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Evaluation of erythropoietin hormone and hematological profiles in end-stage renal disease patients on dialysis: Correlation with biochemical indices

Hind Mahmood Jumaah *

Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq.

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Abstract

Background: In dialysis cohort, it still ambiguous whether individual patient characteristics play a critical role in determining clinical consequences related to alterations in hematological profiles and other biochemical indices, and whether these factors directly contribute to increased mortality rates.

Objectives: The objectives of our study are framed to compare the hematological and biochemical profiles of dialysis patients versus healthy individuals as a control group, assessment the status erythropoietin (EPO), serum iron, and Unsaturated Iron Binding Capacity (UIBC), Also, to investigate the effects of renal failure on mineral metabolism by evaluating the levels of serum calcium (Ca) and phosphate (PO_4).

Methodology: This case-control study involved collecting 100 blood samples, including 60 samples from ESRD patients undergoing dialysis at Hamida Al-Musaffah Dialysis Center at Ima main Al-Kadhim in Medical City, and 40 samples were collected from healthy donors.

Results: Dialysis patients and control groups were age-matching, where non-significant (p=0.926) differences were recorded between their ages. Dialysis patients demonstrated significant shifts in studied hematological and biochemical parameters compared to control group. White blood cell profiles exhibited reduced total counts and LYM percentages, along with increasing MID % and GRAN %. The RBCs indices exhibited noticeable anemia, with significantly decrease RBCs count, HGB, HCT, RDW-CV, RDW-SD alongside mean corpuscular indices. As well as, the platelet parameters were consistently lessened in dialysis patients. Biochemically, studied patients demonstrated significantly higher FBS levels and PO_4, diminished Ca. Renal function markers were notably altered in dialysis patients, with both urea and creatinine levels significantly elevated in patients compared to healthy controls. As for liver function tests, they demonstrated mixed patterns, where total serum bilirubin (TSB) was significantly (p=0.000) reduced in patients than controls. Alkaline Phosphatase (ALP) levels were significantly (p=0.000) increased in patients than controls. However, other liver test did not differ significantly (p>0.05) between studied groups. In addition, a highly significant (p=0.000) decrease in serum iron and EPO was observed in patients than in healthy individuals. The correlation analysis showed that serum iron has significant inverse correlations with LYM $X10^9$/L and MID $X10^9$/L, and it also showed significant positive correlations with each of MID $X10^9$/L, MPV fL, PDW fL, and P-LCR %. As for UIBC µg/dL, it exhibits significant inverse correlations with LYM % and MCHC g/dL; and significant positive correlations with RBCs $X10^{12}$ /L, PO_4 mg/dL, and TSB mg/dL. EPO mIU/ml levels have significant inverse correlations with MID% and MID $X10^9$/L. In addition, EPO showed significant positive correlations with Creatinine mg/dL, and AST U/L, ALT U/L. **Conclusion**: The present study emphasized that ESRD patients subjected to dialysis experience undergone from systemic disruptions characteristic to uremic syndrome, including anemia driven by diminished erythropoietin and serum iron levels, and considerable changes in Ca–PO_4 balance along with other biochemical parameters. Overall, the present outcomes highlight thorough disturbances in hematological homeostasis as well as mineral–metabolic balance in studied dialysis patients.

* Corresponding author: Hind Mahmood Jumaah

Keywords: Dialysis; ESRD; Chronic Kidney Disease; CBC; Erythropoietin; Iron; AST; ALT; Kidney Functions

1. Introduction

Chronic kidney disease (CKD) represents a worldwide public health problem [1]. End-stage renal failure (ESRD) is defined as a chronic and ongoing diminish in kidney functions, which considers the ultimate stage of CKD, as the perpendicular dropping in glomerular filtration demands renal replacement therapy [2]. At this stage, the renal replacement therapy with maintenance hemodialysis or chronic peritoneal dialysis is growingly employed in the management of ESRD patients [3]. It is estimated that around two million people or more suffer from ESRD worldwide [4]. Although dialysis is a vital life-sustaining intervention by removing uremic toxins and restoring electrolyte balance, but it cannot fully mimic the endocrinal and metabolic complexities of the functional kidney. As a result, patients subjected to dialysis suffer from systemic "uremic syndrome" that influences almost all the physiological system, with several hematological and biochemical disturbances being among the most thorough relevance challenges [5,6]. Since that dialysis patients are at high risk of mortality [7,8]; thus, the related risk factors across this population must be picked out.

This uremic syndrome regards as a multisystem catalyst for morbidity, as accumulating of nitrogenous waste products and middle molecules induces a cascade of oxidative stress and chronic inflammations. Across this pathological framework, the hematological disorders exceptionally those reflected anemia and disordered leukocytes dynamics interlace [9,10], together with biochemical abnormalities in mineral metabolism like calcium (Ca), phosphate (PO_4), and erythropoietin (EPO) axis [11,12]. Iron metabolism as well as EPO deficiency are exceptionally central to anemia in CKD, with serum iron, unsaturated iron-binding capacity (UIBC), and ferritin often revealing complex patterns affected by inflammations and dialysis practices [13]. The EPO deficiency production had been thought to be the principal cause of anemia in ERSD patients [14]. Anemia is a serious complication in ERSD patients, despite it can be treated. The significance of anemia treatment is linked with minimizing in morbidity and mortality rates owing to reduce occurrence of left ventricular hypertrophy and consecutive heart failure, a condition known as cardiorenal syndrome [15-17].

