Prognostic importance of platelet/lymphocyte ratio and neutrophil/lymphocyte ratio in proteinuria associated with primary glomerular diseases

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ABSTRACT

Objective: Proteinuria is associated with inflammation, endothelial dysfunction, platelet activation, and progression of kidney disease. The biological mechanisms by which platelet/lymphocyte rate (PLR) and neutrophil/lymphocyte rate (NLR) variables play a role in mediating protein excretion are not fully known. Here we aimed to compare NLR and PLR variables between patients with the primary glomerular disease (PPGD) with normal estimated glomerular filtration rate (eGFR) and healthy individuals (HIs). We divided the primary glomerular disease (PGD) participants into three sub-groups according to the level of proteinuria. In addition, a comparison was made between the sub-groups of patients with PGD in terms of these variables.

Methods: This cross-sectional, double arm, single center retrospective study was performed between January 2019 and April 2020. Serum platelet, total, and differential leukocyte analyses were evaluated using an automated cell counter. Biochemical analysis and 24-hour urinalysis in order to measure protein excretion and creatinine (Cr) clearance were performed using a chemistry analyzer. Of 225 participants in the study, 111 were patients with PGD, and 114 were HIs.

Results: A statistically significant difference was found when compared with PPGD and HI participants in terms of red blood cell (RBC), hemoglobin (HGB), white blood cell (WBC), platelet, neutrophil, NLR, and PLR variables. PPGDs revealed higher median C-reactive protein (CRP) and lower median albumin levels compared to HIs. Age, gender, urea, Cr, CRP, WBC, RBC, HGB, platelet, neutrophil, lymphocyte, NLR, and PLR variables between the sub-groups of patients with PGD were not statistically significant. But, there was only a difference between the sub-groups of patients with PGD in terms of albumin levels.

Conclusions: Our data suggested that PLR and NLR can be used as predictors in PPGDs. Higher median CRP and lower median albumin levels were also associated with proteinuria in PPGDs.

Keywords: Proteinuria, neutrophil/lymphocyte rate, platelet/lymphocyte rate, primary glomerular disease, C-reactive protein, serum albumin.

INTRODUCTION

The third cause of end-stage renal disease in the United States is chronic glomerulonephritis, with a 10% portion of dialysis patients [1]. Glomerular diseases are the main cause of proteinuria. Proteinuria, in the general population, increases morbidity and mortality. Glomerulopathies progressing with proteinuria disturb protein processing in the glomerular capillary barrier, and this may worsen the progression of the disease by increasing inflammation. Increased urine protein is associated with increased T lymphocytes mediated tubulointerstitial inflammation, and T-lymphocytes are accepted as a marker for decreased kidney function [2]. Proteinuria is the important sign of renal damage, fibrosis, and glomerulosclerosis in the progression of many kidney diseases [3].

Proteinuria is also associated with platelet activation, inflammation, and endothelial dysfunction [4]. Peripheric leukocyte count is an indicator of systemic immunologic/inflammatory activity. But, information concerning the relations between peripheric leucocyte counts and proteinuria is limited [5-8]. NLR and PLR variables were mostly studied in diabetic patients [9,10]. But in primary glomerulopathies, we did not find any study with these biomarkers. NLR and PLR may be easily evaluated by a simple blood count, and they are novel inflammatory biomarkers.
This study was performed to compare NLR and PLR, as well as serum levels of HGB, RBC, WBC, neutrophil, lymphocyte, platelet, CRP, and albumin between HIs and PGDs. In addition, sub-groups of PGD patients were compared with these variables according to proteinuria status.

**MATERIAL and METHODS**

This single center, double arm, cross-sectional retrospective study was performed in accordance with the Declaration of Helsinki, with permission from the local ethics committee. Informed consents were obtained from all participants.

Study groups: We divided all participants into two main groups.

**Main group 1**: Healthy individuals (HIs); Between January 2019 and April 2020, HIs were selected from healthy volunteers to participate in this study. Demographic characteristics and clinical and biochemical data were recorded on volunteers’ admission. Patients with neoplastic diseases, hypertension, cardiovascular diseases, chronic kidney disease (CKD), endocrine diseases, hematologic diseases, inflammatory disorders, and under anticoagulant/antiaggregant therapy were all excluded from the HIs group.

