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Research Article

Systemic immune inflammation index may predict mortality in dialysis patients

Diyaliz hastalarında sistemik immün inflamasyon indeksi mortaliteyi öngörebilir

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Abstract

Aim: Renal failure patients have increased inflammation. Serum ferritin is an acute phase reactant. Systemic immune inflammation index is a new marker calculated using lymphocyte, neutrophil, and platelet counts and have been shown to be a prognostic marker for cardiovascular disease and cancers.

This study aims to determine the availability of Systemic immune inflammation index in determining the mortality risk of dialysis patients and the relationship between mortality and ferritin levels.

Material and Methods: This retrospective, multicenter study enrolled 84 patients on peritoneal dialysis and hemodialysis. Baseline demographic, clinical and laboratory data, were obtained from medical records. Inflammatory indices were defined as NLR: absolute neutrophil count divided by absolute lymphocyte count and SII: absolute platelet count multiplied by NLR.

Results: Mean age was 51.3 ± 20.1 years and the mean follow-up time was 60 (6 ~ 85) months. During the follow-up period, 45 (53%) patients died.

Study population was analyzed according to median ferritin level. Kaplan-Meier curves showed higher mortality in patients in the high ferritin group (log-rank test, P = 0.029)

Study population was analyzed according to median SII values. Kaplan-Meier survival analysis showed higher mortality in the group with the higher SII (log-rank test, P = 0.029)

In multivariate regression analysis age (HR 1.060, P=0.00), Kt/V(HR 0.161,P=0.014), CRP(HR1.001,P=0.0429 and SII(HR 1.001, P=0.00), and ferritin (HR 1.001, P=0.013) were the most important determinants of all-cause mortality.

Conclusion: SII, a novel inflammatory marker, and ferritin are related to all-cause mortality in dialysis patients. We believe that inflammation can be followed with SII and ferritin levels.

Keywords: Dialysis, Inflammation, Systemic immune inflammation index

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Öz

Amaç: Böbrek yetmezliğinde artmış inflamasyon söz konusudur. Serum ferritini bir akut faz reaktanıdır. Sistemik immün inflamasyon indeksi, kardiyovaskuler hastalıklarda ve kanserlerde prognostic önemi olduğu gösterilen, nötrofil, lenfosit ve trombosit sayılarından hesaplanan yeni bir belirteçtir. Bu çalışma, sistemik immün inflamasyon indeksinin diyaliz hastalarının mortalite riskini belirlemede kullanılabilirliğini ve mortalite ile ferritin düzeyleri arasındaki ilişkiyi belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Çalışmaya 84 hemodiyaliz ve periton diyaliz hastası alındı. Hastaların bazal demografik, klinik ve laboratuvar verileri, tıbbi kayıtlardan elde edildi. Mutlak nötrofil lenfosit oranının, mutlak platelet ile çarpımı ile sistemik immün inflamasyon indeksi elde edildi.

Tartışma: Yeni bir inflamatuar belirteç olan Sistemik immün inflamasyon indeks ve ferritin, diyaliz hastalarında tüm nedenlere bağlı ölümlerle ilişkilidir. Diyaliz hastalarında inflamasyonun Sistemik immün inflamasyon indeks ve ferritin düzeyleri ile takip edilebileceğini düşünüyoruz.

Sonuç: Hastaların ortalama yaşı 51.3 ± 20.1olup, ortalama takip süreleri 60 (6 ~ 85) aydı. Takip süresince hastaların 45(%53) ü öldü. Hastalar medyan ferritin düzeyine göre analiz edildi. Kaplan-Meier analizine göre ferritinin yüksek olduğu grupta mortalitenin daha yüksek olduğu saptandı (log-rank test, P = 0.029).

Yine hastalar medyan sistemik immün inflamasyon indeksine göre analiz edildi. Kaplan-Meier analizine göre sitemik immün inflamasyon indeksinin yüksek olduğu grupta daha yüksek mortalite oranları saptandı (log-rank test, P = 0.029).

