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NEPHROLOGY - ORIGINAL PAPER

The relationship of blood neutrophil-to-lymphocyte ratio with nutrition markers and health outcomes in hemodialysis patients

Janet Diaz-Martinez[1] · **Adriana Campa**[1] · **Ivan Delgado-Enciso**[2] · **Debra Hain**[3] · **Florence George**[4] · **Fatma Huffman**[1] · **Marianna Baum**[1]

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Abstract

Objective Adverse outcomes in hemodialysis patients have been attributed, in part, to the pro-inflammatory state prevalent in this population. This study examines the relationship between blood neutrophil-to-lymphocyte ratio (NLR) with nutrition markers and health outcomes in hemodialysis (HD) patients.

Design This is a 12-month prospective cohort study that recruited 77 participants from May to Jun 2017.

Settings and subjects Patients receiving maintenance hemodialysis.

Main outcomes Hospitalization, transplants and mortality.

Results Of the 77 participants, 63.8% were hospitalized, 10 (13%) died of cardiovascular diseases and 6 (7.8%) had a kidney transplant. Spearman correlations using baseline values showed an inverse significant correlation between the total number of hospitalizations and BMI kg/m^2 (BMI rho = − 0.37, P <0.001); a significant inverse correlation between NLR and albumin (rho = − 0.22, P = 0.028); and a significant direct correlation between baseline NLR and BMI kg/m^2 (rho = 0.22, P = 0.028). Participants were grouped by their NLR value into quartiles for outcomes analysis: quartile 1 (NLR ≤ 1.75), quartile 2 (NLR 1.76–2.6), quartile 3 (NLR 2.7–3.9) and quartile 4 (NLR ≥ 4). The percentage of patients with the lowest level of inflammation (NLR ≤ 1.75) was greater for not hospitalized patients than for hospitalized (39.3% vs 16.3%, P = 0.025) and not hospitalized participants had higher BMI kg/m^2 (mean ± SD*)* at baseline compared to those hospitalized (29.11 ± 5.4 vs 26.22 ± 5.34, P = 0.026). In a multivariate cox regression analysis, participants in the lowest quartile (NLR ≤ 1.75) were compared to the rest on hospitalization, mortality and transplant. Years in dialysis, BMI kg/m^2 and NLR ≤ 1.75 were significant predictors of hospitalization after adjustment (P = 0.021, P = 0.005, P = 0.039; respectively) and we observed an association of low NLR with a hazard ratio (HR 0.44, 95% CI 0.20–0.96, P = 0.039), BMI (HR 0.90, 95% CI 0.85–0.97, P = 0.005) and years in dialysis (HR 0.90, 95% CI 0.83–0.98, P = 0.021) for hospitalization in overall participants. In a further analysis comparing the effect of low NLR in the subgroup of diabetic vs non-diabetics, it was observed that BMI kg/m^2 was a significant predictor for hospitalization in the non-diabetic subgroup (P = 0.040) but not significant in the case of diabetics (P = 0.128) after adjustments. Years in dialysis and NLR ≤ 1.75 were significant predictors of hospitalizations in the subgroup of diabetic before and after adjustment (P = 0.049, P = 0.044; respectively). Having a low NLR decreased 73% the risk for hospitalization (HR 0.27 95% CI 0.07–0.96, P = 0.044) in this subgroup. Survival and hospitalization curves were analyzed by comparing all participants and the diabetic subgroup, in the lowest inflammation quartile vs the rest (NLR ≤ 1.75 vs NLR > 1.75). Participants with NLR ≤ 1.75 had 100% survival rate (log-rank test, P = 0.059) and lower hospitalization rate (log-rank test, P = 0.025); participants with diabetes had lower hospitalization rate (log-rank test, P = 0.039).

Conclusion NLR at baseline was associated with nutritional markers (albumin, BMI). Low NLR at baseline was a predictor of lower risk for hospitalizations in HD patients with diabetes.

