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Original article

A voluntary transfusion recipient registry in Korea as a database for blood group antibodies

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Background - Several types of transfusion-related registries have been developed to improve patient outcomes and blood banks. In Korea, a transfusion program functioning as a blood group antibody database and a reference laboratory has been in operation since July 2013. This study was conducted to determine the current status of blood group antigens and antibodies in Korea and propose a model for registries in the field of transfusion medicine.

Materials and methods - Cases with unexpected red cell antibodies were registered online in the voluntary transfusion registry. Specific antigen-negative frequencies were calculated based on the recorded data. To determine the frequencies of RhCE antigens, data added via the Blood Information Sharing System were also analyzed. Data added to the registries between July 2013 and June 2022 were included in the analysis.

Results - Among 9,048 antibody cases registered from 29 hospitals, anti-E alone was identified most commonly, followed by anti-E and c, anti-C and e, anti-Lea, and anti-M (2,202, 1,792, 757, 618, and 383 cases, respectively). The frequencies of E-, E-c-, C-e-, Le(a-), and M- were 49.1%, 41.6%, 9.1%, 69.4%, and 21.8%, respectively.

Discussion - The distributions of antibodies and antigen frequencies were estimated through the transfusion registry. Antigen frequencies were calculated based on the results of antigen typing of red blood cell components performed at the time of issuing. The online transfusion registry serving as a blood group antibody database is useful for determining the frequencies of blood group antigens and antibodies.

Keywords: *registry, alloantibody, antigen frequency.*

INTRODUCTION

Several types of transfusion-related registries have been developed worldwide, including antibody registries, platelet donor registries, rare donor programs, and hemovigilance registries. For example, a regional network was established in Lombardy, Italy, in 2005 to prepare rare blood units for transfusion to patients with complex immune profiles, including combinations of antibodies against clinically significant antigens or antibodies against high-prevalence antigens[1,2].

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Apart from rare donor programs, registries for unexpected red cell antibodies are also necessary. Patients with clinically significant alloantibodies should be transfused with red blood cell (RBC) units lacking the corresponding antigens to avoid hemolytic transfusion reaction. Titers of antibodies may decrease over time and even fall below the limits of detection[3]. Transfusion of corresponding antigen-positive units to patients with this antibody "evanescent" state can cause delayed hemolytic transfusion reaction (DHTR)[4]. To avoid DHTR, antigen-negative blood should be transfused in cases with a history of antibody, even if no antibody is currently detected. However, if a patient undergoes transfusion at a different facility, the antibody history may not be available. To overcome this, in the Netherlands, a nationwide antibody registry, The Transfusion Register of Irregular Antibodies and Cross (X)-match Problems (TRIX), was implemented in 2007[5,6]. A recent meta-analysis showed that a national antibody registry helped blood banks detect patients with evanescent alloantibodies and reduced the risk of DHTR[4].

The Korean Rare Blood Program (KRBP), which is a patient-centered transfusion registry, has been operating in Korea since July 2013. The KRBP is in fact divided into two separate registries: a transfusion registry named KRBP database and a case registry named KRBP case archive. The transfusion registry is a large database that provides prevalence data for blood group antigens and antibodies. While the transfusion registry mainly includes routinely identifiable red cell antibodies, the case registry consists of challenging cases, such as ABO subgroups, RhD variants, unexpected antibodies unidentifiable with routine tests, and cases with neonatal alloimmune thrombocytopenia. Such challenging cases are registered in the case registry along with the reason for the request, and the KRBP reference laboratory for blood group immunogenetics resolved the cases through molecular analysis and specialized immunohematological tests. Over the past decade, >9,000 antibodies were registered in the transfusion registry, and >800 cases were registered in the case registry and resolved through further analysis.

Our voluntary transfusion registry in Korea was analyzed in regard to the red cell antibodies that were reported. This study was conducted to determine the current status of blood group antigens and antibodies in Korea, and propose a model for registries in the field of transfusion medicine based on our 10-year experience of managing transfusion registries.

