test-guided strategy (control). CI, confidence interval; df, degree of freedom; GI, gastrointestinal; VET, viscoelastometric testing

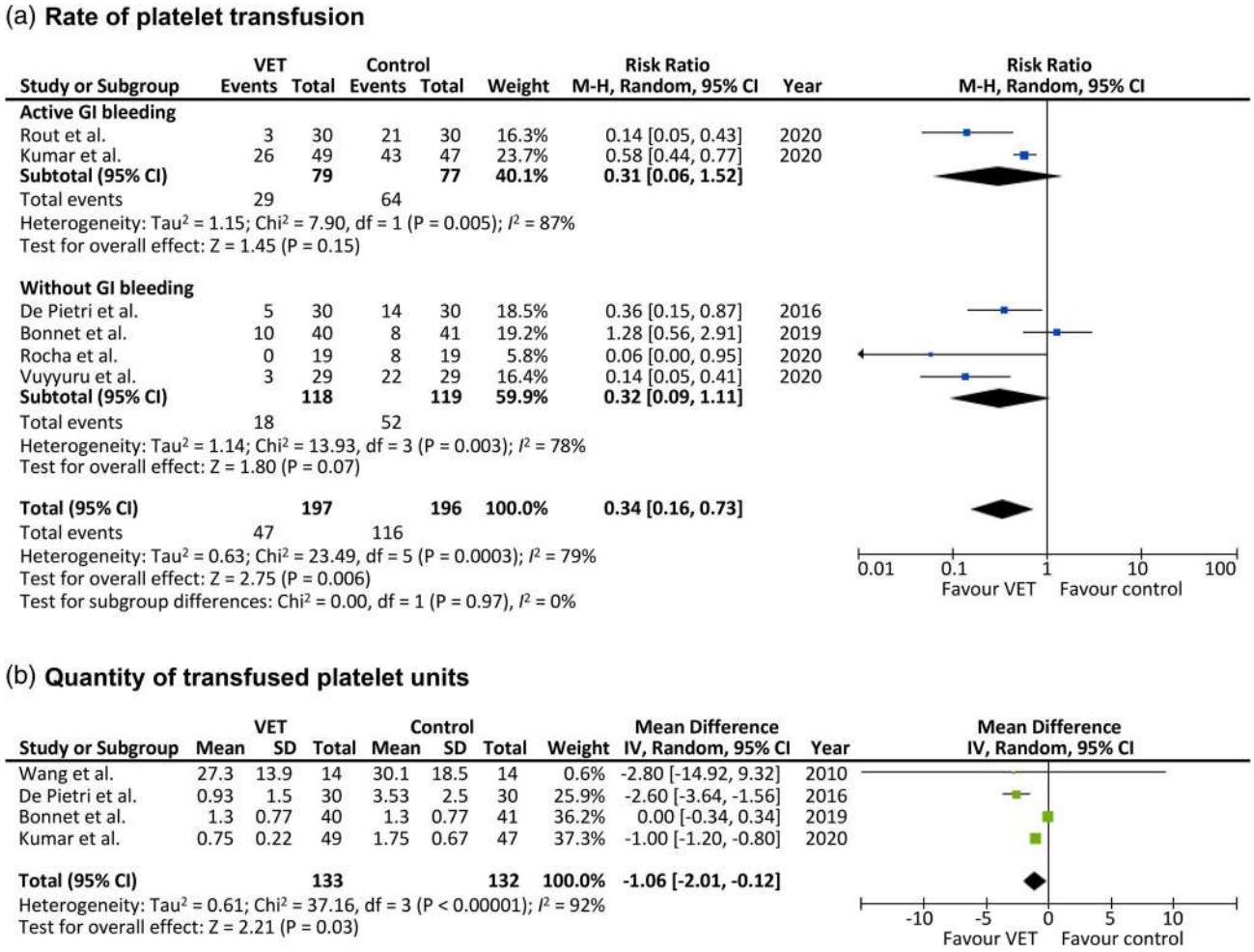

FIGURE 4 Pooled (a) risk ratios of platelet transfusion and (b) differences in mean quantities of transfused platelet units among cirrhotic patients using viscoelastometric test-guided strategy compared with standard coagulation test-guided strategy (control). CI, confidence interval; df, degree of freedom; GI, gastrointestinal; VET, viscoelastometric testing

revealed no significant risk reduction of fibrinogen replacement using VET-specific thresholds (RR 1.31; 95% CI 0.43–3.94; $I^2 = 94\%$). However, the pooled quantity of transfused cryoprecipitate (two RCTs; $n = 124$) [7, 19] was reduced when guided by VET (mean 9.80 units; 95% CI 5.10–14.51; $I^2 = 67\%$) rather than by SCTs (mean 17.65 units; 95% CI 15.75–19.55; $I^2 = 0\%$). The pooled MD of transfused cryoprecipitate was 7.13 units lower in VET group (95% CI −14.20 to −0.07; $p = 0.048$; $I^2 = 71\%$; Figure S1b).

RBC transfusion

Due to haemoglobin (Hb) thresholds of <7–9 g/dl, the pooled rates of RBC transfusion (four RCTs; $n = 297$) [8, 19–21] were not different between VET (53.8%; 95% CI 21.1–78.5, $I^2 = 89\%$) and SCT groups (50.4%; 95% CI 27.2–73.4; $I^2 = 86\%$; Figure S2a). Consistently, among patients with active GI bleeding, the pooled rates of RBC transfusion remain similar between VET and SCT groups (Table S5 and Figure S6a).

Four RCTs ($n = 265$) quantified RBC units delivered perioperatively [7, 19–21]. Corresponding to the pooled transfusion rates, the weighted means of transfused RBC units in VET (3.86 units; 95% CI 2.21–5.51; $I^2 = 95\%$) and SCT groups (3.87 units; 95% CI 1.88–5.85; $I^2 = 95\%$) were not different (Figure S2b). The comparable results were reproducible in active GI bleeding and OLT subgroups (Figure S6b).

Transfusion-related adverse events

Of four RCTs reporting TRAEs, three ($n = 194$) [8, 19, 22] were included in the meta-analysis after excluding the one [23] with zero event. The overall rate of TRAEs in VET group (9.2%; 95% CI 1.3–44.3; $I^2 = 76\%$) was significantly lower than that in SCT group (16.5%; 95% CI 0.7–84.3; $I^2 = 93\%$) with the pooled RR of 0.42 (95% CI 0.27–0.65; $p < 0.001$; $I^2 = 0\%$; Figure S3). Considering TRALI and TACO described solely in the most weighted (95.3%) study of this statistical model ($n = 96$) [19], TRALI and TACO developed in 30.2% and

15.6% of the patients, respectively. When compared with SCT-guided, VET-guided transfusion was significantly associated with a lower risk of TRALI (RR 0.25; 95% CI 0.11–0.56; $p = 0.001$), but not with that of TACO (RR 0.48; 95% CI 0.18–1.30).

Lengths of stay

From two RCTs ($n = 134$) observing LOS [19, 22], when compared with SCT-guided, VET-guided algorithms did not reduce LOS, both in-hospital (MD −0.69 days; 95% CI −5.99 to 4.61; $I^2 = 35\%$) and ICU stay (MD 1.12 days; 95% CI −2.69 to 4.94; $I^2 = 49\%$). Nevertheless, one study of patients with active GI bleeding ($n = 96$) [19] reported shorter in-hospital LOS in VET group (MD −2.00 days; 95% CI −3.49 to −0.51; $p = 0.008$).

Postprocedural mortality

All seven RCTs reported postprocedural mortality among 421 patients. Despite the variable follow-up times (Table S2), the overall mortality rates at the longest follow-ups in VET (30.7%; 95% CI 13.5–55.5; $I^2 = 86\%$) and SCT groups (26.9%; 95% CI 11.2–51.7; $I^2 = 87\%$) were not significantly different (RR 1.04; 95% CI 0.74–1.45; $I^2 = 16\%$). These associations were consistent across procedural subgroups (Figure S7). In addition, the 30-day postprocedural mortality rate (four RCTs; $n = 273$) [19, 21–23] in VET group (14.3%; 95% CI 3.2–46.2; $I^2 = 85\%$) was similar to that in SCT group (12.0%; 95% CI 3.8–32.1; $I^2 = 74\%$).

TEG-specific thresholds and RRs of transfusions

Of six RCTs determining the rates of FFP (Figure 3a) and platelet transfusions (Figure 4a), four ($n = 274$) [8, 19, 20, 23] applied TEG. Due to between-study heterogeneity of TEG-specific thresholds (Table S2), the random-effects meta-regression analyses were performed to examine the impact of r time and MA cut-offs on the pooled RRs of FFP and platelet transfusions, respectively. In linear regression models (Figure S8), using the more prolonged r time cut-off in TEG-guided algorithms was significantly associated with the less RR of FFP transfusion ($p = 0.01$). Meanwhile, using the shorter MA cut-off was related to the less RR of platelet transfusion ($p = 0.04$).

DISCUSSION

In this systematic review and meta-analysis, seven RCTs directly comparing VET-guided with SCT-guided transfusion during the periprocedural period of 421 patients with cirrhosis were accumulated. Transfusion to ameliorate coagulopathy in cirrhosis guided by VET did not alter the risk of postprocedural bleeding-free status, regardless of GI bleeding conditions. Notably, VET-guided algorithms not only decreased the rates of FFP and platelet transfusions but also the quantities of transfused FFP, platelets and cryoprecipitate, resulting in a substantial risk reduction of TRAEs.

As the majority of patients with cirrhosis did not develop postprocedural bleeding (89.5% in VET and 85.7% in SCT groups), plasma and platelet transfusions could be harmlessly avoided using VET-guided thresholds. This advantage of VET on patient blood management in this setting is consistent with the benefits in other groups of patients [9]. Due to the rebalanced haemostasis [4, 5], there is no significant correlation between INR and TEG r time or EXTEM CT [24, 25]. Moreover, FFP transfusion can normalize INR in only 15% of cirrhotic patients with INR ≥1.5, but 34% of those develop impaired thrombin generation, probably due to increasing protein C levels [26]. On contrary, platelet counts and fibrinogen levels show correlations with TEG MA or EXTEM MCF, and TEG alpha angle or EXTEM/FIBTEM MCF, respectively [24, 25, 27]. The speed of fibrin polymerization represented by TEG alpha angle is related to fibrinogen concentration, whereas the clot strength measured by TEG MA or ROTEM MCF are co-influenced by platelets and fibrinogen [28], and can be maintained by fibrinogen replacement during severe thrombocytopenia (≤30×10^9/L) [29]. However, platelet transfusion targeting platelet counts to approximately 50×10^9/L minimally improves ROTEM MCF [30]. In this context, although the preprocedural transfusion thresholds of platelet counts <50×10^9/L and fibrinogen levels <1.0 g/L are recommended for cirrhotic patients, supportive evidence is lacking [31]. Based upon our meta-analysis, VET-specific thresholds on impaired clot formation and strength, rather than the cut-offs on prolonged INR, thrombocytopenia and hypofibrinogenaemia, helpfully prevent unnecessary periprocedural FFP, platelet and cryoprecipitate transfusions in cirrhosis.

VET possibly underestimates deficiencies of the natural anticoagulants, for example, antithrombin and protein C [28]. Therefore, VET may not predict clinically relevant bleeding in cirrhotic patients [32]. Nevertheless, minimizing periprocedural transfusions by VET guidance did not increase bleeding complications in various clinical settings (Figure 2). Our meta-regression analyses of four RCTs [8, 19, 20, 23] revealed the negative correlation between TEG r time cut-offs and the RRs of FFP transfusion, as well as the positive correlation between TEG MA thresholds and the RRs of platelet transfusion. Accordingly, TEG r time >40 min and MA <30 mm can be safely applied for FFP and platelet transfusion thresholds, respectively (Figure S8).

Remarkably, VET did not reduce periprocedural RBC transfusion. A plausible explanation is a general utility of a restrictive RBC transfusion strategy in cirrhosis [33]. An RCT elicited a survival benefit from RBC transfusion when a Hb level <7 g/dl among cirrhotic patients with acute upper GI bleeding [34]. Besides, animal and in vitro studies suggested a futility of excessive RBC transfusion, not only due to rebleeding from portal hypertension but also on no improvement of clot formation [35, 36]. Consequently, the restrictive RBC transfusion strategy should be integrated to maximize the clinical benefits of VET.

Probably attributable to the lower transfusion rates, TRAEs less frequently occurred in the VET group. Evidently, transfused patients

with cirrhosis develop TRALI more commonly than those without cirrhosis [37]. One RCT in our meta-analysis confirmed the remarkably high incidence of TRALI (30.2%), which could be reduced by VET guidance [19]. Despite no reduction in LOS and mortality, VET-guided transfusion helpfully decreases morbidity and cost of TRAEs after invasive procedures [38].

A recent meta-analysis of 17 studies (9 cohorts, 2 published and 6 unpublished RCTs) similarly revealed that the VET-guided approach could reduce the quantities of transfused FFP, platelets and RBCs, as well as the rates of any bleeding in 1753 cirrhotic patients undergoing various procedures [10]. However, biases are possible in observational and unpublished studies. Since our updated analysis included only the published RCTs, sample sizes and baseline data were balanced between VET and SCT groups (Table S3). We discovered that RBC transfusion and postprocedural bleeding were not reduced by VET-guided strategy in RCTs. Moreover, a significant reduction of TRAEs was demonstrated.

Our study has limitations. First, despite the balanced characteristics between two comparative arms, the clinical heterogeneity, including the patient- and/or procedure-specific bleeding risks undeniably varied among RCTs. The subgroup analyses stratified by some specific clinical conditions were conducted. Nevertheless, a few studies were aggregated in each model, leading to inconsistent results among subgroups. Second, the small number and sample sizes of the included RCTs partially caused moderate-to-high degrees of statistical heterogeneity. Thus, the random-effects models were generally applied. Third, VET-specific thresholds were variable; therefore, we performed the meta-regression analyses evaluating the effects of different thresholds. Future large RCTs with uniform VET-guided thresholds should provide robust results for clinical practice.

In conclusion, preprocedural evaluation of coagulopathy in cirrhosis by VET, instead of SCTs, significantly reduces the rates of FFP and platelet transfusions, the quantities of transfused FFP, platelets and cryoprecipitate, as well as the risk of TRAEs, without a harmful increase of postprocedural bleeding, LOS or mortality.

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CONFLICT OF INTEREST

All authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

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ORIGINAL ARTICLE

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Prediction and impact of personalized donation intervals

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Abstract

Background and Objectives: Deferral of blood donors due to low haemoglobin (Hb) is demotivating to donors, can be a sign for developing anaemia and incurs costs for blood establishments. The prediction of Hb deferral has been shown to be feasible in a number of studies based on demographic, Hb measurement and donation history data. The aim of this paper is to evaluate how state-of-the-art computational prediction tools can facilitate nationwide personalized donation intervals.

Materials and Methods: Using donation history data from the last 20 years in Finland, FinDonor blood donor cohort data and blood service Biobank genotyping data, we built linear and non-linear predictors of Hb deferral. Based on financial data from the Finnish Red Cross Blood Service, we then estimated the economic impacts of deploying such predictors.

Results: We discovered that while linear predictors generally predict Hb relatively well, they have difficulties in predicting low Hb values. Overall, we found that non-linear or linear predictors with or without genetic data performed only slightly better than a simple cutoff based on previous Hb. However, if any of our deferral prediction methods are used to assign temporary prolongations of donation intervals for females, then our calculations indicate cost savings while maintaining the blood supply.

Conclusion: We find that even though the prediction accuracy is not very high, the actual use of any of our predictors in blood collection is still likely to bring benefits to blood donors and blood establishments alike.

KEYWORDS
blood collection, donor health, haemoglobin measurement

Highlights

- More refined prediction models, even using genetic data, have only slightly better accuracy than a simple baseline model.
- In our models, the effect of the donation interval on the haemoglobin level was too small to make donor-specific donation intervals possible. However, assigning a temporary fixed-term prolongation of the donation interval when deferral is predicted is likely to bring positive health effects in the vulnerable group of female donors under age 30.
- All prediction models we implemented lead to cost savings when used to determine a temporary fixed-term prolongation of donation interval for females.

INTRODUCTION

Deferring a person from donating due to low haemoglobin (Hb) can be demotivating for the donor, incurs extra costs to blood establishment and may indicate that a donor has donated blood too frequently causing negative health effects such as anaemia [1]. To mitigate these negative effects, it is beneficial to be able to predict the donor's Hb value at a given date or directly predict whether the Hb will be below the deferral limit.

Previously, Baart et al. used logistic regression with non-linear predictors to predict low Hb deferrals [2,3]. Subsequently, Nasserinejad [4] and Fokkinga [5] used Bayesian linear mixed models (LMMs) to predict Hb.

In this study, we aim to develop prediction methods for Hb/deferral to improve donor health and reduce costs due to deferrals without damaging the blood supply. We essentially reimplement the methods of Nasserinejad and Fokkinga and run them on our larger datasets with additional variables. To our knowledge, we are the first to use genetic information as explanatory variables and to estimate the blood supply and economic effects of deploying a low-Hb deferral model. We also publish our model implementations to make it easier to build future research on our results.

