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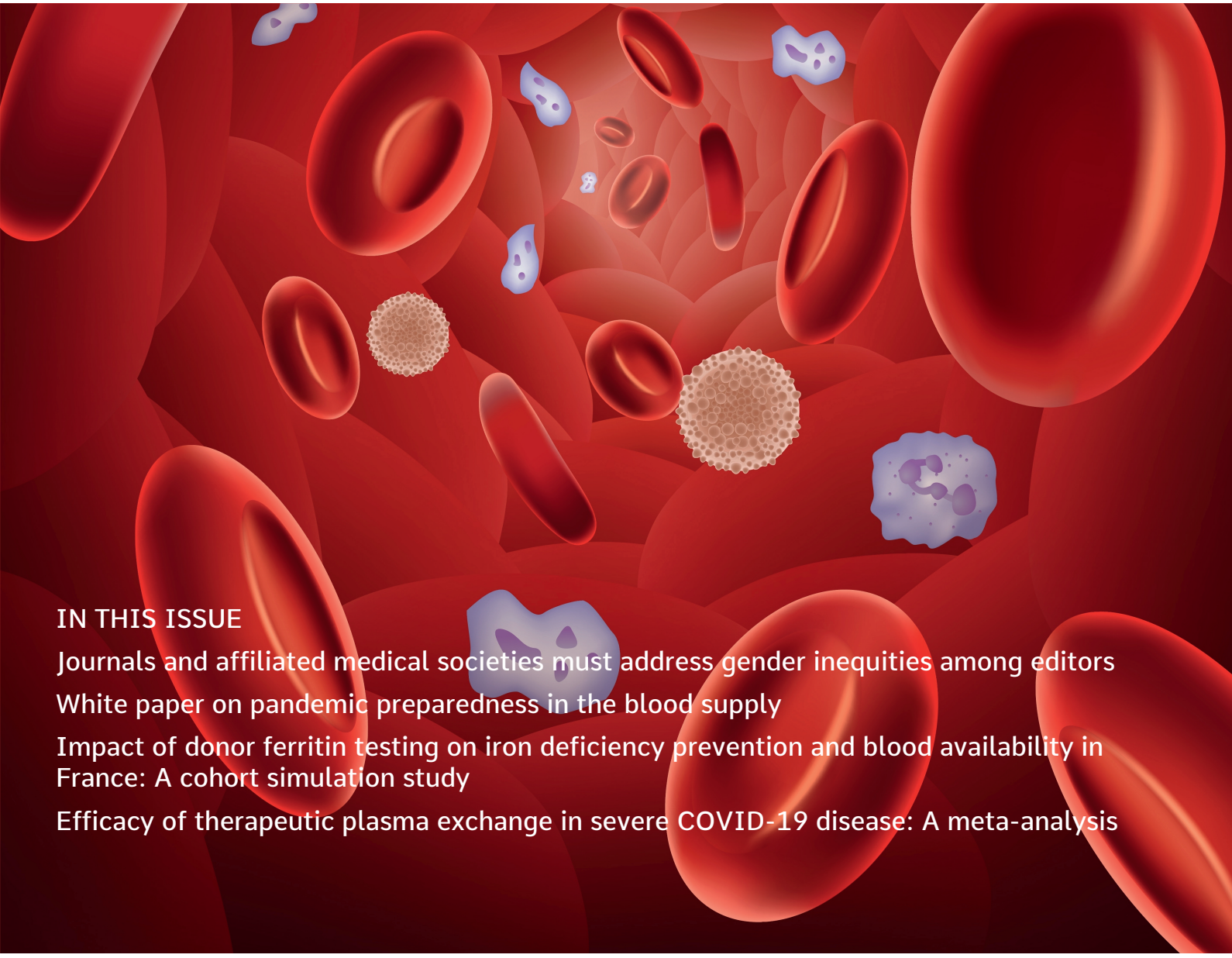

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ISBT International Society of Blood Transfusion

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;

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COMMENTARY

Vox Sanguinis ISBT International Society of Blood Transfusion

Journals and affiliated medical societies must address gender inequities among editors

Gender disparities among journal editors is one of the most fascinating and troubling of the many equity issues, because it has three characteristics that make it unique among workforce equity concerns: (1) a remarkably well-documented problem with dozens of papers published in medical journals over more than two decades; (2) a proven track record of being fixable within a relatively short time frame (i.e., numerous articles published by editors have documented their efforts); and, (3) a journal does not incur any additional cost based on the gender of an editor [1, 2]. Many equity issues share one or even two of these characteristics, but few, if any, share all three. Thus, a reasonable question to ask is: If there is a well-documented gender-equity problem that is easy and inexpensive to fix, then why have so many journal leaders not fixed it?

In 2019, Lally et al. [3] found an underrepresentation of women editors among seven blood banking and transfusion medicine (BBTM) journals. In this issue of *Vox Sanguinis*, Jacobs et al. [4] report their 'Analysis of gender representation on transfusion medicine journal editorial boards: Comparison between 2019 and 2022', analysing nine BBTM journals with 398 editorial positions, significantly more men than women (68.8% vs. 31.2%). The new study includes a re-analysis (3 years later) of the seven journals assessed by Lally et al.—demonstrating minimal change despite adding 54 new positions (2019: 30.1% vs. 2022: 31.9%).

Both *equity* (percent of women in the specialty) and *parity* (50% women) have been used as benchmarks for representation. Equity is often favoured, but in some specialties (e.g., neurosurgery, paediatrics), using parity avoids having mostly men or women editors. Jacobs et al. note that, among the BBTM specialists who passed the American Board of Pathology's BBTM Subspecialty Board Examination between 2016 and 2019, 45% were women physicians, and more than 60% of individuals graduating from BBTM fellowship programmes in the United States (US) are women. Notably, all benchmarks have limitations and the aforementioned do not account for the proportions of women in BBTM who are more senior (likely somewhat lower than the 45% and 60% marks) or benchmarks in other countries that may be higher or lower. Binary benchmarks do not account for the gender spectrum, including people who identify as non-binary (or other identity characteristics such as race).

When the inclusion of women editors is below both equity and parity benchmarks, this deserves scrutiny. In the study by Jacobs et al., several journals are far below the parity benchmark and appear to be well below equity benchmarks: *Journal of Clinical Apheresis* (22% women editors), *Transfusion Medicine and Hemotherapy* (16%) and *Transfusion and Apheresis Science* (9%) (Figure 1). Courts in the United States have used a concept called 'inexorable zero', which can be a true zero or a very low proportion, to infer discrimination [5].

In contrast, two journals approximate parity and, if benchmarks were available, would likely demonstrate near equitable inclusion of women editors: *Vox Sanguinis* (49%) and *Transfusion Medicine Reviews* (47%). Of these, only *Vox Sanguinis* was analysed in 2019 and 2022, and re-analysis found that the number of women editors increased from 3 to 19. In early 2022, the new Editor-in-Chief, Miquel Lozano, MD, PhD, explained his vision for editorial board expansion [6]. In an email communication, he told me he was intentional about recruiting more women editors and said that it was easy to recruit them because 'Transfusion Medicine has been one of the medical specialties where women first started occupying eminent positions' (M. Lozano, email communication, November 2022).

HOW PROFESSIONAL SOCIETIES PERPETUATE INEQUITIES

My work has focused on professional societies (including medical societies; hereafter 'societies') and their role in perpetuating gender disparities for women in medicine, because these organizations are important in academia and support numerous aspects of career development and advancement. Medical schools and academic medical centres pay large sums of money covering professional expenses associated with society membership fees, conference attendance, and so forth [5]. Counter-intuitively, the more a dean or chair recruits diverse faculty, the lower the return on investment for society-related expenses if these organizations do not treat them fairly. As stewards of an institution's financial resources, leaders of academic institutions must insist on fair treatment of diverse faculty—for ethical and financial reasons.

A landmark study showed no narrowing of the gap in promotion to professor for women physicians at US academic medical centres over a 35-year period [7], leading to the conclusion that every metric used in the promotion process deserves examination—including society and journal metrics. For example, recognition awards are often considered in academic rank promotion dossiers, and my colleagues and I have demonstrated zero and near-zero levels of women recipients across many societies [5]. Women are also underrepresented for

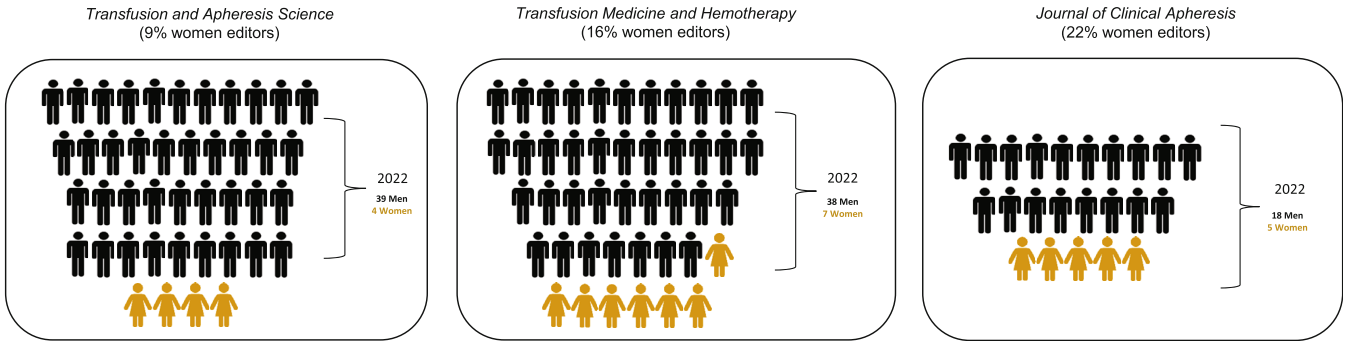

FIGURE 1 Journal editors by gender. Examples of transfusion medicine journals analysed by Jacobs et al. in 2022 that are well below the gender parity and equity benchmarks for the specialty [1].

recognition awards among BBTM societies [8]. Publications are important in promotion, and women are underrepresented as commentary authors—an important category not tied to research funding so disparities may be related to explicit (conscious) or implicit (unconscious) bias of journal editors—even among specialties with more women than men [9]. I co-chaired a women's task force for the Association of Academic Physiatrists and published a report listing society and journal metrics; in less than 3 years with intervention, women members were represented more equitably [10].

Gender bias is unethical, and both societies and journals have an obligation to ensure qualified women physicians and scientists are treated fairly. Societies that own or are affiliated with journals may have concerns about interfering with editorial independence; however, the International Committee of Medical Journal Editors has codified owner obligations that include ensuring journal editors act in a manner that is compatible 'with a position of trust' [2].

MOVING BEYOND SELF-GOVERNANCE

As I studied the relationships among gatekeeper organizations influencing medicine, it became clear to me that, to address diversity and inclusion concerns, organizational self-governance was necessary but not sufficient. *Should a medical society that is behaving in an ethical manner support a journal that is not behaving similarly?* Of course not. The literature is full of descriptions of problematic interorganizational relationships (IORs) [11]. For example, issues related to industry influence at research institutions—a topic explored in many papers including a new study titled 'Analysis of Industry-Related Payments Among Editors of Pathology Journals' [12]. Disrupting IORs that may cause harm is a well-established remedy that goes beyond medicine (e.g., the Fair Trade movement encourages businesses to avoid supporting suppliers engaging in behaviours such as employing child labour or paying unfair wages).

For firmly entrenched equity issues, increasingly the lens has turned towards assessing *structural discrimination* (SD), which focuses on policies and practices embedded within organizations and affects IORs. In a recent commentary titled 'Organizations in Science and Medicine Must Hold Each Other Accountable for Discriminatory Practices', I convened a large team of diverse co-authors who are equity experts and coined the term *interorganizational structural discrimination* (ISD)—defining it as having three features: (1) two or more organizations intentionally work together; (2) one or more of them has an obvious issue consistent with SD; and, (3) that issue is known to be remediable. We explained that relationships with organizations that deviate from established ethical practices can involve considerable reputational, financial and legal risks. Societies support ISD if they are engaged in collaborative relationships with journals that have not sufficiently addressed gender equity among editors, so we recommended journals that have failed to self-regulate should be put on notice that they need to change now. There is no doubt that science and patients suffer when half of the world's most brilliant minds are not at the table. Many journals, including *Vox Sanguinis*, have shown that once the situation is identified it can be modified and gender equity (or parity) reached. The only thing that is needed is a willingness to equitably include women editors.

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CONFLICT OF INTEREST

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REFERENCES

1. Silver JK. Gender equity on journal editorial boards. Lancet. 2019; 393:2037–8.
2. Silver JK. Medical journals must tackle gender bias. BMJ. 2019;367: l5888.
3. Lally K, van den Akker T, Stone EF, Arinsburg SA. Gender representation in editorial boards of transfusion medicine journals. Transfusion. 2020;60:174A.
4. Jacobs JW, Adkins BD, Woo JS, Lally K, Booth GS. Analysis of gender representation on transfusion medicine journal editorial boards: comparison between 2019 and 2022. Vox Sang. 2023;118:93–7.
5. Silver JK, Slocum CS, Bank AM, Bhatnagar S, Blauwet CA, Poorman JA, et al. Where are the women? The underrepresentation of women physicians among recognition award recipients from medical specialty societies. PM&R. 2017;9:804–15.
6. Lozano M. Revamping Vox Sanguinis. Vox Sang. 2022;117:5.
7. Richter KP, Clark L, Wick JA, Cruvinel E, Durham D, Shaw P, et al. Women physicians and promotion in academic medicine. N Engl J Med. 2020;383:2148–57.
8. Jacobs JW, Adkins BD, Stephens LD, Woo JS, Booth GS. Gender inequities in transfusion medicine society recognition awards. Transfus Med Rev. 2022;36:82–6.
9. Silver JK, Poorman JA, Reilly JM, Spector ND, Goldstein R, Zafonte RD. Assessment of women physicians among authors of perspective-type articles published in high-impact pediatric journals. JAMA Netw Open. 2018;1:e180802.
10. Silver JK, Cuccurullo S, Weiss L, Visco C, Sowa G, Oh-Park M, et al. Association of Academic Physiatrists women's task force follow-up report. Am J Phys Med Rehabil. 2021;100:610–619.
11. Silver JK, Booth GS, Chatterjee A, Crusto CA, El-Sayed N, Fleming TK, et al. Organizations in science and medicine must hold each other accountable for discriminatory practices. Cell. 2022;185:3073–8.
12. Jacobs JW, Martin AA, Larson AR, Gehrie EA, Silver JK, Booth GS. Analysis of industry-related payments among editors of pathology journals. Am J Clin Pathol. 2022; in press. https://doi.org/10.1093/AJCP/AQAC147

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REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

White paper on pandemic preparedness in the blood supply

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Abstract

Background and Objectives: In March 2020, the WHO declared the SARS-CoV-2 corona virus a pandemic which caused a great disruption to global society and had a pronounced effect on the worldwide supply of blood.

Materials and Methods: In 2022 an on-line meeting was organised with experts from Austria, Canada, Germany, Greece, Netherlands and United States to explore the opportunities for increasing preparedness within blood systems for a potential future pandemic with similar, or more devastating, consequences. The main themes included the value of preparedness, current risks to the blood supply, supply chain vulnerabilities, and the role of innovation in increasing resiliency and safety.

Results: Seven key recommendations were formulated and including required actions at different levels.

Conclusion: Although SARS-CoV-2 might be seen as a unique event, global health risks are expected to increase and will affect blood transfusion medicine if no preparedness plans are developed.

Keywords

innovation, pandemic, preparedness, safety, supply chain vulnerability

Highlights

- To develop pandemic planning with the involvement of public health and resource sharing.
- To build larger donor bases, revise donor referral criteria based on evidence, develop surveillance systems and prioritize implementation of pathogen inactivation.
- To reflect on convalescent plasma with learnings from SARS-CoV-2.

INTRODUCTION

On 11 March 2020, the World Health Organization (WHO) declared the SARS-CoV-2 coronavirus a pandemic, expressing deep concern for the alarming levels of spread and severity and inaction [1]. In many countries, preventive measures were taken in healthcare, business affairs, travel, local movement and education with great disruption to global society. Although measures impacted all aspects of life, blood collection was not consistently included in the preparedness and resiliency projects at the national and international levels [2].

Although the SARS-CoV-2 virus is not transfusion transmissible, the pandemic has had a pronounced effect on the global supply of blood [3–5]. Experience in developing emergency plans for influenza A in 2010 was foundational in implementing the mitigation measures for COVID-19. Existing preparedness strategies and disaster emergency plans, however, did not sufficiently consider the effect of such a virus on society or on the behaviour of people, including blood donors. The objective of this meeting was to anticipate the future, whether the next pathogen is transfusion-transmitted or not, and to provide a holistic analysis of the blood system and what it means to be prepared. The initiative of the meeting was taken by the corresponding author, who also drafted the questions and

coordinated the meeting. The initiative was based on the consequences of the SARS-CoV-2 pandemic. Although drastic measures were taken, which affected public life worldwide, the impact on the blood supply and transfusion practices was not uniformly anticipated, recognized and addressed. The experts from different countries were selected based on their expertise with (risks of) interruptions of the blood supply due to different reasons, including transfusion-transmitted infections (TTIs). The recommendations were formulated as a result of the discussions.

Questions discussed

1A. How would you describe the role of transfusable blood and blood products in ensuring health system resiliency?

Access to donors and donor availability

In most of the countries represented, preventive measures were taken to minimize the risk of transmission of SARS-CoV-2 in the general population, such as keeping 1.5–2 m distance between people and closing the venues where people congregated. These measures were a serious hurdle for the collection of blood and plasma.

All collections, at least for a time, were concentrated in dedicated fixed-site environments where the flow and spacing of people could be controlled, and the risk of respiratory transmission could be minimized. The number of beds at these sites was reduced to comply with social distancing rules. New locations were needed, and 'pop-up' sites [6] were easy to secure with the abundance of spaces (athletic stadiums, storefronts and conference rooms) not being used during the lockdowns.

The pandemic showed that access to donors stands out as a weak point in guaranteeing and securing the blood supply. Donors could not always attend the sites made available because they were infected, had been exposed and had to quarantine or were afraid of being exposed in the blood collection settings. For those who required public transit, there were risks in transportation. In Greece, donors had to be asymptomatic, and strict pre-donation screening procedures with a physical examination of each candidate donor and temperature evaluation were performed. Medical staff who had close contact with the infected donors underwent molecular screening for the presence of SARS-CoV-2 and self-quarantined. Any post-donation information that revealed subsequently diagnosed asymptomatic donors and personnel possibly exposed to the virus led to the recall of blood components donated by infected individuals and screening of exposed personnel and close contacts of diagnosed donors for the presence of SARS-CoV-2 by means of collection and molecular testing of throat swabs, with precautionary self-quarantine for 14 days.

In Canada, there was a 3-week deferral if hospitalized with COVID-19.

In Canada and the United States, later in the pandemic, vaccinations were recommended for donors along with requirements for being asymptomatic and having had no exposure to contact with coronavirus symptoms in the prior 2 weeks.

Luckily, SARS-CoV-2 posed no risk to transfusion recipients, and its infectivity, morbidity and mortality rates for the population of healthy donors were not high enough to prevent all donors from braving the blood collection establishments. In a pandemic with much higher mortality and risk to the donor, the blood centres could suddenly be confronted with no blood donations.

In preparing for the future, a higher percentage of donors needs to be secured in the population. With more individuals identified as active donors, the system is less susceptible to disruption when donors become ineligible, even if only temporarily. Temporary deferrals compound the problem, as individuals interpret them as a permanent lack of eligibility [7].

Just as donors were kept away from the donor centres, employees were likewise affected by illness and quarantine after SARS-CoV-2 exposure, further limiting donors' opportunities to donate. Healthcare employee availability is becoming a general problem, exacerbated by sick leave during outbreaks, which will require contingency plans.

Alongside the pandemic and related preventive measures, Greece experienced other elements, such as severe heat and large wildfires that negatively influenced the blood supply. Plans must consider multiple challenges confronting the system simultaneously.

1B. Do you think this is understood at the level of blood bankers and policymakers?

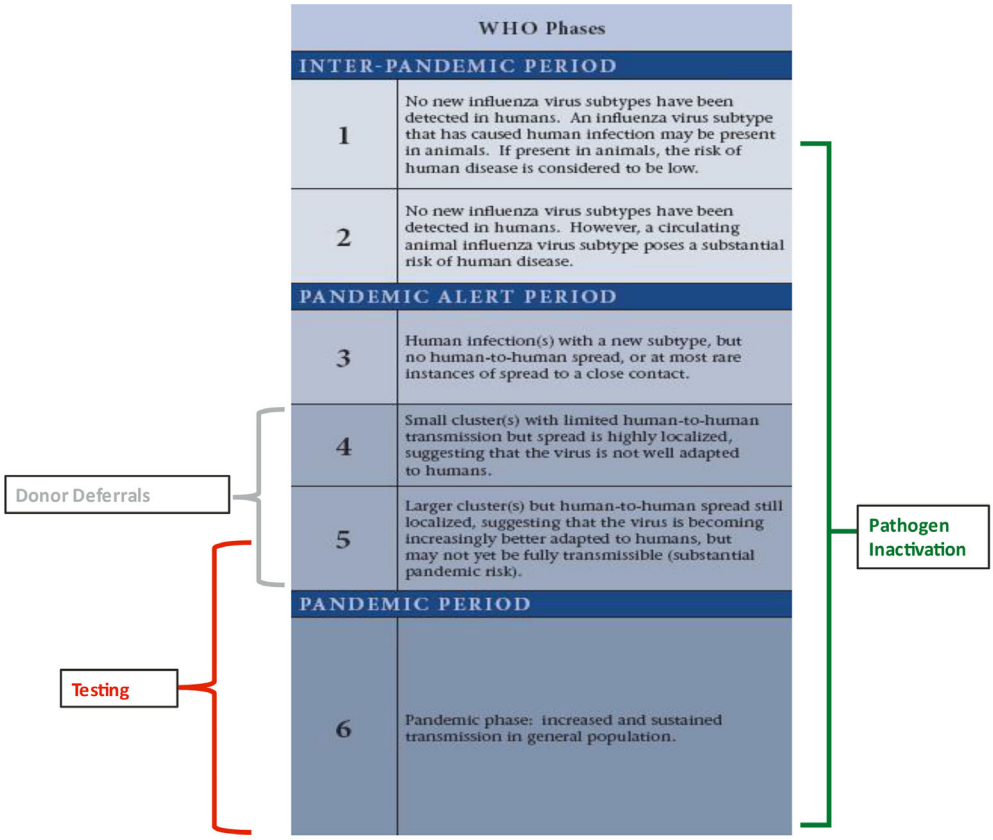
Expertise within the blood banking industry

Both in the Americas and in Europe, blood-related issues are respected as being important. The specific issues, however, are complicated and knowledge is highly specialized. For example, how to manage donor acceptance criteria for whole blood versus apheresis blood collections, how to manage various products with varied blood groups and different storage requirements, and how to balance supply with limited visibility to demand. Blood bankers understand the importance of blood for health system resiliency but senior level policymakers are more apt to take it for granted.

Health authorities

In a resource-rich country, overly cautious policies are sometimes instituted and not always justified by the evidence. On blood availability, the introduction of rulemaking has, in part, been calibrated by awareness of the meaningfully negative impact that new restrictions might have. Contingency plans were less developed for risks outside of TTIs, such as insufficient blood supplies.

Collaboration with and responsiveness from health regulators allowed for changes to donor deferral criteria (e.g., decreasing the deferral for travel to a malaria-endemic area from 12 to 3 months in the United States and Canada [8]), recognition of blood collection staff as essential workers to ensure early vaccinations, and awareness of the importance of blood and need for donation (as in Greece with the mobilization of patient associations). Interaction with authorities



Donor safety measures have varying levels of effectiveness depending on the pandemic phase. Donor deferrals can be useful in the pandemic alert period when at risk individuals can be identified and deferred without impacting the blood availability. Once the pandemic has taken hold in an area, deferrals no longer work because everyone is at risk. Hopefully, before that happens, a test can be developed. That is why testing can be more effective in phases 5 and 6 of the pandemic. For products that can be pathogen inactivated, and for pathogens that are susceptible to PI, it can be effective in all phases of a pandemic.

FIGURE 1 World Health Organization (WHO) pandemic phases and corresponding blood safety measures

and decision-makers was critical to maintaining blood donation. Because of the pandemic, hospitals realized again the dependence on blood donors, blood components and blood centres. Information on how our society can protect blood transfusion medicine is of greater concern than prior to the pandemic. Politicians, however, are unaware of this dependency, and the pandemic should trigger further discussions.

Although the European Union (EU) legislation on blood, tissues and cells and the European Committee on Blood Transfusion (CD-P-TS) of the Council of Europe sets guidance on best practices in blood transfusion, every national European regulatory agency currently can make its own decisions. The European Directorate for the Quality of Medicines & Health Care published a standardized toolkit for contingency and emergency preparedness to support European countries in ensuring continuity of blood and blood components [9]. Revision of donor criteria should be a priority, in general, with relaxation wherever unnecessarily stringent, to promote better donor retention even in non-pandemic times.

2. In general, are blood programs/systems in Europe and North America as prepared as they could be for an emerging TTI? If not, what is holding them back?

Disaster management plans were present but no pandemic plans

Developed during the influenza pandemic in 2010, the WHO has defined six phases of a pandemic and the actions to be taken during each phase to reduce the spreading of disease (see Figure 1) [2]. In Austria, the emergency plan was drafted based on these six phases but using it turned out to be unnecessary for COVID-19. The Omicron

variant was like influenza in that the virus was very infectious, the disease itself was less severe, and the spread was rapid and wide-ranging. Both the staff and the donors were implicated. In Canada, an existing pandemic plan was revised early in the pandemic, focusing on the response to the epidemiology of the virus. Government responses, including dramatic shutdowns, were, however, difficult to foresee.

For the blood system, two different situations should be explored when anticipating a future pandemic: (1) When a pathogen is not a TTI but negatively impacts blood collections by limiting the availability of donors and blood centre staff, and (2) when a pathogen is a TTI and recipients face risk of transmission from a transfusion.

Both situations bring increased risk to donors and patients and could mean a lack of supply resulting in patients not receiving adequate levels of treatment. Great care should be taken to establish measures to prevent such a catastrophe. What is needed is an emergency master plan drafted in collaboration with health authorities for any pandemic, with special attention given to the blood donation program.

3. What should blood establishments, policymakers and governments do to help ensure blood programs and health systems are ready for an emerging TTI?

Donor motivation

Initiatives were developed in all represented countries to generate publicity on blood donation and to increase the number of donations. A recruitment plan is a key aspect of balancing demand and supply. On the other hand, the perception of donors is changing. Just communicating that donating is lifesaving is not always motivating donors to show up. Different generations require different approaches to information, both what is said and how it is delivered. In Canada, extra attention was given to recruitment planning and methods to engage a surplus of potential donors. Donating blood was one of the few options available for people to actively contribute during pandemic lockdowns.

In Greece, a strategy was developed in conjunction with municipalities and donor associations with the continuous support of the National Blood Centre and the National Public Health Organization to commence a joint national TV and radio campaign, 'We Together We Can' in March 2020, providing information and inviting people to make appointments. Donors expressed interest in learning more and found inspiration from understanding the effect of the pandemic on the blood supply.

Repeat versus first-time donors and appointments

Currently, blood safety is high, and first-time donors do not pose the same risk they once did. First-time donors represent less than 10% of total donations in many countries [10]. Typical proposals for securing blood inventories aim at more donations from the existing donor population, but we need to increase the number of donors from the general population.

The structure of blood donation was changed in Germany to avoid large congregations of donors. Normally, donors are invited and are free to come to the collection centre any time they choose, but during the pandemic, it was important to control the number of donors appearing at the same time. Therefore, appointments were introduced, assigning donors to specific time slots and supporting the continuation of collections. A similar operation was installed in Austria, Greece, Netherlands and the United States.

Appointments are also used in Canada, where donors may book online or through a national call centre. Previous donors are contacted to make an appointment via email, text or telephone call. As a result, there is control over who is invited to donate and when. This system was not originally designed for safety but rather for ensuring operational efficiency and donor satisfaction. In the past, having reliable donors donating more times per year was considered desirable, but more recently, the risk of iron loss to such donors has prompted revision of donation frequency. In Canada, as in some European countries, women cannot donate whole blood as frequently as men. A shift in the strategy may be required to better support the supply while still ensuring safety.

Demand

During the first wave of COVID-19 early in 2020, the volume of operations was reduced and there were no elective surgeries. The number of patients requiring transfusion decreased, and sufficient blood was available. Initially, the rapid drop in demand resulted in oversupply and large inventories.

Concern was raised about access for patients requiring transfusions, such as emergency or oncology patients, when COVID-19 patients occupied most of the hospital beds. In Greece, the government faced complaints that all patients should have equal rights to healthcare, including hospital beds, transfusions, laboratories and so on.

As restrictions on movement eased, an increase in blood collection followed, but the use of blood increased faster, and the insufficiency of supply had a severe impact. Ramping down collections (and even expiring products in the beginning) and then ramping back up, with constant calibration to the needs of the hospitals, was challenging for 18 months. In Canada, there was no shortage. The experience in Germany with patient blood management (PBM) has created the impression that transfusion is a risk for the recipients instead of lifesaving. During the pandemic, the hospitals became aware that this perception was not justified, and they were once again confronted with the need for blood. As other countries encountered at the beginning of 2020, blood inventories were large because of the lockdown situation in hospitals.

Resource sharing

An international exchange of surplus blood must be realized in the EU to guarantee supply across Europe. Greece, Italy, France and the Netherlands prepared a full proposal that was accepted by the EU

Commission; based on that proposal, the EU Commission adapted the appropriate strategies to EU legislation and disseminated them across Member States in an attempt to harmonize and improve current practices [11]. With a renewed focus on proactive measures, this proposal is currently being discussed again. Mechanisms to facilitate international cooperation should be in place in case of an eventual crisis or pandemic.

In Canada, where regions help each other, a national blood supply program is in place. The organization in the United States is geographically quite large and diverse. A lot of coordination is involved in staying abreast of needs, but within-country resource sharing is a frequent and well-established means of ensuring balance in supply and demand.

Centralization of testing for blood screening poses an added risk during a pandemic, as the staff could become infected and be unable to perform testing. Standardization, exchange programs and backup systems, therefore, should be established with support by the governments to secure the blood supply.

4. Infected individuals who are asymptomatic can become blood donors. What is the role of the blood establishment in public health surveillance?

Risk modelling

Canada has experience in keeping up with emerging pathogen surveillance. With Zika, risk modelling was used to determine appropriate deferral policies. Every week a simple deterministic model was updated to evaluate whether further risk mitigation was necessary. An area of focus in the future should not only be just on when to institute measures, but also on when to remove them.

With West Nile virus (WNV) in Greece, Canada and the United States, the interaction between blood providers and public health authorities was exemplary as screening of donors allowed for signals of new cases ahead of public health. Identifying asymptomatic WNV carriers in the blood donor population was essential to national surveillance and monitoring of infections [12].

Haemovigilance should be more consistently integrated with public health monitoring of pathogenic infections, such as malaria, Zika, dengue, WNV, hepatitis E virus and so on. Risk modelling is advantageous and efficient; people proficient in these methods are well prepared to recognize and respond to a novel TTI.

Serosurveillance: Are donors representative?

COVID-19 epidemiology in the Netherlands based on samples from healthy blood donors [13] has prompted the question of whether blood donors are a representative group and whether the prevalence of antibodies in donors is a good criterion.

Blood donor seroprevalence has been central to monitoring infection in both the United States and Canada. Blood donor SARS-CoV-2 seroprevalence rates tend to be similar to general population studies, but representativeness needs to be evaluated for each infection [14–16].

Donors represent a healthy and well population that excludes various groups such as people who are sick, who are in nursing homes or who are incarcerated. Although there is no systematic analysis on representation, data on donors should be used more widely to inform both risk modelling and public health policy. Healthy donors might be an underused resource for mining health data. If a large segment of the population is infected and asymptomatic, screening questionnaires would be less effective than screening tests, and blood donors would be an ideally representative group. A disease of great morbidity and mortality will not, however, be present in the donor population.

Another approach to blood collection establishments serving public health, being used for SARS-CoV-2 seroprevalence and being considered for other pathogens, is biobanking. The proposal is to maintain a blood donor biobank for monitoring new and emerging infections. As the pandemic continues, samples from different points in time will be retained. This is still in development in the United States and under consideration in Canada, and researchers are studying the possibilities. The ISBT Working Party on TTI will also be discussing the role of biobanking.

5. What is the role of the blood establishment in crafting novel treatments for an emerging pathogen? What have we learned during the SARS-CoV-2 pandemic regarding the use of convalescent plasma? How should we plan for future needs?

Donor motivation for COVID-19 convalescent plasma collection

During emergency situations, donors want to help; the COVID-19 pandemic is no exception. In all countries represented, the request for COVID-19 Convalescent plasma (CCP) donors was well publicized and heavily supported by the media, health authorities and donors.

In Greece, convalescent patients showed great interest in coming to the blood centre to lend their help, bringing with them touching stories. The blood service stopped publicizing the need for CCP collections when the national committee declined to grant a product licence for CCP due to a lack of convincing clinical efficacy data.

In Canada, CCP donor recruitment was complicated by the limited sites with plasma apheresis capacity [17], requirements for donors with high titres of antibodies and the lack of familiarity with plasma apheresis among the general population.

In other countries, there were many more CCP donors than needed and the surplus plasma was either sold to the industry for the production of COVID-19-specific immunoglobulins for fractionation or was used as fresh frozen plasma for transfusion.

As with any public health issue, the need to communicate clearly and constantly to the public is important. Gaps in communication existed, particularly regarding eligibility.

COVID-19 convalescent plasma

In all countries, clinical studies were performed for the treatment of patients with CCP. Outcomes for patients with a severe disease

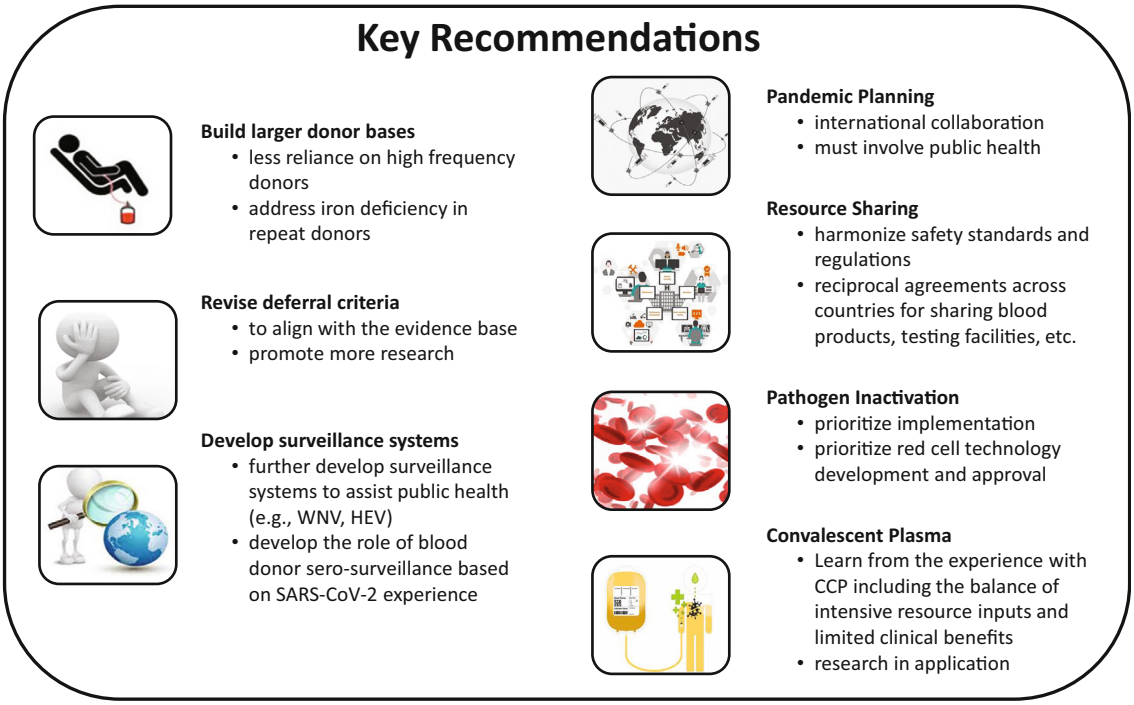


FIGURE 2 Summary of the key recommendations. CCP, COVID-19 convalescent plasma; HEV, hepatitis E virus; WNV, West Nile virus

showed no difference in mortality, morbidity or hospital stay between the treated and untreated patient groups calling into question the general efficacy of CCP. On the other hand, patients with an early-stage disease who were treated with high titre CCP benefited significantly [18].

Going through the process of answering the outstanding questions regarding CCP product characterization and patient eligibility is both interesting and challenging. The complexity surrounding the level of antibodies, severity of symptoms, duration of symptoms and level of medical intervention is important for characterization. This knowledge is foundational to being better prepared to characterize donor material for efficacious use in a future outbreak [19].

The outcomes of the clinical studies might be influenced by the lack of data on neutralizing antibodies. With no available assay for neutralizing SARS-CoV-2 antibodies, most trials commenced with no data on the quality of the product being evaluated. The treatment with convalescent plasma was blinded. Also, sufficient information on the expected course of the disease was lacking.

Plasma may be the key to bridging a gap in treatments; it may be the best usable option to treat patients in a novel pandemic until other treatments can be made available.

Convalescent plasma for other viruses

Convalescent plasma may not always be the first option, but it should be considered an important tool. In another pandemic, a different response might be appropriate [20, 21]. Convalescent plasma should be considered when no other treatments are available and financial resources are low; however, prior to large-scale programs promoting its use, feasibility, safety and efficacy need to be established.

The need for pathogen inactivation (PI) should be noted. The licence for plasma in Germany was linked to quarantine plasma. Because of the need to start early, an emergency licence for non-quarantined and non-inactivated plasma took a lot of time and required lots of discussion with authorities.

6. Understanding that increased safety measures (e.g., donor deferrals) can decrease blood and blood product availability, what blood establishment strategies can be deployed to secure blood supplies? What regional/national level strategies are needed to support the local programs?

Techniques to protect against emerging pathogens

PI is currently commercially available for plasma and platelet products in >100 countries worldwide, with red blood cell and whole blood systems under development. Iceland, France, Belgium and Switzerland are examples of countries that have universally implemented PI. The US Food and Drug Administration (FDA) has put out a very robust statement on PI to support blood safety [22]. Greece wants to adopt PI as one of the solutions to protect against emerging pathogens. In Canada, PI is being introduced as part of routine operations, and it will be valuable in the context of emerging pathogens.

The German view is that most pathogens, except prions, could be suppressed by PI. Two to three adequate PI technologies for blood components are needed. Since the introduction of PI for clotting factor concentrates, the products for haemophilia care have been safe. The reputation of blood centres, in comparison with the plasma

industry, will also be improved with the introduction of PI. If a COVID-19 vaccination program for the whole world can be developed, it should be feasible to develop PI programs for all blood components that would cover most emerging pathogens. Such programs would help significantly to guarantee the blood supply during a future pandemic.

Additionally, politicians and governments should be urged to financially support PI technology research and implementation. PI requires time and resources to operationalize. Like the furtherance of PBM policies, policymakers should support the development of new technologies for blood safety regarding emerging pathogens, not only for a potential pandemic but also for local and regional epidemics.

Testing or no testing

When nationwide testing of blood donors for the Zika virus was introduced in the United States, many people believed that such testing in some states, such as Alaska, was excessive. There was some regionality in case reports, which was not reflected in the policy. These are the challenges with mosquito- and tick-borne infections in a large country with different climatic zones and with the option to test individual donors or pools. Similar discussions persist regarding the appropriateness of year-round testing for WNV or implementing testing for certain arboviruses across the country with no regional differentiation.

New polymerase chain reaction tests for COVID-19 were developed [23]. On the outset of the pandemic the possibility the virus could be transfusion-transmitted was unknown, therefore, a test was prepared in anticipation of a need. If PI technology was available for all components, there would be no need for a test to be developed.

Similar alignment is seen in Austria on PI and the need for a common standard of testing to allow for the exchange of blood. The existing standard for testing blood in Europe is generally very low. Revision of the legislation on blood, tissues and cells is underway and presents an opportunity to elevate and unify the standard for testing [24].

7. Did the lifting of donor exclusion criteria show that the arguments for these donor exclusion criteria were not sufficiently strong? Should donor criteria include measures to prevent supply risks?

Donor exclusion criteria

The donor health criteria are quite variable among different countries. Lifting some of the donor criteria was suggested during the pandemic to increase the number of donors; however, removing donor deferral criteria is complicated, and such a change needs to be considered very carefully.

The US FDA and Health Canada are not under any requirement to consider sufficiency or blood availability in their decision-making process, although they are not precluded from doing so. Nevertheless, decisions on blood safety are often made independently of sufficiency. In the United Kingdom and France, however, there is a stronger connection between epidemiologists who work in public health and those who work in the blood service; this is an advantage. From time to time, complaints about losing blood donors due to donor deferrals are received from local Greek authorities and even some patients. Alternatives to blood donor deferrals, however, are available to manage the blood supply sufficiently.

Early in the pandemic, the deferrals in the United States for men-who-have-sex-with-men (MSM) and for travel to malaria-endemic regions were decreased from 12 to 3 months, and PI was allowed as a substitute for the travel deferral [8, 25]. Other countries, including United Kingdom, France and the Netherlands, had previously made similar changes to the MSM deferral, setting a precedent that a shorter deferral period was reasonable. This was under consideration at the FDA for a long time, and they were looking at what the rest of the world was doing.

Making decisions in isolation is potentially risky. When implementing a donor travel deferral for variant Creutzfeldt Jakob disease (United Kingdom, France and Ireland) in the 1990s, the United States and Canada had to account for the risk that the deferral could lead to a lack of sufficiency of the blood supply [26]. A donor loss of about 3% could assumably be absorbed without a substantive impact on supply. This value has been discussed in relation to the proposed deferral criteria.

Donor health criteria have historically been difficult to remove. Out of the pandemic came renewed thinking on donor deferral criteria. Abnormal blood pressure was stopped in Canada, where healthcare is free, and no need exists for such a health check. Some donor screening parameters are largely for attracting donors rather than ensuring their suitability as a donor. In Greece, frequent health checks are required and important for donor satisfaction. Donor vigilance should be in place, and exclusion criteria should be set only for the safety of the donor and of the product.

SUMMARY

The country-specific data showed that there was no real consensus on all questions; however, based on the discussions, seven key recommendations were formulated, as shown in Figure 2. The opportunities for increasing preparedness within blood systems for a potential future pandemic require actions at different levels. Although the SARS-CoV-2 pandemic might be seen as a unique event, global health risks are expected to increase and will affect blood transfusion medicine if no preparedness plans are developed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. WHO Director-General's opening remarks at the media briefing on COVID-19. 2020 Mar 11. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
2. WHO pandemic influenza preparedness and response. A WHO guidance document. Available from: https://apps.who.int/iris/bitstream/handle/10665/44123/9789241547680_eng.pdf?sequence=1.
3. Loua A, Kasilo OMJ, Nikiema JB, Sougou AS, Kniazkov S, Andrews AE. Impact of the COVID-19 pandemic on the blood supply and demand in the WHO African Region. Vox Sang. 2021;116:774–84.
4. Chandler T, Neumann-Böhme S, Sabat I, Barros PP, Brouwer W, van Exel J, et al. Blood donation in times of crisis: early insight into the impact of COVID-19 on blood donors and their motivation to donate across European countries. Vox Sang. 2021;116:1031–41.
5. Shopsowitz KE, Lim C, Shih AW, Fishbane N, Berry BR, Bigham M, et al. Impacts of COVID-19 and elective surgery cancellations on platelet supply and utilization in the Canadian Province of British Columbia. Vox Sang. 2022;117:251–8.
6. Bloodworks Northwest. Find a Pop-Up Donor Center. Available from: https://www.bloodworksnw.org/donate/find-mobile-blood-drive.
7. Clement M, Shehu E, Chandler T. The impact of temporary deferrals on future blood donation behavior across the donor life cycle. Transfusion. 2021;1–10:1799–808.
8. US FDA. Revised recommendations to reduce the risk of transfusion-transmitted malaria. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/revised-recommendations-reduce-risk-transfusion-transmitted-malaria.
9. European Directorate for the Quality of Medicines & Health Care of the Council of Europe. Blood supply contingency and emergency plan. Recommendations and model preparedness plan. 2022. Available from: Blood Supply Contingency and Emergency Plan (B-SCEP). Survey Report (edqm.eu).
10. Mowla SJ, Sapiano MRP, Jones JM, Berger JJ, Basavaraju SV. Supplemental findings of the 2019 National Blood Collection and Utilization Survey. Transfusion. 2021;61:S11–35.
11. Politis C, Kioupi S, Liumbruno G, Sandid I, Linden F, Escoval MA, et al. Surplus blood exchange: intra-member states agreements and inter-country contracts. 2010 Final Draft.
12. Murphy EL, Wright DJ, Custer BS, Tobler LH, Stramer SL, Kleinman SH, et al. West Nile virus infections projected from blood donor screening data, United States, 2003. Emerg Infect Dis. 2006;12:395–402.
13. Slot E, Hogema BM, Reusken CBEM, Reimerink JH, Molier M, Karregat JHM, et al. Low SARS-CoV-2 seroprevalence in blood donors in the early COVID-19 epidemic in the Netherlands. Nat Commun. 2020;11:5744.
14. Jones JM, Stone M, Sulaeman H, Fink RV, Dave H, Levy ME, et al. Estimated US infection- and vaccine-induced SARS-CoV-2 seroprevalence based on blood donations, July 2020–May 2021. JAMA. 2021;326:1400–9.
15. Reedman CN, Drews SJ, Yi QL, Pambrun C, O'Brien SF. Changing patterns of SARS-CoV-2 seroprevalence among Canadian blood donors during the vaccine era. Microbiol Spectr. 2022;10:e0033922.
16. Grant R, Dub T, Andrianou X, Nohynek H, Wilder-Smith A, Pezzotti P, et al. SARS-CoV-2 population-based seroprevalence studies in Europe: a scoping review. BMJ Open. 2021;11:e045425.
17. CBC. Canadian Blood Services to open plasma donation sites to secure supply for patients. Available from: https://www.cbc.ca/news/health/plasma-cbs-collection-centres-1.5238969.
18. Körper S, Weiss M, Zickler D, Wiesmann T, Zacharowski K, Corman VM, et al. Results of the CAPSID randomized trial for high-dose convalescent plasma in patients with severe COVID-19. J Clin Invest. 2021;131:e152264.
19. Wood EM, Estcourt LJ, McQuilten ZK. How should we use convalescent plasma therapies for the management of COVID-19? Blood. 2021;137:1573–81.
20. van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med. 2016;374:33–42.
21. Hung IF, To KK, Lee C-K, Lee K-L, Chan K, Yan W-W, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis. 2011;52:447–56.
22. US FDA. Statement from FDA Commissioner Scott Gottlieb, M.D., and Director of FDA's Center for Biologics Evaluation and Research Peter Marks, M.D., Ph.D., on efforts to promote and foster blood pathogen reduction technologies. Available from: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-director-fdas-center-biologics-evaluation-and.
23. Mack CD, Wasserman EB, Hostler CJ, Solomon G, Anderson DJ, Walton P, et al. Effectiveness and use of reverse transcriptase polymerase chain reaction point of care testing in a large-scale COVID-19 surveillance system. Pharmacoepidemiol Drug Saf. 2022;31:511–8.
24. European Commission. Revision of the EU legislation on blood, tissues and cells. Available from: https://ec.europa.eu/health/blood-tissues-cells-and-organs/overview/revision-eu-legislation-blood-tissues-and-cells_en.
25. US FDA. Revised recommendations for reducing the risk of human immunodeficiency virus transmission by blood and blood products. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/revised-recommendations-reducing-risk-human-immunodeficiency-virus-transmission-blood-and-blood.
26. Canadian Blood Services. Changes to the donation criteria. Available from: https://www.blood.ca/en/blood/am-i-eligible/changes-donation-criteria-blood-donation.

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REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

Systematic reviews on platelet transfusions: Is there unnecessary duplication of effort? A scoping review

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Abstract

Background and Objectives: Platelet transfusions are used across multiple patient populations to prevent and correct bleeding. This scoping review aimed to map the currently available systematic reviews (SRs) and evidence-based guidelines in the field of platelet transfusion.

Materials and Methods: A systematic literature search was conducted in seven databases for SRs on effectiveness (including dose and timing, transfusion trigger and ratio to other blood products), production modalities and decision support related to platelet transfusion. The following data were charted: methodological features of the SR, population, concept and context features, outcomes reported, study design and number of studies included. Results were synthesized in interactive evidence maps.

Results: We identified 110 SRs. The majority focused on clinical effectiveness, including prophylactic or therapeutic transfusions compared to no platelet transfusion (34 SRs), prophylactic compared to therapeutic-only transfusion (8 SRs), dose, timing (11 SRs) and threshold for platelet transfusion (15 SRs) and the ratio of platelet transfusion to other blood products in massive transfusion (14 SRs). Furthermore, we included 34 SRs on decision support, of which 26 evaluated viscoelastic testing. Finally, we identified 22 SRs on platelet production modalities, including derivation (4 SRs), pathogen inactivation (6 SRs), leucodepletion (4 SRs) and ABO/human leucocyte antigen matching (5 SRs). The SRs were mapped according to concept and clinical context.

Conclusion: An interactive evidence map of SRs and evidence-based guidelines in the field of platelet transfusion has been developed and identified multiple reviews. This work serves as a tool for researchers looking for evidence gaps, thereby both supporting research and avoiding unnecessary duplication.

Keywords

decision support, haemostasis, platelet apheresis, platelet transfusion, scoping review, thrombocytopenia, viscoelastic

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Highlights

- This scoping review identified a total of 110 systematic reviews (SRs) and mapped them in interactive evidence maps according to clinical context and concept.
- Several areas, for example, platelet transfusion in intracerebral haemorrhage and the ratio of blood products in massive transfusion and viscoelastic testing to guide platelet transfusion, are served by multiple overlapping SRs.
- Scoping reviews can be a tool to avoid research waste. This work provides a comprehensive overview of the available research in the field of platelet transfusion.

INTRODUCTION

Platelets are the second most commonly transfused cellular blood component. Platelets are involved in haemostasis, but also have other roles [1]. Thrombocytopenia, or disorders of platelet function, may result in bleeding, which can be life-threatening [2]. Thrombocytopenia is often defined by a platelet count <100 to 150 $\times$ 10^9/L, whereas severe thrombocytopenia is defined by a platelet count <50 $\times$ 10^9/L [2, 3]. Thrombocytopenia can occur due to increased use (e.g. in severe bleeding), decreased production (e.g., haematological disorders) or immune-mediated destruction of platelets (e.g., neonatal alloimmune thrombocytopenia). Therefore, platelets are widely used across multiple clinical settings in hospitalized patients [4, 5], and can be administered either therapeutically, to stop bleeding, or prophylactically, to prevent bleeding [6]. Platelet transfusions are most often used in patients with haematological malignancies, undergoing cardiac surgery or before procedures in intensive care settings [7]. The increased demand and limited supply of platelet products show that judicious use of platelet transfusions is crucial.

