

Role of inflammation, nutritional status and body mass index in the development of resistance to erythropoiesis-stimulating agents (ESAs) in patients under regular hemodialysis

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ABSTRACT

Renal anemia in chronic kidney disease (CKD) is a common complication in hemodialysis patients, primarily due to erythropoietin (EPO) and iron deficiencies. EPO is the preferred treatment for renal anemia. A reduction in the efficacy of EPO, referred to as EPO hyporesponsiveness, could be linked to nutritional deficiencies, heightened inflammatory states, and an elevated risk of mortality. The current study aims to elucidate the correlation between the inflammatory biomarkers (high-sensitive C-reactive protein [hs-CRP] and all of the Erythropoietin Resistance Index (ERI), tumor necrosis factor-alpha [TNF- α], interleukin-6 [IL-6]), nutritional indicators (serum albumin, body mass index [BMI] and normalized protein catabolic rate [nPCR]). **Methods:** The study involved 60 participants (35 males, 25 females; mean age 48.78 ± 14.60 years) who were subjected to consistent hemodialysis treatments over a period exceeding six months, conducted three times per week, within the Nephrology Department at the Theodor Bilharz Research Institute. Medical history and the physical examinations were documented. EPO dosage (units/week) was recorded, and BMI (kg/m^2) was calculated. Serum TNF- α and IL-6 levels were measured using the ELISA method. **The results** indicated that the mean BMI was 26.21 ± 7.18 . Primary causes of renal failure included glomerulonephritis (13.33%), diabetic nephropathy (36.67%), hypertension (25%), polycystic kidney disease (3.33%), and unknown causes (21.67%). The mean duration of dialysis was 8.78 ± 3.11 years. Key lab values included Hb 11.35 ± 1.32 , transferrin saturation 35.10 ± 11.88 , ferritin 572.01 ± 259.68 , serum albumin 3.91 ± 0.39 , intact parathyroid hormone (iPTH) 575.56 ± 356.17 , serum calcium 8.96 ± 0.78 , serum phosphorus 5.72 ± 1.88 , and URR 73.97 ± 8.71 . Significant inverse correlations were found between ERI and BMI, serum creatinine, hemoglobin, serum albumin and nPCR. Also there was positive correlation between ERI and hs-CRP. **Conclusion:** It was concluded from the results that EPO hyporesponsiveness is associated with low BMI, serum albumin, nPCR, and high hs-CRP levels. No linkage was established between the ERI and the duration of dialysis sessions.

Keywords: Erythropoietin hyporesponsiveness, Erythropoietin resistance index, Body mass index, Hemodialysis.

INTRODUCTION

Renal anemia is frequently encountered as a concomitant disorder in chronic kidney disease (CKD), with its severity escalating in tandem with the progressive decline in renal function. Studies indicate that more than 90% of individuals with end-stage renal disease (ESRD) suffer from anemia¹ (Li *et al.*, 2016). This pathological condition not only deteriorates the quality of life but also markedly increases the likelihood of cardiovascular events and elevates the mortality rates (Hauber *et al.*, 2017).

The principal pathogenic factors underlying anemia in patients subjected to maintenance hemodialysis (MHD) are predominantly associated with insufficiencies in erythropoietin synthesis and iron assimilation (Mikhail *et al.*, 2017). The therapeutic landscape for anemia in MHD cohorts has been significantly enhanced through the administration of erythropoiesis-stimulating agents (ESAs), including recombinant human erythropoietin (rHuEPO). Nonetheless, a specific subset of these patients manifests inadequate responsiveness to erythropoietin, denoted as EPO hyporesponsiveness or EPO resistance. This phenomenon is delineated by the failure to attain the designated hemoglobin concentrations despite the application of supra-therapeutic doses of EPO, or the necessity to sustain elevated doses of EPO to preserve desired hemoglobin thresholds (Kim *et al.*, 2018). The Erythropoiesis Resistance Index (ERI), derived from the administered EPO dose relative to the hemoglobin level, is employed as an essential metric to assess EPO responsiveness.

Multiple determinants modulate EPO responsiveness, encompassing serum albumin concentrations, inflammatory reactions, secondary hyperparathyroidism, and iron scarcities^[5]. (Ogawa and Nitta,

2015). Elevated dosages of EPO have been associated with a heightened prevalence of hypertension, cerebrovascular accidents, and thromboembolic occurrences among CKD patients (Koulouridis *et al.*, 2013).

