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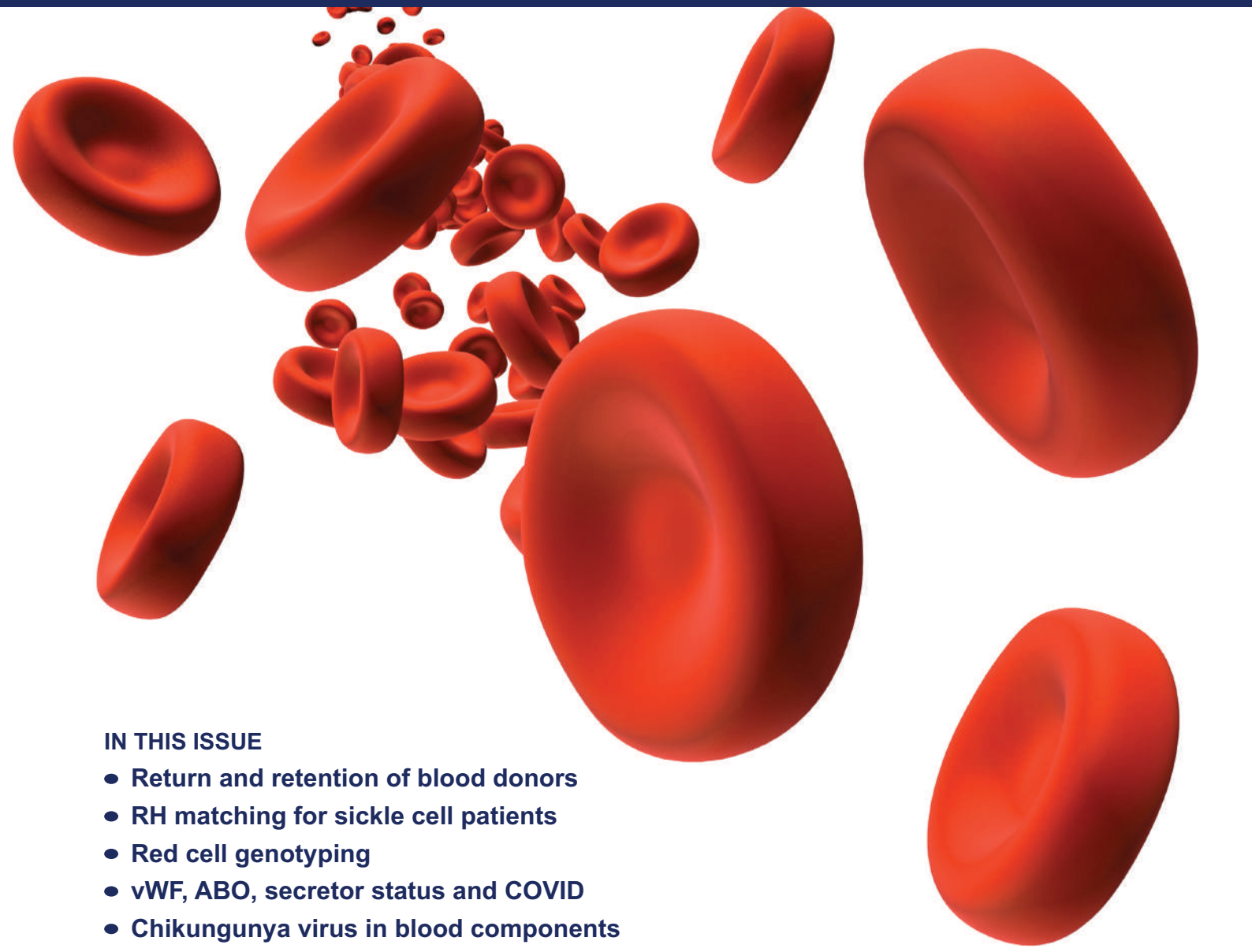

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Transfusion Medicine

An international journal published for the British Blood Transfusion Society

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COMMENTARY

TRANSFUSION MEDICINE WILEY

Red cell genotyping: real world use

Kaoru Takasaki[1] | **Stella T. Chou**[12]

In this issue of Transfusion Medicine, Hui et al describe the experiences at two London trusts (ICHNT, LNWH) of obtaining an extended red cell antigen profile by genotype for patients with sickle cell disease (SCD), with a focus on RH variants and associated alloimmunization.[1] Overall, approximately half of the patients had extended red cell genotypes performed and 20% had RH variants. A small proportion of these patients (10%) had antibodies associated with the RH variant identified. Their work highlights several questions for hematologists and transfusion medicine specialists who care for patients with SCD. First, should all patients with SCD have a red cell antigen genotype, and how comprehensive does it need to be? Second, how should the red cell antigen genotype be used to better inform transfusion support and donor choice for alloimmunized and non-alloimmunized patients with RH variants?

In the United Kingdom (UK), a centralized transfusion service and universal health care allow for more uniform testing and a single laboratory database. Despite this, Hui et al found that only 71% of patients at ICHNT (372 of 482) and 61% of patients at LNWH (211 of 346) had either genotypic or serologic red cell antigen profiles in accordance with British Society of Haematology (BSH) guidelines.[2] Red cell antigen genotyping was the predominant method used: 64% (311 of 481) and 52% (181 of 346) of patients in the two trusts, respectively. Most but not all patients had additional genotyping assays to identify RH variants. Pediatric patients were less likely than adults to have had a red cell antigen genotype or serologic phenotype (85% vs. 65% in ICHNT and 64% vs. 55% in LNWH), even though children have the potential to receive more blood transfusions over their lifetimes.

Both the BSH[2] and the American Society of Hematology (ASH)[3] guidelines for transfusion of individuals with SCD recommend that all patients have red cell antigen typing performed at initial presentation. Having this information at baseline is needed to provide Rh (C, E or C, c, E, e) and K-matched transfusions. ASH guidelines suggest than an extended red cell antigen profile be obtained for all patients with SCD at the earliest opportunity, and that genotyping is preferred over serologic phenotyping as it provides additional antigen information and increased accuracy for C and Fy^b antigens. The extended antigen profile also guides antibody evaluation and donor selection when patients are at high risk of a hemolytic transfusion reaction (HTR). Genotyping platforms may test over 30 red cell antigens, including many for which no serologic testing is available (ie. Doa, Dob, U),[4] but immunization against which can be associated with an HTR. Knowledge of the antigens that a transfused individual lacks can facilitate antibody identification and guide donor red cell selection for subsequent transfusion

In the United States (US), patient insurance coverage varies considerably, provider practices are non-uniform, and hospitals typically have contracts with one or more donor blood centers and immunogenomic reference laboratories. One practical barrier in the US is the frequent need for insurance pre-authorization for red cell antigen genotyping. While the Human Erythrocyte Antigen (HEA) assay is a Food and Drug Association (FDA) approved test in the US for an extended red cell antigen profile, the variants assayed by higher resolution RH genotyping is highly dependent on reference laboratory. RHD and RHCE arrays (Immucor) test for the majority of common variants found in individuals of African background, but laboratory-developed tests supplement the RH arrays to identify several frequent single nucleotide polymorphisms (SNPs) that result in partial antigen expression and thus have clinical significance.[5] This includes the RHD c.1136T change that identifies DAU variants in RHD and the RHCE c.254G change associated with a partial e antigen, which have an allele frequency of 20% and 5%, respectively, among individuals of African descent.[6]

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Red cell genotyping: real world use

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Clinical guidelines for transfusion support for SCD from both the BSH2 and ASH[3] recommend prophylactic Rh (C, E or C/c, E/e) and K matching, which reduces but does not eliminate Rh alloimmunization. The persistence of Rh alloantibody formation despite serologic Rh matching results from a high prevalence of RH variants in both patients and donors that result in partial antigen expression (missing an epitope(s) of RhD or RhCE proteins), loss of high-prevalence Rh antigens (hrB, hrS), or expression of Rh antigens with novel epitopes (ie. V/VS, Goa).[5-8] A high index of suspicion should be maintained for the presence of RH variants in patients who have antibodies to Rh antigens despite exclusively receiving Rh- and K-matched red cell transfusions. These patients should have RH genotyping performed to inform future transfusions. In our experience, Rh antibodies also form in patients who have conventional alleles corresponding to the Rh antibody formed, and we suspect exposure to donor cells expressing variant Rh and subsequent anti-Rh immunization.[5,6]

There are a few scenarios for which prophylactic antigen matching based on the RH genotype can prevent alloimmunization and associated HTRs. Patients identified by genotype with the hybrid RHD*DIIIa-CE(4-7)-D or RHCE*CeRN alleles, which encode partial C antigen and do not have a conventional RHCE*Ce or *CE allele, should be transfused with red cells lacking C antigen to prevent allo-anti-C development.[3,9] Increasing experience also suggests providing prophylactic RhD-negative red cells to RhD+ patients who have RHD variants and exclusive expression of partial D antigen. Examples of "at risk" RHD alleles are DAU3, DAU4, DAU5, and DOL.

Not all patients with RH variants will form alloantibodies and not all alloantibodies associated with RH variants will cause clinically significant HTRs.[5] The number of red cell exposures prior to antibody formation varies considerably and may reach hundreds of antigen-positive red cell units before a patient with the corresponding antigen variant becomes immunized. The authors note that 4 of 8 patients with RH variants and the corresponding Rh antibody received many transfusions with antigen-positive red cells but had no clinical or laboratory evidence of hemolysis, suggesting that these Rh antibodies are not uniformly associated with poor transfusion outcome.[1] However, this was a small study with a limited number of patients, and each of the 4 patients had unique RH genotypes and transfusion strategies. Three of the patients had partial e, two of whom had an anti-e antibody identified and one who had a pan-reactive antibody but no antigen specificity. One of the patients who formed anti-e was subsequently transfused with multiple e+ red cells without any clinical event. The other patient with anti-e was also re-exposed to e+ red cells but treated concomitantly with intravenous immunoglobulin (IVIG) and steroids to prevent HTRs. The fourth patient reported had formed anti-D and anti-C but her genotype showed partial C only. She was subsequently transfused only D- and C- red cells after the antibodies were detected. We caution that the risks associated with transfusion of antigen-positive red cells to immunized patients with the corresponding partial Rh protein require further study with a significantly larger cohort. Individual outcomes are likely highly dependent on the patient's RH genotype and which Rh epitopes their red cells lack.

For patients with RH variants associated with partial Rh antigen expression and who form the corresponding antibody, we recommend providing antigen-negative units if possible to prevent recrudescence of the antibody and potential HTR. Finding compatible red cells lacking D, C, or E for those immunized against D, C or E antigens is straightforward. For patients with anti-e who are E+, transfusion with E+ e− red cells is appropriate. However, for patients with anti-e who are E−, exposing them to E+ e− red cells carries significant risk for anti-E development and associated hemolysis. E− e+ red cells that are RH genotype-matched would be the ideal choice, but this is available only in very limited circumstances. If the anti-e is still demonstrable in the patient's plasma and transfusion cannot be avoided, one should consider concomitant treatment with immunosuppressive therapy (steroids, IVIG), particularly if the patient had clinical or laboratory evidence of red cell hemolysis at the time of anti-e formation. At our institution, we have several E− patients with partial e who formed anti-e, and were subsequently re-exposed with e+ red cells once the antibody was no longer demonstrating and did not show evidence of poor transfusion outcome.

As the number of patients and donors for whom RH genotyping has been performed grows, additional insight will be gained for the specific RH variants that pose the greatest risk for alloimmunization and poor transfusion outcomes. This will better inform how to

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REVIEW

TRANSFUSION MEDICINE WILEY

ABO(H) and Lewis blood group substances and disease treatment

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Abstract

Since the early 20th century, scientists have determined that blood group antigens can be inherited. With more and more studies have been devoted to finding the relationship between blood groups and diseases, the relationship of ABO(H) and Lewis blood groups and the development of human diseases have been summarised. In addition, many studies have shown that blood group substances, such as blood group antigen or related antibody, play an important role in disease prevention and treatment. This review focuses on the advances of ABO(H), Lewis blood group substances in the treatment of diseases, which has important significance for the development of novel therapeutic methods.

KEYWORDS
antibody, antigen, blood group, disease treatment

1 | ABO(H) AND LEWIS BLOOD GROUP SUBSTANCES

The phenotypes of both ABO(H) and Lewis blood groups are determined by the specific carbohydrate structures in red blood cells, vascular endothelial cells, and other tissues. The expression of blood group system in these tissues is controlled by *FUT1* (19q13.3), *FUT2* (19q1.3), *FUT3* (19p13.3) and *ABO* (9q34.1) gene, which encode H(*FUT1*), glycosyltransferase secretory (*FUT2*), Lewis (*FUT3*) and ABO, respectively. The precursor of antigen A and B are oligosaccharide chain with two patterns. The type 1 chain ends with galactose β1-3-*N*-acetylgalactosamine-β1-R sequence and mainly exists in urogenital tract and gastrointestinal epithelial cells. The synthesis of type 1 chain requires α-1,2-fucosyltransferase encoded by *FUT2* that preferentially recognises gal-β1-3-*N*-acetylgalactosamine receptor. *Se* and *se* are the historical names for active and non-active *FUT2* alleles, respectively. Individuals could be typed as secretors with secreted ABO(H) antigen in fluids if inherited *Se*, and non-secretors without secreted ABO(H) antigen if inherited *se*. In addition, this mechanism is highly regulated and can be down regulated under the conditions of inflammation and tumour.[1,2] The type 2 chain mainly expresses in erythrocytes, platelets and endothelial cells and are not affected by secretory state.[3] The synthesis of type 2 chain requires the *FUT1/H* gene, an α1,2-fucosyltransferase that adds a terminal fucose to lactosamine to form Fucα1-2-galactose-β1-4-*N*-acetylgalactosamine-β1-R sequence. H antigen can then serve as a substrate for ABO, which adds a *N*-acetylgalactosamine in an α-13 linkage to form A antigen, or a galactose to the same subterminal galactose to form B antigen.