MATERIALS AND METHODS

The blood donation and blood product information of the Finnish Red Cross Blood Service (FRCBS) until 2020 was collected in the eProgesa database (MAKSYSTEM, Paris, France). Here, the eProgesa dataset contains the donation histories of Finnish blood donors from the last 20 years: 6,414,193 donation attempts from 940,831 donors. These data are collected at every blood donation event, and they contain information about the Hb value (pre-donation point-of-care capillary finger-prick sample) [6], time of day, donation location, type of donation and amount of blood collected.

We pre-processed the raw eProgesa data (Figure 1) to obtain a clean dataset for building models. Outliers, missing values and other problematic cases were handled by dropping instead of imputing them (Figure S2). We also derived several new variables from the raw variables (Figure 1c). After pre-processing, we were left with 2,157,733 donations and 449,008 donors .

The Biobank dataset contains genome-wide SNP genotyping data obtained from the Blood Service Biobank and height, weight and smoking variables from the Biobank enrolment questionnaire of 20,222 donors. The FinDonor [7] dataset contains more information about donation events such as blood counts, iron indices and questionnaire data. This dataset is much smaller than the eProgesa data, having a total of 7994 donation events from 2580 donors.

The variables from the eProgesa, Biobank and FinDonor datasets used for training our models are described in Tables S1–S3, respectively. Later in this paper, we refer to the combinations of eProgesa with the Biobank and FinDonor datasets with just Biobank and FinDonor, respectively. Further discussion about the variables used and pre-processing can be found in Section S1.

As the donation history is a longitudinal dataset, we can apply LMMs (where some parameters can be stochastic instead of being fixed, as in normal linear models) to predict Hb. Our model has the form $y_{it} = x_{it}\ \beta + c_i\ \phi + b_i + \varepsilon_{it}$, where i refers to a donor and t to a donation time. The donation and donor-specific variables are stored in matrices x_{it} and c_i, respectively. The donor-specific intercept b_i is the only random effect, and it allows deviation between donors caused by unobserved variables. If the previous Hb is among the predictors, then the model is called a dynamic linear mixed model (DLMM). Stan [8] is used to train these models in a Bayesian setting with weakly informative conjugate priors. To estimate the linear models' capability to predict deferral, the predicted Hb is dichotomized with the deferral limits used in Finland (135 g/L for men and 125 g/L for women).

To test whether the dependence of Hb is non-linear with respect to the predictors, we use a random forest (RF) model [9]. Because deferrals are rare in Finnish donation history (approximately 3.2% of donations), in the RF algorithm, we oversample the deferrals so that the trees are created from samples where 50% of the donors have deferral as their last donation to make it easier to train a classifier for deferral. As an RF cannot directly model time series, we add to each donation event information about the previous Hb and the number of lifetime donations. We use randomForest [10] to train an RF whose hyperparameters were optimized with caret [11] using four-fold cross-validation. Details about the linear and RF models and their implementations can be found in Section S2.

We measured the accuracy of Hb prediction with root mean square error (RMSE) and mean absolute error (MAE) and the performance of the binary classifier of deferral with area under the receiver operating characteristic curve (AUROC), area under the precision-recall curve (AUPR) and F-score (F1) metrics. More details of the performance measures used can be found in Section S2.4.

Personalized donation intervals can be applied either by estimating a truly personal donation interval for each donor or by creating predetermined donation interval categories and assigning donors to them. In either case, the total adjustment a_{tot} in the population of returning donors is given by the mean of adjustments a_i. If we extend the donation interval of donor i by 10%, for example, then $a_i = 1.1$. This adjustment has a direct inverse effect on the flow of returning donors, which we find by subtracting the influx of new donors from the total influx of donors. Thus, the total influx after adjustments is given by

$$F_{\text{adj}} = (F - F_{\text{new}})/a_{\text{tot}} + F_{\text{new}}.$$

If donor recruitment efforts are not simultaneously increased, then the lowered influx is directly proportional to the supply level, for example, halving the total influx means halving the supply level, on average. Assuming that the supply level is held at the optimum before adjustments, the negative effects from donation interval personalization need to be compensated.

While marketing efficacy is not constant over long periods and while the cost of recruitment might increase with the size of the compensation, we can calculate estimates for the costs of this compensation for small enough adjustments by assuming a direct inverse relationship between the lowered influx of donors and the marketing efforts/budget:

$$M_{new} = F/F_{adj}\, M.$$

In addition to increased donor recruitment costs, we need to consider the savings from avoided deferrals after personalizing donation intervals, as deferring a donor may negatively impact donor retention. Avoiding deferrals decreases the negative impact on donor retention, which we otherwise would have had to compensate in marketing. The full marketing-related economic effects of interval personalization can then be summarized as

$$E_M = F/F_{adj} - 1 - (1 - F_{new})\, d\, q\, r_{loss},$$

where we signify the negative impact of deferral on donor retention with r_{loss}, the rate of avoided deferrals with q and the population deferral rate with d.

By finding the costs for marketing (per successful donation) and deferrals, we can expand this formulation into an equation that outputs the operational cost of deploying a type of personalization model in units of cost per donation:

$$E = P_M\left(F/F_{adj} - 1 - (1 - F_{new})\, d\, q\, r_{loss}\right) - P_D\, d\, q,$$

where P_M represents the estimated marketing cost of a single successful donation, and P_D is the cost of a deferred donor. The boundary for financial gain is then at $E = 0$, with $E < 0$ indicating savings and $E > 0$ costs incurred. The parameter values that apply to the FRCBS are listed in Table 1. Our economic effect formulation allows us to adjust for the model performance via the terms a_{tot} and q. A good model needs to extend the total donor influx only by very little to avoid most of the possible deferrals in the population (so $a_{tot} = 1 + \varepsilon$, $0 \le \varepsilon \ll 1$). If we let a_{tot} and q vary between chosen value ranges, then we can calculate the cost surface between these axes. Figure S38 presents the cost surface for the FRCBS drawn using values given in Table 1.

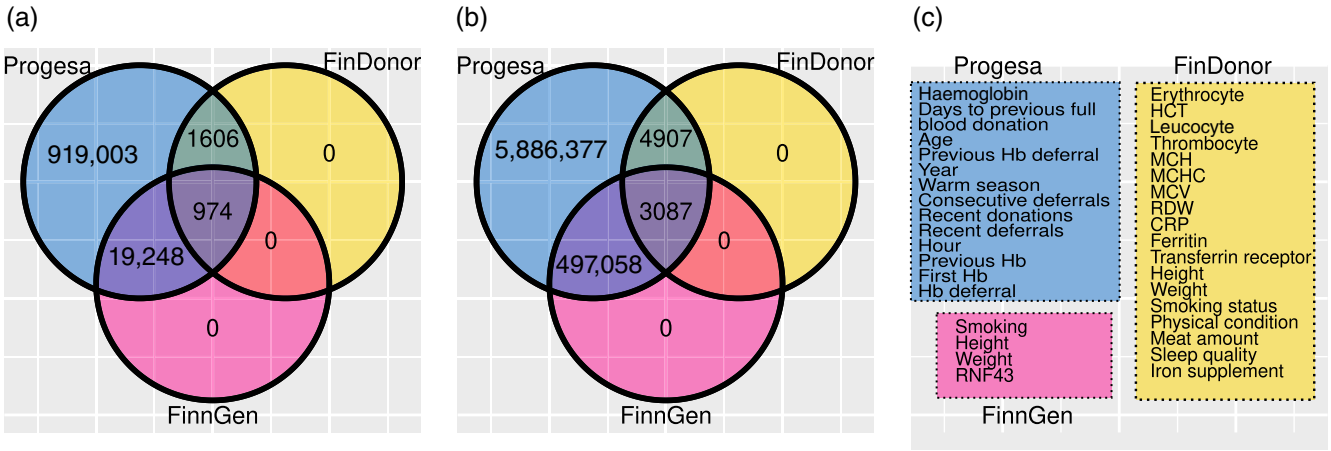

FIGURE 1 The intersections of the three datasets. (a) The number of donors and (b) the number of donations. The eProgesa dataset is shown in the raw form, before any pre-processing was done. (c) The variables of each dataset

TABLE 1 The description of parameters in the cost effect formula and the parameter values specific to Finnish Red Cross Blood Service

Variable	Explanation	Value	Comment
q	Rate of avoided deferrals	[0,1]	From none to all.
d	Rate of deferrals in the population	0.032	From donor history data between 2018 and 2020.
a_{tot}	Total adjustment effect due to interval extension	>1	
P_M	Estimated marketing cost of a successful donation	2.287	Euros. An approximation based on the price of targeted and untargeted marketing per donation and response rates to targeted marketing.
P_D	Cost of a deferred donor	20.342	Euros. Comprises costs of materials, marketing and work time.
F	Total influx of donors	1	As in 100%.
F_{new}	Influx of new donors	0.107	Currently, new donors comprise about 10% of the donor influx.
r_{loss}	Impact of deferral on donor retention	0.167	Low Hb deferrals are currently estimated to have approximately 16.7% negative impact on donor retention. This analysis is detailed in Section S3.3.1.

RESULTS

To determine, which subset of full data are best suited as the input for fitting LMMs, we performed three experiments: effect of time series length, effect of amount of data and effect of the imbalance of the division of the donations into accepted and deferred classes on Hb prediction. In addition, to determine whether the rules for selecting the input subset generalize, we divided the data into two equal-sized halves: an exploration part and a final model fitting and testing part. The three experiments described below were all performed on the exploration part of the data.

The distribution of time-series length of female donors in eProgesa data is shown in Figure S8. The number of donors decreases exponentially as a function of the time-series length. To model the data and predict the last donation of each time series, the minimum theoretical time series length is three. This requirement already dropped 50% of the donors from further consideration. To test the effect of the time-series length on Hb prediction, we partitioned the female eProgesa data

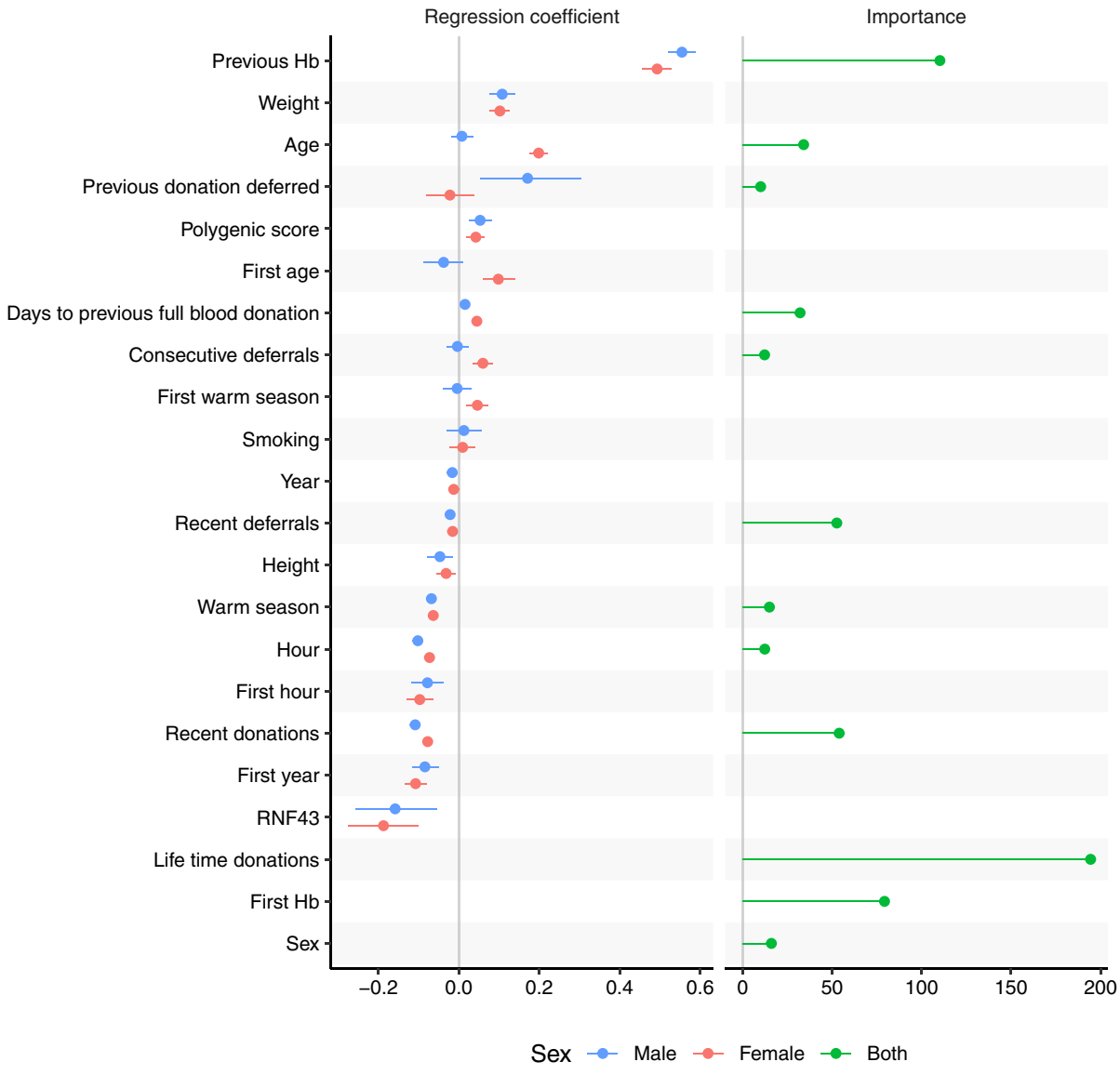

FIGURE 2 The effect sizes and importance of variables in haemoglobin and deferral prediction. On the left panel, the regression coefficients of the DLMM when predicting haemoglobin on variables of the combined eProgesa and Biobank data. The dots and the lines denote the posterior means and the 95% highest posterior density intervals (HPDIs), respectively, for each variable and sex. In order to make the regression coefficients comparable, we left the binary variables as they are but scaled other variables by 2 SD. Hence, the units of the regression coefficients are two times the standard deviation. On the right, the importance of variables, when predicting deferral using a random forest model on eProgesa data, are marked with dots. With the random forest model, we did not train separate models for the male and female subsets but instead used sex as a predictor. Note that for both DLMM and random forest (RF) models the previous haemoglobin was clearly the most important variable. The difference of effect size between sexes seems to be mostly small, the age being a notable exception

into subsets based on time-series length, with each subset having donors with the same number of donations. We fitted a DLMM on each of these datasets and predicted the Hb of the last donation of the time series. The results are shown in Table S6. On the one hand, the results seemed to improve as the time-series length increased. On the other hand, the data were scarcer with longer time series. As a compromise, we decided to use the data from donors with at least seven donations in our later analyses of eProgesa and Biobank data.

We also experimented with the effect of the amount of data on the prediction. We randomly took three samples from female

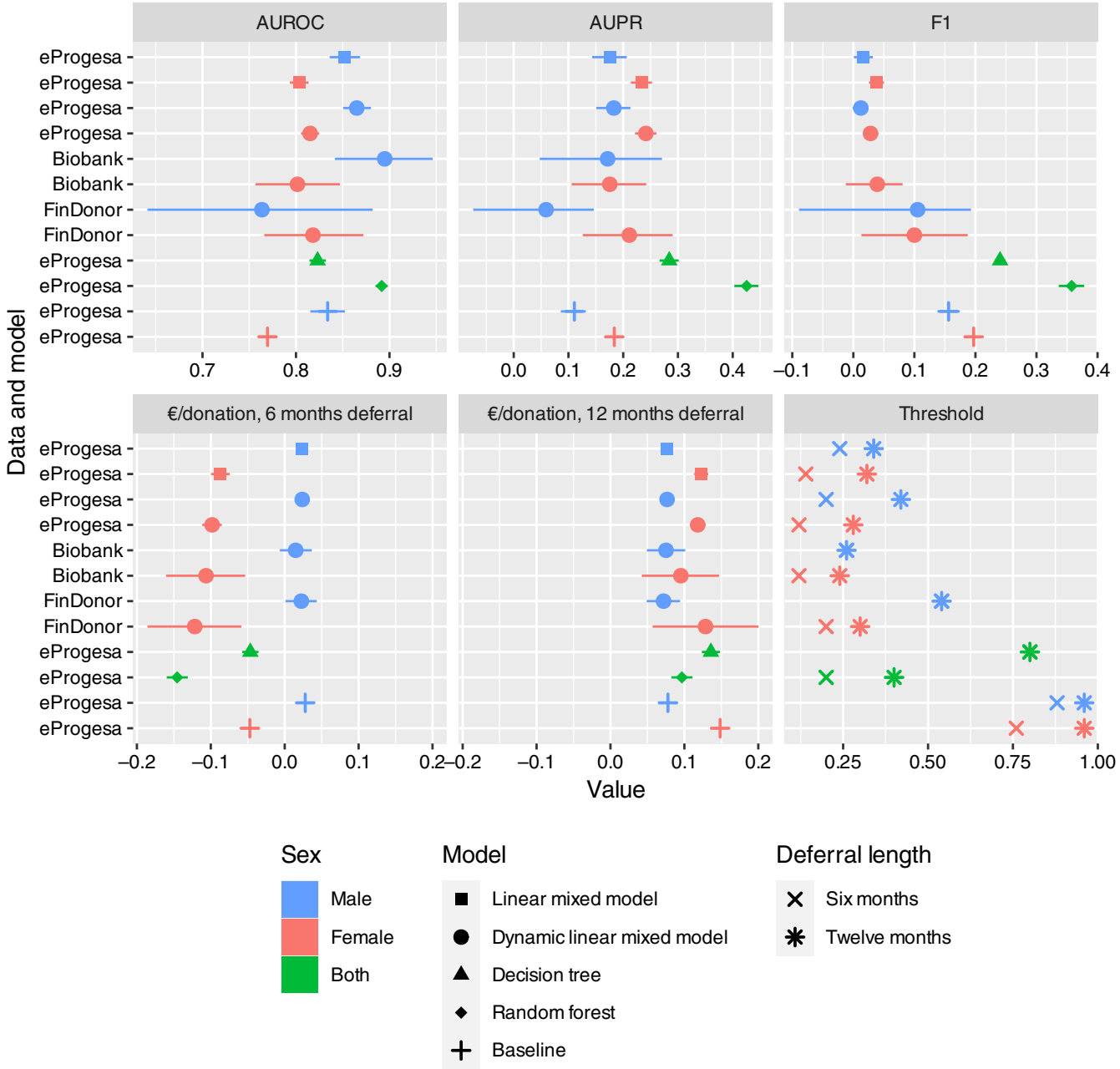

FIGURE 3 Performance metrics and economic effects for the models. The AUROC, AUPR and F1 are standard metrics measuring the performance of a binary classifier. We also show the economic effect of assigning either a 6- or 12-month donation interval to donors who are predicted to be deferred. A negative effect means savings in units of euro per donation. From the Hb prediction of the Bayesian linear mixed models, we calculate the probability of deferral based on Finnish deferral limits, while the random forest model outputs probabilities of deferrals directly. To calculate economic effects, these probabilities of deferrals need to be dichotomized into a deferral status by a cutoff value. The threshold panel shows, which cutoff for the probability of deferral, applied to a given model, gave the optimal savings (shown on the economic effect panels), where the candidates for cutoffs were 0.02, 0.04, ..., 0.98. For all the panels except the threshold panel, 95% confidence intervals computed using bootstrapping are shown. Most of the savings come from avoiding female deferrals

eProgesa data with 10,000, 30,000 and 50,000 donors. The amount of data did not show any clear effect on the prediction results (see Table S7).

