Clin. Lab. 2023;69:XXX-XXX

REVIEW ARTICLE

Correlation of Serum Ferritin Level with Heart T2 MRI in Transfusion Dependent Thalassemia: a Systematic Review and Meta-Analysis

Mahnaz Hosseini-Bensenjan [1], Sezaneh Haghpanah [1], Mehrab Sayadi [2], Mohammad Eghtedari [3]

[1] *Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[2] *Cardiovascular Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[3] *Breast Imaging Division, The University of California San Diego Health, La Jolla, California, USA*

SUMMARY

Background: **Cardiac complications in patients with transfusion-dependent thalassemia (TDT) are one of the major causes of mortality in these patients which annually impose economic burden on the endemic countries. Heart T2 MRI is a good modality for evaluating iron overload. Our aim was to investigate the pooled correlation between the serum ferritin level and heart iron overload in TDT patients and compare the effect size in different geographical areas.**
Methods: **PRISMA checklist was used to summarize the literature search. Three major databases were used for the papers and exported into endnote for screening. Data were extracted into an Excel spreadsheet. The data were analyzed using STATA software. CC was considered as the effect size, and the amount of heterogeneity was indicated by I-squared. Meta-regression was used for age. Also, sensitivity analysis was performed.**
Results: **The present study showed a statistically significant negative correlation of the serum ferritin level with heart T2 MRI: -0.30 (95% CI -0.34, -25). This correlation was not significantly affected by the patients' age (p-value: 0.874). Given different geographic area, most of the studies from different countries indicated that the correlation between the serum ferritin and heart T2 MRI was statistically significant.**
Conclusions: **The pooled analysis showed a significant negative moderate correlation between the serum ferritin level and heart T2 MRI in patients with TDT, regardless of their age. This issue underscores the importance of periodical evaluation of serum ferritin level in patients with TDT in developing countries with low financial supports and limited resources. Further studies are suggested to evaluate the pooled correlation of the serum ferritin level with iron concentration of other vital organs.**
(Clin. Lab. 2023;69:xx-xx. DOI: 10.7754/Clin.Lab.2022.220916)

Correspondence:
Mohammad Eghtedari, MD, PhD
University of California San Diego Health
Department of Radiology
9400 Campus Point Drive #7316
La Jolla, CA, 92093
USA
Phone: + 1 858-245-1719
Fax: + 1 858-249-3070
Email: meghtedari@health.ucsd.edu

Review Article accepted October 20, 2022

KEYWORDS

correlation, ferritin, heart T2 MRI, transfusion dependent thalassemia

INTRODUCTION

Beta-thalassemias are a group of hereditary autosomal recessive disorders which occur through mutation of beta globin genes [1]. Ineffective erythropoiesis in thalassemia patients leads to their need for blood products, especially in transfusion-dependent thalassemia (TDT) [2]. Regular blood transfusion causes iron overload and

excess iron deposition in vital organs including the heart, liver, and endocrine glands [3].
Cardiac complications in TDT patients are one of the major causes of mortality in these patients, which annually imposes economic burden on the endemic countries [4]. Measuring the heart iron overload can be an effective tool for early detection and prevention of further complications [5]. Heart T2 MRI is a confirmed method for evaluating the heart iron overload, but the cost, availability, and frequency of its follow-up, especially in developing countries in the thalassemia belt, may be problematic [6-8]. Hence, available and cost-effective methods for assessing iron overload in TDT patients can be helpful in countries with low financial resources. Association of serum ferritin level as a biomarker of the heart iron overload has been evaluated in several studies with controversial results [9-11]. However, there was no meta-analysis to calculate the pooled correlation between the serum ferritin level and cardiac iron overload. This study aimed to investigate the pooled correlation between the serum ferritin level and heart T2 MRI in TDT patients, considering the effect of age and different geographical areas.

MATERIALS AND METHODS

This systematic review and meta-analysis was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [12]. The review was registered at International Prospective Register of Systematic Reviews (PROSPERO) with the registration number: CRD42022348619.

Search strategy

Searched databases: An electronic search was done in databases including Web of Science (ISI), Scopus, and Medline via PubMed, for papers from the inception to 24th of January 2022. A combination of the following medical subject headings (MeSH), terms, and keywords was used to conduct comprehensive literature searches (Thalassemia*" OR "Beta-thalassemia*" OR "beta thalassemia major*" OR "Transfusion dependent thalassemia*") AND ("Iron overload*" "Serum ferritin*" OR "Iron deposition*" OR "Hepcidin" OR "Sidoresis*" OR "Iron Concentration*") AND ("MRI" OR "Magnetic resonance imaging*" OR "T2 Magnetic Resonance Imaging*" OR "T2 MRI") AND ("Heart*" OR "Myocardial*" OR "Iron cardiomyopathy*" OR "Cardiac*" OR "Myocardium*) (Supplementary 1). Moreover, a manual review of the reference lists of the relevant articles and previously performed reviews was conducted for additional pertinent studies.
Inclusion and exclusion criteria: Two authors (MH-B and SH) independently screened the papers by endnote software, version 9. The inclusion criteria included the human observational studies which reported the correlation between the serum ferritin level and heart T2 MRI in patients with TDT and those in the English language. Studies such as case reports, review studies, and those without complete data for calculating the correlation were excluded. Also, population of non-TDT patients and also studies using a multiple linear regression model for reporting the correlation were excluded. The data shown in graphs were not reported, and only correlations reported in articles were used.

