ORIGINAL ARTICLE

SYSTEMIC IMMUNE INFLAMMATION INDEX AND NEUTROPHIL TO ALBUMIN RATIO CAN PREDICT LEFT VENTRICULAR HYPERTROPHY IN GERIATRIC HEMODIALYSIS PATIENTS

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Abstract

Introduction: A link exists between inflammation and left ventricular hypertrophy, which is a risk factor for cardiovascular disease in patients with end-stage renal failure. Neutrophil, lymphocyte, and platelet counts are used to calculate the systemic immune inflammation index. To calculate the neutrophil to albumin ratio, we divided the total number of neutrophils by the albumin concentration. Some articles have illustrated the value of systemic immune inflammation index and neutrophil to albumin ratio for diagnosing disorders associated with inflammation. The purpose of this study was to investigate whether a connection exists between left ventricular hypertrophy and inflammation, as measured by systemic immune inflammation index and neutrophil to albumin ratio, in hemodialysis patients aged >65 years.

Materials and Method: This study included 51 patients who had been receiving HD for at least three months. Test results and echocardiography measurements were obtained from patient files.

Results: Average patient age was 72.88±5.12 years. Patients were divided into two groups based on left ventricular hypertrophy status. C reactive protein, systemic immune inflammation index and neutrophil to albumin ratio were considerably lower in the left ventricular hypertrophy (-) group, and multivariate logistic regression analysis revealed that high neutrophil to albumin ratio was an independent predictor of left ventricular hypertrophy (odds ratio [OR]:8.83, 95 percent confidence interval [CI]:1.32-28.83, P .0005), in conjunction with a high C reactive protein level (OR:3.45, 95 percent CI:1.905-6.645, P .005).

Conclusion: Neutrophil to albumin ratio correlates with C-reactive protein and left ventricular hypertrophy, thereby predicting the inflammation characteristic of left ventricular hypertrophy.

Keywords: Inflammation; Hypertrophy, Left Ventricular; Renal Dialysis.

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INTRODUCTION

At least 40 percent of deaths caused by end-stage renal illness can be attributed to cardiovascular causes. Left ventricular hypertrophy (LVH) is a significant health concern and risk factor for mortality (1). Inflammation is the body's first line of defense in response to excessive volume and pressure (2, 3).

Individuals with end-stage renal illness experience risk factors unique to uremia in addition to traditional cardiovascular risk factors. Increased production of endothelial adhesion molecules, chemokines, and cytokines has been observed in these tissues. The inflammatory marker C-reactive protein (CRP) has been linked to LVH and cardiovascular mortality (4, 5).

Neutrophils are known to participate in inflammatory processes (6). The recently established systemic immune inflammation index (SII) is computed by first multiplying platelet and neutrophil levels, then dividing this product by the number of lymphocytes. Studies have demonstrated SII's diagnostic utility for a number of malignancies and inflammatory disorders (7, 8).

Inflammation and cardiovascular mortality are known to correlate with blood albumin levels (9). Neutrophil numbers are also known to correlate with inflammation and cardiovascular mortality. To date, the predictive usefulness of integrating these two features is not completely clear. SII and NAR may both be easily approximated by utilizing the amounts of albumin, neutrophils, lymphocytes, and platelets obtained from routine blood testing. The use of these values as inflammatory indicators is not complicated and does not incur excessive costs. The purpose of this study was to determine whether there are connections between LVH, NAR, and inflammation detected by SII in hemodialysis patients.

MATERIALS AND METHOD

Fifty-one ESRD patients undergoing hemodialysis treatment were recruited to participate in this study. Patients with ESRD who lacked any residual renal function and had been undergoing HD (three times per week for four hours per session with standard bicarbonate dialysate) for a minimum of three months were considered eligible for inclusion. Patients were not included in this study if they had a history of using statins, steroids, or immunosuppressant medications; heart failure; a recent acute coronary or cerebrovascular incident; an autoimmune illness; malignancy; liver cirrhosis; or a current infection at the time of HD. Patients with moderate-to-severe valve pathologies were also excluded from this study.

The study was approved by the regional ethics board and was carried out in compliance with the ethical principles outlined in the Helsinki Declaration. All patients provided consent after being fully informed. Patient files were reviewed to obtain demographic information such as age at the time of the research, length of time spent on dialysis, and the existence of diabetes mellitus in the background. Data from laboratory and echocardiography measurements were gathered and placed in the patient's dossier. Thirty minutes after finishing their weekly hemodialysis session, the patients' blood pressure was measured using either a shunt arm or non-arteriovenous fistula.

