Nephro-Urol Mon. 2023 August; 15(3):e136753. https://doi.org/10.5812/numonthly-136753.

Published online 2023 September 1. **Research Article**

Plasma CRP-hs and Ferritin Concentration Related to Kidney Injury in Adult Patients with Beta-Thalassemia: A Cross-Sectional Study in Vietnam

Loan Do Thi Thanh [1], Quyen Dao Bui Quy [2], Huong Pham Thu [3], Kien Nguyen Trung [4], Dung Nguyen Huu [5], Huong Nguyen Thu [6], Huong Nguyen Thi Mai [7], Ngoc Nguyen Thi [6], Ha Le Thu [8] and Thang Le Viet [9,*]

[1]Department of Internal Medicine, Hai Phong University of Medicine and Pharmacy, Hai Phong, Vietnam
[2]Department of Nephrology, Cho Ray Hospital, Ho Chi Minh, Vietnam
[3]Department of Clinical Hematology, Viet Tiep Friendship Hospital, Hai Phong, Vietnam
[4]Center of Hematology and Blood Transfusion, Military Hospital 103, Vietnam Military Medical University, Ha Noi, Vietnam
[5]Center of Hemodialysis, Bach Mai Hospital, Ha Noi, Vietnam
[6]Department of Nephrology and Dialysis, National Children's Hospital, Ha Noi, Vietnam
[7]Department of Clinical Hematology, National Children's Hospital, Ha Noi, Vietnam
[8]Department of Nephrology and Rheumatology, 108 Central Military Hospital, Ha Noi, Vietnam
[9]Department of Nephrology and Hemodialysis, Military Hospital 103, Vietnam Military Medical University, Ha Noi, Vietnam

[*]*Corresponding author*: Department of Nephrology and Hemodialysis, Military Hospital 103, Vietnam Military Medical University, Ha Noi, Vietnam. Email: lethangviet@yahoo.co.uk

Received 2023 April 15; **Revised** 2023 July 08; **Accepted** 2023 August 05.

Abstract

Background: Kidney injury (KI) is one of the complications of β-thalassemia patients.
Objectives: To determine the rate of KI and its relationship with plasma ferritin and CRP-hs in β-thalassemia patients.
Methods: A total of 142 patients diagnosed with β-thalassemia (58.5% minor, 17.6% intermedia, and 23.9% major) were included in our study. In all patients, we measured plasma ferritin, CRP-hs, urine albumin, and serum creatinine and calculated the urine albumin to creatinine ratio (uACR). Based on uACR, we divided the patients into 2 groups: with KI (n = 19, uACR $\geq$ 3.0 mg/mmol) and without KI (n = 123, uACR $<$ 0.3 mg/mmol).
Results: The ratio of KI in β-thalassemia patients was 13.4%. The median concentrations of plasma ferritin and CRP-hs in the KI group were significantly higher than in the non-KI group ($P < 0.001$). Plasma ferritin and CRP-hs were independent risk factors for KI ($P < 0.001$). At a cut-off value of 2.35 mg/L, plasma CRP-hs had a predictive value for KI (AUC = 0.841, $P < 0.001$). Similarly, plasma ferritin at the cut-off value of 2394.95 μg/L showed a predictive value for KI (AUC = 0.789, $P < 0.001$).
Conclusions: The rate of KI was low in adult patients with β-thalassemia. Plasma ferritin and CRP-hs had a good predictive value for KI in β-thalassemia patients.

Keywords: β-Thalassemia, Kidney Injury, Plasma Ferritin, CRP-hs

1. Background

Beta-thalassemia (β-thalassemia) is an inherited disorder of hemoglobin synthesis caused by β-globin gene mutations and a common condition in Southeast Asian countries, such as Vietnam (1). The clinical and hematologic spectrum of β-thalassemia includes major, intermedia, and minor forms, where the severe form is divided into two subtypes, blood transfusion-dependent and transfusion-independent (2-4). The leading cause of mortality in thalassemia patients is heart failure secondary due to chronic iron overload, and patients usually die in the first or second decade of life (5-7). However, with acquiring a better understanding of the disease and advances in blood transfusion practice and iron chelation, the prognosis of β-thalassemia has been markedly improved.