**Main group 2**: It consisted of "patients with the primary glomerular disease (PPGD) " participants. Participants with PGD were also recruited between January 2019 and April 2020 from patients admitted to our nephrology clinic. Demographic characteristics and clinical and hematologic-biochemical data were recorded on patients’ admission. The inclusion criterion for the patients' group is newly diagnosed PGD with urinary protein excretion >1 g/ day, who had proteinuria for more than six months and did not take any definitive medication. The renal biopsy results of the patients with PGD were as follows: focal segmental glomerulosclerosis (FSGS) (n:22), membranous glomerulonephritis (MN) (n:45), membranoproliferative glomerulonephritis (MPGN) (n:12), minimal change disease (MCD) (n:5), and immunoglobulin A nephropathy (IgA nephropathy) (n:27).

The eGFR, serum Cr and urea values of the PGD participants were within the normal range. Exclusion criteria were the presence of chronic or systemic disorders [e.g., diabetes mellitus (DM), hypertension], as well as a history of thrombosis or active infection. During patient examination or admission (case note review has been reviewed), none of the participants reported alcohol use, smoking, use of anti-inflammatory drugs, antiaggregant, anticoagulant, antihypertensive, steroids, and immune-suppressive because all drugs may have negative effects on bone marrow and blood cells.

According to the amount of proteinuria, all PGD participants were divided into 3 groups as follows:

**Sub-group 1**: 45 participants, proteinuria amount 1-1.99 g/ day (mild proteinuria);

**Sub-group 2**: 27 participants, proteinuria amount 2-3.49 g/ day (moderate proteinuria);

**Sub-group 3**: 39 participants, proteinuria amount>3.5 g/ day (nephrotic range proteinuria).

**Laboratory tests**: Patient data, including routine biochemical parameters, complete blood count, and demographic characteristics, were obtained from medical records. Blood samples were collected after a 12-hour fasting period. RBC, WBC, neutrophil, lymphocyte, and platelet analyses were performed using blood samples that had been collected in tubes with EDTA, using an automatic blood counter (Mindray BC6800 Auto Hematology Analyzer Device [Shenzhen Mindray Bio-Medical Electronics Co.Ltd., Shenzhen, P.R, China]); HGB was quantified spectrophotometrically without cyanide using the same device. Biochemical parameters including serum urea, Cr, albumin, and CRP were analyzed by spectrophotometer using a Beckman Coulter Chemistry Analyzer AU5800 Device (Beckman Coulter Mishima K.K., Tokyo, Japan).

Patients with PGD received an explanation about how to collect a proper 24-hour urine sample. The first morning urine sample of the collection day was excluded, and 24- hour urine was collected, which included the first urine of the following day. Patients were warned to keep urine samples in a cool and dark environment. In the end, the urine containers were transferred to the laboratory within 4 hours. Urinary protein (mg/day) was analyzed by spectrophotometry using a Beckman Coulter Chemistry Analyzer AU480 Device (Beckman Coulter Mishima K.K., Tokyo, Japan).

**Definitions**: Plasma proteins are important components of blood. The kidneys play an important role in the preservation of these proteins, using kidney tubules to reabsorb the proteins passing through the glomerule filtration barrier. Herewith, the detection of abnormal types or quantities of urinary protein is considered an early indicator of severe renal or systemic disease. Proteinuria is defined as a 24-hour urinary protein excretion of more than 150 mg [11]. PGD has many causes, including MCD, MN, FSGS, IgA nephropathy, and MPGN [12].

NLR and PLR variables: They are indicated as inflammation markers in the literature. [13,14]. The NLR and PLR were calculated by dividing absolute neutrophil or platelet counts by absolute lymphocyte count [15].

**Statistical Analysis**

Statistical analysis were done with SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Numerical data were expressed as mean ± median or standard deviation (minimum-maximum), and categorical data expressed as absolute number (%). Chi-Square Test was used for categorical data, T-Test for numerical data or Mann-Whitney U Test were used as the significance test of the difference between the groups. Kruskal Wallis test was used to compare sub-groups. Tukey test was used for Post Hoc analysis. A ROC curve analysis was performed to identify the sensitivity and specificity of NLR and PLR cutoff values in prediction of proteinuria associated with PGD. Pearson Correlation Analysis was used in the correlation analysis. P <0.05 was considered statistically significant.
RESULTS

