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ORIGINAL ARTICLE

Malnutrition and Inflammatory Markers among Anemic Hemodialysis Patients

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ABSTRACT

Background: Anemia is a common complication of ESRD. Anemia may be caused by a reduction in erythropoietin in end-stage renal disease (ESRD). This work aimed to focus on evaluating the relationship between malnutrition-inflammation scores (MIS), anemia management, and resistance to erythropoietin therapy in cases with CKD undergoing hemodialysis.

Methods: This was a prospective cross-sectional, non-randomized research performed in the Internal Medicine Department of Faculty of Medicine, Zagazig University Hospitals and Nasr City Police Hospital at a duration of two years from September 2019 to September 2021.

Results: High MIS is strongly correlated ($p<0.05$) with poor nutritional and inflammatory markers, such as low albumin, high CRP, and high ferritin. MIS is negatively correlated with hemoglobin and TIBC, reflecting its impact on anemia. Erythropoietin resistance is closely linked to elevated MIS, inflammation (CRP, ferritin), and malnutrition (albumin).

Conclusions: The research highlights the critical role of malnutrition and inflammation in the management of chronic kidney disease (CKD) cases undergoing hemodialysis. Elevated MIS is correlated with poor nutritional status (low serum albumin) and heightened inflammatory markers (CRP, serum ferritin, and triglycerides).Malnutrition and inflammation exacerbate anemia and impair response to erythropoietin therapy.

Keywords: Malnutrition; inflammation score; End stage renal disease; Anemia.

INTRODUCTION

Chronic kidney disease (CKD) is characterized as a reduction in the function of the kidneys, as evidenced by a glomerular filtration rate (GFR) of below sixty ml/minute/1.73 m^2 or kidney damage markers, or both, for a minimum of three months, irrespective of the root reasons. The main reasons for CKD are diabetes and hypertension [1].

Anemia is a common complication of ESRD. There are possible reasons for anemia in ESRD, as decreased erythropoietin. Other possible reasons for anemia in ESRD include iron deficiency, inflammation, bleeding during dialysis and increasing uremic toxins [2].

Inflammation and malnutrition often coexist in HD patients as malnutrition-inflammation syndrome (MIS). This syndrome is strongly linked to increased mortality, hospitalization rates, and poor clinical outcomes, including refractory anemia and diminished quality of life. MIS contributes to elevated serum ferritin, an acute-phase reactant influenced by inflammation, independent of iron stores. High ferritin levels and pro-inflammatory cytokines, involved tumor necrosis factor-alpha and interleukin-1, inhibit erythropoiesis and reduce responsiveness to erythropoietin (EPO) therapy[3].

Despite the well-documented prevalence of MIS among hemodialysis (HD) cases and its association with poor clinical outcomes, significant gaps remain in fully understanding the interplay between malnutrition, inflammation, and anemia management [4].This study aims to address these gaps by investigating the relationships between inflammatory markers, nutritional status, and anemia responsiveness in HD patients, thereby providing insights to improve patient management and outcomes.

METHODS

This was a prospective cross-sectional, non-randomized research involved 70 patients on regular hemodialysis, the research was performed in the Internal Medicine Department of Faculty of Medicine, Zagazig University Hospitals and Nasr City Police Hospital at a duration of two years from September 2019 to September 2021.All subjects provided written informed consent, and the research ethical committee of the Faculty of Medicine, Zagazig University, approved the study. Research was performed in accordance with IRB#: 5329-1-4-2019 which is the code of ethics for studies involving human subjects as established by the World Medical Association (Declaration of Helsinki).

Inclusion criteria: End-stage renal disease cases on regular hemodialysis for more than three months.

Exclusion criteria: Systemic or autoimmune disease, rheumatic heart disease, patients with thyroid diseases, peritoneal dialysis and inability to give informed consent.

All cases have been exposed to the following; Detailed history taking, History: General Investigation: Including nutritional state assessment (weight- height- mid-upper arm circumference) and malnutrition inflammation score were performed to discover associated medical conditions. The malnutrition-inflammation syndrome involves the seven components of Subjective Global Assessment of nutrition and a semi quantitative scale with severity levels of BMI, serum albumin, and total iron binding capacity. It is a beneficial instrument for predicting morbidity and death and for risk stratification among hemodialysis cases.

Laboratory Assessment: Complete blood count (CBC), kidney function tests (urea-creatinine),Liver function tests and blood glucose concentrations: Fasting, postprandial blood glucose, glycosylated hemoglobin (HbA1c), electrolytes (Na - K - Ca - phosphorus - Mg) and total iron profile (serum iron concentrations-Total iron binding capacity TIBC - serum ferritin) , serum Albumin, C-reactive protein ,lipid profile (Total cholesterol, HDL-Ch, LDL-Ch, Triglycerides) ,bleeding profile and Kt/V.

