Frequency of Iatrogenic Iron Overload in Hemodialysis Patients at Qena University Hospital

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Abstract

Background: Iron overload (IO) appears in cases with end-stage renal disease (ESRD) treated with erythropoiesis-stimulating agents (ESA) & parenteral iron, with liver iron storage concentrations closely related to total body iron stores.

Objectives: To estimate the frequency of iatrogenic iron overload among end-stage chronic kidney disease patients undergoing regular HD and to ascertain the primary determinants of risk & complications associated with iatrogenic iron overload in hemodialysis cases at Qena University Hospital.

Patients and Methods: This was a cross-sectional study involving 96 adult ESRD subjects undergoing maintenance dialysis for at least three months at the nephrology unit of Qena University Hospital, from 1/12/2022 to 1/6/2023. All patients were submitted to full history taking, Full clinical examination, Estimation of body mass index, Laboratory investigation including CBC, Iron profile, Kidney function test, glomerular filtration rate, Liver function, C-reactive protein, liver fibrosis indices, inflammatory indices and liver ultrasonography.

Results:58.3percentmen& 41.7 percentwomen were included;the mean age was 53.32 ± 13.60 years, and 66.7% had less than 5 years of dialysis duration. The common causes of their CKD were hypertension (41.7%), idiopathic (28.1%), and diabetes (18.8%). They have a mean serum ferritin level of 721.96 ± 626.72 ng/ml**,** which was correlated with the patient's age and dialysis duration. 60 patients (63.22%) utilized blood transfusion; 46 (47.9%) received parenteral iron; and 42 (43.8%) got ESA. 47.22%of patients had hyperferritinemia, and 29.16% had IO. Liver ultrasonography revealed diffuse hepatic pathology (21.9%), mild hepatomegaly (6.3%),and 2.1% had a fatty liver.Out of 22 patients with normal ferritin levels, 4 have diffuse hepatic pathology (18.18%), 3 have diffuse hepatic pathology with mild hepatomegaly (13.64%), and 1 hasa bright liver (4.55%). Of 46 hyperferritinemia patients, 5 have diffuse hepatic pathology (10.87%), 2 have diffuse hepatic pathology with mild hepatomegaly (4.35%), and 5 have a bright liver (10.87%). Of 28 IO patients, 11 have diffuse hepatic pathology (39.29%), 1 has diffuse hepatic pathology with mild hepatomegaly (3.57%), 1 has liver cysts (3.57%), and 2 have fatty liver (7.14%). Patients with IO have significant heart symptoms.

Conclusion: Out of 96 ESRD patients, 29.16% had IO, and 47.92% had hyperferritinemia associated with the presence of hepatic pathology. It is necessary to monitor blood or organ siderosis, use parenteral iron cautiously, and find a safe cut-off value for ferritin.

Keywords: Hepatic siderosis; Hyperferritinemia; Liver iron concentration; Secondary iron overload.

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Introduction

Chronic kidney disease (CKD) is gaining globalrecognition as a significant public health concern **(Ghonemy et al., 2016).**

Iron deficiency anemia affects all CKD patients,especiallyas the disease progresses in long-term hemodialysis (HD) patients **(Polin et al., 2013)**. This is often due to various factors, including elevated levels of hepcidin, dietary limitations, reduced iron absorption, blood loss during the HD procedure, enteropathy associated with end-stage renal disease (ESRD), impaired platelet function due to uremia, and regular blood sampling for laboratory testing.Nearly all HD patients are treated with parenteral iron whichforms the backbone of anemia treatment to enable the full therapeutic outcome of ESA to overcome functional iron deficiency & to compensate for true iron deficiency **(Rostoker et al., 2016)**.

Shibata and Taniguchi (2013) reported iron overload (IO) with varying degrees as a commoncomplication in HD patients.In addition, excessive iron accumulation may lead to atherosclerotic plaque instability, impaired immune function, increased cardiovascular risks, increased infection susceptibility, and non-alcoholic fatty liver disease (NAFLD)**(Li et al., 2017)**. Hepatic fibrosis risk increases in patients with ferritin >1000 ng/ml and abnormal liver function tests; these patients should be further investigated **(Fitzsimons et al., 2018).**Thus, observing iron biomarkers is crucial in treating HD patients to promptly identify and mitigate risks associated with IO**(Kuo et al., 2012).**

The research intended to determine the prevalence of iatrogenic IO in ESRDcases receiving regular HDand identify risk factors and consequences.

Patients and methods

This cross-sectional trial was performed on 96 adult subjects 18 years of age or older who were undergoing maintenance dialysis for at least three months at the Department of Clinical Pathology, Qena Faculty of Medicine, South Valley University from 1/12/2022 to 1/6/2023.

