

Survey of Red Cell Transfusion Therapy and Immunohematology Services for Patients with Hemoglobinopathies in Türkiye

Türkiye’de Hemoglobinopati Hastalarında Eritrosit Transfüzyon Tedavisi ve İmmünohematoloji Hizmetleri Araştırması

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Abstract

Objective: Transfusion therapy is critical for many patients with β -thalassemia or sickle cell disease (SCD). We aimed to review current practices and document chronic transfusion therapy for patients with hemoglobinopathies in the transfusion service centers of Türkiye.

Materials and Methods: A survey with 16 structured questions was distributed electronically to adult and pediatric hematologists in Türkiye. Responses were received from 37 centers across 18 cities, representing 1449 patients diagnosed with β -thalassemia major, β -thalassemia intermedia, and SCD.

Results: Although 79% of centers reported performing extended red cell antigen typing prior to the first transfusion, adherence to national transfusion guidelines was inconsistent. Only 16% of centers routinely performed indirect antiglobulin testing before each transfusion despite guideline recommendations. Antibody identification capabilities varied, with 26% of centers lacking the capability onsite. Elution and adsorption testing were always performed at 13% of centers only, predominantly including university hospitals. Nearly half of the centers were always able to provide D, C, E, c, e, and Kell compatible red cell units, but one-fourth reported that they were unable to consistently provide compatible units due to limited supply. There was no access to red cell genotyping in the country.

Conclusion: Our survey revealed disparities in transfusion practices and transfusion service laboratory infrastructure across Türkiye. There is a need for national policy initiatives to mandate adherence to national and international guidelines, expand immunohematology testing capabilities, and ensure the equitable distribution of phenotype-matched red cell units. These findings will contribute to discussions on establishing a centralized immunohematology reference laboratory and enabling red cell genotyping within the country to improve transfusion safety and health equity in hemoglobinopathy care.

Keywords: Thalassemia, Sickle cell disease, Red cell transfusion, Red cell genotyping, Immunohematology

Öz

Amaç: Transfüzyon tedavisi, β -talasemi veya orak hücre hastalığı (OHH) olan birçok hasta için kritik öneme sahiptir. Bu çalışmada, Türkiye’deki transfüzyon merkezlerinde hemoglobinopatili hastalara yönelik kronik transfüzyon tedavisinin güncel uygulamalarını ortaya koymayı amaçladık.

Gereç ve Yöntemler: Türkiye’deki yetişkin ve pediatrik hematologlara 16 sorudan oluşan yapılandırılmış bir anket elektronik olarak gönderildi. Yanıtlar, 18 ildeki 37 merkezden, β -talasemi majör, β -talasemi intermedia ve OHH tanısı almış 1449 hastayı kapsayacak şekilde alındı.

Bulgular: Merkezlerin %79’u ilk transfüzyondan önce genişletilmiş eritrosit antijen tiplendirmesi yaptığını bildirmiş olsa da, ulusal transfüzyon kılavuzlarına uyum tutarsızdı. Kılavuz önerilerine rağmen, merkezlerin sadece %16’sı her transfüzyondan önce rutin olarak indirekt antiglobulin testi yaptığını bildirdi. Antikor tanımlama testi olanakları çeşitlilik göstermekte olup, merkezlerin %26’sında bu olanak bulunmamaktaydı. Elüsyon ve adsorpsiyon testleri, çoğunluğu üniversite hastaneleri olmak üzere merkezlerin yalnızca %13’ünde her zaman yerinde yapılabilmekteydi. Merkezlerin yaklaşık yarısı hemoglobinopati hastalarına her zaman D, C, E, c, e ve Kell uyumlu eritrosit konsantreleri sağlayabiliyordu, ancak dörtte biri yetersiz tedarik nedeniyle devamlı olarak uyumlu eritrosit sağlayamadıklarını bildirdi. Ülkede eritrosit genotipleme yapılamamaktaydı.