Next, we considered the imbalance between accepted and deferred donation classes. In the pre-processed eProgesa data, only 12% of the donors had at least one deferral and the number of donors with more deferrals decreased rapidly, as shown in Figure S9. Since we want to be able to accurately predict Hb values that are below the accepted threshold, it is vital that there are enough examples of low Hb donations in the training data. We tried to artificially enrich the fraction of deferrals by dropping out donors with no deferrals. This resulted in a subset of female eProgesa data with the fraction of donors with at least one deferral being 50%. We fitted a DLMM on these data, and the prediction results are shown in Table S8. The results worsened after the enrichment.

As a result of the above exploration, we decided not to enrich the training data used for fitting LMMs. In addition, we only included donors who had donated at least seven times. The resulting dataset was already small enough, so fitting a model on these data was feasible in terms of time and memory required. Hence, no further

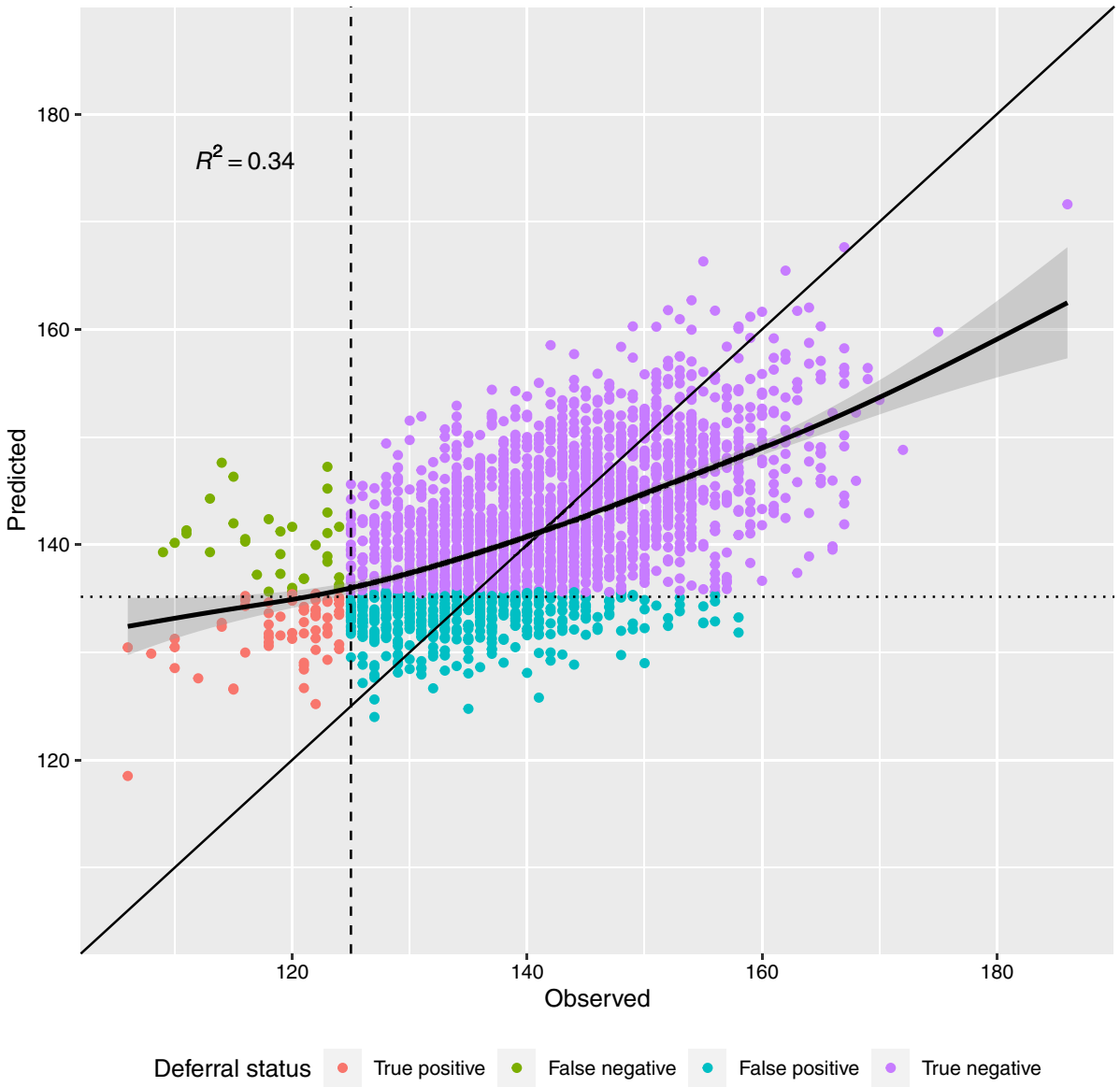

FIGURE 4 The observed and predicted Hb values given by the Biobank female DLMM are plotted with the R^2 correlation value. The fitted smooth curve (generalized additive model) and its 95% confidence intervals show the difficulty in predicting extreme Hb values. The donations are classified into deferred (positive) and accepted (negative) classes first by comparing the observed values and the standard female threshold 125 g/L (dashed vertical line). Second, the probability of the haemoglobin deferral is compared to the 6-month deferral probability cutoff of 0.12 (found by maximizing savings, see Figure 3 panel threshold), which corresponds roughly to the predicted Hb value 135.2 g/L (dotted horizontal line). Note that had we used the same threshold for predicted Hb as for observed Hb (125 g/L), we would have been able to predict only one deferral correctly

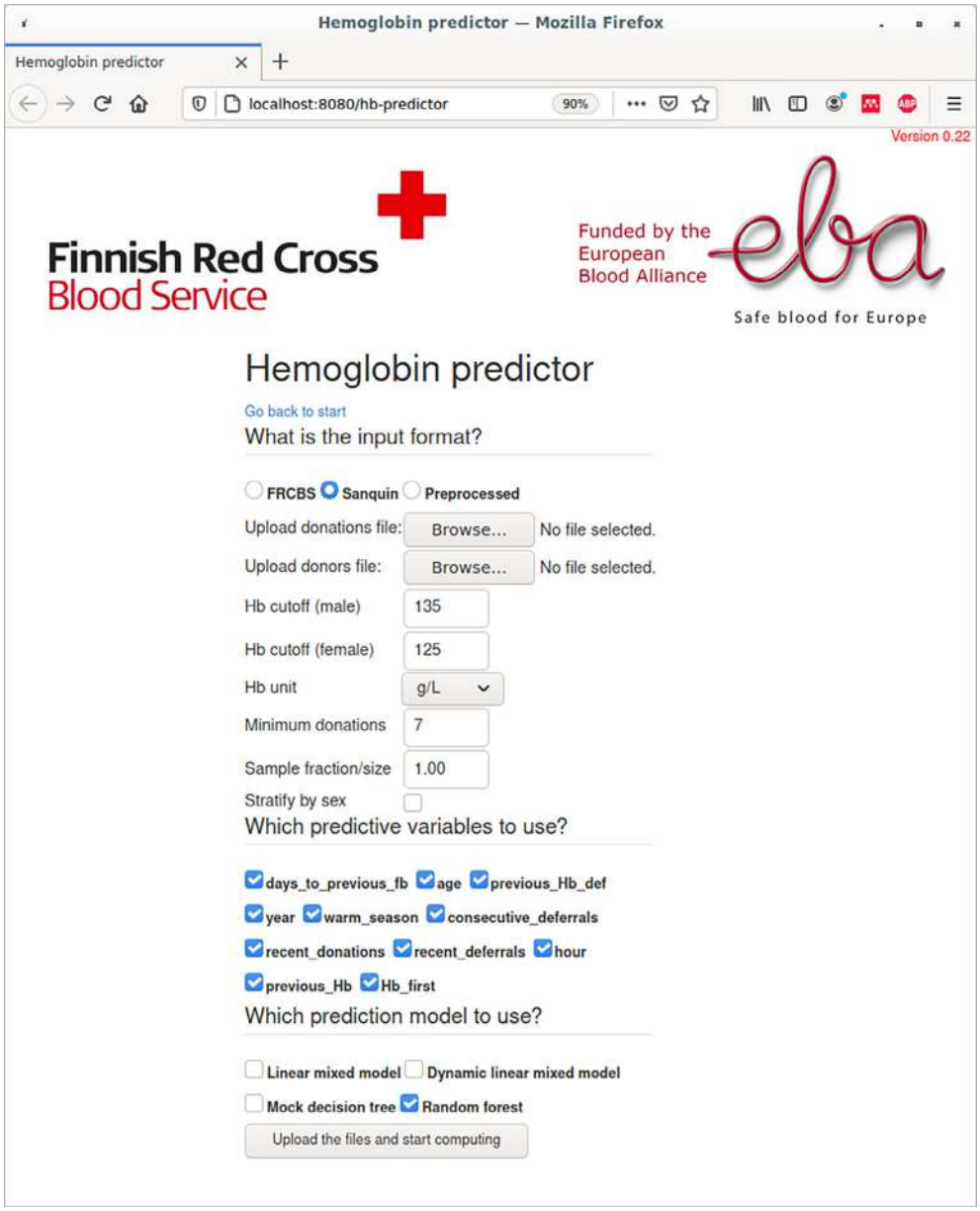

FIGURE 5 The user interface to the prediction models works in any web browser. After the parameters are configured and the input data are uploaded, the computation begins. The result is given as both html and pdf documents that contain plots and tables, with the possibility of downloading the results in a raw form for further processing

subsetting of the data was needed. The resulting final testing data had 695,658 donations (398,803 female and 296,855 male) from 47,820 donors (29,298 female and 18,522 male). This dataset was used in the final analyses of the eProgesa data and the Biobank data. A different scheme, explained in Section S3.2.4, was used for FinDonor data, as that data had a very small number of donors and donations.

Figure 2 illustrates the effect sizes of variables of Biobank data in DLMM and the importance of eProgesa variables in RF. Other models gave similar results (Figures S10, S11, S20, S26, S31 and S34). There were no large differences in effect sizes between men and women except for the age-related variables. In both models, previous Hb was clearly the most important variable. The SNP rs199598395 on gene RNF43 had a large influence, but a polygenic score of Hb calculated from UK Biobank data had a smaller effect size than whether the donation was given in April–September.

The effect of the "days to previous full blood donation" was so small that varying it and other time-dependent variables accordingly did not affect deferral prediction enough to enable fully personalized donation intervals. Hence, we analysed the effect of donation activity by demographic group on the low Hb deferral rate for all donations in Finland (Figure S6) and the effect of donation on the iron deficiency rate in FinDonor data (Figure S7). Although no clear association existed between deferral rate and donation activity, a fixed deferral of 12 months is likely to reduce deferrals in the most

vulnerable group, that is, women younger than 30 (Figure S6). For ferritin levels of the same group, even a 6-month deferral would decrease the number of yearly donations by up to two or three and hence significantly decrease the prevalence of low iron (Figure S7). In general, a 6-month interval, possibly with supplemental iron, has previously been shown to allow ferritin recuperation for most donors [12, 13].

To estimate the economic effects of deferral prediction, we subsequently used these two alternative donation intervals in case a model predicted a donor to be deferred. When we temporarily extended the donation intervals of all true and predicted deferrals to either 6 or 12 months, we obtained a rough but concrete estimate of the cost effect of the model performance.

The deferral prediction results and economic effects are summarized in Figure 3 and Table S14. According to the AUROC metric, RF performed better than the other models except for the male DLMM with Biobank data. However, there were no large differences in the performance of the LMM and RF, and each was only slightly better than our baseline model, that is, logistic regression with previous Hb as the only predictor.

In addition, all female models and the RF model resulted in cost reductions when a 6-month deferral was applied for those predicted to be deferred (Figure 3). For RF, the economic effect was −0.15 euro per donation, that is, an economic savings of 0.15 euro per donation, and the average interval extension was 1.1. Deployment of this model would result in avoiding 51% of the deferrals. In the models that were trained by stratifying by sex, the average cost effect for males was 0.02 euro per donation, whereas, for women, the effect was −0.11 euro per donation. If both male and female models were applied, then the DLMM with FinDonor data gave the second-largest savings at approximately 0.1 euro per donation, with the average donation interval length being 1.12-fold. This model enabled us to avoid 51% of deferrals.

As the baseline model predicts based on previous Hb only, the probability thresholds that were found to provide the largest savings correspond to specific Hb values. For 6-month deferral, these were 147 g/L for men and 135 g/L for women; and for 12-month deferral, 141 g/L for men and 122 g/L for women.

DISCUSSION

Our reimplementation of the LMMs gives equal or slightly weaker results in terms of MAE and RMSE (Table S13) but better results in terms of AUROC than in Fokkinga [5]. This is probably due to larger data and more variables, but these approaches still fail to predict lower Hb values. For example, the female DLMM on Biobank data predicts for all but one donation where Hb is below 125 g/L higher than 125 g/L Hb. However, if the deferral threshold that gives optimal economic effects is used instead, then we can avoid 49% of the deferrals while falsely predicting as deferred only 18% of the viable donations (Figure 4). We expect the prediction results to be more accurate in countries where the deferral rate is higher than in Finland since the ratio of accepted and deferred donations is more balanced. Although the incorporation of genetic information as predictors improves the prediction (Figure 3, Table S14), the effect appears small in relation to the costs of genotyping. The SNP rs199598395 in the RNF43 gene was discovered by the FinnGen project as a lead SNP for iron deficiency anaemia (http://r4.finngen.fi/pheno/D3_ANAEMIA_IRONDEF). Its effect size is large, but the minor allele is only present in ∼2% of donors. Overall, in Finns, it is present in ∼1% of people, in Europeans (non-Finnish) ∼0.01% and it is not found in other populations [14]. This highlights the possibility that further study of population-specific or rare genetic variation could considerably increase the value of genetic predictors.

Our RF model performs similarly to logistic regression with non-linear predictors [3] in predicting deferral but is simpler and easier to train. There is no apparent performance difference between the LMMs and RF in predicting deferral. Importantly, these complicated models seem to have little benefit over a simple one-predictor logistic regression (baseline model).

Due to the low accuracy in Hb prediction and the fact that the effect of the "days to previous full blood donation" variable is small, we were unable to define completely personalized donation intervals. However, our calculations on the blood supply and economic effects indicate that cost reduction is still possible through a fixed deferral (6 months) given to donors (especially female donors) predicted to be deferred. To our knowledge, this is the first report that estimates the blood supply and economic effects of deploying a deferral prediction model. However, our calculations are based on two assumptions: (1) that every euro spent on marketing will result in a proportional number of new donors coming in and (2) that the Hb values recover as a function of time. Although assumption (1) is certainly not universally valid, we believe that it is very likely to be valid for the small adjustments we make here.

