Original article

Factors involved in identifying matched unrelated Thai stem cell donors: a retrospective study from 2016 to 2022

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Abstract:

Introduction: *Allogeneic hematopoietic stem cell transplantation (HSCT) is beneficial in treating patients with hematological disorders. The chance of identifying an unrelated donor depends on several factors, such as patient characteristics, resolution of HLA typing, and registry size. However, the data in the Thai Stem Cell Donor Registry (TSCDR) remain unclear. This study aimed to determine factors that affect identifying an HLA-matched unrelated donor in the TSCDR during the first search for wait-listed patients.* ***Materials and Methods:*** *Demographic and laboratory data of unrelated donors and wait-listed patients from 2016 to 2022 were included. The likelihood of identifying a 6/6 HLA-matched unrelated donor during the initial search was assessed.* ***Results:*** *Among 1,232 patients, only 640 (51.9%) found a 6/6 matched donor. Of these, 634 patients (99.1%) were Thai and those who registered with high-resolution HLA typing had a higher opportunity to identify a 6/6 matched donor compared with those who registered with low-or intermediate-resolution typing. In addition, for every 10,000 increase in the number of donors, patients' chance of identifying a donor increased by 1.035-fold. Multivariate logistics analysis revealed that those two independent variables including the high-resolution of HLA typing and an increased number of donors in the registry were significantly associated with the likelihood of identifying a matched donor during the first search in the TSCDR ($p < 0.01$).* ***Conclusion:*** *This study demonstrated that key factors associated with successfully identifying 6/6 HLA-matched unrelated donors for HSCT wait-listed patients during the initial search from the TSCDR included Thai ethnicity, high-resolution typing of HLA-A, -B and -DRB1 alleles and the expansion of the donor registry.*

Keywords : ● *Involving factors* ● *Human leukocyte antigens* ● *Unrelated stem cell donors* ● *Thai*

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นิพนธ์ต้นฉบับ

ปัจจัยที่ส่งผลให้ได้รับเซลล์ต้นกำเนิดเม็ดโลหิตไทยที่เข้ากันได้จากผู้บริจาคที่ไม่ใช่ญาติ: การศึกษาข้อมูลย้อนหลังตั้งแต่ปี พ.ศ. 2559 ถึง พ.ศ. 2565

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บทคัดย่อ

บทนำ *การปลูกถ่ายเซลล์ต้นกำเนิดเม็ดโลหิตจากผู้บริจาคที่ไม่ใช่ญาติมีประโยชน์ในการรักษาผู้ป่วยโรคทางโลหิตวิทยา โอกาสที่ผู้ป่วยจะพบผู้บริจาคที่ไม่ใช่ญาติขึ้นอยู่กับปัจจัยหลายชนิด ได้แก่ ลักษณะผู้ป่วย ผลการตรวจ HLA และจำนวนผู้บริจาคที่ลงทะเบียน แต่อย่างไรก็ตามข้อมูลดังกล่าวในโครงการรับบริจาคเซลล์ต้นกำเนิดเม็ดโลหิตจากผู้บริจาคที่ไม่ใช่ญาติ (Thai National Stem Cell Donor Registry; TSCDR) ยังไม่ชัดเจน* ***วัตถุประสงค์*** *เพื่อศึกษาปัจจัยที่เกี่ยวข้องกับโอกาสพบผู้บริจาคที่มี HLA-matched กับผู้ป่วยที่ขึ้นทะเบียนของ TSCDR เมื่อหาข้อมูลครั้งแรก* ***วัสดุและวิธีการ*** *รวบรวมข้อมูลทั่วไปและผลตรวจทางห้องปฏิบัติการของผู้บริจาคและผู้ป่วยตั้งแต่ ปี พ.ศ. 2559 ถึง ปี พ.ศ. 2565 และวิเคราะห์โอกาสพบผู้บริจาคที่เป็น 6/6 HLA-matched ในการค้นหาข้อมูลครั้งแรกใน TSCDR* ***ผลการศึกษา*** *ผู้ป่วยที่ขึ้นทะเบียน จำนวน 1,232 ราย พบว่ามีผู้ป่วย 640 ราย (51.9%) เท่านั้น ที่พบผู้บริจาค 6/6 matched โดยผู้ป่วยจำนวน 634 ราย (99.1%) เป็นคนไทยและเป็นผู้ที่ขึ้นทะเบียนผลตรวจ HLA typing แบบ high-resolution ซึ่งมีโอกาสพบผู้บริจาค 6/6 matched สูงกว่าผู้ที่ขึ้นทะเบียนด้วยผลตรวจ low- หรือ intermediate-resolution typing นอกจากนี้ จำนวนผู้บริจาคที่เพิ่มขึ้นทุก 10,000 ราย จะเพิ่มโอกาสผู้ป่วยในการพบผู้บริจาคที่มี HLA-matched 1.035 เท่า จากการวิเคราะห์ข้อมูลด้วยพหุตัวแปรพบว่า ปัจจัยสองชนิดคือ ผลการตรวจ HLA แบบ high-resolution และการเพิ่มจำนวนผู้บริจาคในโครงการมีความสัมพันธ์กับโอกาสการพบผู้บริจาคที่เป็น HLA-matched อย่างมีนัยสำคัญทางสถิติ ($p < 0.01$)* ***สรุป*** *การศึกษานี้พบว่า ปัจจัยหลักที่สัมพันธ์กับการพบผู้บริจาค 6/6 HLA-matched ของผู้ป่วยที่รอการปลูกถ่ายเซลล์ต้นกำเนิดฯ ในการค้นหาข้อมูลครั้งแรกคือผู้ป่วยคนไทยที่มีผลการตรวจอัลลีล HLA-A, -B และ -DRB1 แบบ high-resolution และจำนวนผู้บริจาคที่เพิ่มขึ้นในโครงการ*