Keywords Hemodialysis · Inflammation · NLR · Mortality · Hospitalization

✉ Janet Diaz-Martinez
jmart556@fiu.edu

Extended author information available on the last page of the article

Introduction

Patients with end-stage renal disease (ESRD) receiving dialysis exhibit a high hospitalization rate—approximately two admissions per patient annually—and a 20–25% mortality rate with a 5-year survival rate of 35% [1, 2]. In this population, cardiovascular and infectious diseases account for approximately 50% of hospitalizations and 20% of deaths [1]. These outcomes have been attributed, in part, to the pro-inflammatory state that afflicts patients living with dialysis, as well as co-existing protein energy wasting (PEW) [3]. A number of factors of the uremic milieu contributes to the high prevalence of inflammation, including elevated levels of circulating pro-inflammatory cytokines, oxidative stress, carbonyl stress and increased incidence of comorbidities such as infections, and anemia [4]. Inflammation has been implicated in the initiation and progression of atherosclerosis and may also promote cardiovascular mortality through leukocyte adhesion and infiltration of the vascular endothelium [5, 6]. In hemodialysis patients, *T*-lymphocytes and the antigen-presenting cells (APC) functions are frequently impaired producing immune disturbances that may promote inflammation and metabolic imbalances that lead to malnutrition [7]. The vicious cycle that is closed by the interaction of malnutrition, infections and inflammatory cytokines, may lead to more frequent hospitalizations and ultimately to death. The important role of the impaired immune system in these events may explain the relationship of malnutrition and inflammation with the neutrophil-to-lymphocyte ratio (NLR).

Neutrophil-to-lymphocyte ratio (NLR) has emerged as a subrogate marker for systemic inflammation in chronic kidney disease (CKD) and ESRD [8, 9]. It is obtained by dividing neutrophil count by lymphocyte count, which makes it a cost effective, simple parameter that allows to easily assess the inflammatory status of a subject [8]. NLR has demonstrated potential diagnostic ability in settings where *C*-reactive protein is not measured routinely or it is not an accurate marker [10]. NLR has been useful in the stratification of mortality in major cardiac events [11], as a strong prognostic factor in several types of cancers [12], and in the prediction of worsening renal function in patients with diabetes [13]. While the use of NLR as a predictor of cardiovascular and all-cause mortality in patients receiving dialysis has gained recognition, many barriers still remain to its robust application [14]. The correlation between NLR value and a higher adverse risk has not been thoroughly defined, as it remains unknown which cutoff value will discriminate normal from abnormal results, and for which population NLR will be a better predictor of adverse outcomes. The aim of this study was to examine in detail the relationship of blood neutrophil-to-lymphocyte ratio with nutrition markers and health outcomes in hemodialysis patients.

Methods

Design

A 12-month prospective cohort study was conducted at one hemodialysis clinic located in South Florida. The study protocol was approved by the Florida International University Institution Review Board (FIU-IRB #105733) and informed consent was obtained from each participant. The sample consisted of all adult male and female patients recruited from May to Jun 2017, who agreed to participate in the study and met the inclusion criteria: participants were 19 years of age or older, undergoing hemodialysis three times per week for at least 3 months and being medically stable without acute infection. Excluded from the study were patients receiving nutrition support through intradialytic parenteral nutrition or tube feedings, those with dementia interfering with completing the nutritional questionnaire, or those who refused or were unwilling to participate in the study.

Demographic and clinical data

Clinical and demographic data were collected from clinical charts and through interviews with the patients. The demographic data collected included age, gender, ethnicity, hemodialysis start date, BMI kg/m^2, and diagnosis of diabetes mellitus.

The biochemical data included serum albumin, net protein catabolic rate (nPCR), neutrophils and lymphocytes percent, total iron binding capacity (TIBC), and dialysis adequacy (Kt/*V*). All these values were collected at multiple time points during the 12 months of the study.

Endpoints: hospitalization, transplants and mortality

Hospitalization was defined as any hospital stay lasting one night or longer. The occurrences of hospitalization, kidney transplant and death (all-cause mortality) were collected during the 12-month follow-up.

