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Association between Neutrophil-Lymphocyte Ratio (NLR) and Clinical Outcomes among Filipino Patients with End-Stage Renal Disease (ESRD) Secondary to Diabetic Nephropathy on Maintenance Hemodialysis

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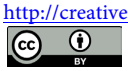

Abstract

The incidence of end-stage renal disease (ESRD) is increasing in the Philippines. The presence of diabetes mellitus further worsens ESRD prognosis. The neutrophil-to-lymphocyte ratio (NLR) is a reliable prognostic marker for mortality, but its usefulness as a prognostic biomarker in diabetes patients with chronic kidney disease is yet to be clarified. This study aimed to determine the association between NLR and morbidity among Filipino patients with end-stage renal disease (ESRD) secondary to diabetic nephropathy on maintenance hemodialysis. This was an observational descriptive, prospective cohort study that evaluated outpatient Filipino citizens aged > 18 years diagnosed with ESRD secondary to type 2 diabetes mellitus (T2DM). All patients had good compliance with their hemodialysis regimen (*i.e.*, at least twice weekly dialysis within the past 3 months). The patients were divided into two groups according to the baseline NLR value at a cut-off of 3.5 as the high NLR group (≥3.5) and the low NLR group (<3.5). The cutoff was based on data that a high NLR of ≥3.5 was correlated with increased inflammatory states leading to higher morbidity. Patients were followed up after 6 months, and data on the primary outcome measure of disease occurrence were collected. Of the 63 patients evaluated, the majority (n = 39, 61.9%) had a baseline NLR value of <3.5. The high NLR group included 24 (38.1%) patients; among them, 9 developed diseases. In the low NLR group (n = 39), only 2 patients developed disease. NLR was significantly correlated with clinical disease outcomes ($p \leq 0.05$). A baseline NLR of ≥3.5 was associated with disease occurrence. In conclusion, patients with a high baseline NLR have an increased inflammatory state and a higher risk of developing disease conditions than pa-

tients with an NLR < 3.5. Thus, the baseline NLR value can be used to predict prognosis in T2DM patients with ESRD.

Subject Areas

Nephrology, Endocrinology

Keywords

Neutrophil-Lymphocyte Ratio, Diabetic Nephropathy, Maintenance Hemodialysis, Filipino, ESRD

1. Introduction

End-stage renal disease (ESRD) is the final stage of chronic kidney disease characterized by kidney failure necessitating renal replacement therapy. The global incidence of ESRD increases annually by 8%, and more than 1.4 million ESRD patients undergo renal replacement therapy. In the Philippines, data from the 2016 Philippine Renal Disease Registry show an increasing trend in the incidence of ESRD [1]. The heightened inflammatory state in these patients contributes to the high mortality rate. Chronic inflammation plays a vital role in the initiation and progression of debilitating illnesses, including chronic kidney disease, that lead to adverse clinical outcomes [2]. The etiology of systemic inflammation in ESRD is multifactorial. Inflammation in this condition is attributed to various factors including the decreased clearance of pro-inflammatory cytokines, oxidative stress, uremic environment, leukocyte adhesion, infiltration of the vascular endothelium, dialysis-related factors, and the presence of infections [3]. Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and C-reactive protein (CRP) are among the representative inflammatory markers. However, their clinical measurement is costly [3].

The neutrophil-lymphocyte ratio (NLR) is a novel inflammatory biomarker calculated by dividing the neutrophil count by the absolute lymphocyte count. NLR has been established as a reliable prognostic marker for mortality in patients with solid organ malignancies, peripheral vascular diseases, and acute coronary syndromes [3]. However, there have been few studies on the use of NLR as a prognostic marker in diabetes patients with chronic kidney disease. The presence of comorbidities such as diabetes mellitus type II (T2DM) in ESRD is one of the leading causes of its poor prognosis. The 2018 Philippine Health Statistics ranked diabetes mellitus as the fifth leading cause of mortality in adults [4]. Chronic hyperglycemia along with the underlying inflammation in ESRD contributes to worse clinical outcomes. The survival rate of ESRD patients with DM is comparable to that of patients with cancer [5].

