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ORIGINAL ARTICLE

Correlation between hepatomegaly and transfusion frequency in thalassemia patients: A cross-sectional study.

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ABSTRACT… Objective: To investigate the relationship between transfusion frequency, serum ferritin levels, and hepatomegaly in beta-thalassemia major patients. **Study Design:** Cross-sectional study. **Setting:** Thalassemia Center, Liaquat University Hospital, Hyderabad. **Period:** January 2023 to June 2023. **Material & Methods:** Among 158 patients, age until 19 years, and β-thalassemia type major was considered as inclusion criteria. Data regarding hematological parameters and hepatomegaly was collected after informed consent. Data was analyzed using SPSS (version 22). Chi-square test was used to investigate the association between ferritin levels and hepatomegaly while Pearson's correlation was used assess the correlation between ferritin levels and transfusion frequency. P-Value ≤ 0.05 was considered as statistically significant. **Results:** Majority of the participants were males (58.22%) as compared to females (41.77%). The mean age of the study participants was 9.31±4.47 years, and the mean age at first transfusion was 8.98±0.93 years. Majority of the participants were underweight 107(67.72%). Monthly transfusion rate was 1.95±0.31.The mean serum ferritin levels among the study participants were 2033.06±1309.36 ng/mL. Hepatomegaly was found to be present in 99 (62.65%) of the study participants. Statistically significant positive correlation between the frequency of transfusion and serum ferritin levels ($r = 0.71$, $p<0.05$) was observed. The difference of hepatomegaly in low-ferritin vs high-ferritin was also found to be statistically significant ($p<0.05$). **Conclusion:** It was concluded that higher transfusion rates were associated with elevated ferritin levels, and there was a significant association between higher serum ferritin levels and the presence of hepatomegaly.

Key words: Blood Transfusion, Hepatomegaly, Hemoglobinopathies, Iron Overload, Thalassemia.

INTRODUCTION

Thalassemia is a genetic blood disorder caused by the mutations in the genes responsible for the synthesis of α- or β-globin chains, resulting in a decreased level of hemoglobin and other alterations in the red blood cells.[1] Among the different thalassemia variants, β-thalassemia is more prevalent as only two chains of β-globin are present, each inherited by a parent, in contrast to α -globin, which has four chains, two from each parent.[2] Depending on the number of β-chains involved, β-thalassemia is divided into three types: Thalassemia Minor, Intermedia, and Major, which is the most severe of the three. It affects populations in the Mediterranean, African, and Asian region, where malaria is endemic most often.[3]

It is estimated that 270 million people worldwide are projected to be carriers of thalassemia with 80 million inheriting β-thalassemia alleles. Over 6,000-7,000 β-thalassemia babies are born in Pakistan, which is attributed to our society's high rate of consanguinity, resulting in the accumulation of damaging genes within a family.[5] Chronic blood transfusions are the only choice of treatment because β-thalassemia major manifests as severe anemia, usually after six months of age as the transition between HbF (α2 γ2) and HbA (Hbα2, Hbβ2) occurs.[6] Due to chronic transfusion, the iron stores of the body rapidly increase with each transfusion episode, for which iron chelating agents are usually prescribed to avoid secondary hemochromatosis, which leads to hepatosplenomegaly.[6]

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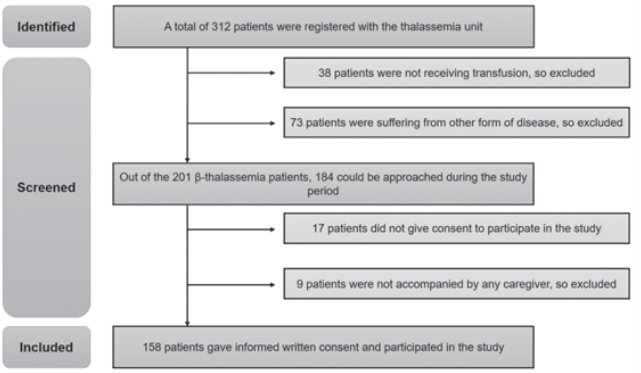
These increased iron levels in the liver, as reflected by a significant rise in serum ferritin, the major iron storage protein, which may disrupt many physiological processes occurring in the liver. This can trigger inflammation and oxidative stress damaging the hepatic architecture leading to hepatocellular injury and subsequent hepatomegaly.[7] Prolonged iron overload can also cause fibrosis and worsening of hepatomegaly. Additionally, some iron chelating therapies, although necessary, also cause hepatomegaly as a potential side effect.[8]

