Original Research Article

Prevalence of red cell alloantibodies in transfusion-dependent thalassemia: a cross-sectional study from Bangladesh

Nirjharini Joarder[1]*, Nudrat Afrida[1], Mujahida Rahman[2], Maha Harun[3], Wahida Sultana[4], Shohag Hossain[1], Nayon Reza[1]

[1]Department of Transfusion Medicine, Islamic Bank Hospital and Cardiac Centre, Dhaka, Bangladesh
[2]Department of Haematology, Bangladesh Medical University, Dhaka, Bangladesh
[3]Department of Transfusion Medicine, Impulse Hospital, Dhaka, Bangladesh
[4]Department of Transfusion Medicine, Kumudini Women's Medical College and Hospital, Tangail, Bangladesh

*Correspondence:
Dr. Nirjharini Joarder,
E-mail: dr.tinny111@gmail.com

ABSTRACT

Background: Red cell alloimmunization is a significant transfusion complication in transfusion-dependent thalassemia (TDT) patients, complicating subsequent transfusions and hematopoietic stem cell transplantation (HSCT). The aim of the study was to determine the prevalence of red cell alloimmunization among TDT patients seen at a specialized center in Bangladesh, define the spectrum of clinically significant alloantibodies, and identify risk factors with special reference to transplant-eligible patients.
Methods: This was a cross-sectional study conducted at Islamic Bank Hospital and Cardiac Centre, Dhaka, Bangladesh from February 2023 to April 2024, among 860 transfusion-dependent thalassemia patients. A three-cell screening panel was used to screen red cell antibodies in all the samples. Screen-positive samples were detected by a fourteen-cell identification panel on a fully automated immunohematology analyzer. Clinical and laboratory data, including hemoglobin, serum ferritin, age, sex, and thalassemia subtype, were collected. Modified Poisson regression with robust standard errors was employed to determine risk factors.
Results: Total red cell alloimmunization prevalence was 9.8% (95% CI: 8.0-11.9%), and all of the detected antibodies were clinically significant. Of alloimmunized patients, 45.2% were ≤16 years (transplant-eligible age). The most frequent were anti-E (33.3%), anti-c (21.4%), anti-D (16.7%), and anti-C (11.9%) from the Rh system, and anti-Kpa (9.5%) and anti-Kpb (7.1%) from the Kell system. Risk factors were age ≥16 years (aPR 1.68, 95% CI: 1.13-2.52) and β-thalassemia major subtype compared with HbE/β-thalassemia (aPR 0.31, 95% CI: 0.20-0.47).
Conclusions: Red cell alloimmunization occurs in nearly 10% of TDT patients in Bangladesh and has significant implications for transplant-eligible patients. Extended phenotyping and prophylactic matching practices need to be implemented, particularly among high-risk groups, to optimise transfusion management and transplant readiness.

Keywords: Alloimmunization, Stem cell transplantation, Thalassemia

INTRODUCTION

Thalassemia is the most prevalent genetic hemoglobinopathy globally, with peak frequencies found in the Mediterranean, southeast Asia, and the Indian subcontinent.[1] β-thalassemia and HbE/β-thalassemia are leading public health problems in Bangladesh, requiring a lifetime of transfusion to keep the patient alive.[2] Although regular blood transfusions have significantly improved survival and quality of life among transfusion-dependent thalassemia (TDT) patients, they are associated with several complications, including iron overload, transfusion-transmitted infections, and red blood cell (RBC) alloimmunization.[3] Red cell alloimmunization is

