ORIGINAL ARTICLE

# Correlation of Serum Ferritin and Cardiac Iron Toxicity with Cardiac Function in Transfusion Dependent Beta-Thalassemia Major Patients

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## ABSTRAK

***Latar Belakang:*** *Toksisitas besi pada jantung merupakan penyebab utama kelainan jantung pada pasien-pasien thalassemia. Modalitas utama untuk mendeteksi toksisitas besi pada jantung adalah dengan magnetic resonance imaging (MRI) T2* yang ketersediaannya terbatas. Penelitian ini bertujuan untuk mengetahui korelasi antara serum ferritin dan toksisitas besi pada jantung dengan fungsi jantung (fraksi ejeksi dan rasio E/A) pada penderita thalassemia beta bergantung transfusi.* ***Metode:*** *Penelitian potong lintang dilakukan di Poliklinik Thalassemia Dewasa Rumah Sakit Cipto Mangunkusumo, Indonesia dari Desember 2017 hingga Maret 2018. Analisis statistik menggunakan uji korelasi Pearson atau Spearman antara nilai MRI T2* dengan fraksi ejeksi dan rasio E/A.* ***Hasil:*** *Median dari rerata 4 bulan kadar ferritin serum adalah 5130 ng/mL. Rerata nilai MRI T2* jantung adalah 24,96 ms. Hemosiderosis jantung berat terjadi pada 11,3 % subjek. Kadar ferritin serum berkorelasi lemah dengan toksisitas besi pada jantung (r=-0,272, p=0,032) dan fraksi ejeksi (r=-0,283, p=0,026), tetapi toksisitas besi pada jantung tidak berkorelasi dengan fraksi ejeksi dan rasio E/A.* ***Kesimpulan:*** *Kadar ferritin serum berkorelasi lemah dengan toksisitas besi dan fungsi sistolik jantung, tetapi toksisitas besi pada jantung tidak berkorelasi dengan fungsi sistolik dan diastolik jantung.*

***Kata kunci:*** *Tosksisitas besi pada jantung, ferritin serum , fungsi sistolik, fungsi diastolik, MRI T2* jantung.*

## ABSTRACT

***Background:*** *Cardiac iron toxicity is a major cause of mortality in transfusion-dependent beta-thalassemia major patients. The main modality for detecting cardiac iron toxicity is MRI T2* with limited availability. This study aims to obtain iron toxicity profiles in transfusion-dependent beta-thalassemia patients; to see a correlation between iron toxicity and cardiac function.* ***Methods:*** *We conducted a cross-sectional study at the Adult Thalassemia Polyclinic of Cipto Mangunkusumo Hospital, Indonesia from December 2017 to March 2018. We performed the statistical analysis using Pearson/Spearman Test comparing MRI T2* values with ejection* *fraction and E/A ratio.* ***Results:*** *The median of 4-months mean of ferritin levels was 5130 ng/mL. The mean for cardiac T2* was 24.96 ms. Severe cardiac hemosiderosis (mean cardiac MRI T2* < 10 ms) occurred in 11.3% of the subjects. There was weak correlation between serum ferritin with cardiac iron toxicity (r=-0.272, p=0.032) and ejection fraction (r=-0.281, p=0.013). But, there was no correlation between cardiac iron toxicity with ejection fraction and E/A ratio.* ***Conclusion:*** *Serum ferritin correlated weakly with cardiac iron toxicity and cardiac systolic function. Meanwhile, there was no correlation between cardiac iron toxicity with cardiac systolic and diastolic function.*

***Keywords:*** *cardiac iron toxicity, serum ferritin, systolic function, diastolic function, cardiac MRI T2*.*

## INTRODUCTION

Thalassemia is one of the most common genetic disorders, affecting 4.83% of the population worldwide.[1] Advances in the treatment of thalassemia major has resulted in better prognoses of the patients. Therefore, those with thalassemia major could survive up to third or fourth decade of life. A long-term study reported that 68% of patients with thalassemia major could survive to their mid-30s.[2,3] Severe anaemia in thalassemia major requires regular transfusion since early age.[4] Regular transfusion leads to an improvement in the quality of life; however, it results in new problems; these include iron overload, which may cause cardiac disease, endocrinopathy, and liver disease.[5]

