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ORIGINAL RESEARCH

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Complications in patients with transfusion dependent thalassemia: A descriptive cross-sectional study

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Abstract

Background and Aims: One of the most common hemoglobinopathies globally related to blood transfusion and iron overload in the body is thalassemia syndrome. Increasing ferritin levels can cause severe damage to the patient's body organs. This study aims to evaluate the complications of iron overload on vital body organs in patients with transfusion-dependent beta-thalassemia.

Methods: This descriptive cross-sectional study was performed in Iran University of Medical Sciences Hospitals on patients with a beta-thalassemia major with frequent blood transfusions. To evaluate the effect of iron overload on vital body organs, hematologic and blood analysis, echocardiography with measurement of pulmonary artery pressure (PAP) and ejection fraction (EF) tests, bone densitometry, and audiometric tests were performed for all patients.

Results: Of the 1010 patients participating in this study, 497 (49%) were males, 513 were (51%) females aged 5–74 years, and the majority of participants (85%) were over 20 years old. This study demonstrated that increasing ferritin levels had no notable correlation with sex, cholesterol, low-density lipoprotein, parathyroid hormone, T4, and aspartate aminotransferase. However, elevating ferritin levels had significant correlations with increasing triglyceride, phosphorus, thyroid stimulating hormone, alkaline phosphatase, alanine transaminase, and PAP levels, age, hearing disorders, splenectomy, osteoporosis, and decreasing high-density lipoprotein, body mass index, calcium, and EF levels.

Conclusion: Improvement in beta-thalassemia patients' survival and quality of life can be due to multidisciplinary care in a comprehensive unit through regular follow-up and early complication detection.

KEYWORDS

beta-thalassemia, cardiac complications, iron chelators, multiendocrine dysfunction

1 | INTRODUCTION

Transfusion-dependent thalassemia (TDT) is a hereditary hemoglobin disorder that is particularly prevalent in the Middle East and Africa. Beta-thalassemia is more common than alpha-thalassemia and has major and minor subtypes in Iran.[1,2] The most severe form of beta-thalassemia, known as Cooley's anemia, is characterized by a lack of beta protein in hemoglobin and requires frequent blood transfusions for survival.[3–5] Complications associated with beta-thalassemia include iron overload, splenomegaly, growth retardation, immune system disorders, heart and renal failure, and liver disease.[6,7] Iron overload is a major concern for patients with TDT, as it can lead to severe complications such as endocrinopathy, cardiomyopathy, diabetes, auditory abnormalities, osteoporosis, and growth failure.[6,8] This occurs due to increased intestinal absorption of iron due to erythropoiesis, leading to its accumulation in various organs.[9] Patients with TDT are particularly susceptible to iron overload, and iron levels in TDT patients can reach as high as 200 mg per unit. In contrast, healthy individuals absorb only around 0.05 g of iron annually.[10] Iron overload disrupts the body's iron homeostasis, increasing extracellular nontransferrin-bound iron and intracellular labile iron pool. This increase in iron levels leads to the production of reactive oxygen species by the Fenton and Haber–Weiss reaction, which subsequently induces oxidative damage to vital components of the cells.[11,12] This cellular injury can cause serious complications such as heart and renal failure, immune system disorders, growth retardation, and liver disease.[13,14] In low-resource countries, blood transfusions with concomitant administration of iron chelators, such as Deferoxamine, L1, and Deferasirox (DFX) medications, are the most common treatment for patients with major thalassemia. However, monitoring serum ferritin levels is essential to prevent iron overload and its associated complications.[15–19]

This study aims to evaluate the impact of iron overload on vital body organs in patients with transfusion-dependent beta-thalassemia, taking into account age and sex differences. While previous studies have discussed these complications individually, this study aims to identify the correlation between these complications and serum ferritin levels in our patient population.

2 | METHODS

2.1 | Study description

We conducted a descriptive cross-sectional study on 1010 transfusion-dependent beta-thalassemia patients diagnosed by clinical and hemoglobin electrophoresis on referral centers. The patients were referred to the Institute of Endocrine Diseases, Rasool-e-Akram Hospital, and Zafar Adult Thalassemia Center, which are affiliated with the Iran University of Medical Sciences and the Iranian Blood Transfusion Organization in Tehran, Iran. The study aimed to evaluate the correlation between iron overload and its complications in vital body organs and was conducted between January 2015 and December 2022.

2.2 | Study design

The study participants provided 20 mL blood samples that were randomly collected. A questionnaire was designed to obtain demographic and clinical information, including sex, age, types, and chelator medication doses (oral, injectable, or combined). Audiometric tests, hematologic and blood analyses such as complete blood count and ferritin level, echocardiography with measurement of pulmonary artery pressure (PAP) and ejection fraction (EF) tests, and bone densitometry were performed for all patients. Additionally, hepatic and cardiac iron concentrations were measured using dynamic MRI. The patients were categorized into four subgroups based on sex and age (under 20 years and over 20 years) to demonstrate the effects of iron overload on vital organs such as heart, liver endocrine. Splenectomy was performed in all patients who required transfusion over 240 mL/kg/year or had hypersplenism.