Çok değişkenli regresyon analizinde yaş (HR 1.060, P=0.00), Kt/V (HR 0.161, P=0.014), CRP (HR1.001, P=0.0429) ve Sistemik immün inflamasyon indeksi (HR 1.001, P=0.00) ve ferritin (HR) 1.001, P=0.013) tüm nedenlere bağlı ölümlerin en önemli belirleyicileriydi.

Anahtar kelimeler: Diyaliz, Enflamasyon, Sistemik immün inflamasyon indeks

Introduction

CKD is a public health problem with a high risk of mortality and morbidity. Patients with CKD have increased inflammatory mediators, probably because of excessive oxidative stress and extracellular fluid overload (1).

Serum ferritin level is considered as an acute phase reactant that is increased in inflammatory conditions such as CKD, liver disease, and cancer (2-5). A high ferritin level can lead to macrophage accumulation causing an increase in reactive oxygen metabolites (6). The association between serum ferritin and mortality in hemodialysis patients has been reported before (6-7).

Several traditional inflammatory cytokines, such as C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α, are positively correlated with poor survival (7,8). The neutrophil-to-lymphocyte ratio is a marker of inflammatory status and is considered to be a predictor of mortality in cardiovascular disease, end-stage renal disease, and cancer (9-12). The systemic immune inflammation index (SII), on the other hand, is a new marker calculated using lymphocyte, neutrophil, and platelet counts and have been shown to be a prognostic marker for cardiovascular disease and cancers (13-16).

This study aims to determine the availability of SII in determining the mortality risk of dialysis patients and the relationship between mortality and ferritin levels.

Material and Methods

This retrospective, observational, multicenter study enrolled 84 patients with end-stage kidney disease (ESKD) on peritoneal dialysis and hemodialysis at……. and…….. All patients with anemia were treated with erythropoiesis-stimulating agents (ESA) and received iron supplementation (intravenously or orally) when transferrin saturation (TSAT) was ≤30% and ferritin ≤500 µg/L. This study was conducted at .....from November 2014 to November 2021. Patients with a duration of maintenance dialysis of fewer than three months, with known malignancy and chronic inflammatory diseases, were excluded.

The study protocol was approved by the Medical Ethics Committee. We reviewed and followed up on the medical data according to the guidelines of our ethics committee. The patients were analyzed retrospectively, and the time of the death was recorded if mortality occurred.

Baseline demographic and clinical parameters, including age, sex, body mass index (BMI), primary kidney disease, and laboratory data, were obtained from medical records. Blood samples at the dialysis initiation were obtained from the medical records. Available laboratory data included systolic blood pressure (SBP), diastolic blood pressure (DBP), Kt/V, blood urea nitrogen (BUN), creatinine, phosphorus, calcium, cholesterol, triglycerides, LDL-C, HDL-C, serum ferritin, uric acid, CRP, albumin, hemoglobin, neutrophil count, lymphocyte count, and platelet count. Inflammatory indices were defined as NLR: absolute neutrophil count divided by absolute lymphocyte count and SII: absolute platelet count multiplied by NLR. Laboratory tests are recorded from the patient files at the beginning of the dialysis.

Descriptive results of continuous variables are reported as mean ± standard deviation (SD), and categorical variables are reported as percentages and numbers. Comparisons between groups were analyzed using a one-way analysis of variance and the chi-square test. The Spearman rank test was performed to estimate correlations. All-cause mortality was determined by Kaplan-Meier survival analyses with the log-rank test. Multivariate Cox regression analysis with forwarding regression was performed to adjust for confounding factors. A P value < 0.05 was considered statistically significant. All statistical analyzes were performed with the Statistical Package for the Social Sciences (SPSS) version 25.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

A total of 84 patients were included in the study. Baseline demographic, clinical, and laboratory parameters are shown in Table 1. The mean age was 51.3 ± 20.1 years, the male/female ratio was 49/35, and the mean follow-up time was 60 (6 ~ 85) months. During the follow-up period, 45 (53%) patients died. The underlying renal diseases were chronic glomerulonephritis (16.7%), diabetic nephropathy (13.1%), hypertensive nephropathy (29.8%), polycystic kidney disease (4.8%), chronic pyelonephritis (8.3%), and unknown (27.4%).

