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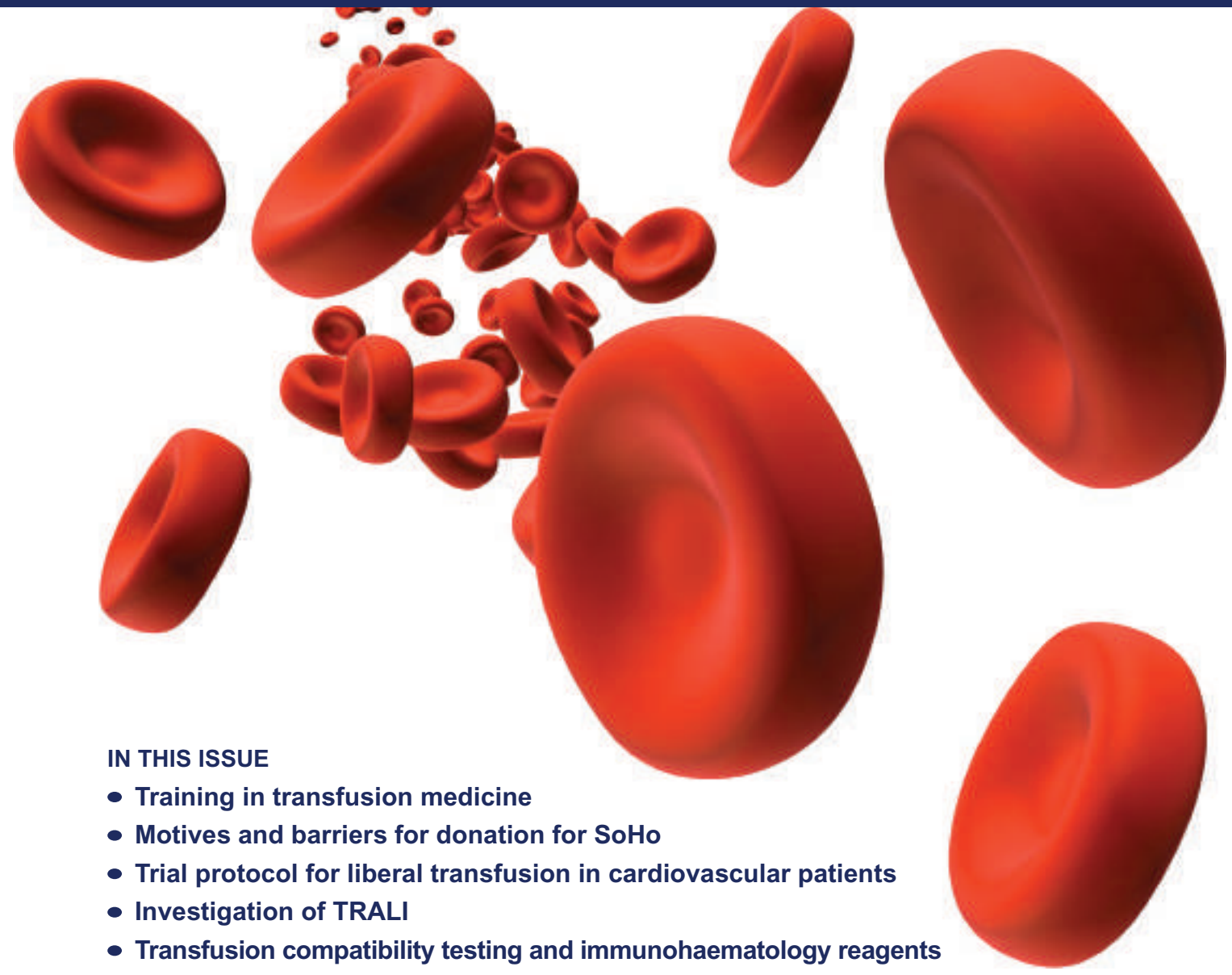

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Transfusion Medicine will publish articles on transfusion medicine in its widest context, including blood transfusion practice (blood procurement, pharmaceutical, clinical, scientific, computing and documentary aspects), immunohaematology, immunogenetics,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

A rapid review of strategies to manage low iron levels in adults donating whole-blood: A focus on donor behaviour

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Abstract

In recognition of the impact of whole-blood donation on body iron stores, there has been an increased focus assessing the efficacy of strategies to minimise the risk of iron deficiency (ID). Whilst donor behaviour is an important determinant of success, this literature is yet to be fully synthesised to help guide blood collection agencies when implementing these strategies into routine practice. This rapid review identifies strategies for management of low iron, how they have been communicated to donors, donor compliance with advice, donor use of external health services and their effect on donor retention. Web of Science, Medline, CINAHL and Wiley online library databases were searched from 2012 to November 2023, with 29 studies meeting inclusion criteria. Five iron management strategies were identified: oral iron supplementation (IS), education, dietary advice, lengthening inter-donation interval and switching donation type. Most studies (n = 16) focused on IS, with only four reporting how they communicated this to donors. Donor use of IS was high in controlled research environments but has not been evaluated when implemented into routine practice. None of the four studies on dietary advice included findings on donor acceptability. The proportion of donors consulting their doctor about a low iron result or their risk of ID was found to be suboptimal. However, in general, the identified strategies and communications had a positive effect on donor retention. More evidence is needed on how to increase donor knowledge and awareness of donation-related risk of ID as well as to identify how to effectively communicate strategies to donors to ensure optimal acceptability and use

Keywords: iron supplementation; blood donor deferral; neutralisation test.

1 | INTRODUCTION

In 2020, the emergence of the severe acute respiratory syndrome Coronavirus 2 (SARS CoV-2) resulted in significant disruption to the US healthcare system. During March April 2020 and extending through 2020, mitigation measures intended to control virus transmission resulted in reduced utilization of healthcare services.1-3 The Centers for Medicare & Medicaid Services (CMS) issued recommendations to delay all nonessential medical procedures.4 Subsequently, this recommendation along with the implementation of other mitigation measures resulted in a reduction in patients seeking routine preventive

and screening measures, emergency services, surgical procedures, and other hospital-based

care.1-3,5,6their lifetime. Therefore, asymptomatic HTLV-1 carriers could be at risk of becoming blood donors in Japan. Regarding the

other mitigation measures resulted in a reduction in patients seeking routine preventive and screening measures, emergency services, surgical procedures, and other hospital-based care.[1-3,5,6]

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

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

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

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

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

2 | OBJECTIVE

To evaluate the evidence for the safety and effectiveness of using convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) to treat severe respiratory disease caused by coronaviruses or influenza. With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR

1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1). We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

3 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for inter- action (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

3.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing

stud- ies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Sci- ence). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11] With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR
1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

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3.2 | Selection criteria

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

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

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR
1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

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3.3 | Data extraction

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

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

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

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

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

3.4 | Risk of bias assessment

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

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

3.5 | Data analysis

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

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

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

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

3.5.1 | Subgroup and sensitivity analysis

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

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

We also subgrouped COVID-19 studies by their use of high titre or low titre/unselected plasma (see Appendix A3 in Data S1) in response to emerging research that highlighted the wide variability in CP titres used in practice. With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR
1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

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

3.5.2 | *Post hoc* analysis of seropositivity

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

4 | RESULTS

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

4.1 | Study Characteristics

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

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

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

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

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

4.2 | Comparisons

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

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

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

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

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

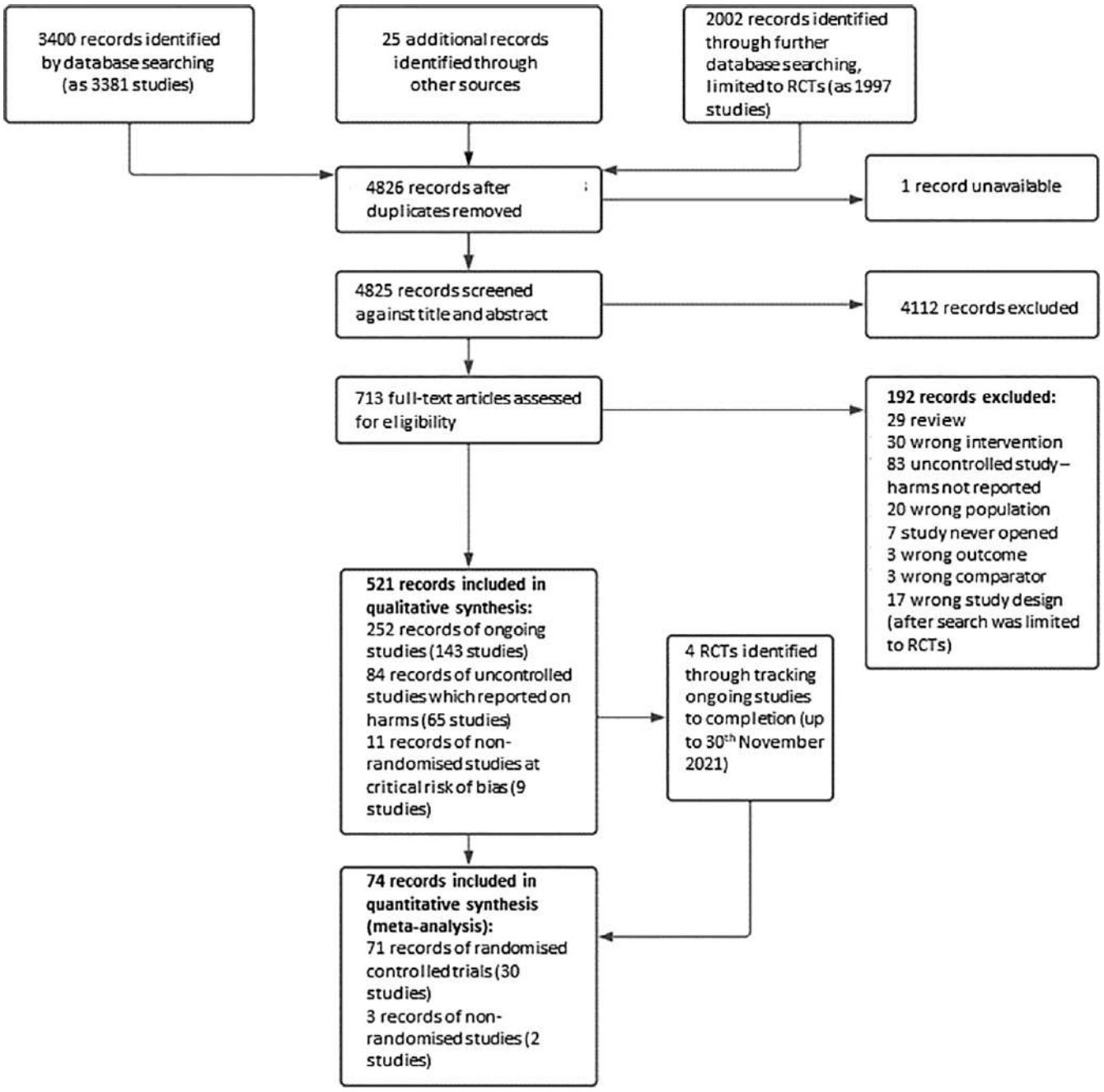

FIGURE 1 PRISMA flow diagram. Caption: The reasons for exclusion at each stage are shown with arrows to the right.

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

4.3 | Outcomes

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

Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which prevents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned —1, people who were on MV at

randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

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

4.4 | ROB in included studies

4.4.1 | RCTs (using Cochrane ROB1)

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

4.4.2 | Non-RCTs (using ROBINS-I)

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

4.5 | Certainty of the evidence (GRADE)

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

4.6 | Effect of the Intervention

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

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

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

All-cause mortality

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

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

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

Improvement of clinical symptoms

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

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

Length of stay (LOS): hospital and ICU

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

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

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

Adverse events

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

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

There was no evidence of an effect on reported SAEs[3,23-31,35,36,39]

(13 RCTs, n = 16 730, very-low certainty of evidence) (Figure A3B). Data were not available on SAEs in seven RCTs.[7,22,32-34,37,38]

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

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

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

All-cause mortality

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

Adverse events

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

Improvement of clinical symptoms

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

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

4.6.3 | Comparison 3: hyperimmune immunoglobulin versus control

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

All-cause mortality

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

Adverse events

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

Improvement of clinical symptoms

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

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

4.6.4 | Comparison 4: early CP versus deferred CP

One RCT assessed early CP compared to deferred CP.

All-cause mortality

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

Adverse events

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

Improvement of clinical symptoms

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

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

4.7 | Results from uncontrolled studies (for safety only)

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

4.8 | Post hoc subgroup analysis: seropositivity at baseline

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

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

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

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

5 | DISCUSSION

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

5.1 | Main findings

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

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

5.2 | Quality (certainty) of the evidence

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

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

SAEs were also downgraded for inconsistency as the heterogeneity was significant between studies, this is likely to be due to the variation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring

varying levels of AE reporting including the need to use a grading sys- tem (e.g., MedDRA[64]). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR
1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

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

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1. We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the

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There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1. We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for inter- action (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

5.3 | Strengths and Limitations of this review

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

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for inter- action (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups. With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for inter- action (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

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We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification. We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

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

5.4 | Interpretation and context

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

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

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

Similarly, between trials, there was heterogeneity of patient groups and severity of illness on admission to hospital (Table 1). The RCTs in

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

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

5.5 | Implications for research and practice

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

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

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention. We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1). With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR With almost all the information coming from the two large, high- quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

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

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

6 | CONCLUSION

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

AUTHOR CONTRIBUTIONS

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

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

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

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Impact of introduction of a goal directed transfusion strategy in a patient blood management program: A single cardiac surgery centre experience

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Abstract

Background: The aim of this retrospective and observational study was to analyse the impact of the introduction of a goal directed transfusion (GDT) strategy based on a viscoelastic test (ROTEM®) and specific procoagulant products in a patient blood management (PBM) Program on blood product use and perioperative bleeding in a single cardiac surgery centre.

Study Design and Methods: Patient population underwent cardiac surgery from 2011 to 2021 was divided in two groups based on PBM protocol used (G#11–14, years 2011–2014, G#15–21, years 2015–2021) and compared for the following variables: intraoperative and postoperative transfusions of packed red blood cell and any procoagulant products, postoperative drain blood loss volume and rate of re-exploration surgery.

The second program was defined after the introduction of a GDT protocol based on viscoelastic tests and specific procoagulant products.

Results: After the introduction of a GDT protocol, about 80% less amongst patients were transfused with fresh frozen plasma and any procoagulant product ($p < 0.001$ for both phases). Moreover, similar results were obtained with PRBC transfusions ($p < 0.001$) and drain blood loss volume ($p = 0.006$) in the postoperative phase.

The main factors affecting the use of any procoagulant and PBRC transfusion in the multivariate logistic regression analysis was Group (2 versus 1, OR 0.207, $p < 0.001$) and preoperative haemoglobin (OR 0.728, $p < 0.001$), respectively.

Discussion: In our experience, a GDT strategy for the diagnosis and treatment of the coagulopathy in patients undergone cardiac surgery led to a significant reduction in bleeding and transfusion.

KEYWORDS

cardiac surgery, coagulopathy, patient blood management, postoperative blood loss, procoagulant products, viscoelastic tests

1 | INTRODUCTION

Cardiac surgery is known to have one of the highest bleeding risks and, consequently, a high rate of blood product transfusions.[1,2] This is mainly due to preoperative patient characteristics (i.e., antiplatelet or anticoagulant therapy), the great invasiveness of the procedures, the exposure to high doses of anticoagulation drugs during surgery, and Cardiopulmonary bypass (CPB)—induced haemodilution.

A quantitative and qualitative coagulation derangement resulting from the abovementioned factors can lead to an increased risk of bleeding and allogeneic transfusion related to adverse clinical outcomes (i.e., infections, acute renal failure and stroke) and a high risk of death.[3–6]

Over the last two decades, patient blood management (PBM), defined as a '*patient-centred, systematic, evidence-based approach to improve patient outcomes by managing and preserving a patient's own blood, while promoting patient safety and empowerment*',[7] has been widely and effectively applied in cardiac surgery through the 'three pillars' strategy: 1. optimisation of the patient's endogenous red cell mass 2. minimisation of bleeding and blood loss 3. optimisation of the patient-specific physiological tolerance of anaemia. Focusing on the second 'pillar', the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC) Guidelines on PBM in cardiac surgery recommend evidence-based algorithms for bleeding management.[8]

In this context, point-of-care (POC) viscoelastic tests play a pivotal role in the timely and goal-directed treatment of coagulopathy in comparison with standard coagulation tests.[9–11]

Moreover, transfusion medicine has improved over the last decades by offering new procoagulant products to identify the cause and achieve bleeding control.[10]

Aim of this single-centre, observational, retrospective study is to analyse the impact of the introduction of a goal directed transfusion (GDT) strategy in a new PBM program, based on rotational thromboelastometry and new procoagulant products, on hemocomponent and hemoderivatives consumption, blood loss and reoperation rates in patients undergoing cardiac surgery on CPB.

2 | PATIENTS AND METHODS

2.1 | PBM protocols

The hospital of Legnano is a community hospital with all the main medical and surgical specialities, including the Cardiac Surgery Department. The PBM program has continuously changed and improved since the opening of the Cardiac Surgery Unit in 2000. In 2011, a local protocol was drawn up (#1) based on international guidelines and good clinical practice.[3,12–15] In 2015, the POC coagulation test ROTEM® sigma® (produced by Werfen, Munich, Germany) was introduced to provide an alternative approach to assess perioperative coagulation disorders employing viscoelastic analysis of blood clotting assessment in vitro. Four tests are performed simultaneously with a citrated blood sample: EXTEM, which tests the blood activated with tissue factor and allows the analysis of the maximum lysis (ML) to establish the need for antifibrinolytic drugs, INTEM by testing the blood activated with phospholipid and ellagic acid, HEPTEM is an INTEM test with the addition of heparinase and tests the need for protamine after CPB and FIBTEM that is an EXTEM test with the addition of platelet inhibitor cytochalasin D to evaluate functional fibrin polymerisation separately without platelet activity. Both tests can neutralise up to 5 IU/mL of unfractionated heparin.

Since 2015, other blood procoagulant products have been introduced in the PBM program with definitive indications: Cryoprecipitate (Cryo), fibrinogen concentrate (Fc) and prothrombin complex concentrate (PCC).

With the introduction of ROTEM® and these specific procoagulant products, a new PBM protocol (#2) based on a Goal-Directed Strategy was defined in 2015 to correct the causes of coagulopathy and bleeding and determine the correct products to transfuse and the best dosage. ROTEM® tests were performed for specific cases: active or massive bleeding after extracorporeal circulation or predictable bleeding procedures on specific patients (see Table 1B for definitions). For active or massive bleeding, patient's blood was tested with ROTEM® during bleeding and after transfusion, up to bleeding stops. For predictable bleeding procedures, patient's blood was tested with ROTEM® routinely during or immediately after CPB and after transfusions. Table 1A summarises the main characteristics of the two PBM protocols, #1 used from 2011 to 2014 and #2 used from 2015 to 2021. The specific triggers to perform a ROTEM® test and to use blood haemostatic products and their dosage are illustrated in Table 1B.