Several methods for preparing platelets, platelet dosing, platelet transfusion threshold and platelet product specifications have been investigated in studies [8–14]. This demonstrates the importance of considering the best available evidence on the effectiveness and cost-effectiveness of procedures, collected in systematic reviews (SRs), to guide the development of evidence-based guidelines for clinical practice [15]. A current overview of existing SRs and topics for which no SR is as yet published is not available. Therefore, the aim of this scoping review is to develop an evidence map informing future SRs in the field of platelet transfusion.

MATERIALS AND METHODS

A completed (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA])-Scoping Reviews reporting checklist can be found in Appendix S1. A concise methods section is presented below, and a full version can be found in Appendix S2.

Selection criteria

We included patients of any age eligible for platelet transfusion. We included any SR of controlled research, with an explicit methods section, in the field of platelet transfusion, in any clinical context, without language restrictions. We included SRs comparing the effectiveness of platelet transfusion to no platelet transfusion, prophylactic to therapeutic platelet transfusion, different doses and timings of platelet transfusion, different ratios of platelets to other blood products in major transfusion and different production modalities for platelet transfusions, decision support systems for platelet transfusion and the impact of platelets on refractoriness or alloimmunization.

Search strategy and study selection

We searched for SRs on 5 May 2021, without applying date limits, in PubMed, Embase, Web of Science, Cumulated Index to Nursing and Allied Health Literature, Cochrane Database of Systematic Reviews, Transfusion Evidence Library and International Prospective Register of Systematic Reviews (PROSPERO).

Studies were assessed for eligibility by two independent reviewers at the title and abstract and full-text levels. Discrepancies were resolved by discussion or consulting a third reviewer. We screened the reference lists and the first 20 'similar articles' in PubMed of included studies for additional eligible studies.

Data charting, synthesis and presentation

Data charting from eligible SRs was done by two independent reviewers. We analysed data by population, concept, outcome type, methodological features, patient age and outdatedness. Data are presented in interactive evidence maps using EPPI-Mapper v2.1.0 [16].

RESULTS

Search results

A total of 9199 records were identified from the database searches, leading to a total of 5583 unique records that were reviewed. Following exclusions, 169 records, reporting on 110 unique SRs, were included, 13 of which were identified through screening of reference lists and 'similar articles' in PubMed of included records (Appendix S3). Multiple records reporting on the same topic area were

noted, including previous versions of the SRs, protocols and PROSPERO registrations and conference abstracts. The eligibility of another 48 records, reporting on 40 SRs, could not be ascertained due to a lack of information (mainly review protocols and conference abstracts of ongoing SRs). These records have an 'awaiting classification' status and may be assessed for eligibility again in future updates of this scoping review (Appendix S4). An overview of studies not meeting eligibility criteria can be found in Appendix S5.

Characteristics of the included SRs

An interactive evidence map describing the characteristics of the included SRs can be accessed online through this link: https://www.cebap.org/storage/cebap/20220110-eppimap-studydesign.html. A static overview is included in this article as Figure 1. A detailed overview of charted characteristics can be found in Appendix S6.

Of the 110 included SRs, 11 were SRs embedded in evidence-based guideline projects [9, 17–26], and three were overviews of reviews concerning the management of traumatic brain injury [27, 28] or trauma-induced coagulopathy [29]. The remainder were SRs of primary research, either experimental studies, observational studies or both. The majority of SRs were conducted in the United Kingdom (20%), Canada (19%) and the United States (18%).

Populations studied

Nine SRs included studies on intensive care unit (ICU) patients, of which one specifically included dengue patients. Fifty-three SRs focused on emergency care patients, including spontaneous or traumatic brain injury patients or patients defined as 'trauma' or 'massive bleeding' patients. Furthermore, 31 SRs included studies conducted in a haematological or oncological setting. Eighteen SRs studied general oncology/haematology patients, five SRs focused on haematopoietic stem cell transplant patients, nine SRs on hypoproliferative bone marrow disorders, three SRs on thrombotic or immune thrombocytopenia purpura, one SR on disseminated intravascular coagulation, two SRs on heparin-induced thrombocytopenia and five SRs on foetal/neonatal alloimmune thrombocytopenia. Thirty-seven SRs concerned surgery patients, 19 of which concerned cardiac surgery patients, eight concerned liver surgery patients, five concerned patients undergoing minor procedures and 16 concerned other or unspecified elective surgery patients. Finally, three SRs included studies with healthy volunteers, and the context of studies included in four SRs was classified as 'other'.

Four SRs specifically focused on the paediatric population, and a further five investigated platelet transfusion in foetal/neonatal alloimmune thrombocytopenia. The remainder either did not specify or specifically included studies in an adult population. The interactive evidence map, segmented by population age, can be accessed through this link https://www.cebap.org/storage/cebap/20220110-eppimap-age.html; a static overview can be found in Figure 2.

Concept studied

Fifty-eight SRs addressed the clinical effectiveness of platelet transfusions. Thirty-four SRs investigated the effectiveness of platelet transfusions compared to no platelet transfusions to prevent or treat bleeding, while eight compared prophylactic to therapeutic-only platelet transfusions. Eleven SRs focused on the dose and timing of platelet transfusions, and 15 included studies on platelet transfusion thresholds in prophylactic platelet transfusion. Finally, 14 SRs included studies comparing the ratio of platelets to other blood products in massive transfusion. Thirty-four SRs looked at decision support systems to guide platelet transfusions. Twenty-six SRs focused on point-of-care viscoelastic testing (thromboelastography and/or rotational thromboelastometry), while eight looked at other decision supports, mainly the use of formal transfusion protocols. Twenty-two SRs were identified that included information on platelet production modalities. Seven SRs included studies on the impact of platelet storage duration, while two searched for studies on the storage temperature of platelets. Four SRs included studies on derivation methods of platelets (whole blood derived vs. apheresis derived), six SRs concentrated on pathogen inactivation of platelets and four SRs assessed leucodepletion. Finally, five SRs investigated the clinical impact of platelet matching by ABO type or human leucocyte antigen cross-matching.

Outcomes reported

Regarding outcome types included, 76 SRs reported a death-related outcome (e.g. 30-day mortality), 69 SRs reported morbidity (e.g., bleeding, re-operation due to bleeding), 62 SRs reported outcomes related to transfusion (e.g., number of blood products used, transfusion requirement, transfusion interval), 33 SRs reported a haematological outcome (e.g., platelet count increment), 37 SRs reported length of stay outcomes (e.g., length of hospital stay or ICU stay), 48 SRs reported at least one adverse event (e.g., acute transfusion reactions), 7 SRs reported an economic outcome (e.g., costs associated) and 13 SRs reported an outcome that did not fit in any of the prior categories (e.g., quality of life).

Methodological features

The included SRs differed from each other in terms of methodological features. Only 66 SRs had a clearly defined research question, including elements of a population, intervention, control and outcomes question. The vast majority searched more than one database, but 15 SRs searched only in PubMed/Medline. A formal quality appraisal of included studies was conducted in 80 SRs, and 33 also assessed the certainty of the body of evidence, all but one, using the grading of recommendations, assessment, development and evaluation methodology [15]. Fifty-two of the included SRs were published before 2017, while 58 were published in 2017 or later. For the SRs supporting an

FIGURE 1 Evidence map illustrating the number of identified systematic reviews, mapped by clinical context and concept, segmented by study design included

evidence-based clinical practice guideline, eight were published in 2017 or later, and only three were from before 2017.

Regarding the outdatedness of the searches, 36 SRs had a search date less than 5 years old, while 69 SRs had a search date older than 5 years old, and therefore, considered outdated. The search data of five SRs were not sufficiently reported to assess outdatedness. An interactive evidence map segmenting the SRs by outdatedness can be accessed via https://www.cebap.org/storage/cebap/20220714-eppimap-outdatedness.html; a static version is shown in Figure 3.

DISCUSSION

This scoping review mapped the currently available SRs in the field of platelet transfusion. It not only provides an overview of the evidence but is also an important reference for clinician education. Moreover, it promotes new research by identifying research gaps and redundancy. We have identified 110 SRs. The high number of reviews, many published in the last few years, raises important questions as to which reviews should be accessed by busy clinicians. We labelled 40 SRs as 'awaiting' classification, which demonstrates that this is clearly an active and ongoing field of research.

About a third of the identified SRs had a search date less than 5 years old, which has been suggested to be a relevant cut-off for considering a SR as up-to-date [30]. If resources allow, the interactive versions of our evidence maps that are online available will be updated regularly. Future updates of the evidence map resulting from this project will likely have an important impact on the completeness of this overview.

It is clear that some areas of research are better served by SRs than others. This may correspond to the amount of underlying primary research available, the need to combine studies in meta-analyses when sample sizes are small or when outcomes are infrequent, or in areas of controversy. Several indications, for example, the use of viscoelastic testing to guide transfusion in cardiac surgery or the effectiveness of therapeutic platelet transfusion in traumatic brain injury, are covered by several overlapping SRs. This demonstrates the added value of a scoping review, which can serve as a tool to minimize future redundancy. Chalmers and Glasziou highlighted that many trials are conducted and reported without reference to existing literature,

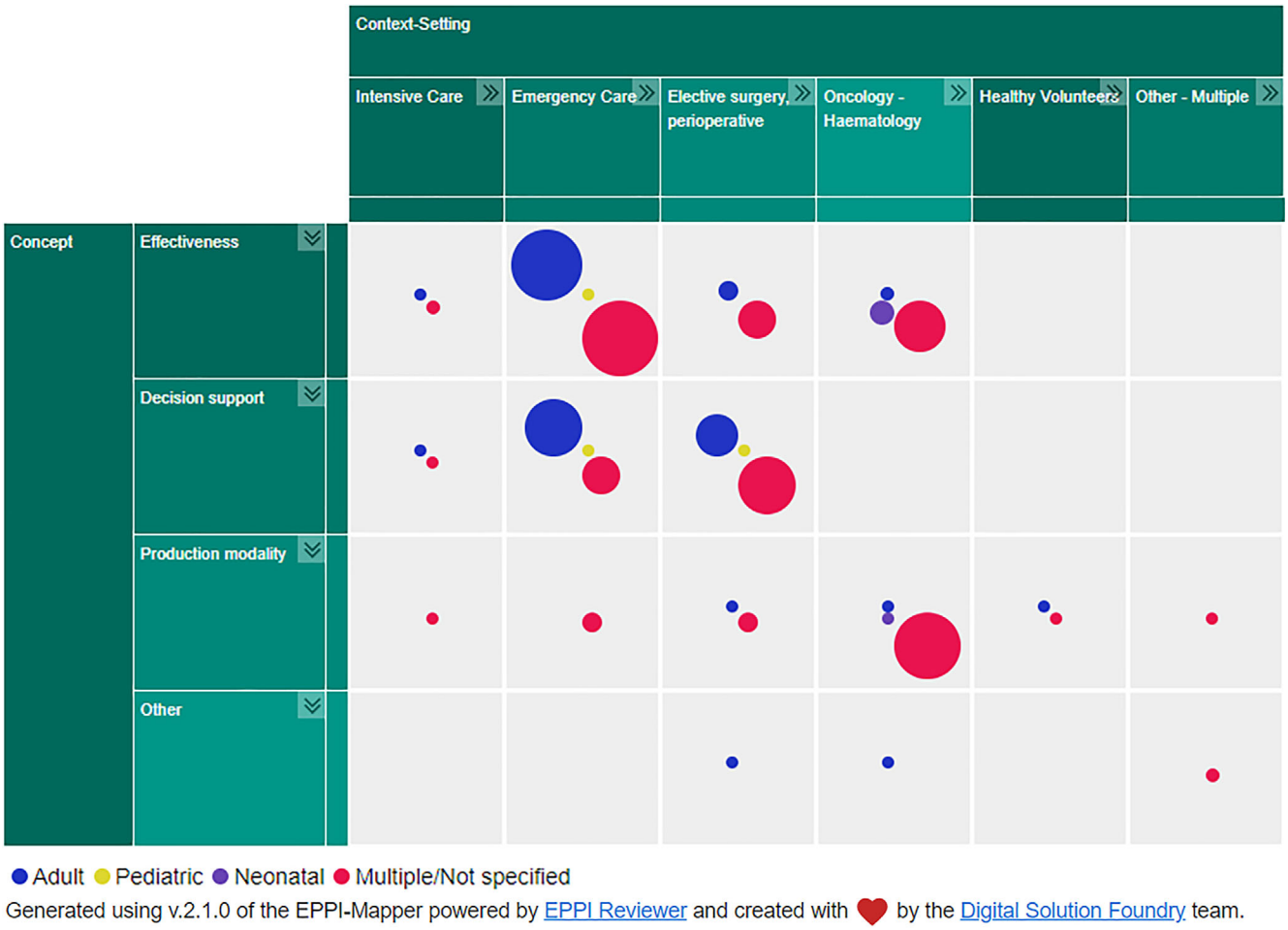

FIGURE 2 Evidence map illustrating the number of identified systematic reviews, mapped by clinical context and concept, segmented by age category

thereby potentially leading to studies answering already solved research questions [31]. Our scoping review identified a similar concept for SRs. In addition, several authors demonstrated that the number of published SRs and meta-analyses had grown steadily over the years [32, 33]. In order to avoid overlap and duplication in evidence syntheses, an initial consideration of whether a new SR is actually needed should be the first step in the set-up of a potential new SR protocol. Scoping reviews and evidence gap maps might be useful tools to answer this need [34, 35], especially if they include a search in the international prospective register for SRs, PROSPERO, for ongoing SRs [36].

Our approach has several advantages. First, we used elaborate search methods and a rigorous methodology [37], thereby aiming to obtain as complete an overview of the state-of-the-art in platelet transfusion as possible. Furthermore, our approach to visually display the identified SRs in interactive maps has the advantage of usability, whereby users can quickly scan the existing evidence for their topic of interest using the different filtering options available. Finally, our work directly demonstrates the research gaps in this field and can thereby inform future reviewers and researchers as to where useful work may be undertaken. When looking at the outcomes reported in the SRs, it is clear that few existing SRs pay attention to economic aspects related to platelet transfusion and production modalities or quality of life. Five of the seven SRs, including an economic outcome, focus on decision support systems [38-42], and two on platelet dose [9, 43]. The few SRs that defined quality of life as an outcome of interest actually did not identify any primary research study reporting this outcome [2, 6, 12, 39, 43-48]. Although a minority of SRs report at least one adverse event, no SR was identified with platelet transfusion-related adverse events as the main focus, despite the fact that platelets are regularly associated with adverse events and carry a higher risk of bacterial contamination than other blood products [49, 50]. Other potential research gaps may include prophylactic versus therapeutic-only platelet transfusion in the paediatric patient population [51], cardiac surgery or critical illness.

Limitations include an initial scope that included alternatives to platelet transfusion (e.g., tranexamic acid). Second, our scoping review is secondary research. It does not show whether there are primary research studies available in a given field of work. Finally, given that we have conducted a scoping review, the purpose of this exercise is to map the existing evidence and not a formal critical appraisal and evaluation of effectiveness.

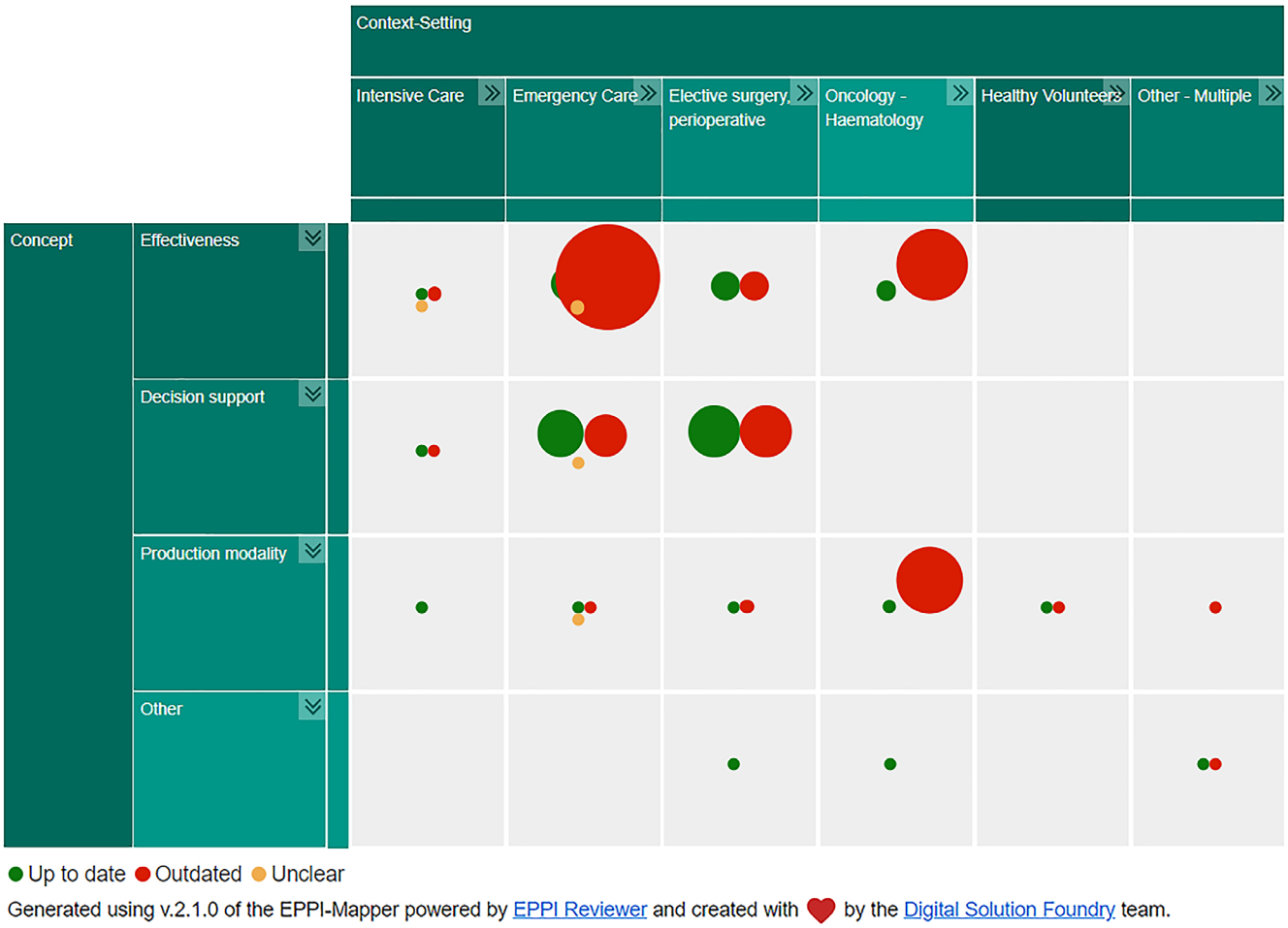

FIGURE 3 Evidence map illustrating the number of identified systematic reviews, mapped by clinical context and concept, segmented by outdatedness

In conclusion, we have mapped the currently available secondary research in the field of platelet transfusion using a rigorous scoping review methodology. This work serves both clinicians, researchers and guideline developers in search for a quick and clear overview regarding the state-of-the-art in themes related to platelet transfusion, from clinical effectiveness to production modalities and decision support.

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CONFLICT OF INTEREST

Relevant financial conflicts of interest directly related to this review: Bert Avau, Dorien O, Koen Veys, Hans Van Remoortel, Jørgen Georgsen, Nadine Shehata, Simon J. Stanworth, Emmy De Buck, Veerle Compernolle and Philippe Vandekerckhove declared not having any relevant direct financial conflict of interest. Susan Nahirniak declared to have received travel reimbursements from the Canadian Blood Services for travel to Scientific Research Advisory Committee, which occasionally discusses International Collaboration for Transfusion Medicine Guidelines (ICTMG) projects.

Relevant financial conflicts of interest not directly related to this review: Bert Avau, Dorien O, Koen Veys, Hans Van Remoortel, Emmy De Buck, Veerle Compernolle and Philippe Vandekerckhove are employees of Belgian Red Cross-Flanders, which is responsible for supplying adequate quantities of safe blood products to hospitals in Flanders and Brussels on a continuous basis and is funded by the Ministry of Social Affairs. Belgian Red Cross-Flanders received a grant from the European Blood Alliance to conduct this review.

Nadine Shehata reported having received personal fees from the ICTMG for the development of the ICTMG platelet guideline. Simon J. Stanworth declared being an employee of the NHSBT, a blood service supplier for England, which manufactures platelets and having received grants for the conduct of trials of platelets in neonates and platelets and tranexamic acid in haematological cancers. Jørgen Georgsen and Susan Nahirniak declared not having any other relevant financial conflicts of interest.

Relevant intellectual conflicts of interest: Bert Avau, Dorien O, Koen Veys, Hans Van Remoortel, Jørgen Georgsen, Emmy De Buck, Veerle Compernolle and Philippe Vandekerckhove declared not having any intellectual conflict of interest. Simon J. Stanworth declared having authored multiple systematic reviews (SRs) on the use of platelets and tranexamic acid in haematology—none within the last three years and being involved in a new guideline on platelets and plasma in critically ill children. Simon J. Stanworth and Susan Nahirniak declared being the co-chair of the platelet guideline revision working group of the ICTMG. Nadine Shehata declared having been a co-author on previous SRs and a guideline on platelet transfusion.

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REFERENCES

1. Macfarlane RG. An enzyme cascade in the blood clotting mechanism, and its function as a biochemical amplifier. Nature. 1964;202:498–9.
2. Estcourt LJ, Malouf R, Hopewell S, Doree C, Van Veen J. Use of platelet transfusions prior to lumbar punctures or epidural anaesthesia for the prevention of complications in people with thrombocytopenia. Cochrane Database Syst Rev. 2018;4:CD011980.
3. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117:4190–207.
4. Freireich EJ. Origins of platelet transfusion therapy. Transfus Med Rev. 2011;25:252–6.
5. Murphy S, Gardner FH. Effect of storage temperature on maintenance of platelet viability—deleterious effect of refrigerated storage. N Engl J Med. 1969;280:1094–8.
6. Crighton GL, Estcourt LJ, Wood EM, Trivella M, Doree C, Stanworth S. A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. Cochrane Database Syst Rev. 2015;9:CD010981.
7. Estcourt LJ. Why has demand for platelet components increased? A review. Transfus Med. 2014;24:260–8.
8. Al-Shahi Salman R, Law ZK, Bath PM, Steiner T, Sprigg N. Haemostatic therapies for acute spontaneous intracerebral haemorrhage. Cochrane Database Syst Rev. 2018;4:CD005951.
9. Nahirniak S, Slichter SJ, Tanael S, Rebulla P, Pavenski K, Vassallo R, et al. Guidance on platelet transfusion for patients with hypoproliferative thrombocytopenia. Transfus Med Rev. 2015;29:3–13.
10. Cid J, Lozano M. Lower or higher doses for prophylactic platelet transfusions: results of a meta-analysis of randomized controlled trials. Transfusion. 2007;47:464–70.
11. Kreuger AL, Caram-Deelder C, Jacobse J, Kerkhoffs JL, van der Bom JG, Middelburg RA. Effect of storage time of platelet products on clinical outcomes after transfusion: a systematic review and meta-analyses. Vox Sang. 2017;112:291–300.
12. Estcourt LJ, Malouf R, Doree C, Trivella M, Hopewell S, Birchall J. Prophylactic platelet transfusions prior to surgery for people with a low platelet count. Cochrane Database Syst Rev. 2018;9:CD012779.
13. Vamvakas EC. Meta-analysis of the studies of bleeding complications of platelets pathogen-reduced with the intercept system. Vox Sang. 2012;102:302–16.
14. Vogt KN, Van Koughnett JA, Dubois L, Gray DK, Parry NG. The use of trauma transfusion pathways for blood component transfusion in the civilian population: a systematic review and meta-analysis. Transfus Med. 2012;22:156–66.
15. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490.
16. Digital Solution Foundry and EPPI-Centre. EPPI-mapper, version 1.2.2. London, UK: EPPI-Centre, UCL Social Research Institute, University College London; 2021.
17. Lieberman L, Greinacher A, Murphy MF, Bussel J, Bakchoul T, Corke S, et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. Br J Haematol. 2019;185:549–62.
18. Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, et al. Guidelines for the use of platelet transfusions. Br J Haematol. 2016;176:365–94.
19. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol. 2017;34:332–95.
20. Kumar A, Mhaskar R, Grossman BJ, Kaufman RM, Tobian AA, Kleinman S, et al. Platelet transfusion: a systematic review of the clinical evidence. Transfusion. 2015;55:1116–27; quiz 5.
21. Schiffer CA, Bohlke K, Delaney M, Hume H, Magdalinski AJ, McCullough JJ, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2018;36:283–99.
22. Al-Riyami AZ, Jug R, La Rocca U, Keshavarz H, Landry D, Shehata N, et al. Quality of evidence-based guidelines for platelet transfusion and use: a systematic review. Transfusion. 2021;61:948–58.
23. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. 2019;23:98.
24. Curry N, Davenport R, Pavord S, Mallett S, Kitchen DP, Klein AA, et al. The use of viscoelastic haemostatic assays in the management of major bleeding: a British Society for Haematology Guideline. Br J Haematol. 2018;182:789–806.
25. Bugaev N, Como JJ, Golani G, Freeman JJ, Sawhney JS, Vatsaas CJ, et al. Thromboelastography and rotational thromboelastometry in bleeding patients with coagulopathy: practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2020;89:999–1017.
26. Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2017;82:605–17.
27. Moore L, Tardif PA, Lauzier F, Bérubé M, Archambault P, Lamontagne F, et al. Low-value clinical practices in adult traumatic brain injury: an umbrella review. J Neurotrauma. 2020;37:2605–15.
28. Synnot A, Bragge P, Lunny C, Menon D, Clavisi O, Pattuwage L, et al. The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: a comprehensive evidence map. PLoS One. 2018;13:e0198676.

29. Curry N, Stanworth S, Hopewell S, Doree C, Brohi K, Hyde C. Trauma-induced coagulopathy—a review of the systematic reviews: is there sufficient evidence to guide clinical transfusion practice? Transfus Med Rev. 2011;25:217–231.e2.
30. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007;147:224–33.
31. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet. 2009;374:86–9.
32. Hoffmann F, Allers K, Rombey T, Helbach J, Hoffmann A, Mathes T, et al. Nearly 80 systematic reviews were published each day: observational study on trends in epidemiology and reporting over the years 2000-2019. J Clin Epidemiol. 2021;138:1–11.
33. Siontis KC, Ioannidis JPA. Replication, duplication, and waste in a quarter million systematic reviews and meta-analyses. Circ Cardiovasc Qual Outcomes. 2018;11:e005212.
34. Snilstveit B, Vojtkova M, Bhavsar A, Gaarder M. Evidence gap maps? A tool for promoting evidence-informed policy and prioritizing future research. Washington, DC: The World Bank; 2013.
35. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol. 2018;18:143.
36. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. Syst Rev. 2012;1:2.
37. Peters MDJ, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: scoping reviews (2020 version). In: Aromataris E, Munn Z, editors. JBI manual for evidence synthesis. Adelaide, Australia: JBI; 2020.
38. Mitra B, O'Reilly G, Cameron PA, Zatta A, Gruen RL. Effectiveness of massive transfusion protocols on mortality in trauma: a systematic review and meta-analysis. ANZ J Surg. 2013;83:918–23.
39. Wikkelso A, Wetterslev J, Moller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev. 2016;2018:CD007871.
40. Kovalic AJ, Khan MA, Malaver D, Whitson MJ, Teperman LW, Bernstein DE, et al. Thromboelastography versus standard coagulation testing in the assessment and reversal of coagulopathy among cirrhotics: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2020;32:291–302.
41. Bianchi P, Beccaris C, Norbert M, Dunlop B, Ranucci M. Use of coagulation point-of-care tests in the Management of Anticoagulation and Bleeding in Pediatric Cardiac Surgery: a systematic review. Anesth Analg. 2020;130:1594–604.
42. Whiting P, Al M, Westwood M, Ramos IC, Ryder S, Armstrong N, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2015;19:v–vi.
43. McQuilten ZK, Crighton G, Brunskill S, Morison JK, Richter TH, Waters N, et al. Optimal dose, timing and ratio of blood products in massive transfusion: results from a systematic review. Transfus Med Rev. 2018;32:6–15.
44. Estcourt LJ, Desborough M, Hopewell S, Doree C, Stanworth SJ. Comparison of different platelet transfusion thresholds prior to insertion of central lines in patients with thrombocytopenia. Cochrane Database Syst Rev. 2015;12:CD011771.
45. Estcourt LJ, Stanworth S, Doree C, Trivella M, Hopewell S, Blanco P, et al. Different doses of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. Cochrane Database Syst Rev. 2015;10:CD010984.
46. Estcourt LJ, Stanworth SJ, Doree C, Hopewell S, Trivella M, Murphy MF. Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. Cochrane Database Syst Rev. 2015;11:Cd010983.
47. Estcourt LJ, Malouf R, Hopewell S, Trivella M, Doree C, Stanworth SJ, et al. Pathogen-reduced platelets for the prevention of bleeding. Cochrane Database Syst Rev. 2017;7:CD009072.
48. Gurusamy KS, Pissanou T, Pikhart H, Vaughan J, Burroughs AK, Davidson BR. Methods to decrease blood loss and transfusion requirements for liver transplantation. Cochrane Database Syst Rev. 2011;12:CD009052. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009052.pub2/full
49. Narayan S (Ed) D. Poles et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2020 Annual SHOT Report. Available from: https://www.shotuk.org/wp-content/uploads/myimages/Interactive_SHOT-REPORT-2020_V2.1.pdf.
50. Levy JH, Neal MD, Herman JH. Bacterial contamination of platelets for transfusion: strategies for prevention. Crit Care. 2018;22:271.
51. Saini A, West AN, Harrell C, Jones TL, Nellis ME, Joshi AD, et al. Platelet transfusions in the PICU: does disease severity matter? Pediatr Crit Care Med. 2018;19:e472–e8.

SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Impact of donor ferritin testing on iron deficiency prevention and blood availability in France: A cohort simulation study

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Abstract

Background and Objectives: Implementing a ferritin testing policy for whole blood (WB) donors may prevent iron deficiency (ID, ferritin <26 ng/mL) and anaemia, but may induce donation losses. As part of a national prevention plan in France, we aimed to estimate its impact on ID, anaemias and WB donations among donors at high risk of ID.

Materials and Methods: A micro-simulation model was developed to evaluate different scenarios compared to the current situation without ferritin testing as a reference scenario. The following scenarios were simulated: a minimum scenario with a 6-month deferral for donors with absent iron store (AIS, ferritinemia <15 ng/ml), a main scenario with additional delayed invitations for donors with ferritinemia 15–25 ng/ml and a supplementation scenario with additional iron supplementation for 50% of the donors with AIS.

Results: In the main scenario, 52,699 WB donations per year were estimated to be lost after 1 year (−8%), falling to 27,687 (−4.7%) after 5 years. IDs and anaemias were reduced by 13.6% and 29.3%, respectively, after 1 year. The supplementation scenario increased the number of prevented IDs and anaemias to 24.1% and 35.4%, respectively, after 1 year, and halved the number of anaemias at 5 years. The latter scenario also had the least impact on the number of donations (−3.2% after 5 years).

Conclusion: A ferritin testing policy resulting in delayed donations for ID donors is effective in reducing IDs and anaemias, but significantly impacts the number of donations, thereby posing a self-sufficiency challenge.

Keywords

blood collection, blood donation testing, donor health

Highlights

- A ferritin testing policy resulting in delayed donations for iron-deficient donors is effective in reducing iron deficiencies (IDs) and anaemias.
- Iron supplementation in 50% of high-risk donors has a substantial positive impact.

- Donations recovered from donors in whom ID and anaemia have been prevented do not compensate for the loss of donations resulting from extended inter-donation intervals, prolonged deferral periods and changes in donor behaviour.

INTRODUCTION

Approximately 3 million blood donations are carried out annually by Etablissement Français du sang (EFS) to treat 1 million patients. As whole blood (WB) donation leads to a 1 g/dl decrease of haemoglobin (Hb) levels [1], various measures are implemented in France to prevent anaemia in WB donors: (1) a mandatory 8-week inter-donation interval; (2) donations limited to four per year for women and six per year for men; (3) investigation into anaemia history and symptoms during the pre-donation interview; (4) pre-donation Hb testing in defined cases (initial donation or no donation in the previous 2 years, past donation Hb <12.5 g/dl for women or 13.5 g/dl for men, history or symptoms of anaemia) and (5) systematic post-donation Hb testing. Below a Hb threshold of 13 g/dl for males and 12 g/dl for females, defining anaemia, donors are deferred for 6 months. These thresholds are 0.5 g/dl below the European thresholds considering French West Indies donors whose Hb values are lower than those of the Caucasian populations [2].

Each donation of a WB unit results in an iron loss of 200–250 mg [1]. Iron stores are a key element in efficient erythropoiesis to compensate for red blood cell losses. Post-WB donation anaemia is due not only to direct Hb loss but primarily to iron loss.

The prevention of iron deficiency (ID), defined by ferritinemia <26 ng/ml [3], is expected to improve donor retention and donations.

The Canadian Blood Services and the Dutch national blood service Sanquin questioned blood product availability further to the implementation of a ferritin monitoring policy and subsequent donor deferral. The introduction of a ferritin monitoring policy to mitigate the effects of repeat donations on iron stores led to a significant decrease in donor availability and reduced donations in the Netherlands [4, 5]. A simulation model assessed the impact of ferritin testing on Canadian WB donors and concluded there would be a strong likelihood of a decline in WB donations [5].

ID in French WB donors was investigated in the FERRIDON research study. The prevalence was estimated to be 39.5% for women and 18.0% for men [6]. Four subgroups of donors at high risk of ID were determined (Table 1). Ferritin testing in these high-risk subgroups was implemented in early 2022 to further prevent ID in WB donors in France.

The aim of this study was to estimate in these subgroups the number of IDs and anaemias detected and the impact on the number of WB donations arising from these new measures with a specific focus on the long-term impact on WB availability to ensure national self-sufficiency.

MATERIALS AND METHODS

Overview

A patient-level micro-simulation model was designed using Visual Basic for Applications. The model was structured to run different scenarios focusing on WB donation, ID, absent iron store (AIS) and anaemia following the implementation of ferritin testing in the high-risk donor population. AIS was defined by ferritinemia <15 ng/ml. Donors with AIS were deferred for 6 months and advised to consult their general practioner (GP) for follow-up and possible iron supplementation. A moderate ID (15–25 ng/ml ferritinemia) led to delayed donation invitations, from 8 weeks to 3 months for male and to 4 months for female donors.

TABLE 1 Definition of groups of whole blood donors at high risk of iron deficiency (<26 ng/ml)

Group	Population	Definition of high-risk subgroups	Proportion among all donors (%)
G1	Repeat female donors	Women with last donation under 4.5 months ago, TCMH at last donation ≥30 pg and aged <31.5 years old	1.21
G2		Women with last donation under 4.5 months ago and TCMH at last donation <30 pg	9.65
G3	New female donors	Women aged <29.5 years old and with a pre-donation Hb level <13.7 g/dl	2.37
G4	Repeat male donors	Men with at least two donations within last year and: • Last donation under 3.5 months ago and TCMH at last donation <29.5 pg • Or last donation more than 3.5 months ago and TCMH at last donation <27.4 pg	7.23

Abbreviation: Hb, haemoglobin; TCMH, mean corpuscular hemogobin content.

Several scenarios were compared, with and without ferritin testing, to determine the impact of changes in inter-donation interval and deferrals as a result of ferritin testing.

Simulation model

The micro-simulation model was an open cohort model comprising donors simulated individually and independently on a weekly basis. The model allowed new donors to enter the cohort and current donors to drop out of the cohort each week. Donors could exit the cohort if they did not return to donation before 24 months. Entry cohorts were assumed to encompass several subgroups of donors, such as repeated donors who transit from low-risk to high-risk, persistent AIS and drop-out donors returning to donation. Every new donor was assigned to a risk group and to different time-dependent states following the initial donation (at-risk for testing, ID, anaemia and drop out for the next donation). Pre-donation Hb testing was simulated, and donors with anaemia were deferred for 6 months. A fall in ferritin levels was assumed post-donation with a return to levels ≥26 ng/ml after several weeks, depending on risk factors for ID, such as gender, pre-donation ID and time to the next donation [7]; an ID occurred in the model when a donation was given before ferritin levels had returned to normal. Donors with anaemia were counted once, and the model did not count them for ID.

The model was structured with two loops: a weekly cohort loop, simulating new high-risk donors every week and updating results (Figure 1a), and an individual donor loop, simulating the course of donations and various time-dependent states (Figure 1b) for each donor. New high-risk donors were followed until their next donation, unless they dropped out and were included in the new weekly repeat donors for their additional donations thereafter. The model assessed total donations, total IDs at the time of donations and pre- and post-donation anaemias per week for each risk group over the model period for each scenario.

Once a donor was assigned to a risk group, time-dependent states, interval to the next donation and ferritin level recovery period were simulated. Donors no longer at risk for testing were kept in the cohort; the model accounted for their next donations so that they could switch to high-risk groups again at any time. Time-dependent states were simulated from the uniform distribution, donation intervals from gamma distributions and ferritin recovery periods from normal distributions (Table S1). An ID was assumed when the time to donation occurred before the ferritin recovery period. Two classes of ID were considered: <15 ng/ml and 15–25 ng/ml distributed according to the prevalence observed in the FERRIDON study. The ferritin recovery period was assumed to be longer for a level of ferritin <15 ng/ml compared to 15–25 ng/ml.

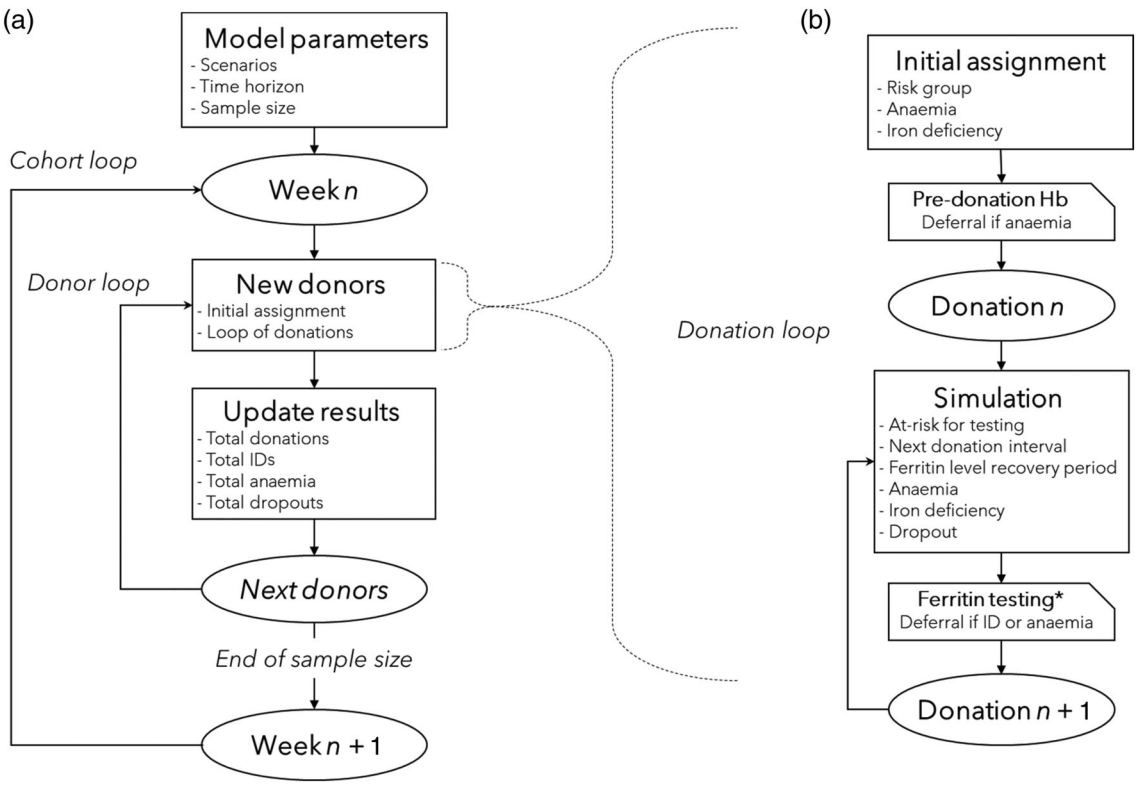

FIGURE 1 Structure of the patient-level micro-simulation model. *Only in scenarios with ferritin testing: <15 ng/ml: 6 months deferral. 15–25 ng/ml: informed by letter advising them to consult their GP and to postpone their next donation for at least 3 months for men and 4 months for women. Hb, haemoglobin; ID, iron deficiency

TABLE 2 Clinical inputs from FERRIDON study

Variables	G1	G2	G3	G4
Prevalence of ID				
15–25 ng/ml	32.2%	26.0%	22.1%	25.5%
<15 ng/ml	38.9%	45.6%	24.0%	31.2%
Prevalence of anaemia at initial donation, by ID status				
15–25 ng/ml	6.6%	11.5%	5.7%	4.0%
<15 ng/ml	9.1%	16.5%	9.3%	6.8%
No ID	3.0%	2.0%	3.9%	0.5%
Prevalence of anaemia at subsequent donations, after ID				
15–25 ng/ml	0.0%	2.0%	7.1%	0.5%
<15 ng/ml	0.0%	2.0%	7.1%	0.5%
Drop out, by ID status				
No ID, no anaemia	35.0%	20.4%	56.6%	20.0%
15–25 ng/ml	35.0%	20.4%	56.6%	20.0%
<15 ng/ml	49.7%	32.1%	65.0%	27.8%
Anaemia	49.7%	32.1%	65.0%	27.8%

Abbreviation: ID, iron deficiency.

Model data

ID prevalence was derived from a national, cross-sectional, multicentre study (FERRIDON study) that estimated ID risk factors in French WB donors [6]. Four groups of donors at high risk of ID were determined based on the following independent risk factors: gender, age, donor status (new or repeat donor), mean corpuscular haemoglobin, Hb level, number of donations in the previous 12 months and interval since previous donation (Table 1). Model inputs from the FERRIDON study are presented in Table 2.

In the FERRIDON study, ID donors (<26 ng/ml) received a letter advising them to consult their GP and to postpone their next donation for at least 6 months. Their follow-up in the EFS database provided inter-donation interval data according to donor status, with and without ID and risk group. Gamma distributions were used and calibrated to reproduce the empirical distribution of donation intervals observed in the FERRIDON study for each risk group by ID status (Figure S1).

The time required for ferritin to revert to normal levels (>26 ng/ml) was taken from the HEIRS study published by Kiss et al. [7]. The study aimed to determine the effect of oral iron supplementation on the recovery of iron stores in donors with 'low ferritin' (≤26 ng/ml) and 'higher ferritin' (>26 ng/ml) levels. It was found that, following a 500-ml donation of WB, ferritin levels fell by approximately 30 and 8 ng/ml over a 30-day period in the high and low ferritin groups, respectively. Among blood donors with normal Hb levels, low-dose iron supplementation versus no supplementation reduced the ferritin recovery period to approximately 1 month in the low ferritin (≤26 ng/ml) or higher ferritin (>26 ng/ml) groups. Another study showed that without iron supplementation, iron stores were not replenished for approximately 84 and 168 days plus in the high and low ferritin groups, respectively [8]. Normal distributions were used to simulate recovery intervals for each risk group according to ID status (Table S1).

Internal validation

Model validation was conducted by calibrating the scenario without ferritin testing, which is the current situation in France, using annual data for each risk group (Figure S2). The model was calibrated to reproduce the overall annual number of donations from donors at high risk of ID, for whom a 20,000 reduction in annual donations was considered to reflect the donation trend. IDs and anaemias were calibrated for each risk group and were stable over time. Simulated model data were compared to historical data (Figure S2).

Statistical analysis

Four scenarios were simulated for each risk group:

1. *A reference scenario*: current situation without ferritin testing and a minimum inter-donation interval of 8 weeks.
2. *Minimum scenario*: implementation of ferritin testing for every donor of each risk group, involving a 6-month deferral period only for donors with ferritin levels <15 ng/ml. No specific intervention is planned for donors at 15–25 ng/ml.
3. *Main scenario*: minimum scenario, plus an additional intervention for donors at 15–25 ng/ml, involving a minimum return interval of 3 and 4 months for male and female donors, respectively.
4. *Supplementation scenario*: main scenario, plus an oral iron supplementation for 50% of donors with ferritin levels <15 ng/ml.

The model was simulated over a 5-year period. Results were calculated separately for each risk group and aggregated for the first, second and fifth year in terms of WB donations, IDs and anaemias. The dispersion was measured with the half-width used to estimate the confidence interval, which measures the error in the estimate of the true mean and is defined as the 95% confidence coefficient times the standard deviation over the square root of the sample size. A sampling rule of 1:10 donors was simulated to reflect monthly donations from high-risk donors.

Sensitivity analyses were conducted to assess uncertainty relating to various data sources for the following outcomes: rates of anaemia, ferritin recovery period, time to next donation and drop-out rate. Deterministic sensitivity analyses were performed for each type of input by applying ±25% of the reference input value to all risk groups (the error margin was assumed to be similar between the risk groups).

RESULTS

Reference scenario

For the first year, the model estimated around 660,000 donations in the high-risk population for the reference scenario, with 230,000 AISs (<15 ng/ml), 140,000 IDs of 15–25 ng/ml and 60,000 anaemias. Estimated changes over time for these high-risk groups are presented in Figure S2 and Table 3.

TABLE 3 Estimated results in high-risk donors eligible for ferritin testing over a 5-year timeline

	Reference scenario	Minimum scenario	Main scenario	Iron supp. <15 ng/ml
WB donations				
First year	662,286	615,973	609,587	632,122
Second year	651,431	607,795	607,352	620,153
Fifth year	594,627	567,209	566,940	575,394
Difference versus reference scenario (loss of WB donations)				
First year change	-	**−46,313**	**−52,699**	**−30,164**
% Change	-	−7.0%	−8.0%	−4.6%
Second year change	-	**−43,636**	**−44,079**	**−31,278**
% Change	-	−6.7%	−6.8%	−4.8%
Fifth year change	-	**−27,418**	**−27,687**	**−19,232**
% Change	-	−4.6%	−4.7%	−3.2%
ID				
Total (<26 ng/ml)				
First year	369,847	328,114	319,532	280,612
Second year	316,828	265,229	258,428	235,498
Fifth year	296,411	250,459	243,078	222,006
<15 ng/ml				
First year	228,094	200,828	196,256	173,168
Second year	195,806	162,586	158,727	145,551
Fifth year	184,774	154,308	150,266	137,750
15–25 ng/ml				
First year	141,753	127,286	123,276	107,445
Second year	121,022	102,643	99,701	89,947
Fifth year	111,637	96,151	92,813	84,256
Difference versus reference scenario (prevented ID)				
Total				
First year change		**−41,733**	**−50,315**	**−89,235**
% Change		−11.3%	−13.6%	−24.1%
Second year change		**−51,599**	**−58,400**	**−81,330**
% Change		−16.3%	−18.4%	−25.7%
Fifth year change		**−45,952**	**−53,333**	**−74,406**
% Change		−15.5%	−18.0%	−25.1%
<15 ng/ml				
First year change		**−27,266**	**−31,838**	**−54,927**
% Change		−12.0%	−14.0%	−24.1%
Second year change		**−33,220**	**−37,079**	**−50,256**
% Change		−17.0%	−18.9%	−25.7%
Fifth year change		**−30,466**	**−34,508**	**−47,024**
% Change		−16.5%	−18.7%	−25.4%
15–25 ng/ml				
First year change		**−14,466**	**−18,476**	**−34,308**
% Change		−10.2%	−13.0%	−24.2%
Second year change		**−18,378**	**−21,321**	**−31,075**
% Change		−15.2%	−17.6%	−25.7%
Fifth year change		**−15,486**	**−18,825**	**−27,381**
% Change		−13.9%	−16.9%	−24.5%

(Continues)

TABLE 3 (Continued)

	Reference scenario	Minimum scenario	Main scenario	Iron supp. <15 ng/ml
Anaemia				
First year	60,215	43,755	42,589	38,876
Second year	49,121	35,849	35,004	32,786
Fifth year	44,115	33,449	32,709	30,820
Difference versus reference scenario (cases of anaemia prevented)				
First year change	-	**−16,460**	**−17,626**	**−21,339**
% Change	-	−27.3%	−29.3%	−35.4%
Second year change	-	**−13,272**	**−14,117**	**−16,335**
% Change	-	−27.0%	−28.7%	−33.3%
Fifth year change	-	**−10,666**	**−11,406**	**−13,295**
% Change	-	−24.2%	−25.9%	−30.1%

Abbreviations: ID, iron deficiency; WB, whole blood.

Minimum scenario

The expected number of donations, IDs and anaemias for the minimum scenario and the estimated difference compared to the current scenario are presented in Table 3. Following the extended 6-month deferral for donors with ferritin <15 ng/ml, a loss of approximately 46,000 donations was estimated in the first year compared to 27,000 in the fifth year, corresponding to a reduction of 7.0% and 4.6%, respectively.

This scenario could prevent around 42,000 IDs in the first year (−11.3%) and 46,000 in the fifth year (−15.5%) (of which 65% AIS). An overall reduction of around 16,000 anaemias (−27.3%) was estimated for the first year and 11,000 (− 24.2%) for the fifth year.

Main scenario

When the delayed donation was applied for donors with ferritin levels ranging from 15 to 25 ng/ml, losses ranging from approximately 53,000 donations (−8.0%) in the first year to 28,000 (−4.7%) in the fifth year were estimated, with the highest impact being observed for G2, followed by G4 (Figure 2).

Around 50,000 IDs (−13.6%) could be prevented in the first year and 53,000 (−18.0%) in the fifth year. An overall reduction of around 18,000 anaemias (−29.3%) was estimated in the first year and 11,000 (−25.9%) in the fifth year.

Compared to the minimum scenario, the additional extended deferral period increased losses by one point (6500 donations) in the first year, with quite no differences in the fifth year. This scenario could prevent almost 10,000 additional IDs per annum over the 5-year period.

Supplementation scenario

In addition to the main scenario, this scenario assumed that 50% of donors with ferritin levels <15 ng/ml received iron supplements. A loss of around 30,000 donations (−4.6%) was estimated in the first year, falling to 19,000 (−3.2%) in the fifth year.

The supplementation could prevent 40,000 additional IDs and 4000 anaemias in the first year compared to the main scenario and 20,000 IDs and 2000 anaemias in the fifth year.

Sensitivity analyses

Deterministic sensitivity analyses are presented (Figure S3) and highlight the impact on WB donations during the first year of ferritin testing and the fifth year on a cumulative basis. In cases where the normal ferritin level recovery period was increased by 25%, additional losses of 35% and 39% were observed in the first and fifth years, respectively; conversely, when it fell by 25%, 20% and 32% of WB donations were saved. Decreasing inter-donation intervals and drop-out rates had a substantial impact, with additional losses ranging from 24% to 43% in the first year and 28% to 33% in the fifth year.

DISCUSSION

ID is a common issue in the general population. Of the 18–74-year-old French adults, 6.9% present AIS, mostly affecting women (11.9%) rather than men (1.5%) [9]. Donors at high risk of ID were investigated in France. AIS was found to be more prevalent in WB donors, with women being affected in 19.3% of cases and men in 6.4% of cases, this figure increasing to 45.6% in the high-risk group of repeat female donors [6].

