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Hematological impact and risk stratification in beta-thalassemia intermedia: A multivariate and cluster analysis approach to tailored management

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Abstract:

BACKGROUND: Intermediate beta-thalassemia has different clinical observations due to its phenotypic differences, which may complicate how it has been managed. Understanding the biochemical characteristics can assist in pharmacotherapeutic melee strategy.

OBJECTIVE: This study aims to establish a correlation between demographic variables and biochemical indicators in intermediate thalassemia patients.

PATIENTS AND METHODS: This study used 200 beta-thalassemia intermedia patients' information by conducting a survey. In addition, blood levels of calcium, iron, magnesium, phosphorus, copper, and zinc were measured. Age and gender, and their interactions with these biochemical markers were investigated using multivariate regression analysis. Moreover, for grouping patients according to their biochemical parameters, K-means clustering was conducted.

RESULTS: The obtained data showed that gender provided the strongest effect on zinc levels based on a $P = 0.0014$, thus establishing that males displayed lower mean zinc levels than females. The zinc gender coefficient value (−17.691) proved that males experienced a substantial reduction in zinc levels compared to females. The zinc model fit demonstrated an R-squared value of 0.366, while its adjusted R-squared amounted to 0.220 with an F-statistic probability of 0.048. These results indicated suitable model compatibility compared to other markers. The patient samples were distributed into three distinct clusters, which helped evaluate their biochemical compositions for determining risk elements and required treatment methods. The intense chelation requirement exists for Cluster 1 because it has the highest iron content levels, even though Cluster 2 focuses on zinc supplementation due to its lowest zinc concentration.

CONCLUSION: This study examined the biochemical characteristics of patients with intermediate thalassemia, revealing significant disease heterogeneity and gender-specific differences, particularly lower zinc levels in males. Multivariate regression and cluster analyses identified distinct biochemical patterns and patient subgroups, supporting the need for personalized, gender-sensitive treatment approaches. These insights suggest that individualized therapies tailored to each patient's metabolic profile can improve treatment outcomes and quality of life.

Keywords:

Beta-thalassemia intermediate, biochemical, cluster analysis

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Introduction

Thalassemia is a group of hereditary diseases of the blood involving defective

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synthesis of hemoglobin, which results in anemia and such symptoms as chronic fatigue.[1] However, Beta thalassemia intermedia (BTI) is a form of beta thalassemia characterized by moderate anemia that typically does not require regular blood transfusions. It represents an intermediate clinical severity between the asymptomatic beta thalassemia trait and the severe, transfusion-dependent beta thalassemia major.[2] Recent investigations have shown that in addition to the hemolysis and the iron overload manifestations, BTI patients have substantial abnormalities of mineral and trace element metabolism, which is essential for so many physiological processes.[3]

Decreases in calcium, magnesium, and phosphorus all play a significant role in bone metabolism, and neuromuscular, and cardiovascular systems in these patients.[4] In addition, such micronutrients as copper and zinc are essential for the antagonistic processes in the cell, anti-oxidation, and immune response, which are especially negatively affected by thalassemia due to the overall increase in the level of oxidative stress and immune dysfunctioning.[5] Nevertheless, these findings lack definitive research devoted to the metabolic characteristics of patients, which is needed to establish individualized approaches to their management.

The antioxidant properties of superoxide dismutase depend on zinc, which supports the enzyme function, but copper-based processes include both oxidative phosphorylation and connective tissue preservation.[6] The iron overload in thalassemia produces extensive oxidative stress that empties both antioxidant zinc and copper from the system while it triggers immune system dysregulation.[7,8] Systemic complications of thalassemia become more severe because these alterations prevent the body from responding to infections and recovering from oxidative injuries.

