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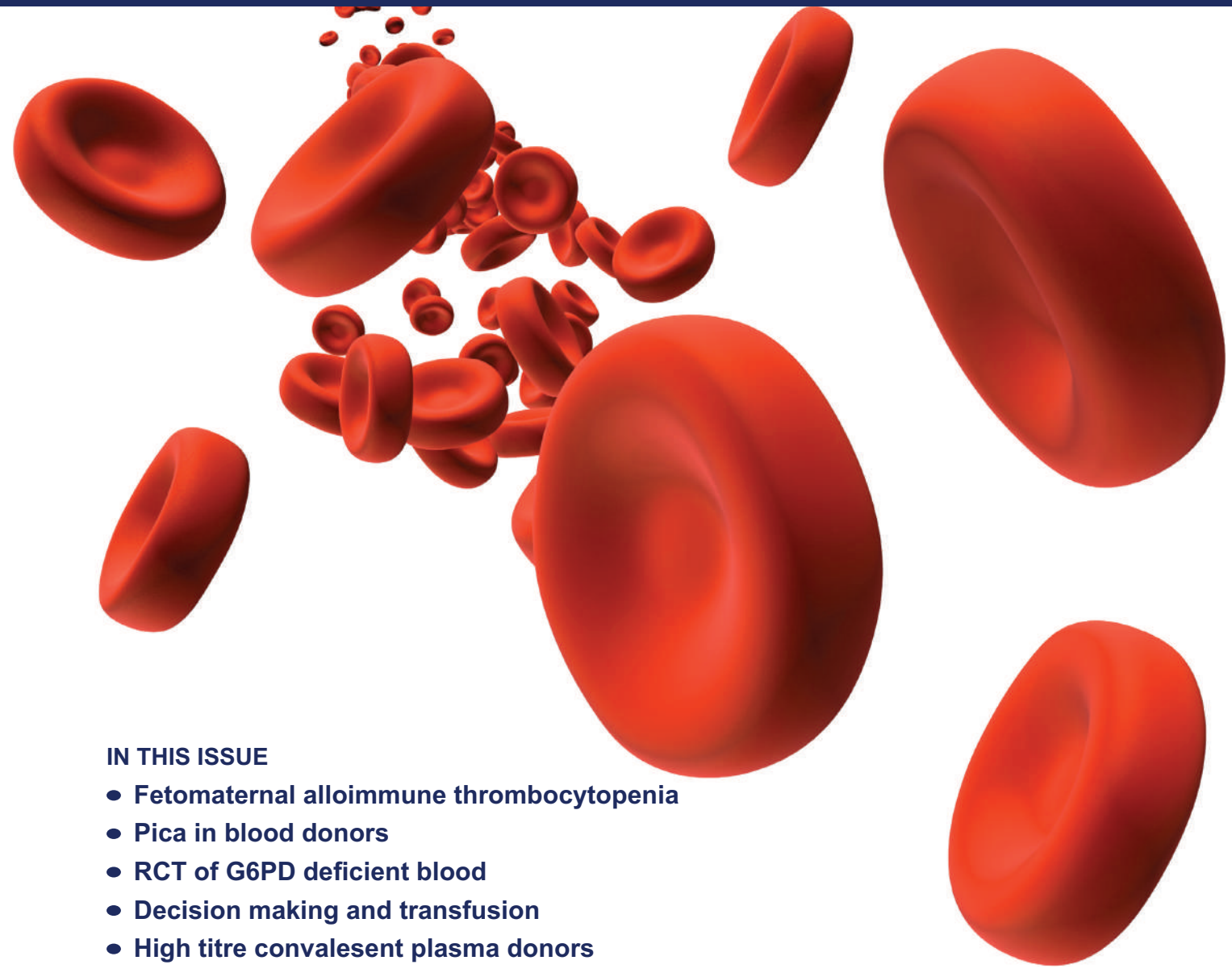

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REVIEW ARTICLE

Severe intracranial haemorrhage in neonatal alloimmune thrombocytopenia due to antibodies against human platelet antigen 1b: Case report and literature review

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Abstract

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) is a rare life-threatening disorder, leading to severe thrombocytopenia and potentially bleeding, with intracranial haemorrhage (ICH) being the most serious complication. We report on a FNAIT case with fourth-degree ICH that arose due to antibodies against human platelet antigen (HPA)-1b. The male infant, born to an otherwise healthy mother, presented with severe signs of ICH soon after delivery. Since only moderate thrombocytopenia was noted and there were no active signs of bleeding, the infant did not receive intravenous immunoglobulins (IVIg) or platelet transfusion. Spontaneous recovery of platelets was noted on the eighth day of life, but permanent neurological impairment remained as a consequence of ICH. We report the results of HPA and human leukocyte antigen (HLA) antibodies in the mother's and the infant's sera, the family's HPA genotype and the mother's HLA genotype, and summarise previously described cases of FNAIT due to anti-HPA-1b antibodies in the literature. FNAIT with severe ICH due to anti-HPA-1b antibodies is rarely diagnosed. An association between HLA genes and sensitization to HPA-1b antibodies was not demonstrated. The severity of FNAIT and the occurrence of ICH is often difficult to predict. In this case, the infant presented with moderate thrombocytopenia and ICH, with subsequent permanent consequences.

KEYWORDS
Blood donor, non-blood donors, transfusion

1 | INTRODUCTION

The demand for plasma products is constantly increasing all over the world and the need will rise in the future due to the significant increase of the need of patients with coagulopathy, immunological and metabolic diseases, as well as new treatments with plasma-derived medicines (http//apps.who.int/medicinedocs/en/d/Js21936 en/pdf, 2015).[1,2] About 9.3 million litres of recovered plasma are discarded in the world every year (http//apps.who.int/medicinedocs/en/d/Js21936 en/pdf, 2015).[2] In 2010, over 33 million litres of plasma were fractionated by 78 fractionators.[1] Countries without a domestic fractionation plant can perform contract plasma fractionation with fractionators abroad to decrease the plasma wastage and improve the access of patients to plasma-derived medicines (http//apps.who.int/medicinedocs/en/d/Js21936 en/pdf, 2015).[1,2]

The Iranian Blood Transfusion Organisation (IBTO) is a national non-profit, centralised organisation, which was established in 1974.

aim to generate high-quality evidence to inform and guide clinical practise during the ongoing pandemic.[3] However, even a year and half after it was initially described, COVID-19 is still largely managed empirically worldwide with few effective or proven therapies. Dexamethasone was the first drug to demonstrate significant reduction in mortality in COVID-19 patients requiring ventilatory support or supplemental oxygen.[4] Recently, remdesivir become the first drug to receive United States (US) Food and Drug Administration (FDA) approval for the treatment of hospitalised COVID-19 patients based on significant reduction in the duration of hospitalisation[5] for COVID-19 patients of varying disease severity. Amongst various other promising therapies, convalescent plasma[6,7] enriched in human antibodies against COVID-19 from recovered patients and humanised monoclonal antibodies[8] have received emergency use authorization (EUA) from US FDA till date.

The use of convalescent blood products (whole blood, plasma, serum, and isolates such as immunoglobulins and antibodies) collected from recovered patients to confer passive immunity in the recipients is not entirely new and has strong scientific rationale and historical precedence.[9,10] Convalescent plasma therapy is a passive antibody therapy that involves the transfusion of plasma rich in antibodies against a given pathogen to a susceptible individual for the purpose of preventing or treating an infectious disease. Efficacy of such therapy largely correlates with titres of anti-SARS-CoV-2 specific neutralising antibodies present in convalescent plasma.[7,10,11] In addition to the neutralising antibodies, other components in donor plasma such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, and pentraxins may also provide further benefit through their immunomodulatory effects and amelioration of systemic inflammatory response. [11] Convalescent plasma with neutralising antibodies has previously demonstrated clinical efficacy[9,10] against other virus-borne illnesses such as Ebola, human influenza A (H1N1), SARS, and Middle East respiratory syndrome (MERS). Over 50 RCTs are currently underway testing convalescent plasma against the present standard of care therapy in COVID-19 disease. However, many of these trials have limitation of numbers (small sample size) which would be inadequate to detect clinically meaningful and/or statistically significant differences, if any. Timely provision of COVID-19 convalescent plasma in resource-constrained settings poses significant logistic difficulties, challenges, and impediments in clinical trial accrual.[12,13] In addition, the unexpected presence of neutralising immunoglobulin G (IgG) antibodies against SARS-CoV-2 in recipients can even result in premature termination of the study, affecting statistical power and rigour. Given the context, a structured systematic review with appropriate statistical pooling of data in a direct comparison meta-analysis of all RCTs evaluating the safety and efficacy of convalescent plasma therapy in COVID-19 was necessary to create an evidence-base and facilitate rapid translation of research findings into clinical practise to inform and guide therapeutic decision-making globally.

2 | MATERIALS AND METHODS

This systematic review was carried out in accordance with Cochrane methodology for systematic reviews of interventional studies.[14] The analysis, interpretation, and reporting included a risk of bias assessment using the Cochrane Risk of Bias tool that assigns studies as having low, unclear, or high risk of bias. Quality of evidence and strength of recommendation was based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[15] that involves consideration of methodological quality, directness of evidence, heterogeneity, precision of effect estimates, and publication bias.

Literature search strategy: For the purpose of this systematic review, priority sources for retrieval of relevant studies included PubMed (https://pubmed.ncbi.nlm.nih.gov) and its curated version LitCOVID; National Library of Medicine database of clinical studies (https://clinicaltrials.gov); WHO International Clinical Trials Registry Platform (https://www.who.int/ictrp/en/); medRxiv (https://www.medrxiv.org); Cochrane living registry of COVID-19 studies (https://covid-19.cochrane.org) and Living mapping and living systematic review of Covid-19 studies (https://covid-nma.com). A systematic search of the medical literature (Table S1) without any language restrictions was conducted on 25 September 2020 and later updated from December 2020 through March 2021 in accordance with international guidelines. A reference list of selected articles was also screened for identifying additional potentially eligible studies.

Study eligibility: Only prospective clinical trials randomly assigning patients with COVID-19 infection to convalescent plasma plus standard of care therapy (test arm) versus placebo/standard of care therapy (control arm) were included. Given the lack of globally accepted standard of care therapy, this could vary across trials, but needed to be similar in both the arms within individual studies. Multi-arm trials were eligible if they directly compared convalescent plasma versus standard of care therapy, with appropriate arms being included in the meta-analysis. Trials allowing co-enrolment of patients across multiple studies were also eligible provided the co-interventions (concurrent medical treatment) were delivered similarly in each of the randomised arms. Emulated RCTs, quasi-randomised trials, propensity matched analyses, nonrandomised comparative studies, or observational studies were not considered in this review. Trials testing complementary and alternative medicines, traditional Chinese medicine, nutraceuticals, phytoceuticals, and herbal formulations were also ineligible.

Outcome measures: The selection of outcome measures for this systematic review was based on the outcome sets developed by WHO for research in COVID-19 hospitalised patients identified through COMET initiative (http://www.comet-initiative.org/Studies/Details/1538). The primary outcomes of interest included clinical benefit as measured on WHO[16] or similar ordinal scale and all-cause mortality. Clinical improvement was defined as becoming asymptomatic and/or discharged (achieving a score of 1 or 2 on the ordinal scale). Relevant endpoints included clinical improvement rate (CIR) on specified days (defined as proportion of patients with clinical improvement by Day7, Day14, Day28 of randomization), time-to-clinical improvement (TTCI), and death due to any cause by Day28 of randomization. Secondary outcomes included viral negativity rate on specified days (defined as proportion of patients with viral negativity on Day3, Day7, Day14 of randomization) and time to viral clearance based on COVID-19

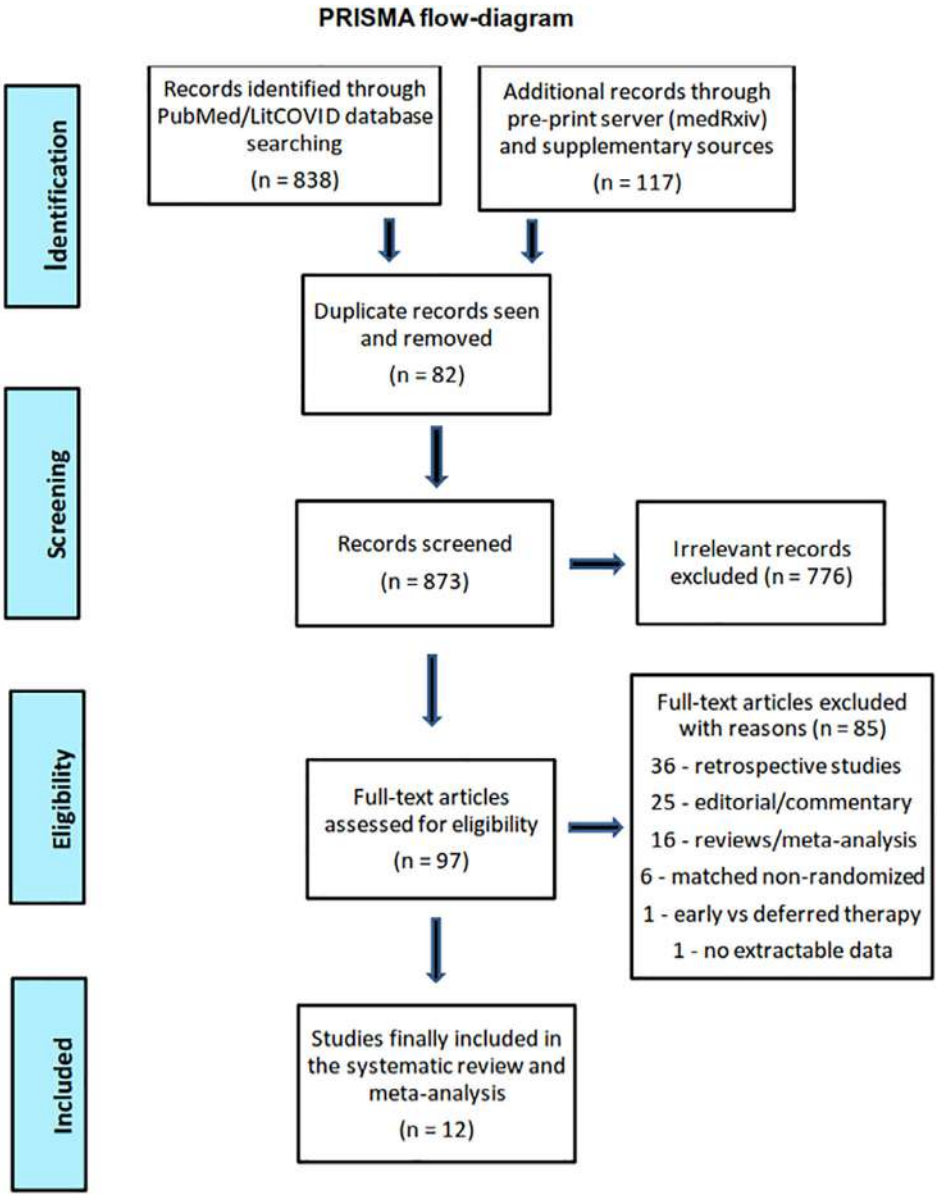

FIGURE 1 Flow-diagram of study selection and inclusion in the meta-analysis as per PRISMA guidelines [Color figure can be viewed at wileyonlinelibrary.com]

negativity as assessed by reverse transcriptase polymerase chain reaction (RT-PCR). In addition, safety outcomes included comparison of infusion-related serious adverse events between the two arms.

Data extraction and analyses: Two reviewers (BK and PT) independently read each preprint, publication, protocol, or any other available study report and extracted relevant data from individual primary studies. Discrepancy, if any, was resolved through consensus interpretation by a third reviewer (TG). In case of publication following a preprint report, data from the peer-reviewed article was used for statistical pooling. Extracted data included study characteristics (such as first author, publication year and journal), number of participants randomised, patient characteristics (severity of clinical presentation), intervention details (class and type of treatment), and outcome measures. For all dichotomous outcomes (CIR, viral negativity rate, adverse event rate, and mortality), the number of events of interest and the number of participants in each study arm were extracted per outcome. Data was pooled using the random-effects model and expressed as risk ratio (RR) with 95% confidence interval (CI). For continuous outcomes (TTCI and time to viral clearance), mean/median values with their dispersion as reported were extracted and expressed as difference in median time (in days) with 95% CI. Any p-value <0.05 was considered as statistically significant. Sensitivity analysis, subgroup analysis, and publication bias was also assessed as appropriate. All analyses were done using Review Manager (RevMan) version 5.3 & GRADE profiler (GRADEpro) version 3.6.1 (The Nordic Cochrane Centre, Cochrane Collaboration, 2008), Stata 14.0 (StataCorp LP, TX, USA) and R Studio. All data were reported in accordance with Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] No source of funding was involved in study conduct, data extraction and analysis, or reporting of results. The protocol is registered with the International Platform of Registered Systematic Reviews and Meta-analysis Protocols (INPLASY202090092).

TABLE 1 Baseline patient and disease characteristics in randomised controlled trials of convalescent plasma therapy in COVID-19

Author [reference] (study name)	Treatment arms	Patient numbers (N)	Disease severity	Median/mean age (years)	Comorbidity[a] (%)	Male patients (%)	Baseline swab positivity (%)
Agarwal A [18] (PLACID)	Convalescent plasma	235	Moderate disease	52	71.1%	75%	100%
	Standard of care	229		52	64.2%	77%	100%
AlQahtani M [19]	Convalescent plasma	20	Severe disease	52.6	35%	85%	100%
	Standard of care	20		50.7	45%	75%	100%
Avendano-Sola C [20] (ConPlas)	Convalescent plasma	38	Mild to moderate	61.3	52.6%	52.6%	68.4%
	Standard of care	43		60.3	27.9%	55.8%	79.1%
Bajpai M [21]	Convalescent plasma	14	Severe disease	48.1	Not known	78.6%	100%
	Fresh Frozen pasma	15		48.3	Not known	73.3%	100%
Gharbharan A [22] (ConCOVID)	Convalescent plasma	43	Moderate to severe	61	30%	67.4%	100%
	Standard of care	43		63	26%	76.7%	100%
Horby P [23] (RECOVERY)	Convalescent plasma	5795	Moderate to severe	63.6	55%	63%	96%
	Standard of care	5763		63.4	56%	66%	96%
Li L [24]	Convalescent plasma	52	Severe disease	70	29%	51.9%	100%
	Standard of care	51		69	27%	64.7%	100%
Libster R [25]	Convalescent plasma	80	Mild disease	76.4	86.2%	32.5%	100%
	Placebo	80		77.9	77.5%	42.5%	100%
O'Donnell M [26]	Convalescent plasma	150	Severe disease	60	37%	64%	100%
	Normal plasma	73		63	38%	70%	100%
Rasheed M [27]	Convalescent plasma	21	Severe to critical	55.7	47.6%	Not known	100%
	Standard of care	28		47.8	39.3%	Not known	100%
Ray Y [28]	Convalescent plasma	40	Severe disease	59	Not known	75%	100%
	Standard of care	40		61	Not known	67.5%	100%
Simonovich V [29] (PlasmAr)	Convalescent plasma	228	Severe disease	62.5	64.9%	71.6%	100%
	Placebo	105		62	64.8%	61%	100%

[a]Percentages represent either any morbidity or highest proportion of one morbidity as reported in each arm of individual studies.

TABLE 2 Summary efficacy and safety outcomes in RCTs comparing convalescent plasma versus placebo/standard of care therapy in COVID-19 included in the meta-analysis

Author [reference] (study name)	Treatment Arms	Patient numbers (N)	Day7 CIR (%)	Day14 CIR (%)	Day28 CIR (%)	TTCI (in days)	Day28 Mortality (%)	Day3 VNR (%)	Day7 VNR (%)	Infusion-related severe toxicity (%)
Agarwal A [18] (PLACID)	Convalescent plasma	235	75.2%	Not known	Not known	14	14.5%	42.9%	67.6%	1.3%
	Standard of care	229	65.7%	Not known	Not known	13	13.5%	36.6%	55%	0%
AlQahtani M [19]	Convalescent plasma	20	Not known	Not known	Not known	Not known	5%	Not known	Not known	0%
	Standard of care	20	Not known	Not known	Not known	Not known	10%	Not known	Not known	0%
Avendano-Sola C [20] (ConPlas)	Convalescent plasma	38	42.1%	76.3%	89.5%	8.5	0%	34.6%	50%	5.3%
	Standard of care	43	39.6%	86%	90.7%	9	9.3%	11.8%	26.5%	0%
Bajpai M [21]	Convalescent plasma	14	Not known	Not known	Not known	12.1	21.4%	Not known	Not known	0%
	Fresh frozen plasma	15	Not known	Not known	Not known	16.1	6.7%	Not known	Not known	0%
Gharbharan A [22] (ConCOVID)	Convalescent plasma	43	37.2%	55.8%	76.7%	12.5	13.9%	Not known	Not known	0%
	Standard of care	43	32.6%	51.2%	72.1%	13.5	25.6%	Not known	Not known	0%
Horby P [23] (RECOVERY)	Convalescent plasma	5795	Not known	Not known	66.4%	11	24%	Not known	Not known	3.3%
	Standard of care	5763	Not known	Not known	66.7%	11	24%	Not known	Not known	3%
Li L [24]	Convalescent Plasma	52	9.6%	32.7%	51.9%	28	15.7%	87.2%	Not known	1.9%
	Standard of care	51	9.8%	14.6%	43.1%	30	24%	37.5%	Not known	0%
Libster R [25]	Convalescent plasma	80	Not known	Not known	Not known	Not known	2.5%	Not known	Not known	0%
	Placebo	80	Not known	Not known	Not known	Not known	5%	Not known	Not known	0%
O'Donnell M [26]	Convalescent plasma	150	Not known	Not known	72%	5	12.6%	Not known	Not known	2.7%
	Normal plasma	73	Not known	Noy known	65.8%	7	24.6%	Not known	Not known	4.2%
Rasheed M [27]	Convalescent plasma	21	Not known	Not known	Not known	19.3	4.8%	Not known	Not known	0%
	Standard of care	28	Not known	Not known	Not known	23.4	28.6%	Not known	Not known	0%
Ray Y [28]	Convalescent plasma	40	9.5%	51.3%	75.7%	13	25%	Not known	Not known	Not known
	Standard of care	40	2.8%	41%	61.8%	17	35%	Not known	Not known	Not known
Simonovich V [29] (PlasmAr)	Convalescent plasma	228	21.2%	56.3%	74%	12	10.9%	Not known	Not known	5.7%
	Placebo	105	29.4%	55.1%	76.2%	12	11.4%	Not known	Not known	1.9%

Abbreviations: CIR, clinical improvement rate; COVID-19, coronavirus disease 2019; RCT, randomised controlled trials; TTCI, time to clinical improvement; VNR, viral negativity rate.

3 | RESULTS

The flow-diagram of study selection and inclusion in the meta-analysis as per the PRISMA guidelines is depicted in Figure 1. Detailed PRISMA cheque-list is also provided as online a Table S2. Systematic search of PubMed/LitCOVID identified 838 records with an additional 117 records being retrieved through supplementary search of other sources. After removing duplicates (n = 82) and excluding irrelevant/inappropriate records (n = 776) through rigorous screening all titles/abstracts, a total of 97 full-text articles (including preprints) were assessed for eligibility, of which 12 RCTs[18–29] were finally included and pooled in this systematic review and meta-analysis.

Description of included studies: Patient characteristics, treatment details, and relevant outcomes of all 12 RCTs randomly assigning COVID-19 patients to convalescent plasma plus standard of care therapy versus placebo/standard of care therapy are briefly summarised in Tables 1 and 2 respectively. These trials were conducted between February 2020 to January 2021 in various parts of the world ensuring good geo-ethnic representation. Patients included in these RCTs were largely representative of the typical COVID-19 patient population seen in routine clinical practise. Trials enrolled patients with wide range of severity ranging from mild/moderate illness to severe/critical and life-threatening disease with varying primary endpoints and outcome measures. Convalescent plasma was administered only once

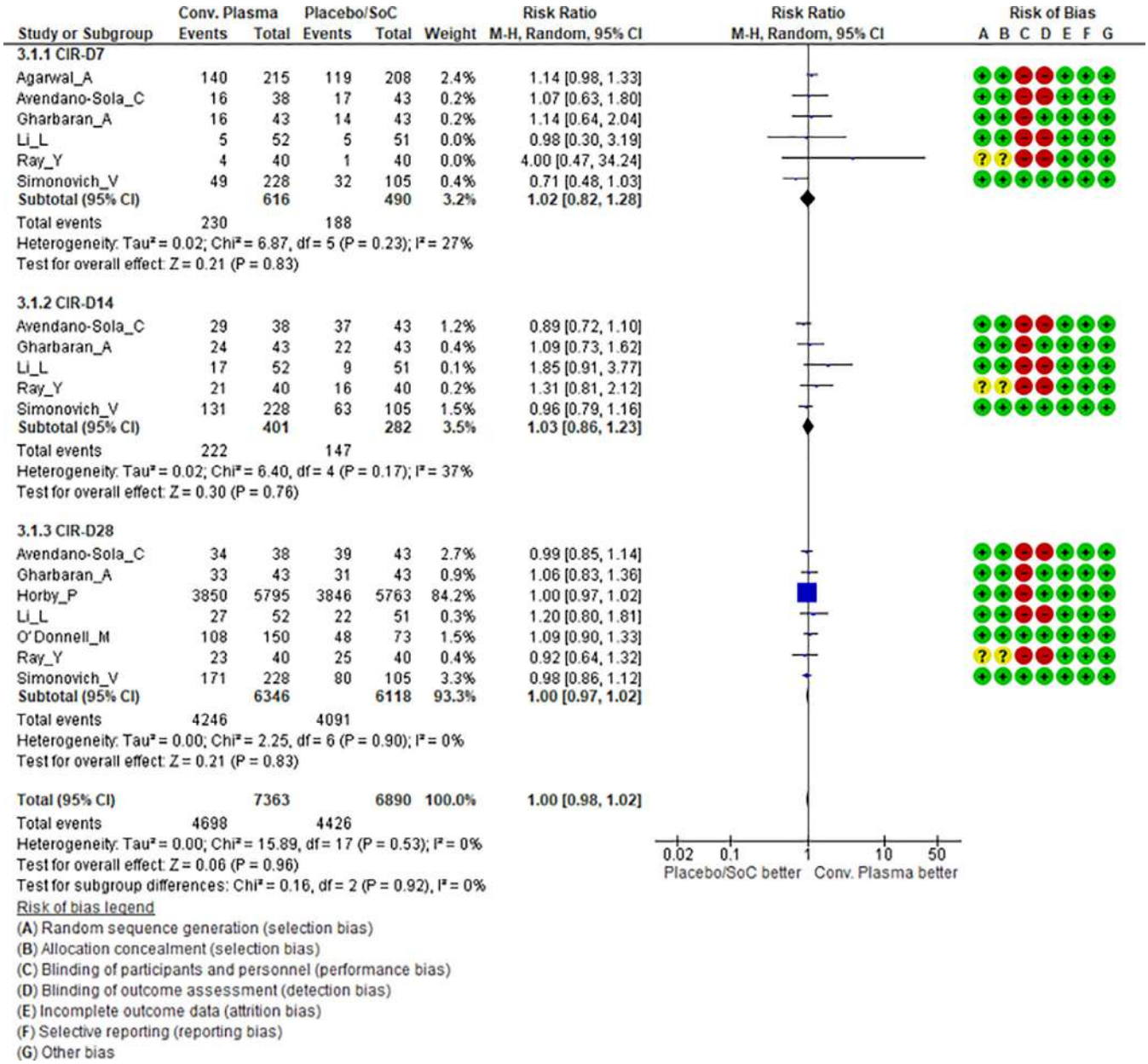

FIGURE 2 Forest plots including risk of bias in individual studies comparing convalescent plasma plus standard of care therapy versus placebo/standard of care therapy for clinical improvement rate (CIR) on specified days from randomization (Day7, Day14, Day28) and overall CIR in COVID-19 [Color figure can be viewed at wileyonlinelibrary.com]

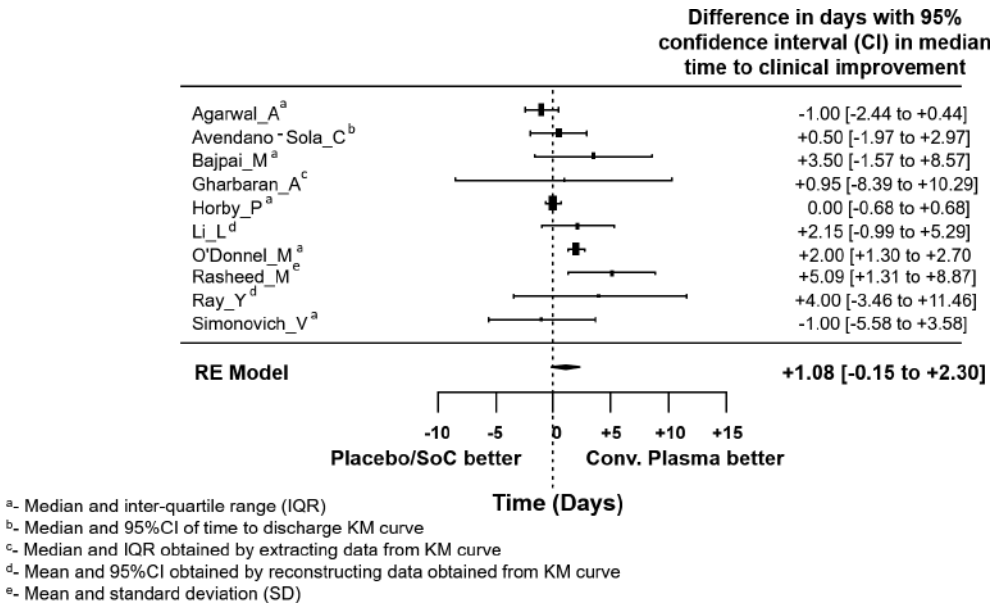

FIGURE 3 Median difference (in days) in time to clinical improvement (TTCI) between convalescent plasma plus standard of care therapy versus placebo/standard of care therapy in COVID-19

either using fixed dose of 250–500 ml[20,25–27,29] or 4–13 ml/kg body weight[24] or twice at a fixed dose of 200–275 ml given 12 to 24-h apart. [18,19,21,23,28] One trial[22] gave a single fixed dose of 300 ml convalescent plasma on day of inclusion but allowed a second such dose 5 days later in patients without clinical response and persistently positive RT-PCR. Only one trial[29] used convalescent plasma with very high neutralising antibody titres (minimum 1:800) while two other studies[23,26] used plasma with antibody titres >1:100 for transfusion. The standard of care though different in the included trials were in keeping with institutional protocols and national guidelines dictated by the best available evidence at the time and comprised of antimalarials (chloroquine, hydroxychloroquine), anti-virals (oseltamivir, lopinavir/ritonavir, remdesivir), broad-spectrum antibiotics (azithromycin), immunomodulators (steroids, tocilizumab, anakinra), traditional herbal medicines, and supportive care (oxygen inhalation and ventilatory support) as appropriate.