This study aimed to assess the impact of a ferritin testing policy on WB donations, IDs and anaemias through patient-level simulation and data observed in the real-world setting.

Our simulation showed encouraging results: between 15% and 25% of IDs could be prevented in high-risk ID groups depending on the scenario. Regardless of the scenario, approximately one third of anaemia cases were prevented during the first year (Table 3).

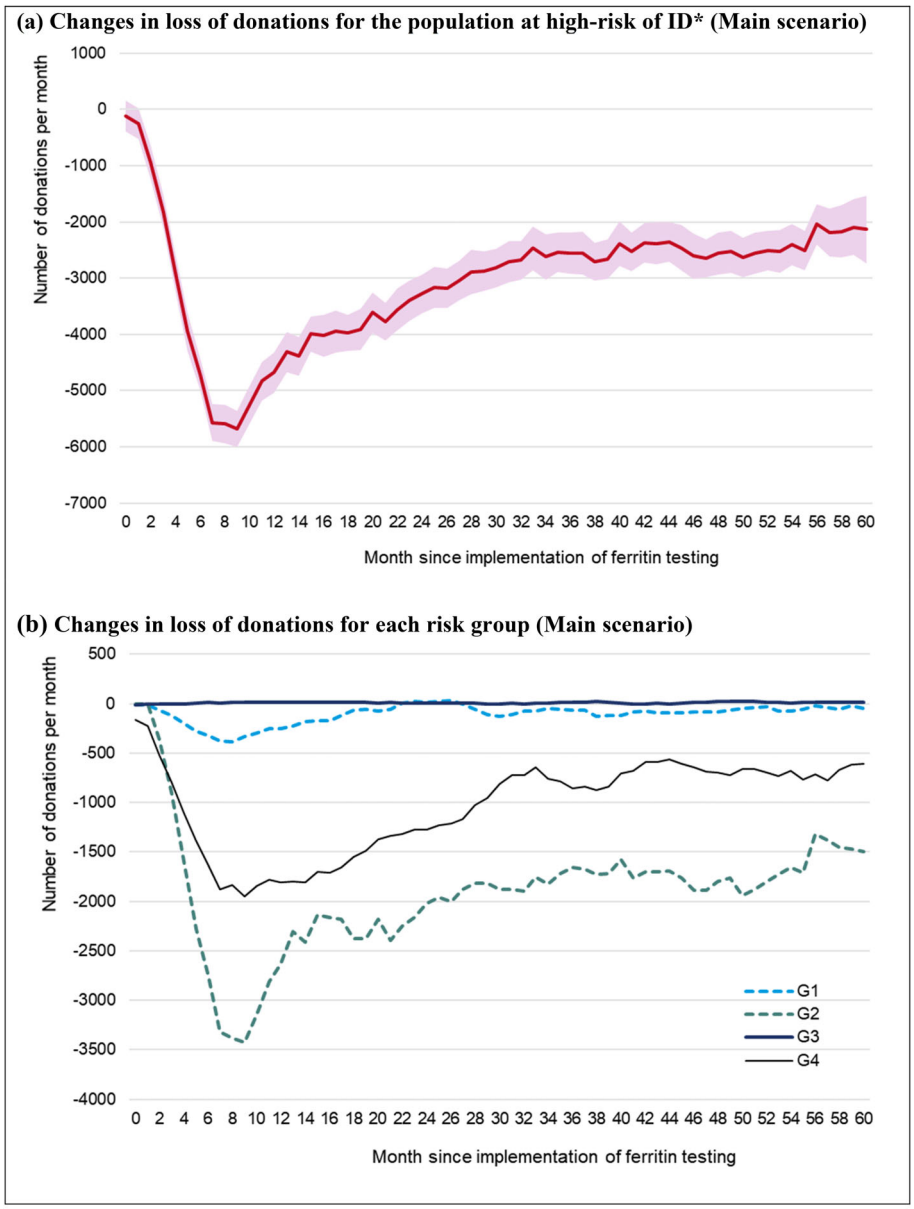

FIGURE 2 Changes in the loss of donations after implementation of ferritin testing (main scenario). (a) Changes in loss of donations for the population at high risk of iron deficiency (main scenario). (b) Changes in loss of donations for each risk group (main scenario)

Compared to the current situation, the number of anaemia cases in these groups fell to almost 50% after 5 years. These figures are underestimated since they only refer to ID and anaemia prevented among WB donors who return to donation, while data are censured for donors lost to follow-up.

Our study highlighted the fact that, after 5 years, donations recovered from donors in whom ID and anaemia have been prevented do not compensate for the loss of donations resulting from deferral and drop out. The maximum of WB donation loss occurred during the first year, decreasing thereafter over time, while the reduction in ID was stable over time (~50,000 IDs per year). Our study also showed that the impact of iron supplementation in 50% of donors with very low ferritin levels (<15 ng/ml) had a substantial positive impact on donations (+20,000) and IDs (−40,000) in the first year.

In a Canadian study [5] using a different simulation model with a higher threshold of ferritinemia for deferral (<26 ng/ml), an extended 6-month deferral period, an increased drop-out rate and reduced donation frequency, the authors estimated a donation loss of 17% and a new donor requirement of 29%. These scenarios, based on a pilot study [10], could be pessimistic since return rates could improve with further retention and educational effort. In a scenario with no reduction in donation frequency, which may be overly optimistic, they estimated a donation loss of 9.5%.

In the Netherlands, donors undergo ferritin testing at entry and every five donations. Ferritin levels between 15 and 30 ng/ml are

deferred for 6 months, and those below 15 ng/ml for 12 months [4]. This new ferritin monitoring policy in the Netherlands resulted in fewer donations and lower response rates to donation drives [11]. These results revealing a high percentage of lost donations have led EFS to defer only WB donors with AIS for 6 months and to delay invitations for moderate ID to avoid jeopardizing self-sufficiency in blood products.

One strength of our study lies in the fact that assumptions regarding donor behaviour were derived from the FERRIDON study, an observational study performed in 2019, including over 9000 WB donors representative of our donor population [6]. This should mitigate the impacts resulting from the unknown proportion of donors already using iron supplementation, having a low ferritin level unrelated to blood donations or from different behaviours depending on the site of donation.

Another strength of our study is that various scenarios have been considered and sensitivity analyses conducted. A delayed period to the next donation and an increase in drop-out rate were considered for donors based on ID level. Sensitivity analyses showed that a shorter inter-donation interval (−25%) and a lower drop-out rate (−25%) had a more adverse impact on WB donation from repeat donors (Figure S3). This was confirmed by the 8% reduction in the average number of annual donations for repeat donors for all risk groups (data not shown). A very recent Finish study corroborated these results, showing that donation activity accounted for most of the variation in ferritin levels [12].

Another key assumption was derived from the HEIRS trial, which studied the time to recovery of Hb and iron levels following a single donation [7]. Without iron supplementation, recovery of iron stores to pre-donation levels took longer than 24 weeks on average. In contrast, donors assigned to receive iron pills (38 mg) in this study displayed uniformly accelerated recovery of both Hb and iron levels. These results were applied in our model, and sensitivity analyses showed that when the ferritin recovery period was shortened by 25%, 32% of WB donations were saved over the 5 years.

In France, the monitoring policy recommends a GP visit for donors with ferritin levels <15 ng/ml. Iron supplementation will be given at the discretion of both patients and GPs. In the STRIDE study—a 2-year randomized controlled trial of 692 donors assigned to educational groups or interventional groups with iron supplementation—a small increase in de-enrolment at 60 days for interventional groups was observed. No difference was observed in donors receiving iron and placebo tablets, which suggests that some donors will not comply with regular dosing regimens [13]. Follow-up data of up to 24 months after the final STRIDE visit [14], however, showed increased donations and decreased Hb deferrals in donors receiving iron supplementation compared to controls. In addition, 57% of donors who received a letter advising of low ferritin levels with recommendations to take iron supplements or delay future donations initiated iron supplementation. This figure was five times higher compared to those who received letters with no specific recommendation. Another study suggested that informing donors of their iron status might be sufficient to stimulate donor initiation of iron supplementation [15] and could increase further with the dispensing of iron supplements [16] or after phoning the donors [17]. In line with these results, iron supplementation for 50% of AIS donors seems to be a realistic expectation that would have a significant impact, although 3.8% of the general French population was shown to take an iron supplementation [9].

In conclusion, our study shows that the prevention of anaemia and ID with a strategy of ferritin testing in donors at risk for ID significantly improves donor health: at least 11%–24% of ID and 27%–35% of anaemias will be prevented among high-risk WB donors. Because of extended inter-donation intervals, prolonged deferral periods and changes in donor behaviour, its implementation will, however, reduce the amount of WB collected from 5% to 8% in the high-risk subgroups after 1 year. The impact on WB donations could even be higher if donors were encouraged to convert to plasma donation, especially for those donating at fixed blood sites. This will need to be offset by combined efforts in terms of retention, education and recruitment of donors. Without public health policies for the prevention of ID in the general population, a significant proportion of donors, especially young women, will, however, continue to present with an ID unrelated to blood donations. Every blood establishment implementing a ferritin testing policy to improve donor health should be aware of the ensuing challenge of maintaining a sufficient blood supply.

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P.R. designed the research study, analysed the results and wrote the paper. A-M.F. wrote the draft of the paper. L.M. performed the statistical analysis, contributed to the design and wrote the paper. C.L., C.C., G.W., C.J. and P.M. reviewed the final draft of the paper. H.L. performed the statistical analysis. A.V. designed the research study, analysed the results and wrote the paper.

CONFLICT OF INTEREST

No conflict of interest to declare.

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REFERENCES

1. Boulton F. Evidence-based criteria for the care and selection of blood donors, with some comments on the relationship to blood supply, and emphasis on the management of donation-induced iron depletion. Transfus Med. 2008;18:13–27.
2. Malard L, Richard P, Maire F, Djoudi R, Gross S, Fillet A-M. Factors associated with recovery of haemoglobin levels after whole-blood donation in the French West Indies in 2015. Transfus Med. 2019;29:72–5.
3. Mei Z, Addo OY, Jefferds ME, Sharma AJ, Flores-Ayala RC, Brittenham GM. Physiologically based serum ferritin thresholds for iron deficiency in children and non-pregnant women: a US National Health and Nutrition Examination Surveys (NHANES) serial cross-sectional study. Lancet Haematol. 2021;8:e572–82.

4. Vinkenoog M, Hurk K, Kraaij M, Leeuwen M, Janssen MP. First results of a ferritin-based blood donor deferral policy in the Netherlands. Transfusion. 2020;60:1785–92.
5. Blake JT, O'Brien SF, Goldman M. The impact of donor ferritin testing on blood availability in Canada. Vox Sang. 2021;117:17–26.
6. Fillet A, Martinaud C, Malard L, Le Cam S, Hejl C, Chenus F, et al. Iron deficiency among French whole-blood donors: first assessment and identification of predictive factors. Vox Sang. 2021;116:42–52.
7. Kiss JE, Brambilla D, Glynn SA, Mast AE, Spencer BR, Stone M, et al. Oral iron supplementation after blood donation: a randomized clinical trial. JAMA. 2015;313:575–83.
8. Schotten N, Pasker-de Jong PCM, Moretti D, Zimmermann MB, Geurts-Moespot AJ, Swinkels DW, et al. The donation interval of 56 days requires extension to 180 days for whole blood donors to recover from changes in iron metabolism. Blood. 2016;128:2185–8.
9. Study of health on environnement, biosurveillance, physical activity and nutrition (Esteban), 2014–2016. Nutrition portion. Chapter biological dosages: vitamins and mineral. Saint-Maurice: Santé Publique France; 2019. 61p. Cited 2020 February 4. Available from: https://www.santepubliquefrance.fr/determinants-de-sante/nutrition-et-activite-physique/documents/rapport-synthese/etude-de-sante-sur-l-environement-la-biosurveillance-l-activite-physique-et-la-nutrition-esteban-2014-2016-.-volet-nutrition.-chapitre-dosages
10. Goldman M, Uzicanin S, Scalia V, O'Brien SF. Iron deficiency in Canadian blood donors. Transfusion. 2014;54:775–9.
11. Spekman MLC, Ramondt S, Sweegers MG. Whole blood donor behavior and availability after deferral: consequences of a new ferritin monitoring policy. Transfusion. 2021;61:1112–21.
12. Lobier M, Castrén J, Niittymäki P, Palokangas E, Partanen J, Arvas M. The effect of donation activity dwarfs the effect of lifestyle, diet and targeted iron supplementation on blood donor iron stores. PLoS One. 2019;14:e0220862.
13. Bialkowski W, Bryant BJ, Schlumpf KS, Wright DJ, Birch R, Kiss JE, et al. The strategies to reduce iron deficiency in blood donors randomized trial: design, enrolment and early retention. Vox Sang. 2015;108:178–85.
14. Cable RG, Birch RJ, Spencer BR, Wright DJ, Bialkowski W, Kiss JE, et al. The operational implications of donor behaviors following enrollment in STRIDE (Strategies to Reduce Iron Deficiency in blood donors). Transfusion. 2017;57:2440–8.
15. Mast AE, Bialkowski W, Bryant BJ, Wright DJ, Birch R, Kiss JE, et al. A randomized, blinded, placebo-controlled trial of education and iron supplementation for mitigation of iron deficiency in regular blood donors. Transfusion. 2016;56:1588–97.
16. Gorlin J, Katz L, Elsmore D, Kirbach K, Erickson Y, Hove A, et al. Prevalence of blood donor iron deficiency and feasibility ferritin-based iron replacement: a blood collection agency-based study. Vox Sang. 2016;111:206–8.
17. Magnussen K, Ladelund S. Handling low hemoglobin and iron deficiency in a blood donor population: 2 years' experience. Transfusion. 2015;55:2473–8.

SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

A positive blood culture is associated with a lower haemoglobin increment in hospitalized patients after red blood cell transfusion

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Abstract

Background and Objectives: Abundant clinical evidence supports the safety of red blood cell (RBC) concentrates for transfusion irrespective of storage age, but still, less is known about how recipient characteristics may affect post-transfusion RBC recovery and function. Septic patients are frequently transfused. We hypothesized that the recipient environment in patients with septicaemia would blunt the increase in post-transfusion blood haemoglobin (Hb). The main objective was to compare the post-transfusion Hb increment in hospitalized patients with or without a positive blood culture.

Materials and Methods: A retrospective cohort study using data from the Transfusion Research, Utilization, Surveillance, and Tracking database (TRUST) was performed. All adult non-trauma in-patients transfused between 2010 and 2017 with ≥1 RBC unit, and for whom both pre- and post-transfusion complete blood count and pre-transfusion blood culture data were available were included. A general linear model with binary blood culture positivity was fit for continuous Hb increment after transfusion and was adjusted for patient demographic parameters and transfusion-related covariates.

Results: Among 210,263 admitted patients, 6252 were transfused: 596 had positive cultures, and 5656 had negative blood cultures. A modelled Hb deficit of 1.50 g/L in blood culture-positive patients was found. All covariates had a significant effect on Hb increment, except for the age of the transfused RBC.

Conclusion: Recipient blood culture positivity was associated with a statistically significant but modestly lower post-transfusion Hb increment in hospitalized patients. In isolation, the effect is unlikely to be clinically significant, but it could become so in combination with other recipient characteristics.

Keywords

blood culture, haemoglobin, red blood cells, regression, septicaemia, transfusion

Syed M. Qadri and Yang Liu contributed equally to this work.

Highlights

- Septic patients are often anaemic and are frequently transfused with red blood cell concentrates (RCCs).
- The septic milieu is highly inflammatory, and exposure to inflammatory mediators may trigger red cell dysfunction.
- In a retrospective study, we found that a positive blood culture was associated with a small but statistically significant decreased haemoglobin increment (−1.5 g/L) after RCC transfusion. The effect is unlikely to be clinically significant but could become so in association with other risk factors.

INTRODUCTION

Red blood cell (RBC) concentrates are transfused to patients to alleviate anaemia and restore tissue oxygenation [1]. National and clinical society guidelines recommend RBC transfusion in hospitalized, haemodynamically stable adult patients with haemoglobin (Hb) levels ≤7, or 8 g/dL in those undergoing orthopaedic or cardiac surgery and in those with pre-existing cardiovascular disease [2–5]. Separate guidelines apply to those patients suffering from major haemorrhages [6]. Since 2012, multiple randomized clinical trials have confirmed the safety of RBC units transfused to paediatric or adult patients at any time during the approved shelf life of up to 42 days of refrigerated storage [7–11].

In contrast to the abundance of high-quality evidence of RBC safety throughout the storage period, much less is known about how recipient characteristics may affect post-transfusion RBC recovery and functionality. Endogenous RBC clearance is enhanced in chronic inflammation, and this mechanism may apply to transfused RBC in a sick and inflamed patient [12]. Post-transfusion RBC recoveries are lower in the sick than in healthy volunteers, as shown in studies of patients with haematological malignancies [13, 14] and febrile patients [15, 16].

Septic patients are frequently anaemic with reduced Hb and haematocrit levels [17]; 45% of a prospective cohort of Scandinavian septic patients received RBC transfusions [18]. RBC dysfunction in sepsis is conferred by a wide array of cellular changes, such as reduced deformability [19], enhanced cytoplasmic calcium levels [20], deranged antioxidant capacity [21], and increased phosphatidylserine externalization [22–24], leading to reduced lifespan of circulating RBCs. If the transfused RBCs are exposed to the septic milieu in critically ill patients, it is possible that at least some RBC would be rapidly lost, diminishing the efficacy of the intervention as measured by the Hb increment.

In this study, we tested the hypothesis that the recipient environment in patients with septicaemia would blunt the desired increase in post-transfusion blood Hb. We used data from the Transfusion Research, Utilization, Surveillance, and Tracking (TRUST) database to perform a retrospective cohort study of patients with or without positive blood cultures tested prior to RBC transfusion, for whom pre- and post-transfusion complete blood counts (CBCs) were available. Our results suggest an association between positive blood cultures and reduced post-transfusion Hb increments in patients transfused with RBC.

METHODS

Study design and setting

This retrospective cohort study was approved by the Hamilton Integrated Research Ethics Board (HiREB #5084). The study was conducted using data in the TRUST database [25], which contains demographic, medical, laboratory and transfusion information on all patients admitted to three tertiary care academic hospitals in Hamilton, Ontario, Canada, with a combined catchment area population of >2.3 million persons.

Transfusion recipient cohort and characteristics

Inclusion criteria: adult in-patients transfused with at least one RBC unit between 1 April 2010, and 31 March 2017; availability of a CBC both before (pre-) and after (post-) the first transfusion episode; and availability of blood culture results from samples cultured prior to the first RBC transfusion episode. We excluded trauma patients, defined as those having a most responsible diagnosis (MRD, the diagnosis contributing the most to patient length of stay in hospital) of injury, poisoning and certain other consequences of external causes according to groupings of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [26]. A transfusion episode was defined as a calendar day when a patient was transfused with at least one RBC unit. We defined the pre-transfusion CBC as the latest laboratory test taken within 24 h before the blood bank issue time of the first RBC unit for each transfusion episode, for which there was no other RBC transfusion recorded between the laboratory test and the transfusion episode. We defined the post-transfusion CBC as the earliest laboratory test taken within 0–24 h of the blood bank issue time of the last RBC unit for each transfusion episode, for which there was no other RBC transfusion recorded between the transfusion episode and the laboratory test. Where multiple blood culture results were available, we defined blood culture positivity or negativity as that of the last culture result

sampled prior to transfusion. All patients were followed for the duration of their time in the hospital.

Patient characteristics that were recorded included: age; sex; ABO blood group; Hb; haematocrit; erythrocyte count; number of RBC units transfused in the transfusion episode; number of RBC transfusion episodes; number of CBC tests; number of blood cultures tested; number of positive blood cultures; refrigerated storage time of RBC units; time from CBC test pre-transfusion to start of transfusion episode; and time from the end of transfusion episode to CBC test post-transfusion. CBC test results were reported at baseline (i.e., the first CBC test during hospitalization), and pre- and post-transfusion as defined above. MRD (ICD10 code indicating the reason for the hospital stay) was captured and grouped into seven categories: certain infectious and parasitic diseases; neoplasms; diseases of the blood and blood-forming organs and certain disorders involving the immune system; diseases of the circulatory system; diseases of the respiratory system; diseases of the digestive system; and other. A comorbidity score was assigned to each patient comprising five levels (no comorbidities or level 1–4) based on case mix grouping (CMG+), a methodology developed by the Canadian Institute for Health Information (CIHI) to aggregate and describe acute-care hospital patients with similar clinical and resource utilization characteristics [27].

Outcomes

The primary outcome was the change in Hb after an RBC transfusion episode. Change in Hb was calculated as the difference in the pre-transfusion and post-transfusion Hb levels. Secondary outcomes included the recipient's change in haematocrit and the recipient's change in erythrocyte count.

Statistical analysis

Categorical data were presented as counts and percentages, and continuous data were presented with medians and interquartile ranges (IQR).

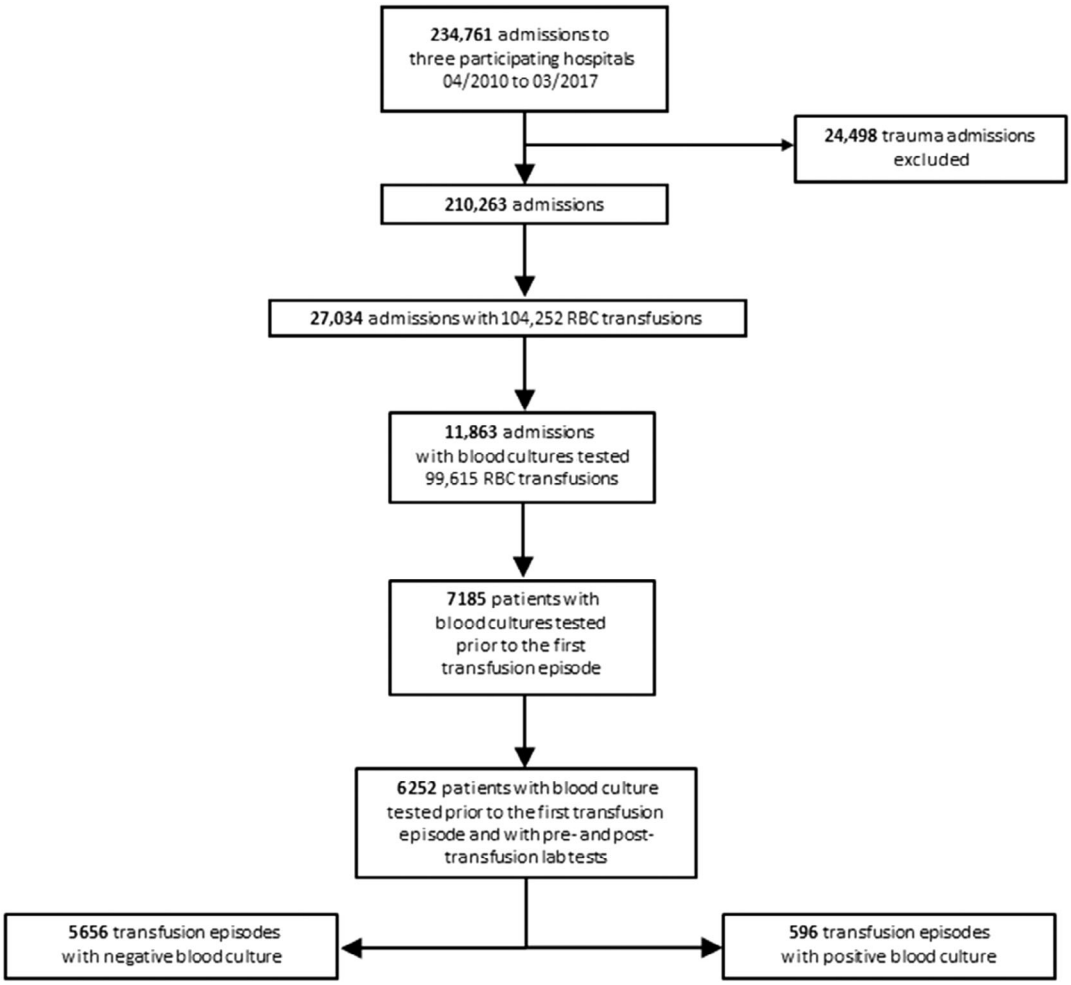

FIGURE 1 Study flow diagram. Boxes oriented vertically describe the winnowing of the total adult inpatient population to select those with temporally appropriate blood culture and complete blood count results, separated into two populations by blood culture positivity. Horizontal stream describes the exclusion of trauma patients. RBC, red blood cell

TABLE 1 First transfusion episodes by blood culture result

Variables	Episodes with negative blood culture, $N = 5656$	Episodes with positive blood culture, $N = 596$
Female, *n* (%)	2656 (47.0)	276 (46.3)
Male, *n* (%)	3000 (53.0)	320 (53.7)
Age (years), median (IQR)	66 (55–76)	66 (55–77)
Most responsible diagnosis, *n* (%)		
Certain infectious and parasitic diseases	560 (9.9)	156 (26.2)
Neoplasms	998 (17.6)	82 (13.8)
Diseases of the blood and blood-forming organs etc.	393 (6.9)	45 (7.6)
Diseases of the circulatory system	1031 (18.2)	104 (17.4)
Diseases of the respiratory system	647 (11.4)	32 (5.4)
Diseases of the digestive system	725 (12.8)	65 (10.9)
Other	1302 (23.0)	112 (18.8)
Comorbidity scores, *n* (%)		
No comorbidity	1280 (22.6)	112 (18.8)
Comorbidity level 1	782 (13.8)	92 (15.4)
Comorbidity level 2	1064 (18.8)	98 (16.4)
Comorbidity level 3	1204 (21.3)	132 (22.1)
Comorbidity level 4	1326 (23.4)	162 (27.2)
Surgical patients, *n* (%)	1608 (28.4)	167 (28)
Length of stay (days), median (IQR)	17 (8–31)	17 (8–33)
No. of RBC units transfused	2 (1–2)	2 (1–2)
No. of RBC units transfused, *n* (%)		
1 unit	1865 (33.0)	199 (33.4)
2 units	3281 (58.0)	346 (58.1)
3 units	219 (3.9)	22 (3.7)
4 units	140 (2.5)	15 (2.5)
5 or more units	151 (2.7)	14 (2.3)
Storage of the oldest RBC (days)	24 (16–33)	24 (17–33)
2–20 days	2282 (40.3)	237 (39.8)
21–42 days	3374 (59.7)	359 (60.2)
Storage of the freshest RBC (days)	20 (14–28)	20 (15–28)
Time from test pre-transfusion to start of transfusion episode (hours), median (IQR)	5.3 (2.9–8.1)	4.8 (2.5–7.9)
Haemoglobin (g/L) pre-transfusion	76 (70–80)	75 (70–80)
Haematocrit pre-transfusion	0.227 (0.212–0.243)	0.223 (0.208–0.240)
Erythrocyte count ($\times 10^{-15}$/L) pre-transfusion	2.52 (2.30–2.80)	2.49 (2.27–2.78)
Time from end of transfusion episode to test post transfusion (hours)	8.4 (4.0–14.2)	7.0 (3.2–12.3)
Haematocrit post transfusion	0.276 (0.254–0.299)	0.270 (0.246–0.297)
Haemoglobin (g/L) post transfusion	92 (85–100)	90 (83–98)
Erythrocyte count ($\times 10^{-12}$/L) post-transfusion	3.09 (2.81–3.41)	3.04 (2.74–3.34)
Change in haemoglobin (g/L)	16 (10–24)	15 (8–23)
Change in haematocrit	0.048 (0.028–0.069)	0.043 (0.023–0.068)
Change in erythrocyte count ($\times 10^{-12}$/L)	0.55 (0.33–0.80)	0.49 (0.27–0.76)

Note: Data are *n* (%) or median (IQR), unless otherwise specified.
Abbreviations: IQR, interquartile range; RBC, red blood cell.

To determine the association between change in Hb and blood culture positivity, a general linear model was fit for continuous Hb increment after the first transfusion episodes with complete data. The models included binary blood culture positivity and were adjusted for patient demographics such as sex, age, MRD, pre-transfusion Hb value, and transfusion-related covariates, including the number of units transfused, and age categories of transfused RBCs (2–15, 16–21, 22–30 or 31–42 days). The regression analysis was repeated with the subset of patients whose transfusion episode comprised a single RBC unit.

The analysis of change in haematocrit and erythrocyte counts was conducted separately by fitting linear regression models with the same criteria as the analysis for Hb. All analyses were carried out in SAS 9.4 (Gary, NC).

RESULTS

Of the 210,263 non-trauma patients admitted to the three tertiary care hospitals contributing data to TRUST, 27,034 received RBC transfusions (Figure 1). Among transfused patients, 11,863 had blood cultures tested; 6252 had CBC test results available pre- and post-their first transfusion episode and had at least one blood culture tested prior to the first transfusion episode. Among 6252 patients, 596 (9.5%) patients' blood culture tested positive prior to transfusion and 5656 (90.5%) tested negative. Patients selected for the study, therefore, represented 2.97% of the total patient population.

At the time of hospital admission, the study patients had a median Hb of 99 g/L, IQR 86–115 (Table S1); during their hospital stay, the median Hb of culture-positive patients fell to 76 g/L, IQR 70–80, and that of culture-negative patients to 75 g/L, IQR 70–80 (Table 1). The demographics of the culture-positive and culture-negative groups were similar. Both groups had a few more male patients than female patients (53.0% vs. 47.0%) and the median age was identical. RBC transfusion requirements were similar in the two groups for number of transfusions and the age of RBCs transfused. The proportion of surgical patients was very similar in the two groups (28.4% in culture-negative and 28% in culture-positive). The length of stay was identical, at a median of 17 days (IQR 8–31 and 8–33, respectively). There was a similar distribution of comorbidity scores between the two groups, although the proportion of patients with no comorbidities was higher in the culture-negative group than in the culture-positive group (81.2% vs. 77.4%), and there were also more patients with the highest comorbidity score, level 4 (27.2% vs. 23.4%) in the culture-positive

TABLE 2 Linear regression results for haemoglobin increment

	First transfusion episodes (all units)				First transfusion episodes (one unit)			
Covariates	Mean difference in increment	95% CI		*p*-Value	Mean difference in increment	95% CI		*p*-Value
Sex: female versus male	4.2227	3.6752	4.7702	<0.0001	3.0050	2.2925	3.7174	<0.0001
Age (years)	0.0713	0.0541	0.0884	<0.0001	0.0595	0.0368	0.0823	<0.0001
Most responsible diagnosis				<0.0001				<0.0001
Certain infectious and parasitic diseases versus Other	−0.9786	−1.9730	0.0158	0.0538	−0.8307	−2.0723	0.4110	0.1898
Neoplasms versus other	0.9659	0.0929	1.8389	0.0301	−0.5112	−1.8066	0.7842	0.4392
Diseases of the blood and blood-forming organs versus other	−1.2202	−2.4079	−0.0325	0.0441	−2.8972	−4.9857	−0.8088	0.0065
Diseases of the circulatory system versus other	−3.6456	−4.5134	−2.7778	<0.0001	−1.1611	−2.2002	−0.1221	0.0285
Diseases of the respiratory system versus other	−0.2214	−1.2294	0.7865	0.6668	0.3572	−0.8715	1.5858	0.5689
Diseases of the digestive system versus other	0.2051	−0.7509	1.1610	0.6742	0.1890	−1.0160	1.3941	0.7585
Haemoglobin pre-transfusion	−0.5895	−0.6152	−0.5639	<0.0001	−0.3726	−0.4068	−0.3383	<0.0001
Number of RBCs transfused	1.2029	0.9779	1.4278	<0.0001				
Storage duration of oldest RBCs				0.1965				0.3366
16–21 days versus 2–15 days	−0.0803	−0.9061	0.7454	0.8488	0.5044	−0.5568	1.5656	0.3516
22–30 days versus 2–15 days	−0.0235	−0.8144	0.7673	0.9535	0.9298	−0.0716	1.9312	0.0688
31–42 days versus 2–15 days	−0.6825	−1.4430	0.0780	0.0786	0.3864	−0.5913	1.3641	0.4386
Blood culture: positive versus negative	−1.4971	−2.4323	−0.5618	0.0017	−1.6193	−2.8236	−0.4149	0.0084

Abbreviations: CI, confidence interval; RBC, red blood cell.

group. There were some differences in MRD, most notably in the infectious and parasitic disease category (26.2% in the blood culture-positive group compared to 9.9% in the blood culture-negative group). The post-transfusion increment in Hb levels was less in the culture-positive group than the culture-negative group, by 1 g/L, and a similar lower increment was also observed in the secondary measures of change in haematocrit and change in erythrocyte number.

Table 2 shows that the primary outcome, Hb increment, was significantly affected by blood culture status, with a modelled deficit of −1.50 g/L (95% confidence interval [CI] −2.4 to −0.56, $p = 0.0017$) in blood culture-positive patients after any transfusion episode, after adjustment for covariates. All covariates had a significant effect on Hb increment except for the age of the transfused red cells. The effect of blood culture positivity, while small, was relatively robust, in that a modelled deficit of −1.62 g/L (95% CI −2.8 to −0.41, $p = 0.008$) was found to be significant when the regression analysis was repeated with the subset of patients whose transfusion episode comprised a single red cell unit. The same pattern of results with respect to the regression estimates was observed with the secondary measures of haematocrit and erythrocyte number, as shown in Tables S2 and S3, for all transfusion episodes and for single-unit episodes.

DISCUSSION

Critically ill patients are frequently anaemic. Anaemia can arise due to reduced RBC production, increased loss of RBC via haemorrhage, or increased RBC destruction via intravascular or extravascular haemolysis [28]. Patients with bacterial or fungal infections are subjected not only to the pathological effects of substances released by pathogens but may also be harmed by an exaggerated response to infection. Some infected individuals develop sepsis, defined in 2016 by the Sepsis-3 Task Force as a 'life-threatening organ dysfunction caused by a dysregulated host response to infection' [29]. Both RBC dysfunction and cell death in critically ill septic patients can potentially contribute to the development of anaemia. RBC transfused into the septic patient vascular environment may therefore be exposed to multiple stressors hastening their clearance and diminishing the value of the transfusion to the patient. RBC cell death has been documented from a wide variety of pathological stressors and in association with multiple human diseases [30]. Other potential explanations for accelerated loss of RBCs in the infected patients include exposure to reactive oxygen species [31], neuraminidases [17, 32] and histones [33] formed either by pathogens or by host cells and by stimulation of purinergic signalling in RBCs [34].

Our findings indicate a small but statistically significant deficit in Hb increment in patients with a positive blood culture versus those with a negative blood culture. By adjusting for covariates, this deficit was modelled as −1.50 g/L overall, or −1.62 g/L in the subset of patients transfused with a single RBC concentrate. The increase in Hb concentration after transfusion of a single unit of RBC has been estimated at 10 g/L per unit of packed RBC, with some uncertainty due to variations in the Hb content per unit [35, 36]; this was consistent with our observation of an unadjusted change in Hb of 15–16 g/L post-transfusion. Thus, the modelled deficit comprised approximately 10% of the increase in Hb elicited by a transfusion in a patient with a negative blood culture. As such, it is unlikely to be clinically significant; for instance, it would, in most cases, not prompt the transfusion of an additional unit because of failure to reach a clinically desirable Hb level. This is particularly true in the era of guidelines promoting transfusion of a single packed RBC unit per transfusion episode [37, 38].

While not clinically significant, our findings are consistent with an effect of the patient environment on the transfusion outcome, an emerging paradigm in transfusion medicine. Roubinian et al. examined 6 years' of RBC transfusion data in over 130,000 patients, finding that individual donor, component and recipient characteristics played a small role in Hb increments but that together they accounted for the variation in response to RBC transfusion seen in clinical practice [13]. With respect to recipient characteristics, these investigators found that recipient age, sex, body/mass index, Rh type and pre-transfusion Hb level significantly affected Hb change after transfusion, after adjustment for covariates. The modelled effects were smaller than those we observed for blood culture positivity (−1.5 g/L) except for pre-transfusion Hb (−1.8 g/L) and female recipient sex (+2.8 g/L). Karafin et al. reported similar findings in a secondary analysis of the prospective red cells in outpatient transfusion outcome (RETRO) trials [39]. In this study of 195 patients with haematological malignancies, 75% failed to exhibit the expected 1 g/dL increase in Hb concentration. Blood volume was negatively related to modelled Hb increment (−2.1 g/L), as was pre-transfusion Hb (−2.8 g/L), while recipient age made a smaller, although still statistically significant contribution.

It did not seem that patients in the positive blood culture group were sicker than those in the negative blood culture group. At least from the perspective of the length of stay in the hospital, there was no difference between the groups. There was some indication that, based on comorbidity scores, culture-positive patients may have been sicker, in that there was a slightly lower proportion of patients with no comorbidities than in the culture-negative group. Whether this status might have predisposed the latter group to bacterial infection or whether it exacerbated the deficit in Hb increment is not clear.

Our findings diverged from those of Rydén et al., who examined pre- and post-transfusion Hb values in patients with myelodysplastic syndromes or myeloproliferative neoplasms over a 10-year period, with a focus on the age of transfused blood [14]. Using mixed effect linear regression, these investigators found modelled Hb deficits of −0.83, −0.92, −1.33 and −1.51 g/L for RBC units stored 5–9, 10–19, 20–29 or >30 days, respectively, versus RBC units stored <5 days. In contrast, we found no statistically significant difference between Hb increments in RBC units stored 2–15 days versus 16–21 days, 22–30 days, or 31–42 days. This discordance could have arisen due to differences in modelling approaches, defined storage intervals, manufacturing processes, or our examination of all non-trauma patients and the contrasting focus of Rydén et al. on patients with haematological malignancies, many of whom were chronically transfused. Interestingly, in a retrospective analysis of a septic shock cohort, Rygård et al. observed no mortality disadvantage related to long storage time [40].

There are limitations to our study. First, it is retrospective in nature and may, therefore, be subject to bias. This concern is mitigated somewhat by the number of patients in the study and the similarities in general characteristics between the patient groups in the positive versus negative blood culture cohorts. Second, there are some uncertainties with respect to the quality of the blood culture results. False positive blood cultures can arise, for instance, due to skin contamination during venipuncture, although improved skin decontamination procedures have reduced false positivity rates in recent years [41]. Our study employed a single blood culture result; while older practice emphasized the value of multiple tests in a 24-h period [42], more recent studies have shown that a single blood draw of sufficient volume results in higher sensitivity and specificity than multiple draws [43]. False negatives in blood culture can also occur if the volume of sampled blood is insufficient [44]. Finally, we did not interrogate our database to stratify patients with initially positive blood cultures into those who continued to be bacteremic and those who subsequently showed negative blood cultures (perhaps due to successful antibiotic treatment). We speculate that those with the most persistent bacteraemia might exhibit the most blunted response to RBC transfusion but addressing this possibility will require future studies.

Our study was unable to contribute specific information concerning the effect of fever on the Hb increment because body temperature data were not recorded in the database that we interrogated. Wendelbo et al. addressed this question in a small prospective observational trial of 29 patients with or without fever treated with multiple red cell transfusions [15]. These investigators found a small but statistically significant reduction in Hb increment in patients with fever (0.79 g/dL in the 'no fever' group vs. 0.49 g/dL in the 'fever' group, a difference of −0.3 g/dL), with fever defined as body temperature ≥38°C. Fever is a common symptom in hospitalized patients with infectious or non-infectious aetiology [45]; thus, some febrile patients will have a positive blood culture, and some will not. While large database studies should be able to stratify patients into those with a positive blood culture with and without fever and probe any association with Hb increment, this was not possible in our study and must await future investigations. By no means should our findings indicate that sepsis should be downplayed in the management of critically ill patients; instead, clinicians should focus on issues other than uncertainty as to whether RBC transfusions will have a durable effect in the septic setting.

In conclusion, our findings support the general concept that the increase in recipient Hb following RBC transfusion can be influenced by recipient factors and provides evidence that blood culture positivity can be added to the growing list of such factors. The reduction in Hb increment, while statistically significant, was not likely clinically significant in isolation but was of a similar magnitude to other recipient factors reported in the literature.

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S.M.Q., Y.L. and R.L.B. performed the research, S.M.Q., N.M.H. and W.P.S. designed the research study, Y.L. acquired and analysed data and W.P.S. wrote the first draft of the manuscript. All authors reviewed and revised the manuscript and approved its submission in final form.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Goodnough LT, Panigrahi AK. Blood transfusion therapy. Med Clin North Am. 2017;101:431–47.
2. Napolitano LM, Kurek S, Luchette FA, Corwin HL, Barie PS, Tisherman SA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. Crit Care Med. 2009;37:3124–57.
3. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA. 2016;316:2025–35.
4. Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R, et al. Patient blood management: recommendations from the 2018 Frankfurt consensus conference. JAMA. 2019;321:983–97.
5. Mo A, Stanworth SJ, Shortt J, Wood EM, McQuilten ZK. Red cell transfusions: is less always best? How confident are we that restrictive transfusion strategies should be the standard of care default transfusion practice? Transfusion. 2021;61:2195–203.
6. Vlaar APJ, Dionne JC, de Bruin S, Wijnberge M, Raasveld SJ, van Baarle F, et al. Transfusion strategies in bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. Intensive Care Med. 2021;47:1368–92.
7. Fergusson DA, Hebert P, Hogan DL, LeBel L, Rouvinez-Bouali N, Smyth JA, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. JAMA. 2012;308:1443–51.
8. Lacroix J, Hebert PC, Fergusson DA, Tinmouth A, Cook DJ, Marshall JC, et al. Age of transfused blood in critically ill adults. N Engl J Med. 2015;372:1410–8.
9. Steiner ME, Ness PM, Assmann SF, Triulzi DJ, Sloan SR, Delaney M, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med. 2015;372:1419–29.
10. Dhabangi A, Ainomugisha B, Cserti-Gazdewich C, Ddungu H, Kyeyune D, Musisi E, et al. Effect of transfusion of red blood cells with longer vs shorter storage duration on elevated blood lactate levels in children with severe anemia: the TOTAL randomized clinical trial. JAMA. 2015;314:2514–23.
11. Heddle NM, Cook RJ, Arnold DM, Liu Y, Barty R, Crowther MA, et al. Effect of short-term vs. long-term blood storage on mortality after transfusion. N Engl J Med. 2016;375:1937–45.
12. Straat M, van Bruggen R, de Korte D, Juffermans NP. Red blood cell clearance in inflammation. Transfus Med Hemother. 2012;39:353–61.

13. Roubinian NH, Plimier C, Woo JP, Lee C, Bruhn R, Liu VX, et al. Effect of donor, component, and recipient characteristics on hemoglobin increments following red blood cell transfusion. Blood. 2019;134:1003–13.
14. Rydén J, Clements M, Hellstrom-Lindberg E, Hoglund P, Edgren G. A longer duration of red blood cell storage is associated with a lower hemoglobin increase after blood transfusion: a cohort study. Transfusion. 2019;59:1945–52.
15. Wendelbo O, Netland Opheim E, Felli Lunde TH, Bruserud O, Hervig T, Reikvam H. A prospective observational study on effects of fever on red cell transfusion outcome. Vox Sang. 2017;112:484–6.
16. Wendelbo O, Opheim EN, Hervig T, Felli Lunde TH, Bruserud O, Mollnes TE, et al. Cytokine profiling and post-transfusion haemoglobin increment in patients with haematological diseases. Vox Sang. 2018;113:657–68.
17. Fagerberg SK, Patel P, Andersen LW, Lui X, Donnino MW, Praetorius HA. Erythrocyte P2X1 receptor expression is correlated with change in haematocrit in patients admitted to the ICU with blood pathogen-positive sepsis. Crit Care. 2018;22:181.
18. Rosland RG, Hagen MU, Haase N, Holst LB, Plambech M, Madsen KR, et al. Red blood cell transfusion in septic shock – clinical characteristics and outcome of unselected patients in a prospective, multicentre cohort. Scand J Trauma Resusc Emerg Med. 2014;22:14.
19. Reggiori G, Occhipinti G, De Gasperi A, Vincent JL, Piagnerelli M. Early alterations of red blood cell rheology in critically ill patients. Crit Care Med. 2009;37:3041–6.
20. Todd JC 3rd, Mollitt DL. Effect of sepsis on erythrocyte intracellular calcium homeostasis. Crit Care Med. 1995;23:459–65.
21. Bateman RM, Sharpe MD, Singer M, Ellis CG. The effect of sepsis on the erythrocyte. Int J Mol Sci. 2017;18:1932.
22. Zhang Y, Meng H, Ma R, He Z, Wu X, Cao M, et al. Circulating microparticles, blood cells, and endothelium induce procoagulant activity in sepsis through phosphatidylserine exposure. Shock. 2016;45:299–307.
23. Qadri SM, Donkor DA, Bhakta V, Eltringham-Smith LJ, Dwivedi DJ, Moore JC, et al. Phosphatidylserine externalization and procoagulant activation of erythrocytes induced by *Pseudomonas aeruginosa* virulence factor pyocyanin. J Cell Mol Med. 2016;20:710–20.
24. Kempe DS, Akel A, Lang PA, Hermle T, Biswas R, Muresanu J, et al. Suicidal erythrocyte death in sepsis. J Mol Med. 2007;85:273–81.
25. Pai M, Cook R, Barty R, Eikelboom J, Lee KA, Heddle N. Exposure to ABO-nonidentical blood associated with increased in-hospital mortality in patients with group A blood. Transfusion. 2016;56:550–7.
26. World Health Organization. ICD-10: international statistical classification of diseases and related health problems. 2nd ed, 10th revision ed. Geneva: World Health Organization; 2004.
27. Perry S, Homan C. Use of case mix tools for utilization management and planning. Stud Health Technol Inform. 2009;143:496–500.
28. Sankaran VG, Weiss MJ. Anemia: progress in molecular mechanisms and therapies. Nat Med. 2015;21:221–30.
29. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315:801–10.
30. Qadri SM, Bissinger R, Solh Z, Oldenborg PA. Eryptosis in health and disease: a paradigm shift towards understanding the (patho)physiological implications of programmed cell death of erythrocytes. Blood Rev. 2017;31:349–61.
31. Bissinger R, Bhuyan AAM, Qadri SM, Lang F. Oxidative stress, eryptosis and anemia: a pivotal mechanistic nexus in systemic diseases. FEBS J. 2019;286:826–54.
32. Piagnerelli M, Boudjeltia KZ, Rapotec A, Richard T, Brohee D, Babar S, et al. Neuraminidase alters red blood cells in sepsis. Crit Care Med. 2009;37:1244–50.
33. Qadri SM, Donkor DA, Nazy I, Branch DR, Sheffield WP. Bacterial neuraminidase-mediated erythrocyte desialylation provokes cell surface aminophospholipid exposure. Eur J Haematol. 2018;100:502–10.
34. Semeraro F, Ammollo CT, Esmon NL, Esmon CT. Histones induce phosphatidylserine exposure and a procoagulant phenotype in human red blood cells. J Thromb Haemost. 2014;12:1697–702.
35. Elzik ME, Dirschl DR, Dahners LE. Correlation of transfusion volume to change in hematocrit. Am J Hematol. 2006;81:145–6.
36. Pieracci FM, Barnett CC Jr, Townsend N, Moore EE, Johnson J, Biffl W, et al. Sexual dimorphism in hematocrit response following red blood cell transfusion of critically ill surgical patients. ISRN Hematol. 2012;2012:298345.
37. O'Brien SH, Badawy SM, Rotz SJ, Shah MD, Makarski J, Bercovitz RS, et al. The ASH-ASPHO choosing wisely campaign: 5 hematologic tests and treatments to question. Pediatr Blood Cancer. 2021;68:e28967.
38. Kron AT, Collins A, Cserti-Gazdewich C, Pendergrast J, Webert K, Lieberman L, et al. A prospective multi-faceted interventional study of blood bank technologist screening of red blood cell transfusion orders: the START study. Transfusion. 2021;61:410–22.
39. Karafin MS, Bruhn R, Roubinian NH, Chowdhury D, Qu L, Snyder EL, et al. The impact of recipient factors on the lower-than-expected hemoglobin increment in transfused outpatients with hematologic diseases. Transfusion. 2019;59:2544–50.
40. Rygård SL, Gronlykke L, Perner A, Winkel P, Lange T, Brokso Holst L, et al. Storage time of red blood cells among ICU patients with septic shock. Acta Anaesthesiol Scand. 2019;63:1366–77.
41. Lamy B, Dargere S, Arendrup MC, Parienti JJ, Tattevin P. How to optimize the use of blood cultures for the diagnosis of bloodstream infections? A state-of-the art. Front Microbiol. 2016;7:697.
42. Washington JA. An international multicenter study of blood culture practices. The International Collaborative Blood Culture Study Group. Eur J Clin Microbiol Infect Dis. 1992;11:1115–28.
43. Dargere S, Parienti JJ, Roupie E, Gancel PE, Wiel E, Smaiti N, et al. Unique blood culture for diagnosis of bloodstream infections in emergency departments: a prospective multicentre study. Clin Microbiol Infect. 2014;20:O920–7.
44. Connell TG, Rele M, Cowley D, Buttery JP, Curtis N. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. Pediatrics. 2007;119:891–6.
45. Laupland KB, Shahpori R, Kirkpatrick AW, Ross T, Gregson DB, Stelfox HT. Occurrence and outcome of fever in critically ill adults. Crit Care Med. 2008;36:1531–5.

SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

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Basophil activation test for allergic and febrile non-haemolytic transfusion reactions among paediatric patients with haematological or oncological disease

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Abstract

Background and Objectives: Allergic transfusion reactions (ATRs) and febrile non-haemolytic transfusion reactions (FNHTRs) are common, although their mechanisms remain unclear. Immunoglobulin E (IgE)-mediated type I hypersensitivity may be involved in the pathogenesis of ATR. A basophil activation test (BAT) may help elucidate this process.

Materials and Methods: The BAT was based on peripheral blood samples from paediatric patients with a haematological or oncological disease and on samples of residual blood products transfused in each case. Dasatinib was used to evaluate whether basophil activation was mediated by an IgE-dependent pathway.

Results: Twenty-seven patients with and 19 patients without ATR/FNHTR were included in this study, respectively. The median BAT values associated with ATR- ($n = 41$) and FNHTR-causing ($n = 5$) blood products were 22.1% (range = 6.1%–77.0%) and 27.8% (range = 15.2%–47.8%), respectively, which were higher than the median value of 8.5% (range = 1.1%–40.9%) observed in blood products without a transfusion reaction. Dasatinib suppressed basophil activity. BAT values were comparable in patients with ATR regardless of severity. Meanwhile, BAT values analysed with blood products non-causal for ATR/FNHTR were higher in patients with ATR/FNHTR than in those without.

Conclusion: The IgE-mediated type I hypersensitivity may be involved in the pathogenesis of ATR and FNHTR. BAT analyses may help elucidate the underlying mechanisms and identify patients at risk.

Keywords

allergen, allergic transfusion reactions, anaphylaxis, febrile non-haemolytic transfusion reactions, hypersensitivity, IgE

Highlights

- Immunoglobulin E-mediated type I hypersensitivity may be involved in the pathogenesis of not only allergic transfusion reactions (ATRs) but also febrile non-haemolytic transfusion reactions (FNHTRs).
- Patients prone to ATRs and FNHTRs may already be at risk of basophil activation.