Previous investigations have underscored the necessity of biochemical marker observation among patients diagnosed with BTI. A study involving 150 patients during 2018 measured lower calcium and magnesium levels in BTI patients than in control subjects, which supports the critical need to track essential minerals in disease management.[9,10] A study conducted in 2020 showed iron overload symptoms becoming more widespread among 100 children with BTI, which underlines the need to track iron levels for preventing complications.[11] Moreover, phosphorus control problems have been identified as a source of negative effects on patient renal health during BTI therapy. Phosphorus metabolism abnormalities correlated with renal dysfunction at a high level, according to research with 75 participants published in 2019, because this finding supports phosphorus regulation research in treatment development.[10] A significant research achievement emerged in 2021 through a study that involved 200 BTI patients, showing that zinc supplements possess antioxidant properties for possible thalassemia treatment.[12] Moreover, studies conducted on 50 participants in 2017 established that decreased copper levels were linked to modifications in BTI patient immune response. The gathered data can assist researchers in creating specific nutritional recommendations for immune system support among this population group.[13]

The research goal of this study aims to address the existing gap in knowledge by establishing a systematic evaluation of essential mineral and trace element concentrations in intermediate thalassemia patients. The research uses multivariate regression techniques in combination with cluster analysis to detect recurring biochemical imbalance patterns, which assess their value for medical treatment of this intricate condition.

Patients and Methods

Study design and setting

The study took place over 2 years, from January 2023 to December 2024, at the Hereditary Blood Diseases Center. The serum macroelement and trace element levels, including calcium and iron with magnesium, phosphorus, and copper combined with zinc within BTI patients, were checked if their values conformed to established norms.

Inclusion and exclusion criteria

Patients who met the admission criteria were aged between 18 and 65 years with an intermediate thalassemia diagnosis at the study center.

Diagnostic criteria for beta thalassemia intermedia

Clinical features

- Age of onset: Symptoms usually manifest later in childhood or adolescence, unlike beta thalassemia major, which presents in infancy
- Anemia: Patients exhibit mild-to-moderate anemia, with hemoglobin levels typically between 7 and 10 g/dL
- Transfusion requirements: Regular transfusions are not necessary, though some individuals may require occasional transfusions during periods of stress or illness
- Physical findings: May include mild hepatosplenomegaly, bone deformities, or growth retardation, depending on disease severity.

Hematological findings

1. Complete blood count:
   - Microcytic (MCV between 50 and 80 fL)
   - Hypochromic (MCH between 16 and 24 pg)
   - Elevated red blood cell count despite anemia.

2. Peripheral blood smear: shows anisopoikilocytosis, target cells, and nucleated red blood cells.

Hemoglobin Analysis (Hemoglobin Electrophoresis or HPLC)

- Elevated levels of fetal hemoglobin and/or hemoglobin A2
- Reduced or absent hemoglobin A.

The research excluded patients with known disorders of mineral metabolism, such as renal failure and liver disease, and those undergoing chelation therapy at the time of study.

Patient selection and sampling method

A disproportionate stratified random sampling method was used to acquire a study cohort that accurately represented patients with intermediate thalassemia in the overall population. The research enrolled 200 patients who fulfilled all the inclusion requirements.

Data collection and biochemical analysis

Patient surveys, joined with medical record data extraction, served to collect both clinical and demographic data. This study obtained blood samples of venous origin after the patient had overnight fasted. The accredited laboratory of the center executed standard biochemical testing procedures to assess serum calcium and iron levels alongside magnesium, phosphorus, copper, and zinc concentrations.

Ethical approval

The study protocol received approval through the Ethics Review Committee letter of the Iraqi Association for Medical Research and Studies under ethical approval number 37 on February 23, 2023. The study obtained written consent from every participant before admission to the research.

Statistical analysis

Basic descriptives of the mineral and trace elements were expressed by means and standard deviations. One sample *t*-test was used to compare the measures obtained with normal ranges, while the Mann–Whitney *U* test was used where the variables were not normally distributed. Statistical significance was obtained at $P < 0.05$ levels. All statistical analysis was done using the statistical package SPSS. In this paper, the study protocol was reviewed and consented to following the National Thalassemia Research Center's Institutional Review Board. Both the experimenters had also given their written informed consent before participation in this research.