Moreover, Ca and PO_4 imbalance engages to secondary hyperparathyroidism and vascular calcification, connecting the mineral metabolism directly to cardiovascular risk [12]. Several observational investigations have illustrated an association between disrupted serum Ca/PO_4 levels and an increasing risk of mortality in dialysis patients [18-20].

These disruptions are not merely secondary symptoms, but being primary drivers of cardiovascular calcification and immunological dysfunction that two key factors across dialysis experience [21]. Given to disproportionately increasingly mortality rate in the dialysis populations, therefore identifying the associated risk factors within this biochemical web and investigate the correlations between these parameters provides valuable insights into the interconnected physiology of ESRD undergoing dialysis and has a clinical imperative.

Accordingly, the present investigation designed to estimate the interaction between hematological profiles, mineral bone parameters, and principle regulatory factors like EPO and serum iron in a cohort of dialysis patients.

2. Methodology

2.1. Study settings and samples

This case-control study involved collecting 100 blood samples, including 60 samples from ESRD patients undergoing dialysis at Hamida Al-Musaffah Dialysis Center at Ima main Al-Kadhim in Medical City, affiliated with the Baghdad Al-Karkh Health Directorate. Along with$_4$0 samples were collected from healthy donors with no health problems or chronic diseases. After obtained the informed consent from all participants, the blood samples were collected and separated by centrifugation to get sera that frozen at −20°C until later biochemical analysis for studied parameters.

2.2. Biomarkers analysis

The hematological parameters were measured after collected the blood specimens EDTA, and then employing the Hemolyze Analytical (Germany) automatic blood analysis device to evaluate these parameters. Fasting blood sugar (FBS), PO_4, and serum urea levels were evaluated using specific kits from Linear/ Spain. Calcium and creatinine levels were measured using kits from Randox/UK. The levels of TSB were measured by spectrophotometer employing the $AU_4$80 Beckman Coulter/USA device. The levels of ALP, ALT, and AST have been assessed utilizing the enzymatic colorimetric procedure employing the kit from Bio Diagnostic, Egypt. The evaluation of serum albumin levels has been followed the instructions of Manufacturer Company (bt products/Turkii) of albumin-Kit. Colorimetric method was

applied to measure TP levels employing the kit from SPINREACT/Spain. To evaluate iron levels, the kit from Bio Labo/ French has been used. The levels of UIBC were assessed employing Roche Cobas analyzer 6000, Switzerland. EPO levels have been measured based on instructions of manufacturer company (My BioSource/USA).

2.3. Statistical analysis

Data had presented as mean ± standard deviation and analyzed using SPSS (26) version. The mean of the investigated biomarkers was compared between the studied groups using t-Test; Chi-Square analysis was employed to significant compare between sexes; as well as the Pearson correlation analysis was performed to investigate the correlations between studied markers

3. Results and discussion

3.1. Demographic Characteristics of Study Population: Age and Sex Distribution

The mean ± SD of age in dialysis patients was 54.1 ± 14.605, while mean ± SD of age in healthy individuals was45.625 ± 14.068. Statistical analysis with t-test demonstrated non-significant differences between groups (p=0.926) (Figure 1)

In dialysis patients, males comprised 70% and females 30%; while in controls, males accounted for 32.5% and females 67.5%. Statistical analysis using the chi-square test demonstrated that this difference in sex distribution between studied groups was highly statistically significant (p=0.000) (Figure 2)

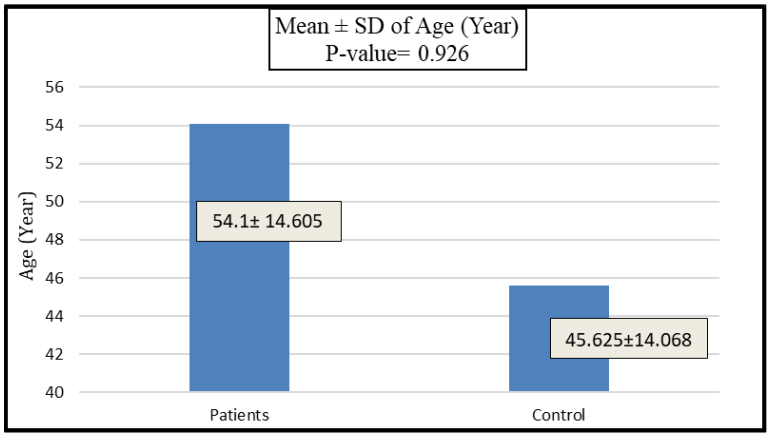

Figure 1 Comparison of age between Dialysis Patients and Healthy Participants

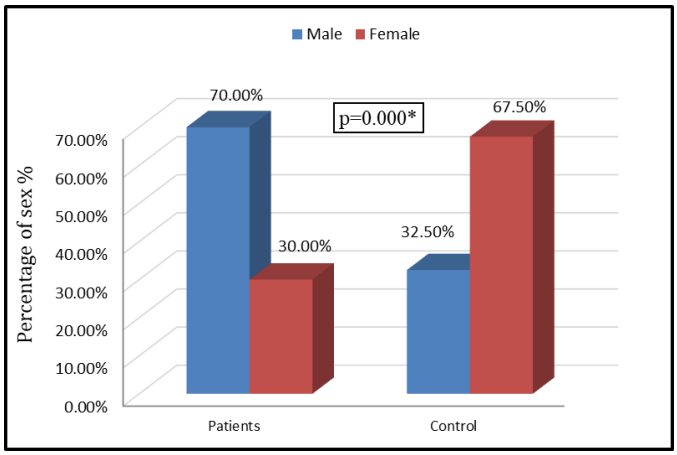

Figure 2 Distribution of Dialysis Patients and Healthy Participants According to sex

