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Neutrophil-Lymphocyte Ratio as Predictor of Mortality in Regular Hemodialysis Patients at Tabanan General Hospital

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Abstract: The risk of mortality in chronic kidney disease (CKD) patients is higher than in normal population. Inflammation has an important role in the high mortality in CKD patients undergoing hemodialysis (HD). The neutrophil lymphocyte ratio (NLR) is a simple parameter and has been widely associated with poor outcomes in HD patients but has not been widely implemented in Indonesia, especially in Bali. This research prospectively analyzed survival of 186 patients aged 18-90 years undergoing regular HD 2x/week for at least 3 months. NLR was calculated by dividing the absolute number of neutrophils and lymphocytes. The Survival test was performed by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate tests were performed to assess the prognostic impact of NLR and other clinical factors on all-cause mortality in HD patients. Mortality was found higher in the group with high NLR values (p-value 0.003). High NLR was significantly associated with all-cause mortality (HR 3.206; 95% CI 1.467 – 7.004; p value 0.003) and remained an independent factor on mortality in routine HD patients after adjustment to other variables (aHR 2.696, 95% CI 1.176 – 6.182, p-value: 0.019). In conclusion, High NLR is independently associated with all-cause mortality in CKD patients undergoing regular HD. NLR can be used as an inflammation marker that is considered easy and affordable and can be used to help determine populations that require special attention in order to reduce the mortality of patients with HD.

Keywords: neutrophil lymphocyte ratio, inflammation, mortality, chronic kidney disease, hemodialysis.

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Introduction

Chronic kidney disease (CKD) is a chronic, progressive and persistent disease and in its course can develop into a condition of terminal renal failure or end-stage renal disease (ESRD). CKD is one of the most prominent causes of death in the 21st century, affecting around 843.6 million people worldwide in 2017 (Kovesdy, 2022). Based on Indonesian Renal Registry 2018, there are 132,142 patients undergoing hemodialysis (HD), of which 66,433 patients are new patients (Perkumpulan Nefrologi Indonesia, 2018).

The risk of mortality in patients with ESRD is higher than in the normal population. The Global Burden of Disease Study reported that in 2013 as many as 956,200 deaths worldwide were directly caused by CKD increasing by 134.6% from 1990. In addition, CKD was ranked 19th as the highest cause of death in 2013 (GBD 2013 Mortality and Causes of Death Collaborators, 2015).

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Hemodialysis has long been an alternative modality of kidney transplantation to reduce and prevent the death of ESRD patients from fatal uremia. Although the mortality rate of patients undergoing HD is said to be decreasing from year to year, the survival rate is still low (Sameiro-Faria et al., 2013). There was a sharp 17% increase in adjusted mortality rate in HD patients between 2019 and 2020 after having a decrease of nearly 13% between 2010 and 2019 (United States Renal Data System, 2022).

Conditions related to uremia contribute to high mortality in HD patients, such as fluid overload, anemia, left ventricular hypertrophy, hyperphosphatemia, oxidative stress, and inflammation. Inflammation has an important role in the high mortality of ESRD patients (Ebert et al., 2020, 2021). Proinflammatory conditions, characterized by increased proinflammatory cytokines such as TNFa, IL6 and CRP, have been shown to play an important role in the process of leukocyte adhesion and infiltration to the vascular endothelium and form atherosclerosis which is the main cause of death in ESRD patients (Adejumo et al., 2016; Kamińska et al., 2019). These proinflammatory factors have an important role as predictors but cannot be used widely and routinely due to their high costs so a simple laboratory examination is needed that can provide a similar role.

The neutrophil lymphocyte ratio (NLR) has been widely studied and has a role as a marker of poor prognosis in several diseases such as malignancy, cardiovascular disease, and kidney disease (Imtiaz et al., 2012). NLR is a simple parameter that can provide functional relationship of the two fundamental white blood cell components, neutrophils and lymphocytes. Neutrophils provide an overview of the innate immune system and lymphocytes provide an overview of the adaptive immune system, hence the ability of NLR to represent systemic infection.

