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Establishing an HLA-Typed Plateletpheresis Donor Registry at the Iranian Blood Transfusion Organization

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ABSTRACT

Administering human leukocyte antigen (HLA)-compatible platelets is a tactic for treating patients with poor responses to random platelet injections. HLA-matched platelet provision requires many donors with HLA-typed and organized information. This study, the first of its kind in Iran, aimed to develop a registry system of HLA-typed platelet donors to facilitate the provision of compatible platelets to patients, leveraging the diversity of *HLA* alleles across Iran's various provinces.

This study involved the HLA-typing of 1850 plateletpheresis donors, who were also registered as unrelated stem cell donors, across all blood centers in Iran from 2015 to 2022. *HLA-A* and *HLA-B* genotyping was conducted at a low-resolution using polymerase chain reaction-sequence specific primers (PCR-SSP) and real-time PCR. Statistical analysis was performed to determine allelic genotypes and donor profiles.

The majority of the donors were male (99.7%), with a mean age of 36 years. The high donor rate in Tehran indicates a larger pool of potential HLA-platelet donors due to a denser population and more donation facilities. The donors were recruited for HLA-compatible plateletpheresis. The frequency of *HLA-AB* alleles among donors was relatively consistent with those documented by Iranians.

Our findings can be utilized to create a foundational HLA database. A registry system for HLA-typed platelet donors is crucial due to high HLA polymorphism and ethnic diversity. This system facilitates the rapid identification of compatible donors based on HLA typing. Additional inquiries are needed to expand the plateletpheresis registry and make a request-supply mechanism between the Iranian Blood Transfusion Organization and hospitals.

Keywords: HLA-A antigens; HLA-B antigens; Donors; Platelet transfusion

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INTRODUCTION

Platelets are the smallest blood particles that initiate a coagulation cascade and play a crucial role in hemostasis.[1] Reducing the blood platelet count increases the risk of bleeding and the need for platelet transfusion, driving alloimmunization complications.[2] Platelet transfusion refractoriness (PTR), a major concern in blood transfusions,[3] can occur even when leukoreduced products are used.[4,5] This issue is characterized by an insufficient increase in the patient's platelet count after transfusion, owing to multiple factors, including immune and non-immune causes. Immune factors contribute to platelet failure in 10% of patients, including antibodies against human leukocyte antigens (HLA) class I, human platelet antigens, and *ABO* system antigens.[6] Anti-HLA–mediated destruction of transfused platelets is a major cause of immune platelet refractoriness.[7] Platelets primarily express *HLA-A* and *HLA-B* antigens of HLA class I, with low expression of *HLA-C* antigens and no expression of HLA class II antigens.[8,9] Due to the high number of platelets in the bloodstream, two-thirds of HLA class I molecules are associated with platelets, potentially stimulating the recipient's immune system and leading to alloimmunization. [10] Alloantibodies against HLA antigens make matching HLA units crucial for reducing the risk of alloimmunization when receiving a platelet transfusion.[11]

Administering HLA-compatible platelets is a tactic for treating patients who do not respond well to random platelet injections.[12] Moreover, apheresis platelet transfusion reduces the risk of alloimmunization because the patient receives platelet products from a single donor.[13] However, finding a suitable HLA-matched donor may be difficult because the features of HLA alleles vary among individuals. Nevertheless, many plateletpheresis donors must be pre-typed with HLA to provide patients with compatible platelet products at the correct time. Hence, HLA-matched platelet provision requires many donors with HLA-typed and organized information, which is only feasible for blood transfusion centers.[14] Therefore, establishing a registry system for multiple HLA-typed plateletpheresis donors is crucial.

The main objective of this study was to develop a registry system of HLA-typed plateletpheresis donors to supply compatible platelets to individuals with immune platelet refractoriness. The HLA Gene Bank was comprised of platelet donors of various Iranian ethnicities. By studying the frequency of HLA alleles in different ethnic groups and urban regions, identifying a compatible plateletpheresis donor for patients with platelet refractoriness will become simpler. This study was the first to investigate the prevalence of HLA alleles in plateletpheresis donors in Iran. According to the Iranian Blood Transfusion Organization (IBTO) policy to establish an HLA database of platelet donors, we focused on platelet donors registered as unrelated stem cell donors and identified 1850 donors. HLA typing was available for 47% of these donors (870 individuals) when we intended to create an HLA database, and typing of the remaining 53% of donors (980 individuals) was performed selectively. The data contained each donor's *HLA-A* and *HLA-B* typing information, enabling us to match platelet donors with platelet recipients. This research represents the first study of HLA-typing in a population group of HLA-plateletpheresis donors in Iran.