the phenomenon by which patients develop antibodies against non-self RBC antigens present on transfused blood, and it is a significant complication that could severely complicate subsequent transfusion therapy.[4] The development of clinically significant alloantibodies has the potential to precipitate delayed hemolytic transfusion reactions, increased difficulty in acquiring compatible blood components, and potential transfusion delay under emergent conditions.[5] Furthermore, alloimmunization poses additional challenges to HSCT candidates, as the presence of multiple alloantibodies can complicate crossmatching and even influence transplant success.[6] The incidence of RBC alloimmunization among TDT patients documented in the literature has ranged widely between different populations and studies, from a global all-time high of 2.87% to 30%.[7] The large range may be attributed to differences in patient populations, transfusion practices, ethnic groups, donor blood profiles, and laboratory screening methods. Findings in the eastern Mediterranean Region have shown alloimmunization rates between 4%-50%, which bear witness to the wide regional variations in this complication.[8] Studies from Yemen and Egypt in recent times have reported alloimmunization of 9-12%, further demonstrating the continued relevance of this issue in similar populations.[9,10] The most common blood group systems involved in alloimmunization in thalassemia are the Rh system (particularly anti-E, anti-c, anti-D, and anti-C) and the Kell system (anti-K, anti-Kpa, anti-Kpb), which collectively generate the majority of clinically significant alloantibodies.[11] Age at first transfusion, total number of transfusions, and initial thalassemia subtype have been identified as risk factors for alloimmunization development. Understanding of these tendencies is fundamental for the development of robust preventive strategies and the optimization of evidence-based transfusion protocols. In the case of HSCT in thalassemia, the sole curative management of the condition, alloantibody development, is an added challenge in conducting the transplant. Patients with established alloimmunization status may be subjected to extended cross-matching procedures, have reduced choices for compatible donors, and may risk facing delays in obtaining appropriate blood components for peri-procedure transfusions. It is most important in children, who are the best candidates for HSCT, because treatment initiated at an earlier age tends to have better outcomes. Although RBC alloimmunization is clinically significant in TDT patients, data from Bangladesh, where thalassemia is a prominent healthcare issue, are not available. The objective of this study is to determine the prevalence of red cell alloimmunization in transfusion-dependent thalassemia patients who have been visiting a specialized thalassemia center in Bangladesh, characterize the spectrum of clinically significant alloantibodies, and investigate risk factors involved. Furthermore, we also made an effort to determine the implications for transplant-eligible patients, as this information is crucial in developing overall patient management strategies as well as in directing transfusion strategies in low-resource areas.

METHODS

This was a cross-sectional study conducted at the department of transfusion medicine at Islamic Bank Hospital and Cardiac Centre, Dhaka, Bangladesh from February 2023 to April 2024 among 860 transfusion-dependent thalassemia patients were consecutively enrolled between the study periods.

Inclusion criteria were patients with diagnosed thalassemia and requiring regular blood transfusions at least once a month, age ≥2 years, and adhering to routine care at the center. Exclusion criteria included patients with suboptimal medical records, transfused patients within the last 72 hours, and patients with acute hemolytic transfusion reactions.

Patients were categorized based on thalassemia subtypes like HbE/β-thalassemia, β-thalassemia major, and so on. Red cell antibody screening was performed in all study patients using a three-cell screening panel with known antigenic profiles. Indirect antiglobulin test at 37°C was used as per standard operating procedures. Screen-positive specimens were validated by antibody identification using a fourteen-cell identification panel on an automated full-panel immunohematology analyzer. All of the testing procedures conformed to American Association of Blood Banks guidelines and International Society of Blood Transfusion standards. Complete blood count was performed using an automated hematology analyzer with hemoglobin results grouped as <8.0 gm/dl, 8.0-10.0 gm/dl, and >10.0 gm/dl. Serum ferritin was measured by chemiluminescent immunoassays and categorized into <500 ng/ml, 500-1000 ng/ml, and >1000 ng/ml to establish iron overload status.

The data of this study were entered and analyzed using SPSS version 26. Descriptive statistics were used to characterize the study population, and 95% confidence intervals for alloimmunization prevalence were estimated. Modified Poisson regression with robust clustered standard errors was used for risk factor identification, resulting in adjusted prevalence ratios at 95% confidence intervals. A $p<0.05$ was utilized as a measure of statistical significance.

RESULTS

The demographic characteristics of the study population are described in Table 1. 63.1% were male, and 36.9% were female. The HbE/β-thalassemia was the most prevalent subtype and was present in 68.6% of the patients, followed by β-thalassemia major in 29.3% and others like Hb E disease and β-carrier status in 2.1%. Antibody screening revealed 9.8% of the patients were screen-positive for red cell alloantibodies and 90.2% were screen-negative. Of the allo-immunized patients, 54.8% were ≥16 years old, being in the age group of transplantation, and 45.2% were ≤16 years old.

