Association between neutrophil-to-lymphocyte ratio and survival rate patient hemodialysis in Adam Malik general hospital in 2016

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Abstract. Hemodialysis patients’ survival rate is influenced by many factors. Some study showed an association between the neutrophil-to-lymphocyte ratio (NLR) and the progression to ESRD. The aim of this study was to find the role of Neutrophil-to-Lymphocyte ratio in hemodialysis patients’ survival rate. It was a cohort retrospective with survival analysis to all patients undergoing dialysis in HAM hospital in January 2016. Patients were followed until December 2016 to find out whether they are dead or alive. Survival rate was as the time when the blood sample was from January 2016 until the patients die or the study stopped. The patients were mostly male (58\%) with mean age of 48 ± 13 yo, mean dialysis was 9.6 ± 3.7 months. Patients who were still alive until the study stopped were 68 persons (61\%). There was an association between NLR and patients’ survival rate with a p-value of 0.001, HR: 1.168, 95\%CI: 1.092–1.249.

1. Introduction
Chronic kidney disease (CKD) is a serious problem and associated with mortality, quality of life and high cost. World Health Organization mentioned the increasing number of CKD in 2013 about 50\% from the previous year.\textsuperscript{1,2,3,4} National basic health research 2013 calculated prevalence of CKD was 0.2\% and 60\% treated by dialysis.\textsuperscript{5} Mortality and morbidity in CKD usually caused by cardiovascular (50\%) and infection (20\%) complication. Infection associated with immune disturbance by many factors. Its known well about 30 – 50\% patient with hemodialysis has chronic systemic inflammation.\textsuperscript{6,7,8,9,10}

In CKD, inflammation may be induced by multiple causes, including dialysis-related factors such as membrane bio-incompatibility and back-filtration of endotoxins from the dialysate and non-dialysis-related factors such as non-access related infections and comorbidities. While dialysis techniques have progressively developed to decrease dialysis-related risk factors, including inflammation, the rate of infections has not diminished. The infectious disease depends on the individual patient’s conditions, including immune dysfunction, PEW, comorbid conditions, dental illness, use of immunosuppression drugs, and, not least, the presence of vascular access devices. Many patients with CKD have increased serum levels of inflammatory mediators including C-reactive protein (CRP), tumor necrosis factor-\alpha (TNF-\alpha), interleukin (IL)-6, and pentraxin-3. Monitoring CRP level is still not routine in many dialysis centers, other most of which are time-consuming and expensive.
NLR was introduced as a potential marker to determine inflammation in cardiac and noncardiac disorders has been examined as a novel measure of inflammation in distinct populations and has been showed to have prognostic and predictive values especially in those with systemic inflammation. In various cancer patients, NLR has been found to be a cost-effective biomarker to stratify the risk of recurrence and mortality.9,10,11,12,13

Complication of cardiovascular worsening as the degree of CKD from 3 – 5 times in ESRD and 20 times in hemodialysis compare to thenormal population. Patient prefers to die by cardiovascular complication to CKD own complication. Coronary artery disease increases 50% in CKD. Inflammation and oxidative stress is connected directly to pathogenesis formation and rupture of plaque.14

Inflammation of patient with CKD is caused by excess ureum level in the blood that influences immune system and risk of bacterial infection. The imbalance immune is also caused by a complication of using drugs that control adverse disease, bad nutrition, dialysis procedure and disturbance in skin and mucosa. Infection in CKD 3 times greater than thenormal population. Mortality caused by sepsis is 100 – 300 times in dialysis population. Urinary tract and skin became source of infection, besides that treatment in water dialysis, reuse dialyzer become source of infection in several patient.14

Anemia in apatient with CKD when hemoglobin<10 gr/dL (PERNEFRI, 2011). Hemoglobin decrease in dialysis, for example, losing from taking a blood sample and because of dialysis process. Latifah (2012) mentioned that group patient die has average hemoglobin less than living group.15

Survival rate patient dialysis decelerates as increasing age where good prognosis is in group < 45 yo and the worst prognosis in elderly with 5 and 10 years survival only 10 and 5% (Muzasti, 2011).

2. Methods

2.1. Participants
This study is cohort retrospective and using survival analysis. Collecting data was started in January 2016 and follow up until December 2016. Location was in HAM Hospital because it is class A and referred hospital in North Sumatera. Inclusion criteria were patients treated by hemodialysis with the complete medical record. Exclusion criteria were patient missing from follow up. All primer data were collected from medical record department in HAM hospital in January 2016 including identity, age, sex, duration dialysis, laboratory finding.

2.2. Definition of NLR
Complete blood counts with automated differential counts, which included total WBCs, neutrophils, and lymphocytes, were obtained at the time of admission. The normal value for neutrophils and lymphocytes are 2.0–7.0×10^9/l (40–80%) and 1.0–3.0×10^9/l (20–40%). NLR was calculated as the ratio of the neutrophils and lymphocytes, both obtained from the same automated blood sample at the admission of the study.10 Some study use studies used definite NLR cutoff points (e.g. NLR ≥ 2.5, NLR ≥ 2.7, NLR ≥ 3, NLR ≥ 4, and others used NLR ≥510,15. In this study, patients were separated into two groups according to a median value of NLR (group 1 NLR < 3.0 and group 2 NLR ≥ 3.0).

2.3. Statistical Method
Kaplan–Meier curves were generated to show the survival of each outcome by monocyte count quartile. Incidence rates were calculated as a number of events per 100,000 person-years, and 95% confidence intervals (95% CIs) were built on the basis of the normal distribution. Univariate analysis was performed to assess independent and non-independent variable to determine the central value (mean, median and standard deviation). The proportional hazard assumption was assessed through the use of log-negative log plots and deemed to have been met in all models. P values for trends were obtained by adding quartiles as a continuous variable to models. We repeated all analyses in a subcohort of participants with white blood cell counts between 4 and 10 thousand cells per cubic
millimeter (counts considered in the normal range). In survival analyses, a 95% CI of a hazard ratio (HR) that does not include unity was considered statistically significant. In all analyses, a P value of < 0.05 was considered statistically significant.