Evidence syntheses: There was no significant methodologic heterogeneity across the 12 included studies allowing statistical pooling of data from a total of 13 206 randomised patients in the meta-analysis. The addition of convalescent plasma to standard of care therapy was not associated with any significant or meaningful clinical benefit. There were no significant differences in rates of clinical improvement (Figure 2) between convalescent plasma plus standard of care therapy (test arm) versus placebo/standard of care therapy (control arm) either in terms of overall CIR (RR = 1.00, 95% CI: 0.98–1.02, $p = 0.96$) or CIR on Day7 (RR = 1.02, 95% CI: 0.82–1.28, $p = 0.83$); Day14 (RR = 1.03, 95% CI: 0.86–1.23, $p = 0.76$); and Day28 (RR = 1.00, 95% CI: 0.97–1.02, $p = 0.83$) respectively. Similarly, there was no significant difference in TTCI between the two arms (Figure 3) with a median difference of 1.08 days (95% CI: −0.15 to +2.30 days) favouring the convalescent plasma arm. The use of convalescent plasma was not associated with significantly reduced risk of death (Figure 4); RR of Day28 mortality was 0.81 (95% CI: 0.65–1.02, $p = 0.08$). Convalescent plasma however resulted in higher rates of viral clearance early after randomization, although based on a much smaller dataset comprising of just over 500 patients enrolled in three RCTs. Viral negativity rates both overall (RR = 1.55, 95% CI: 1.16–2.06, $p = 0.003$) and on Day3 (RR = 1.82, 95% CI: 1.02–3.23, $p = 0.04$) from randomization were higher in the convalescent plasma arm (Figure S3). Data regarding time to viral clearance was not reported consistently precluding statistically pooling of results. Reassuringly, the overall incidence of convalescent plasma transfusion-related serious adverse events was low with a weighted-mean pooled estimate of 3.25% (95% CI: 2.82–3.72%) confirming the safety of convalescent plasma transfusion. There was no significant difference (RR = 1.14, 95% CI: 0.93–1.22, $p = 0.22$) in treatment-related toxicity (Figure 5) between convalescent plasma plus standard of care therapy compared to placebo/standard of care therapy. Sensitivity analysis showed that no single trial was driving the results, inferences, and conclusions of the meta-analysis (Figure S4). Subgroup analysis stratified by disease severity (mild–moderate vs. severe-critical), timing of transfusion (early vs. later), sample size (small vs. large trials), and study design (open-label vs. placebo-controlled) suggested that the risk of dying was reduced with convalescent plasma transfusion in patients with more severe disease (RR = 0.62, 95% CI: 0.42–0.90, $p = 0.01$, 855 patients) and with early transfusion (RR = 0.51, 95% CI: 0.30–0.89, $p = 0.02$, 383 patients), based on much smaller patient numbers precluding definitive conclusions. A formal statistical analysis did not show any asymmetry in the funnel plot (Figure S5) indicating lack of significant publication bias.

Strength of recommendation: All RCTs[18-29] were of moderate to good quality with low risk of bias for most domains for the relevant outcomes of interest excepting high risk of performance and detection bias due to open-label nature of most included studies without placebo controls with lack of blinding of patients and/or physicians. Based on the above, there is low to moderate certainty evidence that the addition of convalescent plasma to standard of care therapy is not associated with significant clinical benefit or harm in patients with COVID-19 (Table 3).

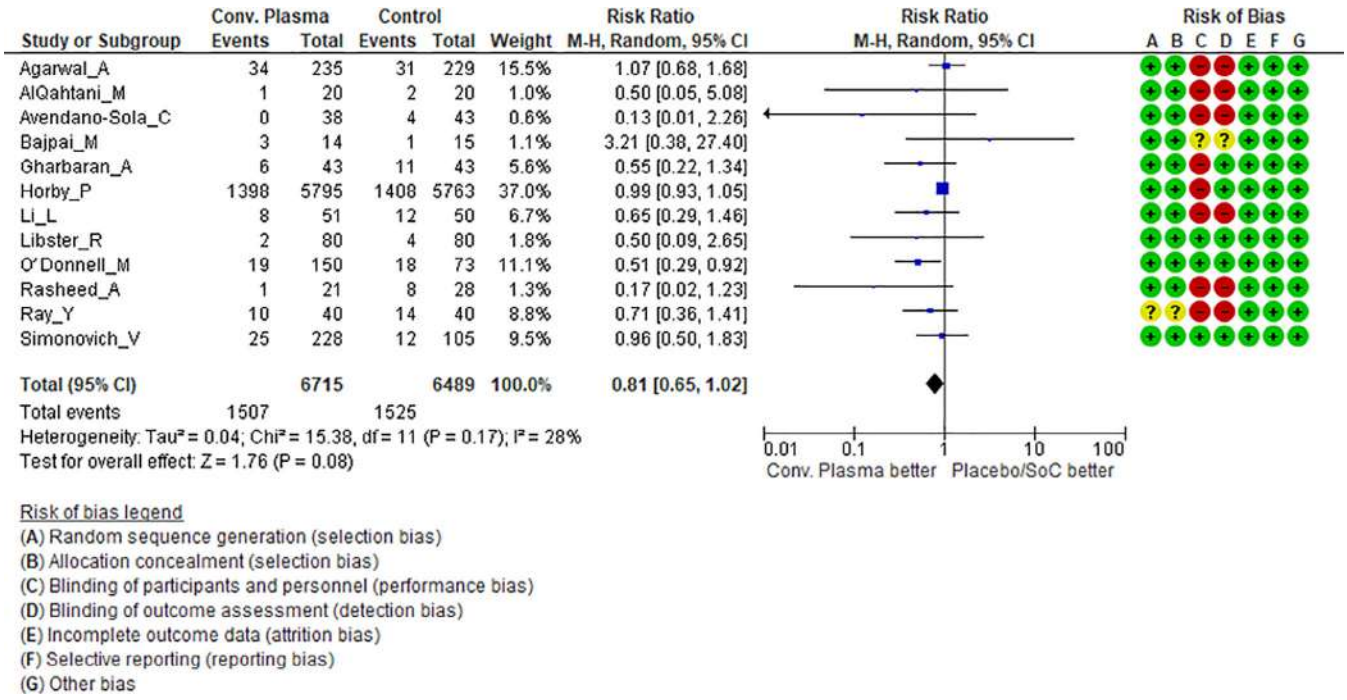

FIGURE 4 Forest plots including risk of bias in individual studies comparing convalescent plasma plus standard of care therapy versus placebo/standard of care therapy for all-cause mortality (by Day28 of randomization) in COVID-19 [Color figure can be viewed at wileyonlinelibrary.com]

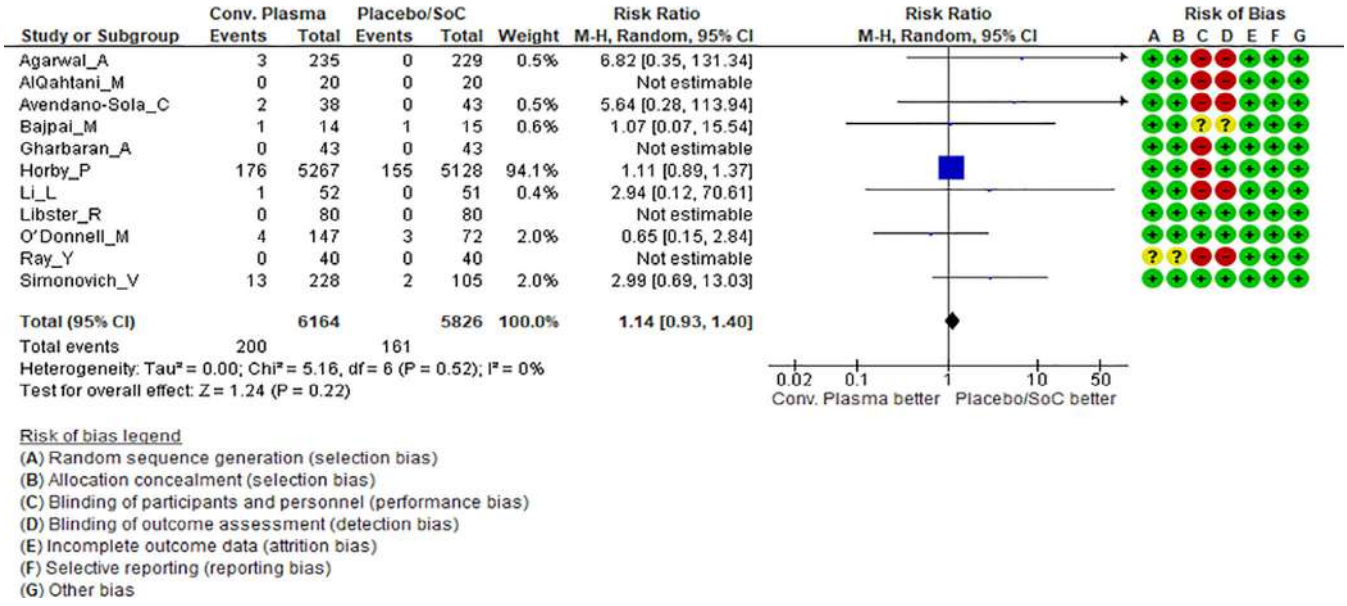

FIGURE 5 Forest plots including risk of bias in individual studies comparing convalescent plasma plus standard of care therapy versus placebo/standard of care therapy for infusion-related serious adverse events in patients with COVID-19 [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The lack of an effective prophylactic and/or therapeutic agent against COVID-19 infection combined with strong scientific rationale and historical precedence demonstrating clinical benefit with convalescent plasma therapy in previous viral outbreaks[9,10] has prompted its widespread use hoping that this might be the magic potion for COVID-19 pandemic.[30]

Quite understandably, the use of convalescent plasma in COVID-19 infection has gained significant traction not only within the medical

TABLE 3 Summary of findings including relative effect and anticipated absolute effects with quality of evidence for benefits or harms of convalescent plasma therapy in COVID-19

Convalescent Plasma for COVID-19					
Outcomes	No of participants (studies) follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with convalescent plasma (95% CI)
Clinical improvement rate (Clinical)	14 253(8 studies)	⨁⨁◯◯LOW[a,b]due to risk of bias, imprecision	RR 1.00 (0.98 to 1.02)	Study population	
				642 CIR per 1000	0 fewer per 1000(from 13 fewer to 13 more)
				Moderate	
				542 CIR per 1000	0 fewer per 1000(from 11 fewer to 11 more)
Day28 mortality (Clinical)	13 206(12 studies)	⨁⨁⨁◯MODERATE[b]due to imprecision	RR 0.81 (0.65 to 1.02)	Study population	
				235 per 1000	45 fewer per 1000(from 82 fewer to 5 more)
				Moderate	
				188 per 1000	36 fewer per 1000(from 66 fewer to 4 more)
Serious adverse events (Clinical)	11 990(11 studies)	⨁⨁◯◯LOW[a,b]due to risk of bias, imprecision	RR 1.14 (0.93 to 1.4)	Study population	
				28 per 1000	4 more per 1000(from 2 fewer to 11 more)
				Moderate	
				0 per 1000	-

Note: The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *GRADE Working Group grades of evidence*: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Abbreviations: CI, confidence interval; RR: risk ratio.

[a]Most studies were open-label with no placebo-control resulting in potential performance bias.

[b]The 95% CI straddles the line of unity and increases/decreases the RR by more than 25% in several studies.

and scientific community across the globe but also within the lay public.[31] Despite lack of definitive evidence of efficacy, convalescent plasma was granted EUA by US FDA in late August 2020. Prior to this authorization, large scale clinical usage in the US was regulated through FDA's expanded access program,[32,33] that collected data on clinical outcomes and side effects in over 100 000 patients from 2700 hospitals across US in a span of 5 months (April to August 2020) and judged that convalescent plasma 'may be effective' and hence should be eligible for wider use under EUA. Safety data was derived from 20 000 patients initially and then over 35 000 hospitalised patients in the US which reported a very low incidence (<1%) of adverse events related to transfusion (circulatory overload, acute lung injury, severe allergic reactions), in the first few hours which was no different from standard blood/plasma transfusions.[32,33] Reassuringly, it largely eliminated concerns exacerbation of illness due to antibody-dependent enhancement. Further mining of this data suggests that patients who receive convalescent plasma early (within 3 days of their diagnosis) fared better than those who receive it later.[34,35] However, this observation has recently been challenged by a small RCT[33] that failed to report any significant benefit in the composite primary outcome of mechanical ventilation, hospitalisation for >14 days, or death in patients treated with upfront convalescent plasma at diagnosis compared to deferred therapy at further clinical deterioration for COVID-19 infection with an odds ratio (OR) of 0.95 (95% CI: 0.32–2.94, $p > 0.99$). There is some suggestion of a dose–response relationship, as those who receive plasma units with high titres of neutralising antibodies having lower mortality rate than patients receiving units with lower titres.[34,35] A minimum neutralising antibody titre in convalescent plasma needs to be determined to achieve desired efficacy yet maintain safe and sufficient supply[36] despite the negative impact of COVID-19 pandemic and resultant disruption of blood bank services.[37] The US FDA currently recommends anti-SARS-CoV-2 specific neutralising antibody titre >1:160 in donor plasma which corresponds to high efficacy based on the plaque reduction neutralisation test (PRNT) assay. It is now increasingly being recognised that evolutionary strain on the viral genome through the use of monoclonal

antibodies targeting the spike protein or convalescent plasma with low levels of neutralising antibodies for COVID-19 infection can potentiate immune escape allowing newer and novel mutations[38,39] with potential for increased infectivity, disease severity and even mortality. Consequent to the EUA, it has now become increasingly difficult to recruit patients on clinical trials evaluating convalescent plasma therapy clearly reflecting a missed opportunity to firmly establish its efficacy in COVID-19.[35]

An updated living Cochrane review[40] of convalescent plasma in COVID-19 involving 38 160 participants enrolled in 19 studies (two RCTs, eight nonrandomised controlled studies, and nine uncontrolled studies) reported an overall high risk of bias (due to study design, types of participants, and other previous or concurrent treatment) and concluded that the beneficial effects (improvement of clinical symptoms and reduction in mortality) or harms (severe/serious adverse events) of convalescent plasma therapy in patients with COVID-19 infection were very uncertain at the present time. More recently, Janiaud et al.[41] reported no significant clinical benefit (decrease in all-cause mortality, increase in rates of clinical improvement, or reduced length of hospitalisation) with convalescent plasma in COVID 19 infection compared to placebo/standard of care therapy in a pooled analysis of 1060 patients from four RCTs published in peer-reviewed journals, 316 patients from five RCTs posted on preprint servers and 10 406 patients from one RCT reported via press briefing. The summary risk ratio (RR) for all-cause mortality with convalescent plasma in the four peer-reviewed RCTs was 0.93 (95% CI: 0.63–1.38) with low certainty of the evidence due to imprecision. After adding results of six more RCTs (from preprints/press release), the summary RR was 1.02 (95% CI: 0.92–1.12) with moderate certainty of evidence. The authors further reported that limited data on clinical improvement, clinical deterioration, and serious adverse events showed no significant differences between the two treatments.

The current meta-analysis provides the most robust and best contemporary evidence regarding the safety and efficacy of convalescent plasma in the treatment of COVID-19 infection. The addition of convalescent plasma to the current standard of care therapy is not associated with statistically significant clinical improvement or reduction in mortality. Overall, the risk of infusion-related serious adverse events is quite low and not significantly different compared to placebo/standard of care therapy. The clinical significance of early viral negativity following convalescent plasma transfusion is unknown and its benefit when given early in the course of the disease and in patients with more severe disease should be considered exploratory findings from this meta-analysis based on much smaller cohort size for such analyses.

Strengths and limitations: Despite being the largest dataset (comprising over 13 000 patients) derived only from RCTs and pooled using modern meta-analytic methods, certain caveats and limitations remain. The efficacy of convalescent plasma largely correlates with high titres of neutralising antibodies in the donor plasma and lack/low-level of such antibodies in recipients. Only three RCTs transfused convalescent plasma with high titres of neutralising antibodies (measured quantitatively using the PRNT assay), while others did not mandate a quantitative estimation of such antibodies prior to transfusion. This was further confounded by the presence of anti-SARS-CoV-2 specific IgG antibodies in a significant proportion of convalescent plasma recipient patients even prior to transfusion in four studies. Detection of such neutralising IgG antibody was an exclusion criterion in only a single RCT, with other trials allowing such patients to be randomised. It is also hypothesized that early transfusion (within few days of symptom onset and/or disease of mild to moderate severity) of convalescent plasma is more effective than delayed/deferred transfusion (>7 days of symptom onset and/or severe to critical illness). However, most trials included patients somewhat late in the course of their illness with median time from symptom onset to transfusion being beyond 7 days in most studies. Four of the included RCTs were exploratory pilot studies with relatively small sample size and four others were terminated prematurely without achieving the specified target accrual further reducing statistical power and rigour. Only three of 12 included RCTs used placebo-controlled design, with remaining nine studies being open-label without blinding of patients/physicians with potential for performance and detection bias leading to downgrading of the quality of evidence. Finally, evidence synthesis and subgroup analyses were primarily based on data reported in preprints/publications without access to individual patient data which would be a more robust method to identify subgroups that might benefit with convalescent plasma transfusion.

Implications for research: Key considerations in clinical trials evaluating convalescent plasma for COVID-19 should include timing of administration relative to onset of disease, timing of donation relative to resolution of symptoms in the donor, severity of disease, pretransfusion serology, and antibody titres.[42,43] A scoping review[44] of registered clinical trials of convalescent plasma therapy for COVID-19 infection was conducted early in the course of the pandemic to provide a framework for accelerated synthesis of trial evidence. The review identified 48 such registered trials (29 controlled studies) projected to enrol over 5000 patients, combined analysis of which would be sufficient to determine meaningful improvements in mortality, intensive-care admission, or mechanical ventilation faster than any individual RCT determining effectiveness of convalescent plasma therapy. A more recent search of clinical trial registries identified 64 studies in 22 countries using convalescent plasma therapy for COVID-19 infection during an international survey.[45] Twenty of the 64 centres responded to the survey, of which only nine were RCTs, the remaining being single arm prospective case series. Only four RCTs planned to include over 400 patients (adequately powered) and only three RCTs were blinded (low risk of bias). The survey reported significant variability in donor antibody testing with no consensus towards an optimal cut-off of anti-SARS-CoV-2 IgG neutralising antibody titres in the donor plasma for transfusion.[45] Current trials of convalescent plasma therapy include patients with wide spectrum of COVID-19 illness (from mild to critical), have variable need for molecular evidence of viral infection, use nonstandardised intervention (differing antibody titres, dose, and timing), have no universally accepted standard of care (as comparator), are mostly open label without placebo control (such as normal plasma) with key differences in primary outcomes between trials.[46] It is conceivable that the treatment effect of convalescent plasma may differ by illness severity, by

dose in terms of volume, concentration of neutralisation antibody, and the risk of antibody dependent enhancement along with other adverse events during COVID-19 illness. The National Institutes of Health (NIH) COVID-19 treatment guidelines panel[47] recently stated that it cannot recommend convalescent plasma as a standard of care for treating COVID-19 at this time as currently the data are insufficient to recommend for or against its usage. Their report further states that prospective, well controlled, and adequately powered RCTs are needed to determine whether convalescent plasma and other passive immunotherapies are safe and effective in COVID-19.

Since the press release declaring closure of RECOVERY trial to recruitment on the convalescent plasma arm, three other RCTs, the REMAP-CAP (NCT02735707), CONCOR-1 (NCT04348656), and NIH-led C3PO study (NCT04355767) have issued public statements announcing cessation of recruitment based on reaching prespecified endpoints of statistical futility on interim analysis of available data. Many more RCTs of convalescent plasma including an ongoing large placebo-controlled trial of 1000 patients (PassITON)[48] are currently underway; an updated living pooled analysis[49] of yet unreported trials might further enhance the certainty of evidence and improve the strength of recommendation in the future.

The next generation of convalescent plasma trials should also determine desirable product attributes, optimal dose and timing of administration, as well as appropriate patient population for its usage.[46,50] All reported RCTs evaluating convalescent plasma in COVID-19 till date have included only hospitalised adults with mild/moderate to severe/critical disease, excepting one study conducted in the outpatient setting for elderly patients with milder disease to prevent symptomatic worsening. If the main mechanism of action of convalescent plasma is through virus neutralisation, it would possibly be most efficacious when used very early in the course of the disease and/or even for prophylaxis in high-risk individuals.[50] In addition, there may be specific groups who are more likely to benefit such as those with impaired immune responses secondary to an immunocompromised state (inherited or acquired immunodeficiency, cancer patients, transplant recipients on suppressive medication) leading to delayed viral clearance.[50] Continuous monitoring of pooled international trials of convalescent plasma for COVID-19 hospitalised patients (COMPILE) project is presently pooling individual patient data from RCTs of convalescent plasma in real-time[49] under a shared regulatory and statistical framework (http://nyulmc.org/compile). A similar initiative from the European Union COVID-19 convalescent plasma platform (https://www.euccp.dataplatform.tech.ec.europa.eu/) could be considered to further strengthen the evidence-base.

5 | CONCLUSIONS

There is low to moderate certainty evidence that the addition of convalescent plasma to current standard of care therapy is generally safe with low risk of transfusion-associated serious adverse events but does not result in significant clinical benefit or reduction of mortality in patients with COVID-19 infection. An updated meta-analysis including other ongoing large RCTs of convalescent plasma therapy may help improve this evidence-base in the future.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Tejpal Gupta: Conceptualization, methodology, analysis, and writing–original draft. **Sadhana Kannan**: Methodology, literature search strategy, and analysis. **Babusha Kalra**: Data curation and writing–review & editing. **Prafulla Thakkar**: Data curation and writing–review & editing.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

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Trust and distrust: Identifying recruitment targets for ethnic minority blood donors

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Abstract

Background: We explore the role of trust, distrust, and the prevailing socio-political context to better understand why people from ethnic minority communities are less likely to be blood donors compared to people from White communities. Recruiting more ethnic minority donors will enhance representativeness, reduce inequality, and help meet the clinical need to increase the proportion of blood with Ro Kell antigen to treat Sickle Cell Disease (SCD).

Study design and methods: A 2 (donor-status: current donor; non-donors) by 4 (ethnicity: People from Asian, Black, Mixed and White ethnic backgrounds) quasi-experiment ($N = 981$) was conducted to examine perceptions of trust/distrust and their influence on willingness to donate blood, within the socio-political context of the Windrush scandal and Brexit.

Results: We identified five domains of trust ('National Health Service [NHS] and staff,' 'NHS Blood and Transplant,' 'outgroups,' 'individuals' and 'politics'), and a single domain of conditional distrust domain. Trust across all the domains was lower, and 'conditional distrust' higher for ethnic minorities. Trust in 'individuals' and 'NHSBT' predicted willingness to donate in non-donors from ethnic minorities and White non-donors, respectively. Concerns about the Windrush scandal were related to lower political trust. Viewing Brexit as 'positive for the UK' was related to lower trust across domains and reduced willingness to donate in White non-donors through its influence on reduced trust in NHSBT.

Conclusion: Distinct domains of trust and distrust are identified, and targeting 'trust in others' through conditional cooperation is recommended as a strategy to increase donor numbers from ethnic minority communities.