All the examinations were conducted with the ethical code of (IR. IUMS. REC. REC.1396.30247) certified by the ethical committee of the Iran University of Medical Sciences.

2.3 | Inclusion criteria

Beta-thalassemia major patients with iron overload due to frequent blood transfusions were referred to Rasool-e-Akram Hospitals, Zafar Adult Thalassemia Center, and the Institute of Endocrine Disease.

2.4 | Exclusion criteria

Patients with unspecified age or ferritin level and patients with more than three missing variables were excluded from the study (Figure 1).

2.5 | Data analysis

Correlations between the variables were analyzed using Chi-Square and Fisher's exact tests and two-way analysis of variance. The mean of continuous variables was reported with standard deviation (SD),

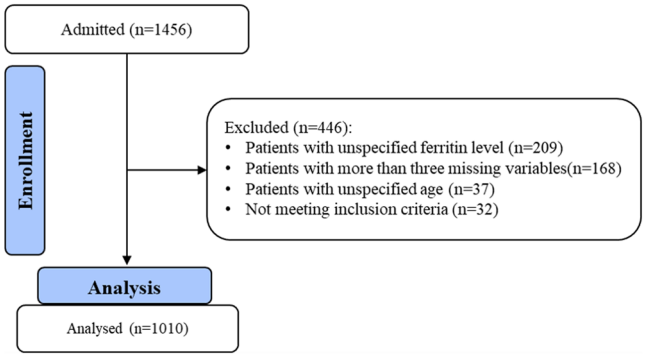

FIGURE 1 Flow diagram.

while frequency percentages were used for qualitative variables. Statistical analysis was performed using SPSS 20 software, and a $p < 0.05$ was considered significant.

3 | RESULTS

3.1 | Overall analysis

The study population consisted of 1010 patients, comprising 497 (49%) males and 513 (51%) females aged 5–74 years (mean ± SD: 28.48 ± 7.76 years). The median age at diagnosis was 5.5 months (45 days to 23 months). A total of 862 of participants (85%) were over 20 years old and received regular blood transfusions every 2–5 weeks, with a pretransfusion hemoglobin level maintained between 8.5 and 10 (g/dL) in 74% of patients. Hemolytic complications were observed in (2.5%) of patients, while extramedullary hematopoiesis was seen in (1.5%).

The ferritin levels of the participants were measured and categorized as follows: 6.24% (63 of patients) had a ferritin level below 300 (ng/dL), 26.73% (270 of patients) had a ferritin level of 300–1000 (ng/dL), 26.44% (267 of patients) had a ferritin level of 1000–2000 (ng/dL), and 40.59% (410 of patients) had a ferritin level above 2000 (ng/dL). There was a significant correlation between increasing age and ferritin levels ($p < 0.05$). Deferoxamine was used by the 990 of patients (98%) with L1 (63%) or DFX (32%) as iron chelator medication to prevent chronic iron overload.

Audiometric tests were performed on all patients, and 402 (39%) were diagnosed with hearing loss (mean ± SD: 0.5), with most patients exhibiting high-frequency sensory hearing loss. Furthermore, 595 (58%) patients underwent splenectomy (mean ± SD: 0.49). Interestingly, patients diagnosed with hearing disorders or who had undergone splenectomy were older than the other groups. Most patients with hearing disorders or splenectomy had higher ferritin levels, with only 18 and 26 participants having a ferritin level below 300 (ng/dL), respectively. These findings suggest a direct and significant correlation between hearing disorders and splenectomy in thalassemia patients, with increased ferritin levels and age ($p < 0.05$) (Figure 2). Additionally, thrombosis occurred in 69 of the splenectomized patients.

3.2 | Iron overload

Hepatic and cardiac iron concentrations were measured using T2-star (T2*) Dynamic MRI in 980 (97%) of patients, while serum ferritin levels were measured in all patients. The mean serum ferritin level was 2153.69 ± 1758.45 ng/mL (range: 138–9982 ng/mL). The mean cardiac T2* dynamic MRI was 21.27 ± 11.2 ms (range: 6.78–42.17), and the mean hepatic T2* dynamic MRI was 4.5.22 ± 3.13 ms (range: 0.84–18.83). However, there was no significant association between ferritin levels and dynamic MRI measurements of the heart and liver.

3.3 | Lipid profile

The patients' cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride levels were evaluated. The analysis showed that LDL and cholesterol levels were within the normal range. However, HDL levels were lower than 50 (mg/dL) in 406 females and under 40 (mg/dL) in 413 males.[18] Triglyceride levels were over 160 (mg/dL) in 169 patients (mean ± SD: 0.76) (20), revealing a significant correlation between increasing ferritin levels and triglyceride levels and decreasing HDL levels ($p < 0.05$). The body mass index (BMI) analysis demonstrated that 569 (94%) of patients with ferritin levels above 1000 (ng/dL) had a BMI below 25. These results highlight the importance of monitoring lipid profile and BMI in patients with beta-thalassemia to manage complications associated with iron overload. These changes clarify the lipid profile measurements and their correlation with ferritin levels and the importance of monitoring BMI in patients with beta-thalassemia.