The function of NLR as a predictor of mortality in patients undergoing HD has not been widely implemented in Indonesia, including in Bali. This study aims to prove the role of NLR in predicting mortality among population of CKD patients undergoing HD so that the results can help determine populations that require special attention in order to reduce mortality rate in HD patients.

Materials and Methods

This research is a one-year prospective cohort study conducted at the Hemodialysis Unit of Tabanan General Hospital, Bali, Indonesia. All patients who underwent hemodialysis in April 2022 and met the inclusion criteria which were 18-90 years of age, scheduled for regular HD twice a week for 4.5 hours per session with standard bicarbonate dialysate, and had HD for at least 3 months during the cohort started were recruited. We excluded HD patients who also underwent Continuous Ambulatory Peritoneal Dialysis (CAPD), had a history of kidney transplantation, had active infections, autoimmunity, malignancy, cirrhosis of the liver, and who received aspirin, steroids, immunosuppressants and chemotherapy. Demographic and laboratory data were collected once at the start of the study, then patients were followed until event occurs (mortality) or drop out, or end of follow-up period on March 31, 2023.

The exposure variable in this study was the neutrophil-lymphocyte ratio (NLR) obtained by dividing the absolute value of neutrophils by lymphocytes. The outcome in this study was all-cause mortality. Univariate, bivariate and multivariate analysis were done. Numerical data with a normal distribution are presented in the mean with a standard deviation, otherwise are presented in median and interquartile range. We used the student's T test or the Mann Whitney test to compare means of numerical variables between the low and high NLR groups according to normality of the distribution. Comparison of categorical variables was done using the chi square or fisher's exact test. Then, we used the Kaplan-Meier method and the log-rank test to compare the survival function of low NLR and high NLR and calculated the crude and adjusted hazard ratios with Cox regression analysis. Crude and adjusted hazard ratio calculations used 95% confidence intervals. Variables with p value <0.15 in the bivariate analysis were included as confounding variables in the adjusted hazard ratio model. All tests were performed using the SPSS statistical application version 20.0.

This research has obtained ethical approval from the Research Ethics Committee of the Tabanan Regional General Hospital No: 800/0690/KEPEG/RSUD.

Result and Discussion

Of the 257 patients who underwent regular hemodialysis in April 2022, 186 patients met the criteria for this study. The average age of patients was 56.3 ± 11.1 years with most being male (59.1%) and having undergone HD for an average of 32 months and mostly using AV fistula for vascular access (86.6%). The leading cause of CKD was chronic pyelonephritis (34.4%) followed by diabetic kidney disease (21%).

The NLR cut-off value was obtained at 3.65 based on ROC analysis with a sensitivity of 63% and specificity of 66%. Based on the NLR cut-off value, 70 patients (37.6%) had high NLR values. Subjects with high NLR values tended to have lower hemoglobin values (10.0 vs 10.4 mg/dl, p value = 0.02) and had undergone HD longer than subjects with normal NLR values (55.9 vs 39.7 months, p value = 0.01) (table 1).

At the end of the study, 27 patients (14.5%) died. Mortality was found to be more prevalent in the group with high NLR (24.3%) than normal NLR (8.6%) (p value = 0.03). As many as 37% of patients died at home so the cause of death is unknown. Among subjects who died in hospital, the leading cause of death were uremic encephalopathy (27.7%) followed by sepsis (14.8%) (Figure 1). Hemoglobin and hematocrit levels in the deceased group were significantly lower than in the group that survive until the end of the study (Hb 9 vs. 10.3 mg/dl, p value 0.001; HCT 27.1 vs 30.7%, p value 0.01). Absolute lymphocyte value was also significantly lower in the deceased group. Similarly, serum creatinine value was also lower in the group who died than those who survived until the end of the study (table 2).