KEYWORDS
blood donation, ethnicity, recruitment, trust

1 | INTRODUCTION

People from ethnic minorities are less likely to donate blood.[1–4] In England, for example, of those registered to donate blood in 2019–2020, blood donors from Black ethnic backgrounds made up 1.2% of all blood donations, and donors from Asian or Mixed ethnic backgrounds 2.1%. Greater diversity within blood donors can result in psychological (e.g., increased well-being)[5–6] and clinical (e.g., improved

treatment of sickle cell disease [SCD]) benefits.[1–3,7] For example, better outcomes for SCD are observed with donor-recipient matching on Ro Kell antigens, which are more common in Black (52%) than White (2%)[1–3] people. However, while demand for Ro antigen blood increases by 10%–15% each year, only 2% of blood donors in England have Ro antigens.[7] Thus, a better understanding of why people from minority communities are less likely to donate blood will inform recruitment strategies that will help realise these potential benefits.[4,8–9] To address this issue, this article focuses on the one key dimension known to influence interactions with healthcare in minority communities: *trust*.[4–6]

2 | TRUST, ETHNICITY, HEALTHCARE AND BLOOD DONATION

While many barriers and motivators for donating blood are similar between minority and non-minority donors and non-donors,[10–14] lower levels of trust in healthcare and donation services could partly explain the lower donation rates in ethnic minority communities.[4,8–21] A lack of trust in medicine is also a demotivating factor for engaging with healthcare generally,[18–19] specifically for people from ethnic minority communities.[4,15–16,20–21] Thus, a broader understanding of the role of trust in the context of blood donation should help to uncover new insights and inform recruitment strategies.[18,22]

3 | DOMAINS OF TRUST

Trust operates across many different domains in life.[23] For example, people express varying degrees of trust in strangers (*individuals*),[24–26] diverse communities, nationalities, and faiths (*outgroups*),[27–28] physicians,[18,29] and organisations of various types, including healthcare providers and the apparatus-of-states (e.g., police, judiciary, Government).[28] These domains are all potentially important when individuals are considering donating blood. For example, blood donation is a public good, where a few donate blood to benefit all.[30] A significant predictor of public good giving is trust in the generosity of *individuals* and members of *other groups*.[31] Furthermore, historical betrayals of ethnic minority groups (e.g., Tuskegee, Windrush) reduce trust in the state (e.g., Government, law-enforcement),[14,32–33] which may undermine donation decisions, especially if the state and healthcare systems are perceived as linked.[14] However, at present, the existing research on trust and blood donation has focused on a narrow set of domains, specifically trust in *healthcare* or *physicians*.[4,8–10,15–17] To fully appreciate how trust impacts decisions about blood donation, we need to understand how trust (including trust outside the domain of healthcare) varies by ethnicity and donor status.

4 | TRUST AND DISTRUST

It is essential to recognise that trust and distrust are separate constructs. While both function to reduce social complexity,[23,34–35] trust creates positive expectations with desirable acts perceived with certainty.[25–26,36–38] In contrast, distrust is not just a lack of trust but is linked to feelings that others are active harmful agents who cannot be relied on, leading to distrust, suspicion and alienation.[23,35]

5 | DONOR DECISION MAKING: WILLINGNESS TO INTENTIONS

Blood donors progress through a career from a non-donor to a new/novice donor (one to four donations) to an experienced donor (five or more donations).[36] Therefore, questions concerning decisions to donate blood need to be commensurate with the stage of the donor career being studied.[37] For people who are inexperienced in a particular domain (e.g., blood donation), decisions are based on behavioural willingness (i.e., an individual's openness to behavioural opportunities and willingness to consider a behaviour); however, as the person becomes more experienced, decisions based on intentions become more important.[38] As a primary focus of this article is to explore the predictive power of trust in non-donors, behavioural willingness is assessed as the most appropriate decision-making index.

6 | SOCIO-POLITICAL CONTEXT

Perceptions of trust and distrust are influenced by the contemporary cultural and political landscapes.[3] However, previous work on trust and blood donation has not considered the influence of the broader socio-political context. To account for the political context at the time of the study, we examined how perceptions of Brexit and the Windrush scandal influence trust in donors and non-donors.

Brexit concerns the UK's exit from the European Union (EU) following a national referendum on the 23rd of June 2016. This issue has dominated the political landscape in the UK since, leading to divided public opinion.[39] The Windrush Scandal emerged in 2017, when hundreds of Black Commonwealth citizens, who came to the UK between 1948 and 1973 on their parent's passport, were erroneously classed as 'illegal' immigrants because the relevant documentation was lost. They were denied legal rights, detained, and deported.[34]

We test the conjecture that reduced trust in the political establishment is linked to perceiving leaving the EU as 'a positive step for the UK.'[40–41] We explore if this generalises to concerns about the Windrush scandal and the broader domains of trust. Finally, we explore if the reduced level of trust reported by ethnic minorities is, in part, accounted for by their beliefs about Brexit and the Windrush Scandal.

7 | AIMS OF THIS PAPER

This article explores how domains of trust (from individual to political) vary by ethnicity and donor status and whether they predict willingness to donate in non-donors. Furthermore, we explore how trust and willingness to donate are associated with perceptions of Brexit and the Windrush Scandal.

TABLE 1 Sample characteristics

		All			
		n or mean	Non-donors	Donors	Non-donors versus donors
NHSBT donors	All ethnic minorities (excluding White minorities	376		376	
	White people	343		343	
Code 3 (market research)	All ethnic minorities (excluding White minorities	132	103	21	
	White people	122	111	19	
Community group	People from an Asian background	8	6	2	
Donor status	Current donors	761			
	Non-donors	220			
Ethnicity					
	Asian	182	38 (17.3%)	144 (19.4%)	$\chi^2_{(3)} = 24.43$, $p = 0.000$. There were fewer donors from Black communities than expected. There were fewer non-donors from Asian communities than expected
	Black	141	53 (24.1%)	88 (11.9%)	
	Mixed	182	27 (12.3%)	155 (20.9%)	
	White	456	102 (46.4%)	354 (48.8%)	
	Missing data	20			
Sex	Male	339	42 (19.3%)	297(39.4%)	$\chi^2_{(1)} = 30.15$, $p = 0.000$. There were more male donors than expected and fewer female non-donors than expected
	Female	633	176 (89.7%)	457 (60.6%)	
	Missing data	9	2	7	
Age		$M = 44.65$ (SD = 14.57) range 18–89	$M = 46.05$ (SD = 14.15)	$M = 44.23$ (SD = 14.67)	t (963) = 1.63, $p = 0.193$

Note: Current donors = donated within the last 2 years. Asian = People from Asian ethnic backgrounds, Black = People from Black and Caribbean backgrounds, Mixed = People from mixed ethnic backgrounds, White = People from White backgrounds (excluding White minorities).

8 | METHODS

8.1 | Design and sample frame

A 2 (*Donor status*: current vs. non-donor) by 4 (*Ethnicity*: People from Asian, Black, Mixed and White ethnic backgrounds), quasi-experiment was conducted. The donor sample was recruited from the UK National Health Service Blood and Transplant (NHSBT) database; a sample of 3500 people from ethnic minorities, and 2500 White people, who had donated in the last 2 years, were *randomly* selected. Non-donors were primarily recruited through a market research company (Code 3: www.code3research.co.uk). A random sample of 4, 300 people from ethnic minorities and 4300 White people were selected (Supplementary File S1 for details, justification of sample sizes, and power calculations). Initial survey invitations were sent on the 14th of June 2019, with a reminder 4 weeks later (12 July 2019). An additional reminder was sent to the ethnic minority sample on the 2nd of August 2019. The study was designed to explore a wider set of variables (Supplementary File S2), but this paper focuses on trust. There was no payment for participating in the surveys. However, five participants from the Code 3 sample were selected at random to receive a £25 gift voucher.

8.1.1 | Current donor status

Current donors were defined as those who had given blood within the last 2 years. All donors recruited via the NHSBT database were selected to have donated in the last 2 years. However, all participants were asked if they had donated: (1) Less than a month ago, (2) 2–12 months ago, (3) 12 months to 2 years ago, (4) Longer than 2 years ago, (5) Cannot remember. Current donors from Code 3 were identified as those who reported one of: (1) Less than a month ago, (2) 2–12 months ago, (3) 12 months to 2 years ago. These participants were added to the current donors derived from the NHSBT sample.

8.1.2 | Coding ethnicity

Participants were sampled based on the ethnicity data recorded by NHSBT and Code-3 (Supplementary File S1). Participants were also asked to self-describe their ethnicity. These self-descriptions were coded using the UK Office of National Statistics (ONS) criteria (Supplementary File Text S3, Supplementary Table S1). While there was a wide range of descriptions (Supplementary File S3), we coded

TABLE 2 Exploratory factor analysis of trust in donors and non-donors

	Trust NHS and staff	Trust NHSBT	Trust individuals	Conditional distrust	Trust politics	Trust outgroup
I completely trust the National Health Services' (NHS) judgements about my medical care	**0.509***	0.256*	0.031	−0.144*	0.101*	−0.120*
Patients receive high-quality medical care from the National Health Service (NHS)	**0.543***	0.185*	0.102*	−0.139*	0.035	−0.118*
I trust my GPs judgements about my medical care	**0.931***	−0.058	−0.044*	0.073*	−0.011	0.085*
My GP would always tell me the truth about my health even if there was bad news	**0.795***	−0.007	−0.035	0.019	−0.082*	0.143*
I feel respected by the National Health Service (NHS)	**0.633***	0.154*	0.019	−0.055	0.008	−0.014
I trust the blood and transplant service to provide blood for all patients who need it.	0.023	**0.876***	0.010	−0.002	−0.015	−0.054*
I trust the blood and transplant service to take care of blood donors	0.020	**0.967***	−0.006	0.043*	−0.025	0.035*
I trust the blood and transplant service to screen blood to ensure it is safe.	−0.021	**0.945***	−0.030	0.009	0.017	0.006
I trust the blood and transplant service to treat people from my ethnic group fairly	0.027	**0.840***	−0.037	−0.115*	0.006	0.011
The National Health Service (NHS) experiments on patients without them knowing	−0.053	−0.177*	−0.049	**0.467***	0.119*	−0.007
Rich patients receive better care in hospitals than poor patients	0.014	−0.149*	−0.088*	**0.562***	−0.025	0.133*
People of my ethnic group cannot trust doctors and healthcare workers	−0.033	−0.173*	−0.089*	**0.656***	0.063*	0.073
To what extent do you trust people from the police	0.009	−0.021	−0.042*	**−0.677***	0.430*	0.140*
To what extent do you trust people from the courts	0.003	−0.040	−0.053*	**−0.665***	0.534*	0.128*
To what extent do you trust people you meet for the first time	−0.036	−0.014	**0.852***	−0.045	−0.010	0.082*
To what extent do you trust a stranger	0.028	−0.046	**0.845***	0.061	0.012	−0.021
In general, one can trust people	0.077	0.141*	**0.448***	−0.011	0.111*	0.079*
When dealing with strangers, it is better to be careful before you trust them:	0.024	0.074	**−0.626***	−0.001	0.039	0.072
To what extent do you trust people of another religion	−0.005	0.024	0.468*	−0.092	0.003	**0.885***
To what extent do you trust people of another nationality	0.013	0.027	0.464*	−0.028	0.014	**0.836***
To what extent do you trust people from the government	−0.025	0.045	0.046*	−0.034	**0.893***	−0.032
To what extent do you trust people from political parties	0.033	0.013	0.174*	0.074*	**0.812***	−0.047*
Latent correlations						
Trust in NHS & staff	1					
Trust NHSBT	0.626*	1				
Trust individuals	0.195	0.162*	1			
Conditional distrust	−0.484*	−0.491*	−0.231*	1		
Trust politics	0.215*	0.094*	0.193*	−0.168*	1	
Trust outgroup	0.107*	0.202*	−0.036	−0.163*	0.078	1

*$p < .05$.

these into the higher-order ONS groups in terms of people from: (1) an *Asian* background (Indian, Pakistani, Bangladeshi, Chinese, any-other-Asian), (2) a *Black and Caribbean* background (African, Caribbean, any other Black/African/Caribbean), (3) a *Mixed Ethnic* background (White-and-Black-Caribbean, White-and-Black-African, White-and-Asian, Black-and-White, Arab, any-other-mixed) and (4) a *White* background (English/Welsh/Scottish/Northern Irish/British/Irish/other White). The White sample did not include any White minorities defined as Gypsy, Roma or Irish traveller groups (see Supplementary Files S3).

8.2 | Measures

8.2.1 | Assessment of trust and distrust

Questions were derived from existing measures of trust to represent seven domains of trust in: (1) the UK National Health Service (NHS), (2) physicians, (3) National Health Service Blood and Transplant (NHSBT), (4) the equality of healthcare provision, (5) the apparatus of the state (police, courts, government), (6) outgroups and (7) individuals[24–27,29,42–48] (Supplementary File S4 details the items and supporting references). Each item was answered on a 5-point scale, where higher scores equate to greater trust, except for trust in individuals,[25] which was responded to on a 4-point scale.

8.2.2 | Willingness to donate

Participants were asked, 'Would you consider donating blood in the future?' yes (1) or no (0).

8.2.3 | Socio-politicalcontext

In terms of perceptions of Brexit, participants were asked: "Do you think Brexit is a positive or negative step for the future of the UK?" (positive [1] or negative [0]; 23.7% thought that Brexit was a positive step).

In terms of perceptions of the Windrush Scandal, participants were asked to what extent: "The Windrush Scandal shows that the authorities still have a negative view about ethnic minorities in the United Kingdom"? This was responded to with 'not sure what this is,' 1 = 'strongly disagree' to 5 = 'strongly agree.' Seventy-four people (55% White people, 25% people from an Asian background, 17% people from a mixed ethnic background and 3% people from a Black and Caribbean background) stated that they were not sure what the Windrush Scandal was.

8.3 | Statistical analyses

8.3.1 | Latent variable and path modelling

M*Plus* 8.4[49] was used to specify factor analytic models to explore the dimension of trust and run path models. In all analyses, a diagonally weighted least squares with means and variance adjustment (WLSMV) extraction algorithm was used to account for the ordinal nature of these data. Fit statistics were used to assess the best fitting model, with the best model having a TLI and CFI >0.95 and RMSR of <0.05.[50]

8.3.2 | Exploratory factor analysis

While the items used to cover the domains of trust are derived mainly from existing measures, they have never been combined or applied in these samples or contexts. Under such circumstances, an exploratory approach has been recommended.[51] As such, exploratory factor analysis was conducted on the trust items with Geomin rotation (Table 2), with an item classed as loading on a factor if it loaded 0.40 or greater.

8.3.3 | Exploratory path models

Path models were specified to examine if perceptions of Brexit and the Windrush Scandal indirectly linked ethnicity, age and sex to perceptions of trust, with perceptions of trust acting as proximal predictors of willingness to donate blood.

9 | RESULTS

9.1 | Sample characteristics

The final sample consisted of 981 participants (Table 1, Supplementary File S3).

9.2 | The structure and dimensionality of trust

Results from the exploratory factor analysis are shown in Table 2. The amount of missing data was small (0.1%–0%) and missing completely random (Little's MCAR test: = ($\chi^2_{[480]} = 519.53$ $p = 0.103$). As such, missing data were treated using Full Information Maximum Likelihood (FIML). A six-factor model best fit these data (TLI = 0.934, CFI = 0.967, RMSR = 0.038: Table 2), which was a better fit than a five-factor model ($\chi^2_{[114]} = 1367.05$; $p = 0.000$), which was in turn a better fit than a 4-factor model ($\chi^2_{[131]} = 1961.38$; $p = 0.000$). However, this six-factor model did not conform to the primary scales, with combined and new factors observed, justifying the exploratory approach.

The resultant factors were summed to create scales. As these scales are based on different numbers of items and some on a 5-point and some on a 4-point response format, scores were standardised to vary between 0 (no trust at all or complete lack of distrust) and 1 (complete trust or distrust) (Supplementary File 5).

The first factor focuses on trust in 'NHS and Staff,' measuring honesty and whether the NHS provides high-quality care. The second factor, 'Trust in NHSBT,' reflects trust in the blood service to provide for patients, take care of blood donors and recipients, and ensure

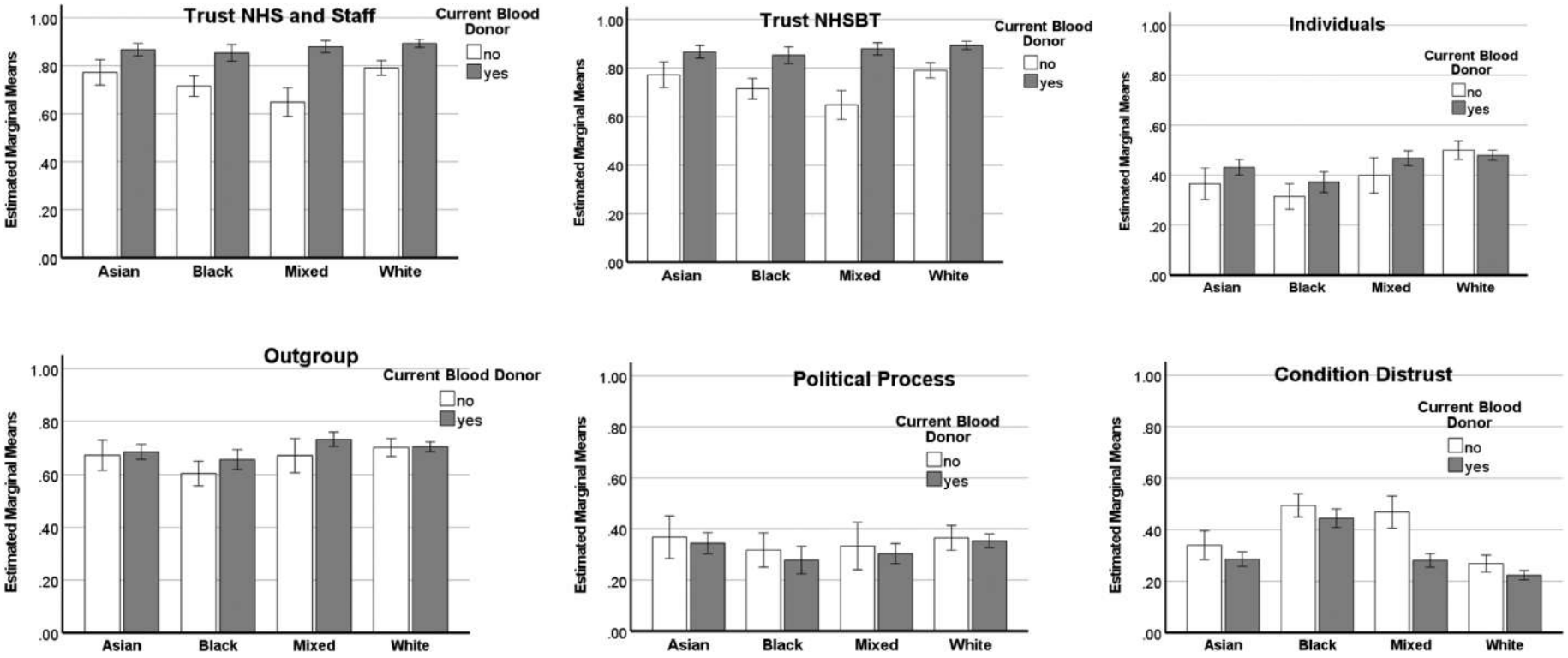

FIGURE 1 Dimensions of trust by donor status and ethnicity (error bars = 95% CIs)

TABLE 3 Predictors of trust and distrust

	Trust								
	NHS & staff			NHSBT			Individuals		
	B	*p*=	95% CI	B	*p*=	95% CI	B	*p*=	95% CI
Age	−0.0008 (0.0005)	0.085	−0.0017, 0.0001	**−0.0009 (0.0004)**	**0.027**	**−0.002, −0.0001**	**0.003 (0.0005)**	**0.000**	**0.002, 0.004**
Sex	**0.043 (0.012)**	**0.000**	**0.019, 0.067**	0.009 (0.010)	0.442	−0.012, 0.030	**0.048 (0.014)**	**0.000**	**0.021, 0.075**
Current donor	**0.043 (0.021)**	**0.039**	**0.002, 0.084**	**0.011 (0.019)**	**0.000**	**0.061, 0.138**	−0.024 (0.022)	0.257	−0.067, 0.018
Ethnicity									
Asian	−0.071 (0.041)	0.088	−0.152, 0.010	−0.069 (0.035)	0.052	−0.139, 0.0005	**−0.100 (0.042)**	**0.017**	**−0.183, −0.018**
Black	**−0.078 (0.037)**	**0.034**	**−0.150, −0.006**	**−0.098 (0.039)**	**0.011**	**−0.174, −0.022**	**−0.156 (0.035)**	**0.000**	**−0.225, −0.088**
Mixed	**−0.108 (0.038)**	**0.004**	**−0.182, −0.034**	**−0.146 (0.043)**	**0.001**	**−0.231, −0.061**	−0.068 (0.040)	0.093	−0.149, 0.011
Interaction									
Donor*Asian	0.013 (0.043)	0.773	−0.073, 0.099	0.022 (0.038)	0.551	−0.052, 0.098	0.074 (0.075)	0.099	−0.014, 0.163
Donor*Black	0.001 (0.042)	0.979	−0.081, 0.083	0.051 (0.042)	0.222	−0.031, 0.135	**0.089 (0.089)**	**0.023**	**0.012, 0.167**
Donor*Mixed	**0.089 (0.040)**	**0.042**	**0.003, 0.160**	**0.109 (0.046)**	**0.017**	**0.019, 0.199**	**0.105 (0.044)**	**0.017**	**0.019, 0.191**
Brexit	**−0.034 (0.015)**	**0.008**	**−0.068, −0.009**	**−0.035 (0.014)**	**−0.012**	**−0.063, −0.008**	**−0.0423 (0.015)**	**0.004**	**−0.072, −0.138**
Windrush	−0.002 (0.007)	0.807	−0.016, 0.012	−0.004 (0.006)	0.531	−0.016, 0.08	−0.005 (0.007)	0.479	−0.19, 0.009
Constant	**0.760 (0.040)**	**0.000**	**0.681, 0.839**	**0.870 (0.038)**	**0.000**	**0.795, 0.944**	**0.357 (0.041)**	**0.000**	**0.276, 0.439**
R^2	0.08			0.16			0.24		
N	854			857			850		
	Trust						**Distrust**		
	Outgroup			**Political process**			**Conditional distrust**		
	B	***p*=**	**95% CI**	**B**	***p*=**	**95% CI**	**B**	***p*=**	**95% CI**
Age	0.005 (0.0004)	0.307	0.0004, 0.001	0.0006 (0.0006)	0.368	−0.0007,0.002	**−0.0008 (0.0004)**	**0.049**	**−0.002, −0.000003**
Sex	0.0007 (0.012)	0.951	−0.023, 0.025	−0.009 (0.018)	0.627	−0.044, 0.027	−0.002 (0.012)	0.881	−0.025, 0.022
Current donor	0.013 (0.020)	0.510	−0.026, 0.052	−0.004 (0.028)	0.892	−0.058, 0.051	**−0.053 (0.018)**	**0.004**	**−0.089, −0.017**
BAME status									
Asian	−0.064 (0.039)	0.089	−0.139, 0.010	0.042 (0.062)	0.490	−0.078, 0.163	0.050 (0.038)	0.200	−0.026, 0.124
Black	**−0.120 (0.036)**	**0.001**	**−0.190, −0.049**	0.003 (0.048)	0.944	−0.091, 0.098	**0.180 (0.038)**	**0.000**	**0.104, 0.256**
Mixed	−0.033 (0.035)	0.343	−0.103, 0.036	0.027 (0.052)	0.606	−0.075, 0.128	**0.159 (0.042)**	**0.000**	**0.076, 0.242**
Interaction									
Donor*Asian	0.020 (0.041)	0.626	−0.061, 0.101	−0.024 (0.064)	0.711	−0.151, 0.103	0.005 (0.040)	0.711	−0.074, 0.085
Donor*Black	0.046 (0.042)	0.275	−0.037, 0.129	−0.0003 (0.057)	0.995	−0.109, 0.109	−0.016 (0.044)	0.624	−0.103, 0.070
Donor*Mixed	0.050 (0.038)	0.186	−0.024, 0.125	−0.043 (0.056)	0.436	−0.151, 0.066	**−0.124 (0.044)**	**0.003**	**−0.211, −0.037**

TABLE 3 (Continued)

	Trust						Distrust		
	Outgroup			Political process			Conditional distrust		
	B	*p*=	95% CI	B	*p*=	95% CI	B	*p*=	95% CI
Brexit	−0.027 (0.014)	0.052	−0.054, 0.0002	−0.0004 (0.019)	0.835	−0.045, 0.036	**0.055 (0.013)**	**0.023**	**0.029, 0.080**
Windrush	0.006 (0.006)	0.311	−0.006, 0.019	**−0.053 (0.010)**	**0.000**	**−0.073, −0.034**	**0.037 (0.006)**	**0.000**	**0.025, 0.049**
Constant	**0.671 (0.038)**	**0.000**	**0.594, 0.745**	**0.513 (0.057)**	**0.000**	**0.402, 0624**	**0.170 (0.035)**	**0.000**	**0.101, 0.240**
R^2	0.06			0.053			0.16		
N	860			858			853		

Note: Sex (0 = female, 1 = male). Ethnicity: people from a White background are the comparison population. Current donor (0 = No, 1 = Yes), Brexit (0 = negative influence, 1 = positive influence). Windrush ("The Windrush Scandal shows that the authorities still have a negative view about ethnic minorities in the United Kingdom" 1 = 'strongly disagree' to 5 = 'strongly agree.') Asian = People from Asian ethnic backgrounds, Black = People from Black and Caribbean backgrounds, Mixed = People from mixed ethnic backgrounds, White = People from a White backgrounds (excluding White minorities).

safety. The third factor, 'Conditional Distrust,' represented a belief that the NHS experiments on patients without their knowledge, that wealthy patients receive better care than poor patients, and that people from their ethnic community cannot trust NHS staff. This is combined with a general lack of trust in the police and judiciary. We term this 'distrust' as it reflects perceptions that others will actively harm the patient or person based on their ethnicity and social status (wealth) and, therefore, cannot be relied on.[21,36] The fourth factor, 'Trust in Individuals,' focuses on trust in strangers and encounters people have in their everyday lives. The fifth factor, 'Trust in Outgroups,' focuses on trust in people from other faiths and nationalities. The sixth factor, 'Trust in Politics,' reflects levels of trust in the Government and political parties.

9.3 | Levels of perceived trust and distrust

The highest levels of trust were observed for 'NHSBT' (Mean = 0.85, SEM = 0.005; Mode = 1.0; *N* = 975), followed by the 'NHS and staff' (Mean = 0.72, SEM = 0.005; Mode = 0.75; *N* = 972), 'Outgroups' (Mean = 0.69, SEM = 0.005; Mode = 1.0; *N* = 977), 'Individuals' (Mean = 0.45, SEM = 0.006; Mode = 0.50; *N* = 966) and lowest in 'Politics' (Mean = 0.34, SEM = 0.008; Mode = 0.25; *N* = 974). Conditional distrust was also found to be relatively high (Mean = 0.29, SEM = 0.006; Mode = 0.25; *N* = 968).

Means scores for each standardised dimension of trust, split by ethnicity and donor status, are shown in Figure 1A–F (Supplementary File 6 for Tables).

9.4 | Predictors of trust and distrust

Table 3 (Supplementary File S7, for sensitivity analysis) shows the results of a series of OLS regressions detailing the effects of sex, age, donor status, ethnicity and the interaction between donor status and ethnicity on the different domains of trust.

Men are more trusting than women with regards to 'NHS and Staff' and 'Individuals.' Current donors are more trusting of the 'NHS and Staff' and 'NHSBT' and express lower 'Conditional Distrust' than non-donors. Older participants were more trusting of 'Individuals' and had lower 'Conditional Distrust' and trust in NHSBT. Those who viewed Brexit as a 'positive benefit for the UK' were less trusting of the 'NHS and Staff,' 'NHSBT,' 'Individuals' and displayed higher 'Conditional Distrust.' Therefore, it could be suggested that those who saw the UK leaving the EU as a benefit were less trusting of UK systems that could be construed as supporting the campaign to remain in the EU.[43–44] Concerns about the Windrush scandal were associated with reduced trust in politics and greater conditional distrust (Supplementary File S8 for more detail on cultural context).

