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Review

Red cell alloimmunization in transfusion-dependent and transfusion-independent beta thalassemia: A review from the Eastern Mediterranean Region (EMRO)

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ABSTRACT

Background: β-Thalassemia is considered one of the common hemoglobin disorders in the Arabian Peninsula. Red blood cell (RBC) transfusion is a crucial component of the management of transfusion-dependent β-Thalassemia patients. Patients with Thalassemia Intermedia (TI), also known as non-transfusion dependent β-thalassemia, have a wide clinical presentation and variable transfusion dependence. Rates of RBC alloimmunization and its risk factors in transfusion-dependent β-thalassemia patients varied between different reports. Risk of alloimmunization is higher in TI patients.

Material and methods: A literature review on existing reports on alloimmunization rates and risk factors in transfusion dependent and non-transfusion dependent β-thalassemia in the Eastern Mediterranean region was performed.

Results: A total of 17 publications were found. Reported rates of alloimmunization among transfusion-dependent β-Thalassemia patients ranged between 2.87 and 30 % and between 6.8 and 19.5 % among TI patients. Most centers utilize ABO and RhD matched RBCs. The most common antibodies described are anti-K and anti-E. The risk factors described included age at onset of transfusion, gender, history of splenectomy, duration of transfusion and number of units transfused. Rate of autoantibody formation ranged between 0.1 and 45 %.

Conclusion: Our review showed variable alloimmunization rates and risk factors in thalassemia patients and scant data on TI patients. The commonest antibodies are anti-K and anti-E. Further studies are required in addressing the rate of alloimmunization, cross-match requirements and role of genotyping in this group of patients. Transfusion support of patients with thalassemia necessitates the availability of blood bank facilities and specialized expertise.

1. Introduction

β-Thalassemia is a genetically inherited hemoglobinopathy characterized by hemolysis and ineffective erythropoiesis. β-Thalassemia is caused by a complete or partial reduction in β-globin chain synthesis, leading to β-thalassemia major (TM) and β-thalassemia intermedia (TI) respectively. In TM, red blood cell (RBC) transfusion is crucial in the treatment as a life sustaining measure, hence the name "Transfusion Dependent β-Thalassemia". Patients with TI, however, have a variable profile, and unique complications that are rarely seen in patients with TM [1]. The clinical profile of TI patients is influenced by several factors including the genotype, level of synthesized hemoglobin (Hb), and other genetic modifiers [2]. This group of patients is currently included in the group of "Non-Transfusion Dependent Thalassemias" (NTDT) as requirement for RBC transfusion is not as stringent as in TM. Unlike TM patients, patients with TI can maintain their hemoglobin (Hb) levels without transfusion support. Treatment is individualized, tailored to the severity of the disease and differs from one patient to another. The current approach in managing TI patients is to reserve RBC transfusion until later in the disease course, unless the patient has a more severe phenotype that requires regular RBC transfusion from an earlier age [3]. The risks of alloimmunization should be considered [4]. Patients might also require intermittent RBC transfusion during specific clinical situations, such as sepsis, pregnancy and pre-operatively. Regular RBC transfusions can be considered in TI patients with severe clinical profile such as growth failure, extramedullary hematopoiesis, congestive heart

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failure with or without pulmonary hypertension and leg ulcers [1,2,5]. Other treatment modalities that are currently available for TI patients include chelation therapy, hydroxycarbamide and splenectomy [6].