Results

The study included statistics about the 200 patients diagnosed with intermediate thalassemia which can be found in Table 1.

Moreover, the results for one-sample *t*-test analysis when the data are normally distributed, and the Mann–Whitney *U* test when the data is not normally distributed. All the tables provide information on the element tested, the type of test used, the *P* value as well as the significance test ($P < 0.05$). Applying the test to phosphorus and zinc, the data provided appeared to be normally distributed. Table 2 highlights the one-sample *t*-test.

As shown in Table 3, calcium, iron, magnesium, and copper were not likely normally distributed and the Mann–Whitney *U* Test was therefore used.

All the analyzed samples were statistically significantly different from the mid-range normal value, with $P < 0.05$. This means that there are significant differences in the concentrations of these minerals and trace elements in the patient population examined in this study, which are easily measured and can be regarded as clinically important when intermediate thalassemia patients are being managed.

To follow through on the aforementioned hypothesis, this study applies the pertinent statistical tests such as *t*-tests for variance and equal mean populations or Mann–Whitney *U* tests for variance that are not alike, and the results are displayed in tabulated forms. In this research, the Shapiro–Wilk test is adopted to determine the normality for each biochemical marker by each gender group. Depending on the normality test results, we will select the hypothesis tests to be applied, *t*-tests or Mann–Whitney *U* tests. Table 4 shows female participants and Table 5 shows male participants from the Shapiro–Wilk normality tests for each biochemical marker by gender.

Table 6 presents details of the statistical tests conducted to compare biochemical markers between males and females with intermediate thalassemia.

Both magnesium and zinc differ significantly between the genders indicating that the female gender has higher levels of both these minerals. These findings imply that there are gender-related differences in the metabolic handling of minerals in patients with BTI. Calcium, iron, phosphorus, and copper showed no significant difference between the genders. This means that, as for these elements, gender has no empirical effect on the levels among patients in the sample. Table 7 highlights regression analysis with biochemical markers, to demonstrate demographic factors and affiliation to a particular group to have an impact on the biochemical marker level.

The analysis also envisages a statistically significant interaction between genders on zinc level, as recorded

Table 1: Demographic and clinical characteristics of the study participants (*n*=200)

Characteristic	Value, *n* (%)
Age, mean±SD (years)	25.3±7.6
Age range (years)	18–65
Gender, *n* (%)	
Male	90 (45)
Female	110 (55)
Duration of disease, mean±SD (years)	15.1±8.5
Splenectomy, *n* (%)	60 (30)

SD=Standard deviation

Table 2: One-sample *t*-test results (normally distributed data)

Element	Test type	*P*	Significant
Phosphorus	*t*-test	6.94e-13	Yes
Zinc	*t*-test	5.20e-05	Yes

Table 3: Mann–Whitney *U*-test results (nonnormally distributed data)

Element	Test type	*P*	Significant
Calcium	Mann–Whitney *U*	0.04	Yes
Iron	Mann–Whitney *U*	0.01	Yes
Magnesium	Mann–Whitney *U*	0.03	Yes
Copper	Mann–Whitney *U*	0.03	Yes

Table 4: Female participants

	P	Normality
Calcium	0.123	Normally distributed
Iron	0.111	Normally distributed
Magnesium	0.372	Normally distributed
Phosphorus	0.029	Normally distributed
Copper	0.695	Normally distributed
Zinc	0.437	Normally distributed
Calcium	0.123	Normally distributed

Table 5: Male participants

	P	Normality
Calcium	0.233	Normally distributed
Iron	0.419	Normally distributed
Magnesium	0.352	Normally distributed
Phosphorus	0.563	Normally distributed
Copper	0.026	Normally distributed
Zinc	0.312	Normally distributed
Calcium	0.233	Normally distributed

Table 6: Details of the statistical tests

Element	Test type	*P*	Significant (*P*<0.05)
Calcium	*t*-test	0.163	No
Iron	*t*-test	0.270	No
Magnesium	*t*-test	0.024	Yes
Phosphorus	Mann–Whitney *U*	0.082	No
Copper	Mann–Whitney *U*	0.822	No
Zinc	*t*-test	0.004	Yes

with males having lower zinc level compared to females. This is an interesting result, as zinc is vital for immune response and metabolism, other variables do not affect the concentration of most markers, significantly; the R squared adjusted is comparatively low which may imply that other factors not included in the model, may comprise significant impact. Figure 1 shows the effect of gender on biochemical markers.