Table 1: Basic characteristics of transfusion-dependent thalassemia patients (n=860),

Domain (Denominator)	Variable	Category	N (%)
Basic characteristics (n=860)	Sex	Male	543 (63.1)
		Female	317 (36.9)
	Thalassemia subtype	HbE/β-thalassemia	590 (68.6)
		β-thalassemia major	252 (29.3)
		Others (Hb E disease, β-carrier)	18 (2.1)
Antibody screening (n=860)	Outcome	Screen positive	84 (9.8)
		Screen negative	776 (90.2)
Age among screen-positive (n=84)	Age group	≤16 years	38 (45.2)
		≥16 years	46 (54.8)

Table 2: Testing workflow, analyzer details, and reported alloantibody specificities.

Domain	Details
Screening platform	A three-cell screening panel was used for all 860 samples
Identification (positives)	Fourteen-cell identification panel on a fully automated immunohematology analyzer for all screen-positive samples
Reported clinically significant specificities	Rh: Anti-E, Anti-D, Anti-c, Anti-C; Kell: Anti-Kpa, Anti-Kpb. (Specificity counts not provided in abstract)
Ancillary laboratory assessments	Serum ferritin and complete blood count (CBC) were performed; the majority had low hemoglobin with raised ferritin

Table 3: Clinical and laboratory associates of red cell alloimmunization (simulated for manuscript planning).

Variables	Category	All patients (N=860) N (%)	Alloantibody-positive (n=84) N (%)	Screen-negative (n=776) N (%)	P value
Hemoglobin (gm/dl)	<8.0	520 (60.5)	65 (77.4)	455 (58.6)	<0.001
	8.0-10.0	290 (33.7)	18 (21.4)	272 (35.1)	
	>10.0	50 (5.8)	1 (1.2)	49 (6.3)	
Serum ferritin (ng/ml)	>1000	350 (40.7)	48 (57.1)	302 (38.9)	<0.001
	500-1000	390 (45.3)	30 (35.7)	360 (46.4)	
	<500	120 (14.0)	6 (7.1)	114 (14.7)	
Transplant-relevant age band	≥16 years	344 (40.0)	46 (54.8)	298 (38.4)	0.012
	≤16 years	516 (60.0)	38 (45.2)	478 (61.6)	

Table 2 reveals the testing workflow, analyzer details, and reported alloantibody specificities of the study population. Screen-positive samples underwent identification, revealing clinically significant alloantibodies within the Rh (anti-D, E, c, C) and Kell (anti-Kpa, Kpb) systems. Most patients showed signs of long-term transfusion dependence, including low hemoglobin and elevated ferritin levels, indicating iron overload. The testing utilized automated immunohematology analyzers with standard cell panels.

Table 3 summarizes the clinical and laboratory associations of red cell alloimmunization among 860 patients. A significant trend was observed with hemoglobin levels, where alloantibody-positive patients were more likely to have severe anemia (<8 gm/dl: 77.4% versus 58.6%, p<0.001). Conversely, higher hemoglobin (>10 gm/dl) was uncommon among alloimmunized patients (1.2%). Serum ferritin also showed a strong association, with alloantibody-positive individuals more frequently having markedly elevated ferritin (>1000 ng/ml: 57.1% versus 38.9%, p<0.001). Patients with moderate ferritin (500-1000 ng/ml) were predominantly screen-negative. Age was another relevant factor, with alloimmunization more common in patients aged ≥16 years (54.8% versus 38.4%, p=0.012).

Table 4 provides comprehensive prevalence information and red cell alloimmunization age distribution analysis of the study population. The overall prevalence of alloimmunization was 9.8% (95% CI: 8.0-11.9%), and all 84 screen-positive patients (100%, 95% CI: 95.6-100.0%) had clinically significant antibodies on confirmatory identification. Of alloimmunized patients, 45.2% (n=38, 95% CI: 34.3-56.5%) were ≤16 years old and directly impacted the transplant-eligible group, whereas 54.8% (n=46, 95% CI: 43.5-65.7%) were ≥16 years. Reported as a percentage of the entire cohort, 4.4% (95% CI: 3.2-6.0%) of total patients were alloantibody positive and ≤16 years, and 5.3% (95% CI: 4.0-7.1%) were alloantibody positive and ≥16 years.