Data extraction

Two authors (SH and MH-B) independently extracted the required data from the included papers using the sheet form of Excel. Any controversy between the data extractors was resolved by the third author. The following data were extracted: name of the first author, publiccation year, number of patients, percentage of male patients, the patients' mean age, mean serum ferritin level, percentage of patients with splenectomy, and Correlation Coefficient (CC).

Study quality assessment

Two independent authors assessed the quality of the included studies based on the Newcastle Ottawa Scale (NOS) checklist (Supplementary Table 1). This scale encompasses three items of selection, comparability, and outcome [13]. If there was any disagreement between the assessors, it was resolved by the third author.

Statistical analysis

Meta-analysis was run via STATA 13 (College Station, TX, USA). CC was considered as the effect size. The amount of heterogeneity of the studies was indicated by I-squared [14]. The random effects model was used where heterogeneity was significant (p-value less than 0.05). Also, the forest plot was provided for each study and pooled data publication bias was assessed by Egger's test [15]. The p value extracted from this test was compared with 0.05 significance level. Also, 95% confidence interval was provided for bias value. In addition, sensitivity analysis was done. Weighted Least Square (WLS) linear regression model was used for age meta-regression on CC as the effect size. Moreover, subgroup analysis was done based on different countries.

RESULTS

Literature search and study characteristics

Figure 1 shows the PRISMA flowchart of the data selection process. The systematic search resulted in 2,153 initial records, of which 1,095 were excluded as duplicates and 777 as irrelevant records due to their title/abstract. Two hundred eighty-one full-text articles were assessed for eligibility according to our inclusion criteria. Finally, 58 articles [9,10,16-71] (60 studies) were found to be appropriate for quantitative synthesis. The main characteristics of the studies are summarized in Supplementary Table 1. The study design mainly included cross-sectional methods. According to Eggers'

Table 1. Correlation coefficient subgroup analysis by countries.

Country	Weight %	Study ES (95% conf. interval)	Test(s) of heterogeneity I-squared, p
Italy	12.59	-0.350 (-0.399, -0.301)	1.8%, 0.0001
India	6.28	-0.369 (-0.484, -0.255)	0.0%, 0.0000
Iran	24.59	-0.311 (-0.373, -0.250)	20.4%, 0.0030
Indonesia	8.88	-0.309 (-0.373, -0.245)	0.0%, 0.0000
Egypt	11.35	-0.356 (-0.573, -0.140)	85.7%, 0.0719
Malaysia	1.39	-0.252 (-0.518, 0.014)	0.0%, 0.0000
Thailand	4.14	-0.229 (-0.801, 0.342)	96.4%, 0.1639
Turkey	4.36	-0.268 (-0.406, -0.131)	0.0%, 0.0000
Tunisia	1.78	-0.031 (-0.229, 0.167)	0.0%, 0.0000
China	4.13	-0.348 (-0.453, -0.243)	0.0%, 0.0000
Pakistan	1.79	-0.441 (-0.636, -0.246)	0.0%, 0.0000
Taiwan	4.19	-0.285 (-0.505, -0.066)	51.8%, 0.0196
Brazil	1.89	0.220 (0.040, 0.400)	0.0%, 0.0000
Australia	1.08	-0.420 (-0.756, -0.084)	0.0%, 0.0000
UK	6.28	-0.167 (-0.377, 0.042)	84.1%, 0.0284
Hong Kong	1.31	-0.110 (-0.391, 0.171)	0.0%, 0.0000
Greece	3.98	-0.208 (-0.455, 0.040)	57.3%, 0.0273

test, publication bias was not statistically significant. Chi-squared test showed that there was heterogeneity between the studies (I^2 = 69.3, p-value < 0.001). Because of heterogeneity, we used random effect models for all data analyses.

A total of 6,429 (50.1% male) TDT patients were included in this study. The overall mean age ± SD was 23 ± 6.76 years. The overall mean ± SD of serum ferritin level was 2,430 ± 2,531 ng/mL, and the mean percentage of patients with splenectomy was 35.4%.

Main outcomes

Correlation

The pooled CC of the included studies was -0.30 (95% CI: -0.34, -25, p < 0.001) (Figure 2). The heterogeneity was statistically significant (I^2 = 69.3%, p-value < 0.001), and the publication bias was not statistically significant (p-value: 0.150). The results of sensitivity analysis showed that none of the studies significantly changed the direction of the results.

Age

Meta-regression was done for evaluating the effect of the patients' age on the pooled CC which showed no significant association between the patients' age and the pooled CC: -0.0005 (95% CI -0.006, 0.005, p-value = 0.874).