Analysis of survival with the Kaplan-Meier curve

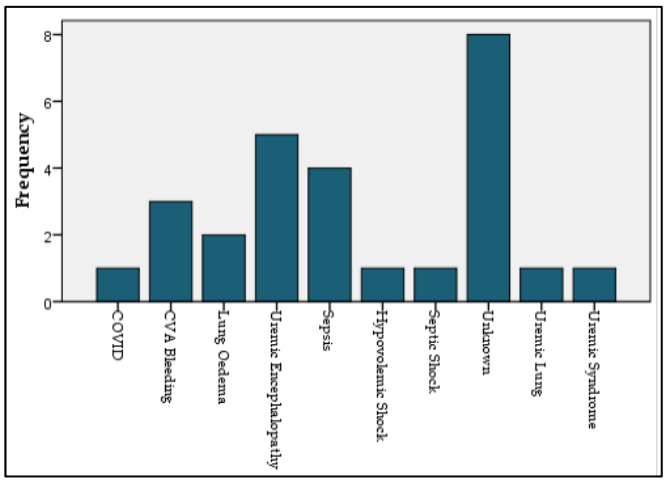

Figure 1. Cause of deaths

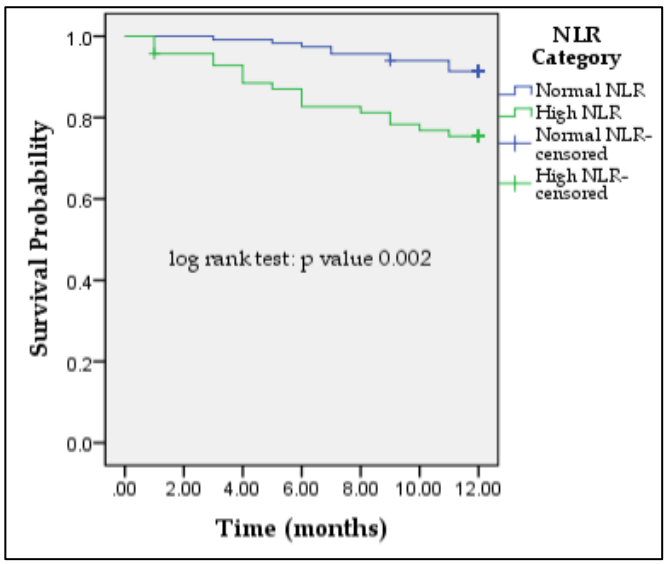

Figure 2. Kaplan-Meier curve

showed statistically significant worse survival function in subjects with high NLR at the end of the follow-up period (log-rank test p value 0.02) (Figure 2). In cox regression analysis with the crude model, high NLR was significantly associated with all-cause mortality (HR 3,206; 95% CI 1,467 – 7,004; p value 0.003) and after adjusting for age, DKD (Diabetic Kidney Disease), PNC, AV fistula vascular access, pre-HD respiratory rate, pre-HD temperature, hemoglobin, hematocrit, serum creatinine, and uric acid, NLR remained an independent factor for mortality among regular HD patients. (aHR 2.696, 95% CI 1.176 – 6.182, p value: 0.019) (Table 3).

High NLR was found in 37.6% of patients of which 24.3% died during the cohort period. Patients who underwent HD longer were found to have significantly higher NLR levels (p value 0.017). This suggests that there is a relationship between inflammation and HD duration. The longer the patient undergoes hemodialysis, themore likely the exposure to inflammation because the HD process itself causes inflammation. However, a study held at RSUD Ulin Banjarmasin showed different results where there was no relationship between inflammatory factors and the duration of hemodialysis. But in that study, the inflammatory factor used was CRP rather than NLR (Ningrum et al., 2023).