Echocardiography was performed two to twenty-four hours after hemodialysis. Echocardiography and computation of dimensions and various heart volumes were performed in accordance with the recommendations of the American Society and European Association of Echocardiography. Echocardiographic assessment comprised the endo-cavitary dimensions of the left ventricle and other cardiac chambers. The left ventricular mass was calculated using the Devereux formula 17:1.04 [(LVID + PWT + IVST)3 - LVID3] 0.8 + 0.6, where LVID represents the left ventricular internal diameter, PWT represents the thickness of the posterior wall, and IVST represents the thickness of the intraventricular septum. Men with a left ventricular

mass index (LVMI) > 115 g/m^2 and women with an LVMI of greater than 95 g/m^2 were diagnosed with left ventricular hypertrophy.

The systemic immune inflammation index (SII) was calculated by multiplying the platelet count by the neutrophil count and dividing the product by the number of lymphocytes. NAR was calculated by dividing the number of neutrophils by the concentration of albumin present in the sample.

For the purpose of statistical analysis, SPSS (Statistical Package for the Social Sciences, Chicago, Illinois) version 25.0, for Windows was used. Continuous variable data are typically presented using mean and standard deviation, unless a different format is specifically required. To compare groups, either the student's t-test (where the data had a normal distribution) or the Mann–Whitney U test (for data without normal distribution) was performed. The Chi-square test was used to compare categorical variables. Estimates of the effects of the different variables on mortality were obtained using univariate analysis. In univariate analysis, the model contained parameters with a P-value of 0.05, which enabled its use in multivariate regression analysis. Cutoff levels of SII and NAR for predicting LVH were accurately determined by analyzing receiver operating characteristic (ROC) curves. The value that corresponded to the highest sensitivity and specificity values in the ROC analysis was chosen as the optimum cutoff value. P.05 on both sides were considered statistically significant.

RESULTS

Males comprised 29 (56.9%) of the 51 participants in the study. The average age was 72.88 ± 5.12 years. Nine patients were diagnosed with diabetes (21.4%), 24 with hypertension (59.5%). Five participants (11.9%) smoked. The average systolic blood pressure was 129.5 ± 11.7 mmHg, while the average diastolic blood pressure was 75.01 ± 6.6 mmHg. The mean CRP was 15.3 ± 9.5 mg/dl, and 68.6 percent of the patients had LVH. Table 1 shows the clinical results and laboratory data for the study cohort.

Dividing participants into two groups based

Table 1. Demographic, clinical and echocardiographic parameters in HD patients and control group

Parameter	HD patients (n=51)
Age (years)	72.88 ± 5.12
Gender (male, n, %)	29 (56.9%)
Comorbidites	
Diabetes (n, %)	9 (21.4%)
Hypertension (n, %)	24 (59.5%)
SBP (mmHg)	129.5 ± 11.7
DBP (mmHg)	75.01 ± 6.6
Kt/V	1.48 ± 0.24
Hemoglobin (g/dL)	11.19 ± 1.12
Glucose (mg/dl)	145.46 ± 52.59
Albumin (g/dL)	4.2 ± 3.3
TC (mg/dl)	158.48 ± 41.71
TG (mg/dl)	161.59 ± 100.18
HDL-C (mg/dl)	37.34 ± 12.66
LDL-C (mg/dl)	91.16 ± 33.03
CRP (mg/L)	15.3±9.5
SII	788.69±601.6
LVMI	149.52±48.86
LVH (n, %)	35(67.9%)
NAR	1.57±0.99

Abbreviations: HD, hemodialysis; 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; LVMI, left ventricular mass index; LVH, Left ventricular hypertrophy; SII, systemic immune inflammation index; NAR, neutrophil-to-albumin ratio.

on the presence or absence of LVH resulted in no difference between groups in sex or age.

Systolic and diastolic blood pressure and ultrafiltration volumes were comparable between groups. The LVH (+) group had a lower Kt/V (1.53 ± 0.2 versus 1.45 ± 0.25; p 0.05).

CRP and SII levels were considerably lower in the LVH group, although albumin levels were not significantly different. LVH (+) patients were found to have significantly higher NAR levels (Table 2).