Statistical analysis

We reported absolute and relative frequencies, mean, standard deviation, median, and interquartile range assuming data normality. For the inferential statistics, normal data distribution was first determined using the Kolmogorov–Smirnov test and the equality of variances was confirmed using Levene's test. One-way ANOVA, Student's t tests, Chi-square tests, or Mann–Whitney tests were used to compare variables among groups, as appropriate. Only baseline values were included in the correlation analysis of albumin, nPCR, NLR, TIBC and Kt/V and in the statistical models for endpoint analysis. Spearman correlations were used for bivariate analysis. Significant outcome's predictors were identified and further analyzed in a multivariable model, and then a forward stepwise Cox regression identified the most parsimonious model. The probability used for the stepwise regression was set at 0.05 for entry of variables and 0.10 for removal. Survival and hospitalization (time to first hospitalization) curves were estimated by Kaplan–Meier analysis and compared using the log-rank test. The hazard ratios were obtained from Cox regression analysis. The level of statistical significance was $P < 0.05$. All statistical tests were performed with SPSS version 20 software (IBM Corp., Armonk, NY, USA).

Results

Demographic analysis

Seventy-seven hemodialysis participants were enrolled in this study, with a mean age of 63.2 ± 15.7 years; 28.8% were female, 18.2% were Hispanics, 39% were African Americans, 31.2% were Whites and 11.7% were West Indians. Their average time receiving dialysis was 6.2 ± 4.2 years, and 58.4% of the patients had diabetes. In terms of dialysis parameters, the hemodialysis doses and duration were similar for all patients.

Endpoints analysis: hospitalization, mortality and transplant

During the studied 12-month monitoring period, six participants (7.8%) had a kidney transplant, one participant (1.2%) was transferred to another dialysis center, and 10 (13%) died of cardiovascular diseases (CVD).

The percent of participants who were hospitalized during the study was 63.8% with a mean ± SD of 1.1 ± 0.73 hospitalizations per patient per year (PPY); 38% participants were admitted only once, 10% were admitted twice, and 14.2% were admitted three times or more. The causes of hospitalizations were varied, a major cause was infection (48.5%). Other causes (51.5%) were related to gastrointestinal issues, access-related issues, fluid overload and programmed surgeries among others. The length of the hospitalization was not recorded for any case. The mean values of the biochemical variables included albumin, nPCR, NLR, TIBC and Kt/V, at baseline, 6 months, 12 months as well as annual averages were compared and no statistically significant differences were detected ($P > 0.05$, data not shown).

Spearman correlations were determined among total number of hospitalizations registered in 12 months and baseline values of BMI kg/m^2, albumin, nPCR, NLR, and TIBC. There was an inverse significant correlation between the total number of hospitalizations and BMI kg/m^2 (BMI: rho = −0.37, P <0.001). The correlations between total numbers of hospitalizations with albumin, nPCR, NLR, and TIBC did not achieve (albumin: rho = − 0.04, P = 0.36; nPCR: rho = − 0.13, P = 0.14; NLR: rho = 0.16, P = 0.07; TIBC: rho = 0.18, P = 0.06). We found a significant inverse correlation between NLR and albumin (rho = − 0.22, P = 0.028; and a significant direct correlation between NLR and BMI kg/m^2 (rho = 0.22, P = 0.028).

Participants were grouped by their NLR value into quartiles for the analysis of NLR as a marker of inflammation and endpoints (Table 1): quartile 1 (NLR ≤ 1.75), quartile 2 (NLR 1.76–2.6), quartile 3 (NLR 2.7–3.9) and quartile 4 (NLR ≥ 4). Baseline cohort characteristics, including demographic and baseline biochemical variables, are summarized in Table 1.

Table 2 shows a comparison between hospitalized and not hospitalized patients during the study period. The BMI kg/m^2 (mean±SD) for not hospitalized patients was significantly higher than for hospitalized (29.1 ± 5.4, 26.2 ± 5.3; P =0.026). The percent of patients with the lowest level of inflammation (NLR ≤ 1.75) was greater for not hospitalized patients than for hospitalized (39.3% vs 16.3%, P =0.025). No statistically significant difference was detected between participants who had at least one hospitalization and participants who did not have any hospitalization during the period of the study by age, gender, years in dialysis, diabetes, ethnicity, albumin, nPCR, TIBC and Kt/V(all $P_s > 0.05$).