MATERIALS AND METHODS

Design of the transfusion registry

The transfusion registry is a database for red cell antibodies accumulated by voluntary registration. Blood bank managers across Korea were invited to voluntarily register data online (*http://bloodgroupimmunogenetics.org*) that satisfy all of the following three conditions: i) antibodies were detected, ii) antibody identification was performed, and iii) RBCs were transfused. Recorded data included the specificities of identified antibodies, methods of antibody screening and identification, and numbers of RBC units requested, antigen-typed, and obtained. The date of request, date of the test, and name of the hospital were also recorded. Date of birth was recorded but the patient's name was obscured with special characters; there was no personally identifiable information (PII) such as patient's full name, identification number, and contact information. Although individuals were not identifiable, the data could be distinguished from each other through the above information. Samples obtained and tested on different days, even for the same patient, were considered independent cases and registered separately. Invalid data were corrected or excluded from analysis and curated data accumulated over 10 years (July 2013-June 2022) were analyzed. This study was approved by the institutional review board of Seoul National University Bundang Hospital in 2017 and is being extended on an annual basis (approval number: B-1705-396-109).

Distribution of unexpected antibodies and calculation of specific antigen-negative frequencies

Antibodies recorded in the transfusion registry were sorted according to their specificities. The number of specific antigen-typed RBC units was recorded. The number of corresponding antigen-negative RBC units actually obtained was also recorded. The specific antigen-negative frequencies were calculated using the following equation:

$$\text{Specific antigen-negative frequency (\%)} = \frac{\text{No. of RBC units obtained}}{\text{No. of antigen-typed RBC units}} \times 100$$

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Then, the average number of required units to be antigen-typed to obtain one specific antigen-negative unit was calculated by taking the reciprocal of the specific antigen-negative frequency and rounding up to the next integer.

Frequencies of RhCE antigens

To determine the true frequencies of RhCE antigens, the frequencies from several references other than the above calculation were analyzed. In addition to ABO and RhD types, the Korean Red Cross Blood Services (KRCBS) has provided the RhCE (C, E, c, and e) types of RBC units through the Blood Information Sharing System (BISS) since June 2016[7]. Users can query information on blood products supplied to their blood banks. Data added to BISS between June 2016 and June 2022 and accessible via the BISS account of our blood bank, were analyzed. The frequencies of RhCE antigens differ significantly between D+ and D- individuals[8], and the frequency of D- individuals is very low in Korea (0.15-0.30%)[9]. Therefore, the frequencies of RhCE antigens among D+ individuals were analyzed and compared with several references.

Survey of transfusion practices and registries

To understand the current status and requirements of blood banks in Korea, a survey was conducted among the KRBP workshop participants. An online survey link was distributed via e-mail to participants of the KRBP workshop between 27th September and 12th October 2022, and the responses were collected. The survey items included the number of screening cells and availability of screening cells with a specific phenotype. The survey results were analyzed by facility and individual.

RESULTS

Overview of the transfusion registry and frequencies of red cell antibodies and antigens

A total of 9,048 cases from 29 general hospitals across the country were registered in the transfusion registry (**Figure 1**). Among the participating hospitals, 19 superior general hospitals were included; the median number of the beds in these hospitals was 1,048. Among all cases with alloantibodies, the most common alloantibodies were as follows: anti-E (4,272 cases, 53.5%), anti-c (1,935 cases, 24.2%), anti-C (912 cases, 11.4%), anti-e (905 cases, 11.3%), anti-Le[a] (738 cases, 9.2%), and anti-M (420 cases, 5.3%) (**Table I**).

The top 20 most commonly identified alloantibodies were listed. Antigen typing was performed on hundreds to thousands of RBC units for each antigen and antigen-negative frequencies were calculated (**Table II**).

RhCE antigen frequencies

In the BISS, information was available regarding 213,691 RBC units (**Table III**). RhCE frequencies were comparable between the BISS and the previous study using genotyping[8]. The antigen-negative frequencies based on the transfusion registry in the present study were overestimated (**Table II**).