Cardiac disease could be manifested by cardiomyopathy. Cardiomyopathy due to iron overload is the leading cause of death in thalassemia major patients. In several countries, this mortality may be up to 70%.[5] Cardiac siderosis usually progresses without symptoms for several years. The onset of symptoms of heart failure is associated with a high likelihood of mortality. The time between the onset of symptoms and death is usually quite short and ranges from 6 - 12 months. If patients with cardiac iron accumulation can be identified early, this would be very helpful because chelation therapy could be started aggressively.[6,7] Several international publications showed that cardiac iron toxicity in various countries vary greatly, with a range of 30-85 %.[8] During the Coronavirus 2019 (COVID-19) pandemic, people with haemoglobin disorders, including thalassemia are considered high risk for severe disease.[9] Mortality in COVID-19 is also linked to cardiovascular disease. Therefore, assessment of cardiac function is critical in determining the prognosis of such patients.

Cardiac magnetic resonance imaging (MRI) T2* is the recommended modality for detecting iron toxicity and is the only non-invasive way to identify the severity of iron deposition in the myocardium. The cardiac T2* is the time taken for the signal decay from the myocardium and is expressed in milliseconds. The more iron deposits in the myocardium the lower the value of T2*. Thus, the more severe the cardiac iron toxicity the lower the cardiac T2* value. The values used as a reference are <10ms as severe hemosiderosis, 10 - 20ms as mild to moderate hemosiderosis, and normal if T2*>20ms. In addition to diagnosing iron toxicity, cardiac MRI T2 * is also used to determine and monitor iron chelation therapy. Cardiac MRI T2 * can also be used to predict the occurrence of heart failure. A value of less than 10 ms predicts heart failure, while a value of more than 20 ms predicts that heart failure will not occur for the following year. A Cardiac MRI T2 * is recommended once a year to assess iron toxicity and effectiveness of iron chelation.[10,11] However, in Indonesia, the MRI T2* examination is only available in four centres, i.e. Aceh, Jakarta, Bandung and Surabaya (three of them in the Java Island). MRI is not available in the central and eastern region of Indonesia. Therefore, some centres utilize serum transferrin saturation and ferritin as surrogate markers of iron overload.

Cardiac iron toxicity is associated with cardiac dysfunction. Echocardiography can give a picture of the patient's systolic and diastolic function. The systolic function is assessed from the left ventricular ejection fraction. An ejection fraction below 50% indicates impaired ventricular contractility. Damage caused by iron mediated generation of free radicals is one of the main mechanism of cardiomyocyte damage.[12] The higher the cardiac iron toxicity, the lower the ejection fraction or left ventricular systolic function and the higher the risk of heart failure.[11,13] Some echocardiographic parameters can be used to assess diastolic function. One of them is the blood flow through the mitral valve, which is the ratio of the blood flow velocity in the early diastolic phase to the advanced diastolic phase or known as the E / A ratio.[14] According to several studies, diastolic dysfunction occurs earlier than systolic dysfunction in adult transfusion dependent thalassemia patients.[14] Echocardiography is a simple bedside diagnostic procedure which is available in every regional hospital. The device is portable, lightweight, and can be operated even in remote healthcare facilities. In addition, echocardiography can detect diastolic dysfunction, which is known to be related to cardiac siderosis.[15]

Limited availability of MRI T2* inspired to study correlation of serum ferritin and cardiac iron toxicity with cardiac function; systolic and diastolic in adults with transfusion-dependent beta thalassemia major. This study describes data of Thalassemia's cardiac function patients in Indonesia because differences in transfusion practices such as inadequate transfusion due to donor shortage might interfere with cardiac function by causing anemic heart disease.

## METHODS

This was a cross-sectional study of 62 patients with transfusion-dependent beta thallassema major, conducted by evaluating the medical records of beta-thalassemia patients ≥18 years of age who were transfusion dependent and who came for a reguler check at the Adult Thalassemia Polyclinic, Department of Internal Medicine, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. The study was conducted from December 2017 to March 2018.

The diagnosis of thalassemia had been made with high-performance liquid chromatography / HPLC or microcapillary method included in this study. We excluded patients who had acute inflammation (temperature> 38°C), congenital heart abnormalities, acute heart failure, and claustrophobia.