คำสำคัญ : ● *ปัจจัยที่เกี่ยวข้อง* ● *Human leukocyte antigens* ● *ผู้บริจาคเซลล์ต้นกำเนิดเม็ดโลหิตที่ไม่ใช่ญาติ* ● *คนไทย*
วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2568;35:179-87.

Introduction

Allogeneic hematopoietic stem cell transplantations (HSCT) have been recommended for patients with malignant and non-malignant hematological diseases, especially those without a related donor who can receive stem cells from a matched unrelated donor (MUD).[1-4] Concerning successful HSCT, the donor and recipient should have optimal human leukocyte antigen (HLA) matching including HLA-A, HLA-B, HLA-C, and HLA-DRB1 (8/8 antigen matches).[5] Stem cell transplants with a mismatch at one of these loci are relatively associated with a higher mortality risk.[2,6] Currently, 103 stem cell registries are available from 54 countries globally, with more than 42 million donors registered at the World Marrow Donor Association (WMDA) search and match database,[7] and those donors are available for any patient in need of HSCT. However, the donor search and selection process is crucial owing to the variations in HLA alleles and haplotype frequencies among populations.

In Thailand, the National Blood Centre of the Thai Red Cross Society (NBC-TRCS), the principal organization under supervision by the Medical Council Association, established the Thai National Stem Cell Donor Registry (TSCDR) Program in April 2002 to promote the recruitment of unrelated stem cell donors in the donor's pool and search for a suitable donor for Thai patients without a matched family donor.[8] HLA-A and -B typing using serological techniques were initially set up among unrelated stem cell donors.[9] Subsequently, HLA-DRB1 low-resolution typing (serology-equivalent) was implemented from 2003 until now, with a minimum HLA-A, -B, and -DRB1 typed donor's pool in our database. In 2010, HLA-A, -B, and -DR antigen and haplotype frequencies (HFs) among 16,807 donors were reported, and only 8% of the patients found matched donors within one month.[10] It has been predicted that approximately 80% of patients identified as HLA-A, -B, and -DRB1-matched unrelated donors would depend on the registry size when the stem cell registry contained up to 100,000 volunteer donors.

With the continued support of the Budget Bureau of Thailand, the Office of the Prime Minister and the Thai Red Cross Society, the number of registered donors in TSCDR increased to 228,063 donors in 2020.[11] In addition, from 2018 until now, next-generation sequencing has been used to provide high-resolution HLA typing for volunteer donors in the TSCDR. As a result, the prevalence of high-resolution typing results has increased to 28% in the TSCDR, compared with 42% in the WMDA report.[7] Even though the donor pool size increased, race was also a significant variable in wait-listed patients for predicting the chance to meet an unrelated donor in each registry.[12,13] Demographic data of wait-listed patients in the TSCDR, including age, sex, and diagnosis, may support an opportunity to find MUD, but the data remain undefined. This study aimed to determine factors that affect identifying an HLA-matched unrelated donor in TSCDR during the first search for wait-listed patients.