In conclusion, our results suggest that pre-donation Hb data could be used much more efficiently to bring savings and health benefits. Furthermore, savings to donors will result in saved time and travel expenses [15], although we did not include them in our estimation. If the pre-donation Hb value is found to be below the threshold for economic effects but above the deferral limit, then the donor can donate but is deferred, for example, for 6 months. We do not find that the more complicated computational predictors could greatly improve on this. However, more predictive data such as ferritin measurements at every donation, more informative genetic data, or iron consumption and menstruation data could bring significant improvements. We have started evaluating the deployment of the threshold-based system at the FRCBS. This includes assessing the effect of varying the cost parameters, risk analysis and possible testing of the procedure at a single donation site.

The source code of the model implementations is available at GitHub (see Supporting Information for details) and Zenodo [16]. Furthermore, a ready-to-use prediction application as a Docker [17] software container is also provided. Its user interface, which runs in a web browser, facilitates easy use for non-programmers (see Figure 5).

These resources allow others to test our models with their data and develop them further; see Section S2.3 for more details.

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CONFLICT OF INTEREST

There are no conflicts identified.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Clinical practice for outpatients that are chronically red cell dependent: A survey in the Netherlands

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Abstract

Background and Objectives: Limited data are available to guide physicians on how to determine the red blood cell (RBC) transfusion regimen in chronically transfusion-dependent patients. The lack of clarity on thresholds and targets to be used for transfusion could easily result in either under or over transfusion in these patients. The aim of our survey is to investigate (1) transfusion thresholds; (2) number of RBC units given per transfusion episode; (3) interval between transfusions and (4) patient factors, like decreased cardiac function modulating the former.

Materials and Methods: We sent a web-based 44-question survey to members of the Dutch Haematology Association.

Results: Fifty physicians responded between June and October 2020 (response rate 30%), well-distributed between community and academic hospitals. A wide variation in transfusion strategies was reported: Most patients have transfused 1–2 RBC units (range: 0–3 units) every 2–4 weeks (range: 1–12 weeks) with a median threshold of 8.0 g/dl ranging from 6.4 to 9.6 g/dl. Patient-specific clinical factors that are most frequently reported to influence the transfusion strategy are angina pectoris, cardiac failure and dyspnoea, softer parameters that are of influence are the quality of life and self-sustainability.

Conclusion: The results of this survey indicate a broad variation in RBC transfusion strategies in Dutch patients with chronic transfusion dependency. While the current variation in transfusion strategies may be unavoidable in an individualized approach, randomized trials and better defined usable parameters to evaluate the effect of transfusion strategies are required to reach a consensus on how to determine the transfusion strategy.

KEYWORDS
chronic anaemia, patient blood management, red blood cell transfusion, survey, transfusion dependency

Highlights

- Great variability in transfusion strategies for chronic anaemic patients was found.
- Parameters associated with changes in transfusion strategies, like angina pectoris and self-sustainability, are identified.
- The outcomes allows professionals to benchmark their transfusion strategies and practices and reflect on them, and can be used in training.

INTRODUCTION

Patients who receive red blood cell (RBC) transfusions on a regular basis typically suffer from diseases like myelodysplastic syndrome (MDS), myeloproliferative diseases (MPN), thalassaemia, sickle cell disease or aplastic anaemia. Although these patients receive 20%–30% of all RBC transfusions in Europe [1, 2], limited data are available to guide physicians on how to determine a chronic RBC regimen [3–7]. As studies on restrictive RBC transfusion strategies show no disadvantages in other patient categories [8–12], physicians tend to use a restrictive transfusion policy based on the perceived Quality of Life (QoL) of the individual patient [13–15]. The effect of this individualized transfusion policy is hard to quantify and depends on the haemoglobin (Hb) threshold, the timing of transfusion and the number of RBC units administrated [6, 7, 16]. Factors like anaemia related symptoms, the (estimated) cardiopulmonary compensation capacity and the presence of iron overload might further influence the transfusion policy [17, 18]. The lack of clarity on thresholds and targets to be used for transfusion, will easily result in either under or over transfusion in these patients. Both moreover, will have negative effects, with on one hand anaemia-related QoL [19–22] and on the other iron-overload and other transfusion-specific side effects [23–25].

We performed a survey amongst haematologists in the Netherlands to investigate their current standard of care for patients dependent on chronic transfusions, regarding the applied (1) transfusion thresholds; (2) number of RBC units given per transfusion episode; (3) interval between transfusions and (4) patient factors, like decreased cardiac function modulating the former.

MATERIALS AND METHODS

Study design

In this cross-sectional study, a structured, 44-question online survey was conducted amongst members of the Dutch Society of Haematology (NVvH) that treat patients with chronic transfusion dependency due to a haematological disorder. The questionnaire was sent to 169 haematologists in the Netherlands (Appendix S1). The questions were related to both clinical and soft outcomes that might influence the transfusion policy, that is, the Hb threshold, amount of transfusions given and the interval between transfusions. In addition, respondents were asked to fill out a set of questions about one or more of their own transfusion-dependent patients to test for consistency of actual practice with responses to similar general questions. To allow for quantitative answers, Likert scales were used [26]. Incomplete surveys were included in the analysis. Free-text responses were interpreted and summarized by the authors. The study was conducted using a Castor Electronic Data Capture (Castor, Amsterdam, the Netherlands) based survey (Appendix S1).

Statistical analysis

Categorical variables are summarized as frequencies and percentages or median with range and statistically evaluated with the chi-square test, continuous variables are reported as means and standard deviations and were statistically evaluated with unpaired *t*-test, Welch's *t*-test and Pearson's correlation coefficient. Statistical methods were conducted using SPSS (version 25.0, SPSS Inc., Chicago, IL), *p*-values <0.05 were considered significant.

RESULTS

Study cohort

We sent out a survey to 169 members of the NVvH in the Netherlands of which 50 physicians responded between June and October 2020 (response rate: 30%). A total of 56% of the responding physicians work in an academic medical centre, 44% in a community hospital. Seven out of eight academic centres in the Netherlands were represented in the responses. The physicians completed questions on a cumulative total of 58 transfusion-dependent patients. Out of the respondents, 42/50 were haematologists, 6 were haematologists in training and 2 were specialists in internal medicine. Including the years in training, 12 respondents had <5 years of experience with transfusion-dependent patients; 19 respondents between 5 and 10 years; 9 between 10 and 19 years and 10 respondents had >20 years of experience.

General response

In the first part of the survey, we asked physicians to indicate, which of a set of 19 given factors affects their transfusion strategy in general. In Figure 1, these factors are depicted. Clinical factors that are reported to strongly influence the transfusion threshold are angina pectoris, cardiac failure and dyspnoea. Soft outcomes that are reported to influence the threshold mostly are a decreased quality of life and self-sustainability. Factors that are reported to be of no, or little, influence are gender, emotional state (fear and depression), renal disease, peripheral vascular disease, iron parameters and a bleeding tendency.

We stratified for years of experience of the haematologist and academic versus community hospital to evaluate for effect-modification by these factors. While responses from academic- and community hospitals yielded comparable outcomes, the amount of experience of physicians did have influence on the weight they attributed to certain factors: patient activity, mobility and self-sustainability were scored as 'moderate-strong influence on the Hb-threshold' in 8/9 (89%, $p = 0.01$), 10/10 (100%, $p < 0.01$) and 9/10 (90%, $p = 0.17$) by physicians with >20 years of experience, while physicians with <20 years of experience scored 17/39 (44%), 23/39 (59%) and 29/40 (74%), respectively.

Long-term outcomes were taken into consideration more often by physicians with <5 years of experience: they scored a 'moderate-strong influence' in 9/11 (82%) cases versus 20/37 (54%) for >5 years of experience ($p = 0.07$). Furthermore, 8/48 (17%) of the respondents

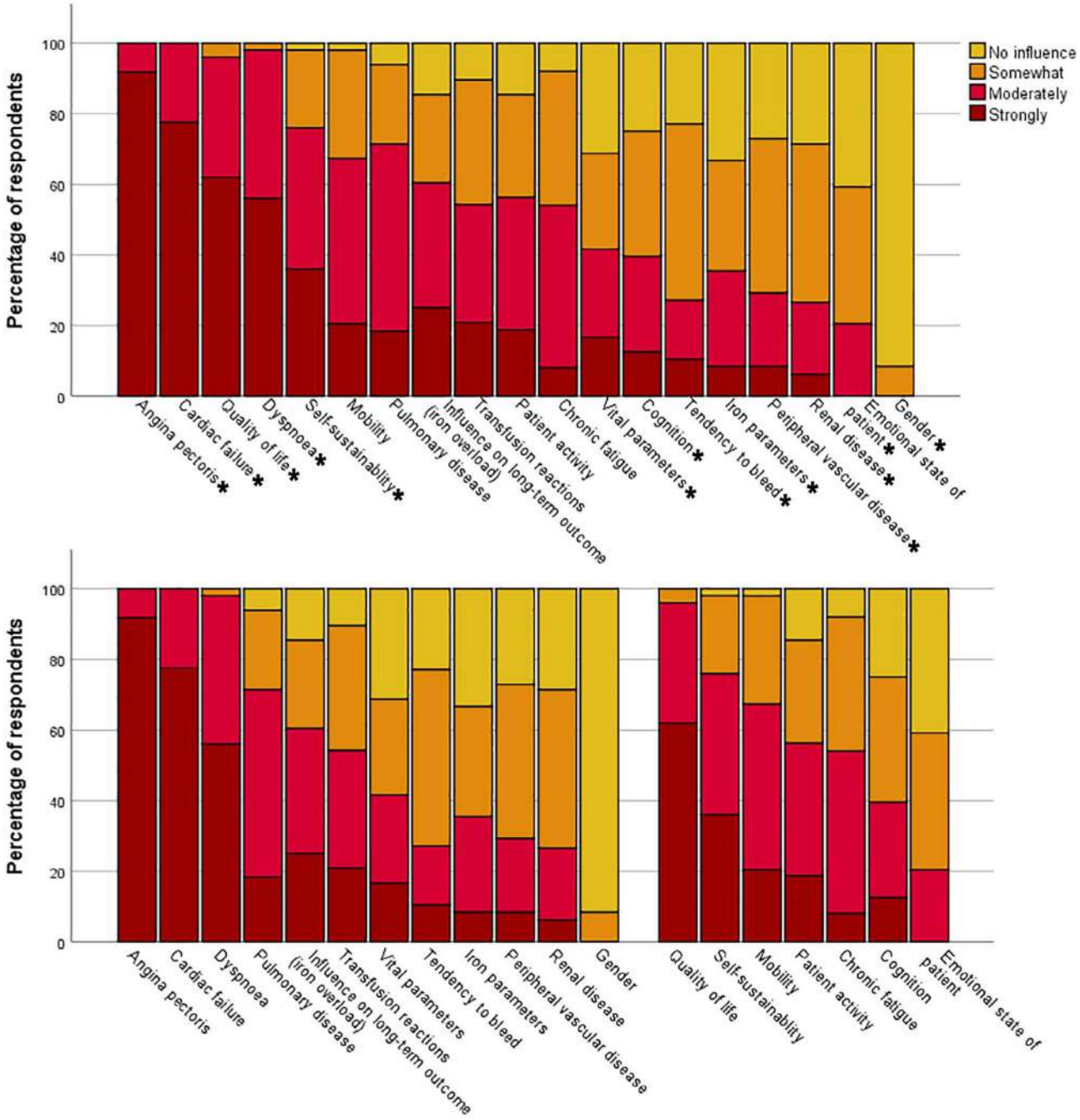

FIGURE 1 Responses to how much the indicated factors affect the choice for a red blood cell transfusion threshold, arranged from strongly to least influential (top); and subdivided in clinical and soft parameters (bottom). *$p < 0.05$ compared to the responses of all other parameters

(all of which have <10 years of experience) reported to measure post-transfusion Hb-levels.

Patient-specific response

The reported Hb thresholds for RBC transfusion-dependent patients are depicted in Figure 2. The most-reported threshold (28/58; 48%) was 8.0 g/dl (range: 6.4–9.6 g/dl). Four patients received transfusions only when their Hb dropped below 6.4 g/dl, seven patients had a threshold of 7.2 g/dl. Sixteen patients had a threshold higher than the median, of these; eight were transfused when their Hb-level dropped below 9.6 g/dl.

Regarding the transfusion interval: 7/56 patients (13%) received transfusions on a weekly basis, 11/56 patients (20%) every 2 weeks, 13/56 (23%) patients every 3 weeks, 13/56 (23%) patients every

4 weeks and only 12/56 (21%) patients have an interval of at least five or more weeks (Table 1).

The number of transfused units was strongly correlated with the pre-transfusion Hb-level ($p < 0.001$). Table 2 shows the amount of RBCs transfused per episode, depending on how much the Hb-level dropped below the patient's threshold. When the pre-transfusion Hb is <0.8 g/dl below the patient's personal threshold, a mean of 1.6 RBC units was transfused. When the observed Hb-level was between 0.8 and 1.6 g/dl below the threshold, a mean of 2.0 RBC units were transfused. When the Hb-level was >1.6 g/dl below the threshold, the mean number of transfused units was 2.6.

The threshold, interval and number of units transfused together to form a transfusion strategy. The various transfusion strategies are cross-tabulated in Table 1 and depicted in Figure 3. The mean threshold/(interval × transfusion amount) does not show a particular trend, suggesting that the variation in thresholds is independent of these two factors and more dependent on patient-specific parameters. Although no single strategy prevails most, a common frame can be identified: 63% of the reported patients are transfused 1–2 units every 2–4 weeks.

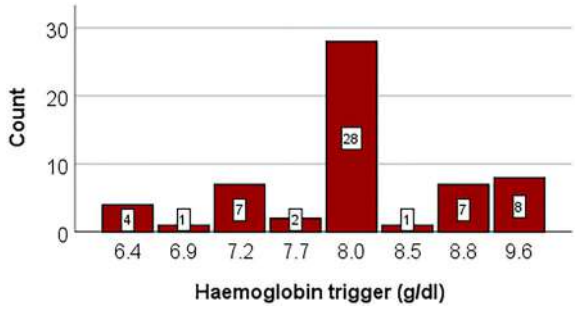

FIGURE 2 Haemoglobin thresholds used in daily practice ($n = 58$)

TABLE 1 Overview of various individual transfusion regimes

	Number of RBC transfused		
	1 RBC, g/dl ± SD (*n*)	2+ RBCs, g/dl ± SD (*n*)	Total, g/dl ± SD (*n*)
Interval (weeks)			
1	8.3 ± 1.0 (4)	8.6 ± 0.9 (3)	8.4 ± 0.9 (7)
2–4	8.0 ± 0.7 (15)	8.3 ± 0.7 (22)	8.2 ± 0.7 (37)
5–12	8.9 ± 1.1 (2)	7.9 ± 1.2 (10)	8.1 ± 1.2 (12)
Total	8.1 ± 0.8 (21)	8.2 ± 0.9 (35)	8.2 ± 0.8 (56)

Note: A mean threshold is given per transfusion regime.
Abbreviation: RBC, red blood cell.

Parameters associated with changes in transfusion strategies

We asked the respondents to complete a set of questions on a patient of theirs to test for consistency with the general responses on the abovementioned factors. For patients without angina pectoris, the mean threshold was 8.0 g/dl whereas patients with moderate angina had a threshold of 8.8 g/dl ($p = 0.047$). This suggests that physicians indeed increase the transfusion threshold when a patient suffers from angina. Whether or not patients had any form of cardiac failure only did not impact the threshold in a significant manner ($p = 0.28$): a mean threshold of 8.1 g/dl for no cardiac failure versus 8.4 g/dl for patients with cardiac failure. Pulmonary disease had an, if any, inverse effect: 8.2 g/dl was the mean threshold for patients without the pulmonary disease, 8.0 g/dl for patients with pulmonary disease. The patient group without pulmonary disease did, however, have a higher prevalence of cardiac failure and angina pectoris.

The underlying disease, the cause for the patient's chronic anaemia, strongly impacts the transfusion strategy. While the overall median transfusion interval is 3 weeks, for 5/8 thalassaemia patients, the transfusion interval is 5 weeks or more (median = 6 weeks, range: 2–12, $p = 0.038$). Thalassaemia and sickle cell patients ($n = 8$ and 3, resp.) also have a lower transfusion threshold (7.2 ± 0.7; $p = 0.001$, and 7.5 ± 1.2 g/dl; $p = 0.19$, respectively). Other disease groups (MDS $n = 22$, MPN $n = 13$, AML $n = 2$, CMML $n = 2$, and other

TABLE 2 Amount of red blood cells (RBCs) transfused when the haemoglobin level drops <0.8, 0.8–1.6 or >1.6 g/dl below the patient's personal threshold

	Number of RBCs transfused per transfusion episode				
	0 RBCs, *n* (%)	1 RBC, *n* (%)	2 RBCs, *n* (%)	3 RBCs, *n* (%)	Cumulative count of transfused RBCs (*mean per patient*)
Hb-level below the patients personal threshold					
<0.8 g/dl	1 (2%)	21 (36%)	34 (59%)	2 (3%)	95 (*1.6 pp*)
0.8–1.6 g/dl	0	8 (14%)	41 (71%)	9 (16%)	117 (*2.0 pp*)
>1.6 g/dl	0	0	26 (45%)	32 (55%)	148 (*2.6 pp*)

Note: A significant increase in transfused RBCs is seen with lower Hb-levels ($p < 0.001$, for both <0.8 compared to 0.8–1.6 and >1.6 g/dl, and 0.8–1.6 compared to >1.6 g/dl).
Abbreviation: RBC, red blood cell.