Investigations conducted by Chung *et al.* (2012) have demonstrated that in patients undergoing maintenance hemodialysis (MHD), resistance to EPO is linked with alterations in the left ventricular mass index, the functionality of left ventricular systole, and the occurrence of cardiovascular events. Furthermore, EPO hyporesponsiveness has been recognized as a prognostic marker for all-cause mortality among MHD patients (Okazaki *et al.*, 2014).

Notwithstanding these insights, the intricate relationship between EPO hyporesponsiveness and other potential contributory factors, as well as the associations between all-cause and cardiovascular mortality, demands further scholarly scrutiny. Thus, this study was designed to elucidate the correlations between ERI and specific inflammatory markers (hs-CRP, TNF- α , and IL-6), as well as nutritional parameters (BMI, serum albumin, and nPCR).

PATIENTS AND METHODS

Study design and population:

This observational cross-sectional research was carried out within the Nephrology Department at the Theodor Bilharz Research Institute, located in Giza, Egypt. A total of 60 subjects, all with ESRD on regular HD for more than 6 months (three times weekly), were enrolled. Participation was voluntary, with all participants providing signed informed consent before enrolment.

Inclusion Criteria: Subjects aged 18 years or older with ESRD on regular HD for more than 6 months (three times weekly).

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Exclusion Criteria: Subjects with a recent history of trauma, acute coronary injury, malignancy, acute hepatitis, acute infection, active bleeding, or those unable to provide informed consent were excluded.

Data Collection:

Information such as demographics, EPO administration, and dosage (units/week) was recorded. All participants underwent medical history and clinical examination.

Each participant commenced HD sessions with a blood flow rate ranging from 250-300 ml/minute and a bicarbonate stream rate of 500 ml/minute. Dialyzer dimensions were tailored based on the individual's body mass. The dialysate formula incorporated glucose at 100 mg/dl, along with concentrations of calcium at 1.25%, magnesium at 0.5%, and potassium at 2.0%. Anticoagulation was managed with 2600-5000 international units of heparin per 4-hour HD session.

Blood tests:

Blood tests included hemoglobin, serum albumin (Alb), serum urea (pre- and post-dialysis), serum creatinine, calcium, phosphorus, serum ferritin, transferrin saturation, iPTH, hs-CRP, TNF, IL-6 by ELISA, cholesterol, and triglycerides (TGs).

BMI:

BMI was computed by dividing BW (in kg) by the square of H (in m). BW was specified as the 'dry weight', ascertained subsequent to the HD session.

Normalized protein catabolic rate (n-PCR)

n-PCR is a calculation commonly used in HD patients to detect dietary protein intake and assess nutritional adequacy in dialysis patients:

$$\text{nPCR(g/kg/day)} = C_0 / (a + bKt/V + c/[Kt/V]) + 0.0168$$

Where;

C_0 signifies the initial blood urea nitrogen concentration before dialysis (mg/dL), Kt/V refers to the single-pool approximation of the dialysis treatment dose.

The constants a, b, and c were modified to accommodate discrepancies in the interdialytic duration for individuals receiving dialysis sessions three times per week.

Urea reduction ratio URR:

URR quantifies the relative decrease in BUN or urea during dialysis. It is formulated as:

$$\text{URR} = 100\% \times (\text{predialysis BUN} - \text{postdialysis BUN}) / \text{predialysis BUN}$$

A minimum URR of 65% to 70% is recommended for adequate HD.

The URR is usually measured only once every 12 to 14 treatments, which is once a month.

Kt/V

Kt/V , like URR, is a measure of dialysis adequacy.

It is a single pool estimate of the dialysis dose. K = clearance—the amount of urea your dialyzer can remove (liters/minute)

t = time—the duration of treatment (minutes)

V = volume—the amount of body fluid (liters)

Per the national guidelines set forth by the Kidney Disease Outcomes Quality Initiative (K/DOQI), it is advised that for individuals receiving hemodialysis thrice weekly, the delivered Kt/V should achieve a minimum threshold of 1.2.

Erythropoiesis resistance index (ERI):

ERI was ascertained by calculating the ratio of the average weekly administration of erythropoietin, quantified in international units, to the patient's clinical dry weight in kilograms and their hemoglobin concentration, expressed in grams per decilitre.

Statistical analysis:

Statistical analyses were performed using SPSS version 24 (SPSS Inc., IL, USA). Quantitative data were summarized using means and standard deviations, while qualitative data were summarized using frequencies and percentages. The student t-test was used to assess statistical significance between two data sets. One-way ANOVA and Tukey's test were applied to identify statistically significant differences. A p-value threshold of 0.05 was established for all statistical evaluations.