Countries

The results of subgroup analysis divided by countries are shown in Table 1. The highest weight in this analysis belonged to Iran, Italy, and Egypt with CC values of -0.311 (95% CI: -0.373, -0.250), -0.350 (95% CI: -0.399, -0.301), and -0.356 (95% CI: -0.573, -0.140), respectively. Also, the highest CC was observed in Pakistan with a value of -0.441 (95% CI: -0.636, -0.246).

DISCUSSION

This meta-analysis aimed to investigate the pooled correlation between the serum ferritin level and heart T2 MRI in patients with TDT. Our study showed a significant negative moderate correlation between the serum ferritin and heart T2 MRI. Also, the results demonstrated that this correlation was not affected by the patients' age. In subgroup analysis based on different countries, the results were similar in the majority of countries. As there was a moderate negative correlation between the serum ferritin level and heart T2 MRI, serum ferritin level can be a cost-effective method for estimating the heart iron overload, especially in developing countries.

Similar to the result of this meta-analysis, several studies have reported a statistically significant correlation between the serum ferritin level and liver T2 MRI [31,43,72], as well as other vital organs such as the pancreas [64] and hypophysis in thalassemia patients [73]. Frequent blood transfusions in TDT patients cause deposition of excess iron in different organs [3]. The metabolism of non-transferring bound iron leads to the production of reactive oxygen species [3]. Heart disease

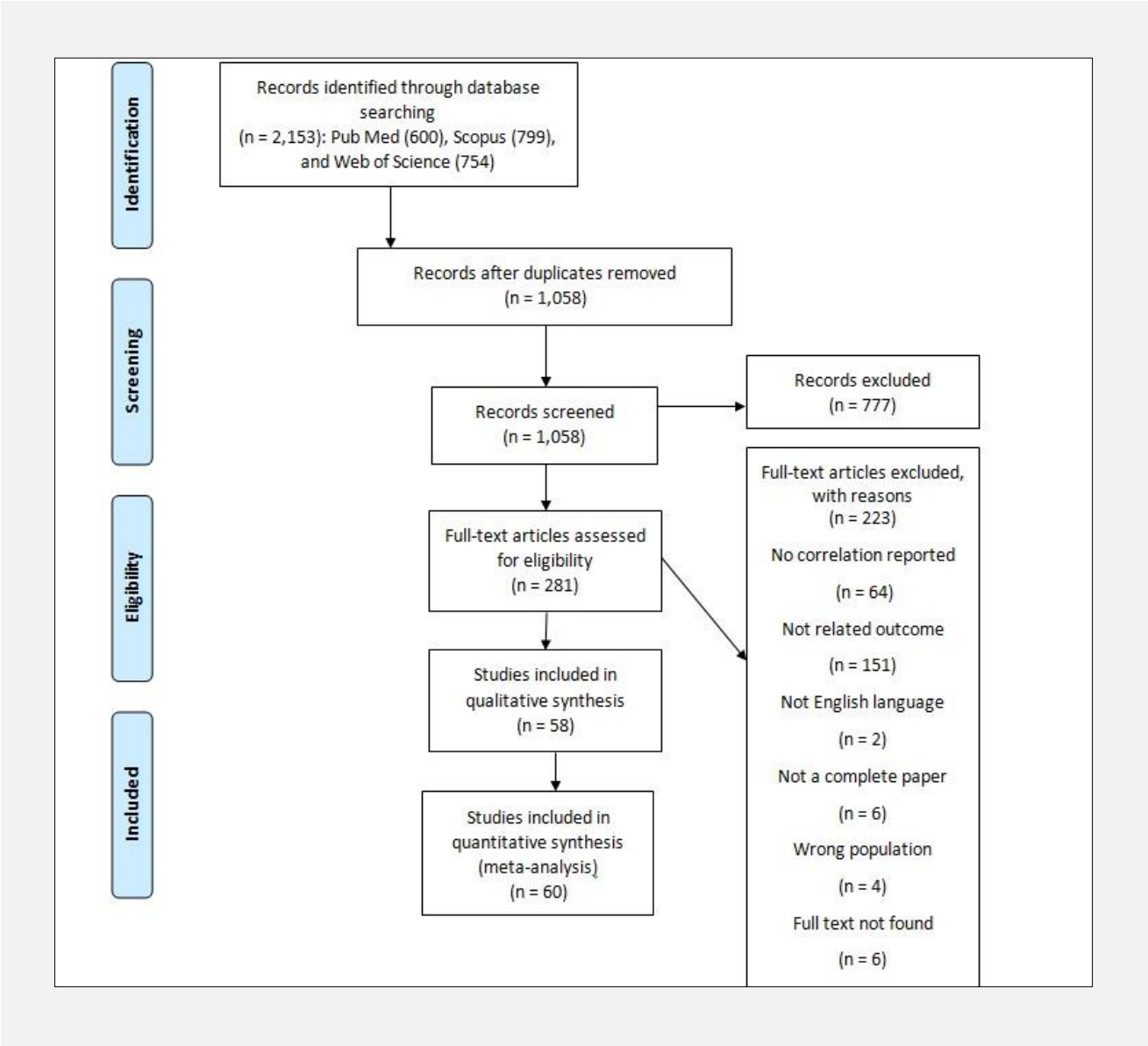

Figure 1. PRISMA flowchart of the study identification and selection process.

was among the most lethal causes of death in TDT patients [74].