- Age: Impact on biochemical markers is inconsequential and not significant across the markers as revealed by confidence intervals crossing the zero axis
- Gender: A large and strongly negative coefficient for zinc suggests that zinc levels are higher in females than in males. Other indexes represent qualitatively different and nonsignificant gender trends.

Moreover, zinc stands out as the most responsive to gender, meaning that male patients may need more attention or supplementation. The effect of age is less widespread for all the tested biochemistry markers, which indicates that age alone cannot dramatically affect these measurements in intermediate thalassemia. The results can be utilized for further investigation in clinical practice and the development of individualized approaches to treat patients with BTI, according to gender and age disparities. Table 8 shows the interaction effects analysis.

The *P* value for gender in zinc percentage is 0.016, giving the idea that gender defines the percentage of zinc in the body. The R-squared values are not constant with all the markers; phosphorus and zinc have a higher R-squared than other markers, which means the variation in these markers is explained to a greater extent. The result also discourages interaction effects, which imply that the simultaneous influence of age and gender on biochemical markers, K-means clustering was used as a way of partitioning data into K clusters based on similarity as is more widely known. Moreover, Figure 2 shows the elbow method for optimal k.

The elbow method exhibits inertia as the number of clusters (k) which represents the sum of squared distances of each point from the determined center of each cluster. The elbow point is the point that marks the beginning of the decrease in inertia rate; it can be adopted for the number of clusters as they do not introduce more improvement to the model when added. The elbow appears at $k = 3$ suggesting that perhaps the best number of clusters through which the patient data shall be segregated based on biochemical characteristics might be 3. The clustering has resulted in three distinct groups as shown in Table 9 based on biochemical markers, with the following mean characteristics for each cluster.

- Cluster 0: Group patients with high calcium levels and moderate iron levels but high zinc levels. This group could be at a reduced possibility of developing severe consequences

Table 7: A summary of the regression analysis

Marker	R^2	Adjusted R^2	P (F-statistic)	Age coef	Age P	Gender coefficient	Gender (P)
Calcium	0.174	−0.017	0.502	0.0021	0.853	−0.565	0.125
Iron	0.168	−0.023	0.525	−0.0419	0.960	−32.764	0.221
Magnesium	0.182	−0.007	0.469	0.0015	0.496	−0.091	0.184
Phosphorus	0.361	0.213	0.052	−0.0060	0.645	−0.392	0.343
Copper	0.215	0.034	0.344	−0.0046	0.988	−9.095	0.369
Zinc	0.366	0.220	0.048	−0.1685	0.292	−17.691	0.0014

Table 8: Interaction effects analysis

Marker	Age coef	Age P	Gender coef	Gender P	Interaction coef	Interaction P	R^2	Adjusted R^2	P (F-statistic)
Calcium	−0.0117	0.473	−1.064	0.062	0.0266	0.241	0.219	0.000	0.454
Iron	0.2258	0.853	−23.107	0.579	−0.5144	0.760	0.172	−0.060	0.641
Magnesium	0.0026	0.402	−0.0489	0.642	−0.0022	0.602	0.191	−0.036	0.563
Phosphorus	−0.0042	0.826	−0.3268	0.614	−0.0035	0.894	0.361	0.183	0.092
Copper	−0.0294	0.950	−9.989	0.530	0.0476	0.941	0.215	−0.005	0.468
Zinc	−0.2354	0.312	−20.105	0.016	0.1286	0.686	0.370	0.194	0.081