MATERIALS AND METHODS

Selection of Common Donors of Registered Stem Cell and Platelet

Between 2015 and 2022, a list of apheresis platelet donors who were verified as unrelated stem cell donors from all blood centers in Iran was made. Donors aged between 19 and 59 years signed an informed consent form.

Human Leukocyte Antigen Test

Nucleic Acid Extraction

Whole blood samples (10 mL) were collected from all donors using ethylenediaminetetraacetic acid (EDTA). The samples were then stored at a temperature of 1–10°C before being referred to our laboratory. Genomic DNA was extracted from the buffy coat layer using a MagCore Genomic DNA Whole Blood Kit and an automated nucleic acid extractor (Magcore, HF16 Plus, Taiwan) as well as a manual DNJia Plus blood and cell kit (ROJE, Iran), according to the manufacturer's instructions. DNA quality (A260/A280 and A260/A230 absorbance) and concentration were measured using a spectrophotometer device (Nanodrop 2000c, Thermo Fisher Scientific, USA).

Genomic HLA Typing

The plateletpheresis donors were genotyped for *HLA-A* and *HLA-B* loci at the low-resolution (2-digit) level using polymerase chain reaction with sequence-specific primers (PCR-SSP) and TaqMan real-time PCR. In conditions of platelet refractoriness, matching for *HLA-A* and *HLA-B* alleles at the 2-digit level is considered standard.[15] HLA-typing was performed using PCR-SSP (low-intermediate resolution, Olerup, Caerdx, Sweden) kits and TaqMan real-time PCR assay (HISTO TYPE Rainbow, BAG, Germany) purchased from the BAG company. PCR products were analyzed using 2.0% agarose gel electrophoresis. HLA genotyping results were interpreted using the manufacturer's datasheets and software.

Statistical Analysis

Statistical analysis to determine allelic genotypes for *HLA-A* and *HLA-B* loci and donor profiles was performed using IBM SPSS version 17 (IBM Corp). The significance of the differences was determined using the chi-square test.

Searching for HLA-Compatible Platelet Donors

When the laboratory receives the request for HLA-matched platelet products from hospitals, fully matched plateletpheresis donors are first searched in the software at low resolution based on 4 alleles (*HLA-A* and *HLA-B*). Based on the HLA-matched platelet classification, a Grade A match is obtained when all 4 *HLA-A* and *HLA-B* antigens are identical. A Grade BU match occurs when the 3 antigens are similar, and the fourth antigen is unknown. A Grade BX match occurs when 3 antigens are identical, and the fourth antigen is cross-reactive. A Grade C match is when 1 antigen is mismatched, and a Grade D match is when 2, 3, or all antigens are mismatched.[6,16]

The donor's blood group and city of residence are carefully evaluated when searching for HLA-compatible recipients. These details help ensure that donated platelet units reach the hospital quickly and efficiently. In cases with insufficient potential plateletpheresis donors, donors with at least 3 of 4 HLA-compatible alleles are selected. After identifying an appropriate donor, the next step is guaranteeing the platelet product's availability. If not, the donor must visit the closest blood donation center and donate the platelet unit if healthy conditions are allowed.

Supply of HLA-Compatible Platelet

During the development of the registration system, a juvenile patient with myelodysplastic syndrome (MDS) was referred to our institution to identify an HLA-compatible donor. The patient had not exhibited any rise in blood circulation platelet count despite receiving multiple repeated random platelet transfusions. Although data were incomplete and analysis was still in progress, a pool of 900 HLA-typed plateletpheresis donors was available. We carefully screened potential donors for compatibility based on the *HLA-AB* alleles in the patient. Initially, we checked for grade A compatibility, but unfortunately, no suitable matched donors were identified. We then changed our search to grades B1U and B1X to identify appropriate donors.

RESULTS

HLA-Compatible Plateletpheresis Donors' Registration Status

In Iran, 1850 HLA-compatible plateletpheresis donors were officially enlisted from all provinces of Iran. The age distribution showed that most of these donors were male (99.7%), with only a small percentage being female (0.3%). Their ages ranged from 19 to 59 years, with an average of 36 years. Most donors were in their thirties (51.1 %), while donors in their twenties and forties accounted for approximately a similar percentage (as shown in Table 1). Table 2 presents information on the donor status based on donation history and frequency. Among these individuals, 69.5% were regular plateletpheresis donors with multiple donations annually, 23.8% had a documented donation record, and 6.6% were newcomers to the donation process.