The parameters that were used to determine ferritin level, the iron toxicity, systolic function, and diastolic function were cardiac MRI T2*, ejection fraction and E/A ratio. The mean ferritin serum was obtained from medical records for four months and categorized into values of <1000ng / mL, 1000-2500 ng / mL, and >2500 ng / mL. MRI T2* values were grouped as severe hemosiderosis (T2* <10 ms), mild-moderate hemosiderosis (T2* 10-20 ms) and normal (T2* >20 ms). The E/A ratio was categorized as mild, moderate and severe diastolic dysfunction (E / A <1; 1-2; and >2).

Data collection was processed by using the SPSS 20 program for Windows. The analysis was performed by testing the Pearson conversion coefficient (r) for normal distribution data or Spearman conversion coefficient (rho) for abnormal data distribution. All patients were given an oral and written explanation of the objectives, benefits, and research procedures. All patients agreed and gave their informed consent. This study was approved by the Ethical Committee of Faculty of Medicine, Universitas Indonesia.

## RESULTS

Sixty-two patients who had undergone MRI and echocardiography were willing to take part in the study, 26 (41.6%) were females and 36 (58.1%) were male. The median age was 22 (18-39) years. The number of patients with beta-thalassemia was 34 (54.8%) and beta-thalassemia HbE was 28 (45.2%). The medan of 4-months mean of ferritin level was 5130 ng/mL (741-18605). The number of patients with serum ferritin above 2500 ng / mL was 52 (83.9%), 1000-2500 ng / mL was 9 (14.5%), and under 1000ng / mL was 1 (1, 6%). Iron overload (Transferin saturation ≥50%) was found in 59 patients (95.2%). Twenty-nine patients used Deferiprone; five used Deferasirox, five used Deferoxamine and 23 used combination iron chelators. (**Table 1**)

The mean value of cardiac MRI T2* was 24.96 ms. Cardiac iron toxicity (Cardiac MRI T2* < 10 ms and 10-20 ms) was seen in 38.7%

patients. Mild-moderate hemosiderosis (Cardiac MRI T2* 10-20 ms) was found in in 27.4% patients. Severe hemosiderosis (Cardiac MRI T2* < 10 ms) was found in 11.3% patients. The mean ejection fraction was 67.55 %. Mean Diastolic dysfunction E/A 1-2 and >2 was seen in all patients, 57 (91,9%) patients with moderate diastolic dysfunction and five patients with severe diastolic dysfunction E/A > 2 (**Table 1**).

### Correlation Between Cardiac Iron Toxicity with Cardiac Function

There was no correlation between cardiac T2 * and ejection fraction (r = -0.076, p = 0.556). There was no correlation between cardiac T2 * and E / A ratio (r = -0.136, p = 0.292). Thus, there was no correlation between cardiac iron toxicity with cardiac function (**Figure 1**).

### Correlation Between Iron Overload with Iron Toxicity, Systolic Function, and Diastolic Function

There was a weak negative correlation between serum ferritin and MRI T2* (r = -0.272, p = 0.032). However, no correlation was found between transferrin saturation and MRI T2* values (r =-0.084, p = 0.514). (**Figure 2**)

This study also found weak negative correlation between ferritin and ejection fraction (r = -0.283, p = 0.026). There was no correlation between transferrin saturation and ejection fraction (r = 0.097, p = 0.453). (**Figure 3**) Also, no correlation was found between ferritin and transferrin saturation with diastolic function (r = 0.073, p = 0.575 and r = 0.009, p = 0.946, respectively). (**Figure 4**)

