## Original Article

# Iron Status in Chronic Kidney Disease Pediatric Patients on Hemodialysis.

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## ABSTRACT

**Introduction:** Iron overload is a well-known complication in chronic kidney disease (CKD) patients, especially on regular hemodialysis, where that can lead to harm to different organs, necessitating the search for an optimal evaluation method. This work was to screen the iron status in pediatric patients with CKD5d, assessing the degree of iron overload by biochemical iron profile and non-invasive quantitative magnetic resonance imaging (MRI) spectrometry to the liver and heart.

**Methods:** This analytical cross-sectional study was conducted on pediatric CKD patients on regular hemodialysis (HD) (CKD5d), at Pediatric Dialysis and Nephrology Unit, Children's Hospital, Ain Shams University. All patients were subjected to detailed history including the frequency of iron and blood transfusion, investigations including iron profile [serum iron, total iron binding capacity, and serum ferritin (SF)], and myocardial and hepatic iron status using quantitative MRI imaging R2* of liver iron (LIC), and myocardial iron content (MIC).

**Results:** Our study included 23 pediatric CKD5d patients with a mean (±SD) age and dialysis duration of 13.83 (± 1.90), and 6.83 (± 2.81) years, respectively. Blood transfusion was given to 4 patients (17.4%) more than 5 times during the whole dialysis duration, 17 patients (73.9%) less than 5 times, while 2 patients (8.7%) had never been transfused. All our patients received intravenous iron, in addition to Erythropoietin. Eighteen patients had iron overload, where 7 patients (30.4%) had SF between 500 -1000 ng/mL, & 11 patients (47.8%) had SF >1000 ng/mL while 5 patients (21.7%) had SF < 500 ng/mL. LIC revealed that 13 (56.5%) CKD5d patients had mild liver iron overload, 2 (8.7%) had moderate liver iron overload, and 4 (17.4%) had severe liver iron overload. Cardiac iron overload was less frequent (one patient, 4.3%). LIC had correlated positively with the age of the patients, serum iron, SF, and TSAT (r=0.483, 0.748, 0.829, 0.78 and p-value 0.020, <0.001, <0.001, <0.001 respectively).

**Conclusions:** Iron overload is a common problem in CKD5d pediatric patients, blood transfusions should be restricted, and iron supplementation should be taken very cautiously in anemic CKD patients.

**Keywords:** CKD, Ferritin, HD, Iron,

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## INTRODUCTION

A high frequency of iron overload was noted in children with different stages of CKD; therefore, a careful assessment of iron for anemia management, in addition to avoidance of overload, is very important to be determined [1]. Serum iron & ferritin are routinely used for assessing the degree of iron overload in CKD patients [2], though the accuracy is questionable, being affected by many factors, including inflammation and hepatic disease, in addition to there is no consensus on the most reliable marker of iron status in patients with pediatric CKD patients. Magnetic resonance imaging (MRI) is now the best non-invasive method of detecting tissue iron deposition in patients with iron overload [3]. MRI T2* is the one of its kind, non-invasive technique for diagnosing hepatic & cardiac iron content, determining the degree of iron deposition, and the success of iron chelator therapy, with a high level of precision [4]. However, in CKD patients, there is no published consensus on the requirements for performing MRI T2*, and the frequency. In addition to that, in pediatric CKD patients, the relationship between serum ferritin and cardiac iron centration (CIC) and liver iron concentration (LIC) has not been well investigated, lacking a set cut-off value, which necessitates more precise workups. Further investigation with more accurate methods. Therefore, this study aimed to screen the iron status in pediatric patients with CKD5d by routine iron profile & by noninvasive quantitative MRI spectrometry, in addition to determine their correlations, also with other variables.

## METHODS

Analytical cross-sectional study was carried out at Pediatric Dialysis and Nephrology Unit, Children's Hospital, Ain Shams University, where an informed written consent was obtained from the parents of the patients, with approval of the Ethics Committee of Faculty of Medicine, Ain Shams University with approval number of FMASU MS 373/2021. It was conducted on pediatric patients under regular HD for at who received 3-hour HD sessions thrice per week, where patients received a combination of Online Hemodiafiltration (OL-HDF), and high flux HD sessions. Most of our patients were receiving medications for hypertension, erythropoietin stimulating agents (ESA) in a dose of 150 IU/kg/dose thrice per week, intravenously, in addition to phosphate binders, calcium, vitamin D supplements, and L-carnitine. A total of 23 pediatric CKD patients were included from March 2021 to September 2022. Sample size was calculated using epi, version 3. Open-source calculator and based on a study carried out by Atkinson et al. (2010) [15], which was sufficient to achieve study objectives given that the hypothesized % frequency of outcome factor in the population (p) is 93%, with margin of error +/- 10, confidence level 95%, and design effect (for cluster surveys-DEFF) =1. Noncompliant patients who have chronic hemolytic anemia, HCV positive, organomegaly and skin pigmentation were excluded from the study. Patients were allocated into 3 groups according to their SF level at the start of the study, where group 1 had patients with levels less than 500 ng/ml, group 2; levels above 500 ng/mL and up

to 1000 ng/mL, while group 3 had levels more than 1000 ng/mL.

All patients were subjected to detailed history including the cause, age of onset of CKD, duration, frequency of regular HD, blood transfusion frequencies, the use of erythropoietin stimulating agents (ESAs), iron therapy including the route, and frequency. Detailed clinical examination including anthropometrics, and blood pressure z scores. Laboratory investigations were done pre-dialysis session in the midweek, including complete blood count, iron profile, bone profile. Echocardiography was performed for all patients after HD sessions, to assess their cardiac status. Quantitative MRI R2* and T2* for calculation of liver & myocardial iron contents respectively (LIC, MIC) were performed after termination of hemodialysis session.