Those examined variables that showed significance levels with a $P \leq 0.2$ (one-way ANOVA and Chi-square test) and pre-determined variables, were further analyzed in multivariate and a stepwise Cox regression models. Table 3 shows a multivariate Cox regression analysis that was constructed to test the contribution of each pre-determined variable to the dependent variable (all cause-hospitalization) in the entire cohort. Significant predictors were subsequently added to the multivariable model and forward stepwise Cox regression, which identified the most parsimonious model. The probability used for the stepwise regression was set at 0.05 for entry of variables and 0.10 for removal. The covariates years in dialysis, BMI kg/m^2 and NLR ≤ 1.75 were significant predictors of hospitalization after adjustment (P = 0.021, P = 0.005, P = 0.039; respectively). In this model, we observed an association of low NLR with hospitalization in overall participants, with a hazard ratio (HR 0.44, 95% CI 0.20–0.96, P =0.039), BMI (HR 0.90, 95% CI 0.85–0.97, P = 0.005) and years in dialysis (HR 0.90, 95% CI 0.83–0.98, P = 0.021) (Table 3).

Table 1 Table of characteristics for the overall participants and comparing participants grouped into NLR quartiles: quartile 1 (NLR ≤ 1.75), quartile 2 (NLR 1.76–2.6), quartile 3 (NLR 2.7–3.9) and quartile 4 (NLR ≥ 4.0)

Variable	Overall *N* = 77	Quartile 1 NLR (≤ 1.75) *N* = 19	Quartile 2 NLR (1.76–2.6) *N* = 21	Quartile 3 NLR (2.7–3.9) *N* = 18	Quartile 4 NLR (≥ 4.0) *N* = 19	*P* values
Baseline	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age	62.3 ± 12.7	62.4 ± 12	61.3 ± 16	64.8 ± 13.9	64.8 ± 20.3	0.861*
Female	28.6%	36.8%	14.3%	22.2%	42.1%	0.174**
Years in dialysis	6.2 ± 4.2	6.4 ± 4.8	6.8 ± 3.9	6.5 ± 5.0	5.1 ± 2.9	0.598*
BMI	27.2 ± 5.5	26.8 ± 5	25.6 ± 4.7	28.8 ± 5.9	28.1 ± 5.2	0.290*
Diabetes	58.4%	42.1%	47.6%	66.7%	78.9%	0.068**
Ethnicity						
Hispanic	18.2%	10.5%	19.0%	22.2%	21.1%	0.024**
Black	39.0%	52.6%	52.4%	33.3%	15.8%	
White	31.2%	15.8%	14.3%	44.4%	52.6%	
West Indian	11.7%	21.1%	14.3%	0.0%	10.5%	
Albumin	3.8 ± 0.3	3.8 ± 0.3	3.9 ± 0.2	3.7 ± 0.3	3.7 ± 0.3	0.098*
Kt/*V*	1.4 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	1.5 ± 0.2	0.396*
TIBC	214 ± 30	214 ± 31	210 ± 27	217 ± 31	218 ± 32	0.845*
nPCR	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.3	1.1 ± 0.34	0.147*
NLR	2.9 ± 1.8	1.1 ± 0.4	2.2 ± 0.2	3.2 ± 0.3	5.4 ± 1.7	0.000*
#Hosp. per patient	1.1 ± 0.73	0.9 ± 1.6	1.4 ± 1.1	2.0 ± 0.4	1.4 ± 1.1	0.628*
Hospitalized	63.8%	42.1%	90.5%	38.9%	78.9%	0.043**
Transp.	7.8%	10.5%	4.8%	11.1%	5.3%	0.820**
Mortality	13%	0%	33.3%	11.1%	5.3%	0.001**

*One-way ANOVA test

**Likelihood ratio Chi-square test

#Total number of hospitalizations

Table 2 Table of characteristic comparing not hospitalized vs hospitalized

Variable	Not hospitalized (*N* = 28)	Hospitalized (*N* = 49)	*P* values
Baseline	Mean ± SD	Mean ± SD	
Age	63.2 ± 14.7	63.3 ± 16.4	0.981*
Female	28.6%	28.6%	0.607**
Years in dialysis	7.1 ± 4.8	5.6 ± 3.7	0.132*
BMI	29.1 ± 5.4	26.2 ± 5.3	0.026*
Diabetes	50.0%	36.7%	0.185**
Ethnicity			
Hispanic	17.9%	18.4%	0.373**
Black	46.4%	34.7%	
White	32.1%	30.6%	
West Indian	3.6%	16.3%	
Albumin	3.7 ± 0.3	3.8 ± 0.3	0.501*
Kt/*V*	1.5 ± 0.2	1.4 ± 0.2	0.828*
TIBC	207.5 ± 30.3	218.6 ± 29.8	0.141*
nPCR	0.9 ± 0.2	0.9 ± 0.3	0.862*
NLR	2.6 ± 1.7	3.2 ± 1.8	0.215*
NLR ≤ 1.75	39.3%	16.3%	0.025**