3.4 | Infection diseases

The study results showed the frequency of viral infections among TDT patients, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Among the patients studied, 97, 59, and 52 were infected with HCV, HBV, and HIV, respectively. The results showed that most infections occurred in older patients. Before 1990, many patients in Iran received blood products that were infected with viruses, including HIV and hepatitis, which were imported from France.[20] In response to this issue, the Iranian Blood Transfusion Organization implemented stricter standards for donors and implemented measures to reduce the risk of viral transmission through blood transfusions. As a result, the incidence of viral infections through blood transfusions in Iran has decreased significantly. In the past, some patients who received blood transfusions were infected with viruses, including HIV and hepatitis, which were transmitted through the blood. This is a serious issue that has had a significant impact on public health. In the decade before 2000, many patients in Iran who received blood transfusions became infected with viruses, including HIV and hepatitis.[21] However, since then, the rate of viral infections through blood transfusions has decreased significantly, thanks to the implementation of stricter standards for donors and measures to reduce the risk of viral transmission. As a result, the incidence of viral infections through blood transfusions in Iran is now very rare. The Iranian Blood Transfusion Organization has implemented international protocols for producing and distributing blood products and has achieved 100% self-sufficiency in voluntary blood donations. All blood products produced by the Iranian Blood Transfusion Organization were examined for viral infections before they were released for use.[22,23] These measures have helped to ensure the safety and quality of blood transfusions in Iran. There was no significant correlation between viral infection rates and either age or sex,