2.2 | Patient population and data collection

The study included all patients undergoing cardiac surgery interventions from 2011 to 2021 that accepted to participate in hospital observational studies. Demographic and clinical data of all patients undergoing elective or emergency cardiac surgery over 11 years were collected, and they were treated by a specific trial office, in order to use—for the statistical analysis—only data completely anonymized.

Data were extracted from the clinical charts of all subjects who had undergone cardiac surgery. Informed consent about using personal data for scientific purposes was collected.

2.3 | Anaesthesia procedures and surgical techniques

All patients received general anaesthesia: anaesthesia maintenance with sevoflurane and propofol, avoiding sevoflurane during CPB time.

According to international guidelines, three boluses of 15 mg/kg tranexamic acid were administered before, during and after the CPB time.[16–18]

TABLE 1A List of strategies based on the 'three pillars' patient blood management principles applied in the 2 periods.

Phase and strategy	Application	
Preoperative	#1 (2011–2014)	#2 (2015–2021)
Preoperative anaemia correction (for acquired deficiency anaemia)	✓	✓
Discontinuation of antiplatelets/anticoagulants drugs in accord with the current guidelines	✓	✓
VASP for evaluation of platelet aggregation for patients in DAPT therapy	✓	✓
Intraoperative	#1 (2011–2014)	#2 (2015–2021)
Routine use of antifibrinolytics	✓	✓
DDAVP (suspected acquired von Willebrand disease)	✓	✓
Routine use HMS for establish heparin and protamine dose	✓	✓
Routine use of cell salvage and use of ultrafiltration in hypervolemic and/or renal failure patients	✓	✓
Routinely restrictive PRBC transfusion thresholds (8 g/dL for CAD patients, 7 g/dL for non-CAD patients)	✓	✓
Protamine infusion (usually 50 mg iv) after extracorporeal circulation if uncontrolled bleeding	✓	x
Viscoelastic test-guided transfusion therapy (FFP, PCC, Cryo, Fc) (Table 1B)	X	✓
PLTs and FFP transfusion according to the most probable cause of coagulopathy guided by preoperative lab tests and CPB duration time	✓	X
Postoperative	#1 (2011–2014)	#2 (2015–2021)
Routinely restrictive PRCB transfusion thresholds (8 g/dL for CAD patients, 7 g/dL for non-CAD patients)	✓	✓
Viscoelastic test-guided transfusion therapy ((FFP, PCC, Cryo, Fc) (Table 1B)	X	✓
PLTs and FFP transfusion according to the most probable cause of coagulopathy guided by preoperative lab tests and CPB duration time	✓	X

Over the 11 years, CPB circuits did never change: two types of circuits, respectively, for roller and centrifugal pump were always used. They are composed by disposable components and cannulas, forming a heparin-coated tip-to-tip circuit. For the priming volume, of about 1200 mL, it was used ringer's lactate solution. Heparin and protamine dosages were calculated with the HMS platform by Medtronic (Hemostasis Management System) according to lean body weight; the ACT target for the CPB phase was 480 s at least.

TABLE 1B ROTEM test protocol.

Indications to immediately perform the ROTEM tests during intraoperative and postoperative phases:

- Active bleeding: more than 3 mL/kg/h for the first 2 h or 1.5 mL/kg/h for the next 4 h after extracorporeal circulation
- Massive bleeding: more than 200 mL per 30 min in the first hour and/or 200 mL/h in the next hours) after extracorporeal circulation
- Predictable bleeding: CPB time > 150 min, redo patients, previous coagulation disorders

Clinical interventions guided by ROTEM:

• CT INTEM >240 s and CT HEPTEM <80% CT INTEM	→	Protamine 50 mg iv
• MCF FIBTEM <9 mm	→	Fc or Cryo 2 g iv
• MCF FIBTEM >9 mm and CT EXTEM >90 s	→	FFP 10 mL/kg iv or PCC 20 UI/kg iv
• MCF FIBTEM >9 mm and A10 EXTEM <40 mm	→	PLTs 1 pool unit iv
• MCF FIBTEM >9 mm and CT EXTEM <90 s and A10 EXTEM >40 mm	→	DDAVP 0.3 mcg/kg iv
• ML EXTEM >15%	→	Tranexamic acid 15 mg/kg iv

Note: A10 = clot amplitude after 10 min.
Abbreviations: CAD, coronary artery disease; CPB, cardiopulmonary bypass; Cryo, cryoprecipitate; CT, coagulation time; DAPT, dual antiplatelets therapy; DDAVP, desmopressin acetate; Fc, fibrinogen concentrate; FFP, fresh frozen plasma; HMS, heparin monitoring system; MCF, maximum clot firmness; PCC, prothrombin complex concentrate; PLTs, platelets; PRBC, packed red blood cell; VASP, vasodilator stimulated phosphoprotein.

All the described procedures were performed with CPB, since heart valves replacement and aortic surgery were open-heart procedures. Surgical incision was median sternotomy for most of the patients, while only a small part was performed via mini-thoracotomy (3%). The same surgeon performed almost 95% of the operations; the anaesthesiologist team consisted of seven physicians.

2.4 | Blood products transfusion

Packed red blood cell (PRBC) transfusion therapy was always performed if haemoglobin was less than 8.0 g/dL in patients with coronary artery disease (CAD) and less than 7.0 g/dL for other patients.

In the first protocol (#1, 2011–2014), fresh frozen plasma (FFP) was transfused prophylactically in redo surgeries and emergency aortic surgeries in deep hypothermic circulatory arrest or according to the results of standard coagulation tests (intraoperative and postoperative), namely PT or aPTT ratio >1.5 or for any cases of uncontrolled bleeding. Platelet pools were transfused according to perioperative laboratory tests if the platelet count was less than 50.000 mcL.

In the second protocol (#2, 2015–2021), transfusion therapy was guided by employing a specific decisional algorithm (Table 1B) based on the results of viscoelastic tests (ROTEM® sigma, IL Werfen, Munich, Germany) and the availability of Cryo, PCC and Fc.

TABLE 2 Patients population in the two groups.

	G#11–14 $N = 1599$	G#15–21 $N = 3291$	p
Age (years)	70 (44–83)	70 (46–81)	0.504
Male sex *N* (%)	1000 (62.5)	2276 (69.2)	<0.001
Weight (kg)	73.1 (±16.9)	74.8 (±14.8)	<0.001
BMI (kg/m^2)	25.5 (19.6–34.3)	25.7 (19.8–34.2)	0.213
Hypertension *N* (%)	853 (61.2)	2163 (73.4)	<0.001
Diabetes *N* (%)	292 (21.0)	707 (24.0)	<0.001
Chronic kidney disease N (%)	89 (6.4)	295 (10.0)	<0.001
Past miocardial infarction *N* (%)	261 (18.6)	487 (16.5)	0.072
COPD *N* (%)	186 (13.4)	348 (11.8)	0.148
Creatinine (mg/dL)	1.1 (0.7–14.0)	1.1 (0.7–15.0)	0.095
Preop EF (%)	55 (32–65)	57 (30–65)	0.002
Preop Hb (g/dL)	13.1 (±1.8)	12.9 (±1.9)	<0.001
Emergency surgery *N* (%)	223 (16.0)	233 (11.3)	<0.001
Redo surgery *N* (%)	94 (6.8)	213 (7.2)	0.562
Coronary surgery *N* (%)	599 (37.5)	1449 (44.0)	<0.001
Isolated valve surgery *N* (%)	536 (33.5)	1174 (35.7)	0.139
Isolated ascending aorta *N* (%)	53 (3.1)	183 (5.6)	0.01
Combined surgery *N* (%)	359 (22.5)	464 (14.1)	<0.001
CPB time (min)	96 (62–156)	97 (65–157)	0.005
X-clamp time (min)	71 (42–116)	74 (46–127)	<0.001
Patients CPB > 150 min *N* (%)	77 (4.8)	319 (9.7)	0.145
SAPS II *N*	24 (13–40)	23 (13–37)	0.728
SOFA score *N*	4 (1–8)	5 (2–8)	<0.001
Euroscore I log *N*	5.5 (0.9–59.0)	5.4 (1.3–49.0)	0.376

Note: Categorical variables are presented as absolute numbers (percentage) and compared by χ^2 test. Continuous, non-normally distributed variables are presented as median [interquartile range] and compared by Mann–Whitney *U* test. Continuous, normally distributed variables are presented as median (±standard deviation) and compared by *t*-student test.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; EF, ejection fraction; Euroscore I log, logistic euroscore I; Hb, haemoglobin; SAPS II, simplified acute physiologic score II; SOFA, sequential organ failure assessment; X-clamp time, aortic cross clamp time.

Four units of cryoprecipitate were pooled in a single transfer bag to obtain a measured total amount of fibrinogen between 1 and 2 g.

We used a 3-factor PCC (Human Complex D.I.-Kedrion, Castelvecchio Pascoli, Italy) that contains clotting factors II (25 U/mL), IX (25 U/mL) and X (20 U/mL) and Haemocomplettan P (CSL Behring, Marburg, Germany) as a source of fibrinogen.

Based on the two protocols described, our patients were divided into two groups: G#11–14 (2011–2014) and G#15–21 (2015–2021).

We compared the two groups by the percentage of transfused patients with any product (PRBC, FFP, PLTs, Cry, or Fc, PCC) in intraoperative and postoperative phases. We then studied the percentage of patients receiving any procoagulant blood product: FFP for G#11–14 and FFP plus Cryo-Fc and/or PCC for G#15–21.

For the postoperative period, we studied the drain blood loss and the percentage of re-exploration surgery patients in the two groups. The postoperative period was defined as the first 12 h after ICU admission.

2.5 | Statistics

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean (standard deviation) if normally distributed and median (interquartile range) if non-normally distributed variables. Student's *t*-test compared continuous, normally distributed variables; continuous non-normally distributed variables were compared by Mann–Whitney *U* test; categorical variables were compared by χ^2 test.

A two-step logistic regression path was used to correct the statistical analysis for any possible confounder. First, all available characteristics were studied by monovariate tests. Second, two multivariate logistic regression models were built with a step-down approach, describing all features significantly associated with using any coagulation product and PRBC transfusion.

The statistical significance level was established at $p < 0.05$ for all analyses. STATA 14 (STATA, College Station, TX) statistical package was used.

TABLE 3 Results: intraoperative and postoperative transfusions, drain blood loss volume and re-exploration surgery.

	Intraoperative			Postoperative		
	G#11–14 (*N* = 1599)	G#15–21 (*N* = 3291)	*p*	G#11–14 (*N* = 1599)	G#15–21 (*N* = 3291)	*p*
Transfused patients *N* (%)	208 (21.3)	555 (18.8)	0.950	133 (9.6)	124 (4.2)	<0.001
PRBC Transfused patients *N* (%)	201 (12.6)	522 (15.9)	<0.002	105 (6.6)	86 (2.6)	<0.001
PRBC Transfused units *N*	2.2 (1–4)	2.6 (1–4)	0.528	2.1 (1–4)	1.9 (1–4)	<0.001
FFP Transfused patients *N* (%)	127 (7.9)	30 (0.9)	<0.001	86 (5.3)	43 (1.3)	<0.001
FFP Transfused volume (mL)	789 (400–1250)	883 (250–2500)	0.245	866 (500–1500)	832 (250–2000)	0.714
PLTs Transfused patients *N* (%)	30 (1.9)	64 (1.9)	0.870	20 (1.3)	45 (1.4)	0.738
PLTs Transfused pool units *N*	1 (1–2)	1 (1–2)	0.285	1 (1–2)	1 (1–2)	0.665
Cryo/Fc Transfused patients *N* (%)	Not used	13 (0.4)	ND	Not used	5 (0.2)	ND
PCC Transfused patients *N* (%)	Not used	20 (0.6)	ND	Not used	1 (0.03)	ND
Procoagulant products transfused patients (FFP-Cryo/Fc-PCC) *N* (%)	139 (8.7)	108 (3.3)	<0.001	88 (5.5)	76 (2.3)	<0.001
Postoperative drain blood loss volume (mL)				200 (80–850)	200 (50–700)	0.006
Re-exploration surgery patients *N* (%)				20 (2.0)	60 (2.2)	0.727

Note: Categorical variables are presented as absolute numbers (percentage) and compared by χ^2 test. Continuous, non-normally distributed variables are presented as median (interquartile range) and compared by Mann–Whitney *U* test.
Abbreviations: Cryo/Fc, cryoprecipitate/fibrinogen concentrate; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; PLTs, platelets; PRBC, packed red blood cell.

3 | RESULTS

During the 11 years considered (from 2011 to 2021), all 4890 patients who underwent cardiac surgery on CPB in the Legnano Hospital were enrolled in the study. G#11–14 included 1599 patients, while G#15–21 included 3291 patients.

Table 2 reports the demographic and clinical characteristics of the two groups. Some features regarding population aging and worsening of preoperative clinical status have a significantly higher prevalence in the second group: male sex, hypertension, diabetes mellitus, chronic kidney disease, SOFA score and preoperative haemoglobin level. On the contrary, the second group's preoperative ejection fraction is higher. Moreover, surgery has changed over the years: coronary and isolated ascending aorta surgery are more represented in the second group than combined and emergency surgery, which are more represented in the first group; CPB time and aortic cross-clamping (X-clamp) times are higher in the second group. As just mentioned, for evaluate the impact of each population characteristic as cofounder, we proceeded with a two-step logistic regression statistical analysis.

In Table 3, the two groups were compared by the prevalence of patients transfused and relative amount of any blood product or haemostatic agent in intraoperative and postoperative phases and for the postoperative drain blood loss and rate of re-exploration surgery.

In Tables 4 and 5, all the available variables were analysed in two subsequent steps: first, with monovariate logistic regressions, the associations between each characteristic and the two main outcomes (transfusion of any procoagulant agent and transfusion of PRBC). Second, two different multivariate logistic regression models identify the variables independently associated with the outcomes. Figures 1 and 2 represent the results of multivariate models.

4 | DISCUSSION

4.1 | Improvement in local PBM protocol

Cardiac surgery with CPB is characterised by an increased risk of bleeding and transfusions due to acquired coagulopathy and high-risk surgery. Both perioperative bleeding and transfusion requirements are associated with adverse outcomes and morbidity.[19–22]

PBM in cardiac surgery patients is a difficult challenge, but the diagnostic and therapeutic tools available have improved in the last few years. The two protocols here compared are similar regarding test and transfusion triggers and indications for procoagulant products and protamine supplementation in bleeding patients.

In the first protocol, transfusions or protamine supplementation had some prophylactic indications based on bleeding risk and intraoperative/postoperative bleeding indications according to the most probable cause of the coagulopathy and laboratory tests. In the second protocol, these indications were overcome using the viscoelastic test ROTEM® performed on specific cases at high risk of bleeding and for all bleeding patients undergoing either massive (i.e., bleeding over 200 mL/h in the first 30 min and/or over 200 mL/h in the following hours) or active haemorrhage (over 3 mL/kg/h in the first 2 h and/or

TABLE 4 Logistic regression model for association with any procoagulant transfusion.

	Monovariate logistic regressions		Multivariate logistic regression	
Variable	**OR [95% CI]**	***p***	**OR [95% CI]**	***p***
Age (year)	1.001 [0.991–1.010]	0.827		
Male sex	0.776 [0.610–0.987]	0.039	0.550 [0.365–0.828]	0.004
Weight (kg)	0.998 [0.995–1.005]	0.619		
Logistic euroscore I (point)	1.003 [1.001–1.005]	0.003	1.004 [1.000–1.007]	0.035
SOFA score (point)	1.086 [1.027–1.148]	0.003	1.086 [1.005–1.173]	0.037
SAPSII (point)	1.013 [0.998–1.028]	0.071		
Hypertension	1.806 [1.380–2.363]	<0.001	2.300 [1.356–3.902]	0.002
Diabetes mellitus	1.404 [1.117–1.764]	0.004	0.832 [0.406–1.704]	0.617
COPD	1.427 [1.058–1.925]	0.020	1.283 [0.602–2.737]	0.518
Chronic kidney disease	0.921 [0.620–1.368]	0.687		
Preop EF (%)	0.989 [0.979–1.000]	0.060		
Preop Hb (g/dL)	0.910 [0.849–0.975]	0.007	0.822 [0.749–0.903]	<0.001
Emergency surgery	1.668 [1.272–2.239]	<0.001	1.159 [0.698–1.925]	0.567
Combined heart surgery	1.909 [1.481–2.460]	<0.001	1.478 [0.703–3.104]	0.302
Coronary surgery	1.825 [1.465–2.274]	<0.001	1.307 [0.801–2.133]	0.282
Redo surgery	1.356 [1.025–1.794]	0.033	1.206 [0.784–1.855]	0.393
CPB time (min)	1.007 [1.005–1.009]	<0.001	1.012 [1.006–1.019]	<0.001
X-clamp time (min)	1.007 [1.005–1.009]	<0.001	0.992 [0.983–1.000]	0.078
Group #2015–2021	0.352 [0.282–0.439]	<0.001	0.207 [0.137–0.312]	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CPB time, cardiopulmonary bypass time; Preop EF, preoperative ejection fraction; Preop Hb, preoperative haemoglobin value; SAPSII, simplified acute physiologic score; SOFA score, sequential organ failure assessment score; X-clamp time, aortic cross clamp time.

over 1.5 mL/kg/h in the following hours). Moreover, since 2015 procoagulant blood products like Cryo, Fc and PCC have been locally introduced.

Regarding primary outcomes, the second group of patients had a significant reduction in (Table 3): the prevalence of total and PRBC postoperative transfusions; the prevalence of intraoperative and postoperative transfusions of FFP and any procoagulant transfusions (FFP in the first group vs. FFP, Cryo/Fc and PCC in the second group); and drain blood loss volume in the postoperative phase. On the contrary, intraoperative PRBC transfused patients were significantly increased in the second group without difference in the number of transfused units, probably due to lower preoperative haemoglobin levels. No significant difference in the amount of blood products transfused were noted, except for postoperative PRBC that were lower in the second group.

4.2 | The effects of GDT-strategy

For PRBC transfusion, the haemoglobin cut-off was the same in both groups: 8 g/dL for CAD patients underwent coronary surgery and 7 g/dL for patients underwent the other type of cardiac surgeries.

A mandatory ROTEM® test before transfusion was required for FFP, PLTs, Cryo, Fc and PCC transfusion.

The intraoperative PRBC transfusion indication was the same, dependent only on haemoglobin levels. The reduction of PRBC transfused patients in the postoperative phase can be explained by better coagulopathy and bleeding management in the intraoperative phase; moreover, the amount of units transfused were lower, too.

A significant reduction of postoperative blood loss was reported in the second group, but it could not further reduce the prevalence of re-exploration surgery, which was globally lower than reported in the literature (3.1%–4.5%).[23]

FFP transfused patients were reduced both in the intraoperative and postoperative phases with no significant difference in transfused volume. This could be attributed to a better diagnostic evaluation of the coagulopathic process and/or to the availability of other haemostatic products in the PBM Protocol of the second group (PCC, Cryo and Fc). This last hypothesis could be excluded because, despite the introduction of PCC, Cryo and Fc, the prevalence of transfused patients with any procoagulant product in the second group (FFP vs. FFP + PCC + Cryo-Fc) was significantly lower.