**T* Student test

**Chi-square test

Table 4 shows a multivariate Cox regression analysis that was constructed to evaluate the contribution of each predetermined variable to the dependent variable (all cause-hospitalization) in the diabetic subgroup compared with non-diabetic participants. Following the same analysis for models that included all participants, significant predictors were subsequently added to the multivariable model and forward stepwise Cox regression identified the most parsimonious model. The probability used for the stepwise regression was set at 0.05 for entry of variables and 0.10 for removal. In this sub-analysis, BMI kg/m^2 was a significant predictor for hospitalization in the non-diabetic subgroup ($P = 0.040$) but not significant in the case of diabetics ($P = 0.128$) after adjustments. Two covariates, years in dialysis and low-inflammation levels (NLR ≤ 1.75), were significant predictors of hospitalizations in the subgroup of diabetic participants after adjustment ($P = 0.049$, $P = 0.044$; respectively). Thus, the effect of low NLR (NLR ≤ 1.75) was only significant among diabetics, but not among non-diabetics. Having a low NLR decreases 73% the risk for hospitalization in this subgroup of participants (HR = 0.27 95% CI 0.07–0.96, $P = 0.044$) (Table 4).

In addition, to analyze the effect of NLR on hospitalization and mortality, survival and hospitalization curves were

Table 3 Multivariate Cox regression model for all-cause of hospitalization in all participants

Covariate	Unadjusted HR	95% CI		P	Adjusted HR	95% CI		P
		Lower	Upper			Lower	Upper	
Age	0.99	0.98	1.01	0.869	–	–	–	–
Sex	1.00	0.54	1.87	0.985	–	–	–	–
Ethnicity	1.16	0.84	1.59	0.349	–	–	–	–
Diabetic	1.42	0.79	2.55	0.229	–	–	–	–
Years in dialysis	0.94	0.88	1.01	0.134	0.90	0.83	0.98	0.021
BMI*	0.94	0.89	0.99	0.044	0.90	0.85	0.97	0.005
Albumin*	1.39	0.49	3.92	0.525	–	–	–	–
nPCR*	0.74	0.26	2.08	0.573	–	–	–	–
TIBC*	1.00	0.99	1.01	0.137	–	–	–	–
Kt/*V**	0.82	0.19	3.53	0.794	–	–	–	–
NLR ≤ 1.75*	0.44	0.20	0.95	0.038	0.44	0.20	0.96	0.039

*Baseline

Table 4 Multivariate Cox regression model for all-cause of hospitalization in diabetics and non-diabetics patients

Covariate	Unadjusted HR	95% CI		P	Adjusted HR	95% CI		P
		Lower	Upper			Lower	Upper	
Non-diabetic								
Age	1.01	0.98	1.04	0.458	–	–	–	–
Sex	1.48	0.52	4.18	0.452	–	–	–	–
Ethnicity	1.04	0.63	1.71	0.873	–	–	–	–
Years in dialysis	0.99	0.89	1.09	0.856	0.97	0.87	1.08	0.593
BMI*	0.91	0.83	1.00	0.050	0.90	0.83	0.99	0.040
Albumin*	1.66	0.24	11.51	0.606	–	–	–	–
nPCR*	0.57	0.06	5.23	0.619	–	–	–	–
TIBC*	1.00	0.98	1.02	0.561	–	–	–	–
Kt/*V**	3.45	0.19	60.36	0.395	–	–	–	–
NLR ≤ 1.75*	0.63	0.22	1.79	0.394	0.60	0.21	1.72	0.347
Diabetic								
Age	0.98	0.96	1.00	0.240	–	–	–	–
Sex	0.72	0.33	1.58	0.425	–	–	–	–
Ethnicity	1.20	0.82	1.90	0.295	–	–	–	–
Years in dialysis	0.91	0.83	1.01	0.082	0.89	0.80	0.99	0.049
BMI*	0.97	0.90	1.04	0.398	0.93	0.85	1.02	0.128
Albumin*	1.45	0.43	4.87	0.540	–	–	–	–
nPCR*	0.93	0.28	3.06	0.911	–	–	–	–
TIBC*	1.00	0.99	1.01	0.240	–	–	–	–
Kt/*V**	0.50	0.08	2.89	0.441	–	–	–	–
NLR ≤ 1.75*	0.33	0.10	1.11	0.075	0.27	0.07	0.96	0.044