Lewis antigens reflect the action of *FUT2* and *FUT3*.[4] *FUT3* encodes a glycosyltransferase, which catalyses a fucose to secreted H type 1 substance to produce Le^b antigen if it is a secretory type. If it is a non-secretory type without H antigen in the secretion, glycosyltransferase catalyses a fucose to the type 1 precursor to produce Le^a antigen. Le^x and Le^y antigens are isomers of Le^a and Le^b, respectively,[5,6] which are less present on red blood cells.[7]

2 | THE ROLE OF ABO(H) AND LEWIS BLOOD GROUP IN DISEASES TREATMENT

ABO(H) and Lewis antigens are widely distributed throughout the body, they also be referred to as histo-blood group antigens for they evolved earlier in ectodermal and endodermal tissue than in RBCs and haematopoietic cells.[8] Antibodies to these tissue antigens cause rejection of transplanted tissues and organs[9] and can cause spontaneous.[8] ABO(H) and Lewis antigens are not only related to the adverse reactions of blood transfusion and the rejection of organ transplantation such as kidney transplantation,[10] but also to the infection of pathogenic microorganisms such as Norovirus and *Helicobacter pylori*,[3] and the occurrence and development of tumours.[11,12] In recent years, more and more

attention has also been paid to the relationship between ABO(H) and Lewis blood groups and the treatment of diseases.[13,14]

2.1 | Neutralisation of antibodies in transplant

Organ transplantation is the most effective therapy method for end-stage organ failure. ABO(H) blood group matching is a necessary step before organ transplantation.[15] ABO(H) antigen is expressed on almost all cells and all body fluids except cerebrospinal fluid because secrete, cells die and the breakdown of glycocalyx structures of some substances. The body produces antibodies to those antigens it does not express itself. Antigen and antibody combination can activate complement, and then cause inflammation and thrombosis, which can lead to organ failure and even death. Although organ transplantation is mainly based on the same ABO(H) blood group, ABO(H) blood group incompatibility (ABOi) organ transplantation has made great progress through plasma exchange, injection of immunoglobulin, use of immunosuppressant and splenectomy.[16] Current practice for ABOi transplantation is the use of A2 solid organs in Group B and Group O recipients, and A2B in group B.[17,18]

In living donor kidney transplantation, 30%–40% of potential donors are rejected because of ABOi, and many of them may need splenectomy after transplantation. Besides, A2 incompatible transplantation may not address the need for solid organs in Group B and (or) O recipients. Kumlien et al. designed an ABOi kidney transplantation scheme without splenectomy and with ABO antibody–antigen specific adsorption effect, which does not require nonspecific plasma exchange and the ABOi practice were not limited to A2 incompatible.[19–21] They performed antigen-specific immunosorbent and passed the patient's plasma through the glycosorb ABO column, a low-molecular-weight carbohydrate column containing synthetic terminal trisaccharide A or B blood group antigen linked to a Sepharose matrix. It can effectively and specifically eliminate anti-A or anti-B antibodies without any obvious side effects. After infusion of rituximab and intravenous immunoglobulin and antigen-specific immunoadsorption, ABOi renal transplantations can be performed with standard immunosuppression and without splenectomy. A recent retrospective observational cohort study on ABOi living donor transplants also found ABO column immunoadsorption with specific columns is a safe and effective method.[22] However, Yoneyama et al. considered that in ABOi renal transplantation, the overuse of immunosuppressants would make the clinical condition of ABOi renal transplantation difficult to control. In order to reduce the use of immunosuppressants, they explored a new blood group antigen neutralisation therapy. ABO blood group antigen-targeting peptide (BATP) was screened from T7 phage-displayed peptide library,[23] it can inhibit the hemagglutination reaction of red blood cells and with very low toxic effect. Moreover, ex vivo perfusion of BATP in kidneys excised from renal cell carcinoma patients caused significant suppression of anti-blood group antibody binding to antigen and IgG and IgM deposition in renal glomerular capillaries after ABOi blood reperfusion. Their approach may enable the development of a novel blood group antigen-neutralising therapy to overcome the challenges of ABOi renal transplantation. However, more data are needed to evaluate the stability and systemic side effects of BATP in vivo.

2.2 | Inhibition of infection by soluble blood group substances and mimics

The structures of ABO(H) and Lewis blood group antigens on red blood cells and other tissues can interact with microorganisms, including bacteria, viruses and parasites.[3] *H. pylori* is a kind of Gram-negative bacteria and more than 50% of the world's population are infected. *H. pylori* can cause a variety of gastric diseases, such as chronic gastritis, peptic ulcer and gastric cancer.[24] As early as 1954, research indicated that individuals with O blood group were more likely to suffer from peptic ulcer. Subsequent studies showed that *H. pylori* seemed to have specificity for O-Le^b. Compared with A-Le^b, the binding affinity of *H. pylori* to O-Le^b was about five times higher.[25] Previous experimental studies have shown that *H. pylori* could expresses adhesin and adhere to fucoidated blood group receptors in gastric mucosa.[26,27]

The blood group antigen-binding adhesin (BabA) is one of the most studied adhesins of *H. pylori*, which can bind the carbohydrate of ABO(H)/Le^b blood group in gastrointestinal mucosa and adhere to the surface of stomach and increase the virulence of bacteria.[28] Younson et al. have isolated a human domain antibody for BabA that inhibit the binding of BabA and Le^b antigen, and the adhesion of *H. pylori* to human gastric epithelium.[29] In addition, they found Le^b oligosaccharides covalently linked to poly-D-lysine also inhibited the binding of BabA to Le^b. Poly-D-lysine-Le^b hexasaccharide and Le^b human serum albumin conjugate can not only inhibit the adhesion of *H. pylori* to gastric epithelium, but also replace the adhesion bacteria. They believe that domain antibody inhibitor may have potential for prophylactic, and treatment of drug-resistant *H. pylori* when combine with Le^b oligosaccharides. An experimental study[30] found that bovine colostrum (BIC) hyperimmune preparation could bind with Le^b blood group antigen, and inhibit the binding of *H. pylori* to human gastric mucosa tissue sections, and the blocking activity was almost 90%. In addition, the experiments confirmed that BIC can eradicate or reduce the number of bacteria in *H. pylori* infected mice. Another study evaluated the efficacy and safety of oral bovine anti-milk anti *H. pylori* antibodies. It was found that oral bovine milk antibody is safe for human body and has obvious scavenging effect on adults with blood group O gastric *H. pylori* infection.[31] According to the relevant research results, some scholars proposed that the "humanised" animal milk with fucosylated antigen introduced by transgenic technology may provide an alternative treatment and prevention measure for *H. pylori* infection.[32]

Susceptibility to norovirus infection is the most cause of acute gastroenteritis in humans. Norovirus can recognise human tissue blood group antigen (HBGA) as receptor,[33] and the fucosylation of HBGA plays an important role of norovirus in the binding to the host.[34] Adhesion of norovirus to gastrointestinal epithelial cells through HBGA receptor is considered as the first step of norovirus infection. Human norovirus is highly diverse with a variety of types, and with different binding patterns with ABO(H), secretor and Lewis

antigens. Studies have found that norovirus (NV, GI-1) was more likely to infect group O individuals,[35] and it preferred H type 1 and Le^b, rather than H type 2 antigen, and did not bind to Le^a and Le^x antigens.[36] Subsequently, two major gene groups were found in human norovirus strains: the first group (GI), which mainly recognised A, H and Le^b epitopes; the second group (GII) was quite different from the receptor recognition.[37] Further studies also showed that GI-1 was able to bind to type O secretors saliva, while GII-3 and GII-4 strains well combined with A secretors saliva.[38] Inhibiting the adhesion of Nov to gastrointestinal epithelial cells or reducing the fucosylation of HBGA can be effective methods for the treatment of this disease.

In recent years, there have been many studies about candidate drugs to inhibit the binding of norovirus and HBGA.[39] ABO(H) blood group substances prepared from pig and squid tissues were found effective in preventing the specific binding of norovirus virus like particles (VLPs) to ABO blood group specific binding of salivary and mucosal samples.[40] These blood group substances may have the potential to prevent and treat norovirus infection. It should be noted, however, that these compounds contain foreign substances that may trigger immune responses in the human body. Other studies found the clearance of chronic norovirus infection was related to the strain specific HBGA blocking antibodies produced in patients' serum.[41] The antibodies can be IgG or IgA,[42] and one of their mechanisms is to block the HBGA binding site on the viral capsid through physical action.[43] In addition, antisera from mice inoculated with norovirus VLPs could block the binding of tissue blood group antigens H-1, Le^b and H-3.[44] These results suggesting the potential mechanism of neutralisation of norovirus mediated by these antibodies and possible therapeutic methods for norovirus infection. Several researchers found that nanoantibodies nano-7 and nano-94 of human norovirus can prevent VLPs from binding with HBGAs, and inhibiting the binding of VLPs with HBGAs is the main way to inhibit norovirus infection.[45] In addition, experimental results showed that the inhibition effects of nano-7 or nano-94 were enhanced after added with 2′-Fucosyllactose.[46] For gastrointestinal norovirus with high genetic polymorphism, drug therapy based on blood group antigen epitopes provides a new method to combat norovirus infection.[47]

2.3 | The use of targeted antibodies/lectins in cancer

Some researchers have early noticed that abnormal expression of blood group antigens is related to tumorigenesis, development and metastasis.[11] It has been found that the morphology of carbohydrate on the surface of tumour cells significantly affects its metastatic potential, and the surface carbohydrate of some normal tissue cells may be involved in the regulation of tumour cell metastasis through the interaction between specific recognition molecules and certain carbohydrate structure of tumour cells.[48] Aberrant glycosylation and the overexpression of certain carbohydrate moieties is a consistent feature of cancers, and tumour-associated oligosaccharides are actively investigated as targets for immunotherapy.[49] Cancer cells exhibit abnormal glycosylation patterns during carcinogenesis, and the abnormal carbohydrate chains produced by them are called tumour associated carbohydrate antigens (TACAs). The Lewis type TACA including Le^y, Le^x and KH-1 antigens. KH-1 antigen is relatively cancer-specific,[50] it was first isolated from adenocarcinoma cells and has not been detected from normal cells. The structural difference between Le^y and Le^x is that the former has an extra α-L-Fucose linked to the 3-O site of galactose residue at the non-reducing end of the latter antigen, while KH-1can be considered as the heterodimer of Le^y and Le^x. As an isomer of Le^b blood group antigen, Le^y antigen expresses on 60%–90% of human epithelial carcinoma surface,[44] including breast cancer, colon cancer, gastric cancer and lung cancer. 40%–77% of small cell lung cancer (SCLC) overexpress Le^y.[51,52] It has been reported that the increased intercellular rejection of Le^y expression may be related to cell migration ability.[53] Antibody target for Le^y has potential for tumour treatment. Although Le^y also expresses in normal tissue, it is limited to the secretion boundary of epithelial surface, and not easy to be approached by circulating antibodies.[54] Some lectins such as galectin-9 and its isoforms were overexpressed in pancreatic cancer cells, breast cancer cells and melanoma.[55,56] These lectins bind to specific, complex oligosaccharides, such as sialic acid Le^x (sLe^x) antigen derived from sialylation of Le^x antigen. It has been confirmed that sLe^x is a ligand of E-selectin, which participates in the adhesion of tumour cells to vascular endothelial cells or lymphatic endothelial cells and promotes metastasis.[12]

Danishefsky et al. synthesised KH-1 antigen in vitro, which opened up a new possibility for the development of anti-cancer vaccine.[57] Subsequently, they synthesised a Le^y protein conjugate and verified its immunogenicity in mice.[58] After that, they synthesised KH-1 analogues by replacing the ceramide part of KH-1 with allyl group, and then combined with carrier protein keyhole limpet hemocyanin (KLH) to form two vaccine constructs, together with the immunological adjuvant QS21(a saponin derivative from the bark of the *Quillaja saponaria* Molina tree) to immunise mice. Both vaccines stimulated the production of antibodies, one of which only produced IgM antibodies, while the other produced high titers of IgM and IgG antibodies. The antibody recognised not only KH-1 antigen, but also Le^y antigen, and had strong reaction with KH-1/Le^y positive melanoma cell line MCF-7, but not with KH-1 and Le^y negative melanoma cell lines.[59] Then, a phase I clinical trial was performed by inoculating the Le^y-pentasaccharide-KLH conjugate vaccine in 25 patients with QS21 adjuvant. It was found that some patients had strong anti-tumour cell response, and the vaccine was well tolerated. No gastrointestinal, haematological, renal or liver toxicity related to the vaccine was observed.[60] Subsequent research synthesised other KH-1 or Le^y related tumour vaccines, which were well-tolerated or induced functional antibodies.[50,61,62] Therefore, Le^y-KLH should be considered as an appropriate component of multivalent vaccine for the treatment of cancer. The recent study also found that the presentation of Le^x, Le^y and KH-1 antigens on cancer cell can be different from that in synthetic conjugates,[50] which should be taken into consideration during the design and optimization of related cancer vaccines.

The expression change of Le^y in cancer tissue makes it an attractive target for monoclonal antibody therapy. Humanised 3s193 (hu3s193), a monoclonal antibody of Le^y, has good complement dependent cytotoxicity and antibody dependent cytotoxicity, and with low risk of immune response in human body.[63] Krug et al. injected two different doses of hu3s193 into patients with advanced SCLC to detect its targeting and pharmacokinetics in patients.[64] They found the antibody has good targeting and significant immune effect function. Another study found hu3S193 variants generated via site-directed mutagenesis could improve therapeutic ratio for radioimmunotherapy of epithelial cancers.[65] This suggested that the drug is expected to be a part of combined immunotherapy and chemotherapy. However, a phase II trial with hu3S193 for the treatment of ovarian, it did not show sufficient activity and with some treatment-related adverse events such as fatigue, nausea and vomiting.[66,67] More data are needed to investigate the efficacy and safety of hu3S193.

Cyclooxygenase-2 (COX-2) and Le^y are correlative sources of specific gastric biomarkers in gastric cancer, which is up-regulated in gastric cancer through MAPKs pathway.[68] Anti Le^y antibody can significantly down regulate the expression of COX-2 through MAPKs pathway and reduce the infection of *H. pylori*, which is helpful for the treatment of gastric cancer.[69] In addition, studies have confirmed that anti le^y antibody can enhance the inhibitory effect of celecoxib on the proliferation of gastric cancer cells, which is also a new feasible method for the treatment of gastric cancer.[70] Daly et al. developed a synthetic method for the incorporation of bioactive carbohydrates, including tissue blood group antigen trisaccharide Le^x, into porphyrin skeleton and screened the PDT activity of these compounds on human oesophageal cancer cell lines.[71] The compounds did not show significant toxicity in the selected cell lines. The synthesised glycoporphyrins without phototoxic effect have potential as imaging dyes and could be used in normal sunlight without side effects. However, it was found that glycoporphyrin can produce singlet oxygen after irradiation, but the level is lower than foscan, so further research is needed to optimise the irradiation time.

3 | CONCLUSIONS AND FUTURE PERSPECTIVES

The relationship between ABO(H), Lewis blood group and disease susceptibility have been extensively studied, but there is a lack of the advance summary about the relationship between ABO(H), Lewis blood group substances and disease treatment. In this review, we have searched and summarised literatures about ABO(H) and Lewis blood group substances that related to disease treatment. With the rapid development of scientific research. We believed that there will be more clinically applicable treatment substances and methods associated with ABO(H) and Lewis group in the future. These have great significance for the further research of blood group substances, and also provides the basis for the treatment of clinical related diseases and the development of novel target and drugs.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTION

Junting Liu did the scientific literature review and drafted the manuscript. Deqing Wang critically revised the entire manuscript and approved the final version. Jie Lin and Yang Yu provided some writing suggestions.

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ORIGINAL ARTICLE

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On consciousness of the decision to discontinue blood donation: Intention to return and effective recovery activities

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Abstract

Objectives: This study aims to (1) explore the consciousness of blood donors' decision to stop donating blood, (2) analyse the association with the donors' intention to return to blood donation and the various reasons for discontinuation, and (3) identify effective activities for the recovery of donors who are no longer donating blood.

Materials/methods: Survey data of former German blood donors who did not donate blood for >36 months were collected ($n = 1263$). The data were analysed using multivariate linear regression and mediation analyses.

Results: This study provides new insights into the consciousness of blood donors' decision to stop donating blood. Former blood donors may be located at distinct stages of consciousness about their decision of discontinuation. The results indicate that 44.9% of the former blood donors did not consciously decide to stop blood donation. Of the lapsed donors, 16.9% decided consciously and 18.2% were in between. Furthermore, 25.2% of the respondents who did not consciously decide to stop donating blood were willing to restart the same. The most effective activities for recovery are more flexible donation hours (29.1%), appointment-scheduling online (24.8%), and sending out reminders (18.1%).

