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Report

Unlocking Insights into Alloantibodies in Thalassemia: Findings from a Single-Center Study

Nabilah Rameli[1], Rusliza Othman[1], Mohd Hanapi Ruslan[1], Nurul Asyikin Nizam Akbar[2], Razan Hayati Zulkeflee[2], Rabiatul Adawiyah Abdul Rohim[3], Adibah Daud[4], Sumaiyah Adzahar[4,*]

[1]*Pathology Unit, Hospital Dungun, Terengganu, Malaysia*

[2]*Department of Haematology, School of Medical Sciences, Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia*

[3]*Faculty of Medicine, Universiti Sultan Zainal Abidin, Kuala Terengganu, Terengganu, Malaysia*

[4]*Department of Pathology and Medical Laboratory, Faculty of Medicine, Universiti Sultan Zainal Abidin, Kuala Terengganu, Terengganu, Malaysia*

Correspondence

Sumaiyah Adzahar, Department of Pathology and Medical Laboratory, Faculty of Medicine, Universiti Sultan Zainal Abidin, Kuala Terengganu, Terengganu, Malaysia

Email: srikandimaya11@gmail.com

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ABSTRACT

Background: Thalassemia is a common inherited hemoglobin disorder in Malaysia. Regular transfusions of packed red cells are required to treat transfusion-dependent thalassemia. These transfusions, although lifesaving, may lead to complications such as red blood cell (RBC) alloantibody formation. This study aimed to determine the incidence of RBC alloantibodies in thalassemia patients who regularly received blood transfusions at our center. **Methods:** This study included 33 thalassemia patients who received regular transfusions at Dungun Hospital, Terengganu, Malaysia, from 2017 to 2023. Laboratory data and clinical presentation information were obtained. Antibody screening was conducted to identify potential alloantibodies that could react with donor blood. All samples that tested positive for alloantibodies were investigated further to determine antibody specificity. **Results:** The rate of RBC alloimmunization in the studied thalassemia patients was 36.4%. Six alloantibodies were detected in the patient cohort, with some individuals developing antibodies of single or multiple specificities. The most frequently present alloantibodies were against the Rh blood group system. **Conclusion :** The development of alloantibodies related to blood transfusions can create challenges in managing transfusion-dependent thalassemia patients. It is advisable to incorporate extended-matched phenotyping into care protocols to mitigate the risk of alloimmunization and minimize the chances of these patients developing blood transfusion-related alloantibodies.

Key words: Alloantibody, blood transfusion, thalassaemia, antibody specificity

INTRODUCTION

Thalassemia is a most common autosomal recessive disorder that affects a significant proportion of the population in tropical countries like Malaysia. As per current estimates, around 6.8% of Malaysians are thalassemia carriers, which puts them at risk of developing anemia to varying degrees[1]. Hb E thalassemia and beta thalassemia are the predominant inherited hematological disorders of beta-globin in Malaysia[2,3].

Patients with severe thalassemia rely on blood transfusions every 3–4 weeks to treat anemia[4].According to the current guidelines of the Thalassemia International Federation, blood transfusions are recommended for pre-transfusion Hb levels of 9–10 g/dL in patients with transfusion-dependent thalassemia[5]. Recent studies have shown that the incidence of red cell alloantibodies is higher among thalassemia patients than in the general population, which could be attributed to the frequent blood transfusions required by thalassemia patients[6].Such alloantibodies arise when the immune system recognizes surface antigens on donor RBCs as foreign, thereby triggering the production of antibodies targeting these antigens[4].

The existence of alloantibodies can add complexity by delaying the process of matching blood for transfusion and potentially increasing the risk of hemolytic transfusion reactions. Managing these risks during transfusions becomes even more challenging when autoantibodies coexist with alloantibodies[7].

Thalassemia patients need to be closely monitored for the development of alloantibodies, as this can increase the risk of transfusion reactions and make it more difficult to find compatible blood for future transfusions. Regular blood tests and screening for alloantibodies should be performed to ensure the safety and effectiveness of transfusions for thalassemia patients.

Hence, this study aimed to (1) determine the incidence of RBC alloantibodies and (2) identify the types of alloantibodies among thalassemia patients who received regular blood transfusions at our center, Dungun Hospital, Terengganu, Malaysia. Knowing the incidence of alloantibodies among thalassemia patients will assist clinicians and transfusions in predicting the level of difficulty in searching for compatible blood.

