Evaluation of immune system in patients with transfusion-dependent beta-thalassemia in Rasoul-e-Akram Hospital in 2021: A descriptive cross-sectional study

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Abstract

Background and aims: Thalassemia syndromes are the most common hemoglobinopathy globally related to blood transfusion and iron overload in the body. Splenectomy, excessive iron overload, and repeated exposure to antigens in blood transfusions can cause severe damage to the patient’s immune system making the patient prone to frequent infection. This study evaluates the immune system status and infection rate in beta-thalassemia major patients receiving iron chelators.

Methods: This descriptive cross-sectional study was performed in Rasoul-e-Akram Hospital on patients with a beta-thalassemia major who had iron overload due to frequent blood transfusions. The percentage of lymphocyte markers was determined by flow cytometry. Serum levels of immunoglobulin were measured by nephelometric assay. Also, Nitro blue tetrazolium and dihydrorhodamine assays were used to evaluate the phagocytic function.

Results: Of the 106 patients participating in this study, 59 (55.7%) and 47 (44.3%) are male and female, respectively. The mean age ± SD of participants was 24.7 ± 12.1 years with 4 to 55 years. There was no significant correlation between sex, the C3 and C4 complements, the lymphocyte markers, and the immunoglobulin levels. Furthermore, all of these variables increased significantly over 30 (p < 0.05). Moreover, there was a strong positive correlation between splenectomy and IgG immunoglobulin (p < 0.001) and CD16 (p = 0.005) lymphocyte marker.

Conclusion: Iron chelator agents effectively improve patients' immune system with thalassemia major. The increase in IgG and IgM immunoglobulins levels is due to frequent blood transfusions, which stimulate the immune system.

KEYWORDS

cellular immunity, humoral immunity, iron chelators agents, phagocytosis, thalassemia major
1 | INTRODUCTION

Infections are a significant and fatal complication in transfusion-dependent thalassemia patients. Thalassemia is an inherited hemoglobin disorder, and its prevalence is more common in the Middle East and Africa. It includes different types and subtypes. Beta-thalassemia is much more common than alpha-thalassemia and divided into major and minor thalassemia. Major beta-thalassemia or Cooley’s anemia is the most severe form of beta-thalassemia, in which a severe deficiency of beta protein in hemoglobin leads to life-threatening and requires frequent regular blood transfusions and extensive treatments of complications.

Moreover, it is associated with many complications, including iron overload, bone deformity, splenomegaly, growth retardation, immune system disorders, liver disease, and heart failure. Mortality from infection among these patients worldwide depends on several factors, including quality of treatment and strategies, epidemiology of various infections, and the rate of income in that country. Infections are almost the second leading cause of death after cardiac problems due to iron overload in thalassemia patients. Several factors, such as thalassemia, immunological abnormalities, blood transfusions, iron overload, chelation therapy, hematopoietic stem cell transplantation, nutritional deficiency, and splenectomy, could increase the rate of infection in these patients. Iron overload causes abnormalities such as endocrinopathy, cardiomyopathy, and other organ dysfunction. Administration of iron chelators in conjunction with blood transfusions is the most common treatment for major thalassemia patients in limited budget countries. Previous studies have demonstrated that iron chelators improve the immune system and phagocytic role of neutrophils and reduce iron overload. As a result, iron overload in thalassemia major patients may be related to an abnormal immune system and increased infection rate.

This study aimed to evaluate the immune function status of the transfusion-dependent major beta-thalassemia taking iron-chelators; and associate factors that cause infection. Most of the studies focus on infection rates with some demographic factors. However, any direct relationship between altered immune function and infection rate was not recognized.

2 | MATERIALS AND METHODS

2.1 | Study description

This descriptive cross-sectional study was conducted on 106 transfusion-dependent major beta-thalassemia patients referred to Rasoul-e-Akram Hospital, dependent on Iran University of Medical Sciences, Tehran, Iran. This study was done to assess the immune function system with infection rate from January to December 2021.

2.2 | Study design

Samples (20 ml of blood) were randomly and consistently collected from patients who volunteered to participate in the study. After selecting patients, a questionnaire was provided that included all demographic and clinical information, such as age, sex, types, and doses of chelators drug administration (oral, injectable, or combined) extracted for each patient. Hematologic and blood tests such as complete blood count (CBC), level of ferritin, erythrocyte sedimentation rate, C-reactive protein, Immunological parameters such as C3 and C4 complements, IgG, IgM, IgA, IgE, antinuclear antibody (ANA), B lymphocytes markers (CD19, CD20) and T lymphocytes markers (CD3, CD4, CD5, CD4, CD8), were measured for all patients.