The first PBM protocol based transfusion choices on the empirical evaluation of the most probable cause of coagulopathy in bleeding patients or to a 'prophylactic approach' to transfusions linked to the type of surgery at the most significant risk of bleeding and may have led to an unnecessary rate of FFP transfusions. In the second group, patients were transfused only with a diagnosed deficiency of one of

TABLE 5 Logistic regression model for association with packed red blood cells transfusion.

	Monovariate logistic regressions		Multivariate logistic regression	
Variable	**OR [95% CI]**	***p***	**OR [95% CI]**	***p***
Age (year)	1.009 [1.002–1.016]	0.006	0.999 [0.988–1.010]	0.919
Male sex	1.392 [1.188–1.632]	<0.001	1.117 [0.870–1.433]	0.383
Weight (kg)	0.986 [0.980–0.991]	<0.001	0.990 [0.982–0.998]	0.022
Logistic euroscore I (point)	1.001 [0.999–1.003]	0.112		
SOFA (point)	1.114 [1.072–1.158]	<0.001	1.060 [0.999–1.125]	0.054
SAPSII (point)	1.017 [1.006–1.027]	0.001	1.009 [0.993–1.026]	0.250
Hypertension	1.264 [1.106–1.504]	0.008	1.244 [0.926–1.672]	0.145
Diabetes mellitus	1.197 [1.012–1.416]	0.035	1.032 [0.733–1.453]	0.856
COPD	1.247 [0.997–1.559]	0.053		
Chronic kidney disease	0.987 [0.752–1.297]	0.930		
Preop EF (%)	0.987 [0.980–0.994]	0.001	0.986 [0.975–0.996]	0.010
Preop Hb (g/dL)	0.744 [0.709–0.780]	<0.001	0.728 [0.685–0.773]	<0.001
Emergency surgery	1.192 [0.954–1.488]	0.121		
Combined heart surgery	1.119 [0.978–1.464]	0.080		
Coronary surgery	1.172 [1.003–1.137]	0.045	0.952 [0.692–1.308]	0.762
Redo surgery	1.458 [1.186–1.794]	<0.001	1.399 [1.064–1.839]	0.016
CPB time (minute)	1.004 [1.003–1.006]	<0.001	1.006 [1.001–1.011]	0.017
X-clamp time (minute)	1.005 [1.002–1.007]	<0.001	0.997 [0.990–1.004]	0.443
Group #2015–2021	1.004 [0.851–1.185]	0.960		

Abbreviations: COPD, chronic obstructive pulmonary disease; CPB time, cardiopulmonary bypass time; Preop EF, preoperative ejection fraction; Preop Hb, preoperative haemoglobin value; SAPSII, simplified acute physiologic score; SOFA score, sequential organ failure assessment score; X-clamp time, aortic cross clamp time.

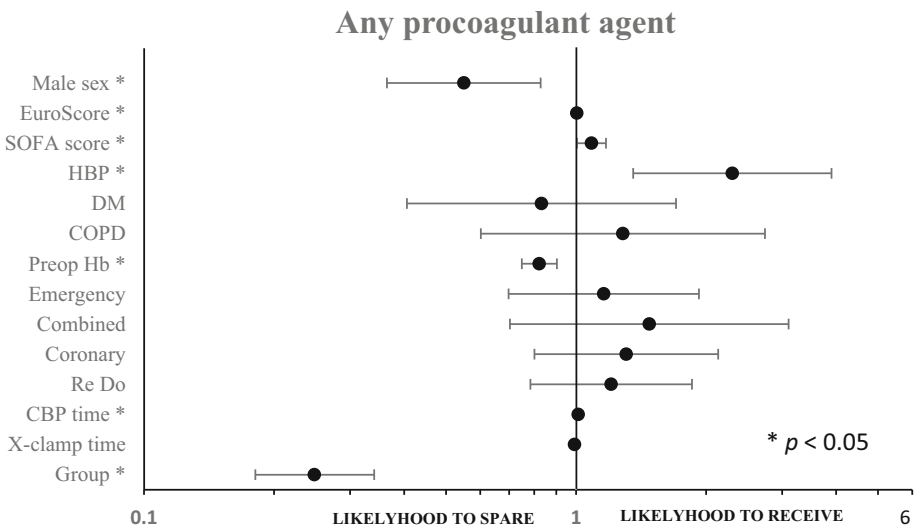

FIGURE 1 Forest plot about procoagulant transfusion risk. Dots represent the Odd's Ratios; lines describe the 95% confidence intervals, on a logarithmic scale. The variables were first selected by univariate logistic regressions; the significantly associated ones were then put in the present multivariate logistic regression model, where * shows the variables still significantly associated with the administration of any procoagulant agent. COPD, chronic obstructive pulmonary disease; CPB time, cardiopulmonary bypass time; DM, diabetes mellitus; HBP, high blood pressure; Preop Hb, preoperative haemoglobin value; Re Do, redo surgery; SOFA score, sequential organ failure assessment score; X-clamp time, aortic cross clamp time.

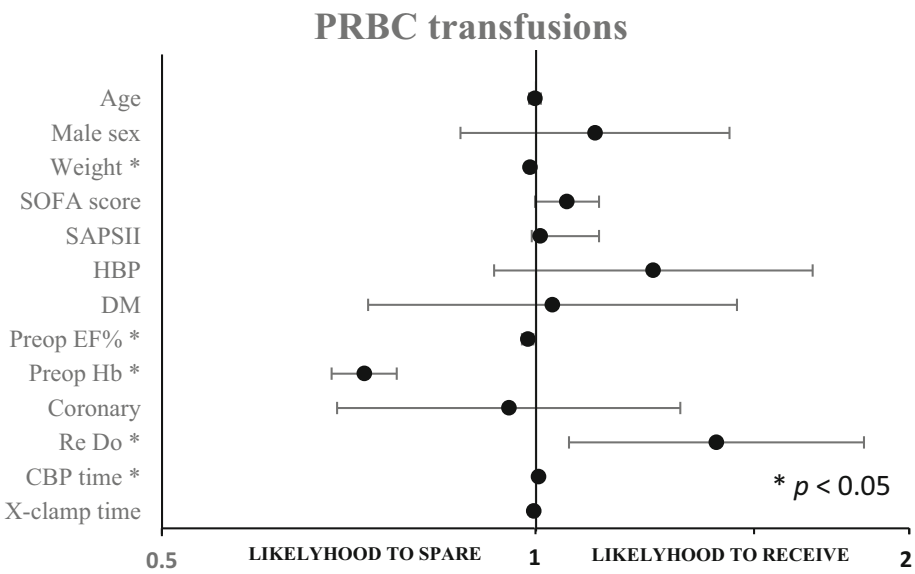

FIGURE 2 Forest plot about packed red blood cell transfusion risk. Dots represent the Odd's Ratios; lines describe the 95% confidence intervals, on a logarithmic scale. The variables were first selected by univariate logistic regressions; the significantly associated ones were then put in the present multivariate logistic regression model, where * shows the variables still significantly associated with the administration of packed red blood cells. PRBC, packed red blood cell transfusion; Preop EF%, preoperative ejection fraction; Preop Hb, preoperative haemoglobin value; Re Do, redo surgery; SAPSII, simplified acute physiologic score; SOFA score, sequential organ failure assessment score; X-clamp time, aortic cross clamp time.

the elements of coagulation pathways on the ROTEM® test, both in bleeding patients or in specific cases at a high risk of bleeding. These results were expected, according to the international literature.[24–26]

Introducing the viscoelastic test guaranteed more accuracy in identifying and treating the specific causes of bleeding and coagulopathy.[27,28] Furthermore, the ROTEM® test could also be performed during CPB time, reducing the time between diagnosis and the proper optimisation of the coagulopathic process, just from the first minutes after the end of CPB. Moreover, introducing other procoagulant products (Cryo, Fc and PCC) in addition to FFP has contributed to reducing transfusion needs and optimising the goal-directed transfusion strategy.

4.3 | Path characteristics conditioning transfusions

Two multivariate logistic regressions were built with a stepwise approach to describe the effect of each available gathered data. The second protocol showed a significant impact by correcting all possible confounders by reducing the need for any procoagulant in almost four out of five patients (Table 4). Along with belonging to #G15-21, the other characteristics associated with a decrease in procoagulant use were: (1) the actual severity of organ failures, as described by the SOFA score and logistic Euroscore I[29–31]; (2) the shortness of extracorporeal circulation, as described by the length of CPB time; (3) the preoperative haemoglobin level, both due to the inflammatory response and to the hypothetical preoperative blood loss that means a decrease in red blood cells concentration and dilution of endogenous coagulation factors; (4) other anamnestic characteristics, like sex and past medical history of hypertension (Figure 1). A better understanding and optimisation of any coagulopathic process can explain the reduction of overall transfusion requirements in the second group despite longer CPB time, usually related to a higher risk of bleeding and reoperation surgery.[32,33]

Statistical significance for some clinical characteristics in monovariate analysis was not confirmed in multivariate analysis. Past medical history (diabetes mellitus, COPD), type of cardiac surgery performed (emergency, coronary, redo and combined surgeries), and X-clamp time, which depend on the surgeon and intervention, did not result statistically significant. Other clinical features describing the patient's functional status (age, SAPSII, pre-operative EF, CKD and weight) were not significant. Considering that a single operator performed most of the surgical procedures, we can safely assume that surgical variability did not cause an increased bleeding risk in our population.

Regarding PRBC transfusions (Table 5), the variable of belonging to the second protocol was not significant, as expected, since the GDT PBM protocol was not devoted to improving this therapy. The patient characteristics significantly associated with a higher probability to receive PRBC transfusions in multivariate analysis were: (1) the lower body weight because of the different hemodilution effect due to the use of a fixed extracorporeal circuit priming volume; (2) the lower preoperative functional reserve, as described by preoperative EF and the redo surgery; (3) the higher probability of blood loss, due to the longer CPB time; (4) and above all, the preoperative haemoglobin level (Figure 2).[34]

As previously stated, the other surgical characteristics were shown not to be significantly associated with PRBC transfusions in building the multivariate logistic model because of the relatively higher association with patient preoperative status, like for demographical variables (age and sex) and history features (SOFA score, SAPSII, high blood pressure and diabetes mellitus).

4.4 | Building a shared algorithm

The update of the PBM program in the second protocol configured a new approach to bleeding management: transfuse less and transfuse

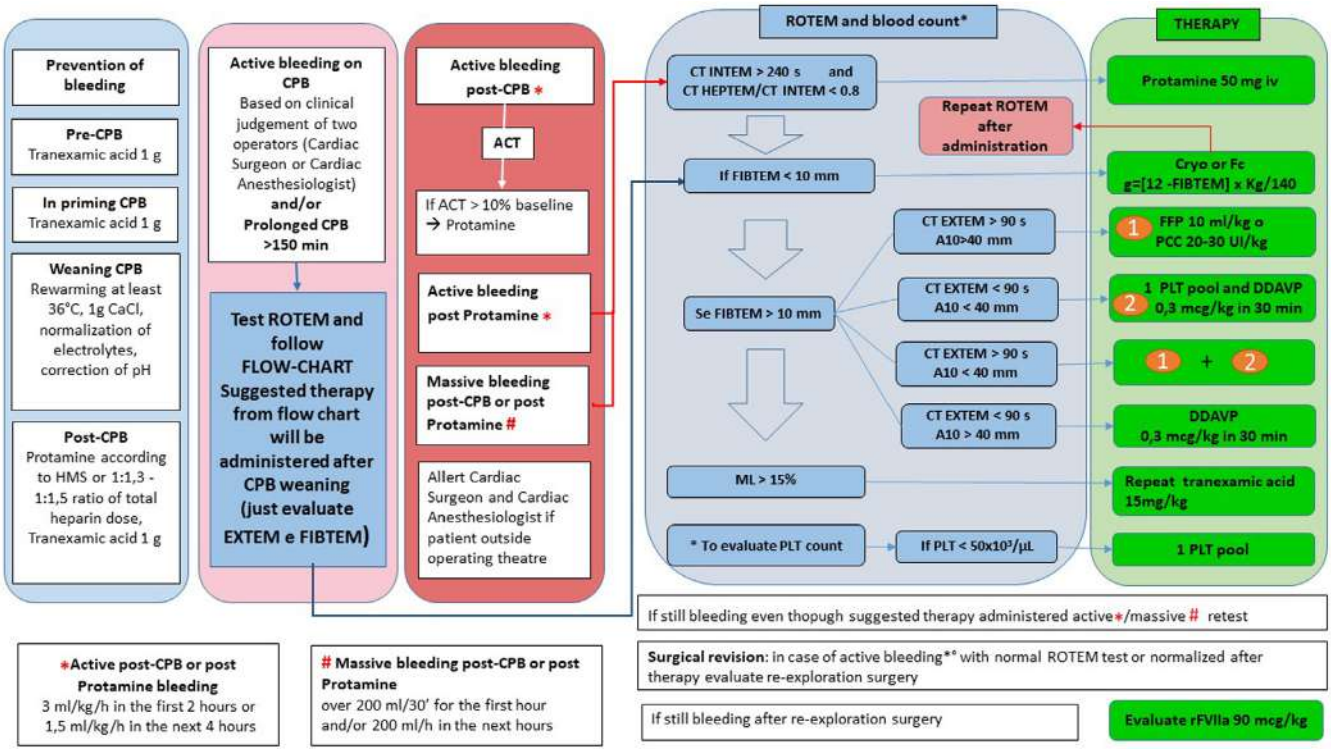

FIGURE 3 Goal directed transfusion algorithm. ACT, activated clotting time; CPB, cardio-pulmonary by pass; Cryo, cryoprecipitate; CT, clotting time; DDAVP, desmopressin; Fc, fibrinogen concentrate; FFP, fresh frozen plasma; HMS, heparin management system; ML, maximum lysis; PCC, prothrombin complex concentrate; PLT, platelets; rFVIIa, recombinant activated factor VII.

more appropriately. The significant reduction of postoperative drain blood loss volume has also verified the effectiveness of this approach.

To improve compliance with the PBM Program, the indications and doses of procoagulant blood products and drugs for bleeding prevention and management for active and massive perioperative bleeding were summarised in a shared algorithm (Figure 3) whose effectiveness could be a topic of discussion in future papers. According to recent reports, the fibrinogen dose calculation (cryoprecipitate or fibrinogen concentrate) was changed from the 2015 PBM protocol to better offset fibrinogen deficiency.[35] The formula was adapted according to the correlation of normal values of fibrinogen level on laboratory tests.[36]

4.5 | Limitations and strengths of the study

Our study has a series of limitations. Firstly, it is monocentric and retrospective: all the results could be due to improvements in peri-procedural care over the last decade. Secondly, this study was limited to the intraoperative phase and the first 12 h of the postoperative period, and this could be a confounding factor, especially for PRBC transfusions caused by postoperative anaemia. Thirdly, although 2011 and 2015 were marked as the years when the two PBM protocols were introduced, operators' compliance with its application may have been variable, especially in the early years. Despite the limitations abovementioned, the study has some strengths. The observational period was over 11 years and concerned all 4000 patients admitted to the Cardiac Surgery Department. The bleeding risk was not influenced by the variability of the surgeon (that was the same operator in more than 90% of cases), and transfusion thresholds were upheld accurately in the ROTEM® protocol.

5 | CONCLUSIONS

The introduction of a new PBM protocol for cardiac surgery patients with the use of viscoelastic tests and specific procoagulant factors (such as cryoprecipitate, fibrinogen and PCC) built a goal-directed transfusion strategy for the diagnosis and treatment of the coagulopathic diseases able to reduce both the prevalence of transfused patients and the postoperative bleeding.

AUTHOR CONTRIBUTIONS

R.F., M.L., C.N. and I.B. conceived the Patient Blood Management protocol valid since 2015 and the idea of the study. R.F. developed the theory and performed the computations. G.M., V.S and M.G. verified the analytical methods. V.S, F.O, M.G., B.M. and F.M. contributed to apply the goal directed transfusion strategy. G.M. supervised the findings of this work and reviewed the paper. All authors discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, M.L., upon reasonable request.

PATIENT CONSENT STATEMENT

Generic informed consent about using personal clinical data for scientific purposes was collected.

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ORIGINAL ARTICLE

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Healthcare provider's perceptions of bleeding in patients with acute leukaemia undergoing induction chemotherapy: A qualitative study

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Abstract

Background: Bleeding is a primary outcome for many transfusion-related trials in acute leukaemia (AL) patients, typically graded using the World Health Organisation (WHO) bleeding scale (clinically significant bleed (CSB) is ≥grade 2). This composite outcome fails to differentiate minor bleeds that may not be significant, poorly represents the total burden of bleeding and lacks input from healthcare providers (HCPs) and patients. As part of a multi-step project to create a better bleeding tool for trials, our objective was to identify HCPs' perspectives on the components of CSB in AL patients.

Study Design and Methods: Using qualitative description, we interviewed 19 physicians and nurses who care for AL patients undergoing induction chemotherapy.

Participants were recruited from professional organisations, networks and social media. An inductive approach to conventional content analysis was used.

Results: HCPs identified features of CSB as the anatomical site of bleeding, amount of bleeding, need for intervention and changes in vital signs. Using these characteristics, bleeding events were categorised into three groups: clinically significant, could evolve into a CSB and not clinically significant. HCPs considered the patient's condition, bleeding history and clinical intuitions when deciding whether a bleed could escalate into serious bleeding.

Discussion: Using data from HCPs, we categorised bleeds as clinically significant, could evolve into a CSB, and not significant. A study of patients' perspectives on the importance of different kinds of bleeding is the next step to creating a bleeding definition that is informed by evidence, clinicians and patients.

KEYWORDS
acute leukaemia, bleeding, healthcare provider perspectives, qualitative

1 | INTRODUCTION

Acute leukaemia (AL) is a rapidly progressive disease that is fatal if not treated.[1] Induction chemotherapy is a standard treatment for most AL cases, but it can lead to anaemia and thrombocytopenia, causing an increased risk of serious bleeding.[2,3] Factors such as abnormal coagulation parameters and disseminated intravascular coagulation (DIC), hyperleukocytosis, and age may also increase the likelihood of bleeding.[4,5] To address the high bleeding risk for AL patients, red blood cell and platelet transfusions and other interventions are commonly used to treat bleeding in AL patients undergoing treatment.[6,7]

Clinical trials have identified that up to 70% of patients with haematological malignancies will experience significant bleeding, assessed by the World Health Organisation (WHO) bleeding scale, which measures the severity of bleeding as a clinically important outcome.[8–10] The scale categorises bleeding signs and symptoms from 0 (no bleeding) to 4 (bleeding that could cause death or permanent morbidity). In transfusion clinical trials, bleeding categorised as grades 2, 3 and 4 are combined into a single clinical outcome referred to as a composite outcome; however, the use of this composite outcome poses challenges.[11]

Grade 2 bleeding events (e.g., epistaxis >1 h, haematuria not requiring transfusion) are more frequent and less severe than grades 3 and 4 bleeding. The inclusion of grade 2 bleeds in the clinically significant category improves the feasibility of studies as it increases the frequency of the outcome measure allowing for an achievable sample size for clinical trials. However, it is uncertain whether all grade 2 bleeds are considered clinically significant by healthcare providers (HCPs) that treat AL and whether some grade 2 bleeds are even risk factors or predictive of future bleeding events that are more severe.[8,11–13] The WHO bleeding scale was designed to categorise bleeding during cancer treatment, but it has never been validated as a trial outcome measure overall or in the AL population.[9] The scale may be useful for other cancer populations, but it may not capture and characterise bleeding events experienced by AL patients, where bleeding occurs both as a disease manifestation and treatment outcome. Although other evidence-based tools have been developed to evaluate clinically significant bleeding (CSB) more accurately, they do not adequately distinguish minor bleeds and the total burden associated with multiple or recurring bleeding events.[9,14,15] Hence, the current definition of CSB is suboptimal and presents methodological challenges in conducting clinical trials.