Conclusion: Addressing unconsciously lapsed donors is promising. Blood donation service providers should implement measures that support busy people; such measures may include appointment scheduling or pause-options. The implementation of a systematic recovery management, entailing an analysis of the decision to discontinue blood donation with subsequent segmentation is advisable. This can help to foster individualised communication with blood donors.

KEYWORDS

blood donors, consciousness of the decision to discontinue blood donation, intention to return, lapsed donors, reasons for discontinuation, recovery activities

1 | INTRODUCTION

A thorough understanding of how the relationship between blood donors and blood donation service ends is particularly important for at least two reasons. First, it is crucial to counter the trend of steadily shrinking donor bases, which is mainly a result of demographic changes and the COVID-19 pandemic.[1–3] Second, the demand for blood products is expected to increase within the next few years due to the aging population.[4] A number of previous studies have identified several reasons why blood donors stop donating. The most important reasons are health

issues, negative physical experiences, fear, inconvenience, deferral, or a busy lifestyle.[5–8] In contrast, very little is known about the consciousness of the decision to dicontinue the donor career from the perspective of the donor. The few studies that have investigated this, such as Van Dongen et al.[9] or Klinkenberg et al.,[10] found that there was a difference between consciously ended and passively lapsed donors. This is an important distinction, because a 'wrong' assessment by blood donation services may lead to inappropriate and ineffective recovery activities.

Consequently, this study focuses on whether the decision of former blood donors to stop blood donation was made deliberately or unintentionally. To determine how conscious the decision to stop donating was, we apply the transtheoretical model,[11,12] which explains the process of change in behaviour and has been applied to various health behaviours, including blood donation.[13–16] The model posits that changes in human behaviour occur in a sequence of discrete stages. These include precontemplation, a stage at which individuals do not think of changing their behaviour, contemplation, where change is considered, the preparation or decision-making stage, where the actual change is planned, the action of performing the change in behaviour, and the maintenance of that behaviour.[17]

The intention to return and the consequent chances of regaining lost blood donors are dependent on the consciousness of the decision to stop donating. Van Dongen et al.[9] found that 51% of people who had actively decided to end the relationship and were deregistered from the donor pool were willing to restart blood donation. For passively lapsed donors, the percentage of people willing to return increased to 80%. Knowledge of the intention to return and of the differences in reasons for discontinuing blood donation help blood donation services target those with the highest potential for recovery.

Finally, on knowing which people to target, insights into effective recovery activities are needed. Blood donation services need to identify the most beneficial activities for different groups of lost donors.[18–20] Previous studies highlight the potential of stage-matched interventions.[12] In the preceding literature on blood donation, however, most interventions predominantly focused on activities for blood donor retention. Godin et al.[21] reported that motivational or reminder-based activities were the most effective for donor recruitment or retention. Drawing from the existing literature and our own findings, our study contributes to a better understanding of effective recovery activities and their application.

In sum, the purpose of the study is threefold: (1) to explore the consciousness of blood donors' decision to stop donating blood, (2) to analyse the association with the donors' intention to return to blood donation and the various reasons for discontinuation, and (3) to identify decision stage-matched effective activities for the recovery of donors who no longer donate blood.

2 | MATERIALS AND METHODS

2.1 | Data collection and sample

Data for this quantitative study were collected from October 2020 to January 2021 via an online survey. A total of 1263 responses were obtained from former blood donors. In this study, the relationship between a former blood donor and the donation service was considered to have ended if the person had not made any donation in the past 36 months and had neither been permanently deferred from future donations for medical reasons.[22] This definition was supported in internal discussions with the German Red Cross (GRC) Blood Donation Services, which organise approximately 75% of the total blood collection in Germany and rely on a non-remunerated donor base. The other 25% of the German blood donation market is served by the public (for instance, at public hospitals) or for-profit blood donation services. Public institutions sometimes provide monetary incentives, and for-profit services mostly pay the donor.

We recruited respondents from two sources: (1) through an online panel, which had the advantage of receiving responses from individuals who had donated at all possible blood donation services (n = 766), and (2) among former donors of the GRC Blood Donation Services (n = 497). In their donor database, the GRC Blood Donation Services identified 9277 former donors and invited them to participate in the survey by postal mail. Among them, 523 lost donors successfully completed the questionnaire, which led to a successful response rate of 5.6%. As 26 respondents indicated that they did not stop donation but only switched to another blood donation service, they had to be excluded from the mail sample. Considering the incomplete answers of those who withdrew in the beginning or were screened out of the questionnaire because they reported donating blood in the past 36 months at the GRC or did not consent to the data protection policies, the resultant response rate was 12.7%. This rate lies below the response rate of 25% among passively lapsed donors by Van Dongen et al. (2012). One explanation for this could be that the donors received a postal letter from which they had to scan a QR-code or type in a link to the questionnaire on the browser on their mobile phone or computer, which may have seemed a bothersome process to some potential participants. The final sample (n = 1263) consisted of whole blood donors (86%), plasma donors (6%), and donors who made different donations (8%). Among the respondents, 34% were 20–40 years old, 46% were 41–60 years old, and 20% were 61–73 years old. The characteristics of all study samples are detailed in Table A1.

2.2 | Questionnaire and measurement

The online questionnaire comprised the following elements: an introduction, request to consent to the data protection policies, questions on the consciousness of the decision to stop blood donation, individual reasons for discontinuing the donor career, intention to restart donation, and recovery activities former donors found attractive. The questionnaire also investigated the donor's personal donation history and sociodemographic characteristics. In general, items were measured on a 7-point Likert scale ranging from 1 (does not apply at all) to 7 (applies entirely). The relevant items are presented in Table A2. The questionnaire was administered via the open-source survey tool, LimeSurvey (2017).

2.2.1 | Consciousness of the decision to stop donating

According to the transtheoretical model,[17] we assume that blood donors who stop donating can, at the same time, be located at different stages of consciousness about the decision. Critics of this model put forward the notion that behavioural changes do not always follow the sequential process in an orderly manner and that the different stages are not mutually exclusive.[15,23] We suppose that a person may have stopped blood donation but is not thinking about the change (precontemplation stage), has stopped, and is thinking about it (contemplation stage), or has consciously decided and stopped donation (postcontemplation stage). Therefore, the consciousness of the decision to stop blood donation was measured using three items, each targeting one of these three stages of consciousness. Regarding the pre-contemplation stage, we asked the respondents to rate their agreement with the statement, "*I did not consciously decide to terminate blood donation but rather did not go for a while*." For the contemplation stage we asked, "*I am still in the process of deciding whether I should go again*", and for the postcontemplation stage, the statement was, "*I consciously decided to no longer donate blood*."

2.2.2 | Intention to return and reasons for discontinuation

Lost donors' intention to return to blood donation was also assessed using three items,[24,25] with respondents evaluating, for instance, the applicability of the statement, "*I firmly intend to start donating blood again*." To examine the actual willingness to take immediate action, respondents were asked, at the end of the questionnaire, if they would like to be forwarded to a blood donation appointment scheduling system after completing the survey. In order to obtain information on individual reasons for discontinuing blood donation, respondents were asked to indicate how much each statement about a single reason for discontinuation applied to them. These questions followed the questions on decision consciousness. To examine as many relevant reasons as possible, we compiled a comprehensive list of 59 different reasons for ending the relationship based on a review of the extant literature.[5,9,10,26–28] Among these, 32 were donor-related reasons, and 27 were blood donation service-related reasons.

2.2.3 | Recovery activities

We presented 10 possible recovery activities to the respondents and requested them to select which ones would convince them to return to blood donation: (1) text message with information regarding the usage of the donated blood,[20] (2) personal phone calls with employees of the blood donation service,[29] (3) the option to book appointments online,[30] (4) more flexible donation hours,[10] (5) little gifts,[31] (6) support to avoid adverse events during the blood draw,[32,33] (7) reminder messages,[34] (8) modern advertising campaigns,[35] (9) stronger public relation activities, and (10) appreciation of the donation (e.g., in the form of acknowledgements). The activities used in our study were discussed with the GRC Blood Donation Services.

2.3 | Data analysis

Our data analysis comprised three steps: First, we analysed the consciousness of the blood donor's decision to stop donating blood. Different levels of consciousness were identified; therefore, we applied independent samples t-tests to obtain the first insights on group differences regarding the intention to return as well as individual reasons for discontinuation. We further applied multivariate linear regression to analyse the association between the reasons for discontinuation and the consciousness of the decision. To prepare for this, we employed an exploratory factor analysis to form clusters of the aforementioned reasons. Bivariate correlations among these clustered reasons as well as their association with the responses to the three consciousness variables and the intention to return are reported in the Table A3. Second, we performed a mediation analysis to assess whether the association among the reasons and the intention to return was mediated by the consciousness of the decision to stop blood donation. Third, to reveal consciousness stage-matched effective activities for recovery, we examined recovery activities depending on group affiliation. Analyses were conducted using the IBM SPSS Statistics version 26.

3 | RESULTS

3.1 | Consciousness of the decision to discontinue blood donation

Table A2 reports the descriptive statistics of the three consciousness items. In the following, we describe our approach to building groups of donors with different levels of consciousness about the decision to stop blood donation, from our data. This allows us to get a first-hand understanding of the distribution of the population of former donors among the different stages of consciousness.

We grouped the respondents into mutually exclusive categories based on their consciousness regarding their decision to donate blood. Therefore, we considered all three consciousness items simultaneously. We interpreted a score of 5, 6, or 7 on the Likert scale ("does not apply at all" to "applies entirely") as consent. Depending on these top-3-scores, we determined the individual association with one or more of the consciousness stages and allocated each respondent to a category. Figure 1 provides an overview. Of the total sample, 15.7% ($n = 198$) could not be assigned to any category. We found that the majority of respondents were located at a single stage. In the first stage, precontemplation, 567 respondents (44.9%) explained that they did not consciously decide to end their donor career but rather absented themselves from blood donation. In the next stage, contemplation, 42 (3.3%) individuals were still in the process of deciding to no longer donate blood. Regarding the stage of postcontemplation,

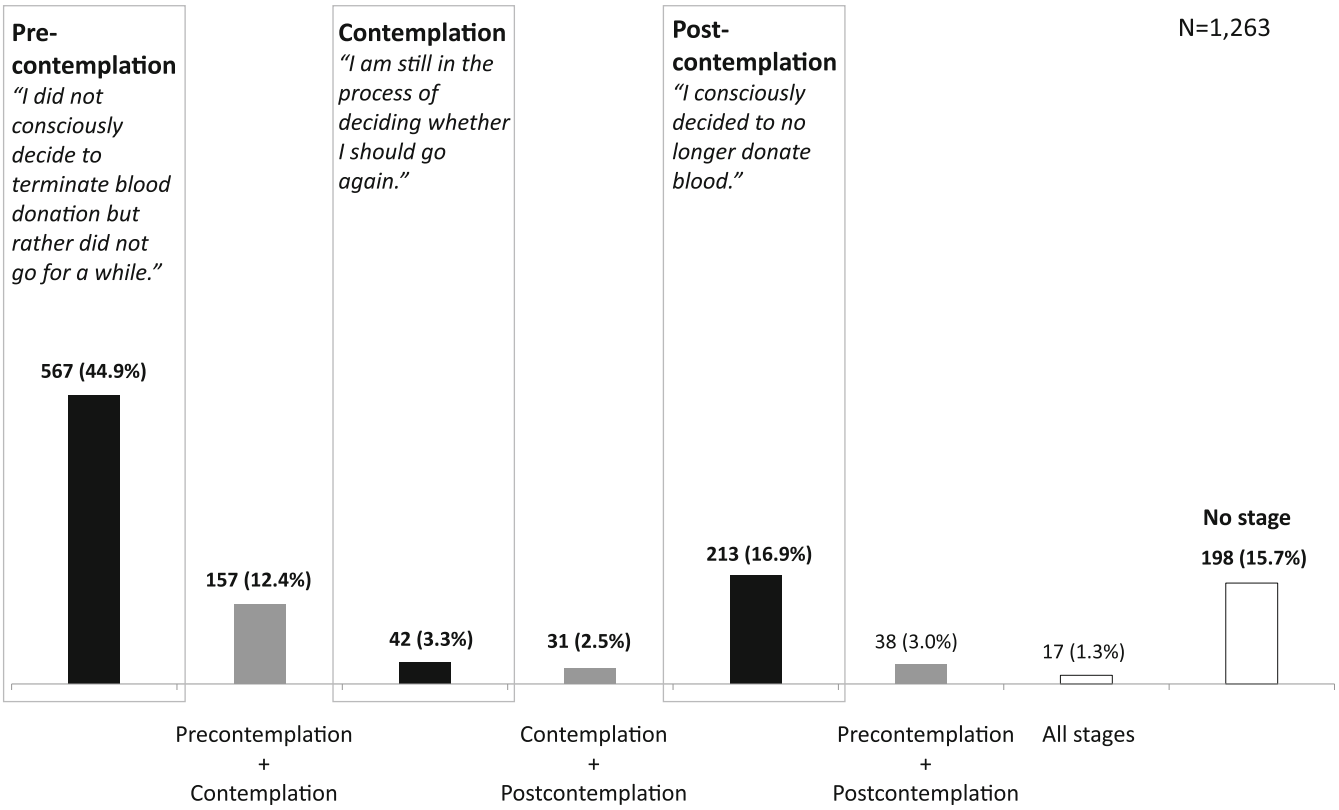

FIGURE 1 Distribution of blood donors among the stages of consciousness of the decision to end

16.9% of the respondents indicated that they had consciously decided to stop blood donation ($n = 213$). Here, we found that some donors were located at two stages at the same time: 23.4% ($n = 157$) at the overlap between precontemplation and contemplation, and 2.5% ($n = 31$) at the overlap between contemplation and postcontemplation. Very few respondents indicated that they were situated at all three stages: 1.3% ($n = 17$) or the non-adjacent stages of precontemplation and postcontemplation, 3% ($n = 38$). These findings indicate that the process of ending a donor career is mostly unconscious or passive.

3.2 | Intention to return and reasons for discontinuation with respect to consciousness

Table 1 reports the group differences in the respondents' intention to resume and the most important reason for discontinuing blood donation. We compared the mean values for all single-or double-stage groups of consciousness and the no-stage group using independent samples t-tests. This test compares the means of two independent groups, accounting for different sample sizes. The postcontemplation group served as the reference category in every comparison. In general, the intention to return may be considered moderate, with a mean value of 4.05 in the total sample. Looking at the different groups, we found a significant difference in intention when comparing the two ends of our consciousness continuum, displayed by a mean value of 4.68 in the precontemplation group versus 2.28 in the postcontemplation group. When asked to indicate their willingness to be forwarded to the appointment scheduling system of a blood donation service after the survey, every fourth respondent in the precontemplation group said yes (25.2%), whereas those in the postcontemplation group predominantly declined (2.3% yes). From these results, we conclude that even if we consider the social desirability bias, which might problematise asking questions related to blood donation,[36] a non-negligible number of respondents are willing to resume blood donation.