The levels of lymphocyte markers in peripheral blood were determined by flow cytometry. The nephelometry method was used to evaluate the level of IgG, IgM, IgA, and IgE immunoglobulins serum. Nitro blue tetrazolium (NBT) and dihydrorhodamine (DHR) assay were designed for phagocytosis function. To evaluate the immune status, patients were divided into four subgroups: patients under 10 years, 10 to 20 years, 20 to 30 years, and over 30 years.

2.3 | Patients

The patients with transfusion dependent beta-thalassemia were included. All patients’ care has been in the thalassemia daycare clinic in Rasoul Akram hospital. The criteria for transfusion therapy were the maintenance of hemoglobin levels above 9 gr/dl for all patients.

2.4 | Inclusion criteria

Rasoul-e-Akram Hospital patients with a beta-thalassemia major that suffered from iron overload due to frequent blood transfusions, with no history of recurrent bacterial or viral infections, hepatitis, other chronic diseases, diabetes, and patients who did not use immunosuppressive drugs such as corticosteroids or hydroxyurea capsules.

2.5 | Exclusion criteria

Patients with a history of recurrent bacterial or viral infections, hepatitis, other chronic diseases, diabetes, and those who used immunosuppressive drugs such as corticosteroids or hydroxyurea capsules were excluded from the investigation (Figure 1).

2.6 | Data analysis

χ² and Fisher’s exact test analyzed the correlation between the variables. The mean of continuous variables was reported with standard deviation. Furthermore, qualitative variables were declared with frequency percentages. The t-test and Kolmogorov–Smirnov test were used to compare two independent quantitative with normal and abnormal distributed variables, respectively. Mann–Whitney U and Kruskal–Wallis test analyzed the comparison of two and three
independent variable groups, respectively. Statistical analysis was conducted using SPSS 20 statistical software. \( p < 0.05 \) was considered significant.

## RESULTS

Demographic and clinical immune status of 106 patients with beta-thalassemia major who received iron chelator drugs were analyzed. Patients were divided into 59 (55.7%) males and 47 (44.3%) females aged 4 to 50 years, with the mean age of participants being 24.7 years (Figure 2A).

### 3.1 Overall hematology results of study participants

Complete blood tests demonstrated the level of ferritin and the function of NK cells and neutrophils normal (Figure 2A). Lymphocyte and neutrophil counts were evaluated in all 106 patients with beta-thalassemia major. Lymphopenia in all patients and neutropenia in 93 patients were observed. Also, all patients reported negative (ANA) and normal phagocytosis function. The level of T lymphocytes markers, immunoglobulins, and C3 and C4 complements were evaluated (Figure 2B,C,D).

### 3.2 Effect of splenectomy in thalassemia patients

Thirty-six patients underwent splenectomy (Figure 3B,C,D). Splenectomy had a significant correlation with age, IgG, IgM, IgA, CD16, neutrophil counts, and the level of lymphocyte markers. The mean age of patients in the splenectomy group was higher than in the other groups. Also, most patients who had a splenectomy had high levels of IgG, CD16, and neutrophil counts (Figure 3A).

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**Figure 1** Consort flow diagram

**Figure 2 (A)** The number of patients was demonstrated by sex and age. YO mean years old. (B, C, D): C3 and C4 complements, IgG, IgM, IgA, IgE, and lymphocyte markers were shown by percentage.
FIGURE 3  (A) C3 and C4 complement, IgG, IgM, IgA, IgE, and lymphocyte markers were classified by ferritin level and patients who had a splenectomy. (B, C, D) The number of patients who had splenectomy was demonstrated by sex and age. The Independent-samples t-test, $\chi^2$ test, Fisher’s Exact test, and Mann–Whitney U-test were used to analyze the correlation between splenectomy and the immune system. (E, F, G) The number of patients was displayed by ferritin level, sex, and age. YO mean years old. Ferritin level was demonstrated in (mg/dl).