Inclusion criteria: Patients with CKD-5D on regular HD for at least 6 months, four hours per session, three times per week, of both sexes and between 18and 87 years of age;most casesreceived regular rHuEpo (6-8 x 10^3 units), concomitant with IV 100 mg ferric hydroxide sucrose complex (ferric saccharate) (VENOFER, Vifor International Inc., St. Gallen, Switzerland) once weekly during the HD session.

Exclusion criteria: persons under 18 years old**,** acute kidney injury**,** stage 1–4 CKD patients under conservative treatment**,** persons with major comorbidities or concomitant malignancies, cases with renal transplantation, incomplete information, & refusal to participate in the research.

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All cases were exposed to the subsequent:

1. **History:** includes the underlying etiology of CKD, associated comorbid disorders such as liver and cardiac diseases, duration of dialysis, and medication taken, including medication for anemia treatment (EPO therapy, iron, and blood transfusion).
2. **Full Clinical Examination:**this involves evaluating the patient's overall general condition and vital signs such as pulse, blood pressure, respiratory rate, and temperature. Examining the abdomen, chest, and heart with attention on chronic liver disease manifestations such as jaundice, ascites, organomegaly, flapping tremors, and lower limb edema.
3. **Body mass index assessment (BMI):**Once determining weight and height, BMI was computed (kg/m2).
4. **Blood sampling for laboratory investigations:**
   Blood samples for the assessment of iron biological markers were obtained at least one week after the last iron infusion. 5 milliliters were drawn from arteriovenous fistulas at the insertion of the arterial needle after an overnight fasting period, about one hour from the session beginning, and were divided into 2 vacutainer tubes as follows: (2 ml) on an EDTA tube for a CBC and (3 ml) on a plain tube was left to clot and then serum was separated after centrifuging at 2000 × g for 10 minutes at room temperature for clinical chemistry evaluation.
   - **Complete blood count (CBC):** using cell dyne-Ruby (Abbott Diagnostics, Santa Clara, California, USA).
   - **Iron profile:** serum ferritin (normal levels < 200 ng/ml); using the Architect i1000SR-Abbot Diagnostics; serum iron;transferrin saturation ; total iron-binding capacity (TIBC). IO is considered if serum ferritin is > 1000 ng/ml, transferrin saturation is >45% in women and >50% in men, and hyperferritinemia (serum ferritin levels between 200 & 1000 ng/ml)**(Fitzsimons et al., 2018).**
   - **Kidney (KFT) and liver function tests (LFT):** serum urea, alanine,creatinine, and aspartate aminotransferase (AST &ALT), alkaline phosphatase (ALP) using the automated chemistry analyzer Pentra c400 (HORIBA ABX SAS, France).
   - **C-reactive protein (CRP)** using a Beckman Coulter AU480 chemistry analyzer (Beckman Coulter, Inc., USA).

5- Calculation of scores and inflammatory indices

a) **Platelet-lymphocyte ratio (PLR)(Smith et al., 2008)**.
b) **Neutrophil lymphocyte ratio (NLR) (Walsh et al., 2005).**
c) **Liver fibrosis index: Fibrosis-4 (FIB-4)(Vallet-Pichard et al., 2007).**
d) **Calculation of glomerular filtration rate**: estimatedutilizing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation**(Levey et al., 2009).**

7- Imaging: All patients were deferred to a liver ultrasound (US) evaluation. However, the use of the US for assessing hepatic IO is not viable due to its inability to identify iron deposition. However, the ultrasound can identify non-specific long-term alterations brought on by hepatic IO, such as portal hypertension, cirrhosis, or hepatocellular carcinoma(**Matheson et al., 2007).**

Ethical approval: The research gets agreement from the Ethical Committee of the Faculty of Medicine - South Valley University. The approval code was

SVUMEDCCP0311212130. Each participant gave written consent after receiving full information about the purpose and details of the study.

Statistical analysis:

The data were analysed utilising Version 27 of the Statistical Programme for Social Science (SPSS). In order to examine the distribution of the variables, the Kolmogorov-Smirnov test is applied. The standard deviation for quantitative data was given as mean ±SD. In expressing qualitative data were frequency and percentage. The ranges of non-parametric variables were represented as medians. When applicable, employ one-way analysis of variance (ANOVA) or the Kruskall-Willis test. Fisher's exact test, also known as the chi-square test, was employed to examine categorical variables. When applicable, differences between the two groups were analysed using the Mann-Whitney U test or an independent student t-test. For determining correlations between variables, Pareason's correlation coefficient (or Spearman's when some variables were ordinal and/or not normally distributed) was utilised. The objective of the regression analysis was to identify predictors of IO in HD patients. P-values with two tails less than 0.05 were deemed significant.