There are several significant effects of ethnicity. People from Asian ethnic backgrounds had less trust in 'Individuals' than White people. People from a Black ethnic background had less trust in 'NHS and Staff,' 'NHSBT,' 'Individuals' and 'Outgroups,' and expressed greater

TABLE 4 Logistic regression for willingness to donate in non-donors

	B (S.E.)	*p*=	B (S.E.)	*p*=
Age	**−0.104 (0.026)**	**0.000**	**−0.114 (0.030)**	**0.000**
Sex	0.812 (0.733)	0.268	0.859 (0.786)	0.275
Ethnicity	7.200 (4.483)	0.108	8.243 (5.069)	0.104
Trust NHS and staff	0.692 (3.025)	0.819	0.985 (3.120)	0.752
Trust NHSBT	**5.899 (2.788)**	**0.034**	**7.124 (3.348)**	**0.033**
Condition distrust	3.558 (2.818)	0.207	4.686 (3.213)	0.145
Trust individuals	−1.082 (2.488)	0.664	−0.320 (2.535)	0.900
Trust outgroup	4.379 (2.911)	0.133	3.695 (3.154)	0.241
Trust politics	1.556 (1.782)	0.383	1.122 (1.889)	0.552
Ethnicity* Trust NHS and staff	2.299 (3.681)	0.532	1.944 (3.751)	0.604
Ethnicity* Trust NHSBT	**−7.289 (3.650)**	**0.046**	**−8.407 (4.180)**	**0.044**
Ethnicity*Condition distrust	−2.678 (3.726)	0.472	−3.095 (4 0.100)	0.450
Ethnicity* Trust individuals	**6.763 (3.359)**	**0.044**	**6.654 (3.431)**	**0.052**
Ethnicity*Trust outgroup	−6.696 (3.715)	0.072	−6.313 (3.977)	0.112
Ethnicity*Trust politics	−2.824 (2.408)	0.241	−2.568 (2.496)	0.304
Brexit			−0.113 (0.667)	0.866
Windrush Scandal			−0.297 (0.323)	0.358
Constant	−2.070 (3.425)	0.546	−1.596 (4.318)	0.712
R^2	0.362		0.395	
n	176		164	

Note: Sex (0 = female, 1 = male). Ethnicity: People from a White background are the comparison population. Brexit (0 = negative influence, 1 = positive influence). Windrush ("The Windrush Scandal shows that the authorities still have a negative view about ethnic minorities in the United Kingdom" 1 = 'strongly disagree' to 5 = 'strongly agree'). White minorities are not represented.

'Conditional Distrust' than White people. Finally, compared to White people, people from mixed-ethnic backgrounds had less trust in 'NHS and Staff' and 'NHSBT' and expressed greater 'Conditional Distrust.'

The effects of donor status and ethnicity were qualified by a series of significant interactions for trust in 'NHS and Staff,' 'NHSBT,' 'Individuals' and 'Conditional Distrust.' These interactions were explored using *margins* in Stata 16 (Supplementary File Text S7 for the full margin table relating to Table 3 and for sensitivity analysis). These show that compared to non-donors, donors from White or mixed-ethnic backgrounds had greater trust in 'NHS and Staff.' Compared to non-donors, donors from Asian, Black, mixed-ethnic or White backgrounds had greater trust in 'NHSBT.' Compared to non-donors, donors from mixed-ethnic backgrounds had greater trust in 'Individuals.' Donors from White or mixed-ethnic backgrounds have lower 'Conditional Distrust' than non-donor.

9.5 | Indirect effects of socio-politicalfactors

We explored if the perception of Brexit and the Windrush scandal indirectly linked demographics (age, sex and ethnicity) to the domains of trust (Supplementary File 9 for model fit, and detailed results). In summary, perceptions that Brexit is 'likely to be beneficial for the UK' was the mechanism linking increased age to low trust in 'NHS and Staff,' 'NHSBT,' 'individuals' and 'outgroups' and greater 'conditional distrust.' Perceptions that the Windrush Scandal indicated that 'the UK government holds negative views of people from ethnic minority backgrounds' linked being a woman and/or being from an ethnic minority community to low trust in individuals, politics and greater conditional distrust.

9.6 | Predicting donation willingness in non-donors

Table 4 details two exploratory logistic regression models that examine predictors of willingness to donate in non-donors. The first (columns 2 and 3) explores the effects of age, sex, ethnicity, and the interaction of ethnicity by trust. The second (columns 4 and 5) includes the effects of Brexit and the Windrush scandal. The results show that younger non-donors were more willing to donate and that overall, trust in NHSBT predicted greater willingness to donate.

There were two significant moderating effects of ethnicity on trust, one for NHSBT and one for trust in individuals. The margins for these interactions are in Tables S8 and S9 in Supplementary File S10. These show that greater 'trust in individuals' predicts willingness to donate for people from ethnic minority backgrounds (Table S8) and that trust in NHSBT predicts willingness to donate in people from White communities (Table S9).

Finally, an overall path model to summarise the main predictor of willingness to donate in non-donors was specified (Figure 2). This model included the two main trust dimensions (NHSBT and individuals) predicting willingness in non-donors and the potential indirect effects of

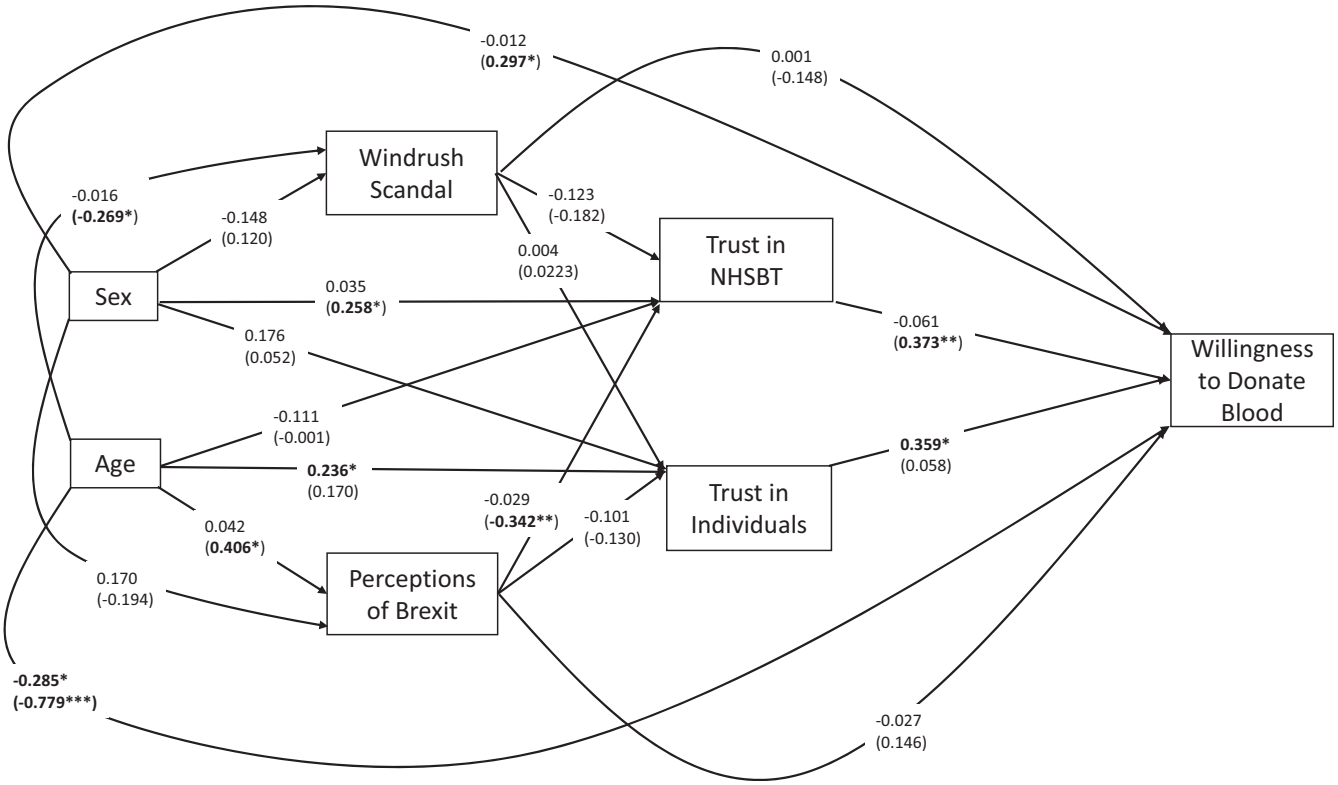

FIGURE 2 Path model to represent the downstream effects of age, sex, perceptions of Brexit and the Windrush Scandal on trust and willingness to donate blood in non-donors. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Parameter estimates for people from all ethnic minority backgrounds are the upper coefficients not in parentheses. The parameter estimates for people from White backgrounds are the lower coefficients in parentheses (*n* for the ethnic minority people is 96, and for the White people, *n* is 71)

demography on trust via indirect paths such as perceptions of Brexit and the Windrush (See Supplementary File S11 for full details). This model shows that 'trust in individuals' predicts willingness to donate in ethnic minority people and 'trust in NHSBT' for people from White communities. There is also evidence of a potential indirect effect of Brexit on willingness to donate through its influence on "trust in NHSBT' for White people, such that perceiving Brexit as a positive move for the UK' was linked to lower "trust in NHSBT" and through this, reduced willingness to donate blood ($\beta_{standardised} = -0.130$, $p = 0.083$).

10 | DISCUSSION

This article demonstrates why a broader conceptualisation of trust is, in part, important for understanding why people from ethnic minority communities are less likely to donate blood. We explored these findings and their implications below.

10.1 | Trust, distrust and blood donation

The results show a clear differentiation between trust and distrust, with trust separating into five domains: (1) politics, (2) healthcare organisations and their staff (e.g., NHS), (3) blood services (e.g., NHSBT), (4) outgroups (e.g., peoples of other nationalities and religions), and (5) individuals (e.g., strangers). The results show that people do not differentiate healthcare organisations (NHS) and their staff. This may reflect the uniqueness of the UK health service with a single national organisation employing medical staff, and staff are seen as representatives of that organisation. In other countries, with private healthcare providers, the link between the healthcare organisation and staff may be less clear. However, trust in the blood service (NHSBT) was seen as separate from the NHS. Thus, while NHS and NHSBT are related organizationally, psychologically, they are considered distinct.

A separate conditional distrust[23] factor emerged that linked the idea that healthcare providers may actively harm patients or treat them differentially based on their ethnicity and wealth, combined with low trust in the police or judiciary.[14] This conditional distrust can lead to a culture of distrust, suspicion, and alienation,[23,35] and is important as it shows a clear link between distrust in healthcare and the apparatus of the states (e.g., police and judiciary). Together, this indicates that reducing distrust in the healthcare system is not as simple as targeting interventions on healthcare but involves a broader consideration of distrust in society. Thus, widespread societal interventions that target distrust are needed, and blood services should consider working with outside government agencies to bring about effective change.

People from ethnic minorities, regardless of their blood donor status, reported significantly less trust across the domains, especially people from Black and Caribbean backgrounds. Lower levels of trust expressed by

ethnic minorities were not only focused on organisations but also on individuals.[17,52] It should be noted that while ethnic minorities had lower trust in 'NHS and Staff' and 'NHSBT' compared to White people, levels of trust were still extremely high. Nevertheless, this was not the case for trust in 'individuals,' which was lower for all participants and especially people from Black and Caribbean backgrounds.

Additionally, 'Conditional Distrust' was higher in people from Black and Caribbean communities. This may reflect the 'hostile environment' around migration and the implications of Brexit.[53] Indeed, concerns about the Windrush scandal were associated with higher 'conditional distrust.' It is often reported that the distrust that may arise from historical betrayals and distrust in various institutions and the apparatus of the state (police and courts) are key features of conditional distrust.[17,23]

10.2 | Implications for donor recruitment from minority communities

Trust in 'individuals' predicted willingness to donate blood for non-donors from all ethnic minorities, which has clear implications for interventions. Critical here is the idea of conditional cooperation.[54] Conditional cooperation occurs when people are aware that other people are cooperating, which motivates them to cooperate.[54] As such, conditional cooperation is a powerful phenomenon that could be harnessed to increase cooperative behaviour, such as blood donation.[55] One way to achieve this is via social media status updates such as—'I have just donated blood' or a blood donation status icon on Facebook, WhatsApp or Instagram, which would inform people that the individual has just donated blood and thereby encourage others to consider donating blood. This approach is effective in increasing opt-in organ donor registrations.[56] Thus, conditional cooperation may be particularly effective at recruiting non-donors as it is a strong social force when free-riding is high, which is the case for blood donation.[57]

10.3 | Caveats

We showed that 'Trust in Individuals,' not trust in healthcare, predicts willingness to donate in non-donors from ethnic minority communities. However, we must acknowledge that we grouped ethnicity into broad categories, minimising any effect of heterogeneity and wider diversity. Furthermore, the sample sizes for the analyses supporting the moderation and mediation analyses are small, and as such underpowered.[58] Thus, while this work offers a starting point, it needs to be refined to explore trust and concomitant interventions in different ethnic communities and replicated in larger samples and cross-validated with other methods.

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CONFLICT OF INTEREST

None of the authors have declared any conflicts of interest.

DATA AVAILABILITY STATEMENT

Data reported in this article is available from the first author on request.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

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A prospective interventional study to assess the impact of a 'structured compact training' on knowledge and skills of safe blood transfusion practices among nurses working in a tertiary care institute

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Abstract

Introduction: There is scarce information on the baseline knowledge and practices of nursing officers in relation to administration of blood components. We set out to evaluate the influence of training on their knowledge and skills through Kirkpatrick's levels of Training Evaluation.

Materials and Methods: This interventional cross sectional study of 7 months duration conducted in a tertiary care teaching institute involved 200 nursing officers. Hundred were assigned to study/intervention group and 100 were assigned to control/ comparison group by systematic random sampling. Knowledge was tested in different domains—blood components, pre-transfusion checks, transfusion process, post-transfusion process and blood administration practice.

Results: The baseline knowledge scores of intervention and control group were similar—15.16 ± 4.11 and 15.02 ± 4.75 ($p = 0.831$). Post-intervention (phase I) after 1 month, the scores improved significantly for domain A, B, C, D and E to 4.3 ± 2.21 ($p = 0.0001$), 3.46 ± 2.15 ($p = 0.0001$), 7.02 ± 3.55 ($p = 0.0001$), 2.51 ± 1.46 ($p = 0.0012$), and 5.86 ± 3.61 ($p = 0.0018$) respectively. In phase II, after 3 months of training, and the scores were significantly better from baseline for all domains except E. For domain A, B, C, D and E, scores were 3.82 ± 2.46 ($p = 0.0001$), 3.53 ± 1.98 ($p = 0.0001$), 7.38 ± 3.87 ($p = 0.0001$), 2.48 ± 1.55 ($p = 0.0035$), and 5.86 ± 3.61 ($p = 0.95$) respectively.

Conclusions: Our study showed that baseline scores were low in the nursing officers. No significant difference was found in baseline scores in subject and control population. However, post-intervention, a significant improvement in scores was observed in the study group across all domains.

KEYWORDS
attitude, knowledge, nursing, practice, transfusion

1 | INTRODUCTION

Blood transfusion is an integral part of the health care system. Nursing officials have an important role in blood safety as they are pivotal personnel involved in blood administration process—pre-transfusion/ bedside checks, administering the blood component, patient monitoring, identifying the transfusion reactions and documentation.[1] Therefore, it is expected that they are familiar with the norms and

is indispensable considering their direct involvement with patients. Therefore, measuring this knowledge has become a current trend between researchers. Misidentification accounts for the common morbidity rate during the transfusion procedure. Consequently, in order to perform a safe transfusion, evaluation of nurse's knowledge could be a useful approach to reduce the risk and decrease blood components wastage. A survey undertaken in the United Kingdom in 1993 and a similar one in the United States revealed that wrong identification and transfusion to the wrong patients account for the majority of fatality rate.[3] Qualified clinical staff include midwives and particularly nurses whose role is important in right and safe transfusion. Therefore, the expertise (or the lack thereof) of this staff could be the Achilles' heel in blood transfusion. Blood transfusion administration has five interwoven stages four of which directly related to nursing role including preparation before collecting blood units from the storage site, blood bag collection, pre-transfusion activities, post transfusion activities and monitoring patients.[4] To date, there have been only limited studies about the knowledge and expertise of the nurses performing blood transfusion. The majority of articles published in the Middle East point to the fact that the nurses suffer from insufficient knowledge in this regard.[2,4–7] Since there was no study preformed in this area in Tehran city, capital of Iran country it was deemed that a study must be undertaken to evaluate the knowledge of nursing staffs about blood transfusion so we can make sure the least people will be affected by low-level nurses' knowledge. The present research has been carried out on university based hospitals affiliated to Shahid Beheshti University of Medical Sciences.

2 | METHODS

2.1 | Design

This was a descriptive study carried out by field-related interviewers (the first and second authors) using the valid questionnaire. Our target participants are nurses who worked and are involved in the administration of blood transfusion in eight wards including intensive care unit, emergency, oncology, orthopaedics, surgeries, internal medicine, urology and paediatrics in 13 university affiliated training public hospitals.

The study subjects included about 2000 registered nurses with experience at in-patient areas and with at least 5 months of work experience. The required sample size is 325 nurses (Setting $\alpha = 0.05$, confidence level = 95%, and bound on error = 5%) which was performed using simple random sampling by SPSS software version 19 (United States) (www.raosoft.com/samplesize.html).

2.2 | Measurement tool

We used a pre-made and used questionnaire by Mr Hijji who had modified and developed this Routine Blood Transfusion Knowledge Questionnaire (RBTKQ) earlier (for which we have his kind permission).[6,7] The questionnaire was then supervised and confirmed by the elite scientists in this field based on Iranian Blood Transfusion Organization Standards. The questionnaire includes seven sections with 43 questions related to blood transfusion knowledge. All nurses accepted to complete the questionnaire. There are three yes/no questions concerning hospital policy and the importance of regulating transfusion rate, whilst the rest of the questions are designed as multiple choices. Each correct answer is given one score and there were no negative scores for questions left unanswered. The total score was determined to be 55 for those who had experience in both adults and infant's units and the figure was 54 for the nurses with the working experience just in one. Furthermore, there are two correct answers to the question 9 in section E which concerns the agents administered with transfusion (b. normal saline 0.9% and d. morphine 1 mg/ml in NS). However, since in accordance with Iranian Blood Transfusion Organization policy doctors should avoid direct morphine compound injections with transfusion, in this questionnaire we limited the correct answer to only one choice (normal saline 0.9%) rather than two.

The current version of RBTKQ included 32 knowledge multiple-choice questions (2 true-false; 20 multiple-choice; 10 multiple-response). Demographics and training information are asked in section A and other sections (B–G) are listed as follows respectively: knowledge aspects of blood bag collection from blood bank and patient preparation prior to it, pre-transfusion initiation nursing responsibilities, post transfusion initiation nursing responsibilities, complications related to blood transfusion (33 items) and the issues related to hospitals' blood transfusion policies and procedures.[7]

2.3 | Validation and pilot study

Readability, validity and content clarity of the questionnaire were evaluated as a pilot study by 50 readers consisting of qualified registered nurses, post-graduate students, and the relevant specialists. They all indicated that content is understandable and readable, and that it had a content validity index of 90% which is well within the acceptable range. All these 50 questionnaires filled out as the pilot were not counted in the main final results. In order to check the internal consistency, we obtained an excellent Cronbach's alpha which was 0.91. We also checked its readability using the Flesch Reading Ease Index (yielding an index of ~68). All modifications were applied after the pilot study.

2.4 | Data collection

After obtaining permission from Director of Nurses in each hospital, two qualified haematology and blood banking students collected the questionnaire data. Besides, the questionnaire was completed by volunteer nurses during 30–60 min in presence of the research assistant. In order to keep anonymity, the involved nurses' names were not asked and the data were collected in 2017–2018.

2.5 | Data analysis

The total score in this questionnaire was 55 points and each correct response gains one point. Since the population did not have normal distribution, non-parametric analyses were carried out. By the time the questionnaires were completed, the data were entered onto SPSS software (United States) and then the descriptive analyses were carried out. For each section, the mean knowledge score was calculated and the overall knowledge score was reported. The chi-squared test was used in order to check the relation between nurses' characteristics (such as age, number of transfusions in year, experience, education) and the knowledge mean score. Statistical significance was set at $p < 0.05$.

2.6 | Ethical considerations

An official permission from the responsible authorities in Shahid Beheshti University of Medical Science by the Ethics Approval Code no: IR.SBMU.RETECH.REC.1395.1034 was obtained to legally start the study. Each nurse participated voluntarily in the study. Anonymity and confidentiality were all guaranteed.

3 | FINDINGS AND DISCUSSION

3.1 | Participants' characteristics and trainings

The number of nurses who answered the questionnaire was 325, out of which 251 (77%) were female. Most of the nurses were in the age group of 20–29 ($n = 190$, 58%). Out of the total number of the participants, 58% (188 nurses) had clinical experience between one to five years; besides, there were 89 nurses (27%) with more than five years of experience. Of the studied nurses, nearly 50% ($n = 153$) acknowledged that they had in-service training on blood transfusion, whereas the rest of them ($n = 170$) had never have such trainings and 156 and 148 (48% and 46%) of them expressed a strong need for training in haemovigilance and adverse reactions, respectively.

3.2 | Overall knowledge

The obtained scores on nurses' knowledge were scaled to 100%; the results showed that the scores of nurses ranged from 24% to 85% (mean 56.16, standard deviation: 5.92) indicating that no one had correctly answered all the questions. Based on previous studies we categorised knowledge scores in three groups where lower than 30% (<30%) indicates poor ($N = 10$, 3%), from thirty to sixty-five (30%–65%) indicates moderate ($N = 262$, 81%) and more than 65% (>65%) indicates good knowledge ($N = 53$, 16%).[4] According to this category the majority of nurses (81%) have been located in the average group.

In comparison with similar conducted studies in the Middle East, all the nurses have an average and insufficient knowledge score. Our results were congruent with other studies including one on 117 nurses in medical training hospitals of Shahrekord University of Medical Sciences in 2004[5] which reported only 51.6% of nurses had good knowledge score.[5] The other conducted by Mr Hijii in Abu Dhabi Emirates (2011) and Jordan (2009) also reported the mean knowledge scores being 40.8 and 51.8, respectively[6,7] and finally, one study performed in Morocco in 2014 on 42 nurses showed the same insufficiency in the overall knowledge of nurses.[8] In addition, in Egypt a survey on 286 nurses showed 61.2 as the mean knowledge score which is higher than other Middle East countries.[2] Furthermore, results obtained from another survey conducted in turkey on 100 health care staffs which 71% of them were nurses, revealed that the average knowledge is adequate. Also they reported that the knowledge of health care professionals was higher than the mean.[9] In another hand, there were reports from Qazvin University of Medicals Science which showed that the average knowledge of 124 nurses calculated to be as medium level.[10]

3.3 | Correlations

3.3.1 | Work experience

In order to measure the strength and correlation that exist between variables, non-parametric tests were performed. The spearman correlation analysis revealed that there is a significant and positive correlation between nurse's work experience and the obtained scores ($p = 0.000$, rs $= 0.229$). Also, Kruskal-Wallis H test confirmed that there was a statistically significant difference in work experience between the different knowledge groups, χ^2 (2) $= 14.458$, $p = 0.001$, with a mean rank work experience of 129.41 for poor, 149.07 for moderate and 197.83 for good. Based on the results and the personal communication of nurses, the more the work experience in blood transfusion, the more the knowledge in that field that is most likely through learning from experienced reactions and interactions between colleagues. But the point is 'what's more important: qualifications or experiences?'.

Generally, learning through academic courses brings about deeper and better understanding whilst the experience only teaches you what happens in practice. Consequently, due to the vital role of blood transfusion even making a simple mistake is inexcusable. SHOT program also provided a checklist which should be completed before transfusion is indicated. However, the errors are inevitable even with years of experience and seniority.[3]

3.3.2 | Degree and transfusion attempts

Mann–Whitney test also was performed to find the possible correlation between the academic degree with the knowledge score. Results illustrated that nurses who have master degree ($N = 59$, mean rank $= 195.46$) tend to have more knowledge score in comparison with the nurses with bachelor degree ($N = 255$, mean rank $= 148.72$)

($p = 0.000$, Mann–Whitney $U = 5283.000$). Moreover, as shown in Table 1 and estimated by Kruskal-Wallis test, the majority of nurses who had administered more than 12 times ($N = 111$, Mean rank = 161.45) of transfusion attempts within the last 6 months showed no higher mean rank than the other nurses with lower experience. The finding illustrated that there was no significant correlation between the number of experiences in administering transfusion and the obtained knowledge score ($p = 0.203$, Kruskal-Wallis = 5.952). The results stressed that academic knowledge is really more important than experience.

3.4 | Issues relating to patient preparation

This section stresses the proper timing for blood collection, availability of intravenous access line and, the appropriate times for vital sign recording. Table 2 shows that nurses lacked the awareness about incomplete medical orders with only 12% ($N = 39$) of nurses refusing to collect and authorise the blood; most likely because of the low knowledge level of nurses and their busy workload. Consequently, this could result in the increasing fatality rate of blood transfusion. On the contrary, about the aspects of information given to patients and baseline vital signs recording, the nurses had enough knowledge. About checking patency of IV after blood bag collection, the results showed a really low knowledge that might be because of hospital crowding and lack of time for nurses which could lead to increase in the holding time of blood units in ward and may raise the bacterial infection potential.

Sufficient knowledge in patient preparation field can prevent the occurrence of complications and blood transfusion reactions. The mean score for this section was 55.78% which is insufficient and as we know, this score illustrates the importance of patient preparation to be neglected most likely due to shortage of personnel in the departments and the hospital crowding. Similar studies including ones conducted by Hamed Abd Elhy et al.[2] and Tetteh[11] showed that nurses' knowledge was fair enough in patient preparation.[11]

3.5 | Blood bag collection

In this section which is about transporting blood units, we have got the highest mean score (83.48%) of all the other sections of the questionnaire.

Table 3 shows that almost all nurses (92%, $n = 299$) would transport blood bags with validated special boxes. About information to ensure collecting the right blood from the blood bank, 84% of nurses ($n = 274$) would check the identification details which are identical on the blood bag and blood request form. In the case of receiving A− blood bag from blood bank for A+ patient, 241 nurses (74%) would check with the physician and obey their orders. Since the earliest blood transfusions, it has always been a concern to transfuse compatible blood type to the recipient. With the advancement in blood typing, it is expected to have only few fatalities caused by incompatible transfusion. Yet, according to global reports human error is still a considerable factor in incorrect transfusion. This is why it is crucial for all hospitals to have very strict policies. Although the nurses in this study have shown a sufficient level of ABO-terminology knowledge, there needs to be more assessment.