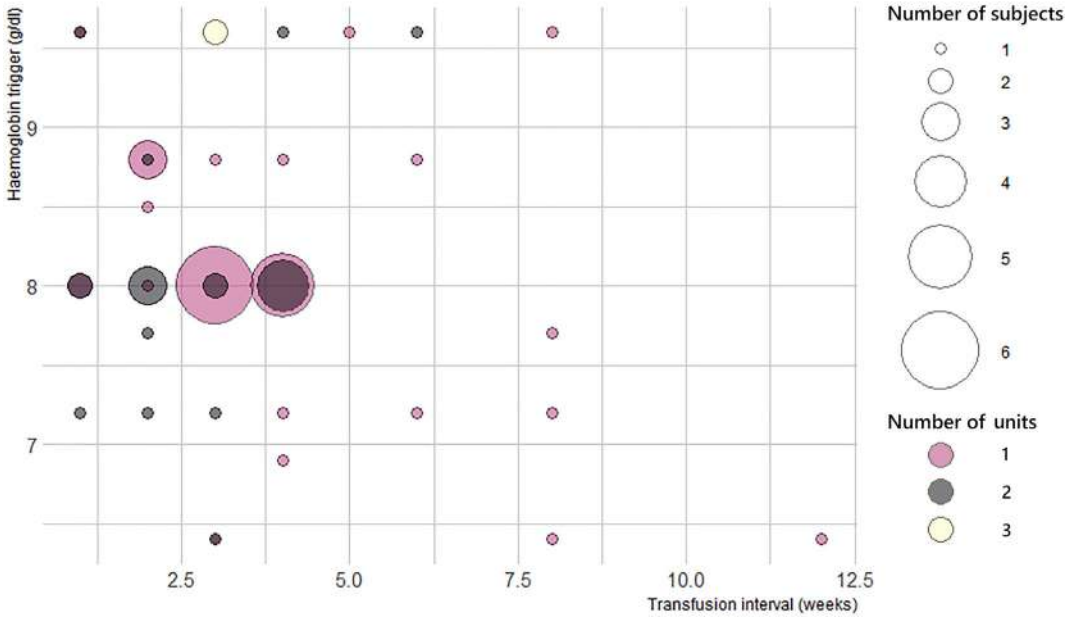

FIGURE 3 Bubble plot of the reported transfusion strategies. Most responses were focussed on a threshold of 8 g/dl every 2–4 weeks. Patients with thalassaemia and Sickle Cell Disease were reported to receive transfusions with a larger interval with also a lower mean threshold, which explains some of the outliers

$n = 7$) all had a mean threshold between 8.2 and 8.6 g/dl with a median interval of 3 weeks (range: 1–8 weeks), except for one aplastic anaemia patient: threshold 9.7 g/dl, interval 1 week. Not all patients have a structured transfusion strategy: 2/3 sickle cell patients receive transfusions on demand.

Whether a patient received active treatment other than RBC transfusions for their underlying disease appears to affect the threshold too. The mean threshold for patients that received a form of chemotherapy was 7.6 ± 0.6 g/dl ($n = 11$, $p = 0.02$ compared to no treatment), while receiving immunomodulatory drugs leads to a threshold of 8.5 ± 0.6 g/dl ($n = 8$) and no treatment to 8.3 ± 0.9 g/dl ($n = 38$).

Although most physicians report that they try to adjust transfusion strategies to avoid long-term negative outcomes due to iron overload, they also report not necessarily taking iron parameters into the equation (Figure 2). Nonetheless, our data do show a mild effect of ferritin level on the threshold. When patients had a ferritin <1000 μg/L, the mean threshold was 8.3 ± 0.6 g/dl, while ferritin levels >1000 μg/L lead to a mean threshold of 8.0 ± 0.4 g/dl ($p = 0.24$). In addition, we evaluated the ferritin levels per response to the question 'how much RBC units the physician would transfuse to their patients if the Hb-level would drop more than 1.6 g/dl below their personal threshold': the 32 patients that would receive three RBCs had a mean ferritin level of 1140 ± 944 μg/L while the 25 patients that would receive 2 RBCs had a mean ferritin level of 1647 ± 1948 μg/L ($p = 0.20$). Stratification for the transfusion burden yielded the same results. While the main cause for elevated ferritin levels is the transfusion burden, it is also dependent on how effective and/or tolerated chelation therapy is (Figure 4). Interestingly, the

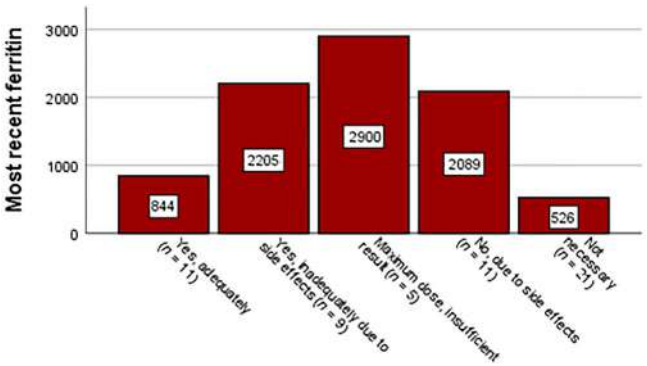

FIGURE 4 Mean ferritin per response to the question of whether the patient receives chelation therapy. The mean transfusion burden is given per response group. Patients that do not require chelation therapy have the highest mean transfusion burden ($p = 0.042$ compared to those who do receive chelation therapy)

patients that were deemed not to need chelation therapy because of the still low mean ferritin levels did have the highest transfusion burden (2.9 units/4 weeks; $p = 0.046$ compared to patients that do receive chelation therapy). These three findings suggest that patients with higher ferritin levels are in fact transfused more restrictively.

Most parameters individually did not render an association with the transfusion threshold, interval or number of units transfused. However, trying to pinpoint what type of patients are most likely to deviate from the mean, we noticed that patients with a threshold <7.2 g/dl did not suffer from pulmonary or cardiac problems, and had few risk factors overall. Amongst patients with thresholds up to

8.0 g/dl, 3/14 (21%) suffered from cardiac and/or pulmonary problems, compared to 26/44 (59%) patients with thresholds above or equal to 8.0 g/dl ($p = 0.014$). This indicates that an important prerequisite for maintaining a maximally restrictive transfusion policy is sufficient (estimated) in cardiopulmonary compensation capacity. Conversely, as stated before, the presence of angina pectoris and cardiac failure may lead to a higher threshold. Other than that, we could not identify consistent motives for increasing the threshold above 8.0 g/dl.

Regarding physician factors, academic hospitals and community hospitals reported similar strategies. There are, however, some nuanced, non-significant, differences: academic hospitals transfuse every 3.6 weeks (mean), while community hospitals transfuse every 4.4 weeks without a change in the mean transfusion threshold (both 8.2 g/dl). Physicians with <5 years of experience in the field appear to transfuse more units (1.8 units every 3.9 weeks) but at a more restrictive = lower threshold (8.0 g/dl), compared to colleagues with more experience, especially compared to those with >20 years of experience (1.6 units every 3.9 weeks, threshold 8.2 g/dl). We found no correlation between outliers in thresholds and the experience level of the physicians.

Because we included incomplete surveys, we performed a non-response error analysis to evaluate whether bias might have been introduced by non-responders. A relatively high amount of respondents failed to report the patient's most recent ferritin (5/58; 9%). We did not find a difference between those who did not report the ferritin level and those who did. Other questions were not left unanswered more frequently than others.

DISCUSSION

This survey amongst Dutch haematologists shows an average transfusion strategy of 1–2 RBC units (range: 0–3 units) every 2–4 weeks (range: 1–12 weeks) with a median threshold of 8.0 g/dl but a large reported variation (range: 6.4–9.6 g/dl). Patient-specific clinical factors that affected the found variability in the transfusion strategies are angina pectoris, cardiac failure and dyspnoea, but also ferritin levels, underlying disease and the concurrent treatment influenced transfusion regimen. Softer parameters of influence are quality of life and self-sustainability. More experienced physicians take patient activity, mobility and self-sustainability into account more often than less experienced colleagues.

Regarding the underlying disease, patients suffering from sickle cell disease and thalassaemia had a lower mean threshold (7.2 and 7.5 g/dl, resp.) and higher interval (median 6 weeks) compared to the other included patients (Hb-threshold >8.2 g/dl, interval = 3 weeks). This may be explained by a lifelong need of these patients to cope with lower Hb-levels but also by the known higher alloimmunization levels of these patients and thus more focus on restriction. In addition, transfusion goals differ between different indications: whereas an MDS patient receives transfusions to improve the oxygen-transportation capacity, the aim in patients with sickle cell disease is also to decrease the proportion of sickle Hb relative to Hb A to prevent or reverse vaso-occlusive disease.

Patients receiving chemotherapy are transfused at a lower mean threshold (7.6 g/dl) as compared to those with immunomodulatory drugs or no active therapy (8.5 and 8.3 g/dl, resp.). The suppression of haematopoiesis by chemotherapy, although more severe, is also more likely to be reversible. Physicians may thus accept a lower Hb level as a rise is to be expected when the chemotherapy's side effects wear off.

There may be various arguments to transfuse at a higher more liberal threshold: a physician might aim to increase the patient's QoL; or to counter a patient's poor tolerance of low Hb-levels. Vice versa, restrictiveness with thresholds below 8 g/dL seems only enforced if there are no clear risk factors such as a reduced estimated cardiopulmonary compensation capacity (Figure 5).

Clearly, the exact effect of a transfusion on the patient is hard to quantify. As few physicians report to measure post-transfusion Hb-levels, this also appears to be a parameter of little value. Therefore, there is a dire need for clinically relevant outcome measures to evaluate transfusions and transfusion strategies.

Interestingly, an increased ferritin level did somewhat influence the threshold and transfusion burden, in spite of the fact that physicians score ferritin as one of the least influential factors. A possible relation indeed is not clear-cut. Indeed, high ferritin levels could cause a more restrained transfusion strategy to avoid iron overload and consequent long-term organ damage, while for patients with lower ferritin levels, a more liberal transfusion strategy could be allowed. On the other hand,

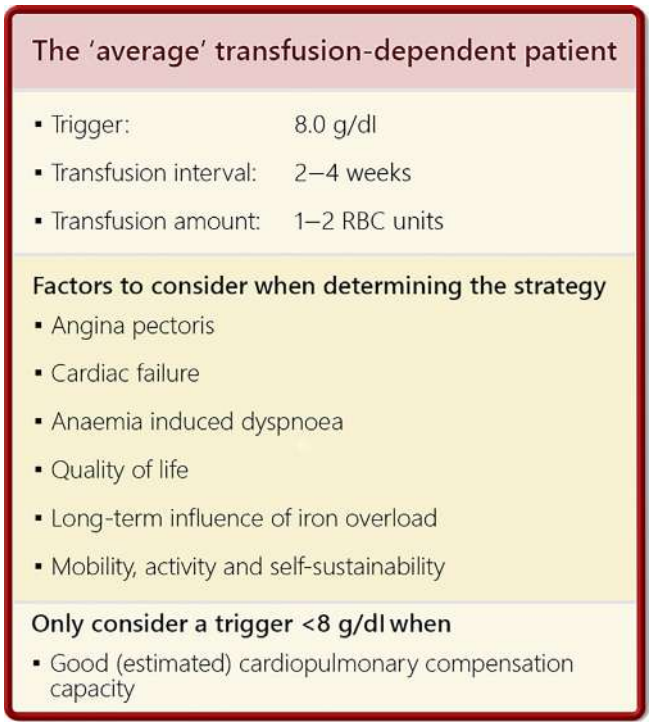

FIGURE 5 The average transfusion-dependent patient according to the present survey. RBC, red blood cell

the need for chronic transfusions is bound to lead to higher ferritin and iron overload, which could already urge the physicians to transfuse more restrictively as a precaution. Therefore, the observed but only moderated impact of elevated ferritin levels on the transfusion strategy might be an underestimation of iron overload awareness. In addition, whether chelation therapy is used, effective and/or tolerated further complicates this question, as it greatly affects ferritin levels. Assuming transfusion burden should be guided by the present or expected iron overload a new question could be raised: could patients in which chelation therapy is effective to be transfused at a higher threshold? The theoretical benefits of a higher Hb level, which have yet to be established, may indeed outweigh the side effects if they can be limited. In addition, an established gain in quality-adjusted life years's might balance the extra labour and costs of transfusions. Clearly, not all variations of transfusion strategies can be accounted for by the investigated factors. Beside patient factors, the current variation in transfusion strategies is likely also due to lack of evidence-based guidelines for this group of patients. Some physicians may base their choice to transfuse more restrictively on multiple studies conducted in other patient groups where restrictive RBC transfusion strategies show no disadvantages on the accumulated parameters like morbidity and mortality [8–12]. Others may choose a more liberal strategy because a higher Hb-level is believed to be beneficial for the transfusion-dependent patient [27]. While variability in transfusion strategies between patients may not be a problem at all, the lack of guidelines should not lead to large interphysician differences, as this will cause both under and over transfusion. Nevertheless, the observed range of thresholds does not find a base in Dutch or international guidelines [13, 28]. Currently, the Dutch guideline advises to use a threshold between 7.0 and 8.0 g/dl for reversible anaemia of haematological patients other than the chronically dependent group; importantly, its only advice for chronic anaemia is to apply an individual strategy based on the perceived quality of life.

This is the first survey amongst haematologists in the Netherlands in which important questions regarding RBC transfusion support in chronic transfusion-dependent patients are addressed. Though some presented results may have been expected, it is important that they are documented in search of proper guidelines.

Regarding this paper's limitations, first, as is the case in most surveys, this study is limited by the moderate response rate. Aiming for respondents who take an interest in transfusion policies, and are, therefore, likely to treat a relatively high number of the low-prevalent transfusion-dependent patients, we believe, we have included a representative portion of the target population. Second, our data may be subject to response bias as physicians who do not maintain standard transfusion strategies, or who do not use transfusion thresholds may not have responded. Third, as only the responses of the physicians were collected, the actual clinical practice could differ. We should, for example, be cautious with the interpretation of ferritin levels, since we have no means of verifying these numbers. Fourth, because we included incomplete surveys, bias could have been introduced by non-response errors. However, our non-response error analysis suggests that this is not the case.

A survey looking into the transfusion thresholds of patients with haematological malignancies in general in the Netherlands yielded similar results [29]. However, the median threshold for outpatient care was lower—7.2 g/dl. Mo et al. performed a survey investigating thresholds for specifically MDS patients in Australia. In agreement with our results, they concluded a typical transfusion threshold of 8.0 g/dl, with higher thresholds typically used for patients with cardiovascular disease or anaemia symptoms [30]. In both the abovementioned surveys, the investigation of parameters associated with changes in transfusion strategies, however, was much more limited than the present study. Both these previous surveys reported on existing institutional transfusion guidelines and/or used case scenarios to elicit transfusion thresholds. The present study, in contrast, asked for actual patient examples, which might be a better reflection of the true spectrum of currently used transfusion strategies for chronic transfusion-dependent patients. These new, original data could allow professionals to benchmark their transfusion practices and reflect on them, and maybe helpful in organizing haematologists' training.

The observed variation in less restrictive transfusion strategies ultimately stems from the variable use of non-evidence-based parameters to counter the cons of transfusions. While it is clear that fewer transfusions prevent transfusion reactions and iron overload, this results in a lower Hb-level, which negatively impacts patients' well-being [10, 19–22]. Softer outcomes describing well-being like health-related quality of life, though reportedly important as shown by Figure 2, however, are harder to quantify.

Our findings hence address the need for prospective randomized trials to develop evidence-based guidelines for RBC transfusions in patients with chronic transfusion dependency with the goal of improving their QoL while limiting unnecessary transfusions without compromising the outcome. To date, there have only been two small randomised controlled trials (13 and 38 patients) comparing restrictive versus liberal thresholds in chronic transfusion-dependent patients. Although not adequately powered to detect clinically relevant differences, results are suggestive of an improved QoL with higher Hb-levels [31, 32]. Currently, several studies with chronic transfusion-dependent patients are conducted (REDDS-2, ACTRN12619001053112; REMOTE 2, NL9289; EnhanceRBC, NCT02099669; SMD-Transfu, NCT03643042; PTQA, NCT03660228). Results of these studies will yield better insight into the effects of transfusion strategies on the well-being of this chronically transfused group of patients. We encourage international collaborations for trials investigating patients with chronic transfusion requirements. Such collaboration is likely required to achieve a large enough sample size to detect meaningful, clinically relevant differences in transfusion strategies.

In conclusion, the results of this survey indicate a broad variation in RBC transfusion strategies in Dutch patients with chronic transfusion dependency. While the current variation in transfusion strategies may be unavoidable in an individualized approach, randomized trials and better defined usable parameters, amongst, which a measure for QoL, to evaluate the effect of transfusion strategies are required to reach a consensus on how to determine the transfusion strategy.

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R.T., M.S. and J.J.Z. conceived the study design. R.T. performed the research and wrote the first draft. M.R. and J.J.Z. supervised the research, and reviewed and edited the manuscript.