Results

The study involved a total of 96 ESRD cases with a mean age of 53.32 ± 13.60 years(56 male (58.3%), 40 female (41.7%)). The recorded common causes of their CKD were hypertension (41.7%), idiopathic (28.1%), and diabetes (18.8%).64 (66.7%) of patients had less than 5 yearsof HD duration, 28 (28.1%) had 5-10 years, and 4 (5.2%) had more than 10 years of dialysis duration. The common comorbidities were cardiac disorders, hypertension, and gastrointestinal disorders, accounting for 36.5%, 29.2%, and 14.73%, respectively. Twenty-six (27.1%) of patients had viral hepatitis. 60 (63.22%) received a blood transfusion, 42 (43.8%) used EPO, and 46 (47.9%) received parenteral iron supplementation. Total iron binding capacity (519.63 ± 750.50 µg/dL),serum ferritin level (721.96 ± 626.72 ng/ml), serum iron level (101.79 ± 122.07 µg/dL), transferrin saturation (24.83 ± 24.02), mean BMI (24.14 ± 3.59 kg/m^2). (**Table.1**).

Table 1. Patients' demographic and clinical features (N=96)

Parameters		**Number**	**Percent %**
	Mean ± SD	53.32 ± 13.605	
	Median (range)	53.50 (25-87)	
Gender	**Male**	56	58.3%
	Female	40	41.7%
Causes of Chronic Kidney Disease	**Hypertension**	40	41.7%
	Diabetes	18	18.8%
	Polycystic kidney	3	3.1%
	Atrophic kidney	3	3.1%
	Urine retention	2	2.1%
	Urine retention and stones	2	2.1%
	Chemotherapy	1	1.0%
	Idiopathic	27	28.1%
Dialysis duration (years)	**Mean ± SDMedian (range)**	4.40 ± 2.69	4 (0.5-15)
Associated comorbidities	**Bone abnormalities**	5	5.2%
	Cardiac disorders	35	36.5%
	Hypertension	28	29.2%

	Diabetes	4	4.2%
	Liver diseases	10	10.5%
	GIT complications	14	14.74%
	Fluid and water retention	7	7.37%
Hepatitis (HCV or HBV)	**Yes**	26	27.1%
	No	70	72.9%
Duration of dialysis (years)	**<5**	64	66.7%
	5-10	28	29.2%
	>10	4	4.2%
Body mass index (kg/m^2)	**Underweight**	4	4.2%
	Normal weight	55	57.3%
	Overweight	34	35.4%
	Obese	3	3.1%
Blood transfusion	**Yes**	60	63.22%
	No	36	37.50%
Erythropoietin use	**Yes**	42	43.8%
	No	54	56.8%
Iron supplementation	**Yes**	46	47.9%
	No	50	52.6%
Serum ferritin level (µg/L)	**< 200**	22	22.92%
	200-1000	46	47.92%
	> 1000	28	29.16%
Serum iron level (µg/dL)	**< 50 µg/dL**	42	43.8%
	50-200 µg/dL	41	42.7%
	> 200µg/dL	13	13.5 %
Transferrin saturation (%)	**<45%**	82	85.4%
	>45%	14	14.6%
Iron overload	**Yes**	29	30.2%
	No	67	69.8%

All studied cases	**Mean ± SD**	**Median (range)**
Total iron binding capacity (µg/dL)	519.63 ± 750.50	380(66.2-7369.2
Serum ferritin level ng/ml	721.96 ± 626.72	544.1 (12.8-2000)
Serum iron level (µg/dL)	101.79 ± 122.07	57 (5-850)
Transferrin saturation (%)	24.82± 24.02	16.82(0.45-134.74)
BMI (kg/m^2)	24.14 ± 3.59	24.14(16.38-38.6)

Liver ultrasonography findings:Out of 96 ESRD patients, 21 (21.9%) had diffuse hepatic pathology, 6 (6.3%) had diffuse hepatic pathology with mild hepatomegaly, 6 (6.3%) had bright liver, 2 (2.1%) had fatty liver, and 1 (1.04%) had cystic liver(**Table.2**).

Table 2.Liver US of the studied patients (N=96)

Radiological findings	Number	Percent %
Normal liver	60	62.5%
Diffuse hepatic pathology	21	21.9%
Diffuse hepatic pathology with mild hepatomegaly	6	6.3%
Fatty liver	2	2.1%
Cystic liver	1	1.04%
Bright liver#	6	6.3%

indicatesacute hepatitis or toxic shock syndrome.

Most patients, 46 (47.92%), had hyperferritinemia, 28 (29.16%) had IO, and 22 cases had normal ferritin levels. 82 (89.6%) had a transferrin saturation of less than 45%(**Table.3**).

Table 3. Demographic and clinical features concerning ferritin level (N=96).