INTRODUCTION

Blood transfusion is an important form of supportive care in clinical practice; however, it is associated with adverse reactions, such as allergic transfusion reaction (ATR) and febrile non-haemolytic transfusion reaction (FNHTR) [1–3]. Although the pathogenesis of ATR remains unknown, allergen-specific immunoglobulin E (IgE) is often detected in ATR cases [4, 5], and blood products that cause ATR have been associated with basophil activation [6]. Basophil activation may be suppressed by dasatinib, which selectively inhibits IgE-dependent pathway activity [6, 7]. In addition, omalizumab may support the treatment of patients with recurrent severe ATR [8, 9]. These findings suggest that type I hypersensitivity is the main mechanism of ATR development [1–3]. However, this evidence comes from small studies; larger studies are required to confirm the generalizability of these findings.

An ATR may involve anaphylaxis; however, identifying patients at risk remains a challenge. A study involving a passive immune-basophil activation test (BAT) using samples derived from healthy individuals reported basophil activation in response to blood products that caused moderate to severe ATR [10], suggesting that BAT may help predict severe ATR.

Meanwhile, FNHTR is associated with plasma leucocyte antibodies and biological response modifiers that accumulate in blood products during storage [1–3]. Patients with ATR may develop FNHTR with another blood transfusion. The onset of ATR is sometimese accompanied by fever [11]. In addition, allergic sensitization-associated single-nucleotide polymorphisms (SNPs) may contribute to ATR. One of the SNPs has been found to be associated with FNHTR and ATR accompanied by febrile symptoms [12]. This evidence suggests that FNHTR may be accompanied by fever via mechanisms similar to those observed in ATR. It also indicates that BAT for patients with ATR or FNHTR or blood products associated with ATR or FNHTR may help elucidate the underlying mechanisms and identify patients at risk. This study aimed to use BAT on residual blood products and samples acquired from paediatric haematology or oncology patients who had received a transfusion to elucidate the relationship between BAT findings and ATR and FNHTR incidence.

MATERIALS AND METHODS

Patient selection

Paediatric haematological or oncological patients aged <20 years who had undergone multiple transfusions at Nagano Children's Hospital or Shinshu University Hospital between August 2020 and April 2022 were included in the study. Some patients included in this study had been included in a previous study [5]. The study protocol was approved by the institutional ethics review board of each participating institution (Nagano Children's Hospital: 31–59; Shinshu University Hospital: 5198).

Transfused blood products

Transfused red blood cell (RBC) or platelet (PLT) concentrates were analysed in this study. Blood products were obtained from the Japanese Red Cross Blood Society. All RBC and PLT concentrates were ABO- and RhD-matched between patients and donors. RBC concentrates were prepared from 200 or 400 ml of whole blood from single donors. PLT concentrates were derived from single-donor apheresis. RBC and PLT concentrates were transfused within 21 and 4 days of blood collection from the donors, respectively. Pre-storage leucocyte reduction and diversion of the first aliquot of blood were performed for all blood products [13]. The leucocyte count in the final products was $<1 \times 10^6$. All blood products were irradiated before transfusion. Serological crossmatching was analysed for RBC concentrates.

ATR, FNHTR and ATR severity definitions

In general, ATR or FNHTR were defined based on previous reports [2, 11]. ATR was diagnosed when at least one symptom, such as rash, pruritus, urticaria, flushing or respiratory distress, occurred during the transfusion or within 4 h of its completion. FNHTR was diagnosed when fever (≥1°C temperature elevation) accompanied by chills, rigour, hypertension, tachycardia or dyspnoea without other clinical symptoms occurred during the transfusion or within 4 h after transfusion end without homolysis or bacterial infection [5]. The severity of ATR was determined based on a previous report [2, 11]: grade I, only transient symptoms corresponding to minor ATR; grade II, ATR requiring discontinuation of blood transfusion, showing improvement with symptomatic treatment and grade III, anaphylaxis with symptomatic bronchospasm with or without urticaria, parenteral intervention indicated, allergy-related oedema/angioedema and hypotension [5].

BAT analysis

Residual transfused blood products (RBC or PLT) were centrifuged, and the supernatant was frozen at −80°C. Most patients were myelosuppressed at the time of transfusion; thus, BAT was performed after leucocyte levels recovered in the peripheral blood. In cases with ATR and FNHTR, we also performed BAT with randomly selected blood products without ATR/FNHTR in these cases. The blood products from patients in whom ATR or FNHTR did not develop during the study period were also randomly selected for BAT analysis as internal group controls. Basophils were obtained from residual samples stored in anticoagulant K2-ethylenediaminetetraacetic acid blood collection tubes for complete blood count analysis. Blood samples were used within one day of blood collection. BAT was performed using Allergenicity kit (Beckman Coulter Inc, Brea, CA, USA), according to the manufacturer's instructions. Samples of 20 µl of negative control (phosphate-buffered saline), positive control (anti-IgE antibody) and blood product were added to 100 µl of peripheral blood sample per condition, mixed, incubated, haemolysed and washed. The expression

TABLE 1 Patient characteristics

Patient no.	Sex	Age[a]	Disease	Allergy history	Total number of transfused products[b]		Transfusion reaction[b] (ATR grade)
					RBC	PLT	
1	M	4	ALL	None	17	21	ATR (II)
2	M	5	NHL	None	39	42	ATR (I)
3	M	3	ETMR	Drug	17	23	FNHTR
4	F	13	Rhabdomyosarcoma	None	38	35	ATR (I, I), FNHTR
5	M	11	Histiocytic sarcoma	Food	30	86	ATR (I, II)
6	F	13	Rhabdomyosarcoma	Food	45	103	ATR (I, I, I, I)
7	F	8	Medulloblastoma	Drug	18	30	ATR (I, I)
8	F	1	AML	Food, drug	18	23	ATR (I)
9	F	13	Germinoma	Atopic dermatitis	7	7	ATR (I, II, III), FNHTR
10	F	2	Hepatoblastoma	None	7	8	ATR (I, I)
11	M	14	NHL	None	14	22	ATR (II)
12	F	4	Neuroblastoma	None	29	41	ATR (I, I), FNHTR
13	M	0	AT/RT	Food	24	24	ATR (I, I)
14	F	6	Medulloblastoma	None	11	29	ATR (III)
15	M	14	NHL	Food	0	2	ATR (I)
16	F	11	Hepatoblastoma	Hay fever	18	21	ATR (II)
17	M	2	AML	Food	10	14	ATR (III)
18	M	12	Neuroblastoma	None	9	17	ATR (I)
19	F	4	Mixed phenotype acute leukaemia	None	13	14	ATR (I, II, III)
20	M	0	NHL	Food	3	2	ATR (I, II)
21	M	5	MHL	None	8	8	ATR (I)
22	F	0	AML	Food	35	9	ATR (I, I, II)
23	M	10	AA	None	8	15	ATR (I), FNHTR
24	M	15	ALL	None	8	16	ATR (I)
25	F	9	ALL	Food	9	12	ATR (I, I, II)
26	M	15	AML	Food	14	19	ATR (II)
27	F	11	ALL	None	16	40	ATR (I)
28	F	0	Medulloblastoma	None	38	75	None
29	M	3	ALL	None	8	6	None
30	M	0	Neuroblastoma	None	5	0	None
31	M	11	Ewing sarcoma	None	6	9	None
32	F	3	Ewing sarcoma	None	15	4	None
33	M	4	Neuroblastoma	Hay fever	29	22	None
34	M	3	ALL	Food	23	29	None
35	F	0	AML	Food	10	9	None
36	F	16	Rhabdomyosarcoma	Food	2	0	None
37	M	4	ALL	None	5	1	None
38	M	4	Wilms tumour	None	3	2	None
39	M	2	Neuroblastoma	None	3	4	None
40	F	3	AA	Atopic dermatitis	4	7	None
41	M	13	ALL	Allergic rhinitis, drug	23	22	None
42	F	5	ALL	Food	5	0	None
43	M	8	ALL	None	19	28	None
44	M	1	WAS	None	6	12	None

(Continues)

TABLE 1 (Continued)

Patient no.	Sex	Age[a]	Disease	Allergy history	Total number of transfused products[b] RBC	PLT	Transfusion reaction[b] (ATR grade)
45	F	9	ALL	None	13	7	None
46	M	1	HLH	None	3	0	None

Abbreviations: AA, aplastic anaemia; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ATR, allergic transfusion reaction; AT/RT, atypical teratoid/rhabdoid tumour; ETMR, embryonal tumour with multi-layered rosettes; F, female; FNHTR, febrile non-haemolytic transfusion reaction; HLH, haemophagocytic lymphohistiocytosis; M, male; NHL, non-Hodgkin lymphoma; PLT, platelet; RBC, red blood cell; WAS, Wiskott–Aldrich syndrome.
[a]At the time of the first transfusion.
[b]Data covers the entire period of blood transfusion (up to end of April 2022) of each case, including data outside of the scope of the study.

TABLE 2 Comparisons between the ATR/FNHTR and non-ATR/FNHTR groups

Clinical parameters	ATR/FNHTR (*n* = 27)	Non-ATR/FNHTR (*n* = 19)	*p*-value
Age, years; median (range)	8 (0–15)	3 (0–16)	0.063
Sex, male:female	14:13	12:7	0.551
Haematological disease and others:solid tumour	16:11	11:8	1.000
Allergy history, yes:no	13:14	7:12	0.551
Total number of transfused products per case			
RBC, median (range)	14 (0–45)	6 (2–38)	0.040
PLT, median (range)	21 (2–103)	7 (0–75)	0.003

Abbreviations: ATR, allergic transfusion reaction; FNHTR, febrile non-haemolytic transfusion reaction; PLT, platelet; RBC, red blood cell.

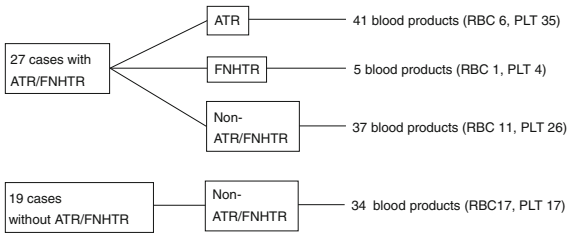

FIGURE 1 Summary of cases and the blood products analysed in this study. ATR, allergic transfusion reaction; FNHTR, febrile non-haemolytic transfusion reaction; PLT, platelet; RBC, red blood cell.

intensity of CD203c on basophils (CD3-negative cells and CRTH2-positive cell fraction) was evaluated by flow cytometry. Flow cytometric data were acquired by BD FACSCanto™ II (Becton Dickinson, Franklin Lakes, NJ). According to previous reports, a cursor was set at 5% positive CD203c on the histogram of negative control cells and the positive percentage of CD203c was measured per condition [6, 10]. The cut-off value for the positivity of BAT was 10% of CD203c expression levels [14]. In addition, we evaluated whether basophil activation by blood products was mediated by an IgE-dependent pathway, using 3 μM of dasatinib [6, 7]. Dasatinib was obtained from Cayman Chemical (Item No. 11498; Ann Arbor, MI, USA). Cases lacking sufficient basophil counts (<100 per condition) were excluded from the analysis.

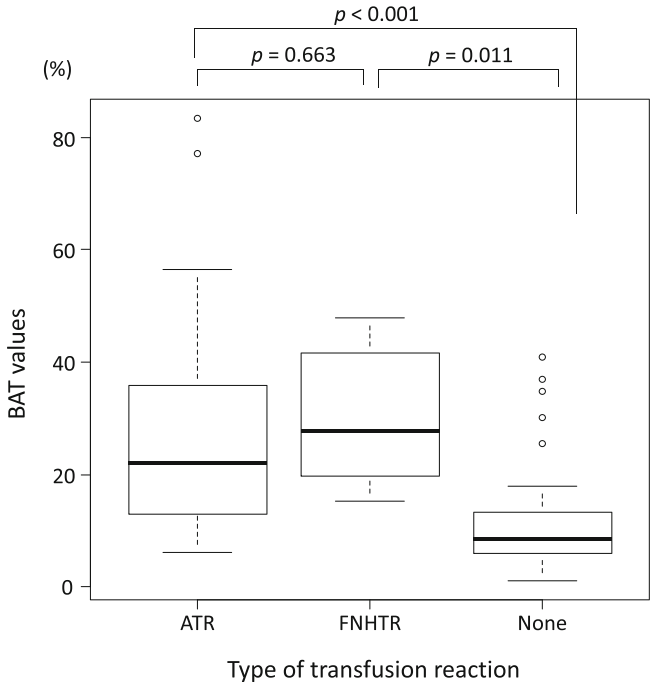

FIGURE 2 Comparison of basophil activation test (BAT) results between blood products associated with allergic transfusion reaction (ATR) or febrile non-haemolytic transfusion reaction (FNHTR)

Statistical analysis

Comparisons between patients with and without ATR/FNHTR were performed with the Fischer exact test or Mann–Whitney test. BAT results were compared using the Mann–Whitney *U* test or the Kruskal–Wallis test, depending on the number of groups. The Steel–Dwass test was used for multiple comparisons among groups after the Kruskal–Wallis test. BAT values were compared between samples with and without dasatinib using the Wilcoxon signed-rank test. Statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan) [15]. Statistical significance was defined as *p*-values of <0.05.

RESULTS

The patients' characteristics are presented in Table 1. Comparisons between groups are presented in Table 2. In total, 27 (14 males and 13 females; median age = 8 [range = 0–15] years) patients developed ATR/FNHTR. In addition, 12 males and 7 females were included in the non-ATR/FNHTR ($n = 19$) group (median age = 3 [range = 0–16] years). Thirteen (48.1%) ATR/FNHTR cases and 7 (36.8%) non-ATR/FNHTR cases had a history of allergies. Age, sex, primary diagnosis and allergy history distributions were comparable between the groups. However, patients in the ATR/FNHTR group received more transfusions of both RBC and PLT concentrates than those in the non-ATR/FNHTR group.

BAT results in total analysis

The BAT analysis was performed on a total of 117 blood products transfused in 46 patients (Figure 1). The patient's median peripheral blood leucocyte count at the time of analysis was 3240/μl (range = 710–12,830/μl). The median basophil count for BAT analysis for each blood product was 375 (range = 100–3973). Of the 117 blood products, 83 were administered to the 27 patients who developed ATR/FNHTR. Of the administered 83 products, 46 (RBC 7 and PLT 39) were associated with the development of ATR/FNHTR, while 37 (RBC 11 and PLT 26) were not. For the 19 patients who did not develop ATR/FNHTR, 34 blood products (RBC 17 and PLT 17) were included in the analysis. First, we analysed the BAT results for each blood product classified according to whether it was associated with the development of ATR/FNHTR or not. However, there was no difference in the BAT results when patients' sex, age (≤10 years or >10 years), disease (solid tumour or others), allergic history, concomitant use of anticancer drugs or immunosuppressive drugs at the time of BAT analysis, transfused blood products type (RBC or PLT), white blood cell counts in peripheral blood of patient's samples (<3000/μl vs. 3000–6000/μl vs. ≥6000/μl) and analysed basophil counts (<250 vs. 250–500 vs. ≥500) in the comparison within the analysis dependent on the products associated with the development of ATR/FNHTR, or those that were not associated with ATR/FNHTR.

BAT results in the ATR/FNHTR group

Twenty-two, one and four patients developed ATR only, FNHTR only and both ATR and FNHTR, respectively (Table 1). BAT results from

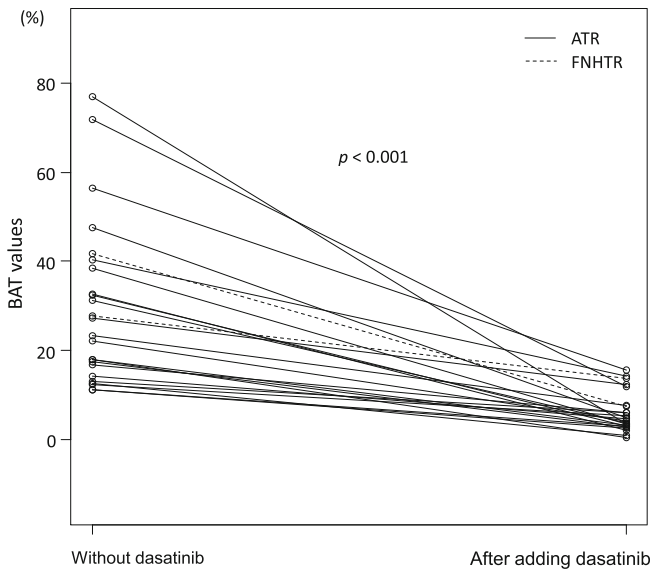

FIGURE 3 Dasatinib inhibited basophil activation test (BAT) when added to allergic transfusion reaction (ATR)- or febrile non-haemolytic transfusion reaction (FNHTR)-causing blood products in BAT-positive cases

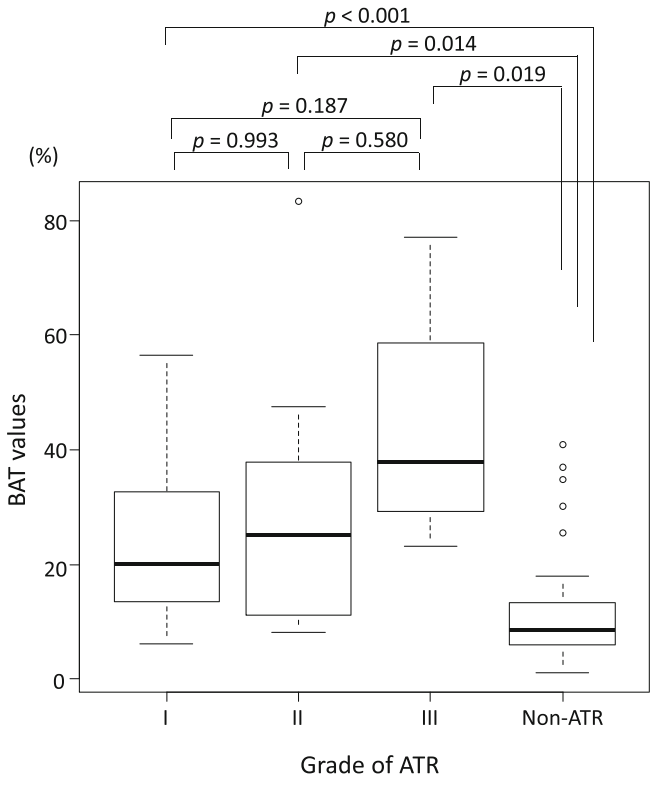

FIGURE 4 Basophil activation test (BAT) results stratified by allergic transfusion reaction (ATR) severity

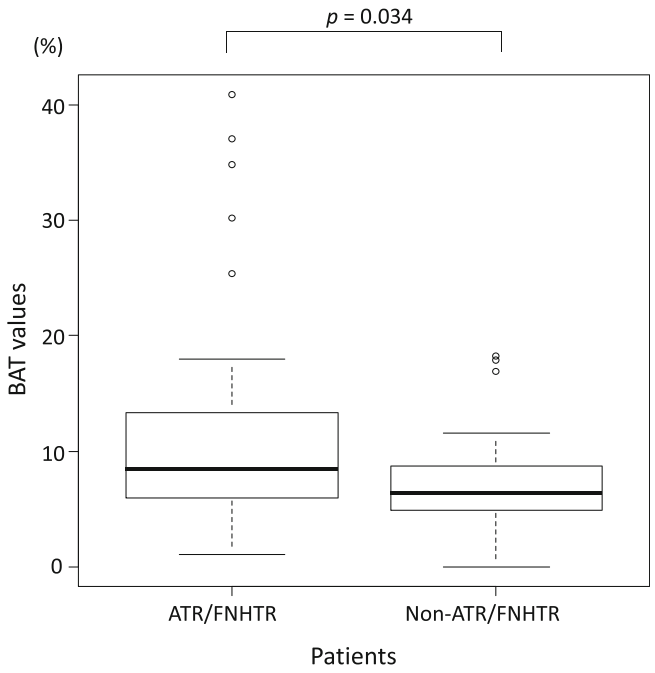

FIGURE 5 Basophil activation test (BAT) results associated with non-allergic transfusion reaction (ATR)/febrile non-haemolytic transfusion reaction (FNHTR) products in ATR/FNHTR and non-ATR/FNHTR cases

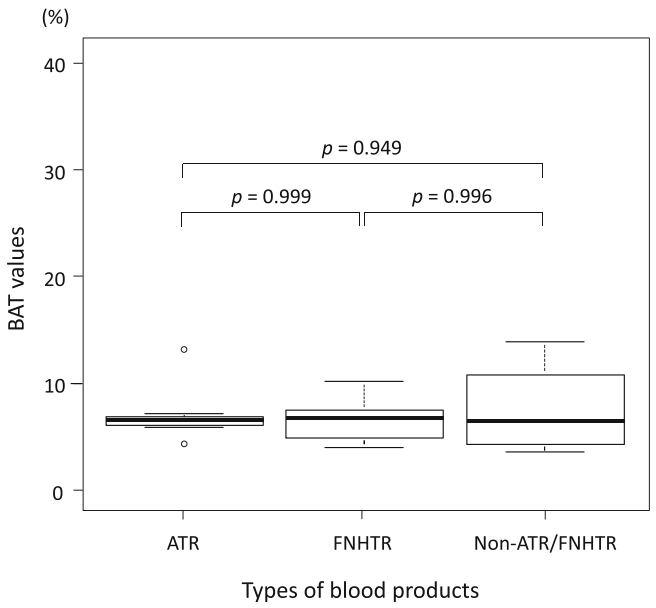

FIGURE 6 Basophil activation test (BAT) results analysed on healthy subjects using blood products that caused allergic transfusion reaction (ATR), febrile non-haemolytic transfusion reaction (FNHTR) or non-ATR/FNHTR in transfusion patients

blood products that caused ATR or FNHTR and those that did not cause clinical reactions in patients with ATR/FNHTR are shown in Figure 2. The median BAT values from blood products that caused ATR ($n = 41$) and FNHTR ($n = 5$) were 22.1% (range = 6.1%–77.0%) and 27.8% (range = 15.2%–47.8%), respectively ($p = 0.663$). Meanwhile, blood products that caused neither ATR nor FNHTR ($n = 37$) had the median BAT value of 8.5% (range = 1.1%–40.9%) (ATR vs. no reaction, $p < 0.001$; FNHTR vs. no reaction, $p = 0.011$). Dasatinib suppressed basophil activation in ATR ($n = 22$) and FNHTR ($n = 2$) ($p < 0.001$, Figure 3).

BAT results according to ATR severity

The BAT results for ATR ($n = 41$) were classified as grades I, II and III in 27 (65.9%), 10 (24.4%) and 4 (9.8%), respectively (Figure 4). Although BAT values were increased in blood products associated with all grades of ATR, they were comparable among severity grades.

BAT results in ATR/FNHTR and non-reaction cases

The BAT values were compared between 37 transfusion products that did not cause ATR/FNHTR in cases with ATR/FNHTR and 34 products in cases without ATR/FNHTR. ATR/FNHTR cases had higher BAT values than non-cases, even with blood products that did not cause clinical reactions in either group ($p = 0.034$, Figure 5).

Follow-up data of patients

For the initial analysis of BAT after the occurrence of ATR/FNHTR, the median time period was 14 (range = 2–62) days. In some cases, additional BAT analyses using the same blood products in each patient were performed a few days later to confirm the persistent duration of the positivity of BAT results. Twenty patients with ATR/FNHTR could be analysed for BAT more than once using 32 blood products that caused ATR/FNHTR. In these analyses, with remaining positive results of BAT, the median time period during which follow-up was discontinued was 204 (range = 23–601) days from the onset of ATR/FNHTR. On the other hand, the shifting of positive to negative results with BAT in these analyses was confirmed during the median duration of 249.5 (range = 48–469) days from the date of ATR/FNHTR onset. As of August 2022, from the 27 ATR/FNHTR cases, six cases developed ATR and/or FNHTR from transfusions after the initial study period. Seventeen patients did not develop ATR/FNHTR, and nine were prevented from transfusion reactions by using washed PLT concentrate. No further transfusions were performed in the remaining two cases. In contrast, 3 of the 19 patients without ATR/FNHTR developed ATR and/or FNHTR with subsequent transfusions after the initial study period, 13 patients did not develop any further ATR/FNHTR and 3 patients did not require subsequent transfusions.

BAT analysis in healthy subjects

Finally, BAT was performed using basophils from nine healthy subjects (five of whom had no history of allergy). We selected one of each of the blood products that caused grade III ATR, FNHTR and non-

ATR/FNHTR. However, there were no differences in BAT results between the blood products (Figure 6).

DISCUSSION

Unlike skin or challenge tests for allergic diseases, BAT is performed in vitro and is safe. In addition, BAT is characterised by its ability to analyse changes in basophils stimulated with antigens in whole blood, which is similar to in vivo conditions [16]. Therefore, BAT has been applied to various allergic diseases, such as food, drug, insect venom and respiratory allergies [17, 18]. In children, it is also used to diagnose food allergies, such as peanuts, cow milk and eggs [17, 18]. BAT tests have become common, and analysis kits are now commercially available, making them easier and quicker to perform than previously. However, in the field of transfusion medicine, BAT has been studied only in a small number of adult cases and few studies in children.

In this study, most ATR cases showed basophil activation associated with the ATR-causing blood product. Furthermore, dasatinib inhibited this activation, suggesting that IgE-mediated type I hypersensitivity may be involved in ATR. Furthermore, patients who developed ATR tended to have active basophils even without blood products that did not cause ATR. It remains unclear whether this phenomenon is an inherent patient characteristic, disease or treatment result, or property acquired via repeated blood transfusions. However, patients with primed basophils may be susceptible to ATR [4]. In fact, in non-ATR cases, the incubation of transfused blood products and basophils resulted in non-activation. Therefore, BAT using peripheral blood and blood product samples may help identify patients at risk of ATR. On the other hand, basophil activation was not observed in BAT performed on healthy subjects using the blood product that caused ATR/FNHTR in transfusion patients. This suggests that there is a clear causal relationship between the development of ATR/FNHTR and the related blood products. Furthermore, in the present study, activation of patient basophils was also observed in the blood products responsible for FNHTR. These results may support the association of FNHTR with allergic sensitisation-associated SNP, and results of a previous study show that ATR is accompanied by febrile symptoms at the time of onset [11, 12]. These findings suggest that BAT can explain the causal relationship between the transfused blood products and symptoms such as allergic or febrile symptoms that occur after blood transfusion. It is also expected to further elucidate the pathogenesis of ATR and FNHTR, which are still largely unknown.

However, BAT against ATR/FNHTR still has some challenges in terms of test accuracy. In this study, it was not possible to discriminate between mild and severe ATR by BAT. One of the differences between ATR and other allergic diseases is that the causative allergen is unknown in ATRs. Therefore, it is impossible to validate BAT accuracy for ATRs based on the allergen concentration of interest. Even in clinical practice, severe ATRs with anaphylaxis do not always occur immediately after blood transfusion [11, 19]. This may be related to both the type and concentration of the causative allergen; that is, even if there is an anaphylaxis-causing allergen in the blood product, it may not elicit a reaction until much of the product has been transfused, and the allergen concentration exceeds a specific threshold. Similarly, at low blood concentrations, allergens associated with ATR may not be detected by BAT. Furthermore, in some cases, positive BAT persisted for a long period of time, while in other cases, BAT became negative after a certain period of analysed time. This may be due to the fact that in most cases in this study, the treatment for the underlying disease also affected BAT. However, further studies on not only sensitivity and specificity but also reproducibility are needed for BAT against ATRs or FNHTRs.

The onset of ATR and FNHTR cannot be predicted in advance; thus, this study was retrospective and is associated with several limitations. First, the timing of ATR or FNHTR onset and BAT testing differed among patients. Using such samples might produce false negative results. Second, the volume of residual samples was limited, and not all of them could undergo suppression with dasatinib. The basophil counts in this study were also not enough for comparison with other analyses for allergic disease in adults [20, 21]. Third, the method of obtaining blood products used for BAT was not standardised. These limitations may have biased the BAT results. Fourth, because of the limited number of samples in this study, it was not possible to explain the differences in BAT results according to the type of blood products. Fifth is the relationship between BAT and IgE, which could not be evaluated in this study. Future large studies are required to validate these findings and to standardise handling and testing procedures in this context. Finally, this study included paediatric haematological and oncological patients; the generalisability of these findings requires further research.

In conclusion, blood products associated with ATR activated basophils; dasatinib suppressed this activation. These findings suggest that ATR may be associated with IgE-mediated type I hypersensitivity. Although BAT results were not always consistent with ATR severity, ATR was more common in cases whereby basophil activation was observed despite the use of blood products that did not cause ATR. Furthermore, in patients with FNHTR, the basophil activation was observed depending on the causative blood product. Despite some limitations, these findings may help identify patients at risk of ATR and support further research into ATR and FNHTR mechanisms.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to declare.

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REFERENCES

1. Goel R, Tobian AAR, Shaz BH. Noninfectious transfusion-associated adverse events and their mitigation strategies. Blood. 2019;133:1831–9.
2. Yanagisawa R. Preventing adverse reactions in pediatric transfusions using washed platelet concentrate. Pediatr Int. 2021;63:391–403.
3. Savage WJ. Transfusion reactions. Hematol Oncol Clin North Am. 2016;30:619–34.
4. Savage WJ, Tobian AA, Savage JH, Hamilton RG, Ness PM. Atopic predisposition of recipients in allergic transfusion reactions to apheresis platelets. Transfusion. 2011;51:2337–42.
5. Yanagisawa R, Ishimine N, Komori K, Kurata T, Saito S, Tanaka M, et al. Relationship between allergic transfusion reactions and allergic predisposition among pediatric patients with hematological/oncological disease. Transfusion. 2022;62:1035–44.
6. Okamura I, Matsuyama N, Yasui K, Hirayama F, Ikeda T. Clinical utility of the basophil activation test for analysis of allergic transfusion reactions: a pilot study. Vox Sang. 2017;112:114–21.
7. Matsuyama N, Yasui K, Amakishi E, Hayashi T, Kuroishi A, Ishii H, et al. The IgE-dependent pathway in allergic transfusion reactions: involvement of donor blood allergens other than plasma proteins. Int J Hematol. 2015;102:93–100.
8. Choi Y, Byun JM, Kim I, Park JH, Kim KH, Kim JS, et al. Successful management of severe allergic reactions to platelet transfusion with omalizumab: a case report. Medicine (Baltimore). 2021;100:e27724.
9. Shi S, Han J, Yao Y, Xu Y, Wu D, Wang Y. Successful prevention of severe allergic transfusion reactions with omalizumab. Transfusion. 2020;60:1639–42.
10. Yasui K, Takihara Y, Matsuyama N, Kato H, Oka K, Imada K, et al. Sensitivity and specificity of passive immune-basophil activation test to detect allergic transfusion reactions. Transfusion. 2019;59:3308–13.
11. Yanagisawa R, Tatsuzawa Y, Ono T, Kobayashi J, Tokutake Y, Hidaka E, et al. Analysis of clinical presentations of allergic transfusion reactions and febrile non-haemolytic transfusion reactions in paediatric patients. Vox Sang. 2019;114:826–34.
12. Ide Y, Yanagisawa R, Kobayashi J, Komori K, Matsuda K, Amano Y, et al. Relationship between allergic sensitisation-associated single-nucleotide polymorphisms and allergic transfusion reactions and febrile non-haemolytic transfusion reactions in paediatric cases. Blood Transfus. 2022;20:94–102.
13. Yanagisawa R, Shimodaira S, Sakashita K, Hidaka Y, Kojima S, Nishijima F, et al. Factors related to allergic transfusion reactions and febrile non-haemolytic transfusion reactions in children. Vox Sang. 2016;110:376–84.
14. Yasui K, Enami T, Okamura-Shiki I, Ueda T, Fukushima K, Matsuyama N, et al. Passive immune basophil activation test for the identification of allergic episodes from various adverse events elicited by haematopoietic cell transplantation: a pilot study. Vox Sang. 2022;117:119–27.
15. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
16. Nagao M, Hiraguchi Y, Hosoki K, Tokuda R, Usui T, Masuda S, et al. Allergen-induced basophil CD203c expression as a biomarker for rush immunotherapy in patients with Japanese cedar pollinosis. Int Arch Allergy Immunol. 2008;146:47–53.
17. Hemmings O, Kwok M, McKendry R, Santos AF. Basophil activation test: old and new applications in allergy. Curr Allergy Asthma Rep. 2018;18:77.
18. Santos AF, Alpan O, Hoffmann HJ. Basophil activation test: mechanisms and considerations for use in clinical trials and clinical practice. Allergy. 2021;76:2420–32.
19. Yanagisawa R, Yamanaka R, Shimodaira S. Analysis of clinical factors associated with the occurrence time of allergic transfusion reactions or febrile non-hemolytic transfusion reactions. Ann Clin Lab Sci. 2022;52:382–90.
20. Li J, Best OG, Rose MA, Green SL, Fulton RB, Fernando SL. Integrating basophil activation tests into evaluation of perioperative anaphylaxis to neuromuscular blocking agents. Br J Anaesth. 2019;123:e135–43.
21. Curto-Barredo L, Yelamos J, Gimeno R, Mojal S, Pujol RM, Giménez-Arnau A. Basophil activation test identifies the patients with chronic spontaneous urticaria suffering the most active disease. Immun Inflamm Dis. 2016;4:441–5.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Efficacy of therapeutic plasma exchange in severe COVID-19 disease: A meta-analysis

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Abstract

Background and Objectives: Therapeutic plasma exchange (TPE) has been used in severe COVID-19 disease to eliminate the cytokine storm. This meta-analysis aims to assess the effectiveness of TPE in reducing mortality in severe COVID-19 disease compared to standard treatment.

Materials and Methods: A comprehensive literature search was performed in PubMed, the Cochrane database and the International Clinical Trial Registry Platform (ICTRP). The random-effect model was used to calculate the risk ratio and standardized mean difference (SMD) as pooled effect size for the difference in mortality and length of the intensive care unit (ICU) stay. The risk of bias and publication bias were assessed in R version 4.1.0. The certainty of the evidence was calculated using the GradePro tool.

Results: The database identified 382 participants from six studies, including one randomized control trial. Egger's test did not detect any publication bias ($p = 0.178$). The random model analysis for mortality evaluated a risk ratio of 0.38 (95% CI: 0.28–0.52) with a significant reduction in the TPE group. The certainty of the evidence was moderate, with a risk ratio of 0.34 (95% CI: 0.24–0.49). Length of ICU stays between TPE versus standard care showed an SMD of 0.08 (95% CI: −0.38, 0.55) and was not significant.

Conclusion: The length of ICU stay in the TPE group was not different from standard care. However, this meta-analysis revealed a significant benefit of TPE in reducing mortality in severe COVID-19 disease compared to standard treatment.

Keywords

COVID-19 treatment, hypercytokinaemia, mortality, plasma exchange, SARS-CoV-2

Highlights

- Therapeutic plasma exchange (TPE) has been used to treat diseases with cytokine storms.
- To date, definitive treatment for severe COVID-19 disease is unavailable.
- This meta-analysis revealed a significant benefit of TPE in reducing mortality in severe COVID-19 disease with moderate certainty of evidence.

INTRODUCTION

The disease COVID-19 caused by SARS-CoV-2, a single-stranded RNA virus of the beta coronavirus genus, was first reported in December 2019 in Wuhan city of China [1]. The droplet-mediated spread of novel coronavirus from human to human through the respiratory route has resulted in worldwide suffering in the form of increased mortality and morbidity. On 11 April 2022, the World Health Organization (WHO) reported 6,179,104 cumulative deaths due to COVID-19 [2]. Many studies and trials conducted worldwide have failed to find a specific cure for the disease. This virus enters with angiotensin converting enzyme (ACE2) receptors distributed widely in the epithelium and endothelium of the lungs, kidney and gastrointestinal, and it can potentially lead to multiorgan involvement and death in some cases [3]. The severe COVID-19 disease manifests as cytokine release syndrome, resulting in elevated interleukin (IL)-1 and IL-6, TNF- α, lactate dehydrogenase, D-dimer, ferritin and C-reactive protein (CRP) [4]. The condition is also associated with microvascular thrombosis and clot formation features. The severe diseased state in COVID-19 is defined as having a respiratory rate of >30/min, breathlessness or SpO_2 of <90% on room air by the Indian Council of Medical Research-COVID-19-National Task Force [5].

Many drugs like azithromycin, doxycycline, supplements like zinc and vitamin C and other drugs like hydroxychloroquine, ivermectin, favipiravir and injection remdesivir, were used to attenuate the disease severity with debatable effects [5]. It has also been observed that approximately half of the patients with cytokine storms gradually develop severe acute respiratory distress syndrome (ARDS), and mortality in the severe category range from 40% to 50% [6, 7]. Tocilizumab, an IL-6 antagonist, was used to reduce the disease progression in the severe category but only provided conflicting results [8]. The convalescent plasma (CP) from the recovered donor also failed to provide conclusive evidence in various studies and trials [9].

Therapeutic plasma exchange (TPE) is recommended to address the hyperinflammation in sepsis with multiorgan failure and haemophagocytic syndrome in haemophagocytic histiocytosis for the removal of cytokines and immune complexes involved in deranged coagulation and clot formation [10]. Various studies and trials conducted across the world find some favourable evidence [11], and this meta-analysis was planned to generate evidence from published observational studies and trials exploring the efficacy of TPE in attenuating disease progression in severe COVID-19, which will eventually help in framing the therapeutic guideline.

MATERIALS AND METHODS

Search strategy

A systematic literature search was performed independently by four review authors (S.P., S.M., A.S. and S.S.R.) using PubMed, the Cochrane database and the International Clinical Trial Registry Platform (ICTRP). The literature search included prospective clinical trials and observational studies on the efficacy of TPE procedures in reducing morbidity (length of intensive care unit [ICU] stay) and mortality in severe COVID-19 patients. The search strategy was not restricted by the date of publication and the clinical or genetic variants of COVID-19. However, articles published in the English language only were included for meta-analysis. Population, intervention, control and outcomes (PICO) scheme was followed for reporting inclusion criteria. The key elements used in our search using MESH terms are the 'P' (COVID-19, SARS-CoV-2), the 'I' (Plasma exchange, Plasmapheresis, TPE), the 'C' (Coronavirus infections/therapy, Oxygenation) and the 'O' (Efficacy), that is, mortality in TPE group versus non-TPE control group, ICU stay, inflammatory markers, such as IL-6, CRP, D-dimer and Ferritin. The adverse events associated with the TPE procedure, for example, hypocalcaemia, hypotension and vasovagal attack, were also included for review.

The meta-analysis research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) vide registration number CRD42021273748 and approved by the institutional ethics committee (IEC), All India Institute of Medical Sciences, Bhubaneswar [12, 13].

Study selection criteria

Types of studies

Prospective clinical trials, observational studies and retrospective studies that had evaluated the effect of plasma exchange on mortality as a primary outcome were included in this meta-analysis. Review articles, letters to the editor, comments, case reports and studies where it was impossible to retrieve or calculate data of interest were excluded from this review.

Types of participants

Severe COVID-19 patients who had undergone TPE were compared with patients on conventional therapy and not undergone the TPE procedure.

Types of interventions

- *Experimental*: TPE procedure, in addition to conventional therapy performed on COVID-19 patients with ARDS in different clinical conditions.
- *Control*: COVID-19 patients with ARDS on conventional therapy and have not undergone TPE.

Outcome measures

Primary outcome

1. Effect of TPE in reducing mortality.

Secondary outcomes

1. Length of ICU stay (in days)
2. Change in the cytokine level of IL-6 and CRP after TPE.
3. TPE procedure-related adverse events, for example, vasovagal syncope, hypocalcaemia, hypotension, etc.

Data extraction and risk of bias statement

For this meta-analysis, four review authors (S.P., S.M., A.S. and S.S.R.) independently screened the titles, abstracts and keywords of all references retrieved. The authors then obtained and assessed the full text from all selected studies and assessed the quality using guidelines published by the Cochrane Collaboration [14]. The risk of bias assessment of included studies was separately performed for randomized controlled trials and observational studies with the 'ROB2' and 'ROBINS-I' tools of the 'robvis' package in R programming using the Cochrane Risk of Bias Assessment tool and judged them as low, moderate, serious, critical and low, some concern and high, respectively. Any disagreement between the review authors was resolved by consensus or consultation with the clinical pharmacologist cum statistical advisor (R.M.). The authors converted the median and interquartile range from the studies into mean and standard deviation with the help of an online calculator formulated and described by Luo et al.[15] and Wan et al. [16]. Extracted data includes:

- Publication type and source
- The trial design includes timing, follow-up, sequence generation and allocation concealment
- Setting including country, level of care
- Participants including selection criteria, number of dropouts
- Interventions, that is, TPE and related adverse events
- Outcome measures include mortality, ICU stays (in days), inflammatory cytokine markers before and after TPE, and drugs used for standard care.

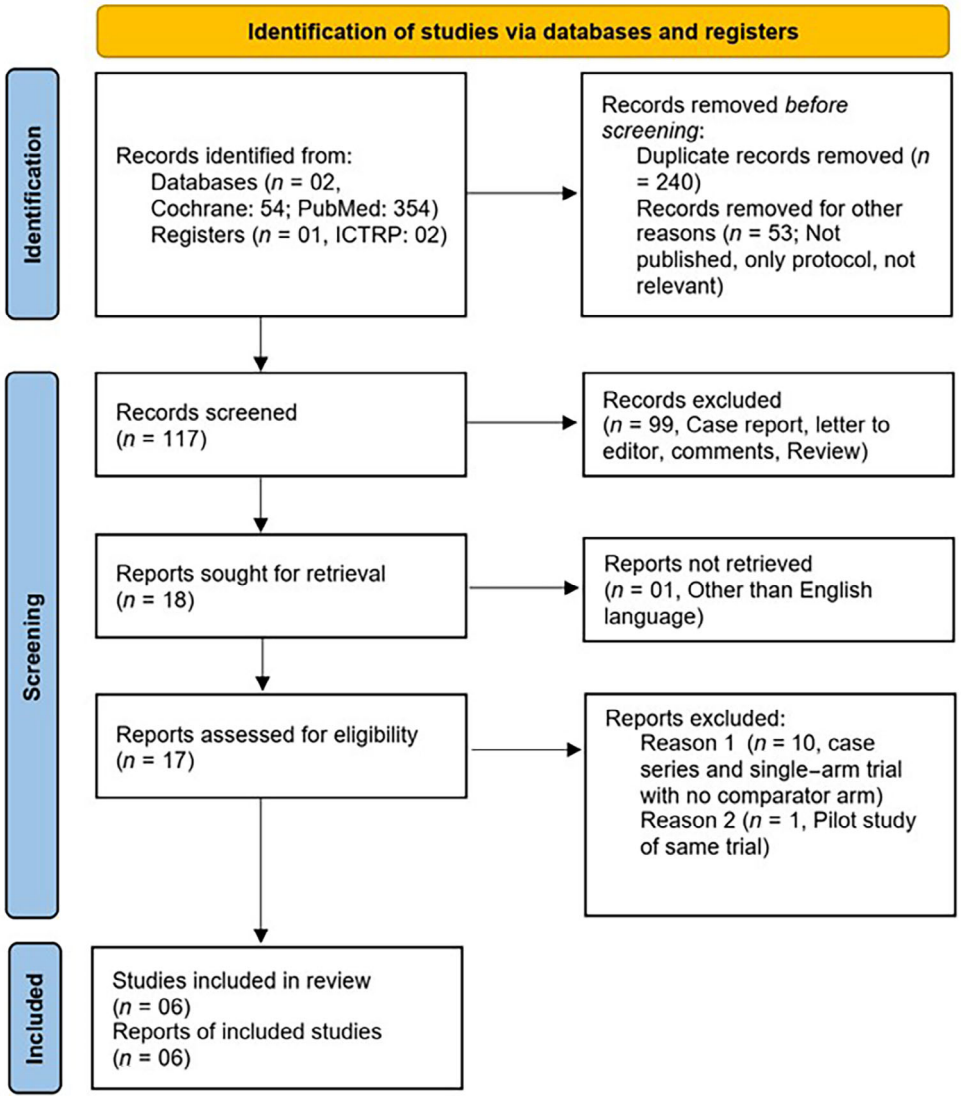

FIGURE 1 Study identification and selection process as per PRISMA guideline 2020

Statistical analysis

This meta-analysis was conducted using the various package in the R programming language (version 4.1.0) [17].

The risk ratio and standardized mean difference (SMD) were calculated to estimate the effect size for mortality and length of ICU stays (in days), respectively. The forest plot was prepared using the random-effect model for between-group analyses. The outcome has been depicted as a point estimate with a 95% confidence interval. The chi-square test was used to assess whether observed differences in results are compatible with chance alone. I^2 statistics, an estimate due to heterogeneity, was done to quantify inconsistency. A prediction

TABLE 1 Characteristics of included studies comparing mortality in the intervention versus standard care

Author name, year and location	Study type	No. of participants	Intervention/ apheresis machine	Outcome (mortality)	
				Intervention arm	Standard care
Dai et al., 2020, China	Prospective case control	101	TPE/not mentioned	16% (8/50)	50.98% (26/51)
Faqihi et al., 2021, Saudi Arabia	Open-label randomized trial	87 in intervention and 43 in standard care	TPE/centrifugal 'Spectra optia'	20.9% (9/43)	34.1% (15/44)
Gucyetmez et al., 2020, Turkey	Retrospective	24	TPE/not mentioned	8.3% (1/12)	58.3% (7/12)
Kamran et al., 2021, Pakistan	Retrospective (propensity-matched control)	90	TPE/centrifugal 'Cobe Spectra'	8.9% (5/45)	38.5% (18/45)
Khamis et al., 2020, Oman	Prospective (with hypothetical control; medical records)	31	TPE/centrifugal 'Spectra Optia'	9.1% (1/11)	45% (9/20)
Nusshag et al., 2021, Germany	Retrospective case control	49	TPE/centrifugal 'Comtech'	39.28% (11/28)	95.23% (20/21)

Abbreviation: TPE, therapeutic plasma exchange.

TABLE 2 Characteristics of excluded studies comparing mortality in the intervention versus standard care

Author name, year and location	Study type	Total no. participants	Intervention	Outcome (mortality)	Reasons for exclusion
Adeli et al., 2020, Iran	Prospective	8	TPE	12.5% (1/8)	No comparator
Zhang et al., 2020, China	Case series	3	TPE	Nil	Comparator not available
Dogan et al., 2020, Turkey	Case series	6	TPE	16.6% (1/6)	No comparator
Fernandez et al., 2020, Spain	Case series	4	TPE	Nil	No comparator
Gluck et al., 2020, USA	Single-arm trial without placebo randomization	6 of 10	TPE on Spectra Optia apheresis system	Nil	No comparator
Faqihi et al., 2020, Saudi Arabia	A pilot study of a randomized trial	10	TPE	(1/10) 10%	No comparator and (main study trial included for meta-analysis)
Hashemian et al., 2020, Tehran	Prospective	15	Plasmapheresis with haemodialysis machine	40% (6/15)	No comparator
Jaiswal et al., 2021, United Arab Emirates	Prospective	14	TPE followed by CP transfusion	28.6% (4/14)	No comparator
Morath et al., 2020, Germany	Retrospective	5	Plasma exchange	40% (2/5)	No comparator
Matsushita et al., 2021, Japan	Retrospective	5	TPE and haemodiafiltration	60% (3/5)	No comparator
Roshandel et al., 2021, Iran	Prospective	5	TPE followed by CP transfusion	20% (1/5)	No comparator

Abbreviation: TPE, therapeutic plasma exchange.

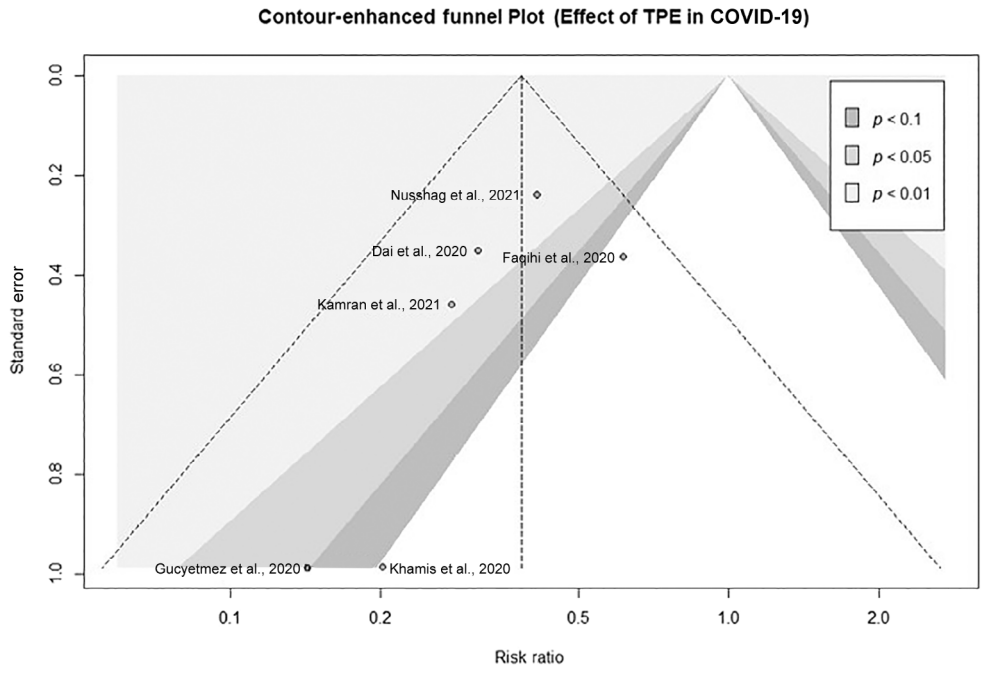

FIGURE 2 Contour-enhanced funnel plot of the effect estimate. TPE, therapeutic plasma exchange

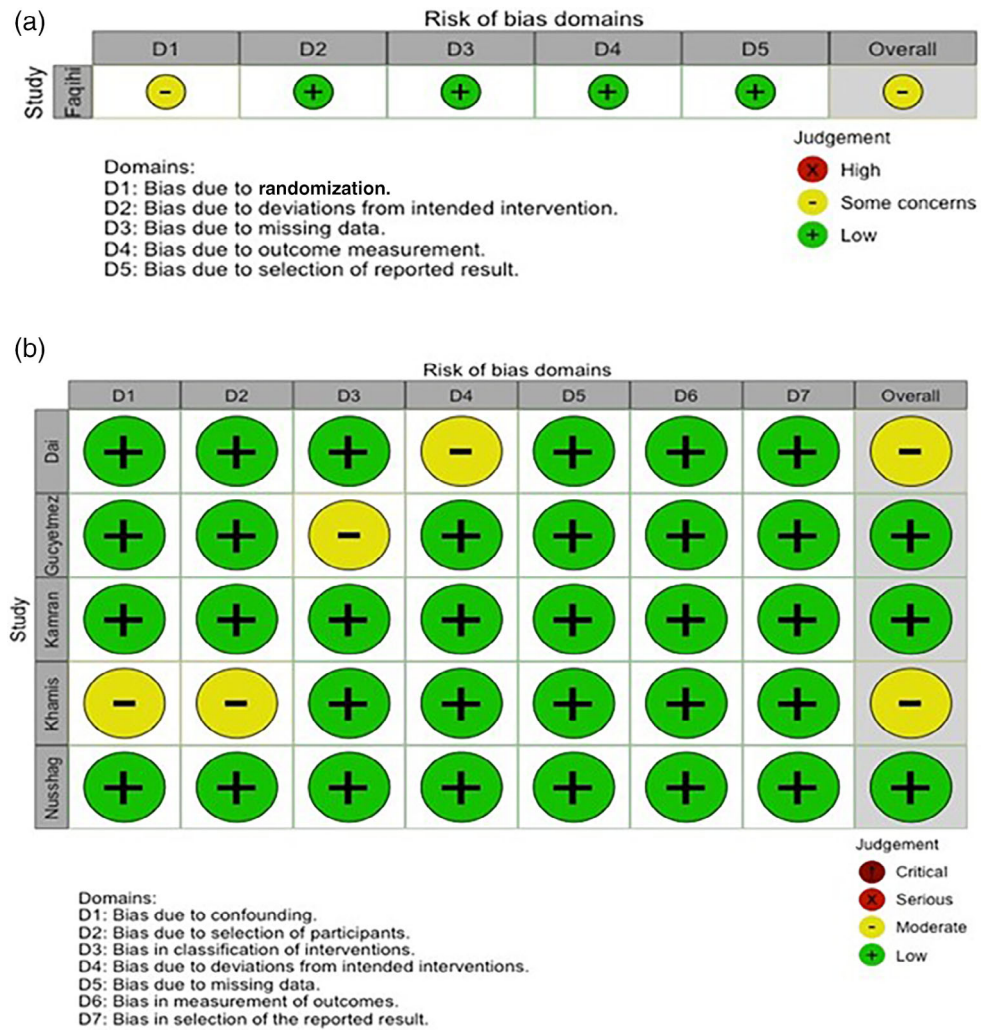

FIGURE 3 Risk of bias graph, clinical trial (a), observational study (b)

interval was also calculated to predict the outcome probability of a new observation later.