To understand what constitutes a CSB for patients with haematological malignancies, it is important to gather the perspectives of HCPs who work with this population, as there is a need for outcomes that are relevant to patients and those involved in their care.[16] In recent years, other measures for bleeding conditions have started to incorporate the perspectives of patients and HCPs to gain a better understanding of the nuances of bleeding.[17–19] Thus, our objective for this study was to identify, from the HCPs' perspective, the components of CSB in the AL population undergoing induction chemotherapy.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This study is part of a larger multi-methods study aiming to develop a bleeding measurement tool by combining a secondary exploratory analysis of bleeding data from four previously published RCTs[20–23] and qualitative interviews of HCPs and patients. As part of this larger study, we conducted a qualitative descriptive study to understand HCPs' perspectives on CSB in AL patients undergoing induction chemotherapy.[24,25] We opted to explore this objective using a qualitative methodology to obtain a clear and concise understanding of bleeding, while exploring the meaning and relevance through analysis and interpretation. We obtained ethics approval from the Clinical Trials Ontario

streamline review process with the Hamilton Integrated Research Ethics Board as REB of record (Project # 3713).

We recruited physicians, nurse practitioners (NP) and registered nurses (RN) who provide care to AL patients undergoing induction chemotherapy in Canada. NPs in Canada are RN with graduate-level education, capable of working independently while also collaborating with physicians as necessary. RNs primarily offer bedside patient support and consult with NPs and physicians when assisting patients experiencing bleeds. Eligible participants were those who could communicate in English and provided written informed consent to participate in the study. We used a combination of purposeful sampling, maximum variation and snowball sampling to recruit HCPs.[26,27] Purposeful sampling involves selecting knowledgeable participants on the topic (bleeding), while maximum variation ensures diversity across factors like profession, experience, location and gender.[26,27] Recruitment notices were circulated by organisations including the Canadian Hematology Society, the Canadian Leukemia Study Group and the Canadian Nurses Association of Oncology, as well as through professional networks and on social media. We also used a chain referral (snowball) sampling approach to recruitment, asking participants to share information about the study with their networks. Interested participants were directed to an online consent form to collect demographic information. Study information was collected and managed on REDCap hosted at the McMaster Centre for Transfusion Research.[28,29]

2.2 | Data collection

Participants completed a single semi-structured interview that was conducted by one of three female qualitative interviewers (S.L., M.K. and S.T.), none of whom were clinicians and none of whom had a prior relationship with the participants. Non-clinician interviewers were chosen to provide a neutral standpoint on the topic in order that participants felt comfortable to share any perspective, even those which may diverge from clinical norms and standards. Interviewers received relevant training on the clinical content from clinician collaborators. Interviews were completed between October 2022 and February 2023 over Zoom conference or on the phone. Interviews were audio-recorded and transcribed verbatim. We interviewed participants until we reached data sufficiency. We defined data sufficiency as the point where no further characteristics of significant bleeding were mentioned and the provided rationale for those bleeds was sufficient to adequately answer the research question.[30]

During the interviews, participants were asked open-ended questions about their perceptions and clinical knowledge of bleeding in AL patients. Two interview guides (one for nurses and one for physicians) (Appendix 1) were developed by the research team consisting of clinicians, methodologists, a biostatistician, research staff and students and a patient partner. Physicians were asked about their clinical knowledge of bleeding, while nurses were asked about their clinical knowledge and how they assessed and evaluated bleeding in patients. The interview guides were piloted with three HCPs on the study team and were revised based on feedback. The interview guides were continually refined throughout the study as new theoretical insights developed. Participants received a $20 gift card.

2.3 | Data analysis

Data collection and analysis occurred concurrently, using an inductive approach to conventional content analysis.[31,32] Content analysis is a technique for interpreting the content of text, in this case, participant interviews, by summarising and categorising text to yield interpretations and understanding across the entire dataset. We applied an inductive and conventional approach where we generated categories and codes from the data, rather than grouping the data to conform to an existing theory or framework. The analytic team (S.T., M.K.and S.L.) open-coded transcripts using NVivo software[33,34] to identify how participants described the clinical significance of different kinds of bleeds. Open coding involves reading and re-reading transcripts to identify common aspects of the content. Afterwards, the analytic team shared their insights with the larger team and developed a coding framework. Similar codes were collapsed or parsed out into categories and written into analytic memos. Additionally, a constant comparison analysis was conducted to compare HCPs' perspectives on CSB.[35]

3 | RESULTS

3.1 | Participant characteristics

Nineteen HCPs, including 12 physicians, four NPs and three RNs from eight hospital centres participated in this study (Table 1). During the interview, the participants described their understanding of CSB in the AL population. They provided details on the characteristics of CSB, and the factors that could be relevant for identifying patients who are more likely to develop a serious bleed.

3.2 | Characteristics of CSB

Participants identified a variety of characteristics that they considered when determining whether a bleed was important. These included factors such as the anatomical site and or the need for intervention. Through inductive analysis, we transformed these characteristics into a series of criteria that describe whether a bleed was considered clinically significant, based on participants' descriptions of specific bleeds or their understanding of clinical significance. Table 2 describes our criteria which differentiate bleeds between those that are, could be, or are not clinically significant.

3.2.1 | Clinically significant bleeds

Participants based their assessment of whether a bleed was clinically significant on characteristics, which included the amount of blood loss, the duration and ability to gain control of the bleeding, the level

TABLE 1 Healthcare provider (HCP) characteristics.

HCP characteristics	Physicians (*n*)	Nurses (*n*)
Gender		
Female	5	7
Male	7	0
Province		
Alberta	3	0
British Columbia	2	0
Ontario	6	7
Quebec	1	0
Number of years practicing as a HCP		
0–5	6	3
6–10	1	1
11–15	1	0
16–20	2	0
21–25	1	2
31+	1	1
Number of years practicing in acute leukaemia		
0–5	5	2
6–10	2	3
16–20	3	0
21–25	1	2
31+	1	0
Number of inpatients seen per year		
0–50	9	3
51–100	1	1
101–150	1	2
201–250	0	1
No response	1	0

of intervention required, the impact on vital signs, changes or persistently low haemoglobin and platelet counts, and the location of the bleed in areas that posed a risk to the individual's life. The requirement of medical intervention was a commonly mentioned characteristic among participants. For instance, participants stated that the need for red blood cell or platelet transfusions, surgical interventions, specialist consults and diagnostic testing were indicative of a significant bleeding event. Some participants also considered the use of tranexamic acid or pressure bandages/packing as indicative of significant bleeding.

Perceptions of CSB varied somewhat by HCPs. Physicians and NPs had a mutual understanding of the characteristics of significant bleeds. They stated changes in vital signs, the use of interventions including specialist consultations, uncontrolled and prolonged bleeding, the amount of blood loss, overt bleeding and the potential damage to other organs were characteristics of significant bleeding. RNs had limited consensus among themselves on the characteristics of CSB. They considered the presence of overt blood, changes in vital signs, significant blood loss, uncontrolled bleeding and the use of interventions to be important characteristics.

3.2.2 | Could evolve into a clinically significant bleed

Participants had varying opinions on the characteristics and clinical significance of certain bleeds resulting in the creation of a 'could evolve into a clinically significant bleed' category. Some believed that bleeds, such as melena, petechiae, mucosal bleeding, epistaxis, moderate bruising and haematuria, could potentially predispose individuals to CSB, while others felt that notwithstanding predisposition to more serious bleeding these bleeds sufficiently met the criteria for a CSB. These varying perspectives could be influenced by the HCP's level of knowledge, experience in treating AL or time spent with the patient. For instance, these differences were also noted between physicians and nurses on whether petechiae were considered clinically significant.

The 'could evolve into a clinically significant bleed' category encompasses characteristics that raised clinical suspicion for some participants or that some participants felt were already clinically significant. These bleeds were seen as signals that warranted clinical attention to identify if worse or more severe bleeding would occur. For instance, NPs indicated that they would notify the team if there was active bleeding that could be potentially concerning, such as melena or haematochezia, signs of potential intracranial bleeding, overt bleeding, haematuria, petechiae, uncontrolled bleeding or changes in vital signs that may be related to a bleed that warranted a physician's attention.

3.2.3 | Not clinically significant

Participants described features of bleeds that made them less worried, such as bleeds that resolved on their own, or if the reason behind the bleed was known and not concerning. There was a consensus among participants that minor bruising, haemorrhoidal bleeding, cutaneous bleeding, such as superficial skin manifestations, subconjunctival bleeding, self-limited epistaxis or gingival bleeding that resolved on its own, and vaginal bleeding that was a typical menstrual flow for menstruating patients was not clinically significant.

3.3 | Predicting a serious bleed

HCPs were asked about factors that might enable them to predict whether a bleed would escalate into a serious bleed. They explained that predicting whether a bleed could escalate was closely linked to the assessment of the patient's condition and bleeding characteristics but was also influenced by a certain level of randomness or unpredictability. Some participants mentioned relying on their clinical intuition, formed from past knowledge and experience, as part of their prediction and assessment strategies.

For instance, when asked about their confidence level in predicting a serious bleed, many participants said it is often challenging, as it depends on the patient's disease and presentation. In some cases,

TABLE 2 Qualitative criteria for clinically significant bleeding in patients with acute leukaemia undergoing induction chemotherapy.

Category	Criteria	Quote Examples
Not clinically significant	Bleeding is not clinically significant if it meets one or more of the following: • Bleeding resolves on its own or with minimal intervention (e.g., applying light pressure) • Small volume bleed (e.g., streaks of blood, microscopic blood on urine dip, slight oozing) • Petechiae or bruises (smaller than a fist) or caused by known trauma (e.g., line insertion)	'I would say post-procedural bleeding, things after a bone marrow, biopsy site or a skin biopsy that resolves with a few minutes of pressure is not as significant to me.' P03 'I mean, it's all sort of context, dependent. So often people will have petechiae at diagnosis, and not that you're not worried about it, but you often kind of know why they're having it. You know their platelets are low, or while they're getting chemo, their platelets are low. They might have some they might have minor epistaxis or that resolves. They might have gums bleeding, especially at diagnosis. Sometimes their gums can be inflamed and infiltrated.' P05
Could evolve into a clinically significant bleed	Bleeds that could evolve into a clinically significant bleed, predict future clinically significant bleeding or be a clinically significant bleed. These bleeds should be monitored or have further investigations if it meets one or more of the following: • A bleed that signifies the potential for a severe bleed (e.g., melena, haemoptysis, haematuria, purpura, mucosal bleeding, epistaxis, rectal bleeding) • Multiple or recurring small bleeds (e.g., streaks of blood, slight oozing) • Bleeds that are unresponsive to treatment or had delayed treatment • Unexpected bleeding with no changes in blood work (e.g., no changes in haemoglobin or platelets, but bleeding occurs) or known trauma • Thrombocytopenia, hyperleukocytosis, use of antiplatelet drugs and anticoagulants, or the patient has concurrent health conditions	'So I mean, if people have for recurrent small bleeds or if they're having abnormal clotting, or if they- I'm not generally concerned about minor bruising, but if bruising is extending or requiring repeat compression or anything like that, then yeah, it would be concerning.' P04 '[…] I think that sometimes it's a constellation of symptoms that go together that make you more concerned about, "Hmm, I wonder if something is happening". So, we could think about the brain bleed again, people that drop their pressure or, their level of consciousness drops and you can't really quite explain it. You start thinking broadly about what this could represent. […]' N05 'Well, starting from the top, I would say that spotting, coughing, or spitting up blood could—it could be only a small amount, but that coming from inside that certainly would be concerning. You wouldn't know whether—because it could be coming from the lungs or the throat—so, that's a type of bleeding that, minor bleeding that could be of concern. I think any gastrointestinal bleeding, bleeding with bowel movements, although it's most often from haemorrhoids and fissures around the bottom end that are not going to be that serious, but any sort of bleeding that comes at all even if it's minor—patient reports, "I went to the bathroom, and there was some blood in the toilet", then that is definitely a warning. That is definitely a warning.' P09
Clinically significant bleeding	Bleeding is clinically significant if it meets one or more of the following: • Bleeding that cannot be controlled even after 10 min • Bleeds that require an intervention (e.g., diagnostic testing, medications, specialist consults, platelet or red blood transfusion, surgery) • Bleeds resulting in a drop in haemoglobin by 10–20 g/L in a day • Changes in vital signs or blood work (e.g., drop in BP, increases in HR or RR, neurologic signs) • Bleeding in particular sites that could pose a risk to an individual's life (e.g., brain, rectum, thoracic or abdominal cavity)	'I think, just in general, wherever it is, if you have bleeding that's uncontrolled, then that would be clinically significant to me just because then it requires prompt intervention and monitoring.' N10 'So, for me, clinically significant bleeding would be anything that requires intervention. So, either with blood product administration, or administration of other medications to prevent bleeding, or intervention like using pressure bandages, requiring an endoscopy to look in the stomach if there's bleeding from the stomach or the bowels, so anything that really requires us to intervene.' P03 'And, so to me, whenever I see haematuria in the context of thrombocytopenia that association it is concerning, the other things that if you're requiring a transfusion, you're losing a significant volume of blood which is concerning as a function just general.' P02

Abbreviations: BP, blood pressure; HR, heart rate; RR, respiratory rate.

bleeds could occur if a patient experiences unexpected physical trauma, making bleeding difficult to predict.

> 'I think it's actually pretty difficult to predict a serious bleed, that's the thing, these are semi-random events, especially things, a lot of cases [of] significant bleeds will happen after a bit like, after a fall, and I've seen intracranial bleeding in an AL patient occurring after a fall. It's difficult to predict the fall, and some of the falls that I've seen happened in people who are, mid 40's no pathology suspect, but they trip on bed clothing or something'. P12.

Two RNs mentioned predicting a serious bleed often relied on their nurse's 'inkling' or 'gut feeling'. They explained that despite a patient's normal vital signs or lab results, they could sense that

something was not right, often through subtle changes in the patient's behaviour. This intuition frequently prompted additional assessments to determine if a bleed was occurring.

> 'Yeah, it's funny, because we really do talk about this whole gut feeling in haematology like if you sense that something is off. Sometimes you can't even explain it. Sometimes the vital signs may seem completely normal but you just know that there's something not right with the patients with their lengthy stays at the hospital'. N08.

Participants also described factors which predisposed patients to a higher risk of bleeding and bruising, including the use of anti-platelet drugs and anticoagulants, other types of leukaemia (e.g., acute promyelocytic leukaemia), high white blood count, thrombocytopenia and concurrent health conditions (e.g., ulcers or other malignancies).

4 | DISCUSSION

In this study, we aimed to investigate HCPs' perceptions of the components of CSB in AL patients receiving induction chemotherapy. After conducting interviews with 19 HCPs, our analysis led to the creation of three categories to differentiate bleeds based on their clinical significance: those that were clinically significant, those that could evolve into a CSB and required vigilance and those that lacked clinical significance. A category of could evolve into a CSB reflects opinions among HCPs about the severity of the bleed and the presence of signs, such as melena, that were not definitive but required more evaluation and investigations as they may indicate, evolve or predict a significant bleeding event. The components of CSB events influenced HCPs' assessment strategies and the information they conveyed to patients.

Although this is the first exploratory study to investigate the reasoning behind HCPs' perceptions of CSB in AL patients, our findings resemble the items identified in the Bleeding Severity Measurement Scale (BSMS), a scale designed for clinical trials.[14] The BSMS was developed by surveying 48 experts who identified key determinants of CSB in chemotherapy-induced thrombocytopenia patients, to create a scale to measure bleeding severity. Our findings align with the BSMS in that bleeding requiring interventions, invasive procedures or investigations or increased monitoring were considered clinically significant. Additionally, the BSMS considers central nervous system bleeding, significant pain, haemodynamic instability, vision loss, significant morbidity or bleeding contributing to a patient's death as CSB. However, our participants did not identify pain as a characteristic of CSB. The differences in our findings could be attributed to the varying expertise of HCPs and the different sources of information used to develop the BSMS.[14] It is also possible our participants did not consider significant pain as meaningful or important when describing CSB, as the most frequent bleeds experienced by AL patients include skin, eye, epistaxis, gingival and gastrointestinal bleeding.[36] HCPs may not perceive these bleeds to be painful, if not communicated by the patient. Future research should investigate if patients associate significant pain with bleeds considered clinically significant by HCPs.

In our study, participants outlined the factors influencing their assessment of whether a bleed might evolve into a severe bleed. For some, this was informed by the patient's conditions, drawing upon their understanding of established risk factors and their clinical intuition. For instance, participants described factors such as thrombocytopenia and hyperleukocytosis, which have been associated with an increased likelihood of severe bleeding.[4] Participants relied on their knowledge of these risk factors to inform decisions about whether to monitor the situation or intervene. Two RNs discussed the role of their clinical intuition in predicting if a bleed would worsen, acknowledging the difficulty in articulating this intuitive judgement. We also saw participants implying intuition with phrases such as a patient 'not looking quite right' in terms of behaviour or referring to other tacit signs of distress. Clinical intuition, also referred to as a gut feeling, inkling or hunch is a concept recognised in medical and nursing education, described as a sense of knowing that something is true in absence of articulated evidence.[37,38] Nurses have described this intuition as informed by their knowledge, experience and relationship with the patient.[37,38] This aligns with the discussions from the two RNs in our study, who described a gut feeling used to identify or predict a severe bleed. RNs often have a close relationship with patients, allowing them to grasp patient's normal patterns and behaviours, which can help them recognise when something is amiss.[39] This relationship between RNs and patients differs from the relationship that patients have with their physicians and NPs, who are not as often physically present for extended periods. Nurses emphasised that they do not rely solely on their intuition, but also look for evidence-based clinical signs. In situations where the evidence was lacking, they communicated their concerns to the healthcare team for further input and guidance. Previous literature has indicated that physicians often struggle with articulating their intuition and tend to focus on easily identifiable components, such as evidence of risk factors.[40,41] This could explain why only the nurse participants described their clinical intuition explicitly unlike the physician participants. While the concept of clinical intuition in the context of haematology has not been reported, our findings suggest that clinical intuition may play a role in identifying and predicting severe bleeds and can be further explored to understand the relationship.