**Table 1.** Clinical, biochemical and cardiac characteristics of the patients of Thalassemia β-dependent transfusion.

| Characteristics | N= 62 |
|---|---|
| Sex, n (%) | |
| - Male | 36 (58.1) |
| - Female | 26 (41.6) |
| Age (years), median (min-max) | 22 (18-39) |
| Genotype diagnosis, n (%) | |
| - Beta-thalassemia | 34 (54.8) |
| - Thalassemia beta/HbE | 28 (45.2) |
| Pre-transfusion haemoglobin, Mean (SD) | 8.51 (1.23) |
| Transferrin saturation (%), median (min-max) | 100 (34-107) |
| - ≥50%, n (%) | 59 (95.2) |
| - <50%, n (%) | 3 (4.8) |
| 4 Months-mean of Ferritin serum,(ng/mL), median (min-max) | 5130 (741-18605) |
| - <1000 ng/mL, n (%) | 1 (1.6) |
| - 1000-2500 ng/mL, n (%) | 9 (14.5) |
| - >2500 ng/mL, n (%) | 52 (83.9) |
| Iron chelation, n (%) | |
| - Deferiprone | 29 (46.8) |
| - Deferasirox | 5 (8.1) |
| - Deferoxamine | 5 (8.1) |
| - Combination | 23 (37.1) |
| Cardiac MRI T2*, mean (SD) | 24.96 (12.13) |
| - <10 ms | 7 (11.3) |
| - 10-20 ms | 17 (27.4) |
| - >20ms | 38 (61.8) |
| Ejection fraction, mean (SD) | 67.55 (6.50) |
| E/A ratio | 1.51 (1.10-2.70) |
| E/A category, n (%) | |
| - <1 | 0 (0) |
| - 1-2 | 57 (91.9) |
| - >2 | 5 (8.1) |

