

Original Article

Impact of Malnutrition and Inflammation on Mortality in Hemodialysis Patients: A Prospective Study

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Abstract

Background: Malnutrition and inflammation are common conditions in patients undergoing hemodialysis (HD) that contribute to poor health outcomes, although their impact on mortality among South Asian populations is limited. This paper discusses how these factors interact and how they affect patient survival.

Objective: To examine the relationship between malnutrition, inflammation and mortality in HD patients, the relationship between these three variables, as well as their impact on clinical outcomes.

Methods: This is a prospective cohort study, which was carried out at the department of Nephrology, Mayo hospital Lahore between September 2023 and October 2024. The sample consisted of 134 patients who were over 18 years old and on maintenance hemodialysis (MHD) for at least three months. Nutritional status was identified using the Malnutrition-Inflammation Score (MIS) and CRP, and ferritin was used to identify inflammation. Anthropometric and biochemical data were recorded at the beginning of the research. Patients were followed for a year, and Kaplan-Meier curves and Cox regression were used as survival outcomes to analyse the results.

Results: Among the 134 patients, 82.8% of the patients were malnourished and 38.8% were classified as severely malnutrition (MIS>9). During the one year follow-up period, 17 patients (12.8%) died. Mortality was strongly associated with higher MIS scores and elevated CRP levels ($p<0.001$). Compared to survivors, deceased patients had lower MAMC, hemoglobin, and albumin, but higher ferritin levels ($p<0.05$).

Conclusion: Malnutrition and inflammation are strongly linked to higher mortality in HD patients. Key indicators are severe malnutrition, elevated CRP and ferritin, and low albumin levels. Regular nutrition screening, effective management of inflammation and early dietary interventions can help reduce mortality risk.

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Introduction

The global prevalence of end-stage renal disease (ESRD) is rising, with over two million individuals

currently undergoing dialysis and HD is the primary renal replacement therapy (RRT) for 70% to 90% of patients in most countries.^{1,2} Malnutrition is a critical yet often overlooked issue in chronic HD patients, which frequently coexists with metabolic alterations, leading to declines in energy reserves and protein levels, ultimately resulting in protein-energy wasting (PEW). Causes of malnutrition are multifactorial, including non-iatrogenic factors such as poor appetite, inadequate



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dietary intake, decreased physical activity, depression, and lack of social support, as well as iatrogenic factors like dialysis-induced nutrient losses and hyper-catabolism.³

Inflammation also significantly impacts HD patients and is a major risk factor for PEW.⁴ Inflammatory markers, including cytokines and C-reactive proteins, increase as renal function deteriorates, indicating that ESRD represents a “low-grade inflammatory process.”⁵ Several stimuli caused inflammation, including the loss of antioxidant potential, the diminished clearance of pro-inflammatory cytokines and dialysate exposure that may contain contaminants.⁶ Malnutrition and inflammation reinforce each other, resulting in a detrimental cycle where inflammation accelerates catabolism and suppresses appetite, ultimately leading to a further decline in nutritional status.⁷ The interaction is of particular concern as it compromises the immune system and elevates the infection risk that subsequently results in higher morbidity and mortality.⁸

The clearer understanding of the relationship between malnutrition and inflammation, together with early diagnosis and targeted treatment, plays a key role in improving the survival of HD patients. To date, the combined impact on the HD population in Pakistan has received limited attention. In order to fill this gap, our research prospectively examined the interaction between malnutrition and inflammation on mortality risk among HD patients, aiming to implement effective and patient-centred interventions.

Methods

This research was a prospective cohort study that was designed in the Department of Nephrology, Mayo Hospital, Lahore, in the period of September 2023 to October 2024. The ethics was approved by the IRB of King Edward Medical University, Lahore (No. 361/RC/KEMU, dated September 18, 2023). The patients who underwent MHD (n=141) and met the inclusion criteria, were included. The study included patients aged between 18 and 70 years who had been taking MHD for at least three months. Patients who switched to alternative treatment regimens during the study, were lost to follow-up, had a history of stroke or had previously used corticosteroids (n= 7) were excluded. The participants were followed up on for a year after the baseline data were collected. Based on the medical records and patient interviews, a pre-designed survey form was developed to collect demographic information including age, gender, education level, marital status, family size, and socioeconomic status.