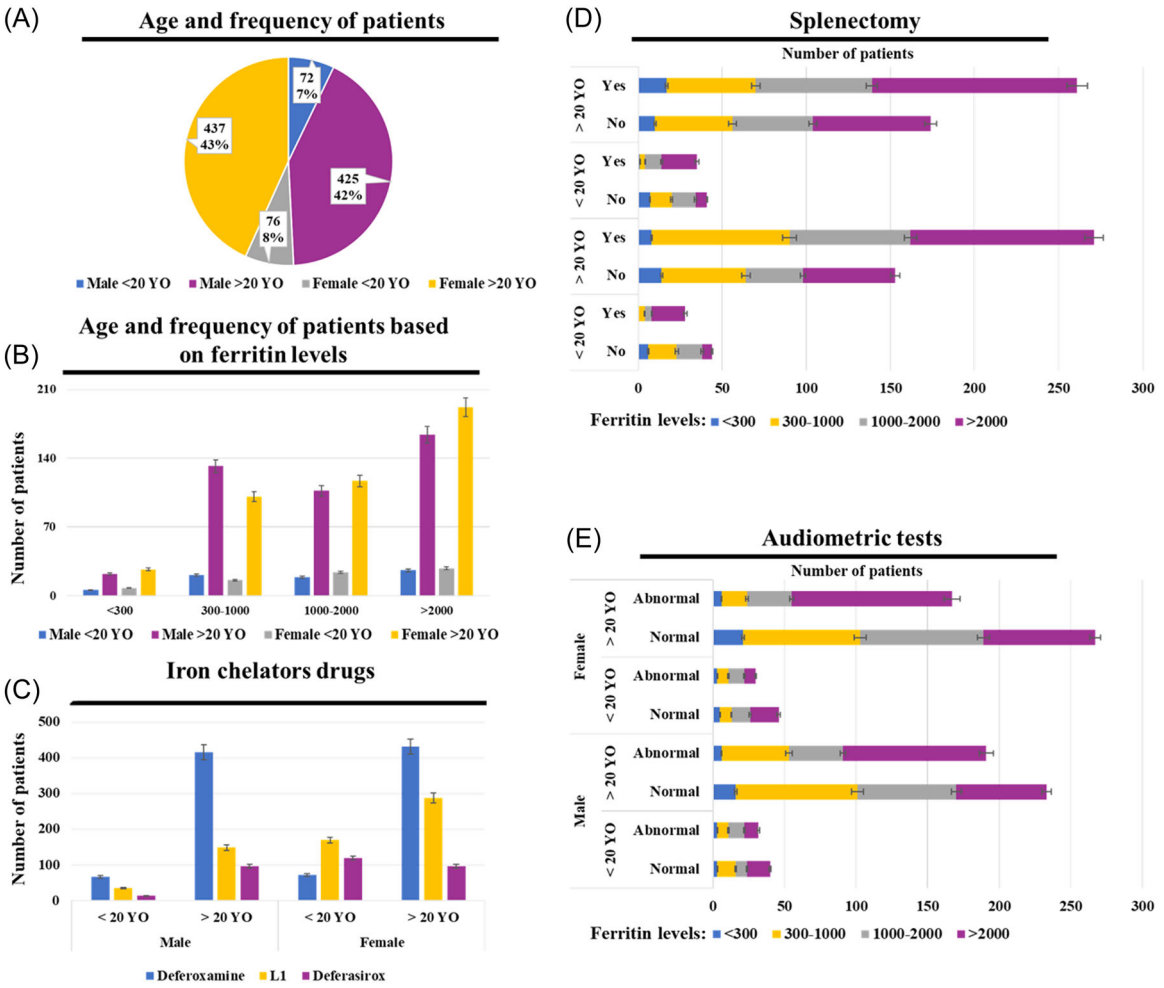

FIGURE 2 (A) The age and frequency of patients. (B) The study participants were categorized based on ferritin levels and analyzed by two-way analysis of variance. (C) Iron chelators medications of this study showed that most of the patients used Deferoxamine. (D) The number of patients who had splenectomy was demonstrated by sex and age, and ferritin levels. (E) Patients with hearing disorders were classified by age and sex, and ferritin levels. Chi-Square and Fisher's Exact tests analyzed the correlation between splenectomy and hearing disorders with increasing ferritin levels and age. YO means years old.

suggesting that all TDT patients are at risk of acquiring these viral infections (Figure 3).

3.5 | Endocrine disease

Calcium, phosphorus, T4, thyroid-stimulating hormone (TSH), and parathyroid hormone (PTH) levels were measured in patients, and their normal ranges were set to (9–10.5 mg/dL), (3–4.5 mg/dL), (0.5–12 g/dL), (0.35–4 mIU/mL), and (10–65 ng/L), respectively.[18,20-23] T4 and PTH levels were mainly normal among the patients. However, an upward trend in phosphorus (467 of patients) and TSH (437 of patients) levels and a downward trend in calcium (517 of patients) levels were observed with increasing ferritin levels of more than 300 ng/dL. Osteoporosis was evaluated in patients based on age and Z-scores under (−2 SD),[24] and it was significantly higher in 449 patients with higher ferritin levels who had a significantly increased risk of osteoporosis ($p < 0.05$). Alendronate and pamidronate drugs were used to prevent the progression of osteoporosis in 355 and 46 patients, respectively.

The study found a high frequency of hypogonadism, with 227 (22.4%) males and 147 (14.5%) females showing abnormal pubertal maturation. Amenorrhea occurred in 98 (9%) females, while azoospermia and oligospermia were observed in 138 (13.6%) male patients. Moreover, replacement hormonal therapy was performed in 137 males and 114 females. Pregnancy was achieved through spontaneous ovulation and in-vitro fertilization in 12 and five participants, respectively. The overall frequency of diabetes mellitus among the patients was 19.37%. The study found that high ferritin levels (over 2500 ng/dL) and increased BMI (over 30) significantly affected the frequency of diabetes ($p < 0.05$). The study also found that hypothyroidism, hypoparathyroidism, and hyperparathyroidism were observed in 19.7%, 14.1%, and 3.3% of patients, respectively. Endocrinopathies were reported in both sexes, but infertility was more common in males (Figure 4).