Based on the results of this study, age had no significant effect on the correlation of serum ferritin level and cardiac iron overload. As to geographical distribution of thalassemia, Mediterranean, Middle East, and Southeast Asia are known as thalassemia belt regions. However, due to migration, the number of thalassemia cases is also increasing in other regions including North America, and northern Europe [75]. Similarly, Iran, Italy, and Egypt accounted for the largest number of patients in this meta-analysis; however, studies from Australia, Brazil, and United States were also included in our analysis. Based on the results of pooled analysis, the significant correlation between the serum ferritin and heart T2 MRI, which was observed in the majority of countries, indicates inconsiderable effect of geographical area on this correlation.

Our study has certain limitations. First of all, we only included papers with English language full text. Secondly, the full texts of a small number of papers were not found, and we had to exclude them. Third, there was heterogeneity among the included studies. However, random effects model and sensitivity analysis was used to decrease the heterogeneity effect.

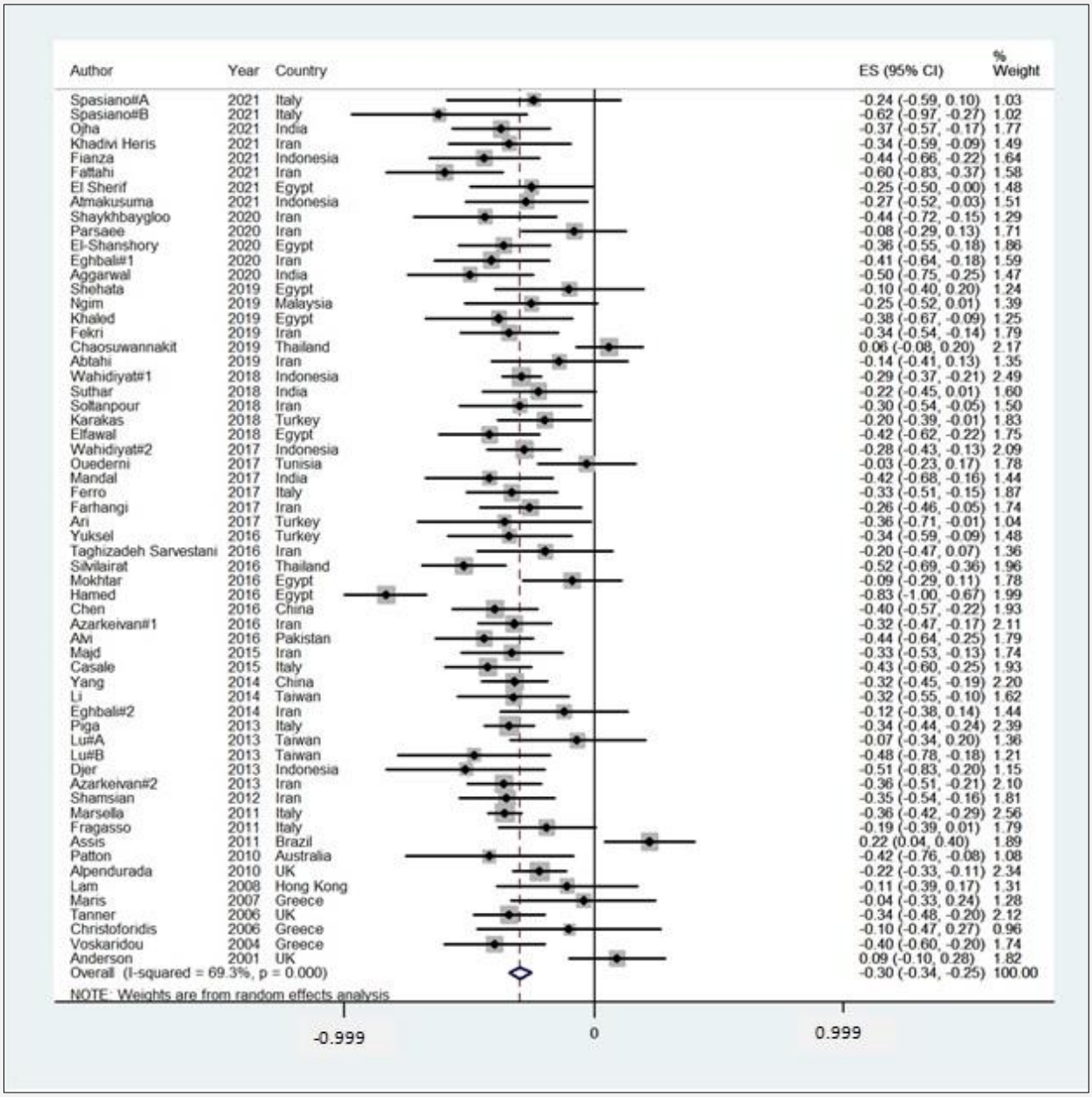

Figure 2. Pooled analysis of correlation coefficient of the included studies.

