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Original Article

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Prevalence of Alloimmunization Events in Thalassemia Patients With Repeated Transfusions in the Rhesus Blood Group System: A Systematic Review and Meta Analysis

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Abstract

Background: Alloimmunization presents a significant challenge for patients with β-thalassemia major who depend on regular transfusion therapy. This systematic review and meta-analysis aimed to evaluate the frequency of alloimmunization within the Rhesus blood group system and identify the most prevalent alloantibodies.

Methods: A comprehensive search across multiple databases was conducted to locate epidemiological studies reporting alloimmunization in thalassemia patients undergoing repeated transfusions, specifically focusing on Rhesus antibodies. Statistical analyses were performed using R software, and heterogeneity was assessed using I^2 statistics.

Results: This review included 20 studies with a total of 4,650 patients. The overall prevalence of alloimmunization was 5.4% (95% confidence interval (CI): 3.1-9.3%) across all ages, with a prevalence of 9.1% (95% CI: 5.3-15.2%) in children and 25% (95% CI: 12.7-41.2%) in adults. The pooled overall prevalence was 6.6% (95% CI: 4.2-10.2%). Among the 488 alloimmunized patients, 310 developed Rhesus-specific antibodies, with anti-E (34.58%) and anti-D (13.69%) being the most frequent.

Conclusions: This study underscores the substantial prevalence of Rhesus antibodies among alloimmunized thalassemia patients. Implementing extended phenotype matching for transfusions could significantly reduce the risk of alloantibody formation in this population. Future analyses should explore factors influencing alloimmunization rates, such as ethnic diversity, matching protocols, and age-related variations, to inform clinical practice better.

Keywords: Alloimmunization; Antibodies; Rhesus; Thalassemia; Transfusion

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Introduction

β-Thalassemia is an inherited blood disorder characterized by insufficient production of β-globin chains, leading to hemolysis and ineffective erythropoiesis [1, 2]. This deficiency in β-globin synthesis, a key component of adult hemoglobin, results in severe anemia, particularly in patients with β-thalassemia major (TM), who become dependent on regular blood transfusions from an early age (a condition known as transfusion-dependent β-thalassemia (TDT)). In contrast, individuals with β-thalassemia intermedia (TI) typically do not require regular transfusions but may need them during specific complications, such as illness or pregnancy [1, 3].

Although transfusion therapy has significantly improved survival and quality of life for thalassemia patients, it is associated with complications, including iron overload, alloimmunization, infections, and adverse transfusion reactions [4, 5]. Frequent transfusions expose patients to foreign antigens, increasing the risk of alloimmunization, where the immune system generates antibodies (alloantibodies) against donor red blood cells (RBCs) [6]. Alloimmunization is influenced by factors such as the immunogenicity of RBC antigens, the patient's immune status, and the timing and frequency of transfusions [7].

Once developed, alloantibodies can complicate future transfusions, making blood cross-matching more difficult, shortening the lifespan of transfused RBCs, exacerbating iron overload, and delaying access to safe blood products [8]. Reported rates of alloimmunization in thalassemia patients vary widely, ranging from 4% to 50%, with lower rates generally observed in populations, where donors and recipients share similar genetic backgrounds [5]. Alloimmunization against RBC antigens, es-

pecially within the Rhesus (Rh) blood group system, poses a significant clinical challenge in β-thalassemia patients [9].

Studies indicate that the most frequently encountered alloantibodies target Rh antigens, particularly anti-E, anti-D, and Kell. The Rh blood group, second only to the ABO system in immunogenicity, is highly polymorphic, which may explain the high alloimmunization rates even when major Rh antigens are matched between donor and recipient due to the presence of Rh variants [10-12].

Given the critical role of Rh antibodies in alloimmunization, understanding their prevalence and distribution among TM patients is essential for improving transfusion strategies. This systematic review and meta-analysis aim to provide valuable insights into the frequency of alloimmunization within the Rh blood group system and identify specific Rh variants common in TM patients undergoing repeated transfusions. While our study focused primarily on Rh blood group alloimmunization, HLA does indeed play a role in alloimmunization events. HLA molecules are highly polymorphic proteins that present peptides to immune cells, particularly T cells. The significant variability in HLA alleles between individuals makes them highly immunogenic. HLA antibodies can develop in response to transfusions and may contribute to transfusion reactions. The recipient is exposed to donor HLA antigens that differ from their own, the immune system can mount an alloimmune response. Although our review did not specifically address HLA-related alloimmunization, it is an important aspect of transfusion medicine.

Materials and Methods

Protocol and registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on June 6, 2024, under the registration number CRD42024552701.

Eligibility criteria

Studies were included if they met the following criteria: 1) focused exclusively on human subjects; 2) employed cross-sectional or retrospective cohort designs; and 3) involved patients diagnosed with TM who received repeated transfusions. Only articles published in English were considered. Diagnoses of TM were confirmed via patient history, clinical examinations, and hemoglobin electrophoresis. Studies that did not specifically address alloimmunization within the Rh blood group system or lacked full-text availability were excluded.