Regarding the reasons for discontinuation, Table 1 reports the 30 most frequently reported reasons and presents group differences against the postcontemplation group as the reference category. We distinguish two dimensions of reasons based on their different spheres of influence: donor-related (18) and service-related reasons (12). We report only those reasons that applied to more than 5% of the total sample. Regarding the most important donor- and service-related reasons for each group of consciousness, in Table 1, the 5 highest-ranked reasons for both dimensions are marked in bold. Within the dimension of donor-related reasons, the most frequently reported reason for discontinuing the relationship was a lack of motivation to donate blood, with a mean value of 3.68 in the total sample. Looking at the precontemplation and postcontemplation groups, we observed different core themes regarding the most important reasons for discontinuation. Respondents in the precontemplation group indicated mainly timely obligations: work, housework (mean value 3.74), switching jobs (2.32), caring for children (2.16), and moving away (2.67) as personal reasons for discontinuation. With respect to the blood donation service, they were deterred by inconvenient donation

TABLE 1 Differences regarding consciousness groups in reported intention to return and reasons for relationship ending (*t* test)

	Total sample ($n = 1263$)	PreC ($n = 567$)	PreC+C ($n = 157$)	C ($n = 42$)	C + PostC ($n = 31$)	PostC ($n = 213$)	PreC + PostC ($n = 38$)	No stage ($n = 198$)
Intention to return (summed score)	***4.05 (1.88)***	**4.68 (1.66)****	**4.57 (1.53)****	**4.35 (1.56)****	**3.49 (1.52)****	**2.28 (1.57)**	**3.54 (1.89)****	**3.88 (1.84)****
Choose to be forwarded to the appointment reservation system of the blood donation service[1]	*228 (18.1%) [15.9–20.1]*	143 (25.2%) [21.4–28.6]	28 (17.8%) [12.0–24.0]	8 (19.0%) [7.1–30.9]	7 (22.6%) [8.2–37.8]	5 (2.3%) [0.7–5.3]	7 (18.4%) [6.5–31.5]	28 (14.1%) [9.2–18.8]
Most important donor-related-reasons								
Know that blood is needed but missing motivation	***3.68 (2.31)***	**3.65 (2.21)**	**4.40 (2.15)**	**3.93 (2.16)**	**3.81 (2.29)**	**3.98 (2.60)**	**3.79 (2.41)**	**2.76 (2.10)****
Obligations: work, housework, study	***3.09 (2.36)***	**3.74 (2.43)****	**3.89 (2.40)****	**2.79 (2.24)***	**2.90 (2.12)***	1.84 (1.69)	**2.47 (1.94)***	**2.25 (1.99)***
Moved away from initial donation site	***2.55 (2.39)***	**2.67 (2.48)****	**3.18 (2.56)****	2.50 (2.34)	2.81 (2.32)	2.05 (2.09)	2.39 (2.25)	**2.26 (2.22)**
Fear of circulatory problems	***2.27 (2.05)***	1.88 (1.69)**	**2.72 (2.20)**	**2.95 (2.19)**	**3.74 (2.74)***	**2.51 (2.28)**	**2.76 (2.26)**	2.20 (2.11)
Physical health problems	***2.20 (2.04)***	1.89 (1.81)*	2.03 (1.84)	**2.93 (2.20)**	2.48 (2.06)	**2.34 (2.24)**	**2.95 (2.30)**	**2.74 (2.32)**
Self-deferral	*2.09 (2.01)*	1.50 (1.42)**	1.48 (1.31)**	2.31 (2.05)	2.48 (2.19)	**3.04 (2.49)**	**3.32 (2.58)**	**2.86 (2.37)**
Obligations: new job/ switching jobs	*2.02 (1.95)*	**2.32 (2.15)****	2.37 (2.21)**	1.55 (1.52)	2.10 (1.99)*	1.49 (1.37)	1.66 (1.56)	1.71 (1.64)
Blood donation not important to me anymore	*2.02 (1.59)*	1.90 (1.39)*	2.17 (1.58)	1.93 (1.37)	2.35 (2.03)	2.32 (2.01)	2.16 (1.79)	1.87 (1.55)*
Obligations: receiving, caring for children	*1.98 (2.01)*	**2.16 (2.18)***	1.92 (1.99)	2.48 (2.36)*	2.19 (2.24)	1.76 (1.85)	1.53 (1.54)	1.74 (1.64)
Blood donation is annoying	*1.96 (1.56)*	1.91 (1.43)	2.52 (1.94)*	1.76 (1.41)	2.26 (1.95)	1.92 (1.66)	2.05 (1.74)	1.69 (1.32)
Emotional health problems	*1.96 (1.76)*	1.83 (1.62)	2.43 (2.03)**	**2.52 (2.24)***	2.42 (2.14)	1.69 (1.62)	1.97 (1.87)	2.02 (1.75)
Contributed enough	*1.95 (1.55)*	1.71 (1.25)**	2.09 (1.60)	1.69 (1.16)*	2.52 (2.14)	**2.38 (1.95)**	2.34 (1.95)	1.84 (1.48)*
Decision where to donate was difficult	*1.93 (1.66)*	1.89 (1.58)*	**2.55 (2.06)****	2.00 (1.50)	2.48 (2.25)*	1.52 (1.34)	2.13 (1.83)	1.85 (1.55)*
Fear of medical disqualification	*1.89 (1.80)*	1.55 (1.40)**	2.11 (1.92)	2.33 (2.03)	**3.00 (2.48)***	2.11 (2.07)	2.39 (2.15)	2.07 (1.90)
Obligations: hobbies, sports, leisure activities	*1.85 (1.60)*	2.04 (1.72)**	2.22 (1.89)**	1.67 (1.43)	2.03 (1.82)*	1.30 (1.03)	2.03 (1.85)*	1.57 (1.30)*
Fear has worsened	*1.80 (1.62)*	1.44 (1.14)**	2.39 (2.00)	2.43 (2.04)	2.81 (2.39)*	2.04 (1.87)	2.03 (1.90)	1.76 (1.59)
Preferred to do good differently	*1.79 (1.50)*	1.63 (1.30)	2.08 (1.69)*	2.33 (1.80)*	**2.90 (2.36)***	1.71 (1.45)	2.05 (1.80)	1.75 (1.44)
Obligations: family events	*1.67 (1.55)*	1.57 (1.40)*	2.10 (1.95)**	2.45 (2.21)*	2.26 (2.11)*	1.29 (1.12)	2.00 (2.05)*	1.66 (1.45)*
Most important service-related reasons								
Donation hours	***2.86 (2.22)***	**3.44 (2.28)****	**3.25 (2.30)****	**2.79 (2.19)***	2.48 (2.11)*	1.58 (1.41)	**2.79 (2.28)***	**2.38 (2.05)****
Too few invitations	***2.71 (2.18)***	**3.07 (2.30)****	**3.08 (2.26)****	**3.07 (2.28)***	2.58 (2.19)	**1.87 (1.65)**	**2.29 (1.93)**	**2.34 (2.01)***
Place is inconvenient	***2.58 (2.16)***	**2.87 (2.22)****	**3.29 (2.43)****	**2.69 (2.23)***	**2.74 (2.32)***	**1.84 (1.74)**	1.95 (1.83)	**2.09 (1.85)**
Not enough advertisement	***2.48 (2.04)***	**2.76 (2.13)****	**2.92 (2.22)****	2.45 (1.97)	2.32 (2.09)	1.84 (1.60)	**2.24 (2.01)**	**2.15 (1.85)**
Negative physical experiences at blood drive	***2.37 (2.10)***	2.05 (1.80)**	**2.72 (2.20)**	**2.60 (2.02)**	**4.32 (2.75)****	**2.68 (2.34)**	**2.84 (2.32)**	**2.27 (2.13)**
Missing knowledge where, when to donate	*2.16 (1.87)*	**2.48 (2.01)****	2.61 (2.14)**	1.79 (1.60)	2.48 (2.31)*	1.43 (1.19)	1.84 (1.87)	1.82 (1.52)*
Waiting times too long	*2.15 (1.63)*	2.15 (1.61)**	2.63 1.95)**	**2.69 (1.85)***	2.48 (1.86)*	1.76 (1.31)	**2.21 (1.63)**	2.01 (1.52)

(Continues)

TABLE 1 (Continued)

	Total sample ($n = 1263$)	PreC ($n = 567$)	PreC+C ($n = 157$)	C ($n = 42$)	C + PostC ($n = 31$)	PostC ($n = 213$)	PreC + PostC ($n = 38$)	No stage ($n = 198$)
Wish material or monetary compensation	*2.09 (1.80)*	1.95 (1.63)	2.58 (2.13)*	2.12 (1.60)	**2.71 (2.38)**	**2.12 (1.92)**	2.08 (1.65)	1.98 (1.70)
No donation hours offered	*2.06 (1.96)*	2.25 (2.06)**	2.38 (2.22)**	2.33 (2.06)*	2.42 (2.38)*	1.41 (1.32)	1.95 (2.03)	1.82 (1.68)*
Health/Lifestyle questions inappropriate	*1.84 (1.57)*	1.76 (1.50)	1.92 (1.67)	2.10 (1.46)	2.19 (2.14)	1.75 (1.47)	2.05 (1.79)	1.92 (1.58)
Complications during blood draw	*1.75 (1.52)*	1.61 (1.30)	1.74 (1.55)	2.14 (1.73)	**2.74 (2.21)***	**1.85 (1.76)**	1.79 (1.53)	1.76 (1.52)
Deferred one or more times	*1.74 (1.55)*	1.62 (1.44)	1.99 (1.86)*	2.00 (1.51)*	**2.94 (2.16)***	1.46 (1.28)	1.61 (1.37)	1.94 (1.62)*

Note: Data are reported as mean (SD); 7-point Likert scale (1 = does not apply at all, 7 = applies entirely)[1]; Data are reported as n (%) [95% Confidence Interval]; Reasons mentioned by less than 5% in total are not shown (top 2 values); PreC, precontemplation; C, contemplation; PostC, postcontemplation; the five highest means per group per dimension are marked in bold; Independent samples *t* test: reference group = PostC; *p <0.05, **p <0.001.

hours (3.44) or places (2.87) and simply received too few invitations (3.07). In contrast, respondents from the postcontemplation group often quit because of self-deferral (3.04), knowing themselves that they could not donate anymore. In this group, health problems (2.34) and fear of circulatory problems (2.51) were likely or the opinion that one had contributed enough (2.38). Within the dimension of service-related reasons, the most prominent reason was negative physical experiences at the blood drive (2.68).

3.2.1 | Factor analysis

To further examine the relationship between the reasons for discontinuation and the consciousness of the decision, we first reduced the dimensionality and formed clusters of reasons by applying a factor analysis (principal axis factor analysis extraction, varimax rotation). Table A3 provides details on the allocation of single reasons for why the relationship ended, factor loadings, and potential cross-loadings. To test the applicability of factor analysis to our data, we assessed the Kaiser-Meyer-Olkin measure of sampling adequacy (0.926) and single MSA values (all > 0.5). The results of Bartlett's test of sphericity were considered significant ($p < 0.000$). Following Kaiser's criterion, we extracted 13 factors that explained 55.01% of the variance in the data. We calculated the Bartlett scores for all factors and saved them as single variables.[37] The factors extracted are shown in Table 2, together with their zero-order correlations.

3.2.2 | Correlations

In addition to the correlations among the clustered reasons, in Table 2, we report the correlations among these reasons, the consciousness items, and the intention to return. We found several significant correlations among the clustered reasons and the items of the different stages of consciousness. They often work in opposite directions for the precontemplation and postcontemplation phases. The reason to stop because of a busy lifestyle is, for example, positively correlated with precontemplation but negatively correlated with postcontemplation. Precontemplation is a significant positive correlate of intention to return, whereby the correlation between postcontemplation and intention is significant and negative.

3.2.3 | Multivariate linear regression

Table 3 shows the results of the multivariate linear regression analysis in an overview, which we applied to examine the association between the consciousness of the decision and the clustered reasons. We analysed two different models: one involving agreement with the item assessing precontemplation as outcome variable and another involving agreement with the item assessing postcontemplation as the outcome variable. Clustered reasons served as the predictor variables. Furthermore, we considered three control variables in the models: age,

TABLE 2 Correlations between consciousness of the decision variables, intention, and clustered reasons ($N = 1263$)

	Intention to return	PreC	C	PostC	1	2	3	4	5	6	7	8	9	10	11	12	13
Intention (summed score)	**0.889**																
Consciousness of decision																	
Precontemplation	0.388**		0.120**	−0.553**													
Contemplation	0.058*			−0.044													
Postcontemplation	−0.484**																
Clustered reasons for ending																	
Busy life	0.297**	0.280**	0.095**	−0.222**	**0.681**	0.073*	−0.036	−0.016	−0.006	−0.048	−0.031	0.009	−0.100**	−0.047	−0.002	0.006	0.029
Health and deferral	−0.110**	−0.179**	0.076*	0.139**		**0.528**	−0.089**	−0.103**	0.056*	−0.052	−0.034	0.020	0.008	−0.020	−0.007	−0.027	0.002
Fear	−0.044	−0.002	0.132**	0.064*			**0.833**	−0.004	−0.071*	−0.027	−0.017	−0.007	0.001	0.019	−0.063*	0.006	0.005
Social norm	−0.100**	−0.134**	0.022	0.138**				**0.767**	−0.040	−0.064*	0.004	−0.032	−0.012	0.004	−0.009	0.016	−0.023
Negative attitude to blood donation	−0.361**	0.004	0.130**	0.173**					**0.720**	−0.062*	0.002	0.000	−0.028	−0.046	0.006	−0.004	−0.051
No knowledge about need for blood	−0.049	−0.071*	0.009	0.099**						**0.818**	−0.002	−0.016	0.018	0.025	0.025	−0.008	−0.016
Deficient service quality tangibles	−0.021	−0.007	0.048	0.011							**0.915**	−0.045	−0.019	−0.029	0.002	0.015	−0.018
Deficient service quality employees	−0.008	−0.015	0.060*	0.033								**0.930**	0.000	−0.023	−0.011	−0.006	−0.031
Problems with the place	0.071*	0.193**	0.116**	−0.152**									**0.742**	0.002	0.003	−0.132**	−0.017
Waiting time	0.035	0.046	0.070*	−0.059*										**0.801**	−0.021	−0.011	−0.028
Adverse events	−0.139**	−0.075*	0.099**	0.138**											**0.739**	0.011	0.006
No solicitation	0.148**	0.122**	0.034	−0.126**												**0.881**	−0.001
Scepticism towards organisation	−0.086**	−0.061*	0.019	0.106**													**0.835**

Note: Pearson Correlation, Cronbach's alpha reported at diagonal.
Significance: *$p < 0.05$, **$p < 0.001$.
Abbreviations: C, contemplation; PreC , precontemplation; PostC, postcontemplation.