TABLE 1 Correlation of categorised knowledge scores with demographic data

	Total knowledge			
Variable	**Poor ($N = 17$)**	**Moderate ($N = 254$)**	**Good ($N = 54$)**	**Test result**
Sex				0.071
Female	17 (6.8%)	139 (76.9%)	41 (16.3%)	
Male	0 (0%)	61 (82.4%)	13 (17.6%)	
				0.246
Age, median, range	28 (26–41)	28 (22–45)	29 (23–41)	
Score, median, range	15 (13–19)	15 (13–19)	30 (21–35)	0.000
Work experience, median, range	2.35 (1–6)	3 (0.1–24)	4 (0.9–12)	0.001
Degree				$X^2(2) = 5.878$ $p = 0.05$
B.S.	13 (5.1%)	204 (80%)	38 (14.9%)	
MSC	1 (1.7%)	42 (71.2%)	16 (27.1%)	
Transfusion				$X^2(8) = 16.889$ $p = 0.031$
0	2 (11.8%)	20 (8.7%)	0 (0%)	
1 to 4	9 (52.9%)	54 (25.6%)	10 (31.5%)	
5 to 8	0 (0%)	43 (16.5%)	4 (24.1%)	
9 to 12	0 (0%)	25 (14.2%)	6 (14.8%)	
More than 12	6 (35.3%)	64 (35%)	15 (29.6%)	

TABLE 2 Issues relating to patient preparation

Section B	Question	Correct answer	Number of correct answers	Percentage of correct answers
1	Checking patency of IV after blood bag collection	F	96	30%
2	Collecting blood bag from blood bank should take place before the administration of any prescribed pre-medication	F	182	56%
3	Decisions to be taken by the nurse with incomplete order	Refuse to collect and administer blood	39	12%
4	Three aspects of information given to patient	Reasons for blood	272	84%
		Transfusion risk of blood transfusion	149	46%
		Reaction symptoms	246	76%
5	Baseline vital signs recording	Within ½ h before transfusion	285	88%

TABLE 3 Blood bag collection

Section C	Question	Correct answer	Number of correct answers	Percentage of correct answers
1	Information to ensure collecting the right blood from blood bank	Patient's identification details are identical on the blood bag and blood request form	274	84%
2	Blood bag transport method	Validated special box	299	92%
3	Receiving A− blood bag from blood bank for A+ patient	Check with the physician and obey their orders	241	74%

TABLE 4 Pre-transfusion initiation nursing activities

Section D	Question	Correct answer	Number of correct answers	Percentage of correct answers
1	Most important nursing action before starting the transfusion	Patient identification	**177**	**54%**
2	Clinical indications for blood warming	Exchange transfusion for infant	**213**	**66%**
		Rapid transfusion	**159**	**49%**
		Patient with cold agglutinins	**106**	**33%**
3	Best time to start the transfusion if delivered to the ward at 4 PM	4:10 PM	**109**	**34%**
4	Blood handling after delivery to ward	Start immediately	**68**	**21%**
5	Steps for patient identification	Ask patient to state name and date of birth	**274**	**85%**
		Patient's identification details are identical on ID band	**207**	**65%**
		Blood request form	**182**	**56%**
6	Suitable filter size of transfusion set	170–200 micron	**96**	**30%**
7	Omitting the final bedside identity check	Never acceptable	252	78%

Note: Bold values indicate the nurses' activities before starting the blood components transfusion.

The promising results in this section may indicate the existence of strict rules and standards in hospital blood banks.

Based on similar studies conducted in Menoufia University Hospital, they also reported a good situation on blood bag collection and it is not in the same line with Hijji which reported that the majority of their targeted nurses lacked knowledge with basic ABO terminology.[2,7]

3.6 | Pre-transfusion initiation nursing activities

This part is about proper patient identification, documentation, use of warm blood, and determination of the right time to start the transfusion.

As shown in Table 4, only 68 nurses (21%) would start transfusion immediately after blood is delivered to the ward. In the clinical

TABLE 5 Post transfusion initiation nursing activities and issues

Section E	Question	Correct answer	Number of correct answers	Percentage of correct answers
1	Three activities for nurses to perform routinely after starting the blood transfusion	Setting up the flow rate	218	67%
		Documentation of relevant information	261	80%
		Observation for transfusion reaction	199	61%
2	The rate to initiate a transfusion on an adult patient	Not more than 120 ml/h	78	27%
3	Regulation of blood transfusion is important	Yes	320	98%
	Regulation of transfusion flow rate	Manual	226	69%
		Via electronic pump	94	28%
4	Maximum duration of using a blood administration set for continuous multiple transfusions	4 h	243	75%
5	The rate to initiate a transfusion at on an infant	Not more than 0.5 ml/kg/h	52	28%
6	Maximum duration for completing a unit of blood.	4 h	249	77%
7	Indications for slow blood transfusion	Patients with heart disease	279	86%
		severe anaemia	94	29%
8	Agents compatible with blood	Normal saline 0.9%	304	94%
9	Vital signs recording after starting a transfusion at 2:00 PM	2:05 and 2:15	280	86%
		3:15	167	51%
		4:15	107	33%
		5:00	72	22%
10	Timing and duration when it is essential to physically observe a patient for possible transfusion reaction	First 10–15 min	151	46%

Note: Bold values indicate clinical complications/complains after starting blood components transfusion.

indications for blood warming only 106 nurses (33%) are aware of patients with cold agglutinins. A high percentage of nurses ask patients to state their date of birth ($n = 274$, 85%) and then also check for identical details on ID bands for proper identification.

Section D has got 51.58% as the mean knowledge score and this almost moderate percentage can lead to many transfusion complications such as acute haemolytic transfusion reactions and microbial infections. There is a crisis about 'blood handling after delivery to ward' because most of the nurses think they should wait for half an hour and then start the transfusion but in fact, this is a common mistake because in principle there is a maximum of half an hour to onset the transfusion. Another remarkable issue is about suitable filter size of transfusion set about which most of nurses do not exactly know and can definitely be due to lack of knowledge in this area.

We had the lowest score for this section of questionnaire and in comparison with other undertaken studies namely Hamed Abd Elhy et al.[2] The majority of participants would act inappropriately regarding pre transfusion responsibilities and as we said earlier this irresponsibility accounts for the high fatality rate. Moreover, Hijji also reported a skimped knowledge base in Jordanian nurses about pre-transfusion initiation nursing activities.[7]

3.7 | Post transfusion initiation nursing activities and issues

Section E is about setting a convenient flow rate, proper duration of transfusion, simultaneous use of drug/solutions with blood and surveillance over the patient for plausible transfusion reactions.

Almost all the nurses are aware of the importance of the regulation of the flow rate of blood transfusion but only 27 percent ($N = 78$) and 28 percent ($N = 52$) of nurses are aware of the suitable rate to initiate a transfusion respectively on adult and infant patients. Seventy-five percent ($N = 243$) acknowledged that maximum duration for completing a unit of blood is 4 h. Concerning the importance of using warm blood to avoid serious side effects such as ischaemia 86% and 29% ($N = 279$, $N = 94$) of nurses respectively know that setting the slow transfusion rate is necessary for patients with heart disease and severe anaemia.

Section E has got 59.11% as the mean knowledge score.it is almost fair or moderate level of knowledge but a poor awareness about blood administration rate can definitely be due to lack of awareness and can leads to blood transfusion complications for example in patient with transfusion-associated circulatory overload which setting a slower administration rate can be helpful.[12]

TABLE 6 Complications related to blood transfusion

Section F	Question	Correct answer	Number of correct answers	Percentage of correct answers
1	Nursing interventions that could minimise the risk of developing transfusion reaction	Administering compatible blood	**266**	**82%**
		Starting transfusion within 20 min	**102**	**31%**
		Total duration of administration 4 h	**67**	**21%**
		Avoid incompatible drugs/solutions	**179**	**55%**
2	Signs and symptoms of acute haemolytic reaction	Tachycardia	**272**	**84%**
		Chest pain	**234**	**72%**
		Hypotension	**122**	**38%**
		Nausea/vomiting	**197**	**61%**
3	Nursing management of AHTR	Stop blood transfusion	**314**	**97%**
		KVO with N/S	**107**	**33%**
		Check V/S	**274**	**84%**
		Notify the doctor and begin emergency treatment	**253**	**78%**
4	A unit of blood was kept in nurses' station for 90 min without starting the transfusion, what should the nurse do?	Not to start the transfusion, notify the blood bank and return the blood	185	57%
5	The usual presenting complaint of a mild allergic transfusion reaction	Urticarial rash	239	74%
6	The first action the nurse should take with mild allergic transfusion reaction	Slow the transfusion rate and notify the doctor	72	22%
7	The commonest cause of fatal transfusion reaction	Identification error of patient	89	27%
8	Complication of rapid transfusion of cold blood	Cardiac arrhythmia	**166**	**51%**

Abbreviations: AHTR, acute hemolytic transfusion reaction; KVO, keep the vein open.

TABLE 7 Issues related to blood transfusion policies and procedures

Section G	Question	Correct answer	Number of correct answers	Percent of correct answers
1	Availability of a written policy for the administration of blood.	Yes	267	82%
		No	30	9%
		I do not know	22	7%
2	If yes, have you read the policy?	Yes	255	95%
		No	52	16%

Our findings were aligned with Hamed Abd Elhy, Hijji and Khalil[2,7,13] which all revealed theirs finding scores were generally inadequate (Table 5).

3.8 | Complications related to blood transfusion

Section F is about sign and symptoms and actions to be taken when acute hemolytic transfusion reaction (AHTR) and allergic transfusion reactions happen.

Administering compatible blood, starting transfusion within 20 min, administering blood during 4 h and avoiding incompatible drugs/solutions are four things that are less likely to lead to a transfusion reaction with timely intervention by nurses with the scores for these four being 82%, 31%, 21% and 55% ($N = 266$, $N = 102$, $N = 67$ and $N = 179$), respectively. About the sign and symptoms of a haemolytic reaction, 84% ($N = 272$) knows that tachycardia is one of the signs, that chest pain, hypotension and nausea/vomiting are the other important symptoms about which the awareness of nurses was 72% ($N = 234$), 38% ($N = 122$) and 61% ($N = 197$), respectively. Only 27% ($N = 89$) believe that the error of patient identification is the commonest cause of fatal transfusion reaction.

Here we got 56.81% as the mean score for this important section. Lack of knowledge in this area can be very disastrous, so continuous

education about the effects of blood transfusion should be given to nurses (Table 6).

3.9 | Issues related to blood transfusion policies and procedures

As we all know presence of a written policy is necessary in the wards of hospitals (http://www.southend.nhs.uk/media/64178/administration_of_blood_and_blood_components.pdf). In this questionnaire the availability of a written policy for the administration of blood was asked and 82% ($N = 267$) said yes out of whom 95% declared that they have read the policy. Nine percent ($N = 30$) of nurses said they have not seen any (Table 7).

4 | CONCLUSION

Annually extensive efforts have been taken in order to collect and produce blood components, encourage people to donate their blood and of course to screen them to obtain a safe donation. Consequently, the role of nurses in this chain is really crucial to reach the optimum efficiency with regard to patient treatment and to reduce component wastage. All the conducted surveys illustrated that the majority of nurses have suffered from insufficient knowledge concerning blood transfusion in all aspects. The main reason for this knowledge deficit is the lack of such factors as supervision policy for nurses and course units on blood transfusion in their curricula. There has also been a lack of a system for regular observations of the nurses to keep them abreast with the latest developments. In comparison with other similar studies on nurses' knowledge level, our target population knowledge was considered to be between the poor and average score border. However, with respect to the vital role of safe and proper transfusion in patient treatment, this knowledge score is inadequate and a post-qualification training is highly recommended to improve nurses' knowledge and skill.

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AUTHOR CONTRIBUTIONS

Amir Yami and Arezoo Darbandi: analysis. **Esmaeil Saber:** collecting data. **Mehdi Tabrizi:** some proofing and addressing a part of questionnaire. **Ahmad Gharehbaghian:** main analytical and discussion issues.

CONFLICT OF INTEREST

The authors have no competing interests.

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ORIGINAL ARTICLE

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Changing red blood cell transfusion practice in obstetrics and gynaecology: A before and after study of hospital-wide education

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Abstract

Objectives: To assess transfusion practices at a Canadian tertiary care center before and after a hospital-wide blood management educational campaign based on the Choosing Wisely toolkit.

Background: Red blood cell (RBC) transfusions are an essential intervention in obstetrics and gynaec ology (O&G). However, with limited guidelines outlining the appropriate use of RBC transfusions, clinicians routinely transfuse based on haemoglobin values and habits.

Methods/Materials: We conducted a retrospective chart review of all patients who received a RBC transfusion while admitted under an O&G provider in two 12-month periods—before and after the intervention. The campaign consisted of Grand Rounds, formal and informal teaching, and posters placed within the hospital. We judged appropriateness from a set of criteria guided by the status of ongoing bleeding, pre-transfusion haemoglobin, and the number of units ordered simultaneously.

Results: Transfusion appropriateness was poor in pre- and post-intervention periods (46% vs. 51%, $p = 0.59$). The overall rate of RBC transfusion was reduced from 1.8% to 1.2% (83/4610 vs. 55/4618, $p = 0.02$) after the intervention. There was a 52% reduction in the total number of RBC units of transfused (229 vs. 111, $p < 0.001$), a 33% reduction in the number of patients transfused (83 vs. 55, $p = 0.016$), and fewer multiple-unit transfusions without reassessment (39 vs. 13, $p = 0.005$).

Conclusion: RBC transfusion appropriateness remained low after a hospital-wide educational campaign. However, there was a marked decrease in overall transfusion use, reflecting the adoption of more restrictive transfusion practices. The low rate of transfusion appropriateness represents an opportunity for further improvement.

KEYWORDS
anaemia, blood transfusion, gynaecology, obstetrics

1 | INTRODUCTION

Red blood cell (RBC) transfusion is a common and potentially life-saving intervention.[1] Each RBC unit transfused carries significant risk, including alloimmunization, acute and delayed transfusion reactions, infection, lung injury, and increased hospital length of stay.[1,2] Alongside these risks, a single unit of blood has an estimated cost of over CAD 600 in Canada.[3] Patient blood management is essential in

A 2017 addendum to the British Society of Haematology (BSH) Pre-Transfusion Compatibility Procedures in Blood Transfusion Laboratories describes a model laboratory investigation protocol for patients who are being treated with targeted therapeutic monoclonal antibodies (TMAb)[6]. The protocol requires patients who are due to undertake a course of anti-CD38 TMAb treatment to be tested as follows:

- ABO and D group
- Antibody screen/identification
- DAT
- Extended phenotype or genotype (C, c, E, e, K, (k if K+), MNSs, Jk^a, Jk^b, Fy^a and Fy^b)

Once the patient has commenced anti-CD38 therapy, the protocol then makes the following recommendations regarding pre-transfusion compatibility testing and provision of blood components, if required:

- ABO and D typing as per normal method.
- Antibody screening, and antibody identification if required, using a strategy to avoid the effect of anti-CD38, for example, reagent cells treated with 0.2 M Dithiothreitol (DTT). Other strategies and techniques for overcoming the effect of anti-CD38 on red cells may become available in the future.
- Red cells should be matched for Rh and K as well as for any alloantibodies.

The overall aim of the protocol is to aid in the timely investigation and provision of blood components, and to mitigate against alloimmunisation in these patients. In addition, before beginning treatment with a drug which is known to interfere with pre-transfusion testing, it is helpful to establish phenotype and antibody status because it will be difficult to do so once treatment has begun. Performing this testing provides information and assurance when selecting RBCs for transfusion. The outcomes of this pre-therapy compatibility testing protocol should be documented in the transfusion laboratory, in the patient's notes and ideally on a patient-held shared-care record. In practice, however, this does not always occur, with lapses and failures in communication a common theme in transfusion-related incidents.[7]

Alternative mitigation strategies to remove pan-reactivity in pre-transfusion compatibility testing include the use of the reducing agent 0.2 M Dithiolthreitol (DTT)[8] which denatures the CD38 antigen, removing pan-reactivity and allowing the identification of underlying alloantibodies. However, treatment of reagent Red Blood Cells (RBCs) with 0.2 M DTT also removes antigens in the Kell, Lutheran, YT, JMH, LW, Cromer, Indian, Dombrock and Knops blood group systems.[9] This prevents recognition by corresponding alloantibodies, where present. Other mitigation strategies include the use of trypsin treated RBCs,[10] chloroquine diphosphate, soluble recombinant proteins and FAB fragments.[11] In addition, the use of cells that express reduced levels of CD38 antigen has been described; including cord cells or Lu(a−b−) cells of the dominant In(LU) phenotype.[12] However, most of these investigative strategies are undertaken in reference laboratories due to the expense and availability of many of the reagents involved. Due to the complexity of pre-transfusion compatibility testing, many of the MM patients in England who are on DARA are referred to the specialist NHS Blood & Transplant (NHSBT) Red Cell Immunohaematology (RCI) laboratories for investigation and provision of Red Blood Cell (RBC) components for transfusion.

Studies in the available literature report favourable outcomes to transfusion in this cohort of patients where ABO/RH/K matched or extended phenotype matched units have been given, with very few transfusion reactions reported and instances of alloimmunisation reported to be low, once daratumumab therapy has commenced. Published rates of alloimmunisation are between 0% and 3% in this cohort of patients[13–20] (see Table I) and studies report a variety of transfusion approaches, including providing RBCs matched for ABO/Rh/K antigens, which is congruent with current BSH guidance, or routine provision of extended matched RBCs to this cohort of patients.

However, a limitation of published studies to date has been the size of the cohorts studied, and data obtained may not reflect the true rate of alloimmunisation. Additionally, the use of extended phenotype matched blood in these studies is not reflective of current BSH guidance,[6] and therefore, does not reflect alloimmunisation rates under current practice. Routine extended matching for all antigens is not achievable with most hospital blood bank stock and may deplete blood service extended phenotype matched stock for other transfusion dependent patients who are at a greater risk of alloimmunisation (e.g., those with sickle cell anaemia).[21]

NHSBT RCI laboratories routinely perform investigations on patients undergoing anti-CD38 TMAb treatment. Therefore, NHSBT is in a unique position to analyse this cohort's data. RCI laboratories have seen an increase in requests for the investigation of patients undergoing anti-CD38 TMAb therapy. However, it is not yet known exactly how many of these patients RCI laboratories are investigating and how many units of blood are being issued, nor the frequency of transfusion and importantly, the frequency of alloimmunisation in this cohort. In order to answer these questions, the authors undertook a retrospective cohort study over a 4-month period in 2019.

2 | METHODOLOGY

Over a 4-month period in 2019 (June–Sept), patients who were referred to RCI laboratories in England were identified either on the RCI test request form by the referring hospital laboratory as due to commence or currently on anti-CD38 therapy, alternatively, they were identified by RCI through the result of serological investigation and further enquiry. Once identified, the patients were flagged on the RCI Laboratory Information Management System (LIMS) as being on an anti-CD38 TMAb. At the end of the 4-month data collection period, the cohort of patients was identified using a Business Objects (BObs—business intelligence software) search to enable the extraction of the discrete data set, using the CD38 LIMS flag.

TABLE I Published rates of alloimmunisation in cohorts of MM patients receiving treatment with anti-CD38 therapeutic monoclonal antibodies

Study	Number of patients transfused	Alloantibodies detected pre-therapy	Underlying rate of alloimmunisation before anti-CD38 therapy commenced (%)	New alloantibodies detected post-therapy	Rate of alloimmunisation once anti-CD38 therapy commenced (%)	Extended phenotype matched blood Y/N
Chari et al.[14]	14	anti-D, anti-E, anti-K, anti-Jk^b, anti-Fy^a, anti-Fy^b, anti-S and anti-Knops	14% ($n = 2$)	None	0%	Y
Deneys et al.[15]	11	None	0%	None	0%	Y
Bub et al.[16]	5	None	0%	None	0%	Y
Ye et al.[17]	45	None	0%	None	0%	Y[a]
Solves et al.[18]	44	None	0%	None	0%	N—ABO/Rh/K matched only
Anani et al.[19]	62	Anti-Jk^a	1% ($n = 1$)	None	0%	
Cushing et al.[20]	91	Alloantibodies/ Autoantibodies—Specificities not given	26.4% ($n = 24$) Alloantibodies 6 (6.6%) Warm autoantibodies 12 (13.2%) Cold autoantibodies 9 (9.9%) Nonspecific reactivity 5 (5.5%)	Anti-C anti-S and anti-Co^b	3% ($n = 3$)	N—ABO/K matched only
Carreño-Tarragona et al.[21]	33	anti-D, anti-C, anti-E and anti-c	9% ($n = 3$)	None	0%	Y

[a]ABO-Rh compatible and ABO compatible plus phenotypically matched RBcs were given. Ratios of each not stated.

Data extracted was collated onto an Excel spreadsheet for further analysis. Interrogation of data was performed independently by two subject matter experts, with discrepancies solved through further discussion and enquiry. Crossmatch requests received by RCI over the 4-month period were analysed to establish the average number of units requested and subsequently provided by RCI to capture patients who had received repeated transfusions over an extended period, for example, at least 3 months. Patient samples received during the audit period who were identified as being alloimmunised once anti-CD38 therapy had begun had their transfusion history examined and followed up with the referring hospital to establish potential sources of alloimmunisation. Other patient data, such as samples received, and number of crossmatch requests was analysed from the 4-month study period only.

3 | RESULTS

Over the 4-month course of the study period, samples were received by RCI labs in England from a total of 734 patients who were flagged on the LIMS as being on Daratumumab. The number of Males was 418 (57%); Females was 296 (41%); sex unknown, 20 (2%). The average age of patients seen was 68 years (68y Males; 69y Females). The range of ages seen was 9–91 years (9–88 years males; 12–91 years females).

The total number of samples received for these patients over the 4-month study period was 1629. The average number of samples received per patient was 2.2 (range 1–13), with some regional variation in sample referral frequency observed.

A total of 46% (341/734) of patient referrals were accompanied by a request for crossmatched units. Over the 4-month study period, the average of units requested and subsequently provided by RCI per patient was 2.8 (range 1–13) although it is not known if all units issued were subsequently transfused.

The majority of patients had an extended phenotype or genotype performed. This comprised of the following; an extended phenotype (58%, $n = 426$); extended genotype (32%, $n = 234$) or neither (10%, $n = 74$). Patients who had no extended typing by RCI labs may indicate testing is being performed by some hospital transfusion laboratories, or alternative local transfusion strategies (limiting to ABO, Rh/K matching) are being employed.

Antibodies to red cell antigens were detected in a total of 4% (30/734) patients seen over the course of the study period. Antibodies to both self antigen (autoantibodies) and non-self antigen

(alloantibodies) were detected. Of the 30 patients in whom RBC antibodies were detected, antibodies where a specificity could not be determined (SNDT) were excluded ($n = 4$), leaving a total of 3% (26/734) of patients on anti-CD38 TMAb therapy who had an identifiable specific underlying allo or autoantibody(ies). Patients were shown to have developed single and multiple specificities of RBC antibodies (see Figure 1).

The detected antibodies can be divided into two categories; pre-existing (before commencement of Dara) or newly formed (detected after the initiation of Dara treatment). In 80% (21/26) of patients with an underlying antibody, the antibody detected was pre-existing in samples received prior to the start of anti-CD38 treatment. The five remaining patients developed newly-formed antibodies whilst on anti-CD38 therapy. The specificities of these identifiable antibodies were as follows:

- 1 x allo anti-D
- 1 x allo anti-E
- 1 x allo anti-Fya
- 1 x auto anti-C (detected in eluate only)
- 1 x auto anti-M (detected in eluate only)

Autoantibodies were then excluded from the dataset, as in the absence of haemolysis, RBC are not selected to take into account autoantibody specificity, as prevention of the development of alloantibodies is usually of more importance.[6]

Therefore, the rate of RBC alloimmunisation for patients whilst on anti-CD38 therapy is 0.4% (3/734 patients included in the study).

4 | CONCLUSION/DISCUSSION

The findings of this study, the largest of its kind to date, found a rate of RBC antigen alloimmunisation in patients whilst on daratumumab of 0.4% (3/734). This is concordant with other, much smaller cohort group studies.[13–20] The overall rate of alloimmunisation in the cohort, defined as the presence of an antibody to a RBC antigen, either existing or newly-formed once daratumumab therapy had begun, was 4% (30/734).

This alloimmunisation rate is lower than in other transfusion dependent cohorts, where alloimmunisation rates as high as 60% of regularly transfused patients are reported.[21] The decreased rate of RBC alloimmunisation in the study cohort may be due to a combination of the disease pathology and immunosuppressive therapeutic regimen. Reduced alloimmunisation has been reported in patients with immunosuppression.[22–23]

Alloimmunisation to RBC antigens occurred despite matching RBC in accordance with BSH guidelines.[6.] In particular, 2 out of the 3 alloimmunised patient were alloimmunised to Rh blood group system antibodies despite receiving RBC fully matched for Rh antigens which would suggest prior alloimmunisation and senescence or sensitisation through an alternative immunological stimulus. In examining the instances of alloimmunisation whilst on Dara more closely, all alloimmunised patients were female and their past medical and serological history was as follows.

The patient who developed alloanti-D started Daratumumab in March 2019. No alloantibodies were detected at the end of April 2019 in the 1st sample received by RCI. Allo anti-D was first detected by RCI in July 2019 and once again in August 2019. The hospital

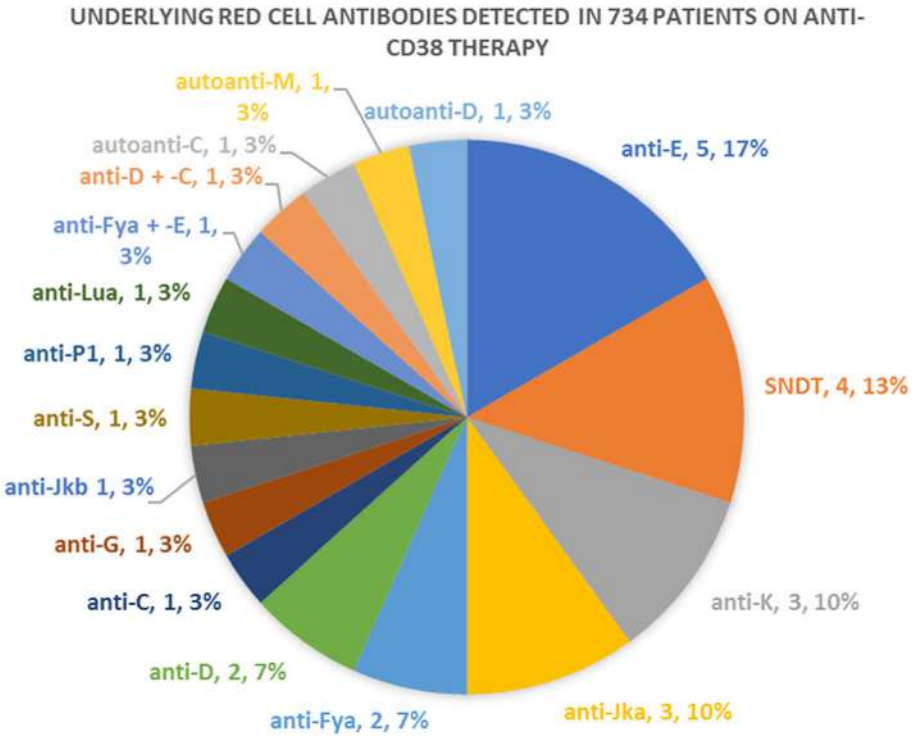

FIGURE 1 Pie chart showing underlying red cell antibodies detected in 734 anti-CD38 TMAb patient referrals to RCI, June 2019-Sept 2019. The most frequently detected, identifiable alloantibodies were Anti-E, Anti-K, anti-Fy^a and Anti-Jk^a. Alloantibodies were detected both prior to commencing Daratumumab therapy (pre-existing, $n = 21$), and once Daratumumab therapy had commenced (newly-formed, $n = 3$). The specificities of the newly-formed alloantibodies were as follows; 1 x alloanti-D, 1 x alloanti-E and 1 x alloanti-Fy^a

confirmed the patient only received D negative RBCs during the course of their treatment, but they did receive one unit of group A, D positive pooled platelets at the beginning of April 2019. Therefore, the formation of alloanti-D was either due to RBC contamination of the pooled platelets,[24] or possibly following a previous pregnancy/sensitising event the anti-D became senescent, and an anamnestic response was subsequently stimulated by administration of D positive pooled platelet components. Modern blood component manufacturing and processing methods now result in very low residual RBC contamination in pooled and apheresis platelet components, however, the risk of antibody alloimmunisation to residual RBCs in these components is not totally obviated. The age/sex of the patients in the study may have meant that a dose of RAADP (250 IU to cover 5 ATD of platelets in a 6-week period) was not issued following the D incompatible platelet transfusion described above, but this should be considered if a patient is D negative, of childbearing potential and D negative platelets cannot be supplied.