Multivariate analysis was used to determine the significance of several LVH risk variables. These variables were age, sex, NLR, CRP, SII, albumin, NAR, SBP, DBP, and HT. Multivariate logistic regression analysis revealed that a high NAR score was an independent predictor of developing LVH (odds ratio [OR]:8.83, 95 percent confidence interval [CI]:1.32-28.83, P .0005), as was high CRP

Table 2. Demographic and clinical parameters in HD patients with and without LVH

Parameter	LVH (-) (n=16)	LVH (+) (n=35)	P
Age (years)	73.8 ± 5.1	72.5 ± 5.1	>0.05
Gender (male, n, %)	9 (56%)	20 (57%)	>0.05
Diabetes (n, %)	3 (19%)	6 (17%)	>0.05
Hypertension (n, %)	7 (43%)	17 (48%)	>0.05
Ultrafiltration(ml)	2980 ± 940	2850 ± 950	>0.05
Hemoglobin (g/dL)	11.01 ± 1.22	11.27 ±1.08	>0.05
Glucose (mg/dl)	144.39 ± 48.9	145.95 ± 54.88	>0.05
Albumin (g/dL)	4.4 ± 0.3	4.1 ± 0.6	>0.05
Cr (mg/dl)	8.02 ± 1.56	8.13 ± 1.94	>0.05
Ferritin (ng/mL)	475.39±284.9	393.68±262.15	>0.050
Kt/V	1.53 ± 0.2	1.45 ± 0.25	0.03
CRP (mg/L)	6.82 ± 5.77	9.18 ± 2.22	0.004
SII	610.33±431.68	870.22±422.11	0.003
NAR	0.96 ± 0.42	1.84 ± 1.05	0.002
PTH (pg/ml)	736.67±517.68	628.45±463.72	>0.05
TG (mg/dl)	165.95±145.08	159.6±76.01	>0.05
HDL-C (mg/dl)	40.35 ± 14.8	35.96 ± 11.52	>0.05
LDL	88.51 ± 29.9	92.37 ± 34.68	>0.05

Abbreviations: LVH, left ventricular hypertrophy; HD, hemodialysis; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cr, creatinine; PTH, parathyroid hormone; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; LVMI, left ventricular mass index; SII, systemic immune inflammation index; NAR, neutrophil-to-albumin ratio.

level (OR:3.45, 95 percent CI:1.905-6.645, P .005). SII and the presence of HT were not significant factors (OR:0.999 percent, 95 percent CI:0.994-1.004, P > 0.05; OR:1.001 percent, 95 percent CI:0.928-1.001, P > 0.05, respectively) (Table 3).

Analysis of the area under the receiver operating characteristic curve revealed an optimal cutoff value of 0.986 for use of NAR to predict the development of LVH, with 69 percent sensitivity and 72.5 percent specificity (area under the ROC curve:0.757 [95 percent confidence interval:0.627-0.887], P .005). An optimal CRP cutoff value of 4.65 predicted the development of LVH with a sensitivity of 56% and specificity of 44%, and the area under the curve was 0.695 (95 percent confidence interval:0.549-0.840; P .005; Figure 1).

Table 3. Binary logistic regression analysis

			95% C.I.for EXP(B)	
	Sig.	**Exp(B)**	**Lower**	**Upper**
NAR	,0032	9,741	1,32	28,83
SII	,933	0,999	,994	1,004
CRP	,004	3,45	1,905	6,675
KTV	,500	,290	,008	10,555
ht(1)	,832	,830	,148	4,653

Abbreviations: NAR, neutrophil-to-albumin ratio; SII, systemic immune inflammation index; CRP, C-reactive protein; ht- presence of hypertension.

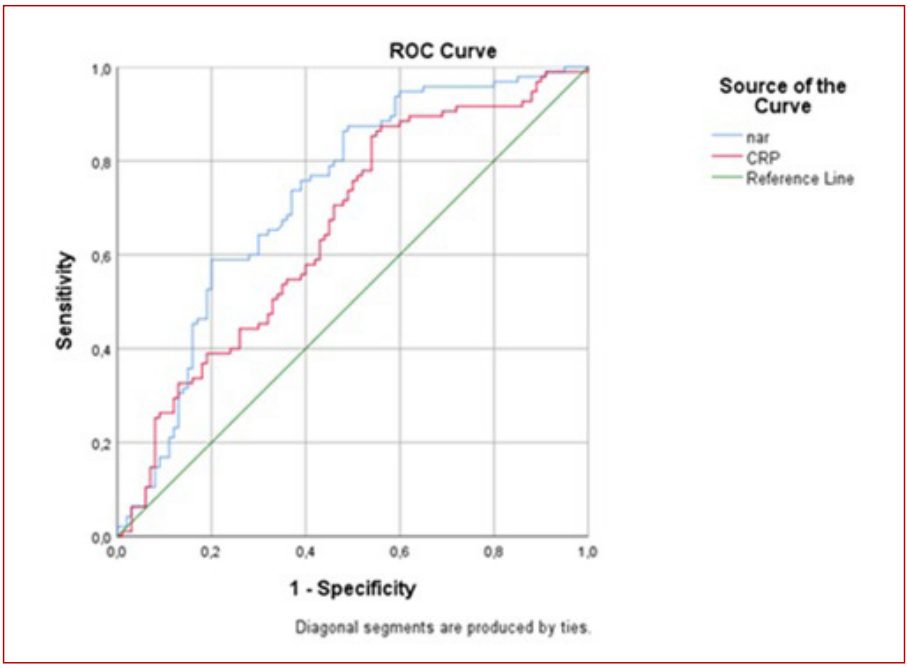

Figure 1. ROC curve

DISCUSSION

The most significant finding of this study was that the NAR score, which is an innovative method for measuring inflammation, can independently predict LVH.