As shown in Table 1, of the 225 patients incorporated in the study, 131 (58.2%) were male, and 94 (41.8%) were female; the mean age was 36.49±11.33 years. HIs included 114 participants (75 male, 39 female) aged 18 to 79 years (mean age, 34.68±12.26 years). Male gender dominant found in the HIs (p=0.020). There was a significant difference in PPGDs compared to HIs in terms of WBC, RBC, HGB, platelet, neutrophil, NLR, and PLR variables. However, there were no statistically significant differences in lymphocytes between groups. The average age of the HIs was significantly higher than the PPGDs (p=0.019). PPGDs revealed higher median CRP and lower albumin levels in comparison with HIs (respectively p<0.001, p<0.001). Average levels of WBC, platelet, neutrophil, CRP, NLR, and PLR variables were higher, but the average levels of RBC and HGB variables were low in PGD participants. ROC analysis was completed to investigate the relationship between NLR-PLR variables and PGD. NLR; AUC: 0.60, P = 0.009; a value of 2.1 for NLR gave 58% sensitivity and 70% specificity.

Table 1: Comparison of demographic and laboratory data of the main groups

| Variable        | Total (n=225) | Healthy individuals (HIs) (n=114) | Patients with primary glomerular disease (PPGDs) (n=111) | P    |
|-----------------|--------------|-----------------------------------|-------------------------------------------------------|------|
| Gender (M/F)    | 131/94       | 75/39                             | 56/55                                                 | 0.020|
| Age (years)     | 36.49±11.33  | 38.25±8.77                        | 34.68±13.26                                           | 0.019|
| Albumin (g/dL)  | 3.94±0.84    | 4.4±0.23                          | 3.47±0.96                                             | <0.001|
| WBC (x10^9/L)   | 8.18±2.03    | 7.77±1.47                         | 8.59±2.43                                             | 0.002|
| RBC (x10^12/L)  | 4.92±0.56    | 4.99±0.49                         | 4.85±0.61                                             | 0.047|
| HGB (g/dL)      | 14.22±1.65   | 14.58±1.32                        | 13.85±1.86                                            | 0.001|
| Platelet (x10^9/L) | 272.76±78.04 | 251.66±52.28                      | 294.43±93.05                                          | <0.001|
| Neutrophil (x10^9/L) | 4.6 (1.79-15.8) | 4.3 (2.0-8.97)                    | 4.9 (1.79-15.8)                                       | 0.009|
| Lymphocyte (x10^9/L) | 2.48±0.77    | 2.47±0.66                         | 2.48±0.86                                             | 0.886|
| CRP (mg/L)      | 2.8 (0.3-11.0) | 2.1 (1-5)                         | 5.0 (0.3-11)                                          | <0.001|
| NLR             | 1.93 (0.73-17.22) | 1.83 (0.73-10.30)              | 2.14 (0.76-17.22)                                     | 0.009|
| PLR             | 105.63 (36.73-991.89) | 100.41 (51.46-242.72)             | 110 (36.73-991.89)                                    | 0.019|

Abbreviations: M: Male, F: Female, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio.

Figure 1: ROC curves for NLR and PLR. Abbreviations: ROC: receiver operator curve; NLR: neutrophil / lymphocyte rate; PLR: platelet / lymphocyte ratio

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were compared in terms of the same variables among themselves.