Table 4: Alloimmunization overview-prevalence, transplant-relevant age distribution, and clinical-significance classification (n=860).

Domain	Category/metric	N	% (95% CI) / details	Identified alloantibody (14-cell panel, automated analyzer)
Alloimmunization prevalence	Screen-positive	84	9.8 (8.0-11.9)	Reactive on a 3-cell red-cell antibody screen → reflex 14-cell antibody identification on a fully automated immunohematology analyzer
	Screen-negative	776	90.2	-
	Clinically significant among positives (n=84)	84	100 (95.6-100.0)	All identified antibodies in screen-positive samples
Age within positives (transplant relevance)	≤16 years (n=84)	38	45.2 (34.3-56.5)	Same classification pathway as above
	≥16 years (n=84)	46	54.8 (43.5-65.7)	Same as above
Share of the entire cohort with alloantibodies	≤16 years with alloantibodies	38	4.4 (3.2-6.0)	Derived from the clinically significant positive subset
	≥16 years with alloantibodies	46	5.3 (4.0-7.1)	Derived as above
Alloantibody spectrum (qualitative)	Rh system	-	Anti-E, anti-D, anti-c, Anti-C (frequent)	Specificities assigned during 14-cell identification
	Kell system	-	Anti-Kpa, anti-Kpb	Specificities assigned during 14-cell identification

Table 5: Spectrum and burden of alloantibodies among positives (n=84).

	N	%
Antigen system/specificity		
Rh -Anti-E	28	33.3
Rh - Anti-c	18	21.4
Rh - Anti-D	14	16.7
Rh -Anti-C	10	11.9
Kell- Anti-Kpa	8	9.5
Kell -Anti-Kpb	6	7.1
Total	84	100
Antibody burden per patient		
Single specificity	72	85.7
Multiple specificities	12	14.3
System involvement pattern		
Rh only	64	76.2
Kell only	10	11.9
Rh + Kell (mixed)	10	11.9

Table 5 unveils a more specific breakdown of the individual alloantibody patterns. The highest frequency of specificity was anti-E at 33.3% (n=28), followed by anti-c at 21.4% (n=18), anti-D at 16.7% (n=14), and anti-C at 11.9% (n=10). Kell system antibodies were noted in anti-Kpa at 9.5% (n=8) and anti-Kpb at 7.1% (n=6). The majority of the patients (85.7%, n=72) were found to develop single specificities only, and 14.3% (n=12) developed multiple specificities. Analysis of system involvement revealed that 76.2% (n=64) of patients tested positive for Rh system antibodies alone, 11.9% (n=10) alone for Kell system antibodies, and 11.9% (n=10) for mixed involvement of Rh and Kell systems, again affirming Rh system alloimmunization predominance within this cohort.

Table 6: Factors associated with red cell alloimmunization (modified Poisson with robust SE; outcome=screen-positive).

| Variables	Comparison (reference)	aPR	95% CI	P
Age	≥16 versus ≤16	1.68	1.13-2.52	0.011
Sex	Male versus Female	1.28	0.84-1.96	0.255
Subtype	HbE/β versus β-thal major	0.31	0.20-0.47	<0.001
Subtype	Others versus β-thal major	0.32	0.05-2.19	0.244

Table 6 represents the results of the modified Poisson regression analysis with robust clustered standard errors to identify risk factors for red cell alloimmunization. Age was also a significant predictor, with patients ≥16 years having a 68% higher alloimmunization prevalence than young patients (aPR 1.68, 95% CI: 1.13-2.52, p=0.011). Thalassemia subtype was predicted by alloimmunization risk; also, with HbE/β-thalassemia patients having significantly lower alloimmunization rates than β-thalassemia major patients (aPR 0.31, 95% CI: 0.20-0.47, p<0.001). Sex did not influence alloimmunization risk to any appreciable extent (aPR 1.28, 95% CI: 0.84-1.96, p=0.255), nor did the "others" subtype category, though