In addition to conventional risk factors, ESRD patients have risk factors uniquely associated with uremia. Risk factors include hypertension, anemia, volume load, phosphorus metabolism, uremic toxin accumulation, and inflammation. These factors all have the potential to play a role in left ventricular damage and hypertrophy (2, 3).

Among the patients who participated in our study, 68.6% were diagnosed with LVH. These findings are consistent with those obtained by Foley et al. (10) and London et al. (11), who discovered that approximately 75% of individuals diagnosed with end-stage renal illness had LVH.

Renal patients who suffer from anemia also tend to have left ventricular hypertrophy (11). Hemoglobin level is a good indicator of the degree of left ventricular hypertrophy (LVH), and each g/dl drop in HB level is associated with a 50% decrease in LV systolic performance (12). During our examination, we found that Hb levels were identical between groups. This may occur as a secondary effect of anemia therapy.

KT/V and URR ratios were used to evaluate the dialysis dose, which is related to the quality of hemodialysis. The measurement of urea before and after HD is at the core of both techniques (13). Urea levels are evaluated at least once per month, although frequency may vary from center to center. According to the findings of Manuel et al., CRP levels are much higher in people who are unable to achieve an ideal Kt/V ratio (14). We concluded that the LVH group had lower Kt/v. This may be due to inflammation caused by a uremic environment, or it may be because people in this demographic have a propensity to consume an excessive amount of water.

Inflammation, fibrosis, and oxidative stress are known to be involved in left ventricular remodeling (15). LVH has been linked to elevated CRP levels (15). The neutrophil-lymphocyte ratio, often known as the NLR, is a measurement of inflammation that has seen a significant increase in popularity over the past several years (16). The systemic immunological inflammation index (SII) is a recently developed measure generated by multiplying platelets with NLR. As a result, the number of platelets in the blood and NLR were combined to obtain an improved indicator of inflammation.

Activated neutrophils increase levels of myeloperoxidase, matrix metalloproteinases 2 and 9, and reactive oxygen metabolites (17). These compounds may accelerate the progression of early atherosclerosis and contribute to plaque instability by exerting effects on the endothelium (18-20). Throughout the course of this inflammatory process, chemokines, secreted proteins, and microRNAs work together to activate platelets (17). As a direct result, platelet counts increase (17). Because SII takes into account NLR and platelet count, it is thought that this value is more sensitive than others (18). However, in our study, no significant difference in SII was observed between groups with and without LVH. It is possible that this was due to the use of heparin, which resulted in fewer platelets being detected in the blood.

Approximately 60 percent of serum protein content is albumin, which has a half-life of 19 days (19,20). Low levels are linked to malnutrition, kidney and liver disorders, cancer, and inflammation (21). Recent studies have suggested that one indicator of chronic inflammation, rather than a dietary condition, is reduced blood albumin levels (21). It is possible that the longer half-life of albumin in comparison with other blood features enhances its usefulness for identifying chronic inflammation.

NAR is a relatively new measure of inflammation. NAR was calculated using albumin and neutrophil counts. Our study found it to be the most valuable

factor in identifying LVH. CRP level was also useful. The diagnostic value of NAR is greater than that of CRP. This may be because its computation incorporates many parameters.

The inflammatory aspect of LVH development may result in increased NAR. Although LVH is commonly associated with hypertension, HT was not identified as a predictor of LVH in our multivariate analysis.

Activation of the inflammatory response enhances cytokine production. Inflammatory cytokines and cells help to alter the cardiovascular system. Wu et al. revealed that neutrophil-produced S100a8/S100a9 proteins increase Ang II-induced cardiac inflammation and fibrosis regardless of the blood pressure response (21). HT was not a predictor of LVH, and LVH may be produced by enhanced inflammation of the angiotensin pathway.

There are some limitations to this investigation. Small sample size and a cross-sectional study approach necessitated the concurrent calculation of SII levels and NAR. Only one center was used for this study. Expanded follow-up studies with more patients at several centers are needed.

The inflammatory nature of LVH might be predicted by NAR owing to its association with CRP. However, our results need to be verified in other large-scale prospective studies.

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