Original Article

Mediating Effects of Inflammatory Markers on the Relationship Between Malnutrition and Depression in Haemodialysis Patients

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Abstract

Background: In hemodialysis (HD) patients, malnutrition and depression are prevalent issues often influenced by inflammatory markers such as CRP, ferritin and albumin. Extensive research has exhibited the robust connection between malnutrition and depression. However, there is a gap in research within Pakistan concerning how inflammatory markers might mediate this relationship.

Objective: To evaluate the mediating role of the inflammatory markers on the relationship between malnutrition and depression in patients undergoing maintenance hemodialysis (MHD).

Methods: This cross-sectional study was performed at the Nephrology Department, Mayo Hospital, Lahore from October 15, 2023 to January 15, 2024. The research incorporated patients aged ≥18 years with end-stage renal disease (ESRD) going through MHD for more than 3 months. However, patients with stroke, prior psychiatric illness, corticosteroid medication and non-consent were excluded. Malnutrition was assessed through Subjective Global Assessment-Dialysis Malnutrition Score (SGA-DMS), depression was measured using the Patient Health Questionnaire-9 (PHQ-9). The data analysis involved descriptive statistics, Pearson's correlation while the mediation analysis was performed using the PROCESS macro.

Results: The study comprised 145 patients. CRP mediated the relationship between malnutrition and depression significantly (a*b= 0.2609, 95% CI: 0.1170-0.4263, p<0.001). Ferritin represented a marginal mediating effect (a*b= 0.0805, 95% CI: 0.0142-0.1609, p= 0.0524) while albumin showed a negative mediating effect (a*b= 0.1107, 95% CI: -0.0090-0.2219, p=0.0429).

Conclusion: Elevated CRP and ferritin levels enhanced the relationship between malnutrition and depression, implying that higher inflammation worsens depressive symptoms in malnourished patients. In contrast, higher albumin levels were inversely associated with depressive symptoms, indicating a possible protective effect in malnourished patients.

Received: 19-09-2024 | **1st Revision:** 10-01-2025 | **2nd Revision:** 25-05-2025 | **Accepted:** 28-07-2025

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Keywords | Malnutrition, Depression, Hemodialysis, CRP, Ferritin, Albumin.

How to cite: Ahmad Z, Anees M, Asif I, Pervaiz MS. Mediating Effects of Inflammatory Markers on the Relationship Between Malnutrition and Depression in Haemodialysis Patients. Ann King Edw Med Univ.2025;31(3): 296-301

Production and Hosting by KEMU

https://doi.org/10.21649/akemu.v31i3.5841

2079-7192/

Introduction

Over two million individuals worldwide are receiving dialysis treatment due to the progressive increase in prevalence of end-stage renal disease (ESRD).[1] Hemodialysis (HD) is the most widely adopted renal replacement therapy for 70% to 90% of patients in most

countries.[2] On one end, HD maintains the life of ESRD patients and on the other end it is associated with inflammation, nutrient imbalance, and various psychological impacts on patients receiving it.[3] Limitation of specific food categories, depletion of water-soluble nutrients during HD, and elevated catabolism due to increased inflammatory markers may result in compromised nutritional status among HD patients.[4] Moreover, there is evidence from several sources that toxins that build up with renal failure might decrease appetite and lead to malnutrition.[5] The prevalence of malnutrition in HD patients is 71% based on Hemodialysis-Associated Systemic (HAS) criteria.[6]

Patients on HD undergo distressing psychological symptoms as a result of the demanding nature of chronic hemodialysis treatment, which has a detrimental impact on their mental health.[7] Depression is the leading psychiatric condition among patients undergoing HD, with its prevalence varying in accordance with the method used for diagnosis. It ranges from 22.8% in standardized psychiatric interviews to 39.3% when measured through screenings for depression symptoms.[8]