The non-significant differences in age between dialysis patients and healthy individuals reflect the deliberate design of current investigation. Since age is a critical determinant for many physiological markers, the study population was selected to ensure age matching across studied groups; where this age matching minimized the likelihood that observed differences in physiological markers are attributable to age rather than dialysis status.

Corresponding findings were reported by Wu *et al*. [22], who revealed that while advanced age interacts with dialysis duration to affect the survival outcomes, but age-matched comparisons are crucial to separate the impacts of disease from age-associated physiological decline. Likewise, matched-pair analyses in transplantation field underscored that age balance between groups is indispensable to elucidate outcomes precisely [23].

The present finding of mean age for patients is (54.1 year) line up the local demographic patterns reported in Iraq, where a cross-sectional study conducted by Alhajim [24] showed that 73% of hemodialysis patients were older than45 years; most of them fall into middle-aged alongside elderly categories. Moreover, consistent with age profile observed in our investigation, Shaheen *et al*. [25] revealed that ESRD prevalence in Middle Eastern countries displays a demographic skew toward patients at their 5th and 6th decades of life. Additionally, our finding is in line with recent study reported that dialysis cohorts often include middle-aged as well as elderly individuals [26].

The significant disparity in sex distribution detected between dialysis patients and controls aligns with the epidemiological trends in chronic kidney diseases; the predominance of male among those had been consistently documented, with physiological and behavioral determinants leading to this disparity. Males are more susceptible to hypertension and cardiovascular diseases, which accelerate the decline of renal functions, while hormonal and genetic impacts may as well predispose males to progressive nephropathy. In contrast, females often manifest slower progression of kidney diseases, likely owing to protective impacts of estrogen hormone on renal hemodynamics as well as pathways of oxidative stress [27].

Jha *et al*. [28] have revealed similar distribution; strengthen the notion that sex differences in dialysis prevalence are not merely demographic artifacts but mirror underlying physiological and clinical risk profiles. In addition, comparable results have been reported in the study of Saran *et al*. [29], which reported that male usually predominate females in dialysis patients.

The significant difference in sex distribution in the current investigation therefore highlights the significance to consider the sex-specific factors in both the pathophysiology and management of renal failure.

3.2. Comparison of studied parameters between dialysis patients and controls

Table (1) illustrates the comparison of complete blood count (CBC) parameters and biochemical parameters of mineral metabolism in patients and controls. According to the results of statistical analysis, dialysis patients showed lower mean white blood cell counts (WBCs) (6.3567 ± 2.281 vs. 7.57± 1.284 × 10^9/L, p = 0.003), decreased lymphocyte (LYM) percentage (22.023 ± 6.728 vs. 34.065± 7.341%, p =0.000), and higher mid-cell (MID) percentage (12.126 ± 4.991 vs. 6.257 ± 1.691%, p =0 .000). Granulocyte (GRAN) percentage was also elevated in dialysis patients (64.653 ± 12.864 vs. 59.678 ± 7.398%, p = 0.029). Absolute lymphocyte and mid-cell counts were significantly lower and higher, respectively, in patients as compared with healthy individuals (p = 0.000 for both). Granulocyte counts did not differ significantly (p =0.629).

Indices of Red blood cells (RBCs) showed notable lessening in patient's RBCs count (3.432 ± 0.581 vs.4.692± 0.374 ×10^{12}/L, p = 0.000), hemoglobin (HGB) (9.477± 1.722 vs. 13.956 ± 0.781g/dL, p = 0.000), and hematocrit (HCT) (30.207 ± 5.384 vs.43.861 ±2.801%, p = 0.000). While mean corpuscular volume (MCV) increased in patients (88.257 ± 5.663 vs. 84.778 ± 3.617 fL, p =0 .001), mean corpuscular hemoglobin (MCH) showed non-significant (p =0 .125). Mean corpuscular hemoglobin concentration (MCHC) showed decreased values in patients as compared with controls (31.627 ± 0.691 vs. 33.533 ± 0.774 g/dL, p = 0.001). Red cell distribution width (RDW-CV and RDW-SD) showed significantly increase in control group than patients (p = 0.000 for both).

As well as, the platelet's parameters demonstrated significant differences, as patients had lower platelet counts (PLT) (188.367 ± 64.926 vs. 253.825 ± 43.499 × 10^9/L, p =0 .000), lower mean platelet volume (MPV) (7.313 ± 1.228 vs. 8.933 ± 0.673 fL, p =0 .000), and lower platelet distribution width (PDW) (8.973 ± 1.587 vs. 11.218 ± 0.728 fL, p =0 .001). Plateletcrit (PCT) and platelet large cell ratio (P-LCR) were also significantly reduced in patients (p = 0.000 for both), as was platelet large cell count (P-LCC) (p =0 .001).