Materials and methods

Study populations

The populations used in this retrospective study included the demographic and laboratory data of unrelated Thai stem cell donors and wait-listed patients at the NBC-TRCS from January 1, 2016, to December 31, 2022, retrieved from the MatchPoint Program of Stem Cell Donors Australia. This study was conducted according to the principles of the Declaration of Helsinki. The requirement for informed consent was waived by the Research Ethics Committee, National Blood Centre, Thai Red Cross Society, Bangkok, Thailand (COA No. NBC 2/2023).

Data analysis

The baseline demographic data of wait-listed patients, including race, sex, age, diagnosis, ABO blood group, and HLA type was concluded using descriptive analysis and expressed in numbers and percentages.

The time for identifying HLA-A, -B, and -DRB1-matched stem cell donors followed the first registration through the MatchPoint Program at the NBC-TRC, which was validated and supervised by Stem Cell Donors Australia.

Identifying a donor who was not a relative of the patient constituted a dependent variable. The patient and donor have HLA matches in at least three loci: HLA-A, -B, and -DRB1 (6/6 antigen matches) in the first donor search with HLA typing from low-resolution levels and above. Moreover, independent variables among wait-listed patients were categorized, including race (non-Thai and Thai), sex (male and female), ages (< 18 years and ≥ 18 years), diagnosis (malignant and non-malignant diseases), according to the Center for International Blood and Marrow Transplantation Research (CIBMTR) and ABO types. The resolution of HLA-A, -B, and -DRB1 typing results among registered donors were divided into two categories: low- or intermediate- and high-resolution typing, according to the typing results at the first registration. The donor count was the cumulative number of donors each month who were HLA-typed and fully registered in the MatchPoint Stem Cell Donor Search Program.

Statistical analysis

A descriptive analysis was conducted to characterize the baseline demographic data of wait-listed patients and expressed in numbers and percentages.

Formal comparisons of categorical characteristics between groups were performed using Pearson's Chi-square test and Fisher's exact likelihood Chi-square test. Trends across ordered groups were evaluated using Cuzick's non-parametric test for trend with rank scores. Univariate and multivariate models assessed factors associated with identifying unrelated stem cell donors. Covariates assessed in logistic regression included race, sex, age, diagnosis, ABO blood group, HLA type and the number of cumulative donors. Variables with $p < 0.10$ in univariable screening were adjusted for in multivariable models. Statistical significance was defined as a two-sided $p < 0.05$. All analyses were performed using SPSS Software, Version 18 (SPSS Inc., Chicago, USA).

Results

From January 1, 2016, to December 31, 2022, a total of 1,232 patients requiring stem cell transplantation without a family donor were included. The baseline characteristics of all patients are shown in Table 1. Among them, 1,201 patients (97.5%) were Thai, and 31 patients were non-Thai (2.5%); the proportion of Thai patients was significantly higher than non-Thai patients ($p < 0.01$). The male-to-female ratio among wait-listed patients was 656/576 (1.1: 1). Their ages ranged from 8 months to 78.64 years (27.96±19.20 years). When dividing patients by age (18 years), we found that the population proportion of patients ≥ 18 years was significantly higher than patients < 18 years (63.1% vs. 36.9%, $p < 0.01$). Strikingly, high-resolution HLA typing was performed in 85.2% of participants.

Regarding the diagnosis of patients, the most prevalent involved malignant diseases (76.7%), while non-malignant diseases totalled 23.3%. For the malignant disease group, acute myeloid leukemia was the most common (n = 443, 35.96%), followed by acute lymphoblastic leukemia (n = 241, 19.56%) and myelodysplastic syndrome (n = 88, 7.14%), respectively. Regarding the non-malignant group, thalassemia was predominant (n = 172, 13.96%), as shown in Figure 1. ABO blood grouping was performed in 1,202 patients (97.6%). Unsurprisingly, group O was the most common, followed by group B, group A, and group AB, consecutively. The patient HLA typing results at registration were divided in low- or intermediate-resolution typing (n = 182, 14.8%) and high-resolution typing (n = 1,050, 85.2%), as shown in Table 1.