Statistical analysis:

SPSS (Statistical Package for the Social Sciences) version 28 was utilized to conduct data analysis. The absolute frequencies of categorical variables were utilized for describing them, and the chi-square test and Monte Carlo tests were utilized if appropriate. The chi square trend test was utilized for comparing ordinal data among two groups. The assumptions for parametric tests were verified using the Kolmogorov–Smirnov test. Quantitative variables have been explained utilizing their standard deviations and mean values or median and interquartile range, depending on the type of data. Independent sample t-test (for normally distributed data) and Mann-Whitney test (for not normally distributed data) have been utilized to evaluate quantitative data among two groups. To compare quantitative data between more than two groups, Kruskal Wallis test (for not normally distributed data) was used. When the difference is significant, pairwise comparison was used to detect difference between each two individual groups. Spearman rank correlation coefficient was used to measure strength and association of correlation between two continuous not normally distributed variables. To determine the independent factors that are correlated with the dependent factor, linear regression analysis was utilized. The level for statistical significance was established at P-value <0.05. If p-value ≤ 0.001 , a highly significant variance was observed.

RESULTS

The study included 70 CKD cases on HD (52.9% male, 47.1% female) with a mean age of 54.2 years. Causes of renal impairment included hypertension (27.1%), combined hypertension and diabetes (20%), diabetes (14.3%), glomerulonephritis (11.4%), and others. Most patients had comorbid hypertension (71.4%) or diabetes (40%).MIS score was classified into tertiles; first tertile (good) in 28.6%, second tertiles (moderate)in 51.4% and third tertiles (poor) in 20% **(Table 1).**

A statistically significant negative correlation was discovered among malnutrition inflammation score and UF volume **(Table 2).**

Malnutrition-Inflammation Score (MIS) negatively correlated with hemoglobin, albumin, and TIBC, positively correlated with CRP, triglycerides, transferrin saturation, and serum ferritin.**(Table 3)**, **(Table 4).**

Serum albumin, triglycerides, serum ferritin, hemoglobin, and C-reactive protein (CRP) are significantly and independently associated with the malnutrition-inflammation score (MIS) among anemic hemodialysis patients **(Table 5).**

A statistically significant relationship was discovered between the tertiles of the malnutrition-inflammation score (MIS) and both CRP and serum ferritin. **(Table 6)**

The study found that resistance to a full dose of erythropoietin in hemodialysis patients was linked to lower hemoglobin and TIBC levels, higher MPV, and higher serum ferritin levels. Positive

CRP levels and higher malnutrition-inflammation scores (MIS) were more common in resistant patients. **(Table 7)**

Table(1): Distribution of cases according to baseline characteristics and according to malnutrition inflammation score.

	N=70	**Percent**
Gender		
Females	33	47.1%
Males	37	52.9%
Cause of renal impairment		
Hypertension	19	27.1%
Hypertension,diabetes	14	20%
Diabetes	10	14.3%
Glomerulonephritis	8	11.4%
Obstruction	7	10%
NSAIDs abuse	5	7.1%
ADPKD	2	2.9%
Recurrent UTI	2	2.9%
Unknown	2	2.9%
Lupus nephritis	1	1.4%
Co-morbidities:		
Diabetes	28	40%
Hypertension	50	71.4%
	Mean ±SD	**Range**
Age(year)	54.2±12.34	23– 77
	Median(IQR)/n=70	**Range/%**
MIS score	4(2– 6)	1–20
Good(1st tertiles)	20	28.6%
Moderate(2nd tertiles)	36	51.4%
Poor(3rd tertiles)	14	20.0 %

Table (2): Correlation between malnutrition-inflammation score and baseline data.

	R	**P**
Age(year)	0.131	0.278
Dry weight(kg)	-0.16	0.185
Kt/V**	0.028	0.818
UF volume***	-0.326	0.006*

R, Spearman rank correlation coefficient, *p<0.05is statistically significant.

** K is the dialyzer clearance of urea, t is the treatment time, and V is the patient's volume of urea distribution.

***Ultrafiltration (UF) Volume

Table(3): Correlation among malnutrition-inflammation score and CBC-related data and iron indices.