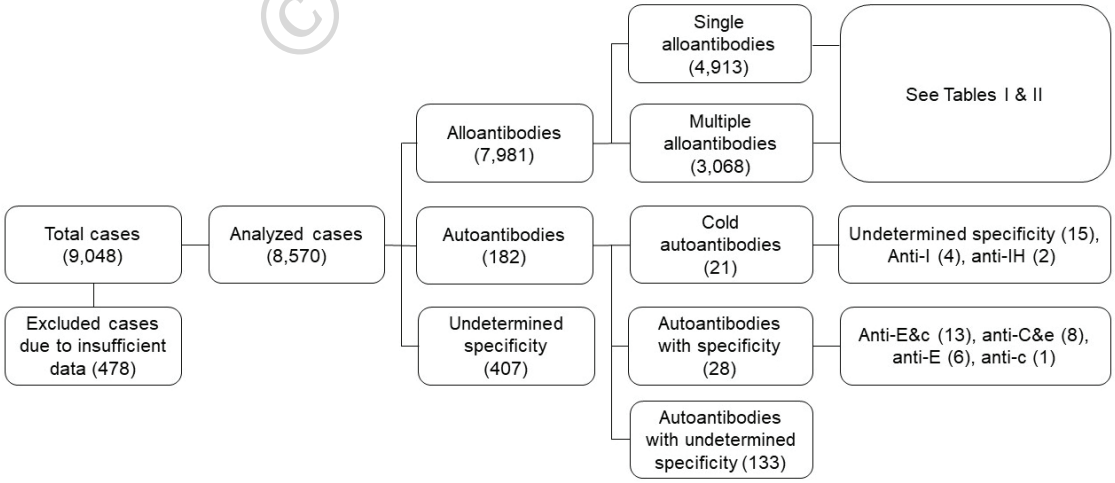

Figure 1 - Schematic of analyzed cases from the transfusion registry
The 9,048 total cases included 7,981 of alloantibodies and 182 of autoantibodies. See **Tables I** and **II** for detailed alloantibody results.

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Table I - *Specificities and numbers of cases with alloantibodies*

Specificity	Cases
Single antibodies	**(No.=4,913)**
Anti-E	2,202
Anti-Le^{a}	618
Anti-M	383
Anti-Jk^{a}	323
Anti-Fy^{b}	283
Anti-Le^{b}	278
Anti-P1	202
Anti-Di^{a}	116
Anti-c	113
Anti-Jk^{b}	94
Anti-S	87
Anti-C	67
Anti-e	59
Anti-D	31
Anti-Xg^{a}	15
Anti-N	13
Anti-Lu^{a}	11
Anti-Fy^{a}	7
Anti-K	4
Anti-Lu^{b}	4
Anti-Di^{b}	2
Anti-k	1
Two antibodies	**(No.=2,862)**
Anti-E, c	1,792
Anti-C, e	757
Anti-Le^{a}, Le^{b}	62
Anti-E, Fy^{b}	42
Anti-E, Jk^{a}	32
Anti-e, Fy^{b}	19
Anti-E, Jk^{b}	16
Anti-Le^{a}, P1	16
Anti-E, M	15
Anti-Fy^{b}, Le^{a}	14
Anti-E, K	12
Anti-E, Le^{a}	7
Anti-D, E	6
Anti-C, c	6
Anti-C, Jk^{a}	5
Anti-Jk^{a}, S	5
Anti-D, C	4
Anti-E, P1	4
Anti-E, S	4
Anti-C, E	3
Anti-C, Fy^{b}	3
Anti-E, Xg^{a}	3
Anti-e, Le^{a}	3
Anti-P1, M	3
Anti-C, Le^{a}	2
Anti-E, Le^{b}	2
Anti-c, e	2
Anti-Fy^{a}, Le^{a}	2
Anti-Jk^{a}, Le^{a}	2
Anti-Le^{a}, S	2
Anti-E, Di^{a}	2
Anti-C, Jk^{b}	1
Anti-C, Le^{b}	1
Anti-E, Kp^{a}	1
Anti-c, Le^{a}	1
Anti-e, Jk^{a}	1
Anti-e, Jk^{b}	1
Anti-f, Le^{a}	1
Anti-K, M	1
Anti-Fy^{b}, Jk^{a}	1
Anti-Le^{a}, N	1
Anti-Le^{a}, Lu^{a}	1
Anti-Lu^{a}, Lu^{b}	1
Anti-Di^{a}, S	1
Anti-E, Di^{b}	1
Anti-E, Wr^{a}	1
Three antibodies	**(No.=197)**
Anti-C, e, Jk^{a}	37
Anti-E, c, Jk^{a}	33
Anti-E, c, Jk^{b}	30
Anti-E, c, Le^{a}	24
Anti-E, c, N	9
Anti-E, c, M	8
Anti-E, c, S	8
Anti-C, e, Jk^{b}	7
Anti-E, c, Le^{b}	7
Anti-E, c, Fy^{b}	6
Anti-C, e, Di^{a}	5
Anti-C, e, S	4
Anti-C, e, M	3
Anti-E, Jk^{b}, M	3
Anti-C, e, Le^{a}	2
Anti-E, c, P1	2
Anti-E, c, Di^{a}	2
Anti-C, e, Fy^{b}	1
Anti-C, K, Js^{a}	1
Anti-E, Jk^{a}, S	1
Anti-c, e, S	1
Anti-Fy^{a}, M, S	1
Anti-Fy^{b}, Jk^{a}, S	1
Anti-Fy^{b}, Di^{a}, Lu^{a}	1
Four antibodies	**(No.=9)**
Anti-E, Jk^{b}, Le^{a}, M	3
Anti-E, c, Le^{a}, Le^{b}	2
Anti-C, E, c, e	1
Anti-C, e, K, Jk^{b}	1
Anti-C, e, Fy^{b}, S	1
Anti-E, c, Fy^{b}, Jk^{a}	1