The improved survival of β-thalassemia patients has enabled us to detect previously uncommon complications, such as kidney injury (KI). Chronic anemia, hypoxia, and iron overload are the main mechanisms of KI

in β-thalassemia. In addition, undesirable effects of iron chelators may contribute to KI in β-thalassemia patients (8-11). In patients with β-thalassemia, serum ferritin levels >1000 μg/L indicate iron overload and are associated with increased mortality, higher risk of cardiac events, hepatic complications, and renal complications (12, 13). Chronic low-grade systemic inflammation is a condition characterized by persistently elevated circulating inflammatory markers such as C-reactive protein (CRP) and is seen in coronary artery disease (14), renal disease (15, 16), and β-thalassemia (17).

2. Objectives

In order to better understand the mechanisms of KI in patients with β-thalassemia, we investigated if elevated plasma ferritin and CRP-hs levels could be related to KI in adults with β-thalassemia.

3. Methods

3.1. Patients

We included all 217 adults with β-thalassemia, including patients with major, intermedia, and minor clinical presentations, who were admitted and treated at Viet Tiep Friendship Hospital, Hai Phong, Vietnam, from January 2020 to December 2022. We excluded < 16-year-old patients, those with underlying kidney disease unrelated to β-thalassemia, patients suffering from acute inflammation (pneumonia, acute viral infections, etc.), and pregnant or lactating women. We provided written informed consent to all 142 remaining patients before their participation in the study.

All clinical and laboratory indices at the baseline time were collected. Based on interviews and follow-up records, the time of β-thalassemia detection, family history, blood transfusion status, and iron chelation drugs were documented. Comorbidities such as hypertension and diabetes were also collected.

We also withdrew peripheral blood samples to determine the serum concentrations of glucose, urea, creatinine, cholesterol, triglyceride, HDL-C, LDL-C, ALT, AST, electrolytes, iron, ferritin, transferrin, and CRP-hs. A complete blood count was also performed to determine the status and severity of anemia.

Urinary albumin was also determined for each patient, and then the urine albumin to creatinine ratio (uACR) was calculated. The glomerular filtration rate (eGFR) was calculated for all patients based on the Epi-CKD formula. Kidney injury was established when ACR was $\geq$ 3.0 mg/mmol based on KDIGO clinical practice guidelines (18).

We divie all 142 patients into two groups: group 1 (n = 19): KI patients with uACR $\geq$ 3.0 mg/mmol and group 2 (n = 123): Non-KI patients with uACR < 3.0 mg/mmol.

3.2. Statistical Analyses

We presented all continuous data by mean and standard deviation (for normally distributed data) or median and interquartile range (for non-normally distributed data). Two continuous variables were compared between the study groups using either the student *t*-test or the Mann-Whitney U test. For more than two groups, variables were compared using the ANOVA or Kruskal-Wallis test. We presented categorical data by frequency and percentage and compared them between the study groups using the chi-square test. Multivariable-adjusted regression analysis was used to identify independent factors related to KI. Receiver operating characteristic (ROC) curve models were performed to identify the predictors of KI. The data were analyzed by Statistical Package for Social Science (SPSS) version 20.0 software (Chicago, IL, USA). A P-value < 0.05 was considered statistically significant.

4. Results

The results (Table 1) showed that the ratios of transfusion-dependent patients, β-thalassemia major, increased ALT, and increased AST were significantly higher in the KI group than in the non-KI group (P < 0.05). The median values of serum iron, ferritin, CRP-hs, urine albumin, and uACR were also significantly higher in patients with KI than in those without KI (P < 0.01). Moreover, blood hemoglobin and urine creatinine concentrations were significantly lower in the KI group than in the non-KI group (P < 0.01).

As shown in Table 2, elevated plasma ferritin, increased CRP-hs, low hemoglobin, and less using iron chelating agents were independent factors associated with KI in adults with β-thalassemia.

Based on the ROC curve (Figure 1), plasma CRP-hs, ferritin, and hemoglobin had good predictive values for KI in adults with β-thalassemia (P < 0.001).