The median ferritin level was 419 ng/ml. The study population was analyzed according to ferritin level (ferritin level (group 1: ferritin < 419, group 2: ferritin > 419). A comparison of the groups with low and high ferritin levels at baseline can be seen in Table 2. The number of patients receiving hemodialysis was higher in group 2 (31% vs. 87%; p=0.00). EPO consumption was higher in group 2 (54.8% vs. 81%; p=0.01). SBP was lower in group 1 (121.19±19.1 vs. 131.8±16.5; p=0.007). There was a statistically significant difference between the two groups in Hb level, blood glucose, and neutrophil to lymphocyte ratio (11.0±1.5 vs. 10.2±1;p=0.005, 87±22 vs. 80±23; p00.036 and 3.86±2.01 vs. 4.07±2.14,p00.019, respectively) (Table 2).

İn correlation analysis, ferritin was not correlated with CRP, NLR, albumin, SII, or Hb levels (Table 3).

Table 1. Demographic, clinical and labarotory parameters in study population

Parameter	patients (n=87)
Age (years)	51±20
Gender (male, n, %)	35(41.7%)
BMI (kg/m2)	24.6±4,8
Comorbidites	
Diabetes (n, %)	13(15%)
Hypertension (n, %)	47 (56%)
Ischemic heart disease (n, %)	22 (26.2%)
Cause of CKD (n, %)	
Diabetes	11 (13.1%)
Glomerulonephritis	14(16.7%)
Hypertension	25(29.8%)
Polycystic kidney disease	4(4.8%)
Chronic pyelonephritis	7 (8.3%)
Unknown	23 (27.4%)
SBP (mmHg)	126.7±18.5
DBP (mmHg)	79.1±10
Kt/V	1.73±0.44
Hemoglobin (g/dL)	10.6±1.3
Glucose (mg/dl)	83±22
Albumin (g/dL)	3.9±0.4
TC (mg/dl)	166±38
TG (mg/dl)	168±114
HDL-C (mg/dl)	40±14
CRP(mg/L)	8.58±8.1
Ferritin(ng/ml)	424±252
NLR	3.96±2.06
SII	1278.14±1105.86

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CRP, C reactive protein; NLR; neutrophil lymphocyte ratio; SII, serum immune inflamation index

Table 2. Comparision of low and high ferritin groups at the baseline

	Group1 (ferritin<419)	Group2 (ferritin>419)	p
Parameter			
Age (years)	50±15	51±17	0.922
Gender (male, n, %)	19(45.2%)	16(38.1%)	0.567
Dialysis type(HD)	13(31%)	36(87%)	0.00
EPO	23(54.8%)	34(81%)	0.01
BMI (kg/m2)	25.1±5	24.2±4.6	0.269
Comorbidites			
Diabetes (n, %)	8(18%)	5(11.9%)	0.365
Hypertension (n,%)	24(57.1%)	23(54.8%)	0.826
SBP (mmHg)	121±19.1	131.8±16.5	0.007
DBP (mmHg)	77±12	80±23	0.104
Kt/V	1.94±0.46	1.51±0.28	0.00
Hemoglobin (g/dL)	11.0±1.5	10.2±1	0.005
Glucose (mg/dl)	87±22	80±23	0.036
Albumin (g/dL)	3.9±0.4	3.9±0.3	0.896
TC (mg/dl)	170±39	163±37	0.338
TG (mg/dl)	167±113	169±116	0.717
HDL-C (mg/dl)	41±16	38±11	0.312
LDL-C (mg/dl)	90±27	84±27	0.352
CRP (mg/L)	8.83±8.32	8.32±7.95	0.553
NLR	3.86±2.01	4.07±2.14	0.019
SII	1212.32±754.15	1343.95±776.65	0.774