RESULTS

A total of 60 patients with ESRD on regular HD were included, comprising 35 males (58.3%) and 25 females (41.7%), with a mean age of 48.78 ± 14.60 years. The mean body mass index (BMI) was 26.21 ± 7.18 . The primary causes of renal failure were glomerulonephritis (13.33%), diabetic nephropathy (36.67%), hypertension (25%), polycystic kidney disease (3.33%), and unknown causes (21.67%). The mean duration of dialysis was 8.78 ± 3.11 years (Table 1).

Table 1: Socio-demographic data of the studied group:

Items	Mean±SD/median	Range/IQR
Age (years)	48.78±14.60/48.50	59/22
BMI [kg/m ²]	26.21±7.18/25.95	30.6/11.1
Male	35(58.3%)	
Female	25(41.7%)	
Duration of dialysis(years)	8.78±3.11/9.00	13.00/4.75
Causes of renal failure		
Glomerulonephritis	8 (13.33%)	
Diabetic nephropathy	22 (36.67)	
Hypertension	15(25%)	
Polycystic kidney	2(3.33)	
Unknown	13 (21.67%)	

Not normally distributed data is represented as median and IQR. DS: standard deviation, BMI; body mass index.

The mean Hb value was 11.35 ± 1.32 g/dL, transferrin saturation was $35.10 \pm 11.88\%$, and ferritin was 572.01 ± 259.68 ng/mL. Serum albumin was 3.91 ± 0.39 g/dL, iPTH was 575.56 ± 356.17 pg/mL, serum Ca was 8.96 ± 0.78 mg/dL, serum phosphorus was 5.72 ± 1.88 mg/dL, serum creatinine was

9.92 ± 2.98 mg/dL, and hs-CRP was 14.73 ± 12.74 mg/L. Pre-dialysis urea was 61.68 ± 17.97 mmol/L, and post-dialysis urea was 18.21 ± 14.23 mmol/L. IL-6 was 6.88 ± 1.93 pg/mL, TNF was 47.71 ± 24.76 pg/mL, TG were 142.45 ± 55.45 mg/dL, and cholesterol was 173.40 ± 41.66 mg/dL (Table 2a).

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Table 2a: Laboratory data of the studied group.

Item	Mean \pm SD/ Median	Range / IQR
Urea pre dialysis[mmol/L]	61.68 \pm 17.97/64.50	87.0/27.5
Urea post dialysis	18.21 \pm 14.23/15.00	92.0/11.0
Hemoglobin (g/dl)	11.35 \pm 1.32/11.450	5.9/1.7
Transferrin saturation (%)	35.10 \pm 11.875/34.00	59/14
Ferritin [μ g/L]	572.01 \pm 259.68/553.30	1086.77/474.43
Creatinine	9.92 \pm 2.98/9.72	13.79/3.93
Alb [g/L]	3.91 \pm .39/3.90	2.3/.4
iPTH (pg/ml)	575.56 \pm 356.17/530.80	1711.44/383.20
Calcium	8.96 \pm 0.78/9.00	4.1/1.1
Phosphrus	5.72 \pm 1.88/5.35	8.5/2.5
hs-CRP	14.73 \pm 12.74/12.00	66/12
IL6	6.88 \pm 1.93/7.00	8.4/2.6
TNF- α	47.7145 \pm 24.75941/42.5500	178.52/9.90
TGs	142.45 \pm 55.45/136.00	234/92
Cholesterol	173.40 \pm 41.66/170.50	196/59

Not normally distributed data is represented as median and interquartile range (IQR). DS;standard deviation, BMI; body mass index. hs-CRP;high sensitive C-reactive protein, iPTH; intact parathyroid hormone,TNF- α ; tumor necrosis factor-alpha, Alb; albumin, TGs; triglycerides.

The value of URR was 73.97 \pm 8.71, was 1.36 \pm 0.27 and ERI was 15.85 \pm 10.21 as Kt/V was 1.6675 \pm 0.458, N-PCR [g/kg/day] shown in Table (2b).

Table 2b: Laboratory data of the studied group.

Item	Mean \pm SD/ Median	Range / IQR
URR	73.97 \pm 8.71/73.0	47.30/13.00
Kt/V	1.6675 \pm .458/1.56	2.58/.66
N-PCR [g/kg/day]	1.36 \pm .27/1.36	93/.46
ERI	15.85 \pm 10.21/12.7750	51.79/12.13

Not normally distributed data is represented as median and interquartile range (IQR). DS; standard deviation, N-PCR; normalized protein catabolic rate, URR; urea reduction ratio, ERI; erythropoietin resistance index.