The numbers of stem cell volunteer donors registered from 2016 to 2022 totalled 173,982, 180,057, 201,210, 235,273, 266,208, 297,096, and 324,646, respectively. Moreover, data of wait-listed patients from 2016 to 2022 gradually increased to 96, 100, 146, 183, 215, 209 and 283, respectively. From 2016 to 2022, the number of patients who could find 6/6 antigen-matched donors were as follows: 51, 45, 47, 47, 51, 54 and 60, respectively. The proportion of wait-listed patients who found 6/6 antigen-match donors relative to the overall growth of

Table 1 Characteristics of wait-listed stem cell patients from 2016-2022 (n = 1,232)

Characteristic	Frequency	%
Race*		
Non-Thai	31	2.5
Thai	1,201	97.5
Sex		
Male	656	53.2
Female	576	46.8
Age*		
< 18 years	454	36.9
≥ 18 years	778	63.1
Diagnosis		
Non-malignant diseases	287	23.3
Malignant diseases	945	76.7
ABO blood group (n = 1,202)		
O	451	37.5
B	402	33.4
A	272	22.6
AB	77	6.4
Not applicable	30	2.4
HLA typing result at registration		
Low- or intermediate-resolution typing	182	14.8
High-resolution typing	1,050	85.2

*Comparing the population proportions in each year using Pearson Chi-square test and Fisher exact test likelihood Chi square statistics ($p < 0.01$).

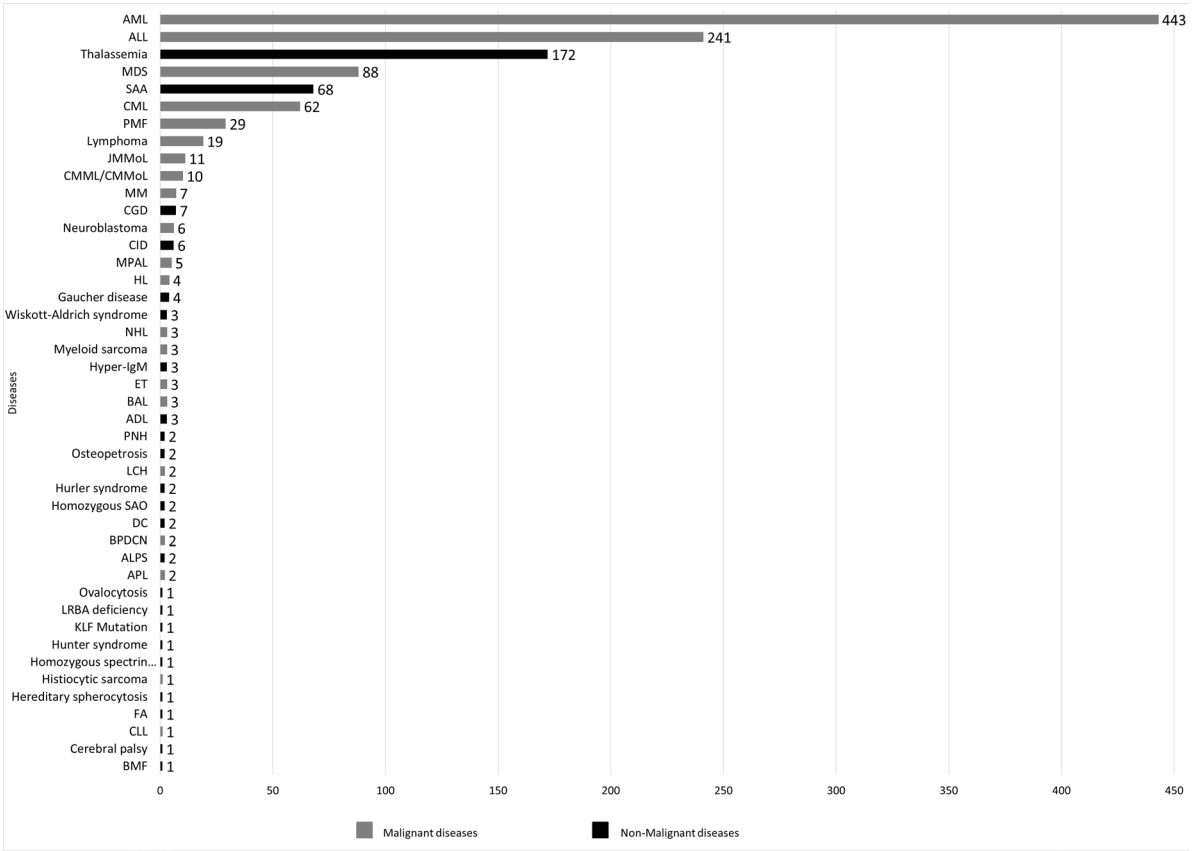

Figure 1 Type of diseases among wait-listed patients (N = 1,232)