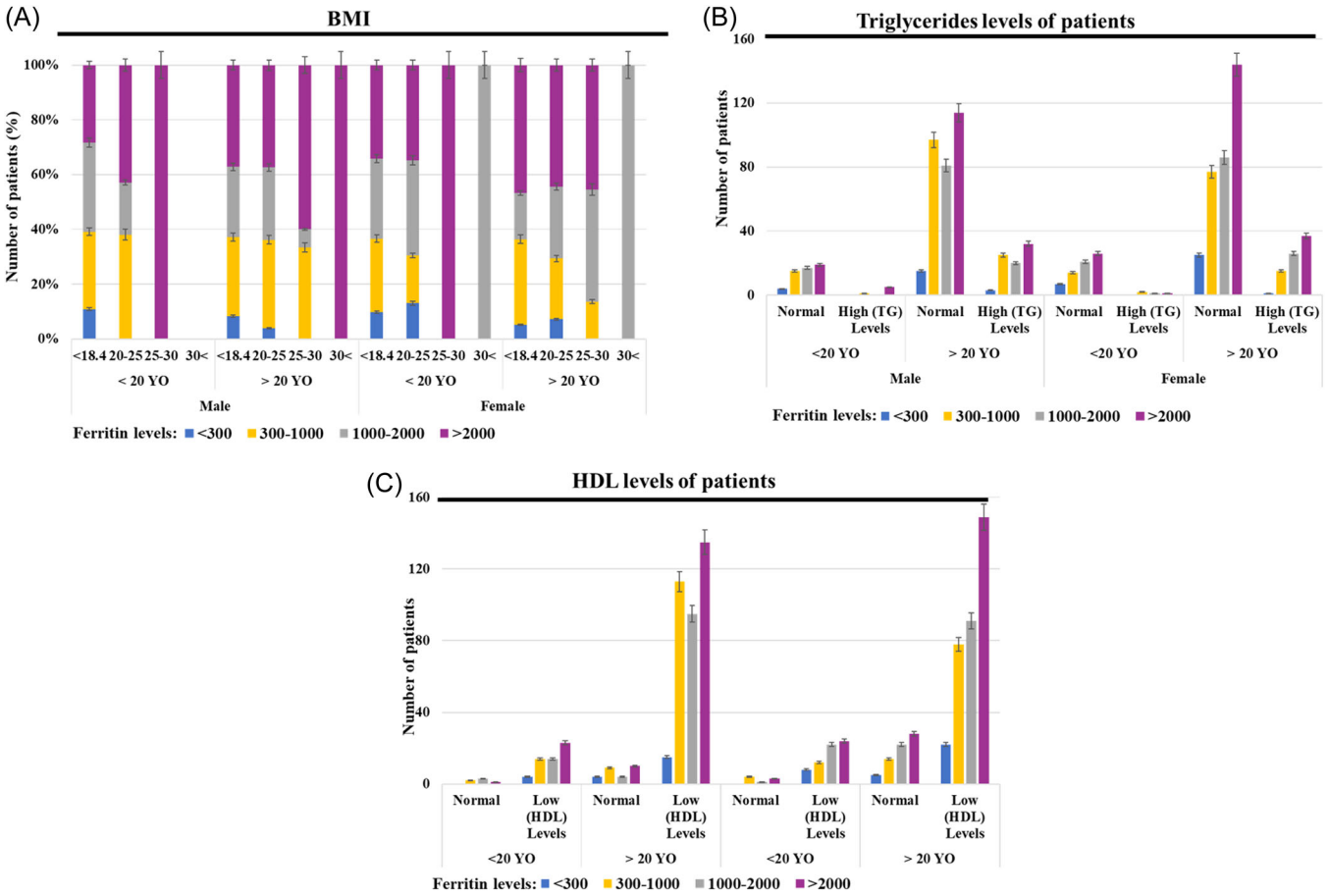

FIGURE 3 (A, B, and C) The body mass index and the levels of triglycerides and high-density lipoprotein were demonstrated by age, sex, and ferritin levels and analyzed with Chi-Square and Fisher's Exact tests. YO means years old.

3.6 | Liver disorders

This study investigated the correlation between ferritin levels and liver enzymes, including alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine transaminase (ALT). In children, ALP levels are typically higher than the normal range of 147 IU/L.[18] The results showed that ALP levels were elevated in most patients under 20 years old. However, they were also high in patients over 20 years of age, and the number of patients with high ALP levels increased significantly with increasing ferritin levels ($p < 0.05$). The number of patients with ALT levels higher than the normal range of 4–36 U/L[20] also increased significantly with age and ferritin levels. Additionally, 390 patients had ferritin levels above 300 ng/dL (mean ± SD: 0.96, $p < 0.05$). On the other hand, AST levels were within the normal range of 8–45 IU/L[21] in 718 of patients, without any correlation with ferritin levels or age (mean ± SD: 0.86).

The study also reported that liver cirrhosis was encountered in 12.3% of thalassemic patients, and hepatocellular carcinoma was reported in three patients with a history of hepatitis C infection.

3.7 | Cardiovascular diseases

PAP and EF are important indicators of cardiovascular health, with normal ranges of 20 mmHg or less and 52% to 72%, respectively.[18,20] The prevalence of cardiovascular disease was found to be 62.8%. Cardiomyopathy and heart failure were observed in 12.2% and 17.53% of patients, respectively. The findings showed that 434 of patients had increased PAP (mean ± SD: 0.64), and 13% had arrhythmia. Analysis of PAP and EF revealed that increasing ferritin levels above 300 ng/dL led to an upward trend in the number of patients with high PAP levels (81%) or low EF levels (46%), without any notable association with age or sex ($p < 0.05$) (Figure 5).

4 | DISCUSSION

Iron overload is a significant concern for patients with thalassemia who require chronic blood transfusions. Multicenter studies have identified various complications associated with transfusion-dependent beta-thalassemia, including hemosiderosis and splenectomy.[24] The