Chronic systemic inflammation is common among patients undergoing HD that cause a persistent inflammatory state which contributes to anorexia, decreases caloric intake and protein levels in the body. In clinical practice, inflammatory markers like C-reactive protein (CRP), ferritin, and albumin are commonly used to assess inflammation and malnutrition in HD patients. These inflammatory markers may play a role as mediators by transducing the impacts of malnutrition into inflammatory responses that afterward affects the onset or severity of depression.[9] Elevated ferritin and CRP levels positively correlate with the markers of inflammation and malnutrition whereas, low serum albumin levels potentially due to amino acid depletion may contribute to malnutrition in HD patients.[10,11] In patients with ESRD, studies have reported a noticeable association between higher levels of serum CRP and ferritin with depressive symptoms, while an inverse relationship is observed between depression and serum albumin levels.[12] These findings emphasize the relevance of inflammatory markers in the psychological profile of kidney patients.

This association highlights the crucial link between body's inflammatory response and psychological health, reflecting the complexity involved in the treatment of HD patients. Identification of the intricate interplay between the inflammatory markers, malnutrition and depression can significantly improve the survival chances and lessen the morbidity and mortality rates. Given the absence of local studies, this research seeks to investigate how inflammatory markers mediate the association between malnutrition and depression in HD patients.

Methods

This cross-sectional study was conducted in the nephrology department, Mayo Hospital Lahore from 15th October, 2023 to 15th January, 2024 following ethical approval from the Institutional Review Board (IRB) of King Edward Medical University, Lahore. All patients aged ≥ 18 with ESRD who had been receiving maintenance hemodialysis (MHD) for more than 3 months were enrolled in the study. Those individuals having a prior history of psychiatric illness, stroke, corticosteroid medication, and those who didn't consent to participate were excluded. Patient demographics, including age, gender, education, marital status, and socioeconomic status, were collected using a predesigned survey form following the acquisition of written informed consent. To ensure precision, the demographic and clinical data were acquired through patient interviews and a comprehensive review of medical records. At the start of research work, all blood samples (serum albumin, serum ferritin and CRP levels) were collected pre-dialysis immediately before the mid-week HD session, in order to minimize the potential impact of recent dialysis on serum concentrations on the measurement of inflammatory markers. Malnutrition was assessed using Subjective Global Assessment–Dialysis Malnutrition Score (SGA-DMS). The SGA-DMS serves as a comprehensive tool that evaluates nutritional status in HD patients as it assesses seven key characteristics, including weight alterations, nutritional consumptions, gastrointestinal upsets, functional abilities, subcutaneous fat, co-morbidity, and evidence of muscular atrophy. The scores of each component ranged from 1 (normal) to 5 (extremely severe), yielding in an overall malnutrition score that ranges from 7 (normal) to 35 (extremely malnourished).

Depression was assessed with the Patient Health Questionnaire-9 (PHQ-9), a standardized tool that ensures an accurate reflection of the psychological health of the patient. The PHQ-9 evaluated nine symptoms in the last two weeks, with scores ranging from 0 (no symptoms) to 3 (symptoms nearly every day). The total score, which could range from 0 to 27, was the sum of individual item scores, with higher scores reflecting intensity of depressive symptoms.

The data entry and statistical analysis were performed with SPSS version 23.0 (IBM Corp. Armonk, NY, USA), which provided detailed data processing and in-depth data analysis. The assessment of participants' general

characteristics, age, nutritional status, and depression was carried out using descriptive statistics. Continuous variables were presented as Mean ± SD to provide understanding of the central tendency and variability, while categorical variables were represented as frequencies and percentages to depict the distribution of these characteristics within the participants. The relationships between continuous variables were assessed using Pearson correlation coefficient, following conformation that the data met key assumptions including normality (via Shapiro-Wilk test), linearity, and homoscedasticity, based on scatter plot and Q-Q plot evaluations. The mediating effect of clinical parameters was assessed utilizing PROCESS macro version 3.5.3 which supports advanced mediation analysis. This analysis was conducted via bootstrapping (model 4, 5,000 samples) in order to determine the impact of mediating effects. The magnitude of mediating effect was calculated by examining the proportion of mediation (PM) in relation to both the indirect and total effects, providing a nuanced interpretation of the role of mediators. A variable was considered to have a mediating effect if the bootstrapped confidence intervals did not include zero. Statistical significance was set at $p < 0.05$.