CONFLICT OF INTEREST

All authors attest that they have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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ORIGINAL ARTICLE

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Preventing alloimmunization using a new model for matching extensively typed red blood cells

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Abstract

Background and Objectives: Alloimmunization is a well-known adverse event associated with red blood cell (RBC) transfusions, caused by phenotype incompatibilities between donor and patient RBCs that may lead to haemolytic transfusion reactions on subsequent transfusions. Alloimmunization can be prevented by transfusing fully matched RBC units. Advances in RBC genotyping render the extensive typing of both donors and patients affordable in the foreseeable future. However, the exponential increase in the variety of extensively typed RBCs asks for a software-driven selection to determine the 'best product for a given patient'.

Materials and Methods: We propose the MINimize Relative Alloimmunization Risks (MINRAR) model for matching extensively typed RBC units to extensively typed patients to minimize the risk of alloimmunization. The key idea behind this model is to use antigen immunogenicity to represent the clinical implication of a mismatch. Using simulations of non-elective transfusions in Caucasian donor and patient populations, the effect on the alloimmunization rate of the MINRAR model is compared with that of a baseline model that matches antigens A, B and RhD only.

Results: Our simulations show that with the MINRAR model, even for small inventories, the expected number of alloimmunizations can be reduced by 78.3% compared with a policy of only matching on antigens A, B and RhD. Furthermore, a reduction of 93.7% can be achieved when blood is issued from larger inventories.

Conclusion: Despite an exponential increase in phenotype variety, matching of extensively typed RBCs can be effectively implemented using our MINRAR model, effectuating a substantial reduction in alloimmunization risk without introducing additional outdating or shortages.

KEYWORDS
alloimmunization, matching, mathematical model, red blood cells

Highlights

- Extended matching is feasible in practice.
- Novel strategy for issuing extensively typed RBCs.

- Extended matching can substantially reduce alloimmunization risks.

INTRODUCTION

Red blood cells (RBCs) are the most common transfused blood product. In most Western countries, between 20 and 40 RBC units per 1000 inhabitants are transfused per year [1]. Nevertheless, blood transfusion can have side effects, of which alloimmunization is one of the most common [2, 3]. Selection of matched blood units is often restricted to the ABO blood group and RhD antigen, and only for certain recipients, more extensively matched units are routinely selected. In case a unit that is mismatched for certain blood group antigens is transfused, there is a risk that the immune system of the recipient will produce red blood cell alloantibodies (alloimmunization) that might result in the destruction of transfused RBCs in subsequent transfusion episodes [4–6]. Therefore, once a patient is alloimmunized against a specific antigen, all subsequent transfusions must be matched for this antigen to prevent acute or delayed transfusion reactions.

Recent advances have resulted in affordable RBC genotyping technology that can be applied on a large scale [7, 8]. In the near future, this technology will allow extensive typing of donors, thereby increasing the availability of typed antigen negative RBC units. But more importantly, when more patients are typed as well, preventive matching for antigens other than A, B and RhD will become possible for more, if not for all patients. However, with the exponential increase in the number of possible phenotype profiles with respect to the antigens considered (for each additional antigen considered, the number of different blood products will roughly double which implies exponential growth per definition), the likelihood of being able to provide all recipients with matched products will diminish.

Another challenge for large-scale extensive matching is that different patient groups have different priorities for receiving extensively matched RBCs. For example, in the Netherlands, female blood recipients aged <45 years receive cEK-matched blood to prevent antibody-mediated haemolytic disease of the foetus and new-born [9]. In many countries, including the Netherlands, certain patient groups at high risk of alloimmunization, such as those with high level of transfusion support (myelodysplasia [10] and thalassemia) and those with higher tendency of alloimmunization (autoimmune haemolytic anaemia [11] and sickle cell disease (SCD) [12]), receive additional matching. The latter group is notoriously hard to match with RBCs of a mainly Caucasian population, as they have a different RBC phenotype profile due to their predominantly African roots [13]. A requirement for the introduction of large-scale extensive matching is that the availability of antigen matched units for the aforementioned patient groups should not decrease when more patients receive extensively matched RBCs.

The feasibility of large-scale extensive antigen matching has not yet been widely studied. When investigating the matching of extensively typed RBC units to patients, previous studies first define several stringency levels of antigen matching and subsequently investigate the availability of units for these levels under strict matching regimes [14–16]. In terms of maximizing the matching potential of an extensively typed RBC inventory and patient population, these approaches all have the same limitation: the availability of matching RBC units (and thereby the overall matching quality) is heavily influenced by the (often non-trivial) choice of matching levels. In this study, we present a novel and more flexible issuing strategy that can be used to assign RBC units to patients. The aim of this issuing strategy is to provide all patients with suitable RBC units without introducing any additional shortages or outdating of RBCs. Thus, the objective is to minimize the expected number of alloimmunizations over all transfused patients. This is achieved by using a penalty-based approach to prevent mismatches, instead of forcing strict matching requirements for a fixed set of minor antigens. Although the model does not differentiate between patients of different categories, its penalty-based structure should pave the way for more refined issuing strategies where patient-specific circumstances are taken into consideration as well.

MATERIALS AND METHODS

Managing an RBC inventory involves carefully balancing supply and demand. Hospitals receive daily requests for RBC units that must be allocated from the hospital inventory. To avoid shortages, the inventory is periodically supplied with fresh RBC units, usually triggered by inventory levels. The distribution centres from the blood supplier have a similar balancing process, but instead of daily requests, they must satisfy hospital orders and invite new donors to ensure a steady flow of RBC units. For the purpose of this research, we presume an RBC inventory that is presented with direct requests from patients, and that can only order ABO-RhD-specific blood units. Each day, requests become known at the beginning of the day and a predefined allocation strategy assigns units to requests. As a baseline, we will use the FIFO/MROL model for ABO-RhD matching (further referred to as

TABLE 1 Antigen immunogenicity

Minor antigens	C	c	E	e	K	Fy^a	Fy^b	Jk^a	Jk^b	M	S
Number of alloimmunizations per 1000 patients exposed to two mismatching units (a_k)	2.1	4.3	14.6	5.1	23.4	2.7	0.8	5.1	0.2	1.8	0.8

Note: Clinically relevant minor antigens and their immunogenicity expressed as expected number of patients alloimmunized per 1000 mismatched patients (after exposure to two antigen positive units) [4].

ABOD) of van Sambeeck et al. [14]. This issuing policy forces all units to be matched for ABOD and computes a maximal assignment, meaning that as many matched units are issued as possible. This model ignores all other antigens and is therefore comparable to the matching strategy currently applied for the majority of RBC transfusions in the Netherlands. For further details on the FIFO/MROL model, we refer the reader to the original publication. [14] Our proposed allocation strategy uses antigen immunogenicity to determine the penalty for mismatching on a particular antigen. The antigens considered and their immunogenicities as estimated by Evers et al. [4] in an incident new-user cohort of 21,512 previously non-transfused, non-alloimmunized Caucasian patients receiving ABOD matched red cell transfusions are shown in Table 1. We restricted ourselves to 11 (minor) antigens, as alloimmunization against these antigens represent 95% of the induced clinically relevant alloantibodies. We used the alloimmunization incidence reported for exposure to two units, as this was the only exposure level where data for all 11 antigens considered were available.

The majority of hospitalized patients require more than one RBC unit per transfusion episode (61%, based on Dutch historical in-hospital data from 2012 until 2019) [17]. This implies that the exposure to foreign antigens can range from one to multiple units. In our model, mismatches are presumed to be binary events: a patient is either exposed to a foreign antigen within a transfusion episode or not, and the probability of antibody development is not dependent on the number of mismatched transfusions given during one transfusion episode. This assumption is in line with the recent publication of Yazer et al. who found no significant dosage effect in RhD-alloimmunization rates among exposed transfusion recipients [18]. By ignoring the level of exposure, we maximize the proportion of patients for which exposure is prevented. With these assumptions, we can define the daily allocation problem as an integer linear programming (ILP) model [19] which is solved using Gurobi Optimization software [20].

Matching strategy model

First, we define the decision variables that represent the decisions that must be taken in the allocation problem

$$x_{ij} = \begin{cases} 1 & \text{if patient } i \text{ is assigned unit } j \\ 0 & \text{otherwise} \end{cases}$$

$$s_i = \begin{cases} 1 & \text{if patient } i \text{ cannot beassigned(shortage)} \\ 0 & \text{otherwise} \end{cases}$$

$$y_{ik} = \begin{cases} 1 & \text{if patient } i \text{ is mismatched on antigen } k \\ 0 & \text{otherwise} \end{cases}$$

And the following parameters:

$$u_i = \text{the number of units requested by patient } i$$

$$\varphi_i(k) = \text{presence of antigen } k \text{ in phenotype of patient } i \quad (1 \text{ if present}, 0 \text{ if not present})$$

$$\varphi_j(k) = \text{presence of antigen } k \text{ in phenotype of unit } j \quad (1 \text{ if present}, 0 \text{ if not present})$$

$$\widehat{a}_k = \frac{a_k}{\sum_{k'} a_{k'}} = \text{normalized immunogenicity}$$

$$c_{ij} = \begin{cases} 1 & \text{if unit } j \text{ is ABOD matched with patient } i \\ 0 & \text{otherwise} \end{cases}$$

Now, we can define the objective function to be minimized. This function should firstly minimize the number of shortages and secondly minimize the total mismatch cost:

$$\text{minimize } M\sum_i s_i + \sum_i \sum_k y_{ik}\widehat{a}_k \quad (1)$$

Here, M is a large number to ensure that the prevention of shortages is always prioritized. Lastly, we define the valid solution space by defining the constraints that govern the validity of the decision variables.

$$\sum_j x_{ij} + s_i u_i = u_i \ \forall i \quad (2)$$

$$\sum_i x_{ij} \le 1 \ \forall j \quad (3)$$

$$\sum_j x_{ij}\varphi_j(k) \le y_{ik} u_i \ \forall i \forall k \text{ if } \varphi_i(k) = 0 \quad (4)$$

$$x_{ij} \le c_{ij} \ \forall i \forall j \quad (5)$$

$$x_{ij}, y_{ik}, s_i \in \{0,1\} \ \forall i \forall j \forall k \quad (6)$$

Constraint (2) forces all demand to be satisfied or a shortage is incurred. Constraint (3) allows each unit to be issued no more than once. Constraint (4) forces y_{ik} to one if patient i is mismatched on antigen k. Constraint (5) forbids any ABOD mismatches and constraint (6) forces all variables to be binary. This ILP, which we will refer to as the MINRAR model (MINimize Relative Alloimmunization Risks), can be used to optimally allocate units to patients on a single day. Note that the scope of the model does not have to be a single day. Instead, it can be any period (e.g., the time between two supply moments).

The issuing of RBC units to patients is not a standalone problem as decisions made on the current day will also affect the matching potential for the next day(s). To account for this, we adjust the MINRAR model to perform in an *online* setting. An online problem is one that requires iterative solving as the problem presents itself. In this case, the inventory changes whenever units are being added or issued. This requires taking into account two additional factors:

1. Prevention of outdating: RBC units have a maximum shelf life of 35 days. Thus, there should be a preference for issuing older units.
2. Limiting antigen substitution: The issuing of antigen negative blood to a positive patient (substitution) should be avoided to prevent an accumulation of antigen positive units.

To make older RBC units preferable for issuing, we use the First In First Out (FIFO) discount function as proposed by van Sambeeck et al. [14]:

$$o(r_j) = \left(\frac{1}{2}\right)^{\frac{r_j}{5}} \tag{7}$$

Here, r_j is the remaining shelf life of unit j. This exponential implies that the discount factor for issuing unit j doubles every 5 days, until it is one when the remaining shelf life is zero. Limiting antigen substitution is more complex, as different antigens have different clinical implications. Major antigens A, B and RhD determine whether a match is possible and heavy substitution leads to a reduction of O type blood in inventory which potentially leads to subsequent shortages. Minor antigen substitutions have no effect on shortages. Instead, these will only lead to a reduction of antigen negative blood in stock which will likely increase the number of future mismatches. Hence, we add two penalty terms to address each of these problems separately.

First, we define the *usability* of a phenotype, which is the probability that the phenotype is matched with a random phenotype on the antigens in set Λ [14].

$$U_\Lambda(\varphi) = \sum_{\varphi' \leq_\Lambda \varphi} p(\varphi) \tag{8}$$

Here, $p(\varphi)$ denotes the prevalence of phenotype φ in the population, and $\varphi' \leq_\Lambda \varphi$ are all phenotypes φ' matching with φ on the antigens in Λ. We can now define the *Major antigen substitution* penalty as the difference in usability between the phenotype of a candidate unit for matching (φ_j) and the phenotype of the patient (φ_i):

$$A_{\text{Major}}(\varphi_j, \varphi_i) = U_{\{A,B,D\}}(\varphi_j) - U_{\{A,B,D\}}(\varphi_i) \tag{9}$$

The value of this term represents the transfusion potential lost by assigning unit j to patient i.

The *Minor antigen substitution* penalty is not determined by the usability of the product, but by its immunogenicity:

$$A_{\text{Minor}}(\varphi_j, \varphi_i) = \sum_{k \mid k \notin \{A,B,D\}} \hat{a}_k (1 - \varphi_j(k)) \varphi_i(k) \tag{10}$$

The penalty is the sum of all minor antigen substitutions, weighted by their immunogenicity ($\hat{a}_k$). A match without any negative-to-positive antigen combinations will thus have a penalty of zero.

We extend the original objective function (Equation (1)) with these three new terms (FIFO penalty and Major and Minor antigen substitution) as shown in Equation (11). However, we do not change any constraints or decision variables, as the solution space (all allowed combinations of variable values) remains the same, which means that the conditions from Equations (2)–(6) still apply. Note that the additional penalty terms will improve the performance of the model in the long run.

$$\begin{aligned} \text{minimize } & M \sum_i s_i + \sum_i \sum_k [y_{ik} \hat{a}_k] - \sum_j o(r_j) \\ & + \sum_i \sum_j \left[A_{\text{Major}}(\varphi_j, \varphi_i) + A_{\text{Minor}}(\varphi_j, \varphi_i) \right] \end{aligned} \tag{11}$$

Simulations

To assess the performance of the proposed allocation strategy, multiple one-year simulations of different sized RBC inventories were performed. Each simulation is preceded by an initialization period of 1 month to allow the inventory to reach a steady-state distribution for the ABOD blood types. During each simulation, RBC units and patients with random phenotypes are generated. The antigen profiles of RBC units were sampled in accordance with the historical ABOD blood type distribution of RBC units in the Netherlands. The remaining antigens were sampled according to the antigen prevalence in the Caucasian population (also considering the linkage between *RHD* and *RHCE* alleles) [21]. The prevalence per antigen corresponds to the actual distribution of antigens in the donor population, as these play no role in donor selection. Patient phenotypes were fully sampled Caucasian phenotype prevalences [21]. The number of units requested per patient was sampled from an empirical distribution of historical in-hospital requests obtained from the Dutch Transfusion Datawarehouse and consisted of 438,260 transfusions given between January 2012 and December 2019 in six Dutch hospitals [17]. Requests for five or more units (3.07%) were omitted, as these are deemed out of scope for an extensive matching algorithm. Such requests are often not elective, and extensive matching is of less value, since the primary concern in these cases is to maintain the patient's RBC volume. Emergency requests can be allocated from a separate smaller emergency inventory or from the regular inventory followed by a new optimization to reallocate the remaining units to regular patients. Patients with a periodic (chronic) demand for RBC units were not explicitly included, and neither were patients with alloantibodies, mainly due to the absence of historical data for the frequency of these patients and their corresponding alloantibodies.