CONCLUSION

The pooled analysis showed a significant negative moderate correlation between the serum ferritin level and heart T2 MRI in patients with TDT, regardless of their age. This issue underscores the importance of periodical evaluation of the serum ferritin level in patients with TDT of all age groups in developing countries with low financial support and limited resources. Further studies are suggested to evaluate the pooled correlation of the serum ferritin level with iron concentration of other vital organs.

Acknowledgment:
The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

Declaration of Interest:
None.

References:

1. Thein SL. Molecular basis of β thalassemia and potential therapeutic targets. Blood Cells Mol Dis 2018;70:54-65. (PMID: 28651846)

2. Longo F, Piolatto A, Ferrero GB, Piga A. Ineffective Erythropoiesis in β-Thalassaemia: Key Steps and Therapeutic Options by Drugs. Int J Mol Sci 2021;22(13):7229. (PMID: 34281283)

3. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. Hematology Am Soc Hematol Educ Program 2017;2017(1):265-71. (PMID: 29222265)

4. Shafie AA, Wong JHY, Ibrahim HM, Mohammed NS, Chhabra IK. Economic burden in the management of transfusion-dependent thalassaemia patients in Malaysia from a societal perspective. Orphanet J Rare Dis 2021;16(1):157. (PMID: 33827621)

5. Mainous AG 3rd, Diaz VA, Everett CJ, et al. IRon Overload screeNing tool (IRON): development of a tool to guide screening in primary care. Am J Hematol 2011;86(9):733-7. (PMID: 21800355)

6. Kumar I, Aggarwal P, Gupta V, Verma A, Kumar S, Shukla RC. Cardiac T2* magnetic resonance analysis of membranous interventricular septum in assessment of cardiac iron overload in pediatric thalassemia patients: A pilot study. Indian J Radiol Imaging 2019;29(1):33-9. (PMID: 31000939)

7. Hutubessy RC, Hanvoravongchai P, Edejer TT; Asian MRI Study Group. Diffusion and utilization of magnetic resonance imaging in Asia. Int J Technol Assess Health Care 2002;18(3):690-704. (PMID: 12391959)

8. De Sanctis V, Kattamis C, Canatan D, et al. β-Thalassemia Distribution in the Old World: an Ancient Disease Seen from a Historical Standpoint. Mediterr J Hematol Infect Dis 2017;9(1): e2017018. (PMID: 28293406)

9. Azarkeivan A, Hashemieh M, Akhlaghpoor S, Shirkavand A, Yaseri M, Sheibani K. Relation between serum ferritin and liver and heart MRI T2* in beta thalassaemia major patients. East Mediterr Health J 2013;19(8):727-32. (PMID: 24975358)

10. Wahidiyat PA, Liauw F, Sekarsari D, Putriasih SA, Berdoukas V, Pennell DJ. Evaluation of cardiac and hepatic iron overload in thalassemia major patients with T2* magnetic resonance imaging. Hematology 2017;22(8):501-7. (PMID: 28218005)

11. Chen X, Zhang Z, Zhong J, et al. MRI assessment of excess cardiac iron in thalassemia major: When to initiate? J Magn Reson Imaging 2015;42(3):737-45. (PMID: 26154874)

12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264-9, w64. (PMID: 19622511)

13. Luchini C, Stubbs B, Solmi M, Veronese N, editors. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale2017. https://www.wjgnet.com/2308-3840/full/v5/i4/80.htm

14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60. (PMID: 12958120)

15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109):629-34 (PMID: 9310563)

16. Abtahi F, Abdi A, Jamshidi S, Karimi M, Babaei-Beigi MA, Attar A. Global longitudinal strain as an Indicator of cardiac Iron overload in thalassemia patients. Cardiovasc Ultrasound 2019; 17(1):24. (PMID: 31684963)

17. Aggarwal P, Kumar I, Jain A, Verma A, Gupta V. Relation Between Cardiac T2* Values and Electrocardiographic Parameters in Children With Transfusion-dependent Thalassemia. J Pediatr Hematol Oncol 2020;42(7):e610-4. (PMID: 32032245)

18. Alpendurada F, Carpenter JP, Deac M, et al. Relation of myocardial T2* to right ventricular function in thalassaemia major. Eur Heart J 2010;31(13):1648-54. (PMID: 20413399)

19. Alvi N, Tipoo FA, Imran A, et al. Burden of Cardiac Siderosis in a Thalassemia-Major Endemic Population: A Preliminary Report From Pakistan. J Pediatr Hematol Oncol 2016;38(5):378-83. (PMID: 27164519)

20. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001;22(23):2171-9. (PMID: 11913479)

21. Ari ME, Ekici F, Cetin, II, et al. Assessment of left ventricular functions and myocardial iron load with tissue Doppler and speckle tracking echocardiography and T2*MRI in patients with beta-thalassemia major. Echocardiography 2017;34(3):383-9. (PMID: 28139073)