*Baseline

analyzed by comparing participants in the lowest quartile of inflammation vs the rest (NLR ≤ 1.75 vs NLR > 1.75). Figure 1a shows the Kaplan–Meier curve for mortality for all participants. Participants with NLR ≤ 1.75 had a 100% survival rate (log-rank test, $P = 0.059$) compared with participants with NLR > 1.75. Figure 1b shows the Kaplan–Meier curve for hospitalization for all participants. Participants with NLR ≤ 1.75 had a lower hospitalization rate (log-rank test, $P = 0.025$) compared with participants with NLR > 1.75. Figure 1c shows the Kaplan–Meier curve for hospitalization for the subgroup of diabetics. Participants with diabetes and in the lowest quartile of inflammation (NLR ≤ 1.75) had lower hospitalization rate compared with participants with diabetes in the higher quartile of inflammation (NLR > 1.75) (log-rank test, $P = 0.039$). In total, there were ten deaths in this cohort in 12 months: seven of them

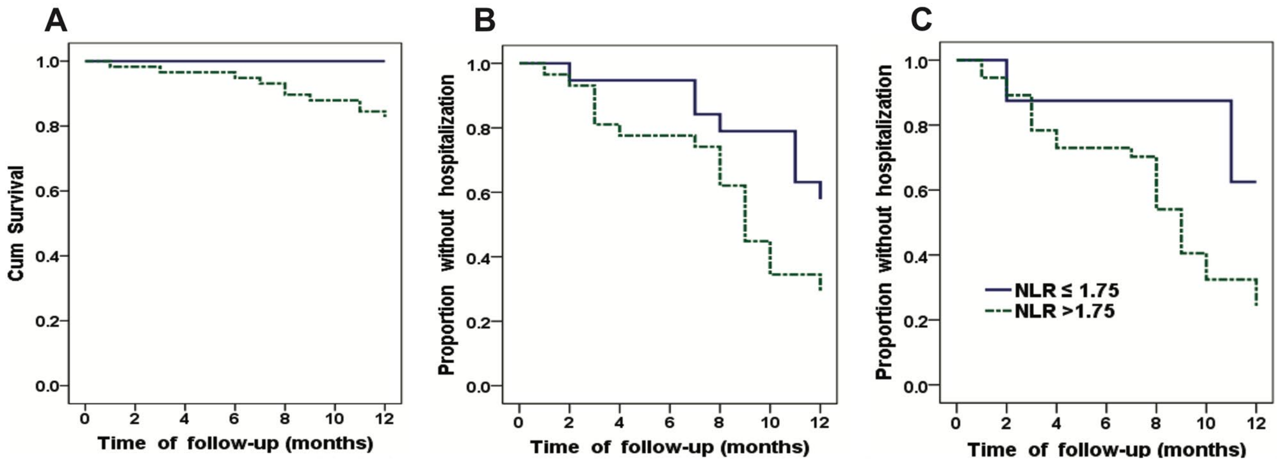

Fig. 1 Kaplan–Meier estimates of mortality and hospitalization. Participants stratified by two groups based on the neutrophil–lymphocyte ratio (NLR): quartile 1 corresponding to the lowest inflammation quartile (NLR ≤ 1.75) vs the rest of quartiles (NLR > 1.75). **a** Kaplan–Meier estimates of mortality for overall participants showed that NLR was not associated with mortality (log-rank test, P = 0.059). **b** Kaplan–Meier estimates of hospitalization for overall participants showed that NLR was associated with hospitalization (log-rank P = 0.025). **c** Kaplan–Meier estimates of hospitalization for participants with diabetes showed that NLR was associated with hospitalization in participants with diabetes (log-rank test, P = 0.039)