Sonuç: Araştırmamız Türkiye genelinde transfüzyon uygulamaları ve kan bankası laboratuvar altyapısı açısından farklılıklar olduğunu ortaya koymuştur. Standardize transfüzyon protokollerine uyulmasını zorunlu kılmak, immünohematoloji test olanaklarını genişletmek ve fenotipik uyumlu eritrosit konsantrelerinin her bölgeye dağıtımını sağlamak için ulusal politika geliştirilmesine ihtiyaç vardır. Bu bulgular, merkezi bir immünohematoloji referans laboratuvarı kurulması ve ülke çapında eritrosit genotiplemenin sağlanması konusundaki tartışmalara katkıda bulunacak ve hemoglobinopati tedavisinde transfüzyon güvenliğinin ve sağlık eşitliğinin iyileştirilmesine yardımcı olacaktır.

Anahtar Sözcükler: Talasemi, Orak hücre hastalığı, Eritrosit transfüzyonu, Eritrosit genotipleme, İmmünohematoloji



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Introduction

Hemoglobinopathies are a group of inherited blood disorders characterized by abnormalities in the hemoglobin molecule that can result in impaired ability to transport oxygen, leading to hemolysis [1]. The absence or diminished synthesis of β -globin in β -thalassemia major or intermedia results in a shortened lifespan of red cells; these patients should receive regular red cell transfusions for normal growth and development. The clinical features of sickle cell disease (SCD) reflect the tendency of erythrocytes to adopt a sickle shape in deoxygenated blood, resulting in reduced red cell survival and a tendency of the blockage of small blood vessels. Therefore, red cell transfusion is a critical therapeutic intervention for avoiding complications of SCD [2].

Türkiye made progress in the safe provision and use of blood and blood products with the Blood and Blood Products Law (2007), followed by the Implementing Regulation on Blood and Blood Products (2008); the Guide on Blood and Blood Products (2009); the National Guides on Preparation, Use, and Quality Assurance of Blood Components (2016); Standards for Blood Service Units (2016); the Quality Management System for Blood Service Units (2016); and Hemovigilance (2020). Türkiye is an active member of the Council of Europe, and its national guidelines are in compliance with European Union legislation on blood and blood products. The Turkish Red Crescent has the main responsibility in this field with 13 temporary regional blood centers supporting blood supply throughout the country by collecting and processing voluntary blood donations. Adult or pediatric hematology clinics have been established in 75 of the 81 provinces of Türkiye [3]. Hematologists and transfusion medicine specialists are actively involved in optimizing transfusion care through the use of uniform blood bank practices across the country.

According to the International Thalassemia Federation (TIF), the Turkish Thalassemia Diagnosis and Follow-up Guidelines, and the American Society of Hematology guidelines for SCD, patients should undergo extended red cell antigen typing, at least including ABO, D, C, c, E, e, and Kell, before starting transfusion therapy [4,5,6]. All patients with transfusion-dependent β -thalassemia major and intermedia should be transfused with leukocyte-reduced red cells that are ABO, D, C, E, c, e, and Kell compatible in volumes of 10-15 mL/kg every 3-4 weeks [4,5]. Antibody screening should also be performed before each transfusion, as alloimmunization rates have been reported to range from 2.9% to 37% in various populations [7].

In this study, we aimed to survey current practices and document chronic transfusion therapy for patients with hemoglobinopathies in the transfusion service centers of Türkiye.

Materials and Methods

Participants

Survey participants were recruited by members of the Turkish Society of Hematology. Pediatric hematologists who were members of the Turkish Society of Pediatric Hematology also participated in the survey. Invitation e-mails were repeatedly sent to approximately 600 specialists of adult or pediatric hematology between January 15 and February 15, 2025. Respondents from 37 of a total of 75 centers voluntarily participated in the survey, representing 5 of 7 geographical regions of Türkiye, and also replied to subsequent correspondence (Table 1). These respondents consented to voluntary participation and became authors of the study as the Turkish Hemoglobinopathy Survey Investigators. The demographics of the non-respondents remained unknown. Hence, no ethics approval for human subjects research was required.

All e-mails contained a link to a website with an electronic version of the survey (Supplementary Table S1).