TABLE 3 Multivariate linear regression models of consciousness on reasons

	Outcome variable: consciousness of the decision to end					
	Model 1: agreement with the item assessing precontemplation			Model 2: agreement with the item assessing post contemplation		
Predictor variables	**B**	**SE (B)**	**β**	**B**	**SE (B)**	**β**
Reasons for ending						
Busy life	0.661**	0.360	0.326	−0.460**	0.049	−0.244
Health and deferral	−0.425**	0.053	−0.230	0.290**	0.044	0.169
Fear	−0.060	0.048	−0.028	0.205**	0.051	0.103
Social norm	−0.333**	0.055	−0.164	0.324**	0.047	0.172
Negative attitude to blood donation	0.001	0.051	0.001	0.361**	0.049	0.192
No knowledge about need for blood	−0.197**	0.053	−0.091	0.238**	0.051	0.118
Deficient service quality tangibles	−0.001	0.054	−0.001	0.031	0.053	0.015
Deficient service quality employees	−0.044	0.057	−0.020	0.086	0.052	0.041
Problems with the place	0.494**	0.056	0.239	−0.363**	0.049	−0.189
Waiting time	0.114	0.052	0.053	−0.125*	0.050	−0.063
Adverse events	−0.168*	0.054	−0.075	0.296**	0.053	0.143
No solicitation	0.323**	0.057	0.150	−0.287**	0.050	−0.143
Scepticism towards organisation	−0.147*	0.054	−0.067	0.263**	0.051	0.129
Controls						
Age (years)	0.008	0.005	0.046	0.001	0.005	0.006
Gender (1 = men, 2 = women)	−0.046	0.132	−0.010	0.158	0.123	0.035
Frequency of donation in the past	−0.024	0.035	−0.019	0.028	0.033	0.024
Constant	4468**			2348**		
Observations	1263			1263		
R^2	0.237			0.239		
F test	24.053			24.296		

*$p < 0.05$. **$p < 0.001$. *Note*: 7-point Likert scale (1 = does not apply at all, 7 = applies entirely).
Abbreviations: B, regression coefficient, β, standardised regression coefficient, SE, Standard error.

gender, and frequency of donation in the past. Klinkenberg et al.[10] found that these characteristics are associated with differences regarding the process of discontinuing blood donation. In general, the models explain about 24% of the variance in the consciousness variables ($R^2_{Precontemplation} = 0.237$, $R^2_{Postcontemplation} = 0.239$). We found several significant associations between the reasons for and the consciousness of the decision to stop. They work in an antagonistic manner in both models. Reasons that had a significant positive association with precontemplation showed a significant negative association with post-contemplation and vice versa. For example, a busy lifestyle, a situation in which time is restricted due to other commitments, was associated with greater agreement with the item assessing precontemplation ($\beta = 0.326$, $p = 0.000$) and with lower agreement with the item assessing post-contemplation ($\beta = -0.244$, $p = 0.000$). Unfavourable social norms were negatively associated with the item assessing precontemplation ($\beta = -0.164$, $p = 0.000$) but showed a positive association with the item assessing postcontemplation ($\beta = 0.172$, $p = 0.000$). A negative attitude towards blood donation had a significant positive association with

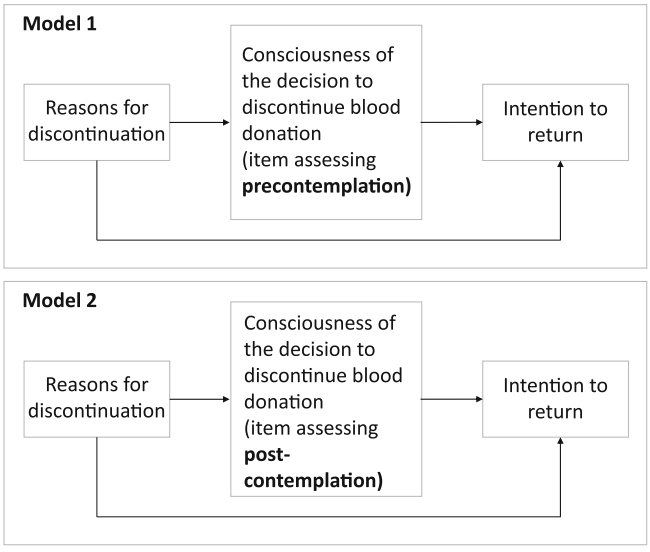

FIGURE 2 Mediation models

TABLE 4 Mediation models: reasons, consciousness, and intention (N = 1263)

	Precontemplation as mediator (Agreement with the item assessing precontemplation)				Postcontemplation as mediator (Agreement with the item assessing postcontemplation)			
	Coefficients ß	BootSE	95% CIs LLCI	ULCI	Coefficients ß	BootSE	95% CIs LLCI	ULCI
Direct effects								
Reasons for ending → Intention								
Busy life	0.311**	0.039	0.234	0.388	0.324**	0.037	0.251	0.397
Health and deferral	−0.088*	0.034	−0.155	−0.021	−0.098*	0.033	−0.162	−0.033
Fear	−0.096*	0.038	−0.171	−0.021	−0.055	0.038	−0.129	0.019
Social norm	−0.157**	0.036	−0.228	−0.086	−0.14**	0.035	−0.209	−0.07
Negative attitude to blood donation	−0.524**	0.037	−0.596	−0.452	−0.429**	0.037	−0.502	−0.357
No knowledge about need for blood	−0.086*	0.038	−0.16	−0.011	−0.063	0.037	−0.137	0.01
Deficient service quality tangibles	−0.028	0.039	−0.106	0.049	−0.021	0.039	−0.096	0.055
Deficient service quality employees	−0.034	0.039	−0.11	0.043	−0.02	0.038	−0.095	0.055
Problems with the place	0.086*	0.038	0.012	0.159	0.09*	0.036	0.019	0.162
Waiting time	0.005	0.037	−0.068	0.078	−0.005	0.037	−0.077	0.067
Adverse events	−0.211**	0.04	−0.29	−0.133	−0.168**	0.04	−0.245	−0.09
No solicitation	0.226**	0.038	0.152	0.301	0.217**	0.037	0.143	0.29
Scepticism towards organisation	−0.157**	0.038	−0.232	−0.083	−0.118*	0.038	−0.192	−0.044
Consciousness item → Intention	0.201**	0.02	0.163	0.24	−0.261**	0.021	−0.302	−0.22
Controls → Intention								
Age (years)	−0.019**	0.004	−0.026	−0.012	−0.017**	0.004	−0.024	−0.01
Gender (1 = men, 2 = women)	0.102	0.092	−0.078	0.282	0.134	0.09	−0.043	0.31
Frequency of donation in the past	0.121**	0.025	0.073	0.17	0.124**	0.024	0.077	0.171
Indirect Effects								
Reasons → Consciousness → Intention								
Busy life	0.133	0.019	0.097	0.173	0.12	0.017	0.088	0.153
Health and deferral	−0.086	0.014	−0.114	−0.061	−0.076	0.015	−0.106	−0.049
Fear	−0.012	0.011	−0.035	0.009	−0.054	0.015	−0.083	−0.026
Social norm	−0.067	0.013	−0.094	−0.043	−0.085	0.016	−0.118	−0.056
Negative attitude to blood donation	0	0.011	−0.022	0.023	−0.094	0.015	−0.125	−0.066
No knowledge about need for blood	−0.04	0.011	−0.062	−0.018	−0.062	0.014	−0.09	−0.036
Deficient service quality tangibles	0	0.012	−0.024	0.024	−0.008	0.013	−0.034	0.016
Deficient service quality employees	−0.009	0.012	−0.032	0.015	−0.022	0.014	−0.05	0.007
Problems with the place	0.099	0.015	0.072	0.132	0.095	0.015	0.067	0.125
Waiting time	0.023	0.011	0.002	0.045	0.033	0.012	0.01	0.057
Adverse events	−0.034	0.012	−0.061	−0.011	−0.077	0.017	−0.111	−0.046
No solicitation	0.065	0.013	0.041	0.094	0.075	0.015	0.047	0.105
Scepticism towards organisation	−0.03	0.012	−0.054	−0.006	−0.069	0.016	−0.101	−0.037
Model Fit (Total effect model)								
R^2 Intention	0.342				0.342			
MSE	2.351				2.351			
F	40.214				40.214			

Note: Outcome variable: intention to return; mediator: consciousness (precontemplation or postcontemplation). *$p < 0.05$; **$p < 0.001$; p values were derived by bootstrapping with 5000 samples within 95% confidence intervals. 7-point Likert scale (1 = does not apply at all, 7 = applies entirely). Abbreviations: LLCI, lower limit confidence interval; ULCI, upper limit confidence interval.

postcontemplation ($\beta = 0.192$, $p = 0.000$), but no significant association with precontemplation ($\beta = 0.001$, $p = 0.980$). This implies that the more the former donors think that donating blood is not important, the higher the agreement with the statement that they consciously decided to stop donating blood.

3.2.4 | Mediation analysis

To evaluate whether consciousness mediated the relationship between the reasons for discontinuing donation and the intention to return, we assessed the direct and indirect effects of the reasons with mediation analysis using Hayes' PROCESS macro.[38] As Figure 2 shows, clustered reasons served as the predictor variables here. The intention to resume blood donation was the outcome variable. In Table 4, we present the results for two models: Model 1 involving agreement with the item assessing precontemplation as mediator and Model 2 involving agreement with the item assessing postcontemplation as the mediator. We controlled again for age, sex, and frequency of past donations. To obtain 95% confidence intervals, we applied bootstrapping with 5000 samples. As quality criteria, we considered the R^2 values, MSE, and F statistics as the goodness-of-fit indicators of our models.

As reported in Table 4, the direct associations between the reasons and the intention to return to blood donation were similar in both models. Specifically, stopping blood donation because of a busy lifestyle was associated with a higher intention to return ($\beta_{Precontemplation} = 0.311$, $p = 0.000$). In contrast, the strongest negative correlate of the intention to return was an unfavourable attitude towards blood donation ($\beta_{Precontemplation} = -0.524$, $p = 0.000$). The direct association between consciousness and intention was positive in the precontemplation condition ($\beta_{Precontemplation} = 0.201$, $p = 0.000$) and negative in the postcontemplation condition ($\beta_{Postcontemplation} = -0.261$, $p = 0.000$).

Table 4 illustrates indirect effects as indicator for the mediating role of consciousness. We found that the association between the reasons for discontinuation and the intention to return was mediated by the consciousness of the decision to stop donating. In the precontemplation model, 9 of the 13 clustered reasons had a significant indirect association with intention mediated by consciousness. In the postcontemplation model, 11 of the 13 clustered reasons had a significant indirect association with intention, mediated by consciousness. This finding further supports the assumption that the former blood donor's awareness of their decision to stop is an important factor for the future intention to donate blood.

3.3 | Recovery activities

Table 5 presents the respondents' recovery activities that they stated to be encouraging in resuming blood donation. We first present the results for the total sample, followed by the seven categories of consciousness. In particular, the respondents in the precontemplation group – those who simply did not go to the donation anymore but did not think of themselves as having discontinued donation – value the offer of more flexible donation hours (39.5%) or the possibility to book appointments online (31.7%). Reminders to an appointment (23.5%) or text messages with information on donated blood usage (20.5%) were also seen as adequate recovery actions. In the postcontemplation group, populated by former donors who had consciously decided to stop donation and had a generally low intention to

TABLE 5 Reported recovery activities

Variable[1]	Total sample ($n = 1263$)	PreC ($n = 567$)	PreC + C ($n = 157$)	C ($n = 42$)	C + PostC ($n = 31$)	PostC ($n = 213$)	PreC +PostC ($n = 38$)	No stage ($n = 198$)
More flexible donation hours	367 (29.1)	224 (39.5)	56 (35.7)	15 (35.7)	5 (16.1)	18 (8.5)	8 (21.1)	38 (19.2)
Possibility to book an appointment online	313 (24.8)	180 (31.7)	55 (35.0)	14 (33.3)	5 (16.1)	17 (8.0)	6 (15.8)	32 (16.2)
Reminder to appointment	229 (18.1)	133 (23.5)	37 (23.6)	8 (19.0)	3 (9.7)	14 (6.6)	3 (7.9)	29 (14.6)
A text message with information about blood usage	183 (14.5)	116 (20.5)	31 (19.7)	11 (26.2)	3 (9.7)	5 (2.3)	1 (2.6)	15 (7.6)
Little gift	155 (12.3)	75 (13.2)	33 (21.0)	10 (23.8)	5 (16.1)	12 (5.6)	1 (2.6)	17 (8.6)
Greater appreciation of donation	131 (10.4)	58 (10.2)	23 (14.6)	8 (19.0)	4 (12.9)	18 (8.5)	4 (10.5)	15 (7.6)
Support to avoid adverse events during the blood draw	119 (9.4)	39 (6.9)	29 (18.5)	8 (19.0)	8 (25.8)	15 (7.0)	2 (5.3)	18 (9.1)
Stronger public relation activities	94 (7.4)	54 (9.5)	15 (9.6)	2 (4.8)	2 (6.5)	11 (5.2)	1 (2.6)	7 (3.5)
Personal phone call with employee of blood donation service	76 (6.0)	30 (5.3)	11 (7.0)	2 (4.8)	2 (6.5)	10 (4.7)	1 (2.6)	18 (9.1)
Modern advertising campaign	45 (3.6)	18 (3.2)	11 (7.0)	5 (11.9)	2 (6.5)	3 (1.4)	0 (0.0)	6 (3.0)
None of these measures	340 (26.9)	115 (20.3)	17 (10.8)	7 (16.7)	10 (32.3)	107 (50.2)	16 (42.1)	64 (32.3)

Note: [1]Data are reported as number (% of group).
Abbreviations: C, contemplation; PreC, precontemplation; PostC, postcontemplation.

return, every second respondent indicated that no recovery activity could convince them to resume blood donation (50.2%). This finding also corresponds to the results of our previous analyses, which indicated that those donors are likely to have discontinued blood donation because of self-deferral or health problems.

4 | DISCUSSION

4.1 | Research discussion

Our study provides new insights into the consciousness of blood donors' decision to donate blood. We find that former blood donors can be located at distinct stages of consciousness about their decision to stop blood donation. These insights are consistent with the core logic of the stages of change in the transtheoretical model.[11,12] While previous studies on blood donation behaviour, such as by Ferguson and Chandler[16] or Amoyal et al.,[13] deliver valuable insights on the applicability of the transtheoretical model regarding the blood donor career as a whole, we find support for the assumption that the core logic works similarly for the group of lost donors. Our empirical evidence contributes to the existing knowledge by delivering a nuanced perspective on donors who are most commonly defined by the researchers as having actively or passively lapsed based on their behaviour.[9,10,39] Future research should investigate which cognitions and behaviours of the lapsed donors have the power to trigger their return to blood donation in order to identify further leverage points for successful relationship management activities.

Our analysis of the association between donors' consciousness of the decision to stop donating and their intention to return to blood donation matches previous findings. We find that intention decreases with growing consciousness about the decision. Even then, our results lie significantly below those of Van Dongen et al.,[9] who found for their passively lapsed condition that 80% were willing to return and 51% of the actively lapsed. We find that when prompted to choose to be forwarded to an appointment reservation system, percentages range from 25.2% to 2.3% in the different groups of consciousness.

The evidence we find regarding the various reasons for discontinuation and their association with the consciousness groups is also in line with previous findings. For unconscious or passively lapsed donors, we support previous findings in that a busy lifestyle represents the main reason to discontinue donation.[8,9] Regarding the conscious, or actively ended donors, our data support results from existing studies in that negative physical experiences and health issues were the main hindrance to making donations.[9,10] We present novel insights into how the intention to return is associated with the preceding reasons to stop blood donation and what role the consciousness of the decision to stop plays. Our results suggest that some reasons are associated with higher intention, whereas others point towards a lower future intention. The reasons significantly affect the consciousness of the decision to stop, which mediates the relationship to intention to return.

Regarding effective activities for recovery, nominated by the former donors, we find differences between the different stages of consciousness. Some of the strategies nominated by donors with the highest likelihood of returning were already tested for their potential for successful donor recovery. Regarding reminders sent via telephone calls or text messages, researchers found that in general, the reception of reminders was positively associated with the return of inactive donors, while text messages led to sooner returns and were more cost-efficient than telephone calls.[19] The use of text messages with information regarding donated blood usage was found to be effective for donor retention, for example, by Gemelli et al.[40] and Fosgaard et al.[20] To the best of our knowledge, no studies have explicitly examined their effectiveness for donor recovery. Similarly, the offer of flexible donation hours has been suggested by some previous studies but has not yet been tested in an experimental setting.[10,41] The same applies to the possibility of booking an appointment online, which was supported by Yuan et al.[30] We call for more research that tests these interventions precisely for donor recovery in the long term.