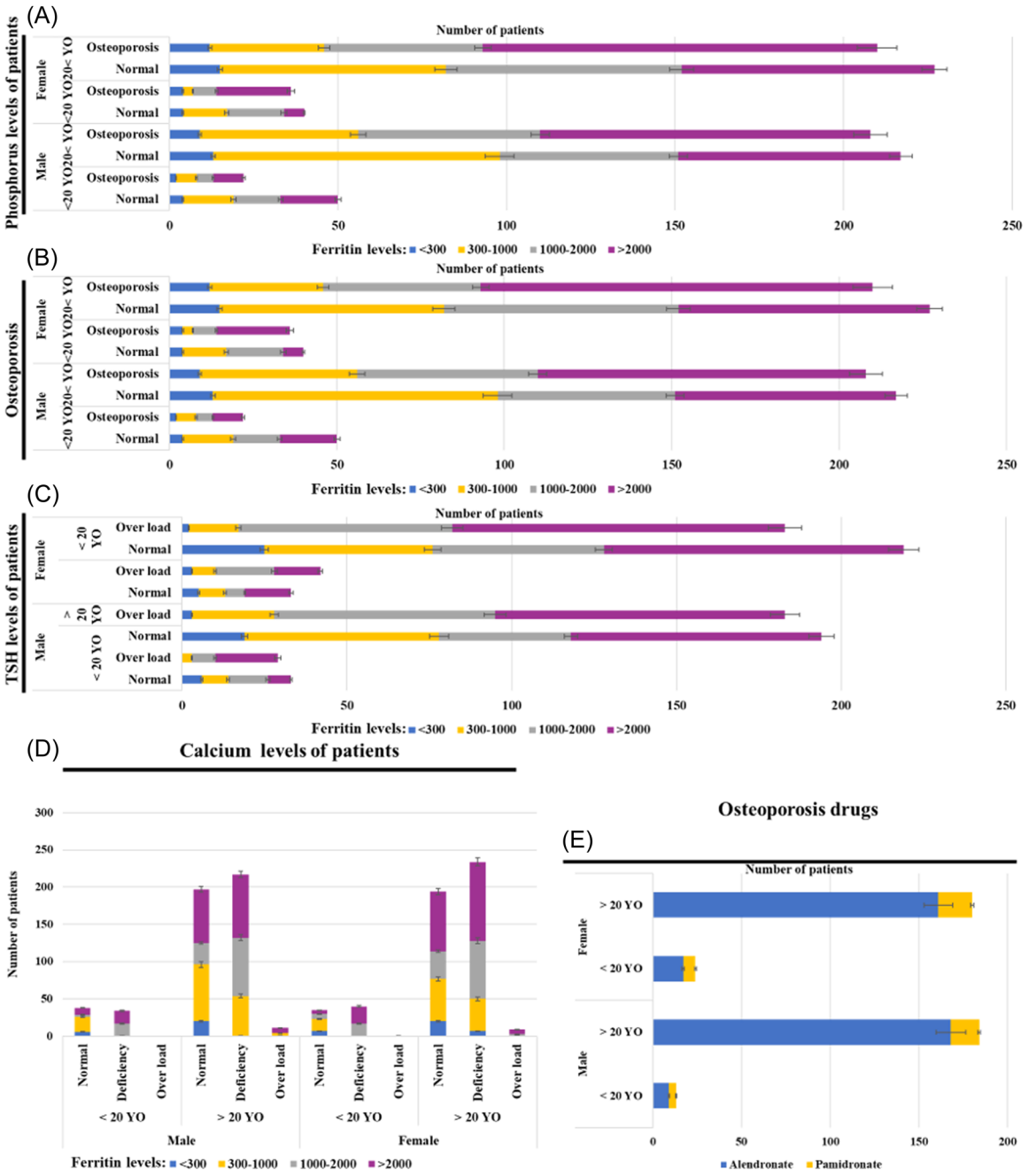

FIGURE 4 (A, B, C, D, and E) The number of patients with osteoporosis, the type of medicine used, and the levels of phosphorus, thyroid stimulating hormone, and calcium were categorized by age, sex, and ferritin levels and investigated with Chi-Square and Fisher's Exact tests. YO means years old.

present study demonstrated the data analysis of the treated patients with a focus on complications of hemosiderosis and splenectomy. While high standards of care have improved the quality and duration of life for thalassemia patients in many countries, iron overload and the nature of the disease continue to pose significant problems. Complications of thalassemia due to iron overload and the nature of the disease are still substantial common problems, including cardiac issues (cardiomyopathy, heart failure, increased PAP, and arrhythmias), hepato-biliary disease (hepatitis, cirrhosis, gallstone, cholecystitis, and hepatocellular carcinoma), endocrinopathy (delay puberty, growth deficiency, hypogonadism, hypothyroidism, diabetes, hypoparathyroidism, and osteoporosis), thrombophilia, iron chelator adverse reaction, and pregnancy problems.[25,26] However, developing potent oral iron chelators, dynamic MRI imaging techniques, safe and appropriate blood transfusion methods, and increased patient education have helped reduce the incidence of complications in thalassemia patients.[27,28] Currently, the Iranian Blood Transfusion Organization plays a critical role in providing appropriate and safe blood for thalassemia patients in Iran. It is essential