Among the patients, we identified several correlations; an inverse correlation between ERI and BMI ($r = -0.328$, $p = 0.011$), an inverse correlation between ERI and serum creatinine ($r = -0.380$, $p = 0.003$), an inverse correlation between ERI and hemoglobin ($r = -0.570$, $p < 0.001$), an inverse correlation between ERI and serum albumin ($r = -0.352$, $p = 0.006$), and an

inverse correlation between ERI and nPCR ($r = -0.303$, $p = 0.018$). Additionally, there was a positive correlation between ERI and hs-CRP ($r = 0.708$, $p < 0.001$). These findings indicate that EPO hypo-responsiveness is linked to low BMI, low serum albumin, low nPCR, and high hs-CRP levels as shown in Table (3).

Table 3: Correlation between ERI and other parameters.

		BMI [kg/m ²]	Urea pre dialysis [mmol/L]	Serum creatinine [mg/dL]	Hemoglobin [g/dL]	Serum albumin [g/L]	N-PCR [g/kg/day]	hs-CRP
ERI	r	-.328*	-0.291*	-0.380**	-0.570**	-0.352**	-0.303*	0.708**
	P	0.011	0.024	0.003	< 0.001	0.006	0.018	0.000

ERI; erythropoietin resistance index, BMI; body mass index, deviation, N-PCR; normalized protein catabolic rate, hs-CRP; high sensitive C-reactive protein.

In multiple linear regression analysis, serum creatinine, haemoglobin level, and hs-

CRP were independent correlated factors of ERI as shown in Table (4).

Table 4: Multiple linear regression analysis with erythropoietin resistance index as dependent variable.

	Unstandardized Coefficients		standardized Coefficients	t	Sig.
	B	Std Error	Beta		
constant					
Serum creatinine [mg/dL]	-0.887	0.407	-0.259	-2.178	0.036
Hb- [g/dL]	-3.436	0.778	-0.444	-4.415	0.000
Hs-CRP	0.293	0.092	0.365	3.163	0.003

DISCUSSION

The etiology of renal anemia is complex, principally attributed to an absolute or relative insufficiency of endogenous EPO. This disorder not only precipitates symptoms such as fatigue, palpitations, and dyspnea, significantly impairing the quality of life for patients on hemodialysis, but it also serves as a pivotal prognostic marker indicative of adverse outcomes in these patients (Fishbane and Spinowitz, 2018; Nangaku, 2017).

Clinically, a subset of patients with renal anemia demonstrates only marginal enhancement in hemoglobin concentrations subsequent to administration of weight-dependent recombinant human erythropoietin (rHuEPO), or they necessitate considerably elevated dosages of rHuEPO per unit body weight to sustain normative hemoglobin values relative to their counterparts with renal anemia. This clinical condition is identified as EPO hyporesponsiveness or resistance (Bamgbola, 2012). It is posited that the

insufficiency of substrates for hemoglobin synthesis, attributable to absolute or functional iron deficits, plays a crucial role in the suboptimal effectiveness of rHuEPO in managing renal anemia. While erythropoiesis-stimulating agents (ESAs) have been validated to ameliorate anemia and augment the quality of life in patients undergoing maintenance hemodialysis (MHD), resistance to ESAs is acknowledged as a primary factor for escalated ESA dosages and might elucidate the observed correlation between ESA utilization and increased mortality rates (Fukuma *et al.*, 2012; Pan *et al.*, 2022; Sakaguchi *et al.*, 2019).

The study of this investigation underscored the association between comorbid conditions and erythropoietin resistance in patients undergoing MHD, as well as its detrimental effects on survival outcomes. ERI was utilized to assess ESA hyporesponsiveness, serving as a prognostic indicator for mortality. Suboptimal responsiveness to ESA may be associated

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with an aggravated inflammatory condition, marked by heightened concentrations of inflammatory biomarkers like (CRP, IL-6, IL-1 and TNF- α) in patients with CKD (Santos *et al.*, 2018).

Cytokines can disrupt iron metabolism, leading to functional iron deficiency (de Francisco *et al.*, 2009). They also affect various stages of erythropoiesis and mediate apoptosis, suggesting that pro-inflammatory cytokine signaling impairs EPO activity (de Francisco *et al.*, 2009)

Chronic inflammation not only directly impacts erythropoiesis and erythropoietin responsiveness but also worsens nutritional status (Bandach *et al.*, 2021; Virzi *et al.*, 2022).