Results

In this study, out of all patients receiving MHD, 145 patients who adhered to our inclusion criteria were included. Of these, 61.4% were male and 38.6% female. The mean age was 46.85±12.46 years. The majority were married (85.5%), while 14.5% were unmarried. Diabetes mellitus was most common cause of ESRD in most patients (40.3%). Regarding the employment, 20% were employed, 57.2% unemployed, and 22.8% housewives. Participants had a mean SGA-DMS of 11.01±4.81, and a mean depression score of 9.57± 5.79. Pearson correlation analysis showed a significant positive correlation between SGA-DMS and depression scores ($r = 0.514$, $p < 0.001$), showing that higher malnutrition levels were associated with increased depressive symptoms. Socioeconomic status (SES) was analyzed in relation to nutritional status, depression, and inflammatory markers. No statistically significant associations were found ($p > .05$), suggesting SES did not notably influence the outcomes assessed in this cohort.

While investigating mediating effect of CRP, Ferritin and albumin when finding the relationship between malnutrition (using SGA scale), a significant positive relationship ($a = 4.53$, $p<0.001$) was found between CRP (as dependent variable) and malnutrition (as independent variable). A significant relationship ($b=0.0576$, $p<0.001$) was observed between CRP and depression when malnutrition and CRP jointly taken as predictors and depression as dependent variable (Figure 1). The direct effect of malnutrition on depression demonstrated a statistically positive significant relationship ($c/ = 0.333$, 95% CI: 0.1211-0.5450, $p=0.002$). Additionally, a statistically significant positive mediating effect of malnutrition on depression through CRP was observed ($a*b=0.2609$, 95% CI: 0.1170-0.4263). It is to say that malnutritional status has significant direct and indirect effect on depression. The size of mediating effect is, therefore, 0.2609.

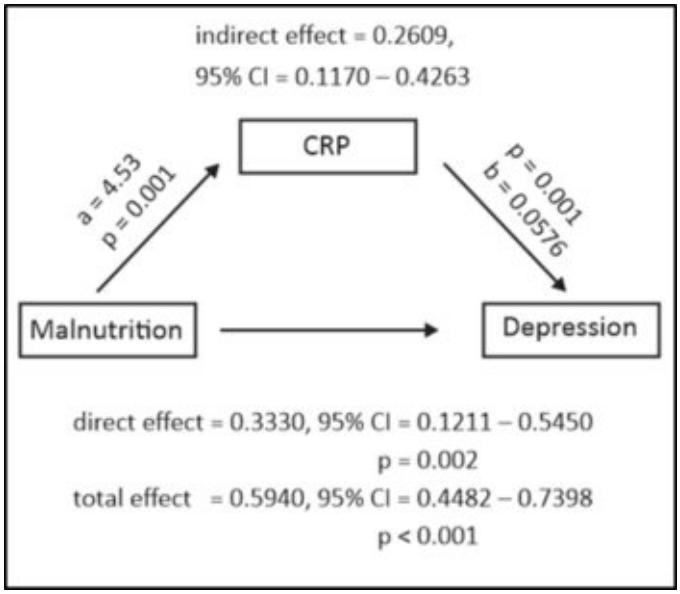

Figure-1: *The "a" is regression coefficient of malnutrition while predicting CRP, "b" and "c" are regression coefficients of malnutrition and CRP for predicting depression, total effect is effect of malnutrition on depression which is sum of direct effect and indirect effect, a*b is indirect effect of nutrition on depression. SGA is abbreviation of Subjective Global Assessment for malnutrition; CRP is C-reactive protein, and 95% confidence interval.*

A mediating analysis was also carried out between malnutrition (SGA), Ferritin and depression (Figure 2). A significant relationship was found between malnutrition and ferritin ($a=19.926$, $p<0.001$) but ferritin has a marginally mediating effect on depression ($b=0.0029$, $p=0.0524$).