Table 3. Cox regression analysis

	Sig.	Exp(B)	95,0% CI for Exp(B)	
			Lower	Upper
Hb	,948	,991	,746	1,316
NLR	,291	,892	,721	1,103
Alb	,916	1,085	,236	4,981
SII	,000	1,001	1,000	1,001
Ferritin	,013	1,001	1,000	1,002
Age	,000	1,060	1,028	1,094
Kt/v	,014	,161	,037	,693
Glucose	,670	1,004	,986	1,022
CRP	,042	,930	,867	,997

SII was found to be positively correlated with NLR and CRP and negatively correlated with albumin levels

The ability of serum ferritin to predict mortality during a median follow-up of 60 months was investigated. Of the 84 patients, 45 died during follow-up. Kaplan-Meier curves showed higher mortality in patients in the high ferritin group (log-rank test, P = 0.029 (Figure 1).

The median value of SII was 1091.67, and the study population was divided into two groups: < 1091.67 (group 1) and > 1091.67 (group 2). Kaplan-Meier survival analysis was performed to understand the effect of SII on survival, and higher mortality was found in the group with the higher SII (log-rank test, P=0.01) (Figure 2).

To determine the independent predictors of all-cause mortality in dialysis patients, a Cox proportional hazard model was applied. After adjustment for age, sex, and other confounders (factors with P < 0.10 in univariate analysis), multivariate analysis was performed.

Age (HR 1.060, P=0.00), Kt/V(HR 0.161,P=0.014), CRP(HR1.001,P=0.0429 and SII(HR 1.001, P=0.00), and ferritin (HR 1.001, P=0.013)were the most important determinants of all-cause mortality..

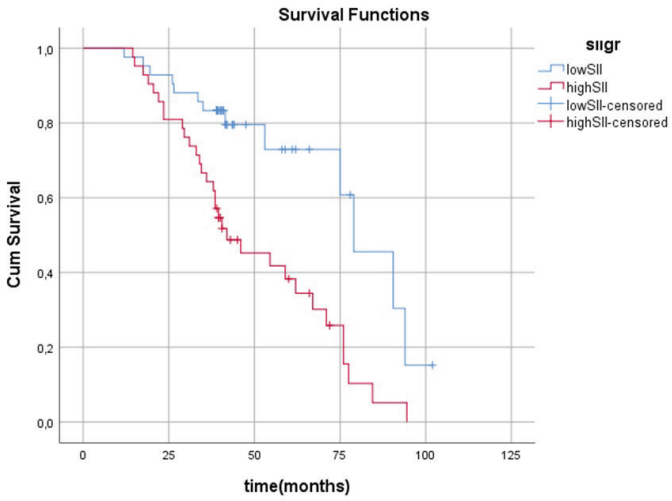

figure 1: Kaplan-Meier analysis of ferritin groups

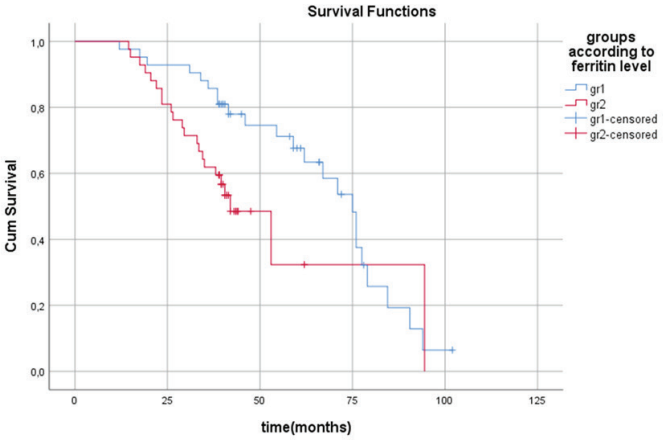

figure 2: Kaplan-Meier analysis of SII groups

Discussion

The most important finding of this study is the predictive value of ferritin and SII for mortality in dialysis patients.