4.1 | Strengths and limitations

To our knowledge, this is the first qualitative study that explored Canadian HCP perceptions of CSB in the AL population. This study is unique as it included perspectives from a wide range of physicians with varying experiences working in AL and different geographical regions in Canada. It also validates some of the previous findings published by Webert et al. in the development of the BSMS.[14] We believe our findings may be transferable to HCPs caring for other haematological malignancies, or to other groups that identify significant

bleeding. The results of this study provide valuable insights, which may contribute to the development of a new tool to measure CSB in transfusion and haematological malignancy clinical trials.

However, this study was limited by the sample we were able to obtain. Despite our best efforts to recruit, the final sample included 12 physicians and 7 nurses. Senior physicians in other geographic regions may have different perspectives. We were not able to recruit NPs and RNs beyond two institutions in the same geographical region. The perspectives of the nurses in this study may not represent those of all nurses in similar or different geographical regions. However, we also acknowledge the distinctions in the clinical roles of NPs and RNs, and how this may elicit different perspectives of CSB. Interpretations from this study are influenced by the historical and geographical context in which the research was conducted and may not apply to all settings.

5 | CONCLUSION

HCPs identified characteristics that were taken into consideration for assessing whether a bleed was clinically significant. In our analysis process, we generated three categories to group common characteristics of HCPs' perceptions of the clinical significance of bleeding that were elicited in this study: clinically significant, those that could evolve into clinically significant and those that lacked clinical significance. To determine if a bleed was significant, HCPs relied on their understanding of these characteristics. HCPs considered the patient's condition, bleeding history and clinical intuition to predict whether a bleed would escalate into a serious bleed.

AUTHOR CONTRIBUTIONS

N.M.H., C.H., M.V., D.K., D.A., H.Z., K.W., L.H., R.C., S.S. and T.G. received funding and conceptualised the larger project. N.M.H., C.H., M.V. and S.T. designed this study. S.T., M.K. and S.L. collected data and completed data analysis with input from N.M.H., C.H., M.V., D.K., D.A., H.Z., K.W., L.H., R.C., S.S., T.G., D.M. and S.T. wrote the original manuscript with critical revision and input from M.V., N.M.H., C.H., S.L., M.K., D.K., D.A., H.Z., K.W., L.H., R.C., S.S., T.G., D.M. and D.M. All authors approved the final version.

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CONFLICT OF INTEREST STATEMENT

R.C. has consulted for Terumo BCT on trials with bleeding-based outcomes, but they had no contribution or influence on this methodological work. C.H. has received financial honorariums from Novartis, Janssen, Pfizer, Paladin, and Bristol-Myers Squibb, has sat on advisory boards for Novartis, Pfizer, Paladin, Bristol-Myers Squibb and Janssen, and received grants from Sierra Oncology, Novartis, Astra Zeneca, and Lundbeck. None of these organisations provided any influence on this methodological work. T.G. has provided consultancy services for Cellphire Corporation, which had no influence on this methodological work. The remaining authors have no conflict of interest to declare.

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APPENDIX 1

A.1 | Physician interview guide

1. What do patients with newly diagnosed acute leukaemia need to know about the potential for bleeding when they are first diagnosed and ready to start induction chemotherapy?
   - (1a) Do you tell patients about the risk of bleeding and how it may present?
   - (1b) Are there particular bleeds you mention and why?
   - (1c) Do you differentiate between bleeding as a disease manifestation or a treatment side effect?
2. Do patients discuss their concerns about signs and symptoms of bleeding? If YES, what are they?
   - (2a) Do patients discuss their concerns about bruising? If YES, what are they?
3. When caring for patients with acute leukaemia undergoing chemotherapy, what bleeding is clinically significant?
   - (3a) What about this bleed is concerning?
   - (3b) What is this bleed a sign or symptom of?
   - (3c) Is there any bruising that is clinically significant?
4. What bleeding are you less worried about?
5. Thinking about patients with APL, do they experience the same types of clinically significant bleeds as other AML patients and ALL patients?
   - (5a) Are there certain types of clinically significant bleeds that primarily tend to occur, or only occur in patients with APL? Which ones?

6. What are the characteristics of a clinically significant bleed (i.e., serious bleed)?
   (6a) When you see bleeding in a patient, what signs or indications tell you whether or not this bleeding is severe? Probes: For example, these could be signs and symptoms, impacts on the patient or tests/treatments that might have to be ordered.
   (6b) ometimes bleeding might be significant enough to need treatment. Are there particular interventions that would make you think that a bleed was significant?
   (6c) Of the treatments and tests you just mentioned, which ones might have a large impact on the patient?
   (6d) Are there types of minor bleeding that based on your experience serve as a cue or hint or that tip you off that a worse, more significant bleed may develop?
   (6e) In your DCF, you mentioned ___ serious bleeding event. Can you tell me a little more about that?
   (6f) What do you perceive to be the impact or clinical significance of a patient experiencing multiple bleeds, occurring on the same day?
7. Are signs and symptoms of bleeding documented when they occur? If YES, are all types of bleeding documented? (i.e., mild bleeding, like petechiae, or only more severe bleeding)?
8. How do you assess bruising? Is it the same for darker skin tones or do you do something different?
9. How well do you think you are able to predict a serious bleed?
   (9a) Are you able to put your finger on signs or symptoms that give you the signal of a serious bleed developing in the future?
10. Do you have any other perceptions or comments about bleeding in this patient population that we have not discussed during this interview that you would like to share?
11. Would you be willing to be contacted again about this study?
12. Would you be willing to circulate an email invitation about the study through your professional networks?

A.2 | Nurse interview guide

A.2.1. | Bleeding perceptions questions

1. What do patients with newly diagnosed AL need to know about the potential for bleeding when they are first diagnosed and ready to start induction chemotherapy?
   (1a) We know that clinical life is very busy in an ideal world what do you teach your patients about bleeding?
   (1b) Is there anything you think your patients should know that you don't usually teach them?
   (1c) Do you tell patients about the risk of bleeding and how it may present Probe: Are there particular bleeds you mention, and why?
   (1d) When speaking with patients do you differentiate between bleeding as a disease manifestation or a treatment side effect?
2. As a nurse caring for patients with AL do you assess bleeding? If YES, ask 2a-d. If NO, proceed to question 3.
   (2a) How often do you assess bleeding?
   (2b) How do you perform that assessment?
   (2c) What is the clinical purpose of the assessments?
   (2d) Do you involve patients in assessments? Why or why not?
   (2e) Are there certain signs/symptoms of bleeding that you would notify other members of the healthcare team about immediately? If yes, which ones and why?
3. Do you document bleeding? YES/NO.
   (3a) If YES, are all types of bleeding documented? (i.e., mild bleeding, like petechiae, or only more severe bleeding).
4. Do patients discuss their concerns about signs and symptoms of bleeding with you? If YES, what are they?
   (4a) Do patients discuss their concerns about bruising? If YES, what are they?
5. How do you assess bruising? Is it the same for darker skin tones or do you do something different?
6. When caring for patients with AL undergoing induction chemotherapy, what bleeding is clinically significant?
   (6a) What about this bleed is concerning?
   (6b) What is this bleeding a sign or symptom of?
   (6c) Is there any bruising that is clinically significant?
   (6d) What do you perceive to be the impact or clinical significance of a patient experiencing multiple bleeds, occurring on the same day?
7. What bleeding are you less worried about?
8. Thinking about patients with APL, do they experience the same types of clinically significant bleeds as other AML patients and ALL patients?
   (8a) Are there certain types of clinically significant bleeds that primarily tend to occur, or only occur in patients with APL? Which ones?
9. What are the characteristics of a clinically significant bleed (i.e. serious bleed)?
   (9a) When you see bleeding in a patient, what signs or indications tell you whether or not this bleeding is severe? Probes: For example, these could be signs and symptoms, impacts on the patient, or tests/treatments that might have to be ordered.
   (9b) Sometimes bleeding might be significant enough to need treatment. Are there particular interventions that would make you think that a bleed was significant?
   (9c) Of the treatments and tests you just mentioned, which ones might have a large impact on the patient?
   (9d) Are there types of minor bleeding that based on your experience serve as a cue or hint or that tip you off that a worse, more significant bleed may develop?
   (9e) In your intake survey, you mentioned ___ serious bleeding event. Can you tell me a little more about that?
10. How well do you think you are able to predict a serious bleed?
   (10a) Would you be able to put your finger on the symptoms or signs that give you the signal that this may be a serious bleed?
11. Do you have any other perceptions or comments about bleeding in this patient population that we have not discussed during this interview that you would like to share?

12. Would you be willing to be contacted to again about this study?
13. Would you be willing to circulate an email invitation about the study through your professional networks?

Legend: AML, acute myeloid leukaemia; AL, acute leukaemia; APL, acute promyelocytic leukaemia; ALL, acute lymphocytic leukaemia.

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TRANSFUSION MEDICINE WILEY

ORIGINAL ARTICLE

Perioperative transfusion study (PETS): Does a liberal transfusion protocol improve outcome in high-risk cardiovascular patients undergoing non-cardiac surgery? A randomised controlled pilot study

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Abstract

Background: Small studies have shown that patients with advanced coronary artery disease might benefit from a more liberal blood transfusion strategy. The goal of this pilot study was to test the feasibility of a blood transfusion intervention in a group of vascular surgery patients who have elevated cardiac troponins in rest.

Methods: We conducted a single-centre, randomised controlled pilot study. Patients with a preoperative elevated high-sensitive troponin T undergoing non-cardiac vascular surgery were randomised between a liberal transfusion regime (haemoglobin >10.4 g/dL) and a restrictive transfusion regime (haemoglobin 8.0–9.6 g/dL) during the first 3 days after surgery. The primary outcome was defined as a composite endpoint of all-cause mortality, myocardial infarction or unscheduled coronary revascularization.

Results: In total 499 patients were screened; 92 were included and 50 patients were randomised. Postoperative haemoglobin was different between the intervention and control group; 10.6 versus 9.8, 10.4 versus 9.4, 10.9 versus 9.4 g/dL on day one, two and three respectively ($p < 0.05$). The primary outcome occurred in four patients (16%) in the liberal transfusion group and in two patients (8%) in control group.

Conclusion: This pilot study shows that the studied transfusion protocol was able to create a clinically significant difference in perioperative haemoglobin levels. Randomisation was possible in 10% of the screened patients. A large definitive trial should be possible to provide evidence whether a liberal transfusion strategy could decrease the incidence of postoperative myocardial infarction in high risk surgical patients.

KEYWORDS
myocardial infarction, red blood cell transfusions, troponin, vascular surgery

1 | INTRODUCTION

Myocardial infarction and ischemic cardiac complications are common after high-risk non-cardiac surgery patients. Studies show that the incidence of perioperative myocardial infarction varies roughly between 4% and 30%, depending on the patient population.[1–3] A major concern is that in most patients, ischemic cardiac events occur without symptoms and that these patients therefore do not receive adequate treatment.[4] The hospital mortality rate for perioperative myocardial infarction is estimated to be up to 35%.[1,2,4–6] The majority of perioperative myocardial infarctions present within the first 4 days of surgery and nearly 90% by the end of the first week after surgery.[7] A preventive strategy for perioperative myocardial infarction is therefore of the utmost importance.

Prevention of perioperative ischemic events is mainly achieved through optimization of the imbalance between coronary oxygen supply and demand by cardiovascular medication.[8] Beta blockers, aspirin and statins remain the cornerstone of optimization in the non-surgical setting but large trials have not shown a reduction in outcome by preventive use of these medications.[6,9]

Studies suggest that preoperative anaemia as well as a restrictive transfusion strategy might adversely affect outcomes in patients at a high risk for postoperative cardiovascular complications.[10,11] No studies are available with regard to optimization of perioperative haemoglobin levels in high-risk cardiovascular patients. We therefore performed a pilot study to assess the feasibility of a blood transfusion study in high-risk patients who are scheduled for non-cardiac surgery.

2 | MATERIALS AND METHODS

2.1 | Design

We conducted a single-blinded, single centre, randomised controlled trial at the Erasmus University Medical Centre, Rotterdam, The Netherlands from June 2015 until May 2017.

Ethical approval for this study (Ethical Committee Number NL52055.078.14) was provided by the Ethical Committee of the Erasmus University Medical Centre, Rotterdam, The Netherlands (chairman: Prof. Dr. H. W. Tilanus) on 21 May 2015. This trial was registered in trialregister.nl on 17 January 2012 and modified on 18 October 2015 (ID NTR3244). This trial was conducted in accordance with the relevant articles of the declaration of Helsinki. Written informed consent was obtained from all patients.

2.2 | Subjects studied

Patients, aged above 40 years, were eligible if they were presenting for non-urgent, non-cardiac vascular surgery in combination with a high-sensitive troponin T value above 99th percentile (i.e., >14 ng/L) measured at rest during preoperative visit at the outpatient clinic. The following vascular procedures were included; open or endovascular aneurysm repair, peripheral bypass surgery and lower limb amputation. Exclusion criteria were: (1) patients who refused blood transfusions for religious or other reasons, (2) patients who had clinically recognised acute myocardial infarction within 30 days before study entry, (3) patients who are currently enrolled in a trial or previously participated in this trial, (4) patients who were actively bleeding at the time of randomisation or (5) patients who refused to provide an informed consent.

2.3 | Laboratory measurements

Preoperative haemoglobin level was measured as part of standard care the day before surgery. During surgery, haemoglobin level was measured after every 500 mL of blood loss. After surgery, haemoglobin as well as high-sensitive troponin T concentrations were obtained daily for the first 3 days following inclusion or until discharge. Fifth-generation high-sensitive troponin assay was used (Elecsys Troponin T hs, Roche Diagnostics, Basel, Switzerland).

2.4 | Informed consent and randomisation

All patients had their preoperative workup according to the 2014 ESA/ECS guidelines.[8] Eligible patients were approached by study staff preoperatively and written consent was obtained. If any haemoglobin level was below the threshold of 10.4 g/dL during the period of the evening before surgery until the third postoperative day, patients were randomised to either a liberal transfusion regime (haemoglobin >10.4 g/dL) or a restrictive transfusion regime (haemoglobin 8.0–9.6 g/dL). Randomisation was performed by a computer-based system using block randomisation with varying blocks from four till eight patients. During allocation, each patient received a unique randomisation code. Research staff involved in the randomisation process, the treating physician as well as the patient were non-blinded to the intervention. Research staff assessing outcomes as well as analysing data were blinded.

2.5 | Intervention

Patients were randomised to a liberal transfusion regime or a restrictive transfusion regime. The lowest acceptable haemoglobin level in the liberal transfusion group was set at 10.4 g/dL. If a patient was randomised to the restrictive control group, blood transfusions were according to standard care as specified in the Dutch CBO guidelines.[12] This guideline advises a perioperative haemoglobin level between 8.0 and 9.6 g/dL. All patients were allowed to receive preoperative blood transfusions regardless of the assigned study group. Patients allocated to the control group were permitted to receive red blood cells transfusions above the restrictive transfusion threshold, if patients developed symptoms of anaemia. The assigned transfusion strategy was followed until the third postoperative day or discharge from hospital, whichever occurred first. After ABO cross-match, each

unit of red blood cells consisting of 260 mL was administered one at a time, followed by a haemoglobin measurement.

2.6 | Study outcome

The primary endpoint of the study was the incidence of Major Adverse Cardiac Events (MACE) within 30 days of randomisation. MACE was defined as a composite endpoint of all-cause mortality, myocardial infarction or unscheduled coronary revascularization. Secondary endpoints were the individual components of the MACE as well as peak high-sensitive troponin T levels. Myocardial infarction was defined according to the third universal definition.[13] Unscheduled coronary revascularization was defined as any coronary intervention (diagnostic as well as acute percutaneous revascularization).

2.7 | Follow up

Patients were followed up for 30 days postoperatively. Primary and secondary outcome data were obtained by using the electronic medical record.

2.8 | Sample size calculation

A total number of 100 patients randomised or a maximum inclusion period of 24 months was planned for this pilot study, although no formal group size calculation was possible.

2.9 | Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Chicago, IL, USA). Normality of continuous data was tested with the Shapiro-Wilk test. Categorical data were compared using Fisher's exact test. Continuous data were compared using Kruskal-Wallis tests. A P-value below 0.05 was considered significant. All patients were analysed according to an intention-to-treat analysis.

3 | RESULTS

In total, 499 patients were screened for eligibility (Figure 1). The majority of patients were excluded from the study because of high-

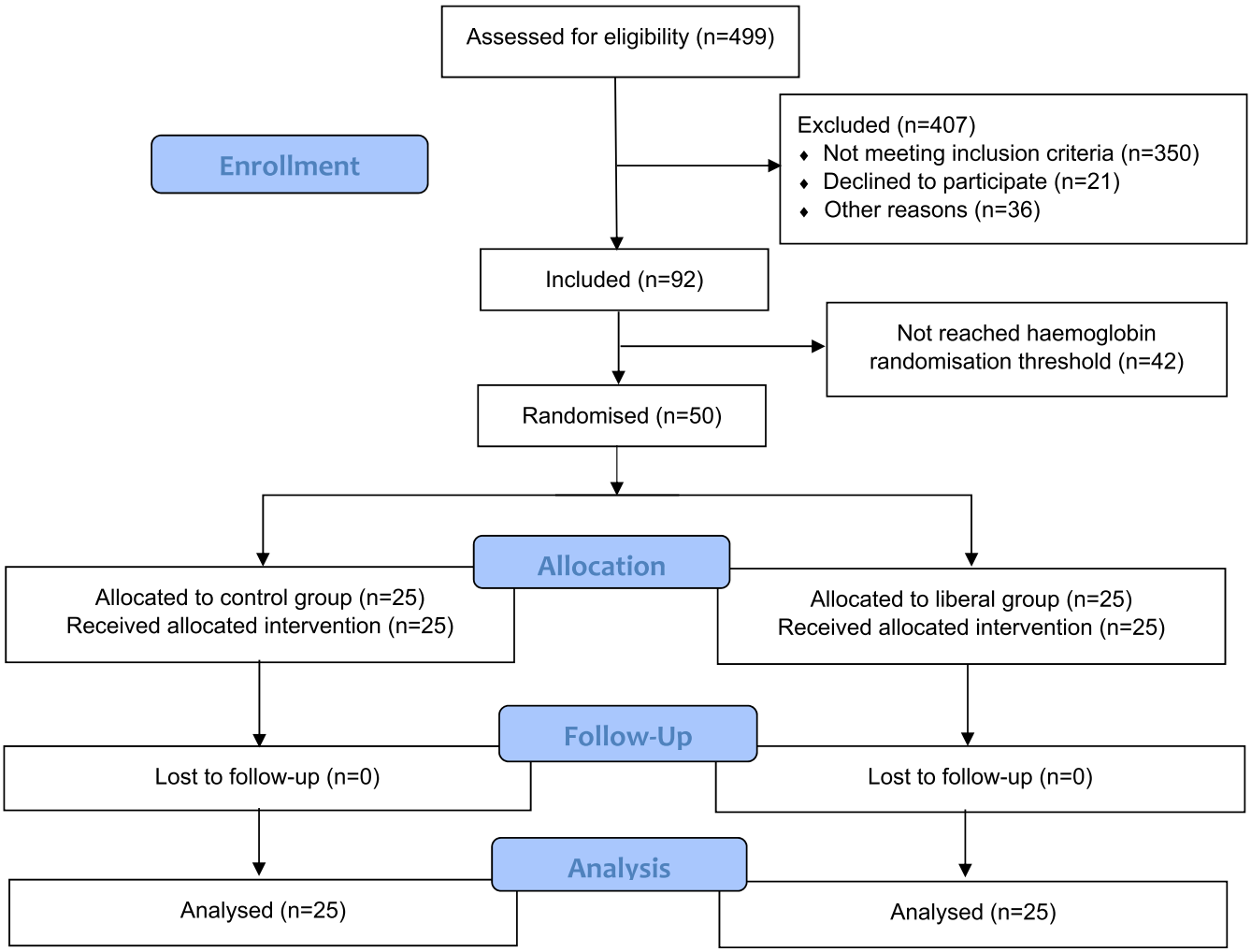

FIGURE 1 Study flow diagram.