With regard to biochemical parameters, dialysis patients had significantly increased fasting blood sugar (FBS) (152.212 ± 56.489 vs. 95.725± 5.81 mg/dL, p =0.000). Serum calcium (Ca) levels were significantly (p=0.000) decreased in patients (8.644 ± 0.891mg/dL) as compared with control group (9.276 ± 0.579 mg/dL, while phosphate (PO_4) demonstrated notably increased in studied patients than controls (5.361 ± 1.711 vs. 3.522± 0.585 mg/dL, p =0 .000).

Table 1 Comparison Hematological and Biochemical parameters between patients and controls

Parameters	**Dialysis Patients (n=60)**		**Control (n=40)**		**P value**
	Mean	Std. Deviation	Mean	Std. Deviation	
Haematological parameters					
WBCs $\times 10^9$/L	6.356	2.281	7.57	1.284	0.003*
LYM %	22.023	6.728	34.065	7.341	0.000*
MID%	12.126	4.991	6.257	1.691	0.000*
GRAN%	64.653	12.864	59.678	7.398	0.029*
LYM $\times 10^9$/L	1.29	0.393	2.398	0.583	0.000*
MID $\times 10^9$/L	0.707	0.256	0.433	0.180	0.000*
GRAN $\times 10^9$/L	4.433	2.118	4.608	0.989	0.629NS
RBCs $\times 10^{12}$ /L	3.432	0.581	4.692	0.374	0.000*
HGB g/dL	9.477	1.722	13.956	0.781	0.000*
HCT %	30.207	5.384	43.861	2.801	0.000*
MCV FL	88.257	5.663	84.778	3.617	0.001*
MCH PG	27.86	2.029	28.428	1.391	0.125NS
MCHC g/dL	31.627	0.691	33.533	0.774	0.000*
RDW-CV%	3.753	0.246	12.308	0.757	0.000*
RDW-SD FL	23.087	2.036	45.548	4.944	0.000*
PLT $\times 10^9$/L	188.367	64.926	253.825	43.499	0.000*
MPV FL	7.313	1.228	8.933	0.673	0.000*
PDW Fl	8.973	1.587	11.218	0.728	0.000*
PCT%	0.132	0.041	0.222	0.037	0.000*
P-LCR %	15.307	6.347	20.138	4.667	0.000*
P-LCC $\times 10^9$/L	26.60	10.575	51.10	13.538	0.000*
Biochemical Parameters					
FBS mg/dL	152.212	56.489	95.725	5.81	0.000*
Ca mg/dL	8.644	0.891	9.276	0.579	0.000*
PO_4 mg/dL	5.361	1.711	3.522	0.585	0.000*
*Significant difference under p ≤ 0.05 by T-test, NS: Non-significant					

The outcomes of Table (2) showed significant disturbances in hematological and biochemical indices among dialysis patients compared to healthy individuals. The significant reductions in RBCs count, HGB, and HCT indicate the well-established anemia of chronic kidney diseases (CKD), which owing to impaired iron dysregulation alongside chronic inflammations, Portolés *et al*. [11] stated that these mechanisms collectively engaged with diminished oxygen-carrying capacity and escalated morbidity in dialysis patients.

Our findings in line with several reports demonstrated the prevalence of anemia among kidney dialysis patients and it's correlated with a minimize life quality (30), a reduced kidney survival [31], and an escalate in morbidity and mortality [11]. In addition, a previous study conducted by Portolés *et al*. [32] demonstrated that patients that had developed anemia notably progressed to CKD stages4–5, and they had high hospitalization's rates, major cardiovascular diseases as well as mortality. Moreover, Inker *et al*. [33] reported that anemia expanded with progressing of CKD from 8.40% at stage 1 to 53.40% at stage 5. Besides, the fluctuation observed in mean corpuscular indices and RDW further emphasize erythropoiesis heterogeneity in cases with renal failure, theses finding in agreement with previous report of anisocytosis and microcytic changes in dialysis patients [34].

The present study as well documented significantly reduction in platelet parameters, where such findings are clinically relevant, since uremia lessens both platelet function and survival, participating to bleeding likelihood in dialysis patients. Similar findings in platelet indices were reported in previous studies that highlighted the systemic impacts of uremic toxins on hematopoiesis and hemostasis [35,36].

Additionally, the alterations present in the current study, particularly anemia, disturbed minerals metabolism, as well as metabolic imbalance are compatible with a large observational investigation from Swedish Renal Registry conducted by Evans *et al*. [37] which established that anemia is prevalent in CKD, especially among dialysis cases, and its management is intricate by inflammations, variable response to erythropoiesis-stimulating factors, and suboptimal iron utilization, these registries outcomes, revealing that our findings reflect the established clinical pattern in dialysis patients. Furthermore, our findings agree with those reported by Al-khafaji *et al*. [38], who also revealed a significant decrease in WBCs, RBCs, Hb and PLT and concluded that CKD directly influenced the hematological parameters.

In the present study, the assessment of fasting blood sugar showed increased FBS in patients than controls. Hyperglycemia is common in dialysis patients due to high prevalence of diabetes as an implicating cause for renal failure and impaired glucose metabolism during dialysis itself [39,40]. This finding agrees with concept that glycemic control in ESKF is of remarkable diagnostic significance [41].

