Neutrophil to lymphocyte ratio as the main predictor of peripheral artery disease in regular hemodialysis patients

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Abstract. Cardiovascular disease is the most inducer of morbidity and mortality of chronic kidney disease (CKD) patients who have undergone dialysis. Today, neutrophil to lymphocyte ratio (NLR) is considered an indicator of the severity and extent of systemic inflammation and atherosclerosis in patients with renal and cardiovascular disorders. To examine the relationship between NLR with PAD in regular hemodialysis patients, a cross-sectional study, Ankle-Brachial Index (ABI) measurement and peripheral blood examination was on 72 regular hemodialysis patients > 6 months. The ABI value <0.9 is considered PAD. NLR >3.5 is considered abnormal based on some pre-existing research. Prevalence of PAD is 29.16%. Chi-square test showed significant correlation between NLR with PAD (p = 0.0001), multiplication of Calcium and Phosphorus (p = 0.0001), and type 2 Diabetes Mellitus (T2DM) (p = 0.039), multivariate analysis showed that NLR was an independent predictor for PAD in regular hemodialysis patients (RR = 2.271 p = 0.027). In conclusion, NLR, a new inflammatory marker of peripheral blood examination may serve as a marker of PAD in a regular hemodialysis patient, in addition to the multiplication of Calcium and Phosphorus as well as T2DM.

1. Introduction
Chronic Kidney Disease (CKD) is a health problem, associated with mortality, quality of life and increase healthcare costs. Its prevalence increased with the increasing number of patients with hypertension and diabetes mellitus. The World Health Organization (WHO) said growth some patients with kidney failure in 2013 had increased 50% from the previous year. Based on data from the Ministry of Health of the Republic of Indonesia, Riskesdas, the national prevalence of CKD patients in 2013 amounted to 0.2%.[1]

Chronic kidney disease is a pathophysiological process with diverse etiology, resulting in a progressive decline in renal function, and generally, end up with kidney failure. Also, kidney failure is a clinical condition characterized by the irreversible decline in kidney function, to a degree requiring renal replacement therapy were fixed, in the form of dialysis or kidney transplantation.[2]

Hemodialysis is the main renal replacement therapy, in addition to peritoneal dialysis and kidney transplantation in most countries in the world. There are more than 2 million patients currently undergoing hemodialysis worldwide.[2]

Cardiovascular disease is a cause of morbidity and mortality of patients with kidney disease, an estimated 43% of all causes of death. The increased risk of cardiovascular disease also occurs in
patients with CKD who had been undergoing dialysis. Atherosclerosis is an independent predictor of cardiovascular disorders as the cause and all-cause mortality in patients with CKD.[3,4,5]

Atherosclerosis is the leading cause of peripheral arterial disease, both patients with normal renal function and patients with CKD. The Atherosclerosis Risk in Communities (ARIC) study noted that there are events of 8.4 people per 1000 patients with CKD who undergo Peripheral Arterial Disease (PAD).[6]

PAD are all diseases that occur in the blood vessels of non-syndrome coronary acute after coming out of the heart and aorta-iliac, so that the blood vessels, the location of the PAP are blood vessels all four extremities, carotid arteries, renal arteries, mesenteric artery, aorta abdominal, and all the vessels that branch out from the aorta-iliac.[7]

PAD can occur due to the change in the structure or function of blood vessels. PAP is often part of the process of systemic diseases that affect multiple arterial abnormalities. The presence of PAD in an artery into a strong predictor of their PAD in other arteries, including the coronary arteries, carotid and cerebral.[7]

PAD is required to diagnose an objective examination. Doppler examination by calculating the ankle-brachial index (ABI) is very useful to know the PAD.[7]

Micro-inflammatory as a component of the syndrome Malnutrition-Inflammation-Atherosclerosis-Calcification (MIAC syndrome) also associated with the risk of cardiovascular disease in patients with CKD.[2]

Today, the ratio of neutrophils to lymphocytes (NLR), calculated as the ratio of the number of neutrophils and lymphocytes in peripheral blood is a considered indicator of the severity and extension of systemic inflammation and atherosclerosis in patients with renal impairment and cardiovascular.[2]

Based on the description above, it is necessary to investigate the relationship between inflammation with PAD through the value of NLR and the value of ABI on regular hemodialysis patients.

2. Methods
This study was observational analytic with cross sectional design, which is looking for a relationship with the independent variables and the dependent variable confounding variables by measuring instantaneous on March 2017 in Haji Adam Malik General Hospital Medan.

2.1. Population and Sample
2.1.1. Study Population. The population in this study were all patients who undergo hemodialysis in Haji Adam Malik General Hospital Medan.

2.1.2. Sample. All samples were patients undergoing hemodialysis in Haji Adam Malik Hospital in March 2017 and met the inclusion and exclusion criteria.

2.1.2.1. Inclusion and Exclusion Criteria. The inclusion and exclusion criteria were as follows:
1) Inclusion Criteria
   a. Hemodialysis patients who have undergone at least 6 months
   b. Willing to follow the peripheral blood laboratory tests and ABI measurement
2) Exclusion Criteria
   a. Patients who have a sedimentation rate of more than 60 mm/hour
   b. Patients with increased leukocyte more than 11,000/µl

2.2. Methods of Collecting Data
The data in this study are primary data from peripheral blood laboratory examination and measurement of ABI. The data collected from the sample who are willing to be the sample after getting an explanation and informed consent of study.
2.3. **Statistical Analysis**

All data were analyzed using the statistical software SPSS 22. Demographic data is in numbers and percentages, then when the normal distribution of the data will be reported in the mean ± standard deviation while when data distribution is not normal will be reported with the median values (minimum-maximum). The relationship between neutrophil to lymphocyte ratio with peripheral artery disease was analyzed using Chi-square test and multivariate using binary logistic regression analysis. The p value < 0.05 indicates significant statistically.