In current study, correlation analysis revealed a highly significant positive correlation between ERI and serum hs-CRP ($r = 0.708$, $p < 0.0001$), consistent with findings from Lu *et al.* (2020) and Sewefy *et al.* (2019). Analytical methodologies including correlation analysis and multiple linear regression revealed a pronounced linkage between hs-CRP, an indicator of inflammation, and ERI, with a correlation coefficient (r) of 0.708 and a statistically significant p -value ($p < 0.0001$), findings that are in alignment with those reported by Lu *et al.* (2020). Previous research involving continuous ambulatory peritoneal dialysis (CAPD) patients identified hs-CRP as a critical predictor of EPO hypo-responsiveness. Locatelli *et al.* (2004) discerned that subject with serum high-sensitivity C-reactive protein (hs-CRP) concentrations ≥ 2 mg/dL required an augmentation of epoetin administration by 80% relative to those presenting lower CRP values. In contrast, Hara *et al.* (2015) discerned no substantive correlation between the ERI and hs-CRP, potentially due to a selection bias influenced by the exclusion of participants who had experienced infections

in the month preceding the investigation. Furthermore, Sewefy *et al.* (2019) reported elevated hs-CRP levels in patients who demonstrated a lack of therapeutic response to ESA treatments.

Endemic low-grade inflammation is frequently encountered among individuals on dialysis, precipitated by factors such as oxidative stress, the deposition of uremic toxins, metabolic anomalies, and assorted pathophysiological conditions, which collectively induce imbalances in cytokine level (Ahmadmehrabi and Tang, 2018; Cozzolino *et al.*, 2018). Cytokines with pro-inflammatory properties, including IL-1, IL-6, and TNF- α , are identified as negative regulators of the erythropoiesis pathway. Augmented concentrations of IL-6 and TNF- α impede the processes of iron metabolism and its accumulation within the reticuloendothelial framework. Additionally, these cytokines may directly impact the structural integrity of erythrocytes and catalyze apoptotic processes in marrow-derived cells. It is imperative to prevent bacterial contamination of dialysates in dialysis patients, and attention must be paid to additional inflammatory mediators, as their cumulative presence could elevate the likelihood of resistance to ESAs.

However, the present results indicated no correlation between ERI and TNF- α or IL-6. Feret *et al.* (2022) also found no association between TNF- α and ERI but did report a correlation with IL-6. They elucidated that IL-6 enhances the synthesis of hepcidin, a molecule that degrades ferroportin, thereby obstructing the release of iron and consequently impeding effective hematopoiesis. The reduction of IL-6 levels in serum is viewed as a promising strategy for mitigating resistance to erythropoietin. However, other studies reported positive correlations between ERI and both TNF- α

and IL-6. (Goicoechea *et al.*, 1998; Solid *et al.*, 2007).

The mean Kt/V in our patients was 1.6675 ± 0.458 , and we found no significant correlation between Kt/V and ERI, consistent with the findings of López-Gómez *et al.* (2008).

Malnutrition among HD patients is attributed to a confluence of factors. Stringent dietary regimens required for those with ESRD, coupled with often inadequate nutritional guidance from clinical dieticians, significantly undermine their nutritional health. These patients encounter difficulties in maintaining proper fluid homeostasis and are likely to have deficient caloric and protein consumption. The restriction of certain food items, alongside the reduced appetite commonly induced by uremia, predisposes them to protein-energy wasting (PEW) (Feret *et al.*, 2022). Unlike the general population, malnutrition in patients undergoing renal replacement therapy poses a higher mortality risk than obesity, a phenomenon known as reverse epidemiology (Hanna *et al.*, 2020; Zha and Qian, 2017).

The current research sought to delve deeper into the impact of nutritional status on erythropoietin responsiveness and there was an elevated ERI among the present hemodialysis patients typically correlates with diminished nutritional status.

The current results demonstrated a significant inverse correlation between ERI and serum albumin levels ($r = -0.352$, $p = 0.006$), indicating that a reduction in serum albumin is concomitant with an elevation in ERI. Similarly, there was a negative correlation between ERI and serum creatinine ($r = -0.380$, $p = 0.003$). A comparable single-center study in Japan reported analogous findings, revealing that serum albumin levels and BMI are inversely related to ERI. However, their study diverged from ours by establishing a direct association

between dialysis vintage and ERI (Okazaki *et al.*, 2014).