Also, the assessment of other biochemical markers demonstrated significantly reduced Ca, and increased PO_4 in patients. This imbalance in Ca and PO_4 indicates the mineral bone upset of CKD, driven by decreased renal excretion of PO_4, secondary hyperparathyroidism, and changed vitamin D metabolism. These interferences are robustly associated with vascular calcification and cardiovascular risk in dialysis patients [12]. Several studies had reported that high-PO_4 and high-FBS medium caused more severe Ca deposits in vascular smooth muscle cells, probably via upregulation of a PO_4 transporters or cellular-senescence-associated agents [42,43]. Furthermore, van der Vaart *et al*. [44] investigated non-dialysis diabetes patients and found a vigorous association between high plasma PO_4 concentrations and all-cause mortality in patients with type 2 diabetes. While our study revealed a significant increase in PO_4 concentrations in dialysis patients, a previous study, however, suggested that higher PO_4 combined with adequate protein intake was associated with better prognosis in dialysis cases, while low PO_4 and poor nutrition status predicted worse consequence [45].

The observed reduced Ca levels in dialysis patients can be justified by the complex disturbances in mineral metabolism that happen in CKD. One of the principal mechanisms is the macerated ability of affected kidneys to convert vitamin D into its active form (1, 25-dihydroxyvitamin D). Because active vitamin D is crucial for intestinal Ca absorption, its deficiency leads to lessen Ca uptake from the gastrointestinal tract and as a result decrease serum Ca levels. Moreover, some dialysis-related factors can as well lead to lessen Ca levels; where usage of low-Ca dialysate, which is often utilized to avert hypercalcemia and vascular calcification, may directly reduce serum Ca during treatment [46].

3.3. Comparison of the Renal and Liver Functions Tests between Dialysis Patients and Controls

Table (2) compares the renal and liver functions markers between patients and controls. Renal function markers were notably altered in dialysis patients, with both urea and creatinine levels significantly elevated in patients (144.005±44.801 and4.801±3.328 mg/dL, respectively) compared to healthy controls (34.625±5.908 and 0.8649±0.203 mg/dL, respectively), indicating impaired excretory capacity.

In the context of liver function tests, they demonstrated mixed patterns, where total serum bilirubin (TSB) was significantly ($p=0.000$) reduced in patients than controls (0.3778±0.144 vs. 0.645±0.243 mg/dL). Alkaline Phosphatase (ALP) levels were significantly ($p=0.000$) increased in patients than controls (395.247 ± 27.885 vs. 93.250 ± 22.652 U/L). While other studied markers including Aspartate Transaminase (AST) and Alanine Transaminase (ALT), albumin and Total protein (TP) did not differ significantly ($p>0.05$) between studied groups.

Table 2 Comparison the Renal and liver functions Tests and other biochemical related parameters between patients and controls

Parameters	Patients (n=60)		Control (n=40)		P value
	Mean	Std. Deviation	Mean	Std. Deviation	
Urea (mg/dL)	144.005	44.801	34.625	5.908	0.000*
Creatinine (mg/dL)	8.371	3.328	0.8649	0.203	0.000*
TSB mg/dL	0.37780	0.144	0.645	0.243	0.000*
ALP U/L	395.247	27.885	93.250	22.652	0.000*
AST U/L	19.190	2.169	22.353	8.287	0.273NS
ALT U/L	17.080	2.553	18.515	6.715	0.660NS
ALB g/dL	3.868	0.282	3.861	0.335	0.918NS
TP g/dL	6.395	0.558	6.64	0.445	0.172 NS
*Significant difference under $p \leq 0.05$ by T-test, NS: Non-significant					

The observed alterations of renal and liver biomarkers in dialysis patients highlight the intrinsic systemic physiological disruptions of ESRD. The significance rising of urea and creatinine in those patients serves as a principal indicator of severely affected glomerular filtration and excretory failure. These findings agree with those reported by Gulavan *et al*. [47], who revealed that in spite of the intervention of hemodialysis, re-dialysis levels of these nitrogenous metabolites continue notably higher than physiological reference ranges owing to the persistent catabolism of endogenous proteins and the incompetence of damaged nephrons to sustain clearance. At the physiological context, this azotemia condition reflects an intense loss of functional nephron mass, as even doubling of creatinine levels signify a loss of roughly 50% of renal capacity [48].

On the other hand, despite the obvious renal findings, liver function tests exhibited a more complex and varied clinical patterns. The significant depletion in TSB in dialysis patients is a noteworthy finding often assigned to chronic oxidative stress. Bilirubin is an effective endogenous antioxidant; nevertheless, at uremic environment distinctive of ESRD, stable exposure to reactive oxygen species (ROSs) could exhaust the systemic antioxidant reserves [49], which explains the sub-normal levels present in the current study.

This inverse association between progression of ESRD and bilirubin levels has been reinforced by clinical evidence stating that reduced circulating bilirubin levels may even linked with boosted cardiovascular risk in dialysis patients [50].

Contrariwise, the significant increment in ALP levels seems to reflect the secondary mineral and bone disorders rather than primary liver injury. In dialysis patients, high ALP levels are frequently a surrogate indicator for high-turnover bone diseases like osteitis fibrosa cystica that resulting from secondary hyperparathyroidism [51]. A similar finding reported by Fan *et al*. [52], who also found a significant increased levels of ALP in dialysis patients. Furthermore, Smout *et al*. [53] revealed that higher ALP levels were independently linked with expanded all-cause mortality and vascular calcification in CKD patients.