Transfusion can create significant challenges in the management of thalassemic patients including iron overload and RBC alloimmunization [7]. Alloimmunization is a complication that has major clinical significance due to its association with acute hemolytic transfusion reactions, delayed hemolytic transfusion reactions and hemolytic disease of the fetus and the newborn [8]. Crucially, the development of RBC antibodies can complicate transfusion support, may lead to delays in obtaining compatible RBCs for transfusion, and potentially accelerate iron overload [9,10]. Alloimmunization is common in TI patients and the risk is increased if the transfusion is started after the age of 12 months [11]. It has been hypothesized that intermittent transfusion for TI patients, which often is given at the time of a coexisting inflammatory status such as surgeries and pregnancy, may predispose to alloimmunization, though the exact mechanism is not fully understood [12]. Autoantibodies in TM patients were reported in number of studies [13–31]. Although development of autoantibodies is less common compared to alloantibodies, they can cause significant hemolysis and difficulties in obtaining compatible blood. Little is known about the prevalence and causes of autoantibody formation among thalassemic patients or the appropriate interventions for prevention. Singer et.al reported an association between autoantibody formation and the risk of alloimmunization, exposure to non-leukoreduced RBCs and splenectomy [13].

The prevalence of thalassemia extends from the Mediterranean region through the Middle East, Arabian Gulf, India and Southeast Asia [32–36]. RBC alloimmunization among transfused TM patients has been addressed in many reports with 5.2%–37% overall reported rates [9–11,13–24,27,28,31–33,35–44]. Many of the reports were in Western or Mediterranean populations and may not translate well to the patient and donor population in the Arabian Peninsula [45]. There is limited data on the rates of RBC alloimmunization from the Arabian Gulf and among thalassemia patients of Arab descent [17]. We aim to review the existing literature from the EMRO region to examine the published alloimmunization rates among TM and TI patients and to compare these with what has been published elsewhere. Data on autoimmunization was also included. Reported risk factors that might predict increased risk of RBC alloimmunization were reviewed.

2. Materials and methods

A Pubmed search for existing literature on RBC allo- and autoimmunization in β-thalassemia patients from the Eastern Mediterranean Region (EMRO) as defined by the World Health Organization was performed. The literature search included papers that were published up to 2018. Search terms included; alloimmunization, risk factor, thalassemia, beta thalassemia, thalassemia major, transfusion dependent thalassemia, thalassemia intermedia and transfusion independent thalassemia. Obtained literature were screened for publications from the EMRO region and were summarized. Reported data of RBC alloimmunization rates and alloimmunization risk factors in transfusion dependent β-thalassemia major (including β thalassemia β/β, E/β thalassemia) and non-transfusion dependent β-thalassemia were examined. Details examined included patients' age, type of RBC components transfused (leukoreduced or not), extent of crossmatch, presence or absence of any autoantibodies or alloantibodies, antibody specificity, and identified risk factors for alloimmunization. Clinically significant RBC alloantibodies were defined as those that are known to cause acute or delayed hemolytic transfusion reaction or hemolytic disease of the fetus or newborn [46]. Rates of alloimmunization were examined for TM and TI patients separately in the reporting literatures, and were adjusted, where possible, based on the number of alloimmunized patients per group to allow comparison between the different reports.

3. Results

Table 1 summarizes the demographics of the patients in the available literature. A total of 17 manuscripts that examined frequencies of alloimmunization in TM and TI were found (6 from Egypt, 5 from Iran, 2 from Pakistan, 2 from Oman, 1 from Kuwait, and 1 from Tunisia). A total of 4142 T M patients and 379 TI patients where included in this review. Sample sizes ranged from 36 to 711 for TM, and 14–79 for TI. The type of crossmatch was specified in 12/17 of the reports with all reporting the use of ABO and D matched units upfront. A center in Oman utilized extended phenotype matched units for all TI patients [31,47]. Leukoreduction was reported in 8/17 reports and was universal for all patients in two centers, one in Kuwait and one in Oman. Among the TI patients, one center reported 65 % need of blood transfusion at some stage during patients' follow up, with the most common blood transfusion indication being pregnancy [47]. Of the 51 successful pregnancies in this cohort, 25 (49 %) required transfusion support.