Information sources and search strategy

We conducted a comprehensive literature search across multiple databases, including EBSCO, Proquest, PubMed, ScienceDirect, Wiley, and Scopus. The search covered all available data from the inception of each database up to February 15, 2024. The search strategy was based on the population, intervention, and outcome (PIO) framework and employed a combination of medical subject headings (MeSH) terms and keywords such as ("Thalassemia" (MeSH terms) OR "beta-Thalassemia" (MeSH terms) OR "thalassemia*"(title/abstract) OR "beta thalassemia*" (title/abstract)) AND ("Blood Transfusion" (MeSH terms) OR "blood transfusion*" (title/abstract) OR "regular transfusion"(title/abstract) OR "repeated transfusion" (title/abstract)) AND ("Rh-Hr blood-group system" (MeSH terms) OR "rh hr blood group system*" (title/abstract) OR "Rh" (title/abstract) OR "Rhesus" (title/abstract)) AND ("isoantibodies" (MeSH terms) OR "isoantibodies*" (title/abstract) OR "alloantibody*" (title/abstract) OR "allo antibody*" (title/abstract) OR "alloimmunization*" (title/abstract) OR "alloimmunisation*" (title/abstract)).

Data collection process and data items

One reviewer (V.I.) was responsible for extracting data from the included studies, which was then verified by a second reviewer (L.A.C.). Any disagreements during this process were resolved through discussion, and if consensus could not be reached, we consulted with verifiers (T.T., B.M., and A.E.H.). The extracted data included study characteristics, patient demographics, and outcomes related to alloimmunization in the Rh blood group system. Additionally, we contacted the authors of conference abstracts to inquire about the availability of full texts for inclusion.

Risk of bias assessment

Two reviewers (V.I. and L.A.C.) independently assessed the risk of bias in the included studies using the Joanna Briggs Institute (JBI) critical appraisal checklist designed for cross-sectional studies [13]. Each potential source of bias was rated as "yes", "no", "unclear", or "not applicable". Disagreements were resolved through discussion, and in cases where consensus could not be reached, a third or fourth reviewer was consulted.

Synthesis of results

A meta-analysis was conducted using logit-transformed proportions and random-effects models in the R software for our analysis. We categorized studies by age into three groups: 1) all-population; 2) children; and 3) adults. Heterogeneity was evaluated using both I^2 and T^2 statistics. Additionally, we performed tests for subgroup variances and carried out descriptive analyses to summarize supplementary data, including age at first transfusion, duration between transfusions, and intervals. These analyses were aimed at guiding future research.

Ethics and dissemination

The study is grounded in a synthesis of existing published

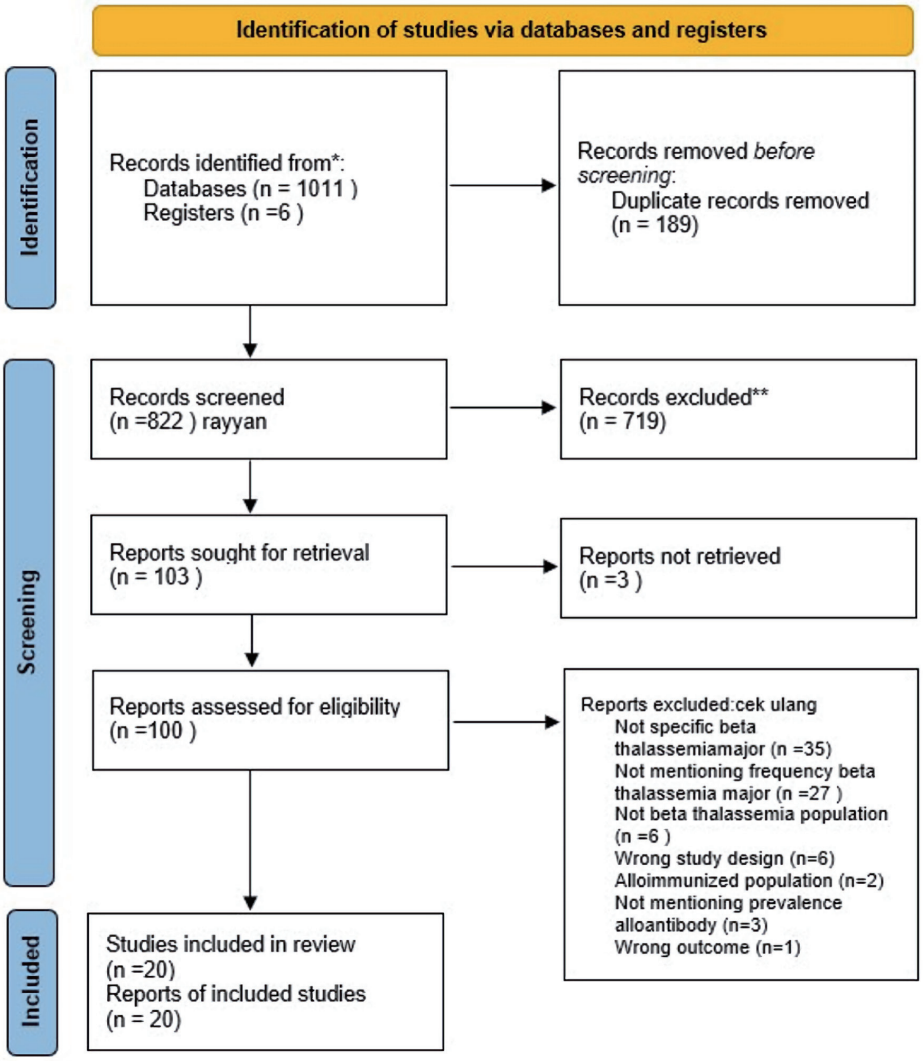

Figure 1. Study selection according to PRISMA flowchart. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

data, thereby rendering ethical approval unnecessary. We intend to disseminate our findings through publication in a peer-reviewed journal and presentations at pertinent academic conferences