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Table 1: Demographic and clinical characteristics of the patients

Demographic data	Frequency	Percentage
Gender		
Male	14	42.4
Female	19	57.6
Age		
< 12 years	12	36.4
12 – 18 years	7	21.2
>18 years		42.4
Diagnosis		
Beta thalassemia major	11	33.3
Alpha thalassemia	3	9.1
Hb E Beta thalassemia	15	45.5
Hb Adana Pakse	2	6.1
Beta thalassemia trait with ESRF	1	3.0
Hb H Constant Spring	1	3.0
Numbers of transfusions		
< 50	20	60.6
51 - 100	11	33.3
101 - 150	1	3.0
>150	1	3.0
Blood group		
A	8	24.2
B	8	24.2
AB	4	12.1
O	13	39.4

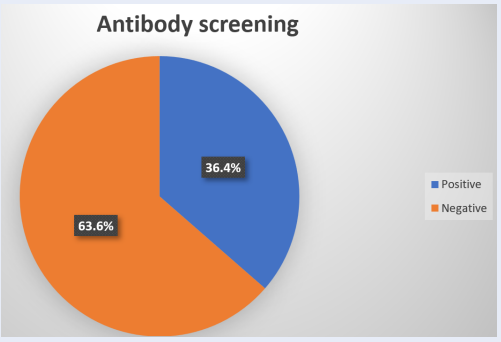

Figure 1: Antibody screening result for thalassemia patients who received blood transfusion (n = 33).

Table 2: The alloantibody specificities in immunized patients (n=12)

Alloantibody specificities	Number (Percentage %)
Anti-E	4 (33.3)
Anti-Jka	1 (8.3)
Anti-Mia	1 (8.3)
Anti-E, anti-c	4 (33.3)
Anti-E, anti-Jka	1 (8.3)
Anti-E, anti-c, anti-Leb	1 (8.3)

Table 3: Frequency of alloantibodies in the studied patients in relation to demographic and clinical data

Parameters	Antibody		P - value
	Positive n (%)	Negative n (%)	
Gender			
Male	6 (42.9)	8 (57.1)	0.506
Female	6 (31.6)	13 (64.8)	
Age			
<12 years	4 (33.3)	8 (66.7)	0.915
12 – 18 years	3 (42.29)	4 (57.1)	
>18 years	5 (35.7)	9 (64.3)	
Number of transfusions			
<50	6 (30.0)	14 (70.0)	0.382
51-100	5 (45.5)	6 (54.5)	
101-150	0 (0.0)	1 (100.0)	
>150	1 (100.0)	0 (0.0)	
Blood group			
A	4 (50.0)	4 (50.0)	0.581
B	3 (37.5)	5 (62.5)	
AB	2 (50.0)	2 (50.0)	
O	3 (23.1)	10 (76.9)	

MATERIALS AND METHODS

Study design

This retrospective study was conducted in the Pathology Unit of Dungun Hospital from 2017 to 2023. Secondary data from thalassemia patients who received regular transfusions and were screened for alloantibody formation were collected. A total of 33 patients were enrolled, and their demographic data, including gender, age, blood group, total number of transfusion units, frequency of transfusion, and clinical diagnosis, were extracted from the e-Delphyn Blood Bank System. The inclusion criteria for this study were patients with thalassemia who had previously received at least one blood transfusion. Patients with thalassemia who had already passed away were excluded. Approval for this study was obtained from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (ID: NMRR ID-22-02377-NMR). The study was conducted following the principles outlined in the Declaration of Helsinki.

Laboratory procedures

Blood samples were collected from patients in EDTA tubes for ABO/RhD blood grouping and antibody screening/identification following standard protocols. ABO and RhD blood groupings were done using the ABO-D/reverse grouping system (Bio-Rad Laboratories, DiaMed GmbH, Cressier, Switzerland). Antibody screening and identification were performed to detect alloantibodies that may react with donor blood. The screening was done using a three-cell panel (Diacell, Bio-Rad, Switzerland) in three phases: immediate spin, 37 °C, and anti-human globulin. All samples that tested positive for alloantibodies underwent further investigation to ascertain antibody specificity using a commercial 11-cell identification panel (Diapanel, Bio-Rad, Cressier sur Morat, Switzerland). Regarding the transfusion policy, all patients received ABO and Rh(D) crossmatch-compatible blood transfusions. If alloantibodies were detected, antigen-negative crossmatch-compatible blood was given.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 26. The prevalence of RBC alloimmunization and the alloantibody specificities were described using descriptive statistics. A chi-squared analysis was performed to evaluate the correlation of gender, age, number of blood transfusions, and blood group with the development of alloantibodies.