The NLR is a biomarker that incorporates two types of inversely related immune pathways. Specifically, it can be calculated from the differential white blood cell (WBC) count, which is a more reliable measurement than the indi-

vidual WBC count as it is less influenced by conditions that could modify the individual cell counts [6]. Given that neutrophils have short half-lives, NLR can reflect the immediate severity of systemic inflammation and can thus be used as an effective marker of acute inflammation [7]. NLR determines the balance between neutrophils (the active inflammatory component) and lymphocytes (the regulatory and "protective component). As such, a higher NLR correlates with a greater level of inflammation [8]. Okyay *et al.* conducted a large cohort study of hemodialysis patients and found that an increased neutrophil count and a decreased lymphocyte count were useful predictors of poor outcomes [9].

The 2014 Nagoya Immunity System in End-stage renal disease study concluded that a higher NLR was associated with an increased risk for cardiovascular-related events in hemodialysis patients [6]. Erdem *et al.* in 2013 and also found a higher mortality rate in dialysis patients with high neutrophil and low lymphocyte counts; they concluded that these parameters were independent predictors of mortality in hemodialysis patients [10]. In addition, the Dialysis Outcomes and Practice Pattern Study reported that patients with a lower baseline lymphocyte count and higher baseline and 6-month increase in neutrophil count had significantly higher mortality rates [10].

A 2012 study by Imtiaz showed that patients with comorbid conditions associated with a high NLR had a higher level of systemic inflammation. Endothelial dysfunction was found to be the common etiology in patients with metabolic syndrome, obesity, and diabetes. Inflammation modifies endothelial function and its capability to produce vasodilator substances such as nitric oxide, prostacyclin, and antithrombotic and anti-atherogenic properties of the vascular endothelium [11]. Inflammation interacts with malnutrition, and imbalances in protein-energy nutritional status leads to protein-energy wasting, resulting in the high mortality among hemodialysis patients [2].

Between 2008 and 2014, the top three causes of ESRD in the Philippines were diabetic nephropathy, hypertensive nephrosclerosis, and glomerulonephritis [12]. DM causes worse clinical outcomes and complications. In a study by Balta *et al.*, patients with DM had significantly higher NLRs than did the healthy control group. The NLR of the DM patients with diabetic retinopathy was also higher than those of the DM patients without diabetic retinopathy [8]. Soleymanian *et al.* reported that among hemodialysis patients, those with diabetes have worse clinical outcomes and health-related quality of life, and this was mainly attributable to the higher frequency of cardiovascular events in these patients [13]. Given this adverse impact of DM, the current study focused on DM patients with ESRD.

No standardized criteria for defining a high NLR have been established. However, a study by Neuen *et al.* showed that patients with an NLR value of more than 3.0 were significantly more likely to have diabetes and have a higher white cell count and a lower hemoglobin count [3]. A 2013 prospective cohort study by Erdem *et al.* used an NLR cutoff of 3.48 and concluded that high NLR was associated with high short-term overall mortality risk and thus may be used

as a predictor of all-cause mortality in patients with ESRD [10]. An NLR of >3.5 indicates concurrently elevated TNF-a levels [14]. The study by Han Li et al further emphasized that an NLR ≥ 3.5 was associated with high all-cause and cardiovascular death in patients on chronic hemodialysis [15].