Results

Study selection

During the initial database search, we identified 1,011 articles. After the removal of 189 duplicates, 822 articles remained for screening. Using Rayyan automation tools, we reviewed the titles and abstracts, excluding 719 articles based on criteria such as the absence of an abstract, a focus on the thalassemia intermedia population, or a lack of relevance to alloimmunization. Of the remaining 103 articles, three could not be retrieved despite attempts to contact the corresponding authors. After evaluating the remaining 100 articles, 80 were excluded for reasons such as irrelevance to TM, incorrect population, inappropriate study design, or irrelevant outcomes. Ultimately, 20 studies met the inclusion criteria. A detailed PRISMA flow diagram illustrating this selection process can be found in Figure 1 [14].

Study characteristics

The 20 studies included in this review were published between 2011 and 2024 [15-34]. Geographically, four studies originated from Pakistan, four from India, four from Iran, and one each from Egypt, Tunisia, Israel, Albania, Canada, Sri Lanka, China, and Yemen. These studies were categorized into three age groups: all-population (14 studies; 70%, age range 0 - 40 years), children (five studies; 25%, age range 1 - 18 years), and

adults (1 study; 5%, age range 20 - 47 years). While we recognized the importance of ethnic diversity in blood group antigen distribution, our ability to categorize populations based on ethnicity was limited by the data reported in the original studies. The sample sizes varied widely, ranging from 32 to 1,147 patients across the studies. In terms of methodology, most studies utilized agglutination techniques for RBC antibody screening, with products such as Diamed and Diacell. Alloantibody identification was primarily performed using the Diamed-Diapanel 11 identification panel in 75% of the studies (15 studies). Leukoreduction was reported in six studies, with five applying it universally across all patients. The age at which patients received their first transfusion varied significantly: from 0.3 to 12 years in the all-population group, 0.9 to 8.5 years in children, and 0.25 to 4 years in adults. The total number of transfused blood units also showed substantial variation, ranging from 12 to 191 units in the all-population group, 12 to over 250 units in children, and 493 to 1,363 units in adults. Blood transfusion intervals ranged from 5 to 90 days across half of the studies. A summary of these study characteristics is presented in Table 1 [15-34].

Prevalence of alloimmunization

Of the 4,650 patients included in the review, 488 developed alloimmunization, translating to an overall prevalence rate of 10.49%. Specifically, within the Rh blood group system, alloimmunization was identified in 309 patients, representing 6.64% of the total. While one study did not report the specificity of alloantibodies, the remaining 19 studies provided data for 4,566 patients, with 466 cases of alloimmunization involving Rh antibodies. In total, 44 types of Rh antibodies were identified. Among these patients, 72.35% (212 patients) developed a single antibody, while 27.39% (80 patients) exhibited multiple antibodies. The most frequently identified Rh antibodies were anti-E (34.58%, or 101 cases), followed by anti-D (13.69%, or 40 cases), anti-C (10.27%, or 30 cases), anti-c (7.87%, or 23 cases), and anti-D combined with anti-C (5.47%, or 16 cases). Detailed information on the specificities of Rh blood group antibodies is provided in Table 2 [15-34].

Risk of bias assessment and level of evidence

The risk of bias was assessed using the Joanna Briggs Institute (JBI) critical appraisal tool across eight key domains. Most studies received high ratings in domains such as inclusion criteria, data collection, outcome measurement, statistical analysis, control of confounders, sample size adequacy, and relevance of conclusions. However, three studies (Chaudhari et al [17], Ebrahimisadr et al [21], and Gholami et al [23]) received a "no" rating in domain two, indicating a lack of sufficient detail on study subjects, which could introduce bias due to limited demographic and clinical context.

Despite this, all studies were deemed methodologically sound and included in the meta-analysis. The overall level of evidence (LOE) ranged from level 3 to 4, with most studies classified as level 4, representing moderate-quality evidence. Although some studies had minor weaknesses, the overall strength of the evidence supports the validity of the meta-analysis findings.

Synthesis of results

A meta-analysis was conducted using logit-transformed proportions and random-effects models in the R software. The studies were categorized by age into three groups: 1) all-population; 2) children; and 3) adults. Heterogeneity was evaluated using both I^2 and T^2 statistics. Additionally, subgroup variance tests and descriptive analyses were performed to summarize supplementary data, including the age at first transfusion, duration between transfusions, and transfusion intervals. These analyses are intended to guide future research.

The forest plot (Fig. 2) illustrates the findings from the meta-analysis of 20 studies investigating the prevalence of alloimmunization in β-thalassemia patients undergoing repeated transfusions. The plot visually represents the individual study estimates, their respective confidence intervals (CIs), and the pooled estimates for various subgroups. The overall pooled prevalence of alloimmunization was 6.9% (95% CI: 4.2% - 11.2%), with significant heterogeneity across studies, indicated by an I^2 value of 94.12% (P = 0.000). This high heterogeneity suggests considerable variability in the reported prevalence, likely due to differences in study populations, transfusion practices, and alloimmunization detection methods.