22. Assis RA, Kay FU, Rosemberg LA, et al. Iron overload in Brazilian thalassemic patients. Einstein (Sao Paulo) 2011;9(2):165-72. (PMID: 26760810)

23. Atmakusuma TD, Kalwani R, Nasution SA, Rumende CM. Correlation of Serum Ferritin and Cardiac Iron Toxicity with Cardiac Function in Transfusion Dependent Beta-Thalassemia Major Patients. Acta Med Indones 2021;53(3):291-8. (PMID: 34611068)

24. Azarkeivan A, Hashemieh M, Shirkavand A, Sheibani K. Correlation between Heart, Liver and Pancreas Hemosiderosis Measured by MRI T2* among Thalassemia Major Patients from Iran. Arch Iran Med 2016;19(2):96-100. (PMID: 26838079)

25. Casale M, Meloni A, Filosa A, et al. Multiparametric Cardiac Magnetic Resonance Survey in Children With Thalassemia Major: A Multicenter Study. Circ Cardiovasc Imaging 2015;8(8): e003230. (PMID: 26253625)

26. Chaosuwannakit N, Makarawate P. The value of magnetic resonance imaging in evaluation of myocardial and liver iron overload in a thalassaemia endemic population: a report from Northeastern Thailand. Pol J Radiol 2019;84:e262-8. (PMID: 31481999)

27. Chen X, Zhang H, Yang Q, et al. Value of severe liver iron overload for assessing heart iron levels in thalassemia major patients. J Magn Reson Imaging 2016;44(4):880-9. (PMID: 27038128)

28. Christoforidis A, Haritandi A, Tsitouridis I, et al. Correlative study of iron accumulation in liver, myocardium, and pituitary assessed with MRI in young thalassemic patients. J Pediatr Hematol Oncol 2006;28(5):311-5. (PMID: 16772883)

29. Djer MM, Anggriawan SL, Gatot D, Amalia P, Sastroasmoro S, Widjaja P. Correlation between T2* cardiovascular magnetic resonance with left ventricular function and mass in adolescent and adult major thalassemia patients with iron overload. Acta Med Indones 2013;45(4):295-301. (PMID: 24448334)

30. Eghbali A, Mehrabi S, Ghandi Y, Eghbali A, Dabiri M, Mousavi-Hasanzadeh M. The correlation between serum ferritin, serum troponin t, cardiac t2* MRI and echocardiographic findings in patients with thalassemia major. Iranian Journal of Blood and Cancer 2020;12(1):1-5.
http://ijbc.ir/article-1-904-en.pdf

31. Eghbali A, Taherahmadi H, Shahbazi M, Bagheri B, Ebrahimi L. Association between serum ferritin level, cardiac and hepatic T2-star MRI in patients with major β-thalassemia. Iran J Ped Hematol Oncol 2014;4(1):17-21. (PMID: 24734159)

32. El Sherif AM, Ibrahim AS, Elsayed MA, Abdelhakim AS, Ismail AM. The impact of magnetic resonance imaging in the assessment of iron overload in heart and liver in transfusion-dependent thalassemic children: Minia experience. Egyptian Journal of Radiology and Nuclear Medicine 2021;52(1).
https://doi.org/10.1186/s43055-021-00645-4

33. Elfawal SK, Emara DM, Shehata AA. Assessment of hepatic and cardiac iron overload in thalassemia patients by magnetic resonance imaging: Our experience in Alexandria University. Egyptian Journal of Radiology and Nuclear Medicine 2018;49(2):323-8.
https://doi.org/10.1016/j.ejrnm.2018.01.016

34. El-Shanshory M, Tolba O, El-Shafiey R, Elgamasy M, Hablas N, Mawlana W. Cardiac Iron Overload by MRI in Children With B-Thalassemia Major and its Correlation With Cardiac Function by Echocardiography. J Pediatr Hematol Oncol 2020;42(6):398-402. (PMID: 32251156)

35. Farhangi H, Badiei Z, Moghaddam HM, Keramati MR. Assessment of Heart and Liver Iron Overload in Thalassemia Major Patients Using T2* Magnetic Resonance Imaging. Indian J Hematol Blood Transfus 2017;33(2):228-34. (PMID: 28596656)

36. Fattahi H, Parsaee M, Rezaeian N, et al. Comparison between two and three-dimensional speckle-tracking echocardiography and cardiac T2*magnetic resonance imaging in ss-thalassemia. Res Cardiovasc Med 2021;10(1):7-13.
https://www.rcvmonline.com/text.asp?2021/10/1/7/319787

37. Fekri K, Asle Rasouli N, Tavallai Zavareh SA, et al. Hepcidin and HFE Polymorphisms and Ferritin Level in β-Thalassemia Major. Int J Hematol Oncol Stem Cell Res 2019;13(1):42-8. (PMID: 31205627)

38. Ferro E, Visalli G, La Rosa MA, et al. The role of anaemia in oxidative and genotoxic damage in transfused β-thalassaemic patients. Hematology 2017;22(3):183-91. (PMID: 27801288)