4.1.1 | Managerial Implications

Based on the insights emerging from our data, we offer the following suggestions for blood donor recovery strategies. (1) Addressing busy people: to engage donors who are positively disposed to donating but have unconsciously lapsed due to their busy lives, we recommend distinct communication regarding this topic. Blood donors showing first signs of lapsing should be approached and given the opportunity to explain their situation, to select a pause-option, and to determine a time period after which they would like to be contacted again. To prevent lapsing and support recovery, we advise implementing and advancing appointment-scheduling solutions that help busy people fit blood donation into their lives. Advertising these possibilities could be a helpful measure, as our results indicate. (2) Implementing a segmentation approach to recovery: in order to target recovery activities, segmentation of former donors, based on their individual consciousness of their decision to stop donating, would be beneficial. Our findings indicate that donors' potential willingness to return and reasons for discontinuing donations vary with the consciousness group. Systematic short surveys could help in this regard. (3) Individualising direct communication: because we find that too few invitations from the blood service provider were an oft-mentioned reason for discontinuation, we suggest furthering the involvement of donors in the optimisation of communication settings. For example, offering individuals the option to adjust how frequently they receive communication mails in the longer term would be an effective measure in this regard.

4.1.2 | Limitations

The present study has some limitations. First, the data gathered in this study is cross-sectional which limits the inferences on causal relationships. Further studies with a longitudinal design are needed to explore the effect mechanisms. Second, the response rate among the former donors invited by mail was low. We thoroughly compared the results

between participants invited per mail and those invited by the panel provider and found congruent results in both groups. These results may have been hampered further by the non-response bias. Third, our most important donor-related reason for discontinuation, a lack of motivation, might bear a measurement problem, as it also contains the agreement with the awareness of the need for blood. Fourth, we based the results on the consciousness of the decision to stop donating on self-reported data. Future research projects could rely on more sophisticated, established scales to measure the constructs of the transtheoretical model. Fifth, the beta coefficients in our regression model, even though significant, were relatively small. This means that the individual reasons for discontinuation do not play a prominent role in explaining consciousness and should be interpreted within the larger context that is presented. For the mediation models, the beta coefficients were slightly higher. It is still important to note that many other factors may also shape the intention to return to blood donation and must be considered. An example of such a factor could be the well-researched constructs from the theory of planned behaviour. Sixth, the differences in blood collection systems across countries may impede the generalizability of our findings to other countries. We are confident that the basic tendencies are transferable. More cross-country research could shed further light on the differences in the donation of blood by donors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Carolin Saltzmann and Silke Boenigk drafted the study, collected and anaysed the data and wrote the manuscript together.

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APPENDIX A

TABLE A1 Sample characteristics

Variable[a]	Overall $N = 1263$	Panel sample $N = 766$	Mail sample $N = 497$
Gender			
Female	659 (52)[1]	354 (46)	305 (61)
Male	601 (48)	411 (54)	190 (38)
Divers	3 (0)	1 (0)	2 (0)
Age			
20–40	424 (34)	229 (30)	195 (39)
41–60	584 (46)	354 (46)	230 (46)
61–73	250 (20)	179 (23)	71 (14)
Missing responses	*5 (0)*	*4 (1)*	*1(0)*
Net household income			
Lower income (< 2000 €)	301 (24)	206 (27)	95 (19)
Middle income (2000–4000 €)	482 (38)	333 (43)	149 (30)
Higher income (> 4000 €)	255 (20)	158 (21)	97 (20)
Missing responses	*225 (18)*	*69 (9)*	*156 (31)*
Blood donation frequency in the past			
1–3 times	408 (32)	268 (35)	140 (28)
4–7 times	325 (26)	211 (28)	114 (23)
8 or more times	530 (42)	287 (37)	243 (49)
Blood donation type			
Whole blood	1086 (86)	622 (81)	464 (93)
Plasma	74 (6)	64 (8)	10 (2)
Thrombocytes	6 (0)	5 (1)	1 (0)
Different donations	97 (8)	75 (10)	22 (4)

[a]Data are reported as number (% of group).

TABLE A2 Overview on measurement and means

	Item (7-point Likert scale ranging from 1 (does not apply at all) to 7 (applies entirely)	Mean (SD)
Conscious-ness	I did not consciously decide to terminate blood donation but rather did not go for a while	4.70 (2.42)
	I am still in the process of deciding whether I should go again	2.67 (1.97)
	I consciously decided to no longer donate blood	2.76 (2.25)
Intention to return	I firmly intend to start donating blood again	4.20 (2.16)
	I think that I will start to give blood again soon	3.76 (2.11)
	How likely would you schedule an appointment after this survey? (Very unlikely - very likely)	4.19 (1.96)
Reasons: Donor-related	I know that I am not allowed to donate blood	2.09 (2.01)
	I am/was hindered due to physical problems, such as difficulties with moving.	2.20 (2.04)
	I am/was hindered due to emotional problems, such as being overstrained or depressed	1.96 (1.76)
	I do not live at the place where I went to the donation anymore	2.55 (2.39)
	I moved abroad or stayed abroad most of the time (travelling, occupational stays)	1.28 (1.10)
	I have/had little time due· · · to receiving and/or caring for children	1.98 (2.01)
	· · · to obligations such as work, housework and/or study	3.09 (2.36)
	· · · to obligations such a new job or switching jobs	2.02 (1.95)
	· · · to hobbies, sports, or other leisure activities	1.85 (1.60)
	· · · to family events, such as elderly care or a funeral	1.67 (1.55)
	· · · to pregnancy/breastfeeding. (women)	2.31 (2.37)
	I did not go to blood donation anymore because of my fear of · · · needles.	1.61 (1.47)
	· · · the sight of blood	1.46 (1.27)
	· · · circulatory problems	2.27 (2.05)
	· · · physical injury	1.41 (1.20)
	· · · infectious diseases	1.65 (1.48)
	· · · medical disqualification	1.89 (1.80)
	This fear has worsened over time	1.80 (1.62)
	I know that blood is needed; I could just no longer motivate myself to go to the donation	3.68 (2.31)
	To donate blood is not important to me anymore	2.02 (1.59)
	I believe I contributed enough	1.95 (1.55)
	I find it annoying to go to the donation	1.96 (1.56)
	My friends and/or family members · · · do not like me to donate blood	1.54 (1.41)
	· · · also wanted to stop or already stopped	1.52 (1.28)
	· · · thought it was better if I stopped donating blood	1.46 (1.31)
	· · · made bad experiences that put me off	1.35 (1.11)
	I think that donating blood is useless	1.24 (0.90)
	I no longer believe in the purpose of donating blood	1.25 (0.95)
	I have the feeling that it does not matter if I give blood or not	1.76 (1.48)
	My blood is not needed	1.59 (1.37)
	I preferred to do good in a different way (volunteering or donating money)	1.79 (1.50)
	The decision where to donate is difficult for me	1.93 (1.66)
Reasons: Service-related	I did not know where and when to donate	2.16 (1.87)
	There were no longer donation hours offered at the place where I used to donate	2.06 (1.96)
	The place where I could donate blood is inconvenient for me	2.58 (2.16)
	I could not donate because of the donation times	2.86 (2.22)

TABLE A2 (Continued)

	Item (7-point Likert scale ranging from 1 (does not apply at all) to 7 (applies entirely)	Mean (SD)
	The blood donation service does not work with up-to-date technology	1.68 (1.36)
	The donation facilities have not been clean enough	1.42 (1.07)
	The donation facilities have not been visually appealing to me	1.71 (1.41)
	The appearance of the donation facilities did not correspond to the occasion	1.59 (1.29)
	I found the atmosphere at the donation facilities unpleasant	1.72 (1.44)
	The friendliness or the appearance of the employees was not adequate	1.59 (1.33)
	The treatment or the service of the employees was not adequate	1.59 (1.34)
	The attention and empathy of the employees were not adequate	1.62 (1.33)
	The employees were not trustworthy	1.41 (1.09)
	The questions about my health and lifestyle were inappropriate	1.84 (1.57)
	I was deferred one or more times what I found demotivating	1.74 (1.55)
	I had one or more negative physical experiences (like vasovagal reactions)	2.37 (2.10)
	I experienced complications during the blood draw (pain, heavy bleeding, or hematoma)	1.75 (1.52)
	The waiting times were too long	2.15 (1.63)
	In general, donating blood took too long	1.94 (1.49)
	The information at the single stations in the procedure had not been sufficient	1.58 (1.25)
	I did not receive enough gratefulness and appreciation by the donation service	1.79 (1.50)
	I was not satisfied with the nature of the appreciation. I wish for a material or money	2.09 (1.80)
	I do not like the organisation itself, its guidelines, policies, or operating principles	1.69 (1.39)
	The blood donation service does not operate at the best interest of donors/recipients	1.74 (1.43)
	I did not see/receive enough advertisement of the blood donation service	2.48 (2.04)
	I received (too) few invitations to donate	2.71 (2.18)
	I received (too) many invitations to donate	1.59 (1.31)

Note: SD, standard deviation; 7-point Likert scale (1 = does not apply at all, 7 = applies entirely); $N = 1263$.

TABLE A3 Overview of the results of the exploratory factor analysis of the reasons

Variable[a]	Busy Life	Health & Defer-ral	Fear	Social Norm	Atti-tude Blood Don.	Need for blood	Serv Qual Tangibles	Serv Qual Employees	Place	Wait time	Ad-verse events	No solicit-ation	Scepticism Organisation
Work/housework/study	0.76												
New job or switching	0.52												
Hobbies, sports	0.47												
Donation timings	0.43								0.40				
Family events	0.33												
Parenting	0.32												
Fear of deferral		0.60											
Self-deferral		0.43											
Physical health		0.40											
Emotional health		0.33											
Deferrals experienced		0.31											
Fear needles			0.79										
Fear sight of blood			0.76										
Fear worsened			0.57										
Fear physical injury			0.57										
Fear infectious diseases			0.46										
Peer pressure				0.71									
Peers believe				0.63									
Peers wanted to stop				0.57									
Peers' bad experiences			0.31	0.39									
Is annoying					0.65								
Not important to me					0.61								
Contributed enough					0.52								
No longer motivate					0.50								
Donating is useless						0.75							
Not important						0.74							
My blood is not needed					0.31	0.50							
Does not matter					0.39	0.47							
Facilities not appealing							0.84						
Correspond occasion							0.83						
Unpleasant atmosphere							0.74						

TABLE A3 (Continued)

Variable[a]	Busy Life	Health & Defer-ral	Fear	Social Norm	Atti-tude Blood Don.	Need for blood	Serv Qual Tangibles	Serv Qual Employees	Place	Wait time	Ad-verse events	No solicit-ation	Scepticism Organisation
Facilities not clean							0.70						
Old technology							0.50						
Service employees								0.80					
Attention/empathy								0.77					
Appearance								0.77					
Trustworthiness							0.36	0.63					
Place inconvenient									0.78				
Know where/when									0.62			0.30	
No donation hours									0.48				
Moved									0.48				
decision where difficult									0.40				
Waiting times										0.78			
Took too long										0.72			
Lack of information							0.31			0.33			
Adverse event											0.89		
Fear vasovagal reaction			0.38								0.64		
Complications			0.30								0.33		
Few invitations									0.37			0.79	
No advertisement									0.31			0.78	
Organisation selfish													0.81
Guidelines, policies, etc.													0.78
Not enough appreciation								0.32					0.44
Other appreciation					0.30								0.44

[a]Factor loadings $\lambda < 0.3$.

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SHORT COMMUNICATION

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Designing and testing an ethnic-ancestry question for Australian blood donors: Acceptability, feasibility, and understanding

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Abstract

Objectives: We aimed to evaluate the acceptability, feasibility, and understanding of a donor ethnic-ancestry question with Australian blood donors.

Background: Ethnic-ancestry assists blood collection agencies to meet the demand for rare blood-types. However, there is no standard ethnicity question used by health/blood services around the world and we do not know how blood donors in Australia will respond to being asked for this information.

Methods/Materials: A survey and ethnic-ancestry question was administered to a sample of donors ($n = 506$) to evaluate their views on being asked for their ethnic-ancestry, test a comprehensive ethnic-ancestry list, and determine the level of information required by donors.

Results: Donors reported being very comfortable providing their ethnic-ancestry and the majority of donors found an ethnic-ancestry option they were happy with (91.3%). Overall donors reported a high level of understanding of why ethnic-ancestry was important to blood donation. However, when provided more information on why ethnic-ancestry is required, donors reported increased understanding.

Conclusion: The findings from this study demonstrated that it is acceptable and feasible to introduce a comprehensive ethnic-ancestry question for Australian blood donors. We also found that a greater understanding is achieved when a more comprehensive explanation for inclusion of the question is provided.

KEYWORDS
blood donors, ethnicity, ethnic-ancestry

1 | INTRODUCTION

Information on donor ethnicity is critically important in assisting blood collection agencies (BCA) to adequately meet the demand for rare blood-types. Between 2017 and 2020, Australian Red Cross Lifeblood (Lifeblood) experienced a 50% increase in demand for phenotyped red blood cell units, most commonly required for patients needing chronic transfusion support.[1] Increased migration has resulted in more minority groups requiring blood types that are not present in the majority populations of their new countries[2]—for example, the phenotype Fy(a-b-) found among those with West African ancestry. A survey of 42 BCAs worldwide revealed that many do not record blood donors' ethnicities, either because they are not legally allowed, or because the data has not yet been of interest.[2] Although Lifeblood routinely

collects information on donors' country of birth, this information is not sufficient for identifying which donations to perform extended phenotyping on to locate rare blood-types. While the majority of Lifeblood's donors were born in Australia and people from sub-Saharan Africa, Melanesia/Polynesia, or East/South-East Asia are underrepresented in the donor panel,[3] country of birth is not a reliable indication of donors' ethnic-ancestry. For instance, in the 2016 Australian census, a fifth of people born in Australia (21%) had at least one parent born abroad and over 300 ancestries were separately identified.[4] For these reasons, Lifeblood identified the need to introduce an ethnic-ancestry question for donors.

The Australian Privacy Principles guidelines (APP) classify racial or ethnic origin as sensitive information.[5] In an Australian context, these sensitivities are layered in a history of colonisation and racial government policies that have shaped people's experiences and understanding of race and ethnicity.[6,7] Accordingly, the APP requires that for organisations to legally collect this information, the data must be reasonably necessary for one or more of their functions or activities and that the individual is adequately informed before consenting to the collection.[5] Consequently, prior to commencing routine collection of donor ethnic-ancestry, it is important to ensure that donors understand why it is required and are comfortable providing it.