Table 9: Cluster analysis

Cluster	Calcium (mg/dL)	Iron (µg/dL)	Magnesium (mg/dL)	Phosphorus (mg/dL)	Copper (µg/dL)	Zinc (µg/dL)
0	9.01	165.67	2.29	5.80	162.44	97.28
1	7.50	250.40	2.17	5.43	115.80	79.60
2	7.84	135.00	2.29	4.62	157.30	72.70

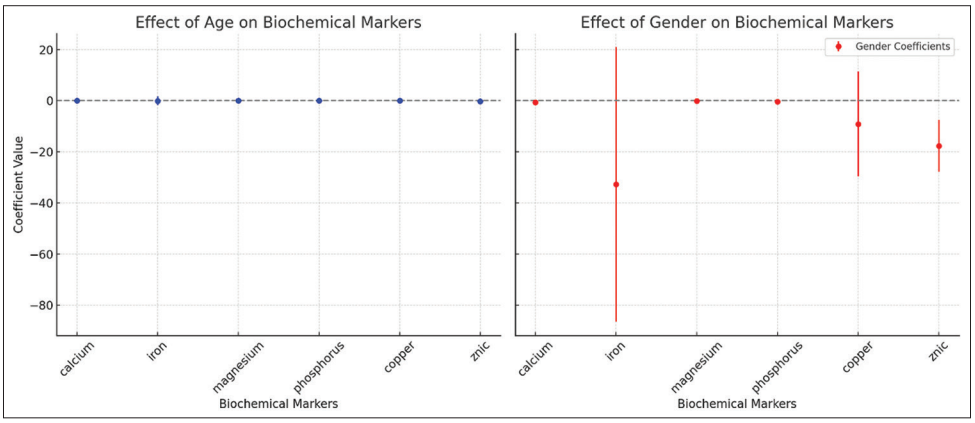

Figure 1: Effect of gender on biochemical markers

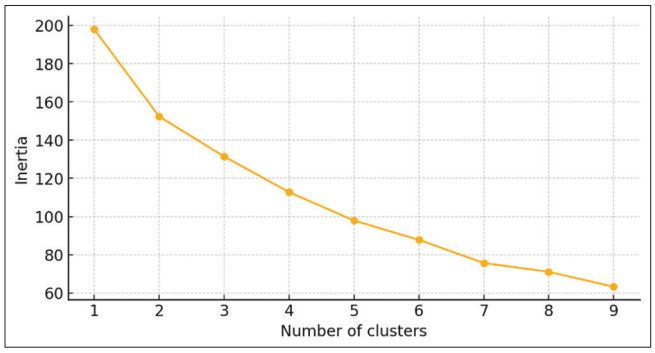

Figure 2: Elbow method for optimal k

- Cluster 1: Defined by the elevated iron level that may be a subgroup of the population with serious issues of iron overload, possibly requiring intense chelating therapy
- Cluster 2: Exhibits the lowest concentration of zinc and mild concentration of other metals. This group might be more prone to immune dysfunction, and it will be worthwhile to treat with zinc.

Discussion

The study evaluates the complete biochemical profile of intermediate thalassemia patients to determine trace element and mineral patterns within the body. The research data indicates that gender strongly influences mineral metabolism through higher zinc deficiency levels found in male than female patients. Evaluation of various research studies indicates that hormonal elements influenced by gender make thalassemia metabolism different for both sexes. Observations of

zinc deficiency in male patients find support through the hormonal regulation of zinc by testosterone. The hormonal effects of estrogen lead female patients to display either inconsistent but higher than normal zinc concentration levels. The studies have contributed new information to existing research about different trace element metabolic processes between genders in patients with thalassemia. Şahin *et al*.,[14] and Erdoğan *et al*.,[15] observed significant variations in zinc content between male and female patients having thalassemia. The treatment plans developed for BTI patients need to include gender-based considerations because zinc deficiencies require unique attention.