The patient who developed anti-E received an autologous Haematopoietic Stem Cell Transplant (HSCT) in early 2019. The patient started Daratumumab in October 2019. RCI crossmatched units for the patient twice in September 2019, and once in October and November 2019 before detection of allo anti-E in November 2019. On all occasions, RBCs provided to the patient from RCI were fully matched for Rh and K antigens, in line with BSH guidance.[6] There was no historical record at the referring hospital of the patient having an allo anti-E prior to commencing Daratumumab. The patient received transfusions of pooled platelets in September (×3), October (×2) and November (×1) 2019. Therefore, formation of alloanti-E may have been due to either of the following; the formation of a naturally occurring alloanti-E, RBC contamination of pooled platelets, or possibly following a previous pregnancy/sensitising event.

The last alloimmunised patient who developed alloanti-Fy^a received an autologous HSCT in 2012, and again in 2016. The patient subsequently started Daratumumab in May 2019. No alloantibodies were detected in May 2019 in the 1st sample received by RCI. RCI first detected alloanti-Fy^a in July 2019. There was no historical record of alloanti-Fy^a at the referring hospital before Daratumumab treatment commenced. The patient received three units of RBC in May and two units of RBC in June. One of the RBC units issued in May was Fy(a+b+), and is, therefore, a possible source of alloimmunisation in this instance.

As discussed, development of autoantibodies did not change the provision of blood components as in the absence of haemolysis, RBC are not selected to take into account autoantibody specificity, as prevention of the development of alloantibodies is usually of more importance.[6] Therefore, they are not considered to be significant in the context of clinical management and are excluded from the scope of these findings. However, it is important to note that despite immunosupression, the patients above were still able to mount an immunological response to RBC derived antigens, producing antibodies to both self and non-self antigenic structures.

These findings come with the caveat that any antibodies detected may have been senescent but present in the patients identified, and that for the purposes of the study alloimmunisation was defined as a newly detected/identified antibody which had not been reported/identified prior to commencement of anti-CD38 therapy. Additionally, as DTT was used for ABID, there may have been an underestimation of the alloimmunisation rate in the patient population, especially for Kell system antibodies and additional specificities not detected by using DTT treated cells, due to antigen removal following DTT treatment. There is also a risk that despite having audited a large number of patients, the time frames studied may not be representative of the exposure and risk, and hence underestimate alloimmunisation. Our data may also underrepresent the number of patients/transfusions, as some labs order extended matched (ABO, Rh, K, MNS, FY, JK) blood directly from NHSBT through the Online Blood Ordering System (OBOS) once a genotype or phenotype has been performed and do not refer samples to RCI for repeat antibody investigation and crossmatching of units.

On the basis of the findings of this study, current protocols to phenotype or genotype all patients prior to commencement of anti-CD38 therapy may be considered excessive given the low rate of alloimmunisation. Particularly when comparing this pre-transfusion testing strategy to antigen matching strategies in other cohorts of patients, for example, in sickle cell anaemia where rates of alloimmunisation are much higher. Consideration should be given to removing the requirement for extended phenotyping or genotyping in all cases prior to the commencement of anti-CD38 therapy, limiting this to those with pre-existing or newly formed alloantibodies. An alternative suggested pre-therapeutic approach to pre-compatibility testing may include the approach shown in Figure 2.

If the initial antibody screen is negative, it is unlikely that alloantibody formation will occur, and therefore, the standard approach of transfusing ABO compatible, Rh/K matched units, issued as suitable would be appropriate for the majority of patients in this cohort.

If the initial antibody screen is positive at commencement of therapy, or becomes positive as a result of antibodies other than the TMAb whilst on treatment, then it would be prudent to phenotype or genotype the patient, as they have previous/current history of antibody formation; and therefore, may make further antibodies if transfused. This would then guide RBC component selection.

Anecdotal reports suggest that some hospital transfusion laboratories already order extended matched RBC routinely, to avoid alloimmunisation and referral of samples to a reference laboratory for investigation and RBC provision. This places additional demand on the stock of extended phenotype units which are needed for other cohorts of transfusion dependent patients who have a higher risk of alloimmunisation, or whom may already have multiple antibodies. This study data should provide confidence that ordering extended phenotype matched units beyond ABO/Rh and K as routine is unnecessary. It also should allow some confidence when assessing the possibility of extending sample validity periods to 7 days from 3 days due to the low risk of alloimmunisation between transfusions. This should enable reduced hospital visits, which with the increased risk of Coronavirus (COVID-19) in these immunocompromised patients is a sensible precautionary measure.

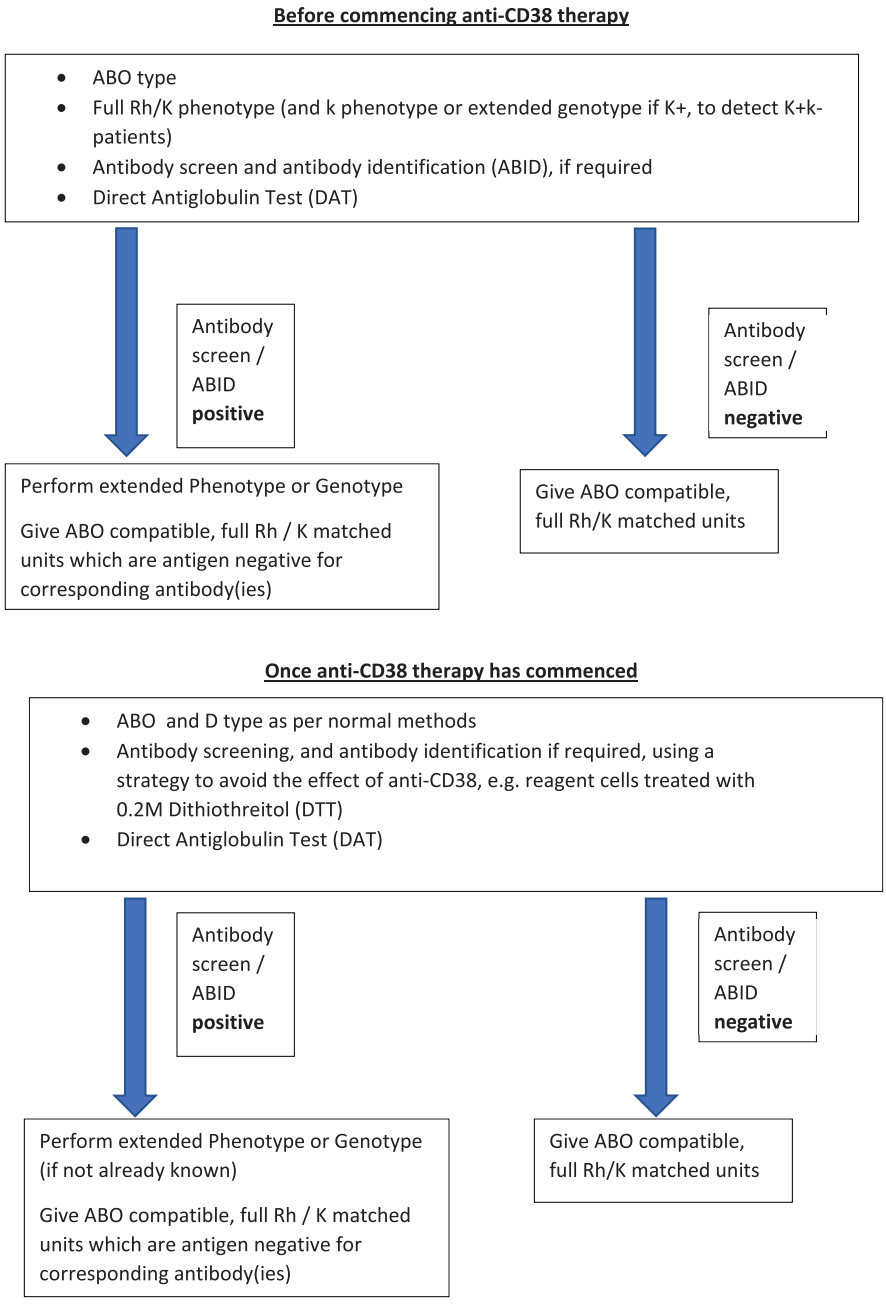

FIGURE 2 Proposed workflow for pre-transfusion compatibility testing for patients on anti-CD38 TMAbs. For each transfusion episode patients should have an ABO Rh/K (and k type, if K+)

The risks of not performing extended typing on MM patients on anti-CD38 therapies who are not alloimmunised may include a delay in blood provision in those few instances when a new antibody is detected, to allow for a phenotype or genotype to be performed. Additionally, it is known that the incidence of MM amongst White populations is significantly lower than Black populations[25] and a genotype may be useful in detecting antigenic variants and guiding RBC selection. A percentage of MM patients also go on to have an allogeneic Stem Cell Transplant and in the long term, a genotype or phenotype would not be beneficial to their treatment due to the different antigenic profile between the recipient and donor. There is also the initiative for personalised medicine which includes genotype-matched blood provision. The current large-scale feasibility of this approach means that it may be limited to transfusion dependent cohorts whom are at greater risk of alloimmunisation. The data from this study indicates that for this cohort, matching routinely beyond ABO/Rh/K may be unnecessary for most MM patients.

Pre-transfusion compatibility testing is necessary to prevent haemolytic transfusion reactions, however, as more TMAbs are developed to treat varying disease states, those working in blood transfusion will need to be aware of any subsequent challenges in blood compatibility testing and supply. Determining the risk of RBC alloimmunisation in patients treated with these novel therapies may help to reduce testing costs and turn-around times and enable evidence-based patient care.

CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

Tom Bullock wrote the paper, analysed and reported the data. Amie Foster contributed to the paper, supplied and analysed the data. Bryony Clinkard contributed to the data analysis.

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ORIGINAL ARTICLE

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Therapeutic apheresis and non-blood donor related apheresis current practices at various blood centres of healthcare organisations of India: A brief online survey

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Abstract

Objectives: To determine the variability in therapeutic apheresis (TA) and non-blood donor related apheresis practices, and the extent of expertise and knowledge of blood centre staff.

Background: Apheresis activity that was earlier limited to therapeutic plasma exchange (TPE) and donor apheresis at few centres in India has seen remarkable surge involving many centres practising TA and non-blood donor related apheresis. The decentralised transfusion medicine practice in country has resulted in wide variability of knowledge and practice of TA. An online survey was conducted to achieve study objectives.

Study design and methods: A 22 questionnaire survey was sent to the 215 blood centres through e-mail link focussing on three aspects; basic information of the participating centres, details of TA procedures and education and training levels of the staff.

Results: Majority (71.9%) of centres were teaching institutions among analysed 57 centres. TPE (85.9%) and therapeutic cytapheresis (71.9%) were the most common TA procedures. The clinical haematology (68.4%) followed by neurology (64.9%) were the specialities utilising TA. The 64.9% centres used continuous flow cell separator and central venous access (52%) was preferred vascular access. A combination of normal saline, fresh frozen plasma and 5% albumin replacement fluid was first choice. Doctors involved in TA were trained in apheresis during their MD/DNB degree, but no structured training program existed for other category of staff.

Conclusion: There was a wide variability in TA practice in India and a dedicated training program for all categories of staff was emphasised by majority of participants.

KEYWORDS
blood centre, survey, teaching and training, therapeutic apheresis, vascular access

1 | INTRODUCTION

Apheresis is a process in which whole blood is withdrawn from a subject and continually separated into components to retain the desired component and return the remainder.[1] The application of apheresis technology has expanded to include both donor and therapeutic apheresis (TA). The donor procedures ensure that a specific blood component is available for transfusion. The TA permit for the reconfiguration of patient's blood that could favourably affect some disease processes.[2] The collection of autologous or allogeneic

1 | INTRODUCTION

Human T-cell leukaemia virus type 1 (HTLV-1) is a causative agent of human T-cell malignancy, adult T-cell leukaemia/lymphoma (ATL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[1–3] The number of HTLV-1-infected individuals is estimated to be 10–20 million worldwide[4] and over 1 million in Japan,[5] and >95% of infected patients will remain asymptomatic throughout their lifetime. Therefore, asymptomatic HTLV-1 carriers could be at risk of becoming blood donors in Japan. Regarding the transfusion-transmission of HTLV-1, a serological test for all blood donors was mandated by the Japanese Red Cross Blood Centre (JRC) in 1986. At the same time, the JRC has permanently declined blood donation from HTLV-1-seropositive donors, and subsequently, in 1999, a notification programme for HTLV-1-seropositive blood donors was started in order to ensure the safety of blood products for transfusion, according to the recommendation from the government committee on notification of HTLV-1 infection. Although a unified document for HTLV-1-seropositive blood donors was prepared in the JRC headquarters, the format and information content were not put practical use among the regions at this point. The reason why uniform materials were not used nationwide is that the required information varies according to the prevalence in the region.

The Kyushu region, located in the south-western part of Japan, is well-known to have the highest prevalence of HTLV-1 among developed countries. In the Kyushu region, we annually detect >300 HTLV-1-seropositive blood donations, and approximately 2% of seropositive donors visit for repeated blood donation. As the only facility to collect and supply blood products in Japan, the JRC has a responsibility to maintain the safety of blood products by instructing HTLV-1-seropositive blood donors to refrain from blood donation. However, whether or not the notified donors correctly understand the results and what information they need has not been investigated. In order to promote the awareness of HTLV-1-seropositive blood donors, it is important to provide accurate and up-to-date information that addresses the unmet needs of notification recipients.

In this study, we conducted a questionnaire survey to define the unmet needs and knowledge on HTLV-1 infection among donors who were notified of HTLV-1-seropositivity. Based on the responses, we created a new information booklet that contains updated information on HTLV-1 and HTLV-1-specialised medical institutions, with a comment instructing the individual to refrain from blood donation in the future. To assess the impact of the new information booklet on the comprehension of notified donors and their consultation of designated medical institutes, a follow-up survey was conducted. And the number of repeating HTLV-1-seropositive blood donors was compared before and after the distribution of the new information booklet.

2 | MATERIALS AND METHODS

2.1 | Study design

From December 2018 to March 2020, 388 donors (male, $n = 222$; female, n = 166) were notified of their seropositivity on a confirmatory test of HTLV-1. We mailed the notification along with an explanation of the purpose of this study, a consent form, a questionnaire survey form (Appendix S1) and a postage-paid envelope to the notified donors.

In the first survey, the donors who received the notification were asked about their knowledge of HTLV-1, their feelings on receiving the notification, their unmet information needs, the tools they used to obtain on-demand information, whether or not they wished to visit a medical institution and any problems they encountered when receiving the notification. When introducing medical institutions for HTLV-1 carrier consultation in the booklet, we referred to accredited institutions registered in the Japanese Society of HTLV-1 and Associated Diseases (JSHAD). Consent to include the name and reception hours of each medical institution designated for consultation in the attachment of the new information booklet was obtained from all nine certified HTLV-1-specialised medical institutions in the Kyushu region.

The new information booklet was created through consideration of the responses to the first questionnaire survey, and distribution with notification of HTLV-1-seropositive test results started in June 2019. We assessed the recipients' impressions and comprehension of the information in the new booklet, as a second survey targeting newly notified seropositive individuals. Next, we investigated the change in the number of the newly notified blood donors who visited the medical institutions listed in the attachment. In addition, the number of repeating HTLV-1-seropositive blood donors was compared before and after receipt of

TABLE 1 Characteristics of the respondents to the questionnaire survey

	Total (*n*)	Age (years) 16–19	20–29	30–39	40–49	50–59	60–69	Median (range)
Male								
Notified donors	222	15	18	36	41	88	24	50.0 (17–65)
Respondents	46	0	2	4	3	31	6	56.0 (20–64)
Response rate (%)	20.7	0.0	11.1	11.1	7.3	35.2	25.0	
Female								
Notified donors	166	8	10	16	28	75	29	52.0 (17–67)
Respondents	57	2	2	8	6	31	8	53.0 (18–66)
Response rate (%)	34.3	25.0	20.0	50.0	21.4	41.3	27.6	

the above booklet as an evaluation study of new information booklet with attachment from January 2017 to March 2021.

2.2 | Ethical approval

Ethical approval for this study was obtained through the JRC Ethics board (Infection-112, 2018-037-1).

3 | RESULTS

3.1 | Questionnaire survey for notified HTLV-1-seropositive blood donors and the preparation of the new information booklet

Of the 388 notified HTLV-1-seropositive donors, 103 donors (male, $n = 46$; female, $n = 57$) gave their consent to participate in this

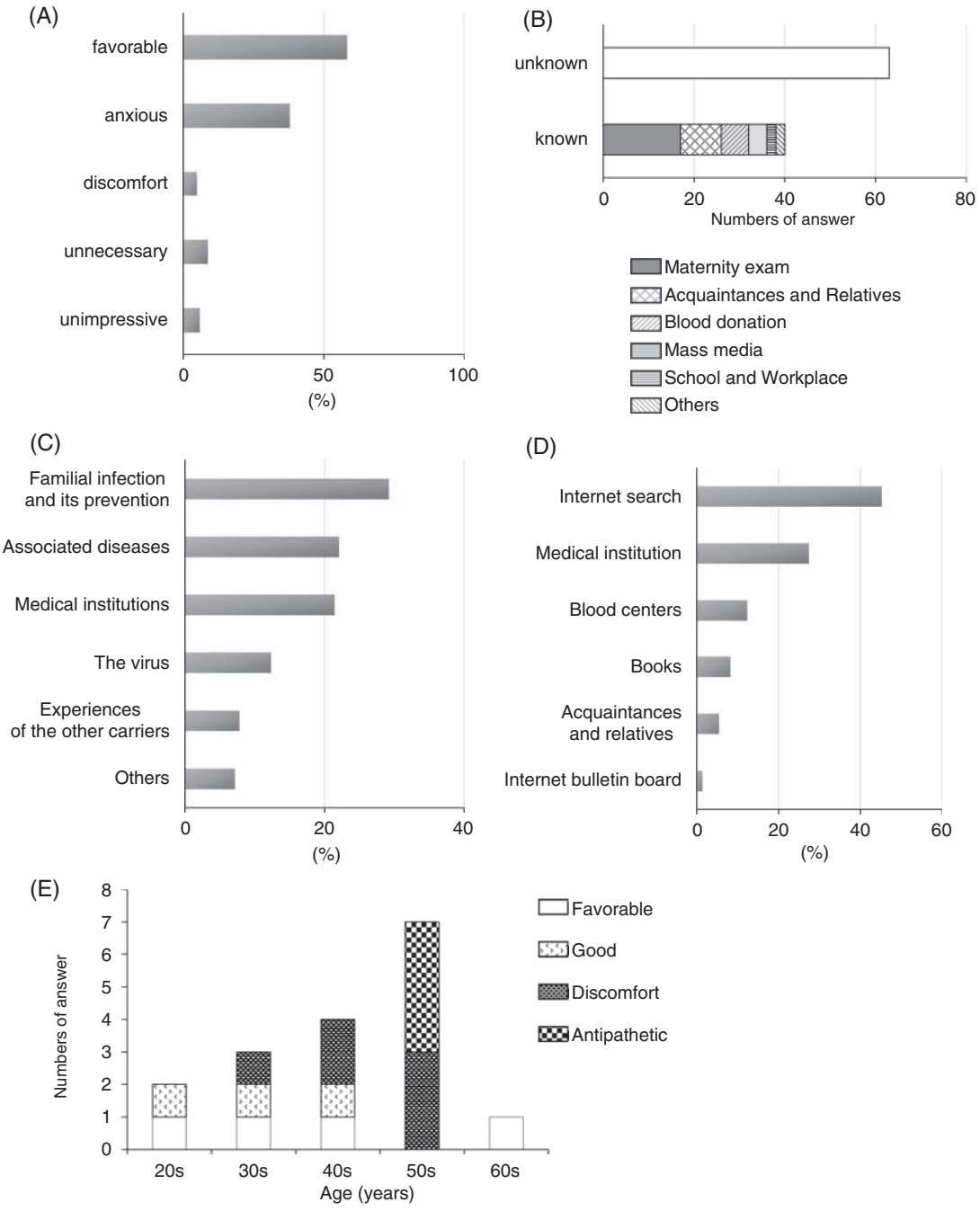

FIGURE 1 Answers to the first questionnaire survey. The questionnaire was sent along with a notification concerning seropositive test results for HTLV-1, and answers were obtained from respondents who consented to participate. (A) Donors' feelings at the time of receipt of the HTLV-1-seropositive notification (numbers of answers: 119), (B) Awareness of HTLV-1 when receiving the notification (numbers of answers: 103; white, did not know about HTLV-1 prior to the receipt of seropositive notification; shaded, knew about HTLV-1 prior to the receipt of seropositive notification). The horizontal axis shows the numbers of respondents. (C) Type of information requested (numbers of answers: 154), (D) Tools for obtaining on-demand information (numbers of answers: 73), (E) Impression about the MHLW Manga material

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

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

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

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

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

As the most important issue for the improvement of the safety of blood products, we explicitly stated in the new information booklet that future blood donations from the notified recipients would be declined.

3.2 | Follow-up survey to assess comprehension after distribution of the new information booklet

The reviewed and revised information booklet (available at: https://www.bs.jrc.or.jp/bc9/bbc/special/m6_05_04_index.html) has been distributed to the HTLV-1-seropositive donors since June 2019. A follow-up survey was conducted to assess the comprehension of the notification recipients and their status of HTLV-1 infection.

For the follow-up survey, we distributed a questionnaire about the notification to 233 HTLV-1-seropositive blood donors, and 58 donors (male, $n = 30$; female, $n = 28$; 24.9%) replied. The median age of the male and female respondents was 56.0 years (range, 20–64 years) and 52.5 years (range, 24–64 years), respectively; and 19 (63.3%) of the male respondents and 16 (57.1%) of the female respondents were in their 50s (Table 2). Fifty-eight respondents reported 66 impressions of the new information booklet; 33 (50.0%) found it 'easy to understand', 11 (16.7%) found it

TABLE 2 Characteristics of the respondents to the follow-up questionnaire survey

	Total (*n*)	Age (years) 16–19	20–29	30–39	40–49	50–59	60–69	Median (range)
Male								
Notified donors	147	12	10	20	29	58	18	50.0 (17–65)
Respondents	30	0	2	2	2	19	5	56.0 (20–64)
Response rate (%)	20.4	0.0	20.0	10.0	6.9	32.8	27.8	
Female								
Notified donors	86	0	5	5	16	44	16	53.0 (20–66)
Respondents	28	0	2	2	4	16	4	52.5 (24–64)
Response rate (%)	32.6	0.0	40.0	40.0	25.0	36.4	25.0	

'useful' and 14 (21.2%) found it 'difficult to understand but still comprehensive', meaning that 87.9% of the respondents were able to gather the necessary information from the contents of the new information booklet (Figure 2). By attachment of the consultation guide for available medical institutions specialising in HTLV-1 consultation, seven of the nine introduced hospitals confirmed that they had outpatient visits from blood donors with an HTLV-1-seropositive notification.

3.3 | Deterrent effect of the new information booklet on repeated donation by HTLV-1-seropositive notification recipients

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

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

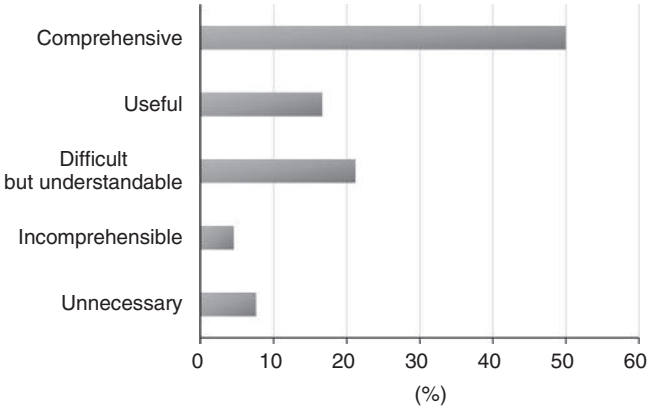

FIGURE 2 Impressions of the new information booklet. After the distribution of the new information booklet with the seropositive notification, a follow-up survey was conducted. Fifty-eight respondents gave 66 answers about their impressions of the new information booklet

4 | DISCUSSION

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

The WHO reported that 37 countries conduct mandatory testing of all blood donors for HTLV-1 and HTLV-2 and that seven countries conduct selective testing of new donors or donors who have not been previously tested.[6] It is a worldwide consensus in blood programmes that the notification and counselling of blood donors who show seropositive test results are important to blood safety; however, there are no fixed standards for either the regulatory requirements (legally prescribed criteria for notification) or the guidelines for notifying blood donors.[7,8] Notification of HTLV-positive blood donors was reported in Canada,[9] Australia[10] and the United States[11] in the 1990s. For example, in the UK,[12] notification recipients are asked to contact the blood service to arrange a discussion about their test results and onward clinical care. In Japan, this notification program started in 1999. The notification of healthy blood donors about seropositive test results can cause confusion, anxiety, and lack of understanding. In the recent report on health-related quality of life among blood donors who were notified viral infection, cases shown anxiety and depression had been 2.67-fold in HTLV carriers comparing to the control uninfected donors.[13] However, we have not adequately followed up the outcomes of notification.

In the present study, we defined the knowledge of HTLV-1 among notified blood donors and the unmet information needs according to the findings of a questionnaire. Taking the respondents' voice into consideration, we then created a new information booklet to provide the most necessary and up-to-date information in an easy-to-understand format. In the new information booklet, with the aim of improving health-related quality of life of the notification recipients, we included phrases to mitigate their anxiety, recommended early consultation to those with any symptoms, and listed the HTLV-1-specialised medical

TABLE 3 A comparison of the numbers of re-visiting recipients before and after the distribution of the new information booklet

	All notified donors in this study		Recipients tracked over 1 year	
	n	Re-visiting recipients (%)	*n*	Re-visiting recipients within 1 year (%)
Before distribution	853	17 (1.99)	853	5 (0.59)
After distribution	530	0 (0.00)	310	0 (0.00)

institutions for the consultation. In addition, we conducted a questionnaire survey to investigate the comprehension of recipients. In this survey, 90% of the respondents answered that the new information booklet was understandable, indicating that their knowledge had dramatically improved thanks to the contents, which coincided with the unmet needs of the notification recipients.

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

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

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

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

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

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

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

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

to improvement of both the health-related quality of life of seropositive blood donors and the safety of blood products.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

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

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

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Utility of pre-operative haemoglobin concentration to guide peri-operative blood tests for hip and knee arthroplasty: A decision curve analysis

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Abstract

Objective: Assess the prognostic value of pre-operative haemoglobin concentration (Hb) for identifying patients who develop severe post-operative anaemia or require blood transfusion following primary total hip or knee, or unicompartmental knee arthroplasty (THA, TKA, UKA).