5. Discussion

5.1. Ratio of KI in Adults with β-thalassemia

Based on urine ACR and according to KDIGO 2012 classification, 19 out of 142 (13.4%) patients had KI (Table 1). Studies on renal function (glomerulus and tubulous) and

Table 2. Multivariate Logistic Regression Analysis of Some Variables Related to KI in Adults with β-thalassemia

Variables	OR	95% CI	P-Value
Hemoglobin (g/L)	0.944	0.893 - 0.998	0.044
Ferritin (μg/L)	1.001	1.000 - 1.001	0.002
CRP-hs (mg/L)	3.301	1.945 - 5.602	< 0.001
Albumin (g/L)	1.165	1.009 - 1.346	0.037
Using iron chelating agents	0.137	0.025 - 0.766	0.024

Abbreviations: KI, kidney injury; CRP-hs, C reactive protein-high sensitive.

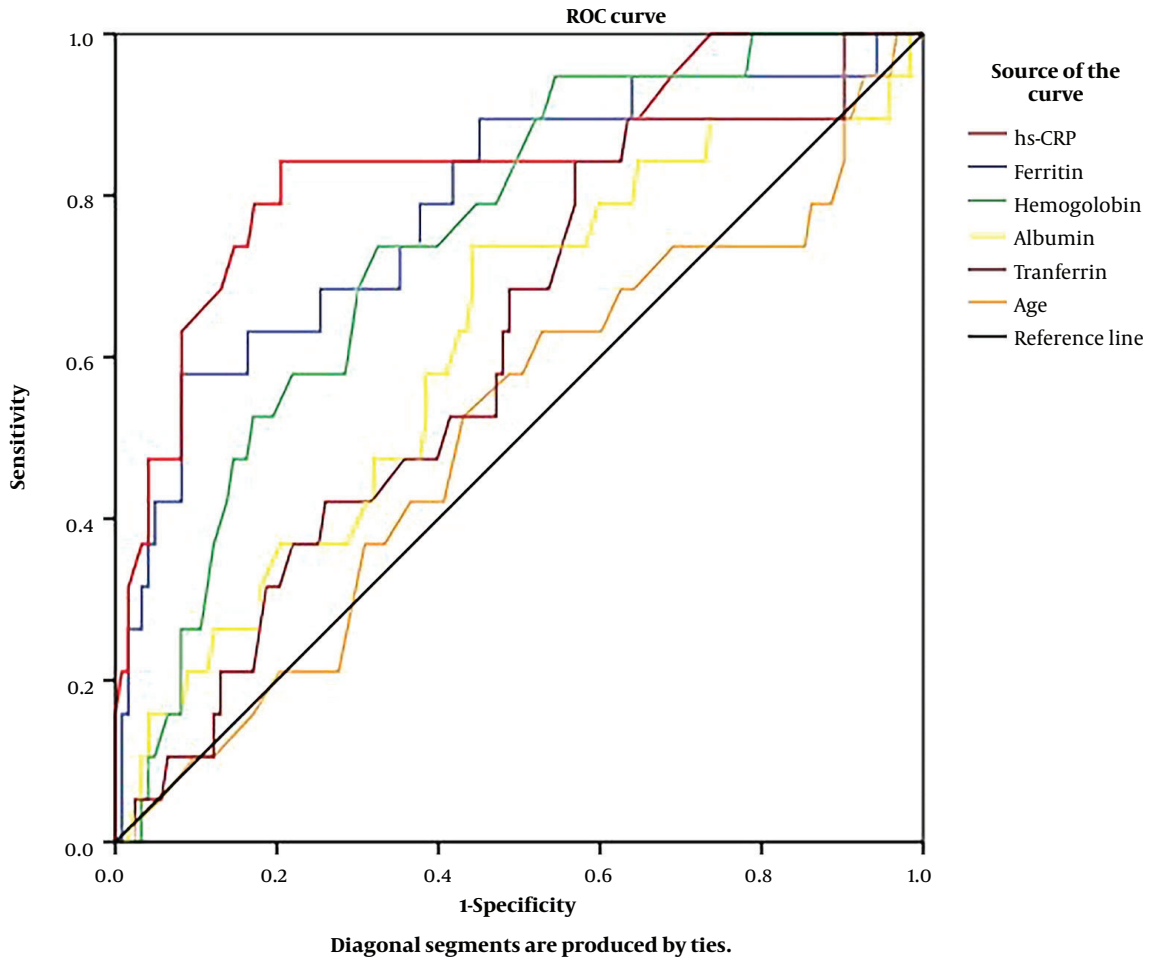

Figure 1. Receiver-operating characteristic curves of age, plasma albumin, hemoglobin, ferritin, transferrin, and CRP-hs for predicting KI in adults with β-thalassemia. (CRP-hs: AUC = 0.841; P < 0.001; cut-off value = 2.35 mg/L; sensitivity = 84.2%; specificity = 79.5%, ferritin: AUC = 0.789; P < 0.001; cut-off value = 2394.95 μg/L; sensitivity = 57.9%; specificity = 91.9%, hemoglobin: AUC = 0.747; P = 0.001; cut-off value = 76.5 g/L; sensitivity = 73.7%; specificity = 67.5%, albumin: AUC = 0.619; P > 0.05, transferrin: AUC = 0.608; P > 0.05, age: AUC = 0.511; P > 0.05).

KI in β-thalassemia patients are scarce. Plasma creatinine is a reliable indicator to assess GFR in patients, and cystatin C, which is not excreted or reabsorbed into the bloodstream by renal tubules, is a sensitive biomarker for GFR. All cells in the body continuously produce cystatin C and cystatin C production is not affected by age, gender, or muscle mass (19, 20). Therefore, many researchers use cystatin C as an early and reliable marker of glomerular filtration dysfunction (21, 22). In addition, urinary β2 microglobulin, which is freely filtered by the glomerulus, reabsorbed by renal tubules, and then eliminated, is also recommended for assessing early renal dysfunction in β-thalassemia patients (23, 24).

Regarding renal tubular function, other classic indicators that can be used as early predictors of renal tubular damage in β-thalassemia patients include the fraction excretion of sodium, potassium, calcium, urine NGAL, and KIM-1 (25, 26). Also, uACR is a valuable indirect indicator of glomerular injury (albumin) and glomerular filtration function (creatinine). This is an easy-to-follow biomarker that has been widely applied in clinical practice. Many authors have also used this index to evaluate KI in β-thalassemia patients (25, 26). An interesting point observed in our study was that although 13.4% of the patients were found to have KI, only 1/142 patients (0.7%) had renal dysfunction (MLCT < 60 mL/min) based on the glomerular filtration rate (Table 1). Based on these results, we recommend clinicians consider uACR during each patient visit to detect renal complications in β-thalassemia patients.