Thalassemia is a genetic disorder that requires lifelong management, and understanding the factors that contribute to disease progression and complications is crucial for optimizing patient care. This study aims to investigate the relationship between transfusion frequency, serum ferritin levels, and hepatomegaly, which are key aspects of thalassemia management.

MATERIAL & METHODS

This cross-sectional study was performed during the period of January 2023 to June 2023 among 158 β-thalassemia type major patients from different cities of Sindh, Pakistan. The study was approved by the ethical committee of Isra University, Hyderabad (IU/RR-10-IRC-23/N/2023/94). Data was collected from the thalassemia center of Liaquat university hospital, Hyderabad. Informed written consent was obtained from the patients who were of age or the parents/guardians of the patients who were underage while the study was conducted in accordance with the principles of the Declaration of Helsinki. The inclusion criteria was age up till 19 years and β-thalassemia major while patients older than 19 years or those having β-thalassemia minor or those having any other hemoglobinopathies were excluded from the study.

Demographic data regarding the diagnostic age, age at receiving first transfusion, family history of thalassemia, annual transfusion rate, serum ferritin levels, hepatomegaly, and splenomegaly were included in the study.



Statistical analysis was conducted on study variables via the assistance of Statistical Package for Social Sciences - SPSS (version 22). The mean and standard deviation values of different parameters were calculated. Pearson's correlation coefficient was calculated to determine the strength and direction of the linear relationship between the frequency of transfusion and ferritin levels. Chi-square test was used to investigate the association between ferritin levels and the presence of hepatomegaly. Significance value was evaluated at $p \leq .05$ with 95% confidence level.

RESULTS

Out of the 158 patients included in the study, 92 (58.22%) were males and 66 (41.77%) were females. The age of the participants ranged from 0 to 19 years while the mean age of the study participants was 9.31±4.47 years. The mean age of β-thalassemia diagnosis was 7.13±0.69 months. Majority of the patients, 107 (67.72%) were underweight while only 51 (32.27%) had a normal BMI. A total of 98 (62.02%) had a positive history of β-thalassemia among family members. The mean age of the patients at the time of receiving the first transfusion was 8.98±0.93 years. HCV positivity was found to be in 61 (38.60%) of the patients.

The rate of transfusions ranged from 12/year to 29/year with a Mean±SD of 23.42±3.80. This resulted in a monthly transfusion rate of 1.95±0.31. The average hemoglobin count prior to transfusion ranged from 5.2-12.3 g/dL.

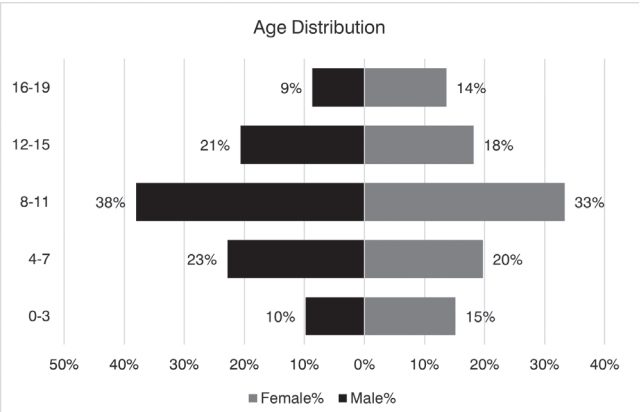


Figure-1. Gender-Based age distribution: Population pyramid of study participants