In the mediating analysis of malnutrition, albumin and depression, albumin has a negative and significant role in malnutrition and depression (Figure 3). When taking malnutrition (SGA) as an independent variable and depression as the dependent variable, a

significant relationship was found between these two variables as already discussed above (b=0.5940, p<0.001), a negative significant relationship was also observed between albumin and depression (b=-1.5863, p=0.0429). The direct effect of malnutrition was noted as statisti-cally positive significant relationship (c/=0.4833, 95% CI= 0.3037-0.6628, p=0.002). The mediating effect of malnutrition on depression through albumin was identified as negative statistically significant, indicating that malnutrition had both direct and indirect effects on depression. The mediation effect size is 0.1107. Our statistical analysis revealed no significant associa-tion between socioeconomic status (SES) and malnu-trition (p=0.45), depression (p=0.39), or inflammatory markers including CRP, ferritin and albumin (p>0.05 for all).

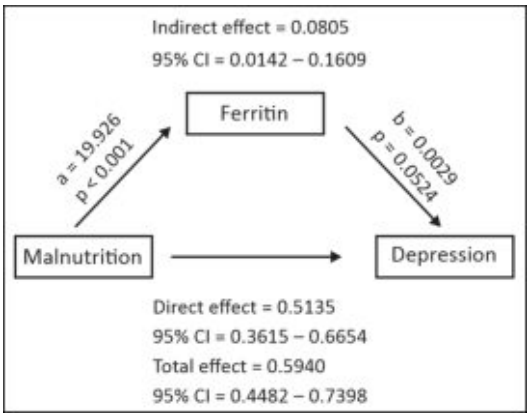

Figure-2: *The "a" is regression coefficient of malnutrition while predicting ferritin, "b" and "c" are regression coefficients of malnutrition and ferritin for predicting depression, total effect is effect of malnutrition on depression which is sum of direct effect and indirect effect, a*b is indirect effect of malnutrition on depression and 95% confidence interval.*

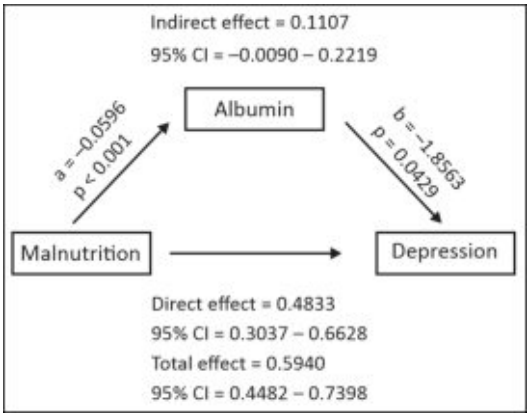

Figure-3: *The "a" is regression coefficient of malnutrition while predicting albumin. "b" and "c" are regression coefficients of malnutrition and albumin for predicting depression, total effect is effect of malnutrition on depression which is sum of direct effect and indirect effect, a*b id indirect effect of nutrition on depression.*

Discussion

The relationship between malnutrition, inflammation, and depression is complex and multifactorial. This study demonstrates a notable mediating effect of inflammatory markers specifically CRP, ferritin, and albumin on the link between malnutrition and depression in HD patients. Our results revealed a significant correlation between malnutrition and increased CRP levels reinforcing that inadequate nutrition can trigger or intensify the inflammatory pathways, consistent with recent studies recognizing CRP as a highly reliable biomarker for both malnutrition and inflammation in this patient population.[13] Evidence from an inpatient medical settings emphasize that inflammation, as elucidated by elevated CRP levels, plays a central role in disease-related malnutrition. It contributes to anorexia, decreased dietary intake, muscle wasting, and cellular insulin resistance. These factors collectively drive catabolic processes and reduce the effectiveness of nutrition-based interventions.[14]