Table 2: Comparison of demographic and laboratory data of the subgroups

| Variable     | Total (n=111) | Sub-group 1 (n=45) | Sub-group 2 (n=27) | Sub-group 3 (n=39) | P     |
|--------------|--------------|-------------------|-------------------|-------------------|-------|
| Gender (M/F) | 56/55        | 26/19             | 9/18              | 21/18             | 0.112 |
| Age (years)  | 34.68±13.26  | 35.6±14.75        | 33.7±12.45        | 34.31±12.22       | 0.930 |
| Urea (mg/dL) | 29 (11-77)   | 32 (14-77)        | 24 (11-49)        | 30 (11-63)        | 0.196 |
| Cr (mg/dL)   | 0.70 (0.2-1.38) | 0.7 (0.23-1.2)   | 0.62 (0.2-1.28)   | 0.70 (0.2-1.38)   | 0.516 |
| Albumin (g/dL) | 3.47±0.96 | 3.95±0.85         | 3.61±0.82         | 2.81±0.81         | <0.001|
| WBC (x10^9/L) | 8.59±2.43 | 8.64±2.23         | 8.73±3.17         | 8.45±2.09         | 0.772 |
| RBC (x10^12/L) | 4.85±0.61 | 4.82±0.59         | 4.88±0.59         | 4.86±0.66         | 0.970 |
| HGB (g/dL)   | 13.85±1.86  | 13.95±1.91        | 13.62±1.68        | 13.88±1.94        | 0.747 |
| Platelet (x10^9/L) | 294.43±93.05 | 276.98±82.24 | 312.78±108.71 | 301.87±92.14 | 0.402 |
| Neutrophil (x10^9/L) | 2.47±1.79 | 5.38±1.91         | 5.55±2.40         | 5.23±1.99         | 0.722 |
| Lymphocyte (x10^9/L) | 2.49±0.87 | 2.5±0.92           | 2.49±1.01         | 2.41±0.99         | 0.621 |
| CRP (mg/L)   | 4.99±2.76   | 5.63±2.66         | 4.29±2.33         | 4.73±3.03         | 0.111 |
| NLR          | 2.15 (0.76-17.22) | 2.09 (0.76-17.22) | 2.48 (0.93-4.79) | 2.30 (0.92-8.35) | 0.722 |
| PLR          | 110 (36.73-991.89) | 102.33 (36.73-991.89) | 120.59 (67.09-278.29) | 109.31 (75.77-585.0) | 0.196 |

Abbreviations: M: Male, F: Female, Cr: Creatinine, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, CRP: C-reactive protein, NLR: Neutrophil/lvmhochtcve ratio. PLR: Platelet/lvmhochtcve ratio.

**DISCUSSION**

Primary and secondary glomerular diseases cause proteinuria. Glomerulopathy caused by secondary causes such as DM and systemic lupus erythematosus is beyond the scope of this article. The mechanisms explaining the PGD are not yet well elucidated. However, proteinuria and inflammation processes are strongly associated. The causes and mechanisms described in each disease pathology are based on predictions. As the amount of proteinuria increases, the risk of kidney damage increases, and life expectancy decreases. The secret of the mechanisms that make the kidney susceptible to damage in increasing proteinuria is unknown. The pathology of PGDs is generally complicated. Even in diagnostic renal biopsies, these diseases can be associated and/or confused, and these factors may complicate treatment. There are some unknowns that need to be clarified in the pathology of these diseases.

For this reason, the relationship between proteinuria and inflammatory processes in PGDs is the center of the studies [16-22]. Our aim in this study was to examine this mysterious pathology of primary glomerulopathy. Early prognostic predictors of proteinuria have not yet been identified. If a predictor involved in this process is found, it can shed light on the diagnosis and treatment of PGDs.

NLR and PLR variables have not been studied in PPGDs. We wanted to investigate the role of these variables in PGGD participants. Significant differences were found when HIs and PPGD groups were compared in terms of WBC, RBC, HGB, platelet, neutrophil, NLR, and PLR variables. CRP variable was significantly higher in PPGDs (p<0.001). Albumin was found significantly lower in PPGDs (p <0.001). No significant difference was found when sub-groups of PGDs were compared in terms of the same variables among themselves.

We find a relationship between NLR-PLR inflammation markers and PGDs with proteinuria. In the process of inflammation and proteinuria, with hypoalbuminemia and CRP elevation. ROC analysis showed the sensitivity and specificity of NLR and PLR in PGD with proteinuria. NLR and PLR can be used as markers in pure glomerulopathies with proteinuria. These new biomarkers can be tried during diagnosis, treatment, and follow-up.

Neutrophils secrete inflammatory mediators, and because of their short life span, neutrophilia is associated with acute inflammation during tissue injury. It was shown that neutrophil activation changes their mobility and increases adherence to the endothelium, all of which lead to capillary occlusion and tissue ischemia [23]. Probably low-grade chronic inflammation, together with other risk factors, lead to increased oxidative stress, vascular damage, endothelial dysfunction, and increased production of cytokines and growth factors, and finally causes renal injury and proteinuria. Where are NLR and PLR involved in the inflammation and proteinuria process? How do changes occur as the amount of proteinuria increases? Due to their similarity to our study, we would like to discuss about previous studies (when we scanned the English literature in detail, we found six studies) on the relationship between these variables and proteinuria.

Afsar B et al. [9], the relationship between proteinuria and NLR in newly diagnosed type-2 DM patients was evaluated, and a significant correlation was determined between proteinuria and neutrophil, lymphocyte, and NLR, and they emphasized NLR as a marker for proteinuria independent of other risk factors in patients with newly diagnosed type-2 DM.
The relationship between proteinuria and NLR in this study supports our study. The difference of our article from this study is that the compared patient group includes PGD participants, and the studied markers are PLR together with NLR.