The nutritional status of HD patients was determined by the Malnutrition-Inflammation Score (MIS); this scale is a valid tool that evaluates nutrition and inflammation. The MIS has 10 elements that, when put together, provide a general assessment of the nutritional and inflammatory state. They assess changes in body weight, functional capacity, nutrition, gastrointestinal symptoms and comorbidity. Physical examination results, such as muscle wasting and subcutaneous fat loss, along with biochemical levels including serum albumin and total iron-binding capacity (TIBC) were included. The lowest and highest possible scores on each of the components were 0 (normal) to 3 (severely abnormal), and the sum of MIS scores ranged from 0 to 30. The patients were categorised as follows: normal (0 to 3), mild (4 to 6), moderate (7 to 9) and severe malnutrition (more than 9). The rate of inflammation was assessed using C-reactive protein (CRP >10 mg/dL) and serum ferritin (>500 ng/mL); a higher level of either of these two indicated a higher rate of inflammation.

The anthropometric measurements were carried out to determine the body composition, including the body mass index (BMI), mid-arm circumference (MAC), mid-arm muscle circumference (MAMC) and triceps skinfold thickness (TSF). The measurements were carried out by members of the research team, who have been trained to adhere to the standard procedures and utilise the calibrated instruments to achieve the measurements in a precise and consistent manner. The medical records gave the baseline laboratory tests, which included CRP, cholesterol, iron, ferritin, electrolytes, iPTH and calcium-phosphate product. HD adequacy was measured based on the ratio of Kt/V. Mortality was measured using a one-year patient follow-up. Deaths were tracked through hospital records and, when needed, by contacting the family. The main outcome was the death rate, which was evaluated in relation to baseline MIS, inflammatory markers and the selected demographics and laboratory variables.

Data were entered and analysed using the assistance of SPSS version 23.0 (IBM Corp. Armonk, NY, USA). Continuous variables were expressed as Mean \pm SD, while categorical variables were represented as frequencies and percentages. The Chi-square test was employed to assess the relationships among participant’s characteristics. An independent t-test was used to analyse differences in mortality between two groups, and a one-way ANOVA was conducted to investigate differences across four groups. The relationship between malnutrition and inflammation with the survival of HD patients was examined through survival analysis using Kaplan-

Meier curves. Cox proportional hazards regression was used to adjust for confounders (age, gender, comorbidities, and dialysis adequacy). A p-value < 0.05 was considered statistically significant.

Results

In this study, out of all patients receiving MHD, 134 patients who adhered to our inclusion criteria, were followed up for one year. The mean age of the patients was 48.49 ± 11.73 years with majority of patients (n=73, 54.4%) were 50 years old or above. Most of the patients were male (n=82, 61.2%), married (n=117, 87.3%), unemployed (n=105, 78.4%) and with education of less than 10th grade (n=85, 63.4%). DM was most common cause of ESRD in most patients (n=54, 40.3%). Malnutrition was found in 111 (82.8%) patients, among which 37 (27.6%), 22 (16.4%) and 52 (38.8%) patients were mild, moderate and severely malnourished respectively.

The malnutrition status along with anthropometric measures and lab parameters of 134 MHD are demonstrated in Table 1. Mid arm circumference, Triceps skin fold, mid arm muscle circumference, Hb levels, CRP,

cholesterol levels, phosphate, albumin, and Ca-P product, were found to be statistically significant across all four malnutrition groups (P-value < 0.001). Ferritin levels (P-value=0.003) and iPTH (P-value<.004) were also significant across all groups.

At one year, 17 patients (12.7%) had died. Compared to survivors, non-survivors were older (55.8 ± 10.7 vs 47.4 ± 11.5 years, $p=0.005$), had higher MIS scores (21.0 ± 5.8 vs 8.1 ± 5.4 , $p<0.001$), and demonstrated significantly lower MAC, TSF, MAMC, haemoglobin, albumin, and cholesterol, along with higher ferritin, CRP, phosphate, Ca-P product, and iPTH as demonstrated in Table 2. In addition, patients with BMI < 18.5 (underweight) had a higher rate of mortality when compared to those in other BMI groups (normal, overweight and obese).

No significant relationship was found between demographic factors (gender, education, marital status, income, employment, family members) or clinical parameters (diabetes, hypertension, kidney stones, ischemic heart disease, chronic liver disease, smoking, frequency of maintenance hemodialysis, and hepatitis C virus) and mortality (all p-value > 0.05).