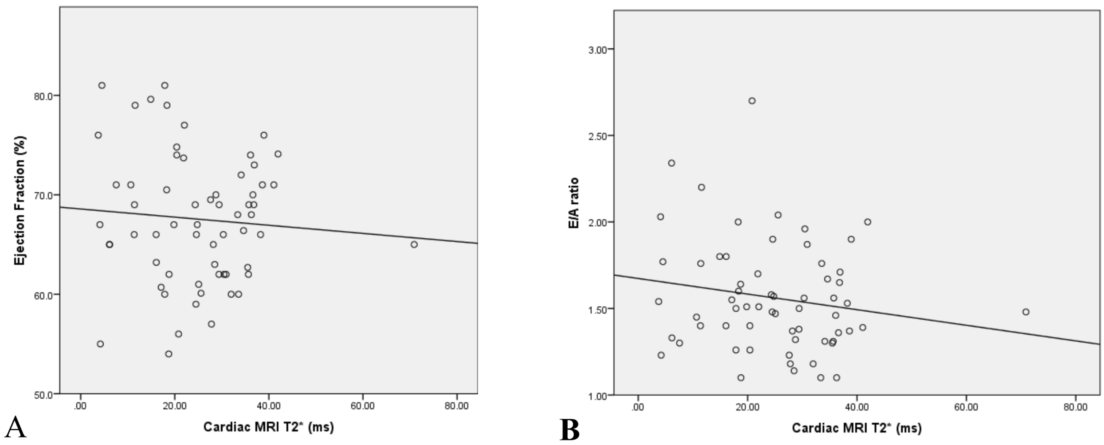


**Figure 1.** Correlation Between Cardiac Iron Toxicity with Ejection Fraction (A) and E/A ratio (B)

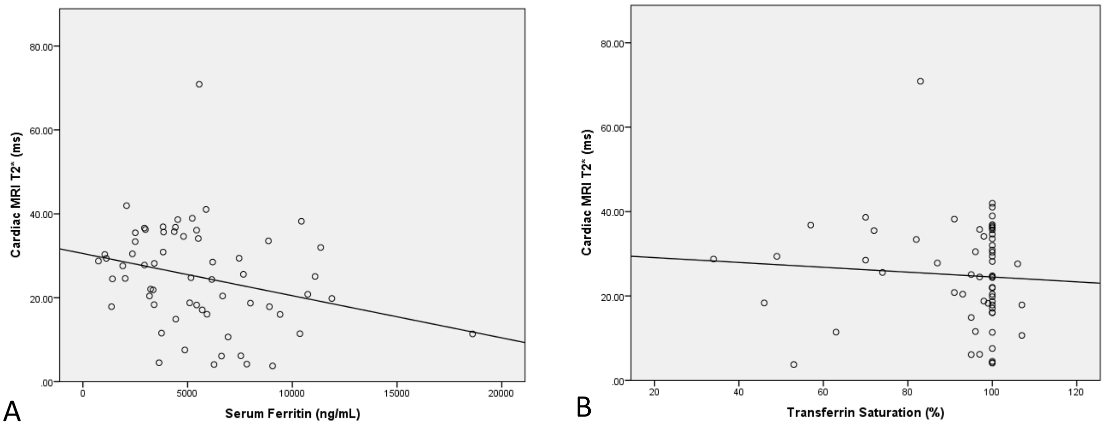


**Figure 2.** Correlation Between serum ferritin with MRI T2* (A) and transferrin saturation with MRI T2* values (B)

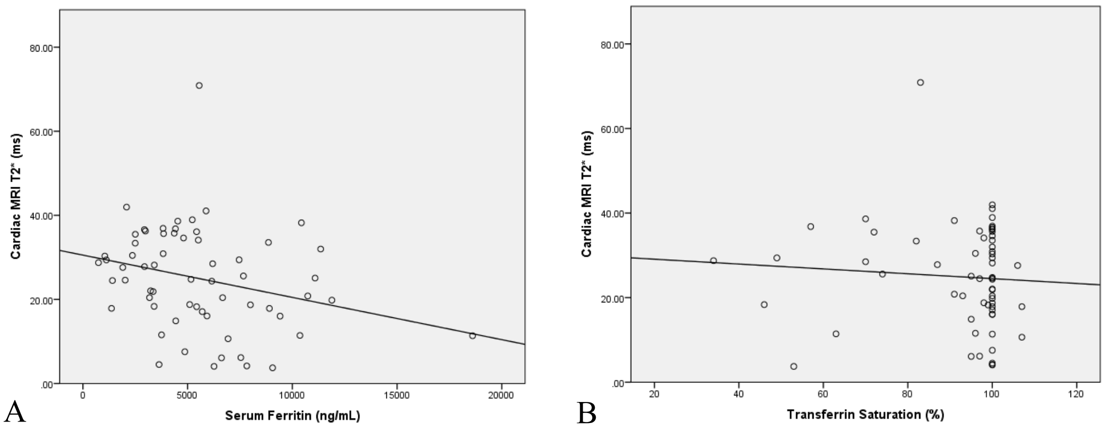


**Figure 3.** Correlation Between serum ferritin with ejection fraction (A) and transferrin saturation with ejection fraction (B)

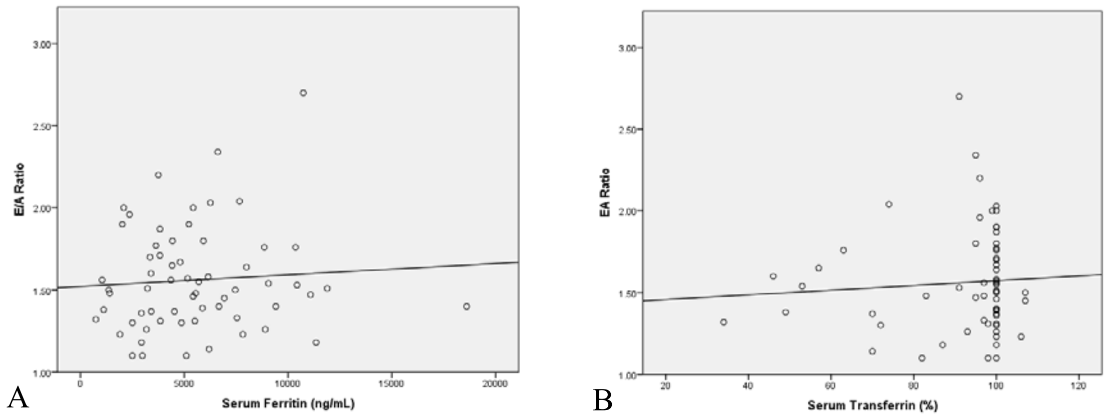


**Figure 4.** Correlation Between serum ferritin with diastolic function (A) and transferrin saturation with diastolic function (B)

## DISCUSSION

The median of 4-months ferritin serum in this study was 5130 ng/mL. Amrita et al[16] in 2020 found that the mean ferritin level in transfusion-dependent beta thalassemia in Surabaya was 5137.8 ng/mL and the median age was 23 years old, which is almost exactly identical to this study because study was done in same country. The Turkish Study found less than both study (2,072 ng/mL).[17]

This study showed 38.7% subjects had mean cardiac T2*<20 ms. Studies in other countries showed 30-85% subjects had mean cardiac T2 * <20 ms.[8] Patton et al showed 74% subjects had the cardiac T2* < 20 ms, while a study in Thailand showed 7.8% subjects had abnormal cardiac T2* MRI values because 12.1% of the subjects were non-transfusion dependent.[18]

The mean ejection fraction of this study was 67.55 % which wasalmost as similar as those in a study by Chinprateep, et al[18] that showed the mean ejection fraction of 63.59%. Chinprateep et al.[18] showed slightly lower ejection fraction values than this study (63.59% vs 67.55%) because the mean age of the subjects was older than this study (27.5 years vs 22 years).