Questionnaire

Prospective participants received the questionnaire (Supplementary Table S1). We requested information including: 1) the number of patients with β -thalassemia major, intermedia, and SCD receiving regular red cell transfusions or exchange transfusions at each institution; 2) the required pre-transfusion serological testing of patients with hemoglobinopathies, such as C, E, c, e, and Kell testing; 3) the frequency of direct antiglobulin tests (DATs) and indirect antiglobulin tests (IATs) and the interpretation of the results; 4) the routine use of antibody identification, elution, and adsorption tests and the interpretation of the results; and 5) information on the level of the supply of C, E, c, e, and Kell compatible red cell units for patients with hemoglobinopathies.

Results and Discussion

A total of 20 adult hematology specialists (54%) and 17 pediatric hematology specialists (46%) from 37 centers in 18 cities in Türkiye responded to the survey (Table 1). The 3 most populated cities in Türkiye, İstanbul, Ankara, and İzmir, accounted for 38% of the responding centers. Among the participating centers, 17 were university hospitals (46%), 17 were public or city hospitals (46%), and 3 were private hospitals (8%); 12 centers were located in the Marmara region (32%), 10 centers in the Central Anatolia region (27%), 8 in the Mediterranean region (22%), 6 in the Aegean region (16%), and 1 in the Southeastern Anatolia region (3%). The specialists contacted in the Black Sea region responded verbally that they did not have any patients with hemoglobinopathy and regular transfusion (data not shown). No data were received from the Eastern Anatolia region. These findings are supported by a previous study indicating that the

Black Sea region had no recorded cases of thalassemia, while the Eastern Anatolia region had the lowest number of documented patients with thalassemia [8]. Hence, the possible impact of missing data from the Eastern Anatolia and Black Sea regions is low. The overall response rate for our 16 questions was 97%.

We collated data for 1449 patients, including 1226 with β -thalassemia major (85%), 130 with β -thalassemia intermedia (9%), and 93 with SCD (6%) from 37 centers (Table 1). Pediatric hematology outpatient clinics in Ankara (Bilkent City Hospital), İzmir (Ege University), and Antalya (Akdeniz University) reported 440 patients with β -thalassemia major (34%), while most adult β -thalassemia major patients (18%) were reported from hematology clinics in İstanbul (İstanbul University) and Hatay (İskenderun Public Hospital). Similarly, β -thalassemia intermedia patients were most commonly reported from İstanbul, İzmir, Antalya, and Konya. However, more than half of the patients with SCD (52%) were followed in adult hematology outpatient clinics in Antalya, Hatay, Muğla, and İstanbul. Previous epidemiological studies from Türkiye reported that the Mediterranean region had the highest rate of SCD while coastal areas had the highest levels of β -thalassemia [9,10], and these findings were confirmed by our survey.

Red Cell Phenotyping

Phenotyping for C, E, c, e, and Kell was always performed in most of the centers (79%) before the first transfusion (Table 2). When transfused patients with hemoglobinopathies were referred from other centers, 27 centers (71%) always performed the C, E, c, e, and Kell typing. Although the existing thalassemia guidelines for Türkiye recommend extended red cell antigen typing including ABO, D, C, c, E, e, and Kell before starting transfusion therapy, 2 adult hematology centers (5%) reported not performing extended phenotyping for patients diagnosed at their center or for those referred from other centers. This finding suggested gaps in the adherence to the established guidelines.

A previous study from the United States revealed inconsistencies in transfusion practices between comprehensive care centers for thalassemia or SCD and other healthcare institutions. Notably, only 20% of non-thalassemia treatment centers and 71% of non-SCD treatment centers were reported to follow the established guidelines by providing Rh- and Kell-matched red blood cell units prophylactically [11]. A hemoglobinopathy survey in England also revealed suboptimal compliance with transfusion guidelines, with only 71% of patients being phenotyped for Rh and Kell antigens [12]. These data highlight potential areas for improvement of transfusion practices, particularly

Table 1. Geographic regions in Türkiye and patients reported by survey respondents.