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Table II - *Top-20 alloantibodies and corresponding antigen(s)-negative frequencies*

Antibody (anti-)	Cases	Proportion	Antigen-typed cases	Antigen-typed units	Obtained units	Antigen(s)-egative frequency	Units required for typing*
E	2,202	27.6%	1,305	4,194	3,027	72.2%**	2
E, c	1,792	22.5%	1,343	4,251	2,957	69.6%**	2
C, e	757	9.5%	555	1,880	1,091	58.0%**	2
Le^a	618	7.7%	110	451	313	69.4%	2
M	383	4.8%	197	1,902	415	21.8%	5
Jk^a	323	4.0%	215	1,741	491	28.2%	4
Fy^b	283	3.5%	228	1,001	743	74.2%	2
Le^b	278	3.5%	62	319	163	51.1%	2
P1	202	2.5%	137	731	421	57.6%	2
Di^a	116	1.5%	37	135	98	72.6%	2
c	113	1.4%	99	425	283	66.6%**	2
Jk^b	94	1.2%	67	811	185	22.8%	5
S	87	1.1%	61	272	180	66.2%	2
C	67	0.8%	29	94	46	48.9%**	3
Le^a, Le^b	62	0.8%	17	132	46	34.9%	3
e	59	0.7%	36	82	64	78.1%**	2
E, Fy^b	42	0.5%	25	108	83	76.9%**	2
C, e, Jk^a	37	0.5%	11	450	28	6.2%**	17
E, c, Jk^a	33	0.4%	22	162	68	42.0%**	3
E, Jk^a	32	0.4%	26	191	54	28.3%**	4

*Mean number of units needed to be typed in order to find one compatible unit. **Antigen(s)-negative frequencies including C, E, c, and/or e were overestimated because many blood banks preselected C-, E-, c-, and/or e-negative units through the Blood Information Sharing System (BISS) and performed retyping (see **Table III**).

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Table III - *RhCE-negative frequencies from several data sources*

Study period	Present study - BISS June 2016 ~ June 2022			Present study - KRBP July 2013 ~ June 2022		Previous study * Not provided	
	No.	Frequency	Required units**	No.	Frequency	No.	Frequency
C-	27,295/213,691	12.8%	8	46/94	48.9%	39/305	12.8%
E-	104,984/213,691	49.1%	3	3,027/4,194	72.2%	159/305	52.1%
c-	89,651/213,691	42.0%	3	283/425	66.6%	127/305	41.6%
e-	19,539/213,691	9.1%	11	64/82	78.1%	35/305	11.5%
C-e-	19,379/213,691	9.1%	11	1,091/1,880	58.0%	35/305	11.5%
E-c-	88,993/213,691	41.6%	3	2,957/4,251	69.6%	126/305	41.3%

*Reference No. 8. Hong YJ *et al.*, Ann Hematol, 2016. **Average number of units required for typing to obtain one antigen(s)-negative unit. BISS: blood information sharing system; KRBP: Korean Rare Blood Program.

Table IV - *Survey results from 73 facilities and 124 participants*

Survey item	No. (%)
1. Responses by facilities (No.=73)	
A) No. of screening cells	
2 cells	55 (75.3%)
3 cells	11 (15.1%)
Not applicable	7 (9.6%)
B) Specific screening cell available	
Di(a+)	18 (24.7%)
Mi(a+)	2 (2.7%)
Not applicable	55 (75.3%)
2. Responses by participants (No.=124)	
A) Database requires patient identifier	
Necessary	115 (92.7%)
Not necessary	9 (7.3%)
B) Reference when searching antigen frequency	
Textbook[10]	102 (82.3%)
Relevant articles	72 (58.1%)
BISS (for C, E, c, e)	46 (37.1%)
Own database	9 (7.3%)

BISS: Blood Information Sharing System.