RESULTS

As seen in **Table 1**, our study involved 33 transfusion-dependent thalassemia patients comprising 14 (42.4%) men and 19 (57.6%) women aged between 4 and 62 years. The majority of patients were 18 years or older. Of the 33 patients dependent on transfusion, 15 (45.5%) had Hb E beta thalassemia and 11 (33.3%) had beta thalassemia major. The quantity of packed cells transfused to patients in this study ranged from 10 to 646 units. Most of the patients (20 [60.6%]) had received <50 units of packed cells. The frequencies of the ABO blood groups were as follows: 13 (39.4%) group O, eight (24.2%) group A, eight (24.2%) group B, and four (12.1%) group AB. All patients were RhD antigen positive.

Of the 33 patients screened for alloantibodies, 12 (36.4%) tested positive (**Figure 1**). The prevalence of alloimmunization was found to be 36.4% (95% CI: 2.80–5.75%).

Six alloantibodies were detected in this study, with some individuals developing antibodies of single or multiple specificities. Among the individuals with single red-cell antibodies, the most common alloantibody was anti-E (33.3%), followed by anti-Jka (8.3%) and anti-Mia (8.3%). Among those with multiple antibodies, anti-E and anti-c were the most common combinations (33.3%; **Table 2**).

There was no significant association between alloantibody formation and gender (p=0.506), age at transfusion (p=0.915), number of blood transfusions (p=0.382), and blood group (p=0.581); see **Table 3**.

DISCUSSION

RBC alloimmunization is an immune response against foreign RBC antigens that can occur after sensitization through multiple blood transfusions or pregnancies. It is one of the complications that patients dependent on RBC transfusions may encounter[8]. The process of alloimmunization is complex and influenced by various factors. The main contributing elements include differences in RBC antigens between the blood donor and recipient, the recipient's immune status, and the immunomodulatory effect of allogeneic blood transfusions on the recipient's immune system[9].

RBC alloimmunization rates have been examined in multi-transfused thalassemia patients in several studies. In a study conducted in Saudi Arabia, the alloimmunization rate in thalassemia patients was 11.97%[10]. Another study in Iran reported an alloimmunization rate of 16.4% in thalassemia patients[11]. A study in Iraq found that 5.8% of transfusion-dependent thalassemia patients experienced alloimmunization[12]. Additionally, a study in Malaysia reported an alloimmunization rate of 8.6% in thalassemia patients[13]. In our study, the rate of alloimmunization was higher at 36.4%. Among the included patients, 45.5% had HbE beta thalassemia, while 33% had beta thalassemia major. These findings highlight the risk of alloimmunization in multi-transfused thalassemia patients and the need for extended phenotyping to prevent complications. This could be attributed to our inability to provide phenotypically matched blood to transfusion-dependent thalassemia patients who test negative in antibody screening. In contrast, in some other developed countries, the practice is to provide phenotypically matched blood as soon as a patient is diagnosed with thalassemia, regardless of their antibody screening status.

In addition, the increased alloimmunization rate can be attributed to several factors: (1) diversity of thalassemia patients: our study included a diverse population of thalassemia patients with varying genetic

backgrounds, treatment histories, and blood transfusion regimens. This diversity may have contributed to the observed differences in alloimmunization rates; (2) genetic factors: thalassemia patients often exhibit genetic variations that may predispose them to higher rates of alloimmunization; and (3) duration of observation and sample size: the duration of our study might have influenced the observed alloimmunization rates. A more extended follow-up period and a larger sample size could provide a more comprehensive understanding of the temporal dynamics of alloimmunization.

RBC alloimmunization is a significant complication that can occur following a blood transfusion. It can lead to delays in transfusions, shortened *in vivo* survival of donated blood, and difficulties finding compatible blood for future transfusions. In addition, RBC alloimmunization can lead to the development of autoantibodies and cause hemolytic transfusion reactions. In some cases, these reactions can be fatal[8].

Over 300 RBC antigens have been identified and categorized into 36 systems, the better known of which include ABO, Rh, Kell, Duffy, Kidd, and MNS. This extensive array of antigens raises the potential for RBC alloimmunization with various antibody specificities[14]**.** Different studies have reported variable antibody specificities in multi-transfused patients. This variability can be attributed to differences in antigen frequencies between populations and the effects of genetics on the response to this antigenic stimulation.