Parameters		Serum Ferritin			p-value
		< 200 µg/L (n=22)	**200-1000 µg/L (n=46)**	**>1000 µg/L (N=28)**	
		N (%)	**N (%)**	**N (%)**	
Gender	**Male**	13 (59.1%)	28 (60.9%)	15 (53.6%)	**0.8236**
	Female	9 (40.9%)	18 (39.1%)	13 (46.4%)	
Diabetes	**Yes**	7(31.82%)	9(19.56%)	4(14.29%)	**0.3038**
	No	15(68.18%)	37(80.43%)	24(85.71%)	
Hypertension	**Yes**	15(68.18%)	19(41.30%)	11(39.29%)	**0.7311**
	No	7(31.82%)	27(58.69%)	17(60.71%)	
Cardiac involvement	**Yes**	8(36.36%)	20(43.48%)	6(21.43%)	**0.1569**
	No	14(63.64%)	26(56.53%)	22(78.57%)	
Bone abnormalities	**Yes**	2(9.09%)	1(2.17%)	2 (7.1%)	**0.4185**
	No	20(90.90%)	45(97.83%)	26 (92.9%)	
Liver disease	**Yes**	3 (13.6%)	7 (15.2%)	0 (0%)	**< 0.0001**
	No	19 (86.4%)	39 (84.8%)	28 (100%)	
Fluid and water retention	**Yes**	1 (4.5%)	2 (4.3%)	4 (14.3%)	**0.2391**
	No	21 (95.5%)	44 (95.7%)	24 (85.7%)	
Viral hepatitis	**Yes**	6(27.27%)	14(30.43%)	6 (21.4%)	**0.6993**
	No	16(72.72%)	32(69.57%)	22 (78.6%)	
Erythropoietin use	**Yes**	13(59.09%)	20(43.48%)	8 (28.6%)	**0.0948**
	No	9(40.91%)	26(56.53%)	20 (71.4%)	
Parenteral Iron supplementation	**Yes**	11 (50%)	24(52.17%)	10 (35.7%)	**0.3668**
	No	11 (50%)	22(47.83%)	18 (64.3%)	

*chi-square test

The enhancein serum ferritin levels was correlated to a substantial rise in MCHC (P = 0.004), a significant parallel increase in serum iron (P < 0.00001), transferrin saturation (P < 0.0001), & TIBC (P < 0.001). Out of 22 patients with normal ferritin levels, 4 (18.18%) have diffuse hepatic pathology, 3 (13.64%) have diffuse hepatic pathology with mild hepatomegaly, and 1 (4.55%) has bright liver US. Out of 46

patients with hyperferritinemia, 5 (10.87%) have diffuse hepatic pathology, 2 (4.35%) have diffuse hepatic pathology with mild hepatomegaly, and 5 (10.87%) have a bright liver. Out of 28 patients with IO, 11 (39.29%) have diffuse hepatic pathology, 2 (7.14%) have fatty liver, 1 (3.57%) has diffuse hepatic pathology with mild hepatomegaly, and 1 (3.57%) has liver cysts(**Table.4**).