Patient preparation: Full clinical history was reviewed. Patients were instructed to lie supine on MRI table, and keep regular quiet breathing, and to avoid swallowing excessively. Skin was cleaned then ECG electrodes were placed. For imaging with multi-element phased-array coils, specific cardiac or thoracic coils were utilized.

Scan protocol: A 1.5-T MR scanner (Philips Medical Systems, Acheiva, Netherlands) was used for the MRI investigation, and single breath-hold multi-echo method was used to gate the respiratory and ECG signals, where single shot dual inversion black blood breath-hold scan (BB-SSh-BH); axial, left anterior oblique (LAO), vertical long axis, four chamber view (P4CH); axial, multiecho Turbo Field Echo (mTFE), Cardiac BB (Black blood) short axis with TE (from 1.2-17.3 msec. ), multiecho Turbo Field Echo (mTFE) Cardiac WB (White blood) short axis, with TE (from 2.3- 19.8 msec.), multiecho Turbo Field Echo (mTFE) Liver FIG (Axial) with TE (from 1-12 msec.). After acquiring transverse localizer pictures, a parasagittal slice was placed through the Left Ventricular (LV) apex and the middle of the mitral annulus at the end of the expiratory phase to create a two-chamber (Vertical Long-Axis (VLA)) cine image.

MRI image acquisition: the right hepatic lobe and mid-septal myocardial T2* values were measured for iron deposition at a slow rate of 200 T m-1 s-1 and a maximum gradient strength of 45 mT m- 1.

Image interpretation: liver and myocardial T2* and R decay were calculated by a semi-automated analysis software using manual analysis in an electronic spread sheet (a plug in of CMR tools, Cardiovascular Imaging Solutions, London, UK). liver iron contents (LIC), and myocardial iron concentration (MIC) were measured, where iron overload risk classification for cardiac T2* values, the cut-off values were; normal if level was >20 ms, low risk if it was between 15-20 ms, intermediate risk between 10-15 ms, and high risk if below 10 ms. Meanwhile for LIC values, cut-off points were normal level: < 2mg/g dry liver, low risk: 2-7 mg/g, intermediate risk: 7-14mg/g, high risk: >14 mg/g **[5].**

## STATISTICAL ANALYSIS

The collected data was analyzed using SPSS v25 (IBM Inc., Chicago, IL, USA). Quantitative data were presented as mean, standard deviation (± SD) and range for parametric data, while median and interquartile range (IQR) for non-parametric data. Qualitative data was

presented as frequency and percentage. Quantitative data was studied using the student t test to compare between two study groups for parametric data and Mann Whitney Test (U test) was used for non-parametric data. To evaluate the degree to which two quantitative variables are associated, correlation analysis was utilized. P value was considered significant if below 0.05.

## RESULTS

The mean (±SD) age of our patients was 13.8 ± 1.9 years, 14 (60.9%) males & 9 (39.1%) females with dialysis duration of 6.83 ± 2.81 years. Our patients were categorized according to their SF level, where we had 5 patients (21.7%) had level < 500 ng/mL, 7 patients (30.4%) 500 -1000 ng/mL, & 11 patients (47.8%) >1000 ng/ml. Anthropometric and blood pressure measurements revealed that most of our patients were underweight, short in stature with controlled hypertension by medications. **Table 1** shows the etiology of CKD and clinico-demographic data of our studied patients.

Congenital anomalies of the kidney and urinary tract (CAKUT) were the most common cause of CKD5d, where 11 patients had CAKUT, where 6 (54.55%) patients had mild hepatic iron overload, 2(18.18%) patients had moderate hepatic iron overload, 1(9.09%) patient had severe hepatic iron overload. Nephronophthisis was found in 4 (17%) patients, where 3(75%) patients had mild hepatic iron overload, 1(25%) patient had severe hepatic iron overload. Podocytopathy was found in 4 (17%) patients, where 1 (25%) of them had mild hepatic iron overload and 2 (50%) patients with severe hepatic iron overload **Figures 1 and 2.** Ciliopathy was found in 2 (9%) patients, both (100%) had mild hepatic iron overload. In 2 (9%) patients the etiology was unknown, and only one of them (50%) had mild hepatic iron overload. All studied patients had no cardiac iron overload, except for one (9.09%) patient with CAKUT, who had mild myocardial iron overload. **Table 2** shows the etiology of CKD with iron overload in liver and heart.

On studying the frequency of blood transfusion, route of iron supplementation and type of erythropoietin stimulating agents (ESA) during the whole dialysis duration, 2 patients (8.7%) hadn't received any blood, while 17 (73.91%) received it, but less than 5 times during the whole dialysis duration, meanwhile 4 (17.39%) patients received it more than 5 times. All our patients received intravenous iron, where 19 (82.6%) patients received it monthly. The frequently used ESA was Eprex (15 patients, 65.2%) and the remaining used Aranesp (8 patients, 34.8%) **Table 3**.

Most of our CKD5d patients had anemia, and high ferritin levels. Echocardiographic examinations showed that the mean ejection fraction (EF %) (±SD) was 66.61 ± 6.6, where 1 (4.3%) patient had left ventricular systolic dysfunction (EF < 40%), and 3 (13%) had left ventricular diastolic dysfunction. Fourteen patients (60.9%) had ventricular hypertrophy. Cardiac and hepatic iron contents were examined by MRI R* and T2* respectively, revealed the mean (±SD) LIC (mg/g) was 7.74 ± 7.5, where 13 (56.5%) CKD5d patients had mild liver iron overload, 2 (8.7%) had moderate overload and 4 (17.4%) had severe liver iron overload. The mean (±SD) of CIC was

26.22 ± 5.29 ms, where only one (4.3%) patient had mild iron overload **Table 4**.