TABLE 1 Patient baseline characteristics.

		Control group $n = 25$	Liberal group $n = 25$	p-value
	Age (years)	75 (68–79)	75 (67–76)	0.44
	Male sex (%)	17 (68)	17 (68)	1.0
	BMI (kg/m^2)	26.2 (23.6–28.5)	24.3 (22.9–26.5)	0.21
Previous medical history and medication				
	Hypertension (%)	21 (84)	20 (80)	1.0
	Hypercholesterolemia (%)	18 (72)	21 (84)	0.50
	Chronic heart failure (%)	6 (24)	7 (28)	1.0
	Prior revascularization(%)	6 (24)	12 (48)	0.14
	Diabetes mellitus (%)	6 (24)	6 (24)	1.0
	Smoking (%)	5 (20)	5 (20)	1.0
	Dialysis (%)	2 (8)	0 (0)	0.49
	Prior CVA (%)	6 (24)	5 (20)	1.0
	P2Y12 inhibitors (%)	4 (16)	9 (36)	0.20
	Ascal (%)	16 (64)	16 (64)	1.0
	Beta-blockers (%)	15 (60)	14 (56)	1.0
	ACE/AT2 inhibitors (%)	15 (60)	15 (60)	1.00
	Diuretics (%)	11 (44)	8 (32)	0.56
	Calcium channel blockers (%)	9 (36)	10 (40)	1.0
	Nitrovasodilator (%)	6 (24)	5 (20)	1.0
	Statins (%)	20 (80)	23 (92)	0.42
Preoperative haemoglobin (g/dL)		10.9 (10.1–12.6)	11.7 (9.2–13.1)	0.61
Preoperative creatinine (μmol/L)		94 (74–165)	93 (79–104)	0.44
Preoperative troponin (ng/L)		28 (22–35)	19 (16–27)	0.05

Note: Values are median (interquartile range) or number of patients (%).
Abbreviations: ACE, angiotensin-converting enzyme; AT2, angiotensin II receptor; CVA, cerebrovascular accident.

TABLE 2 Haemoglobin levels postoperatively.

	Control group $n = 25$	Liberal group $n = 25$	p-value
Haemoglobin first day postoperative (g/dL)	9.8 (9.0–106)	10.6 (10.1–11.2)	0.02
Haemoglobin second day postoperative (g/dL)	9.4 (8.5–10.2)	10.4 (9.8–11.2)	0.001
Haemoglobin third day postoperative (g/dL)	9.4 (8.6–10.2)	10.9 (10.1–11.5)	0.001
Transfusions per patient	0.0 (0.0–1.5)	2.0 (1.0–3.0)	0.003

Note: Values are median (interquartile range).

sensitive troponin T levels below the specified threshold; 21 patients refused to participate or were unable to provide informed consent. Furthermore, 36 patients could not be included due to the lack of administrative support. Of the 92 patients included, 42 patients did not reach a haemoglobin level below the randomisation threshold. This left 50 patients to be randomised. There was no loss to follow up and all patients were analysed. Baseline characteristics were equally distributed between both study groups with the only exception being preoperative high-sensitive troponin T levels (Table 1). Haemoglobin levels throughout the perioperative period are presented in Table 2 and Figure 2. The majority of blood transfusions were given intraoperatively. Seven patients, allocated to the liberal transfusion protocol, received a preoperative blood transfusion. Patients in the liberal strategy group received more transfusions than the control group (64 vs. 23 units of packed cells). The primary endpoint occurred in four patients (16%) in the restrictive group and in two patients (8%) in the liberal group ($p = 0.67$) (Table 3). Myocardial infarction occurred in four patients in the restrictive group and was not present in the liberal study group ($p = 0.11$). Postoperative troponin T levels were significantly higher on the second and third postoperative day in the restrictive group (Table 3).

4 | DISCUSSION

This pilot study tested the feasibility of a liberal red blood cell transfusion regime in vascular surgery patients who have an elevated high-sensitive troponin T before surgery. Of the 499 patients screened,

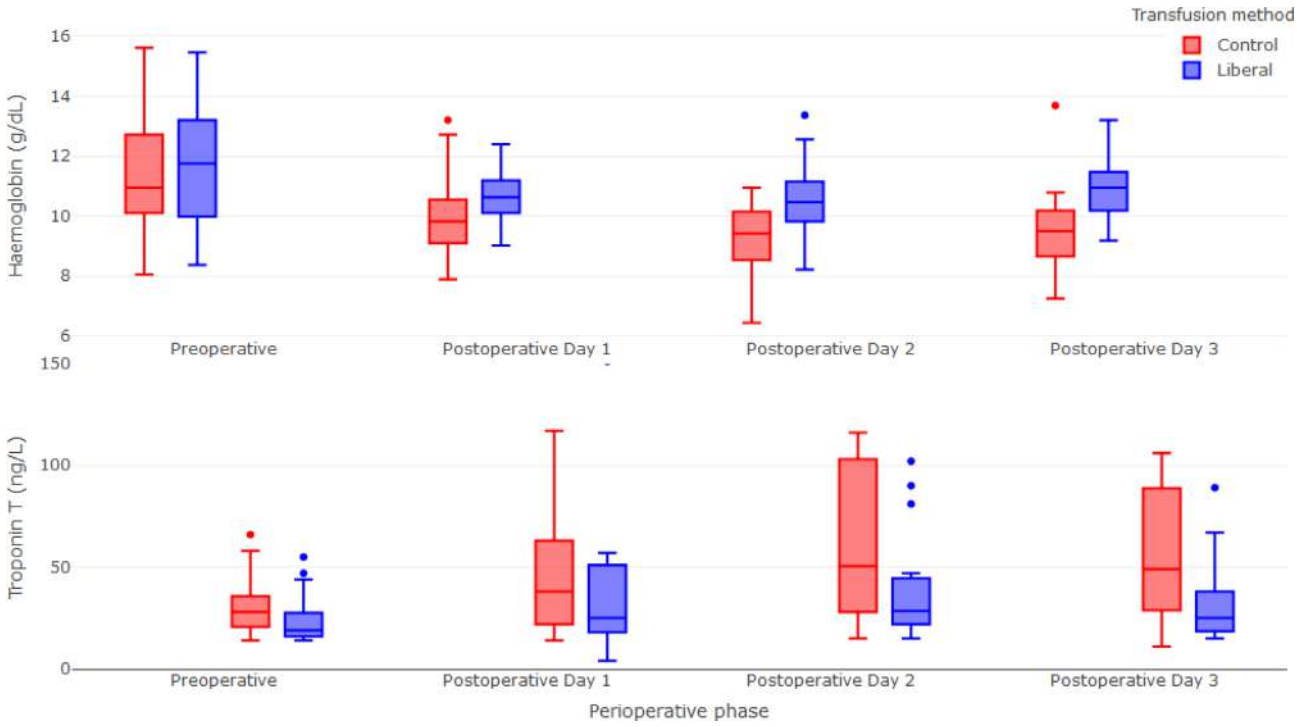

FIGURE 2 Haemoglobin levels (g/dL) between intervention and control group.

TABLE 3 Postoperative outcome and troponin concentrations.

		Control group $n = 25$	Liberal group $n = 25$	p-value
MACE (%)		4 (16)	2 (8)	0.67
	Death (%)	1 (4)	2 (8)	1
	Myocardial infarction (%)	4 (16)	0 (0)	0.11
	Unplanned revascularization (%)	1 (4)	0 (0)	1
Troponin day 1 (ng/L)		38.0 (22.0–65)	25.0 (15.6–51.2)	0.18
Troponin day 2 (ng/L)		50.5 (26.8–106.25)	28.5 (22.0–45.8)	0.03
Troponin day 3 (ng/L)		49.0 (28.5–94.5)	24.9 (18.3–39.0)	0.01

Note: Values are median (interquartile range) or number of patients (%).

49 patients could be randomised. The study protocol was able to create a difference in the perioperative haemoglobin levels. The liberal transfusion group, on average, had a 1.1 g/dL higher haemoglobin level throughout the perioperative period. Consequently, there was a significant difference in the amount of red blood cells transfused between both strategies. The incidence of the primary outcome was 16% in the control group. Although outcome comparisons should be assessed with extreme caution in this study design, there was a trend in the number of myocardial infarctions in favour of the liberal transfusion strategy. In accordance, high-sensitive troponin T levels were also significantly lower in the liberal strategy group on the second and third day postoperatively.

The general belief is that a restrictive strategy is safe in most clinical settings. A comprehensive systematic review and meta-analysis including a mixed non-surgical population of 9813 patients showed no benefit of a liberal transfusion strategy.[14] Furthermore, a Cochrane review including 19 trials involving a total of 6264 patients, showed a reduction in hospital mortality associated with a restrictive transfusion strategy in non-surgical patients.[15] The 30-day mortality, cardiac events, stroke or pneumonia did not differ between both strategies.[15] The same authors published a second Cochrane review including 48 trials involving a total of more the 21.000 surgical and non-surgical patients showed also no difference.[16] Two randomised controlled clinical trials by Hebert et al. reported that a restrictive strategy of red blood cell transfusion (haemoglobin levels maintained between 7.0 and 9.0 g/dL) is at least as effective as a liberal transfusion strategy (haemoglobin level maintained between 10.0 and 12.0 g/dL) in critical ill intensive care patients.[17,18] However, the authors did make (a possible) exception for patients with acute myocardial infarction and unstable angina in both studies. This was confirmed in two independent retrospective studies, which showed that a postoperative (mild) anaemia (<11.0 g/dL) was associated with postoperative cardiac

ischaemia in high-risk cardiovascular patients after non-cardiac surgery.[10,11] The results of this study were in concordance with the pilot study by Carson et al.[19] In this small study patients with symptomatic coronary artery disease were randomised between two transfusion strategies. And although there was no significant difference in MACE, their study showed a clear trend towards fewer major cardiac events in the liberal transfusion group. The recently published MINT trial was a randomised study involving patients with myocardial infarction and haemoglobin levels below 10 g/dL.[20] In this study patients were assigned to either a restrictive transfusion strategy, with target haemoglobin levels set at 7 or 8 g/dL, or a liberal strategy where haemoglobin levels of 10 g/dl and higher were maintained. The primary outcome, a composite of myocardial infarction or death within 30 days, was observed in 16.9% of patients in the restrictive group compared to 14.5% in the liberal group. After multiple imputations for incomplete follow-up no differences were seen between both groups. This led to the conclusion that a restrictive transfusion regimen is non-inferior to a liberal transfusion regimen.

There are several limitations to our study. First, given the small sample size, comparisons between groups should be interpreted very cautiously. Second, we used preoperative elevated high-sensitive troponin T as a reflection marker for the identification of high cardiac risk patients. This hypothesis was based on the fact that an elevated troponin T at rest can be used as a diagnostic marker for extensive coronary heart disease.[21] Furthermore, several studies have also shown a correlation between preoperative elevated troponin T levels and the incidence of postoperative MACE.[5,22–24] Thus, although we believe that an elevated troponin T at rest reflects extensive coronary artery disease, it may be questioned whether this is a valid assumption. Lastly, although this study was randomised, the preoperative troponin levels were marginally significantly higher in the control group which might suggest that the control group had a slightly higher initial risk to develop perioperative MACE, although other baseline characteristics did not differ.

Out of the 499 patients evaluated for eligibility, 50 (10%) were ultimately randomised. The substantial number of exclusions stemmed from two primary factors. First, a considerable portion of patients assessed did not present with elevated troponin T levels at rest (29.9%). Second, due to the increasing utilisation of less invasive percutaneous vascular surgical techniques, many patients did not reach the threshold for randomisation. This should be taken into account when designing a larger trial.

In conclusion, this pilot study shows that the selected transfusion threshold is able to create a difference in perioperative haemoglobin levels in a vascular surgical population. Whether the difference in haemoglobin levels between both groups is clinically meaningful, is debatable. A definitive, larger, randomised trial will be needed in order to prove the superiority of a liberal transfusion regime.

AUTHOR CONTRIBUTIONS

S.A., S.R., S.H., RS.S and F.vL contributed to study design and conduct, acquisition of data, analysis and interpretation of data and writing—original draft. S.V. and A.K. were responsible for the critical revision of the article. All Authors read and approve the final version of the article.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

PATIENT CONSENT STATEMENT

Written informed consent has been obtained from all involved patients.

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ORIGINAL ARTICLE

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Construction of a decision model for donor testing in cases of suspected antibody-mediated transfusion-related-acute-lung-injury

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Abstract

Objective: To propose a rational basis for donor testing in cases of suspected antibody-mediated transfusion-related lung injury (AMT).

Background: Anti-leukocyte antibodies in donated blood are established causes of transfusion-related lung injury (TRALI). However, the question of whether to test donors for antibodies is not identical to whether the case meets definition criteria for TRALI. There is a balance between the potential benefits of testing and the costs of donor deferral and investigation. We propose that a decision-making process based on optimising the balance between risk and benefit requires a subjective choice of the relative value of different outcomes of testing.

Methods: We have developed a formal decision model to illustrate how these choices affect testing decisions.

Results: Using a Bayesian probability model, we show that the diagnostic benefit and TRALI prevention benefit of testing donors have a complex interrelationship with the number of implicated donors and clinical suspicion of antibody-mediated TRALI (AMT) and that rational testing choices vary according to value assigned to outcomes.

Conclusions: The challenges to the use of a formal decision model for clinical testing are discussed and conclude that a formal model is a useful consensus-building tool for improving consistency and openness in decision making.

KEYWORDS

algorithm, antibody, blood donor, decision model, haemovigilance, HLA, HNA, mathematical model, testing, TRALI

1 | INTRODUCTION

Antibodies in transfused blood components against leukocyte antigens such as HLA and HNA are an established cause of transfusion-related lung injury (TRALI).[1] However, these are not synonymous concepts. Demonstrating the presence of leukocyte antibodies in the donors is neither necessary nor sufficient for classification of a reaction as TRALI, and indeed it has no role in the International Revised Consensus definition of TRALI[2] or the earlier international Canadian Consensus definition.[3] TRALI is a clinically defined syndrome which can arise due to interaction between inflammatory insults in the recipient, the fluid load of the transfusion

and biologically-active mediators in the transfusion (including antibodies and other proposed but not proven mediators). Nevertheless, the phenomenon of antibody-mediated-TRALI remains an important concept because it is the only established cause of TRALI which is within the current ability of blood centres to prevent as part of product safety. It is also the only established cause of TRALI for which laboratory testing is routinely available.

The decision to investigate donors in a case of suspected antibody-mediated TRALI (AMT), or indeed any adverse reaction, is more complex than a simple decision to perform a diagnostic test. Investigation may confer benefit to the recipient, since understanding what caused the reaction may alter clinical care. It may also confer benefit to the blood service and future recipients by improving blood product safety, by identifying donors with antibodies who could cause future reactions. However, investigation also has costs in terms of causing anxiety and inconvenience to the donors being investigated, reduction in blood supply because of donor deferral, as well as the analytical cost of the testing itself.

Interpretation of donor testing results is also not straightforward because there is no direct correlation between the finding of antibodies and causation. Leukocyte antibodies are prevalent in the donor population[4] and most transfusions where there is an antibody cognate to the recipient do not cause any reaction.[5] Thus, the finding of cognate antibody does not entail causation. A cognate antibody could also be found as a chance association, and importantly the probability of a chance finding will increase as the number of donors tested and the antibody prevalence increase. The diagnostic performance of testing donors is therefore dependent on the number of donors tested. Furthermore, many recipients who suffer a respiratory deterioration after transfusion are often unwell with multiple possible explanations for the deterioration,[6] and therefore causation is impossible to prove if antibodies are detected.

Blood services are aware of the complex cost-benefit conundrum of testing donors, particularly as recalling donors for testing is labour intensive. They often employ procedures such as expert review of cases before deciding to test donors. However, expert review can attract the criticism that the basis of decision making is not transparent, and as discussed above, the question of whether to test is not the same as whether the case meets TRALI criteria.

In order to address these concerns, we have used a Bayesian probability framework to illustrate the diagnostic benefit obtained by testing donors for antibodies, the benefits of testing in terms of TRALI prevention and the costs in terms of donor deferral. The results are combined into a formal decision model to attempt to answer the question 'in which suspected cases of antibody-mediated TRALI should we test donors?'

2 | CONSTRUCTION OF DECISION MODEL

2.1 | First benefit of testing: Diagnostic information

One aim of testing donors is to provide information about whether the transfusion might have caused the reaction by identifying at least one donor with leukocyte antibodies which match the recipient. The diagnostic benefit of testing can therefore be quantified as the degree to which it changes the requestor's confidence in the diagnosis, which can be calculated using Bayes' theorem.

Bayes' theorem, as applied to diagnostic testing[7] generally states.

$$P(\text{condition}|\text{test result} = x) = \frac{P(\text{test result} = x|\text{condition}) \times \text{pre} - \text{test probability}}{P(\text{test result} = x)}. \quad (1)$$

Informally this captures the idea that our confidence in the diagnosis is related to how likely we thought the diagnosis was before performing a test, and how good the test is.

As applied to antibody testing of suspected AMT, the appropriate formulas are shown in Data S1: Equations 2.1 and 2.2.

To calculate these, we need estimates of the following three probabilities:

a. The probability that a donor positive for antibodies is found in a true case of AMT.
b. The probability that an antibody is found in a donor if the reaction was not an AMT, and thus depends on the number of donors implicated and the prevalence of antibodies in the donor population.
c. The pre-test probability of AMT, which will be clinically determined for each case (by expert review).

We can illustrate the qualitative features of the test performance, choosing placeholder values for these probabilities. Figure 1A shows the likelihood ratio[8] (LR+) for donor testing, as a function of the number of donors involved and the antibody prevalence in the population. Note that the LR+ decreases as the number of donors increases, and as the antibody prevalence increases since both situations increase the probability of finding an antibody purely by chance. The diagnostic value of testing donors decreases as the number of implicated donors and the donor antibody prevalence increase. In contrast, the diagnostic value of a negative test is independent of the number of donors since the post-test probability of a chance positive finding is clearly zero.

Figure 1C,D present the change in pre-test probability following positive and negative test results, respectively. The maximum diagnostic information is achieved when the pre-test probability is intermediate, where there is uncertainty about the diagnosis. Intuitively, this reflects the idea that if you are sure of the diagnosis, no test result will change your opinion Again, the diagnostic information decreases as the number of donors increases.