5.2. Link of Plasma CRP-hs and Ferritin with KI in Adults with β-thalassemia.

Renal complications in β-thalassemia patients are infrequent. We found that only 13.4% of the patients in this study had KI (Table 1). However, the patient's prognosis will not be good when this complication occurs. We divided patients into 2 groups (i.e., KI and non-KI) and identified modifiable risk factors that can be regarded during the treatment process to reduce the rate of this complication. Although there were many univariate indicators related to renal complications (Table 1), multivariate analysis revealed only 2 independent indicators of KI; plasma ferritin (P = 0.002) and CRP-hs (P < 0.001) (Table 2). According to ROC analysis, the results showed that plasma ferritin and CRP-hs were valuable predictors of renal complications in β-thalassemia patients with AUCs of 0.789 and 0.841, respectively (P < 0.001, Figure 1). These findings suggest that we can rely on plasma ferritin and CRP-hs levels to predict renal complications in adults with β-thalassemia.

Plasma ferritin levels in β-thalassemia patients reflect iron overload (ferritin levels > 1000 μg/L) (12, 13). Iron homeostasis is a complicated process, and daily absorption and excretion are maintained at approximately 2 mg/day. Because humans cannot actively excrete iron, excess iron from blood transfusions will be accumulated in body tissues. In β-thalassemia patients, among important factors associated with KI have been noted to be anemia, iron overload, and using iron chelators (27, 28). Here, we identified that elevated levels of CRP-hs, an indicator of subclinical inflammation, were closely related to renal complications in adults with β-thalassemia (Table 1, and 2, Figure 1). Elevated plasma levels of CRP-hs often result from subclinical inflammatory processes, including endothelial injury and deposition of immune complexes in renal parenchyma (29, 30). Our results suggested that plasma hs-CRP was involved in the pathogenesis of KI in β-thalassemia patients. Chronic anemia/hypoxia leads to endothelial and epithelial damage, tubulointerstitial injury, glomerulosclerosis due to iron overload, tubuloglomerular feedback, and hemodynamic changes due to iron chelation (8, 10). The final consequences of chronic anemia, iron overload, and iron chelator toxicity will be damage to glomeruli and renal tubulointerstitium (10).