Subgroup analysis

The meta-analysis was divided into three subgroups based on patient age: all-population, children, and adults. In the all-population subgroup, the pooled prevalence of alloimmunization was 5.5% (95% CI: 2.9% - 10.2%), based on data from 16 studies involving 4,229 patients. This subgroup also exhibited high heterogeneity (I^2 = 95.54%, P = 0.000), indicating variability in the study estimates. In the children subgroup, the pooled prevalence was higher at 9.4% (95% CI: 5.0% - 17.0%) with moderate heterogeneity (I^2 = 70.52%, P = 0.009). This variability suggests that factors such as transfusion protocols and antigen matching may influence alloimmunization rates in children. In the adult subgroup, the pooled prevalence was significantly higher at 30% (95% CI: 17.9% - 45.7%) based on a single study involving 40 patients. Due to the limited number of studies, no heterogeneity measures (I^2 or P values) were reported for this subgroup.

Discussion

This systematic review and meta-analysis of 20 studies, encompassing 4,650 β-thalassemia patients, examined the prevalence of alloimmunization against Rh blood group antigens in repeatedly transfused individuals. The overall prevalence was 10.49% (95% CI: 8.9% - 12.2%), with 6.9% (95% CI: 4.2% - 11.2%) specifically attributed to Rh antibodies. These findings

Table 1. General Characteristic and Outcome of the Eligible Studies

Study	Study design	Sample size	Gender male, n (%)	Age (years), mean ± SD	Blood transfusion interval (days)	Number of transfusions	Duration of transfusion	First transfusion age	Population	Method	Total number of patients with alloantibody	Total number of patients with Rhesus alloantibody	Blood component
Almorish et al, 2024 [15]	Cross-sectional	100	50 (50)	Range 1 - > 20	N/A	> 12 units/year (88), ≥ 12 units/year (12)	< 160 month (71), ≥ 160 months (30)	< 1 yr (42), 1 - 10 yr (53), > 10 yr (5)	Sana'a City - Yemen	11 cell identification panel	6	2	Leukoreduced
Chao et al, 2013 [16]	Retrospective cohort	64	31 (48)	19.2 ± 6.7	N/A	N/A	17.8 ± 4.3 years	5.7 ± 2.2 month	China	LISS	6	5	Leukodepleted
Chaudhari et al, 2011 [17]	Cross-sectional	32	22 (68.75)	12.0 ± 3.8	21 - 35	2 units (1), 15-19 units (2), > 20 units (29)	8.5 ± 4.0 year	2.7 ± 1.3 years	India	11 cell identification panel	6	4	Non leukodepleted whole blood or packed RBC
Davari et al, 2016 [18]	Cross-sectional	49	25 (51)	18.59 ± 8.16	14 - 35	> 50 units	N/A	N/A	Iran	10 cell identification panel	8	2	Leukoreduced and non leukoreduced
Dhawan et al, 2014 [19]	Cross-sectional	319	235 (73.66)	15.18	14 - 28	235.74 units	N/A	14.93 months	India	11 cell identification panel	18	10	Non leukodepleted
Dogra et al, 2015 [20]	Descriptive study	59	N/A	9.27 ± 4.58	14 - 28	Mean ± SD: 132 ± 38.44 units	N/A	4.7 (3.8) years	India	11 cell identification panel	6	4	Non leukodepleted
Ebrahimisadr et al, 2021 [21]	Descriptive study	184	66 (35.86)	Range 0 - > 30	21 - 35	N/A	N/A	N/A	Iran	11 cell identification panel	116	73	Non leukodepleted
El Danasoury, et al, 2012 [22]	Prospective cohort	235	126 (53.61)	12 ± 6.1	14 - 28	N/A	N/A	2 ± 1.2 years	Egypt	11 cell identification panel	46	29	Non leukodepleted
Gholami et al, 2021 [23]	Cross-sectional	1147	N/A	14 ± 6	N/A	> 20 units	N/A	N/A	Iran	IBTO home-made 11-cell panel in LISS solution	97	47	Non leukodepleted
Guirat-Dhouib et al, 2011 [24]	Prospective cohort	130	73 (56.15)	9.9	N/A	N/A	N/A	N/A	Tunisian	Gel filtration test	10	9	Non leukodepleted
Iqbal et al, 2014 [25]	Cross-sectional	130	76 (58.5)	6.28 ± 3.18	5 - 20	N/A	N/A	N/A	Pakistan	3 cell panel followed by 11 cell panel	11	8	Non leukodepleted

Table 1. General Characteristic and Outcome of the Eligible Studies - *(continued)*