39. Fianza PI, Rahmawati A, Widihastha SH, et al. Iron Overload in Transfusion-Dependent Indonesian Thalassemic Patients. Anemia 2021;2021:5581831. (PMID: 33953980)

40. Fragasso A, Ciancio A, Mannarella C, et al. Myocardial iron overload assessed by magnetic resonance imaging (MRI)T2* in multi-transfused patients with thalassemia and acquired anemias. Eur J Intern Med 2011;22(1):62-5. (PMID: 21238896)

41. Hamed AA, Elguindy W, Elhenawy YI, Ibrahim RH. Early Cardiac Involvement and Risk Factors for the Development of Arrhythmia in Patients With β-Thalassemia Major. J Pediatr Hematol Oncol 2016;38(1):5-11. (PMID: 26583617)

42. Karakas Z, Yilmaz Y, Bayramoglu Z, et al. Magnetic resonance imaging during management of patients with transfusion-dependent thalassemia: a single-center experience. Radiol Med 2018; 123(8):572-6. (PMID: 29663188)

43. Khadivi Heris H, Nejati B, Rezazadeh K, et al. Evaluation of iron overload by cardiac and liver T2* in β-thalassemia: Correlation with serum ferritin, heart function and liver enzymes. J Cardiovasc Thorac Res 2021;13(1):54-60. (PMID: 33815703)

44. Khaled A, Ezzat DA, Salem HA, Seif HM, Rabee H. Effective method of evaluating myocardial iron concentration in pediatric patients with thalassemia major. J Blood Med 2019;10:227-33. (PMID: 31372080)

45. Lam WW, Au WY, Chu WC, Tam S, Ha SY, Pennell DJ. One-stop measurement of iron deposition in the anterior pituitary, liver, and heart in thalassemia patients. J Magn Reson Imaging 2008;28(1):29-33. (PMID: 18581349)

46. Li MJ, Peng SS, Lu MY, et al. Diabetes mellitus in patients with thalassemia major. Pediatr Blood Cancer 2014;61(1):20-4. (PMID: 24115521)

47. Lu MY, Peng SS, Chang HH, et al. Cardiac iron measurement and iron chelation therapy in patients with β thalassaemia major: experience from Taiwan. Transfus Med 2013;23(2):100-7. (PMID: 23448138)

48. Majd Z, Haghpanah S, Ajami GH, et al. Serum Ferritin Levels Correlation With Heart and Liver MRI and LIC in Patients With Transfusion-Dependent Thalassemia. Iran Red Crescent Med J 2015;17(4):e24959. (PMID: 26023341)

49. Mandal S, Sodhi KS, Bansal D, et al. MRI for Quantification of Liver and Cardiac Iron in Thalassemia Major Patients: Pilot Study in Indian Population. Indian J Pediatr 2017;84(4):276-82. (PMID: 28233255)

50. Maris TG, Papakonstantinou O, Chatzimanoli V, et al. Myocardial and liver iron status using a fast T*2 quantitative MRI (T*2qMRI) technique. Magn Reson Med 2007;57(4):742-53. (PMID: 17390359)

51. Marsella M, Borgna-Pignatti C, Meloni A, et al. Cardiac iron and cardiac disease in males and females with transfusion-dependent thalassemia major: a T2* magnetic resonance imaging study. Haematologica 2011;96(4):515-20. (PMID: 21228034)

52. Mokhtar GM, Sherif EM, Habeeb NM, et al. Glutathione S-transferase gene polymorphism: Relation to cardiac iron overload in Egyptian patients with Beta Thalassemia Major. Hematology 2016;21(1):46-53. (PMID: 26288192)

53. Ngim CF, Lee MY, Othman N, Lim SM, Ng CS, Ramadas A. Prevalence and Risk Factors for Cardiac and Liver Iron Overload in Adults with Thalassemia in Malaysia. Hemoglobin 2019;43(2): 95-100. (PMID: 31179787)

54. Ojha V, Ganga KP, Seth T, et al. Role of CMR feature-tracking derived left ventricular strain in predicting myocardial iron overload and assessing myocardial contractile dysfunction in patients with thalassemia major. Eur Radiol 2021;31(8):6184-92. (PMID: 33721061)

55. Ouederni M, Ben Khaled M, Mellouli F, et al. Myocardial and liver iron overload, assessed using T2* magnetic resonance imaging with an excel spreadsheet for post processing in Tunisian thalassemia major patients. Ann Hematol 2017;96(1):133-9. (PMID: 27730342)

56. Parsaee M, Khansari N, Azarkeivan A, Chitsazan M, Ghadrdoost B, Mombeini H. Role of left atrial structure and function in the early prediction of cardiac iron overload in transfusion-dependent β-Thalassemia patients. Iranian Heart Journal 2020;21(1):27-33. http://journal.iha.org.ir/article_102258.html

57. Patton N, Brown G, Leung M, et al. Observational study of iron overload as assessed by magnetic resonance imaging in an adult population of transfusion-dependent patients with beta thalassemia: significant association between low cardiac T2* < 10 ms and cardiac events. Intern Med J 2010;40(6):419-26. (PMID: 19460052)