Number of HLA Plateletpheresis Donors by Province in Iran

The Tehran province had the highest number of HLA-plateletpheresis donors, with 696 subjects (37.6%). This demographic is the largest age group within the population, with more than 5 times the number of donors in the next highest province, Qazvin, with 121 donors. Razavi Khorasan, Khuzestan, and Yazd had HLA-plateletpheresis donors up to one-sixth of those in Tehran province. The lowest number of HLA-plateletpheresis donors belonged to Kordestan, North Khorasan, and Ilam, with less than 5 donors. "Kohgiluyeh and Boyer-Ahmad" had no HLA-plateletpheresis donor (data not shown)

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Table 1. Gender and age distribution of HLA-plateletpheresis donors

		Frequency	Percentage (%)
Gender	Male	1844	99.7
	Female	6	0.3
Age	<20	1	0.1
	20–29	384	20.7
	30–39	946	51.1
	40–49	409	22.1
	50–59	110	6.0

Table 2. Donor status categorized by donation history and frequency

Donor Status	Frequency	Percentage (%)
Regular donor	1286	69.5
Recurring donor	441	23.8
First-time donor	123	6.6
Total	1850	100

Frequency of *HLA-AB* Alleles in Plateletpheresis Donors

Table 3 represents the allele frequencies of *HLA-A* types in registered platelet donors. The data showed some significant differences from the blood donor frequencies in Iran. In this study, 21 *HLA-A* alleles were investigated at a low-resolution level. Based on *HLA-A* allele data, *HLA-A**02 (15.7%), *24 (13.2%), *03 (11.3%), and *01 (10.8%) were the most prevalent. By contrast, *HLA-A**34 and *80 (0.027%) were the least common alleles. Some alleles such as *HLA-A**36 and *43 were absent in our donor population. The frequency of *HLA-A* alleles among the recruited donors confirmed the findings of a study on Iranian unrelated stem cell donors.[17]

Table 4 shows the *HLA-B* allele frequencies among platelet donors. By investigating 36 alleles at a low resolution, this study provided information about *HLA-B* frequencies in Iranian platelet donors. The highest frequency of *HLA-B* alleles was related to *HLA-B**35 (17.5%), *51 (12.3%), *52 (5.8%), *18 (5.1%), and the least common alleles were *HLA-B**78 and *81 (0.027%). Alleles of *HLA-B*, such as *B**59, *67, *82, and *83 were not observed in this survey. Our findings verified the outcomes of a study carried out on unrelated stem cell donors registered in Iran.[17]

Report on the Supply of HLA-Compatible Donors for a Patient with Platelet Failure

The initial provision of HLA-matched platelet units through this registration system was observed in a scenario involving a patient diagnosed with MDS. Despite multiple platelet product injections, the patient's platelet count did not increase. Subsequently, in the secondary search phase, eight plateletpheresis donors were identified from the registry data. The selection of potential donors was determined by an assessment of the patient's HLA profile and donor alleles, resulting in the identification of one donor with grade B1U and seven donors with grade B1X. Fortunately, the patient's platelet count showed significant improvement following the infusion of several HLA-compatible platelet products, indicating a positive response to the treatment.

Table 3. Gene frequencies of human leukocyte antigen (*HLA)-A* alleles

HLA-A	Frequency	Percentage (%)
A*01	398	10.8
A*02	582	15.7
A*03	419	11.3
A*11	364	9.8
A*23	88	2.4
A*24	490	13.2
A*25	5	0.1
A*26	200	5.4
A*29	103	2.8
A*30	190	5.1
A*31	67	1.8
A*32	225	6.1
A*33	144	3.9
A*34	1	0.027
A*36	0	0.0
A*43	0	0.0
A*66	24	0.6
A*68	150	4.1
A*69	25	0.7
A*74	5	0.1
A*80	1	0.027

Table 4. Gene frequencies of *HLA-B* alleles

HLA-B	Frequency	Percentage (%)	*HLA-B*	Frequency	Percentage (%)
B*07	145	3.9	B*48	4	0.1
B*08	125	3.4	B*49	124	3.4
B*13	136	3.7	B*50	176	4.8
B*14	109	2.9	B*51	454	12.3
B*15	129	3.5	B*52	215	5.8
B*18	189	5.1	B*53	31	0.8
B*27	56	1.5	B*54	2	0.1
B*35	648	17.5	B*55	136	3.7
B*37	43	1.2	B*56	4	0.1
B*38	179	4.8	B*57	47	1.3
B*39	47	1.3	B*58	65	1.8
B*40	118	3.2	B*59	0	0.0
B*41	136	3.7	B*67	0	0.0
B*42	5	0.1	B*73	12	0.3
B*44	151	4.1	B*78	1	0.027
B*45	11	0.3	B*81	1	0.027
B*46	4	0.1	B*82	0	0.0
B*47	10	0.3	B*83	0	0.0