Study	Study design	Sample size	Gender male, n (%)	Age (years), mean ± SD	Blood transfusion interval (days)	Number of transfusions	Duration of transfusion	First transfusion age	Population	Method	Total number of patients with alloantibody	Total number of patients with Rhesus alloantibody	Blood component
Jariwala et al, 2019 [26]	Retrospective cohort	333	188(56.45)	11.3 (4 - 26)	N/A	17.6 units/year	N/A	N/A	India	11 cell identification panel	4	4	Non leukodepleted
Davoudi-Kiakalayeh et al, 2017 [27]	Retrospective cohort	190	N/A	26 ± 5.9	N/A	N/A	N/A	N/A	Iran	IBTO homemade, 3 RBC cells) and antibody identification panels	47	30	Leukodepleted
Minhas et al, 2022 [28]	Retrospective cross-sectional	84	51 (59.5)	Median 7 (4 - 11)	N/A	Median 64 (26 - 127) units	N/A	N/A	Pakistan	Dia clon3 cell antigen panel	22	17	Non leukodepleted
Pazgal et al, 2020 [29]	Retrospective cohort	40	21 (52.5)	31.8 ± 6.9	14 - 21	Mean 828.5 ± 239.3 units	N/A	0.71 ± 0.93 years	Israel	Automated systems and LISS-IgG cards	17	10	Before 2004 non leukoreduced 2004: leukoreduced
Seferi et al, 2015 [30]	Retrospective study and prospective follow up	118	59 (50)	17	10 - 90	N/A	N/A	N/A	Albania	DiaPanel, Diamed-Biorad	14	10	Pre- and post-storage leukoreduced red cell
Senavirathna et al, 2021 [31]	Retrospective descriptive study	398	188 (47.24)	18.41 ± 11.67	N/A	N/A	N/A	N/A	Colombo	Tube technique	6	4	Non leukodepleted
Usman et al, 2011 [32]	Cross-sectional	800	350 (43.75)	11.5	N/A	N/A	N/A	N/A	Pakistan	DiaMed	30	26	Non leukodepleted
Zaidi et al, 2015 [33]	Cross-sectional	162	97 (60)	Median 6.7 (range: 0·5 - 25)	14.2 - 31.8	N/A	N/A	0.98 ± 0.93 years	Pakistan	3 cell antigen panel	14	11	Non leukodepleted
Zarrabian et al, 2023 [34]	Retrospective cohort	76	44 (58)	12.83 (5.48)	N/A	Mean (range) 145.5 (5 - 598)	95.6 (63.3) months	N/A	Canada	11 cell identification panel	4	4	Non leukodepleted

N/A: not available; yr: years; RBC: red blood cell; IgG: immunoglobulin G.

Table 2. Specificity of Red Blood Cell Antibodies in Rhesus Blood Group

Rhesus bloood group system specificity	Almorish et al, 2024 [15]	Chao et al, 2013 [16]	Chaudhari et al, 2011 [17]	Davari et al, 2016 [18]	Dhawan et al, 2014 [19]	Dogra et al, 2015 [20]	Ebrahimisadr et al, 2021 [21]	El Danasoury et al, 2012 [22]	Gholami et al, 2021 [23]	Guirat-Dhouib et al, 2011 [24]	Iqbal et al, 2014 [25]	Jariwala et al, 2019 [26]	Davoudi-Kiakalayeh et al, 2017 [27]	Minhas et al, 2022 [28]	Pazgal et al, 2020 [29]	Seferi et al, 2015 [30]	Senavirathna et al, 2021 [31]	Usman et al, 2011 [32]	Zaidi et al, 2015 [33]	Zarrabian et al, 2023 [34]	Number of alloimmunized patients (total 292)		Antibody specificity among all studies (total 4,566)	
																					N	%	N	%
E	1	4	2	1	2	3	10	11	21	3	5	0	11	N/A	8	1	3	7	4	4	101	34.58	101	2.21
D	0	0	0	0	2	1	11	6	0	1	2	0	6		2	0	0	8	1	0	40	13.69	40	0.87
C	0	1	0	0	1	0	1	7	8	3	0	2	2		0	0	0	5	0	0	30	10.27	30	0.66
c	1	0	1	1	0	0	0	0	11	0	1	2	0		0	0	0	6	0	0	23	7.87	23	0.50
D + C	0	0	0	0	1	0	7	0	0	1	0	0	3		0	3	0	0	1	0	16	5.47	16	0.35
Cw	0	0	0	0	1	0	2	5	3	0	0	0	0		0	1	0	0	0	0	12	4.10	12	0.26
Kell + E	0	0	0	0	0	0	4	0	0	0	0	0	2		0	0	0	0	1	0	7	2.39	7	0.15
e	0	0	0	0	0	0	1	0	2	0	0	0	0		0	1	0	0	2	0	6	2.05	6	0.12
C + E	0	0	0	0	0	0	5	0	0	0	0	0	1		0	0	0	0	0	0	6	2.05	6	0.12
c + E	0	0	1	0	0	0	0	0	0	0	0	0	0		0	2	0	0	0	0	3	1.37	3	0.08
Cw + E	0	0	0	0	1	0	2	0	0	0	0	0	0		0	0	0	0	0	0	3	1.02	3	0.06
E + Jkb	0	0	0	0	1	0	2	0	0	0	0	0	0		0	0	0	0	0	0	3	1.02	3	0.06
C + e	0	0	0	0	0	0	3	0	0	0	0	0	0		0	0	0	0	0	0	3	1.02	3	0.06
C + K	0	0	0	0	1	0	0	0	0	0	0	0	0		0	1	0	0	0	0	2	0.68	2	0.04
E + K	0	0	0	0	0	0	0	0	2	0	0	0	0		0	0	0	0	0	0	2	0.68	2	0.04
Kell + C + E	0	0	0	0	0	0	0	0	0	0	0	0	2		0	0	0	0	0	0	2	0.68	2	0.04
Kell + C + D	0	0	0	0	0	0	0	0	0	0	0	0	2		0	0	0	0	0	0	2	0.68	2	0.04
C + Kell	0	0	0	0	0	0	2	0	0	0	0	0	0		0	0	0	0	0	0	2	0.68	2	0.04
Kell + Cw + Kpa	0	0	0	0	0	0	2	0	0	0	0	0	0		0	0	0	0	0	0	2	0.68	2	0.04
E + C- + kell	0	0	0	0	0	0	2	0	0	0	0	0	0		0	0	0	0	0	0	2	0.68	2	0.04
E + S	0	0	0	0	0	0	0	0	0	1	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
Kpa + D	0	0	0	0	0	0	0	0	0	0	0	0	1		0	0	0	0	0	0	1	0.34	1	0.02
D + K	0	0	0	0	0	0	0	0	0	0	0	0	0		0	1	0	0	0	0	1	0.34	1	0.02
D + E + C	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	1	0	1	0.34	1	0.02
E + K + C + M + Kpa	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	1	0	1	0.34	1	0.02
C + S	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
D + S	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
D + Kell	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
D + E	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
E + Jka	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02