The rate of alloimmunization in the reviewed literature ranged from 2.87 to 30% in TM patients and 6.8–19.5% In TI patients. That said, there are a few publications that included both TM and TI patients but which did not specify the rate of alloimmunization in each subgroup separately [30,32,38]. Among patients with TM, the highest rate of alloimmunization was reported by Amen et.al from Kuwait, while the lowest was reported by Sadeghian et.al from Iran [17,41]. As for TI, the highest rate of alloimmunization was reported by Abdelrazik et.al (16.4 % on 41 TI patients, age range 2–45 years ; mean 10), while the lowest rate was reported by Ahmed et.al (6.8 % on 59 TI patients, age range 2–24 years; mean 9.3) ; both reports were from Egypt [20,43]. Although the former study discussed higher alloimmunization rates in older patients enrolled in the study, there was no specific analysis of this group of patients to explain this finding compared to what has been reported by Ahmed et.al. The most prevalent alloantibodies detected among TM and TI patients were anti-K and anti-E (Table1). Autoantibodies were reported at rates of 0.1–45%, with the highest rates being reported among Egyptian and Tunisian patients [25,30]. No autoantibodies were found in the TI patients in these reports. Risk factors for alloimmunization in thalassemia were examined in 12/17 of the studied reports and are summarized in Table 1.

4. Discussion

Transfusion therapy is considered an important management pillar in the treatment of thalassemic patients. However, RBC alloimmunization is a known complication that proves a therapeutic challenge in finding compatible blood for patients with hemoglobinopathies. The rate of RBC alloimmunization in patients with sickle cell disease (SCD) receiving ABO and D matched units is variable between reports and ranges from 18 to 76% [10]. This rate was reported to be reduced to 0–7% when extended phenotyped RBCs were provided to these patients [48]. The rate of alloimmunization in TM is also variable, but seems to be lower when compared to the rates in SCD, and is reported at 4–37% [49]. This is probably because transfusion in TM patients is performed on a regular basis and started at a younger age [10,11,13,39]. The rate of alloimmunization among TM patients reported from our region falls within the reported rate above.

Frequency of RBC transfusions in TI patients is variable, and many patients require intermittent transfusions in certain situations such as infection and pregnancy. TI patients on either intermittent or regular transfusion therapy have been reported to have a lower rate of complications including thrombosis, extra-medullary hematopoiesis and pulmonary hypertension than those TI patients not on transfusion [50]. Alloimmunization is a relatively common complication in TI patients, despite the fact that some patients are minimally transfused [3,11]. We found few publications from our region that address rates of alloimmunization among TI patients [20,38,43,47]. Abdelrazik et.al [43] and Azarkeivan et.al [38] reported a higher rate of alloimmunization among

Table 1
Literature review of red blood cell alloimmunization and risk factors in transfusion dependent ß thalassemia in the Arab and Eastern Mediterranean (EMRO) region. Percentage of antibodies is estimated out of number of allo-immunized patients with alloantibodies.