from quartile 2 and two from quartile 3 and one from quartile 4. Survival was 100% in the lowest quartile of inflammation (quartile, NLR ≤ 1.75). Further analysis may be needed with a bigger sample and/or over a longer period to clarify the role of inflammation on these particular health outcomes. Kaplan–Meier hospitalization curves also supported the findings that level of inflammation is a better predictor of hospitalization than of mortality, Fig. 1a–c. Participants with NLR ≤ 1.75 had lower hospitalization rate compared with participants with greater NLR levels (log-rank test, P = 0.025) and this protective effect was more significant for diabetic patients (log-rank test, P = 0.039).

Discussion

Several adverse clinical outcomes have been associated with systemic inflammatory markers in CKD and ESRD, including cardiovascular events, kidney disease progression, anemia, PEW, and all-cause mortality [7, 10, 13]. In this study, we evaluated the predictive value of NLR for health outcomes: hospitalization, transplant, and mortality in patients receiving hemodialysis. The results indicated that NLR was a significant predictor of hospitalization in diabetic patients. Our results support previously reported findings that showed the usefulness of this novel marker in the prediction of outcomes. NLR has been shown to be a strong and independent predictor of cardiovascular disease severity and mortality in the general population [10] In 2012, An X et al. [15] reported the predictive value of NLR for cardiovascular mortality in patients receiving peritoneal dialysis, and more recently, in 2017, Han Li et al. [16] found that NLR was an independent predictor of cardiovascular risk and mortality in patients receiving maintenance hemodialysis. In Turkey, Erdem et al. [17], in 2013, also reported the usefulness of NLR in predicting short-term mortality among patients receiving hemodialysis in a hospital setting. However, in our study, the effect of NLR on mortality did not reach significance.

The hospitalization of hemodialysis patients in the United States varies from 51 to 67% [1]. In our cohort (N = 77), the percent of participants who were hospitalized was 63.8% and the hospitalization patient per year (PPY) was (mean ± SD) 1.1 ± 0.73, which is below the adjusted rate of hospitalizations for hemodialysis patients reported in 2014 (1.7 PPY) [1]. When we compared the hospitalization rate of participants in the lowest level of inflammation vs the rest, we found that a low NLR had a significant protective effect among patients with diabetes. Interestingly, a similar significant effect was not observed in participants without diabetes. Our findings support those of Azab et al. [18], who in two long-term follow-up studies, analyzed the usefulness of NLR specifically for patients with diabetes and reported a correlation between high NLR and worsening of kidney function [13, 18] Furthermore, they found that NLR was a predictor of major adverse cardiac events among patients with diabetes with stage-five kidney disease [18].

While our analyses did not reveal a significant correlation between inflammation and mortality, there seems to be a possible effect that needs further exploration. There was no mortality in the lowest NLR quartile and all the ten deaths registered during the study occurred in the higher

NLR quartiles. The reason behind this finding needs to be studied in the future with a larger sample size.

Our study also showed an unusual relationship between BMI kg/m^2 and number of hospitalizations; as BMI kg/m^2 increased, the number of hospitalizations decreased (rho = −0.37 $P < 0.001$).This trend is contrary to that of the general population, where the higher the BMI, the greater the risk of morbidity and mortality [19] This epidemiological paradox, in which high BMI kg/m^2 is associated with improved survival in patients with CKD–ESRD and undergoing hemodialysis has been reported before [20, 21]. In our cohort, participants with higher BMI kg/m^2 had 10% lower risk for hospitalization (HR 0.90, 95% CI 0.85–0.97, $P = 0.005$), and patients with greater number of years in dialysis had less risk for hospitalization (HR 0.90, 95% CI 0.83–0.98, $P = 0.021$). This might suggest that, in hemodialysis patients with increased BMI, increased body fat, and more years in dialysis are related to less adverse events that ultimately require hospitalizations. The known 5-year survival rate is 35% for ESRD patients; [1] therefore, long-term survivors seem to be more resilient to hospitalization in our cohort. Not hospitalized patients had a mean 7.1 ± SD 4.8 in dialysis vs 5.6 ± SD 3.7 for participants who were hospitalized, at least once, in 12 months. This difference became significant after adjustment ($P = 0.021$) for all participants (Table 3) and for diabetic participants ($P = 0.049$) (Table 4).