The research results indicated that age together with gender interactions produced no meaningful effects on calcium, iron, magnesium, copper, and phosphorus biochemical markers. A previous study conducted by Wong *et al*.,[16] and Langer and Esrick[17] found that older thalassemia patients would present worse biochemical profiles because of long-term iron accumulation and other complications of the disease. Our research findings indicate that the biochemical states of BTI patients mainly depend on disease severity and genetic backgrounds instead of patient age or gender. The genetic makeup of thalassemia along with disease profile severity tends to impact health outcomes more than demographic factors during the treatment process.

A cluster analysis technique revealed different patient clusters that exhibited distinct biochemical features between their samples. The study reveals a vital benefit of cluster analysis because this tool reveals hidden levels of thalassemia heterogeneity which traditional methods commonly miss. The research resulted in three different patient groups to show standardized management practices cannot successfully treat intermediate thalassemia. The different approaches to management diverge according to each patient cluster since individualized approaches are necessary. Patients with thalassemia need thorough chelation therapy due to their high iron amounts since unmanaged iron overload inflicts damage to organs. Personalized iron chelation therapy requires immediate attention according to research by Taher and Cappellini[18] to minimize health complications in patients with thalassemia. The second cluster showed having lower zinc levels presents a chance to evaluate zinc supplementation as a possible therapeutic strategy. Recovery from wounds and protein synthesis together with immune response depend on zinc but these biological functions may be impaired in thalassemia patients. Zinc supplementation shows potential for bettering immune response together with health outcomes in thalassemia patients according to Matter, Elbarbary.[19] The specific administration of zinc supplements to patients in this area shows promise for enhancing health benefits so additional clinical trials should design clear therapeutic protocols. Therefore, different individuals with intermediate thalassemia demonstrate diverse biochemical measurements that create complex metabolic conditions. The unique biochemical profiles of patients with intermediate thalassemia necessitate individualized treatment through medicine adjustments based on their specific biochemical requirements. The results of our analysis demonstrate that present-day thalassemia treatment requiring iron chelation and blood transfusions needs additional intervention strategies that target all metabolic abnormalities found in the disease. Despite the significant findings of this study, some limitations must be acknowledged. First, the cross-sectional design of the study limits the ability to conclude causal relationships between demographic factors and biochemical markers. Longitudinal studies would be needed to examine how these relationships evolve. In addition, while cluster analysis identified distinct patient subgroups, further investigation is required to explore the underlying genetic or environmental factors contributing to these differences. It would also be valuable to extend the study to include other trace elements or biomarkers, which could provide a more comprehensive understanding of the metabolic consequences of thalassemia.

The research findings demonstrate important information about intermediate thalassemia patient biochemistry while confirming the need for custom treatment methods. Understanding how gender influences zinc metabolism together with recognizing different patient clusters gives valuable information for medical care. Research findings point toward a need for customized intermediate thalassemia treatment which requires attending unique biochemical abnormalities of each patient. Future medical studies need to determine how specific mineral supplementation helps patients with thalassemia along with analyzing the prolonged results from these individualized treatment methods.

Conclusion

This study examined the biochemical characteristics of patients with intermediate thalassemia, revealing significant disease heterogeneity and gender-specific differences, particularly lower zinc levels in males. Multivariate regression and cluster analyses identified distinct biochemical patterns and patient subgroups, supporting the need for personalized, gender-sensitive treatment approaches. These insights suggest that individualized therapies tailored to each patient's metabolic profile can improve treatment outcomes and quality of life.

Future studies should include broader genotypic, phenotypic, and dietetics and treatment spectra to

prioritize the outlined biochemical variations among patients with thalassemia in the future. Longitudinal research would, however, be very helpful in tracing the development of the disease and the outcomes of personal treatment plans. In addition, further research must explore genetic and environmental aspects that form the basis for the patient subgroups that cluster analysis has identified. The research should consider additional biomarkers and trace elements for a better evaluation of thalassemia metabolic effects. Thus, a better understanding of common treatment modifiers and the expectation that individually targeted therapies will increase their effectiveness in the context of the specific characteristics of patient subpopulations may help improve the quality of life of those suffering from this difficult disease.

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Conflicts of interest
There are no conflicts of interest.

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