3. **Results**

| Table 1. Patient’s demographic characteristics (clinical characteristics). |
|---------------------------------------------------------------|
| Characteristics                                                   | Total Patient (n = 72) |
|-----------------------------------------------------------------|-----------------------|
| Gender                                                          |                       |
| Male                                                             | 50 (69.44 %)          |
| Female                                                           | 22 (30.55 %)          |
| Age                                                             | 53.5 (19-76) years old|
| NLR                                                             | 3.216 (1.000 – 7.653)  |
| ABI                                                             | 1.00 (0.9-1.12)        |
| Ca x P                                                           | 43.36 (20.02 – 121.20) |
| Hemodialysis duration                                            | 26 (6-54) months      |
| Hypertension                                                     | 64 (88.88 %)          |
| Type 2 DM                                                        | 27 (37.5 %)           |

Table 1 showed that the number of samples is 72 people with male sample of 50 people (69.44%) and female as many as 22 people (30.55%). The median age in this study was 53.5 years old with range (19-75) years old. The median ratio of neutrophils and lymphocytes was 3.216 with range (1000 - 7653). The median value of ABI is 1 with range (0.9-1.12). The mean value multiplication of Calcium-phosphorus is 43.36 with range (20.02 - 121.20). The hemodialysis duration median value is 26 months with range (6-54). In this study, the amount of hypertension patients is 64 people, and patients with type 2 diabetes are 27 people.

| Table 2. Characteristics of hemodialysis patients associated with PAD. |
|---------------------------------------------------------------|
| Variable | N | PAD (n =21) | Without PAD (n=51) | P Value | Value |
|----------|---|-------------|---------------------|---------|-------|
| Gender   |   |             |                     |         |       |
| Male     | 50| 17 (34%)    | 33 (66%)            | 0.177   | NS    |
| Female   | 22| 5 (22.72%)  | 17 (77.27%)         | 0.177   | NS    |
| Age      | 72| 50 (19-72)  | 55 (23-76)          | 0.163   | NS    |
| NLR      | 72| 4.47 (3.507 – 7.65) | 2.91(1-7.618) | 0.0001 | S     |
| Ca x P   | 72| 72.42 ± 14.53 | 37.42 ± 11.07      | 0.0001  | S     |
| Hemoduration | 72 | 27 (9-48) | 24 (6-54) | 0.080 | NS    |
| Hypertension | 64 | 21 (32%) | 43 (67.18%) | 0.056 | NS    |
| Type 2 DM | 27| 4 (14.81%)  | 23 (85.18%)         | 0.039   | S     |

Significant (p value < 0.05)
Table 2 showed that there are significant relationships between NLR (P = 0.0001), Ca x P (P = 0.039) and type 2 DM (P = 0.039) with PAD in regular hemodialysis patients. In addition, there were no differences of gender (P = 0.177), age (P = 0.163), duration of hemodialysis (P = 0.080) and hypertension variable (p = 0.056) in regular hemodialysis patients who had PAD and without PAD.

Table 3. Characteristics of hemodialysis patients associated with NLR.

| Variable      | N   | Abnormal NLR (n=29) | Normal NLR (n=43) | P    | Value |
|---------------|-----|---------------------|-------------------|------|-------|
| Gender        |     |                     |                   |      |       |
| Male          | 50  | 24 (48%)            | 26 (52%)          | 0.045| S     |
| Female        | 22  | 4 (18.18%)          | 18 (81.81%)       | 0.045| S     |
| Age           | 72  | 56 (23 - 76)        | 49 (19 – 72)      | 0.246| NS    |
| Ca x P        | 72  | 63.72 ± 20.35       | 36.78 ± 10.25     | 0.0001| S     |
| HD duration   | 72  | 27 (6 - 54)         | 24 (6 - 51)       | 0.144| NS    |
| Hypertension  | 64  | 22 (34.37%)         | 42 (65.62%)       | 0.866| NS    |
| Type 2 DM     | 27  | 7 (25.92%)          | 20 (74.07)        | 0.156| NS    |

Table 3 showed that gender, multiplication of Ca and P have a relationship with NLR, but there is no relation of age, duration of hemodialysis, hypertension and type 2 DM with NLR.

Table 4. Multivariate association of PAD in regular hemodialysis patients.

| Variable | Standard B | P value | Exp (B) | CI 95%     |
|----------|------------|---------|---------|------------|
| NLR      | 0.820      | 0.027   | 2.271   | 1.100-4.691|
Table 4 showed that NLR is the most influential variable on the occurrence of PAD with p-value<0.05 with an opportunity 2.27 times.

4. Discussion
There is a significant relationship between NLR and PAD, by the previous study from LA Garcia et al. and Teperman et al. which explained that inflammation plays a role in PAD of renal and cardiovascular disorders patients.[8,9]

In this study, there is a significant relationship between multiplication of Ca and P with PAD by Guerin AP et al. in 2000 which explained that elevated serum phosphorus and calcium levels as well as increasing the value of multiplication of calcium and phosphorus products and secondary hyperparathyroidism associated with PAD.[10]

This study showed that there is a relationship between T2DM and PAD which is corresponding to Framingham Heart Study result.[5]

5. Conclusion
There is a relationship NLR, Ca XP, type 2 diabetes patients with PAP on regular hemodialysis. NLR is an inflammatory marker of peripheral blood examination can be a marker of PAD on regular hemodialysis patients, in addition to the value of the multiplication of Ca and P as well as T2DM.

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