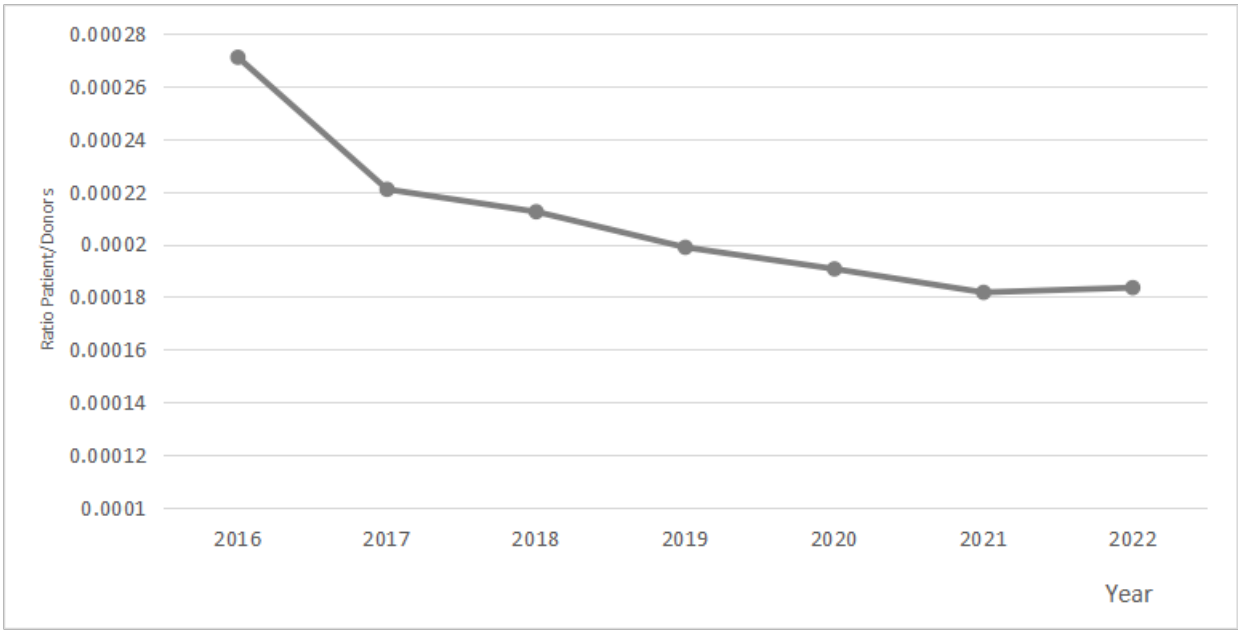

Figure 2 Trend-to-trend analysis between wait-listed patients and matched 6/6 antigen compared with the number of volunteer donors in the TSCDR

the stem cell volunteer donor registry (i.e., Ratio Patient/Donors) decreased over the study period, as illustrated in Figure 2. The tendency for patients to find a 6/6 antigen-match donor was corresponded to an increase in a number of stem cell volunteer donors ($p < 0.05$). Cuzick's test with rank scores was used to determine the trend. The ratio between patients identifying matched unrelated stem cell donor and donors decreased with increasing number of donors ($p < 0.05$).

Among 1,232 patients, 640 (51.9%) identified a 6/6 match donor the first time searching. Of the 640 patients who found a 6/6 match, 634 (99.1%) were Thai. These comprised male (n = 342, 53.4%) female (n = 298, 46.6%), and age ≥ 18 years (n = 399, 62.3%). The most frequent were malignancies (n = 485, 75.8%) and HLA high-resolution typing (n = 563, 88.0%). Calculating the chance of identifying an unrelated donor varied from independent variables including race, sex, age, blood type, disease group, resolution of HLA typing, and the number of donors using the univariate logistics analysis, revealed that race, resolution of HLA typing, and number of donors were significantly related to the chance that the patient would observe a 6/6 match donor at $p < 0.01$, as shown in Table 2. Multivariate logistic regression, after adjusting for other covariates, revealed that race, resolution of HLA typing, and number of donors were significantly associated with the likelihood of finding a 6/6 matched donor ($p < 0.01$). Importantly, Thai patients had a 4.183-fold greater chance of identifying a 6/6 match donor than other races, and patients registered with HLA high- resolution had a 1.547-fold greater chance of identifying a 6/6 match donor than HLA low- or intermediate-resolution. For every 10,000 increase in the number of donors, the patients' chance of identifying a donor increased by 1.035-fold, as shown in Table 3.