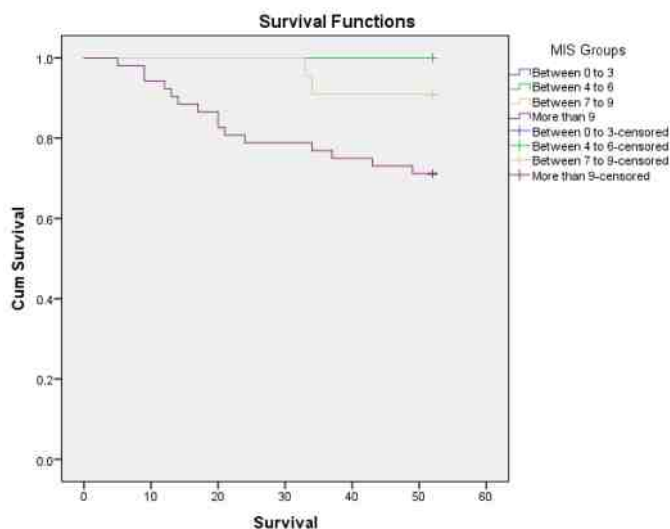
Table 1: Comparison of Nutritional, Anthropometric, and Laboratory Parameters across Malnutrition Categories (n=134)

Variable	Patients	Malnutrition (MIS Score)				F-Ratio	P-value
		Normal (0-3) 23	Mild (4-6) 37	Moderate (7-9) 22	Severe (More than 9) 52		
Age (years)		43.65±10.2	48.24±10.69	47.95±12.64	51.02±12.30	2.190	0.092
MAC (cm)		25.57±8.89	24.34±7.01	23.16±6.13	18.85±5.53	7.590	<0.001
TSF (mm)		13.91±5.43	15.37±6.81	12.86±5.23	8.44±5.18	11.98	<0.001
MAMC (cm)		24.84±6.51	23.98±4.48	22.74±5.31	18.73±4.99	11.00	<0.001
Hb (g/dL)		10.79±1.31	11.16±1.21	10.72±1.26	8.74±1.08	36.97	<0.001
Urea (mg/dL)		112.42±34.84	116.27±41.23	108.77±35.50	116.92±36.84	0.292	0.831
Creatinine (mg/dL)		8.35±2.28	8.39±3.15	7.03±3.24	7.21±2.03	2.380	0.072
Albumin (g/dL)		3.81±0.51	3.86±0.36	3.37±0.33	3.10±0.47	29.01	<0.001
TSAT (%)		22.03±6.77	23.68±14.30	27.56±18.25	23.41±15.65	0.606	0.631
Iron (mcg/dL)		66.83±52.12	61.16±27.05	69.50±57.42	59.25±35.82	0.431	0.744
TIBC(mcg/dL)		247.93±73.17	265.00±76.59	244.59±107.34	251.15±93.42	0.326	0.807
Ferritin (ng/mL)		396.40±207.34	458.58±304	433.79±241.98	631.14±332.21	5.001	0.003
CRP (mg/L)		10.30±17.88	7.81±8.68	13.62±19.01	70.82±44.28	43.52	<0.001
Cholesterol (mg/dl)		193.17±20.48	185.92±25.68	177.27±22.80	152.81±28.69	18.93	<0.001
Sodium (mEq/L)		134.69±4.41	135.16±3.17	136.45±4.03	135.57±4.87	0.724	0.540
Potassium (mEq/L)		5.31±0.89	5.27±1.22	4.95±1.32	5.47±1.19	0.994	0.398
Calcium (mg/dL)		7.68±1.01	7.89±1.04	7.57±0.72	8.11±0.81	2.363	0.074
Phosphate (mg/dL)		6.09±1.85	5.60±1.67	5.33±1.47	7.31±1.72	10.76	<0.001
Ca-P Product		46.85±17.20	43.81±13.07	40.60±12.28	59.39±15.55	7.501	<0.001
iPTH (pg/mL)		573.8±547.7	330.7±251.3	418.0±416.6	626.0±385.9	4.650	<0.004
Kt/V		1.31±0.17	1.26±0.07	1.26±0.08	1.25±0.08	1.843	0.143

Table 2: Differences in MIS, anthropometric measures and lab parameters with respect to outcome (n=134)