NLR is increasingly recognized as a marker of systemic inflammation, but its prognostic value in patients with ESRD secondary to diabetic nephropathy is unknown. Thus, this study aimed to investigate the prognostic value of NLR, as a marker of systemic inflammation, and its association with clinical outcomes and all-cause morbidity and mortality in patients with ESRD secondary to DM nephropathy on maintenance hemodialysis. Particularly, we clarified the association between NLR and clinical outcomes among Filipino patients with ESRD secondary to diabetic nephropathy on maintenance hemodialysis. Towards this goal, the 6-month clinical outcomes in patients with elevated NLR (>3.5) with respect to pneumonia, acute pulmonary edema, acute coronary syndromes, catheter-related blood stream infections, urinary tract infections, hospitalizations, and duration of hospitalization were clarified.

2. Methods

2.1. Study Design and Participants

This observational, descriptive, prospective cohort study was approved by the Institutional Ethics and Review Board (IERB) of Perpetual Succour Hospital (PSH) (Approval code: 2018-007) and was conducted according to the tenets of the Declaration of Helsinki. The need for written informed consent was waived as this was only a chart review study.

This study was conducted in PSH Kidney Service, Gorordo Avenue, Cebu City, Philippines. Adult Filipino patients aged > 18 years diagnosed with ESRD secondary to DM nephropathy with good compliance to hemodialysis were evaluated. Good compliance was defined as meeting the schedule of at least twice weekly hemodialysis for at least 3 months. The exclusion criteria were ESRD secondary to other causes and presence of current infections and autoimmune disease. Patients who had a failed renal transplant and returned to hemodialysis during the study period were also excluded.

The Kidney Service of PSH had accommodated a total of 191 ESRD outpatients as of January 2018; of them, 71 patients had ESRD secondary to diabetic nephropathy.

2.2. Data Collection

Clinicodemographic data, including age, sex, height, weight, body mass index (BMI), medications, and comorbidities, of 63 eligible patients were collected from the medical records. The NLR was measured once from the routine monthly complete blood count (CBC) and then repeated after 6 months. Data collected in this study did not include personal or confidential information, and the patient's privacy was preserved.

2.3. Statistical Analysis

The primary endpoint was mortality. Data were expressed as the mean ± SD for continuous variables and as numbers (percentage) for categorical variables. In testing associations, the Chi square test was utilized with continuity correction for 2 × 2 contingency table. All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered significant.

3. Results

The mean patient age was 63.38 years (range, 35 - 87 years; standard deviation [SD], 11.107), and majority (n = 35; 55.6%) of the patients were male. Table 1 shows the baseline clinicodemographic characteristics of the patients. With respect to comorbidities, 46 (73%), 11 (17.5%), and 2 (3.2%) patients had concomitant hypertension, CAD, and chronic obstructive pulmonary disease (COPD), respectively. There were 3 (4.8%) patients with a history of cerebrovascular diseases. Overall, 58 patients had complete BMI data; of them, majority 37 (58.7%)

Table 1. Patient characteristics (n = 63).

Characteristic	n (%)
Sex	
Male	35 (55.8)
Female	28 (44.4)
Age (years), mean ± SD	63.38 ±11.107
Comorbidities (n = 63)	
Hypertension	46 (73)
Coronary artery disease	11 (17.5)
Cerebrovascular disease	3 (4.8)
Chronic obstructive pulmonary disease	2 (3.2)
Body mass index, kg/m^2 (n = 58) (WHO general population [16])	
<18.5 (Underweight)	2 (3.2)
18.5 - 24.9 (normal weight)	37 (58.7)
>25.0 - 29.9 (pre-obesity)	19 (30.2)
Medications	
Calcium carbonate (CaC03)	57 (90.5)
Erythrocyte-stimulating agent	54 (85.7)
Iron	53 (84.1)
Dipeptidyl peptidase-4 inhibitor inhibitors	37 (58.7)
Calcium channel blockers	34 (54.0)
Angiotensin receptor blockers	32 (50.8)
Antiplatelet	21 (33.3)
Angiotensin-converting enzyme inhibitor	20 (31.7)
Nitrates	16 (25.4)
Insulin	12 (19.0)
Alpha 2 agonists	9 (14.3)
Statins	6 (9.5)
Sevelamer carbonate	3 (4.8)