This study found that high NLR was an independent factor affecting mortality in regular HD patients, with subjects with high NLR having a 2.6 times higher risk of dying than subjects with NLR below cut-off (aHR 2,696, 95% CI 1,176 – 6,182, p value: 0.019). This result is similar to those by Han Li et. al who studied 268 HD patients and Neuen et al. that studied 170 HD patients with a 37-month follow-up that found high NLR as independent predictors of overall and cardiovascular mortality after adjusting for other risk factors (Li et al., 2017; Neuen et al., 2016). However, our study differs from the prospective cohort study conducted by Xiang et al in 355 HD patients where NLR was associated with mortality in univariate regression cox analysis only (HR 1,095; 95% CI, 1,026–1,170; P 5 0.007), and its significance disappears after adjusting for other parameters. In the study, the monocyte-lymphocyte ratio (MLR) played a greater role in mortality than NLR due to cardiovascular events (HR 6,985, 95% CI 1,943–25,115, p 0.003) as well as overall (HR 4,842; 95% CI 2,091–11,214; P<0.001). (Xiang et al., 2018)

Mild and prolonged inflammation have been considered as common comorbidities found in CKD patients, especially in patients undergoing chronic dialysis. There is strong evidence that chronic dialysis patients experience prolonged inflammation that is independently associated with negative clinical outcomes (Nowak & Chonchol, 2018). The causes of

Table 1. Characteristics of Research Subjects by NLR Category

Variable	Total (n = 186)	Normal NLR (n = 116)	High NLR (n = 70)	P value
Age, year	56.3 ± 11.1	56.7 ± 10.5	55.5 ± 12.2	0.485
Gender				
Male	110 (59.1)	65 (56)	45 (64.3)	0.267
Female	76 (40.9)	51 (44)	25 (35.7)	
Hemodialysis duration, months	32 (15 - 64)	28 (12 – 53)	38 (19.5 – 84.8)	**0.017**
CKD Etiology				
Diabetic kidney disease	39 (21)	21 (18.1)	18 (25.7)	0.217
Chronic Glomerulonephritis	18 (9.7)	10 (8.6)	8 (11.4)	0.530
Obstructive nephropathy	24 (12.9)	16 (13.8)	8 (11.4)	0.641
Urate Nephropathy*	4 (2.2)	2 (1.7)	2 (2.9)	0.632