The sensitivity analysis was performed to test the robustness of the results in case of significant heterogeneity in ICU stays. We constructed funnel plots and performed the Eggers' regression test as a quantitative test for publication bias. Standard Cochrane methodology and the GRADE Working Group guidance were followed to create the 'Summary of findings' table. The five grade considerations (risk of bias, consistency, imprecision, indirectness and publication bias) of the included studies were considered to conclude the certainty of the evidence for the outcome [18].

RESULTS

The database identified 410 publications and reduced them to 117 after removing duplicates, trials in progress, only protocol published and irrelevant studies manually. Further screening of the remaining studies and excluding case reports, reviews, letters to editors, comments, and studies in the Chinese language, 17 studies sought eligibility [19–35]. Finally, we included six studies, as shown in the PRISMA flow chart (Figure 1). One was a randomized trial among six studies, and the remaining five were either prospective or retrospective observational studies [30–35]. The details of the included and excluded studies are described in Table 1 and Table 2, respectively. We could not observe any publication bias in the studies. The funnel plot is not asymmetrical, and Eggers' test showed a *p*-value of 0.178(95% CI: −2.66, 0.24; Figure 2). The risk of bias plot has been produced by 'robvis' package via the 'rob_traffic_light' function separately for the randomized trial and observational study, as shown in Figure 3a,b.

The primary outcome, that is, reducing mortality in the intervention arm (TPE), was compared with standard care among six included studies. The test of heterogeneity was not significant (heterogeneity: $\chi 2 = 0$, $I^2 = 0\%$, $p = 0.55$). The random model analysis of the studies evaluated a risk ratio of 0.38 (95% CI: 0.28–0.52; Figure 4a) with a significant reduction in mortality in the TPE group ($p < 0.01$).

The length of ICU stay in included six studies showed significant heterogeneity (heterogeneity: $I^2 = 57\%$, $p = 0.04$). The random model analysis showed a SMD of 0.08 (95% CI: −0.38, 0.55; Figure 4b). The sensitivity analysis was performed because of significant heterogeneity by excluding studies sequentially. However, changes in heterogeneity were minimal, and the overall *p*-value was not significant, as summarized in Table 3.

We could not analyse other secondary outcome measures like change in cytokine level, sequential organ failure assessment (SOFA) score, and adverse events as data obtained from these studies were not adequate. Only a few studies documented hypotension and

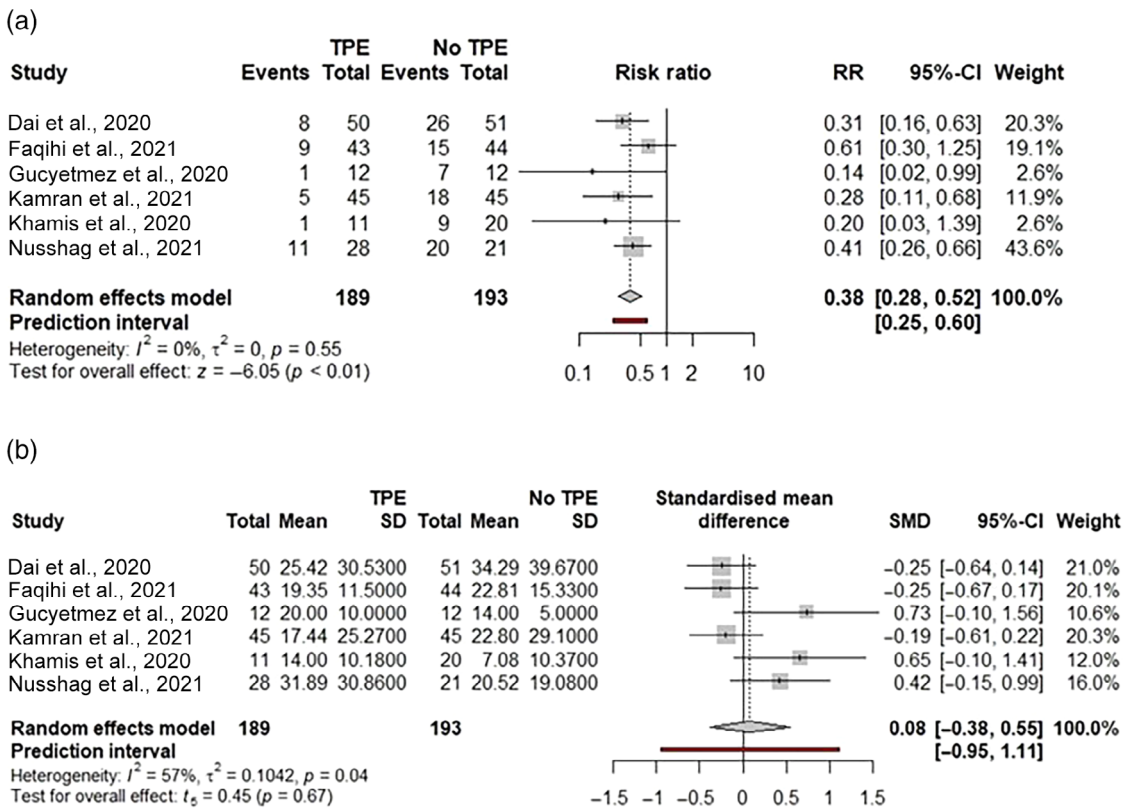

FIGURE 4 Forest plot (a): Analysing the risk ratio of mortality in TPE (intervention) versus no TPE (standard care) group, Forest plot (b): Illustrating the difference in length of ICU stay (in days) between TPE (intervention) and No TPE (standard care) group. CI, confidence interval; ICU, intensive care unit; RR, risk ratio; SD, standard deviation; SMD, standardized mean difference; TPE, therapeutic plasma exchange

TABLE 3 Sensitivity analysis by excluding studies one by one with no change in overall effect (ICU stay in days)

Study excluded	SMD	95% CI	*p* (overall effect)	I^2	*P* (I^2)
Dai et al.	0.18	−0.40, 0.76	0.43	60%	0.04
Faqihi et al.	0.18	−0.40, 0.75	0.44	61%	0.04
Gucyetmez et al.	−0.01	−0.50, 0.47	0.94	51%	0.08
Kamran et al.	0.17	−0.42, 0.76	0.47	63%	0.03
Khamis et al.	−0.02	−0.51, 0.48	0.93	52%	0.08
Nusshag et al.	0.01	−0.55, 0.58	0.96	55%	0.06

Abbreviations: CI, confidence interval; ICU, intensive care unit; SMD, standardized mean difference.

TABLE 4 Grade of evidence for the primary outcome (mortality)

Summary of findings:

[Therapeutic plasma exchange] compared to [Standard care] for [Severe COVID-19 disease patients]

Patient or population: [Severe COVID-19 disease patients]
Setting:
Intervention: [Therapeutic plasma exchange]
Comparison: [Standard care]

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with [Standard care]	Risk with [Therapeutic plasma exchange]				
Mortality	537 per 1000	**183 per 1000** (129–263)	**RR 0.34** (0.24–0.49)	295 (5 observational studies)	⨁⨁⨁◯ Moderate[b]	

Note: **GRADE Working Group grades of evidence**: **High certainty**, we are very confident that the true effect lies close to that of the estimate of the effect; **Moderate certainty**, we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; **Low certainty**, our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; **Very low certainty**, we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Abbreviations: CI, confidence interval; RR, risk ratio.
[a]*The risk in the intervention group* (and its 95% CI) is based on the assumed risk in the comparison group and the *relative effect* of the intervention (and its 95% CI).
[b]The sample size of a few studies was not sufficient.

allergic reaction, and any serious adverse events were not encountered. The evidence was graded using online GradePro software. There were five observational and only one randomized trial, and separate grading was recommended for various types of study. The Grade assessment for the primary outcome was calculated for five observational studies, including 295 participants, and the risk ratio was significant with a moderate grade of evidence shown in Table 4.

DISCUSSION

TPE is one of the life-saving modalities in diseases with underlying cytokine storms such as sepsis and haemophagocytic syndrome. In the initial phase after SARS-CoV-2 infection, lymphocytosis ensues, resulting in a rise in the inflammatory and chemotactic cytokines like TNF- α, IL-6, IL-1β and MCP-1. This hypercytokinaemia was found to lower the lymphocyte count, thus further reducing viral clearance. Immunomodulators like steroids, tocilizumab, cyclooxygenase inhibitors, ACE inhibitors and extracorporeal therapy were used to treat hypercytokinaemia. The direct removal of these inflammatory mediators by TPE may help to prevent T-cell exhaustion [36]. The favourable change in laboratory profile after TPE was evident in many studies. However, few authors opposed the benefits of TPE in reducing mortality and disagree with the assumption of improving survival by simply decreasing cytokine levels of IL-6, CRP and TNF- α [37, 38]. This meta-analysis was planned to see the clinical efficacy of TPE in reducing mortality in severe COVID-19 disease.

The meta-analysis shows a significant reduction in mortality in severe COVID-19 patients despite no change in the ICU stays. The random model analysis reflects no heterogeneity, and overall effects were significantly in favour of the TPE procedure in reducing the mortality in severe COVID-19 patients. The benefit of TPE in reducing mortality was evident clearly with the prediction interval in favour of the intervention group. The insight of improving survival by removing harmful inflammatory mediators and antibodies and replacing the deficient blood components in the TPE procedure was found useful in

many studies. The COVID-19-related coagulopathy was associated with a decrease in antithrombin, disintegrin, metalloproteinases like ADAMTS-13, and the increase in von-Willebrand multimers (vWF) and D-dimers level [39, 40]. The benefit of reducing mortality by TPE in patients with elevated D-dimer levels was shown in the study of Gucyetmez et al. [35]. TPE, thus, may be a rational therapeutic approach by replacing these deficient components and correcting coagulopathy. As sought in some case reports, the removal of inflammatory mediators and harmful antibodies to interferon-I was also found protective [41]. The TPE was proposed by a few authors to cause immune paralysis by reducing IL-10 levels, an immunosuppressive cytokine. However, an elevated level of IL-10 was associated with a decrease in lymphocyte count and increased neutrophil-to-lymphocyte ratio (NLR). Previous studies also quoted decreased lymphocyte count and increased NLR as a poor prognostic marker in COVID-19 [42, 43]. Again, the TPE procedure may help eliminate the elevated IL-10 levels, reverse the NLR and improve the cellular profile. The change in these inflammatory mediators also improved the SOFA score, organ dysfunction and overall survival and was not just a change in laboratory markers, as suggested by a few authors. The claim of immune paralysis by removing protecting antibodies through TPE may also be refuted as the trial on CP fails to provide any mortality benefits in various age groups and severe categories of patients with COVID-19. This evidence further disagrees with the use of CP as a replacement fluid for the TPE procedure [34]. The use of fresh frozen plasma (FFP) as replacement fluid was also debatable due to its hypercoagulable state. However, deficient metalloproteinase and an increase in vWF multimers were also found to cause a hypercoagulable state in COVID-19. Thus, the use of FFP as a replacement fluid may be beneficial. Five out of six studies [30–34] used plasma as the replacement fluid, and one study [35] has not mentioned the type of replacement fluid used for the TPE procedure. Few participants in this meta-analysis were also receiving tocilizumab, and a claim of a decrease in cytokines due to this IL-6 inhibitor was proposed. However, an instant reduction in IL-6 and other cytokines was observed post-TPE procedure in patients who did not receive the tocilizumab [33]. Specific drugs like tocilizumab were not much beneficial in controlling inflammation in COVID-19, and it may be due to a diverse array of immunopathology in COVID-19 [44].

Further, the broad-spectrum oral and inhaled steroid was shown to reduce the severity, morbidity and mortality of COVID-19. TPE treatment also appears to act in a wide spectrum by removing many pathogenic substances and replacing deficient components. Moreover, like many other autoimmune diseases and diseases with inflammatory components, TPE had shown a good response in patients refractory to steroid treatment. Thus, TPE may be used as life-saving last resort therapy in severe COVID-19 refractory to steroid and standard care.

The higher mortality in ICU was associated with a longer length of stay in the previous study. Prolonged immunosuppression, nosocomial infections and protein-energy malnutrition causing myopathy were responsible for poor outcomes with increased ICU stay, irrespective of mechanical ventilation [45]. In this meta-analysis, the length of ICU stay was not different between the intervention and standard care arm. The heterogeneity was high, and the *p*-value of heterogeneity was significant (Figure 4b). However, sensitivity analysis by sequentially excluding the study fails to get an overall significant difference in length of ICU to stay in TPE and non-TPE groups. (Table 3) TPE procedure was performed in 2–5 cycles on a daily or alternate day basis and was responsible for increasing the day of ICU admission. Further, no difference in ICU stay can be explained due to the increased day of admission with associated comorbidities like chronic kidney disease patients on dialysis support, hypertension and diabetes. Random inclusion of more seriously ill patients in the TPE group also contributed to increased days of ICU admission [30, 33].

The TPE procedure's safety has already been established, and the procedure itself had minimal adverse events. Most of the adverse events in TPE are hypotension, allergic reaction to replacement fluid and citrate-related side effects [46]. All these adverse events can easily be managed by medical intervention. In this meta-analysis, mild hypotension and allergic reaction were encountered by a few authors and managed by saline fluid bolus and supportive management. Serious adverse events, including mortality related to the TPE procedure itself, were not found in any of the participants in the intervention arm (TPE). Recent studies mentioned the change in the level of cytokines before and after the TPE procedure, and the change was significant for IL-6, CRP, SOFA score, LDH and ferritin levels [23, 26, 30, 32, 35]. However, we could not conduct a meta-analysis of a few secondary outcomes like adverse events to TPE procedures and the change in the level of various cytokines due to inadequate data in both the intervention and standard care arm.

We have a few limitations in our meta-analysis. This meta-analysis included only one randomized trial and a few observational and retrospective studies. The chance of selection bias, the inadequate sample size in a few studies and other unclear risks of bias may be the drawback of these studies, which could hamper the suitable comparison between intervention and standard care groups. However, most of the included studies in this meta-analysis performed the matching of participants for age, gender, demography, clinical and laboratory parameters. Thus, selection bias may be compensated.

In conclusion, the evidence generated with this meta-analysis suggests TPE as a promising and safe therapeutic approach for a subset of patients with severe COVID-19. However, the certainty of evidence in reducing mortality is moderate. Hence, further high-quality large randomized controlled trials are desirable to attain factual inference on the efficacy of TPE in severe COVID-19.

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draft preparation; S.M. executed the conceptualization, planned the methodology, acquired the software, carried out the formal analysis, performed the data curation and took on the responsibility of writing, reviewing and editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264–6.
2. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. [cited 2022 April 11]. Available from: https://covid19.who.int/
3. Dalan R, Bornstein SR, El-Armouche A, Rodionov RN, Markov A, Wielockx B, et al. The ACE-2 in COVID-19: foe or friend? Horm Metab Res. 2020;52:257–63.
4. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368:473–4.
5. Force/Joint AI-C-19 NT, (Dte.GHS) MG, Ministry of Health & Family Welfare G of I. Clinical Guidance For Management of Adult COVID-19 Patients. [cited 2022 Feb 5]. Available from: https://www.icmr.gov.in/pdf/covid/techdoc/COVID19_Management_Algorithm_22042021_v1.pdf
6. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130:2620–9.
7. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia. 2020;75:1340–9.
8. dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options. Biomed Pharmacother. 2020;129:110493.
9. Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2020;7:CD013600.
10. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice - evidence-based approach from the writing Committee of the American Society for apheresis: the eighth special issue. J Clin Apher. 2019;34:171–354.
11. Patidar GK, Land KJ, Vrielink H, Rahimi-Levene N, Dann EJ, Al-Humaidan H, et al. Understanding the role of therapeutic plasma exchange in COVID-19: preliminary guidance and practices. Vox Sang. 2021;116:798–807.
12. PROSPERO. [cited 2022 Mar 15]. Avialble from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=273748
13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. PRISMA-P group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
14. JPT H, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. (editors)Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester, UK: John Wiley & Sons; 2019.
15. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27:1785–805.
16. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
17. R: The R Project for Statistical Computing. [cited 2022 Jan 14]. Avaialable from: https://www.r-project.org/
18. Guideline Development Tool. [cited 2022 Jan 14]. Avaialable from: https://gdt.gradepro.org/app/#projects
19. Adeli SH, Asghari A, Tabarraii R, Shajari R, Afshari S, Kalhor N, et al. Therapeutic plasma exchange as a rescue therapy in patients with coronavirus disease 2019: a case series. Pol Arch Intern Med. 2020;130:455–8.
20. Zhang L, Zhai H, Ma S, Chen J, Gao Y. Efficacy of therapeutic plasma exchange in severe COVID-19 patients. Br J Haematol. 2020;190:e181–3.
21. Dogan L, Kaya D, Sarikaya T, Zengin R, Dincer A, Akinci IO, et al. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: case series. Brain Behav Immun. 2020;87:155–8.
22. Fernandez J, Gratacos-Ginès J, Olivas P, Costa M, Nieto S, Mateo D, et al. Covid clinic critical care (CCCC) group. Plasma exchange: an effective rescue therapy in critically ill patients with coronavirus disease 2019 infection. Crit Care Med. 2020;48:e1350–5.
23. Gluck WL, Callahan SP, Brevetta RA, Stenbit AE, Smith WM, Martin JC, et al. Efficacy of therapeutic plasma exchange in the treatment of penn class 3 and 4 cytokine release syndrome complicating COVID-19. Respir Med. 2020;175:106188.
24. Faqihi F, Alharthy A, Alodat M, Kutsogiannis DJ, Brindley PG, Karakitsos D. Therapeutic plasma exchange in adult critically ill patients with life-threatening SARS-CoV-2 disease: a pilot study. J Crit Care. 2020;60:328–33.
25. Hashemian SM, Shafigh N, Afzal G, Jamaati H, Tabarsi P, Marjani M, et al. Plasmapheresis reduces cytokine and immune cell levels in COVID-19 patients with acute respiratory distress syndrome (ARDS). Pulmonology. 2021;27:486–92.
26. Jaiswal V, Nasa P, Raouf M, Gupta M, Dewedar H, Mohammad H, et al. Therapeutic plasma exchange followed by convalescent plasma transfusion in critical COVID-19-an exploratory study. Int J Infect Dis. 2021;102:332–4.
27. Matsushita Y, Kusaoi M, Hiki M, Murayama G, Abe Y, Nozawa K, et al. Combination therapy with plasma exchange and glucocorticoid may be effective for severe COVID-19 infection: a retrospective observational study. Ther Apher Dial. 2021;25:390–400.
28. Morath C, Weigand MA, Zeier M, Speer C, Tiwari-Heckler S, Merle U. Plasma exchange in critically ill COVID-19 patients. Crit Care. 2020;24:481.
29. Roshandel E, Sankanian G, Salimi M, Jalili A, Salari S, Sadeghi A, et al. Plasma exchange followed by convalescent plasma transfusion in COVID-19 patients. Transfus Apher Sci. 2021;60:103141.
30. Faqihi F, Alharthy A, Abdulaziz S, Balhamar A, Alomari A, AlAseri Z, et al. Therapeutic plasma exchange in patients with life-threatening COVID-19: a randomised controlled clinical trial. Int J Antimicrob Agents. 2021;57:106334.
31. Kamran SM, Mirza ZE, Naseem A, Liaqat J, Fazal I, Alamgir W, et al. Therapeutic plasma exchange for coronavirus disease-2019 triggered cytokine release syndrome; a retrospective propensity matched control study. PLoS One. 2021;16:e0244853.
32. Dai X, Zhang Y, Yu L, Jiang YA, Chen L, Chen Y, et al. Effect of artificial liver blood purification treatment on the survival of critical ill COVID-19 patients. Artif Organs. 2021;45:762–9.
33. Khamis F, Al-Zakwani I, Al Hashmi S, Al Dowaiki S, Al Bahrani M, Pandak N, et al. Therapeutic plasma exchange in adults with severe COVID-19 infection. Int J Infect Dis. 2020;99:214–8.

34. Nusshag C, Morath C, Speer C, Kaelble F, Zeier M, Boxberger M, et al. Plasma exchange in patients with severe coronavirus disease 2019: a single-center experience. Crit Care Explor. 2021;3:e0517.
35. Gucyetmez B, Atalan HK, Sertdemir I, Cakir U, Telci L. COVID-19 study group. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. Crit Care. 2020;24:492.
36. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 2020;11:827.
37. Stahl K, Bode C, David S. First do no harm-beware the risk of therapeutic plasma exchange in severe COVID-19. Crit Care. 2020;24:363.
38. Memish ZA, Faqihi F, Alharthy A, Alqahtani SA, Karakitsos D. Plasma exchange in the treatment of complex COVID-19-related critical illness: controversies and perspectives. Int J Antimicrob Agents. 2021;57:106273.
39. Lippi G, Henry BM, Sanchis-Gomar F. Plasma Antithrombin values are significantly decreased in coronavirus disease 2019 (COVID-19) patients with severe illness. Semin Thromb Hemost. 2021;47:460–2.
40. Doevelaar AAN, Bachmann M, Hölzer B, Seibert FS, Rohn BJ, Bauer F, et al. von Willebrand factor Multimer formation contributes to Immunothrombosis in coronavirus disease 2019. Crit Care Med. 2021;49:e512–20.
41. de Prost N, Bastard P, Arrestier R, Fourati S, Mahévas M, Burrel S, et al. Plasma exchange to rescue patients with autoantibodies against type I interferons and life-threatening COVID-19 pneumonia. J Clin Immunol. 2021;41:536–44.
42. Prozan L, Shusterman E, Ablin J, Mitelpunkt A, Weiss-Meilik A, Adler A, et al. Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 compared with influenza and respiratory syncytial virus infection. Sci Rep. 2021;11:21519.
43. Qun S, Wang Y, Chen J, Huang X, Guo H, Lu Z, et al. Neutrophil-to-lymphocyte ratios are closely associated with the severity and course of non-mild COVID-19. Front Immunol. 2020;11:2160.
44. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med. 2021;384:1503–16.
45. Moitra VK, Guerra C, Linde-Zwirble WT, Wunsch H. Relationship between ICU length of stay and long-term mortality for elderly ICU survivors. Crit Care Med. 2016;44:655–62.
46. Shemin D, Briggs D, Greenan M. Complications of therapeutic plasma exchange: a prospective study of 1,727 procedures. J Clin Apher. 2007;22:270–6.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Management system of home transfusion in Japan: A nationwide survey in 2019

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Abstract

Background and Objectives: In Japan, there are various opinions on the pros and cons of home transfusion because of safety concerns. We hence aimed to elucidate the safety and availability of home transfusion in Japan, which has not been clarified to date.

Materials and Methods: Clinics throughout Japan that provide home care and have experience in performing blood transfusions were surveyed. The analysis period was February to December 2019. Basic information about the clinics, their collaboration system with core hospitals, storage method of red blood cells (RBCs) and the system for the management of patient information regarding transfusion reactions were investigated.

Results: Detailed information was obtained regarding the implementation of home transfusions by 51 clinics. The proportion of home care clinics performing home transfusions was 17.6%, and they were more frequently performed in urban regions. Approximately half of the clinics collaborated with a core hospital for emergency responses to transfusion reactions. At 84% of the clinics, RBC units were stored in refrigerators that were not exclusively allocated to blood storage. Nurses and family members were involved as patient attendants in 83% and 77% of the home transfusions, respectively. No serious transfusion reactions were reported among the 150 patients in 2019, nor the 623 patients up to 2018.

Conclusion: From data on its availability and safety, home transfusions are considered to be in the developing phase in Japan. Increased cooperation between hospitals and clinics is crucial towards improving the home transfusion system in Japan in the future.

Keywords

blood storage, collaboration system, home transfusion, transfusion management system

Highlights

- The availability of home transfusion services is currently low in Japan.
- Problems were identified in blood storage methods and in collaboration systems between core hospitals and clinics, and there was imbalance between cost and reimbursement.
- No serious transfusion reactions were reported in the 773 home transfusion patients analysed.

INTRODUCTION

In Japan, the need for home transfusion has increased in recent years, owing to the government's policy of promoting home care. In addition, the proportion of older people (individuals aged 65 years or older) in Japan is the highest in the world, at 28.0% in 2019 [1]. Moreover, there is an urgent need to control insurance-covered medical costs, which have been increasing in recent years. Transfusion therapy is usually carried out in hospitals as inpatient or outpatient care because of the possibility of serious transfusion reactions. However, in many countries, home transfusion is regarded as an easily accessible and convenient treatment for frail patients and patients with difficulty walking. Moreover, it is potentially cost-efficient, as patients do not require hospitalization.

Japan's healthcare system enables universal access to medical institutions, and the system of registering with a family doctor has not been legislated. Consequently, effective referral systems between general practitioners and medical specialists in core hospitals are still lacking [2]. Home transfusion fees are inclusive and based on the amount of blood transfused, in accordance with hospital transfusions. Therefore, the storage and transport of blood products and the time spent at the patient's home, which are associated with home transfusions, are not reflected in the cost. Furthermore, even if a cooperative system is established with blood transfusion specialists at core hospitals and local clinics, the specialists cannot charge reimbursements under the current system. Accordingly, these costs are covered by the clinic's budget. A particular challenge for home nursing stations is the lack of reimbursement for the long hours spent at the patients' homes. A common model of home transfusion in Japan includes only an arrangement between a clinic and a regional blood centre. General practitioners are solely responsible for home transfusions, and hence they must organize and manage all steps of the transfusion service, including pre-transfusion testing, ordering blood products, temperature control of the blood products and arranging for nursing staff to monitor transfusion reactions. Only the Japanese Red Cross Society provides blood services in Japan, and there are no blood banks in hospitals. A blood centre is expected to issue blood products that meet the recommended regulations and standards for transfusion management and implementation [3, 4]. Transfusion specialists in core hospitals usually only have minimal collaborations with doctors of clinics, assisting them at times of emergency, including severe transfusion reactions of a patient. Most nurse practitioners are trained to provide blood transfusion work in hospitals and are hence, rarely assigned to home nursing stations. Furthermore, as laboratory technicians are not usually employed by clinics, and blood centres do not perform routine pre-transfusion testing, blood group and crossmatch testing must be outsourced to registered clinical laboratories. Moreover, an outside monitoring system has not been mandated, and hence the true state of home transfusion in Japan remains unclear.

Thus, the Japan Society of Transfusion Medicine and Cell Therapy launched a proposal named Red Blood Cell Transfusion in Home (released in October 2017; excerpts are shown in Table 1) to promote

future improvements in the transfusion implementation system in Japan. The guidelines were determined based on the guidelines and evidence from the United States and countries in Europe [5–11]. The guidelines focused on patient safety and stated the importance of strict temperature control of blood products. The above guidelines of Western countries also stated that it was essential to control blood products within an appropriate temperature range. In Japan, the amount of platelet units transfused at home is approximately 10% of that of red blood cells (RBCs), and plasma is rarely used in the home transfusion setting [12]. Therefore, the Japanese guidelines initially included the use of only RBCs. In this study, with the aim of improving home transfusion care in Japan, we investigated the current state of home transfusion in Japan and evaluated its safety and availability.

MATERIALS AND METHODS

Study background

This study was conducted as a part of the 2019 Health and Labour Science Research entitled 'Comprehensive management system of blood transfusion in the community'. The study group consisted of transfusion specialists from teaching hospitals and clinics, experts from blood centres and a director of a public health centre. The survey and questionnaire were designed and reviewed by these experts, to clarify the problems and to improve the safety of home transfusion in the local healthcare setting.

Study design

Candidate clinics were extracted from a database of the Japanese Red Cross Society, which is the sole manufacturer of blood products in Japan. The database did not include information on whether the clinics performed transfusions on an outpatient basis or at home. Therefore, clinics that provide home healthcare were determined from the clinics' websites. Clinics included those specializing in home healthcare and those that provide both outpatient and home healthcare.

Clinics in all 47 prefectures of Japan were included in the survey. The survey was sent by mail to clinics in January 2019 with a written request. The survey period was from February to November 2019, and survey questionnaires were collected by mail until June 2020. The survey forms were sent out before the survey period in the hope that the survey itself would have an improvement effect.

The full text of the survey is shown in the Data S1 (https://figshare.com/s/77a1537dfcd20f32c9d8). Survey items were generated based on the Japanese guidelines, experts' opinions, a literature review and background factors of transfusion practice in Japan. The survey was prepared in a systematic manner. Experts in various fields, including home healthcare, haematology and transfusion medicine, were consulted in the preparation process. The survey was first tested on two clinic physicians who were acquaintances of the experts before being widely implemented. The primary evaluation item was the proportion of home care clinics performing home transfusions. The secondary evaluation items were the rate of compliance with the guidelines and the extent of the establishment of a haemovigilance system. The survey included two parts. The first part (section A) consisted of items regarding the transfusion management system and safety of home transfusions through 2018 in each facility. The second part (section B) was regarding in-depth data of the patients who received home transfusions in 2019. The first part included questions regarding the facilities that the clinics collaborated with for the implementation of home transfusion and for emergency responses to transfusion reactions, methods for the storage and transport of RBCs, and the average time required for crossmatch testing. Moreover, the number of annual cases of home transfusion and serious transfusion reactions experienced through 2018 was also included. The second part contained the patients' characteristics (such as age group, underlying diseases, reasons for transfusion and physical condition), the specialty of the physician in charge and the purpose of the transfusion. Questions regarding the haemovigilance system included the period of observation by the patient's attendant at the patient's home, the number of cooperators attending to the patient, whether there were any transfusion reactions and the details of these reactions, and how the transfusion reaction information was managed. In section B, data of each patient were included only once; however,

TABLE 1 Red blood cell transfusions performed at home (excerpts)

1. Target diseases
   - Chronic diseases (blood/malignant diseases, kidney diseases, gastrointestinal diseases, anaemia in patients with difficulty visiting hospitals and cared for at home, etc.).
   - Terminal phase (depends on the condition of individual patients).
2. Conditions of implementation
   - The patient must have a history of transfusion for the disease that is presently requiring transfusion and be confirmed to have had no serious adverse events at the time of the previous transfusions, in principle.
   - There is no other treatment that can improve the condition other than transfusion.
   - The patient has no disease in which transfusion is likely to induce serious adverse events and is in a stable condition.
   - The patient must be awake and alert, cooperative, and able to appropriately inform others regarding physical symptoms, in principle.
   - There must be a 'patient attendant' who can stay at the patient's home and observe the patient even after the doctor and nurse have left the patient's home.
   - It is desirable that the healthcare professionals that implement the home transfusion can be contacted 24 h a day.
   - If home transfusion is implemented, it is desirable to have home transfusion conferences that are attended by multiple professionals involved in the home transfusions, including the physician in charge, nurses, staff of the home-visit nursing station, and care manager.

Note: These guides were developed by Task Force on Transfusion Therapy in Small Facilities, Guidelines Committee of the Japan Society of Transfusion Medicine and Cell Therapy, in October 2017. The full text is available on the Society's website (in Japanese).

the request document asked clinics to include all episodes of transfusion reactions. Data of each patient were collected prospectively. Detailed information of the patients will be presented in a separate manuscript.

Ethics

The study was approved by the Institutional Review Board of Tokyo Medical University (study approval no. T2018-0048).

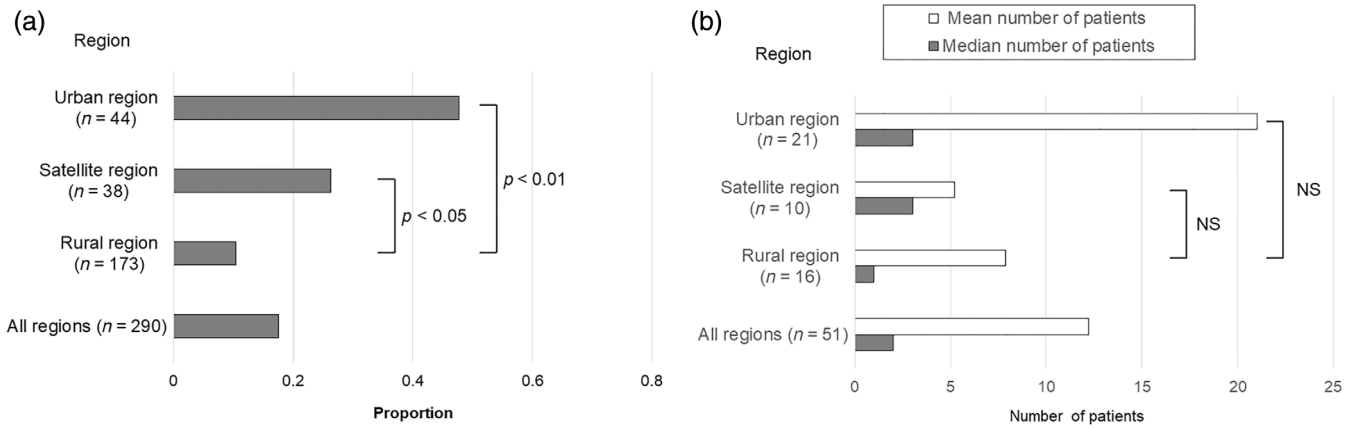

FIGURE 1 Home transfusions performed by clinics in different types of regions in Japan. The proportions of clinics providing home transfusions (a) and the number of patients per facility receiving home transfusions reported during the 2019 survey period (b) among different types of regions in Japan. NS, not significant

TABLE 2 Basic information of the clinics providing home transfusions

Item	Urban region ($n = 21$)	Satellite region ($n = 10$)	Rural region ($n = 18$)	Total[a] ($n = 51$)
Cooperating facilities for the implementation of home transfusions				
Core hospitals	10 (48%)	5 (50%)	10 (56%)	26 (51%)
Clinical laboratories	16 (76%)	8 (80%)	13 (72%)	39 (76%)
Blood centres	13 (62%)	8 (80%)	12 (67%)	35 (69%)
Home-visit nursing stations	15 (71%)	7 (70%)	12 (67%)	35 (69%)
Cooperating hospitals for emergency responses to transfusion reactions				
Core hospitals	13 (62%)	3 (30%)	9 (50%)	25 (49%)
Emergency hospitals	5 (24%)	4 (40%)	2 (11%)	11 (22%)
None	2 (10%)	4 (40%)	6 (33%)	14 (27%)
Time required for obtaining results of crossmatching test				
Less than 3 h	4 (19%)	3 (30%)	9 (50%)	16 (31%)
3 h to within that day	9 (43%)	6 (60%)	7 (39%)	23 (45%)
The next day	8 (38%)	1 (10%)	2 (11%)	12 (24%)
Refrigerator for the storage of red blood cells (RBCs)				
Blood bank refrigerator	6 (29%)	0	1 (6%)	8 (16%)
Refrigerator for medicines	6 (29%)	7 (70%)	11 (61%)	24 (47%)
Others	9 (43%)	3 (30%)	6 (33%)	19 (37%)
Method of transporting RBCs to the patient's house				
With gel ice pack	16 (76%)	8 (80%)	9 (50%)	35 (69%)
With ice	0	0	3 (17%)	3 (6%)
Without refrigerant	4 (19%)	2 (20%)	4 (22%)	10 (20%)
Using portable refrigerator for blood	0	0	1 (6%)	1 (2%)
Experiences of serious transfusion reactions				
Number of experiences	None among 402 cases	None among 52 cases	None among 126 cases	None among 623 cases

Note: The sum of each category may not equal the number of clinics, because some clinics did not respond to some items.
[a]There were two clinics with unknown geographic locations.

TABLE 3 Monitoring system for transfusion reactions in patients undergoing home transfusions

Item	Urban region ($n = 79$)	Satellite region ($n = 38$)	Rural region ($n = 27$)	Total[a] ($n = 150$)
Patient attendant monitoring transfusion reactions (multiple choices allowed)				
A nurse from a clinic	49 (62%)	19 (50%)	11 (41%)	85 (57%)
A nurse from a home-visit nursing station	58 (73%)	17 (45%)	11 (41%)	87 (58%)
A family member	63 (80%)	31 (82%)	20 (74%)	115 (77%)
An acquaintance	1 (1%)	0	1 (4%)	2 (1%)
Observation period by patient attendant				
30 min or less	4 (5%)	0	8 (30%)	12 (8%)
31–120 min	3 (4%)	0	5 (19%)	8 (5%)
Until the end of the transfusion	31 (39%)	15 (39%)	7 (26%)	59 (39%)
Until the night of that day	6 (8%)	1 (3%)	1 (4%)	8 (5%)
Until the next morning	35 (44%)	21 (55%)	5 (19%)	61 (41%)
Recording method of transfusion reactions				
Medical charts with information from a nurse	64[b] (81%)	14 (37%)	22 (81%)	100 (67%)
Medical charts with information from patient/family	19 (24%)	20 (53%)	4 (15%)	43 (29%)
Paper reports	1 (1%)	4 (11%)	0	5 (3%)
Digital reports	3 (4%)	0	0	8 (5%)
No record	2 (3%)	0	1 (4%)	4 (3%)
Transfusion reactions				
Number of patients	0	0	0	0

Note: The sum of each category may not equal the number of clinics, because some clinics did not respond to some items.
[a]There were six clinics with unknown geographic locations.
[b]In 11 cases, information was obtained from both a nurse and a family member.

Statistical analysis

Numerical data were analysed by the Mann–Whitney *U*-test, and categorical data were analysed by the Fisher's exact test and the chi-square test. A *p*-value of less than 0.05 was considered to indicate a statistically significant difference between groups. SPSS Statistics 27 software (IBM Corporation) was used for statistical analyses.

RESULTS

Obtained responses

Of the 856 clinics to which the questionnaires were sent, 290 (33.9%) responded, and 51 answered that they provided a home transfusion service (17.6% of all clinics that responded to the questionnaire). Detailed information on 150 patients receiving home transfusions was obtained.

Availability and cooperating systems for home transfusion services

The surveyed areas were classified into three regions, namely urban regions (4 large prefectures, i.e., Tokyo, Aichi, Osaka and Fukuoka), satellite regions (7 prefectures neighbouring the prefectures containing large cities, i.e., Saitama, Chiba, Kanagawa, Gifu, Shizuoka, Kyoto and Hyogo) and rural regions (the other 36 prefectures). A comparison of the proportion of clinics implementing home transfusions in each region showed significantly higher proportions in the urban and satellite regions (Figure 1a). Although the mean number of home transfusion patients per clinic tended to be higher in the urban regions, the difference was not statistically significant (Figure 1b).

Whereas 70%–80% of the clinics collaborated with clinical laboratories, blood centres and home-visit nursing stations, only 50% of them collaborated with core hospitals for the implementation of home transfusion (Table 2). Thirty per cent of the clinics were not collaborating with a specific hospital for emergency responses to transfusion reactions.

Furthermore, almost half of the clinics required 3 h or more to obtain crossmatch testing results, whereas only 30% of clinics required less than 3 h.

Transfusion management systems

Only eight clinics (16%) stored RBCs in a blood bank refrigerator, and the other clinics stored them in a refrigerator for medicines and other items (Table 2). A blood bank refrigerator was used significantly more frequently in urban regions than in other regions ($p < 0.05$). The temperature of the RBCs was controlled during transport to the patient's house using a gel ice pack at 70% of the clinics and using ice at 6% of

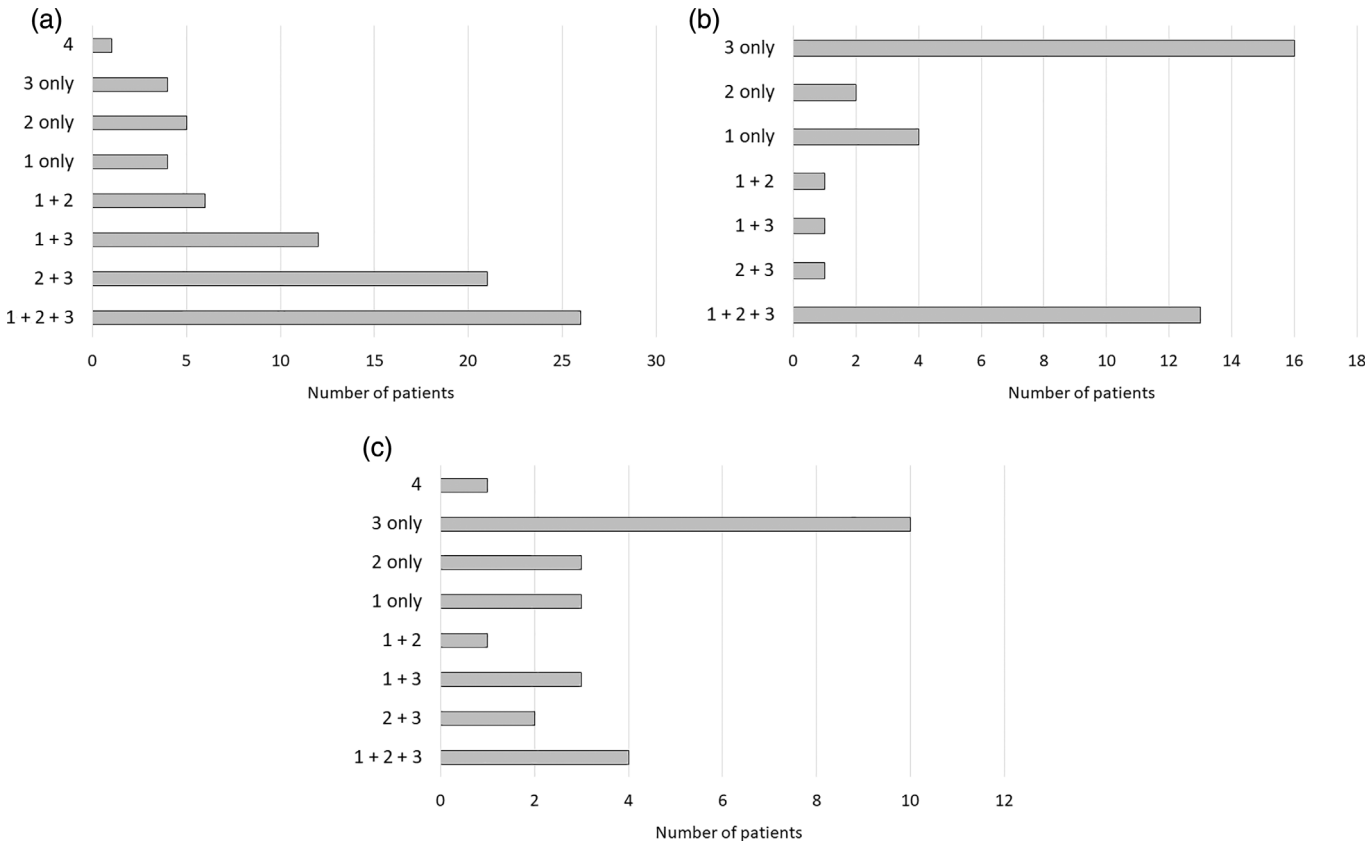

FIGURE 2 Patient attendants for home transfusions among different types of regions in Japan. Patient attendants of home transfusions in urban regions (a), satellite regions (b), and rural regions (c). In the legend shown at the bottom of the figures, 1 indicates a nurse from a clinic, 2 indicates a nurse from a home-visit nursing station, 3 indicates a family member and 4 indicates an acquaintance. Multiple numbers indicate each type of person that was involved

TABLE 4 Suggestions for improving home transfusions

1. Revision of the Japanese guidelines for home transfusion.
2. Training of home care personnel in transfusion techniques.
3. Revision of the health insurance system commensurate with costs.
4. Promotion of collaboration between clinics and core hospitals.
5. Establishment of a supervising system to ensure the safety of home transfusions.

the clinics, whereas 20% of the clinics transported RBCs without refrigeration. No regional differences were found in the method of transporting RBCs to patients' houses.

Monitoring system for transfusion reactions

Almost equal numbers of nurses from clinics and home-visit nursing stations acted as patient attendants during home transfusions (Table 3). Both types of nurses were involved in 41% of the transfusions in urban regions, 37% in satellite regions and 19% in rural regions (Figure 2). Only one type of nurse was involved in 6% of the transfusions in urban regions, 15% in satellite regions, and 22% in rural regions. Family members acted as attendants for 77% of the patients and were more likely to be solely responsible for observing transfusion reactions in rural and satellite regions (Table 4).

The observation period for possible transfusion reactions differed greatly from patient to patient. Specifically, 10% of patients were observed for 30 min or less, 37% were observed until the end of the transfusion and 41% were observed until the next morning. Rural regions had a significantly higher rate of observation periods of 30 min or less ($p < 0.01$) and a lower rate of observations until the end of the transfusion ($p < 0.05$). Furthermore, family members were significantly less likely to be involved in observation until the next morning in rural regions ($p < 0.05$).

Two-thirds of the information regarding transfusion reactions was obtained from the nurses and documented in paper medical records. On the other hand, only 30% of the same information from family members was obtained and documented by nurses, and reports were prepared for less than 10% of them in total.

No transfusion reactions were reported in the 150 patients reported in 2019. There were also no serious transfusion reactions reported in the 623 patients up to 2018. Consequently, no serious transfusion reactions were observed in the 773 home transfusion patients in this survey.

DISCUSSION

In this study, we found that the proportion of clinics that implemented home transfusions in Japan in 2019 was 17.6%, which was similar to that reported in a previous survey conducted by the Japanese Academy of Home Care Physicians [13]. This suggests that facilities providing home transfusion services in Japan have not markedly increased from the survey in 2011 [13].

Availability and cooperating systems for home transfusion services

In the present survey, the proportion of clinics providing home transfusion services was higher in urban and satellite regions than in rural regions, and this was thought to reflect an increase in the older population in these areas. In a survey of patients at the end stage of advanced cancer, the distance from home to the hospital, a low Quality Of Life level and previous experience of home care were reported to be important factors in determining whether they requested home transfusion [14]. One reason for the low rate of home blood transfusion in rural regions may be the distance from the patient's home and the hospitals that provide emergency care for patients with severe transfusion reactions. In Japan, few regional core hospitals have a division that is in charge of home care, and hence clinics need to develop a close partnership with hospitals in case of emergencies. Therefore, improving the cooperation between clinics performing home transfusions and core hospitals and reducing the burden on home care physicians is expected to promote home transfusions.

Transfusion management systems

In home transfusions, it is necessary to strictly control the temperature of the blood products as in the hospital. The importance of temperature control of blood products is also highlighted in the guidelines mentioned above. RBCs were, however, not stored in a blood bank refrigerator at many clinics, and temperature management of the RBCs was considered to have been inadequate in 84% of the clinics. In Japan, as the number of patients receiving home transfusions per clinic is small, strict temperature control of the RBCs may not be recognized as an important issue. The higher rate of use of blood bank refrigerators in urban regions may reflect differences in the perceptions of the physicians in charge and the financial situations of the clinics.

The storage temperature of RBCs is specified as 1 or 2–6°C in the United States, Europe and Japan [3, 15, 16], and must be constantly monitored to remain in this range. These regulations are mainly designed to prevent bacterial growth and preserve RBC function, and clinic physicians should be reminded of the significance of temperature control. In particular, continuous temperature control is essential and should be emphasized in Japan's home transfusion guide.

An appropriate refrigerant was not used for the transport of RBCs to the patients' homes in 20% of the clinics. The transport method of RBCs used by these clinics is hence inappropriate unless the patient's home is located very close to the clinic.

To improve the entire system for the storage and management of blood products in Japan, it would be effective to have a licensing system as in the United States [17, 18]. As transfusion therapy in Japan does not currently require a licence, it may be practical to have an official checklist stating the essential requirements. In addition, a consultation system by transfusion specialists is also worth considering as an initiative to increase the number of clinics performing home transfusions. In New York State, the approval of out-of-hospital transfusion therapy is based on an agreement between the director of the blood bank and the director responsible for implementing transfusions [17]. Although there are approximately 2300 clinics in Japan that perform blood transfusions, only a small proportion of these clinics also perform home transfusions. There are also various limitations to the implementation of home transfusion, including wide variations in clinic physicians' views regarding home transfusion, as well as financial constraints, and hence, it is difficult to manage all transfusions. Therefore, it is crucial to develop a system that enhances collaboration between transfusion specialists and clinic physicians to continually improve patient safety. Moreover, holding multidisciplinary conferences would also be helpful, as indicated in Table 1.

As it often takes several hours or longer to obtain crossmatch test results, collaboration with hospital transfusion departments for transfusion testing should also be encouraged in the future.

System for the management of transfusion reactions

In the present survey, no transfusion reactions that required emergency responses were observed in a total of 623 patients through 2018, and even mild adverse reactions were not reported in the 150 patients in 2019. Consequently, it is assumed that the lack of reported transfusion reactions is associated with short observation periods, particularly in rural regions. Furthermore, more than half of the patients receiving home transfusions were observed until only the end of the transfusion, which suggests a lack of awareness that adverse reactions can occur in the post-transfusion period.

Adverse reactions have been reported after home and palliative transfusions at frequencies of 1.5%–2.6% [19–22], and hence, a system for the appropriate detection and recording of adverse reactions should be developed. In addition, improving the monitoring system for transfusion reactions will require the establishment of cost-effective reimbursement methods [23]. For developing an efficient home transfusion system, there is an urgent need to revise the Japanese guidelines in line with the current situation and to train home care personnel in blood transfusion techniques.

Strengths and limitations

The strength of this study is that it is the first in-depth study of home blood transfusions in Japan. We believe that the findings of this

survey will be useful for promoting clinical practices, research and problem-solving for home transfusions. It must, however, be noted that this study was retrospective, and the number of cases was less. The key uncertainties are clinical and methodological heterogeneity. In particular, serious transfusion reactions were not specifically defined, and their criteria remained at the discretion of the attending physicians.

In conclusion, home transfusion practice is considered to be in the developmental stage in Japan. These data demonstrate that whereas home transfusion is more readily available in large cities, there are disparities in its implementation among individual clinics. Improvements in the collaboration system with core hospitals and temperature management of blood products are key issues for promoting and improving the quality of home transfusion in Japan.