| Variables | Normal (Abnormal) | P-Value | Ferritin | P-Value |
|-----------|------------------|---------|----------|---------|
| C3        | Abnormal (Normal) 15 (30) 9.097 16 (21) 3 5 3 0.564 |
|           | Normal (Abnormal) 21 (40) 0.812 15 (15) 4 1 2 0.356 |
|           | Abnormal (Normal) 26 (49) 0.508 20 (35) 4 7 7 0.382 |
| IgG       | Abnormal (Normal) 32 (33) <0.001 30 (33) 7 7 7 0.382 |
|           | Normal (Abnormal) 4 (35) 14 23 1 1 1 0.333 |
| IgM       | Abnormal (Normal) 21 (41) 0.981 25 (26) 4 7 7 0.333 |
|           | Normal (Abnormal) 15 (29) 19 20 4 1 1 0.771 |
| IgE       | Abnormal (Normal) 1 (2) 0.981 1 0 1 1 0.771 |
|           | Normal (Abnormal) 35 (48) 43 46 7 7 7 0.079 |
| IgA       | Abnormal (Normal) 20 (27) 0.096 23 18 5 7 7 0.079 |
|           | Normal (Abnormal) 16 (43) 21 28 3 7 7 0.079 |
| CD3       | Abnormal (Normal) 11 (20) 0.832 14 11 3 3 0.137 |
|           | Normal (Abnormal) 25 (50) 30 35 5 5 5 0.258 |
| CD4       | Abnormal (Normal) 16 (34) 0.687 15 10 3 3 3 0.258 |
|           | Normal (Abnormal) 20 (36) 20 26 5 5 5 0.258 |
| CD5       | Abnormal (Normal) 8 (14) 0.789 11 9 1 1 0.543 |
|           | Normal (Abnormal) 28 (56) 33 37 7 7 7 0.543 |
| CD7       | Abnormal (Normal) 10 (12) 0.101 13 8 0 1 1 0.119 |
|           | Normal (Abnormal) 26 (56) 31 38 8 7 7 0.119 |
| CD8       | Abnormal (Normal) 11 (18) 0.596 14 11 2 2 0.409 |
|           | Normal (Abnormal) 25 (52) 30 35 6 6 6 0.409 |
| CD15      | Abnormal (Normal) 15 (53) 0.005 36 38 7 7 7 0.879 |
|           | Normal (Abnormal) 1 (17) 8 8 1 1 1 0.879 |
| CD20      | Abnormal (Normal) 9 (22) 0.491 13 15 2 2 2 0.951 |
|           | Normal (Abnormal) 25 (48) 31 31 6 6 6 0.951 |
| CD55      | Abnormal (Normal) 9 (10) 0.039 8 5 0 0 0 0.59 |
|           | Normal (Abnormal) 27 (60) 54 41 8 5 5 0.59 |
| Ferritin  | <1000 (1000–2000) 1000–3000 >3000 | 0.482 |
| Neutrophil| <1000 (1000–2000) 1000–3000 >3000 | 0.482 |
| Neutropenia| <1000 (1000–2000) 1000–3000 >3000 | 0.482 |
3.3 | Effect of ferritin in thalassemia patients

The different levels of ferritin were analyzed in patients. The optimal serum ferritin level is up to 1000(mg/dl), and it was above 1000(mg/dl) despite using iron chelator drugs in more than 50% of the patients (62 patients) (Figure 3E,F,G). There was no direct correlation between patients’ ferritin levels with C3 and C4, lymphocyte markers, and immunoglobulins levels (Figure 3A).

3.4 | Administration of iron chelators drugs

The administration of Iron Chelators drugs in most patients (90 patients) was oral (deferasirox), and the remainder used desferrioxamine or combined with deferiprone. There was only a significant correlation between the administration of iron-chelator drugs and IgG immunoglobulin levels (Figure 4).

3.5 | Age and immune system

The age increase of the patients had a remarkable correlation with the humoral immune system. There was also a significant correlation between age and cellular immunity, NK cells, so upward trends were observed in the CD marker, especially in patients over 30-year-old (Figure 5A,B,C).

CBC test indicated that the number of lymphocytes and neutrophils increased in older patients (Figure 5D). In immunoglobulins analysis, only increasing IgG level by age was demonstrated, and the rest had no meaningful correlation with age (Figure 5E).