Background: Pre-operative group and save (G&S), and post-operative Hb measurement may be unnecessary for many patients undergoing hip and knee arthroplasty provided individuals at greatest risk of severe post-operative anaemia can be identified.

Methods and Materials: Patients undergoing THA, TKA, or UKA between 2011 and 2018 were included. Outcomes were post-operative Hb below 70 and 80 g/L, and peri-operative blood transfusion. Logistic regression assessed the association between pre-operative Hb and each outcome. Decision curve analysis compared strategies for selecting patients for G&S and post-operative Hb measurement.

Results: 10 015 THA, TKA and UKA procedures were performed in 8582 patients. The incidence of blood transfusion (4.5%) decreased during the study. Using procedure specific Hb thresholds to select patients for pre-operative G&S and post-operative Hb testing had a greater net benefit than selecting all patients, no patients, or patients with pre-operative anaemia.

Conclusions: Pre-operative G&S and post-operative Hb measurement may not be indicated for UKA or TKA when adopting restrictive transfusion thresholds, provided clinicians accept a 0.1% risk of patients developing severe undiagnosed post-operative anaemia (Hb < 70 g/L). The decision to perform these blood tests for THA patients should be based on local institutional data and selection of acceptable risk thresholds.

KEYWORDS
blood transfusion, decision curve analysis, haemaglobin, orthopaedics

1 | INTRODUCTION

The number of elective primary hip and knee arthroplasties performed internationally is projected to increase exponentially for hip arthroplasty by 2050 and four-fold for knees by 2030, with comparable projections across 20 Organisation for Economic Cooperation and Development countries.[1–3]

Hip and knee arthroplasties are highly successful procedures at improving quality of life, but the surgery can result in significant blood loss.[4,5] Blood loss can exceed 1 L during the peri-operative period for a primary hip or knee arthroplasty procedures when accounting for visible and hidden blood losses.[6] Despite blood conservation strategies, over 80% of patients are anaemic on discharge from hospital and up to 5% require allogenic red blood cell transfusion.[7–10] The recommended haemoglobin concentration (Hb) threshold for administering allogeneic red blood post-operatively is 70 g/L, or 80 g/L in the presence of acute coronary syndrome.[11]

Routine clinical practice is to perform group and save (G&S) in all patients prior to arthroplasty surgery and a post-operative blood test for Hb prior to discharge from hospital, however, there is limited guidance for when these investigations are indicated or can be omitted. Pre-operative G&S and post-operative Hb measurement may be unnecessary when the risk of requiring a blood transfusion or a patient developing severe post-operative anaemia is acceptably low.

Previous studies have identified pre-operative Hb thresholds that predict blood transfusion using Receiver Operator Characteristics (ROC) curve methodology, choosing pre-operative Hb values associated with the highest combined sensitivity and specificity, and giving equal weighting to true and false positives.[12,13] However, this does not allow clinicians to consider the harm: benefit ratio they feel is appropriate for their patient cohort.

The potential benefits of a targeted approach to peri-operative blood tests include reduced cost, improved patient experience, and shorter length of inpatient stay by preventing delays waiting for blood results and facilitating safe day-case surgery. Potential risks of omitting these investigations include having no blood product available when required and discharging patients with severe undiagnosed anaemia. The acceptable harm: benefit ratio will differ between institutions and clinicians.

The aim of this study was to characterise the prognostic value of pre-operative Hb for identifying patients who develop severe post-operative anaemia or require blood transfusion following elective primary hip or knee arthroplasty. We address four research questions:

1. What are the temporal trends of post-operative Hb below the 70 and 80 g/L transfusion thresholds, and allogeneic blood transfusion following elective primary hip and knee arthroplasty?
2. What is the relationship between pre-operative Hb, and post-operative Hb and blood transfusion?
3. What are the pre-operative Hb thresholds for different risks of severe post-operative anaemia?
4. What is the utility of different strategies using pre-operative Hb to select patients for pre-operative G&S and post-operative Hb measurement?

2 | MATERIALS AND METHODS

We performed a cohort study using electronic health records, reported in accordance to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Reporting Recommendations for Tumour Marker Prognostic Studies (REMARK) statements.[14,15]

2.1 | Subjects studied

Routinely collected data from the Nuffield Orthopaedic Centre (NOC), Oxford, UK, between December 2011 and August 2018 were used. All primary hip and knee arthroplasty procedures at the NOC were included in the study, regardless of approach, implant, blood management strategy or grade of surgeon. Patients undergoing elective primary total hip arthroplasty (THA), total knee arthroplasty (TKA) or unicompartmental knee arthroplasty (UKA) were identified using the Office of Population Censuses and Surveys (OPCS) procedure codes (Classification of Interventions and Procedures, version 4) (Table S1). THA were performed using the anterolateral or posterior approach using cemented and uncemented implants. TKA were mostly performed using the medial parapatellar approach and a tourniquet. UKA were routinely performed with a minimally invasive medial arthrotomy and a tourniquet. Routine tranexamic acid administration was introduced after 2015 as intravenous with or without topical administration. Patients who had a blood transfusion within 3 months prior to surgery were excluded as they are likely to have an underlying medical condition that requires regular Hb measurement. Procedures with a missing date and duplicate entries on electronic health records were also excluded.

2.2 | Outcomes

The primary outcome was the National Institute for Health and Care Excellence (NICE) recommended transfusion threshold of a Hb less than 70 g/L within 7 days following surgery (<70 g/L transfusion threshold: yes/no, binary).[11]

Secondary outcomes were the NICE recommended transfusion threshold for patients with acute coronary syndrome of a Hb less than 80 g/L (<80 g/L transfusion threshold: yes/no, binary)[11]; and administration of a blood transfusion intra- or post- operatively (blood transfusion: yes/no, binary) within 7 days following surgery.

All data collected between 2011 and 2018 were used for Hb measurements. Data collected between 2013 and 2018 were used for the blood transfusion analysis when electronic prescribing for blood transfusion was introduced.

2.3 | Variables

Data were extracted for: age (years, continuous); sex (male/female, binary); pre-operative Hb (g/L, continuous); American Society of

Anesthesiologists (ASA) classification (range: 1–5, ordinal); and post-operative Hb (g/L, continuous). The closest pre-operative Hb value to surgery start date and time was used from within 6 months prior to surgery, and the closest value to surgery end date and time was used from within 7 days following surgery.

Pre-operative and post-operative Hb were categorised according to the World Health Organisation (WHO) and the International Consensus Statement (ICS) definitions of anaemia for descriptive purposes.[16,17] The WHO defines anaemia using a haemoglobin <120 g/L for females and <130 g/L haemoglobin for males; and the ICS defines anaemia using a <130 g/L for both females and males.

2.4 | Sample size

No formal sample size calculation was carried out. The study size was limited by the number of THA, TKA, and UKA procedures undertaken at the NOC between December 2011 and August 2018.

2.5 | Statistical analysis

2.5.1 | Time trends

The proportion of patients with post-operative Hb below the 70 and 80 g/L transfusion thresholds and the proportion of patients receiving blood transfusion were described for all procedures by year of surgery.

2.5.2 | Regression analysis

The association between pre-operative Hb and the outcomes was evaluated using unadjusted and adjusted logistic regression. The variables age, sex, and ASA classification were chosen a-priori to be included in the adjusted logistic regression. We assessed non-linearity and checked the functional form of pre-operative Hb using fractional polynomials of degree 1.[18] Unadjusted and adjusted odds ratios with 95% confidence intervals are presented.

2.5.3 | Decision curve analysis

Decision curve analysis (DCA) was used to assess and compare the utility of four intervention strategies to identify patients with post-operative anaemia and needing a blood transfusion, and therefore, which patients should be selected for G&S prior to surgery and similarly, which patients should have post-operative blood tests to measure their Hb.[19,20]

Intervention strategies were:

1. *Test all patients*: perform pre-operative G&S and post-operative Hb measurement for all patients
2. *Test no patients*: do not perform pre-operative G&S or post-operative Hb measurement for any patients
3. *Test patients with pre-operative anaemia*: perform pre-operative G&S and post-operative Hb measurement on patients with pre-operative Hb < 130 g/L
4. *Test patients according to risk of post-operative anaemia*: select patients for pre-operative G&S and post-operative Hb measurement based on risk of post-operative anaemia (pre-operative Hb threshold for intervention informed by unadjusted logistic regression models).

Risk thresholds—Clinician's preference

We considered a range of 0.1% (clinician is more concerned about undiagnosed post-operative anaemia) to 1% (clinician is more concerned about unnecessary post-operative blood tests) that a clinician may find acceptable for not having performed a G&S when a post-operative blood transfusion is indicated. As the risk threshold decreases there will be more true positives (necessary G&S and post-operative blood tests) at the expense of more false positives (unnecessary G&S and post-operative blood tests). When a risk threshold of 0.1% (1:1000) is used, we perform a G&S and post-operative blood test on at most 1000 patients per one true positive.

Alternatively, the odds of the risk threshold represent the maximum number of false positives that a clinician is willing to accept per true positive; known as the 'harm to benefit ratio'. For the 0.1% threshold, the odds (harm to benefit ratio) are 1:999, hence at most 999 false positives are accepted per one true positive. Therefore, risk thresholds of 0.25%, 0.5%, 0.75% and 1% imply a clinician is willing to unnecessarily perform G&S and a post-operative blood test on 399, 199, 133 and 99 patients to correctly identify one patient where a transfusion is required, respectively.

As the risk threshold decreases, the clinician is more averse to the risk of not having blood available for transfusion or not diagnosing severe post-operative anaemia. The range of risk thresholds refers to the clinician's preference to perform a G&S and post-operative blood test for a given patient, which can be discussed with the patient and thus can vary accordingly.

Net benefit

To assess the utility of the four intervention strategies for selecting patients for G&S and post-operative Hb measurement we calculated net benefit, which is the net proportion of true positives, much like net profit equals revenue minus all expenditures in business.

The benefit of an intervention strategy is that is correctly identifies which patients had a post-operative Hb < 70 g/L, <80 g/L or had a blood transfusion (and hence needed a G&S and postoperative blood test). For example, a net benefit of 0.002 is equivalent to having 2 additional patients correctly identified as needing blood transfusion per 1000 patients, without incorrectly selecting anyone who did not need a blood transfusion.

The net benefit is directly comparable to the 'test none' strategy (do not perform pre-operative G&S or post-operative Hb measurement for anyone) which by definition has a net benefit of 0 because if

you never intervene you do not have any true or false positives. The difference in net benefit between all strategies can also be calculated, for example, if the net benefit increases from 0.001 when using 'Test all: intervention for all patients' to 0.002 when using the 'Test patients according to risk of post-operative anaemia' strategy, the latter has 1 more net detected blood transfusion per 1000 patients for the same number of unnecessary G&S and post-operative blood test carried out.

The net benefit was calculated and presented in a decision curve at risk thresholds between 0.1% and 1%, as it was deemed unlikely a clinician would risk not having blood available when the risk of needing it exceeds 1%. The DCA was informed using an unadjusted logistic regression analysis of pre-operative Hb for the intervention strategy based on institution and procedure specific pre-operative Hb. It is presented for each outcome (Hb < 70 g/L, Hb < 80 g/L, allogeneic blood transfusion) and each risk threshold (0.1%, 0.25%, 0.5%, 0.75%, and 1%).

Net reduction

We also calculated the test trade-off, which is the net reduction in the number of unnecessary G&S and post-operative blood tests (false positives) using procedure and institution specific pre-operative Hb

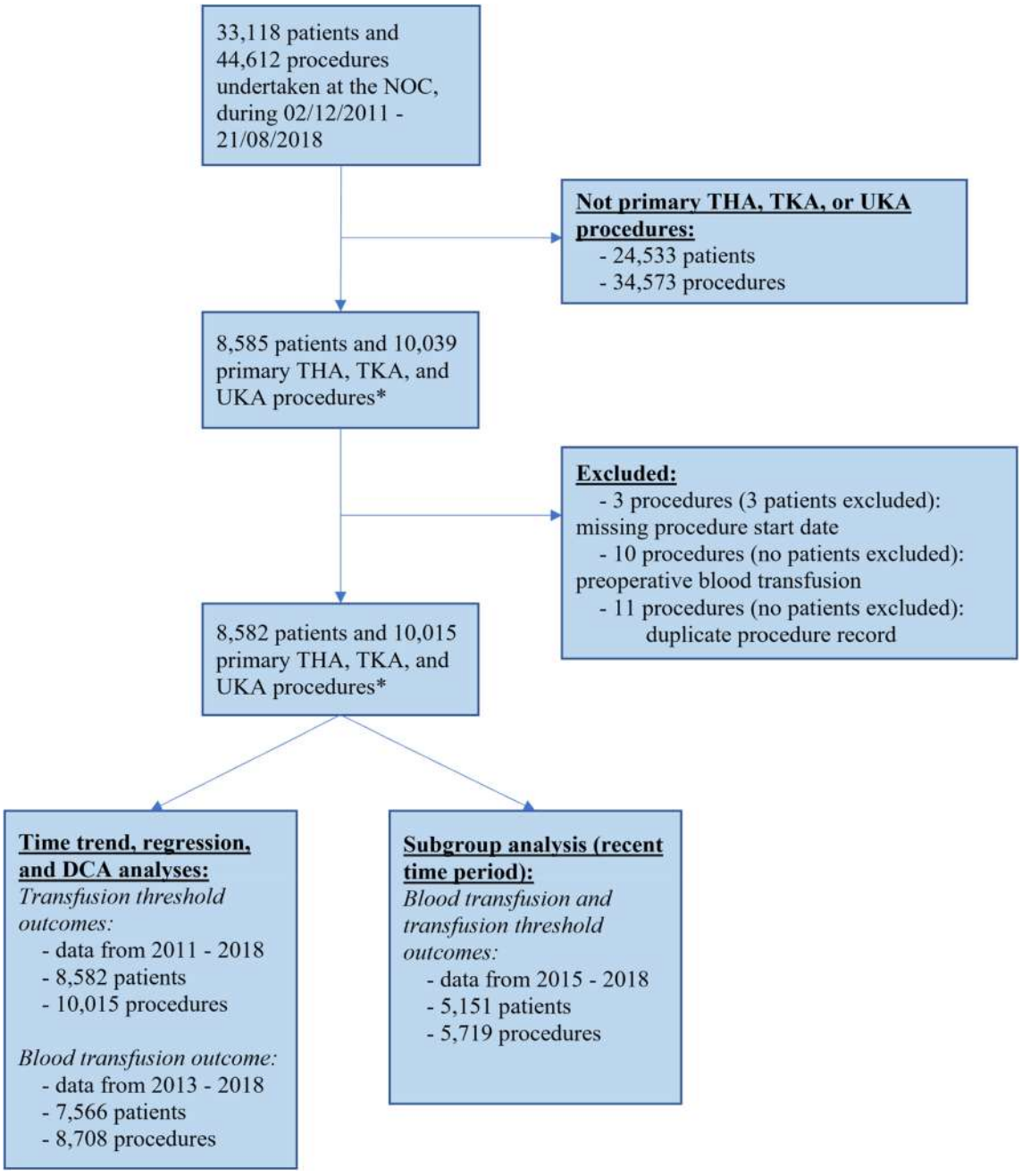


FIGURE 1 Flow of patients and procedures into the study. NOC, Nuffield Orthopaedic Centre, Oxford, UK; THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental (partial) knee arthroplasty; DCA, Decision curve analysis. *OPCS codes used to identify THA, TKA and UKA procedures: W371, W381, W391, W941, W421, W401, W581

cut-offs compared to the 'Test all: intervention for all patients' strategy. This number is equivalent to the number of avoided interventions, whilst keeping the number of true positives the same. For example, a net reduction of 0.04 means that, per 100 patients, four unnecessary G&S and post-operative blood test interventions are avoided for the same level of necessary interventions. We also calculated and plotted the net reduction, over the risk thresholds.

Further details about the net benefit and net reduction calculations are provided in Supporting Information S1: Appendix A. The utility of testing patients according to risk of post-operative anaemia was compared with all other intervention strategies for each outcome and procedure type.

2.5.4 | Additional analyses

We performed a sensitivity analysis using data from years 2015 to 2018 to account for any potential temporal changes in patient blood management and to reflect current practice. We also performed a sensitivity analysis for transfusions that took place prior to a formal postoperative Hb measurement which assumed that these patients had Hb < 70 g/L and Hb < 80 g/L before their transfusion. Missing data were described, and no imputation analysis was performed given the small amount of missing data. All analyses are complete case analyses.

3 | RESULTS

44 612 surgical procedures were undertaken at the NOC between January 2011 and August 2018. Of these, 10 015 procedures were THA, TKA and UKA procedures (Figure 1).

3.1 | Baseline and post-operative characteristics

Of the 10 015 procedures included in the analysis, 49.1% were THA ($n = 4917$), 23.6% were TKA ($n = 2363$), and 27.3% were UKA ($n = 2735$). Patients had a mean age of 68 years (SD 11.7), 59.1% were female. Mean pre-operative Hb was 138.8 g/L (SD 13.7) (Table 1), with 14.8% anaemic according to WHO criteria and 30.4% according to ICS criteria. 4.5% ($n = 388/8708$) patients received allogeneic blood, but only 3.9% ($n = 15/388$) of these patients had a post-operative Hb below 70 g/L and 27.8% ($n = 108/388$) below

TABLE 1 Baseline characteristics of the study sample and procedures undertaken between 2011 and 2018, by procedure.

	THA ($n = 4917$)		TKA ($n = 2363$)		UKA ($n = 2735$)		Total ($n = 10\,015$)	
Baseline characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	68.46	12.66	70.55	10.86	67.61	10.43	68.72	11.72
Pre-operative Hb (g/L)	135.08	13.99	134.58	13.6	138.8	12.84	135.96	13.71
Missing (*n*, %)	39 (0.79)		110 (4.66)		125 (4.57)		274 (2.74)	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Sex								
Female	3021	61.44	1469	62.17	1433	52.39	5923	59.14
Male	1896	38.56	894	37.83	1302	47.61	4092	40.86
ASA								
1	718	14.6	236	9.99	455	16.64	1409	14.07
2	2928	59.55	1585	67.08	1826	66.76	6339	63.3
3	943	19.18	427	18.07	314	11.48	1684	16.81
4	34	0.69	4	0.17	2	0.07	40	0.4
Missing	294	5.98	111	4.7	138	5.05	543	5.42
Pre-operative anaemia (WHO)								
No	4062	82.61	1854	78.46	2340	85.56	8256	82.44
Yes	816	16.6	399	16.89	270	9.87	1485	14.83
Missing	39	0.79	110	4.66	125	4.57	274	2.74
Pre-operative anaemia (ICS)								
No	3240	65.89	1469	62.17	1984	72.54	6693	66.83
Yes	1638	33.31	784	33.18	626	22.89	3048	30.43
Missing	39	0.79	110	4.66	125	4.57	274	2.74

Abbreviations: THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental (partial) knee arthroplasty; Hb, haemoglobin; ASA, American Society of Anesthesiologists; WHO, World Health Organisation; ICS, International Consensus Statement.

TABLE 2 Post-operative characteristics of the study sample for procedures performed between 2011 and 2018 for transfusion threshold analyses and between 2013 and 2018 for the blood transfusion analysis.

	THA ($n = 4917$)		TKA ($n = 2363$)		UKA ($n = 2735$)		Total ($n = 10\,015$)	
Post-operative characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Post-operative Hb (g/L)	107.53	15.3	109.78	14.1	121.13	13.19	110.89	15.51
Missing (n, %)	100 (2.03)		117 (4.95)		908 (33.2)		1125 (11.23)	
Change in Hb (g/L)	27.52	11.25	24.74	10.47	17.16	8.03	24.71	11.21
Missing (*n*, %)	124 (2.52)		157 (6.64)		947 (34.63)		1228 (12.26)	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Post-operative anaemia (WHO)								
No	598	12.16	329	13.92	727	26.58	1654	16.52
Yes	4219	85.8	1917	81.13	1100	40.22	7236	72.25
Missing	100	2.03	117	4.95	908	33.2	1125	11.23
Post-operative anaemia (ICS)								
No	348	7.08	161	6.81	448	16.38	957	9.56
Yes	4469	90.89	2085	88.24	1379	50.42	7933	79.21
Missing	100	2.03	117	4.95	908	33.2	1125	11.23
Post-operative blood transfusion[a]								
No	3946	92.89	1955	95.93	2419	99.88	8320	95.54
Yes	302	7.11	83	4.07	3	0.12	388	4.46
Post-operative blood transfusion given on same day of surgery[b]								
No	224	74.17	72	86.75	3	100	299	77.06
Yes	78	25.83	11	13.25	0	0	89	22.94
Post-operative Hb below transfusion trigger (70 g/L)								
No	4794	97.5	2244	94.96	1827	66.8	8865	88.52
Yes	23	0.47	2	0.08	-	-	25	0.25
Missing	100	2.03	117	4.95	908	33.2	1125	11.23
Post-operative Hb below transfusion trigger (80 g/L)								
No	4678	95.14	2216	93.78	1826	66.76	8720	87.07
Yes	139	2.83	30	1.27	1	0.04	170	1.70
Missing	100	2.03	117	4.95	908	33.2	1125	11.23

Note: Results are presented by procedure.

Abbreviations: THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental (partial) knee arthroplasty; Hb, haemoglobin; ASA, American Society of Anesthesiologists; WHO, World Health Organisation; ICS, International Consensus Statement.

[a]Blood transfusion based on data from 2013 to 2018, $n = 8708$.

[b]Patients who had a blood transfusion based on data from 2013 to 2018.

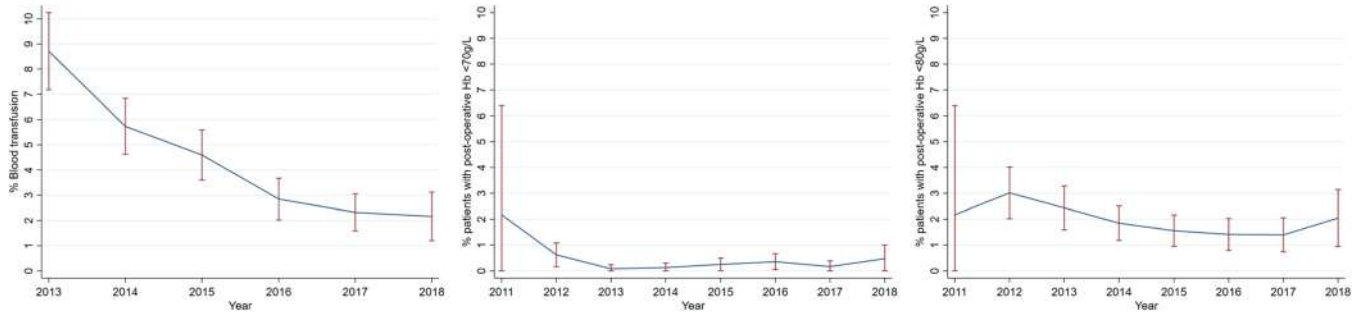


FIGURE 2 Time trends of observed blood transfusion (2013–2018), and post-operative Hb less than 70 and 80 g/L transfusion thresholds (2011–2018) for all procedures.

80 g/L prior to transfusion. 22.9% ($n = 89/388$) of blood transfusions were performed on the day of surgery, of which 12 were performed intraoperatively (13.5%, $n = 12/89$) (Table 2).

Thirty-one blood transfusions were administered on the day of surgery but before a formal postoperative Hb was available and a further 17 blood transfusions were performed after the day of surgery but before a formal postoperative Hb was available. Of these 48 blood transfusions, two patients triggered the post-surgery 70 g/L transfusion threshold despite having received a blood transfusion and nine triggered the post-surgery 80 g/L transfusion threshold.

No patient developed a post-operative Hb below 70 g/L, and one patient (0.04%) developed a post-operative Hb below 80 g/L following UKA. Two patients (0.08%) developed a post-operative Hb below 70 g/L following TKA. Regression and decision curve analysis was not performed for these procedure outcomes due to the small number of cases.

3.2 | What are the temporal trends of post-operative Hb below the 70 and 80 g/L transfusion thresholds, and allogeneic blood transfusion following elective primary hip and knee arthroplasty?

The proportion of patients receiving blood transfusions fell during the period of study, although the proportion of patients developing post-operative anaemia remained stable (Figure 2).

3.3 | What is the relationship between pre-operative Hb, and post-operative Hb and blood transfusion?

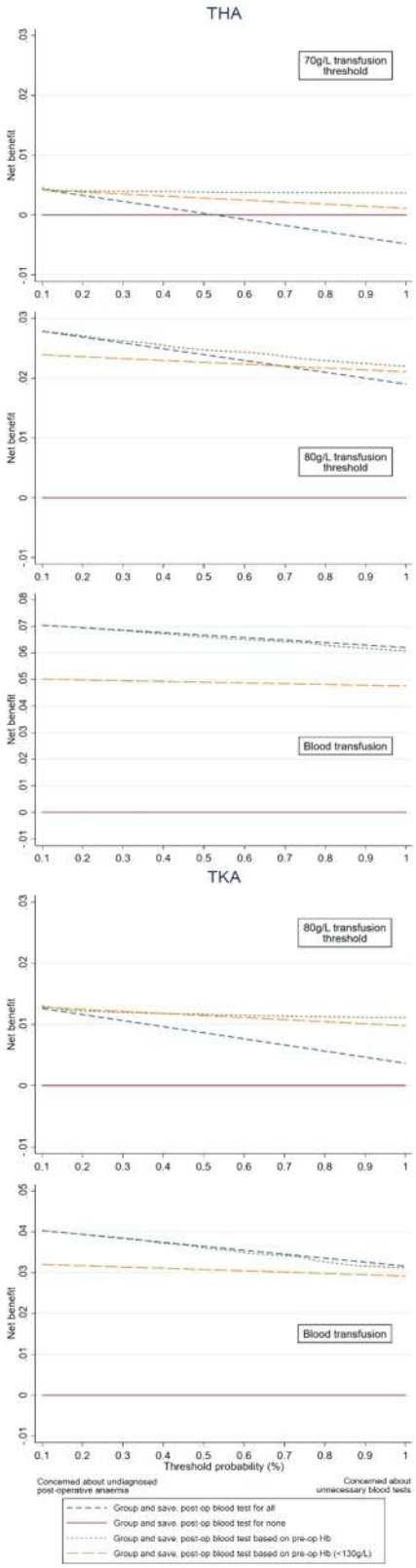
Odds of patients developing a post-operative Hb below 70 or 80 g/L, and patients receiving an allogeneic blood transfusion reduced per unit increase in pre-operative Hb for THA and TKA procedures

TABLE 3 Risk associated pre-operative Hb thresholds and decision curve analysis results for THA and TKA.