The non-significant differences in the levels of transaminases (AST and ALT), albumin, and TP across studied groups suggests that core synthetic and metabolic functions of liver stay relatively preserved in dialysis patients. These findings align with the study of Saleem [54], which showed that unless a concomitant viral hepatitis or congestive hepatopathy is present, classical markers of hepatocellular injury often stay at normal or even diminished ranges in uremic patients due to existence of metabolic inhibitors that could mask liver enzymes activities.

3.4. Comparison of Iron Homeostasis and Erythropoietin Levels between patients and controls

The comparison of iron status and hematopoietic regulatory biomarkers between studied groups is illustrated in Table 3. A highly significant (p=0.000) decrease in serum iron was observed in patients (40.301 ± 13.875 µg/dL) than in healthy individuals (81.133 ± 9.825 µg/dL). Also, the levels of erythropoietin (EPO) showed a profound deficit in

patients as compared with controls (4.37 ± 1.544 vs. 185.788 ± 11.197, p=0.000). On the other hand, Unsaturated Iron Binding Capacity (UIBC) marker showed non-significant differences between studied groups (p =0.874).

Table 3 Comparison of Iron Homeostasis and Erythropoietin Levels between patients and controls

Parameters	**Patients (n=60)**		**Control (n=40)**		**P value**
	Mean	Std. Deviation	Mean	Std. Deviation	
Serum Iron µg/dL	40.301	13.875	81.133	9.825	0.000*
UIBC µg/dL	329.987	65.389	314.318	69.793	0.874^{NS}
EPO mIU/ml	4.37	1.544	185.788	11.197	0.000*
*Significant difference under p ≤ 0.05 by T-test, NS: Non-significant					

In the current research, the analysis of hematological and regulatory markers demonstrated a thorough disruption across erythropoietic axis, which characterized by a statistically significant depletion in both serum iron and EPO levels in dialysis patients compared to healthy individuals. The coincident observation of lack significant differences in UIBC between these groups further complicated the clinical scenery, revealed that the anemia observed in studied patients is resulted from a multifaceted deficiency in substrate availability as well as hormonal stimulation.

With regard to physiological context of ESRD, the substantial reduction in EPO is a direct outcome for losing of peritubular interstitial cells within renal cortex, which represent a primary site to synthesize EPO responding to hypoxia [55]. Where without sufficient EPO levels, bone marrow can't sustain effective RBCs production, regardless of serum iron status.

Our findings align with a number of studies that have reported decreased iron and EPO levels in dialysis patients, highlighting the central impact of renal insufficiency and inflammations in driving anemia. The present findings line up the study of Venkatesan *et al*. [13], who reported notably decrease serum iron in CKD cases as compared to healthy individuals. Also, the findings of Portolés *et al*. [11] supported our result, where they demonstrated that depressed EPO production along with iron deficiency is a hallmark of CKD-associated anemia.

Hanna *et al*. [56] documented nearly similar trends in a hemodialysis patients, they revealed that concurrent of iron loss owing to dialysis-related blood entrapment and defeat of renal EPO production generates a synergistic effect of resistance to anemia therapy. Likewise, Padwal *et al*. [57] had proven that iron deficiency is common in dialysis patients, even so ferritin or transferrin levels may differ based on inflammatory conditions. In addition, the constant levels of UIBC presented in our cohorts agrees with finding of Gulavan *et al*. [47], who revealed that at conditions of chronic inflammations, the ability of liver to synthesize of transferrin (and accordingly iron-binding capacity) is often conquered, thus averting the increase in UIBC levels that expected to present at status of simple iron-deficiency. Also the present finding of non-significant differences between patients and controls in the levels of UIBC agrees with Raoof and Abdalah [58], who also found that UIBC levels did not differ significantly (p=0.697) between hemodialysis patients and healthy individuals, as they were 26.845 ± 12.802 versus 30.582 ± 12.144 respectively.

The study of Todorova *et al*. [59] demonstrated fluctuating EPO levels across dialysis patients, with roughly 29% of those patients exhibited levels under reference range, whereas peritoneal dialysis patients seem to possess higher average levels; these findings highlighted viability across dialysis modalities and patients, but the presence of a considerable proportion of patients had reduced levels of EPO in their patients reinforces our findings that dialysis patients frequently show reduced erythropoietin.

Conversely, other studies demonstrated contrasting findings concerning these markers; [60] documented that iron levels remained relatively stable some cases, like dialysis patients who were obtaining high doses of iron intravenously supplementation, which may explain the inconsistency between their findings and the finding observed in our study.

3.5. Correlation analysis

3.5.1. The correlation analysis of serum iron, UIBC and Erythropoietin with CBC markers among patients

Table (4) illustrates the correlation analysis of serum iron, UIBC and EPO with studied CBC parameters among patients. Regarding to serum iron it showed significant inverse correlations with LYM $\times 10^9$/L and MID $\times 10^9$/L, and it also showed significant positive correlations with each of RDW-SD fL, MPV fL, PDW fL, and P-LCR %.

As for UIBC µg/dL, it exhibits significant inverse correlations with LYM % and MCHC g/dL; and significant positive correlations with RBCs X10^{12} /L. Finally, EPO mIU/ml levels have significant inverse correlations with MID% and MID $\times 10^9$/L. While other association revealed non-significant correlations.