3.6 | Rate and type of infections

The overall adjusted infection rate was 2.16 infections per 100 patient-years. Forty-nine infections were reported. In most infection episodes

![Figure 4](image-url)

**Table 1**

| Variables | Normal/Abnormal | Administration | P-Value |
|-----------|-----------------|----------------|---------|
| C3        | Abnormal        | Oral           | 0.33    |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| C4        | Abnormal        | Oral           | 0.385   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| IgG       | Abnormal        | Oral           | 0.042   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| IgM       | Abnormal        | Oral           | 0.1     |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| IgE       | Abnormal        | Oral           | 0.459   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| IgA       | Abnormal        | Oral           | 0.795   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD3       | Abnormal        | Oral           | 0.702   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD4       | Abnormal        | Oral           | 0.335   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD5       | Abnormal        | Oral           | 0.813   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD7       | Abnormal        | Oral           | 0.998   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD8       | Abnormal        | Oral           | 0.723   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD16      | Abnormal        | Oral           | 0.909   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD19      | Abnormal        | Oral           | 0.423   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD20      | Abnormal        | Oral           | 0.32    |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |
| CD56      | Abnormal        | Oral           | 0.247   |
|           | Normal          | Oral-Injection |         |
|           |                 | Injection      |         |

**Figure 4** (A, B, C) The administration demonstrated the number of iron chelator drugs and IgG levels used. (D) C3 and C4 complements, IgG, IgM, IgA, IgE, and lymphocyte markers were classified by administration of drugs.
(35 episodes), no pathogen was isolated in blood and other sites of cultures. Streptococcus Pneumoniae (7 episodes) was the most common pathogen isolated, Staphylococcus Aureus (5 episodes) and Gram-negative bacteria from sputum, blood, and urine severe bacterial infection were found in three patients (2.83%) with a history of splenectomy and ferritin level over 2000 ng/l. All splenectomized patients had received penicillin prophylaxis for at least 5 years. Septicemia was reported in two patients, and one patient had pneumonia. The other infections, according to frequency, were upper respiratory tract infection (29 episodes), cellulitis on the distal part of lower extremities (5 episodes), cholecystitis due to gall stone (6 episodes), and the remainder include urinary tract infection and gastroenteritis.

History of Hepatitis C virus infection was reported in two patients who were treated.

4 | DISCUSSION

The main finding in this investigation was a notable correlation between the level of immunoglobulin and lymphocyte markers with splenectomy and the age of patients. The rate of infection, in comparison to other studies, was low; despite the immune system dysfunction, hemosiderosis, and splenectomy in thalassemia patients. Prophylactic use of antibiotics may be one of the reasons for reducing the prevalence of infection. Thalassemia is a globin chain genetic disorder associated with severe hemolytic anemia, immune disorders, and infectious diseases still represent a significant challenge for a better quality of life and improved survival. Data showed a decrease in the ratio of CD4 to CD8 and a defect in the function of normal killer cells.

Moreover, hemosiderosis causes suppression of complement performance in both classical and alternative pathways and reduces the level of C3 and C4. Therefore, administering iron chelator drugs in beta-thalassemia major patients reduced their iron deposition and positively affected the immune system. The study of Amin et al. showed that in patients with thalassemia, the levels of immunoglobulins also increase with age. The results of different age groups of patients demonstrated that the level of IgG, neutrophil, and lymphocyte blood counts and the mean level of lymphocyte markers differed in various groups. Previous studies reported the correlation between increasing age and an increase in the level of immunoglobulins such as IgG and IgA and the lymphocyte count. This is similar to our study, especially in patients over 30-year-old. Iron plays a vital role in regulating the expression of T lymphocyte markers. Iron overload due to blood transfusions in patients with thalassemia major
may impair the immune system and increase the proliferation of infectious organisms. Cantinieux's study conveyed that iron chelators could improve some immune system defects. In a 1994 study by Lombardi, levels of interleukins 2 and 6, tumor necrosis factor (TNF), CD4, CD8, CD23, and CD25 were measured in patients with thalassemia major, and the results showed that levels of CD23, CD8, TNF, and CD25 increased and CD4 levels decreased compared to control groups.

Also, splenectomized patients had lower levels of CD8 and CD23 compared to other patients. Furthermore, the finding demonstrated that levels of CD7, CD5, CD8, CD3, and CD19 were normal in most patients, but 82.1% of CD16 cells and 32.1% of CD4 cells were reduced. Moreover, most patients had normal levels of (57.5%) C3 and (70.8%) C4. 29.2% and 32.1% of patients had lower levels of C4 and C3, respectively, and an upward level of C3 was observed in only 10.4% of patients. A study designed by vergin showed no significant difference in C3 and C4 levels between the thalassemia patients and the control group, and a notable reduction in C4 has been observed only in patients with ferritin levels of 3000 mg/dl and more. Iron overload on the skin stimulates the production of IgA as a mucosal surface's antigen. Encounters with antigens due to repeated blood transfusions and infections stimulate the proliferation of IgG, IgM, and IgE.