	R	P
Hemoglobin(gram per deciliters)	-0.406	<0.001**
Hematocrit	0.008	0.948
MCV	0.009	0.939
MCH	0.022	0.855
MCHC	0.121	0.317
RDW	0.026	0.834
Serum iron	-0.004	0.976
TIBC	-0.646	<0.001**
Transferrin saturation	0.337	0.004*
Serum ferritin	0.298	0.012*
WBCs	0.016	0.898
Basophil	-0.136	0.261
Eosinophil	0.082	0.497
Neutrophil	-0.105	0.387
Monocytes	0.013	0.918
Platelets count	-0.089	0.462

Mean Corpuscular Volume (MCV) (fl)
Mean Corpuscular Hemoglobin (MCH)(pg)
Mean Corpuscular Hemoglobin Concentration (MCHC) (g/dl)
Red Cell Distribution Width (RDW)
Total Iron Binding Capacity (TIBC)
White Blood Cells (WBCs)

Table(4): Correlation among malnutrition-inflammation score and the examined parameters

	R	p
Serum albumin	-0.863	<0.001**
Serum creatinine	-0.23	0.055
Sodium	-0.041	0.736
Potassium	0.133	0.273
Phosphate	-0.045	0.714
Pre-dialysis urea	0.082	0.489
Post-dialysis urea	-0.005	0.976
Parathyroid Hormone	0.045	0.712
Total cholesterol	-0.07	0.563
Triglycerides	0.291	0.015*
C-Reactive Protein	0.327§	0.006*

§point biserial correlation.

Table (5): Linear stepwise regression of factors correlated with malnutrition inflammation score

	Unstandardized Coefficients			T	p	95%CI	
	B	SD	Beta			Lower	Upper
Constant	19.519	2.549		7.658	<0.001**	14.427	24.611

Serumalbumin (gram per deciliters)	-3.64	0.42	-0.513	-8.667	<0.001**	-4.479	-2.801
Triglycerides(milligram per deciliters)	0.035	0.008	0.253	4.17	<0.001**	0.018	0.052
Serum ferritin	0.003	0.001	0.239	4.194	<0.001**	0.001	0.004
Hemoglobin(g/dl)	-0.993	0.227	-0.254	-4.378	<0.001**	-1.446	-0.54
C-Reactive Protein	1.58	0.553	0.158	2.862	0.006*	0.478	2.688

CI: confidence interval.

Table(6): Relation among MIS-score and inflammatory markers.

	Good	**Moderate**	**Poor**	**Significance**	
	n=20(%)	**n=36(%)**	**n=14(%)**	χ^2	p
C-Reactive Protein					
Negative	11(55%)	18(50%)	1(7.1%)	6.633	0.01*
Positive	9 (45%)	18(50%)	13 (92.9%)		
	Median IQR	**Median IQR**	**Median IQR**	**KW**	**p**
Serum ferritin	504.5 107.8–884.78	526.5 186.43–871.6	886 650 –1306.3	8.437	0.015*
Pairwise	$P_1$0.597	$P_2$0.011*	$P_3$0.007*		

(KW) Kruskal Wallis test, χ^2Chi square for trend test, p1: difference between good and moderate,p3: difference between good and poor,p2: difference among moderate and poor.

Table(7): Relation between resistance to erythropoietin and CBC data and iron indices, inflammatory markers and MIS-score.

	Resistance		**Test of significance**	
	Absent[n=60]	**Present[n=10]**		
	Mean ±Standard deviation	**Mean ±Standard deviation**	**T**	**p**
Hemoglobin(gramper deciliters)	10.02 ±1.13	8.02 ±0.51	9.191	<0.001**
Hematocrit	31.7±4.34	30.54 ±5.17	0.763	0.448
MCV(fl)	85.44 ±7.08	82.6±10.66	0.814	0.434
RBCs(10^6/mm^3)	3.37 ±0.52	3.73 ±0.69	-0.047	0.963
MCH(pg)	27.45 ±2.72	27.08 ±3.51	0.38	0.705
MCHC(g/dl)	32.14 ±2.15	32.88 ±2.15	-1.001	0.32
RDW	14.94 ±1.87	14.29 ±1.34	1.052	0.296
Serum iron	57 (50 –70)¥	69(40.3–72.3)¥	Z=0.109	0.913
TIBC	238.5 (205–279)¥	190.5 (177.8–203)¥	Z= -3.131	0.002*
Transferrin Saturation Test	24(19.3–30%)¥	31.5(22.2–38%)¥	Z=-1.52	0.128
Platelet count(10^3/mm^3)	235.11±77.02	241.2±49.38	-0.241	0.81