Lu *et al.* (2020) noted an inverse correlation between the ERI and the levels of serum albumin and creatinine measured prior to dialysis. Both albumin and creatinine are recognized as indicators of nutritional status and play roles in the pathogenesis of the malnutrition-inflammation-atherosclerosis (MIA) syndrome (Lu *et al.*, 2020). Hypoalbuminemia is identified as a prognostic marker for both the efficacy of ESA treatment and overall survival outcomes in patients undergoing hemodialysis, likely owing to its linkage with inflammatory mechanisms (Antunes *et al.*, 2016; Katalinic *et al.*, 2019). Contrarily, Kalantar-Zadeh *et al.* (2004) reported no significant association between low serum albumin levels and either the required EPO dose or ERI. Predialysis serum creatinine, which may serve as a proxy for muscle mass, was found to be inversely associated with mortality in both hemodialysis and peritoneal dialysis patients (Park *et al.*, 2013, Walther *et al.*, 2012)

In the current investigation the elevated BMI is linked to an augmented responsiveness to α EPO therapy, a correlation that is supported by outcomes from the study of Santos *et al.* (2018). Previous research indicates that ESA dose requirements and the ERI are inversely proportional to the amount of total adipose tissue in dialysis patients (do Sameiro-Faria *et al.*, 2013; Kotanko *et al.*, 2008). BMI serves as a critical indicator of nutritional status in these individuals. Contrary to trends observed in the general population, higher BMI in hemodialysis patients correlates with a more favorable clinical prognosis (Okazaki *et al.*, 2014; Park *et al.*, 2018); conversely, a lower BMI is associated with a higher burden of uremic toxins (Kotanko *et al.*, 2008).

Previous studies have established that indicators of nutritional status, such as serum albumin and BMI, demonstrate an inverse

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correlation with heightened ERI measurements (Feret *et al.*, 2022; López-Gómez *et al.*, 2008). An extensive study in Spain, covering 1710 patients distributed among 119 hemodialysis facilities, identified inverse relationships between serum albumin concentrations, BMI, and the ERI^I (López-Gómez *et al.*, 2008). Albumin, classified as an acute-phase reactant, undergoes reduction in the presence of inflammatory mechanisms. Therefore, the discernible inverse association between diminished serum albumin levels and increased resistance to ESAs is probably influenced more by inflammatory conditions than by nutritional deficiencies (Zhao *et al.*, 2024). Furthermore, a focused study from a single center in Japan echoed similar results, demonstrating an inverse correlation between serum albumin concentrations and BMI with the ERI. However, it also highlighted a direct relationship between the length of dialysis treatment, referred to as dialysis vintage, and ERI, presenting a discrepancy with our findings (Okazaki *et al.*, 2014).

In the present study it was found that the nutritional supplements can help improve ESA resistance. ESRD cases need regular monitoring of their nutritional status. ESRD patients on MHD frequently experience protein-calorie malnutrition, a key predictor of mortality (Rahman *et al.*, 2022).

Various laboratory parameters are considered to evaluate nutritional status. In stable HD patients, the protein catabolic rate normalized by body weight (nPCR) is periodically used to assess dietary protein consumption (Maduell *et al.*, 2003). An increase in nPCR by 0.1 g/kg/day is associated with a 15% reduction in mortality (Lin *et al.*, 2002; Maduell *et al.*, 2003), making nPCR a crucial risk factor for mortality in this population. Our study detected an inverse correlation between ERI and nPCR ($r = -0.303$, $p = 0.018$), indicating that reduced protein intake is linked to

elevated ERI. Conversely, López-Gómez *et al.* (2008) found a correlation between low ERI values and serum albumin levels but no relation with nPCR. Hara *et al.* reported no significant correlation between ERI and CRP, serum albumin, intact PTH, and nPCR levels (Hara *et al.*, 2015).

In the current study, there was no correlation between the duration of dialysis and ERI. However, a direct relationship between dialysis vintage and ERI was reported, which is inconsistent with our findings (Okazaki *et al.*, 2014).

Secondary hyperparathyroidism (SHP) is increasingly recognized as a cause of ESA-resistant anemia in ESRD patients (Kanbay *et al.*, 2010). SHP can adversely affect EPO synthesis, erythrocyte longevity, and can induce bone marrow fibrosis, all of which contribute to resistance to ESA (Brancaccio *et al.*, 2004). SHP is a prognostic factor for EPO hypo-responsiveness (Al-Hilali *et al.*, 2007; Wei *et al.*, 2007) and, although less commonly acknowledged, it is a significant etiological factor of renal anemia in CKD patients. Parathyroid hormone (PTH) is identified as a uremic toxin, with elevated PTH levels being associated with renal anemia in hemodialysis patients. Recent clinical investigations have shown that addressing SHP with vitamin D receptor activators, calcimimetics, or parathyroidectomy ameliorates anemia, thereby underscoring the pivotal role of PTH in the pathogenesis of renal anemia (Azeem *et al.*, 2020; Tanaka *et al.*, 2018). Anemia resulting from PTH stems from overproduction of PTH, which impairs responsiveness to ESAs by suppressing native EPO synthesis, curtailing the abundance of erythroid progenitor cells within the bone marrow, and abbreviating the survival duration of erythrocytes (Brancaccio *et al.*, 2004; Papayannopoulou and Migliaccio, 2018). Indirect consequences