Table 4. Clinical and laboratory data concerning serum ferritin levels

Parameters (Mean ± SD)	Serum ferritin			P-value
	< 200 ng/ml (n=22)	200-1000 ng/ml (n=46)	>1000 ng/ml (N=28)	
Age (years)	53.50 ± 14.435	54.22 ± 13.187	51.71± 13.976	0.747
Dialysis duration (years)	3.8523 ± 2.27	4.4457 ± 2.459	4.75 ± 2.69	0.502
Body mass index (kg/m^2)	24.8 ± 3.02	24.51 ± 3.92	22.95±3.24	0.11
Hemoglobin (g/dL)	10.58 ± 1.66	10.68 ± 1.93	11.08± 2.12	0.60
MCV (FL)	88.48 ± 12.8	85.76 ± 11.89	92.59 ±12.18	0.07
MCH (pg.)	26.12 ± 3.71	26.81 ± 3.30	28.12±3.43	0.10
MCHC (g/dL)	29.6 ± 1.92	31.4 ± 2.22	30.43 ±2.03	0.004*
Platelets count (×10^3/µL)	266.4 ± 107.6	252.8 ± 105.0	228.93 ±96.09	0.42
WBCs count (×10^3/µL)	8.66 ± 3.99	9.12± 4.77	9.57±4.057	0.76
Monocyte count (×10^3/µl)	0.89 ± 0.46	0.94 ± 0.67	1.06 ±0.52	0.56
Neutrophils count (×10^3/µl)	6.147 ± 3.68	6.76 ± 5.07	6.36±3.487	0.84
Lymphocyte count (×10^3/µl	1.57 ± 0.53	2.03 ± 1.733	2.23±1.30	0.25
NLR	4.56 ± 4.05	6.42 ± 10.62	3.72 ± 2.73	0.2995
PLR	200.71±133.06	215.40±244.11	122.96±65.09	0.116
AST (U/L)	35.39 ± 46.47	29.25 ± 14.67	27.51±16.54	0.53
ALT (U/L)	29.89 ± 31.13	28.41 ± 20.79	27.06±17.82	0.90
ALP (IU/L)	106.36 ± 67.9	108.55± 74.5	112.48 ±75.12	0.95
PT (seconds)	13.48 ± 1.75	13.95 ± 5.01	13.11 ±1.48	0.62
Total bilirubin (mg/dL)	1.18 ± 1.87	0.66 ± 0.35	0.86 ± 0.75	0.14
Albumin (g/dL)	3.94 ± 0.81	4.2 ± 0.82	3.88 ± 0.58	0.17
eGFR (ml/min/1.73 m2)	7.77 ± 3.59	7.43 ± 2.81	7.82 ± 3.56	0.85
Blood urea level (mg/dL)	95.68 ± 36.83	114.56 ± 57.5	106.56 ± 47.21	0.35
Serum creatinine (mg/dL)	7.49 ± 1.334	7.66 ± 1.39	7.51 ± 1.36	0.85
Uric acid (mg/dL)	6.04 ± 1.21	6.06 ± 1.28	6.011 ± 1.22	0.98
Serum iron	49.14 ± 32.47	48.41 ± 25.102	126.68 ± 151.02	<0.001*
Serum iron	48.27 ± 31.59	51.89 ± 28.85	230.86 ±158.86	< 0.00001
Transferrin saturation %	20.52 ± 21.77	16.80 ± 13.92	41.38 ± 29.65	0.0001*
FIB-4 score	1.336 ± 0.814	1.56 ± 1.50	1.594 ± 1.421	0.767
TIBC Median (IQR)	265.2 (223.3)	367.8 (225.4)	691.8 (483.3)	<0.001[a]
Ultrasonography findings	**No (%)**	**No (%)**	**No (%)**	**P-value**
Normal liver	14 (63.63%)	33 (71.74%)	13 (46.43%)	0.0972
Diffuse hepatic	4 (18.18%)	5 (10.87%)	11 (39.29%)	

pathology				
Diffuse hepatic pathology with mild hepatomegaly	3 (13.64%)	2 (4.35%)	1 (3.57%)	
Fatty liver	0	0	2 (7.14%)	
Cystic liver	0	0	1 (3.57%)	
Bright liver#	1 (4.55%)	5 (10.87%)	0	

***:** significant;one-wayANOVA; [a] Kruskall-Wallis test; TIBC: total iron binding capacity; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio.

Patients with transferrin saturation > 45% were significantly older (60.57 ± 12.74 years) compared to patients with transferrin saturation < 45% (52.09 ±13.43 years) (p = 0.030) (**Table.5**).

Table 5. CBC, liver, and kidney functions, concerning transferrin saturation

Parameters (Mean ± SD)	**Transferrin saturation**		P-value
	< 45% (No = 82)	**>45% (No = 14)**	
Age (years)	52.09 ±13.43	60.57 ±12.74	0.03*
Dialysis duration (years)	4.3198 ± 2.39	5.075 ± 4.636	0.404
Body mass index	24.17 ±3.68	23.87 ±3.14	0.78
RBCs count (*10^6/µL)	4.087 ±0.82	4.38 ±1.65	0.53
Hemoglobin (g/dL)	10.74 ±1.82	10.97 ±2.5	0.69
Hematocrit value (%)	35.14 ±6.29	35.82 ± 8.96	0.72
MCV (FL)	88.04 ±12.79	90.36 ±10.06	0.52
MCH (pg.)	26.917 ±3.62	27.74 ± 2.55	0.41
MCHC (g/dL)	30.69 ± 2.22	30.77 ±2.22	0.91
RDW (%)	15.67 ±2.51	15.87 ± 3.46	0.79
Platelets count (*10^3/µL)	250.65±102.82	240.50 ±106.3	0.74
WBCs count (*10^3/µL)	9.35 ± 4.49	7.44 ± 2.75	0.10
Monocyte absolute count (*10^3/µl)	0.98 ± 0.59	0.83 ± 0.56	0.62
Neutrophils absolute count (*10^3/µl)	6.67 ± 4.44	5.033 ± 2.92	0.17
Lymphocyte absolute count (*10^3/µl)	2.04 ± 1.47	1.50 ± 0.712	0.40
AST (U/L)	29.57± 26.33	35.11 ± 21.23	0.96
ALT (U/L)	27.67±22.62	34.21 ± 22.60	0.94
ALP (IU/L)	101.61±61.28	174.42 ±121.6	0.33
PT (seconds)	13.63 ± 3.84	13.34 ± 1.13	0.81
Total bilirubin (mg/dL)	0.83 ± 1.07	0.88 ± 0.36	0.87
Albumin (g/dL)	4.01 ± 0.78	4.31 ± 0.53	0.49
eGFR (ml/min/1.73 m^2)	7.76 ± 3.33	6.50 ± 1.17	0.65
Blood urea level (mg/dL)	107.06 ±49.73	115.13 ± 59.89	0.64
Serum creatinine (mg/dL)	7.55 ± 1.40	7.85 ± 0.91	0.76
Uric acid (mg/dL)	6.006 ± 1.26	6.37 ± 0.93	0.87

*Student t-test; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio.