had a normal BMI, 19 (30.2%) patients were pre-obese, and 2 (3.2%) patients were underweight. The most commonly used medication was calcium carbonate (n = 57, 90.5%), whereas the least commonly used was sevelamer carbonate (n = 3 patients, 4.8%). The other medications were erythropoietin-stimulating agents (n = 54, 85.7%), iron supplements (n = 53, 84.1%), dipeptidyl peptidase 4 inhibitors (n = 37, 58.7%), calcium channel blockers (n = 34, 54%), angiotensin II receptor blockers (n = 32, 50.8%), antiplatelets (n = 20, 33.3%), angiotensin-converting enzyme inhibitors (n = 20, 31.7%), nitrates (n = 16, 25.4%), insulin (n = 2, 19%), alpha 2 agonists (n = 9, 14.3%), and statins (n = 6, 9.5%).

The mean neutrophil count was 63.37% (range, 38% - 91%; SD: 9.161) (Table 2), and the mean lymphocyte count was 21.18% (range, 6% - 36%; SD: 6.77). The mean NLR was 3.36 (SD: 1.66). Majority of the patients (n = 39) had an NLR value of <3.5 (61.9%); 24 participants (38.1%) had an NLR value of ≥3.5.

As shown in Table 3, there was no significant association between baseline patient characteristics and NLR. Particularly, NLR was not significantly associated with sex (p = 0.931), age (p = 0.906), and BMI (p = 0.509). Further, there were also no significant correlation between NLR and the comorbidities of hypertension (p = 0.550), CAD (p = 1.000), CVD (p = 1.000), and COPD (p = 0.275). NLR was also not correlated with the following medications: CaC03 (p = 0.283), ESA (p = 1.000), iron supplement (p = 1.000), DPPIV inhibitors (p = 0.459), calcium channel blockers (p = 0.814), ARBS (p = 0.674), ACEI (p = 1.000), nitrates (p = 0.723), insulin (p = 0.540), alpha 2 agonists (p = 0.491), statins (p = 0.487), and sevelamer carbonate (p = 0.098).

As shown in Table 4, NLR is significantly related to clinical outcomes (p = <0.05). Of the 63 patients, 39 patients had an NLR of <3.5, but only 2/39 patients (0.05%) had clinical outcomes: 1 (0.02%) patient had pulmonary edema, and the other 1 (0.02%) patient had hypertensive emergency. Meanwhile, 24/63 patients had an NLR of ≥3.5, and of 15/24 patients developed disease. Among them, 4 (0.16%), 3 (0.125%), 3 (0.125%), and 2 (0.08%), 1 (0.04%), 1 (0.04%), and 1 (0.04%) patient had diabetic foot, pneumonia, catheter-related blood stream infections, pulmonary edema, coronary artery disease, hypertensive emergency, and calciphylaxis, respectively.

4. Discussion

Evidence on the usefulness of NLR as a prognostic marker in diabetes patients with chronic kidney disease is still scarce to date. This study found that patients with a higher NLR value have an increased inflammatory state and are thus at a

Table 2. Neutrophil and lymphocyte counts.

	N	Minimum	Maximum	Mean	Standard deviation
Neutrophil (%)	63	38	91	63.37	9.161
Lymphocyte (%)	63	6	36	21.18	6.776
Ratio	63	1.17	8.20	3.3608	1.66295

Table 3. Relationship between NLR and patient characteristics.