Although our results met our research objectives, this study had some limitations. First, we did not use these new biomarkers to assess glomerular and tubular dysfunction. Second, we did not analyze the relationship of KI with disease severity and the use of iron-chelating drugs.

5.3. Conclusions

The rate of KI in adults with β-thalassemia was 13.4%. Plasma ferritin and CRP-hs had good predictive values for KI in β-thalassemia patients.

Acknowledgments

We were strongly supported by officials in our hospital and university to conduct this research.

Footnotes

Authors' Contribution: Study concept and design: D. T. T. L., D. B. Q. Q., and L. V. T. Acquisition of data: D. T. T. L., P. T. H., N. T. H, and N. T. M. H. Analysis and interpretation of data: N. T. K. and N. T. N. Drafting of the manuscript: D. T. T. L. and D. B. Q. Q. Critical revision of the manuscript for important intellectual content: N. H. D. and L. V. T. Statistical analysis: N. T. K. and N. T. N. Administrative, technical, and material

support: P. T. H. and N. T. N. Study supervision: N. H. D., L. T. H., and L. V. T.

Conflict of Interests: The authors declare no financial or otherwise conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: This study was approved by the Ethical Committee of Vietnam Military Medical University (No.1232/Q-HVQY).

Funding/Support: We did not receive any funds to conduct this study.

Informed Consent: Informed consent was obtained from all the participants.