Table$_4$ The correlation analysis of serum iron, UIBC and Erythropoietin with CBC markers among patients

Correlations		**Serum iron µg/dL**	**UIBC µg/dL**	**EPO mIU/ml**
WBCs $\times 10^9$/L	Pearson Correlation	-0.167-	0.146	-0.036-
	Sig. (2-tailed)	0.220	0.266	0.784
LYM %	Pearson Correlation	-0.145-	-0.306-*	-0.033-
	Sig. (2-tailed)	0.285	0.017	0.804
MID%	Pearson Correlation	-0.162-	-0.082-	-0.302-*
	Sig. (2-tailed)	0.234	0.533	0.019
GRAN%	Pearson Correlation	0.118	0.215	0.138
	Sig. (2-tailed)	0.387	0.099	0.294
LYM $\times 10^9$/L	Pearson Correlation	-0.264-*	-0.186-	0.027
	Sig. (2-tailed)	0.049	0.156	0.840
MID $\times 10^9$/L	Pearson Correlation	-0.326-*	0.096	-0.256-*
	Sig. (2-tailed)	0.014	0.466	0.048
GRAN $\times 10^9$/L	Pearson Correlation	-0.072-	0.171	0.020
	Sig. (2-tailed)	0.597	0.192	0.882
RBCs $\times 10^{12}$/L	Pearson Correlation	0.173	0.454*	-0.042-
	Sig. (2-tailed)	0.204	0.040	0.750
HGB g/dL	Pearson Correlation	0.104	0.226	0.054
	Sig. (2-tailed)	0.445	0.083	0.680
HCT %	Pearson Correlation	0.160	0.250	0.048
	Sig. (2-tailed)	0.237	0.054	0.716
MCV FL	Pearson Correlation	0.068	0.000	0.148
	Sig. (2-tailed)	0.620	0.997	0.259
MCH PG	Pearson Correlation	-0.018-	-0.075-	0.152
	Sig. (2-tailed)	0.894	0.572	0.246
MCHC g/dL	Pearson Correlation	-0.237-	-0.354-*	0.047
	Sig. (2-tailed)	0.079	0.041	0.724
RDW-CV%	Pearson Correlation	0.143	0.122	-0.129-
	Sig. (2-tailed)	0.293	0.352	0.327

RDW-SD FL	Pearson Correlation	0.334*	0.100	0.102
	Sig. (2-tailed)	0.012	0.448	0.440
PLT $\times 10^9$/L	Pearson Correlation	-0.194-	-0.051-	0.001
	Sig. (2-tailed)	0.151	0.698	0.996
MPV FL	Pearson Correlation	0.407**	0.046	-0.035-
	Sig. (2-tailed)	0.002	0.726	0.788
PDW FL	Pearson Correlation	0.408**	-0.012-	-0.175-
	Sig. (2-tailed)	0.002	0.929	0.180
PCT%	Pearson Correlation	-0.090-	-0.050-	-0.061-
	Sig. (2-tailed)	0.510	0.703	0.641
P_LCR %	Pearson Correlation	0.451**	0.027	-0.082-
	Sig. (2-tailed)	0.000	0.838	0.535
P_LCC $\times 10^9$/L	Pearson Correlation	0.217	0.006	-0.170-
	Sig. (2-tailed)	0.107	0.966	0.194
* Correlation is significant at the 0.05 level				
** Correlation is significant at the 0.01 level.				

3.6. The correlation analysis of serum iron, UIBC and Erythropoietin with biochemical parameters among patients

Table (5) illustrates the correlation analysis of serum iron, UIBC and EPO with studied biochemical parameters among patients. Serum iron showed non-significant correlations with all parameters.

As for UIBC, it exhibits significant positive correlations with PO_4 mg/dL, and TSB mg/dL. Finally, EPO MIU/ml levels have significant positive correlations with Creatinine mg/dL, and AST U/L, ALT U/L. While other associations revealed non-significant correlations.

Table 5 The correlation analysis of serum iron, UIBC and Erythropoietin with biochemical parameters among patients

Correlations		**Serum iron µg/dL**	**UIBC µg/dL**	**EPO mIU/ml**
FBS mg/dL	Pearson Correlation	0.135	-0.088-	-0.175-
	Sig. (2-tailed)	0.322	0.503	0.182
Urea mg/dL	Pearson Correlation	0.097	0.065	0.227
	Sig. (2-tailed)	0.475	0.624	0.081
Creatinine mg/dL	Pearson Correlation	0.128	0.181	0.300*
	Sig. (2-tailed)	0.345	0.166	0.020
Ca mg/dL	Pearson Correlation	0.161	0.003	-0.199-
	Sig. (2-tailed)	0.235	0.983	0.128
PO_4 mg/dL	Pearson Correlation	-0.161-	0.355**	0.162
	Sig. (2-tailed)	0.235	0.005	0.217
TSB mg/dL	Pearson Correlation	0.206	0.436**	0.100
	Sig. (2-tailed)	0.127	0.001	0.445
ALP U/L	Pearson Correlation	-0.044-	0.024	0.095

	Sig. (2-tailed)	0.748	0.857	0.473
AST U/L	Pearson Correlation	-0.262-	-0.140-	0.416**
	Sig. (2-tailed)	0.051	0.285	0.001
ALT U/L	Pearson Correlation	-0.158-	-0.108-	0.442**
	Sig. (2-tailed)	0.244	0.413	0.000
ALB g/dL	Pearson Correlation	0.028	-0.192-	0.233
	Sig. (2-tailed)	0.836	0.142	0.074
TP g/dL	Pearson Correlation	0.123	0.122	0.150
	Sig. (2-tailed)	0.365	0.353	0.254
* Correlation is significant at the 0.05 level				
** Correlation is significant at the 0.01 level.				