Variable	Patients	Outcome		t-value	P-value
		Alive 117	Died 17		
Age (years)		47.42±11.51	55.82±10.73	2.83	<0.005
Malnutrition(MIS)		8.14±5.42	21.00±5.76	9.06	<0.001
MAC (cm)		23.19±7.07	15.61±4.14	4.29	<0.001
TSF (mm)		12.91±6.18	5.88±4.22	4.53	<0.001
MAMC (cm)		22.71±5.60	16.25±3.18	4.63	<0.001
Hb (g/dL)		10.32±1.52	8.44±1.09	4.89	<0.001
Urea (mg/dL)		113.71±36.93	120.92±40.21	0.74	0.458
Creatinine (mg/dL)		7.77±2.68	7.21±2.67	0.80	0.423
Albumin (g/dL)		3.63±0.50	2.96±0.56	4.99	<0.001
TSAT %		23.73±14.44	25.30±15.89	0.41	0.680
Iron (mcg/dL)		62.18±41.93	66.76±34.93	0.42	0.668
TIBC (mcg/dL)		253.22±83.02	254.24±118.38	0.04	0.965
Ferritin (ng/mL)		458.21±259.62	873.40±357.08	5.85	<0.001
CRP (mg/L)		24.01±32.65	99.91±40.36	8.68	<0.001
Cholesterol (mg/dl)		177.14±28.51	143.71±27.55	4.53	<0.001
Sodium (mEq/L)		135.39±4.25	135.88±4.22	0.44	0.658
Potassium (mEq/L)		5.28±1.19	5.47±1.26	0.59	0.552
Calcium (mg/dL)		7.87±0.94	8.00±0.73	0.53	0.596
Phosphate (mg/dL)		6.15±1.84	7.38±1.74	2.58	<0.011
Ca-P Product		48.42±15.95	59.71±17.52	2.69	<0.008
iPTH (pg/mL)		465.02±398.53	751.67±405.68	2.76	<0.007
Kt/V		1.28±0.10	1.21±0.08	2.53	<0.012

The Kaplan-Meier curve clearly demonstrated that mortality was higher in the group with severe malnutrition (i.e. MIS scores >9) compared to the group with normal to mild malnutrition (MIS scores 0-6), a finding supported by log-rank test (P-value < 0.05) as shown in Figure 1.

**Figure 1:** Kaplan–Meier survival curves showing

survival between well-nourished and malnourished patients (Log-rank test, $P < 0.05$)

Discussion

This prospective study explored the association between malnutrition, inflammation and mortality in HD patients. A high prevalence of malnutrition was found in our study group, with a significant portion of the cohort affected by severe malnutrition. Previous researches have reported varying estimates of prevalence of malnutrition in HD patients, with rates ranging from 40% and 70%.⁹ Research conducted at The Kidney Centre, Karachi, Pakistan, 64% of the patients were classified as experiencing mild to moderate malnutrition.¹⁰ Yet, an Indian prospective study reported a broader range (32% to 60%) of malnutrition.¹¹ The consistently high prevalence of malnutrition in south Asian HD population could be due to socioeconomic disparities, low literacy rates, diverse healthcare infrastructure, psychological issues, and lack of adequate social assistance with limited access to proper nutritional support.

The key findings of the present study revealed that the MIS scores are positively associated with mortality in

HD patients and malnutrition. Patients with MIS>9 had significantly lower survival than those with MIS ≤ 6, confirmed by Kaplan-Meier and log-rank analysis. Recent literature shows that malnutrition is not only endemic in the patients suffering from HD but is also a major cause of increased mortality.¹² The duration of HD is a crucial factor linked to malnutrition, as longer duration of HD may result in hyper-catabolism, loss of nutrients, inflammation and worsening of the renal function.¹³

Parameters like BMI and MAMC were significantly lower in non-survivors compared to survivors. Low BMI suggests inadequate nutrition reserves, while reduced MAMC points to muscle wasting which impairs the physical strength and promotes inflammation, contributing to poor outcomes. As noted by Kim et al. in a prospective study, underweight HD patients with a BMI below 18.5 had higher mortality rates in comparison to the overweight group (BMI >25.0)¹⁴ whereas, higher MAMC values are associated with decreased risk of all-cause mortality in MHD patients.¹⁵

To emphasize the strong association between malnutrition and inflammation, the term “Malnutrition Inflammation Complex Syndrome” (MICS) has been proposed.⁶ Bramania et al. found 81.6% HD patients exhibited signs of inflammation, commonly attributed to persistent uraemia. Other multiple triggers include the HD procedure, quality of the dialysate and the bio-incompatibility of the membranes.¹⁶ In addition, malnutrition and inflammation establishes a feed-forward loop which in turn intensifies clinical discord in HD patients by declining muscle mass and impairing immune system which increases mortality risk.^{17,18} Our results reinforce this association, showing that patients with a higher MIS score had significantly higher mortality rates.