There was a negatively significant correlation between cardiac iron content by MRI T2* (ms) and LV systolic dysfunction, where cardiac iron overload is associated with the LV systolic dysfunction. There was a significant difference between liver iron content by MRI T2* (mg/g) and SF levels, where CKD5d patients who had SF levels < 500 ng/mL, had less LIC than those with SF >1000 ng/mL. No similar finding could be found with other parameters **Table 5.**

LIC by MRI R2* had significant positive correlations with the age of the patients, serum iron, SF, and TSAT (r=0.483, 0.748, 0.829, 0.78 and p-value 0.020, <0.001, <0.001, and <0.001 respectively) **Figures 3 and 4**, where older patients, those with high serum iron, SF and TSAT, had a higher LIC, meanwhile CIC correlated negatively with hemoglobin level **Tables 6 and 7.**

We have found that the most significant factors affecting the liver iron content by MRI T2* (mg/g) were serum iron and SF levels, that could be used as markers of assessing LIC in pediatric CKD5d, where the cutoff values should be determined by using larger sample size **Table 8**.

**Table 1:** Etiology of CKD, clinico-demographic data of studied patients (no. = 23)

| | | |
|---|---|---|
| **Etiology** | CAKUT | 11 (48 %) |
| | Nephronophthisis | 4 (17 %) |
| | Podocytopathy | 4 (17 %) |
| | Ciliopathy | 2 (9 %) |
| | Unknown | 3 (13%) |
| **Groups according to serum ferritin level** | Ferritin < 500 ng/mL | 5 (21.7%) |
| | Ferritin 500 -1000 ng/mL | 7 (30.4%) |
| | Ferritin >1000 ng/mL | 11 (47.8%) |
| **Gender** | **Male** | 14 (60.9%) |
| | **Female** | 9 (39.1%) |
| **Age (±SD) years** | | 13.83 ± 1.90 |
| **Duration of hemodialysis (±SD) years** | | 6.83 ± 2.81 |
| **Z score for weight** | | -2.75 ± 1.69 |
| **Z score for height** | | -3.07 ± 1.95 |
| **BMI Z score** | | -0.79 ± 1.50 |
| **Systolic blood pressure Z score** | | 2.18 ± 1.72 |
| **Diastolic blood pressure Z score** | | 3.41 ± 1.72 |

BMI: Body mass index, CAKUT: congenital anomalies of the kidney and urinary tract, Data are presented as mean ± SD or frequency (%).

**Table 2:** Liver and cardiac iron overload according to different etiologies of CKD

| | | **CAKUT** | **Nephronophthisis** | **Podocytopathy** | **Ciliopathy** | **Unknown** |
|---|---|---|---|---|---|---|
| | | 11 (48 %) | 4 (17 %) | 4 (17 %) | 2 (9 %) | 2 (9 %) |
| **Heart** | **No** | 10(90.91%) | 4 (100%) | 4 (100%) | 2 (100%) | 2 (100%) |
| | **Mild** | 1 (9.09%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Liver** | **No** | 2 (18.18%) | 0 (0%) | 1 (25%) | 0 (0%) | 1 (50%) |
| | **Mild** | 6 (54.55%) | 3 (75%) | 1 (25%) | 2 (100%) | 1 (50%) |
| | **Moderate** | 2 (18.18%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | **Severe** | 1 (9.09%) | 1 (25%) | 2 (50%) | 0 (0%) | 0 (0%) |

CAKUT: Congenital Anomalies of the Kidney and the Urinary Tract.