Table 2. Specificity of Red Blood Cell Antibodies in Rhesus Blood Group - *(continued)*

Rhesus bloood group system specificity	Almorish et al, 2024 [15]	Chao et al, 2013 [16]	Chaudhari et al, 2011 [17]	Davari et al, 2016 [18]	Dhawan et al, 2014 [19]	Dogra et al, 2015 [20]	Ebrahimisadr et al, 2021 [21]	El Danasoury et al, 2012 [22]	Gholami et al, 2021 [23]	Guirat-Dhouib et al, 2011 [24]	Iqbal et al, 2014 [25]	Jariwala et al, 2019 [26]	Davoudi-Kiakalayeh et al, 2017 [27]	Minhas et al, 2022 [28]	Pazgal et al, 2020 [29]	Seferi et al, 2015 [30]	Senavirathna et al, 2021 [31]	Usman et al, 2011 [32]	Zaidi et al, 2015 [33]	Zarrabian et al, 2023 [34]	Number of alloimmunized patients (total 293)		Antibody specificity among all studies (total 4,650)	
																					N	%	N	%
Cw + Kell	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
Cw + Kpa	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
E + C + Jka	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
E + Kell + Jkb	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
E + C- + Jkb	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
D + C + S	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
C- + kell + Cw	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
D + C + kell	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
E + S + Jkb	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
D + C + E + K + S + Jkb	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	1	0	0	0	1	0.34	1	0.02
E + C- + kell + M	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
E + kell + Fyb + S	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
D + kell + S + Jkb	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
C + D + E + kell	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02
E + C + Fyb + Jka + S	0	0	0	0	0	0	1	0	0	0	0	0	0		0	0	0	0	0	0	1	0.34	1	0.02