References

1. Fucharoen S, Winichagoon P. Haemoglobinopathies in southeast Asia. *Indian J Med Res*. 2011;**134**(4):498.
2. Origa R. beta-Thalassemia. *Genet Med(Official J American College Medical Genetics Gene Reviews)*. 2017;**19**(6):609–19. [PubMed ID: 27811859]. https://doi.org/10.1038/gim.2016.173.
3. Cao A, Galanello R. Beta-thalassemia. *Genet Med*. 2010;**12**(2):61–76. [PubMed ID: 20098328]. https://doi.org/10.1097/GIM.0b013e3181cd68ed.
4. Taher A, Vichinsky E, Musallam K, Cappellini MD, Viprakasit V, Weatherall D. Introduction and blood. In: Weatherall D, editor. *Guidelines for the Management of Non Transfusion Dependent Thalassaemia (NTDT)[Internet]*. Thalassaemia International Federation; 2013.
5. Borgna-Pignatti C, Cappellini MD, De Stefano P, Del Vecchio GC, Forni GL, Gamberini MR, et al. Survival and complications in thalassemia. *Ann N Y Acad Sci*. 2005;**1054**:40–7. [PubMed ID: 16339650]. https://doi.org/10.1196/annals.1345.006.
6. Makmettakul S, Tantiworawit A, Phrommintikul A, Piriyakhuntorn P, Rattanathammethee T, Hantrakool S, et al. Cardiorenal syndrome in thalassemia patients. *BMC Nephrol*. 2020;**21**(1):325. [PubMed ID: 32746879]. [PubMed Central ID: PMC7398251]. https://doi.org/10.1186/s12882-020-01990-8.
7. Malagu M, Marchini F, Fiorio A, Sirugo P, Clo S, Mari E, et al. Atrial Fibrillation in beta-Thalassemia: Overview of Mechanism, Significance and Clinical Management. *Biology (Basel)*. 2022;**11**(1). [PubMed ID: 35053146]. [PubMed Central ID: PMC8772694]. https://doi.org/10.3390/biology11010148.
8. Demosthenous C, Vlachaki E, Apostolou C, Eleftheriou P, Kotsiafti A, Vetsiou E, et al. Beta-thalassemia: renal complications and mechanisms: A narrative review. *Hematology*. 2019;**24**(1):426–38. [PubMed ID: 30947625]. https://doi.org/10.1080/16078454.2019.1599096.
9. Borgna-Pignatti C, Gamberini MR. Complications of thalassemia major and their treatment. *Expert Rev Hematol*. 2011;**4**(3):353–66. [PubMed ID: 21668399]. https://doi.org/10.1586/ehm.11.29.
10. Musallam KM, Taher AT. Mechanisms of renal disease in beta-thalassemia. *J Am Soc Nephrol*. 2012;**23**(8):1299–302. [PubMed ID: 22677552]. https://doi.org/10.1681/ASN.2011111070.
11. Behairy OG, Abd Almonaem ER, Abed NT, Abdel Haiea OM, Zakaria RM, AbdEllaty RI, et al. Role of serum cystatin-C and beta-2 microglobulin as early markers of renal dysfunction in children with beta thalassemia major. *Int J Nephrol Renovasc Dis*. 2017;**10**:261–8. [PubMed ID: 28979155]. [PubMed Central ID: PMC5602444]. https://doi.org/10.2147/IJNRD.S142824.
12. Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. *Blood Rev*. 2009;**23**(3):95–104. [PubMed ID: 18835072]. [PubMed Central ID: PMC2717717]. https://doi.org/10.1016/j.blre.2008.08.001.
13. Hahalis G, Kourakli A, Gerasimidou I, Kalogeropoulos AP, Sitafidis G, Papageorgiou U, et al. Cardiac mortality in beta-thalassemia major: resting but not dobutamine stress echocardiography predicts mortality among initially cardiac disease-free patients in a prospective 12-year study. *Eur J Heart Fail*. 2009;**11**(12):1178–81. [PubMed ID: 19889689]. https://doi.org/10.1093/eurjhf/hfp152.
14. Dregan A, Charlton J, Chowienczyk P, Gulliford MC. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: A population-based cohort study. *Circulation*. 2014;**130**(10):837–44. [PubMed ID: 24970784]. https://doi.org/10.1161/CIRCULATIONAHA.114.009990.
15. Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, et al. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *J Immunol Res*. 2018;**2018**:2180373. [PubMed ID: 30271792]. [PubMed Central ID: PMC6146775]. https://doi.org/10.1155/2018/2180373.
16. Greenberg JH, Abraham AG, Xu Y, Schelling JR, Feldman HI, Sabbisetti VS, et al. Plasma biomarkers of tubular injury and inflammation Are Associated with CKD progression in children. *J Am Soc Nephrol*. 2020;**31**(5):1067–77. [PubMed ID: 32234829]. [PubMed Central ID: PMC7217410]. https://doi.org/10.1681/ASN.2019070723.
17. Sanchez-Villalobos M, Blanquer M, Moraleda JM, Salido EJ, Perez-Oliva AB. New insights into pathophysiology of beta-thalassemia. *Front Med (Lausanne)*. 2022;**9**:880752. [PubMed ID: 35492364]. [PubMed Central ID: PMC9041707]. https://doi.org/10.3389/fmed.2022.880752.
18. Eknoyan G, Lameire N, Eckardt K, Kasiske B, Wheeler D; Improving Global Outcomes (KDIGO) CKD Work Group. [KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease]. *Kidney int*. 2013;**3**(1):5–14. Russia.
19. Willey JZ, Moon YP, Husain SA, Elkind MSV, Sacco RL, Wolf M, et al. Creatinine versus cystatin C for renal function-based mortality prediction in an elderly cohort: The Northern Manhattan Study. *PLoS One*. 2020;**15**(1). e0226509. [PubMed ID: 31940363]. [PubMed Central ID: PMC6961921]. https://doi.org/10.1371/journal.pone.0226509.
20. Benoit SW, Ciccia EA, Devarajan P. Cystatin C as a biomarker of chronic kidney disease: Latest developments. *Expert Rev Mol Diagn*. 2020;**20**(10):1019–26. [PubMed ID: 32450046]. [PubMed Central ID: PMC7657956]. https://doi.org/10.1080/14737159.2020.1768849.
21. Tantawy AA, El Bablawy N, Adly AA, Ebeid FS. Early predictors of renal dysfunction in egyptian patients with beta-thalassemia major and intermedia. *Mediterr J Hematol Infect Dis*. 2014;**6**(1). e2014057. [PubMed ID: 25237470]. [PubMed Central ID: PMC4165495]. https://doi.org/10.4084/MJHID.2014.057.
22. Arman Bilir O, Kirkiz S, Fettah A, Ok Bozkaya I, Kara A, Cakar N, et al. Renal function and the oxidative status among children with thalassemia major and healthy controls: A cross-sectional study. *Transfus Apher Sci*. 2020;**59**(4):102746. [PubMed ID: 32173278]. https://doi.org/10.1016/j.transci.2020.102746.
23. Kaçar AG, Şilfeler İ, Kacar A, Pekun F, Türkkan E, Adal E. Levels of beta-2 microglobulin and cystatin C in beta thalassemia major patients. *J Clin Analyt Med*. 2015;**6**:269–73.
24. Cetinkaya PU, Azik FM, Karakus V, Huddam B, Yilmaz N. beta2-microglobulin, neutrophil gelatinase-associated lipocalin, and endocan values in evaluating renal functions in patients with beta-thalassemia major. *Hemoglobin*. 2020;**44**(3):147–52. [PubMed ID: 32441176]. https://doi.org/10.1080/03630269.2020.1766486.
25. Sadeghi MV, Mirghorbani M, Akbari R. beta-Thalassemia minor & renal tubular dysfunction: Is there any association? *BMC Nephrol*. 2021;**22**(1):404. [PubMed ID: 34872508]. [PubMed Central ID: PMC8650370]. https://doi.org/10.1186/s12882-021-02602-9.