Baseline patient characteristics	NLR < 3.5	NLR ≥ 3.5	p-value
Sex			
Male	21	14	0.931
Female	18	10	
Age			
Average	63.51	63.17	0.906
Standard deviation	10.933	11.620	
Comorbidities			
Hypertension	30	16	0.550
CAD	7	4	1.000
CVD	2	1	1.000
COPD	0	2	0.275
Body mass index (n = 58)	24.8708	25.3595	0.509
Standard deviation	5.29279	4.49710	
Medications			
$CaCO_3$	37	20	0.283
ESA	33	21	1.000
Iron	33	20	1.000
DPPIV inhibitors	21	16	0.459
Calcium channel blockers	22	12	0.814
ARBS	19	13	0.674
Antiplatelet	15	6	0.409
ACEI	12	8	1.000
Nitrates	11	5	0.723
Insulin	6	6	0.540
Alpha 2 agonists	7	2	0.491
Statins	5	1	0.487
Sevelamer carbonate	0	3	0.098

Note: Significance is set at a p-value of <0.05 alpha.

Table 4. Association between NLR and clinical outcomes.

N = 63		Outcome		Total	p-Value
		Without disease occurrence	With disease occurrence		
NLR category	Low (<3.5)	37	2	39	<0.05*
	High (≥3.5)	9	15	24	
Total		46	17	63	

*Significant difference.

higher risk of developing disease conditions. A higher NLR was significantly correlated to clinical outcomes. Of the 63 patients, 24 patients (38%) had an NLR value of ≥3.5, and 9/24 (0.37%) patients had significant outcomes while 15 (0.62%) had none.

The prognostic value of NLR was investigated from patients who are already on maintenance hemodialysis because these patients were clinically stable at this time, thus reducing the influence of other transient factors at the commencement of hemodialysis that might affect the inflammatory status [6]. The findings of this study will help clarify the prognostic value of NLR in ESRD patients and provide local data regarding the clinical outcomes and incidence of morbidity and mortality in hemodialysis patients. Further, the findings will provide local data on the relationship between NLR and worse clinical outcomes in Filipino patients with ESRD secondary to DM nephropathy on maintenance hemodialysis

A high NLR signifies two major components of chronic inflammation, that is, high neutrophil and low lymphocyte counts. A high neutrophil count is a marker of the ongoing destructive nonspecific inflammatory process, while a low lymphocyte count indicates immune regulation and a quiescent immunity pathway. Therefore, elevated NLR can reveal the functional status of the immune system during chronic inflammation [17]. The current study found that there was no correlation between NLR and medication use, consistent with a previous report that medication use does not influence the NLR [9].

Chronic inflammation is a contributing factor to the development of diabetic neuropathy. Diabetic neuropathy is the most common complication of diabetes. It has an insidious onset and is characterized by symmetrical numbness, pain, and paresthesia at an early stage, with some patients even developing foot ulcers and gangrene [17]. In this study, majority of the patients (4/24 patients) with high NLR developed diabetic foot.

5. Limitations and Recommendations

This study has some limitations. In a study by Shariq *et al.* 2016, HbA1C or glucose-bound glycated hemoglobin is a reliable diagnostic measure for chronic hyperglycemia that correlates with diabetes complications. It has been noted that HbA1C levels are directly proportional to blood glucose levels [18]. However, due to financial constraints, majority of the patients in this study did not undergo HbA1c testing. The determination of HbA1C levels in ESRD patients secondary to DM type II in relation to NLR can be recommended for future prospective studies.

In conclusion, this observational descriptive, prospective cohort study shows that a high NLR of ≥3.5 is associated with disease occurrence in patients with ESRD secondary to DM nephropathy on maintenance hemodialysis. Thus, it can be used to predict prognosis in these patients.

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Conflicts of Interest

This research is not funded. There were no financial conflicts of interest to disclose.

References

[1] Depaynos, T., *et al.* (2019) Quality of Life among End Stage Renal Disease Patients on Hemodialysis and Peritoneal Dialysis in the National Kidney and Transplant Institute. *International Journal of Nephrology and Kidney Failure*, **5**, 1-8.