Variables	N (%)
Age group (in years)	
0-3	19 (12.02%)
4-7	34 (21.51%)
8-11	57 (36.07%)
12-15	31 (19.62%)
16-19	17 (10.75%)
Gender	
Male	92 (58.22%)
Female	66 (41.77%)
Residence	
Urban	61 (38.60%)
Rural	97 (61.39%)
BMI	
Normal	51 (32.27%)
Underweight	107 (67.72%)
Family history of Thalassemia	
Yes	98 (62.02%)
No	60 (37.97%)
Hepatomegaly	
Yes	99 (62.65%)
No	59 (37.34%)
Splenomegaly	
Yes	39 (24.68%)
No	119 (75.31%)8

Table-I. Demographic variables: Summary of study participants (n=158).

The mean serum ferritin levels among the study participants were 2033.06±1309.36 ng/mL (ranging from 395-6425 ng/mL). As shown in Figure-2, our analysis revealed a statistically significant positive correlation between the frequency of transfusion and serum ferritin levels ($r = 0.71$, $p<0.05$). This indicates a strong association between these two variables, suggesting that as the frequency of transfusion increases, serum ferritin levels also tend to rise. These findings suggest that the frequency of transfusion plays a significant role in influencing serum ferritin levels in our study population.

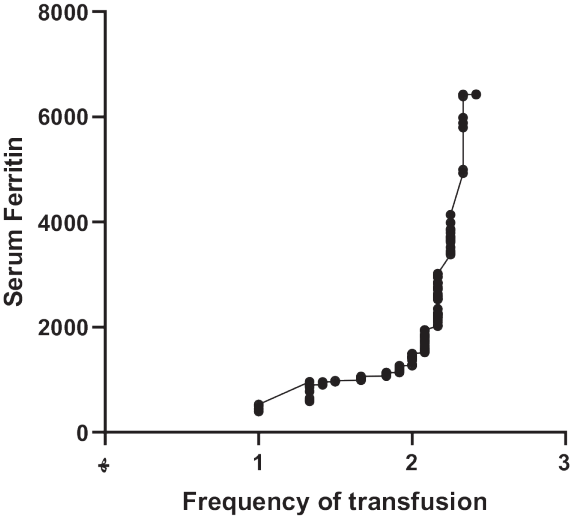


Figure-2. Correlation between frequency of transfusion and serum ferritin levels.

Hepatomegaly was found to be present in 99 (62.65%) of the study participants. Table-II. Shows the association between serum ferritin levels and the presence of hepatomegaly using chi-square analysis. In patients having serum ferritin levels less than 1500 ng/mL, the prevalence of hepatomegaly was found to be 53.94% while the prevalence of hepatomegaly was 70.73% in patients having serum ferritin levels greater than 1500 ng/mL. The difference among the groups was found to be statistically significant ($\chi^2 = 4.05$, $p = <.05$).

	Hepatomegaly		X^2	P-Value
Serum Ferritin	Present	Absent	4.05	.04*
<1500	41	35		
>1500	58	24		

Table-II. Comparison of hepatomegaly prevalence among low and high ferritin groups (n=158).
*** Statistically significant (p-value <0.05) using chi-square**

DISCUSSION

As mentioned above, thalassemia is a hereditary hematological disorder that causes a formation

defect in either the α- or β-globin chains, resulting in decreased levels of hemoglobin and various red cell alterations. Among the various kinds, β-thalassemia major is the most severe variant, typically affecting populations residing in areas with a high malaria incidence rate.[9] Thalassemia is a major healthcare burden, with a substantial global prevalence, especially in countries such as Pakistan, emphasizing the need of a better understanding of the factors that contribute to disease progression and complications in an attempt to optimize patient care.