In several studies, the K and Rh system antigens were predominantly involved in stimulating the production of alloantibodies. This is expected, given the immunogenicity of these antigens[15]. In our study, anti-E and anti-c were the most frequently detected alloantibodies in the Rh blood group system. These findings align with most other studies, which also identified anti-E as the most frequent antibody in these patients[15]. Most of these antibodies are in the form of immunoglobulin (Ig) G. The order of immunogenicity for different Rh antigens is as follows: D>c>E>C>e[2]. Interestingly, no anti-Kell antibodies were detected in this study, in accordance with a previous study by Dhawan *et al*[8]. This may be because, in Western populations, Kell antibodies are frequently detected due to the presence of the K antigen in approximately 10% of Caucasians. In contrast, in Malaysia, over 99% of individuals are Kell-negative; thus, the likelihood of Kell antibody formation is extremely low[16,17].

Another alloantibody detected in our study was anti-Jka, which belongs to the Kidd blood group system. Anti-Jka antibodies pose a significant risk as they can be difficult to detect in routine blood crossmatches because of their amnestic nature. They frequently cause delayed hemolytic transfusion reactions (DHTRs) because they tend to become undetectable between transfusions following sensitization[18]. However, a strong anamnestic response is observed upon subsequent re-exposure through blood transfusion or pregnancy. Studies showed that approximately 52% of Jka antibodies disappear within months. Therefore, it is recommended that individuals who have developed alloimmunization carry a special immunohematology antibody card to ensure they receive antigen-negative blood lifelong[18].

In our study, we observed the presence of anti-Mia antibodies in one patient. According to Prathiba *et al*., anti-Mia antibodies are the third most commonly occurring antibodies in general and antenatal patients in Malaysia[19]. Anti-Mia is most frequently reported in Chinese patients due to its high prevalence in this population (15%)[20]. The significance of the anti-Mia antibody should not be underestimated as there have been reports of clinically significant hemolytic transfusion reactions (HTRs) and hemolytic disease of the fetus and newborn[19].

One patient in this study was found to have anti-Leb, which belongs to the Lewis blood system. These antibodies are categorized as naturally occurring non-red-cell IgM antibodies with a propensity to react at lower temperatures. They are typically generated by individuals possessing the Le (a−b−) phenotype and are occasionally observed in pregnant women during specific temporary periods[21]. Anti-Lewis antibodies typically exhibit non-reactivity at a temperature of 37 °C and are commonly considered clinically insignificant. Nonetheless, it is important to note that clinically significant anti-Lewis antibodies capable of inducing HTRs do exist, and such occurrences have been documented[22].

In this study, six out of 12 patients were identified as having multiple antibodies; five had a mixture of two antibodies, and one had three antibodies. The combination of anti-E and anti-c was the most common among patients with multiple alloantibodies[23]. This is consistent with the findings of other studies, which indicate that the probability of developing additional antibodies is three times higher in alloimmunized patients[19,24]. Therefore, patients who have been transfused multiple times with a single alloantibody are at risk of developing multiple alloantibodies in the future. It is worth noting that anti-E is the alloantibody observed with the highest frequency[19].

Although this study found no correlation between alloantibodies and gender, age, number of blood transfusions, or blood group, which is consistent with the

findings of Kajiyazdi *et al.*, addressing red cell alloimmunization in multi-transfused thalassemia patients remains a significant medical concern[11]. By continually advancing our understanding and clinical practices in this area, we can enhance the quality of life and improve the long-term outcomes for these patients, allowing them to lead healthier and more fulfilling lives.

The present study had a small sample size of only 33 patients, which may limit the generalizability of the findings to a broader population of thalassemia patients. It is important to note that the specific characteristics and diversity of the patient group included in the study may only partially represent the thalassemia population. Therefore, caution should be exercised when extrapolating the results to different settings or demographics. For future studies, it is recommended that the sample be collected in larger centers, such as central hospitals, where more thalassemia patients are available.

CONCLUSION

In conclusion, our investigation of alloantibody incidence among thalassemia patients sheds light on important aspects of the immune response and transfusion outcomes within this population. Despite the limitations of the small sample size, our study provides valuable insights into the dynamics of alloimmunization in thalassemia patients. Our study also highlights the importance of tailored transfusion strategies and ongoing vigilance in managing thalassemia patients to minimize the risks associated with alloimmunization. Future research with larger and more diverse cohorts is crucial to validate and extend our findings, providing a more comprehensive understanding of alloantibody incidence in thalassemia.

ABBREVIATIONS

None.

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

SA and NR are responsible for the writing of the article. MM, MHR and RHZ helped in data collection. RAAR contributed to statistical analysis and data interpretation. AD and NANA participated in sequence alignment. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval for this study was obtained from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia, with the study identified as NMRR ID-22-02377-NMR. The study was conducted following the principles outlined in the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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