The correlation analysis in our study demonstrated a notable and complex associations between serum iron levels and several hematological parameters, emphasized the systemic effects of iron on immunological responses and hemostatic system in dialysis population. The reported significant inverse correlation of serum iron with both LYM and MID indicates that when iron stores exhaust, there is a compensatory driven alteration in WBCs.

In uremic environment of ESRD, serum iron deficiency often coincides with chronic inflammations. This relationship is reinforced by Tiwari and Tiwari [61], who revealed that iron markers were negatively correlated with inflammatory status, suggested that the exhaustion of iron that usually mediated by increased hepcidin is greatly correlated to the activation and redistribution of WBCs throughout inflammatory responses distinctive to dialysis. The present findings in line with Liao *et al*. [62], who revealed that iron deficiency in dialysis patients is associated with increased platelet counts, indicating that iron metabolism directly influences both platelets production and functions. Also, our finding of negative correlation of iron levels with MID aligns with Xie *et al*. [63], who demonstrated that higher inflammatory cell ratios (including monocyte-to-lymphocyte ratio) were linked with reduced serum iron owing to iron sequestration. The positive association between serum iron and RDW-SD is a particular indicator of how dialysis patients reply to iron availability. As iron is supplied, bone marrow boosts erythropoiesis. This process establishes new populations of larger, younger red cells into circulation, which statistically boosted (RDW-SD), while the older and smaller cells remaining [64].

In the studied cohort of dialysis patients, UIBC showed significant inverse correlations with LYM% and MCHC, as well as positive correlations with RBCs. The inverse association between UIBC and LYM% indicates that reduced iron may implicated to immunological dysregulation, harmonious with the inflammatory environment usually present in dialysis patients. Likewise, the inverse association with MCHC mirrors the functional iron deficiency, where decreased iron saturation weakens the hemoglobinization.

On the other hand, the positive correlations with RBCs, PO_4, and TSB point out the broader systemic interactions; as increased PO_4 is regarding a hallmark of CKD-mineral bone disorder, while high TSB might reflect hemolysis or liver dysfunction, both of which could intensify anemia. These findings line up the observations of Padwal, *et al*. [57], they found potent correlations between iron markers such as ferritin and the classical inflammatory markers like C-reactive protein and leukocyte counts in dialysis patients, highlighting the link between iron metabolism and immunological markers. Although their investigation did not specifically assess UIBC, but they supported the concept that iron is closely linked with hematological and inflammatory profiles in CKD.

The correlations between EPO and hematological/biochemical parameters in the current study provide significant insights into the pathophysiology of anemia in our cohort. The significant inverse correlations with MID% and MID counts indicate that lower EPO availability is correlating to impaired regulations of leukocyte precursors, mirroring the suppression of hematopoiesis in CKD. On the other hand, the positive correlations with creatinine, AST, and ALT suggest that decline kidney functions and the hepatic stress are correlated with compensatory increments in serum EPO, albeit inadequate to address anemia.

These correlations align with Portolés *et al*. [11], who demonstrated that lessen kidney EPO production is a key driver for anemia in CKD. Venkatesan *et al*. [13], who revealed that iron together with EPO deficiencies could impair

erythropoiesis. In addition, Padwal *et al.* [57] observed that EPO responsiveness is affected by iron status together with systemic inflammations, align with the current correlations linking EPO to biochemical stress biomarkers. Furthermore, Hanna *et al*. [56] reported that EPO levels were negatively correlated with stress markers, enhancing the concept that EPO has a role that goes beyond simply erythropoiesis, serving as a stabilizer for immunological environment.

4. Conclusion

The current investigation reveals that ESRD patients required dialysis display intense hematological and biochemical disruptions consistent with systemic uremic syndrome. The impaired kidney function tests and $Ca–PO_4$ imbalance, with altered liver function test indicated the inclusive metabolic stress of dialysis. Anemia was evident via outstandingly diminished iron and EPO levels, highlighting the complexity of iron metabolism in those patients. Correlation analyses showed that iron and EPO levels were closely correlated with leukocytes and platelet indices, along with biochemical markers like creatinine, PO_4, and bilirubin, emphasized the interrelated nature of hematopoietic suppression, mineral disorder, as well as systemic inflammations. Overall, our outcomes assured that anemia and mineral imbalance represented main challenges in patients subjected to dialysis. By situating these findings within broader studies, this investigation revealed the demand for integrated check of hematological and biochemical parameters to elucidate risk stratification and management strategies in dialysis patients

Compliance with ethical standards

Disclosure of conflict of interest

The author declares no conflict of interest.

Statement of ethical approval

In the current study, the protocol, individual's data and assent form have been revised and approved by a local ethics committee, College of Science, University of Baghdad as stated by document numbered as CSEC/0326/0032.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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