Five different sized inventories with an average daily demand of 25, 50, 100, 200 and 500 RBC units, respectively, were simulated. In each simulation, the inventory size used is equal to five times the average daily demand, which is most common in the Netherlands. In the Netherlands, hospital inventories are relatively small, as they can have units delivered from Sanquin distribution centres within 1 h if necessary. We have not implemented this feature in our simulations, as it confounds the capability of the matching policy itself. In our simulations, units with major antigens issued (or outdated) on the previous day are replenished at the beginning of each day. Each of these units has a set of randomly assigned minor antigens in accordance

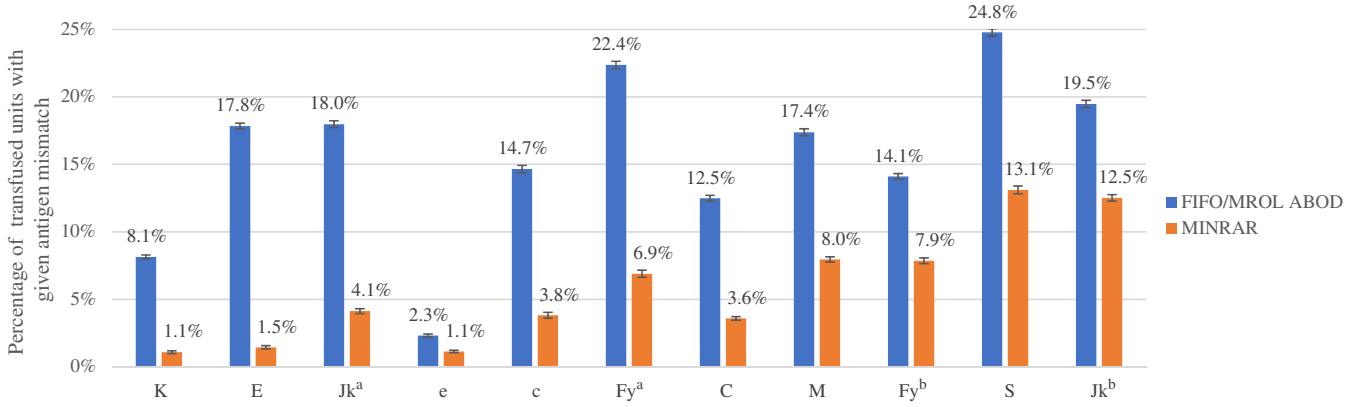

FIGURE 1 Percentage of transfused units with antigen mismatches using the FIFO/MROL ABOD and MINRAR issuing strategies for a random average daily demand of 100 red blood cell units (inventory size 500 units)

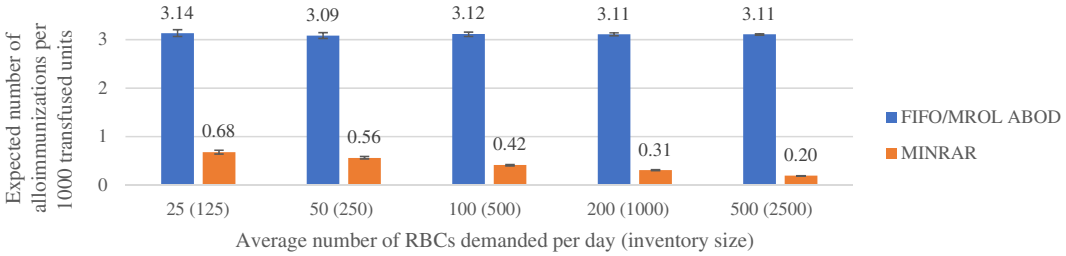

FIGURE 2 Approximation of the expected number of alloimmunizations per 1000 transfused units using the FIFO/MROL ABOD and MINRAR issuing strategies for five different sized inventories

with the donor population prevalence. This policy eliminates shortages and outdating caused by supply irregularities. The daily demand was sampled from fitted distributions per day of the week based on historical data (total issued RBC units per day by Sanquin, the Dutch blood bank, during 2009 and 2019, obtained from *eProgesa*, the ICT management system of Sanquin), and downscaled to match the average daily demand of 25, 50, 100, 200 and 500 RBC units used in the simulations.

For each antigen, we report the percentage of units transfused that mismatch on that antigen. Furthermore, we computed an estimate of the expected number of alloimmunizations per 1000 transfused units. Translating the number of mismatches into an expected number of alloimmunizations is not straightforward. However, an approximation can be made using the alloimmunization incidence estimates from Table 1. First, we assume that within a single transfusion episode, a patient can only be exposed once per foreign antigen, meaning that the transfusion of 1, 2, 3 or 4 mismatching units is treated as one exposure. This approach is used as we presume that in general, the level of exposure needed to potentially trigger alloimmunization is already reached with the transfusion of one mismatching unit. Although the risk of alloimmunization increases with the amount of exposure, this concerns exposures over time rather than the level of exposure within a single transfusion episode. To estimate the total number of alloimmunizations, the number of patients exposed per antigen is multiplied with the corresponding alloimmunization incidence from Table 1. Note that the data presented in Table 1 from the original paper [4] reflect an exposure to two units. As we only model one exposure event, the final penalty is therefore divided by two.

The C++ code for the simulations can be obtained from the corresponding author upon request.

RESULTS

In Figure 1, the percentage of transfused units that mismatch on a particular antigen is shown for both issuing strategies. These results are averages of 1-year simulations of a 500-unit inventory with an average daily demand of 100 random units. The figure shows a reduction in mismatches for every antigen in line with the aim of the MINRAR issuing strategy (which is to minimize the risk of alloimmunization over all patients). The effect of these reductions in terms of the expected number of alloimmunizations prevented is shown in Figure 2. A table with more details on the outcomes of the simulations (including the percentage of shortage and outdating) can be found in Supplementary Materials (Appendix S1). Our results show that the gain of extensive matching with the MINRAR issuing strategy compared with a matching policy limited to antigens A, B and RhD can, even for small inventories, provide a decrease in alloimmunization risk of 78.3%. This risk can be further reduced when the matching is

performed more centralized, for example in distribution centres with larger inventories. In the largest scenario that was analysed (2500 RBC unit inventory and average daily demand 500 units), the expected number of alloimmunizations is 0.20 per 1000 transfused units, compared with 3.11 for the FIFO/MROL ABOD policy, which implies a reduction of the alloimmunization risk of 93.7%. Note that this reduction is achieved without an increase in shortages or outdating and pertains to a demand of RBCs with a previously unknown phenotype profile.

DISCUSSION

In this study, we investigated the feasibility of extensive RBC matching for genotyped donors and patients. We proposed the MINRAR model for allocation of RBC units to patients to minimize the risk of alloimmunization for all patients. Figure 1 shows that substantial reductions in antigen mismatches are possible, while Figure 2 shows that these reductions translate to a substantial reduction in alloimmunization incidence. We note that the approximation used to estimate the expected number of alloimmunizations ignores the magnitude of antigen exposure per transfusion episode. This favours the results of the MINRAR issuing strategy, as this strategy will actively 'bundle' antigen mismatches such that exposure can be prevented for a maximum number of patients whenever mismatch-free issuing is not possible. However, we argue that ignoring the magnitude of antigen exposure within a transfusion episode is both justifiable (as was explained earlier) and favourable for the overall patient population in terms of preventing alloimmunization and therefore the best method of approximation.

As mentioned in the introduction, patient-specific circumstances play an important role in determining the clinical implication of a mismatch on a particular antigen. Currently, mismatch penalties in the MINRAR model are solely based on immunogenicity. However, the MINRAR model can be easily adapted to weigh clinical aspects that determine the implications of a mismatch for a specific patient group. For example, mismatches for SCD patients could be given much larger penalties than similar mismatches for regular patients. Although the effect of such an extension to the MINRAR model with penalties dependent on both the mismatched antigen and transfusion recipient patient group has already been preliminary studied [22], the viability of extended matching hinges on the availability of extensively matched units for patient groups for which there is an increased incentive for preventing alloimmunization. Further research should provide insight into how extended matching can be implemented without a loss of matching quality for those patient groups.

The results in Figures 1 and 2 show that the application of the MINRAR model leads to a substantial reduction in the expected number of alloimmunizations. More difficult to see is how well the MINRAR model performs in absolute sense. To evaluate the quality of allocation, we can compare the matching result to the *best possible allocation* for a given simulation by assigning RBC units to patients retrospectively. Looking back on the RBC supply and demand over a finished simulation, one can determine what the very best allocation possible would have been if one would have been able to look into the future. In Appendix S2, we show a comparison between the MINRAR model and this optimal (retrospective) allocation. These results show that the allocation obtained by the MINRAR strategy is close to the best possible allocation. The amount of alloimmunization preventable by retrospective issuing—relative to the MINRAR strategy—is comparable to the expected alloimmunization induced by ignoring antigens M, S or C. Considering that the MINRAR model has no knowledge of future supply and demand, we can conclude that the MINRAR strategy provides a near-optimal solution.

In addition to optimizing specific allocation strategies, the MINRAR model can also be used to address policy issues. One example is how antigen matching is affected by the heterogeneity of donor and recipient populations. In Appendix S3, we show the impact of a varying mix of Caucasians and individuals of African descent on the level of alloimmunization for both ethnic groups. These results show that the alloimmunization risk for individuals of African descent increases substantially (up to 60%) when supplied from a 98% Caucasian population, whereas in a more heterogeneous population (80% Caucasian, 20% African descent), this increase is limited (4.9%). Lastly, we note that all the results presented are limited to alloimmunization against the antigens included in Table 1, which are most relevant for Caucasians. However, the MINRAR model can be applied for any mixture of ethnic populations and number of antigens, given that their immunogenicity can be estimated.

With the advancements in genotyping technology and foreseen reduction in its costs, the implementation of extensive antigen matching becomes more and more realistic. In contrast, the exponential increase in the number of phenotypes when considering more minor antigens—with the 14 antigens considered, there are 3168 different blood groups in Caucasians alone—would suggest that extensive matching would not be feasible in practice. However, we have shown that matching on all clinically relevant antigens can almost fully eliminate the risk of transfusion induced alloimmunization. Using the MINRAR allocation model to iteratively compute an assignment of RBCs to patients even for a small inventory, one can prevent 78.3%, and possibly even up to 93.7% of expected alloimmunizations that would have occurred when matching for antigens A, B and RhD alone. The decrease in alloimmunization risk for larger inventories indicates that more advanced matching strategies, whereby the decision on RBC allocation is organized at a more centralized level (e.g., at a large distribution centre), may reduce this risk even further. In addition, the model and current simulations presume that all RBC requests are non-elective and that the antigen composition of patient RBCs is unknown until requested. As in practice, a substantial proportion of transfusions are elective; the potential alloimmunization reduction achievable by extended matching will be higher than indicated by our current results. At present, however, most effort should be directed towards investigating the financial viability of large-scale

extensive matching as well as other operational and organizational challenges resulting from changes in matching policy. Nonetheless, our research shows that a substantial reduction in alloimmunization can be achieved without any increase in outdating or shortages, even if RBC allocation remains at hospital level. With such promising results, we have demonstrated the practical feasibility and potential in alloimmunization prevention of extended matching which should lead to an improved safety of future RBC transfusions.

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CONFLICT OF INTEREST

We declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Motivation, blood donor satisfaction and intention to return during the COVID-19 pandemic

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Abstract

Background and Objectives: This study aimed to describe motives as well as donation experiences and the intention to return for further donations of German whole blood donors who donated at the beginning of the COVID-19 pandemic.

Materials and Methods: To describe motives and donor experiences, a retrospective survey was conducted among whole blood donors that had a donation appointment at the German Red Cross Blood Donation Service in the first 4 weeks of the pandemic. A donor questionnaire including 17 retrospective questions was sent to 7500 donors. Donor motivation and donor experiences were compared for different donor groups using chi-square statistics. Finally, in an ordinal logistic regression model predictors for the intention to return were identified.

Results: More than half of the participating donors (56.9%) wanted to contribute to the fight against the pandemic by donating blood. Most of the donors were satisfied with their last donation experience and felt safe during the blood donor appointment. However, some donors would have liked more information on how to deal with the pandemic (20.3%). Intention to return for further donations was strongly associated with overall satisfaction (OR: 1.67, CI: 1.47–1.90) and the feeling of being safe during blood donation (OR: 1.33, CI: 1.05–1.68).

Conclusion: Donor satisfaction with the last donation was high and the vast majority of donors felt very safe. However, those donors who felt unsafe expressed a low intention to return and blood donation services should therefore carefully monitor donor satisfaction.

KEYWORDS
blood donation, COVID-19, donor motivation, donor return, donor satisfaction

Highlights

- 56.9% of the participating donors wanted to contribute to the fight against the pandemic by donating blood.
- Most of the donors were satisfied with their last donation experience and felt safe during the blood donor appointment.
- Intention to return for further donations was strongly associated with overall satisfaction with the last donation experience and the feeling of being safe during blood donation.

INTRODUCTION

Blood donation services have to secure blood supply even in times of crisis. As long-term storage is not possible, blood donors also have to be recruited continuously during extraordinary events. In the case of disasters such as earthquakes, terrorist attacks or tsunamis, the care of a large number of injured people usually requires significantly more blood products. Donor recruitment must be intensified. Previous studies show high solidarity during the first week after a disaster and that many first-time donors can be recruited [1, 2]. In contrast, emerging pandemics may not increase blood demand but impact donor motivation negatively. Due to the ongoing risk of infection, many donors may hesitate to visit a donation facility.

At the beginning of the current COVID-19 pandemic, there was indeed a decline in the number of donations, similar to previous outbreaks of infectious diseases. For example, in the Chinese region Zhejiang, the volume of blood donations at the beginning of 2020 declined by 67% [3]. Declining donation numbers at the beginning of the pandemic were also reported in Italy, Brazil, Spain, Greece and Iran [4–8]. The pandemic studies discuss various causes for the significant decline: First, in many countries, the usual number of mobile donation sites could not be maintained at the beginning of a pandemic [7]. Second, additional reasons for deferral in the context of the pandemic were reported, which led to a reduction in the potential donor base [8]. Third, many donors were afraid of getting infected by COVID-19 during blood donation. In a survey of potential donors in the Chinese Zhejiang province during the COVID-19 pandemic, fear of infection (81.2%) and concern about weakening the immune system (14.1%) were by far the most frequently mentioned barriers [3]. As a result, many donors stayed at home and avoided potential infections.

Donors who gave blood during the pandemic often wanted to contribute to overcoming the crisis and support their health system [9]. How the general motivation to donate changed during the pandemic, however, has hardly been described so far. Furthermore, very little is currently known about donor satisfaction with the measures taken to avoid the risk of infection during blood donation. The German Red Cross Baden-Wuerttemberg—Hessen, for example, implemented numerous changes in donation procedures during the first wave of the COVID-19 pandemic from 22 March 2020. These changes included the introduction of mandatory online appointment booking, moving to larger blood donation sites for at least 5 days instead of daily changing mobile donation sites, measuring body temperature at the entrance and the distribution of surgical face masks to every single donor [10]. It is unclear how these measures influence donor satisfaction and the intention to return for further donations. Therefore, this study aims to describe the motives as well as donation experiences of blood donors who donated at the very beginning of the COVID-19 pandemic. Furthermore, we examined whether the respective donor experience influences the intention to return for further donations.

METHODS

Study population

On 22 March 2020, the German government implemented a partial lockdown in order to limit the number of COVID-19 infections [11]. To describe motives and donor experiences at the beginning of the COVID-19 pandemic, a retrospective anonymous survey was conducted among 7500 German whole blood donors who had a donation appointment between 23 March and 18 April 2020. Both donors who were allowed to donate and deferred donors were included in the sample. The sample size was calculated to assess differences between inexperienced, experienced, and very experienced donors by assuming a response rate of 40%. The sample was drawn using a random number among donors of the German Red Cross Blood Donation Service Baden-Wuerttemberg—Hessen and North-East. The German Red Cross Blood Donation Service collects around 75% of all blood donations in Germany and is divided into six regional units.

In May 2020, a self-administered questionnaire was mailed to the selected donors along with a personalised introduction letter, a data security statement and a stamped, pre-addressed return envelope. Besides this, donors had the opportunity to fill out the questionnaire online. The data collection was stopped on 31 July 2020. No monetary compensation was paid for either the blood donation or the participation in the survey. The study was approved by the Ethical Committee of the Medical Faculty Mannheim, Heidelberg University (2020-572-AF 5).

Survey instrument

The donor questionnaire included questions on donor motivation, donor recruitment, satisfaction with the last donation, experiences with additional safety measures, donation history and sociodemographic characteristics. To assess the motivation of the donors, the participants were asked to rate nine possible motives as "applicable" or "not applicable." The motives included the importance of potential health benefits from donating blood, altruistic motives, motivation by the pandemic and the importance of invitations from others. These motives had already been used in a previous survey among German donors [12].

Further questions were asked about satisfaction with the measures to avoid infection during blood donation. In detail, donors were asked to indicate whether sufficient distance was kept during blood donation, whether they felt safe, whether they thought the temperature measurement was appropriate, and whether they were adequately informed about the handling of the COVID-19 pandemic (see Table 2). A 5-point Likert scale was offered ranging from "totally disagree (1)" that indicates a very low satisfaction to "totally agree (5)" that indicates a very high satisfaction. For the bivariate analysis, the ratings were categorised into "disagree/neutral" (1–3) "agree" (4), and "totally agree" (5). In addition, donors were asked how satisfied they were overall with the last donation experience. Again, the answers were measured by a scale ranging from "very dissatisfied (1)" to "very satisfied (5)." For the bivariate analysis, the ratings were categorised into "low/medium satisfaction" (1–3) "high satisfaction" (4) and "very high satisfaction" (5). To measure intention to return for further donations, the participating donors were asked how likely it is that they continue to give blood at the German Red Cross Blood Service. Responses were captured using a 5-point Likert scale from "very unlikely" to "very likely."

Statistical analysis

First, we calculated the proportion of donors who felt motivated by nine different motives and compared the proportion between younger donors (18–29 years), middle-aged donors (30–54 years) and older donors (55+ years). Second, we analysed whether donor characteristics (sex, age, education, previous donation and donor deferral) were correlated with donor satisfaction with different aspects of the last donation during the pandemic. Multiple chi-square tests were performed to test for bivariate associations, and p values < 0.05 were considered significant. Third, multiple ordinal logistic regression modelling was used to study the association between satisfaction with different aspects of the last donation during the pandemic and the intention to return for further donations. The dependent variable was the intention to return that was measured on an ordinal scale from "very unlikely" to "very likely," whereas very unlikely was the reference category. We calculated odds ratios that a respondent reported a high intention to return for further donations. Separate regression models were estimated for inexperienced, experienced and very experienced donors. All models were adjusted for sex, age, education and donor deferral.