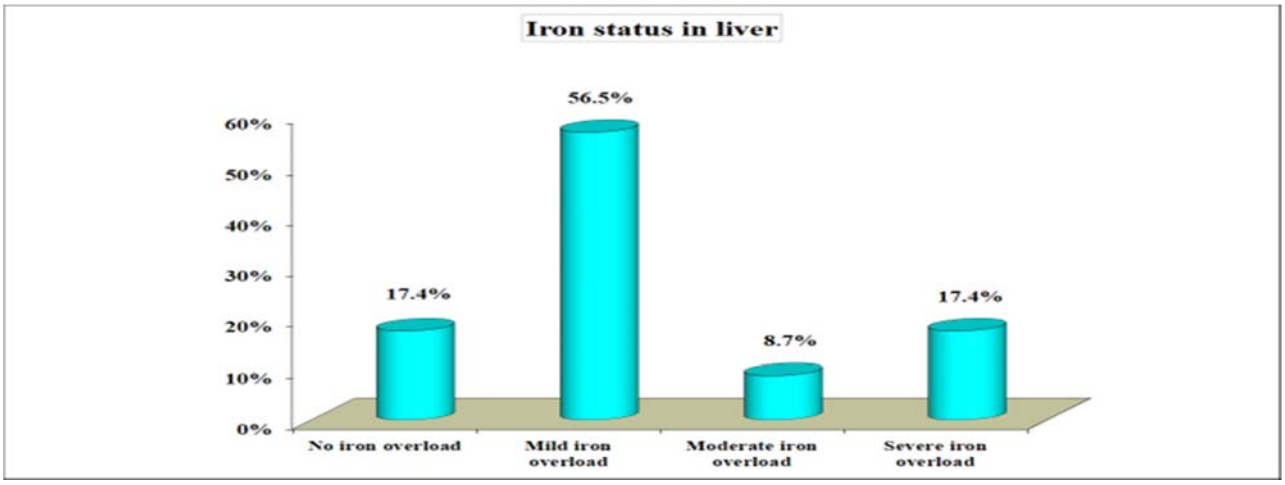


**Figure 1:** LIC in our studied cases

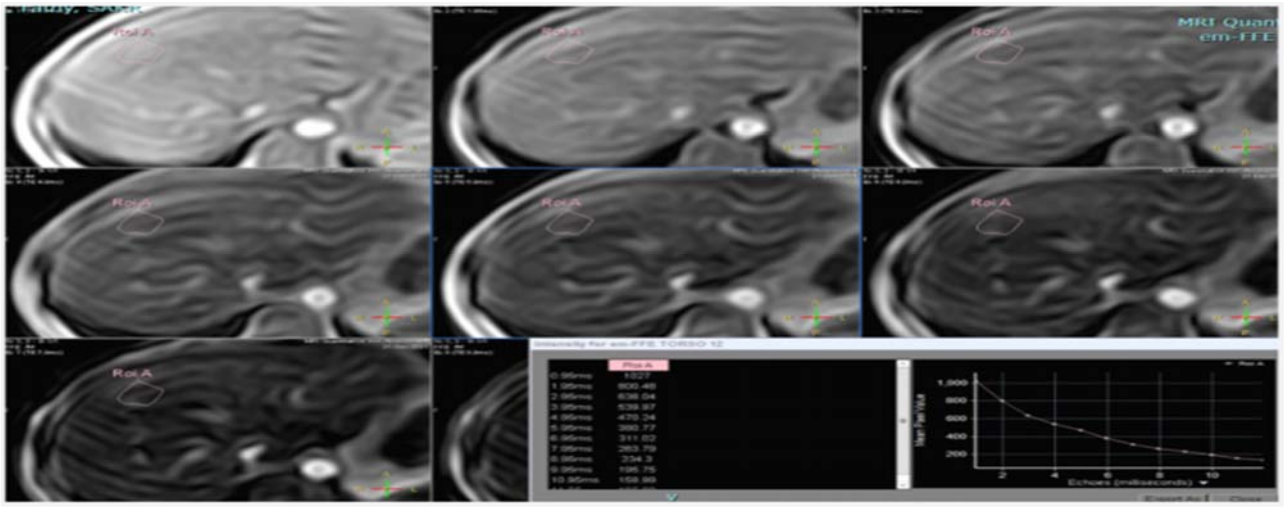

**Figure (2 A):** MRI assessment of hepatic T2* value with a ROI drawn in the periphery of the right hepatic lobe.

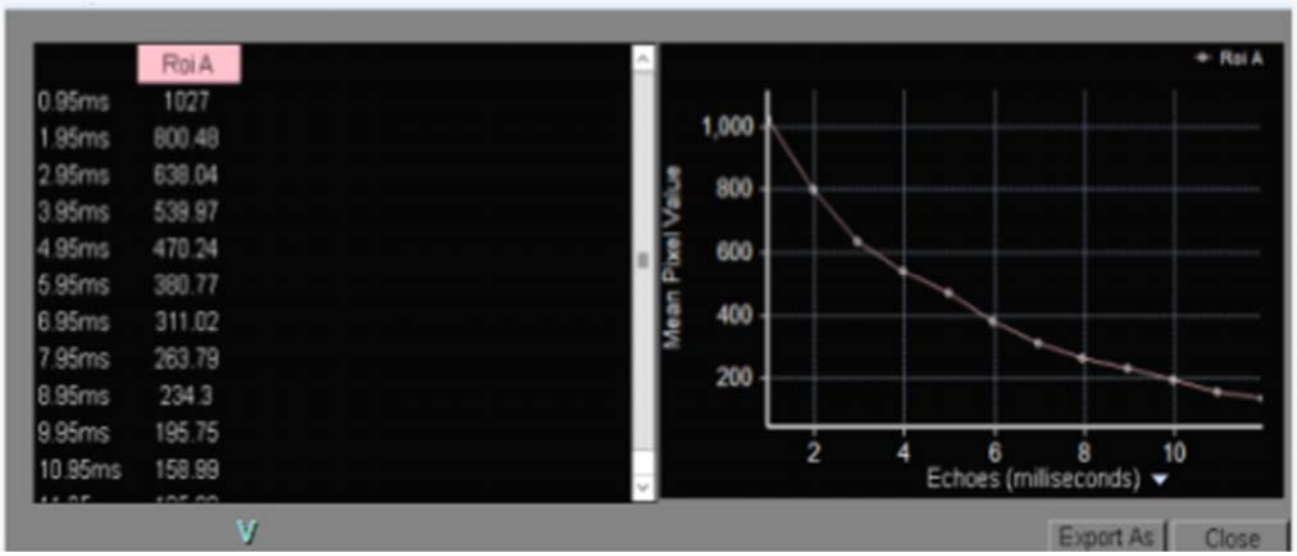


**Figure (2B):** shows slow signal decay over time indicating mild hepatic iron load.

**Table 3:** History of blood transfusion, iron, & ESAs supplementations during the whole dialysis duration (no. = 23)

| | | |
|---|---|---|
| **Blood transfusion frequency** | No blood transfusion | 2 (8.7%) |
| | ≤ 5 times | 17 (73.91%) |
| | >5 times | 4 (17.39%) |
| **Frequency of iron supplementation** | Monthly | 19 (82.6%) |
| **Route of iron supplementation** | IV | 23 (100.0%) |
| | Oral | 0 (0.0%) |
| **Type of ESAs** | Aranesp | 8 (34.8%) |
| | Eprex | 15 (65.2%) |