Our findings indicated that CRP amplified the relationship between malnutrition and depression. Increased CRP was also emerged as a significant mediator in the link between malnutrition and depression, supporting the hypothesis that inflammation may serve as a bridge between nutritional status and psychological health as indicated in the study by higher levels of CRP observed in patients with depressive symptoms.[15] A 2024 cohort study highlighted the significant role of inflammation, depicted by higher levels of CRP and cytokines, in modulating glutamatergic and monoamine neurotransmission in the central nervous system. Additionally, pro-inflammatory cytokines affect the turnover of 5-hydroxytryptamine (5-HT) in the brain, potentially disrupting neuroplasticity and contributing to the development of depressive symptoms[16] as pro-inflammatory cytokines contribute to aggravate the symptoms of depression.[17] The contribution of these cytokines to the higher prevalence of depression in HD patients is noteworthy.[18] Alternatively a recent study conducted by Guenzani revealed that depression along with elevated pro-inflammatory cytokines such as CRP coincides in HD patients however, their association is uncertain.[19] This study conclusively addresses an existing gap in the literature by providing empirical evidence for the mediating role of CRP in the relationship between

malnutrition and depression among HD patients.

Our study also found that ferritin, a common marker of iron stores and inflammation in HD patients,[20] was significantly associated with malnutrition possibly reflecting inflammation induced iron sequestration and catabolism. Higher ferritin levels were linked to greater degrees of malnutrition, and it showed a marginal mediating effect on depression. Elevated ferritin levels are associated with a reduced lean tissue index in dialysis patients and are linked to increased all-cause morbidity and mortality.[21] Recent research further supports the relationship between elevated serum ferritin levels and higher Malnutrition-Inflammation scores (MIS) in dialysis patients, emphasizing its role in the pathophysiology of malnutrition and inflammation in this population.[13] Moreover, elevated serum ferritin levels and impaired iron utilization efficiency can worsen fatigue and lethargy, contributing to depressive symptoms in HD patients.[22] These findings suggest that ferritin may serve as both a biomarker of inflammation and a potential mediator of the complex interplay between malnutrition, inflammation, and depression in this patient population.

In contrast to CRP and ferritin, our study observed that albumin had a negative mediating effect on the relationship between malnutrition and depression. However, Gama Axelsson et al. argue that serum albumin levels may be more significantly influenced by chronic inflammation, a key feature of ESRD, than by nutritional intake, as inflammation inhibits albumin synthesis and accelerates catabolic processes.[23] Thus, low serum albumin levels in HD patients can reflect malnutrition or inflammation consistent with the findings of our study. In a cross-sectional study, patients with serum albumin levels under 3.8g/dL were shown to have twice the risk of depression. Similarly, hypoalbuminemia was linked with depressive status in HD patients, irrespective of the inflammatory markers such as high sensitivity CRP and interleukin-6.[22] A study by Gonzalez-Flores et al. revealed that hypoalbuminemia was linked to malnutrition and both of these conditions were associated with depression which highlights the mutual interdependence between physical and mental health in dialysis patients.[24] A prospective study in Turkey identified that HD patients with depression had higher levels of CRP and ferritin but lower serum albumin levels compared to those without depression[12] Our study emphasize that although biochemical testing adds cost and invasiveness, inflammatory markers like CRP, ferritin and albumin offer mechanistic insights that simple screening tools cannot. In selected cases, their use may help tailor interventions when malnutrition and depression do not improve with standard care. However, the absence of a significant association between SES and malnutrition, depression, or inflammatory markers in our study implied that biological determinants may have played a more dominant role, though the impact of SES still warrants further investigations in diverse cohorts.

The limitations of the study include its restriction to a single institution, which may constrain the generalizability of the findings. Additionally, confounding factors such as patient comorbidities and medication use might have influenced the outcomes.