	Resistance		Test of significance	
	Absent[n=60]	Present[n=10]		
	Mean ±Standard deviation	Mean ±Standard deviation	T	p
MPV(fl)	9.15 ±1.64	7.88 ±2.39	2.104	0.039*
TLC(10^3/mm^3)	7.58 ±2.13	7.78 ±2.57	-0.269	0.789
	N=60 (%)	**N=10 (%)**	**χ^2**	**p**
C-Reactive Protein				
Negative	30(50%)	0(0%)	Fisher	0.004*
Positive	30(50%)	10(100%)		
	Median (IQR)	**Median(IQR)**	**Z**	**p**
Serum ferritin	519.5	1122.5	-	<0.001**
	(181.9–851.5)	(812.8–1475)	3.433	
MIS score	**N=60 (%)**	**N=10 (%)**	**χ^2**	**p**
Good	20 (33.3%)	0 (0%)		
Moderate	36 (60%)	0 (0%)	28.338	<0.001**
High	4 (6.7%)	10 (100%)		
	Median (IQR)	**Median (IQR)**	**Z**	**p**
Score	3(2–5)	16(15–18.5)	-5.079	<0.001**

Z: Mann Whitney test, t: independent sample t-test, ¥ Data is represented as median and IQR.
Total Iron Binding Capacity (TIBC)
White Blood Cells (WBCs)
Mean Platelet Volume (MPV)
Total Leucocyte Count (TLC)
Malnutrition-Inflammation Score (MIS)

DISCUSSION

The study illustrated the role of malnutrition-inflammation syndrome on anemia of hemodialysis patients. The study involved seventy cases with chronic kidney disease on regular hemodialysis; they were 33 females (47.1 %) and 37 males (52.9 %). The age of cases varied to from 23 – 77 years with a mean ± standard deviation of 54.2 ± 12.34 years. About 27%, 20%, 14% and 11% of patients had hypertension, combined hypertension & diabetes, diabetes, and glomerulonephritis respectively as causes of renal impairment. Comorbid diabetes and hypertension prevailed in 40% and 71.4% of them respectively.

Rocha Lemos et,al. Stated that Malnutrition-inflammation is more likely to occur in older people who have lived for extended periods, have undergone renal replacement treatment, and are female [5].

In our study, malnutrition inflammation score (MIS) varied from1 to 20 with median of 4. MIS was classified into tertiles; first tertile (good) in 28.6% ,second tertiles (moderate) in 51.4% and third tertiles (poor) in20%.A statistically significant negative association was discovered among MIS and UF volume, albumin, TIBC, and hemoglobin. A statistically insignificant association among is discovered MIS and either age, dry weight or Kt/V. A statistically significant positive association was discovered among MIS and transferrin saturation and serum ferritin, triglycerides, and CRP. A statistically insignificant association was discovered among MIS and other hematological and laboratory variables.

The occurrence of malnutrition-inflammation in the examined people was 52.2%, as indicated by the MIS. Albumin was identified as a protective factor for high MIS, as reported by Rocha Lemos et al. [5].

Higher MIS levels have been correlated with an older age, a finding that was additionally observed in further research conducted by Hanna et al. [6].

In the multivariate model for this population, the risk of malnutrition increases by 2.4% for each year of life as a result of aging. The anorexia of aging is a term that describes the physiologic alterations that occur in old age as a consequence of decreased energy requirements and expenditure. If an elderly individual acquires a physical or psychological disease, the risk of weight loss and malnutrition is elevated by this physiological anorexia, according to Crogan.[7]

The MIS is a nutritional assessment system that is specific to chronic kidney illness and has been validated. It is valuable for predicting mortality and morbidity of HD cases. The majority of chronic HD cases in stable condition have a low MIS. Kalantar-Zadeh et al. [8].

To more accurately evaluate the influence of elevated MIS on PMN activity, Cohen-Hagai et al. examined both steady-state and acutely hospitalized chronic hemodialysis cases [9].

Consequently, it is predictable that our cohort showed a higher average MIS (9.8 ± 5.44) compared to people examined by Kalantar-Zadeh et al. (6.3 ± 3.9). The difference likely signifies the selection of a varied HD people, which encompasses both stable and severely ailing HD cases [8].

In our study showed that, serum albumin (unstandardizedβ=-3.64,p-value<0.001),triglycerides (unstandardizedβ=0.035, p-value <0.001) ,serum ferritin (unstandardized β=0.003,p-value <0.001), hemoglobin(unstandardized β=-0.993,p-value <0.001)and CRP(unstandardized β=1.58, p-value =0.006) significantly independently associated with malnutrition inflammation score among anemic hemodialysis patients.