encompass the relationship between renal osteodystrophy and bone marrow fibrosis, as demonstrated by the recuperation of bone marrow space and the associated elevation in serum EPO levels subsequent to parathyroidectomy (Gallieni *et al.*, 2000).

In current study, there was no correlation between ERI and iPTH, consistent with the findings of Hara *et al.* (2015). Nevertheless, multiple studies have documented significant ameliorations in severe renal anemia in uremic patient's post-parathyroidectomy (Fujita *et al.*, 1995, Zingraff *et al.*, 1978). Sethi *et al.* (2018) demonstrated that elevated iPTH levels in ESRD patients contribute to bone marrow fibrosis. Moreover, Rao *et al.* (1993) revealed that ESRD patients exhibiting poor EPO responsiveness had increased bone marrow fibrosis. Our patient data and single-center observations indicate considerable variability in the relationship between PTH levels, anemia, and bone marrow alterations. PTH does not exert a direct inhibitory effect on erythropoiesis in humans. Instead, the underlying causes of EPO hypo-responsiveness are attributed to bone marrow fibrosis and the uremic environment (Rao *et al.*, 1993).

The Kt/V ratio, a dimensionless metric representing urea clearance during a single renal replacement therapy (RRT) session, is widely utilized to assess dialysis adequacy. Typically, elevated Kt/V values are presumed to indicate more effective dialysis. However, it is essential to acknowledge that urea is not the sole toxin that needs to be eliminated during dialysis (Feret *et al.*, 2022). In our study, no association was found between ERI and Kt/V, although some studies have shown that low Kt/V values are associated with an increased dose of EPO. An alternative metric for assessing urea removal during dialysis is the Urea Reduction Ratio (URR), which measures the percentage decrease in blood

urea levels over the course of a dialysis session. In our study, there was no association between ERI and URR. However, Santos *et al.* reported that higher URR is associated with a better response to EPO (Santos *et al.*, 2018). A high URR indicates a successful dialysis session, which is linked to a better response to ESA medication (Kanbay *et al.*, 2010; Mallick *et al.*, 2012).

Serum ferritin, which reflects iron reserves, is crucial in mediating resistance to EPO therapy and serves as a prognostic indicator of overall mortality among dialysis patients. As an acute-phase reactant, ferritin levels are modulated by inflammatory activity, and the observed relationship between elevated ferritin concentrations and mortality risk diminishes upon adjustment for inflammatory biomarkers. Patients on regular HD with elevated serum ferritin levels are at risk of EPO resistance (Lu *et al.*, 2020). However, our study showed no relation between ERI and serum ferritin levels. Conversely, research by Joksimovic *et al.* (2022) and Lu *et al.* (2020) indicated that patients exhibiting resistance to short-acting EPO agents (epoetin- α and epoetin- β) possess markedly higher serum ferritin levels compared to those without EPO resistance. Ferritin might engage with inflammatory processes, contributing to ESA hyporesponsiveness by activating the NF- κ B pathway (Simmen *et al.*, 2019). The correlation between ferritin and ERI remains contentious, as the ferritin light chain could confer protection against endotoxemia (Zarjou *et al.*, 2019). This research domain warrants further investigation.

The Cardiovascular Risk in Dialysis (RISCAVID) study data revealed that increased all-cause and cardiovascular mortality rates are significantly associated with elevated ERI values, even after adjusting for various confounding factors. This relationship persisted throughout a median follow-up period of 36 months

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(Rosati *et al.*, 2018). Importantly, they observed that EPO hyporesponsiveness, particularly when coupled with reduced handgrip strength, emerged as a markedly stronger predictor of adverse outcomes (Kobayashi *et al.*, 2022). Nevertheless, our investigation did not establish a connection between the ERI and cardiovascular mortality. This absence of an observed relationship could potentially be ascribed to the limited follow-up period, which resulted in comparatively lower rates of recorded cardiovascular mortality.