26. Romadhon PZ, Ashariati A, Bintoro SUY, Thaha M, Suryantoro SD, Windradi C, et al. Markers of renal complications in beta thalassemia patients with iron overload receiving chelation agent therapy: A systematic review. *J Blood Med*. 2022;**13**:725–38. [PubMed ID: 36467279]. [PubMed Central ID: PMC9717586]. https://doi.org/10.2147/JBM.S387416.
27. Pinto VM, Forni GL. Management of iron overload in beta-thalassemia patients: Clinical practice update based on case series. *Int J Mol Sci*. 2020;**21**(22). [PubMed ID: 33233561]. [PubMed Central ID: PMC7699680]. https://doi.org/10.3390/ijms21228771.
28. Lee YC, Yen CT, Lee YL, Chen RJ. Thalassemia intermedia: Chelator or not? *Int J Mol Sci*. 2022;**23**(17). [PubMed ID: 36077584]. [PubMed Central ID: PMC9456380]. https://doi.org/10.3390/ijms231710189.
29. Adam CA, Salaru DL, Prisacariu C, Marcu DTM, Sascau RA, Statescu C. Novel biomarkers of atherosclerotic vascular disease-latest insights in the research field. *Int J Mol Sci*. 2022;**23**(9). [PubMed ID: 35563387]. [PubMed Central ID: PMC9103799]. https://doi.org/10.3390/ijms23094998.
30. Lousa I, Reis F, Beirao I, Alves R, Belo L, Santos-Silva A. New potential biomarkers for chronic kidney disease management-a review of the literature. *Int J Mol Sci*. 2020;**22**(1). [PubMed ID: 33375198]. [PubMed Central ID: PMC7793089]. https://doi.org/10.3390/ijms22010043.

Table 1. Baseline Demographic and Laboratory Indices of Participants [a]

Clinical and Laboratory Indices	Total (N = 142)	KI (N = 19)	Non-KI (N = 123)	P-Value
Age (years)	30.5 (24 - 41)	29 (25 - 56)	31 (24 - 41)	0.881
Number of males	40 (28.2)	5 (26.3)	35 (28.5)	0.847
Disease detection time				0.081
First time	59 (41.5)	4 (21.1)	55 (44.7)	
1 to < 5 (y)	18 (12.7)	1 (5.3)	17 (13.8)	
5 to < 10 (y)	24 (16.9)	4 (21.1)	20 (16.3)	
10 to < 15 (y)	15 (10.6)	4 (21.1)	11 (8.9)	
≥ 15 (y)	26 (18.3)	6 (31.6)	20 (16.3)	
Use of iron chelators				0.134
Yes	46 (32.4)	9 (47.4)	37 (30.1)	
No	96 (67.6)	10 (52.6)	86 (69.9)	
Blood transfusion				0.011
No	66 (46.5)	4 (21.1)	62 (50.4)	
NTD	53 (37.3)	8 (42.1)	45 (36.6)	
TD	23 (16.2)	7 (36.8)	16 (13)	
Family history				
Yes	11 (7.7)	1 (5.3)	10 (8.1)	1.000
No	131 (92.3)	18 (94.7)	113 (91.9)	
Severity of disease				0.029
Minor	83 (58.5)	6 (31.6)	77 (62.6)	
Intermedia	25 (17.6)	5 (26.3)	20 (16.3)	
Major	34 (23.9)	8 (42.1)	26 (21.1)	
BMI				0.375
< 18.5	42 (29.6)	8 (42.1)	34 (27.6)	
18.5 to 22.9	95 (66.9)	11 (57.9)	84 (68.3)	
≥ 23.0	5 (3.5)	0 (0)	5 (4.1)	
Mean	19.57 ± 2.01	18.91 ± 1.63	19.68 ± 2.05	0.124
Hypertension				0.246
Yes	17 (12)	4 (21.1)	13 (10.6)	
No	125 (88)	15 (78.9)	110 (89.4)	
Diabetic mellitus				1.000
Yes	15 (10.6)	2 (10.5)	13 (10.6)	
No	127 (89.4)	17 (89.5)	110 (89.4)	
Glucose (mmol/L)				
≥ 7.0	12 (8.5)	2 (10.5)	10 (8.2)	0.665
Median	5 (4.4 - 5.8)	5.25 (4.63 - 5.89)	5 (4.36 - 5.8)	0.452
Plasma protein (g/L)	72.19 ± 7.21	77.04 ± 8.99	71.44 ± 6.62	0.001
Plasma albumin (g/L)	40.08 ± 5.03	41.59 ± 5.42	39.85 ± 4.95	0.162
ALT (UI/L)				