Nephrosclerosis*	2 (1.1)	0 (0)	2 (2.9)	0.140
Nephrotic syndrome	27 (14.5)	18 (15.5)	9 (12.9)	0.618
Polycystic kidney disease*	8 (4.3)	6 (5.2)	2 (2.9)	0.712
Chronic pyelonephritis	64 (34.4)	43 (37.1)	21 (30)	0.326
Comorbidities				
Diabetes mellitus, n (%)	38 (20.4)	21 (18.1)	17 (24.3)	0.311
Hypertension, n (%)	170 (91.4)	108 (93.1)	62 (88.6)	0.286
Hepatitis B, n (%)	5 (2.7)	3 (2.6)	2 (2.9)	1.000
Hepatitis C, n (%)	4 (2.2)	1 (0.9)	3 (4.3)	0.151
Hemodialysis Access				
AV fistula	161 (86.6)	104 (89.7)	57 (81.4)	0.111
Femoral	6 (3.2)	2 (1.7)	4 (5.7)	0.200
CDL	19 (10.2)	10 (8.6)	9 (12.9)	0.355
Pre-Hemodialysis Data				
Systolic blood pressure, mmHg	140 (120 - 150)	138.5 (120 - 150)	140 (127.8 - 150)	0.165
Diastolic blood pressure, mmHg	80 (70 - 90)	77.5 (70 - 81.5)	80 (70 - 90)	0.056
Pulse frequency, times/minute	73.5 (66 - 82)	73 (66.3 - 80)	74 (65.8 - 84.3)	0.336
Respiratory rate, times/minute	20 (18 - 20)	20 (18 - 20)	20 (18 - 20)	0.738
Temperature, celcius	36.5 (36 - 36.5)	36.5 (36 - 36.5)	36.5 (36 - 36.5)	0.163
BB pre-HD, kg	58.8 (50.6 - 66.6)	58.7 (50.8 - 66.5)	58.8 (50.4 - 68.2)	0.817
Laboratory				
Hemoglobin, mg/dL	10.3 (9.2 - 11.2)	10.4 (9.6 - 11.2)	10 (8.8 - 11.05)	**0.020**
Hematocrit, %	30.5 (27.3 - 33.5)	30.8 (28.6- 33.6)	29.6 (26.4 - 32.6)	**0.014**
Platelet, x 10^3/uL	192.5 (162.8 - 228.8)	196.5 (165.3 - 232.8)	184.5 (143.8 - 225.3)	0.102
Leucocyte, x 10^3/uL	6.2 (5.1 - 7.7)	6.1 (5.2 - 7.3)	6.6 (5.1 - 8.5)	0.112
Diff count (Absolute)				
Basophils	0.04 (0.03 - 0.06)	0.04 (0.03 - 0.05)	0.04 (0.04 - 0.06)	0.108
Eosinophils,	0.4 (0.2 - 0.5)	0.4 (0.2 - 0.6)	0.3 (0.2 - 0.4)	**0.001**
Neutrophils	3.9 (3.1 - 5.2)	3.6 (2.9 - 4.7)	4.7 (3.8 - 6.6)	**0.000**
Lymphocytes	1.3 (0.9 - 1.6)	1.5 (1.2 - 1.8)	0.9 (0.7 - 1.2)	**0.000**
Monocytes	0.4 (0.3 - 0.5)	0.4 (0.3 - 0.5)	0.4 (0.3 - 0.6)	0.350
BUN	52.1 ± 12.7	51.1 ± 12.1	53.7 ± 13.7	0.201
Serum creatinine	11.3 ± 3.3	11.3 ± 3.1	11.3 ± 3.5	0.986
Uric Acid	7.1 (6.3 - 8.1)	7.1 (6.5 - 8.1)	7 (6 - 8.1)	0.685
NLR	3.2 (2.2 - 4.2)	2.4 (1.9 - 3.1)	4.7 (4.0 - 5.9)	**0.000**
Death	27 (14.5)	10 (8.6)	17 (24.3)	**0.003**