Pearson's correlationrevealed a significant positive correlation between serum ferritin and serum iron (p <0.001, r = 0.885), dialysis duration (p <0.001, r = 0.337), and transferrin saturation (p= 0.002, r = 0.317). There is a significant positive association between transferrin saturation and serum iron (p < 0.001, r = 0.395), ALP

(p = 0.004, r = 0.295), age (p = 0.006, r = 0.277), and a noteworthy negative correlation with TIBC (p = 0.030, r = -0.222) (**Table.6**).

Table 6.Correlation between serum ferritin and transferrin saturation % with dialysis duration, and other laboratory parameters

Parameters	Serum ferritin		Transferrin saturation %	
	r*	P-value	r*	P-value
Serum iron	0.885	**<0.001***	0.395	< 0.001*
Dialysis duration (years)	0.337	**<0.001***	0.137	0.185
Transferrin saturation	0.317	**0.002***	-	-
Total iron binding capacity	0.084	0.415	- 0.222	0.030*
MCH	0.181	0.078	0.070	0.496
MCV	0.112	0.276	0.087	0.399
MCHC	0.095	0.356	- 0.046	0.658
Red blood cells	- 0.173	0.092	- 0.002	0.983
Platelets	- 0.167	0.103	- 0.042	0.684
MPV	0.120	0.246	0.029	0.781
WBCs	- 0.055	0.591	- 0.180	0.079
Absolute neutrophil count	- 0.094	0.361	- 0.170	0.098
Absolute lymphocyte count	0.060	0.562	- 0.103	0.318
Body mass index	- 0.165	0.108	- 0.029	0.776
Age (years)	- 0.151	0.143	277	0.006*
ALP	- 0.041	0.695	0.295	0.004*
ALT	- 0.071	0.493	0.038	0.715
AST	- 0.092	0.373	0.000	0.997
C-reactive protein	- 0.115	0.265	0.155	0.132
INR	- 0.094	0.362	- 0.003	0.978
Prothrombin time	- 0.090	0.385	- 0.005	0.961
eGFR	0.078	0.453	- 0.072	0.484
FIB-4	0.012	0.910	0.110	0.285

*: significant; r: correlation coefficient; AST: aspartate transferase; ALT: alanine transaminase; ALP: alkaline phosphatase;eGFR: estimated glomerular filtration rate; FIB-4: fibrosis-4.

Pearson's correlationrevealed a significant negative correlation between FIB-4 and platelet count (p < 0.001, r = -0.531) and a significant positive correlation between FIB-4 with AST (p < 0.001, r = 0.389), age (P < 0.001, r =0.339), ALT (P = 0.001, r = 0.321), and RDW (P = 0.022, r = 0.233) (**Table.7**).

Table 7.Correlation between FIB-4 with age and laboratory data

Parameters	FIB-4	
	r*	P-value
Platelets	-0.531	< 0.001*
AST	0.389	< 0.001*
Age (years)	0.339	< 0.001*
ALT	0.321	0.001*
RDW	0.233	0.022*
ALP	0.168	0.101
Hemoglobin	0.131	0.204

Total protein	0.125	0.226
Hematocrit value	0.123	0.233

*: significant; r: correlation coefficient

Multivariable logistic regression analysisdemonstratedthat the most significant predictor of elevated serum ferritin is MCH ≥ 27 pg. (p = 0.008), followed by MCHC ≥ 32.4 g/dL (p = 0.024), followed by serum iron (p = 0.025), and the least significant predictor is Hb ≥ 10.9 g/dL (p = 0.037)(**Table.9**).