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CONFLICT OF INTEREST

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

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REFERENCES

1. Health Nutrition and Population Statistics by Wealth Quintile, World Bank Group [cited 2021 Nov 27]. Available from: https://databank.worldbank.org/reports.aspx?source=2&series=SP.POP.65UP.TO.ZS
2. Okamoto E, Miyamoto M, Hara K, Yoshida J, Muto M, Hirai A, et al. Integrated care through disease-oriented clinical care pathways: experience from Japan's regional health planning initiatives. Int J Integr Care. 2011;11:e125.
3. Guideline for blood products (revised version). Available from: https://www.mhlw.go.jp/new-info/kobetu/iyaku/kenketsugo/5tekisei3b.html
4. Implementation Guidelines for transfusion therapy. Available from: https://www.jsaweb.jp/modules/news_topics/index.php?content_id=456
5. Anderson K, Benson K, Glassman A, Fridey JL, Kasprisin CA, Issitt LAM, et al. Guidelines for home transfusion. Bethesda, MD: American Association of Blood Banks; 1997.
6. Guidelines for Home Transfusion.pdf May 2014 Version 2.0 (Nova Scotia Provincial Coordinating Blood Program). Available from: http://www.cdha.nshealth.ca/search/apachesolr_search/home%20transfusion
7. Benson K, Popovsky MA, Hines D, Hume H, Oberman HA, Glassman AB, et al. Nationwide survey of home transfusion practices. Transfusion. 1998;38:90–6.
8. Benson K. Blood transfusions in the home sweet home: how to avoid a sour outcome. Cancer Control. 1997;4:364–7.
9. Craig JI, Milligan P, Cairns J, McClelland DB, Parker AC. Nurse practitioner support for transfusion in patients with haematological disorders in hospital and at home. Transfus Med. 1999;9:31–6.
10. Fridey JL. Practical aspects of out-of-hospital transfusion. Am J Clin Pathol. 1997;107:S64–71.
11. Ademokun A, Kaznica S, Deas S. Home blood transfusion: a necessary service development. Transfus Med. 2005;15:219–22.
12. Data collection of the survey of blood products use in fiscal year 2020. Available from: http://yuketsu.jstmct.or.jp/wp-content/uploads/2021/05/b02c3b3630c1dc791731b4e29c9ff9c5.pdf (in Japanese).
13. Suzuki H, Ishigaki Y, Fujita A, Mori K. Questionnaire survey of home transfusion. J Jpn Assoc Home Care Med. 2011;12:107–12. (in Japanese).
14. Havet N, Morelle M, Remonnay R, Carrere MO. Cancer patients' willingness to pay for blood transfusions at home: results from a contingent valuation study in a French cancer network. Eur J Health Econ. 2012;13:289–300.
15. Guide to the preparation, use and quality assurance of blood components. European Committee on Blood Transfusion, European directorate for the quality of medicines and healthcare. 2020.
16. The Association for the Advancement of Blood & Biotherapies. Standards Program Committee. Standards for Blood Banks and Transfusion Services. 31st ed. Bethesda, MD: AABB; 2022.
17. Limited transfusion services. New York State: Department of Health, Wadsworth Center. 2021. Available from: https://www.wadsworth.org/regulatory/blood-program/limited-transfusion-services
18. Mckenna DJ. Standards for out-of-hospital transfusion administration services. 1st ed. Maryland, USA: Association for the Advancement of Blood & Biotherapies; 2018.
19. To TH, To LB, Currow DC. Can we detect transfusion benefits in palliative care patients? J Palliat Med. 2016;19:1110–3.
20. Martinsson U, Lundström S. The use of blood transfusions and erythropoietin-stimulating agents in Swedish palliative care. Support Care Cancer. 2009;17:199–203.
21. García D, Aguilera A, Antolín F, Arroyo JL, Lozano M, Sanroma P, et al. Home transfusion: three decades of practice at a tertiary care hospital. Transfusion. 2018;58:2309–19.
22. To THM, LeBlanc TW, Eastman P, Neoh K, Agar MR, To LB, et al. The prospective evaluation of the net effect of red blood cell transfusions in routine provision of palliative care. J Palliat Med. 2017;20:1152–7.

23. Charron J, Gouëzec H, Bajeux E. Home blood transfusion in France: benefits and development terms. Transfus Clin Biol. 2019;26:304–8.

SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Blood component ratios in children with non-traumatic life-threatening bleeding

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Abstract

Background and Objectives: In paediatric trauma patients, there are limited prospective data regarding blood components and mortality, with some literature suggesting decreased mortality with high ratios of plasma and platelets to red blood cells (RBCs) in massive transfusions; however, most paediatric massive transfusions occur for non-traumatic aetiologies and few studies assess blood product ratios in these children. This study's objective was to evaluate whether high blood product ratios or low deficits conferred a survival benefit in children with non-traumatic life-threatening bleeding.

Materials and Methods: This is a secondary analysis of the five-year, multicentre, prospective, observational massive transfusion epidemiology and outcomes in children study of children with life-threatening bleeding from US, Canadian and Italian medical centres. Primary interventions were plasma:RBC and platelets:RBC (high ratio ≥1:2 ml/kg) and plasma and platelet deficits. The primary outcome was mortality at 6 h, 24 h and 28 days. Multivariate logistic regression models were used to determine independent associations with mortality.

Results: A total of 222 children were included from 24 medical centres: 145 children (median [interquartile range] age 2.1 years [0.3–11.8]) with operative bleeding and 77 (8.0 years [1.2–14.7]) with medical bleeding. In adjusted analyses, neither blood product ratios nor deficits were associated with mortality at 6 h, 24 h or 28 days.

Conclusion: This paper addresses a lack of prospective data in children regarding optimal empiric massive transfusion strategies in non-traumatic massive haemorrhage and in finding no decrease in mortality with high plasma or platelet to RBC ratios or lower deficits supports an exploratory analysis for mortality.

Keywords

haemorrhage, massive, non-traumatic, paediatric, ratios, transfusion

Highlights

- In children requiring massive transfusions for non-traumatic indications, neither high ratios of plasma and platelets to red blood cells nor low deficits of platelets and plasma are independently associated with decreased mortality at 6 h, 24 h or 28 days.

Callie Marshall and Cassandra D. Josephson are co-primary authors.

- Optimal empiric transfusion strategies for children with life-threatening haemorrhages may differ depending on aetiology: medical, operative or traumatic.
- Massive transfusions in children with non-traumatic bleeds are rare but associated with high mortality; thus, more studies are needed to understand the best blood product approaches.

INTRODUCTION

Life-threatening bleeding in children is uncommon but associated with significant morbidity and mortality [1–3]. Although traumatic injury accounts for more deaths in the paediatric population than any other cause, an international survey of predominantly large, academic medical centres found that more than half of paediatric massive transfusion protocol (MTP) activations stem from non-traumatic bleeding [4]. The initial paper from the massive transfusion epidemiology and outcomes in children (MATIC) study supported this finding in demonstrating 46% trauma, 34% operative and 20% medical indications [1]. The 28-day and in-hospital mortality rates after massive transfusion range from 35% to 65% depending on the aetiology of the bleed [1, 2, 5–7].

Despite the staggering mortality rate, the literature on transfusion strategies for paediatric non-traumatic life-threatening bleeding is sparce [4, 8, 9]. Current management of children with life-threatening bleeding is modelled after damage control resuscitation (DCR), a well-established strategy for haemorrhaging adult trauma patients. Its central tenet is balanced haemostatic resuscitation, either with a blood component-based approach with high ratios of plasma and platelets to red blood cells (RBCs) or low titre group O whole blood with minimization of crystalloids [10, 11]. DCR targets the lethal triad of hypothermia, acidosis and coagulopathy known to herald death in trauma resuscitation [11, 12]. Contrastingly, operative and medical bleeds begin in a controlled setting and include a variety of aetiologies, including gastrointestinal extracorporeal membrane oxygenation (ECMO) complications and cardiothoracic surgeries [1, 4]. Therefore, a one size fits all approach extrapolating adult trauma blood product studies to non-traumatic bleeds in children may not be effective.

Even in adults, only a small subset of massive transfusion studies extends beyond the trauma bay, predominantly to gastrointestinal bleeds and cardiothoracic surgeries. These studies suggest a possible benefit in short- [13] and long-term [14, 15] survival with higher plasma:RBC or platelet:RBC. One study in paediatric burn excisions found that higher ratios correlated with decreased blood product administration after surgery but did not evaluate mortality [16]. The primary objective of this secondary analysis of the MATIC study was to evaluate the independent association of ratios and deficits of plasma and platelets to RBCs to mortality in children with non-traumatic life-threatening bleeding to address this gap in paediatric massive transfusion literature.

MATERIALS AND METHODS

We conducted a secondary analysis of a prospective, multicentre, observational study of children with life-threatening bleeding at 24 children's hospitals in the United States, Canada and Italy between January 2014 and October 2018. Children aged 0 through 17 were eligible if they received greater than 40 ml/kg of total blood products over 6 h (literature suggests 40 ml/kg as an inflection point, after which mortality increases in children with traumatic injury) [17]. Data extracted included demographics, blood type, vital signs, Glasgow Coma Scale (GCS), laboratory values related to coagulation and end-organ function, blood products and haemostatic adjuncts, Pediatric Risk of Mortality score (PRISM III), complications (acute respiratory distress syndrome, sepsis and acute kidney injury [AKI]) and mortality at 6 h, 24 h and 28 days.

This paper analysed children with non-traumatic bleeding, divided into operative (44% cardiothoracic, 15% neurosurgical, 14% general surgery, 7% liver transplant, 3% including otolaryngology/plastic surgery, obstetrics/gynaecology and orthopaedics, 8% 'other' and 14% procedural [biopsies and catheterizations]) and medical (32% gastrointestinal, 18% sepsis, 12% oncologic and 36% 'other') bleeds. Data regarding specific aetiologies described as 'other' were not recorded [1]. 69.9% of operative patients and 82.0% of medical were transfused under MTP [1]. Patients on ECMO were categorized as operative or medical by proximate cause of haemorrhage. Details regarding this cohort have been previously published [1]. An analysis of blood product ratios and deficits in children with traumatic injury from this dataset is detailed in a separate publication [18].

Data before the haemorrhage were gathered in the 24 h before the start of the bleed, and data during the event spans initiation (MTP activation or administration of first blood product if not under MTP) to the conclusion (MTP deactivation or last product with no more in the subsequent 60 min). Data collected after the haemorrhage span the 12 h after event conclusion. Only data collected during the life-threatening bleeding were used to calculate ratios and deficits.

Children were excluded if MTP was activated, but no blood products were transfused, or if they had multiple life-threatening bleeds. Patients were excluded from plasma:RBC analyses if plasma was not transfused, and from platelet:RBC analyses if platelets were not transfused. Blood product ratios were calculated by dividing plasma or platelet (in millilitres per kilogram) by RBC (in millilitres per kilogram). A high ratio was defined as >1:2 plasma:RBC or platelet:RBC as this cut-off is commonly used in transfusion studies, including the pragmatic, randomized optimal platelet and plasma ratios study [10, 19]. Product deficits were calculated as the volume (in millilitres per kilogram) of RBCs minus the volume of plasma or platelets.

Research ethics

This study was conducted under the waiver of informed consent granted by each participating centre's institutional review board.

Statistical analysis

Data were described as counts, percentages, medians and interquartile ranges as appropriate. Tests of association included chi-square for categorical measures and Mann–Whitney *U* for continuous. Many of the pretreatment measures considered as potential confounders had substantial amounts of missing data; thus, we could not meet the assumption of missing at random and did not perform multiple imputation models. Instead, we considered measures with no more than 10% of values missing and regressed these on each mortality endpoint. Any measure associated with mortality ($p < 0.2$) was considered for the multivariate logistic regression models unless there was evidence of collinearity ($r > 0.6$) with potential confounders. Because of listwise deletion, measures were excluded from the final model if including them reduced the sample size by more than 10%. Some categorical measures were excluded if there were too few events to estimate an odds ratio. Statistical significance is defined as $p < 0.05$. Analyses were conducted with Stata Statistical Software, Version 16 (StataCorp, College Station, TX, USA).

Covariates considered for inclusion in the operative model included age, sex, PRISM III, heart disease, mechanical ventilation, cardiac arrest, vasoactive drugs, upper gastrointestinal bleeding, renal disease, haemofiltration, and administration of any component, adjunct or fluid. In the medical cohort, the same measures were considered in addition to white blood cell count, haemoglobin, haematocrit and highest blood urea nitrogen.

RESULTS

A total of 222 children met inclusion criteria, with 145 (65%) experiencing operative bleeding and 77 (35%) medical.

Operative bleeding

Among children with operative bleeding, 67 (46%) had high-plasma ratios and 35 (24%) high-platelet ratios (Table 1). For children with operative bleeding, there were no differences in demographics between high and low plasma:RBC, but the high ratio group had lower platelet counts (98 vs. 155 $\times 10^9$/L, $p = 0.04$) before the event (Table 1). The high-platelet ratio group was younger in median years (0.3 vs. 3.2) and was more likely to receive cryoprecipitate (71.4% vs. 31.9%) or recombinant factor VIIa (31.4% vs. 21.7%).

While there were no differences in complications between plasma high and low ratio groups, in the unadjusted analysis of platelet:RBC, the high ratio group had a higher incidence of AKI ($p = 0.003$) (Table 2).

Medical bleeding

Within the medical cohort, 53 (69%) had a high-plasma ratio and 21 (27%) a high-platelet ratio. Children receiving high plasma:RBC ratios for medical bleeding had lower pre-event GCS (12 vs. 14) (Table 3), and children who received high platelet:RBC were younger (2.2 years vs. 10) (Table 3).

The high platelet:RBC group had a higher median plasma:RBC ratio (Table 4), but children in the high plasma:RBC group did not have significant differences in the volume of platelets or median platelet:RBC ratio (Table 4). There were no differences in transfusion-related complications between the ratio groups.

Multivariate analysis

In the multivariate analysis, after adjusting for the potential confounders shown in the table, high ratios of plasma or platelets to RBC and low

TABLE 1 Demographics and severity of injury measures before life-threatening haemorrhage in children with operative bleeding

	Plasma:RBC ($n = 145$)			Platelet:RBC ($n = 145$)		
	High (≥1:2), ($n = 67$)	Low (<1:2), ($n = 78$)	*p*-value	High (≥1:2), ($n = 35$)	Low (<1:2), ($n = 110$)	*p*-value
Age (year)[a]	2.7 (0–12)	2.0 (0–13)	0.9	0.3 (0–8)	3.2 (0–13)	**0.02**
Male, *n* (%)	35 (52.2)	39 (50.0)	0.8	14 (40.0)	60 (54.5)	0.1
White, *n* (%)	44 (78.6)	43 (63.2)	0.1	24 (77.4)	63 (67.7)	0.4
Hispanic, *n* (%)	12 (19.7)	8 (12.3)	0.3	3 (9.7)	17 (17.9)	0.3
Pediatric Risk of Mortality III[a]	11.0 (6–2)	11.0 (6–17)	0.4	15.0 (7–21)	11.0 (5–17)	0.2
Age-adjusted hypotension, *n* (%)	38 (58.5)	40 (55.6)	0.7	22 (64.7)	56 (54.4)	0.3
Lowest temperature (°C)[a]	36.0 (35–37)	36.2 (36–37)	0.1	36.3 (35–37)	36.1 (36–38)	1.0
Lowest Glasgow Coma Scale[a]	14.5 (6–15)	10.0 (3–15)	0.3	15.0 (6–15)	12.5 (3–15)	0.2
Base excess (mmol/L)[a]	−0.3 (−4 to 5)	0.4 (−4 to 6)	0.7	1.2 (−4 to 5)	−0.6 (−4 to 7)	0.9
Lowest platelets ($\times 10^9$/L)[a]	98 (73–222)	155 (93–245)	**0.04**	117 (62–226)	136 (89–238)	0.3
Lowest haemoglobin (g/dl)[a]	9.6 (7–11)	10.0 (8–12)	0.08	10.5 (9–12)	9.6 (8–11)	0.06
Highest international normalized ratio[a]	1.5 (1–2)	1.4 (1–2)	0.3	1.4 (1–2)	1.4 (1–2)	0.9
Extracorporeal membranous oxygenation, *n* (%)	14 (18.2)	11 (12.6)	0.32	6 (15.8)	19 (15.1)	0.92

Abbreviation: RBC, red blood cell.
[a]Median (interquartile range).
Note: Bold value indicates the statistically significant.

TABLE 2 Interventions during and outcomes after massive transfusion by high and low plasma and platelets to red blood cells (RBCs) for children with operative bleeding

	Plasma:RBC			Platelets:RBC		
	High (≥1:2) ($n = 67$)	Low (<1:2) ($n = 78$)	*p*-value	High (≥1:2) ($n = 35$)	Low (<1:2) ($n = 110$)	*p*-value
Blood products/adjuncts						
RBCs (ml/kg)[a]	47.1 (25–75)	56.6 (24–109)	0.3	47.1 (22–75)	58.3 (28–103)	0.2
Plasma (ml/kg)[a]	39.1 (22–73)	9.04 (0–25)	**<0.0001**	33.5 (18–49)	19.6 (4–48)	0.06
Platelets (ml/kg)[a]	17.0 (7–38)	10.4 (0–28)	0.053	41.9 (23–65)	8.3 (0–21)	**<0.0001**
Any cryoprecipitate, *n* (%)	35 (52.2)	33 (42.3)	0.2	25 (71.4)	43 (31.9)	**0.0008**
Any recombinant factor VIIa, *n* (%)	12 (7.9)	13 (16.7)	0.84	11 (31.4)	14 (12.7)	**0.01**
Any tranexamic acid, *n* (%)	5 (7.5)	4 (5.1)	0.6	3 (8.6)	6 (5.5)	0.5
Complications						
Acute respiratory distress syndrome, *n* (%)	17 (25.4)	19 (24.4)	0.9	12 (34.3)	24 (21.8)	0.14
Sepsis, *n* (%)	4 (6.0)	9 (11.5)	0.2	2 (5.7)	11 (10.0)	0.4
Acute kidney injury, *n* (%)	23 (34.3)	19 (24.4)	0.2	17 (48.6)	25 (22.7)	**0.003**
Mortality						
Died within 6 h, *n* (%)	3 (4.5)	4 (5.2)	0.9	1 (2.9)	6 (5.6)	0.5
Died of haemorrhage within 6 h, *n* (%)	**3 (100)**	**4 (100)**		**1 (100)**	**6 (100)**	
Died within 24 h, *n* (%)	6 (9.1)	9 (11.7)	0.6	3 (8.6)	12 (11.1)	0.7
Died of haemorrhage within 24 h, *n* (%)	**6 (100)**	**8 (88.9)**	**0.4**	**3 (100)**	**11 (91.7)**	**0.6**
Died within 28 days, *n* (%)	14 (21.2)	19 (24.7)	0.6	7 (20.0)	26 (24.1)	0.6
Died of haemorrhage within 28 days, *n* (%)	**14 (21.20)**	**19 (24.7)**	**0.6**	**7 (20.0)**	**13 (50.0)**	**0.7**

[a]Median (interquartile range).
Note: Bold value indicates the statistically significant.

TABLE 3 Demographics and severity of injury measures before life-threatening haemorrhage in children with medical bleeds

	Plasma:RBC ($n = 77$)			Platelet:RBC ($n = 77$)		
Characteristic	High (≥1:2) ($n = 53$)	Low (<1:2) ($n = 24$)	*p*-value	High (≥1:2) ($n = 21$)	Low (<1:2) ($n = 56$)	*p*-value
Age (year)[a]	8.2 (2–15)	7.6 (1–15)	0.7	2.2 (0–13)	10.5 (2–15)	**0.03**
Male, *n* (%)	26 (49.1)	8 (33.3)	0.2	11 (52.4)	23 (41.1)	0.4
White, *n* (%)	34 (73.9)	11 (55.0)	0.3	13 (68.4)	32 (68.1)	0.8
Hispanic, *n* (%)	3 (6.5)	2 (9.1)	0.7	2 (10.5)	3 (6.1)	0.5
Pediatric Risk of Mortality III[a]	19.0 (12–24)	17.5 (11–23)	0.8	21.0 (16–27)	18.0 (12–23)	0.2
Age-adjusted hypotension, *n* (%)	31 (62.0)	19 (79.2)	0.1	15 (71.4)	35 (66.0)	0.7
Lowest temperature (°C)[a]	36.2 (35–37)	36.2 (35–37)	0.9	36.4 (35–37)	36.2 (36–37)	0.8
Lowest Glasgow Coma Scale[a]	12.0 (3–14)	15.0 (14–15)	**0.045**	13.5 (8–15)	13.5 (3–15)	0.9
Base excess (mmol/L)[a]	1.2 (−5 to 11)	0.2 (−16 to 5)	0.098	1.4 (−6–0.5)	1.1 (−7–0.13)	0.8
Lowest platelets ($\times 10^9$/L)[a]	38.0 (19–152)	85.0 (26–134)	0.1	35.5 (19–92)	54.5 (20–159)	0.3
Lowest haemoglobin (g/dl)[a]	8.0 (6–9)	8.2 (6–10)	0.4	8.6 (6–11)	7.4 (6–9)	0.2
Highest international normalized ratio[a]	1.9 (2–4)	1.5 (1–2)	0.1	1.9 (1–4)	1.7 (1–3)	0.5
Extracorporeal membranous oxygenation, *n* (%)	8 (14.3)	2 (7.1)	0.34	3 (13.0)	7 (11.5)	0.84

Abbreviation: RBC, red blood cell.
[a]Median (interquartile range).
Note: Bold value indicates the statistically significant.

deficits were not associated with mortality (Table 5). For both plasma and platelet ratios, PRISM III and ECMO were associated with increased mortality at 28 days. Although none of the ratio associations reached statistical significance, all odds ratios for mortality in patients with medical bleeds were greater than one. In the operative cohort, the opposite non-significant trend was present: odds ratios less than one.

TABLE 4 Interventions during and outcomes after massive transfusion by high and low plasma and platelet to red blood cell (RBC) ratios for children with medical bleeding

	Plasma:RBC			Platelets:RBC		
	High (≥1:2) ($n = 53$)	Low (<1:2) ($n = 24$)	*p*-value	High (≥1:2) ($n = 21$)	Low (<1:2) ($n = 56$)	*p*-value
Blood products/adjuncts						
RBCs (ml/kg)[a]	27.3 (19–52)	36.2 (20–100)	0.2	22.9 (15–40)	28.8 (20–68)	0.5
Plasma (ml/kg)[a]	25.2 (16–46)	6.3 (0–22)	**0.0004**	27.5 (16–39)	18.3 (8–51)	0.3
Platelets (ml/kg)[a]	10.7 (4–20)	11.4 (4–21)	0.6	19.8 (14–36)	7.3 (0–16)	**0.0001**
Any cryoprecipitate, *n* (%)	21 (39.6)	8 (33.3)	0.6	9 (42.9)	20 (35.7)	0.6
Any recombinant factor VIIa[a]	9 (17.3)	4 (16.7)	0.9	4 (19.0)	9 (16.4)	0.8
Any tranexamic acid, *n* (%)	5 (9.4)	3 (12.5)	0.7	1 (4.8)	7 (12.5)	0.3
Platelet:Red blood cells[a]	0.3 (0.1–0.7)	0.22 (0.2–0.4)	0.2	0.77 (0.7–1.0)	0.20 (0.0–0.3)	**<0.0001**
Complications						
Acute respiratory distress syndrome, *n* (%)	13 (24.5)	5 (20.8)	0.7	6 (28.6)	12 (21.4)	0.5
Sepsis, *n* (%)	9 (17.0)	6 (25.0)	0.4	4 (19.0)	11 (19.6)	1.0
Acute kidney injury, *n* (%)	15 (28.3)	10 (41.7)	0.2	9 (42.9)	16 (28.6)	0.2
Mortality						
Died within 6 h, *n* (%)	15 (28.3)	5 (20.8)	0.5	6 (28.6)	14 (25.0)	0.8
Died of haemorrhage within 6 h, *n* (%)	**15 (100)**	**4 (80.0)**	**0.08**	**6 (100)**	**13 (92.9)**	**0.5**
Died within 24 h, *n* (%)	19 (35.8)	7 (29.2)	0.6	10 (47.6)	16 (28.6)	0.2
Died of haemorrhage within 24 h, *n* (%)	**18 (94.7)**	**5 (71.4)**	**0.1**	**9 (90.0)**	**14 (87.5)**	**0.8**
Died within 28 days, *n* (%)	36 (67.9)	13 (54.2)	0.2	15 (71.4)	34 (60.7)	0.4
Died of haemorrhage within 28 days, *n* (%)	**23 (63.9)**	**6 (46.2)**	**0.3**	**9 (60.0)**	**20 (58.8)**	**0.9**

[a]Median (interquartile range).

TABLE 5 Multivariate logistic regression for mortality outcomes at 6 h, 24 h and 28 days in children with operative and medical bleeding

	6-h mortality			24-h mortality			28-day mortality		
Covariates	Odds ratio	Confidence interval	*p*-value	Odds ratio	Confidence interval	*p*-value	Odds ratio	Confidence interval	*p*-value
Operative									
Plasma/RBC ≥ 1:2	0.87	0.2–4.0	0.9	0.76	0.3–2.2	0.6	0.82	0.4–1.8	0.6
Platelet/RBC ≥ 1:2	0.50	0.06–4.3	0.5	0.75	0.2–2.8	0.7	0.79	0.3–2.0	0.6
Plasma deficit	0.99	0.99–1.0	0.8	1.00	0.99–1.0	0.4	1.00	0.99–1.0	0.2
Platelet deficit	0.99	0.99–1.01	0.7	1.00	0.99–1.0	0.4	1.00	1.0–1.0	0.06
Medical									
Plasma/RBC ≥ 1:2	1.50	0.5–4.7	0.5	1.36	0.5–3.9	0.6	1.79	0.7–4.8	0.2
Platelet/RBC ≥ 1:2	1.20	0.4–3.7	0.8	2.27	0.8–6.4	0.1	1.62	0.5–4.8	0.4
Plasma deficit	1.00	0.99–1.0	0.9	1.00	0.98–1.0	0.5	1.00	1.0–1.0	0.4
Platelet deficit	1.00	0.99–1.0	0.6	1.00	1.0–1.0	0.8	1.00	0.99–1.0	0.8

Note: Covariates in operative plasma and platelet ratio models: PRISM III, cardiac arrest, extracorporeal membrane oxygenation and congenital heart disease (CHD). Covariates in operative plasma and platelet deficit models: PRISM III, cardiac arrest, haemofiltration, any blood component, vasoactive drug, hypotension and CHD. Covariates in plasma and platelet ratio models: age, PRISM III, cardiac arrest, highest blood urea nitrogen and gastrointestinal bleed. Covariates in plasma and platelet deficit models: age, sex, highest respiratory rate, haemoglobin and PRISM III.
Abbreviation: RBC, red blood cell.

DISCUSSION

This secondary analysis of the MATIC cohort found no improvement in 6-h, 24-h or 28-day mortality among children with operative or medical bleeding when administered high plasma:RBC or high platelet:RBC, nor were there associations between mortality and lower plasma or platelet deficits. This is the first multicentre, prospective data to evaluate the effect of transfusion

ratios and deficits in children with non-traumatic life-threatening bleeding.

In a separate MATIC analysis of children with traumatic injury, higher plasma:RBC was independently associated with reduced mortality at 6 h and greater plasma deficits with increased mortality at 6 and 24 h [18]. The authors posited that the increase in 24-h mortality with greater plasma deficits without equivalent findings with ratios was due to ratios' inability to account for the product volume. In this analysis of non-traumatic bleeding, however, we did not find any difference in mortality analysed by ratios or deficits.

In trauma-induced coagulopathy, hypoperfusion and endothelial dysfunction from tissue damage constitute prime drivers in the complex cascade causing fibrinolysis, platelet dysfunction and systemic anticoagulation [19]. In operative bleeding, however, the extent of endothelial damage could be less pervasive, considering the controlled nature of surgeries. In non-traumatic bleeding, hypoperfusion is more likely to be rapidly corrected as opposed to traumatic hypoperfusion that can persist unattenuated in the field before medical aid arrival. The observed lack of mortality benefit with higher relative plasma and platelet volumes in non-traumatic haemorrhage may relate to the amelioration of these mechanisms that herald traumatic coagulopathy.

Operative bleeding is also likely addressed via immediate surgical haemostasis, which can outweigh the impact of blood components. Furthermore, the plurality of procedures in this cohort was cardiothoracic; thus, children might have been on cardiopulmonary bypass, often monitored intra-operatively with modalities like activated clotting times, anti-Xa assays and viscoelastic-based testing to guide tailored product selection [20].

By considering the heterogeneity of pathophysiologies and procedures in non-traumatic bleeding, a goal-directed, individualized approach could target clotting derangements and limit unnecessary product transfusion. Studies suggest a superiority of viscoelastic monitoring (VEM) to conventional coagulation tests in describing multifactorial clot formation [21]. In children, goal-directed studies are mostly perioperative, predominantly cardiothoracic, and suggest goal-directed resuscitation with thromboelastography (TEG) or rotational thromboelastometry (ROTEM) may improve morbidity [22] and reduce blood product volume [20, 23]. While adult mortality data in non-traumatic VEM-guided transfusions are limited and inconclusive [3, 24, 25], to the best of the authors' knowledge, no paediatric studies have evaluated mortality. Medical patients who were more thrombocytopenic at baseline but failed to improve with increased platelet:RBC or decreased deficits could benefit from these tests of platelet function. In our study, TEG/ROTEM data were insufficient to include in the analysis.

Children with medical haemorrhage had the highest mortality and the fewest patients. Even among adults, evidence is sparse and primarily limited to gastrointestinal bleeding, for which there is no consensus on blood components [9, 22]. One study in adults with non-traumatic haemorrhage demonstrated higher platelet and plasma ratios in patients with greater haemostatic lab abnormalities but no mortality association [26]. Our study's small sample size also makes interpretation of the trend towards increased mortality with high ratios in medical patients and decreased mortality in operative patients difficult to interpret. A single-centre study of adult non-traumatic massive transfusion found an increase in mortality in medical and non-cardiothoracic, non-vascular surgery patients with *low* ratios [27]. A 2018 meta-analysis of plasma ratios included only two non-trauma studies, one cardiac surgery and one vascular, and showed lower ratios associated with greater mortality at 24 h and 30 days [28]. These discrepancies demonstrate the need for larger studies in both medical and operative paediatric life-threatening bleeding.

Regarding the increased incidence of AKI in children with operative bleeding receiving high platelet:RBC, the literature is mostly in cardiothoracic surgeries. Thrombocytopaenia and AKI are common after cardiopulmonary bypass, and the magnitude of platelet nadir correlates with AKI severity [29]. Haematologic complications also nearly triple the odds of developing AKI after cardiopulmonary bypass in children [30]. Therefore, the relationship between high platelet:RBC and AKI is likely not causal but rather likely reflects thrombocytopaenia associated with AKI leading to increased platelet administration.

Strengths of this study include its prospective design and inclusion of multiple large academic centres in and outside of the United States. Importantly, this is the first study to evaluate blood product ratios for life-threatening medical bleeding in children and the first multicentre study in paediatric operative bleeding. Furthermore, this study reports products in millilitres per kilogram instead of units, as this is standard paediatric dosing. Finally, although data were collected before, during and after transfusion, the analysis evaluated only blood products delivered during the life-threatening haemorrhage.

Limitations of this study include small sample sizes, particularly among medical patients, making multivariate analyses less reliable, and precluding analysis of the data by age groups to account for the range of haemostatic development from infancy to adolescence. Furthermore, although the data were remarkably complete for the most pertinent variables (blood products and mortality), some lab values were missing; thus, the covariates could not be evaluated. Among the incomplete data, cause of death other than haemorrhage was missing; therefore, we are unable to comment on deaths due to central nervous system or multiorgan failure. Other potential covariates, such as the use of anticoagulation and measures of cardiothoracic surgical complexity, were not included in the data collection. Finally, due to the observational nature of the data, we cannot determine causality.

This study suggests that in children with life-threatening bleeding, empiric massive transfusion strategies associated with decreased mortality may differ for trauma, operative and medical patients. It is difficult to make broad recommendations for management of life-threatening haemorrhage, particularly in patients with medical bleeds; thus, treatment should be individualized to the child's evolving disease process, medications and comorbidities. Future studies could evaluate mortality with goal-directed therapies using viscoelastic assays and explore the effects of haemostatic adjuncts, including factor VIIa, fibrinogen concentrates and cryoprecipitate. The pathophysiology of traumatic haemorrhage differs from that in operative and medical settings—two broad categories of bleeding which in and of themselves

have significant differences—and considering the high mortality with paediatric massive transfusions, more research, including clinical trials are warranted to identify blood product relationships to maximize survival in a child acutely decompensating due to non-traumatic exsanguination.

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C.D.J., J.C.L., C.M.L. and P.C.S. supervised the research, conceptualized and executed the original study, analysed the data and reviewed the manuscript. S.R.W. created the study design, supervised the analysis and reviewed the manuscript. J.C.L. conducted statistical analyses and reviewed the manuscript. C.M. authored the manuscript, analysed data, and contributed to methods of analysis. *Group Information for the MATIC Investigators*: Christine Allen, MD, Fabrizio Chiusolo, MD, Adrienne L. Davis, MD, MSc, Robert A. Finkelstein, MD. Julie C. Fitzgerald, MD, PhD, MSCE, Barbara A. Gaines, MD, Susan M. Goobie, MD, FRCPC, Sheila J. Hanson, MD, MS, Hilary A. Hewes, MD, Laurie H. Johnson, MD, MS, Mark O. McCollum, MD, Jennifer A. Muszynski, MD, MPH, Alison B. Nair, MD, Robert B. Rosenberg, MD, PhD, Thomas M. Rouse, MD, Athina Sikavitsas, DO, Marcy N. Singleton, MSN, Marie E. Steiner MD, MS, Jeffrey S. Upperman, MD, Adam M. Vogel, MD, Hale Wills, MD, MS, Margaret K. Winkler, MS, MD.

CONFLICT OF INTEREST

Dr Spinella is a consultant for Secure Transfusion Services, Hemanext and Haima; Dr Leonard receives royalty payments from UpToDate; Dr Josephson is a consultant for Immucor, Octapharma and Cellphire, and has an unrestricted grant from Medtronics. The remaining authors have no conflicts to declare.

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REFERENCES

1. Leonard JC, Josephson CD, Luther JF, Wisniewski SR, Allen C, Fabrizio C, et al. Life-threatening bleeding in children: a prospective observational study. Crit Care Med. 2021;49:1943–54.
2. Kamyszek RW, Leraas HJ, Reed C, Ray CM, Nag UP, Poisson JL, et al. Massive transfusion in the pediatric population: a systematic review and summary of best-evidence practice strategies. J Trauma Acute Care Surg. 2019;86:744–54.
3. Wikkelso A, Wetterslev J, Moller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev. 2016;9:CD007871.
4. Thomasson RR, Yazer MH, Gorham JD, Dunbar NM. International assessment of massive transfusion protocol contents and indications for activation. Transfusion. 2019;59:1637–43.
5. Hwu RS, Spinella PC, Keller MS, Baker D, Wallendorf M, Leonard JC. The effect of massive transfusion protocol implementation on pediatric trauma care. Transfusion. 2016;56:2712–9.
6. Chidester SJ, Williams N, Wang W, Groner JI. A pediatric massive transfusion protocol. J Trauma Acute Care Surg. 2012;73:1273–7.
7. Hendrickson JE, Shaz BH, Pereira G, Parker PM, Jessup P, Atwell F. Implementation of a pediatric trauma massive transfusion protocol: one institution's experience. Transfusion. 2012;52:1228–36.
8. McDaniel LM, Etchill EW, Raval JS, Neal MD. State of the art: massive transfusion. Transfus Med. 2014;24:138–44.
9. Tucci M, Crighton G, Goobie SM, Russell RT, Parker RI, Haas T. Plasma and platelet transfusion strategies in critically ill children following noncardiac surgery and critically ill children undergoing invasive procedures outside the operating room. Pediatr Crit Care Med. 2022;23:e50–62.
10. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313:471–82.
11. Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma. 2007;62:307–10.
12. Giannoudi M, Harwood P. Damage control resuscitation: lessons learned. Eur J Trauma Emerg Surg. 2016;42:273–82.
13. Etchill EW, Myers SP, McDaniel LM, Rosengart MR, Raval JS, Triulzi DJ, et al. Should all massively transfused patients be treated equally? An analysis of massive transfusion ratios in the nontrauma setting. Crit Care Med. 2017;45:1311–6.
14. Unlu A, Yilmaz S, Akbasli IT, Karaagac Akyol T, Akkapulu N, Tumer M. MATRA-A: a study on massive transfusion. Vox Sang. 2021;116:880–6.
15. Johansson PI, Stensballe J. Hemostatic resuscitation for massive bleeding: the paradigm of plasma and platelets—a review of the current literature. Transfusion. 2010;50:701–10.
16. Galganski LA, Greenhalgh DG, Sen S, Palmieri TL. Randomized comparison of packed red blood cell to fresh frozen plasma transfusion ratio of 4:1 vs 1:1 during acute massive burn excision. J Burn Care Res. 2017;38:194–201.
17. Neff LP, Cannon JW, Morrison JJ, Edwards MJ, Spinella PC, Borgman MA. Clearly defining pediatric massive transfusion: cutting through the fog and friction with combat data. J Trauma Acute Care Surg. 2015;78:22–8.
18. Spinella P, Leonard J, Marshall C, Luther J, Wisniewski S, Josephson C, et al. Transfusion ratios and deficits in injured children with life-threatening bleeding. Pediatr Crit Care Med. 2022;23:235–44.
19. Christiaans SC, Duhachek-Stapelman AL, Russell RT, Lisco SJ, Kerby JD, Pittet JF. Coagulopathy after severe pediatric trauma. Shock. 2014;41:476–90.
20. Machovec KA, Joose EH. Pediatric transfusion algorithms: coming to a cardiac operating room near you. J Cardiothorac Vasc Anesth. 2019;33:2017–29.
21. Cohen T, Haas T, Cushing MM. The strengths and weaknesses of viscoelastic testing compared to traditional coagulation testing. Transfusion. 2020;60:S21–8.
22. Donovan K, Stanworth S, Jairath V. The optimal use of blood components in the management of gastrointestinal bleeding. Best Pract Res Clin Gastroenterol. 2019;42–43:101600.
23. Nakayama Y, Nakajima Y, Tanaka KA, Sessler DI, Maeda S, Lida J, et al. Thromboelastometry-guided intraoperative haemostatic management reduced bleeding and red cell transfusion after paediatric cardiac surgery. Br J Anaesth. 2015;114:91–102.
24. Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. Ann Surg. 2016;263:1051–9.

25. Baksaas-Aasen K, Gall LS, Stensballe J, Juffermans NP, Curry N, Maegele M, et al. Viscoelastic haemostatic assay augmented protocols for major trauma haemorrhage (ITACTIC): a randomized, controlled trial. J Intensive Care Med. 2021;47:49–59.
26. Matzek LJ, Kurian EB, Frank RD, Weister TJ, Gajic O, Kor D, et al. Plasma, platelet and red blood cell transfusion ratios for life-threatening non-traumatic hemorrhage in medical and post-surgical patients: an observational study. Vox Sang. 2022;117:361–70.
27. Mesar T, Larentzakis A, Dzik W, Chang Y, Velhamos G, Yeh DD. Association between ratio of fresh frozen plasma to red blood cells during massive transfusion and survival among patients without traumatic injury. JAMA Surg. 2017;152:574–80.
28. Rahouma M, Kamel M, Jodeh D, Kelley T, Ohmes LB, Biasi AR, et al. Does a balanced transfusion ratio of plasma to packed red blood cells improve outcomes in both trauma and surgical patients? A meta-analysis of randomized controlled trials and observational studies. Am J Surg. 2018;216:342–50.
29. Tew S, Fontes ML, Greene NH, Kertai MD, Ofori-Amanfo G, Jaquiss RDB, et al. Natural history of nonimmune-mediated thrombocytopenia and acute kidney injury in pediatric open-heart surgery. Paediatr Anaesth. 2017;27:305–13.
30. Sethi SK, Goyal D, Yadav DK, Shukla U, Kajala PL, Gupta VK, et al. Predictors of acute kidney injury post-cardiopulmonary bypass in children. Clin Exp Nephrol. 2011;15:529–34.

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ORIGINAL ARTICLE

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Dose-dependent effects of red blood cell transfusion and case mix index on venous thromboembolic events in spine surgery

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Abstract

Background and Objectives: Venous thromboembolic (VTE) events represent a major source of morbidity and mortality in spine surgery. Our goal was to assess whether a dose–response relationship exists between red blood cell (RBC) transfusion and postoperative VTE events among spine surgery patients.

Materials and Methods: A total of 786 spine surgery patients at a single institution who received at least 1 RBC unit perioperatively were included (2016–2019). Patients were stratified based on RBC transfusion volume: 1–2 units (39.3%), 3–4 units (29.4%), 5–6 units (15.9%) and ≥7 units (15.4%). Subgroup analyses were performed after stratification by case mix index, a standardized surrogate for patients' disease severity and comorbidities. Multivariable regression was used to assess risk factors for the development of postoperative VTE events.

Results: The overall VTE event rate was 2.4% ($n = 19$). A dose–response relationship was seen between RBC transfusion volume and VTE events (1–2 units: 0.97%, 3–4 units: 1.30%, 5–6 units: 3.20%, ≥7 units: 7.44%; $p < 0.01$). Similar dose–response relationships were seen between case mix index and VTE events (1.00–3.99: 0.52%, 4.00–6.99: 2.68%, ≥7.00: 9.00%; $p < 0.01$). On multivariable regression, larger RBC transfusion volumes (adjusted odds ratio [OR] 1.18 per RBC unit, 95% confidence interval [CI] 1.07–1.29; $p < 0.01$) and higher case mix index scores (adjusted OR 1.39 per unit increase, 95% CI 1.14–1.69; $p < 0.01$) were associated with an increased risk of thrombosis.

Conclusion: Larger RBC transfusion volumes and higher case mix index scores were associated with an increased risk of VTE events. Physicians should be aware of how these dose–response relationships can influence a patient's risk of developing thrombotic complications postoperatively.

Keywords

red blood cell, spine surgery, transfusion, venous thromboembolic events, venous thromboembolism prophylaxis

Highlights

- Venous thromboembolic (VTE) events represent a significant source of morbidity and mortality among hospitalized patients undergoing spine surgery.

- A dose–response relationship exists between red blood cell transfusion and VTE events in spine surgery, as each unit of blood transfused was associated with a ~1.2-fold increased risk of thrombosis.
- Physicians should be aware of how clinical and intraoperative factors can influence a patient's risk of developing postoperative thrombotic events.

INTRODUCTION

Hospital-acquired venous thromboembolic (VTE) events are a significant source of morbidity and mortality among hospitalized patients [1–3]. These events occur when the body's normal balance between prothrombotic and antithrombotic factors becomes skewed, leading to the formation of clots in the venous circulation. Many triggers exist that predispose patients to the development of these venous clots, including malignancy, medications, immobility and surgery. Spine surgery patients, in particular, are at high risk of developing thrombotic complications due in part to their prolonged operative times and significant immobilization in the immediate postoperative period [4–10]. Given that the incidence of VTE events following spine surgery ranges from 0.3% to 31% in the published literature, it is important for physicians to identify and appropriately treat patients at high risk for these complications [11].

One known risk factor for VTE events following spine surgery is red blood cell (RBC) transfusion. Studies have demonstrated that patients receiving RBC transfusions during their hospitalization have worse outcomes, increased costs and prolonged length of stay [12], with much of the morbidity associated with infectious complications and VTE events. It has been hypothesized that the increased endothelial adherence, increased aggregability and decreased cell membrane deformability seen in stored RBCs work in concert to increase this risk of thrombosis [13–16]. While prior studies in general surgery have demonstrated a dose–response relationship between RBC transfusion and VTE events [17], no similar study has been performed among spine surgery patients. It is currently unclear whether the risk of postoperative VTE events among spine surgery patients is differentially impacted by the total number of RBC units transfused.

The purpose of this study was to assess risk factors for the development of postoperative VTE complications among patients undergoing spine surgery, with a particular focus on the potential dose–response relationship between RBC transfusion and VTE events. We hypothesize that spine surgery patients receiving larger volumes of RBCs, and those with higher comorbidity scores, would be at increased risk of developing VTE complications postoperatively.

MATERIALS AND METHODS

Study design

After Institutional Review Board (Johns Hopkins Hospital, Baltimore, MD, USA) approval with waived written informed consent, we conducted a retrospective cohort study of adult patients undergoing elective spine surgery at our institution between July 2016 and May 2019. For assessing the dose-dependent effects of RBC transfusion on VTE events, only patients who were transfused ≥1 RBC unit perioperatively were included. Patients transfused with 0 RBC units, as well as those with a history of deep vein thrombosis or pulmonary embolism who were restarted on a therapeutic dose of anticoagulation, were excluded. This resulted in a final study population of 786 patients (Figure 1).

Variables

Data were extracted from an institutional patient blood management database, which included patient characteristics, such as age, sex and race and clinical characteristics, such as American Society of Anesthesiologists (ASA) classification, case mix index, comorbidities (e.g., hypertension, renal dysfunction, obesity, diabetes mellitus, pulmonary disease and congestive heart failure) and length of stay. Case mix index (APR-DRG [all patient refined diagnosis-related group]) is used by Medicare as an index of the severity of illness and complexity of the disease and has been shown to be predictive of clinical outcomes [18]. Operative factors included operative time, the number of vertebrae operated on, the site of surgery (cervical/thoracic/lumbar) and whether patients presented with a primary indication of malignancy.

Transfusion data, including the total number of RBC units transfused, were obtained from our electronic medical record (Epic, Verona, WI, USA). The Clinical Analytics team at Johns Hopkins Hospital regularly performs quality control for these data sources by comparing electronic medical record data with institutional blood bank data. Additional perioperative characteristics, including tranexamic acid administration and estimated intraoperative blood loss, were also obtained from the electronic medical record (Epic, Verona, WI, USA).

Stratifications

Patients were primarily stratified into four categories based on the total number of RBC units transfused: (1) 1–2 units, (2) 3–4 units, (3) 5–6 units and (4) ≥7 units. We intentionally chose to analyse this as a categorical rather than continuous variable in order to increase the clinical utility of our findings.

Subgroup analyses were performed after stratification by case mix index, a validated surrogate for patients' comorbidities and

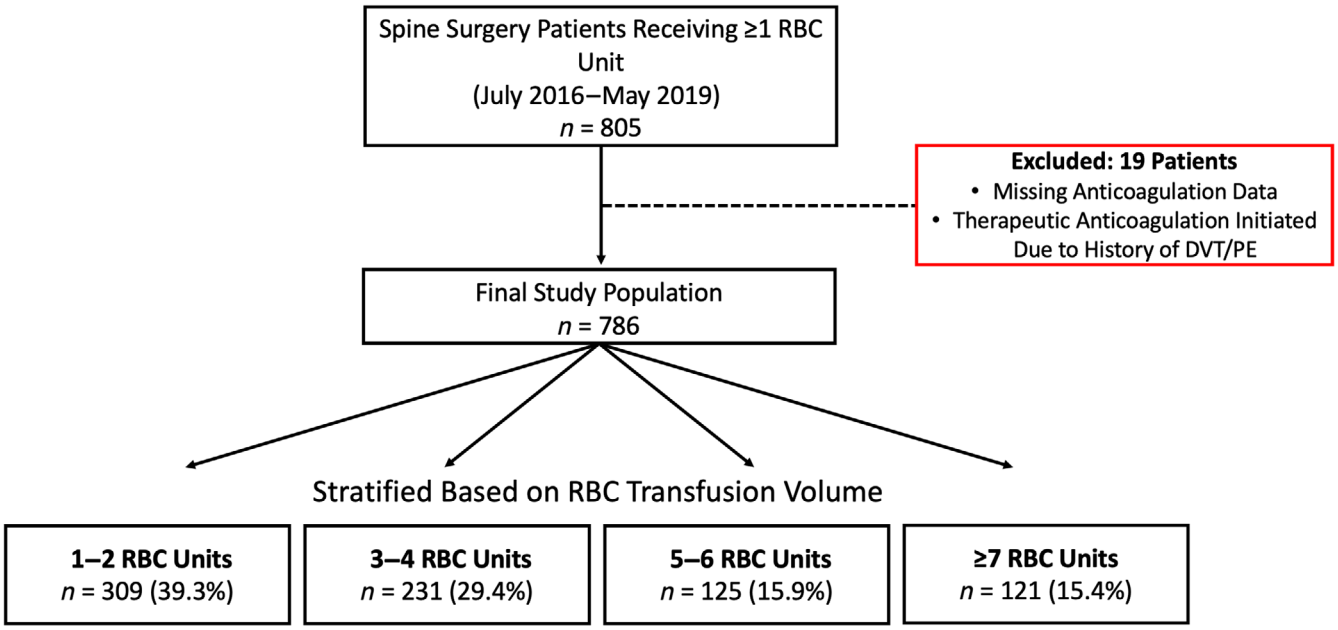

FIGURE 1 Flow diagram outlining inclusion and exclusion criteria for our population of spine surgery patients. DVT, deep vein thrombosis; PE, pulmonary embolism; RBC, red blood cell

TABLE 1 Baseline demographic characteristics of spine surgery patients, stratified by the the number of red blood cell (RBC) units transfused

	1–2 RBC units (*n* = 309)	3–4 RBC units (*n* = 231)	5–6 RBC units (*n* = 125)	≥7 RBC units (*n* = 121)	*p*-value
Age (years), mean ± SD	57 ± 19	60 ± 17	61 ± 16	59 ± 15	0.18
Male sex, *n* (%)	126 (40.8)	84 (36.4)	44 (35.2)	43 (35.5)	0.58
Race, *n* (%)					0.34
White	205 (66.3)	167 (72.3)	100 (80.0)	84 (69.4)	
Black	73 (23.6)	51 (22.1)	18 (14.4)	28 (23.1)	
Asian	12 (3.9)	4 (1.7)	1 (0.8)	1 (0.8)	
Other[a]	19 (6.1)	9 (3.9)	6 (4.8)	8 (6.6)	
ASA classification ≥3, *n* (%)	207 (67.0)	161 (69.7)	89 (71.2)	74 (61.2)	0.31
Case mix index, median (IQR)	3.5 (2.7–5.0)	4.5 (3.3–5.4)	4.9 (3.3–5.4)	5.0 (3.7–7.3)	<0.01
Comorbidities, *n* (%)					
Hypertension	15 (4.9)	16 (6.9)	11 (8.8)	2 (1.7)	0.07
Renal dysfunction	21 (6.8)	19 (8.2)	4 (3.2)	7 (5.8)	0.32
Obesity	71 (23.0)	47 (20.4)	28 (22.4)	30 (24.8)	0.80
Diabetes mellitus	35 (11.3)	22 (9.5)	11 (8.8)	5 (4.1)	0.15
Pulmonary disease	44 (14.2)	37 (16.0)	27 (21.6)	16 (13.2)	0.23
Congestive heart failure	15 (4.9)	16 (6.9)	11 (8.8)	2 (1.7)	0.07

Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range.
[a]American Indian, Alaska Native, Native Hawaiian, Other Pacific Islander or not specified.

disease severity. This composite variable has been shown to be predictive of morbidity and mortality in critically ill patients [18]. Since the median case mix index for our study population was 4.00, we stratified patients into three categories: (1) 1.00–3.99, (2) 4.00–6.99 and (3) ≥7.00.

