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ORIGINAL PAPER

Serum ferritin, bone marrow iron and mortality rate in CKD patients with different methods of dialysis

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Summary ***Background and aim: It is well recognized that one of the most significant public health concerns is chronic kidney disease (CKD). In a cohort of incident CKD patients without dialysis, or on hemodialysis (HD), or on peritoneal dialysis (PD), the complicated interactions between bone marrow iron, serum ferritin levels, and death rates were examined.***

Materials and methods: For this prospective and observational study, 288 CKD patients who were registered in three institutions between January 2022 and December 2023 were initially recruited. The final analysis comprised 200 patients, chosen based on predetermined inclusion and exclusion criteria.

Results: The median age of all patients was 65.52 ± 8.36, with 102 patients (51%) being male. Of the patients followed up, forty (20%) died. Cardiovascular events accounted for 22.5% of deaths (9 patients), and infections accounted for 70% of deaths. An elevated ferritin level (HR 1.528, 95% CI 1.239-1.885, p < 0.001) and advanced age were important risk factors for infection-related cardiovascular disease.

Conclusions: It was demonstrated that higher blood ferritin levels were substantially linked to a higher risk of death and that the most common causes of death of CKD patients in Iraq are infection-related.

KEY WORDS: *Serum ferritin; Bone marrow iron; Mortality rate; CKD patients*

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INTRODUCTION

Globally, *chronic kidney disease* (CKD) is acknowledged as one of the most important public health issues where 13.4% is the estimated prevalence of CKD worldwide (1). CKD is defined as abnormalities of kidney structure or function that have implications for health and have been present for three months (2). Diverse dialysis methods are often used to treat patients with CKD; nevertheless, the effects of different methods on iron and serum ferritin levels and mortality are still being studied.

Few studies had focused on the link between bone marrow iron, serum ferritin, and death rates in patients with CKD using various dialysis modalities (3-5). Serum ferritin has been proven to be a good measure of bone marrow iron reserves in a number of chronic renal failure patient populations (6). Gaining knowledge about the interactions between these variables can help optimize treatment plans and enhance patient outcomes.

End-stage renal disease (ESRD), which is caused by the growing global epidemic of CKD, remains a major concern for nations (7). For ESRD patients, *hemodialysis* (HD) and *peritoneal dialysis* (PD) are the two most popular types of dialysis treatment (8). Thus, to explore the complex relationships between bone marrow iron, serum ferritin levels, and mortality rates in, a cohort of incident CDK patients with no dialysis, HD and PD was used to investigate these relationships.

MATERIALS AND METHODS

Study design

The study is a prospective, observational cohort study of Iraqi patients with CKD. CKD patients from 3 governmental hospitals were enrolled. The inclusion criteria included being registered as CKD patients between January 1, 2022 and December 31, 2023 and undergoing no dialysis or starting HD/PD. The exclusion criteria included patients younger than 20 years of age and patients who rejected follow-up assessments. A total of 42 CKD patients with no dialysis, 76 CKD patients on PD and 82 CKD patients on HD were included (Figure 1).

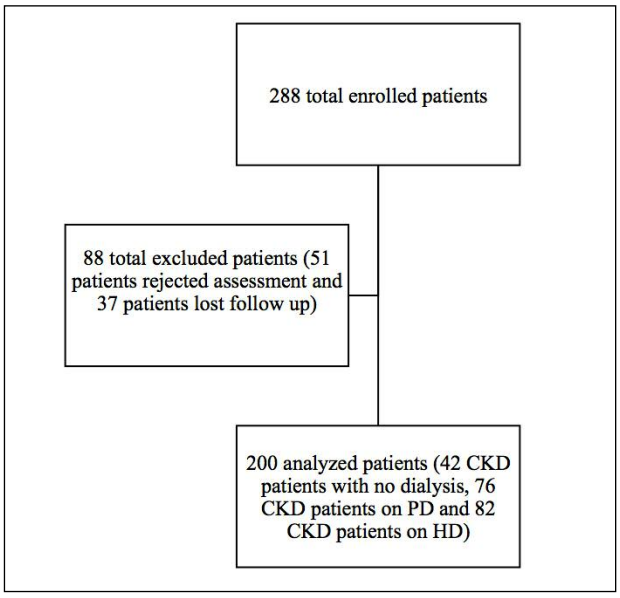
The study strategy at each participating hospital was approved by the Institutional Review Board. Prior to taking part in the research, every patient provided signed informed consent. The study focused on protecting patient privacy by anonymizing data during analysis, according to ethical standards for research involving human subjects.

From January 2022 to December 2023, 288 CDK patients who were registered in the three hospitals were initially recruited for this prospective and observational study. Two hundred patients were included in the final analysis based on inclusion and exclusion criteria. Figure 1 shows the flow diagram of the study.