Cohort data from Zhao *et al.* (2024) similarly indicated a correlation between the ERI and elevated mortality rates in MHD patients. A prospective cohort study in Japan, despite its relatively modest sample size of 248 MHD patients, identified a high ERI score as an independent risk factor for all-cause mortality among HD patients. Similarly, a retrospective study in China reported that higher dosages of ESAs and resistance to ESA therapy were linked to increased all-cause mortality (Okazaki *et al.*, 2014).

There was no link between ERI and transferrin saturation in the current investigation, however, other researchers have demonstrated that transferrin levels are higher in the EPO-sensitive group compared to the EPO-resistant group (Elbadawy *et al.*, 2021). It has been suggested that the deficiency of substrates necessary for hemoglobin synthesis, arising from either absolute or functional iron deficiency, is a significant factor diminishing the efficacy of rHuEPO in the treatment of renal anemia.

Finally, this study presents several limitations. Firstly, the sample size was relatively small, encompassing only 60 patients, which may restrict the generalizability of the results. Secondly, the cross-sectional study design precludes the establishment of causal relationships

between the observed correlations. Third, the study did not account for potential confounding factors such as medication adherence, differences in dialysis protocols, and variations in individual patient health conditions that could influence EPO responsiveness. Additionally, the need for follow-up to assess long-term outcomes and mortality accurately.

Conclusion

This study highlights the significant association between EPO hyporesponsiveness and low BMI, low serum albumin, low nPCR, and high hs-CRP levels in hemodialysis patients. These findings suggest that inflammation and poor nutritional status play critical roles in the development of resistance to erythropoiesis-stimulating agents. Regular monitoring and appropriate management of nutritional and inflammatory status may improve EPO responsiveness and overall patient outcomes. Further research with larger sample sizes and longitudinal designs is needed to confirm these associations and explore potential interventions.

Conflict of interest

The authors have no conflicts of interest to declare.

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دور الإلتهاب والحالة الغذائية ومؤشر كتلة الجسم في تطور مقاومة تحفيز تكون كرات الدم الحمراء لدى المرضى الخاضعين لغسيل الكلى الدموي المنتظم

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المستخلص

فقر الدم الكلوي في مرضى الغسيل الكلوي هو أحد المضاعفات الشائعة ويرجع ذلك في المقام الأول إلى نقص هورمون الإيريثروبويتين ونقص الحديد ولذلك فإن العلاج الأمثل لهؤلاء المرضى هو هورمون الإيريثروبويتين ولكن في بعض الحالات يحدث إنخفاض في فاعلية هذا الدواء نتيجة لأسباب كثيرة مثل الإلتهاب المصاحب لهؤلاء المرضى وكذلك سوء التغذية مما قد يؤدي إلى الوفاة. الهدف من هذه الدراسة هو توضيح العلاقة بين مؤشر مقاومة الهرمون (ERI) و عوامل الإلتهابات مثل بروتين سي التفاعلي (CRP) ، عامل نخر الأورام (TNF- α) ، الإنترليوكين 6 (IL-6) ، وكذلك مؤشرات التغذية مثل مصل الألبومين ومؤشر كتلة الجسم (BMI) ومعدل تقويض البروتين (nPCR) في إنخفاض فاعلية هذا الدواء. شملت الدراسة عدد 60 مريض من مرضى الفشل الكلوي ويعالجون بجلست الغسيل الكلوي الدموي بشكل منتظم ثلاث مرات اسبوعيا على مدى فترة تزيد عن ثلاثة أشهر وتم توثيق التاريخ الطبي والفحوصات البدنية. تم تسجيل جرعة EPO الإيريثروبويتين (وحدات/أسبوع)، وتم حساب مؤشر كتلة الجسم (كجم/م²). تم قياس مستويات TNF- α و IL-6 في الدم باستخدام طريقة ELISA. أوضحت النتائج وجود علاقة عكسية بين مؤشر مقاومة الهرمون (ERI) وكل من مؤشر كتلة الجسم (BMI) والهيموجلوبين (Hb%) والكرياتينين (ERI) ومصل الألبومين ومعدل تقويض البروتين (nPCR). كما وجدت علاقة طردية بين بروتين سي التفاعلي (hs-CRP) ومؤشر مقاومة الهرمون (ERI). ولقد امكن استنتاج وجود ارتباط بين مؤشر مقاومة الهرمون الإيريثروبويتين بنقص مؤشر كتلة الجسم ومعدل تقويض البروتين والهيموجلوبين بين الكرياتينين و مصل الألبومين وزيادة بروتين سي التفاعلي.