Data are presented as frequency (%). ESAs: Erythropoietin stimulating agents, IV: Intravenous,

**Table 4:** The laboratory data, myocardial & liver iron content according to MRI T2* results

| **VARIABLES** | | **Mean ± SD no. (%)** | **Median (IQR)** |
|---|---|---|---|
| **Laboratory data** | Serum albumin (g/dL) | 4.20 ± 0.33 | 4.2 (3.9 - 4.4) |
| | Serum iron (mg/dL) | 99.23 ± 99.46 | 69 (46.7 - 100.9) |
| | Serum ferritin (mg/dL) | 1639.72 ± 1870.23 | 977.1 (509 - 2610) |
| | TIBC (µg/dL) | 224.97 ± 38.44 | 223.1 (202.1 - 246) |
| | TSAT % | 43.54 ± 39.01 | 33.33 (19.97 - 51.22) |
| | Hgb (g/dL) | 10.49 ± 1.65 | 10.5 (9.2 - 11.5) |
| **Cardiac status** | EF% | 66.61 ± 6.68 | 68 (63 - 70) |
| | LV systolic dysfunction | 1 (4.3%) | -- |
| | LV hypertrophy | 14 (60.9%) | -- |
| | LV Diastolic dysfunction | 3 (13%) | -- |
| **Mean (±SD) Liver iron content by MRI R2* (mg/g)** | | 7.74 ± 7.50 | 5.0 (3.85- 8.57) |
| Normal < 2 (mg/g) | | 4 (17.4%) | ---- |
| Mild 2-7 (mg/g) | | 13 (56.5%) | |
| Moderate 7-15 (mg/g) | | 2 (8.7%) | |
| Severe >15 (mg/g) | | 4 (17.4%) | |
| **M ean (±SD) Cardiac iron content by MRI T2* (ms)** | | 26.22 ± 5.29 | 24.7(22.4 - 29.8) |
| Normal >20 (ms) | | 22 (95.7%) | ---- |
| Mild 15-20 (ms) | | 1 (4.3%) | |
| Moderate 10-15 (ms) | | 0(0.0%) | |
| Severe < 10 (ms) | | 0 (0.0%) | |

EF: Ejection fraction, Hgb: Hemoglobin, IQR: Interquartile range, LV: Left Ventricular, MRI: Magnetic resonance imaging, TIBC: Total iron binding capacity, TSAT: Transferrin saturation.

**Table 5:** Relation of liver and cardiac iron content by MRI R2* and T2* respectively (mg/g) with some demographic, clinical & laboratory data

| | | | **Liver iron content by MRI R2* (mg/g)** | | **P-Value** |
|---|---|---|---|---|---|
| | | | **No.** | **Median (IQR)** | |
| **Groups** | **1** | SF <500 ng/mL | 5 | 1.35 (0.72 - 1.84) | 0.002* |
| | **2** | SF 500-1000 ng/mL | 7 | 4.49 (3.85 - 4.6) | |
| | **3** | SF >1000 ng/mL | 11 | 8.57 (5.49 - 19.9) | |
| **Gender** | | Male | 14 | 4.8 (3.85 - 7.4) | 0.753 |
| | | Female | 9 | 5.49 (4 - 8.57) | |
| **LV systolic dysfunction** | | No | 22 | 4.8 (3.85 - 7.4) | 0.366 |
| | | Yes | 1 | 8.57 (8.57 - 8.57) | |
| **LV hypertrophy** | | No | 9 | 5 (4 - 7.4) | 1.00 |
| | | Yes | 14 | 5.02 (3.85 - 8.57) | |
| **LV Diastolic dysfunction** | | No | 19 | 4.6 (3.54 - 7.4) | 0.372 |
| | | Yes | 4 | 7.03 (4.88 - 9.11) | |
| | | Yes | 1 | 7.4 (7.4 - 7.4) | |

**Table 5:** Relation of liver and cardiac iron content by MRI R2* and T2* respectively (mg/g) with some demographic, clinical & laboratory data **(Continued).**

| | | | Cardiac iron content by MRI T2* (ms) | | P-Value |
|---|---|---|---|---|---|
| | | | NO. | Mean ± SD | |
| Group | 1 | SF <500 ng/mL | 5 | 25.14 ± 6.07 | 0.886 |
| | 2 | SF 500-1000 ng/mL | 7 | 26.5 ± 5.04 | |
| | 3 | SF >1000 ng/mL | 11 | 26.53 ± 5.56 | |
| Gender | | Male | 14 | 26.61 ± 5.19 | 0.67 |
| | | Female | 9 | 25.61 ± 5.7 | |
| LV systolic dysfunction | | No | 22 | 25.72 ± 4.84 | 0.032* |
| | | Yes | 1 | 37.10 | |
| LV hypertrophy | | No | 9 | 27.02 ± 5.43 | 0.571 |
| | | Yes | 14 | 25.7 ± 5.34 | |
| LV Diastolic dysfunction | | No | 19 | 26 ± 5.12 | 0.678 |
| | | Yes | 4 | 27.25 ± 6.79 | |
| | | Yes | 1 | 22.70 | |

*Significant as p-value < 0.05. LV: Left ventricle.