Conclusion

In conclusion, this study identifies a significant positive mediating effect of CRP and ferritin on the association between malnutrition and depression in HD patients. However, albumin showed a negative mediating effect on this relationship. These findings can play a pivotal role in understanding the challenges faced by HD patients. By recognizing and addressing inflammation as shared pathway may enhance clinical strategies for managing both malnutrition and depression in this vulnerable population. Our research provides critical insights into the interconnected challenges of malnutrition and depression in HD patients, paving the way for innovative solutions and improved patient care strategies that will significantly enhance their lives.

Ethical Approval: The Institutional Review Board, King Edward Medial University, Lahore, Pakistan approved this study vide letter No.362/ RC/ KEMU.

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

Funding Source: None

Authors' Contribution

ZA: Conception & design, acquisition of data, analysis & interpretation of data, drafting of article

MA: Critical revision for important intellectual content, final approval

IA: Acquisition of data, analysis & interpretation of data

MSP: Acquisition of data, analysis & interpretation of data

References:

1. Agarwal AK, Haddad NJ, Vachharajani TJ, Asif A. Innovations in vascular access for hemodialysis. Kidney Int. 2019;95(5):1053-63.doi: 10.1016/j.kint.2018.11.046.
2. Imamah NF, Lin HR. Palliative Care in Patients with End-Stage Renal Disease: A Meta Synthesis. Int J Environ Res Public Health. 2021;18(20):10651.doi: 10.3390/ijerph182010651.