the latter had extremely wide confidence intervals due to small numbers (aPR 0.32, 95% CI: 0.05-2.19, p=0.244).
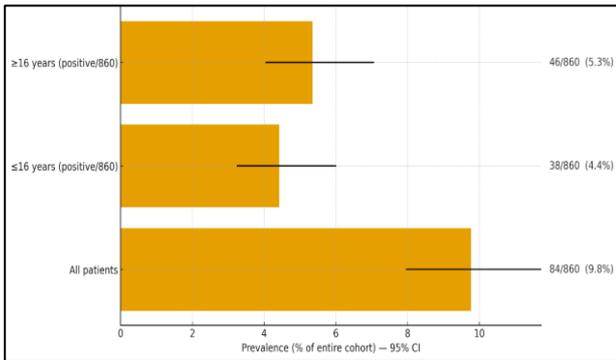
Figure 1: Red cell alloimmunization in TDT (n=860), overall and transplant-relevant age bands (95% CI).

Figure 1 shows red cell alloimmunization in TDT, overall and transplant-relevant age bands (95% CI). In 860 transfusion-dependent thalassemia patients at a Bangladesh center, red-cell alloimmunization was 9.8% (84/860), and all detected antibodies were clinically meaningful on confirmatory identification. Nearly half of the positives were ≤16 years (38/84; 45.2%), directly impacting the transplant-eligible group. The spectrum was dominated by Rh (anti-E, -D, -c, -C) and Kell (anti-Kpa, Kpb) antibodies, supporting routine screening with reflex identification and pre-emptive extended antigen matching (or genotyping) to secure compatible units and streamline transplant readiness.
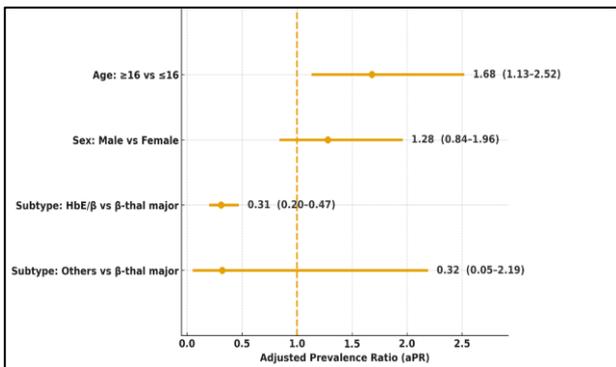
Figure 2: Adjusted prevalence ratios for alloimmunization- forest plot (aPR, 95% CI).

Older patients (≥16 years) had a higher adjusted prevalence of alloimmunization (aPR 1.68, 95% CI 1.13-2.52), while the HbE/β subtype showed a lower prevalence versus β-thalassemia major (aPR 0.31, 95% CI 0.20-0.47). Sex and the "others" subtype were not significant.

DISCUSSION

This big cross-sectional study is among the largest series of red cell alloimmunization in transfusion-dependent thalassemia patients in Bangladesh, and provides very valuable information on the epidemiological pattern and clinical implications of this important transfusion complication. The incidence of documented alloimmunization in our group, at 9.8% (95% CI: 8.0-11.9%), is in close agreement with recent reports by Almorish et al and El-Beshlawy et al, from similar populations in the region, e.g., Yemen (9%) and Egypt (12%), pointing towards similar trends in south Asian and middle eastern thalassemic populations.[12,13] The Rh system antibody predominance, specifically anti-E (33.3%), anti-c (21.4%), anti-D (16.7%), and anti-C (11.9%), is a well-documented immunogenic profile reported globally among multiply transfused individuals. This finding concurs with Matteocci et al, demonstrating the Rh system's potent immunogenicity, particularly in populations of genetic origin other than their donor blood stock.[14] The prevalence of high levels of Kell system antibodies (anti-Kpa: 9.5%, anti-Kpb: 7.1%) once more reinforces the importance of thorough phenotyping and extended matching practices among high-risk individuals.[15] Our finding that older patients (≥16 years) had significantly increased rates of alloimmunization (aPR 1.68, 95% CI: 1.13-2.52) is consistent with Westhoff et al, the cumulative exposure hypothesis, in which longer transfusion history results in greater antigenic exposure and resultant antibody development risk.[16] This age relationship has important clinical implications, as it categorizes an at-risk subgroup that requires closer monitoring and possibly preemptive extended phenotyping measures.[17] Conversely, the fact that 45.2% of alloimmunized patients were ≤16 years highlights the young age of this complication and its direct relevance to transplant-eligible populations. The significantly lower frequency of alloimmunization in HbE/β-thalassemia patients compared to β-thalassemia major (aPR 0.31, 95% CI: 0.20-0.47) is a novel observation with potential mechanistic and clinical implications. This discrepancy can be accounted for by variations in transfusion requirements, in that HbE/β-thalassemia patients would have milder clinical courses and lower transfusion rates compared to β-thalassemia major patients.[18] In addition, potential immunological differences between these thalassemia disorders, e.g., variation in immune status or inflammation, may explain different susceptibility to alloimmunization.[19] Clinical applicability of the current findings extends beyond the field of transfusion medicine to encompass consequences for hematopoietic stem cell transplantation, the sole curative therapy for thalassemia. Identification of alloantibodies in 4.4% of individuals ≤16 years has immediate consequences for the transplant-eligible population and can complicate pre-transplant preparation, intraoperative blood management, and post-transplant support.[20] Recent advances in thalassemia gene therapy and gene editing technology have further highlighted the importance of ensuring optimal transfusional support during these curative procedures.[21] Prevalence of single vs multiple specificities (85.7% versus 14.3%) is useful in transfusion management strategy information. Individuals with single specificities might be managed simply with antigen-matched units,