Author (reference)	Country	N. Cases	Age (years)	Leukoreduction	Compatibility policy	Allo Rate (%)	Rate of reported antibodies (out of total number of allo-immunized patients)	Auto rate (%)	Risk factors
Ameen et. al, 2003 [17]	Kuwait (included Kuwaiti & non-Kuwaiti Arabs)	190 TM	0.25 -33 (mean 12.7)	Yes (post storage)	ABO and D for all Rh matched for those with antibodies	30	anti-K (72%), anti-E (45.6%), anti-D (21.1%), anti-v (21.1%), anti-C (15.8%), anti-Le^{a} (12.3%), anti-JK^{a} (10.5%), anti-c (8.8%), anti-C^{w} (8.8%), anti-Kp^{a} (5.3%), anti-S (5.3%), anti-Js^{a} (3.5%), anti-Fy^{a} (3.5%), anti-Fy^{b} (3.5%), anti-Le^{b} (3.5%), anti-Jk^{b} (1.8%), anti-Lu^{a} (1.8%), anti-Lan (1.8%), anti-Co^{b} (1.8%), anti-Dia^{b}(1.8%)	11	NA
Bilwani et.al, 2005 [62]	Pakistan	97 TM	2-24 (mean 10.6)	NA	ABO and D	9.2	anti-K (33.3%), non-specific (22.2%), anti-D (11.1%), anti-E (11.1%), anti-D + C (11.1%), anti-E + K (11.1%)	NA	NA
Karimi et.al, 2006 [63]	Iran	711 ß thal	1-41 (mean 14.4)	Yes (bedside in a 73% of patients)	ABO and D	5.3	anti-K (50%), anti-D (15.8%), anti-E (10.5%), anti-D + C (7.9%), anti-C (5.3%), anti-c (5.3%), anti-e (2.6%), anti-Lu^{a} (2.6%)	1.7	- Duration of blood transfusion
Sadeghian et.al, 2009 [41]	Iran	313 ß thal	0.7-38 (mean 14.4)	Yes (subset of patients)	ABO and D	2.87	anti-D (88.88%), anti-C (33.33%), anti-E (11.11%)	NA	- Female gender -Splenectomy - RhD negative phenotype
Ahmed et.al, 2010 [20]	Egypt	448 (389 TM 59 TI)	2-24 (mean 9.3)	None for the majority of patients	ABO and D	8.4% TM 6.8% TI	TM: anti-K (42%), anti-E (24%), anti-C (18%), anti-Fya (6%), anti-Kp^{a} (6%), anti-M (3%) TI: anti-K (50%), anti-E (50%)	32.4% TM 8.5% TI	-History of splenectomy
Azarkeivan, et.al,2011 [38]	Iran	835 (707 TM, 128 TI)	Adults: 16-61 (median 23) Pediatrics: 1-15 (median 10)	NA	NA	11.3	anti-K (36.2%), anti-D (11.7%), anti-E (10.6%), anti-c (8.5%), anti-D + C (8.5%), anti-C^{w} (4.2%), anti-K + E (3%), anti-K + Kp^{a} (3%), anti-C (2%), anti-Col^{b} (2%), anti-K + D (1%), anti-E + c (1%), anti-E + Jk^{a} (1%), anti-N + Jk^{a} (1%), anti-C + D+K(1%), anti-E + K + Kp^{a}(1%), anti-e (1%), anti-D + E(1%),unknown(6%)	0.1	-Type of thalassemia -History of transfusion reaction -Result of antibody screen -Age category
N.Guirat-Dhouib et.al, 2011 [25]	Tunisia	130 ß thal	1-26 (mean 10)	None for the majority of patients	ABO and D	7.7	anti-E (30%), anti-C (30%), anti-D (10%), anti-K (10%), anti-E + S(10%), anti-D + C (10%)	40	NA
Saied DA et.al, 2011 [32]	Egypt	95 (74 TM, 21 TI)	1-45 (Mean 17.07)	Yes partial (64%)	NA	28.4	anti-K (48.1%), anti-E (48.1%), anti-C (14.8%), anti-D (11.1%), anti-c (11.1%), anti-S (11.1%), anti-Fy^{a} (11.1%), anti-Jk^{b} (7.4%), anti- Jk^{a} (7.4%), anti-Le^{a} (7.4%), anti-M (7.4%), anti-s (3.7%), anti-Le^{b} (3.7%), anti-Fy^{b} (3.7%), anti-I (3.7%), anti-Yk^{a} (3.7%)	1	-Kell negative phenotype -HbsAg positivity -Male gender
El Danasoury et. al, 2012 [9]	Egypt	235 TM	6-34 (mean 12+/-6.1)	NA	ABO and D	19.6	anti-K (23.9%), anti-E (23.9%), anti-C (15.2%), anti-D (13%), anti-C^{w} (11%), anti-N (4.3%), anti-JK^{a} (4.3%), anti-JK^{b} (2.1%), anti-Le^{a} (2.1%)	NA	-Age > 12 years -Higher transfusion frequency -Splenectomy