Data collection

Demographic including age and gender and clinical data including hemoglobin, bone marrow iron and ferritin levels were recorded at the time of study entry. Pre-dialysis fasting blood samples obtained during a midweek dialysis session within 30 days after the start of HD/PD were

Figure 1.
Flow diagram of the study subjects.



utilized by this study. Within the HD/PD dialysis treatment, patient took oral and *intra-venous* (IV) iron.
Bone marrow aspirates were collected from the sternum or posterior iliac crest, based on physician preference and patient tolerance. The aspirates were fixed in formalin, embedded in paraffin, and sectioned. The sections were stained with Prussian blue to visualize iron stores within the bone marrow. A trained, blinded hematopathologist semi-quantitatively graded the stainable iron on a scale from 1 to 5 to facilitate the comparative assessment of iron stores within the patient cohort. A grade of 1 indicated absent or highly reduced iron stores, 2 indicated moderately decreased stores, 3 indicated normal stores, 4 indicated moderately elevated stores, and 5 indicated highly elevated stores or hemosiderosis.
In case of death, the cause of death was reported within a month following the incident. Cardiovascular death was defined as mortality resulting from myocardial infarction or ischemia, congestive heart failure, pulmonary edema, sudden cardiac death, or cerebrovascular disorders. Infection-related death included mortality events due to septicemia with confirmed microorganisms in blood cultures, as well as fatal infections such as pneumonia, abdominal infections, genitourinary infections, central nervous system infections, and endocarditis.

Statistical analysis

Data are expressed as means ± standard deviation for continuous variables, and as number and percentage for categorical variables. The statistical analysis of mean differences for continuous variables was assessed using the independent t-test. The significance of differences for categorical variables was evaluated using the chi-square test. Univariate analyses were performed to identify the association of potential risk factors with the outcome of cardiovascular and infection-related mortality causes. The variables that were examined in the univariate analyses were as follows: age (continuous), gender (categorical), hemoglobin level (continuous), ferritin level (continuous), and dialysis modality (categorical). The association of continuous and categorical variables with mortality was established by Cox proportional hazards regression and chi-square test, and *hazard ratios* (HR) and 95% *confidence intervals* (CI) were reported. Statistical analysis was carried out with SPSS version 18.0. P values less than 0.05 were regarded as significant.

Results

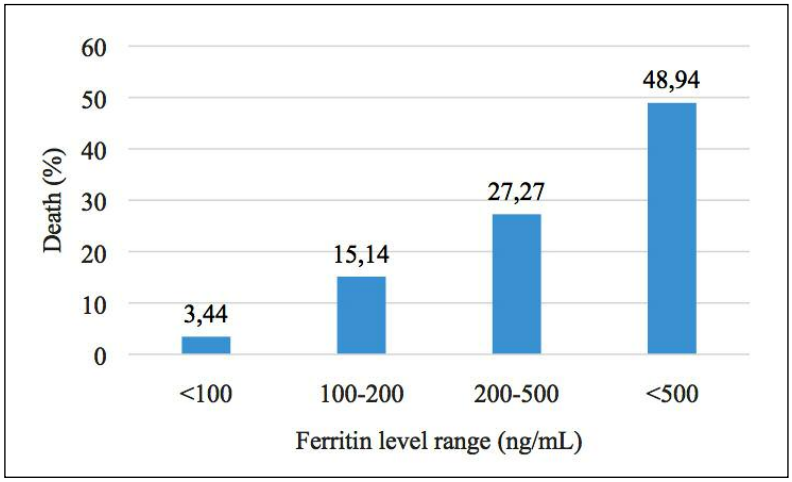
Baseline demographics and laboratory characteristics of the subjects are shown in Table 1. The total median age was 65.52 ± 8.36 and 102 (51%) patients were male. The hemoglobin of CKD patients without dialysis was 7.34 ± 0.57 g/dl lower than that of CKD patients who underwent PD that was 9.18 ± 0.9 g/dl and of CKD patients who underwent HD that was 7.65 ± 0.3 g/dl. Patients were divided into 15 groups according to baseline ferritin levels and bone marrow iron.
Group 1 included 10 CKD patients without dialysis who have markedly decreased bone marrow iron level. Group 2 included 15 CKD patients without dialysis who have moderately decreased bone marrow iron level. Group 3

Table 1.
Baseline characteristics of patients.