Regions*	Patients				Sickle cell disease	
	β -thalassemia			Total	%	n
Major (n)	Intermedia (n)					
Marmara	261	29	290	21%	22	24
Central Anatolia	270	24	294	22%	11	12
Mediterranean	320	52	372	27%	38	41
Aegean	280	15	295	22%	20	21
Southeast Anatolia	95	10	105	8%	2	2
Black Sea	nr	nr	nr	nr	nr	nr
East Anatolia	nr	nr	nr	nr	nr	nr
Total	1226	130	1356	100%	93	100%

*: Geographic regions listed in decreasing order of population size.
nr: No responses received.

Table 2. Routine serologic testing for patients with hemoglobinopathies in Türkiye.

Responses	Transfusion service centers							
	C, E, c, e, and Kell antigens							
	Diagnosed at the center		Referred from another center		Antibody identification		Adsorption and elution	
n	%	n	%	n	%	n	%	
Always	29	79%	26	71%	18	47%	5	13%
Usually	5	13%	9	24%	5	16%	3	8%
Sometimes	1	3%	0	2%	4	11%	6	16%
Never	2	5%	2	5%	10	26%	23	63%
Total	37	100%	37	100%	37	100%	37	100%

to ensure compatibility and prevent alloimmunization among hemoglobinopathy patients.

The transfusion policy for patients referred from another center who were tested for D, C, c, E, e, and Kell and had mixed-field reactions was to transfuse cross-match compatible red cell units in 12 centers (32%) and red cell units negative for mixed-field antigens in 10 centers (27%), to review old subgroup results from the referring center in 4 centers (11%), to consult an experienced center in 3 centers (8%), and to perform DATs, IATs, and antibody identification tests in 2 centers (5%). Another 6 centers (16%) reported having encountered no mixed-field reactions.

DATs and IATs

The frequency of performing DATs and IATs varied widely among centers (Table 3). Before the first transfusion, fewer than one-third of the centers performed either test. For ongoing transfusion therapy, 62% of the centers reported performing the DAT at least once a year. Although the TIF guideline and the Appropriate Clinical Use of Blood Guide recommend an IAT before every transfusion [4,13], only 6 university hospitals (16%) performed an IAT before every transfusion. While many specialized centers were cautious about ensuring compatibility through DATs and IATs (data not shown), all centers should follow consistent protocols for patient safety, such as preventing alloimmunization and hemolytic transfusion reactions [14].

Table 3. Frequency of performing direct antiglobulin test (DAT) and indirect antiglobulin test (IAT) for patients with hemoglobinopathies.

	Transfusion service centers			
	DAT		IAT	
Frequency	n	%	n	%
Before first transfusion only	11	30%	10	27%
Before every transfusion	3	8%	6	16%
Once per year	7	19%	9	24%
2 times a year	7	19%	9	24%
4 times a year	9	24%	3	8%
Total	37	100%	37	100%

Transfusion and typing strategies for DAT-positive patients also varied significantly (Table 4). Only 6 centers (16%) reported giving cross-matched and C, E, c, e, and Kell compatible red cell units; investigating the cause of DAT positivity; and performing elution. An additional 9 centers followed a similar strategy without elution (24%). This suggests that elution, a technique used to detect red cell-bound antibodies, was not widely utilized across the country. Another 6 centers relied solely on cross-match compatible red cell units without additional antigen matching (16%), while 4 centers provided red cell units matched only for C, E, c, e, and Kell (11%).

Elution and Antibody Identification Testing

Nearly two-thirds of the centers (63%) reported being unable to perform elution and adsorption tests (Table 1). Conversely, only 5 centers (13%) consistently performed these tests, with the majority being university hospitals and one being a training and research hospital. Currently, these specialized tests seem largely dependent on institutional resources and expertise. A national resource and an immunohematology reference laboratory could suffice for these non-urgent tests.

Regarding antibody identification, 18 centers always performed this test (47%), whereas 10, mostly city or public hospitals, lacked this capability onsite (26%) and sent their samples to university hospitals (n=8) or laboratory companies (n=2). These findings highlight disparities in laboratory capabilities, which can delay transfusion decisions and patient management. Furthermore, the ability to provide antigen-negative red cell units compatible with antibody identification results was limited, with only 5 centers always (13%), 14 usually (38%), and 13 sometimes (35%) being able to supply antigen-negative red cell units based on antibody identification results. As a result, these centers provided antigen-matched red cells to 42% of their hemoglobinopathy patients based on antibody identification results. However, 5 centers could not provide antigen-matched red cell units based on such results (13%).