**Table 6:** Correlation of liver iron content (LIC) by MRI R2* (mg/g) with some demographic, clinical, & laboratory data.

| | Liver iron content by MRI R2* (mg/g) | |
|---|---|---|
| | r | p-Value |
| Age (years) | 0.483 | 0.020 |
| Frequency of blood transfusion | 0.386 | 0.069 |
| Duration of HD (years) | 0.550 | 0.117 |
| Hgb (g/dL) | -0.048 | 0.829 |
| Serum Iron (mg/dL) | 0.748 | <0.001* |
| SF (mg/dL) | 0.829 | <0.001* |
| TIBC (µg/dL) | -0.037 | 0.868 |
| TSAT % | 0.78 | <0.001* |

*Significant as P-value < 0.05. DBP: Diastolic Blood Pressure, EF: ejection fraction, Hgb: hemoglobin, SBP: Systolic Blood Pressure, TIBC: total iron binding capacity, TSAT: transferrin saturation.

**Table 7:** Correlation between cardiac iron content by MRI T2 *(ms) with some demographic, clinical & laboratory data.

| | Cardiac iron content by MRI T2 (ms) | |
|---|---|---|
| | r | p-Value |
| Age (years) | 0.072 | 0.743 |
| Frequency of Blood transfusion | 0.016 | 0.941 |
| Duration of hemodialysis (years) | -0.063 | 0.776 |
| Hgb (g/dL) | -0.470 | 0.023* |
| Serum iron (mg/dL) | -0.079 | 0.722 |
| SF (mg/dL) | -0.067 | 0.761 |
| TIBC (mg/dL) | -0.391 | 0.065 |
| TSAT% | 0.035 | 0.874 |
| EF% | -0.138 | 0.531 |

BMI: body mass index, DBP: diastolic blood pressure, EF: ejection fraction, Hgb: hemoglobin, SBP: systolic blood pressure, TSAT: transferrin saturation

**Table 8:** Multivariate Regression analysis between liver iron capacity by MRI R2* (mg/g) with other variables.

| | B | Std. Error | Beta | t-test | Sig. |
|---|---|---|---|---|---|
| Age (years) | -0.362 | 0.498 | -0.092 | -0.727 | 0.477 |
| Duration of HD (years) | 0.158 | 0.315 | 0.059 | 0.502 | 0.622 |
| Iron (mg/dL) | 0.110 | 0.044 | 1.455 | 2.477 | 0.025 |
| Ferritin (mg/dL) | 0.003 | 0.000 | 0.734 | 6.762 | < 0.001* |
| TSAT % | -0.185 | 0.115 | -0.960 | -1.607 | 0.128 |