58. Piga A, Longo F, Musallam KM, et al. Assessment and management of iron overload in β-thalassaemia major patients during the 21st century: a real-life experience from the Italian WEBTHAL project. Br J Haematol 2013;161(6):872-83. (PMID: 23600689)

59. Shamsian BS, Esfahani SA, Milani H, et al. Magnetic resonance imaging in the evaluation of iron overload: a comparison of MRI, echocardiography and serum ferritin level in patients with β-thalassemia major. Clin Imaging 2012;36(5):483-8. (PMID: 22920350)

60. Shaykhbaygloo R, Moradabadi A, Taherahmadi H, Rafiei M, Lotfi F, Eghbali A. Correlation of Cardiac and Liver Iron Level with T2*MRI and Vitamin D3 Serum Level in Patients with Thalassemia Major. J Blood Med 2020;11:83-7. (PMID: 32210653)

61. Shehata SM, Amin MI, Zidan ESH. MRI evaluation of hepatic and cardiac iron burden in pediatric thalassemia major patients: spectrum of findings by T2*. Egyptian Journal of Radiology and Nuclear Medicine 2019;50(1). https://doi.org/10.1186/s43055-019-0044-5

62. Silvilairat S, Charoenkwan P, Saekho S, et al. Heart Rate Variability for Early Detection of Cardiac Iron Deposition in Patients with Transfusion-Dependent Thalassemia. PLoS One 2016; 11(10):e0164300. (PMID: 27737009)

63. Soltanpour MS, Davari K. The Correlation of Cardiac and Hepatic Hemosiderosis as Measured by T2*MRI Technique with Ferritin Levels and Hemochromatosis Gene Mutations in Iranian Patients with Beta Thalassemia Major. Oman Med J 2018;33(1):48-54. (PMID: 29467999)

64. Spasiano A, Meloni A, Costantini S, et al. Setting for "Normal" Serum Ferritin Levels in Patients with Transfusion-Dependent Thalassemia: Our Current Strategy. J Clin Med 2021;10(24): 5985. (PMID: 34945281)

65. Suthar K, Goyal VK, Sharma P, Deopa B, Rathore PS, Bishnoi RK. Relationship between T2* magnetic resonance imaging-derived liver and heart iron content and serum ferritin levels in transfusion-dependent thalassemic children. Asian J Transfus Sci 2018;12(1):69-74. (PMID: 29563679)

66. Taghizadeh Sarvestani R, Moradveisi B, Kompany F, Ghaderi E. Correlation between heart and liver iron levels measured by MRI T2* and serum ferritin in patients with β-thalassemia major. International Journal of Pediatrics 2016;4(3):1559-67. https://doi.org/10.22038/ijp.2016.6587

67. Tanner MA, Galanello R, Dessi C, et al. Myocardial iron loading in patients with thalassemia major on deferoxamine chelation. J Cardiovasc Magn Reson 2006;8(3):543-7. (PMID: 16755844).

68. Voskaridou E, Douskou M, Terpos E, et al. Magnetic resonance imaging in the evaluation of iron overload in patients with beta thalassaemia and sickle cell disease. Br J Haematol 2004;126(5): 736-42. (PMID: 15327528)

69. Wahidiyat PA, Iskandar SD, Sekarsari D. Evaluation of Iron Overload Between Age Groups Using Magnetic Resonance Imaging and Its Correlation with Iron Profile in Transfusion-dependent Thalassemia. Acta Med Indones 2018;50(3):230-6. (PMID: 30333273)

70. Yang G, Liu R, Peng P, et al. How early can myocardial iron overload occur in beta thalassemia major? PLoS One 2014;9(1): e85379. (PMID: 24465548)

71. Yuksel IO, Koklu E, Kurtoglu E, et al. The Association between Serum Ferritin Level, Tissue Doppler Echocardiography, Cardiac T2* MRI, and Heart Rate Recovery in Patients with Beta Thalassemia Major. Acta Cardiol Sin 2016;32(2):231-8. (PMID: 27122954)

72. Zamani F, Razmjou S, Akhlaghpoor S, Eslami SM, Azarkeivan A, Amiri A. T2* magnetic resonance imaging of the liver in thalassemic patients in Iran. World J Gastroenterol 2011;17(4):522-5. (PMID: 21274383)

73. Çetinçakmak MG, Hattapoğlu S, Menzilcioğlu S, et al. MRI-based evaluation of the factors leading to pituitary iron overload in patients with thalassemia major. J Neuroradiol 2016;43(4):297-302. (PMID: 27083690)

74. Chern JP, Su S, Lin KH, et al. Survival, mortality, and complications in patients with beta-thalassemia major in northern Taiwan. Pediatr Blood Cancer 2007;48(5):550-4. (PMID: 16972241)

75. Kattamis A, Forni GL, Aydinok Y, Viprakasit V. Changing patterns in the epidemiology of β-thalassemia. Eur J Haematol 2020; 105(6):692-703. (PMID: 32886826)

Additional material can be found online at:
http://supplementary.clin-lab-publications.com/220916/