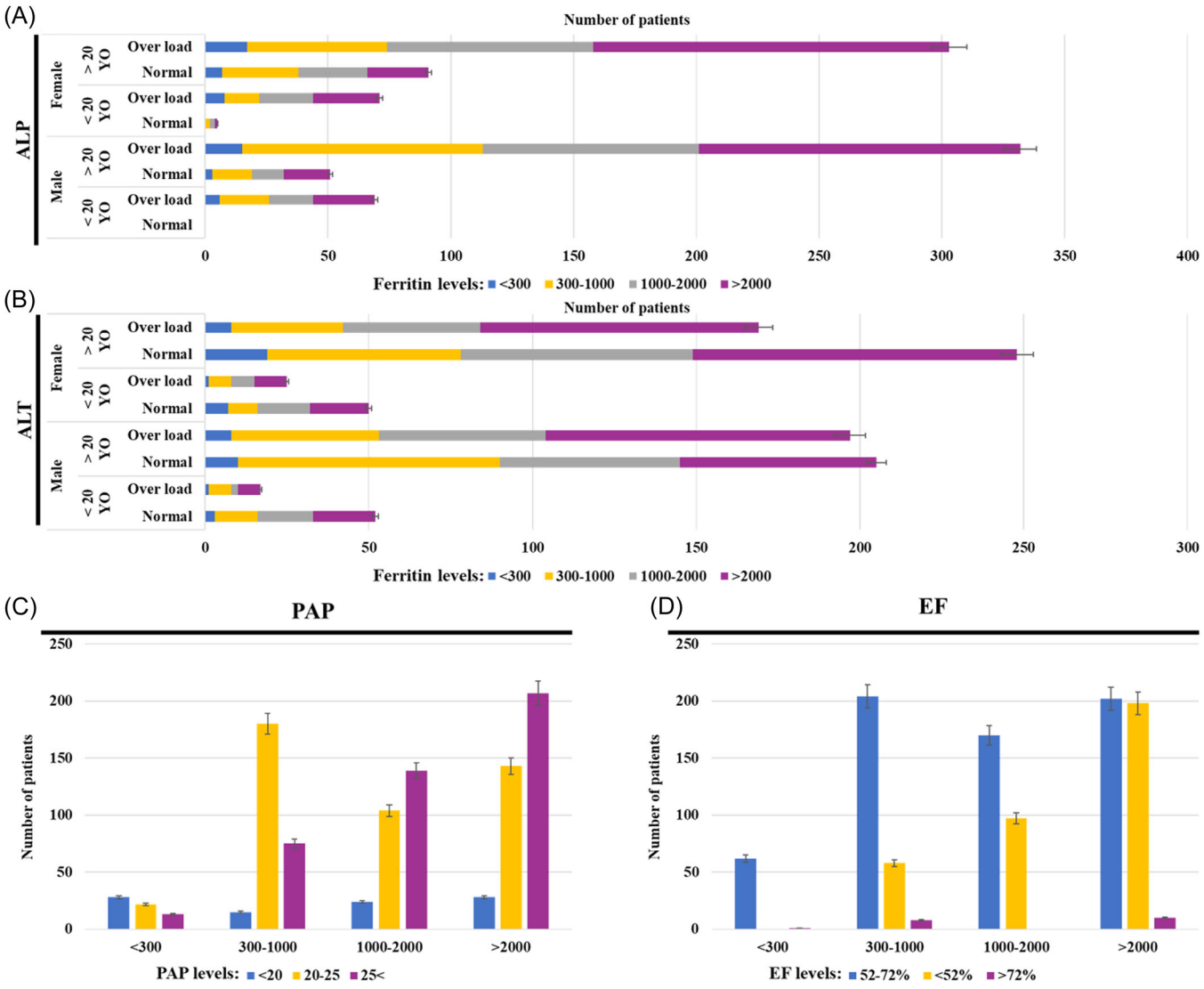

FIGURE 5 (A and B) Chi-Square and Fisher's Exact tests analyzed the levels of alkaline phosphatase and alanine transaminase that were categorized by age, sex, and ferritin levels. (C and D) Pulmonary artery pressure (PAP) and ejection fraction (EF) levels were displayed based on ferritin levels. One-way analysis of variance analyzed the correlation between PAP and EF with ferritin levels. YO means years old.

to ensure that all blood transfusions are performed using safe blood products by a hundred percent of volunteer donors screened for infections and other potential health risks. In addition to providing safe blood products, the organization may also promote public health initiatives to prevent thalassemia and other genetic blood disorders. Overall, the Iranian Blood Transfusion Organization plays a crucial role in the management and prevention of thalassemia in Iran, and its efforts are essential in ensuring the health and well-being of thalassemia patients and their families.[29] Prevention programs and proper care in Iran have led to an increase in the age of thalassemia patients and a decrease in the prevalence of new birth with thalassemia.[29] As a result, our study's mean age of patients exceeded 28 years old.

In our study, more than 40% of patients had ferritin levels above 2000 (ng/dL) and abnormal T2 star MRI which could indicate nonadherence to be treated with iron chelators. Treatment is a considerable challenge in TDT patients, as shown in the meta-analysis of Fortin's study, widely varying adherence rates to iron chelation therapy, and the range of nonadherence rates to Desferrioxamine from 3.9% to 29.4%, Deferiprone from 5.1% to 17.6%, and DFX from 1% to 14.7% were reported.[30,31] Wood's study in 2014 reported that liver and cardiac complications are still significant causes of morbidity and mortality, and most comprehensive thalassemia treatment centers currently offer new methods for diagnosing complications.[32] In this study, T2*MRI was used to measure iron levels in the heart and liver and demonstrated that abnormal cardiac and hepatic T2*MRI was associated with higher ferritin levels and more associated complications. Some studies showed a significant association between increasing cardiac T2*MRI and the mean age and a reverse correlation between T2*MRI and increasing age.[33,34] However, Christoforidis and Fragasso's studies

reported that a significant correlation was not found between cardiac T2*MRI and serum ferritin levels.[35,36]