*Significant as P-value < 0.05. HD: Hemodialysis, TSAT: transferrin saturation

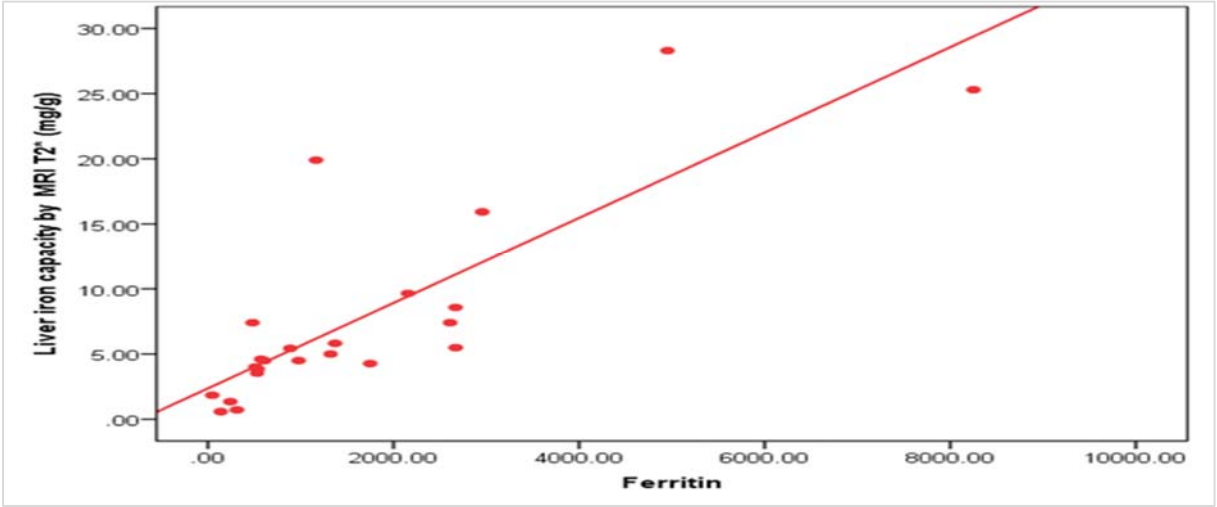


**Figure 3:** Correlation between liver iron content by MRI T2* (mg/g) and SF

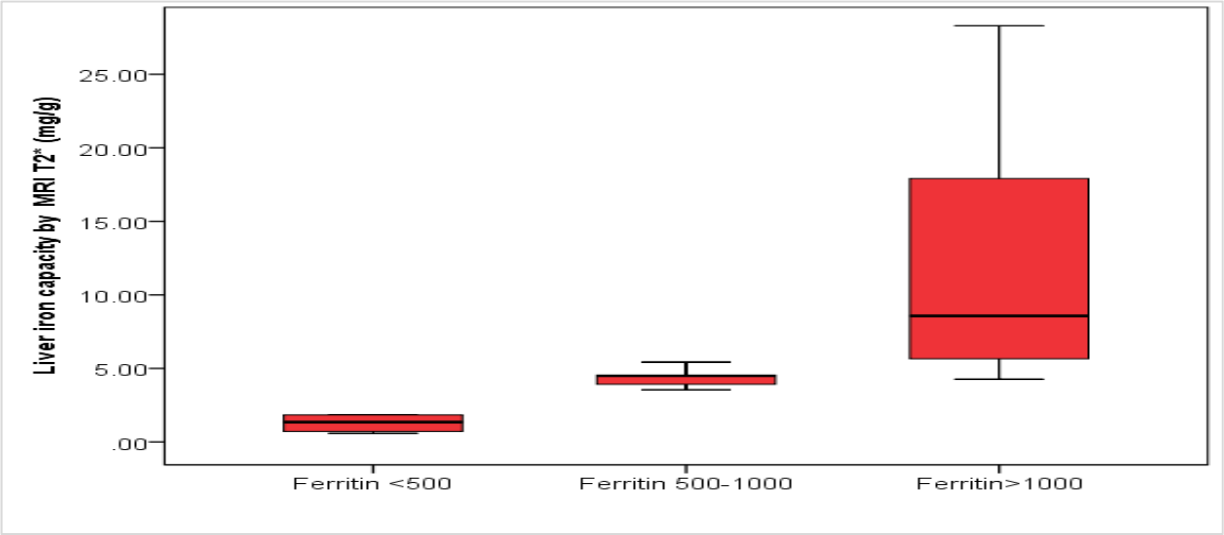


**Figure 4:** Shows the difference between Liver iron content by MRI T2* (mg/g) and SF.

## DISCUSSION

This analytical cross-sectional study was conducted on 23 CKD5d pediatric patients, where patients were allocated into three different groups based on their SF level, where group 1 had level < 500 ng/mL, group 2 level was between 500 ng/ml to 1000 ng/mL, while group 3, level was >1000 ng/mL.

According to our research, the main causes of CKD were CAKUT (48%), nephronophthisis (17%), podocytopathy (17%), and ciliopathy (9%). However, 9% of cases remained unknown. Our results were consistent with studies conducted by Lee et al. [5] and Mohammed et al. [7], which also found that congenital anomalies were the predominant cause of CKD in pediatric patients (41.4% and 47%, respectively). In contrast, Ruiz-Jaramillo et al. [8] reported that the etiology of renal failure was unknown in 106 (74%) of their patients in a cross-sectional study.

There was a male predominance in our study where 60.9% were male, and 39.1% were females, with mean (±SD) age and dialysis duration of 13.83 (± 1.90), 6.83

(±2.81) years respectively. This male predominance may be attributed to the cause of CKD, which was mainly due to CAKUT, that is common in males. Similarly, Lee et al. [6] and Mohammed et al. [7] found that pediatric CKD was predominant in males than in females.

In our studied patients, most of them (16 patients, 70%) had controlled (on medications) systolic hypertension, which is a known complication of CKD. This was almost the same result as in previous study regarding the management of hypertension of CKD pediatric patients where, it was seen in 70.2 % of their studied cases, but all of them were controlled [7].

Echocardiographic examinations for all our studied patients revealed that 4.3% of our CKD5d patients had left ventricular systolic dysfunction (EF% < 40%), 13% had left ventricular diastolic dysfunction, and 60.9% had left ventricular hypertrophy. The measured serum ferritin level showed that 5 (21.7%) patients had level <500 ng/mL, while 7 patients (30.4%) had level between 500-1000, and 11 patients (47.8%) had level >1000. Upon these results, detailed history about iron intake, blood transfusion & other haematinics was taking, where 8.7% of our patients hadn't received any transfusion, while 73.91% received it less than 5 times, and 17.39% received it more than 5 times during the whole dialysis duration. All our CKD5d patients received intravenous iron supplementations, and erythropoiesis stimulating agents (ESA), however, most of our patients had anemia. These findings may be attributed to the status of chronic inflammation in CKD patients, that resulted in dysregulation of iron homeostasis, in addition to the uremia, oxidative stress, and nutritional deficiencies [9], which all causes anemia that necessitated packed RBCs transfusion & hence the development of iron overload. In agreement with our results, previous studies [8, 6] found a significantly increased SF levels among the anemic CDK pediatric patient.

Regarding the non-invasive assessment of iron overload in our studied CKD5d patients, the mean (±SD) liver iron content (LIC) that was measured by MRI R2*, was 7.74 (± 7.5) mg/g, where 56.5% CKD5d patients had mild liver iron overload, 8.7% had moderate overload, and 17.4% had severe liver iron overload, meanwhile the mean (±SD) cardiac iron content was 6.22 (± 5.29) ms, where only one patient (4.3%) had mild iron overload. In the same context, Ambarsari et al. [1] reported that 29% of the children had mild liver iron overload.

Unlike our results, Rostoker et al. [10] had assessed LIC of 119 CKD5d patients, who received iron and erythropoiesis-stimulating agents, by the help of MRI R2 *, which revealed that liver iron overload excess was seen in 84%, where 36% of them had severe iron overload, therefore, they concluded that iron concentration of the hepatic iron overload is strongly associated with to the overall amount of supplemented iron [11].

MRI R2* tests revealed a positive correlation between liver iron content (measured in mg/g) and patient age. Older patients had higher levels of liver iron content, consistent with findings from previous studies on pediatric CKD5d patients. This connection may be due to extended illness and treatment contributing to iron overload. Our findings agreed with Ambarsari et al. [1] and Ishaq et al. [12], noted a positive association between the age of pediatric CKD5d patients and iron overload, that was explained by the

prolonged duration of illness and the therapy, contributing to the iron overload.

We had noted that LIC (mg/g) by MRI R2* was significantly correlated positively with serum ferritin, iron, and TSAT levels, where CKD5d patients who had SF levels less than 500 ng/mL, had less iron over content than those with SF >1000 ng/mL, in addition to that, those who with higher serum iron and TSAT, had more LIC.