3. Jadoul M, Bieber BA, Martin P, Akiba T, Nwankwo C, Arduino JM, et al. Prevalence, incidence, and risk factors for hepatitis C virus infection in hemodialysis patients. Kidney Int. 2019;95(4):939-47.doi: 10. 1016/ j.kint.2018.11.038.
4. Costacurta M, Basilicata M, Marrone G, Di Lauro M, Campolattano V, Bollero P, et al. The impact of chronic kidney disease on nutritional status and its possible relation with oral diseases. Nutrients. 2022; 14(10): 2002.doi: 10.3390/nu14102002.
5. Graterol Torres F, Molina M, Soler-Majoral J, Romero-González G, Rodríguez Chitiva N, Troya-Saborido M, et al. Evolving concepts on inflammatory biomarkers and malnutrition in chronic kidney disease. Nutrients. 2022;14(20):4297.doi: 10.3390/nu14204297.
6. Ramla M, Nadia BA, MongI BM, Adel K, Inès L, Henda J. Prevalence of malnutrition for elderly hemodialysis patients. La Tunisie medicale. 2019;97(4):588-94.
7. Fradelos EC, Alikari V, Tsaras K, Papathanasiou IV, Tzavella F, Papagiannis D, et al. Assessment of psychological distress in end stage renal disease: is it spirituality related? Medicine Pharmacy Reports. 2021; 94 (1):79.doi: 10.15386%2Fmpr-1623.
8. Alencar SBV, de Lima FM, Dias LDA, Dias VDA, Lessa AC, Bezerra JM, et al. Depression and quality of life in older adults on hemodialysis. Braz J Psychiatry. 2020; 42(2):195-200.doi: 10.1590/1516-4446-2018-0345.
9. da Cunha Bandeira SB, Cansanção K, de Paula TP, Peres WAFJCnE. Evaluation of the prognostic significance of the malnutrition inflammation score in hemodialysis patients. Clinical Nutrition ESPEN. 2020;35:109-15. doi: 10.1016/j.clnesp.2019.10.019.
10. Tur K, Güçlü A. Independent Association Between Malnutrition Inflammation Score And C Reactive Protein/Albumin Ratio In Hemodialysis Patients. J Inflamm Res. 2024;17:9325-33. doi: 10.2147/ JIR. S477307.
11. Sahathevan S, Khor B-H, Ng H-M, Abdul Gafor AH, Mat Daud ZA, Mafra D, et al. Understanding development of malnutrition in hemodialysis patients: a narrative review. Nutrients. 2020;12(10):3147.doi: 10.3390/ nu 12103147.
12. Kalender B, Corapcioglu Ozdemir A, Koroglu GJNCP. Association of depression with markers of nutrition and inflammation in chronic kidney disease and end-stage renal disease. Nephron Clin Pract. 2006;102(3-4): 115-21.doi: 10.1159/000089669.
13. Prabhu PP, Siddini V, Bonu R, Prakash G, Sundar S, Ballal S. Correlation of Malnutrition Inflammation Score and Highly Sensitive C-reactive Protein with Mortality and Morbidity in Patients on Maintenance Hemodialysis in a Tertiary Care Center from South India–A Prospective Study. Indian J kid Dis. 2024; 3(3): 84-91.doi: 10.4103/ijkd.ijkd_13_24.
14. Wunderle C, Stumpf F, Schuetz P. Inflammation and response to nutrition interventions. J Parenter Enteral Nutr. 2024;48(1):27-36.doi: 10.1002/jpen.2534.
15. Jayakumar S, Jennings S, Halvorsrud K, Clesse C, Yaqoob MM, Carvalho LA, et al. A systematic review and meta-analysis of the evidence on inflammation in depressive illness and symptoms in chronic and end-stage kidney disease. Psychol Med. 2023; 53(12): 5839-51.doi: 10.1017/S0033291722003099.
16. Liu F, Yang Y, Fan XW, Zhang N, Wang S, Shi YJ, et al. Impacts of inflammatory cytokines on depression: a cohort study. BMC Psychiatry. 2024;24(1):195.doi: 10.1186/s12888-024-05639-w.
17. Nazneen S, Yadla M, Reddy P. Assessment of Depression and Its Correlation with Serum Levels of Interleukin-6 in Patients on Maintenance Hemodialysis. Saudi J Kidney Dis Transpl. 2023;34(5):397-405.doi: 10.4103/ 1319-2442.397201.
18. Yavuz YC, Biyik Z, Ozkul D, Abusoglu S, Eryavuz D, Dag M, et al. Association of depressive symptoms with 25(OH) vitamin D in hemodialysis patients and effect of gender. Clin Exp Nephrol. 2020;24(1):63-72.doi: 10.1007/s10157-019-01794-7.
19. Guenzani D, Buoli M, Caldiroli L, Carnevali GS, Serati M, Vezza C, et al. Malnutrition and inflammation are associated with severity of depressive and cognitive symptoms of old patients affected by chronic kidney disease. J Psychosom Res. 2019;124:109783.doi: 10. 1016/j.jpsychores.2019.109783.
20. Hamdan M, Alwassouf S. The Diagnostic Value of Serum Ferritin in Assessing Iron Status in Syrian Hemodialysis Patients. Bull Pharm Sci. 2022;45(1): 351-7.doi: 10.21608/bfsa.2022.239527.
21. Zhang G, Ma D, Li B, Bao L, Luo H, Cao S, et al. Clinical characteristics of patients with maintenance hemodialysis affected by COVID-19: A single-center retrospective study. Exp Ther Med. 2024;29(1):7.doi: 10.3892/ etm. 2024.12757.
22. Tsuji Y, Suzuki N, Hitomi Y, Mizuno-Matsumoto Y, Tokoro T, Nishimura M. Association of depressive symptoms with iron management in patients on maintenance hemodialysis: a cross-sectional study. Int J Biomed Eng Clin Sci. 2020;6(2):48-54.doi: 10.11648/ j.ijbecs.20200602.14.
23. Maraj M, Hetwer P, Dumnicka P, Ceranowicz P, Mazur-Laskowska M, Ząbek-Adamska A, et al. Acute Phase Proteins and Vitamin D Seasonal Variation in End-Stage Renal Disease Patients. J Clin Med. 2020;9(3).doi: 10.3390/jcm9030807.
24. González-Flores CJ, García-García G, Lerma A, Pérez-Grovas H, Meda-Lara RM, Guzmán-Saldaña RME, et al. Resilience: A Protective Factor from Depression and Anxiety in Mexican Dialysis Patients. Int J Environ Res Public Health. 2021;18(22).doi: 10.3390/ijerph 182211957.