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Table 1 (*continued*)

Author (reference)	Country	N. Cases	Age (years)	Leukoreduction	Compatibility policy	Allo Rate (%)	Rate of reported antibodies (out of total number of allo-immunized patients)	Auto rate (%)	Risk factors
Al Riyami et.al, 2014 [47]	Oman	37 TI	11-59 (median 27)	Yes	Extended match	18.9	anti-E (28.5%), anti-K (14%), anti-D + c (14%), anti-JK^b + E + c (14%), anti-E + K + JK^b + Kp^a + S + Fy^b (14%), non-specific antibody (14%)	None	NA
Hussein et.al, 2014 [28]	Egypt	272 ß thal	NA	Yes (Pre-storage in 40.1% of patients)	ABO and D	22.8	anti-E (29%), anti-D (17.7%), anti-C (17.7%), anti-c (9.7%), anti-Kell (51.6%), anti-MNS (19.4%), anti-Kidd (17.7%), anti-Duffy (16%), anti-Le (11.3%), anti-Lu (4.8%), anti- P1 (3.2%)	1.5	-Number of RBC units transfused -Male gender -Receiving non-leukoreduced blood -Splenectomy
Obaid JM et.al, 2015 [30]	Egypt	40 (36 TM, 14 TI)	TM 7-40 (mean 20.3 ± 7.29) TI 23-57 (mean 36.9 ± 11.42)	No	NA	52.5(including the unidentifiable antibodies)	anti-D (4.76%), anti-c (4.7%), anti-K (4.76%), anti-Kp^a (9.25%), anti-Kp^b (19.52%), anti- Lu^a (9.52%), anti-Lu^b (19.05%), anti-Bg^a (4.76%), unidentifiable (23.8%)	45	NA
Azarkeivan et.al, 2015 [38]	Iran	441 (362 TM,79 TI)	3-61 (mean 22)	NA	NA	11.3 (10.2% in TM, 16.4% in TI)	anti-K (28%), anti-D (16%), anti-E (8%), anti-D + C (8%), anti-c (8%), anti-C^w (6%), anti-Col^b (4%), anti-e (2%), anti-D + E (2%), anti-C (2%), anti-K + E (2%), anti-K + Kp^a (2%), anti-K + D (2%), unknown (8%)	0.2	-History of transfusion reactions
Borhany et.al, 2015 [44]	Pakistan	162 ß thal	0.5-25 (median 6.7)	NA	NA	8.6	anti-E (28.6%), anti-K (21%), anti-e (14%), anti-D (7%), anti-D + C (7%), anti-E + K (7%), anti-D + E + C (7%), anti-E + K + C + M + Kp^a (7%)	NA	None
Davari et.al, 2016 [29]	Iran	49 TM	2-40 (mean 18.59 ± 8.16)	Yes (partial)	ABO and D	16.32	anti-K (75%), anti-E (12.5%), anti-c (12.5%), anti-Le^b (12.5%), nonspecific antibody (12.5%)	2.14	-Lower rate in patients who received leukoreduced blood
Abeer abdelrazik et.al, 2016 [43]	Egypt	188 (147 TM, 41 TI)	2-45 (mean 10)	No	ABO and D	7.98 (4.76% in TM, 19.5% in TI)	anti-D (53%), anti-E (13%), anti-C (13%), anti-c (13%), anti-Fy^a (13%), anti-K (6.6%)	Nil	-Female gender -Age > 20 years -Splenectomy -RhD negative phenotype
Al Riyami, et.al, 2018 [31]	Oman	268 TM	2-43 (median 22)	Yes	-ABO and D matched -Rh and Kell compatible RBC units when pre-transfusion baseline phenotype is available	9.3	anti-E (24%), anti-K (24%), anti-D (12%), anti-c (12%), anti-C (12%), anti-Kp^a (8%), anti-e (8%)	0.4	-Age 19-30 years -Number of units transfused

NA; not available/indicated, Allo; allo-immunization, Auto; auto-immunization, RBC; red blood cell.