[2] Catabay, C., *et al.* (2017) Lymphocyte Cell Ratios and Mortality among Incident Hemodialysis Patients. *American Journal of Nephrology*, **46**, 408-416. https://doi.org/10.1159/000484177

[3] Neuen, B.L., *et al.* (2015) Neutrophil–Lymphocyte Ratio Predicts Cardiovascular and All-cause Mortality in Hemodialysis Patients. *Renal Failure*, **38**, 70-76. https://doi.org/10.3109/0886022X.2015.1104990

[4] The 2018 Philippine Health Statistics https://doh.gov.ph/sites/default/files/publications/2018%20Philippine%20Health%20Statistics.pdf

[5] Kasper, D., *et al.* (2015) Harrison's Principles of Internal Medicine. 19th Edition, McGraw-Hill Education, USA.

[6] Kato, S. *et al.* (2015) Neutrophil/Lymphocyte Ratio: A Promising Prognostic Marker in Patients with Chronic Kidney Disease. *Inflammation and Cell Signaling*, **2**, 1-5.

[7] Malhorta, R., *et al.* (2015). Relationship of Neutrophil-to-Lymphocyte Ratio and Serum Albumin Levels with C-Reactive Protein in Hemodialysis Patients: Results from 2 International Cohort Studies. *Nephron*, **130**, 263-270. https://doi.org/10.1159/000437005

[8] Balta, S., *et al.* (2016) The Relation between Atherosclerosis and the Neutrophil-Lymphocyte Ratio. *Clinical and Applied Thrombosis/Hemostasis*, **22**, 405-411. https://doi.org/10.1177/1076029615569568

[9] Okyay, G., *et al.* (2013) Neutrophil to Lymphocyte Ratio in Evaluation of Inflammation in Patients with Chronic Kidney Disease. *Renal Failure*, **35**, 29-36. https://doi.org/10.3109/0886022X.2012.734429

[10] Erdem, E., *et al.* (2013) Neutrophil to Lymphocyte Ratio in Predicting Short-Term Mortality in Hemodialysis Patients. *Journal of Experimental and Clinical Medicine*, **30**, 129-132.

[11] Imtiaz, F., *et al.* (2012) Neutrophil Lymphocyte Ratio as a Measure of Systemic Inflammation in Prevalent Chronic Diseases in Asian Population. *International Archives of Medicine*, **5**, 2.

[12] Situational Analysis and Priority Setting. Renal Disease Control Program (ReDCoP) Department of Health-Cordillera Administrative Region 2016.

[13] Soleymanian, T., *et al.* (2017) Clinical Outcomes and Quality of Life in Hemodialysis Diabetic Patients versus Non-Diabetics. *Journal of Nephropathology*, **6**, 81-89. https://doi.org/10.15171/jnp.2017.14

[14] Turkmen, K., *et al.* (2012) The Relationship between Neutrophil-to-Lymphocyte Ratio and Inflammation in End-Stage Renal Disease Patients. *Renal Failure*, **34**,

155-159. https://doi.org/10.3109/0886022X.2011.641514

[15] Li, H., *et al.* (2017) High Neutrophil-to-Lymphocyte Ratio Predicts Cardiovascular Mortality in Chronic Hemodialysis Patients. *Mediators Inflammation*, **2017**, Article ID: 9327136. https://doi.org/10.1155/2017/9327136

[16] Body Mass Index (BMI) Classification by World Health Organization (WHO). https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations

[17] Tingting, X., *et al.* (2017) The Relationship between Neutrophil-to-Lymphocyte Ratio and Diabetic Peripheral Neuropathy in Type 2 Diabetes Mellitus. *Medicine* (*Baltimore*), **96**, e8289. https://doi.org/10.1097/MD.0000000000008289

[18] Sherwani, S.I., *et al.* (2016) Significance of HbA1C Test in Diagnosis and Prognosis of Diabetic Patients. *Biomarker Insights*, **11**, 95-104. https://doi.org/10.4137/BMI.S38440