Procedure	Outcome	Risk thresholds (%)	Harm to benefit ratio	Associated Hb cut-off (g/L)	No. true positives	No. false positives	No. true negatives	No. false negatives	NB per 1000 patients: Hb (g/L) vs. none	NR per 100 patients: Hb (g/L) vs. all
THA	Post-operative Hb below transfusion trigger (70 g/L)	1	1:99	<116	16	434	4336	7	2.4	76
		0.75	1:133	<118	18	533	4237	5	2.9	74.6
		0.5	1:199	<122	19	817	3953	4	3.2	67.6
		0.25	1:399	<127	20	1334	3436	3	3.5	46.7
		0.1	1:999	<139	23	3003	1767	0	3.9	10.5
	Post-operative Hb below transfusion trigger (80 g/L)	1	1:99	<136	130	2478	2177	8	22	30.1
		0.75	1:133	<138	132	2755	1900	6	23.2	23.1
		0.5	1:199	<143	135	3393	1262	3	24.7	16.5
		0.25	1:399	<149	137	3950	705	1	26.5	6.4
		0.1	1:999	<164	138	4576	79	0	27.9	5
	Post-operative blood transfusion[a]	1	1:99	<153	292	3552	368	9	60.7	−12.4
		0.75	1:133	<156	297	3677	243	4	63.8	−6.8
		0.5	1:199	<162	298	3823	97	3	66.1	−11.6
		0.25	1:399	<169	300	3886	34	1	68.8	−8.6
		0.1	1:999	<185	301	3917	3	0	70.4	0.2
TKA	Post-operative Hb below transfusion trigger (80 g/L)	1	1:99	<123	29	443	1733	1	11.1	74.1
		0.75	1:133	<125	29	538	1638	1	11.3	68.3
		0.5	1:199	<128	29	681	1495	1	11.6	58.7
		0.25	1:399	<132	29	922	1254	1	12.1	38.8
		0.1	1:999	<143	30	1588	588	0	13	39.1
	Post-operative blood transfusion[a]	1	1:99	<144	77	1450	479	6	31.2	−3.5
		0.75	1:133	<147	80	1581	348	3	33.8	−2.4
		0.5	1:199	<152	82	1754	175	1	35.9	−9.7
		0.25	1:399	<159	83	1868	61	0	38.9	3
		0.1	1:999	<177	83	1929	0	0	40.3	0.3

Abbreviations: THA, total hip arthroplasty; TKA, total knee arthroplasty; Hb, haemoglobin; NB, net benefit; NR, net reduction.
[a]Blood transfusion based on data from 2013 to 2018.

(Figure S1 and Table S2). After adjustment, the odds of receiving allogeneic blood were 7% (OR 0.93, 95% CI 0.92–0.94) lower after THA and 8% lower (OR 0.92, 95% CI 0.90–0.94) lower after TKA per unit (g/L) increase in pre-operative Hb.



3.4 | What are the pre-operative Hb thresholds for different risks of severe post-operative anaemia?

Pre-operative Hb thresholds for different risks of post-operative anaemia differed between THA and TKA (Table 3). An example scenario based on these results is a clinician who does not wish to unnecessarily collect blood for pre-operative G&S in more than 99 patients to identify 1 patient with a post-operative Hb less than the 80 g/L transfusion threshold (1% risk threshold). They would select a pre-operative Hb < 136 g/L to decide whether to perform a pre-operative G&S for THA. In our cohort, a threshold of <136 g/L would have meant 130 patients who subsequently required a blood transfusion had a pre-operative G&S performed preoperatively, and eight patients who subsequently required a blood transfusion did not have a G&S performed preoperatively and would need one prior to transfusion. G&S from 2478 patients would have been collected but not required, and no G&S would have been collected from 2177 patients who did not require a blood transfusion.

3.5 | What is the utility of different strategies using pre-operative Hb to select patients for pre-operative G&S and post-operative Hb measurement?

Decision curve analysis showed that for THA and TKA, using the 'Test patients according to risk of post-operative anaemia' strategy resulted in improved net benefit across all risk thresholds for the 70 and 80 g/L transfusion threshold outcomes, when

FIGURE 3 Decision curves for the four intervention strategies for THA and TKA, by outcome. The four intervention strategies are performing a G&S and post-operative blood test on all patients, on no patients, only on patients with pre-operative anaemia, or on patients at risk of post-operative anaemia. Data are presented for 2011–2018 for transfusion threshold analyses, and 2013–2018 for the blood transfusion analysis. Analysis was not performed for a 70 g/L transfusion threshold for TKR due to the paucity of event rates. The y-axis is the benefit (net benefit), and the x-axis is the preference (threshold probability). The benefit of an intervention strategy is that is correctly identifies which patients had a post-operative Hb < 70 g/L, <80 g/L or had a blood transfusion (and hence actually needed a G&S and postoperative blood test). The preference refers to how clinicians value different outcomes and what risk they are willing to take to not have blood when it is needed for a given patient, which varies. For example, if Clinician A was concerned about undiagnosed post-operative anaemia in their THA (Hb < 70 g/L) patient, they may only be willing to accept a 0.1% risk to not have blood available when it is needed, compared to Clinician B who is more concerned about unnecessary blood test and would be willing to accept a slightly higher 1% risk of not having blood when it is needed. In this case for Clinician A, there is little difference between the intervention strategies of performing a G&S and post-operative blood test on all patients, only on patients with pre-operative anaemia, or on patients at risk of post-operative anaemia. However, Clinician B would be better to use the intervention strategies of performing a G&S and post-operative blood test only on patients at risk of post-operative anaemia based on pre-operative Hb measurement.

TABLE 4 Risk associated pre-operative Hb thresholds and decision curve analysis results for THA and TKA using data limited to 2015–2018.

Procedure	Outcome	Risk thresholds (%)	Harm to benefit ratio	Associated Hb cut-off (g/L)	No. true positives	No. false positives	No. true negatives	No. false negatives	NB per 1000 patients: Hb (g/L) vs. none	NR per 100 patients: Hb (g/L) vs. all
THA	Post-operative Hb below transfusion trigger (70 g/L)	1	1:99	<116	12	240	2408	2	3.7	84
		0.75	1:133	<117	12	268	2380	2	3.8	79.5
		0.5	1:199	<120	12	359	2289	2	3.8	71.0
		0.25	1:399	<124	12	542	2106	2	4	49.1
		0.1	1:999	<134	13	1261	1387	1	4.5	26.2
	Post-operative Hb below transfusion trigger (80 g/L)	1	1:99	<131	61	970	1627	4	19.1	45
		0.75	1:133	<133	61	1130	1467	4	19.7	35.2
		0.5	1:199	<137	62	1459	1138	3	20.7	22.9
		0.25	1:399	<141	65	1744	853	0	22.8	32.0
		0.1	1:999	<154	65	2385	212	0	23.6	16.6
	Post-operative blood transfusion	1	1:99	<146	129	2024	530	11	40.3	−20.8
		0.75	1:133	<149	133	2162	392	7	43.3	−19.8
		0.5	1:199	<154	136	2342	212	4	45.8	−27.8
		0.25	1:399	<161	138	2484	70	2	48.9	−27.0
		0.1	1:999	<179	140	2549	5	0	51.0	0.5
TKA	Post-operative Hb below transfusion trigger (80 g/L)	1	1:99	<120	8	177	1099	1	5.0	79.1
		0.75	1:133	<121	8	200	1076	1	5.1	73.4
		0.5	1:199	<125	8	304	972	1	5.1	62.0
		0.25	1:399	<128	8	394	882	1	5.5	37.6
		0.1	1:999	<139	9	794	482	0	5.8	−25.5
	Post-operative blood transfusion	1	1:99	<139	32	786	489	3	18.7	17.5
		0.75	1:133	<142	34	891	384	1	20.8	19.2
		0.5	1:199	<147	34	1033	242	1	22.1	5.4
		0.25	1:399	<154	35	1180	95	0	24.5	7.3
		0.1	1:999	<170	0	3	0	0	25.8	1.3

Abbreviations: THA, total hip arthroplasty; TKA, total knee arthroplasty; Hb, haemoglobin; NB, net benefit; NR, net reduction.

compared with the 'Test none' and 'Test patients with pre-operative anaemia' strategies (Figure 3). A net reduction in unnecessary blood tests was found for these outcomes when using the 'Test patients according to risk of post-operative anaemia' strategy, compared to the 'Test all' strategy (Figure S2 and Table S3).

Continuing the example scenario above, where a clinician selects a pre-operative Hb threshold of 136 g/L for THA (corresponding to a 1% risk of post-operative Hb < 80 g/L): Compared with a 'test none' approach, 22 additional patients per 1000 would be correctly selected for G&S without any unnecessary blood tests. Compared with a 'test all' approach, 30 additional patients per 100 would correctly have no G&S collected without decreasing the number of patients correctly selected for G&S.

Additional data of net benefit and net reduction comparisons between intervention strategies are provided in Figure S2 and Table S3. Only two patients undergoing TKR developed a post-operative Hb below 70 g/L, and one patient undergoing UKR developed a post-operative Hb below 80 g/L, hence decision curve analysis was not performed for these outcomes.

3.6 | Sensitivity analysis

Thresholds for intervention were lower for TKA and THA using 2015–2018 compared with 2011–2018 data (Tables 3 and 4). Hb thresholds based on the 'Test patients according to risk of post-operative anaemia' strategy demonstrated increased net benefit compared to the other strategies for the 70 and 80 g/L transfusion threshold outcomes (Figures S3 and S4, Table S4).

Thresholds for intervention and the associated net benefit for using Hb thresholds based on the 'Test patients according to risk of post-operative anaemia' strategy increased when THR patients who received a blood transfusion before their postoperative Hb was

measured were assumed to have a Hb < 70 g/L. A smaller increase was found in the thresholds for intervention and associated net benefit when both THR and TKR patients, who received a blood transfusion before their postoperative Hb was measured were assumed to have a Hb < 80 g/L. Full results are provided in Table S5.

4 | DISCUSSION

4.1 | Summary of findings

Only a small proportion of patients have a post-operative Hb less than 70 or 80 g/L following primary hip and knee arthroplasty. The odds of a post-operative Hb less than 70 or 80 g/L or receiving a blood transfusion fall as pre-operative Hb increases for both THA and TKA. We found the optimal strategy for selecting patients for pre-operative G&S and post-operative Hb measurement was to base the decision on a calculated risk of severe post-operative anaemia. This strategy allows clinicians to select a harm to benefit ratio that is most appropriate for their clinical practice, and allows more accurate patient selection than when testing all or no patients, or patients with pre-operative anaemia (Hb < 130 g/L). Although differences in net benefit are small between strategies, there is potential for considerable reduction in unnecessary G&S and post-operative blood tests using a risk-based approach. Only two patients undergoing TKR developed a post-operative Hb below 70 g/L (0.09%) and one patient undergoing UKR developed a post-operative Hb below 80 g/L (0.05%). In the 2015–2018 data, there was a 1% risk of post-operative Hb < 80 g/L if pre-operative Hb was <120 g/L for TKA and <131 g/L for THA.

There has been a reduction in the proportion of patients receiving a blood transfusion with time, likely due to improved blood management and restrictive transfusion strategies. However, the proportion of patients receiving a post-operative blood transfusion remains higher than recommended by national guidelines, with most transfusions administered with a Hb >70 g/L. This observation highlights the need to promote adherence to recommended transfusion thresholds and avoid unnecessary transfusions and related complications.

4.2 | Literature

Routinely performing blood tests for pre-operative G&S and post-operative Hb measurement is potentially unnecessary given the low prevalence of severe post-operative anaemia and blood transfusion.[21] When unnecessary, these blood tests increase cost and impair patient experience through venepuncture. They may also increase pre-operative hospital attendance delay surgery (awaiting G&S), or discharge from hospital (awaiting post-operative Hb). Previous studies with smaller sample sizes proposed thresholds for performing these investigations at 130 g/L or between 121 and 124 g/L depending on age.[12,22] The ROC analysis used in these studies have limited clinical interpretability and assumes true and false positives are equally important, which may not be accurate. When selecting patients for G&S, a true positive potentially has a higher misclassification cost and carry greater importance than a false positive.[23]

The ability to stratify risk using decision curve analysis, enables the selection of a threshold for G&S and post-operative Hb measurement that is deemed appropriate for a specific clinical setting. These thresholds can be used for electronic clinical decision support tools increasingly adopted for preoperative assessment. In addition to the patient population and clinical practice, institutional factors may influence selection of appropriate harm to benefit ratios, such as the availability of electronic blood issue and proximity to blood banks. Clinicians must also assess the risk discharging patients with severe undiagnosed anaemia, and a different harm to benefit ratio Hb threshold may be used to select patients for G&S than for post-operative Hb measurement. Rates of blood transfusion are falling and suggested thresholds for performing pre-operative G&S and post-operative Hb measurement require regular review.[21]

In this study, less than a quarter of transfusions were administered on the day of surgery, hence in most cases there is time to organise a G&S if not already performed. This can be expedited if there is a strong clinical suspicion that a transfusion will be unexpectedly required, such as higher than anticipated on table blood loss or post-operative cardiovascular compromise. If cross-matched blood products are not available in an emergency, the use of blood group O blood will be necessary. A circumstance when a group and save is always indicated is when there is a past medical history of red blood cell antibodies.

4.3 | Strengths and limitations

Our study uses contemporary and clinically relevant statistical methodology to evaluate the utility of different strategies to select patients for pre-operative G&S and post-operative Hb measurement. We build on existing ROC curve analyses that assume true and false positives are equally important[24,25] and use decision curve analysis which better addresses the utility of a prognostic test. Decision curve analysis weights true and false positives separately, and does not require categorisation of pre-operative Hb to derive clinically informed risk thresholds, which minimises the loss of statistical information.[26] We present the results of decision curve analysis for different levels of risk that clinicians may find acceptable.

Our study is limited as we used data from a single centre and only collected data up to 2018 as the study observations have since been used to reduce the number of blood tests performed. No formal sample size calculation was performed. We included all procedures available from when this centre became fully 'paperless' and the sample size was informed by a relevant time interval. We believe any optimism in our estimates are negligible as we use a single continuous predictor for our predictions. Using recent guidance, we estimated that a minimum of 995 patients with five events (events per predictors = 4.68) would be needed to model risk in the THA analyses, based on achieving a conservative 15% of the maximum r-squared and a 0.47% event rate (lowest event rate was found for the 70 g/L

outcome).[27] A minimum of 457 patients with six events (events per predictors = 5.80) is required for the TKA analyses, based on achieving a conservative 15% of the maximum *r*-squared using one predictor and a 1.27% event rate (lowest event rate was found for the 80 g/L outcome). The heuristic shrinkage for each analysis ranged from 0.97 to 0.99, indicating likely very small amounts of optimism in our estimates. Missing data was described in our study but was not imputed. Given the very small amount of missing data present, a complete case analysis was justified.[28] We used an unadjusted logistic regression model to inform the pre-operative Hb thresholds for different risk of severe post-operative anaemia strategy, instead of developing a prediction model for each outcome. However, the purpose of this study was to evaluate the individual effect of pre-operative Hb and identify pre-operative Hb cut-off values that can easily be used in clinical practice when preparing to THA and TKA.

Our analysis includes 48 patients and procedures where a blood transfusion was performed prior to the availability of a formal postoperative Hb. Possible explanations are estimated blood loss and physiological parameters as an indication for blood loss or point of care Hb measurement. This observation may bias our results as the number of patients with a Hb lower than 70 or 80 g/L after surgery may be higher than what is reported. A sensitivity analysis assuming a postoperative Hb < 70 g/L or Hb < 80 g/L in this cohort showed an increase in the transfusion thresholds. We also accounted for this limitation by including postoperative transfusion as a secondary outcome measure, independent of postoperative Hb.

4.4 | Future research

This study was performed on data from a single institution, but the methodology can be applied to different surgical procedures and different institutions. Clinicians overseeing the care of patients receiving primary hip and knee arthroplasty may wish to select an acceptable harm to benefit ratio Hb threshold from our study and then retrospectively validate the performance using their local data. There may be significant financial savings associated with reducing the number of unnecessary G&S and post-operative blood tests, and a formal health economic review may be of value in the future.

4.5 | Conclusions

In summary, our study outlines a means of selecting patients for G&S and post-operative Hb measurement based on the risk of developing severe post-operative anaemia. Pre-operative G&S and post-operative Hb measurement may not be indicated for UKA or TKA when adopting restrictive transfusion thresholds provided clinicians accept a 0.1% risk that patients will develop severe undiagnosed post-operative anaemia (Hb < 70 g/L). The decision to perform these blood tests for THA patients should be based on local institutional data and selection of an acceptable harm to benefit ratio. Decision curve analysis can be adopted for all surgical procedures to accurately select patients who require pre-operative G&S and post-operative Hb measurement, facilitating day-case surgery and reduced cost.

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SUPPORTING INFORMATION

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

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TRANSFUSION MEDICINE WILEY

LETTER TO THE EDITOR

Blood transfusion needs in COVID-19 patients: An observational prospective unicentric study

Dear Editor,

In 2019 a severe acute respiratory syndrome (SARS-CoV-2), caused by a novel coronavirus (2019-nCoV), was described in Wuhan City, Hubei Province, China, which then rapidly spread and evolved into a pandemic. As of 5 July 2021, 183,298,109 confirmed cases of coronavirus disease (COVID-19) and 3,971,687 deaths all over the world have been reported.[1] Italy is one of the most involved countries, reaching 4,259,909 confirmed cases (as of 2 July 2021) and 127,566 deaths.[1]

Clinical presentations of SARS-CoV-2 are various. Most infected patients are asymptomatic, others develop mild symptoms like dry cough, sore throat, and fever, with a spontaneous resolution. Some cases evolve into pulmonary oedema, severe pneumonia, acute respiratory distress syndrome (ARDS), and septic shock resulting in organ failure. Most-used treatments are chloroquine and hydroxychloroquine, claimed to block viral entry into cells and have immunomodulatory effects, lopinavir/ritonavir and other antivirals, corticosteroids, anti-cytokines or immunomodulatory agents (tocilizumab, a monoclonal antibody IL-6 receptor antagonist),[2] low-molecular-weight heparin (LMWH) to limit the risk of an associated coagulopathy and disseminated intravascular coagulation (DIC).

The WHO has published guidelines to manage the blood supply in response to the COVID-19 pandemic. The guidance underlines the role of blood services in assessing, planning, and responding to the outbreak. In fact, lockdown and social distancing may lead to limited blood resources. Moreover, while blood transfusion requirement may decrease as the health care system is focused on treating COVID-19 patients, thus deferring other clinical interventions, transfusions will still be necessary for emergency situations and to support COVID-19 patients with severe sepsis.[3]

Critical patients may develop anaemia as a consequence of multifactorial and complex pathogenesis. Phlebotomies and other surgical procedures, coagulopathies, pathogen-associated haemolysis, hypoadrenalism, and nutritional deficiencies, as well as the concomitant administration of different drugs, may cause Haemoglobin (Hb) to drop. Decreased erythropoietin production and/or activity could be the consequence of inflammatory cytokines such as IL-1 and TNF-α.[4] The risk in COVID-19 patients is even higher due to the well-known pro-haemolytic effect of hydroxychloroquine, especially in G6PDH-deficient individuals, even if there are few findings supporting the necessity for G6PDH deficiency screening before starting this drug.

Here we report the results of a retrospective evaluation of blood transfusion supply in patients (pts) affected by COVID-19, admitted to Policlinico Umberto I, Sapienza University of Rome, during the epidemic outbreak, taking into account treatments, comorbidities, clinical and laboratory parameters, especially those related to RBC transfusion.

From the 1 March 2020 to 27 April 2020, 71 patients with COVID-19 infection were admitted to Policlinico Umberto I, in the departments of Infectious Disease or in the intensive care unit (ICU).

Forty-seven of them, required transfusion support; 30 patients were males, 17 were females; median age was 72 (38–95). Sixteen out of 47 (34%) had blood group type A. Forty-five patients required RBC, with a median of 3 transfusions each (1–20); nine patients received plasma support, with a median of 4 transfusions (3–24). Five out of the 45 patients who required RBC, required plasma supply as well; two patients received only plasma. Two patients received platelets, RBC and plasma (see Figure 1D). Thirty-two patients out of 47 (68%) showed comorbidities such as hypertension and cardiovascular diseases (18 patients), diabetes mellitus (nine patients), oncological/haematological diseases (six patients), autoimmune diseases (three patients).

Twenty-two out of the 47 patients who required transfusion, were admitted to ICU due to severe clinical disease. All of them were treated with the same therapy, consisting of anti-viral drugs, LMWH, and hydroxychloroquine (400 mg/day); one patient did not receive hydroxychloroquine due to G6PDH deficiency.

Considering the pro-haemolytic effect of hydroxychloroquine, we monitored haemolytic markers in patients treated with RBC transfusions, observing the following median values: Hb 12.3 g/dl (7.4–16.6) at admission; Hb 7.5 g/dl (6.7–11) and lactate dehydrogenase (LDH) 383 UI/L (271–781, n.v. 125–225) at the time of first transfusion. Both direct and indirect antiglobulin tests were negative in all patients, thus excluding immune-mediated haemolytic anaemia. The median time between COVID-19 diagnosis and transfusion requirement was 13 days (0–33); all patients showed increasing LDH values starting at a median time of 5 days (1–11) after COVID-19 diagnosis and first hydroxychloroquine administration, with a median peak value of 706 IU/L (301–2805).

In more detail, in Figure 1 we report the trend of values of Hb and LDH of the 22 patients (Figure 1A), and day-by-day LDH and Hb profiles and transfusion requirements of two representative patients.

The first patient (Figure 1B) was a 42-year-old female affected by hypertension and autoimmune hepatitis treated with steroids. In 6 days, Hb and LDH values reached 9.8 g/dl and 1000 IU/L, respectively (at admission, Hb 13 g/dl, and LDH 282 UI/L). Fourteen days after, LDH reached 2285 UI/L value. In the same time frame, with the increasing levels

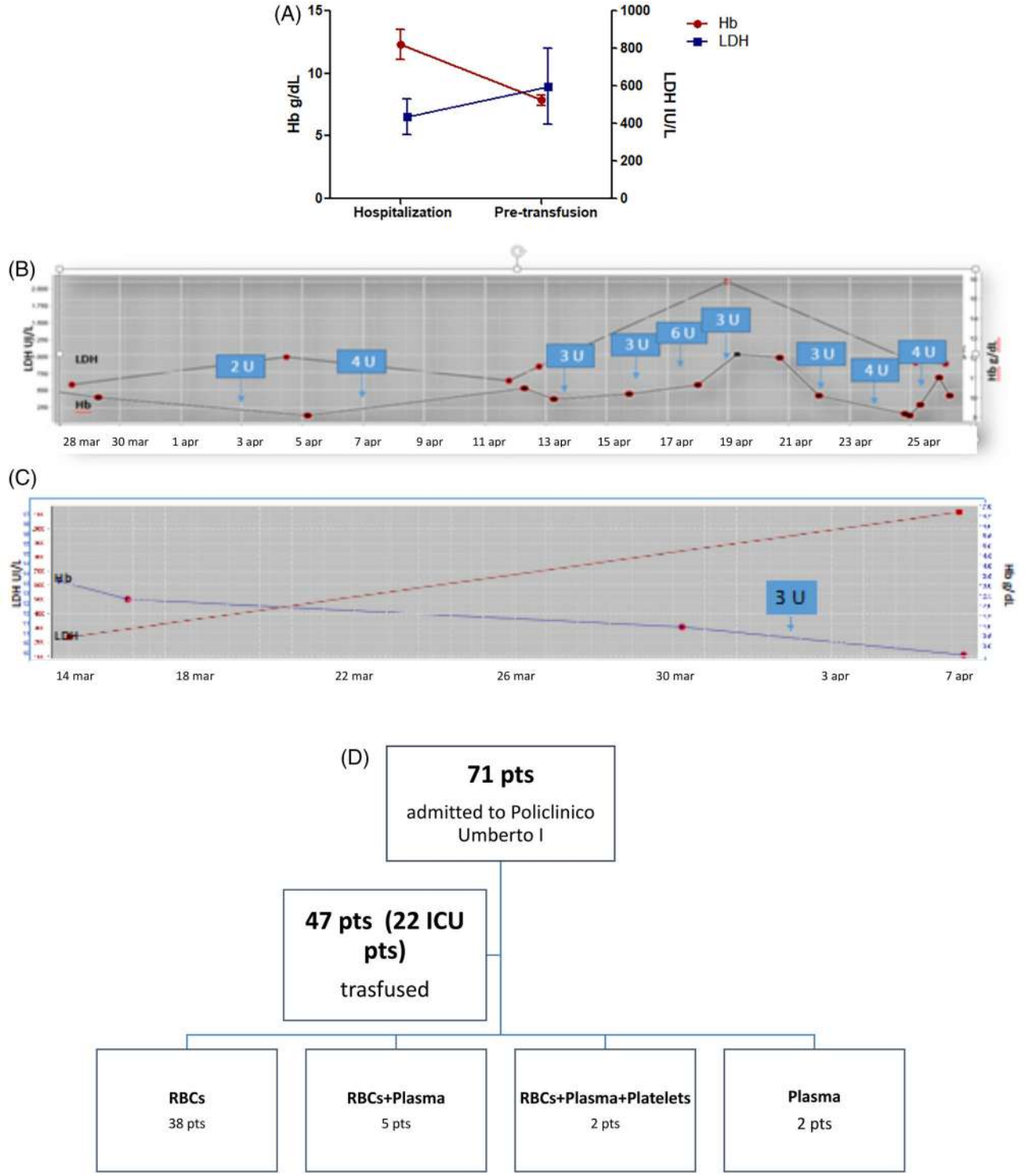

FIGURE 1 The trend of values of haemoglobin (Hb) and LDH of 22 patients (A); LDH, Hb profiles and transfusion requirements of two patients (B,C). Flow-chart of patients enrolled in the study and blood transfusion needs (D)

of LDH, she received 20 RBC units. The second patient (Figure 1C), a 74-year-old male, with ulcerative colitis, hypertension, benign prostatic hyperplasia, and endovascular prosthesis for aortic abdominal aneurysm showed Hb 13.6 g/dl and LDH 255 UI/L at admission. In 18 days, he showed a progressive increase of LDH with a peak of 1100 UI/L.

Overall, at our Institution, in the period analysed, 33.8% of patients admitted to ICU required transfusion support; this data is comparable with other published experiences.[5] We observed a lower request for platelets and plasma with respect to others' reported experiences, maybe reflecting different therapeutic and transfusion

management among patients at different institutions as well as various clinical manifestations and comorbidities.

We compared this 2020 data with those observed in the corresponding period of 2019, noting a lower number of blood products transfused in ICU setting at our Institution. In 2019, there were a total number of transfusion requests for 17 patients, in 16 cases for RBCs, in five cases for plasma and 11 for platelets.

We could suppose that our observations, performed on a larger number of patients with respect to published data, may reflect the role of hydroxychloroquine in the onset of an acute drop in Hb levels, caused by haemolysis.

This effect could be induced by a G6PDH deficiency not yet diagnosed, worsening the critically ill patients' anaemia condition determined by the above-mentioned factors, including the concomitant administration of drugs as well. Notably, the estimated number of G6PDH-deficient individuals is close to 400 million people worldwide, with a global prevalence of 4.9%,[6] highest prevalence in Africa, Asia, Middle East and Mediterranean countries.[6,7] Italian prevalence of G6PDH-deficiency is reported to be 0%–3%, with a higher prevalence among some regions (e.g. Sardinia). A recent Italian prospective study conducted on more than 3000 healthy blood donors identified 1.1% of G6PDH-deficient individuals, characterised by haematological parameters of G6PDH within the normal range.[7]

In other kinds of interstitial pneumonia, haemolysis could be the consequence of immune-mediated mechanisms (e.g. *Mycoplasma pneumoniae* and cold agglutinins), not observed in this experience.

We point out the importance of prospective studies on a larger number of patients to better evaluate the impact of SARS-CoV-2 and its treatments on transfusion requirement, taking into account the COVID-19 local epidemiology and the outbreak spread in different regions and countries.

AUTHOR CONTRIBUTIONS

Study design: ULR, GG, SC. Clinical management of patients: FM, MP, FP. Data Collection: GG, MF. Data analysis and interpretation: ULR, GG, SC. Drafting of manuscript: ULR. Critical revision of manuscript: AA, SC. All Authors interpreted the data analysis, read and approved the final draft.

CONFLICT OF INTEREST

The authors have no competing interests.

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