Serum ferritin is an iron-containing protein. Apart from this function, it is an acute phase reactant and an inflammatory marker (4,17). It has been reported to be elevated in cancer with liver disease, coronary artery disease, and various immunological diseases (2,5,18,19). It is also associated with the rate of progression in patients with renal failure (20-22). Previous studies have demonstrated the association between high ferritin levels and mortality in dialysis patients (23-25).

The association between high ferritin levels and mortality is not fully known, but some mechanisms have been proposed. Serum ferritin escapes from damaged cells and loses most of the iron in the bloodstream. This free iron cannot be bound and increases cellular damage (26). In addition, aminolevulinate, a uremic toxin, can increase oxidative stress by causing the release of iron from ferritin (27).

The causes of inflammation in ESRD are diverse, and uremic toxins, concomitant comorbidities, and the dialysis process are some (28,29). It has been found that inflammation can indicate the long-term prognosis of ESRD patients based on some clinical indicators (30-32). Therefore, in this study, we investigated the use of ferritin as an inflammatory indicator and its effect on mortality.

A ferritin-mediated inflammatory cycle may explain why ferritin is a marker of mortality in dialysis patients. Ferritin molecule includes heavy (H) and light (L) chains. Inflammatory cytokines increase ferritin synthesis by increasing the synthesis of the H and L subunits (33). The increase in ferritin leads to a positive feedback loop with TLR9 activation, and inflammatory signals further increase (33). In addition, chronic inflammation in the uremic milieu has been reported to exacerbate vascular calcification and malnutrition and increase associated risk factors (14).

Although serum ferritin levels are almost always associated with inflammation, we did not find any correlation between inflammatory parameters and ferritin in correlation analysis. This could be the use of a single basal value, the use of iron supplements by patients, and the use of EPO.

The value of SII, an inflammatory marker, may be due to increased neutrophil and platelet counts and decreased lymphocyte counts. An increase in the neutrophil count has been shown to be associated with mortality in both cardiovascular disease and CKD (11-12).

Platelets are formed from the breakdown of megakaryocyte plasma. Megakaryopoiesis is regulated by inflammatory factors such as IL -6 and IL -1 (33). Similarly, inflammation in ESRD can also cause thrombocytosis through the action of cytokines (34). The authors suggested that SII is a more sensitive inflammatory marker because it is calculated with three cell types affected by inflammation (35).

Micro inflammation further accelerates the progression of atherosclerosis and is a crucial factor in the syndrome of malnutrition, inflammation, and atherosclerosis in ESRD patients (36). In inflammation, neutrophils are directly involved in tissue destruction (37). They do this through mediators such as myeloperoxidase and oxygen radicals (37). It has been reported that low lymphocyte count is associated with the progression of atherosclerosis and increased mortality, possibly caused by lymphocyte apoptosis (37).

Some limitations should be noted

1. This was a retrospective observational study conducted at a single center with a small sample size.

2. Only a single serum ferritin concentration was used, determined at baseline.

3. No other biomarkers of inflammation, including IL -1, TNF-α, and IFN-γ, were analyzed in addition to CRP.

Conclusion

Consequently, SII, a novel inflammatory marker, and ferritin are related to all-cause mortality in dialysis patients. We believe that inflammation can be followed with SII calculated from complete blood count parameters, which is a simple and inexpensive test. That ferritin measurement can also be a stimulating factor when the association between inflammation and mortality is considered. Prospective follow-up studies with a more significant number of patients are needed.

Ethics Committee Approval

Ethical Declaration Ethical permission was obtained from the Diskapi Yildirim Beyazit Training and Research Hospital Clinical Research Ethics Committee for this study with the date 12.09.2022 and number 146/10, and Helsinki Declaration rules were followed to conduct this study.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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