while with multiple specificities, more advanced crossmatching strategies and prolonged phenotyping or molecular genotyping strategy would be advantageous.[22] Participation of mixed Rh and Kell system in 11.9% patients is a particularly challenging subgroup requiring special transfusion regimens. From a healthcare system viewpoint, these findings have important implications for organizing transfusion services in low-resource settings. Identification of high-risk patient groups (older patients, β-thalassemia major subtype) enables prevention strategies to be directed, such as extended phenotyping for the Rh (C, c, E, e) and Kell (K) antigens, which have been demonstrated to significantly reduce alloimmunization rates in high-risk populations.[23] The cost of such regimens must be balanced against the eventual cost of caring for alloimmunized patients, including increased transfusion unit usage, increased crossmatching time, and potential delays in treatment. The study findings also highlight the requirement for extensive databases for the identification of rare blood units and the establishment of regional blood banking networks for ensuring the availability of antigen-negative units for alloimmunized patients. This is particularly required in Bangladesh and similar settings where donor population diversity may be restricted to potentially amplify disparities of antigen exposure in patients compared to donors.

The study's single-center design potentially does not reflect the entire breadth of the broader Bangladeshi population with thalassemia due to potential referral bias and variable patient demographics within regions. Transfusion records, including the quantity of blood units transfused and donor characteristics, were not systematically analyzed, which potentially would have yielded additional information on risk factor associations.

CONCLUSION

This study reports 9.8% red cell alloimmunization prevalence among transfusion-dependent thalassemia patients from Bangladesh, with Rh and Kell system antibodies being the most common. Alloimmunization risk factors were age ≥16 years and β-thalassemia major subtype. Nearly half of all immunized patients were in the transplant-eligible age group (≤16 years), which has a direct effect on curative therapeutic options. Results support the use of extended phenotyping and prophylactic matching strategies, particularly in high-risk patient subgroups. All the antibodies identified were of clinical significance, emphasizing the importance of proper screening protocols in thalassemia centers of excellence.

Recommendations

Follow-up multicenter longitudinal studies need to be done for the cumulative transfusion exposure's temporal relationship to alloimmunization development in different thalassemia centers in Bangladesh. Development of national registries for finding rare blood units and elucidation of the cost-effectiveness of prevention on the basis of matching should be prioritized to optimize transfusion management in low-resource settings.