The outcomes showed that non-survivors had higher CRP, ferritin and lower albumin levels. Elevated CRP levels in ESRD patients are a response to systemic inflammation, which is driven by factors such as dialysis membrane exposure, urotoxin accumulation, immune system dysfunction and oxidative stress. Along with increased circulatory overload and metabolic acidosis, these triggers lead to the production of CRP and interleukins which effectively assess the prognosis by reflecting the severity of inflammation.¹⁹ The persistent inflammatory state functions as a catalyst for the progression of cardiac insufficiency and significantly leads to the onset of cardiovascular complications such as strokes and myocardial infarctions which are the leading causes of deaths in HD patients.¹⁷

Our results showed low albumin and high ferritin in severely malnourished patients, reflecting their link with inflammation and mortality. Elevated CRP can suppress albumin synthesis, making hypoalbuminemia a marker of systemic inflammation rather than solely poor nutrition. Comorbid conditions linked to hypoalbuminemia in HD patients, including chronic liver disease, diabetes mellitus, peripheral vascular disease, neoplasms and smoking, intensify this problem. In addition, metabolic acidosis reduces albumin production and increases the breakdown of skeleton muscles in these patients. Chronic inflammation and increased susceptibility to infections lead to higher resting energy expenditure (REE), which results in loss of body tissue mass and perpetuates hypoalbuminemia.²⁰

Cardoso et al. also reported that patients with hypoalbuminemia exhibits elevated inflammatory markers, including serum ferritin and CRP, showing a strong association between malnutrition, inflammation and mortality.²¹ Patients who eventually died also showed higher ferritin levels, reinforcing the relationship between iron dysregulation, inflammation and adverse patient outcomes. Elevated ferritin levels act as an acute phase reactant, indicating inflammation, and are associated oxidative damage and compromised immune function which can contribute to cardiovascular complications. This corroborates existing analysis, showing that elevated serum ferritin levels are associated with a high risk of all-cause death in MHD patients.²²

Moreover, higher serum phosphate and iPTH levels were closely correlated with increased risk of mortality in our follow-up. Elevated iPTH causes high turnover bone disease, disrupts calcium and phosphorous balance, leading to vascular calcifications, hypertension, inflammation and fibrosis that significantly increases the risk of mortality. According to Floege et al. patients with high iPTH, high serum phosphate and Ca had a lower survival chance as compared to controlled levels of these parameters.²³ Contrary to our results, a notable exception was observed in a French study where “iPTH too low” along with high serum phosphate and calcium were associated with increased mortality risk. However, the underlying pathophysiological mechanism is not well known.²⁴

Older age was significantly associated with mortality, reflecting the compounded effect of multiple co-morbidities, decreased physiological adaptability and age – related immune dysfunction, all of which can exacerbate the adverse effects of malnutrition and inflammation. This aligns with a previous research indicating that older age heightens the risk of mortality in HD patients

along with other factors such as blood pressure, race and diabetes status.²⁵

Notably, the influence of variables such as gender, education, marital and employment status did not significantly affect mortality, which indicates that they may not be important factors in the determination of the physiological effects of malnutrition and inflammation in HD patients. These findings suggest the importance of timely assessment of malnutrition and the use of certain interventions to improve outcomes in patients with HD. Routine examinations and regular nutritional treatment might contribute to reducing the risk of mortality and enhancing the life expectancy of this at-risk population. The limitations of the study include the fact that it is a single-centre study, has a small sample, and did not control for other aspects of nutritional and inflammatory status, like dietary intake, physical activity, and dialysis adequacy. The results of this study might have been influenced by other patient related factors, comorbidities and the use of medication.

Conclusion

Malnutrition and inflammation were significant mortality causes in our HD cohort. Patients with high CRP and ferritin levels, low serum albumin, high iPTH and phosphate levels and severely malnourished had poor survival. Proactively addressing malnutrition and inflammation through early intervention and regular monitoring is essential for improving patient outcomes and reducing mortality risk.

Ethical Approval: The Institutional Review Board, King Edward Medical University, Lahore, Pakistan approved this study vide letter No.361/RC/KEMU.

Conflict of Interest: The authors declare no conflict of interest.

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Authors' Contribution

ZA: Concept of the study, design of the study, data collection, drafting of the manuscript, and data interpretation.

MA: Analysing and interpreting data, and critically reviewing the manuscript.

IA: Data collection, analysing and interpreting data, and literature review.

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