Another study by Binnetoğlu E et al. [14] on chronic kidney disease (CKD) patients without DM evaluated the relationship between proteinuria and NLR. It was emphasized that NLR is a prognostic marker for the presence and degree of proteinuria. In this study, unlike the participants in our study, CKD participants were included, and only NLR was studied. Similar to our study, this study also supports the relationship between proteinuria and NLR.

In the study by Emokpae MA et al. [24], the NLR and PLR correlated with the measured traditional inflammatory markers in sickle cell anemia (SCA) patients, with values increasing in SCA patients with macroalbuminuria, and the highest levels were seen in those with impaired renal function. This study highlights the relationship between proteinuria and NLR. The participant group studied is different. Here, similar to our study, the NLR and PLR markers have been studied together. The significance of these markers strongly supports our study.

Yılmaz G et al. [25] investigated the relationship of mean platelet volume (MPV) and NLR with inflammation and proteinuria in patients with CKD Stage 3-4. Their study showed that the NLR is high in the CKD group and is correlated with uric acid and proteinuria, which are known to be associated with atherosclerosis, in patients with CKD. They thought that NLR might be a determinant of inflammation and atherosclerosis in patients with CKD. The participant group in this study is different. MPV was added to the studied NLR marker. This study is different from our study in these aspects. But the relationship between NLR and proteinuria supports our study. Another difference of our study is that PLR was added to the NLR.

Kutlugun AA et al. [15] evaluated the association between NLR, PLR, and microalbuminuria in patients with normal eGFR. Higher NLR levels were found in microalbuminuric patients with normal eGFR. This study is very similar to our study. The markers studied are the same. The patient group is not PGD but microalbuminuric patients. The fact that there is a relationship between proteinuria and NLR-PLR supports the strength of our study.

Kawamoto R et al. [26] examined the relationship between NLR and eGFR and urinary albumin excretion. Their data showed that NLR might be an important factor for evaluating patients with a higher degree of albuminuria among diabetic outpatients. The relationship between NLR and albuminuria in this study supports our study. Differently, the participant patient group consisted of DM participants. The patient group of our study was different, and NLR and PLR markers were studied together.

There were some unique features in the present study. Unlike the studies mentioned above, NLR and PLR were investigated in PGD participants. Patients in our study had proteinuria; the amount of urine protein was at least >1 g/day). Causative diseases included were PGDs, while secondary or systemic causes (e.g., diabetes, lupus) were excluded. Therefore, the patients in this study had pure glomerular diseases. Their diagnosis has been proven by renal biopsy.

Our study has some limitations. One limitation of this study was its cross-sectional design, which limited its ability to infer a causal relationship between total and differential blood counts and inflammation and proteinuria. Besides, analyses were based on a single measurement of total and differential blood counts that may not reflect the relation over time. It would be interesting to measure the serial changes of total and differential blood counts to further clarify the role of WBCs-platelets and sub-populations for the development of inflammation and proteinuria. Secondly, when 111 glomerulopathy participants are grouped among themselves, the number of participants in the sub-groups decreases. The roles of NLR and PLR variables are hidden. If the number of participants in this subgroup was high, the roles of these variables could become evident in severe proteinuric glomerulopathies. However, there was a significant difference between PPGD and HIs in terms of both variables. We aimed to examine the study from this aspect. Third, because our study was retrospective, gender and age matching could not be made. We could not analyze the effect of these variables on the results. Fourth the cut-off values for leukocyte, platelet, and lymphocyte ratios, known as inflammatory markers, are unknown. In similar studies, the limit values of the variables mentioned were not determined.

CONCLUSION

Neutrophils, lymphocytes, and platelets, which are simply examined in the blood count, have important roles in the inflammation process. Their subtypes and rates can guide the inflammation process. We found that WBC, RBC, HGB, platelet, neutrophil, NLR, and PLR levels were statistically significant in primary glomerulopathies. If cut-off values were known, NLR and PLR could be used as predictors in glomerulopathies. Higher median CRP and lower median albumin levels were also associated with proteinuria in PPGDs.

Author Contributions: ZK: Project design, Patient examinations. Data analyses and Literature review. ZK: Manuscript preparation, Revisions.

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Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional research committee.

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