DISCUSSION

When a patient experiences platelet transfusion refractoriness (PTR) due to HLA alloimmunization, 3 approaches are available for selecting a suitable platelet product: platelet cross-matching, using antigen-negative platelets based on the patient's HLA antibodies, and *HLA-A* and *HLA-B* matching.[18] The latter approach is most effective for patients with extensive HLA alloimmunization when a patient is referred to the laboratory, HLA matching eliminates additional tests and minimizes the time to find a compatible donor.[19] HLA-matched platelets are commonly used in other registries and medical centers to assist patients with significant alloimmunization.[4,19,20]

In this study, we created a registry system of platelet HLA genes using low-resolution HLA-typing technology. The HLA genotyping methods employed in our laboratory included PCR-SSP and Real-time PCR. Given the limitations of serological techniques, such as high rates of incorrect or inconclusive results and the failure to detect all known HLA alleles,[21] molecular methods have become the preferred strategy for HLA typing in many centers worldwide.[20,22,23] Molecular typing identifies nucleotide polymorphisms for allelic variants, while serological typing indicates expressed cell molecules.[24]

Our initial registry was created with 1850 HLA-typed platelet donors by March 2024. The platelet donor registry in Korea was established in 2015 with 1029 donors[14] and raised to 4080 in 4 years.[25] Similar registries were set up in the Netherlands with 19 478 donors,[26] , in China with 1000 donors,[27] and in Brazil with 867 platelet donors.[22] Additionally, Xia et al genotyped 864 donors for *HLA-A* and *HLA-B*.[20] Generally, having a minimum plateletpheresis donor reserve of 1000 to 3000 donors can sufficiently supply HLA-compatible platelet products.[28]

The genotype-based platelet donor registration system is critical because of the high polymorphism in the HLA genes and the diversity of ethnic groups in Iran.[17,23] However, obtaining HLA full-matched units is only feasible for blood transfusion centers with a great pool of HLA class I-typed platelet donors.[29,30] In Iran, the IBTO is the only governmental supplier institution of apheresis platelet products for patients. Iran's platelet transfusion strategy is primarily based on the ABO isotype; patients receive random platelet transfusions multiple times, which results in the development of alloimmunization. Many countries have established a registration system for HLA-matched platelet donors to provide compatible platelet products.[14,18,20,22,25] Establishing a registered system or HLA database for supplying compatible platelets can help prevent PTR and reduce excessive treatment costs.[31]

As shown in Table 1, the majority of HLA-plateletpheresis donors across this country were male. Iranian HLA-platelet donors averaged 36 years, Brazilians 39,[22] Chinese 36.5,[27] and Dutch 26.5.[26] Dutch donors were significantly younger than their counterparts from Iran, Brazil, and China. This indicated a young donor population in the Netherlands.[26] Our statistical data highlighted the critical need for young people to become HLA-plateletpheresis donors. The age variation of donors could reflect cultural, societal, or perhaps promotional differences in these countries. Understanding the age demographic of HLA-platelet donors is vital for developing targeted recruitment strategies. Encouraging donors from younger individuals could be beneficial and allow us to have them for more years as potential donors.

The status of plateletpheresis donors according to the history and frequency of donation is displayed in Table 2. Most individuals were regular platelet donors. Because of the short shelf life of the platelet, the steady stream requirement of donations is critical. In this specific aspect, there was no data on Korean,[14] Brazilian,[22] Chinese,[27] or Dutch studies.[26] The high regularity rate of donation indicated effective recruitment and retention strategies used by the donation centers in Iran. Also, there was high awareness and motivation for platelet donation among platelet donors.

The number of HLA-plateletpheresis donors in each province was determined, which was related to the population and the number of available blood donors (data not shown).