Table 2. Characteristics of Research Subjects Based on Vitality Status

Variable	Alive (n = 159)	Dead (n = 27)	P value
Age, year	55.7 ± 10.6	59.9 ± 13.6	0.135
Gender			
Male	92 (57.9)	18 (66.7)	0.389
Female	67 (42.1)	9 (33.3)	
Hemodialysis duration, months	31 (15 - 64)	37 (15 - 92)	0.534
CKD Etiology			
Diabetic kidney disease	30 (18.9)	9 (33.3)	0.088
Chronic Glomerulonephritis	14 (8.8)	4 (14.8)	0.304
Obstructive nephropathy	22 (13.8)	2 (7.4)	0.537
Urate Nephropathy*	3 (1.9)	1 (3.7)	0.469
Nephrosclerosis*	2 (1.3)	0 (0)	1.000
Nephrotic syndrome	24 (12.9)	3 (1.6)	0.771
Polycystic kidney disease*	6 (3.8)	2 (7.4)	0.328
Chronic pyelonephritis	58 (36.5)	6 (22.2)	0.149
Comorbidities			
Diabetes mellitus, n (%)	31 (19.5)	7 (25.9)	0.444
Hypertension, n (%)	146 (91.8)	24 (88.9)	0.708
Hepatitis B, n (%)	3 (1.9)	2 (7.4)	0.154
Hepatitis C, n (%)	3 (1.9)	1 (3.7)	0.469
Hemodialysis Access			
AV fistula	140 (88.1)	21 (77.8)	0.148
Femoral	5 (3.1)	1 (3.7)	1.000
CDL	14 (8.8)	5 (18.5)	0.162
Pre-Hemodialysis Data			
Systolic blood pressure, mmHg	140 (120 - 150)	137 (121 - 150)	0.645
Diastolic blood pressure, mmHg	80 (70 - 90)	78 (66 - 90)	0.615
Pulse frequency, times/minute	73 (67 - 82)	74 (62 - 84)	0.512
Respiratory rate, times/minute	20 (18 - 20)	20 (20 - 20)	**0.008**
Temperature, celcius	36.5 (36 - 36.5)	36.5 (36.5 - 36.5)	**0.044**
BB pre-HD, kg	58.8 (50.9 - 66.5)	56.5 (47.5 - 70.5)	0.607
Laboratory			
Hemoglobin, mg/dL	10.3 (9.5 - 11.2)	9 (8 - 10.4)	**0.001**
Hematocrit, %	30.7 (28.1 - 33.6)	27.1 (23 - 31)	**0.001**
Platelet, x 10^3/uL	194 (163 - 233)	184 (153 - 209)	0.278
Leucocyte, x 10^3/uL	6.2 (5.2 - 7.7)	5.8 (4.9 - 8)	0.679
Diff count (Absolute)			
Basophils	0.04 (0.03 - 0.06)	0.04 (0.03 - 0.05)	0.925
Eosinophils,	0.37 (0.25 - 0.56)	0.34 (0.2 - 0.48)	0.252
Neutrophils	3.87 (3.12 - 5.12)	3.81 (3.21 - 6.6)	0.447
Lymphocytes	1.34 (1.02 - 1.69)	1.01 (0.72 - 1.32)	**0.004**
Monocytes	0.4 (0.33 - 0.53)	0.43 (0.33 - 0.64)	0.554
BUN	52.3 ± 12.4	51.1 ±14.6	0.665
Serum creatinine	11.5 ± 3.1	10.1 ± 3.9	**0.048**
Uric Acid	7.1 (6.4 - 8.2)	6.8 (5.65 - 7.9)	0.121
NLR	3.03 (2.18 - 4.01)	3.96 (3.08 - 5.88)	**0.004**

Table 3. Hazard Ratio Analysis

NLR	Crude analysis			Adjusted analysis (*)		
	HR	95% CI	P value	HR	95% CI	P value
Normal	Ref	-	-	Ref	-	-
High	3.206	1.467 – 7.004	0.003	2.696	1.176 – 6.182	0.019

(*) data adjusted for age, DKD etiology, PNC etiology, AV fistula vascular access, pre-HD respiratory rate, pre-HD temperature, hemoglobin, hematocrit, serum creatinine, and uric acid

elevated inflammatory markers have been studied extensively in the dialysis population and are multifactorial. The HD process itself may directly affect the inflammation (Dheda et al., 2022). Some factors

influencing inflammation in dialysis include exogenous factors such as dialysis membranes, tunneled catheters, vascular grafts and unclean dialysis fluid; cellular factors such as oxidative stress and cellular aging; tissue factors such as hypoxia, changes in fluids and solutes or changes in temperature; and microbial factors such as immune dysfunction and intestinal dysbiosis; and uremic toxin retention. Another possible cause of inflammation is the detection of circulating endotoxin levels in the dialysis population. Pre-existing arterial disease, along with splanchnic vasoconstriction and/or hypotension during dialysis, is thought to compromise the blood-gut barrier, facilitate the entry of intestinal bacteria and endotoxins into the circulation, and trigger inflammation. Intestinal dysbiosis in CKD may also be an additional risk factor (Dheda et al., 2022).

Our study has several limitations, namely patients with subclinical infections or acute interdialytic infections are not well monitored, other possible factors that have the potential to affect mortality, such as nutritional status, albuminuria, cardiovascular disease, obesity, smoking, and acute kidney injury, are not assessed, and ratio measurements are only carried out at the beginning of monitoring so ratio variations over time and the effect of these variations on mortality were not assessed.

Conclusion

There was a relationship between high NLR and all-cause mortality in CKD patients undergoing routine hemodialysis. NLR can be used as an accessible and inexpensive marker of inflammation and can be used to help determine populations in need of special attention to lower mortality rate in HD population.

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