Discussion

To date, HSCT remains a potentially effective treatment for a wide range of malignant and non-malignant hematological disorders.[4, 13] Several studies have investigated factors influencing hematopoietic stem cell yields from unrelated healthy donors. The data indicated that both sex and age impact stem cell collection outcomes.[17-19] Although it was reported that there is no significant effect of donor sex on stem cell yields,[20,21] a related study found that female donors had a lower mean stem cell yield compared with male donors.[19] Besides the number of stem cells taken from unrelated

Table 2 Factors associated with identifying 6/6 antigen-matched donors among 1,232 patients

Variable	Odds ratio	95%CI		*p*-value
		Lower	Upper	
Race				
Non-Thai (ref.)	4.659	1.898	11.439	< 0.001
Thai				
Sex				
Male (ref.)	0.984	0.787	1.231	0.889
Female				
Age				
< 18 years (ref.)	0.930	0.738	1.173	0.542
≥ 18 years				
ABO blood group				
Group O (ref.)	1.107	0.876	1.398	0.395
Non-O				
Diagnosis				
Non-malignant (ref.)	0.898	0.689	1.170	0.425
Malignant				
HLA typing results at registration				
LR or IR typing (ref.)	1.576	1.147	2.167	< 0.001
HR typing				
Donors in TSCDR (x 10,000)	1.000	1.000	1.000	< 0.001

LR, Low-resolution typing; IR, intermediate-resolution typing; HR, high-resolution typing

All data were analysed using univariate logistics regression analysis.

Table 3 Factors associated with identifying 6/6 antigen-matched donors analyzed using multivariate logistics regression analysis.

Variable	Odds ratio	95% CI		*p*-value
		Lower	Upper	
Race				
Non-Thai (ref.)	4.183	1.711	10.619	0.002
Thai				
HLA typing results at registration				
LR or IR typing (ref.)	1.547	1.076	2.071	0.008
HR typing				
Donors in TSCDR (x 10,000)	1.035	1.000	1.000	0.006

LR, Low-resolution typing; IR, intermediate-resolution typing; HR, high-resolution typing; TSCDR, Thai Stem Cell Donor Registry

donors, other important factors affecting the success of allogeneic HSCT include the patient's age, disease stage, the time interval from diagnosis and transplantation, and the compatibility of HLA and ABO blood types between the donor and recipient.[17,22] Moreover, a larger donor registry increases the likelihood of identifying HLA-matched unrelated donors.[10]

In this study, we identified factors influencing the identification of HLA-matched unrelated donors in the TSCDR during the initial search for wait-listed patients. No association was observed between demographic factors, including donor sex and age, and donor matching within the TSCDR. However, when searching for 6/6 HLA-matched donors, the majority (99.1%) of matches

were found for Thai patients, similar to previous study in the TSCDR from 2011 to 2015.[12] These findings support the suitability of recruiting Thai donors for Thai patients, consistent with previously reported similarities in HLA-A, -B, and -DRB1 allele frequencies within different regions of Thailand.[10,16] Previous studies demonstrated that the chance of identifying an HLA-matched unrelated donor depends on the recipient's ethnic background. Hence, estimating the availability of suitable donors within specific populations and expanding the size of donor registries accordingly is recommended.[23-25]

According to an increase in the number of registered donors in the TSCDR from 164,634 in 2017 to 324,646 in 2022, the likelihood of identifying an HLA-matched donor may also be improved.[12] Regarding the resolution of HLA typing in donors and patients, we found a significant association between high-resolution HLA typing and the likelihood of identifying 6/6 HLA-matched donors, compared with patients with low- or intermediate-resolution typing results ($p < 0.01$). These findings highlight the effectiveness of using high-resolution HLA typing among both donors and patients, as demonstrated in other related HSCT studies.[5,12,13]

Conclusion

This study demonstrated that key factors associated with successfully identifying 6/6 HLA-matched unrelated donors for HSCT wait-listed patients during the initial search from the TSCDR included Thai ethnicity, high-resolution typing of HLA-A, -B and -DRB1 alleles, and the expansion of the donor registry.

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