3. Result

The demographic and health characteristics of the overall cohort and according to NLR are in Table 1. Majority patient was male 65 person (58.0%) and female 47 persons (42%). The patient began to have dialysis < 45 yo was 42 persons (37.5%) and ≥ 45 yo was 70 persons (62.5%). The most patients started dialysis with anemia 71 persons (63.4%) and without anemia 41 persons (36.6%). Within an average year patient running dialysis 9.6 ± 3.7 month. NLR count level was both equal.

Table 1. Demographic and clinical characteristics.

| Characteristics | Number ( % ) |
|-----------------|--------------|
| Sex             |              |
| Male            | 65 (58.0%)   |
| Female          | 47 (42.0%)   |
| Age             |              |
| < 45 yo         | 42 (37.5%)   |
| ≥ 45 yo         | 70 (62.5%)   |
| Hemoglobin      |              |
| < 10 g/dl       | 71 (63.4%)   |
| ≥ 10 g/dl       | 41 (36.6%)   |
| HD vintage      | 18 month     |
| Duration HD Follow up | 9.6 ± 3.7 month |
| Leukocyte count | 7.883 ± 3.494 |
| NLR             |              |
| < 3             | 56 (50%)     |
| ≥ 3             | 56 (50%)     |

After 1 year follow up, patient alive 71 persons (63.4%) and die 41 person (36.6%) with average survival rate 9.6 month. RNL was significant associated with survival rate (p=0.001). Age (p=0.996),
sex (p=0.843) and hemoglobin (p=0.881) were not significant associated with survival rate. Statistic analysis with cox regression time independent to determine (Hazard Ratio) HR was = 1.168, 95% CI: 1.092 – 1.249.

![Graphs showing Kaplan-Meier curves for survival rate based on NLR, age, sex, and hemoglobin levels.](image)

**Figure 2.** Kaplan-Meier curve for survival rate. (a) Kaplan-Meier for RNL of survival rate; (b) Kaplan-Meier for age of survival rate; (c) Kaplan-Meier for sex of survival rate; (d) Kaplan-Meier for Hb of survival rate.

4. **Discussion**

In the observational cohort study of 1,594,700 United States veterans followed for a median of 9.16 years, graded association between monocyte count and risk of development of CKD. Prior evidence suggested that total white blood cell count predicts mortality in patients with kidney disease. Higher total white blood cell count is present in the context of infection or inflammation and associated with higher risk of hospitalization, cardiovascular events, and a host of untoward outcomes. There are no data, however, specifically linking elevated total white blood cell count with the risk of development of kidney disease and its progression.

Monitoring CRP level is still not routine in many dialysis centers worldwide, especially in the USA and Canada. Moreover, baseline CRP levels might differ among races. In addition, CRP level measured by the standard technique may not detect low-grade inflammation, especially in Japanese patients with CKD. Procalcitonin (PCT), a precursor of calcitonin and a polypeptide of 116 amino acids (molecular weight, 13 kDa), is a specific biomarker of bacterial infection. Serum PCT (sPCT) has been reported to increase during bacterial infections in patients with CKD.22

CKD has been likened to a clinical model of premature aging as we mentioned, CKD is an early aging disease, a category that also includes chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, chronic heart failure, and autoimmune diseases. The uremic phenotype is
characterized by various features of aging, such as atherosclerosis, protein-energy wasting (PEW), oxidative stress, inflammation, sarcopenia, osteoporosis, and frailty, which all play a role in the increased risk of CVD and infection. Among them, poor nutrition status and inflammation are highly prevalent and mutually entangled in patients with CKD. The condition of poor nutrition status with exhausted body stores of protein and energy, now termed as PEW, is strongly associated with inflammation in patients with CKD\(^5,23\).

Anemia is one of the many complications of chronic kidney disease (CKD). One of the lesser known functions of the kidneys is the production of erythropoietin, a signaling molecule that stimulates red blood cell production, in response to decreased oxygen levels in the blood. Any disruption of this process, e.g., secondary to a functional abnormality due to CKD, has the potential to produce anemia, a condition in which the number of circulating red blood cells, and therefore the level of hemoglobin, is lower than normal. Anemia in CKD associated with cognitive impairment, sleep disturbances, CKD progression, cardiovascular comorbidities, and higher mortality\(^14,24\). In this study, the author predicts there was association RNL and survival rate with proportional Hazard Ratio group with Hb\(>10\) mg/dl had 0.8 HR lower than the group with Hb\(<10\) mg/dl but not significant. The reasons were laboratory test was taken in January 2016 where themost patients had ever given ablood transfusion to maintenanceHb>7 mg/dl.

In this study, gender was not significantly associated with survival rate. It is same with study Carrero JJ concluded that sex did not have a predictive effect on outcome in dialysis\(^25\). Study of Manfred Hacking also proves that Women’s survival on dialysis, however, was equal to or better than men’s survival.\(^26\)

The study has several limitations. There were significant baseline differences in demographic and health characteristics according to monocyte quartiles, in which those in the highest quartile were less healthy. Demographic data: acomorbid disease like DM, hypertension, cardiovascular disease, chronic lung disease, peripheral artery disease, race, BMI etc. Longtimefollow-up and more HD center are very necessary to make the study more representative.

5. Conclusion
NLR was significantly associated with survival rate patient with hemodialysis.

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