TI patients compared to TM patients. It is possible that early and regular transfusion support may become part of the management and prevention of complications in TI patients in the future [3]. It is therefore important that more data is published from different countries in the region to address the current practice and rate of alloimmunization in TI patients.

4.1. Risk factors

Different risk factors for alloimmunization in TM patients were reported by some authors in our region. Risk factors for alloimmunization are complex. At least three contributing elements were hypothesized: the recipient's immunity, the RBC antigenic differences between the donor and the recipient, and the immune-modulatory effect of the transfused RBCs on the recipient [13]. Other risk factors that have been reported are the patient's age at onset of transfusion, cumulative number of units transfused, recipient age at onset of alloimmunization, gender, and genetic background [37]. The variable reported rates of alloimmunization among the different reports in TM patients could be due to the differences in the number of studied patients in these publications; however, the variable age at the initiation of blood transfusion, variable degree of homogeneity of the donor-recipient population and the variation in the testing methods and transfusion management can play a role [14,51].

4.1.1. Leukoreduction

There is no universal standard for the most appropriate selection of RBC units in chronically transfused patients [37]. The role of leukoreduction in reducing the rate of RBC alloimmunization has been discordant among different reports [10,12,13,17,21,29,32,49,52]. However, and considering its benefit in decreasing the risk of febrile reactions and cytomegalovirus transmission, leukoreduction has been increasingly used in most centers caring for patients with thalassemia and sickle cell disease [10,53]. It has been hypothesized that leukoreduction may be associated with a reduced rates of RBC alloimmunization [12]. Unfortunately, not all the reviewed reports from the region documented whether units transfused were leukoreduced or not. Oman reported a lower RBC alloimmunization rate compared to what has been reported among most reports on Egyptian thalassemic patients [9,28]. When compared to these studies, the former adheres to universal leuko-reduction with the utilization of both pre- and post-storage leuko-reduction methods as indicated. The use of leuko-reduced components was not clearly stated in the publication by El-Danasoury et.al [9], and is only utilized in 40 % of patients in the study by Hussein et.al [28]. In the latter study, it was shown that patients who received unfiltered blood had higher RBC alloimmunization rates compared to those who always received leuko-reduced RBCs. In this study, 80.6 % of alloimmunized patients received blood units that are not always leukoreduced [28].

4.1.2. Patient/Donor disparity

High RBC alloimmunization rates with heterogeneous patient-donor background in patients with TM was observed by Singer et.al who examined the ethnic background of the thalassemic patients in their center in the United States and assessed the antigenic difference between the white donors and patients of Asian descent [13]. Considering this factor, the rate of RBC alloimmunization is expected to be lower in more homogenous populations. Unlike the data described by Ameen et.al which included Kuwaiti and non-Kuwaiti Arabs [17], the data from Oman represented a more homogenous population, explaining the lower RBC alloimmunization rate described in the latter report [31]. In Oman, 90–95% of blood donors at present are Omanis, unlike the rates of 40–43% of nationals described in Kuwait [17,47]. Added to that, a subgroup of the patients in the study by Ameen et.al had their blood transfusion outside Kuwait, unlike Omani patients. All these factors may explain the difference observed in the RBC alloimmunization rate between the two centers.