Table 3 shows that the prevalent *HLA-A* alleles in the studied population were *HLA-A**02, *24, *03, and *01. The 2011 IBTO study indicated *HLA-A*B allele frequencies in 1513 registered unrelated stem cell donors, identifying *HLA-A**01, *02, *03, and *24 as the top alleles, similar to our findings but in a different order (*HLA-A**02/01/03/24). Notably, *HLA-A**02 frequency was higher in stem cell donors compared to this study ($p<0.001$).[17] Moreover, the *HLA-A**02 allele was the most prevalent among Brazilians[22] and Koreans.[14] It should be noted that HLA allele frequencies can differ

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significantly across various ethnic populations due to genetic drift and evolutionary impacts that occur over time.[32]

The rarest HLA alleles in this donor group were *HLA-A**34 and *80, each at 0.027%. In the Shaiegan study, *HLA-A**34 was more common at 0.27% ($p<0.001$). *HLA-A**36 was absent in platelet donors but present at 0.2% in unrelated stem cell donors. Both studies did not report *HLA-A**43, indicating its rarity. *HLA-A**80 appeared at 0.027% in our study but was not noted in Shaiegan's.[17] Reporting rare allele frequencies can assist in selecting matched donors. It is proposed that recruiting stem cell donors as platelet donors could enhance the representation of rare alleles in the HLA database. Brazilian platelet donors showed *HLA-A**36 at 0.49%, with *HLA-A**43 absent.[22]

*HLA-B**35 was the most common allele in our study and the analysis of unrelated stem cell donors. Notably, we observed *HLA-B**73 (0.3%) and *78 (0.027%), which were absent in the unrelated stem cell donor study. Both studies did not identify *HLA-B**59, *67, *82, or *83, indicating their rarity in the populations examined. Our study's overall distribution patterns were similar to those found by Shaiegan et al.[17] In Brazil, *HLA-B**35 and *44 were prevalent, while our study and Shaiegan's[17] indicated *HLA-B**35 and *51 as dominant. The Brazilian study found *HLA-B**59 at 0.06% whereas it was not found in our analysis and *HLA-B**81 at 0.43%, differing significantly from our data ($p<0.001$).[22] The Korean study noted *HLA-B**51 and *44 as the most common among HLA-platelet donors, while B*40 and *50 were rare.[14] Variations in HLA genotype distribution across populations may result from sample sizes and ethnic differences. Due to the high genetic diversity of the HLA system, differences between donors and patients with platelet refractoriness are expected. Employing HLA-matched platelets is an effective strategy to manage PTR in these patients.[6,15,28,33]

Establishing an HLA-plateletpheresis donor registry is crucial for improving the availability of HLA-matched platelets for patients unresponsive to random donations. However, there are challenges, such as a limited donor pool, maintaining the privacy and confidentiality of donor information, high costs of HLA typing and registry keeping, and the need for timely donor availability due to the short shelf-life of platelets. Donor commitment is also an issue, as the longer plateletpheresis process and multiple visits can discourage participation. Furthermore, balancing supply and demand is complex, with some rare HLA types being underused while others are in high demand. Despite these hurdles, improving HLA-plateletpheresis registries is essential for better patient care, particularly for those with blood disorders or specific treatments.

To enhance HLA-plateletpheresis donor registries, strategies like developing point-of-care HLA typing devices for donor screening, establishing recognition programs to encourage regular platelet donations, public education campaigns highlighting the importance of HLA-matched platelets, and ethical protocols for managing donor information should be implemented. Moreover, implementing quality assurance measures, utilizing mobile plateletpheresis units, and establishing a system to thank donors, fosters loyalty.

Through this initial study, 1850 individuals were registered as HLA-typed plateletpheresis donors. HLA genotypes may be used for creating a database that can recognize rare HLA types, foster allele diversity among donors, and enhance the availability of compatible platelets for all patients. However, providing full-matched platelet units to each patient with immune thrombocytopenia may not be feasible. By continuously updating and expanding the registry, suitable donors can be quickly identified and selected. Future research is required to enlarge the pool of registered HLA-typed plateletpheresis donors and develop computerized software to manage requests from medical institutions. This will allow us to provide HLA-compatible platelet products to hospitals needing to support patients with platelet refractoriness.

The analysis of HLA class I genotypes of plateletpheresis donors provided an original foundation for the development of an HLA database, crucial for identifying matched donors. This endeavor is expected to enhance patient outcomes and reduce complications associated with repeated platelet transfusions in cases of immune platelet refractoriness. Further investigation is needed to extend the pool of registered donors, create a robust computerized program for efficient management and recovery of HLA-compatible donors, and precise estimate the required size of Iran’s HLA-plateletpheresis donor bank.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of the Iran University of Medical Sciences (Approval

ID: IR.IUMS.REC.1401.1031). All of the participants had informed consent about the survey.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Data Availability

Upon reasonable request from the corresponding author via email.

AI Assistance Disclosure

The authors have used Sider and Grammarly for language editing.

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