RESULTS

A total of 7500 self-administered questionnaires were mailed to whole blood donors who donated or were deferred between 23 March and 18 April 2020. Until the end of July 2020, a total of 4355 (58.1%) completed questionnaires were returned. About 568 (13%) of the questionnaires were completed electronically, which was particularly used by younger and more highly educated donors. Due to missing values for relevant questions, 22 questionnaires were excluded from the analysis. In addition, 778 donors were excluded who reported a second donation during the pandemic. In our survey, we asked the donors about their "last donation" assuming that this was the first donation during the pandemic. Responses of those donors who have already donated twice since March 2020 may not be comparable due to habituation effects to donating during the pandemic. The final sample consisted of 3555 donors, of which 1608 (45.3%) were men, 1941 (54.6%) were women and 3 (0.1%) identified themselves neither as a man nor as a woman. The majority of the participants were either experienced (26.8%) or very experienced donors (47.1%) with 5–15 or more than 15 previous donations. The percentage of inexperienced donors with less than five donations was 26.1%, of which 10.7% were making their very first donation attempt. About 56.6% of the donors reported having a high educational level, and 33.2% reported having a medium educational level. Of all participants, 4.0% were deferred on their last donation attempt.

Regarding their motivation for their last donation, almost all donors (98.1%) reported that they wanted to help others. Therefore, they can be described as altruistically motivated, acting benevolently, or seeking warm glow (Figure 1) [13]. The desire to contribute to the fight against the corona pandemic was mentioned by 56.9% of the participating donors. Especially among young donors (66.3%), as well

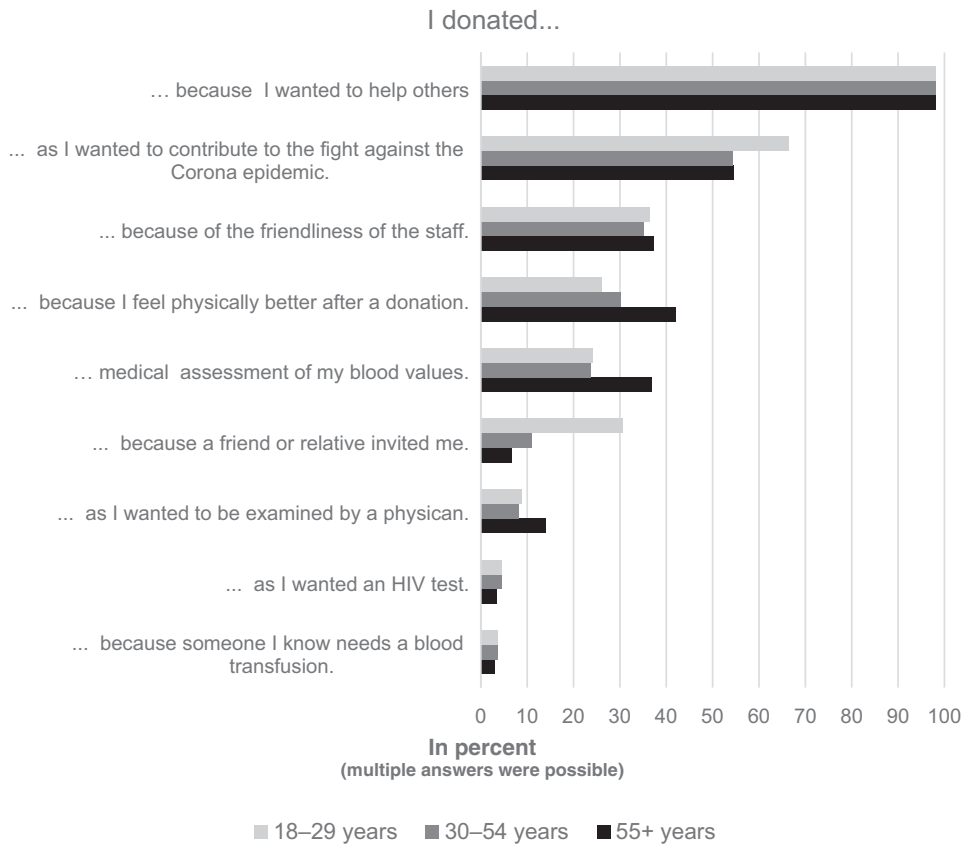

FIGURE 1 Donor motivation by age group

TABLE 1 Satisfaction with safety measures during blood donation

	"During the blood donation, sufficient distance to other donors was ensured."				"I felt safe at the donation appointment."				"I found the temperature measurement at the entrance to be adequate."				"I have received sufficient information on how to deal with the Corona virus."				"Overall, how satisfied were you with your last blood donation appointment?"			
	Disagree/ neutral (%)	Agree (%)	Totally agree (%)	Chi-square	Disagree/ neutral (%)	Agree (%)	Totally agree (%)	Chi-square	Disagree/ neutral (%)	Agree (%)	Totally agree (%)	Chi-square	Disagree/ neutral (%)	Agree (%)	Totally agree (%)	Chi-square	Low/ medium (%)	High (%)	Very high (%)	Chi-square
Total	5.5	17.0	77.5		4.3	15.6	80.1		7.1	18.5	74.3		20.3	26.4	53.3		12.5	28.6	58.9	
Sex				17.5***				12.7**				35.6***				6.0*				18.0***
Men	5.1	19.9	75.0		4.3	18.0	77.7		8.8	21.7	69.5		20.6	28.2	51.2		13.3	31.6	55.1	
Women	5.8	14.6	79.6		4.3	13.6	82.1		5.8	15.9	78.3		20.1	24.8	55.0		11.9	26.0	62.1	
Age				9.6*				5.4				13.2*				23.7***				5.5
18-29	7.3	18.0	74.7		5.1	15.0	79.9		9.0	16.6	74.5		25.2	27.6	47.3		12.7	31.4	55.9	
30–54	5.5	16.6	78.0		4.5	15.0	80.4		7.6	19.3	73.1		20.2	24.8	55.0		12.9	28.1	59.0	
55+	4.2	16.9	78.9		3.4	17.0	79.6		5.1	18.9	76.0		17.0	28.0	55.1		11.9	27.2	60.9	
Education				8.9				0.8				3.2				4.5				13.8**
Low	5.1	12.7	82.2		4.3	15.7	80.1		7.3	18.3	74.4		19.5	23.0	57.6		11.3	23.2	65.5	
Medium	4.5	16.9	78.6		3.9	16.2	79.8		7.4	20.0	72.6		19.8	25.9	54.2		12.3	26.6	61.1	
High	5.9	17.8	76.3		4.3	15.2	80.4		6.8	17.8	75.5		20.5	27.5	52.0		12.6	30.7	56.7	
Previous donations				2.8				6.8				4.0				10.3*				7.4
0–4	6.2	16.7	77.1		5.4	13.7	80.9		6.7	16.8	76.5		22.4	25.8	51.8		13.5	28.9	57.6	
5–15	5.5	16.1	78.4		3.5	15.8	80.7		6.9	18.8	74.4		22.3	26.0	51.7		10.5	30.9	58.6	
16+	4.8	17.5	77.6		4.0	16.2	79.8		7.4	19.6	73.0		17.9	26.9	55.2		13.1	27.2	59.7	
Deferral				4.0				6.5*				0.1				2.0				49.5***
No	5.3	17.0	77.7		4.1	15.7	80.2		7.1	18.6	74.3		20.2	26.6	53.2		11.8	28.4	59.8	
Yes	9.2	17.0	73.8		8.5	13.5	78.0		7.7	17.6	74.6		22.8	21.3	55.9		30.2	33.1	36.7	

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 2 Predictors of a high intention to return for further donations

	Inexperienced donors (0–4 donations)		Experienced donors (5–15 donations)		Very experienced donors (16+ donations)		All donors	
	Adjusted odds ratio[a]	Confidence interval	Adjusted odds ratio[a]	Confidence interval	Adjusted odds ratio[a]	Confidence interval	Adjusted odds ratio[a]	Confidence interval
"During the blood donation, sufficient distance to other donors was ensured."[b]	0.97	0.70–1.32	0.73	0.40–1.31	0.95	0.66–1.38	0.90	0.73–1.12
"I felt safe at the donation appointment."[b]	1.06	0.74–1.52	1.38	0.73–2.62	1.48	1.01–2.18	1.33	1.05–1.68
"I found the temperature measurement at the entrance to be adequate."[b]	1.22	0.95–1.57	0.97	0.68–1.39	1.13	0.86–1.47	1.06	0.91–1.24
"I have received sufficient information on how to deal with the Corona virus."[b]	0.93	0.76–1.15	1.23	0.94–1.62	1.13	0.90–1.42	1.08	0.94–1.23
"Overall, how satisfied were you with your last blood donation appointment?"[c]	1.80	1.46–2.22	1.46	1.10–1.94	1.68	1.36–2.08	1.67	1.47–1.90

Note: Results of an ordinal logistic regression model among inexperienced, experienced and very experienced donors.
[a]Odds ratios adjusted for sex, age, education and donor deferral.
[b]A 5-point Likert scale was offered ranging from "totally disagree (1)" to "totally agree (5)."
[c]A 5-point Likert scale was offered ranging from "very dissatisfied (1)" to "very satisfied (5)."

as among female donors (60.1%), a high proportion of donors wanted to support the health care system through blood donation. The medical assessment of blood values (27.8%) and the doctor's consultation (10.0%) also motivated some donors, mainly older donors. An HIV test, however, was only a motive for very few donors to come to donate (4.1%). Among younger and thus less experienced donors, invitations by friends and relatives were very important (30.5%). Among older donors, many reported that they felt physically better after donating blood and therefore came to donate (42.1%).

The majority of donors (77.5%) were very satisfied with the compliance with the distance regulations during blood donation (Table 1, totally agree). The feeling of safety during donation and the acceptance of the temperature measurement at the beginning of the blood donation were also high. Thus, 80.1% of the donors reported that they felt very safe and 74.3% rated the additional temperature measurement at the entrance as appropriate. Subgroup analysis showed slightly lower scores on these questions only among men and young donors. Satisfaction with information about the novel virus, however, was lower. About 53.3% said they were very satisfied with the information about COVID-19 and 20.3% said they were dissatisfied. Again, the subgroup analysis showed that especially men and young donors would have liked more information. When asked about their overall satisfaction with the last donation experience, 58.9% indicated very high satisfaction. Dissatisfied donors were found mainly among men (13.3%), higher educated donors (12.6%) and deferred donors (30.2%).

The willingness to return to donate was very strong among the participants in the study. About 89.8% of donors reported that they were very likely to return (response 5 on a 5-point Likert scale) and another 6.5% that they were likely to donate again (response 4 on a 5-point Likert scale). To describe correlations with donor satisfaction, a multiple ordinal logistic regression was estimated to explain a high intention to return (see Table 2). The regression model for all donors showed that overall satisfaction with the last donation experience was positively associated with the intention to return for further donations (OR: 1.67, CI: 1.47–1.90). Satisfaction with the different measures to avoid infection with the novel virus during blood donation was only relevant in one respect. The safer the donors felt during blood donation, the greater the intention to return to further donations (OR: 1.33, CI: 1.05–1.68). This association appeared to be significant under adjustment for all other characteristics considered. However, the subgroup analysis suggests that this does not apply to inexperienced donors. The regression model further showed a high intention to return among experienced (OR: 2.50, CI: 1.81–3.46) and very experienced donors (OR: 3.57, CI: 2.56–4.98), whereas donor deferral was associated with a low intention to return (OR: 0.39, CI: 0.25–0.61) (data not shown).

DISCUSSION

To describe motives, donation experiences and the intention to return of blood donors who donated at the beginning of the COVID-19 pandemic, we conducted a retrospective survey among German whole blood donors. Results show that more than half of the participating donors wanted to contribute to the fight against the pandemic by

donating blood. Most of the donors were satisfied with their last donation experience and felt safe during the blood donor appointment. However, some donors would have liked more information on how to deal with the pandemic. Intention to return for further donations was strongly associated with overall satisfaction with the last donation experience and the feeling of being safe during blood donation.

In line with a study from other European countries on donor motivation at the beginning of the pandemic [9], our survey showed that many donors felt motivated because of the pandemic. In particular, female donors and young donors showed a strong desire to contribute to overcoming the crisis by donating blood. The decline in blood donations in many countries at the beginning of the pandemic may therefore not be explained by a lack of willingness to help and solidarity among blood donors. The reduced number of mobile donation sites and the fear of infection among blood donors are more likely to be relevant for the low number of donations in the first weeks of the pandemic. This interpretation is consistent with the results obtained in the European study [9]. Potential donors who were worried about infection during blood donation were less likely to donate.

However, findings from the Netherlands show that new donors can be recruited even during a pandemic [14]. After intensive appeals via social media, a particularly large number of new donors were recruited. A high level of solidarity as well as test-seeking for COVID-19 have been discussed as possible explanations for this finding [14]. From our data, the tendency of greater interest in the results of the blood test or the doctor's consultation cannot be identified. Compared to a survey of German donors from Mecklenburg-Western Pomerania that was conducted before COVID-19 appeared [12], there were significantly lower proportions of respondents in our survey who wanted their blood tested (27.8% vs. 68.2%) or showed up to donate because of the doctor's examination (10.0% vs. 26.0%). Donor's interest in such results seems to be weaker rather than stronger, at least at the beginning of the pandemic. As the pandemic progressed, however, test-seeking behaviour for COVID-19 may have increased, as the Robert Koch Institute began testing 5000 randomly selected blood donations for antibodies every 14 days at the end of April 2020 [15]. Whether potential donors experienced these tests as an additional incentive to donate blood still needs to be clarified [14].

A very high acceptance and satisfaction were shown for the additional measures to avoid infection with the novel virus during blood donation. Body temperature measurement and ensuring physical distance were rated very positively and the majority of donors felt very safe during blood donation. However, not all donors felt sufficiently informed about the blood transfusion service's handling of the pandemic. These concerns reflect the general uncertainty of potential blood donors at the beginning of the pandemic, which has also been described in other studies [9, 16]. Blood transfusion services should therefore try to reduce donor uncertainty through appropriate communication campaigns and do not rely on threat scenarios in donor recruitment. There are examples from the current pandemic of how such communication campaigns can be designed [10, 17]. However, studies evaluating the effectiveness of different styles of communication during the pandemic are still not available.

The results of our ordinal logistic regression model describing predictors of the intention to return for further donations were consistent with previous studies. Experienced donors were more likely to report the intention to return for further donations, whereas donor deferral halves the odds of the intention to return [18, 19]. Overall satisfaction with the last donation experience also proved to be an important predictor of further donations, which has already been described in previous studies [20, 21]. Our analysis, however, also highlights new insights into the intention to return.

The already very high intention to return among donors of the German Red Cross Blood Donation Service seems to be even higher during the pandemic. While in a comparable study before the pandemic 92.2% of the donors stated that they were very likely or likely to return, the proportion in this study was 96.2% [22]. These results suggest that donors who donate during a pandemic might have a very strong connection to their blood service and are very easy to mobilise again. It may also have been important that we conducted our study among donors of the Red Cross, as they are often particularly altruistically motivated and highly committed [23]. The altruistic nature of donating blood to the Red Cross may have been further strengthened by the pandemic.

Furthermore, the feeling of safety during donation was shown to be a predictor of the intention to return for further donations. Although the importance of donor satisfaction for donor retention has been discussed in previous studies [24–26], the feeling of safety during donation seems to be particularly relevant in the context of a pandemic. Further studies should clarify what this feeling of safety depends on and how it can be increased especially among very experienced donors.

In this study, however, only the intention to return and not the actual donor return behaviour was surveyed. The intention to return positively correlated with donor return in previous studies [27, 28]. Interestingly, the extent of the match between intention and actual behaviour was well explained when the experience of the donors was taken into account [29]. However, little is known about donor intention and actual donor return during and after a pandemic. It must also be taken into account that our study was conducted retrospectively. Donors had to evaluate their experience up to 2 months after their donation, which may have led to recall bias. However, this bias should be rather small, as the first donation during the pandemic is expected to be very memorable. In addition, information is only available from 58.1% of the selected donors, which may have led to nonresponse bias. Compared to previous studies, however, the willingness to participate was high [22, 24] and the age structure of the participants largely corresponds to the donor population of the German Red Cross [30].

More than half of the blood donors who donated at the early phase of the pandemic wanted to contribute to the fight against the pandemic. Acceptance with the changed donation procedures was very high and the vast majority of donors felt very safe during the blood donation session. However, those donors who felt unsafe expressed a low intention to return. Blood donor services should adapt pre-donation information material and carefully monitor donor satisfaction of those who donated or intended to donate during a pandemic to avoid donor loss.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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DIARY OF EVENTS

See also http://www.isbtweb.org/congresses/	
10.2.2022	The European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT) - 4th edition of the jointly organized European CAR T-cell Meeting.
15-16.3.2022	The IPFA/EBA Symposium on Plasma Collection and Supply will take place fully physical in Amsterdam, the Netherlands on March 15 - 16, 2022.
23.3.2022	Eye Drops from Human Origin - First EDHO Workshop on Current Standards and Future Developments organized by the ISBT Working Party Cellular Therapies.