4.1.3. Immuno-tolerance

Many reports supported the role of immune-tolerance induced by early exposure to repeated transfusions [11,13,15,17,24,39,54]. Some authors found a decreased alloimmunization risk among those patients who received their first transfusion before 24 months of age [23], less than 3 years [11] and less than 6 years [24]. Others observed that age at first transfusion is significantly higher in allo-immunized than in non-alloimmunized patients. In particular, transfusion before the age of 3 years was found to offer some protection against alloimmunization in patients with thalassemia [13,43]. In contrast to many reports, Davari et.al [29] and Karimi et.al [19] found no significant association between age at onset of transfusion and alloimmunization. On review, different publications in the region reported an association between age and alloimmunization, although the studied age group varied between studies. The study from Oman showed a significant association between age and the risk of RBC alloimmunization in TM patients, with the risk being highest in the age group 19–30 years [31]. El Danasoury et.al [9] and Abderlrazik et al. [43] reported ages > 12 and > 20 years respectively as a risk factor for alloimmunization. In the study from Kuwait, 58 % of the allo-immunized patients formed their first allo-antibody between the age 2 and 10 years [17]; as mentioned earlier, this may have been due to the differences between donor and recipient population. Younger age at time of initiation of transfusion in the Omani patients compared to what has been published in the Egyptian patients may also explain the lower rate of RBC alloimmunization in the Omani cohort [9,28]. Some authors showed increased alloimmunization risk with the number of units transfused including data from Egypt and Oman [9,28,31]. Higher transfusion frequency was reported as a risk factor by El- Danasoury and colleagues [9]. This reflects higher exposure and longer transfusion duration, in concordance with the data obtained by Thompson et.al who observed that transfusion duration of more than 10 years was a significant alloimmunization risk factor [14].

4.1.4. Host factors

Some reports from other regions have shown no association between RBC alloimmunization risk in thalassemia patients and female gender [11,18,23,28,29,31,42,55,56]. Female gender has, however, been identified as a RBC alloimmunization risk factor in TM patients from our region in data from Iran, Egypt and India [26,41,43]. There is no explanation put forward for this finding, except for potential increased transfusion exposure with more units during pregnancy. That said, none of these reports examined this possible association. In contrast, a report from Egypt showed a higher risk among male patients [28]. There are conflicting reports in the literature with some studies showing no association between splenectomy and the alloimmunization risk [16,18,19,24,29,31,39,55], and others reporting an association [9,13,20,28,41]. This variation in the rate of alloimmunization in splenectomized patients can be related to the heterogeneity of the transfusion protocols among the different centers, and merits assessment in a large group of patients with a standardized transfusion protocols. The mechanism by which removal of the spleen increases the risk of alloimmunization is however not clear. It has been hypothesized that post-splenectomy conformational changes in RBC membrane enhances immunomodulation leading to increased risk of alloimmunization [10,13]. There are different reports from the region that reported an association between splenectomy and alloimmunization [9,20,28,41,43].

In patients with TI, reported risk factors for alloimmunization include newly transfused patients and history of splenectomy [57]. Transfusion during pregnancy had additional risks as it is recommended to increase transfusion support in these patients during pregnancy to maintain the Hb level at > 100 g/l, since this is been shown to be optimal for the fetal development [58]. Beside the ethnic and antigenic diversity between donor and recipient populations in studies from other

populations, it has been hypothesized that increased systemic inflammation and dysregulation of the immune system in SCD may be responsible for alloimmunization [48]. The same process may occur in TI patients, in addition to later transfusion in this group of patients. Risk factors for alloimmunization in TI patients were not specifically addressed in the published data examined from the region.

4.1.5. Extended RBC matching

Singer et.al and Spanos et.al have observed a higher rate of RBC alloimmunization in patients who were transfused with non-phenotypically matched RBCs, compared to patients who received phenotypically matched blood [11,13]. Most centers in the EMRO region utilize ABO and RhD matched units for non-alloimmunized TM patients. Compared to the published data on TM, a lower rate of RBC alloimmunization was found among the Omani TI patients, due to the stringent use of extended phenotype matched RBCs upfront for all patients among this group in line with recent guidelines which supports this practice in TI patients to reduce the rate of alloimmunization [31,47]. This included obtaining a baseline phenotype on all patients either at the time of their first presentation, or during follow-up on a pre-transfusion sample and the provision of RBC phenotype match for Rh (C,c,E,e), Kell (K, Kpa, Kpb), Kidd (Jka, Jkb), Duffy (Fya, Fyb), S and s antigens, [47].