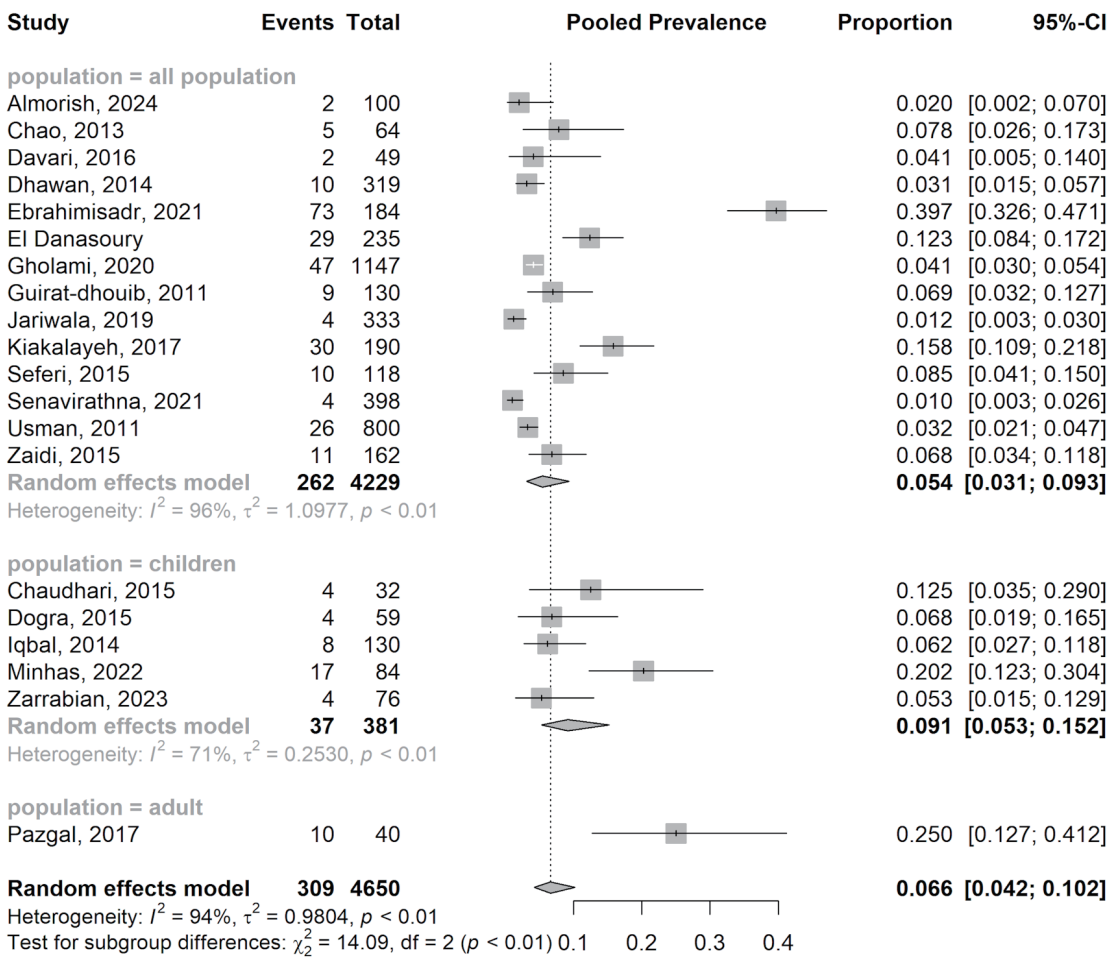

Figure 2. Forest plot of proportion estimate of alloimmunization in rhesus blood group. CI: confidence interval.

align with prior research identifying Rh antibodies as the most frequent alloantibodies in thalassemia patients, underscoring the significant immunological challenges posed by lifelong transfusion dependency.

High heterogeneity (I^2 = 94.12%) reflects variability driven by regional differences, donor-recipient antigenic disparity, and transfusion practices. Populations with limited antigen matching, such as in Egypt and Southwest Iran, exhibit higher alloimmunization rates, whereas nations employing extended matching, like some European countries, report lower rates. Patient-specific factors, including transfusion frequency, splenectomy, and immune maturity, further contribute to this variability, highlighting the need for tailored transfusion strategies [35-37]

Subgroup analysis

Subgroup analysis revealed notable differences in alloimmunization rates between children and adults. In children, the pooled prevalence was 9.4% (95% CI: 5.0% - 17.0%), while adults showed a much higher prevalence of 30% (95% CI: 17.9% - 45.7%). This disparity may be attributed to the cumulative effects of repeated transfusions over time in adults, increasing their risk of alloimmunization. As patients age and are exposed to foreign antigens from multiple donors, their likelihood of developing alloantibodies increases. These results align with existing literature, which indicates that the risk of alloimmunization rises with the number of transfusions and the duration of exposure [38-40]. Sex was not identified as a statistically significant factor influencing alloimmunization in adult or pediatric transfusion-dependent thalassemia patients. Only in Yemen, alloimmunization was found to be significantly associated with sex, with females more likely to develop alloantibodies than males (P = 0.03). This may suggest immune system differences or transfusion patterns influenced by cultural or clinical factors.

High heterogeneity

The substantial heterogeneity (I^2 = 94.12%) observed across studies suggests that factors such as ethnic diversity, transfusion practices, and antigen matching significantly influence alloimmunization rates. Regions with more advanced blood-matching protocols, including extended Rh and minor antigen

matching, tend to have lower alloimmunization rates. In contrast, areas with less comprehensive matching experience higher rates [27-29]. Variations in blood group antigen distribution between donors and recipients, particularly in diverse populations, further increase the risk of alloimmunization due to antigen mismatch. The study by Ebrahimisadr et al [21], which reported a 39.7% prevalence of alloimmunization, likely reflects regional or institutional differences in transfusion practices, whereas the 1% prevalence reported by Senavirathna et al [31] may be attributed to stricter matching protocols or differences in genetic backgrounds and transfusion frequencies.

Variability in prevalence rates

The wide variability in alloimmunization rates across different studies can be explained by several factors. Ethnicity plays a critical role, as ethnic differences within populations significantly impact immunogenicity. For example, the low prevalence (1%) reported in a Sri Lankan study may be due to the ethnic homogeneity of the population and effective local transfusion practices [31]. In contrast, higher prevalence rates, such as the 39.7% reported in Iran, may reflect greater genetic diversity and varying immunogenic responses to Rh antigens [21].

Transfusion protocols and age-related factors

Blood transfusion protocols are crucial in mitigating alloimmunization. Studies have shown that matching blood for Rh and Kell antigens significantly reduces the risk of alloimmunization compared to ABO-D matching alone [8]. International guidelines recommend extended phenotyping for C, c, E, e, and Kell antigens before transfusion to minimize alloimmunization risks [39-40]. Variations in the implementation of these guidelines across different centers may account for some of the inconsistencies observed in the reviewed studies.

Age also plays a significant role in the development of alloimmunization. The adult subgroup had the highest prevalence rate of 30%, which is consistent with findings from Eastern India, where 67.86% of alloimmunized cases occurred in individuals aged 21 - 40 years [41]. This suggests that patients requiring multiple transfusions over several years are more likely to develop alloantibodies. On the other hand, children had a lower rate of 9.1%, possibly due to immune tolerance mechanisms that prevent the formation of alloantibodies upon initial exposure to foreign RBC antigens [42]

Specific antibodies and technical considerations

The most frequently identified Rh antibody in this review was anti-E (34.58%), consistent with findings from other regions like Thailand. Anti-D (13.69%) was the second most common, potentially influenced by technical factors such as testing errors or weak D variants. Accurate antibody screening is crucial for managing thalassemia patients and minimizing alloimmunization risks. Variations in detection methods may explain differences in prevalence rates across studies. Standardizing testing protocols can enhance the accuracy of alloantibody identification, leading to improved clinical outcomes for patients undergoing repeated transfusions.