As well as meeting our legal obligations, adequately explaining to donors why BCAs need this information may result in them being more comfortable about providing the information and therefore increased uptake. In their study exploring the perceptions of general practitioners and patients in Ireland, Roura et al.[8] concluded that the implementation of an ethnicity question requires a strong rationale that makes sense to patients to ensure greater buy-in. Similarly, in the study by Alfridi and Murji[9] exploring the quality and limits of ethnicity data collected by higher education and health services in England, participants suggested that low disclosure rates were, in part, due to a lack of confidence in what the data was being used for.[9] Two studies[10,11] in the USA tested whether giving patients information explaining the rationale for the collection of ethnicity data made them more comfortable providing it. Patients were asked how concerned/comfortable they were towards providing their ethnicity before and after being given information.[10,11] In both studies, information explaining the rationale for the data collection increased patients' comfort level, and in one of the studies the increase was higher among those from ethnic-minority backgrounds.[10,11] While these findings provide valuable insight on the collection of ethnicity data, we have been unable to locate research that evaluates the use and acceptability of an ethnicity question with blood donors.

There is no standard ethnicity question used by health services in Australia or BCAs around the world. Race and ethnicity are complex social constructions[12] resulting in vast differences in the way governments and services have categorised them. For BCAs the need for this data is to help locate specific blood-types found more frequently in certain groups. Unlike race, ethnicity takes into account ancestral homelands[13] and can provide more specific information needed when looking for blood groups and phenotypes which have developed through a combination of environmental factors, migration/isolation of human populations, and in response to contact with infectious diseases that are often regionally specific.[14,15] However, there is no uniform list of ethnicities and due to the subjective, relational, and created nature of ethnic groups, they number in the thousands and can be categorised in different ways.[12,13,16] Research has shown that the options people are presented with to classify themselves can make a difference to their uptake and quality of responses. In Alfridi and Murji,[9] fewer than half of respondents were satisfied with the ethnic categories used by their organisation when collecting this information. Respondents wanted more granularity in the categories and the findings suggested more detailed data can increase the quality of information collected.[9] Burton et al.[17] suggest that it is not only important to focus on what is relevant to those collecting the data, but to ensure it is relevant to the respondent and to consider the impact of acceptability, phrasing, position, and mode. Consequently, while a much smaller list of ethnic categories would be adequate to meet the current needs of a BCA, we decided to develop a more comprehensive list.

Therefore, the aim of our study was to determine donor acceptability of a request to provide their ethnic-ancestry, to test the effect of providing different levels of information on donors' understanding of why the information is needed, and to test whether a comprehensive list of ethnicities was feasible and granular for donors to complete. Given the findings in previous research that people with ethnic-minority ancestry may be less comfortable providing the information, we hypothesised that there will be differences in donors' understanding and acceptability of the ancestry question for Australian donors who reported a European ancestry compared to those with non-European ancestries.

2 | METHOD

2.1 | Procedure

The study was approved by the Lifeblood Human Research Ethics Committee. An online survey was emailed to eligible donors ($n = 3000$; 16.9% response rate) in July 2019. Donors were considered eligible to participate if they had made at least one successful donation in the previous 12 months, had not been contacted for research in the last 6 months, and had a valid email address. To diversify the sample, at least 2000 of the eligible donors had recorded a country of birth other than Australia. Eligible donors were randomised to receive one of two question preambles (a short preamble and a long preamble) about why we were asking for ethnicity using simple randomisation performed in Microsoft-Excel-2016.

2.2 | Ethnicity question and preambles

A list of ethnicities for donors to choose from was created in consultation with Lifeblood's Red Cell Reference Team, to ensure that the information provided would assist in meeting current and future

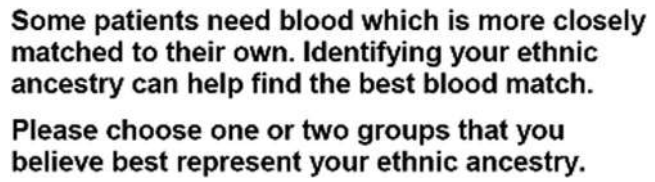

FIGURE 1 Short preamble

transfusion demands. The list was also informed by the recommendations in the literature to provide more granularity and relevance to respondents to ensure greater acceptability and uptake.[9,17] Consequently, we developed a comprehensive ethnic-ancestry list containing 53 choices—including 10 that allowed for a written response (Appendix S1). It was presented to donors via seven regional dropdown lists with headings matching those presented in Appendix S1. Donors were asked to select up to two options that they believed *'best represented their ethnic-ancestry'* or alternatively to select the *'prefer not to say'* option. Donors who selected *'prefer not to say'* were asked to provide the reason why they chose this option. To determine how much information is required for donors to understand why Lifeblood is asking for their ethnic-ancestry, two different question preambles were tested, one that was short with less detail (Figure 1) and a longer version with additional detail on why ancestry information was needed (Figure 2). The two preambles were developed with representatives from Lifeblood's legal and marketing teams to ensure they met their respective requirements.

2.3 | Measures

After participants answered the ethnic-ancestry question, they completed a survey to determine their understanding of why they were being asked to provide their ethnicity, their satisfaction with the options provided, and how easy it was to find an option they were happy with. Donors were asked to indicate *'yes'*, *'maybe'*, or *'no'*, as to whether they understood why information on donors' ethnicity was important to Lifeblood. Donors were asked to indicate *'yes'* or *'no'* to whether they were able to find an option they were happy with. Those who responded *'yes'* to being happy with their choice were asked to rate how easy it was to find the option they were happy with using an 11-point scale (0 = 'very difficult' to 10 = 'very easy'). Those who responded 'no', indicating they were not able to find an option they were happy with, were asked why and were provided with three options: *'I do not know my ethnic-ancestry'*, *'I had to select an "Other" option and write in my ethnic-ancestry'*, and *'something else'*. Donors were allowed to multiselect options and those who selected *'something else'* were provided with an optional textbox to provide details. Lastly, donors were asked to indicate how comfortable they were about providing their ethnic-ancestry information to Lifeblood on an 11-point scale (0 = 'very uncomfortable' to 10 = 'very comfortable').

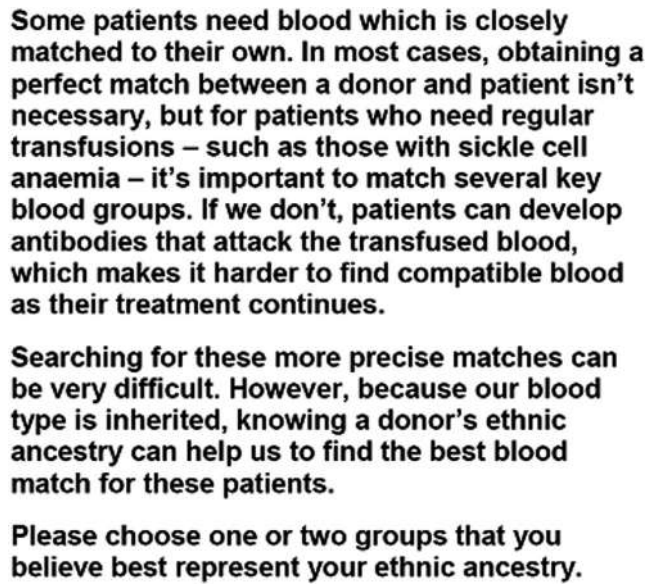

FIGURE 2 Long preamble

2.4 | Analysis methodology

Free text responses were compiled and analysed using inductive thematic analysis in Microsoft-Excel-2016. Coding schemes identifying key categories were revised and expanded, resulting in key themes.

Statistical analyses were performed using statistical software IBM SPSS (IBM SPSS Statistics 23.0; IBM Corporation). Survey responses were described by totals (percentages) for categorical variables, and medians/interquartile ranges Med(IQR) for non-parametric ordinal data. Univariate differences between preambles one and two, and European and non-European ethnic-ancestry were examined using chi-square goodness of fit tests for frequency data, and Mann Whitney U tests for non-parametric ordinal data. European was defined as anyone who selected a European-ancestry as either their first or second choice. Statistical significance was defined at $p \leq 0.05$.

3 | RESULTS

The sample consisted of 506 donors, with 266 receiving the short-preamble and 240 receiving the long preamble. Overall, 68% of donors reported a European ethnic-ancestry for their first selection, with British/Irish the most common response (52.3% short-preamble and 51.2% long-preamble). The majority of donors reported only one ethnic-ancestry for both preambles (79.7% and 80.4%). No notable differences were observed for ethnic-ancestry selection between the short and long preambles. A minority of donors selected *'prefer not to say'*—short-preamble: 6(2.3%) and long-preamble: 5(2.1%). Of these, nine participants provided a written response when asked why they chose *'prefer not to say'* and these responses were grouped into three themes: believing that ethnicity was not relevant to blood donation (all from those who received the short-preamble), being unsure of their

ethnic-ancestry, or confusion between ethnicity and nationality (i.e., looking for their country of birth). An overview of donor response is available in Appendix S3.

3.1 | Finding an ethnic-ancestry option they are happy with

A majority of donors indicated that they found an ethnic-ancestry option they were happy with (91.3%). When asked to indicate how easy it was to find an ethnic-ancestry the were happy with, respondents reported a median score of 8.[8–10]

Only 43 donors (8.4%) reported that they did not find an acceptable ethnic-ancestry option. Of these, 11 reported their reason was having to select *'other'* and write in their ethnic-ancestry, five reported not knowing their ethnic-ancestry, and 30 reported it was *'something else'* with 28 providing a qualitative response. The most common theme from the small number of the qualitative responses was confusion between one's nationality and one's ethnic-ancestry. For example, a small number of donors requested a non-Indigenous Australian or New Zealander ethnic-ancestry. Participants also used the qualitative response to request certain ethnicities to be added to the list. Sinhalese, Tamil, Lebanese, and Hispanic/Portuguese/Latin American received the most mentions and were also the most commonly entered into the write-in *'other'* options when participants answered the ancestry question.

3.2 | Donors' perceptions of providing ethnic-ancestry information

Overall, 74.3% of participants responded *'yes'* to understanding why donors' ethnic-ancestry was important to Lifeblood, while 11.0% responded no, and 14.7% responded maybe. Further, we investigated differences for those who responded yes or no to the question. Looking at differences between the preambles, 83.6% of those who received the short-preamble reported understanding compared to 91.1% who received the long-preamble; $\chi^2 = 5.302$, $p = 0.021$. Additionally, donors with European ancestries reported higher levels of understanding (92.9%) than those with non-European ancestries (74.8%); $\chi^2 = 25.53$, $p < 0.0001$. Lastly, we investigated differences between ethnic-ancestry for the preamble version they were provided; donors with European ancestries who received the short-preamble (90.6%) were more likely to report that they understand than those with non-European ancestries (68.9%; $\chi^2 = 16.08$, $p < 0.0001$). Similarly, donors with European ancestries who received the long-preamble reported higher levels of understanding (95.3%) than those with non-European ancestries (82.0%; $\chi^2 = 8.96$, $p = 0.003$).

Overall, donors reported being very comfortable providing their ethnic-ancestry to Lifeblood (10 [9, 10]), with no notable differences between those who received different preambles. Those reporting European ancestries reported slightly higher median scores (10 [9, 10]) than those reporting non-European ancestries (10 [8–10]; $U = 21200.5$, $p < 0.0001$).

4 | DISCUSSION

To our knowledge, this study is the first to evaluate the use and acceptability of an ethnicity question with blood donors. Our results indicate that overall, donors in Australia are very comfortable providing their ethnic-ancestry to Lifeblood. They demonstrate that while a majority of donors understand why the information is needed regardless of the explanation provided, greater understanding is achieved when a more comprehensive explanation is provided. The findings also confirm that it is feasible to introduce a comprehensive ethnic-ancestry list and that donors find it easy to locate their ancestry within the list and are happy with their choice. Importantly, the findings reveal differences in both comfort and understanding between Australian donors with European and non-European ethnic-ancestries.

Although a majority of donors with non-European ancestry were comfortable providing their ethnic information regardless of the preamble version, they nonetheless had lower comfort levels than those with only European ancestries. This is consistent with the studies by Baker et al.,[10,11] which found that ethnic-minority patients were less comfortable than other patients having their ethnicity recorded. While the difference in our study was minimal, it is nonetheless significant and should be considered when BCAs ask donors for this information. As there were limited qualitative responses in our study, we cannot be certain why comfort was lower among those with non-European ancestry. Baker et al.[10,11] suggest that ethnic-minorities in the USA may have lower comfort providing their ethnic information due to historic and current discrimination; it is plausible that the same could be true for minorities in Australia. Similarly, previous research exploring ethnic-minority blood donation in Australia has shown that for some communities, real and/or perceived experiences of discrimination in their everyday lives can impact their views on blood donation.[18] Increasing the diversity of the donor panel is important to help BCAs identify rare blood types and provide the best match for patients to prevent alloimmunization.[1,3] Therefore, it is important that BCAs address any concerns that ethnic-minority donors may have through relevant, easy to understand information about the collection of ethnicity data. Additional qualitative research with ethnic-minority communities to co-design appropriate messaging and educational materials on the need for ethnic ancestry information may assist in raising comfort and understanding.

The number of participants in our study who selected *'prefer not to say'* was very low, and willingness to provide ethnicity details was high. Nevertheless, our findings can provide lessons that may help improve the uptake further. While only a small number of donors provided a reason for not disclosing their ancestry, the qualitative responses revealed that some participants selected *'prefer not to say'* due to confusion between nationality, country of birth, and ethnicity. Therefore, we recommend that donors are provided with information explaining what ethnic-ancestry is and why it is more useful than country of birth or nationality. The wider literature also suggests that privacy concerns and hesitance about what race/ethnicity data will be used for can impact disclosure.[9–11] While we cannot know from our limited data whether this was a factor in our study, we recommend

that BCAs provide donors with privacy assurances and a detailed understanding what the information will be used for.

A majority of participants indicating that they were able to find an option they were happy with when presented with the comprehensive list of ethnic-ancestries. While only a small number were not happy with their choice because they could not find their specific ancestry and had to use a write-in *'other'* option rather, we have recommended expanding the list to include the ancestries that received the highest write-in responses and which were raised the most frequently within the qualitative responses. This final list of ethnic-ancestries (Appendix S2) will be introduced by Lifeblood.

Although this study provides a critical first insight into donors' acceptability of providing their ethnicity, there were several important limitations. First, donors self-selected to participate in the survey and therefore our data may over-represent those who were strongly motivated by the research topic or who understood the email written in English. Second, a response rate of 16% was obtained for this survey. Although this is on the lower end of response rates, is not unusual for Australian blood donation surveys (27% vs. 10.3%).[19,20] Future studies should consider different survey recruitment methodologies to increase response rates. Third, we were unable to link the survey to the donor records and were unable to determine demographics of those who completed the survey; therefore, we were unable to determine the response rate based on country of birth. Future surveys should include the ability to link through to donation records.

Overall, our results have demonstrated the acceptability of Australian blood donors to provide their ethnicity to Lifeblood to target rare blood-types. A comprehensive list of ethnicities, as well as detailed information, can create greater and willingness to provide the information and understanding about why this information is needed. Lifeblood is progressing towards a full launch of the question with all donors being encouraged to provide their ethnic-ancestry.

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AUTHOR CONTRIBUTION

Luke Gahan: Conceptualization, Methology, Investigation, Formal Analysis, Writing – Original draft, Writing – review and editing, Project administation. Carley Gemelli: Formal Analysis, Writing – Original draft, Writing – review and editing. Sarah Kruse: Formal Analysis, Writing – review and editing. Tanya Davison: Conceptualization, Funding Acquisition, Supervision, Writing – review and editing.

CONFLICT OF INTEREST

The authors have no competing interests.