Table 4. Transfusion strategies for direct antiglobulin testing.

Items	Transfusion service centers (n)* and answers†									
	6	9	4	2	2	1	1	6	4	2
I give cross-match compatible red cell units	x	x		x	x			x		
I give C, E, c, e, and Kell compatible red cell units	x	x	x		x	x			x	
I investigate the reason for DAT positivity	x	x	x	x			x			x
Elution should be done	x					x	x			

*: For a total of 37 centers.
 †: 10 different response patterns are shown together with the number of centers (n=1 to n=9) responding with 1 of the 10 possible response patterns.

Supply of Compatible Red Cell Units

Many centers (n=17) could always provide C, E, c, e, and Kell compatible red cell units for thalassemia patients (n=16) and for alloantibody positive patients (n=1). However, 9 centers reported that they were not able to consistently provide compatible red blood cells to patients with hemoglobinopathies due to a shortage of supply; 13 centers usually provided C, E, c, e, and Kell compatible red cell units for thalassemia (n=2) and SCD patients (n=2); and 6 centers sometimes provided such units for alloantibody-positive (n=4) or DAT-positive patients (n=1). Only 1 center reported not providing compatible red cell units at all, with transfusions limited to DAT-positive patients. These data highlight disparities in transfusion practices and emphasize the need for policy interventions aimed at improving the availability and equitable distribution of phenotype-matched red blood cell units across transfusion service centers.

Red Cell Genotyping

Only 1 center reported sending samples to another country in Europe for red cell genotyping in some cases of complicated alloantibodies in thalassemia patients. No center provided red cell genotyping for their patients onsite or had access to red cell genotyping within Türkiye.

Conclusion

This nationwide survey provided a comprehensive overview of current transfusion practices for patients with hemoglobinopathy across 37 centers in Türkiye. Our survey represented adult and pediatric hematology specialists in nearly equal numbers. Despite national and international guidelines recommending extended red cell antigen phenotyping and antibody screening [4,5], our findings revealed significant variability in the implementation of that recommendation. While the majority of centers performed initial phenotyping and strive to provide C, E, c, e, and Kell compatible red cell units, key practices such as a routine IAT before each transfusion, the use of elution techniques, and access to antibody identification are inconsistently applied and often limited by institutional resources. In addition, blood group identification can be complicated because of mixed-field reactions after recent transfusions, when antigen typing had not been performed before the first transfusion of red cells.

One-fourth of the centers explicitly cited supply limitations as the primary reason for not consistently providing antigen-matched red cell units. This constraint represented a significant systemic barrier to optimal transfusion care and increased the likelihood of alloimmunization and hemolytic transfusion reactions. This inequity of access to patient care particularly affected regions with limited immunohematology infrastructure, suggesting the urgent need for centralized coordination and supply chain improvement. The data presented here may be

used to evaluate the feasibility, cost-effectiveness, and impact on the healthcare system of proposed changes, such as a centralized immunohematology reference laboratory and red cell genotyping, in Türkiye. Developing a centralized policy that mandates red cell antigen typing, alloantibody screening, and red cell genotyping, especially in cases with alloantibodies or complex serology, in cooperation with the Turkish Red Crescent and regional blood banks may help to address these gaps.

Ethics

Ethics Committee Approval: No ethics approval for human subjects research required.

Informed Consent: Not applicable for this survey.

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Footnotes

Authorship Contributions

Concept: D.G.G., N.A., W.A.F.; Design: D.G.G., N.A., W.A.F.; Data Collection or Processing: The Turkish Hemoglobinopathy Survey Investigators, D.G.G.; Analysis or Interpretation: D.G.G., W.A.F.; Literature Search: The Turkish Hemoglobinopathy Survey Investigators; Writing: D.G.G., W.A.F.

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Supplementary Material Link. <https://d2v96fxpocvxx.cloudfront.net/2e2ef1e6-55a4-4774-a230-ade3bb752921/documents/Supplement%20Questionnaire%20US-TR.pdf>