Transfusion practices and alloimmunization

We found that the age at which patients received their first transfusion ranged from 0.25 to 12 years. The age at which patients begin receiving transfusions significantly influences the likelihood of developing alloimmunization. Studies show that younger patients, particularly those starting transfusions before 2 years of age, are less likely to develop alloantibodies compared to those who begin transfusions later in life. For instance, Al-Mousawi et al (2015) observed that the risk of alloimmunization was significantly higher in patients who started transfusions after the age of 2 [43]. Similarly, Yadav et al (2023) reported that patients who received their first transfusion at a median age of 1 year had a higher rate of alloimmunization compared to those who started at 6 months [38]. This phenomenon may be explained by the immune tolerance hypothesis, which suggests that early exposure to foreign antigens during the immune system's developmental stage might reduce immunological responsiveness. However, not all studies consistently identify a significant correlation between age at first transfusion and alloimmunization risk [44]. However, some studies have found no significant link between age and the risk of alloimmunization [36].

The frequency and volume of transfusions are strongly linked to alloimmunization risk. Studies show that shorter transfusion intervals (< 3 weeks) and higher cumulative transfusion volumes significantly increase alloimmunization rates. El Kababi et al (2019) reported that patients with shorter transfusion intervals had a higher likelihood of developing alloantibodies compared to those with longer intervals [44]. Similarly, Yadav et al (2023) found that alloimmunized patients received more units annually and had shorter transfusion intervals than non-alloimmunized patients, further highlighting the association between frequent transfusions and heightened immune response [38]. These findings emphasize the need for tailored transfusion strategies to minimize exposure to foreign antigens and reduce alloimmunization risks.

Furthermore, evidence from Teawtrakul et al (2022) emphasizes that higher transfusion volumes, particularly exceeding 15 mL/kg, strongly increase the risk of alloimmunization. The study underscored that shorter transfusion intervals and higher total transfusion volumes are among the most predictive factors for the development of alloantibodies in thalassemia patients [45]. This finding is consistent with previous research, which indicates that total transfusion volume is a key factor in predicting the development of alloantibodies in thalassemia patients [35, 46, 47].

Implications for clinical practice

This review underscores the critical need for implementing

extended Rh antigen matching protocols in clinical practice. Matching blood for both Rh and K antigens before a patient's first transfusion can significantly reduce the risk of alloimmunization and improve patient outcomes [48]. Given the diverse ethnic backgrounds of thalassemia patients worldwide, transfusion services should consider implementing extended antigen matching protocols that account for the specific antigen profiles common in their patient populations. This approach could potentially reduce alloimmunization rates by minimizing exposure to foreign antigens. Our findings highlight a significant gap in current practices, particularly in developing countries where access to comprehensive blood typing is often limited.

Limitations

While our review provides valuable insights, it has some limitations, including insufficient data for a detailed meta-analysis on alloimmunization related to specific Rh antigen variants and the absence of heterogeneity analysis in adults. The high heterogeneity observed indicates the need for further research to identify factors influencing alloimmunization in diverse populations, including the potential impact of pharmacotherapy for comorbidities. Future studies should aim to standardize alloimmunization reporting and transfusion practices, conduct longitudinal studies to track alloimmunization risk over time considering variables such as age, sex, and ethnicity, and investigate the influence of various medications, particularly immunosuppressive drugs, on alloimmunization rates in thalassemia patients with comorbidities.

Conclusions

This meta-analysis offers crucial insights into the prevalence of alloimmunization in β-thalassemia patients undergoing repeated transfusions. The findings reveal particularly high rates of alloimmunization among adults, emphasizing the urgent need for improved transfusion strategies. Specifically, the use of extended phenotypic matching, including Rh and minor antigens, could significantly lower the risk of alloimmunization in this population.

The considerable heterogeneity across studies highlights the importance of recognizing regional differences in blood group antigen distribution and transfusion practices when implementing these strategies. Adapting transfusion protocols to accommodate these variations could help clinicians reduce alloimmunization rates, improve patient outcomes, and minimize transfusion-related complications in β-thalassemia care. Future research should aim to standardize alloimmunization reporting and explore the long-term effects of transfusion practices in diverse populations.

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Conflict of Interest

The authors declared that they had no competing interest.

Informed Consent

Since this manuscript is a systematic review, informed consent is not applicable.

Author Contributions

V.I. initiated the research idea and wrote the initial draft of the manuscript. V.I and L.A.C. performed the literature review, data extraction, and edited the manuscript. T.T., B.M., and A.E.H. verified and accepted the manuscript before submission.

Data Availability

The data supporting the findings of this study are available within the article. Further inquiries can be made to the corresponding authors regarding data requests.

Abbreviations

β-TM: beta-thalassemia major; TDT: transfusion-dependent β-thalassemia; TI: β-thalassemia intermedia; RBC: red blood cell; Rh: Rhesus; CI: confidence interval; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; PIO: population, intervention, and outcome; MeSH: Medical Subject Headings; JBI: Joanna Briggs Institute; LOE: level of evidence; HLA: human leukocyte antigen; ABO: A, B, and O blood types

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