Two prospective cohort studies on hemodialysis patients who were receiving treatment for anemia with intravenous iron-sucrose and erythropoiesis-stimulating agents, and analysed correlations between iron biomarkers and MRI LIC and tested their ability to diagnose iron overload precisely, where they found that there was significant difference between LIC by MRI R2* (mg/g) and SF levels **[10, 13]**

Our study found mild cardiac iron overload in only one patient measured by MRI T2*. A positive correlation was observed between higher hemoglobin levels and greater cardiac iron overload, possibly due to packed RBCs transfusion to correct anemia. More research with a larger sample size is needed to confirm our findings. In contrast to our results, previous studies found less cardiac iron overload with low hemoglobin and iron profiles. This finding needs more studies with a larger sample size in the future. Unlike our results, Ghoti et al.**[13]**, and Rostoker et al. **[10]** found a significant positive correlation between cardiac iron content and hemoglobin level, where they explained it by the low hemoglobin and low iron profile was associated with less cardiac iron overload.

On assessing the relation of cardiac iron content by MRI T2* (ms) and echocardiographic findings of our studied CKD5d patients, a negative correlation was found with LV systolic dysfunction, where cardiac iron overload was associated with LV systolic dysfunction.

Our research findings align with those of Bayraktaroglu et al., **[14]** who found a significant negative correlation between the left ventricular (LV) end-systolic and diastolic volume indices and the myocardial iron overload MRI T2* value. Additionally, they discovered a negative association between the cardiac MRI T2* value and the LIC. Our own multivariate regression analysis model revealed that the serum levels of both iron and ferritin were the most critical factors affecting the liver iron content by MRI R2* (mg/g) in pediatric CKD5d. This information can serve as a reliable marker for assessing liver iron content, and determining a cut-off value would require a larger sample size. Similar to our findings, Rostoker et al. **[10]** and Lee et al. **[6]** also indicated that the serum levels of both iron and ferritin were the most influential factors affecting the liver iron content by MRI R2* (mg/g).

## LIMITATIONS

Due to the limited scope of our study and small sample size, we were unable to determine the threshold levels of SF and serum iron that indicate the onset of liver and cardiac iron deposition, as confirmed by MRI R and T2* scans respectively. Furthermore, there is no conclusive evidence to establish a maximum safe level of SF. The study was further complicated by the young age of the participants, their non-compliance with MRI instructions, limited access to MRI facilities, and cost constraints, all of which posed significant challenges.

## CONCLUSIONS

We observed that the LIC (mg/g) measured by MRI R2* showed a positive correlation with the levels of serum ferritin, iron, and TSAT. Among CKD5d patients, those with SF levels below 500 ng/mL had lower iron content compared to those with SF levels above 1000 ng/mL. Additionally, patients with higher serum iron and TSAT levels had a higher LIC. Iron overload is common among HD patients with CKD. Careful management is required for those with cardiac iron overload. Blood transfusions and IV iron should be administered with caution. There is no correlation between the degree of iron overload and the underlying kidney disorder. Establishing target values for serum iron and SF is important to prevent iron deposition in tissues.

## RECOMMENDATIONS

Blood transfusion and iron supplementation should be prescribed very judiciously and cautiously in CKD anemic patients. The use of chelation therapy should be commenced and warranted. Myocardial and cardiac iron status should be measured in all CKD dialysis patients. Be cautious with blood transfusions and iron supplements for anemic CKD patients. Consider chelation therapy and assess cardiac iron levels for dialysis patients.

## ABBREVIATIONS

| | | | |
|---|---|---|---|
| **BMI** | Body mass index, | **LAO** | Left anterior oblique |
| **CAKUT** | Congenital anomalies of the kidney and urinary tract | **LIC** | Liver iron contents |
| **Cardiac BB** | Cardiac Black blood | **LV** | Left Ventricular |
| **CIC** | Cardiac iron content | **MIC** | Myocardial iron concentration |
| **CKD** | Chronic kidney disease | **MRI** | Magnetic resonance imaging |
| **CKD5d** | Chronic kidney disease stage 5 on hemodialysis | **mTFE** | multiecho Turbo Field Echo |
| **DBP** | Diastolic Blood Pressure | **RBCs** | Red blood cells |
| **ECG** | Electrocardiogram | **SBP** | Systolic Blood Pressure |
| **EF** | Ejection fraction | **SD** | Standard deviation |
| **ESA** | Erythropoietin stimulating agents | **SF** | Serum ferritin |
| **HCV** | Hepatitis c virus | **TIBC** | Total iron binding capacity |
| **HD** | Hemodialysis | **TSAT** | Transferrin saturation |
| **Hgb** | Hemoglobin | **U test** | Mann Whitney Test |
| **IQR** | Interquartile range | **VLA** | Vertical Long-Axis |
| **IV** | Intravenous | **WBC** | White blood count |

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## AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-authors.
All authors contributed to authorship, have read, and approved the manuscript.
Conception and design of study: 1st & 4th
Acquisition of data: 2nd & 3rd
Analysis and/or interpretation of data: 1st & 4th
Drafting the manuscript: 2nd & 4th
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## STATEMENTS

**Ethics approval and consent to participate.**
This study protocol and the consents were approved and deemed sufficient by an informed written consent was obtained from the parents of the patients, with approval of the Ethics Committee of Faculty of Medicine, Ain Shams University with approval number of FMASU MS 373/2021, and informed written consent was obtained in every case from their legal guardians.

**Consent for publication**
The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

**Availability of data and material**
"Available for your request, anytime"

**Conflict of interest**
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