Also, in this investigation, like the examination conducted by Amin, the IgG and IgM level of 50% of the patients were increased, while a considerable percentage of the patients had normal IgE and IgA levels. Furthermore, immunoglobulin levels were significantly associated with age. Ahoaluwalia reported in 2000 that IgG levels are higher in children with thalassemia major who had a splenectomy than in patients who had not. Also, this investigation demonstrated a significant correlation between splenectomy, and a downward trend in IgG, CD16 levels, and neutrophils count, which cause infection in these patients. Sari's examination indicated that neutrophil count was lower in patients with thalassemia major and who had a splenectomy than in patients without splenectomy. Based on previous studies of chemotaxis, phagocytosis of neutrophils and macrophages was impaired in patients with thalassemia major. Due to inefficient hematopoiesis, the function of the phagocytic system against microorganisms was reduced. Moreover, the WBC and neutrophils count increased were these patients. The reason for using iron chelator drugs in thalassemia patients is the production of a double superoxide anion by neutrophils while the ferritin levels are higher than 1000 mg/dl. Also, Frequent blood transfusions are associated with alloimmunization, autoimmunization, hemolysis, and dysfunction of monocytes and macrophages. NBT and DHR tests, which are associated with phagocytosis function, were reported normal in all patients in this study. The ANA test was negative, indicating the positive performance of iron chelator drugs in thalassemia patients. Moreover, iron overload also increases the rate of some specific infections, for example, Staphylococcus, Yersinia enterocolitica, Klebsiella species, Pseudomonas aeruginosa, Escherichia coli, Streptococcus pneumoniae, Listeria monocytogenes, and Legionella pneumophila.

4.1 | Limitations

One of the most critical limitations of this study was that patients with beta-thalassemia major lacked in history of frequent bacterial or viral infections, hepatitis, other chronic diseases, diabetes, and patients who did not use immunosuppressive drugs. Different results of immune functions have been reported in patients with beta-thalassemia major, as the mechanism of these disorders is still unclear. Immune deficiency in patients with beta-thalassemia involves several components of the immune system. Further studies are necessary to explain the etiology, pathogenesis, and clinical importance of the mechanisms affected in this process.

5 | CONCLUSION

Iron overload is a major cause of immune abnormality in patients with thalassemia major. This study demonstrated no significant correlation between sex and C3 and C4 competent and also between CD7, CD5, CD16, CD8, CD4, CD3, and CD19 lymphocyte markers and IgE, IgM, IgG, and IgA immunoglobulins. Splenectomy affects the immune function of patients with beta-thalassemia major. The mean age of patients who had splenectomy was significantly higher, and their IgG immunoglobulin and CD19 lymphocyte marker levels were abnormal. The increase in IgG and IgM immunoglobulins levels is probably due to frequent blood transfusions in these patients. The complexity of immune function abnormalities needs more cooperation among hematologists, immunologists, and infectious specialties. Moreover, using safe blood at the right time and suitable patients with intense iron chelation play a crucial role in standard care for thalassemia patients.

AUTHOR CONTRIBUTIONS

Fahime Ehsanipour: Conceptualization; formal analysis; writing–review & editing. Pooya Faranoush: Conceptualization; formal analysis; writing–original draft. Mohammad Reza Foroughi Gilvare: Methodology; software; writing–original draft. Negin Sadighnia: Methodology; software; writing–original draft. Morteza Fallahpour: Conceptualization; writing–review & editing. Mona Motamedi: Data curation; formal analysis; writing–original draft. Afsoon Zandi: Data curation; software. Zahra Safaei: Software; writing–review & editing. Ashkan Zandi: Data curation; formal analysis. Mohammad Faranoush: Conceptualization; methodology; writing–review & editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the finding of this study are available from the corresponding author on request.
ETHICS STATEMENT
The ethical committee of the Iran University of Medical Sciences authorized the study, and all the examinations were performed with the ethical code of IR. IUMS. FMD. REC.1398.078.

TRANSPARENCY STATEMENT
The lead author Pooya Faranoush and Mohammad Faranoush affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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