Survey results

Responses were collected from 124 workshop participants in 73 facilities which was more than the number of hospitals participating in the transfusion registry. For antibody screening, more than three quarters of facilities used two cells. Di(a+) cells were available in less than a quarter of facilities. More than 90% of individuals stated that a database including patient identifiable information is necessary (**Table IV**).

DISCUSSION

Overview of the study

In the present study, data accumulated on the Korean transfusion registry over 10 years were analyzed. This study provides statistics for the blood group antibodies, including antibody specificity and specific antigen-negative frequency. Of the 29 general hospitals that participated in the transfusion registry, 19 were superior general hospitals accredited by the Ministry of Health and Welfare in Korea, with a median of >1,000 beds. Many hospitals in densely populated urban areas, such as Seoul, Busan, and Gyeonggi, participated. Although there is a limitation derived from voluntary registration, the statistics provided by this study approximate the current status of blood group antibodies in Korea, considering the size and regional distribution of the participating hospitals.

Frequencies of RhCE antigens

The present (and several previous) studies showed that antibodies to RhCE antigens are commonly identified in Korea[11,12]. To predict the probability of obtaining antigen(s)-negative units, it is necessary to determine the true frequencies of RhCE antigens. In the present study, C-, E-, c-, and e- frequencies were calculated through the BISS, which has provided blood banks with RhCE types of RBC units since June 2016 (**Table III**). The frequencies were calculated using large amounts of data, and the results showed similar frequencies to the previous study[8]. The RhCE-negative frequencies calculated through the transfusion registry were overestimated because many blood banks preselected antigen-negative units with reference to the BISS and retyped them. Therefore, RhCE frequencies based on the BISS currently represent the most reliable data, and it is recommended that they be referred to when searching for RhCE frequencies in the Korean population.

Current status and considerations for antibody screening

According to the United States Food and Drug Administration, for antibody screening, reagent RBCs with no fewer than two donor sources should be used and should include the following antigens: D, C, E, c, e, K, k, Fy^a, Fy^b, Jk^a, Jk^b, Le^a, Le^b, P1, M, N, S, s[13,14]. Among 73 facilities that attended KRBP workshop, 75.3% used cells from two sources and 15.1% used cells from three sources for antibody screening, and Di(a+) and Mi(a+) cells were available in 24.7% and 2.7% of facilities, respectively (**Table IV**). Anti-Di^a was the 10th most commonly identified alloantibody, accounting for 1.5% of all alloantibodies (**Table II**). Di^a antigen is a low-prevalence antigen that differs in frequency according to ethnicity. The gene frequency in East Asians is 1-5%, but *DI*A* alleles have never been found in individuals of unmixed European descent[15]. Considering the clinical significance of anti-Di^a, it is recommended that Di(a+) cells be added to routine

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antibody screening in Korea and other Asian countries. Meanwhile, the Mi^a antigen (MNS7), previously known as Miltenberger subsystem of MNS blood group, is a low-prevalence antigen except in Chinese (7%) and Southeast Asian (10%) populations[16]. In Korea, foreigners can donate blood if they meet the following conditions: lived in Korea for >1 year; can communicate in Korean or through an interpreter; and have identification cards verifying residency in Korea[17]. As the number of immigrants from these countries is increasing each year, the chances of Mi^a antigen exposure and anti-Mi^a formation will increase[18]. There have been two cases of anti-Mi^a in Korea[19,20]. Blood banks should prepare for a time when Mi(a+) cells become necessary.

Red cell antibodies in Eastern countries

There are several previous studies related to red cell antibodies in Eastern countries. The common point of the present study in Korea and the previous studies in China, Thai, India, and Iran was that the anti-E, followed by antibodies against other RhCE antigens, was the most common[21-24]. There were differences between Eastern countries. The frequency of the K antigen was 12% in Iranian Jews and as high as 25% in Arabs, whereas it was very rare in Asians[25]. Unlike in China[21], Thailand[22], and Korea (**Table I**), anti-K was the second most common antibody in India and was considered important due to high immunogenicity, as in Western countries[23,26]. Another difference between Eastern countries lies in MNS system: Mi^a (mentioned in the paragraph above) and Mur antigens. While the Mur antigens have very low frequency in most ethnic groups, the frequency in China and Thailand was is 6-9%[25] and anti-Mur was identified[21]. These racial differences should be taken into account when analyzing blood types of immigrants.

Features of registries in the field of transfusion medicine

To derive a model for registries in the field of transfusion medicine, features of several transfusion-related registries and databases were reviewed (**Table V**)[1,2,5,6,27-37].