In the current study, the distribution of thalassemia patients across different age groups revealed the highest frequency in the 8-11 age group (36.07%) and the lowest frequency in the 16-19 age group (10.75%). This age distribution suggests a broad representation of numerous age ranges within the study. In terms of gender distribution, the majority of the patients were males (58.22%) as compared with the female patients (41.77%). This gender disparity is supported by the findings reported by Gafer A et al.[10], Biswas et al.[11], and Abbas H et al.[12], who also reported a higher prevalence of thalassemia in males among their sample population. Additionally, Biswas et al.[11] and Abbas H et al.[12] also reported a higher prevalence of thalassemia among rural population as compared to urban, which is also consistent with the findings of the current study.
Regarding BMI, a significant portion of the patients (67.72%) were classified as underweight, which is consistent with the findings of Dey et al.[13] The pathogenesis of low BMI in thalassemia is multifactorial and can be attributed to nutritional deficiency, chronic anemia, tissue hypoxia, iron overload in different organs, and endocrinopathies leading to delayed puberty, hypogonadism and dysglycemia, as reported by Soliman et al.[14] However, given that a significant proportion of the study participants resided in economically disadvantaged areas, particularly in remote rural regions, the notable prevalence of malnutrition may be attributed not only to their illness but also to their limited financial resources hindering access to nutritious meals. While specific measurements of household-level food availability were not conducted, factors such as socioeconomic status and educational level could serve as proxy indicators in gauging their potential influence on nutritional status.

The mean transfusion rate in the current study was 1.95±0.31 per month. This is similar to the findings of Saeed et al.[15] who also reported that their study participants were receiving transfusion almost twice every month.

Mean serum ferritin levels in the current study were found to be 2033.06±1309.36 ng/mL. Additionally, there was a significant positive correlation observed between the serum ferritin levels and the frequency of transfusion. These results are consistent with the findings reported by Kouegnigan et al.[16] who also observed that the serum ferritin levels were positively correlated with the transfusion rate and contributed to iron overload among the patients. These results are also consistent with the findings reported by Bhalodiya et al.[17] who also observed a rise in serum ferritin levels with the increase in the transfusion rate.

Increased transfusions lead to iron overload and increased hepatic iron deposits, which in turn can trigger inflammation and oxidative stress, leading to hepatocellular injury and subsequent hepatomegaly, which in one of the most common complications of thalassemia. The prevalence of hepatomegaly in the current study was found to be 62.65%. Similar hepatomegaly rates among thalassemia patients of 67% and 72% have been reported by Ramsha et al.[18] and Umendra et al.[19] in their respective studies. We also found a correlation between increased mean serum ferritin levels and hepatomegaly in our study population. These results are also in consistence with the findings reported by Ramsha et al. and Umendra et al. who found that the incidence of hepatomegaly in thalassemia patients was linked with progressive iron overload as reflected by increasing serum ferritin levels.

There were some limitations of the current study. Firstly, this study focused on samples collected from a single thalassemia center, which leaves room for potential selection bias and may affect

the generalizability of the findings. Secondly, owing to the cross sectional nature of the study as well as time and monetary constraints, only a single sample of serum ferritin was evaluated which might not be an accurate indicator of iron overload. Therefore, further studies are recommended which should strive to include a larger and more diverse sample of thalassemia patients. Moreover, by using a prospective study design, it would be possible to gather data in real-time, lowering the risk of recall bias and ensuring more accurate and thorough data.

CONCLUSION

This study concluded that higher transfusion frequency was associated with increased serum ferritin levels, which, in turn, is positively correlated with Hepatomegaly. The findings underscore the importance of monitoring ferritin levels to identify liver complications and highlight the correlation between hepatomegaly and transfusion frequency. These results also contribute to optimizing thalassemia management.

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1	Adeel Rehman	Study design, Drafting of manuscript, Results write-up.	
2	Kumayl Abbas Meghji	Acquisition, analysis and interpretatin of data, drafting of manuscript, final approval of the version to be published.	
3	Haji Abdullah Memon	Drafting of manuscript and proof reading.	
4	Ahmed Mustafa Burney	Proof reading and review of references.	
5	Wasi Ur Rehman Siyal	Drafting of Manuscript and proof reading.	
6	Muhammad Jawad	Proof reading and review.	