		CKD patients without dialysis (N * = 42)		CKD patients on PD (N = 76)		CKD patients on HD (N = 82)		P value
Mean age ± Standard deviation		64.95 ± 5.74		65.2 ± 9.41		66.1 ± 8.74		0.014
Male N (%)		23 (54.76%)		40 (52.63%)		39 (47.56%)		0.034
Hemoglobin (g/dl)		7.34 ± 0.57		9.18 ± 0.9		7.65 ± 0.3		0.14
		Ferritin level	N (%)	Ferritin level	N (%)	Ferritin level	N (%)	
		(ng/mL, mean ± STD **)		(ng/mL, mean ± STD)		(ng/mL, mean ± STD)		
Bone Marrow Iron	Markedly decreased	9.48 ± 15.49	10 (23.81)	28 ± 16.26	14 (18.42)	98 ± 45.36	14 (17.07)	< 0.001
	Moderately decreased	15.47 ± 17.48	15 (35.71)	53 ± 26.16	17 (22.37)	150 ± 70.71	18 (21.95)	
	Normal	50.89 ± 13.713	17 (40.48)	150 ± 63.54	15 (19.74)	201.45 ± 160.48	21 (25.62)	
	Moderately increased	-	-	312 ± 107.48	12 (15.79)	541.89 ± 201.56	18 (21.95)	
	Markedly increased	-	-	503 ± 143.54	18 (23.68)	751.78 ± 180.71	11 (13.41)	

* N: Number of patients; ** STD: Standard.

Figure 2.
Death rate in relation to the ferritin level.



included 17 CKD patients without dialysis who have normal bone marrow iron level. Group 4 and 5 do not include any patients because none of them have demonstrated moderately or markedly increased bone marrow iron levels. Group 6 included 14 CKD patients on PD who have markedly decreased bone marrow iron level. Group 7 included 17 CKD patients on PD who have moderately decreased bone marrow iron level. Group 8 included 15 CKD patients on PD who have normal bone marrow iron level. Group 9 included 12 CKD patients on PD who have moderately increased bone marrow iron level. Group 10 included 18 CKD patients on PD who have markedly increased bone marrow iron level. Group 11 included 14 CKD patients on HD who have markedly decreased bone marrow iron level. Group 12 included 18 CKD patients on HD who have moderately decreased bone marrow iron level. Group 13 included 21 CKD patients on HD who have normal bone marrow iron level. Group 14 included 18 CKD patients on HD who have moderately increased bone marrow iron level. Group 15 included 11 CKD patients on HD who have markedly increased bone marrow iron level. The median ferritin level for each group is shown in Table 1.

A total of 40 patients were dead during the study assessment. These patients were divided into 4 categories according to their last record of the ferritin level. Figure 2 shows that death rate was associated to the ferritin level.

During the follow-up period, 40 (20%) patients died. The most common cause of death was a cardiovascular event (9 patients, 22.5%), followed by infection (28 patients, 70%) (Table 2). Cardiovascular fatalities were defined as deaths caused by myocardial infarction/ischemia, congestive heart failure, pulmonary edema, sudden cardiac death, or cerebrovascular disease. Deaths from infections included sepsis with blood cultures confirming the presence of microorganisms, as well as deadly illnesses such as pneumonia, endocarditis, genitourinary infections, stomach infections, and infections of the central nervous system.

To determine the association between baseline parameters mortality for different causesunivariate analysis was performed. Older age and high ferritin level (HR 1.528, 95% CI 1.239-1.885, $p < 0.001$) were significant risk factors for both cardiovascular and infection-related mortality. Hemoglobin level and gender were found to be not significant risk factors for cardiovascular and infection-related mortality (Table 3).

Table 2.
Cause of death.

Variable		Total N (%)
All dead patients		40 (20%)
Cause of death	Cardiovascular cause	9 (22.5%)
	Infection-related cause	28 (70%)
	Other	3 (7.5%)

Table 3.
Univariate regression analysis of baseline parameters for the cardiovascular and infection-related cause.

	Cardiovascular cause		Infection-related cause	
	HR * (95% CI)	P value	HR (95% CI)	P value
Age (Years)	1.071 (1.014-1.141)	0.004	1.089 (1.007-1.198)	0.003
Male vs Female	1.741 (0.684-1.948)	0.351	0.841 (0.678-1.127)	0.419
Hemoglobin (g/dL)	0.841 (0.614-1.481)	0.154	0.859 (0.681-1.315)	0.481
Ferritin level (ng/mL)	1.487 (1.089-2.015)	0.041	1.458 (1.201-1.771)	0.002

* *HR: Hazard Ratio.*

Discussion

Elevated serum ferritin levels were shown to be substantially related with an increased risk of death in the current investigation, which observed a prospectively collected cohort of incident patients without dialysis, and with PD, or HD.