NLR had an inverse correlation with albumin (rho = − 0.218, $P = 0.028$); and a direct, significant correlation with BMI kg/m^2 (rho = 0.222, $P = 0.026$). The inverse correlations between several makers of inflammation and albumin are well established [22]. It has been known that albumin levels decrease with inflammation due to reduced synthesis, increased catabolism, and translocation of albumin to extravascular pools [23]. Likewise, the direct correlation between BMI and markers of inflammation has been reported recently in hemodialysis patients [24]. This 12-month cohort study suggested that NLR values were significantly associated with parameters of nutritional status and inflammation (albumin and BMI) and hospitalizations. The lowest quartile of inflammation (NLR ≤ 1.75) predicted lower hospitalizations, and had a stronger protective effect in hemodialysis patients with diabetes than in those hemodialysis patients without diabetes.

Inflammation characterized by increased levels of proinflammatory cytokines has been recognized as having the potential for numerous complications in chronic dialysis, including mortality [25, 26]. The mechanisms behind this observation remain unclear, and they are the subject of current investigations and controversies [27, 28]. In conclusion, this study demonstrates that NLR is associated with nutritional markers (albumin, BMI) and is a predictor of hospitalizations for diabetic patients living with hemodialysis. The mechanism through which high or low inflammation influences the mortality and hospitalization rate of hemodialysis patients, however, needs further elucidation.

Limitations

The generalization of our findings to other hemodialysis populations is limited by a small sample size of participants from only one clinic facility. Despite multiple measures of NLR through 12 months, the longitudinal analyses of this marker were not performed and only baseline values were examined as predictors. This study did not compare the predictive strength of NLR with other potential inflammatory markers, such as C-reactive protein and interleukin-6, only with albumin. Further studies are needed to answer which NLR cutoff values are clinically meaningful and for which population will NLR be a better predictor of adverse outcomes.

Conclusion

Our present study supports the use of neutrophil-to-lymphocyte ratio, an inexpensive and convenient inflammation marker, as outcome predictor in hemodialysis patients. According to our results, this study provides significant information regarding hospitalization risk factors and suggests the protective effect that a low neutrophil-to lymphocyte ratio might have on the risk of hospitalizations in hemodialysis patients with diabetes.

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Compliance with ethical standards

Conflict of interest Author Janet Diaz-Martinez declares that she has no conflict of interest. Author Adriana Campa declares that she has no conflict of interest. Author Ivan Delgado-Enciso declares that he has no conflict of interest. Author Debra Hain declares that she has no conflict of interest. Author Florence George declares that she has no conflict of interest. Author Fatman Huffman declares that she has no conflict of interest. Author Marinna Baum declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. IRB Protocol Approval #: IRB-17-0198-CR01.

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Affiliations

Janet Diaz-Martinez[1] · Adriana Campa[1] · Ivan Delgado-Enciso[2] · Debra Hain[3] · Florence George[4] · Fatma Huffman[1] · Marianna Baum[1]

Adriana Campa
campaa@fiu.edu

Ivan Delgado-Enciso
ivan_delgado_enciso@ucol.mx

Debra Hain
dhain@health.fau.edu

Florence George
fgeorge@fiu.edu

Fatma Huffman
huffmanf@fiu.edu

Marianna Baum
baumm@fiu.edu

[1] Department of Dietetics and Nutrition, Robert Stempel College of Public Health and Social Work, Florida International University, 11200 SW 8th Street, Miami, FL 33199, USA

[2] Department of Molecular Medicine, School of Medicine, University of Colima, Av. Universidad 333, Colonia las Viboras, Colima, Mexico

[3] Christine E. Lynn College of Nursing, Florida Atlantic University, 777 Glades Road, Boca Raton, FL 33431, USA

[4] Department of Mathematics and Statistics, Florida International University, 11200 SW 8th Street, DM 405, Miami, FL 33199, USA