> 40.0	42 (29.6)	10 (52.6)	32 (26)	0.018
Median	23 (14.42 - 47.32)	47 (26 - 85.2)	21.4 (14 - 43)	< 0.001
AST (UI/L)				
> 40.0	44 (31)	12 (63.2)	32 (26)	0.001
Median	31 (22.07 - 50)	58.7 (34.6 - 98.4)	28.5 (21.4 - 43.4)	< 0.001
Na+ (mmol/L)	135.97 ± 3.79	135.7 ± 2.33	136.01 ± 3.97	0.639
K+ (mmol/L)	3.74 ± 0.30	3.85 ± 0.39	3.72 ± 0.28	0.07
Anemia	141 (99.3)	19 (100)	122 (99.2)	1.000
Hemoglobin (g/L)	79.88 ± 16.03	69.15 ± 10.95	81.53 ± 16.09	0.002
Hematocrit (L/L)	0.26 ± 0.04	0.23 ± 0.04	0.26 ± 0.04	0.003
Urea (mmol/L)	4.43 (3.6 - 5.45)	4.5 (3.87 - 6.22)	4.4 (3.55 - 5.34)	0.221
Creatinine (μmol/L)	53.4 (46.2 - 63.75)	53.6 (42.1 - 58.3)	53.4 (46.3 - 64.1)	0.590
eGFR				
< 60 mL/min	1 (0.7)	0 (0)	1 (0.8)	1.000
Mean	120.32 ± 20.28	122.26 ± 22.44	120.02 ± 20.0	0.656
Iron (μmol/L)	22.25 (14.05 - 33.85)	28.1 (24.9 - 41.6)	20 (12.7 - 32.1)	0.002
Ferritin (μg/L)	534.25 (174.74 - 1541.5)	2468 (741.7 - 5125)	400.27 (138.9 - 1392.7)	< 0.001
Transferrin (G/L)	1.88 ± 0.63	1.69 ± 0.49	1.91 ± 0.64	0.167
CRP-hs (mg/L)	1.2 (0.6 - 2.6)	3.5 (2.6 - 4.9)	1.1 (0.5 - 2.1)	< 0.001
Urine Protein (g/24hs)	0.07 (0.05 - 0.17)	0.23 (0.07 - 0.56)	0.07 (0.04 - 0.12)	0.001
Urine albumin (mg/L)	6.44 (4.26 - 10.92)	24.52 (15.5 - 54.23)	5.56 (3.94 - 8.43)	< 0.001
Urine creatinine (mmol/L)	7.21 (4.45 - 10.04)	5.23 (3.73 - 6.58)	7.68 (4.73 - 10.65)	0.01
uACR (mg/mmol)	0.81 (0.52 - 1.6)	4.78 (3.84 - 8.79)	0.71 (0.5 - 1.16)	< 0.001
KI	19 (13.4)	-	-	-

Abbreviations: NTD, non-transfusion-dependent; TD, Transfusion-dependent; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; CRP-hs, C reactive protein-high sensitive; uACR, urine albumin creatinine ratio; KI, kidney injury.
[a] Values are presented as No. (%).