In the present series, mean *hemoglobin* (Hb) concentration in patients on peritoneal dialysis was 9.18 g/dl, a value greater than the value reported in patients of a previous study (9) receiving intermittent peritoneal dialysis that ranged between 8.6 and 8.9 g/dl. Mean Hb concentration in patients receiving conservative care without dialysis or on hemodialysis was 7.34 and 7.65 g/dl respectively. These values were lower than 9.7-10 g/dl 10 or 10.5-12.4 g/dl that were observed in other studies (10, 11). CKD patients in another study (12) showed higher hemoglobin concentrations compared to our series that ranged between 13.0 and 14.5 g/dl.

In patients with CKD receiving no dialysis, serum ferritin levels < 40 ng/mL were associated with reduced bone marrow iron; however, a study (11) stated that serum ferritin levels less than 60 ng/mL were linked to decreased or non-existent bone marrow iron in CKD patients. In patients with CKD receiving PD, serum ferritin levels < 60 ng/mL were associated with reduced bone marrow iron, and in patients with CKD receiving HD, serum ferritin levels < 180 ng/mL were associated with reduced bone marrow

iron. Similarly, in a different study (13), serum ferritin concentrations (mean value, 83 ng/mL) in CKD patients with a bone marrow iron score of 0 were significantly lower than in those with a bone marrow iron score of +2 or greater when bone marrow iron was graded 0 to +4, ranging from absent to diffuse homogeneous iron staining. Additionally, a substantial association between bone marrow iron scores and serum ferritin was observed.

Serum ferritin is commonly used as a measure of iron storage in people with CKD (14). Serum ferritin has been proven to be a good measure of bone marrow iron reserves in a number of populations of patients with chronic renal failure. Our findings imply that in individuals receiving PD or HD, blood ferritin concentrations also positively correlate with stainable bone marrow iron similar to a previous study (15). In the current study serum ferritin levels showed a significant positive correlation with iron levels, which is consistent with results of another study (9) and supports ferritin's well-known function as an iron content proxy. Moreover, the prevalence of high ferritin level was associated with higher rate of death. This also implies that CKD patients with high ferritin levels are more susceptible to death.

Patients with a serum ferritin level of > 250 ng/mL were shown to have a trend toward greater mortality in patients with advanced CKD who were not on dialysis, although there was no statistically significant difference. This does not align with results of another study (16) that stated the opposite. Another study (17) showed that a serum ferritin level < 100 ng/mL was linked to a higher mortality risk than a lower serum ferritin level in a study of patients on hemodialysis in Japan.

In our study, infection-related complications were more common than cardiovascular ones. This might be explained by the spread of infectious diseases favored by poor hygienic conditions. A significant association has been shown between elevated serum ferritin levels and mortality from both infectious and cardiovascular diseases. The many functions of ferritin in the body might account for this association. Iron homeostasis depends on the protein ferritin, which regulates the release and storage of iron. Elevated ferritin levels may be a sign of increased systemic inflammation in the setting of cardiovascular mortality. Cardiovascular disorders, such as myocardial infarction and congestive heart failure, are known to be exacerbated by chronic inflammation. Increased ferritin levels may indicate an inflammatory condition, which increases a the risk of cardiovascular events. Conversely, increased ferritin levels may be a result of the immunological response in case of infection-related death. The immune system produces inflammatory cytokines during infections, which can increase the synthesis of ferritin. Since iron is necessary for microbial development, iron sequestration is a component of the host defensive system to limit its availability to pathogens. On the other hand, hyper inflammatory conditions may cause excessive ferritin formation, increasing the risk of complications and death during severe infections.

In conclusion, the present study demonstrated that higher serum ferritin levels were associated with high mortality outcome and that infection-related cause of mortality is most frequent in patients with CKD in Iraq.

Conclusions

In the current study, a prospectively collected cohort of incident patients with CKD without dialysis, and on hemodialysis and peritoneal dialysis was examined. It was shown that elevated blood ferritin levels were significantly associated with an increased risk of mortality in patients with CKD and that infection-related cause of mortality of CKD patients is the most common in Iraq.

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Declarations

Ethical approval: *Ethical approval was granted by the Research Ethics Committee in the three hospitals to ensure adherence to standards, while safeguarding participants' rights and well-being (O/3/8/2021).*

Availability of data and material: *The datasets generated and/or analyzed during the current study are not publicly available due to data privacy laws, but are available upon reasonable request from the corresponding author.*

Competing interests: *The authors state that there is no conflict of interest.*

Funding: *No external funding.*

Authors' contributions: *Conceptualization: MA; Data curation: BAN; Formal analysis: MAN; Funding acquisition: MA, BAN, MAN; Investigation: BAN; Methodology: MA; Project administration: MAN; Resources: MAN; Software: BAN; Supervision: MAN; Validation: MA; Visualization: BAN; Writing - original draft: BAN Writing - review and editing: MA.*

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