Table 8.Multivariable logistic regression analysis for risk factors of hyperferritinemia and iron overload

Variables	Odds ratio (OR)	95% CI		P-Value
		Lower	Upper	
MCH ≥ 27 (pg.)	3.956	1.432	10.929	0.008*
MCHC ≥ 32.4 (g/dL)	10.714	1.361	84.326	0.024*
Serum iron	1.014	1.002	1.027	0.025*
Hemoglobin ≥ 10.9 (g/dL)	3.221	1.076	9.642	0.037*
Bone abnormalities	5.684	0.886	36.486	0.067
ALP > 117	1.953	0.648	5.890	0.235

*: significant

Discussion

Anaemia is a prevalent complication of chronic kidney disease , & the current treatment options include IV iron, ESA, and blood transfusions **(KDIGO, 2012).** Researchers prioritize monitoring anemia in CKD patients over IO due to iatrogenic iron replacement. Untreated IO can lead to increased ROS production, oxidative damage, and progressive multi-visceral disease **(Deugnier et al., 2021).**

IO increases the risk of hepatic and cardiovascular diseases, infections, and complications (**Nashwan et al., 2022**). Over 70% of total body iron is found in the liver, with liver iron correlated with total body iron, approximately 10.6 times higher than the hepatic iron concentration **(Angelucci et al., 2000).**

Ferritin is a significant risk factor for CKD & HD patients, necessitating control of iron deficiency and overload risks in HD patients on iron therapy (**Rostoker et al., 2015).**

The primarytarget of this study was to find out the frequency of iatrogenic IO in ESRD patients undergoing regular HD and define the associated risk factors and complications.

This study involved 96 ESRD cases, with a mean age of 53.32 ± 13.60 years, 58.3% were males, 40 (41.7%) were females, with 66.7% had HD durations of less than 5 years, 28.1% had 5-10 years, and 5.2% had more than 10 years of duration on dialysis. The most common causes of their CKD were hypertension, idiopathic, & diabetes, accounting for 41.7%, 28.1%, and 18.8%, respectively.

Of the 96 HD patients, 46 patients (47.92%) had serum ferritin levels between 200 & 1000 nanogram per milliliter (hyperferritinemia), 28 (29.16%) had serum ferritin more than 1000 ng/ml (IO), and 22 (22.92%) had serum ferritin below 200 ng/ml.Patients with transferrin saturation > 45% were significantly older compared to patients with transferrin saturation < 45% (p = 0.030).

The present study showed that there was no significant distinctionamong the cases with & without IO as regards comorbidities or causes of CKD. This was in accord with **Luo et al. (2021) and Kang et al. (2023).**

Concerning serum ferritin, there is a substantial rise in MCHC with the increase in serum ferritin level, and a significant parallel increase in serum iron (P < 0.00001), transferrin saturation (P <0.0001), and TIBC (P < 0.001) was related to an increase in serum ferritin levels.As predicted, HD patients with IO have elevated serum levels of iron, ferritin, and TIBC, suggesting that these markers can be used as markers of IO. This was agreed upon by**Kang et al. (2023)**.

The existing study revealed an insignificant association between IO and blood pressure (SBP and DBP). This was in agreement with **Sonet al. (2019),Luo et al. (2021), and Kang et al. (2023).**

In the current research, there wasn't significant association among IO & renal function tests (urea, creatinine, eGFR, and uric acid); this was in concordance with **Sonet al. (2019).** In contrast, **Luo et al. (2021)** showed that HD patients with elevated iron levels have significantly increased renal function test levels of creatinine, urea, & uric acid compared to those with normal iron levels. Yet **Kang et al. (2023)** demonstrated that HD patients with elevated iron levels have significantly lower creatinine compared to those with normal iron levels.

In our study, there is a significant positive associationamong serum ferritin & dialysis duration (p <0.001, r = 0.337). Moreover, there is a significant positive associationamongtransferrin saturation &ALP (p = 0.004, r = 0.295), and age (p = 0.006, r = 0.277). There is a significant positive correlation among FIB-4 and age (P < 0.001, r =0.339), ALT (P = 0.001, r = 0.321), and RDW (P = 0.022, r = 0.233).

Our findings were consistent with the **Canavese et al. (2004)** study, which found a significant correlation between hepatic iron content and ferritin (r = 0.324, P = 0.04). Furthermore, multivariate logistic regression analysis proved that a 100 ng/ml increase in serum ferritin was an independent risk linked with moderate to severe hepatic IO and that CKD patients whose serum ferritin value exceeds 500 ng/ml have a ten-fold increased risk of IO.However, **Ferrari et al. (2011)** found no linkamong serum iron markers &liver iron concentration (LIC) in CKD patients.

Our study revealed a significant enhance in MCV & MCH in IO cases associated with hemoglobin stabilization.Thus indicating iron uptake into the red cells (**Umanath et al., 2015**).

In the current study,we found insignificant differences between the studied groups concerning the inflammatory indices NLR, PLR, and CRP, andthis indicatesthat the group with IO had truly elevated ferritin levels and did not result from the presence of inflammation. In contrast to the findings of **Sonet al. (2019)** and **Luo et al. (2021),**they found a significant increase in CRP levels in HD patients with elevated serum ferritin and iron levels.