Clinical outcomes

The primary outcome of interest was the incidence of hospital-acquired VTE events, defined based on the International Classification of Diseases, Tenth Edition (ICD-10) codes (Table S1). Both deep vein

TABLE 2 Clinical and operative characteristics of spine surgery patients, stratified by number of red blood cell (RBC) units transfused

	1–2 RBC units ($n = 309$)	3–4 RBC units ($n = 231$)	5–6 RBC units ($n = 125$)	≥7 RBC units ($n = 121$)	*p*-value
Operative time (min), mean ± SD	407 ± 132	457 ± 128	536 ± 135	544 ± 163	<0.01
Spine levels, *n* (%)					<0.01
0–2 vertebrae	30 (9.7)	10 (4.4)	2 (1.6)	6 (5.0)	
3–5 vertebrae	136 (44.2)	75 (32.6)	26 (20.8)	26 (21.5)	
6–9 vertebrae	93 (30.2)	80 (34.8)	60 (48.0)	44 (36.4)	
≥10 vertebrae	49 (15.9)	65 (28.3)	37 (29.6)	45 (37.2)	
Spine malignancy, *n* (%)	36 (11.7)	28 (12.1)	17 (13.6)	18 (14.9)	0.55
Surgical site, *n* (%)					0.82
Cervical	8 (2.6)	12 (5.2)	0 (0.0)	7 (5.8)	
Cervical/thoracic	14 (4.5)	13 (5.6)	4 (3.2)	4 (3.3)	
Thoracic	39 (12.6)	24 (10.4)	11 (8.8)	12 (9.9)	
Thoracic/lumbar	44 (14.2)	37 (16.0)	18 (14.4)	21 (17.4)	
Lumbar	26 (8.4)	18 (7.8)	9 (7.2)	7 (5.8)	
Lumbar/sacral	74 (24.0)	51 (22.1)	31 (24.8)	27 (22.3)	
Thoracic/lumbar/sacral	102 (33.0)	75 (32.5)	52 (0.42)	42 (34.7)	
Received tranexamic acid, *n* (%)	103 (33.3)	104 (45.0)	63 (50.4)	57 (47.1)	<0.01
Estimated blood loss (ml)	975 (550–1300)	1250 (850–1600)	1800 (1200–2500)	2500 (1600–3500)	<0.01
Timing of postoperative anticoagulation initiation					0.02
No anticoagulation	56 (18.1)	38 (16.5)	11 (8.8)	10 (8.7)	
0–24 h	42 (13.6)	19 (8.2)	12 (9.6)	11 (9.1)	
24–48 h	157 (50.8)	113 (48.9)	69 (55.2)	64 (52.9)	
48–72 h	37 (12.0)	44 (19.1)	21 (16.8)	23 (19.0)	
>72 h	17 (5.5)	17 (7.4)	12 (9.6)	13 (10.7)	
Number of FFP units transfused	0 (0–0)	0 (0–2)	2 (1–4)	5 (2–8)	<0.01
Number of PLT units transfused	0 (0–0)	0 (0–0)	0 (0–0)	1 (0–2)	0.03
Number of CRYO units transfused	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.06

Note: Data presented as median (interquartile range) unless otherwise specified.
Abbreviations: CRYO, cryoprecipitate; FFP, fresh frozen plasma; PLT, platelets.

thrombosis and pulmonary embolism were included as VTE events. The secondary outcome was in-hospital mortality.

Statistical analysis

Demographic, clinical and transfusion data were presented as a whole number with their respective percentages for categorical variables and as a mean and standard deviation for continuous variables. Median and interquartile range were used for data not normally distributed, as determined by histograms. Chi-square, Fisher's exact and one-way analysis of variance tests were used, as appropriate, to compare data across the RBC transfusion categories. Non-parametric Kruskal–Wallis tests were used for data not normally distributed.

With respect to the primary outcome of interest, Chi-square tests were used to compare rates of VTE events across the four RBC transfusion categories. Multivariable logistic regression models were used to assess risk factors for the development of postoperative VTE events. Clinically relevant characteristics incorporated into the model were identified a priori and chosen based on their potential association with VTE events. These variables included age, sex, obesity, case mix index, RBC transfusion volume, TXA administration, spine malignancy, the total number of vertebrae operated on and timing of postoperative anticoagulation initiation. Results of the multivariable logistic regression are presented as odds ratios (OR) with 95% confidence intervals (95% CIs). Statistical significance was defined as $p < 0.05$ (two-tailed tests). All statistical analyses were performed using JMP version 16.0 (SAS Institute, NC, USA). This manuscript adheres to the applicable STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.

RESULTS

Patient characteristics

Among our study population of 786 spine surgery patients, 39.3% ($n = 309$) received 1–2 RBC units, 29.4% ($n = 231$) received 3–4

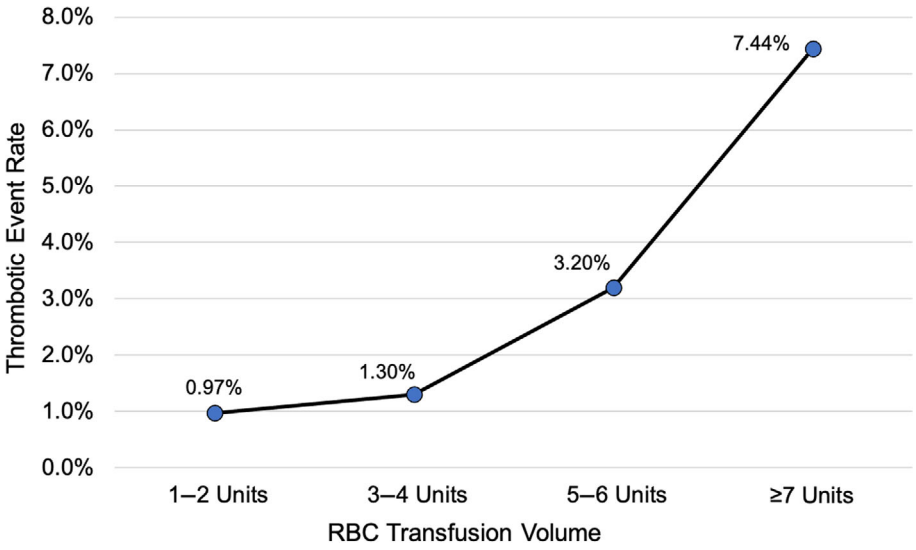

FIGURE 2 Venous thromboembolic event rates among spine surgery patients after stratification by red blood cell (RBC) transfusion volume ($p < 0.01$ for differences between groups)

RBC units, 15.9% ($n = 125$) received 5–6 RBC units and 15.4% ($n = 121$) received ≥7 RBC units (Figure 1). Our patient population was relatively balanced across age, sex, ASA classification and all comorbidities. The only significant difference was that spine surgery patients receiving more RBC units exhibited higher case mix index scores ($p < 0.01$) (Table 1). From a clinical perspective, patients receiving more RBC units also had longer procedures ($p < 0.01$), underwent more extensive procedures ($p < 0.01$) and had a higher estimated intraoperative blood loss ($p < 0.01$) (Table 2).

Since hospital-acquired VTE events were the primary outcome of interest in this study, baseline patient, clinical and operative characteristics of patients who developed VTEs, compared to those who did not, are outlined in Table S2.

Postoperative prophylactic anticoagulation

All patients received mechanical prophylaxis with sequential compression devices in the immediate postoperative period. Among patients receiving pharmacologic anticoagulation, 54.0% ($n = 362$) were started on prophylactic heparin (5000 units), while the remainder received prophylactic enoxaparin (40 mg). The majority of patients receiving heparin were on a q12 (twice a day) dosing regimen, while those receiving enoxaparin were on a q24 (daily) dosing regimen.

With respect to the timing of anticoagulation initiation, patients transfused with larger volumes of RBCs tended to exhibit a longer delay in initiating postoperative anticoagulation. For example, patients transfused with 1–2 RBC units tended to initiate anticoagulation 0–24 h postoperatively, while those transfused ≥7 RBC units tended to initiate anticoagulation ≥72 h following spine surgery (Table 2).

RBC transfusion volume and VTE events

The overall VTE event rate among our patient population was 2.4% ($n = 19$). A dose–response relationship was seen between the number of RBC units transfused and VTE events among spine surgery patients. VTE event rates were 0.97% (3 of 309) for patients receiving 1–2 RBC units, 1.30% (3 of 231) for patients receiving 3–4 RBC units, 3.20% (4 of 125) for patients receiving 5–6 RBC units and 7.44% (9 of 121) for patients receiving ≥7 RBC units ($p < 0.01$) (Figure 2). There was no statistically significant association between RBC transfusion volume and in-hospital mortality (1–2 units: 0.32%, 3–4 units: 0.87%, 5–6 units: 2.40%, ≥7 units: 0.00%; $p = 0.10$).

Case mix index and VTE events

After stratification by case mix index, 49.4% ($n = 388$) of patients had scores between 1.00 and 3.99, 37.9% ($n = 298$) had scores between 4.00 and 6.99 and 12.7% ($n = 100$) had scores ≥7.00. Higher case mix index scores were associated with increased VTE event rates. VTE event rates were 0.52% (2 of 388) for patients with case mix index scores between 1.00 and 3.99, 2.68% (8 of 298) for patients with scores between 4.00 and 6.99 and 9.00% (9 of 100) for patients with scores ≥7.00 ($p < 0.01$) (Figure 3). There was similarly a statistically significant association between higher case mix index scores and increased rates of in-hospital mortality (1.00–3.99: 0.26%, 4.00–6.99: 0.67%, ≥7.00: 3.00%; $p = 0.02$).

Multivariable analysis

After controlling for clinically relevant covariates, multivariable logistic regression demonstrated that patients transfused larger volumes of

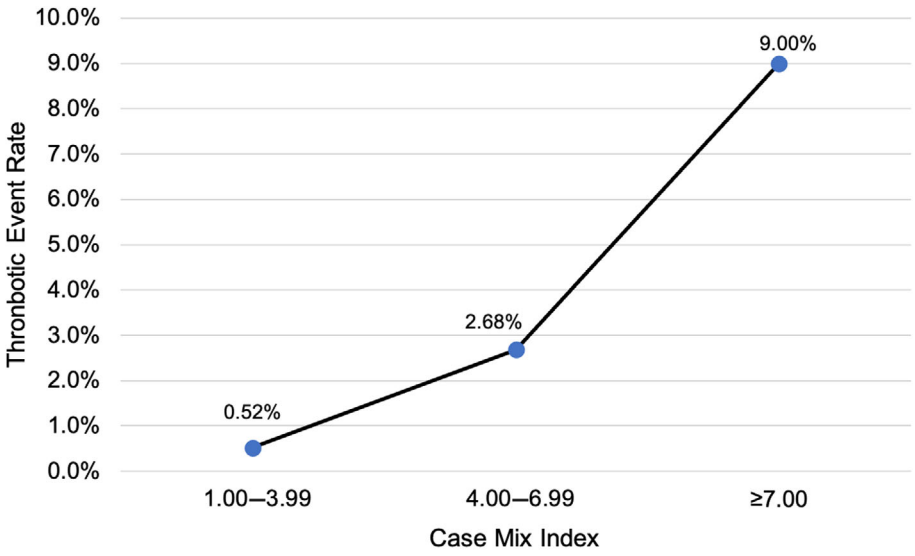

FIGURE 3 Venous thromboembolic event rates among spine surgery patients, after stratification by case mix index ($p < 0.01$ for differences between groups)

TABLE 3 Multivariable logistic regression assessing risk factors for the development of postoperative venous thromboembolic events among spine surgery patients

	Odds ratio	95% CI	*p*-value
Age (per year)	0.99	0.96–1.03	0.59
Male, sex	0.48	0.15–1.55	0.22
Obesity	1.20	0.35–4.05	0.77
Case mix index (per unit increase)	1.39	1.14–1.69	<0.01
Number of red blood cell units transfused (per RBC unit)	1.18	1.07–1.29	<0.01
Tranexamic acid administration	0.78	0.23–2.72	0.70
Spine malignancy	1.48	0.40–5.41	0.55
Number of vertebrae operated on			
0–2 vertebrae	Reference	Reference	Reference
3–5 vertebrae	1.25	0.12–12.6	0.85
6–9 vertebrae	1.14	0.11–11.3	0.92
≥10 vertebrae	0.22	0.01–3.90	0.30
Timing of postoperative anticoagulation initiation			
0–24 h	Reference	Reference	Reference
24–48 h	0.29	0.08–1.07	0.06
48–72 h	0.39	0.07–2.36	0.31
>72 h	0.84	0.17–4.19	0.84

Abbreviations: CI, confidence interval; RBC, red blood cell.

RBCs throughout their hospitalization (adjusted OR 1.18 per RBC unit, 95% CI 1.07–1.29; $p < 0.01$) and those with higher case mix index scores (adjusted OR 1.39 per unit increase, 95% CI 1.14–1.69; $p < 0.01$) were at increased risk for VTE complications (Table 3). There was no association between the timing of postoperative anticoagulation initiation and VTE event rates. Compared to spine surgery patients who initiated anticoagulation 0–24 h after surgery, patients who started anticoagulation >72 h postoperatively (adjusted OR 0.84, 95% CI 0.17–4.19; $p = 0.84$) did not experience an increased risk for VTE events. There was also no increased risk for VTE events among patients undergoing more extensive spine surgeries (Reference: 0–2 spine levels; ≥10 spine levels: adjusted OR 0.22, 95% CI 0.01–3.90; $p = 0.30$; Table 3).

DISCUSSION

Spine surgery patients receiving larger RBC transfusion volumes and those with higher case mix index scores were at a significantly increased risk of developing VTE complications postoperatively. In fact, a dose–response relationship was seen between these variables, demonstrating that the risk of postoperative VTE events may be influenced more so by the baseline characteristics of patients and intraoperative events rather than the extent of the spine surgery itself.

While prior studies have demonstrated that RBC transfusion is associated with an increased risk of composite morbidity [19], our study is one of the first to characterize the dose-dependent effects of RBC transfusion on postoperative VTE events in spine surgery. This study is an update of a preliminary study from our group that used older data (2009–2015) [20]. In the years since the publication of that project, our institution has focused significant efforts on reducing non-essential RBC transfusions through the implementation of a multidisciplinary health-system-wide patient blood management program [21]. This makes the results of the current study more relevant to clinical practice, as our data can be appropriately contextualized within the current medical landscape. The dose–response relationship seen between RBC transfusion and VTE events emphasizes the importance of balancing symptomatic anaemia and the need for transfusion with clinical outcomes when optimizing care.

In a similar vein, we also demonstrated a dose–response relationship between case mix index and postoperative VTE events among spine surgery patients. The case mix index is a standardized metric developed by Medicare and Medicaid in the United States that is representative of a patient's acuity, comorbidities, disease severity and surgical complexity [22]. Multiple studies have shown the case mix index to be predictive of morbidity, mortality and transfusion requirements [18, 23, 24]. Given this, it is understandable that spine surgery patients with higher scores would be at increased risk for VTE events, given their poorer baseline functional status and reduced physiologic reserve. Since a significant proportion of the case mix index is based on a patient's baseline health status before entering the operating room, it may be prudent for physicians to place a larger emphasis on these factors when deciding when to appropriately initiate prophylactic anticoagulation in the postoperative period.

Interestingly, the paradoxical findings in this study regarding a lack of association between delayed postoperative anticoagulation initiation (>72 h postoperatively) and VTE events may be explained by the efficacy of mechanical interventions as a means of VTE prophylaxis. One prospective study assessing patients undergoing major reconstructive spine surgery demonstrated that mechanical prophylaxis alone, with either compression stockings or compression boots, was just as efficacious as chemoprophylaxis at preventing VTE events [25]. Multiple retrospective studies have similarly reported that mechanical prophylaxis and early ambulation are effective at reducing the incidence of VTE events after spine surgery without the need for anticoagulation [26–28]. At our institution, VTE prophylaxis regimens involve mechanical prophylaxis with sequential compression devices in the immediate postoperative period for all patients. The decision on when to specifically initiate postoperative anticoagulation is based primarily on individual surgeon preference, as well as the nature and complexity of the surgery, a patient's comorbidities, and their preoperative functional status.

Taken together, it is critical that physicians understand how these individual preoperative (case mix index) and intraoperative (RBC transfusion volume) factors affect a patient's risk of developing VTE events. Given that delayed initiation of postoperative anticoagulation was not associated with an increased risk of VTE events, it will be important for physicians to ensure that anticoagulation regimens are tailored to the needs of each patient. By incorporating these clinical factors into a risk-stratification model to better predict one's risk of developing VTE events, we may be able to develop targeted interventions to reduce the associated morbidity and mortality associated with this postoperative complication.

Several limitations of this study should be recognized. First, this was a retrospective study at a single institution, which impacts the generalizability of our results. Variables either missing or unaccounted for in our database, such as smoking status, may have confounded the results of our study. Second, due to limitations associated with both our institutional database and ICD-10 coding, we were unable to determine the specific timing of each postoperative VTE event. Although the majority of transfusions occurred in the intraoperative period, it is possible that a small number of RBC units may have been transfused postoperatively after the VTE event occurred, leading to a minor overestimation of the association between RBC transfusion volume and VTE events. Furthermore, we did not analyse patients who received 0 RBC units perioperatively, and therefore, could not calculate the overall transfusion rate or VTE event rate among all spine surgery patients at our institution. We also did not assess the potential association between fresh frozen plasma (FFP) and VTE events, as our primary stratification was based on RBC transfusion volume. Since patients receiving larger numbers of RBC units were more likely to receive FFP, it was challenging to discern whether the transfusion of FFP potentially confounded our results. Finally, we acknowledge that including a broad range of spine surgery patients in this study may have led to some heterogeneity among our patient population. That being said, our results held true even after controlling for multiple clinical and operative factors, implying that our findings were independent of surgical complexity.

In summary, the overall VTE event rate among transfused spine surgery patients was 2.4%. There was a dose–response relationship between RBC transfusion volume and postoperative VTE events, as each unit of blood transfused was associated with a ~1.2-fold increased risk of thrombosis. Furthermore, patients with higher comorbidity scores, as assessed through the case mix index, also exhibited an increased risk of VTE events. It is important for physicians to be aware of how these clinical and intraoperative factors can influence a patient's risk of developing thrombotic events postoperatively.

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All authors were involved in the study design and interpretation of the data. B.D.L. and B.C.C. were responsible for analysing the data and drafting the manuscript. All authors critically revised the manuscript and approved the final version.

CONFLICT OF INTEREST

Steven M. Frank has served on a scientific advisory board for Haemonetics. Nadia B. Hensley has served on a scientific advisory board for Octapharma. All other authors declare no conflicts of interest.

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REFERENCES

1. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12:464–74.
2. Cohen A, Agnelli G, Anderson F, Arcelus J, Bergqvist D, Brecht J, et al. Venous thromboembolism (VTE) in Europe. Thromb Haemost. 2007;98:756–64.
3. Mahan CE, Borrego ME, Woersching AL, Federici R, Downey R, Tiongson J, et al. Venous thromboembolism: annualised United States models for total, hospital-acquired and preventable costs utilising long-term attack rates. Thromb Haemost. 2012;108:291–302.
4. Hohl JB, Lee JY, Rayappa SP, Nabb CE, Devin CJ, Kang JD, et al. Prevalence of venous thromboembolic events after elective major thoracolumbar degenerative spine surgery. J Spinal Disord Tech. 2015;28:E310–5.
5. Smith MD, Bressler EL, Lonstein JE, Winter R, Pinto MR, Denis F. Deep venous thrombosis and pulmonary embolism after major reconstructive operations on the spine. A prospective analysis of three hundred and seventeen patients. J Bone Joint Surg. 1994;76:980–5.
6. Kim HJ, Iyer S, Diebo BG, Kelly MP, Sciubba D, Schwab F, et al. Clinically significant thromboembolic disease in adult spinal deformity surgery: incidence and risk factors in 737 patients. Global Spine J. 2018;8:224–30.
7. Inoue H, Watanabe H, Okami H, Kimura A, Takeshita K. The rate of venous thromboembolism before and after spine surgery as determined with indirect multidetector CT. JBJS Open Access. 2018;3:e0015.
8. Schoenfeld AJ, Herzog JP, Dunn JC, Bader JO, Belmont PJ. Patient-based and surgical characteristics associated with the acute development of deep venous thrombosis and pulmonary embolism after spine surgery. Spine (Phila Pa 1976). 2013;38:1892–8.
9. Akeda K, Matsunaga H, Imanishi T, Hasegawa M, Sakakibara T, Kasai Y, et al. Prevalence and countermeasures for venous thromboembolic diseases associated with spinal surgery. Spine (Phila Pa 1976). 2014;39:791–7.
10. Oda T, Fuji T, Kato Y, Fujita S, Kanemitsu N. Deep venous thrombosis after posterior spinal surgery. Spine (Phila Pa 1976). 2000;25:2962–7.
11. Glotzbecker MP, Bono CM, Wood KB, Harris MB. Thromboembolic disease in spinal surgery. Spine (Phila Pa 1976). 2009;34:291–303.
12. Purvis TE, Goodwin CR, De la Garza-Ramos R, Ahmed AK, Lafage V, Neuman BJ, et al. Effect of liberal blood transfusion on clinical outcomes and cost in spine surgery patients. Spine J. 2017;17:1255–63.
13. Hovav T, Yedgar S, Manny N, Barshtein G. Alteration of red cell aggregability and shape during blood storage. Transfusion. 1999;39:277–81.
14. Cloney M, Dhillon ES, Roberts H, Smith ZA, Koski TR, Dahdaleh NS. Predictors of readmissions and reoperations related to venous thromboembolic events after spine surgery: a single-institution experience with 6869 patients. World Neurosurg. 2018;111:e91–7.
15. Yang S-D, Ding W-Y, Yang D-L, Shen Y, Zhang Y-Z, Feng S-Q, et al. Prevalence and risk factors of deep vein thrombosis in patients undergoing lumbar interbody fusion surgery. Medicine (Baltimore). 2015;94:e2205.
16. Wang TY, Sakamoto JT, Nayar G, Suresh V, Loriaux DB, Desai R, et al. Independent predictors of 30-day perioperative deep vein thrombosis in 1346 consecutive patients after spine surgery. World Neurosurg. 2015;84:1605–12.
17. Goel R, Patel EU, Cushing MM, Frank SM, Ness PM, Takemoto CM, et al. Association of perioperative red blood cell transfusions with venous thromboembolism in a north American Registry. JAMA Surg. 2018;153:826.
18. Baram D, Daroowalla F, Garcia R, Zhang G, Chen JJ, Healy E, et al. Use of the all patient refined-diagnosis related group (APR-DRG) risk of mortality score as a severity adjustor in the medical ICU. Clin Med Circ Respirat Pulm Med. 2008;2:19–25.
19. Zhou JJ, Hemphill C, Walker CT, Farber SH, Uribe JS. Adverse effects of perioperative blood transfusion in spine surgery. World Neurosurg. 2021;149:73–9.
20. Johnson DJ, Johnson CC, Cohen DB, Wetzler JA, Kebaish KM, Frank SM. Thrombotic and infectious morbidity are associated with transfusion in posterior spine fusion. HSS J. 2017;13:152–8.
21. Frank SM, Thakkar RN, Podlasek SJ, Ken Lee KH, Wintermeyer TL, Yang WW, et al. Implementing a health system-wide patient blood management program with a clinical community approach. Anesthesiology. 2017;127:754–64.
22. Center for Medicare and Medicaid Services. Case mix index. 2006 [cited 2022 April 5]. Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Acute-Inpatient-Files-for-Download-Items/CMS022630.
23. Stonemetz JL, Allen PX, Wasey J, Rivers RJ, Ness PM, Frank SM. Development of a risk-adjusted blood utilization metric. Transfusion. 2014;54:2716–23.
24. Hyer JM, Tsilimigras DI, Diaz A, Mirdad RS, Pawlik TM. A higher hospital case mix index increases the odds of achieving a textbook outcome after hepatopancreatic surgery in the Medicare population. Surgery. 2021;170:1525–31.
25. Rokito SE, Schwartz MC, Neuwirth MG. Deep vein thrombosis after major reconstructive spinal surgery. Spine (Phila Pa 1976). 1996;21:853–8.
26. Epstein NE. Efficacy of pneumatic compression stocking prophylaxis in the prevention of deep venous thrombosis and pulmonary embolism following 139 lumbar laminectomies with instrumented fusions. J Spinal Disord Tech. 2006;19:28–31.
27. Takahashi H, Yokoyama Y, Iida Y, Terashima F, Hasegawa K, Saito T, et al. Incidence of venous thromboembolism after spine surgery. J Orthop Sci. 2012;17:114–7.
28. Kurtoglu M, Yanar H, Bilsel Y, Guloglu R, Kizilirmak S, Buyukkurt D, et al. Venous thromboembolism prophylaxis after head and spinal trauma: intermittent pneumatic compression devices versus low molecular weight heparin. World J Surg. 2004;28:807–11.

SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

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Adverse events caused by cord blood infusion in Japan during a 5-year period

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Abstract

Background and Objectives: In Japan, cord blood is used for more than half of all unrelated stem cell transplantations. The public cord blood banks (CBBs) have been collecting information on cord blood transplantation-related adverse events from physicians on a voluntary basis, without common definitions of the adverse reactions. The aims of this study were to compare two classification systems to improve the reporting system and to clarify the actual risk from cord blood infusion, which can then provide the impetus to take appropriate measures to reduce adverse events.

Materials and Methods: We classified the reports according to existing criteria; one is the Proposed Standard Definitions for Surveillance of Non-Infectious Adverse Transfusion Reactions by the International Society of Blood Transfusion (ISBT) Working Party on Haemovigilance, and the other is the Common Terminology Criteria for Adverse Events (CTCAE). There were 140 cases with adverse events reported from April 2014 through March 2019.

Results: Twelve cases, such as donor-derived leukaemia/myelodysplastic syndromes (MDS) and chromosomal aberrations reported after engraftment, were excluded from this analysis. Of the 128 cases with adverse events at cord blood infusion, the CTCAE and ISBT criteria could not classify 6 cases and 68 cases, respectively. Classifying by the CTCAE, the most common side effect was hypertension in 35 cases, followed by anaphylaxis, allergic reactions, nausea, urticaria, etc. Serious adverse events (grades 4 and 5) were mainly anaphylaxis, with a frequency of 0.23%.

Conclusion: It is necessary not only to provide information on adverse events but also to standardize the reporting of adverse events to support measures to reduce them.

Keywords

classification of adverse event, haematopoietic stem cells, infection, umbilical cord blood transplantation

Highlights

- The Common Terminology Criteria for Adverse Events (CTCAE) cover almost all adverse events at cord blood infusion, and their grading matched the physicians' reports.
- For the 5 years up to 2019, the most common adverse event from cord blood transplantation was hypertension, while the most serious was anaphylaxis.
- In addition to hypertension, haematuria was an adverse event characteristic of cord blood infusion.

INTRODUCTION

Cord blood (CB) has been used as a source for unrelated haematopoietic stem cell transplantations, in addition to bone marrow and peripheral blood stem cells. For at least the past 10 years, there have been more cord blood transplantations (CBTs) in Japan than in any other country. According to a World Marrow Donor Association (WMDA) report, 2750 CBTs were conducted worldwide in 2020 [1], of which more than half were done in Japan. In that year, 1496 CBTs, as well as 1092 unrelated bone marrow and unrelated peripheral blood stem cell transplantations, were performed in Japan [2, 3]. That was the first year affected by the COVID-19 pandemic, which made it difficult to coordinate bone marrow and peripheral blood donors. CBTs were used for patients whose disease conditions would not permit them to wait for a matched unrelated donor.

The first CBT was performed on a patient in Japan in 1994 [4], and since 2016, there have been more than 1300 CBTs annually in Japan. The recipients of CBT are over 20 years of age in more than 80% of the cases, which is different from many countries that use CBT mainly for paediatric patients [5]. Also, a single unit is used for one transplantation, and it is thawed in the ward and injected soon after thaw without diluting or washing the cryoprotectant. Only single-unit CBTs are performed in Japan, as no benefit from double CBTs had been shown in an earlier study [6].

In some cases of CBT, we experienced adverse events during or after the infusion of CB or late-onset events such as donor-derived leukaemia. If a patient's symptoms were suspected to be a CBT-related adverse event, the physician in charge was to report them. There was no guidance about the severity of adverse events to be reported, and the physicians' reports have been done on a voluntary basis.

For this paper, to determine an appropriate set of criteria suitable to categorize adverse events specifically for cord blood, the symptoms of the adverse events reported between April 2014 and March 2019 were classified using two sets of criteria, one defined by the International Society of Blood Transfusion (ISBT) and the other was the Common Terminology Criteria for Adverse Events (CTCAE) by the National Cancer Institute in the United States. This provided a comparison of the two systems and enabled us to suggest modifications to make appropriate criteria for reporting adverse events from CBT, which do not exist currently. This study also shows the frequency of severe adverse events and discusses modifications in the reporting system to clarify the actual risk from cord blood infusion, which can then provide the impetus to take appropriate measures to reduce adverse events. Possible changes to make compiling the adverse events more efficient and to give necessary alerts to the transplant community are also discussed.

MATERIALS AND METHODS

Data collection

For a CBT, the designated unit was thawed and infused into the patient in the ward. Since 2014, at the completion of the infusion, the physician in charge reported to the source cord blood bank (CBB) the completion together with any unit-associated problems, such as clot formation or leakage, and whether there were infusion-related adverse events. When there was an adverse event, the CBB requested the physician to report what the symptoms were and the final prognosis on a voluntary basis. The reporting form for the physicians was made by consensus by all six public CBBs. The form had the following choices: symptom, time from infusion to the occurrence of the symptom, severity (mild or severe), recovery, imputability, progress (other symptoms and treatments) and changes to the CB infusion (stopped or continued, volume infused). The form did not list the categories of adverse events nor did it have severity standards. The CBB must report the information received from the physicians to the Ministry of Health, Labour and Welfare (MHLW) and to the Japanese Red Cross (JRC), which has been designated by the MHLW to be the Haematopoietic Stem Cell Provision Support Organization [7, 8]. The JRC must compile adverse event reports and provide the collected information to the MHLW. The yearly summary was published on the JRC website [9].

In a fatal case that showed transfusion-associated circulatory overload (TACO) like symptoms, we also received the age, body weight and progress of the symptoms. This study was to reassess the adverse events related to cord blood infusions for the 5-year period from April 2014 to March 2019. Study protocols for this work were approved by the Institutional Review Board of the Blood Service Department of the JRC (approval number 2019-009).

Classification of adverse events

The CBT-related adverse events were classified twice, once based on the ISBT criteria, the Proposed Standard Definitions for Surveillance of Non-Infectious Adverse Transfusion Reactions by the Working

Party on Haemovigilance of the International Society of Blood Transfusion, adopted in June 2013 [10] and once based on the CTCAE, the Common Terminology Criteria for Adverse Events, version 5, published in November 2017 by the Cancer Therapy Evaluation Program of the National Cancer Institute in the United States [11].

Data analysis using nominal group technique

To assess the adverse events reported during the 5-year study period, the two laboratory technicians and two physicians in charge of the JRC CBT adverse events reporting system would meet, using a nominal group technique to reach a consensus on the adverse event and its severity. After obtaining comments from the CBB in each case, a second meeting was held to reassess them, and for the cases with more information, additional meetings were held. When multiple adverse symptoms were reported for the same patient, one significant or severe symptom was chosen. When there were multiple significant symptoms, two or more were chosen. The severity of each adverse event was also determined using the grading of the ISBT and CTCAE criteria (Table 1).

RESULTS

Data collection

From April 2014 through March 2019, there were 6512 CBTs performed in Japan. All of these CBTs were single-unit transplantations.

TABLE 1 Severity and description of severity for each grade by criteria.

CTCAE		ISBT criteria	
Grade	**Severity**	**Grade**	**Severity**
1	Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	1	Non-severe: The recipient may have required medical intervention (e.g., symptomatic treatment), but lack of such would not result in permanent damage or impairment of a body function.
2	Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.	2	Severe: • the recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; and/or • the adverse event resulted in persistent or significant disability or incapacity; or • the adverse event necessitated medical or surgical intervention to preclude permanent damage or impairment of a body function.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.		
4	Life-threatening consequences; urgent intervention indicated.	3	Life-threatening: The recipient required major intervention following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death.
5	Death related to adverse events.	4	Death: The recipient died following an adverse transfusion reaction.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ISBT, International Society of Blood Transfusion.

TABLE 2 Type and severity grade of adverse events using the International Society of Blood Transfusion criteria.

	Grade					
Adverse events	**1**	**2**	**3**	**4**	**Total**	
Allergic reaction	25	5	14	1	45	35.2%
Hypotensive transfusion reaction	0	0	1	0	1	0.8%
Acute haemolytic transfusion reaction	5	0	0	0	5	3.9%
Febrile non-haemolytic transfusion reaction	1	0	0	0	1	0.8%
Transfusion-associated dyspnoea	4	2	0	0	6	4.7%
Transfusion-associated circulatory overload	0	0	0	1	1	0.8%
Unclassifiable complication of transfusion	61	6	1	1	69	53.9%

Note: After excluding delayed adverse events of cord blood transplantations, 128 cases were classified according to the International Society of Blood Transfusion criteria. By these criteria, adverse events are presented in four levels of severity (Table 1).

The clinical practice is to infuse the thawed CB without washing the cells after thawing. In the 5 years of this analysis, half of the CBT recipients were in their 50s and 60s, and 15% of the recipients were less than 20 years old. For Human Leukocyte Antigen matching at the antigen level, there were 6/6, 5/6 and 4/6 matches for 8, 26 and 66% of the cases, respectively. Adverse events in 140 CBT patients were reported by the transplant centres. Twelve of these cases appeared after the cord blood was engrafted, with six assessed as donor-

TABLE 3 Type and severity grade of adverse events using the Common Terminology Criteria for Adverse Events (CTCAE)

SOC	CTCAE terms	Grade 1	2	3	4	5	Total	
Vascular disorders	Hypertension	11	12	12	0	0	35	27.3%
	Hypotension	1	1	0	0	0	2	1.6%
	Flushing	1	0	0	0	0	1	0.8%
Immune system disorders	Anaphylaxis	0	0	2	14	1	17	13.3%
	Allergic reaction	4	4	1	0	0	9	7.0%
Gastrointestinal disorders	Vomiting	3	0	0	0	0	3	2.3%
	Nausea	8	0	0	0	0	8	6.3%
	Nausea and vomiting	1	0	0	0	0	1	0.8%
	Abdominal pain	1	1	0	0	0	2	1.6%
Skin and subcutaneous tissue disorders	Urticaria	6	3	0	0	0	9	7.0%
	Pruritus	3	0	0	0	0	3	2.3%
	Erythema multiforme	1	1	0	0	0	2	1.6%
Respiratory, thoracic and mediastinal disorders	Dyspnoea	2	0	0	0	0	2	1.6%
	Wheezing	0	1	0	0	0	1	0.8%
	Pulmonary oedema	0	0	1	0	0	1	0.8%
	Hypoxia	0	2	2	0	0	4	3.1%
Not applicable[a] (respiratory, thoracic and mediastinal disorders)	Not applicable (hypoxia)	6	0	0	0	0	6	4.7%
Cardiac disorders	Ventricular arrhythmia	1	0	0	0	0	1	0.8%
	Asystole	1	0	0	0	0	1	0.8%
	Atrial fibrillation	1	0	0	0	0	1	0.8%
	Sinus bradycardia	1	0	0	0	0	1	0.8%
	Sinus tachycardia	0	1	0	0	0	1	0.8%
	Heart failure	0	0	0	0	1	1	0.8%
Renal and urinary disorders	Haematuria	2	1	3	0	0	6	4.7%
General disorders and administration site conditions, or cardiac disorders[b]	Chest pain	1	0	0	0	0	1	0.8%
General disorders and administration site conditions	Fever	1	0	0	0	0	1	0.8%
	Non-cardiac chest pain	1	0	0	0	0	1	0.8%
Infections and infestations	Sepsis	0	0	0	1	1	2	1.6%
Musculoskeletal and connective tissue disorders	Back pain	1	0	0	0	0	1	0.8%
Vascular disorders and cardiac disorders[c]	Hypotension and sinus tachycardia	0	0	0	1	0	1	0.8%
Immune system disorders, and general disorders and administration site conditions[c]	Allergic reaction and neck oedema	0	1	0	0	0	1	0.8%
Gastrointestinal disorders and vascular disorders[c]	Nausea, abdominal pain and flushing	1	0	0	0	0	1	0.8%
Gastrointestinal disorders, and skin and subcutaneous tissue disorders[c]	Abdominal pain and erythema multiforme	1	0	0	0	0	1	0.8%

Note: After excluding delayed adverse events of cord blood transplantations, 128 cases were classified into types of events and system organ class (SOC) according to the CTCAE. By these criteria, adverse events are presented in five levels of severity.

[a]Mild hypoxia with $PaO_2 \geq 88\%$ was counted as grade 1, though the CTCAE do not define grade 1 hypoxia.

[b]The SOC was not clear for the term 'chest pain'.

[c]There were two symptoms that belong to different SOC.

derived leukaemia or MDS, five as chromosomal aberrations and one as food allergy. Excluding these 12 late-onset adverse events, the 128 adverse events, which occurred during or immediately after CB infusion, were included in this analysis and represented 2.0% of the CBTs performed during the 5-year study period.

Classification based on the ISBT criteria

The reported adverse events were classified according to the definition of the ISBT criteria. The most frequent adverse reaction that could be classified with the ISBT criteria was an allergic reaction. Of the 128 adverse events, 60 were classified into seven categories and 68 (53.1%), such as high blood pressure and gastrointestinal disorders, were listed as unclassifiable (Table 2). As we did not receive the blood type information of the CB and the recipient, the possibility of haemolytic transfusion reactions could not be excluded.

Classification based on the CTCAE

Table 3 shows the results of the classification of the 128 CB infusion-related adverse events based on the CTCAE. They were classified under 32 of the CTCAE terms. Very mild hypoxia observed in six patients did not fit any category of the CTCAE because the definition of the CTCAE category for hypoxia did not include cases with $PaO_2 \geq 88\%$. They are shown as 'not applicable (hypoxia)'. There were four cases for which we could not determine the major symptom of the case. Also, for one case with 'chest pain', we could not determine the 'system organ class' (SOC).

The most common adverse events were hypertension, followed by anaphylaxis, allergic reactions, and urticaria. Out of the 128 cases, 109 (85%) were grades 1–3. There were 19 serious adverse events, which were grade 4 or 5. Of these, 14 anaphylaxis, 1 sepsis and 1 hypotension were classified as grade 4 (life-threatening consequences) and 1 anaphylaxis, 1 heart failure and 1 sepsis as grade 5 (death). In the two cases reported as sepsis, bacteria were not detected in samples taken during the preparation of the cord blood.

When adverse events were categorized according to organ classification (SOC; Table 3), vascular disorders were the most common event (31.3%), followed by immune system disorders (21.1%), gastrointestinal disorders (12.5%) and skin and subcutaneous tissue disorders (11.7%) (Figure 1).

Comparison of the classification results using the ISBT criteria and the CTCAE

The comparison of the classification results is shown in Table 4. The ISBT criteria of allergic reaction corresponded to many symptoms in the CTCAE, such as anaphylaxis, urticaria, wheezing, etc. Also, transfusion-related dyspnoea in the ISBT criteria corresponded to the three symptoms of hypoxia, dyspnoea and pulmonary oedema in the CTCAE. With the CTCAE, there were fewer unclassifiable cases. For severity, the CTCAE shows grades numerically, which makes the categorization of symptoms clearer.

Fatal cases

Three fatal cases with anaphylaxis, heart failure and sepsis were reported (Table 3). The case with heart failure was originally reported as anaphylaxis by the physician in charge; however, this was ultimately classified as heart failure because 25 ml of cord blood product had been rapidly (within 3 min) infused into an infant with a body weight of approximately 3600 g. The patient had symptoms and a clinical course similar to TACO, which is a known severe adverse event of blood transfusion. In the case reported as sepsis, no bacterial contamination was detected either by bacterial culture or by a nucleic acid amplification test, with the cord blood samples preserved during the processing. The symptoms and clinical course of the fatal cases are shown in Table 5.

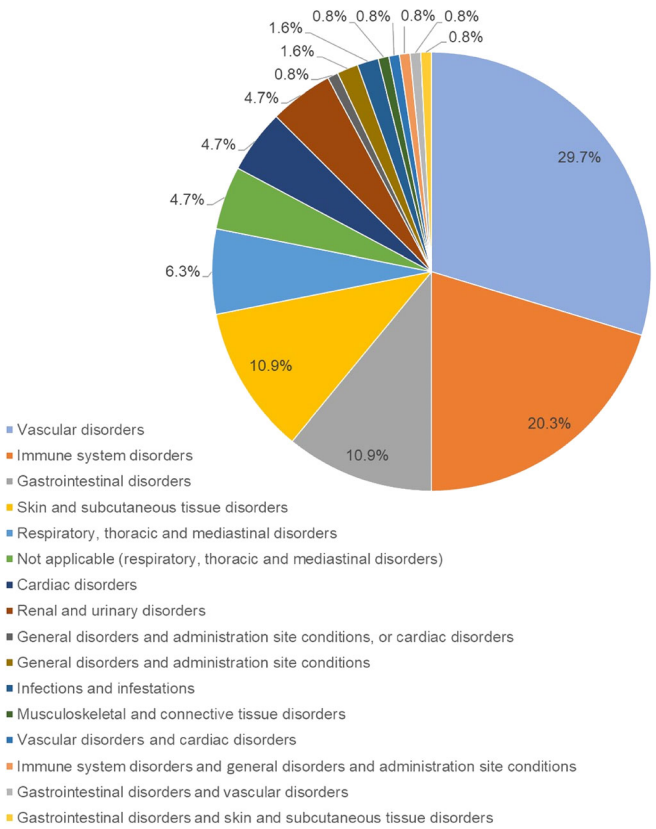

FIGURE 1 Adverse events at cord blood infusion classified by the system organ class (SOC) according to the Common Terminology Criteria for Adverse Events. SOC is identified by the anatomical or physiological system, aetiology or purpose. The most common case was 'vascular disorders', and the second was 'immune system disorders'. Other adverse events that accounted for more than 10% were 'gastrointestinal disorders', 'skin and subcutaneous tissue disorders' and 'respiratory, thoracic and mediastinal disorders'.

TABLE 4 Comparison of two criteria for adverse events from cord blood infusion.

CTCAE	Criteria of ISBT	Cases	Serious cases
Anaphylaxis	Allergic reaction	17	15(1)
Allergic reaction		9	0
Nausea/abdominal pain/flushing		1	0
Allergic reaction/neck oedema		1	0
Urticaria		9	0
Wheezing		1	0
Pruritus		3	0
Erythema multiforme		2	0
Flushing		1	0
Hypotension		1	0
Hypertension	Unclassifiable complication of transfusion	35	0
Nausea		8	0
Not applicable (hypoxia)		6	0
Vomiting		3	0
Sepsis		2	2 (1)
Haematuria		2	0
Abdominal pain		2	0
Nausea/vomiting		1	0
Chest pain		1	0
Ventricular arrhythmia		1	0
Asystole		1	0
Atrial fibrillation		1	0
Hypoxia		1	0
Sinus bradycardia		1	0
Sinus tachycardia		1	0
Back pain		1	0
Non-cardiac chest pain		1	0
Hypotention		1	0
Hypotension/sinus tachycardia	Hypotensive transfusion reaction	1	1
Haematuria	Acute haemolytic transfusion reaction	4	0
Abdominal pain/erythema multiforme		1	0
Fever	Febrile non-haemolytic transfusion reaction	1	0
Heart failure	Transfusion-associated circulatory overload	1	1 (1)
Hypoxia	Transfusion-associated dyspnoea	3	0
Dyspnoea		2	0
Pulmonary oedema		1	0

Note: The adverse events of cord blood infusions were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) and the criteria of the International Society of Blood Transfusion (ISBT). Serious cases were counted based on reports from medical institutions, and the number in parentheses indicates fatal cases.

Discrepancy of adverse event assessment between physicians' reports

Adverse events have been reported at the discretion of each physician in charge. CBBs did not suggest any categories for adverse events or severity standards when they requested information. For the adverse events that we classified as anaphylaxis or an allergic reaction based on the CTCAE, most physicians had reported them using the same terminology. In some cases, however, they had reported them as low blood pressure, respiratory distress, mood discomfort, bradycardia, hypoxia, etc. The CTCAE adverse events of urticaria and hypertension were reported by the physicians using various terms. For example, cases of urticaria were reported as wheal, redness, erythema, pruritus, etc., and some cases of hypertension were described as increased blood pressure, high blood pressure, etc.

TABLE 5 Symptoms and clinical course of fatal cases.

Report by medical institution	CTCAE	Symptoms and clinical course
Anaphylaxis	Anaphylaxis	Shock Progressive intravascular dehydration and metabolic acidosis Death after 1 month of treatment in ICU
Anaphylaxis	Heart failure	Patient's age: 3 months old Patient's weight: 3600 g Infusion rate: 25 ml in 3 min Hypoxia (SpO_2 < 90%) Tachycardia (200/min) Dyspnoea 2.5 h after transplantation Acidosis Loss of spontaneous breathing on day 2 Intracranial haemorrhage on day 5 Death on day 11
Sepsis	Sepsis	Fever Headache Acute respiratory distress syndrome Death from multiple organ failure due to septic shock, approximately 72 h after transplantation Bacterial test Patient: Positive (*Klebsiella pneumoniae*) Cord blood product: Negative

Note: The symptoms of three fatal cases were shown by the Common Terminology Criteria for Adverse Events (CTCAE) classification.
Abbreviation: ICU, intensive care unit.

In the CTCAE, mild hypoxia is not considered to be an adverse reaction, as there is no classification of grade 1; however, the severity of 6 out of 10 hypoxia cases reported by the physicians was mild, with a SpO_2 ≥ 88%. We classified them as grade 1 in this study, as the physicians reported them as adversely reactive to hypoxia.

Adverse reactions were classified by the reporting physicians as either mild or severe. The cases reported as serious corresponded to grades 4 and 5 in the CTCAE.

DISCUSSION

In this study, we classified the adverse events at cord blood infusion according to the ISBT criteria and the CTCAE. When we did so according to the ISBT criteria, which was created for blood transfusions, more than half of the reported adverse events could not be categorized. Adverse events that did not fit into the ISBT criteria were hypertension, gastrointestinal disorders, cardiac disorders and haematuria.

Infusion of cell products has been reported to be associated with the occurrence of adverse events, ranging from mild reactions such as nausea, vomiting, flushing, fever, chills and cough to life-threatening reactions such as effects on the cardiovascular, respiratory and neurological systems [12]. For peripheral blood stem cell transplantation (PBSCT), the frequency was reported to be from 13.5% to 50% [13–17]. Cryopreserved marrow infusion was reported to have adverse events in 76.1% of the cases [18]. Fresh marrow infusions were reported in >50% of the cases [19]. Injection of thawed CB has been reported to have adverse events in 22%–79% of patients [19–21]. As the study by Ikeda et al. covering all haematopoietic stem cell transplants was designed to pick up all adverse events, they could observe very mild symptoms, like malodour, which was reported in 13.1% of patients. This was not a symptom reported to the CBBs in our study, which suggests that the transplant centres did not report all mild events. One report showed 84% of children had a grade 1 adverse event from all sources of stem cell infusion [22]. In our report, the frequency of adverse events was 2% for all CB infusions. Comparing the studies suggests a clear underreporting in our system. Still, in our study, mild adverse events were reported, as 60 of 128 events were graded 1 by the CTCAE, when including the six unclassified hypoxia. A reason for our low percentage of adverse events is that in the forms that the CBBs give to the transplant centres, not all the known symptoms are listed, and there is no guidance about the severity of adverse events to be reported, and our voluntary reporting system depends on the physicians' discretion.

Hypertension was the most reported adverse event in this study. For PBSCT, cardiovascular problems have been reported to be the most frequent adverse event [16]. The serious adverse events for children who received a haematopoietic stem cell transplantation, including CBT, were hypertension, hypoxia, fever, etc [22]. As the most common adverse event of CBT, hypertension was reported with frequencies of 17.9% and 58% [19, 21]. Cardiovascular symptoms (hypertension, bradycardia, etc.) were serious adverse events in CBTs for adults [19, 21].

Among mild adverse events, gastrointestinal symptoms were reported to occur often [22]. The frequency was 15.4% with PBSCT [13] and 71% with cryopreserved bone marrow infusion [18]. CB infusion was reported to result in nausea/vomiting in 9% of the patients [21]. In another study, CB had a lower frequency of nausea and vomiting, 3.7%, compared to 12.3% for allogeneic PBSCT [19].

With our reporting system, there were 15 cases reported with severe adverse events that we categorized as grade 4 or 5 anaphylaxis, a frequency of 0.23%, or one in 435 infusions. Grade 4 or higher adverse events are almost exclusively anaphylactic shocks. Several papers have reported that the cryoprotective solutions, Dimethyl sulfoxide (DMSO) and dextran, which are used for preserving cord blood, contribute to adverse events from stem cell infusion [12, 23–26]. Dextran with albumin, which is used for dilution after thawing, is also reported as the suspected cause of severe anaphylactic and cardiopulmonary reactions [26]. The amount of cryoprotectants included in one CB unit is 2 ml of DMSO and 0.2 g of dextran 40. This indicates the possibility of some sort of allergic reaction to or toxic effect of additives. We have not been able to determine the cause of allergic reactions, such as anaphylactic shock. As blood transfusions also cause

anaphylactic reactions, we cannot attribute all of the cases of anaphylaxis to the cryoprotectant. The basophil activation test (BAT) is useful for verifying allergic reactions [27], although it requires fresh basophils, and it is not possible to prepare the patient's basophils prior to transplantation. The passive immune basophil activation test (pi-BAT) was developed as an alternative test that uses a healthy donor's basophils to which a patient's IgE is bound [28]. By introducing pi-BAT, it may be possible to verify allergic reactions and hopefully apply the test before the CBT for high-risk patients in the future.

There was also a report that showed TACO-like symptoms, which we classified as heart failure using the CTCAE. The cause of TACO is said to be due to excessive volume load or excessive infusion rate load. Because this case resulted in a fatality, we received detailed information through the CBB that supplied the unit. The total CB volume is 25 ml, and if the patient's weight is low, transfusing this amount may produce either volume or velocity overload. The JRC began to add alerts about the injection speed after this case, as there had been no such guidance in Japan previously. As the thawing of the frozen CB unit is done in the ward prior to injection in the recipient, without washing the cryoprotectant, physicians tend to be under pressure to hurry to avoid cell damage from the DMSO. There is a report for CB that the cell quality is maintained for 30 min after thawing [29], and in another report for PBSCT, the risk of adverse events was lower when the product was administered by a drip compared to injecting directly with a syringe [13]. We must communicate with the transplant centres on the best practices.

There were some limitations in our work. One was underreporting due to the lack of standards that the physicians could follow. This meant that some physicians reported only severe adverse events while some also reported mild events, which lowered the frequency of mild adverse events reported. Another was that there was limited information for each case, and we could not open the medical records of each patient at the transplant centres.