Clinical standards for thalassemia care in the United Kingdom include recommendation on antigen matching for transfused thalassemic patients [59]. A recent guideline recommends that ABO D Cc Ee and K–matched RBCs are selected for individuals with β -thalassemia, even in the absence of alloantibodies [60]. In the event that one or more alloantibodies are formed, and if matching doesn't cause undue delays that adversely affect patient healthcare, it is recommended to provide RBCs that are matched for CcEe, K, Fya, Fyb, Jka, Jkb, S and s [60]. However, the ability to find extended antigen-matched RBC units depends on local inventory size and the population donor base [10]. The issue of the cost effectiveness of this approach has been raised considering the low rate of alloimmunization in this group of patients [24]. Molecular RBC antigenic matching is an innovative strategy in the management of SCD patients but the rationale and feasibility of increased matching in other hematological disorders has not been established. Similar practice is less standardized for thalassemia patients [49]. Ultimately, recommendations on RBC alloimmunization prevention need to be individualized for specific countries based on available resources as well as blood group distributions in the various recipient and donor populations [49].

4.2. Antibodies

The most common antibodies observed in thalassemia patients from different countries in regions other than EMRO are those that are directed against antigens in the Rh blood group system and the K antigen. [37] Thompson et.al reported antibodies that are directed mainly against C, E, and K antigens in the Caucasian and Asian patients in his study from the United States [14]. This is comparable with what has been published in thalassemia patients from Greece, Italy, India, Malaysia and Hong Kong [11,16,18,24,26,27,36,39,42]. This predominance is not unexpected given the immunogenicity of these particular antigens. That said, antibodies developing against the other Rh antigens remain common. In Chinese patients, most antibodies reported are against the Milternberger antigens which has been attributed to their prevalence in this population: 15 % for the Mia antigen, and 6–7% of the Mur antigen. [21,37,55] These antibodies can be associated with severe hemolytic disease of the newborn as well as hemolytic transfusion reactions [10].

In the EMRO region, the most frequent RBC alloantibodies identified in TM patients were anti-E and anti-K in a study from Oman, similar to the published data in TI patients from the same institution. [31,47] This is seen to be comparable to what has been described in Kuwait, Egypt and Iran [9,17,20,29]. Unlike published data of Egyptian [23,43], Iranian [19,41] and Indian populations [23], a very low rate of anti-D alloimmunization was reported among Omani patients [47]. This is probably explainable by the existing transfusion policy of provision of Rh negative blood to Rh negative patients, the existing protocols in preventing Rh alloimmunization in Oman [61], and the fact that pregnant TI and TM thalassemia patients were managed and continued to receive their transfusion support in one center.

In summary, we report the rates and risk factors of alloimmunization among β-thalassemia patients from the EMRO region. Our review showed variable rates of RBC alloimmunization. Factors that can be contributory are the donor-recipient homogeneity and the provision of leuko-reduced RBC. Age, female gender, history of splenectomy, duration of transfusion and number of units transfused were significant risk factors for the development of alloantibodies identified in some of the reports. The most common RBC antibodies associated with alloimmunization were directed against the E and K antigens. Anti-D alloimmunization remain an issue in some countries in the region. There is lack of data on the risk of alloimmunization in patients with TI. More studies are required on a larger scale involving other countries in the region to obtain more information on the rates and risk of alloimmunization in patients with thalassemia. Moreover, further studies will be needed to establish the role and cost-effectiveness of extended phenotype-matched and genotype-matched RBCs in our population. Transfusion support of these patients necessitates the availability of needed blood bank facilities and specialized expertise.

Authors' contribution

AZR initiated the research idea, performed the literature review, and wrote the manuscript. SD reviewed and edited the manuscript. All authors reviewed and accepted the manuscript before submission.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest relevant to the manuscript submitted.

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