The current study showed an insignificant association between IO and LFTs in the studied cases. Moreover, the current study showed insignificant associations between IO and the fibrosis marker (FIB4 score). This was in agreement with **Vallet-Pichard et al. (2007), Wish et al. (2018), Coyne (2017), and Macdougall et al. (2016).**

In this study, out of 96 ESRD patients, 21 patients (21.9%) had diffuse hepatic pathology, 6 (6.3%) had mild hepatomegaly, 6 (6.3%) had a bright liver, 2 (2.1%) had a fatty liver, 1 (1.04%) had a cystic liver, and 60 (62.5%) had a normal liver.

In our study, out of 22 HD patients with normal ferritin levels, 4 had diffuse hepatic pathology, 3 had mild hepatomegaly, and 1 had a bright liver US. Of 46 HD patients with hyperferritinemia, 5 had diffuse hepatic

pathology, 2 had mild hepatomegaly, and 5 had a bright liver US. Of 28 HD cases with ferritin levels over 1000 ng/ml, 11 had diffuse hepatic pathology, 1 (3.57%) had diffuse hepatic pathology with mild hepatomegaly, 1 (3.57%) had liver cysts, and 2 (7.14%) had fatty liver. However, the abnormal liver US was non-significantly (p = 0.91) higher among HD patients with iron IO than those without IO.

In our study,out of 96 HD patients,only 2 (2.1%)had fatty liver and were associated with IO (1138 and 1620 ng/ml, respectively). This was compatible with**Rostokeret al. (2019)**,who revealed that IO induced by indiscriminate and unmonitored iron treatment may trigger or worsen NAFLDin HD patients. Thisis produced by the direct role of iron in the activationof liver macrophages& hepatic satellite cells,besides its inflammatory signaling that promotes the synthesis of ferritin and fat accumulation due to cellular lipid uptake that ends with liver cirrhosis(**Yen et al., 2017; Rostokeret al., 2018).**

The study found no significant difference in serum ferritin concentration between groups of anemia management medications in HD patients, out of 22 patients with normal ferritin levels 13 received ESA /11 received parenteral iron, and out of 46 patients with hyperferritinemia 20 received ESA /24 received parenteral iron, and out of 28 patients with IO 8 received ESA /10 received parenteral iron.

In this study, there was no significant difference between groups concerning serum ferritin concentration and anemia management medications used in HD patients.Out of 22 patients with normal ferritin levels, 13 had received ESA/11 of them received parental iron, and out of 46 hyperferritinemia patients 24 received parental iron/20 received ESA, and out of 28 IO cases, 10 received parental iron/8 received ESA.

Our results were in line with**Eisengaet al. (2019),** who found an inverse correlation between EPO level and iron level among HD patients. However, **Sonet al. (2019)** showed that there was no association between ESA use or dose and ferritin levels among HD patients.

The current study showed an insignificant association between IO and liver ultrasonography findings (p = 0.91).
Rostoker et al. (2019) reported a higher LIC and hepatic siderosis in 39 out of 68 HD patients (57%), of which 23 cases were mild, 9 were moderate, and 7 were severe. In addition, **Tolouian et al. (2016)** demonstratedthat iron deposition in the liver was present in 50% of the 17 HD patients. Also, **Holman et al. (2017)** showed that LIC was elevated in 8 of 10 subjects (80%). **Nashwan and Yassin (2023)** revealed a high prevalence of severe hepatic IO in cases with ESRD on HD; the pooled prevalence of severe & mild to moderate hepatic IO quantified by MRI was 23% [95% CI: 8–43%] and 52 [95% CI: 47–57%], respectively**.**
Rostoker (2019) reported that HD patients with IO, without concomitant inflammatory syndrome, exhibited ESA hypo responsiveness, as did patients with iron deficiency.It looks wise to stop parenteral iron and use ascorbic acid, which mobilizes sequestered iron for erythropoiesis**(Peters et al., 2017).** Iron therapy withdrawal with ESA continuation significantly improved iron metabolism biomarkers in HD patients with IO without affecting erythropoiesis **(Ghotiet al., 2012).**
The limitations of the current study are the small sample size, cross-sectional design, being a single-center study, absence of liver evaluation by MRI (the gold standard for monitoring LIC), and the absence of other

organ evaluationsfor IO such as the heart and spleen.

Conclusion

Out of 96 HD patients, 28 (29.16%) haveIO, and 46 patients (47.92%) have hyperferritinemia, which is accompanied by hepatic pathology detected by ultrasonography.It is crucial to monitor blood or organ siderosis,parenteral iron therapy must be used judiciously,patients should receive a minimal dose of parenteral iron, only if they have true iron deficiency (ferritin ≤100 µg/L), and effectively manage IO by holding parenteral iron.Ferritin targets in current guidelines should be lowered to establish a safe cut-off value for serum ferritin to avoid IO and its potentially harmful effects.

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