There were six cases with haematuria. At the time the data was collected for this study, the form used by the transplant centres and CBBs did not include the patient's blood group information. Thus, we could not associate haematuria with haemolytic transfusion reaction due to ABO incompatibility. Haemoglobinuria, rather than haematuria, is expected as the CB unit contains red blood cells that experience freezing and thawing. With Bone marrow and PBSC infusions, all patients were reported to have had haemoglobinuria [30]. Including the term 'haemoglobinuria' as a choice in the reporting form might change the adverse event that is reported.

Blood transfusions often cause allergic reactions. In Japan, more than 60% of the yearly reports of blood transfusion-related adverse events are allergic reactions. This is followed by fever and breathing difficulty [31]. ISBT criteria are designed to classify these adverse events. The conditions that fit an allergic reaction by the ISBT criteria were divided by the CTCAE into the SOC categories of 'immune system', 'vascular', 'skin and subcutaneous tissue', 'gastrointestinal' and 'respiratory, thoracic and mediastinal' disorders. Transfusion-related acute lung injury (TRALI) and TACO are terms for dyspnoea caused by blood transfusion within 6 h, with or without heart dysfunction. We need some proof of lung oedema, heart function or test data to diagnose them, which would add a burden to the physicians if we try to use ISBT criteria in our data collection, as well as to the CBBs and the JRC, which would have to confirm the algorithms used to diagnose them. As half of the infusion-related adverse events were not covered by the ISBT criteria, we gave up our early intention to disseminate the ISBT criteria to the transplant centres.

Currently, a system for reporting adverse events after CB infusion is in place in Japan. As a next step, we must establish the standards for this reporting system. It is necessary to determine the information to be collected, such as the cord blood infusion rate, the presence/absence of drugs administered, blood type and blood pressure values before and after transplantation. The reporting form should include classifications with grades. The physicians in charge should be given the grade definitions of the CTCAE for reporting symptoms that occur with a high frequency. So as not to increase the workload of transplant centres and CBBs, the information we deal with should be concise except for severe or life-threatening events. The collected information needs to be shared with the transplant community.

With this study, the features of reported adverse events at CB infusions can be better understood. By knowing the information that was missing in the past, the reporting system can be updated. Close communication with the transplant centres is necessary to make CBT safer.

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CONFLICT OF INTEREST

The authors have declared that there are no conflicts of interest relevant to this work.

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REFERENCES

1. World Marrow Donor Association. WMDA Global Trends Report 2020. [cited 2022 Mar 10]. Available from: https://wmda.info/wp-content/uploads/2021/05/GTR-2020-Summary-slides.pdf
2. Japanese Red Cross Society. Number of cord blood transplantations. Information service of hematopoietic stem cell transplantation. [cited 2022 Mar 10]. Available from: https://www.bs.jrc.or.jp/bmdc/cordblooddonor/m3_04_statistics.html (written in Japanese)
3. Japan Marrow Donor Program. Number of bone marrow and peripheral blood stem cell transplantations from unrelated donors. [cited 2022 Mar 10]. Available from: https://www.jmdp.or.jp/documents/file/08_data/bank_genjou_isyoku.pdf (written in Japanese)
4. Kato S, Nishihira H, Sako M, Kato K, Azuma E, Kawano Y, et al. Cord blood transplantation from sibling donors in Japan. Report of the national survey. Int J Hematol. 1998;67:389–96.

5. Japanese Data Center for Hematopoietic Cell Transplantation. Hematopoietic Cell Transplantation in Japan Annual Report of Nationwide Survey 2020 Summary Slide. [cited 2022 Mar 10]. Available from: http://www.jdchct.or.jp/en/data/slide/2020/
6. Kai S, Wake A, Okada M, Kurata M, Atsuta Y, Ishikawa J, et al. Double-unit cord blood transplantation after myeloablative conditioning for patients with hematologic malignancies: a multicenter phase II study in Japan. Biol Blood Marrow Transplant. 2013;19:812–9.
7. Takanashi M. Current cord blood transplantation in Japan. Jpn J Transfus Cell Ther. 2017;63:736–40. (written in Japanese).
8. Japanese Red Cross Society. Blood services 2021. [cited 2022 Mar 10]. Available from: https://www.jrc.or.jp/english/pdf/BloodServices2021.pdf
9. Japanese Red Cross Society. CBT information. Information service of hematopoietic stem cell transplantation. [cited 2022 Mar 10]. Available from: https://www.bs.jrc.or.jp/bmdc/medicalpersonnel/files/saitaiisyoku2021.pdf (written in Japanese)
10. Popovsky M, Robillard P, Schipperus M, Stainsby D, Tissot J-D, Wiersum-Osselton J. Proposed standard definitions for surveillance of non infectious adverse transfusion reactions. International Society of Blood Transfusion (ISBT). [cited 2022 Mar 6]. Available from: https://www.zva.gov.lv/sites/default/files/inline-files/ISBT-definitions-for-non-infectious-transfusion-reactions%281%29.pdf
11. The National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). [cited 2022 Mar 10]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50
12. Shu Z, Heimfeld S, Gao D. Hematopoietic SCT with cryopreserved grafts: adverse reactions after transplantation and cryoprotectant removal before infusion. Bone Marrow Transplant. 2014;49:469–76.
13. Mulay SB, Greiner CW, Mohr A, Bryant SC, Lingineni RK, Padley D, et al. Infusion technique of hematopoietic progenitor cells and related adverse events (CME). Transfusion. 2014;54:1997–2003.
14. Calmels B, Lemarié C, Esterni B, Malugani C, Charbonnier A, Coso D, et al. Occurrence and severity of adverse events after autologous hematopoietic progenitor cell infusion are related to the amount of granulocytes in the apheresis product. Transfusion. 2007;47:1268–75.
15. Aladag E, Demiroglu H, Buyukasik Y, Karakulak UN, Tekin F, Aksu S, et al. Cardiac adverse events during stem cell transplantation for hematological malignancies: a single Centre experience. Transfus Apher Sci. 2020;59:102653.
16. Vidula N, Villa M, Helenowski IB, Merchant M, Jovanovic BD, Mehta J, et al. Adverse events during hematopoietic stem cell infusion: analysis of the infusion product. Clin Lymphoma Myeloma Leuk. 2015;15:e157–62.
17. Otrock ZK, Sempek DS, Carey S, Grossman BJ. Adverse events of cryopreserved hematopoietic stem cell infusions in adults: a single-center observational study. Transfusion. 2017;57:1522–6.
18. Stroncek DF, Fautsch SK, Lasky LC, Hurd DD, Ramsay NK, McCullough J. Adverse reactions in patients transfused with cryopreserved marrow. Transfusion. 1991;31:521–6.
19. Ikeda K, Ohto H, Okuyama Y, Yamada-Fujiwara M, Kanamori H, Fujiwara S, et al. Adverse events associated with infusion of hematopoietic stem cell products. A prospective and multicenter surveillance study. Transfus Med Rev. 2018;32:186–94.
20. Hahn T, Bunworasate U, George MC, Bir AS, Chinratanalab W, Alam AR, et al. Use of nonvolume-reduced (unmanipulated after thawing) umbilical cord blood stem cells for allogeneic transplantation results in safe engraftment. Bone Marrow Transplant. 2003;32:145–50.
21. Konuma T, Ooi J, Takahashi S, Tomonari A, Tsukada N, Kobayashi T, et al. Cardiovascular toxicity of cryopreserved cord blood cell infusion. Bone Marrow Transplant. 2008;41:861–5.
22. Truong TH, Moorjani R, Dewey D, Guilcher GM, Prokopishyn NL, Lewis VA. Adverse reactions during stem cell infusion in children treated with autologous and allogeneic stem cell transplantation. Bone Marrow Transplant. 2016;51:680–6.
23. Nagamura-Inoue T, Shioya M, Sugo M, Cui Y, Takahashi A, Tomita S, et al. Wash-out of DMSO does not improve the speed of engraftment of cord blood transplantation: follow-up of 46 adult patients with units shipped from a single cord blood bank. Transfusion. 2003;43:1285–94.
24. Morris C, de Wreede L, Scholten M, Brand R, van Biezen A, Sureda A, et al. Should the standard dimethyl sulfoxide concentration be reduced? Results of a European Group for Blood and Marrow Transplantation prospective noninterventional study on usage and side effects of dimethyl sulfoxide. Transfusion. 2014;54:2514–22.
25. Cooling L, Sankar A, Mody R, Yanik G, Bonifant C, Choi SW. A severe umbilical cord stem cell infusion reaction due to dextran in an atopic pediatric patient. Bone Marrow Transplant. 2017;52:1051–3.
26. Choi SW, Hoffmann S, Cooling L. Another case of acute cardiopulmonary toxicity with cord blood infusion: is dextran the culprit? Transfusion. 2012;52:207–8.
27. MacGlashan DW Jr. Basophil activation testing. J Allergy Clin Immunol. 2013;132:777–87.
28. Yasui K, Matsuyama N, Okamura-Shiki I, Ikeda T, Ishii K, Furuta RA, et al. Clinical utility of a passive immune basophil activation test for the analysis of allergic transfusion reactions. Transfusion. 2017;57:2084–95.
29. Fry LJ, Querol S, Gomez SG, McArdle S, Rees R, Madrigal JA. Assessing the toxic effects of DMSO on cord blood to determine exposure time limits and the optimum concentration for cryopreservation. Vox Sang. 2015;109:181–90.
30. Alessandrino P, Bernasconi P, Caldera D, Colombo A, Bonfichi M, Malcovati L, et al. Adverse events occurring during bone marrow or peripheral blood progenitor cell infusion: analysis of 126 cases. Bone Marrow Transplant. 1999;23:533–7.
31. Japanese Red Cross Society. Haemovigilance in JRCS 2020. [cited 2022 Aug 15]. Available from: https://www.jrc.or.jp/mr/english/pdf/Haemovigilance%20by%20JRCS%202020_en_2022.3.pdf

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Analysis of gender representation on transfusion medicine journal editorial boards: Comparison between 2019 and 2022

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Abstract

Background and Objectives: A 2019 study highlighted significant gender inequities among blood banking and transfusion medicine (BBTM) journal editorial boards. We sought to assess if the representation of women has improved in the intervening 3 years.

Materials and Methods: We analysed the gender composition of nine BBTM journal editorial boards as of 13 September 2022, including the seven journals studied in 2019. We compared this to the proportion of females (term used by authors) on seven BBTM journal editorial boards in 2019 to assess change in the editorial board composition. We also assessed gender composition by editorial position (editor-in-chief [EIC], associate/assistant/titled editors and editorial board members).

Results: Nine BBTM journals have a total of 398 editorial positions and comprise significantly more men than women (68.8%, 274/398 vs. 31.2%, 124/398; $p < 0.001$). Among the seven journals analysed in 2019, the proportion of women on these seven editorial boards has remained unchanged (2019: 30.1%, 81/269 vs. 2022: 31.9%, 103/323; $p = 0.66$) despite the addition of 54 editorial positions.

Conclusion: Women remain inequitably represented on journal editorial boards among all journal editorial positions. Although advocacy efforts are increasing, there has been limited improvement in gender equity in 3 years, despite a 20% increase in editorial positions.

Keywords

biomedical journals, diversity, editorial boards, gender equity, inclusion, transfusion medicine

Highlights

- As of September 2022, nine blood banking and transfusion medicine (BBTM) journals have a total of 398 editorial positions, and these comprise significantly more men than women (68.8%, 274/398 vs. 31.2%, 124/398; $p < 0.001$).
- Significantly more men than women serve as editors-in-chief (90.0%, 9/10 vs. 10.0%, 1/10; $p = 0.011$), as associate/assistant/titled editors (66.7%, 60/90 vs. 33.3%, 30/90; $p = 0.002$) and as editorial board members (68.8%, 205/298 vs. 31.2%, 93/298; $p < 0.001$).
- Among seven BBTM journals analysed in 2019, the proportion of women on the same seven editorial boards has remained unchanged (2019: 30.1%, 81/269 vs. 2022: 31.9%, 103/323; $p = 0.66$) despite the addition of 54 new editorial positions.

INTRODUCTION

The importance of demographic diversity, including but not limited to gender, is being increasingly recognized throughout medicine [1]. Despite recent efforts to rectify longstanding inequities, women and individuals from various groups continue to be disproportionately underrepresented, including among medical society recognition award recipients and journal editorial boards [2–4]. As previously illustrated, blood banking and transfusion medicine (BBTM) award conferral rates demonstrate longstanding gender inequities, which may impact career progression and success [2]. We subsequently analysed the board of directors of 10 BBTM specialty societies as of May 2022 and found that women comprise more positions than men and outnumber men on 6 of 10 society boards [5]. While these findings suggest that women are not underrepresented among society boards, a previous study demonstrated that women were underrepresented on BBTM journal editorial boards in 2019 compared to the number of women receiving BBTM certification [6].

The finding that women were underrepresented on journal editorial boards is salient, as journal editors are involved in all aspects of the publication process, including coordinating and collaborating with peers and colleagues, establishing connections, promoting the journal and potentially authoring editorials. Therefore, women may be at a disadvantage in establishing these connections and advancing their academic and research career. However, given recent diversity, equity and inclusion (DEI) initiatives in BBTM in conjunction with the improved representation of women on society boards, we sought to reassess BBTM journal editorial boards to determine if gender representation had improved over the intervening 3-year period.

MATERIALS AND METHODS

In this cross-sectional study, we assessed the gender composition of nine preeminent (impact factor >1.0 obtained via Journal Citation Reports, Clarivate [7]) BBTM journal editorial boards (all editors-in-chief [EIC], associate/assistant/titled editors and editorial board members) as of 13 September 2022. Journal editorial board members were identified on each respective journal's website. We compared this to the proportion of females (term used by authors) on seven BBTM journal editorial boards in 2019, as reported by Lally and colleagues (Table 1) [6]. We also assessed the gender breakdown by editorial position (EIC, associate/assistant/titled editors and editorial board members). Of note, we analysed all journal editorial board positions, not individuals, as an individual may hold more than one position on an editorial board.

Gender was determined using established materials and methods [2, 3] via a review of online pronouns (i.e., he/she/they); if unavailable, individuals' photographs and names were used in combination. No individuals identified as non-binary; therefore, we report our findings as binary (i.e., he/she) and recognize our inability to account for the entirety of the gender spectrum as a study limitation. Statistical analyses were conducted using GraphPad PRISM version 9.2.0 (GraphPad Software, LLC, San Diego, CA, USA), with a p-value <0.05 considered significant.

TABLE 1 Blood banking and transfusion medicine journals analysed

Journal	IF (2018)	IF (2021)	Country published in	Medical society associated with journal	Editorial board size, *n*		Females/women on editorial board, *n* (%)		EIC	
					2019	2022	2019	2022	2019[a]	2022[b]
Blood Transfusion	3.352	5.752	Italy	SIMTI	54	63	19 (35)	21 (33)	M	M
Transfusion	3.111	3.337	USA	AABB	80	84	28 (35)	30 (36)	M	M
Journal of Clinical Apheresis	3.088	2.605	USA	ASFA	24	23	6 (25)	5 (22)	M	M
Vox Sanguinis	2.364	2.996	England	ISBT	10	39	3 (30)	19 (49)	F	M
Transfusion Medicine	1.9	2.057	England	BBTS	29	28	10 (34)	11 (39)	M	M
Transfusion and Apheresis Science	1.412	2.596	England	WAA	32	43	3 (9)	4 (9)	1 M, 1 F	1 M, 1 W
Transfusion Clinique et Biologique	1.029	2.126	France	FSBT	40	43	12 (30)	13 (30)	M	M
Transfusion Medicine Reviews	N/A	6.969	USA	N/A	N/A	30	N/A	14 (47)	N/A	M
Transfusion Medicine and Hemotherapy	N/A	4.040	Switzerland	GSTMI	N/A	45	N/A	7 (16)	N/A	M

Abbreviations: AABB, Association for the Advancement of Blood and Biotherapies; ASFA, American Society for Apheresis; BBTS, British Blood Transfusion Society; EIC, editor-in-chief; FSBT, French Society of Blood Transfusion; GSTMI, German Society for Transfusion Medicine and Immunohematology; IF, impact factor; ISBT, International Society of Blood Transfusion; N/A, not applicable; SIMTI, Società Italiana di Medicina Trasfusionale e Immunoematologia; WAA, World Apheresis Association.

[a]Coded as M (male) or F (female) [6].

[b]Coded as M (man) or W (woman).

RESULTS

As of September 2022, nine BBTM journals have a total of 398 editorial positions. The gender of 364 (91.5%) editorial positions was identified via pronouns, while 34 (8.5%) were identified via photograph and name in combination. The 398 editorial positions comprised significantly more men than women (68.8%, 274/398 vs. 31.2%, 124/398; $p < 0.001$). The proportion of women on editorial boards ranged from 9.3% to 48.7%. Only two of the nine journals have a near-equal proportion (i.e., parity or 50–50 men and women) of women and men [*Vox Sanguinis* (48.7%) and *Transfusion Medicine Reviews* (46.7%)]. No journal had more women than men on editorial boards. While no data exist for the gender composition of the BBTM workforce as a whole, recent findings show that 45% of BBTM specialists, who passed the American Board of Pathology's BBTM Subspecialty Board Examination between 2016 and 2018, were women [8]. Furthermore, 63% and 61% of individuals graduating from a BBTM fellowship program in 2019 and 2021, respectively, were women [6, 9]. It should, however, be noted that these passage rates for BBTM specialists are reflective of individuals who predominantly practice in the United States and may not be representative of the international BBTM community.

As of 2022, men hold more editorial positions in BBTM journals than women, irrespective of the specific editorial position. Significantly, more men than women serve as EIC (90.0%, 9/10 vs. 10.0%, 1/10; $p = 0.011$), as associate/assistant/titled editors (66.7%, 60/90 vs. 33.3%, 30/90; $p = 0.002$) and as editorial board members (68.8%, 205/298 vs. 31.2%, 93/298; $p < 0.001$) (Figure 1).

Among the seven journals analysed by Lally et al. in 2019, the proportion of women on the same seven editorial boards has remained unchanged overall (2019: 30.1%, 81/269 vs. 2022: 31.9%, 103/323; $p = 0.66$) despite the addition of 54 new editorial positions. One journal increased the proportion of women in editorial positions by more than 5%, while two others increased by 1% and 5%, respectively. The proportion of women decreased in two journals and remained the same in two journals. While journals published in the United States tend to have a marginally greater proportion of women on editorial boards compared to journals based in other countries, the difference is not significant (35.8%, 49/137 vs. 28.7%, 75/261; $p = 0.17$); however, we acknowledge that journal publication country may or may not reflect the citizenship status of the editors.

DISCUSSION

These findings illustrate that despite generally equitable representation on transfusion medicine specialty society boards [5], women are not equitably represented on journal editorial boards, many of which are directly affiliated with or endorsed by these same specialty societies. These inequities are seen among all journal editorial positions, from EIC to board members. Furthermore, we discovered that although advocacy efforts and DEI initiatives are becoming more frequent, there has been limited improvement in gender equity in 3 years, despite a 20% increase in editorial positions among the original seven journals studied over this time period (269–323). This highlights the importance of not only continued advocacy but of holding journals and other stakeholders accountable for ensuring they are actively working to rectify these inequities, as opposed to making empty statements.

Notably, the findings in this analysis mirror those of our previous assessment of gender inequities in BBTM society recognition

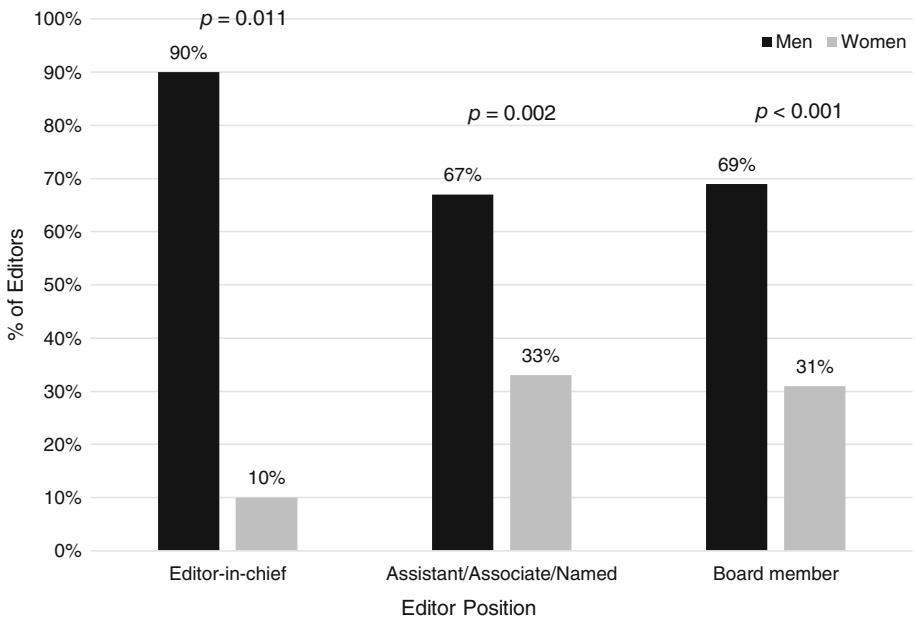

FIGURE 1 Proportion of men and women by editorial position in 2022

awards, wherein women were significantly underrepresented among recipients of research/innovation awards compared to men (17% vs. 83%) [2]. This underscores one of the challenges women face in academia, as studies have shown that women receive fewer awards for research, less money and prestige and may be less likely to be promoted [10–12].

Additionally, the underrepresentation of women on journal editorial boards may hinder career progression, as editorial board appointments are associated with prestige and notoriety, which may, in turn, impact hiring, promotion and tenure, as well as influence opportunities for personal and professional growth via collaboration and networking opportunities [13]. Furthermore, limiting the proportion of women among journal editorial boards not only impacts women's' careers but also affects the entire biomedical research establishment, as previous investigators have found that the presence of a woman EIC is associated with a greater proportion of women on editorial boards and advisory boards and as peer reviewers [14–17]. Finally, previous authors have suggested that a lack of women on editorial boards may reduce the diversity of published ideas and perspectives, as well as the number of individuals deemed qualified to address particular topics [13].

Limitations of this study include the inability to account for other variables that may influence the selection of journal editorial board members, including career stage. Additionally, we were unable to investigate or analyse editorial board terms; thus, it is not known how board terms (or term limits) affect the data and conclusions. We also acknowledge that we identified the perceived gender of individuals, which may not necessarily correlate with their true gender identity, and as is the case with DEI research, we are unable to account for the entirety of the gender spectrum. Nonetheless, these materials and methods are well established and have been used in numerous previous DEI studies. Finally, this observational study is not designed nor intended to assess for causality, as inequities are often multifactorial.

It should be noted that in contrast to previous studies of gender composition among recognition award recipients, which are bestowed on individuals via (an often anonymized and non-transparent) nomination and selection process, journal editorial board positions may be obtained via various avenues (e.g., the application process, invited applications, appointments, etc.). Therefore, the means by which a journal solicits and selects individuals to fill its editorial board may influence the demographic composition of editorial boards, and these processes should be studied further to ensure they are equitable and non-biased. Despite the limitations, these findings demonstrate the inequitable representation of women among journal editorial boards in BBTM, and assessment for causality may be the next step in addressing gender underrepresentation. Journals must commit to improving diversity among editorial boards, and the BBTM community must continue to advocate for women and individuals from historically underrepresented groups. We must continue to strive for equity among boards and governing bodies with respect to gender, race, ethnicity, sexual orientation and other identifying demographics.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Lee TH, Volpp KG, Cheung VG, Dzau VJ. Diversity and inclusiveness in healthcare leadership: three key steps. NEJM Catal. 2021. https://doi.org/10.1056/CAT.21.0166
2. Jacobs JW, Adkins BD, Stephens LD, Woo JS, Booth GS. Gender inequities in transfusion medicine society recognition awards. Transfus Med Rev. 2022;36:82–6.
3. Silver JK, Slocum CS, Bank AM, Bhatnagar S, Blauwet CA, Poorman JA, et al. Where are the women? The underrepresentation of women physicians among recognition award recipients from medical specialty societies. PM R. 2017;9:804–15.
4. Amrein K, Langmann A, Fahrleitner-Pammer A, Pieber TR, Zollner-Schwetz I. Women underrepresented on editorial boards of 60 major medical journals. Gend Med. 2011;8:378–87.
5. Jacobs JW, Adkins BD, Booth GS. Gender equity analysis of board of directors for transfusion medicine professional societies around the world. Vox Sang. 2022; *117*:1240–41.
6. Lally K, van den Akker T, Stone EF, Arinsburg SA. Gender representation in editorial boards of transfusion medicine journals. Transfusion. 2020;60.
7. Journal Citation Reports, Clarivate. Accessed Sept 13, 2022. https://access.clarivate.com/login?app=jcr&detectSession=true&referrer=target%3Dhttps%3A%2F%2Fjcr.clarivate.com%2Fjcr%2Fhome
8. Tanhehco YC, Ipe TS, Booth GS, Adkins BD. Academic productivity of early career transfusion medicine specialists: a workforce study. Transfus Med Rev. 2022; (In press).
9. AAMC. Table B3. Number of Active Residents, by Type of Medical School, GME Specialty, and Sex. Accessed Sept 15, 2022. https://www.aamc.org/data-reports/students-residents/interactive-data/report-residents/2021/table-b3-number-active-residents-type-medical-school-gme-specialty-and-sex
10. Ma Y, Oliveira DFM, Woodruff TK, Uzzi B. Women who win prizes get less money and prestige. Nature. 2019;565:287–8.
11. Patel SR, St Pierre F, Velazquez AI, Ananth S, Durani U, Anampa-Guzmán A, et al. The Matilda effect: underrecognition of women in hematology and oncology awards. Oncologist. 2021;26:779–86.
12. Murphy M, Callander JK, Dohan D, Grandis JR. Women's experiences of promotion and tenure in academic medicine and potential implications for gender disparities in career advancement: a qualitative analysis. JAMA Netw Open. 2021;4:e2125843.
13. Fox CW, Duffy MA, Fairbairn DJ, Meyer JA. Gender diversity of editorial boards and gender differences in the peer review process at six journals of ecology and evolution. Ecol Evol. 2019;9:13636–49.
14. Mauleón E, Hillán L, Moreno L, Gómez I, Bordons M. Assessing gender balance among journal authors and editorial board members. Scientometrics. 2013;95:87–114.
15. Ioannidou E, Rosania A. Under-representation of women on dental journal editorial boards. PLoS One. 2015;10:e0116630.

16. Fox CW, Burns CS, Muncy AD, Meyer JA. Author-suggested reviewers: gender differences and influences on the peer review process at an ecology journal. Funct Ecol. 2017;31:270–80.
17. Pinho-Gomes AC, Vassallo A, Thompson K, Womersley K, Norton R, Woodward M. Representation of women among editors in chief of leading medical journals. JAMA Netw Open. 2021;4:e2123026.

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SHORT REPORT

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The complexities of transfusion reactions: Coexistence of a delayed haemolytic transfusion reaction and post-transfusion purpura

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Abstract

Background and Objectives: Immune-mediated acute or delayed transfusion reactions occur when there is immunological incompatibility between transfused blood products and recipient's antibodies. Acute haemolytic transfusion reactions occur within 24 h and are delayed after 24 h up to 10 days following transfusion, whereas post-transfusion purpura (PTP) typically occurs 7–10 days post-transfusion. We present a case of a previously transfused and recently post-partum female who developed both delayed haemolytic transfusion reaction (DHTR) and PTP.

Case Report: A 42-year-old woman, G2P1, with non-alcoholic liver disease, portal hypertension and previous transfusion history with allogeneic anti-E, developed a severe DHTR and PTP following a complicated post-partum course and multiple transfusions. The antenatal and initial post-partum pre-transfusion antibody screens were negative. Subsequently five red cell antibodies, including anti-c, anti-Fya, anti-Jkb and anti-S and the reappearance of anti-E were, however, identified during follow-up investigations along with the anti-platelet antibody HPA-3a and human leukocyte antigen class I antibodies. Anti-E, anti-Jkb and anti-S were eluted from the circulating red blood cells.

Conclusion: To our knowledge, there have been only two other case reports of DHTR and PTP occurring in the same patient.

Keywords

haemolytic transfusion reaction, immunohaematology, platelet immunobiology, RBC antigens and antibodies, transfusion reactions, transfusion medicine (in general)

Highlights

- We present a rare case of both delayed haemolytic transfusion reaction (DHTR) and post-transfusion purpura occurring in a post-partum patient following the transfusion of seven red blood cell units.
- The patient had a history of anti-E that was not detected in the pre-transfusion antibody screening.
- A nationwide register of red cell antibodies in patients would help to prevent DHTRs due to evanescent antibodies.

INTRODUCTION

Immune-mediated transfusion reactions are infrequent adverse events that can carry significant consequences impacting future transfusions, pregnancy and surgery, including transplants. Delayed haemolytic transfusion reactions (DHTRs) are uncommon, occurring in 1:2500–11,000 transfusions [1] resulting from an anamnestic response to a red cell antigen to which the patient has previously been sensitized through either pregnancy or transfusion, usually becoming obvious 3–10 days post-transfusion [2]. This results in the (re)appearance of an antibody that was below the level of detection of the current pre-transfusion antibody screening. DHTR is clinically suspected if the patient develops clinical signs or laboratory findings of haemolysis in a temporal association with a recent transfusion. The reappearance of previously identified red cell antibodies or the presence of new antibodies in association with transfusion of antigen-positive blood confirms the diagnosis of a DHTR. Most DHTRs have a benign course and do not require specific treatment; however, all future transfusions must be with antigen-negative blood for patients in whom a clinically significant antibody was identified [2].

Transfusion reactions, which generate platelet antibodies, are a greater challenge to manage given the smaller frequency of compatible antigen-negative platelet products and the risk of transfusing small platelet doses in other plasma-containing blood products. Post-transfusion purpura (PTP) is a rare syndrome occurring in 1:24,000–1:100,000 transfusions [3] and characterized by profound thrombocytopaenia occurring 5–14 days post-transfusion of platelet-containing products [2, 4–7]. In many PTP cases, this is due to platelet-specific antibodies with a minority of cases occurring due to human leukocyte antigen (HLA) antibodies. Treatment includes the use of high-dose steroids and intravenous immunoglobulin (IVIg) [4, 5, 8]. Even with transfusion of antigen-negative platelets, there is only a transient or incomplete increment in platelet count (PLT) [8].

PTP occurring with DHTR is extremely rare, with only a small number of case reports described since 1980 [4, 5]. The parallel development of these antibodies is suggestive of a hyperimmune response postulated to occur on a background of autoimmune disease.

MATERIALS AND METHODS

All blood grouping, antibody screening and identification, phenotyping, direct antiglobulin test (DAT) and serological crossmatching were performed using Ortho BioVue® cassettes and manual techniques or the Ortho Vision® automated test system according to the manufacturer's instructions. Red cell blood group genotyping was performed by extracting DNA using the Immucor BioArray HEA Precise BeadChip™ and analysing individual single nucleotide polymorphisms results.

All platelet investigations were performed by the Australian Red Cross Lifeblood reference laboratory. Testing included the platelet immunofluorescence test (PIFT) as an indirect alloantibody test (donor crossmatch) and indirect autoantibody test (maternal specimen); the Glycoprotein assay using Immucor Lifecodes PAK Luminex assay (Pak-Lx); and HPA genotyping performed using polymerase chain reaction sequence-specific primers (PCR-SSP), using LinkSeq HPA typing, the Applied Biosystems Real-Time PCR instrument and PCR-Real Time using TaqMan dual-labelled probes for identification of HPA genotypes (1, 2, 3, 5 and 15).

ADAMTS13 activity assay was performed using the TECHNOZYM® ADAMTS13 Activity ELISA kit for the detection and quantification of ADAMTS13 activity. It uses a vWF73 substrate to which the patient sample is added. The patient's ADAMTS13 activity is proportional to the amount of von Willebrand Factor substrate cleaved and is measured by optical density.

CASE REPORT

A 42-year-old G2P1 female (AB RhD positive) was transferred to a tertiary care hospital from a smaller metropolitan hospital for further evaluation and management of suspected post-partum microangiopathic haemolytic anaemia. She has a history of long-standing asymptomatic non-alcoholic liver cirrhosis with portal hypertension that required red blood cell (RBC) transfusions at an interstate hospital at ages 19 and 23 following acute gastrointestinal haemorrhage arising from oesophageal varices. Following her second transfusion episode, she was informed of the development of an allogeneic anti-E red cell antibody. At age 39 and 17/40 gestation, she suffered a miscarriage of uncertain aetiology and was again informed of the presence of anti-E.

During her recent pregnancy, she had an uneventful antenatal period where her anti-E history was appropriately documented on pathology request forms although her current antibody screen was negative prior to delivery.

At 36-week gestation, a forceps delivery of a live male infant was complicated by an estimated 1-L blood loss when she received two units of crossmatch compatible group A RhD-positive RBC (Figure 1). Over the next 7 days, she remained symptomatically anaemic with no evidence of bleeding. Her haemoglobin continued to fall to 58 g/L requiring a further two units of RBC. RBC fragments were noted on her blood film and there was concurrent thrombocytopaenia (PLT: 77×10^9/L). Additional laboratory results demonstrated evidence of DAT-negative haemolysis (Figure 1). Following the transfusion of a further three units of group A RhD-positive crossmatch-compatible RBC, the haemoglobin incremented poorly (Figure 1). Bilirubin and lactate dehydrogenase (LDH) continued to rise and thrombocytopaenia persisted. On Day 8, post-partum, she was transferred to a tertiary care hospital for therapeutic plasma exchange based on a provisional diagnosis of thrombotic thrombocytopaenia purpura (TTP).

Repeat complete blood picture and biochemistry at the tertiary hospital confirmed haemolysis with ongoing fragmentation and undetectable haptoglobin. Coagulation studies were not indicative of disseminated intravascular coagulopathy (DIC). Based on the available results, a 6-L therapeutic plasma exchange was performed with fresh frozen plasma (AB, apheresis, thawed within 24 h of transfusion). Her DAT was now positive (IgG and C3d), and her indirect antiglobulin test (IAT) antibody screen and 11-cell IAT antibody panel were reactive.

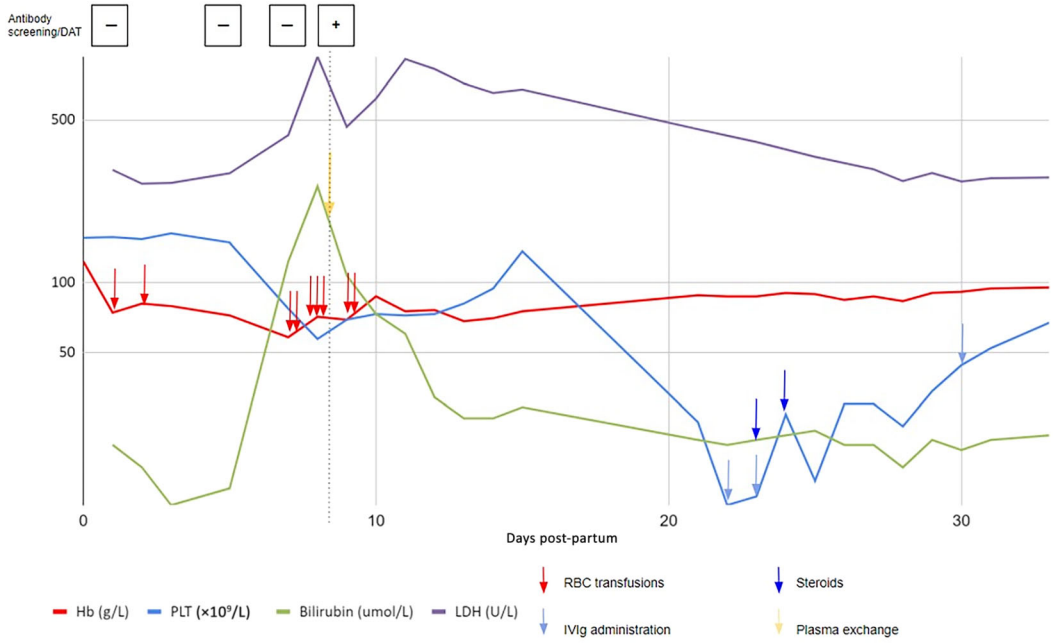

FIGURE 1 Detailed case summary with trends of haemoglobin (Hb), platelet count (PLT), bilirubin and lactate dehydrogenase (LDH) during the patient's post-partum period. Downward arrows depict specific treatment provided. The dotted vertical line demonstrates the day of transfer to a tertiary hospital to facilitate plasma exchange. Plus and minus symbols above the plotted graph show results of direct antiglobulin test (DAT) testing on the days testing was performed. IVIg, intravenous immunoglobulin; RBC, red blood cell.

TABLE 1 Red cell investigations

Blood group	**AB RH(D) positive**
Plasma testing by a range of IAT detection methods (saline, 22C and 37C, enzyme, polyethylene glycol)	Anti-E, anti-c, anti-Fya, anti-Jkb, anti-S
Acid glycine eluate	Anti-E, anti-Jkb and anti-S specificity when tested against panel cells
Phenotype (performed on pre-transfusion specimen)	CCDee, K−k+, Jk(a+b−), Fy(a−b+), NN, ss
Genotype	CCDee, K−k+, Jk(a+b−), Fy(a−b+), NN, ss

Transfused cell characteristics

RBC	**Phenotype**	**Additive**	**Characteristics**	**Days until expiry**
1	Apos, C−E+ c+ e+ K−	SAG-M	Leukodeplete	21
2	Apos, C+ E− c− e+ K−	SAG-M	Leukodeplete	4
3	Apos, C+ E−c+ e+ Cw− K−	SAG-M	Leukodeplete	6
4	Apos, C+ E− c− e+ Cw− K−	SAG-M	Leukodeplete	34
5	Apos, C− E−c+ e+ Cw− K−Fya+ Fyb+ Jka+Jkb+ M+ S− s+	SAG-M	Leukodeplete	11
6	Apos, C−E+ c+ e+ K−	SAG-M	Leukodeplete	14
7	Apos, C+ E− c− e+ Cw− K−	SAG-M	Leukodeplete	36

Note: Red letters in transfused cells phenotype indicate incompatible antigens to the patient's antibodies.
Abbreviations: IAT, indirect antiglobulin test; RBC, red blood cell; SAG-M, saline adenine glucose mannitol.

ABO grouping gave a mixed field reaction in the forward group consistent with recent transfusions of group A RhD RBCs. An extended red cell phenotype performed on the original pre-transfusion sample at the metropolitan hospital was CCDee, K−k+, Jk(a+b−), Fy(a−b+), NN and ss. Her past pregnancy and transfusion history was obtained from the obstetrics team, which guided further investigations, ultimately identifying anti-E, anti-c, anti-Jkb, anti-S and anti-Fya. The phenotypes of the group A RhD-positive RBC units transfused at the metropolitan hospital were obtained and two/seven units were shown to be incompatible with her known anti-E alloantibody (Table 1). Red cell genotyping results confirmed the serologically determined phenotype.

ADAMTS13 activity assay results excluded TTP. The patient improved following the transfusion with two units of phenotype-

TABLE 2 Platelet antibody and genotyping results

PIFT (group O donors)	All four panels reactive
Glycoprotein assay (Pak-Lx)	IIb, IIIa positive HPA-3a specificity
AutoXM (PIFT)	Positive
HLA (Pak-Lx)	Positive
Platelet genotyping	
Patient	1ab 2aa3bb 4aa 5aa 15aa
Partner	1ab 2aa 3ab 4aa 5aa 15ab
Neonate	1aa 2aa 3ab 4aa 5aa 15aa

Note: Red letters patient's antigen, which is incompatible with her partner.
Abbreviations: HLA, human leukocyte antigen; Pak-Lx, PAK Luminex assay; PIFT, platelet immunofluorescence test.

matched blood, remaining well over the next several days. Her blood counts and biochemical parameters improved, and she was commenced on folate supplementation to facilitate red cell recovery; iron status was satisfactory. Adequate reticulocytosis was noted, and she was discharged Day 15 post-partum.

Follow-up haematology and biochemistry blood tests at Day 21 post-partum revealed reticulocytosis (haemoglobin: 88 g/L) and thrombocytopaenia (25×10^9/L). Both bilirubin (21 μmol/L) and LDH (455 U/L) continued to fall. Examination showed no obvious bleeding or bruising. Repeat blood tests excluded DIC and TTP. Thrombocytopaenia continued to worsen (PLT: 11×10^9/L) with new mild haemorrhoidal bleeding. The patient was readmitted for further investigations and IVIg therapy (1 g/kg). The likely differentials for her thrombocytopaenia were autoimmune and alloimmune. Thrombocytopaenia persisted, and a further 1 g/kg IVIg was administered along with 1 mg/kg oral prednisolone. Transient improvement occurred in the PLT (27×10^9/L) before falling to 14×10^9/L requiring IV methylprednisolone. Over the next few days, her PLT remained between 20 and 30×10^9/L with no further bleeding (Figure 1).

Platelet investigations on her pre-treatment samples identified platelet autoantibodies, alloantibodies and HLA antibodies(Table 2). The PIFT showed strongly reactive antibodies to all four donor group O platelets, with reduced antibody activity against HPA-3bb platelets. The glycoprotein assay (Pak-Lx) showed antibody reactivity against glycoprotein IIb/IIIa, which expresses antigens HPA-1, HPA-3 and HPA-4. Anti-HPA-3a was identified, and the patient's genotype was confirmed as HPA-3bb, thus establishing the alloantibody as part of her PTP diagnosis. The PIFT auto-crossmatch was positive, demonstrating an autoantibody and the Pak-Lx assay also demonstrated HLA class I antibodies.

As the antibody continued to react strongly on all testing, a third dose of IVIg was administered on Day 30, after which the platelets continued to rise. By Day 35, her PLT was 93×10^9/L.

DISCUSSION

The parallel development of red cell, leukocyte and platelet antibodies in our patient with resultant severe DHTR and PTP may indicate a hyperimmune response. The exact aetiology of our patient's liver disease is unknown, with no documented evidence of autoantibodies, but an autoimmune background has been previously reported in two cases of DHTR and PTP co-occurrence where both cases had autoimmune thyroid disease [4]. Transfusion of blood products can trigger the release of cytokine mediators from endothelial cells, particularly if these cells have been activated from surgery or trauma. A pro-inflammatory state may have arisen from the birth and transfusion during this immediate post-partum period and may have primed the patient's immune system, lowering the threshold for reaction to the first incompatible product.

Although our patient had a known history of anti-E from prior transfusions, the antibody remained below the detection threshold during her antenatal and initial post-partum period. The transfusion service had not been informed of this history, and the combination of negative antibody screen, negative DAT and lack of antibody history meant that the transfusion provider issued electronically cross-matched RBCs that were ultimately incompatible. Her anti-E antibody was restimulated by incompatible RBC transfusions, only being detected on Day 8 post-transfusion (where her DAT and antibody screen were positive). The first incompatible red cell unit likely triggered a cascade of additional antibody development to the four other antigens described in the case.

Blood group antibodies commonly associated with DHTRs include Rh, Kidd, Duffy, Kell and S in order of decreasing frequency [9]. Any of her antibodies could have contributed to her reaction. The lack of increment to RBC transfusions and rise in biochemical haemolysis markers were likely due to multiple antibody development causing a more severe DHTR presentation. To prevent DHTR, it is important to have a thorough medical history, including previous transfusions, pregnancies, transplants and transfusion reactions and relevant information provided to the laboratory. The sharing of this information across different pathology and transfusion providers or alternatively through a national antibody register may have prevented the described complications.

Our patient returned to the hospital within 2-week post RBC transfusions with profound thrombocytopaenia and mild haemorrhoidal bleeding. Given the development of multiple RBC alloantibodies, alloimmune and autoimmune thrombocytopaenia were suspected as the cause. Although she never received platelet transfusions, it is known that platelet alloantibodies can be generated following transfusion with other blood products, such as RBCs, although the potential platelet antigen dose is small. While further investigations were underway, she was treated with a combination of high-dose steroids and IVIg. Clinical and serological findings established the diagnosis of PTP with HPA-3a platelet antibody detected.

PTP was first described in 1961 by Shulman et al. in two multiparous women who had developed thrombocytopaenia following transfusion [3, 8]. PTP more commonly occurs in multiparous women who have been sensitized to foreign platelet antigens through previous pregnancy or transfusions [2, 3, 6], resulting in a profound secondary response and reaction 5–14 days post-transfusion [3]. It is likely that transfusion was our patient's sensitizing event rather than the

previous pregnancy, given that serum collected antepartum had no evidence of HPA-3a antibody.

PTP is usually associated with mucocutaneous bleeding, haematuria, melaena, vaginal bleeding, abnormal post-operative bleeding and intracranial haemorrhage [3, 6, 7]. HPA-3a antibodies have been reported to be associated with moderately severe bleeding; our patient had minimal signs of haemorrhoidal bleeding. Given the potential for rapid deterioration and a 10%–20% fatality rate (mostly from intracranial haemorrhage), a thorough investigation can cause diagnostic delay so treatment may need to be commenced before workup is completed [7]. Other differentials that require exclusion include drug-induced thrombocytopaenia (such as heparin-induced thrombocytopaenia), DIC, septicaemia, underlying haematologic disease, thrombotic microangiopathies, ITP and splenomegaly with sequestration. Because of clinical overlap with these conditions, it is thought that PTP is underdiagnosed and thus under-reported [3]. The temporal association with RBC transfusion 12 days prior increased the probability of PTP. Although our patient had splenomegaly from liver disease, her pre-delivery PLT had been maintained at >100 $\times$ 10^9/L. The mean platelet volume in these patients is often elevated, indicating higher platelet turnover and activation. It is unknown whether this amplified platelet activity may have contributed to such a high platelet-antibody titre and persistent thrombocytopaenia requiring additional steroids and IVIg to generate an incremental response.

Unlike a DHTR, in PTP, the HPA antibodies destroy platelets with foreign antigens and paradoxically, also, autologous platelets [3]. The mechanisms are poorly characterized; however, the most probable hypothesis suggests a hyperimmune response, which induces the formation of autoantibodies reactive with autologous platelets [3, 5–8, 10]. Falk et al. [10] demonstrated serum collected during the thrombocytopaenic phase of illness reacted with post-recovery autologous platelets, strongly suggesting that platelet destruction was caused by a GPIIb/IIIa-specific autoantibody produced simultaneously or shortly after the two alloantibodies (HPA-1a and HPA-2a). This is also supported by (1) autologous platelets containing elevated levels of platelet-associated IgG, (2) clinical features and responses similar to ITP, (3) platelet autoantibodies detected in the acute phase of PTP that are not detectable at recovery while alloantibodies persist and (4) transfusions with antigen-negative platelets are still cleared with poor platelet incrementation [3]. A similar phenomenon is recognized with RBC antibodies; however, the consequences of autoantibodies against red cells is usually mild due to the large red cell mass in comparison to a much smaller total body platelet mass [10]. Our patient had high-titre alloantibodies and an autoantibody, requiring several treatments before platelet recovery.

HLA antibodies can also frequently develop in association with PTP, with a few reported cases of PTP secondary to HLA antibodies [3, 5]. No autoantibodies to HLA antigens have been convincingly reported; however, HLA antibodies are an important cause of platelet refractoriness and may contribute to the suboptimal response to platelet transfusions even with HPA antigen-negative platelets [3].

Without treatment, the duration of thrombocytopaenia in PTP ranges from 10 days to 3 weeks or more [6, 7]. Although the condition appears to be self-limiting, the duration of thrombocytopaenia can be reduced with specific treatment [8]. In the pre-IVIg era, high-dose steroids have induced dramatic improvements in some patients but have not demonstrated consistent efficacy in others [4, 5]. Plasmapheresis is efficacious in ~80%–90% in removing offending antibodies and can be considered for complex cases or those refractory to IVIg [3, 6, 7]. IVIg is thought to be ~80% efficacious in doses similar to those used in other immunohaematological disorders such as ITP [2, 3, 6, 7, 11]. Most patients achieve remission after 1–4 weeks of therapy, but 15% have fatal outcomes [6, 7, 10, 11].

Red cell availability for elective and emergency settings is conditional on how stringently matched the blood is required to prevent complications. When searching on donor red cell compatibility calculators, Group A phenotype-matched blood in preference to AB phenotype matched is approximately 1:950 (0.11% of the donor population) compared to 1:10,000. Group O phenotype-matched blood has a frequency reported of 1:422 (0.24% of the donor population). Platelet availability for HPA-3bb platelets is scarce. Furthermore, platelet refractoriness and alloimmunization from additional HLA exposure could make liver transplantation difficult or even unviable for our patient. The timing of available platelet units matched for HPA status is ~7 days from request to processing and delivery to the hospital for use [12].

CONCLUSION

This case highlights the challenges of correct diagnosis and management of immune-mediated transfusion reactions and future implications on the patient's care. The best strategy to prevent immune transfusion reactions is the use of sensitive antibody screening methods, sharing of accurate, up-to-date transfusion records through national antibody registers, medical history and notification of special requirements for future transfusions.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DECLARATIONS

Our patient consented to have her relevant demographics, medical history, symptoms and signs, treatments and interventions, and outcomes included in our case report. The patient provided consent to publication given the rarity of the conditions and to provide education on transfusion history documentation.

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REFERENCES

1. U.S. Centers for Disease Control and Prevention. National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol. 2021. Available from: https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf.
2. Ogedegbe HO. A review of immune mediated transfusion reactions. Lab Med. 2002;33:287–95.
3. Hawkins J, Aster RH, Curtis BR. Post-transfusion purpura: current perspectives. J Blood Med. 2019;10:405–15.
4. Maślanka K, Zupanska B. Post-transfusion purpura and delayed haemolytic transfusion reaction. Transfus Med. 1993;3:281–4.
5. Puig N, Sayas MJ, Montoro JA, Villalba JV, Pia A. Post-transfusion purpura as the main manifestation of a trilineal transfusion reaction, responsive to steroids: flow-cytometric investigation of granulocyte and platelet antibodies. Ann Hematol. 1991;62:232–4.
6. Vincent EC, Willett T. Post-transfusion purpura. J Am Board of Fam Pract. 1991;4:175–7.
7. Bhamra JS, Iversen PO, Titze TK, Tjønnfjord GE, Aköok ÇA. A case of posttransfusion purpura with severe refractory thrombocytopenia but no cutaneous manifestations. Case Rep Hematol. 2018;2018:1–3.
8. McCrae KR, Herman JH. Posttransfusion purpura: two unusual cases and a literature review. Am J Hematol. 1996;52:205–11.
9. Australian Red Cross Lifeblood. Delayed Haemolytic Transfusion Reactions (DHTR). 2022 [updated 2021–2022]. Available from: https://www.lifeblood.com.au/health-professionals/clinical-practice/adverse-events/DHTR.
10. Falk G, Winans CG, Bowens K, Bougie DW, Curtis BR, Aster RH. An unexpected development after surgery-post-transfusion purpura! Am J Hematol. 2016;91:848–51.
11. Rafei H, Yunus R, Nassereddine S. Post-transfusion purpura: a case report of an underdiagnosed phenomenon. Cureus. 2017;9:e1207.
12. Australian Red Cross Lifeblood. Red cell compatibility calculator. 2021–2022. Available from: https://www.lifeblood.com.au/health-professionals/testing/red-cell-compatibility-calculator.

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