In our research demonstrated that, a statistically significant correlation is observed among the tertiles of the MIS score and CRP and serum ferritin in our study. Positive CRP prevailed in 45%, 50%, and 92.9% of patients with good, moderate, and poor nutritional status.On pairwise comparison concerning serum ferritin, the difference is significant between patients with poor nutritional status and each other group.

It was demonstrated that a less serum ferritin level is an accurate marker of deficiencies in iron in HD cases. Nevertheless, a high serum ferritin level can't be the most accurate marker of elevated iron stores in dialysis cases. This is due to the fact that ferritin is an acute-phase reactant, and its rise in dialysis cases can be attributed to factors unrelated to iron stores, including inflammation Bárány, [10];Kalantar-Zadehetal. [11]; Rafiean-KopaieandNasri,[12].

Within our research demonstrated that cases with resistance to the full dose of erythropoietin had significantly lesser hemoglobin, serum albumin, calcium, UF volume, and significantly higher triglycerides.

In agreement with our results, Agarwal et al. demonstrated that serum albumin, a substitute inflammatory indicator, was additionally an essential indicator of sensitivity to ESAs and baseline Hb. The suppression of hypoxia-induced erythropoietin (EPO) secretion in Hep3B cells is additionally a mechanism by which the inflammatory state impacts erythropoiesis [13].

In our study revealed that the patients with resistance to the full dose of erythropoietin had a significantly higher CRP (50% versus 100% of patients sensitive and resistant to the full dose of erythropoietin had positive CRP) and also serum ferritin it was significantly higher among those with resistance to the full dose of erythropoietin. There is a statistically significant relation between resistance to full dose of erythropoietin and MIS score (all patients with resistance to full dose of erythropoietin versus 6.7% of those sensitive to full dose of erythropoietin had high MIS score).

In agreement with the se results, an investigation was carried out by Sirken et al. It was discovered that the relative EPO resistance in dialysis cases was correlated with the high concentrations of CRP. [13].

Regarding NKF-KDOQI guidelines,hypo-responsiveness to erythropoietin is the presence of a minimum one of the following 3 conditions: a significant reduction in hemoglobin level at a constant ESA dose, a substantial increase in the ESA dose required to maintain a given hemoglobin concentration, or a failure to elevate the hemoglobin level to a higher than 11 gram per deciliters regardless of an ESA equivalent to erythropoietin greater than 500 international units per kilogram per week. National Kidney Foundation[15].

The points of strength:

The study's strengths include a well-defined patient cohort with diverse demographics and underlying conditions, offering valuable insights into anemia in hemodialysis patients. It provides comprehensive biomarker data, revealing significant correlations between malnutrition-inflammation score (MIS) and key markers like CRP, ferritin, and albumin, as well as important relationships between erythropoietin resistance and comorbid diabetes, inflammation, and nutritional status. The statistical analysis, including correlations between MIS and various clinical parameters, adds depth to the findings,

making the study clinically relevant for improving anemia management in hemodialysis patients.

The limitations:

The limitations of the research include a relatively small sample size (70 patients), which can limit the generalizability of the findings to a larger population. The research also lacks long-term follow-up, meaning it does not address how these associations evolve over time or how they might affect patient outcomes in the long run. Furthermore, factors such as diet and other unmeasured variables influencing nutritional status and inflammation were not fully controlled for, which could introduce potential confounding.

Recommendations:

Based on the study's findings, it is recommended that clinicians closely monitor malnutrition and inflammation markers, such as CRP, serum ferritin, and albumin, in anemic hemodialysis patients, particularly those with comorbid diabetes, to better manage erythropoietin resistance. Regular assessment of the MIS might help identify patients at higher risk of poor outcomes and guide tailored interventions. Future investigations with larger sample sizes and longitudinal follow-up are necessary to establish causal relationships and evaluate the long-term effects of inflammation and malnutrition on erythropoietin response. Additionally, incorporating dietary assessments and addressing other unmeasured confounders could provide a more full understanding of these associations.

CONCLUSIONS

The management of anemia in regular HD cases may require additional attention throughout iron therapy due to the fact that malnutrition-inflammation complex syndrome can elevate serum ferritin level in addition to iron status. The malnutrition-inflammatory score was correlated with a lower quality of life for hemodialysis cases, particularly the elderly. Serum albumin was identified as a protective factor for cases with high MIS.

Author contribution statements:

M.H. and K.H. conceived the presented idea, designed the study. K.H. conducted the computations.

Y.A. and G.E. verified the analytical methods. M.H. encouraged M.M. to investigate [a specific aspect] and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

Conflict of interest statement*:*

The authors declared that there were NO conflicts of Interest.

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