In summary, investigating donors provides the most diagnostic information for the recipient in cases where there is diagnostic uncertainty and where a smaller number of donors are implicated. Test results will have little influence on the confidence that the transfusion caused the reaction in situations where many donors are involved, there is already a high level of confidence that the reaction was caused or not caused by the transfusion, or where there is a high prevalence of antibodies in the donor population.

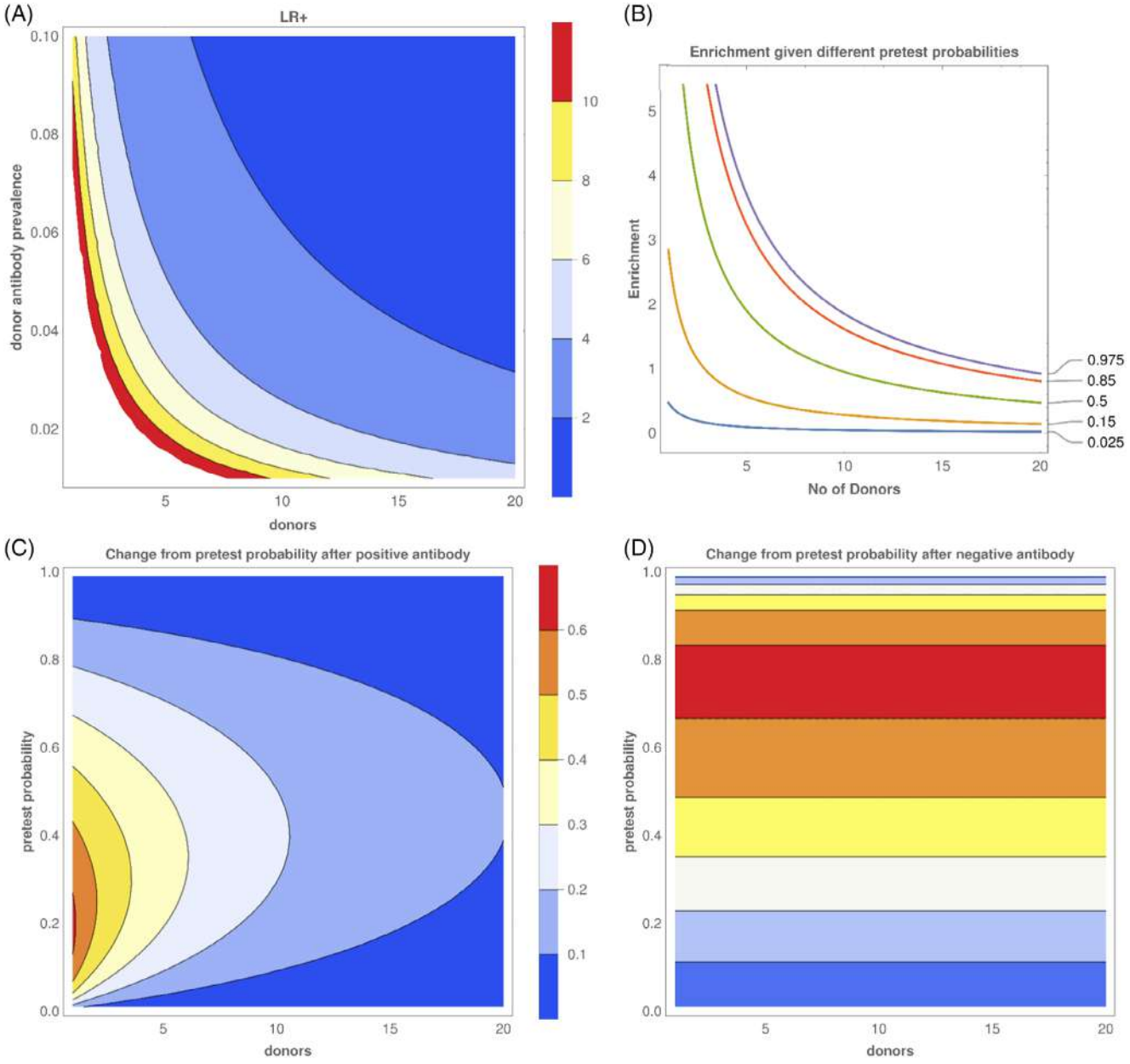

FIGURE 1 Diagnostic performance of donor testing. (A) shows the positive likelihood ratio (LR+) of testing donors, as a function of the number of implicated donors and the donor antibody prevalence, showing that test performance decreases as the number of donors and the donor antibody prevalence increase. Results shown are calculated using a 90% positivity rate for antibody-mediated transfusion-related lung injury. (B) shows the increased proportion of donors with antibodies detected by testing implicated donors relative to testing the same number of random donors ('enrichment') as a function of the number of donors and pre-test probability. The results show that enrichment decreases as the pre-test probability decreases and the number of donors increase. Results shown are calculated using a donor prevalence rate of 5%. (C) and (D) illustrate the change in diagnostic confidence (difference between pre- and post-test probabilities) following a positive and negative test, respectively. The results shown are calculated using a donor antibody prevalence of 5% and that assume 90% of antibody positive transfusion-related lung injury cases are positive for antibodies. Parameter values are chosen to illustrate qualitative features but are within credible limits (see Data S1: Section 9).

2.2 | Second benefit of testing: Donation safety

The second aim of testing donors is to identify donors with antibodies who could be at risk of causing further reactions if they donate blood in the future. The risk of AMT could be maximally reduced by screening all donors, but this would lead to unacceptable increased levels of expense and donor deferral. The rationale for testing donors in a suspected case of AMT must therefore be that investigating cases would have a higher detection rate for donors with antibodies than simply investigating donors at random.

We can calculate the proportional increase in detection of donors with antibodies by testing following a suspected reaction compared

with testing the same number of random donors from the donor population (Data S1: Section 3). This is termed the 'enrichment'.

Figure 1B shows the result of calculating the enrichment for different values of the pre-test probability, as a function of the number of donors involved. Note the increasing relationship between the enrichment and the pre-test probability and the decreasing relationship with the number of donors involved.

In summary, testing donors provides the greatest benefit in terms of increasing the detection rate for donors with antibodies if there are fewer donors involved with the reaction or where there is a high level of suspicion that the transfusion caused the reaction. Alternatively, if there is a higher confidence that the transfusion caused the reaction, it is worth testing a larger number of donors.

2.3 | Disadvantages of testing or not testing

As noted in the Section 1, a decision to investigate a suspected case with a view to deferring donors who have antibodies cognate with the recipient has intrinsic costs. There are costs related to the analytics of investigation and the short-term loss of donations while donors are deferred for investigation. This is simply proportional to the number of donors implicated.

Further cost is incurred by permanent loss of future donations from donors who have antibodies and are permanently deferred. Because of the prevalence of donor antibodies, there is an expected rate of donor loss if a case is investigated regardless of whether the case was caused by donor antibodies or not. This depends on the number of implicated donors and the donor antibody prevalence (Data S1: Section 6).

However, a decision not to test donors also has a cost since there is a risk that a donor with antibodies could continue to donate and cause a TRALI reaction in a future recipient. An expression for estimating the expected number of AMT cases if donors involved with a suspected AMT continue to donate is derived in Data S1: Section 4.

2.4 | Which cases to investigate?—A balance of cost and benefit

How should we make a rational decision whether to investigate donors? The fundamental starting principle is that we should test donors where the expected benefits of testing are greater than the disadvantages of not testing.

In line with this we have developed a formal decision mode[9] to illustrate the information and considerations required to make such a calculation. The model considers three available decision choices, and four outcomes of interest, as summarised in Figure 2A.

Establishing the expected benefit, implicitly, requires a way of comparing the relative value of the different outcomes. The general concept is termed 'utility' and construction of a formal model requires a choice of utility value to be assigned to each outcome. Different utility measures can be chosen such as financial cost, mortality or quality-adjusted life years (QALY), but the key point is that a subjective value judgement needs to be made on the relative value of the different outcomes.

(A)

Decision options	Benefit -increased understanding of what caused reaction	Benefit -reduction in risk of future antibody mediated TRALI	Cost -Investigation of donors and short term deferral	Cost -Permanent deferral of donors with antibodies
1. Do not test. All donors continue to donate.	NO	NO	NO	NO
2. Do not test. Defer all donors	NO	YES	NO	MAXIMUM
3. Test donors. Defer if cognate antibody	YES	YES	YES	YES

(B)

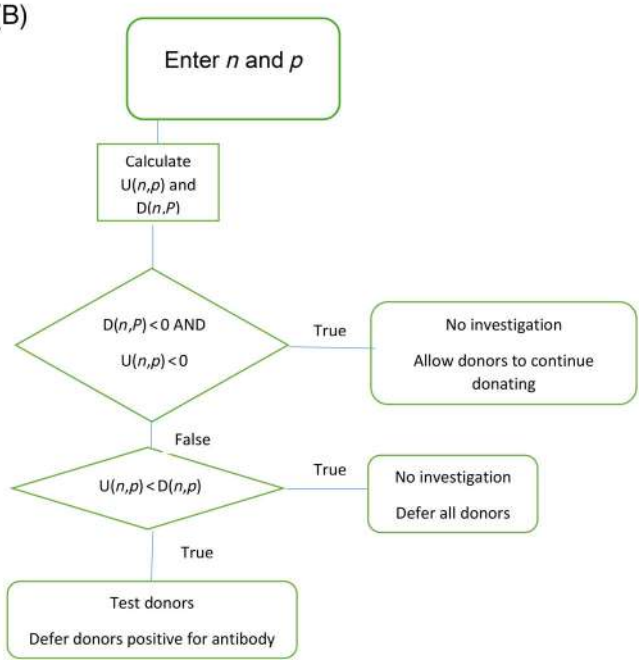

FIGURE 2 Description of decision-making algorithm. (A) summarises the decision options and outcomes used in the decision model. (B) presents the decision-making algorithm, which returns a recommended action when given an input of *n*: the number of implicated donors and *p*: the pre-test probability of antibody-mediated transfusion-related lung injury. The function *U* (*n*, *p*) returns the net utility gain of testing all donors. *D* (*n*, *p*) returns the net utility gain of deferring all donors without investigation. Complete expressions for *U* (*n*, *p*) and *D* (*n*, *p*) and their derivation are given in the Data S1.

In this approach, donor testing is considered worthwhile if the gain of utility obtained by confirming the diagnosis plus reducing the risk of future TRALI is greater than the loss of utility caused by donor deferral and the costs of testing. Mathematically this can be expressed as,

$$[Uc^{*}E(c) + Ut^{*}E(t)] - [Us^{*}E(s) + Ud^{*}E(d)] > 0, \quad (2)$$

where Uc, Ut, Us and Ud are the utility values assigned to the events 'diagnosis is confirmed or excluded', 'future case of TRALI caused by

donor antibody', 'short term donor deferral' and 'permanent donor deferral', respectively. These values are subjectively chosen (Data S1: Section 7) and E(c), E(t), E(s) and E(d) are the expected number of these events, given the decision choice.

Calculation of the net utility requires estimates of three parameters: Pp 'proportion of antibody-mediated TRALI cases where at least one donor has antibodies', Pd 'probability that a random donor is positive for antibodies' and Pt 'probability that a donor with antibodies causes a future antibody-mediated TRALI case'. These parameters may not be accurately known but can in principle be estimated from real world data.

Figure 2B summarises the decision-making algorithm. The full derivation of the decision model and calculation of the utility functions is presented in Data S1: Sections 1–9.

3 | RESULTS OF DECISION MODELLING

The output of the decision model, calculated over a range of possible utility, and parameter values are shown in Figure 3. Figure 3A shows how the recommended testing approach changes with different choices of the utility value for different outcomes. A series of hypothetical 'thought-experiments' B–G illustrate how different utility choices might be made in different contexts.

A- 'Default': Arbitrary choices of utility values are chosen to illustrate all possible decisions outcomes, as a starting point. This is shown in panel A.

B- 'Non-maleficience': Beneficient blood service considers the safety of blood products to be their main concern, allocating a higher value to the utility of TRALI prevention. Panel B shows that this results in testing cases where larger number of donors are implicated. In the limit where almost all cases would be tested despite minimal advantage in donor detection compared to testing a similar number of random donors, the question could be asked whether TRALI prevention would be better achieved by universal screening of donors rather than waiting for cases to occur.

C- 'Fatality': Charles is a lawyer whose mother died after developing pulmonary oedema during her transfusion. An inquest is being held and he is considering legal action against the blood service if it can be shown that blood caused her mother's death. Thus, there is a higher utility value of diagnostic information Uc. Panel C shows that testing is most of value in cases where there is most uncertainty (pre-test probability 0.5) as the testing has the most potential to alter the outcome of the inquest.

D- 'Deferral': Dionysus blood service is pleased to have a plentiful supply of donors for their needs, and so can assign a lower utility value to donor deferral Ud. Panel D shows that here utility is maximised by simply deferring the donors in high-imputability case, thus saving the testing costs and also avoiding the possibility of recurrent TRALI caused by other mediators in the product.

E- 'Disregard': Exclusive hospital only considers the interest of its patients and not donor safety and thus has assigns a TRALI prevention utility of zero. In this scenario, panel E shows that no cases are tested. This admittedly extreme scenario is included to illustrate how testing decisions (as opposed to TRALI diagnosis) may differ between clinicians and blood services and why blood centres may need to promote reporting of suspected cases.

F- 'Slow testing': Frankness blood service appreciates that the time taken to investigate donors is sufficiently long that the results are unlikely to alter management of the recipient, and assigns a low value for the diagnostic utility of testing Uc Panel F shows the number of donors worth testing becomes linearly related to the pre-test probability, with testing decisions being determined by the probability of detecting antibodies in donors.

G- 'Rare donor': Gina is a patient with antibodies to a high-frequency red cell antigen who developed a suspected TRALI reaction. There are only two donors available with this blood type in the country. A higher utility cost of long term donor deferral is assigned. The model suggests that only cases with smaller numbers of donors would be tested-perhaps making an implicit calculus that the increased risk of harm because a donor was unnecessarily suspended leading to unavailable blood is greater than the risk of harm due to TRALI recurrence. If the conclusion feels unconscionable, it suggests a mismatch between the assigned utility values and an instinctive assignment of utility. The thought experiment may reveal that default utility assignments need to be revised, although the possibility that intuition is misleading should also be considered.

Parameter estimates: Figure 3B shows the results of the decision model calculated over a 'reasonably credible' range of values for the parameter estimates Pd and Pp. Sensitivity to Pt is not shown, as qualitatively this will behave similarly to variation in Ut, seen in Figure 3A. The results show that lack of a precise estimate for the proportion of true cases which test positive for antibodies need not be a barrier to use of a decision model since the outputs are not sensitive to variation in this parameter. This is an important observation since this parameter is difficult to estimate given the lack of a gold standard reference test for AMT. In contrast, the output is sensitive to the donor antibody prevalence, suggesting that improving this estimate is an important priority for further study to improve accuracy of the model in a specific donor population. The analysis shows that the qualitative observation that it is rarely beneficial to test large numbers of donors where there is a low suspicion of AMT remains robust over a wide credible range of parameters.

An interactive presentation of the model is available at https://tom-latham-nhsbt.shinyapps.io/TRALI-decision-model/ to allow readers to perform their own exploratory analysis. The model should not be used unmodified for clinical decision-making without agreeing parameter values and utility values which are specific to the user's context. The R source code is freely available at https://github.com/tombob-spam/TRALImodel.

4 | CONCLUSION

We have developed a Bayesian decision-making model to illustrate in qualitative terms how the results of testing donors for leukocyte antibodies could be interpreted, and the considerations needed to decide

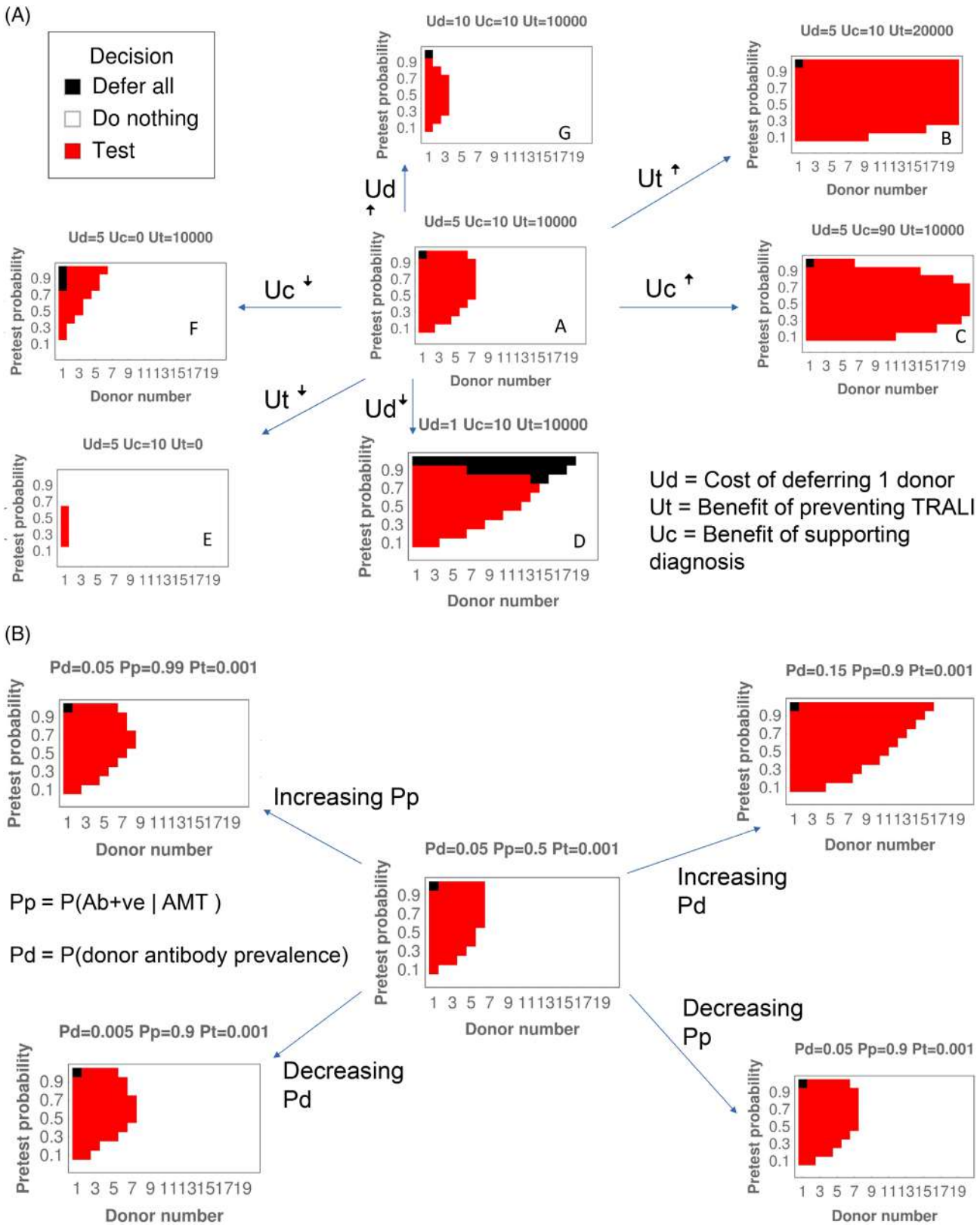

FIGURE 3 Legend on next page.

whether the benefits of testing outweigh the costs. Development of the model illustrates how the decision to investigate depends on a subjective decision regarding the relative values of different outcomes and importantly there is a non-intuitive relationship between the level of clinical suspicion of AMT, the number of implicated donations and the diagnostic value of investigating donors.