All of the subjects in this study had impairment of diastolic function though only 38.7% subjects had abnormal cardiac MRI T2*. Chinprateep, et al[18] found 89.5% subjects with mean age of 27.5 years old already had diastolic dysfunction but only 7.2% subjects had had abnormal cardiac MRI T2*. This data proved that diastolic dysfunction has happened before abnormal cardiac MRI T2*.[18] Therefore, diastolic dysfunction can be used for early detection of iron toxicity.

There was a weak correlation between serum ferritin and cardiac MRI T2* (r=-0.272, p=0.032) in this study. Study by Yuksel et al.[17] found moderate negative correlation between ferritin and cardiac MRI T2* values (r=-0.34, p=0.009). The Turkish study got moderate correlation. Patton et al[19] also showed a moderate negative correlation between serum ferritin and cardiac MRI T2*.

No correlation between cardiac MRI T2* and ejection fraction was found in this study. Patton, et al[19] and Alpendurada, et al[20] showed a correlation between iron toxicity and systolic cardiac function, however mean T2* was lower (13.4 and 18.4 ms) and hemosiderosis was seen in more than 50% of study patients. Patton, et al[19] found that marked decrease in cardiac function was found in subjects with cardiac MRI T2*<10 ms, indicated by median ejection fraction of 49%. According to Penell, et al[8,21], the ejection fraction would decline at an advanced stage of cardiac hemosiderosis. The value of MRI T2* and cardiac function has a weak correlation until it reaches its critical values when the deterioration of cardiac function occurs rapidly.[19] Approximately 61,8% of subjects of this study has normal T2* value, therefore mean of EF of this study was normal. This study failed to show correlation between iron toxicity and cardiac function, particularly ejection fraction. Cardiac failure in thalassemia patients, caused by systolic dysfunction, occurrs at the late stage of the disease.

This study showed no correlation between iron toxicity and diastolic dysfunction. There were no subjects who had normal diastolic dysfunction in this study. However, several other studies showed iron toxicity and diastolic dysfunction correlation. Djer et al[22] found a correlation between MRI T2 * and the E / A ratio. Aessopos et al[23]also showed a weak correlation between MRI T2 and E / A *. Diastolic dysfunction, however, occurrs earlier than systolic dysfunction.[14]

This study showed a weak correlation between serum ferritin and left ventricular ejection fraction. The same as this study, Akpinar et al[20] showed a weak correlation between both. But this study didn't show correlation between serum ferritin and diastolic function because there were no subject who had normal diastolic function. Nisli et al[24] and Akpinar et al[20] found a correlation between serum ferritin and diastolic function, compared the diastolic function with healthy control subjects. This is due to the fact that from the three different forms of iron in myocytes, labile cellular iron (LCI) is the most toxic. It is only when ferritin converts to LCI that it leads to impaired contractility and congestive cardiac failure. Besides that immunoinflammatory and genetic factors also contribute such as myocarditis, the HLA genotype and apolipoprotein E genotype.[11]

This study showed correlation between serum ferritin level and iron toxicity and correlation between serum ferritin level and systolic function, but did not show correlation between iron toxicity and cardiac function. Learning from other studies about iron toxicity and cardiac function, this correlation depends on the proportion of subjects with cardiac iron toxicity. More proportion of subjects with cardiac iron toxicity means stronger correlation to systolic dysfunction. But, correlation between iron toxicity and diastolic dysfunction would be marked if the proportion of subjects with iron toxicity was lesser because diastolic dysfunction has happened before severe iron toxicity.

### Limitation of the Study

This study was a correlation study that did not account for other factors that contribute to cardiac dysfunction in Thallasemia patients beyond iron toxicity. The results from several studies can be concluded that cardiac toxicity in Thallasemia patients were influenced by other factors beyond iron toxicity. Studies that involve many factors beyond iron toxicity should be done.

## CONCLUSION

Serum ferritin correlated weakly with iron toxicity and ejection fraction but did not correlate with diastolic function. There is no correlation between cardiac iron toxicity with cardiac systolic and diastolic function.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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