In our study, 402 (39%) patients were diagnosed with hearing loss, with most exhibiting high-frequency sensory hearing loss. Interestingly, most patients with hearing problems were older and had undergone splenectomy. According to various studies, the prevalence rate of hearing disorders in patients with TDT is approximately 32.3%. This complication has not been found to be related to age, sex, and ferritin level in many studies. However, Tartaglione's study reported a weak correlation between hearing loss, clinical phenotype, and iron chelator.[37]

This investigation demonstrated that the BMI was lower than the normal level in most patients, while the lipids profile was increased, and cardiovascular disease was observed in some patients. Several other factors can affect lipid profile and BMI in beta-thalassemia patients. These include iron overload and its associated complications, chronic inflammation and oxidative stress, hormonal imbalances, and genetic factors. These factors should be considered when evaluating and managing lipid profiles and BMI in beta-thalassemia patients. These findings suggest that beta-thalassemia patients may be at risk of developing metabolic abnormalities, such as dyslipidemia, and despite having a lower BMI, may be due to the underlying pathophysiology of the disease.[38] It is essential to closely monitor lipid levels and BMI in beta-thalassemia patients and other cardiovascular risk factors to identify and manage any potential health complications associated with their condition. It may involve lifestyle modifications, such as dietary changes and increased physical activity, and pharmacological interventions, such as lipid-lowering medications, as needed.[39,40] The results showed a high frequency of endocrinopathies in both sexes without a direct link to hemosiderosis. However, an upward trend in phosphorus and TSH levels and a downward trend in calcium levels with increasing ferritin levels were reported, which may suggest the presence of iron overload. Patients with beta-thalassemia major, also known as Cooley's anemia, are at increased risk for endocrine complications due to chronic anemia and iron overload associated with thalassemia. The incidence of these endocrine complications varies depending on the population studied and the duration and severity of the disease in the world. However, it is estimated that up to 90% of individuals with thalassemia major will develop at least one endocrine complication during their lifetime.[41]

An iron overload could cause damage to various organs, including the endocrine glands, which may lead to endocrinopathies. This study did not directly link endocrinopathies to hemosiderosis, and may iron overload could play a role in the high frequency of endocrinopathies observed in the study population. Nevertheless, liver and cardiac complications remain significant causes of morbidity and mortality, and new diagnostic methods are being developed to detect these complications early. Gene therapy, Jak2 inhibitors, induction of hemoglobin F, and hepcidin agonists are among the promising new treatments being studied to reduce transfusion requirements and decrease iron overload. A multidisciplinary management team is needed to handle the diverse complications associated with beta-thalassemia, particularly in older patients.[42-44]

Due to the diverse complications of beta-thalassemia caused by the nature and treatment results, we need an experienced comprehensive care unit for a multidisciplinary management team, especially for older patients. The national clinical guideline is one of the critical strategies in the timely treatment and prevents morbidity and mortality by the disease.

5 | CONCLUSIONS

Eventually, significant progress in the diagnosis, prevention, and management of beta-thalassemia was reported in the past few decades. However, iron overload remains a critical challenge. In addition, using chelators therapy methods, especially novel agents, can enhance the quality of treatment, life expectancy, and health-related quality of life and reduce overall morbidity and mortality rates. Cardiac, endocrine, and liver complications remain among the primary causes of mortality and morbidity in beta-thalassemia patients. Regular follow-up in a comprehensive thalassemia clinic, providing safe blood transfusions, chelator medication, extended care, and genetic counseling before marriage and prenatal diagnosis are essential prevention strategies. Overall, significant progress has been made in diagnosing, preventing, and managing beta-thalassemia. However, iron overload remains a critical challenge.

6 | LIMITATIONS

In the interest of completeness, it should be noted that due to the large number of patients and the long duration of the study, some variables could not be collected and analyzed. Additionally, a small number of patients were referred to other medical centers, potentially introducing some variability into the data. However, every effort was made to minimize any potential impact of these limitations on the study's overall findings.

AUTHOR CONTRIBUTIONS

Mohammad Faranoush: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing—original draft; writing—review and editing. **Pooya Faranoush**: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing—original draft; writing—review and editing. **Iraj Heydari**: Data curation; funding acquisition; methodology; resources; visualization. **Mohammad Reza Foroughi-Gilvaee**: Conceptualization; data curation; formal analysis; software; writing—original draft. **Azita Azarkeivan**: Conceptualization; data curation; investigation; resources; validation. **Ali Parsai Kia**: Formal analysis; investigation; methodology; software; supervision. **Negin Sadighnia**: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; software; writing—original draft;

writing—review and editing. **Ali Elahinia**: Formal analysis; software; writing—review and editing. **Afsoon Zandi**: Conceptualization; data curation; formal analysis; writing—original draft. **Mohammad Reza Rezvany**: Conceptualization; data curation; formal analysis; funding acquisition; resources. **Nahid Hashemi-Madani**: Conceptualization; data curation; investigation; project administration; resources. **Amir Ziaee**: Conceptualization; data curation; formal analysis; investigation; resources; software. **Reza Nekouian**: Investigation; methodology; resources; software; supervision; writing—original draft. **Farzaneh Rohani**: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

TRANSPARENCY STATEMENT

The lead author Pooya Faranoush affirms 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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