The main purpose of developing the model is to clarify the assumptions needed to make a rational testing decision, and to illustrate quantitatively how decisions may vary according to those assumptions. The next stage of development is to consider using such a decision tool for clinical decision-making. However, there are several challenges to address.

The first barrier to clinical use is determining the parameter and utility values. Although there is uncertainty in the values to assign to utility choices and parameters, the advantage of using such a decision model forces us to explicitly state our assumptions and value judgements. The main value, then, of using a formal decision-making model is as a consensus-building tool and as an important component of the operational implementation for blood services to gain agreement on how utility values and parameters should be chosen.

The second challenge, common to all Bayesian approaches, is that the decision depends on a clinical judgement of the pre-test probability of AMT. Estimating numerical probabilities given uncertain clinical scenarios is likely to be difficult for reviewers, and it has been shown that reviewers from different backgrounds differ in assigning TRALI probability.[10] A practical solution may be to ask reviewers to assign probability in ordinal categories corresponding to probability ranges which may be more intuitive and achieve better intra-rater agreement. A more fundamental concern is whether the clinical assessment of probability as the 'confidence that this case is an antibody-mediated TRALI' corresponds to 'the proportion of similar cases which are genuinely antibody-mediated TRALI'. This paper does not attempt to answer the question but clarifies a well-defined question for future research: 'what features of a transfusion reaction predict antibody-mediated TRALI?' The precise question becomes particularly pertinent given the contemporary concept of TRALI as 'endothelial permeability pulmonary oedema',[11] which may not necessarily predict donor antibodies.

The third challenge is the validity of the mathematical model itself, and whether this can replace clinical judgement and experience. More complex models could certainly be developed involving more parameters, for example, considering relative values of different kinds of donors or considering the possibility of reverse TRALI. However, the intention was to show that a rational decision necessarily involves subjective choices and combining information in non-intuitive ways. Availability of a decision-making tool would appear to be desirable since it is arguably more intuitive for clinicians to estimate the level of suspicion that the case is an AMT than to resolve the complex considerations involved in deciding whether benefits outweigh costs. It improves the clarity of decision making.

A further concern of the decision model might question the implicit utilitarian premise of making a decision that maximises utility across the whole system, with consequent overriding of individual needs. These concerns are in fact implicit in the model, interpreted as 'whose values do we assign to the utility of outcomes'. This is a valid reason for caution, and it is suggested that a decision model should be used to guide decision-making rather than to make rigid decisions. The use of the tool then becomes a 'rule utilitarian' principle rather than an 'act utilitarian' decision and may be overridden if appropriate. For example, in the case of an unexpected recipient death where there is understandably a higher value placed on understanding the cause of death.

It may come as a disappointment that the conclusion is that there can be no objective answer to the originally posed question 'in which cases of suspected antibody-mediated TRALI should we investigate donors?' Nevertheless, we have shown that in principle a formal decision model can be developed which can make a rational recommendation on whether to test a given case. Such a model could be used clinically to help clinicians make decisions in a more consistent manner by applying pre-agreed utility choices and decision processes between cases. The most important advantage of developing a formal model is that the discipline of agreeing a numerical value to assign to the relative value of competing outcomes may be a useful consensus-building tool, as well as increasing openness since the values chosen are explicitly available for criticism.

AUTHOR CONTRIBUTIONS

T.L. designed the modelling and wrote the manuscript. All other authors have provided substantial review of the manuscript and have been involved with the analysis and interpretation of clinical data, which although not directly reported in this manuscript has motivated the development of the modelling.

CONFLICT OF INTEREST STATEMENT

T.L., J.C., A.P., S.N. are employees of NHS Blood and Transplant which is the main provider of TRALI antibody testing in England.

FIGURE 3 Results of decision model. (A) Dependence of decision model output on utility value choice. Illustrates qualitatively how the set of values of the pre-test probability and donor number for which the model recommends different choices of action vary according to the relative importance assigned to different outcomes (utility multipliers Ud, Ut and Uc) in thought-experiment scenarios (A–G). The results shown are calculated using parameters Pd = 0.05, Pp = 0.9 and Pt = 0.001, which are within credible limits but are arbitrarily chosen to illustrate the qualitative features of the output variation. (B) Sensitivity of decision model output to parameter estimates and (B) illustrates how the set of values of the pre-test probability and donor number for which the model recommends different choices of action is sensitive to estimation of the donor antibody prevalence Pd and positivity rate in antibody-mediated transfusion-related lung injury Pp. Results are calculated over the credible ranges Pp = (0.5–0.99), Pd (0.05–0.15). The ranges are chosen primarily to show qualitative variation but the reasoning behind the estimates is given in Data S1: Section 9.

DATA AVAILABILITY STATEMENT

There is no primary data included with this work. The corresponding author has made the R source code freely available which may be used as desired if acknowledgement of this paper is made.

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SUPPORTING INFORMATION

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

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SHORT COMMUNICATION

TRANSFUSION MEDICINE WILEY

Transfusion Camp: The UK experience and its value in improving knowledge of transfusion medicine among postgraduate trainees

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Abstract

Objectives: To report the UK experience of rolling out Transfusion Camp.

Background: Transfusion Camp is a structured education programme developed in Toronto, with the aim of reducing knowledge gaps in transfusion medicine in postgraduate trainees. It consists of didactic lectures viewed online by the participants, then interactive, locally delivered seminars. Since 2015, it has been rolled out in the United Kingdom, and is now available in four centres. Here, we report the UK experience of Transfusion Camp and outcomes.

Methods: Trainees are recruited via the training programme directors in each region. Pre- and post-course assessments are administered using the validated BEST (Biomedical Excellence for Safer Transfusion) test, with possible scores 0–20, and confidence measured on an A-E Likert scale.

Results: Since 2015, 130 trainees have participated in Transfusion Camp in the United Kingdom. Trainees from all specialties significantly improved their BEST-test scores after attending the course (mean score 11.6/20 before the course, compared with 14.3/20 after the course), and confidence in managing transfusion-related issues was also significantly improved.

Conclusion: We recommend that all centres consider offering Transfusion Camp to trainees in haematology and other specialties that frequently use blood transfusions, such as anaesthesia/ICU, Internal Medicine and others.

KEYWORDS
education, postgraduate, transfusion

1 | INTRODUCTION

Blood transfusion is one of the commonest clinical procedures. Whilst potentially lifesaving, blood transfusion can lead to serious morbidity and mortality.[1] Consequently, it is imperative for medical professionals to have a thorough understanding of evidence-based transfusion practice. However, a recent review highlighted significant gaps in knowledge regarding transfusion practice among trainees across various specialties.[2]

To address this knowledge deficit, Transfusion Camp was established at the University of Toronto in 2012. The programme structure includes online lectures delivered by the Toronto team, which are supplemented by seven interactive, locally-conducted seminars in smaller groups. Its primary goal is to enhance transfusion medicine education for trainees, particularly those outside of haematology (Table 1).[3,4]

Building on this foundation, the programme formed partnerships with institutions such as the Centre for Innovation at Canadian Blood Services and the Ontario Regional Blood Coordinating Network. This allowed the programme to broaden its impact such that, by the 2022–2023 academic year, Transfusion Camp was offered to postgraduate trainees in 16 out of the 17 medical schools in Canada.[5] The value of Transfusion Camp in enhancing knowledge of transfusion medicine as well as self-reported positive impact on transfusion practice was reported in 2019.[3]

Outside of Canada, Transfusion Camp has gained traction in the United Kingdom. The University of Oxford was the pioneer in adopting this initiative in 2015. Building on its success, Transfusion Camp has extended its reach to include trainees from two centres in London (Guys & St Thomas's-GSTT, and King's College Hospital) as well as the University Hospitals Birmingham NHS Foundation Trust.[6]

Here, we report the UK experience of delivering Transfusion Camp.

2 | METHODS

2.1 | Recruitment

Eligible postgraduate trainees from a variety of medical specialties are invited to register for Transfusion Camp. In all centres, the programme is advertised by approaching the Training Programme Directors for haematology, emergency medicine, anaesthesia and intensive care, and asking them to inform their trainees. Particular emphasis is placed on recruiting early-stage haematology trainees so that key principles are embedded early and liaison queries may be more easily answered by the trainees.

2.2 | Course format

Transfusion Camp is structured as a combination of 22 centralised didactic lectures over 5 days and seven interactive, locally facilitated seminars. For UK trainees, the pre-recorded lectures are watched during the participants' own time in the week leading up to their seminars. Additional pre-reading materials and reference materials relevant to the topic are provided.

Each modified team-based learning seminar is made up of a series of case studies. Each case is followed by multiple choice questions, on which participants 'vote'. Voting on the questions is conducted by holding up a piece of paper with the answer on to the camera screen, typing in the 'chat' or using online voting systems such as Mentimeter. The questions are designed to stimulate discussion for the group to reach consensus and consolidate the learning from the lectures. The seminar facilitator provides any key learning points not raised in the discussion. The course material was not altered for a UK audience. Any differences in practice were discussed in the interactive sessions.

TABLE 1 Lectures and seminars delivered for Transfusion Camp.

	Lectures and seminars delivered
Day 1	Red cell transfusion
	Platelet transfusion
	Basic blood bank testing
	Albumin
	Plasma, prothrombin complex concentrates and fibrinogen replacement
	Seminar A: RBC and platelet transfusion cases
	Seminar B: Plasma, PCC and fibrinogen cases
Day 2	Acute non-infectious reactions
	Informed consent
	Sickle cell disease: perioperative and acute transfusion
	Seminar A: Transfusion reactions
	Seminar B: Sickle cell disease
Day 3	Pre-operative patient blood management
	Intra-operative patient blood management- tranexamic acid, salvage and triggers
	Congenital coagulation disorders- bleeding history, von Willebrand's disease, haemophilia
	Reversal of antiplatelets and direct anticoagulants
	Seminar A: Patient blood management
	Seminar B: Advanced haemostasis testing and management
Day 4	Massive haemorrhage—pathophysiology and evidence-based management
	Massive haemorrhage protocols—real world application
	New updates in transfusion
	Ask the experts Q&A and review
	Seminar: Major haemorrhage

In Oxford, three dates are offered for each interactive seminar to accommodate for rota constraints. Initially all seminars were delivered by one facilitator, but now seven facilitators lead one seminar each. The seminars were initially in person, but were switched to online in 2020 due to the Covid-19 pandemic, and have remained online since then. In other centres, there is a single facilitator so one date is offered for each seminar.

Table 1 demonstrates the lecture and seminar topics included in Transfusion Camp.

2.3 | Outcome measures

Pre- and post-course knowledge assessments were administered using the validated multiple-choice exam developed by the Biomedical Excellence for Safer Transfusion (BEST) collaborative to measure the change in transfusion medicine knowledge.[7] Possible scores for this test are 0–20. The original BEST test was used until 2019–2020. The test was modified to be more specific to Transfusion Camp for 2020–2021, and was validated by the Toronto team.[5]

TABLE 2 Characteristics of Transfusion Camp attendees.

	2016–17	2017–18	2018–19	2019–20	2020–21	2021–22	2022–23	Total
Centre								
Oxford	13	9	14	15	20	15	12	98
Birmingham						6	11	17
GSTT						6	4	10
Kings							5	5
Specialty								
Haematology	8	3	9	3	10	8	15	56
Anaesthesia/ICU	5	6	5	8	9	12	7	52
Internal medicine				1		6	8	15
Emergency medicine				1			1	2
Obstetrics						1		1
Oncology							1	1
Surgery				2				2
Other					1			1
Total	13	9	14	15	20	27	32	130

Self-reported confidence in eight specific transfusion-related scenarios and overall confidence was gauged with a survey administered before and after the course, each question being answered on an A-E Likert scale.

Participant feedback is in the early stages of collection, with data from only three sessions so far. Trainees are asked to rate each lecture and small-group session, and to answer general questions about their experience of Transfusion Camp.

Informal verbal feedback was collected from UK facilitators in all regions for this publication with regard to recruitment of attendees and their experience of delivering Transfusion Camp.

2.4 | Statistical methods

Statistical analyses were conducted to evaluate the effectiveness of the Transfusion Camp on improving students' knowledge (measured by test scores) and confidence levels (measured by self-reported ratings on an A-E Likert scale).

Descriptive statistics, including means, standard deviations and frequencies, were used to summarise the test scores and self-reported confidence levels. To compare the mean test scores and confidence levels by speciality, Student's *T*-tests were conducted. The significance level was set at 0.05.

Trainees who registered but did not attend any sessions were excluded from the final analysis.

3 | RESULTS

3.1 | Attendees

Between 2016 and 2023, 130 postgraduate trainees attended Transfusion Camp in the United Kingdom. 56/130 (43%) were from haematology, 52/130 (40%) from anaesthetics/ICU, 15/130 (11.5%) from internal medicine and 7/130 (5.3%) from other specialties, including oncology, obstetrics, emergency medicine and surgery. Table 2 shows the characteristics of attendees.

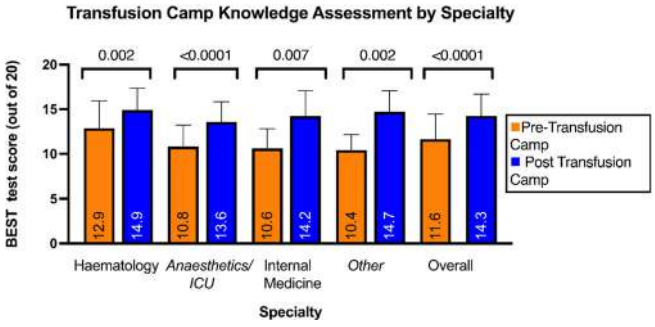

FIGURE 1 Pre- and post-test scores for trainees by specialty. Orange bars represent the pre-Transfusion Camp scores, and the blue bars show the post-Transfusion Camp scores. The number on the bar shows the mean. Specialties in 'other' include emergency medicine, obstetrics and surgery.

3.2 | Knowledge

In the pre-course questionnaire, 51% of attendees rated themselves as a 'beginner', and 46% 'intermediate' with respect to Transfusion Medicine (Figure 1).

The mean pre-test score was 11.6 (out of 20). Better pre-test scores were associated with haematology trainees, with a mean of 12.9, compared with a non-haematology average of 10.7 (SD 2.3, $p = <0.001$).

The mean post-test score was 14.3 out of 20, 2.4 points greater than the pre-test scores (SD 2.4, $p < 0.0001$). The pre- and post-test scores demonstrated significant improvements in knowledge after attending the Transfusion Camp across all specialties. There was no statistically significant difference between specialties in the post-test results.

3.3 | Attitudes and confidence

At the end of Transfusion Camp, 73/75 (97%) of trainees who completed the confidence survey rated their overall confidence in managing transfusion medicine-related patient issues as 'intermediate', 'advanced' or 'expert', compared with 40/95 (42%) before the course.

All trainees felt they could adequately consent a patient for transfusion at the end of the course, compared with 67% beforehand.

3.4 | Participant feedback

Feedback data is available for 3 'days' in total (i.e., lectures and associated small group sessions). All lectures were rated 'Good' or 'Excellent' by those who had watched the session. Of the 20 participants surveyed, 100% of them would recommend Transfusion Camp to colleagues. 13/15 participants felt that they had applied learning from Transfusion Camp in their clinical practice by the end of the course.

4 | CONCLUSION

This study demonstrates that Transfusion Camp was applied in the United Kingdom with comparable increases in attendee knowledge and confidence in managing transfusion-related problems to those found in Canada.[3,4] The material is broadly applicable to both health systems and training structures.

In the United Kingdom, transfusion medicine training is currently offered to haematology trainees by NHS Blood and Transplant (NHSBT) in the form of 'Essential' and 'Intermediate' Transfusion Medicine courses. These focus on the laboratory and theoretical aspects of transfusion medicine. Hospital-based training varies by region. Transfusion Camp complements existing training for early-stage haematology trainees, offering knowledge on practical aspects of transfusion medicine. For other specialties, there is no standardised teaching on transfusion medicine in the United Kingdom.

As demonstrated in Figure 1, trainees in all specialties improved their scores on the BEST questionnaire after attending Transfusion Camp. The improvement was comparable to that seen in the Canadian data.[3] This structured educational programme goes some way to address the knowledge gaps within transfusion medicine across all specialties. However, some deficits in knowledge of transfusion persist, and additional efforts are needed to address these, perhaps in changes to the course format or further educational initiatives. These need to be backed up by continuing education and training and monitoring of compliance with good transfusion practice with feedback to individual physicians and clinical teams.

The most robust outcome data would include long-term evidence of knowledge retention and changes in practice. This is challenging data to collect, but we may be able to tackle this going forward.

Feedback from facilitators has been that Transfusion Camp is 'user friendly' with excellent, informative resources provided, minimising the preparation time required for each session. The online format has some challenges (such as technical issues and equipment availability), but enables attendance for those working in multiple hospitals in a region.

Some attendees have given informal feedback that they have particularly enjoyed being in sessions with trainees from other specialties to understand their perspective. This does not often occur in daily clinical practice, and facilitates an understanding of how different specialties may evaluate the same clinical case, in addition to fostering relationships between trainees who may work together in the same region.

There have been challenges with recruitment to the course in the centres most recently offering Transfusion Camp, particularly from specialties outside of haematology. This may represent an increasingly short-staffed system with low staff morale,[8] in which people are less willing to commit significant periods of time to optional training outside of their working hours. There may also be a lack of awareness of the complexities of transfusion practice outside of haematology, and so trainees in these specialties may feel that further training is not required.

A factor that may limit the ongoing rollout of Transfusion Camp in the United Kingdom, as has been done in Canada, is the availability of transfusion specialists in each region to facilitate these sessions. The Oxford experience of Transfusion Camp has been presented at regional and national transfusion committee meetings but as can be seen from this report the rate of uptake of courses outside Oxford is very slow.

We advocate that Transfusion Camp should be implemented in all centres within the United Kingdom. There is clear benefit not only to haematology trainees but also those in other specialties such as ICU/anaesthetics and internal medicine.

AUTHOR CONTRIBUTIONS

AA wrote the manuscript. AA and KK analysed the data. SM, AD, KG and SR led transfusion camp in their hospitals. CK, SC and YL designed and implemented Transfusion Camp in Canada, and collated the data from all attendees. AA, MD and MFM designed the study. All authors critically reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

Available on request.

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TRANSFUSION MEDICINE WILEY

LETTER TO THE EDITOR

Efficacy and safety of BNT162b2 mRNA vaccine in a cohort of 90 transfusion dependent thalassemia patients

Dear Editor,

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

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

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

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

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

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

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

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

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

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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