REFERENCES

1. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ. 2001;79(8):704-12.
2. Hossain MS, Raheem E, Sultana TA, Ferdous S, Nahar N, Islam S, et al. Thalassemias in South Asia: clinical lessons learnt from Bangladesh. Orphanet J Rare Dis. 2017;12(1):93.
3. Choudhry VP. Thalassemia minor and major: current management. Indian J Pediatr. 2017;84(8):607-11.
4. Thompson AA, Cunningham MJ, Singer ST, Neufeld EJ, Vichinsky E, Yamashita R, et al. Red cell alloimmunization in a diverse population of transfused patients with thalassaemia. Br J Hematol. 2011;153(1):121-8.
5. Matteocci A, Pierelli L. Red blood cell alloimmunization in sickle cell disease and in thalassaemia: current status, future perspectives and potential role of molecular typing. Vox Sanguinis. 2014;106(3):197-208.
6. Borgna-Pignatti C, Marsella M. Iron chelation in thalassemia major. Clin Ther. 2015;37(12):2866-77.
7. Pahuja S, Pujani M, Gupta SK, Chandra J, Jain M. Alloimmunization and red cell autoimmunization in multitransfused thalassemics of Indian origin. Hematology. 2010;15(3):174-7.
8. Singer ST, Wu V, Mignacca R, Kuypers FA, Morel P, Vichinsky EP. Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly Asian descent. Blood J Am Soc Hematol. 2000;96(10):3369-73.
9. Ameen R, Al-Shemmari S, Al-Humood S, Chowdhury RI, Al-Eyaadi O, Al-Bashir A. RBC alloimmunization and autoimmunization among transfusion-dependent Arab thalassemia patients. Transfusion. 2003;43(11):1604-10.
10. Sadeghian MH, Keramati MR, Badiei Z, Ravarian M, Ayatollahi H, Rafatpanah H, et al. Alloimmunization among transfusion-dependent thalassemia patients. Asian J Transfus Sci. 2009;3(2):95-8.
11. Spanos TH, Karageorga M, Ladis V, Peristeri J, Hatziliami A, Kattamis C. Red cell alloantibodies in patients with thalassemia. Vox Sanguinis. 1990;58(1):50-5.
12. Almorish MA, Al-Absi B, Elkhalifa AM, Alhamidi AH, Abdelrahman M. Red blood cell alloimmunization in blood transfusion-dependent β thalassemia major patients in Sana'a City-Yemen. Sci Rep. 2024;14(1):1005.
13. El-Beshlawy A, Salama AA, El-Masry MR, El Husseiny NM, Abdelhameed AM. A study of red

blood cell alloimmunization and autoimmunization among 200 multitransfused Egyptian β thalassemia patients. Sci Rep. 2020;10(1):21079.

14. Matteocci A, Pierelli L. Red blood cell alloimmunization in sickle cell disease and in thalassaemia: current status, future perspectives and potential role of molecular typing. Vox Sanguinis. 2014;106(3):197-208.

15. Chou ST, Liem RI, Thompson AA. Challenges of alloimmunization in patients with haemoglobi-nopathies. Br J Hematol. 2012;159(4):394-404.

16. Westhoff CM. Blood group genotyping. Blood J Am Soc Hematol. 2019;133(17):1814-20.

17. Schonewille H, Van De Watering LM, Brand A. Additional red blood cell alloantibodies after blood transfusions in a nonhematologic alloimmunized patient cohort: is it time to take precautionary measures? Transfusion. 2006;46(4):630-5.

18. Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood J Am Soc Hematol. 2010;115(22):4331-6.

19. De Sanctis V, Kattamis C, Canatan D, Soliman AT, Elsedfy H, Karimi M, et al. β-thalassemia distribution in the old world: an ancient disease seen from a historical standpoint. Mediter J Hematol Infect Dis. 2017;9(1):e2017018.

20. Hongeng S, Pakakasama S, Chuansumrit A, Sirachainan N, Kitpoka P, Udomsubpayakul U, et al. Outcomes of transplantation with related-and unrelated-donor stem cells in children with severe thalassemia. Biol Blood Marrow Transplant. 2006;12(6):683-7.

21. Thompson AA, Walters MC, Kwiatkowski J, Rasko JE, Ribeil JA, Hongeng S, et al. Gene therapy in patients with transfusion-dependent β-thalassemia. N Engl J Med. 2018;378(16):1479-93.

22. Al-Agha AE, Bawahab NS, Nagadi SA, Alghamdi SA, Felemban DA, Milyani AA. Endocrinopathies complicating transfusion-dependent hemoglobinopathy. Saudi Med J. 2020;41(2):138.

23. Vichinsky EP, Luban NL, Wright E, Olivieri N, Driscoll C, Pegelow CH, et al. Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial. Transfusion. 2001;41(9):1086-92.