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SUPPORTING INFORMATION

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SHORT COMMUNICATION

Diagnostic accuracy of Abbott Architect Assay as a screening tool for human T-cell leukaemia virus type-1 and type-2 infection in a London teaching hospital with a large solid organ transplant centre

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Abstract

Aim: In the United Kingdom, organ donors/recipients are screened for evidence of human T-cell leukaemia virus type-1 and type-2 (HTLV-1/2) infections. Since the United Kingdom is a low prevalence country for HTLV infections, a screening assay with high sensitivity and specificity is required. Samples with repeat reactivity on antibody testing are sent to a reference lab for confirmatory serological and molecular testing. In the case of donor screen, this leads to delays in the release of organs and can result in wastage. We aim to assess whether a signal/cut-off (S/CO) ratio higher than the manufacturer's recommendation of 1.0 in the Abbott Architect antibody assay is a reliable measure of HTLV-1/2 infection.

Methods: We conducted a 5 year retrospective analysis of 7245 patients from which 11 766 samples were tested on the Abbott Architect rHTLV I/II assay. Reactive samples (S/CO >1) were referred for confirmatory serological and molecular detection (Western Blot and proviral DNA) at UK Health Security Agency, (formerly PHE, Colindale), the national reference laboratory. Electronic, protected laboratory and hospital patient databases were employed to collate data.

Results: A total of 45 patients had initially reactive samples. 42.2% ($n = 19/45$) had an S/CO ratio > 20, with HTLV infection confirmed in $n = 18/19$ and indeterminate confirmatory results in $n = 1/19$. No samples with an S/CO ratio <4 (48.9%, $n = 22/45$) or 4–20 (8.9%, $n = 4/45$) had positive confirmatory results on subsequent confirmatory testing.

Conclusion: Samples with an S/CO >20 likely represent a true HTLV-1/2 infection. Reactive samples with an S/CO <4 were unlikely to confirm for HTLV infections. Interpretation of these ratios can assist clinicians in the assessment of low reactive samples and reiterates the need for faster access to confirmatory testing.

KEYWORDS
HTLV-1/2, screening, transplant

1 | INTRODUCTION

Human T-cell leukaemia virus type-1 and type-2 (HTLV-1 and HTLV-2) were first isolated in 1979 and 1981 respectively, the former the first retrovirus to be discovered.[1] They are enveloped, single-stranded RNA viruses members of the genus Deltaretrovirus of the Orthoretrovirinae subfamily of the family of Retroviridae.[2] HTLV-1 has been found to cause lifelong infection of T-lymphocytes, and is associated with the development of haematological malignancies and neurological sequelae.[3–5] Although myelopathy is a recognised association with HTLV-2, other disease associations with HTLV-2 are less well established.

It has only been since 2011 that pre-screening for HTLV infection in solid organ transplant recipients and donors was introduced in the United Kingdom because of growing concern about the infection risk and progression to disease by this route.[6–8] Timely and accurate diagnostics are vital given the occasionally short assessment window for serological evaluation at or around the time of organ transplantation.[2]

The aim of this study was to assess whether a signal/cut-off (S/CO) ratio higher than the manufacturer's (Abbott Architect) recommendation of 1.0 is a reliable measure of HTLV-1/2 infection using data from a large UK solid organ transplant centre. Secondary objectives were included which evaluated the diagnostic accuracy of various S/CO ratio categories to improve screening outcomes.

2 | METHODS

A retrospective analysis was performed on data from 11 766 blood serum samples from 7254 patients submitted for HTLV-1 and HTLV-2 testing over a 5 year period between 2013 and 2017 at the Royal Free Hospital (RFH) in London, United Kingdom. Samples were drawn from screening patients from the renal, hepatology and haematology/oncology departments, most of them screened as potential transplant recipients but also included samples from organ donors. Samples were also included from patients screened from immunology and neurology departments. Basic demographic information was recorded from all patients, including co-presenting viral infections such as Hepatitis B, C, D and HIV. Retrospective request for intravenous immunoglobulin (IVIG) therapy was confirmed from the Immunoglobulin Database (https://igd.mdsas.com/) and cross-checked with RFH's pharmacy dispensing records. Ethics approval was not sought as all data were collected routinely for clinical purposes.

2.1 | Primary analysis

Samples were tested using the Abbott Architect rHTLV I/II assay (Abbott Laboratories Weisbaden, Germany) at our laboratory. All samples with values S/CO ≥1.0 were sent to the UK National Reference Department (VRD; Virus Reference Department, UK Health Security Agency) for confirmatory serological testing, where the initial clotted samples were again tested on the Abbott Architect rHTLV I/II, and reactive samples were then tested by Western blot. Where unseparated whole blood on ethylenediaminetetraacetic (EDTA) samples were available from patients who had HTLV I/II reactive serology, the EDTA samples were tested by a nested HTLV DNA polymerase chain reaction (PCR). A final status was determined by the reference lab using the Western blot (WB) and PCR results, and was reported as the following: HTLV-1 positive, HTLV-2 positive, HTLV untyped, HTLV indeterminate or HTLV negative.

The sensitivity, specificity, positive predictive values and negative predictive values were calculated for S/CO ratios in the ranges 1–4, 4.01–20 and >20. The standard was a composite of tests run by the VRD; defined as a positive confirmatory WB or proviral PCR.

TABLE 1 Patient demographics of this study population

Patient demographics	
Patients (%)	Male: 64.4% (29/45)
	Female: 25.6% (16/45)
Mean age (range)	49.8 (19–85)
Reason for testing (%)	
Pre-transplant screening	80% (36/45)
Clinical indication	15.7% (7/45)
Donor screening	2.2% (1/45)
Not documented	2.2% (1/45)
HIV positive (%)	2.2% (1/45)
Hepatitis B positive (%)	6.7% (3/45)
Hepatitis C positive (%)	6.7% (3/45)

2.2 | Secondary analysis

S/CO values were stratified into groups first proposed in the paper by Tosswill & Taylor to aid in the clinical interpretation of results.[2] Values were stratified into the following groups: S/CO 1–4, 4.01–20, and >20. Tosswill & Taylor suggested that an S/CO cut-off of <4 could be considered a negative result as no samples with values in this range subsequently confirmed positive for HTLV-1/2 infection. All samples that had an S/CO value initially >20 were subsequently found to have HTLV infection. Although the samples with S/CO values between 4.01 and 20 were found to have an indeterminate status on additional testing, subsequent repeat sampling found most of these to be false positive results.

	In-house Abbott Architect S/CO values		
	S/CO 1–4	S/CO 4.01–20	S/CO > 20
Western blot testing			
Seropositive	—	—	94.7% (18/19)
Seronegative	90.9% (20/22)	100% (4/4)	—
Indeterminate	9.1% (2/22)	—	5.3% (1/19)
HTLV-1 DNA PCR			
Positive	—	—	63.2% (12/19)
Negative	45.4% (10/22)	50% (2/4)	36.8% (7/19)
Not tested	54.5% (12/22)	50% (2/4)	—

TABLE 2 Western blot and viral PCR testing outcomes across the samples stratified by in-house Abbott Architect S/CO groups

3 | RESULTS

Of the 11 766 samples tested there were 114 samples (1%) from 45 patients that were initially reactive that formed this cohort, with patient demographics described in Table 1. Each patient had an initial serology sample with an Abbott Architect S/CO value ≥1.0. When repeated at the reference lab, all the initial first positive samples had an S/CO value ≥1.0.

A 26.7% (12/45) of patients were bone marrow or stem cell transplant recipients, 15.6% (7/45) were renal transplant recipients, 8.9% (4/45) were liver transplant recipients, 28.9% (13/45) were end-stage renal failure on or being considered for dialysis, 8.9% (4/45) were undergoing plasmapheresis, and 6.7% (3/45) had other medical comorbidities. In addition, one patient (2.2%) was under investigation for spastic paraparesis, and one (2.2%) was a transplant donor.

The Western blot and viral PCR testing outcomes are given in Table 2. Samples tested in WB were seropositive in 40% ($n = 18/45$) of patients, seronegative in 53.3% (24/45) and indeterminate in 6.7% (3/45) of patients. Of the in-house S/CO 1–4 group, 90.9% (20/22) were WB seronegative and 9.1% (2/22) were indeterminate. Of the in-house S/CO 4.01–20 group, 100% (4/4) of patients were WB negative. 94.7% (18/19) of patients in the in-house S/CO >20 group were WB positive, and 1 patient was WB indeterminate on the initial sample but negative by PCR on a subsequent sample.

HTLV-1 DNA was detected by PCR in 26.7% (12/45) of patients, all of whom had S/CO >20 on initial HTLV serology. None of the samples from the 45 patients were positive for HTLV-2 DNA by PCR. In the in-house S/CO 1–4 and 4.01–20 group there were no positive HTLV-1 DNA PCR results, although 53.8% (14/26) of these patients did not undergo PCR testing at the reference lab as an EDTA sample was never sent. In the in-house S/CO 4.01–20 group, 50% (2/4) of the patients had samples which had undergone PCR testing.

Follow-up samples were received for 62.2% (28/45) of patients, totalling 65 samples, of which 50% (14/28) were in the initial in-house S/CO 1–4 group, 7.1% (2/28) in the S/CO 4.01–20 group, and 42.9% (12/28) were in the S/CO > 20. A total of 53.3% (24/45) patients had confirmatory proviral DNA sent, including 71% (10/14) of those in the initial in-house S/CO 1–4 who were followed up, and all the patients followed up in the remaining two groups. It is advised by our laboratory, as well as the reference laboratory, that repeat samples should be sent at least 2 weeks after the initial reactive samples. In our cohort, there were a proportion of patients who had samples sent <2 weeks as well as >2 weeks as recommended. Of all patients who had follow-up samples, 46.4% (13/28) had repeat samples sent <2 weeks after the first sample, of which the majority (76.9%; 10/13) were EDTA samples to confirm proviral DNA. Repeat samples sent >2 weeks were received from 85.7% of follow-up patients (24/28), with 50% (12/24) in the initial in-house S/CO 1–4 group, 4% (1/24) for the S/CO 4.01–20 group, and 45.8% (11/24) in the in-house S/CO >20 group.

Eight patients had IVIG administered before submitting at least one of their samples for HTLV serological testing, equating to a 10.5% (12/114) of samples. In the in-house testing of these samples, 58.3% (7/12) had an S/CO 1–4, 33.3% (4/12) were S/CO 4.01–20, and 8.3% (1/12) was S/CO >20. The one patient with a positive S/CO >20 subsequently had HTLV-1 PCR detected on confirmatory sampling. None of the S/CO 4.01–20 had confirmed HTLV-1 from the reference lab testing.

The diagnostic accuracy against reference lab positive from the initial S/CO ratio of >20, the sensitivity and the PPV of the initial Abbott Architect is 100% (95% CI 79.4%–100%) and 96.3% (95% CI 81%–99.9%) respectively. HTLV infection was not confirmed in any individual with S/CO ratio 1–4, with a negative predictive value of 21.7% (95% CI 7.5%–43.7%). In the S/CO group 4.01–20 there were also no confirmed infections, and this had a negative predictive value of 56.1% (95% CI 39.7%–71.7%).

4 | DISCUSSION

The aim of this study was to describe the experience of HTLV-1/2 screening in a tertiary solid organ transplant centre in the United Kingdom. From the large cohort of samples tested, there were a significant number of confirmed HTLV-1 cases compared with the experience of other research groups both historically and internationally.[5,9]

The goal of screening is to ensure that blood, tissues and organs are safe for donation. Identification of recipients with HTLV is

important, as transplantation and in particular associated immunosuppressive therapy, may be important in altering immunological control of HTLV infection.[6] The majority of local hospital labs that embark on HTLV-1/2 testing only have a screening test such as Abbott Architect rHTLV I/II assay at their disposal. Therefore when samples are tested and reactive results obtained, these patient samples must undergo additional testing before the recipient or donor organs are deemed safe for transplantation. Delays in testing and laboratory processing ultimately lead to delays in donation and in most cases wastage. The ability to draw conclusions about the HTLV status of the patient based on the S/CO value could allow for appropriate risk-stratification and reduced time lost.

Similar to datasets previously described, categorization of S/CO values can aid in rapid identification of cases suggestive of true HTLV-1/2 infection.[2] It is significant that none of the patients with S/CO values ≤4 had detectable virus on subsequent PCR testing. This has potential significant implications on transplantation risk assessments, particularly pertaining to the clinical interpretation of low-titre serological positivity suggestive of low risk of true HTLV infection for a transplant recipient or from donor tissue for an organ recipient facing an imminent transplant. This has ramifications for cost-effectiveness considerations in transplant delay and the avoidance of organ wastage.

Intravenous immunoglobulin therapy (IVIG) is a therapy used in a variety of conditions involving the infusion of donor-derived IgG.[10] False-positive serological testing due to non-specific reactivity of donor IgG is a widely known consequence following IVIG use.[11,12] In our cohort, of those who had received IVIG prior to serological testing only eight had HTLV-1/2 reactive serology. Of the 12 samples with reactive serology, the majority (92%; 11/12) were within the low (1–4) and indeterminate (4.01–20) S/CO value range. The one case with an S/CO value >20 was subsequently demonstrated to be PCR positive for HTLV-1. As HTLV has been routinely screened for in the United Kingdom in blood products since 2002 and donor transmission of HTLV is very low risk from leucodepleted blood components, this was likely to be un-related to IVIG administration.[13] This further supports the stratification of S/CO > 20 as likely representative of true infection despite the use of IVIG, however our data size precludes any concluding statement on contribution of IVIG to HTLV-1 reactivity.

There were some limitations in the analysis of our cohort. The stratification of S/CO is dependent on the use of the Abbott Architect rHTLV I/II assay. However, this is one of the more widely used assays in the United Kingdom and worldwide for HTLV screening. Less than half of the samples sent to the reference lab received HTLV PCR testing because whole blood on EDTA blood was not available, though of the samples tested none were positive in the S/CO 1–4 and S/CO 4.01–20 groups, which supports the findings of Tosswill et al. There was limited demographic information including ethnicity recorded on patients records, therefore it was impossible to assess impact. It should also be noted that our analysis is conducted in a low-prevalence country setting for primary HTLV disease – our proposed cut-off may not be applicable in high prevalence settings but would be worthy of further investigation.

Though our data indicates that low level reactive samples are likely to represent false positives the ideal situation would be a commercially available HTLV PCR test, which would enable laboratories which perform initial HTLV testing and require rapid confirmatory HTLV investigation to more confidently exclude HTLV infection in the event of reactive samples. It is acknowledged that stratification of S/CO values into groups reduced sample sizes resulting in wider confidence intervals in the diagnostic accuracy analysis. However, the significant positive predictive value of the S/CO >20 group aids the role of serological testing, which is known to have limitation in low seroprevalence populations.[14]

5 | CONCLUSION

Samples with an S/CO >20 are likely to represent a true HTLV-1/2 infection. Reactive samples with an S/CO ≤ 4 are unlikely to confirm for HTLV infections. Interpretation of these ratios can assist clinicians in the assessment of low reactive samples. A commercially available HTLV PCR would be a valuable tool in certain hospital settings such as solid organ transplantation where rapid confirmation is desirable.

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CONFLICT OF INTEREST

The authors have no competing interests.

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CORRIGENDUM

The surname of the last two authors were misspelled and the affiliation linked to the last author was incorrect in the poster abstract entitled 'PO5 | Do deferred blood donors with low haemoglobin or low iron stores seek medical care?' by James et al.[1] The correct surnames and affiliation link are presented below.

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