Several registries used patient identifying records; TRIX in the Netherlands[5,6], Centralized Transfusion Services (CTS) in Pittsburgh[27,28], and the centralized transfusion service database (CTS-D) in Seattle[29]. Patient records, such as ABO and Rh type, unexpected antibodies, and special needs, are tracked when a patient visits more than one hospital within the CTS system. When using the historical ABO type data in the CTS, the detection rate of wrong blood in tube (WBIT) errors was 38% higher than when it was not used[28]. The study based on the CTS-D revealed that the proportion of patients with clinically significant antibodies was

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Table V - *Features and available information of transfusion-related registries and databases*

Classification	Features and available information	Reference
Regional registry or centralized transfusion service	Patient identifying records among hospitals - Prevention of DHTR - Additional detection of WBIT errors	5, 6, 27, 28, 29, 30, 31
Databases including transfusion reactions	Transfusion reactions Donor-to-recipient information	29, 36, 37
Cloud-based search engine	Rapid access to historical antigen information for blood products in hospital inventories	32, 33
Rare donor program	Information on rare donors (e.g. high-incidence antigen-negative) Cryopreservation of rare units	1, 2
Transfusion registry in Korea	Antibody statistics - Frequently identified antibodies - Geographic distribution - Specific antigen-negative frequency - Average units that need to be antigen-typed	Present study
Web-based system in Korea	RhCE phenotype of units in inventory RhCE phenotype frequency	34
D-- donor registry in Korea	D-- donor	34, 35

DHTR: delayed hemolytic transfusion reaction; WBIT: wrong blood in tube.

greater in the group using more than one hospital than in the group using one hospital (7.11 *vs* 3.97%)[29].

Registries with patient-trackable data also prevent DHTR. A web-based regional registry was developed to prevent DHTR due to antibody evanescence and fragmentation of records among hospitals. During the first year of operation, this registry prevented four cases of possible DHTR[30]. As another example, in the United States of America, a case was reported in which antibody screening was negative but a history of anti-Jk^a was identified in the local antibody registry. The patient was transfused with a total of 16 Jk(a-) units and no hemolytic transfusion reaction occurred[31].

Facilitating the detection of specific antigen-negative blood units in the hospital inventory streamlines the blood banks. A cloud-based search engine enabled blood banks to access antigen information of the blood products and to prepare antigen-negative units rapidly[32,33]. In Korea, using BISS (which provides data on the RhCE types of blood units), the RhCE phenotype of a specific blood unit in the inventory can be searched and selected using the blood unit identification number. In addition, rare donors with the D--phenotype (lack of RhCE antigens) have been found and a patient with the D-- phenotype transfused with RBC units from the D--phenotype donor[34,35].

As shown by these studies, registries that can resolve the interhospital fragmentation of records will be able to improve their transfusion services. The majority of KRBP workshop participants (92.7%) agreed on the necessity of a patient identifying database (**Table IV**). In future, it will be necessary to establish a database including PII to track the history of antibodies.

Limitations

The present study had several limitations. Firstly, although the blood banks may have been able to save time by referring to the specific antigen-negative frequencies and the number of units required to obtain compatible blood units in **Tables II** and **III**, this was not investigated. Secondly, participation in the transfusion registry was voluntary. A significant proportion of large hospitals participated; smaller hospitals were less likely to participate. If the practical benefits of the registry are publicized through research and promotion, the participation rate of hospitals would increase. Lastly, due to the absence of PII, antibodies from the same patient may be registered in duplicate, especially in patients receiving frequent transfusions along with pre-transfusion tests including antibody identification. Antibody identification interval in the same patient ranges from 1 to 6 months in Korea depending on the hospital. Although it is several months apart, there may be overlapping registrations.

CONCLUSIONS

In conclusion, distributions of antibodies and antigen frequencies were estimated through a website-based transfusion registry functioning as a blood group database. The various features of the registries discussed in this study will serve as references for individuals operating transfusion-related registries.

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ETHICAL CONSIDERATION

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital in 2017 and is being extended on an annual basis (approval number: B-1705-396-109). Exemption of written informed consent was approved by the Institutional Review Board (above). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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AUTHORS' CONTRIBUTIONS

DWS wrote the first draft of the manuscript. JH and EYS collected, analyzed, and interpreted the data. YJH and KUP conceptualized and designed the study, and revised the manuscript critically. All Authors were involved in preparing the final manuscript and approved the submitted version.

The Authors declare no conflicts of interest.

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