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ASSOCIATION BETWEEN PLATELET LYMPHOCYTE AND NEUTROPHIL-LYMPHOCYTE RATIO WITH MORTALITY AND PROGNOSIS IN SUBJECTS WITH RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS: A CLINICAL STUDY

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ABSTRACT

Background*:* RPGN (Rapidly progressive glomerulonephritis) is a clinical syndrome characterized by the features of progressive renal function loss and nephritic syndrome features in a short period.

Aims: The present study was conducted to assess the relationship between pathological findings of renal biopsy, prognostic factors, PLR (platelet-to-lymphocyte ratio), and NLR (neutrophil-to-lymphocyte ratio) in subjects with RPGN (Rapidly progressive glomerulonephritis).

Methods: The present retrospective study analyzed the subjects having newly diagnosed RPGN (Rapidly progressive glomerulonephritis) and had data for the past 6 months minimum were assessed. eGFR (estimated glomerular filtration rate) was evaluated for all the study subjects along with CRP/albumin ratio, CRP (C-reactive protein) levels, and albumin levels.

Results: Significantly higher values in primary crescentic subjects were seen for ferritin, CRP/albumin ratio, CRP, albumin, creatinine, neutrophils, and WBC with respective values of 453.56±79.52ng/ml, 28.43±6.73, 72.87±16.07 mg/dl, 2.87±±0.13 g/dl, 4.47±0.42 mg/dl, 7919.52±620.06 10^3/ul, and 10337.52±652.76 10^3/ul, whereas, significantly lower values in primary crescentic were seen compared to secondary crescentic for MDRD-GFR with values

for primary and secondary crescentic was 26.64±4.03 and 56.62±8.25 respectively. Hematuria, proteinuria, BUN, PLR, NLR, hematocrit, hemoglobin, platelet count, and lymphocytes showed statistically non-significant differences between primary crescentic and secondary crescentic groups with 39 and 13 subjects respectively. Fibrocellular crescent had respective values of 19.19±5.47 and 10.53±2.47 for dialysis dependency and non-dependency and for sclerotic glomeruli, these values were 3.32±1.34 and 1.63±0.36 respectively. A significant correlation was seen for dialysis dependency in fibrocellular crescent and sclerotic glomeruli with a p-value of <0.05

Conclusion: This present study concludes that mortality in subjects with RPGN (Rapidly progressive glomerulonephritis) can be accurately predicted with NLR with the correlation of systemic inflammation. A negative correlation was seen with fibrocellular crescents percentage and can be considered as a measure for glomerular inflammatory condition. Also, PLR (platelet-to-lymphocyte ratio) can be taken as an indicator for assessing disease severity in the acute phase of crescentic glomerulonephritis.

Keywords Crescentic glomerulonephritis, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, renal pathology, RPGN

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is a rare clinical entity with the incidence ranging between 4%-10% in all the subjects undergoing renal biopsy. RPGN is commonly associated morphologically with the formation of the extensive crescent in the Bowman's space. On histopathologic examination, crescentic glomerulonephritis shows three different types where type 1shows linear deposition of immunoglobulin G (IgG) throughout the glomerular basement membrane (GBM; anti-GBM disease), type 2: granular deposits (immune complex disease), and type 3: absence of immunoglobulins is characteristic of pauci-immune GN seen in patients with systemic vasculitis. The disease severity in crescentic GN subjects is associated with the crescent formation degree where advanced renal failure and non-responsiveness to immunosuppressant therapy is seen in subjects with circumferential crescents in >80% of the glomeruli, whereas, in subjects with <50% crescent of glomeruli and non-circumferential crescent shows more remission and indolent cruising.[1]

In the active inflammation stage, the cellular crescent is seen usually after fibrous and fibrocellular crescent formation. This is a clinically vital transition as fibrous crescent shows a disease stage that is non-responsive to immunosuppressive therapy. When non-treated, crescentic glomerulonephritis shows poor clinical outcomes where the majority of the subjects either die or progress to ESRD (end-stage renal disease) within a few months of the disease. Hence, the treatment plan must be planned carefully as the disease rapidly progress from diagnosis to end-stage disease. However, even after aggressive treatment, rapid ESRD development and dialysis dependency is commonly seen.[2]

With the advances in the knowledge about the disease and the factors affecting the disease diagnosis, physicians can plan the treatment effect for the individual and reduce the mortality and morbidity associated with crescentic glomerulonephritis. Factors considered as predictive for the prognosis of crescentic GN are time since diagnosis, interstitial fibrosis, tubular atrophy, anti-GBM antibodies in GBM, fibrinoid necrosis, the crescent of >80% glomeruli,

dialysis dependence at the admission time, raised serum creatinine at the admission time, and anuria or oliguria presence. However, the typical prognostic factors that would predict renal function.[3]

TLC (Total Leucocyte Counts) shows a sensitive and rough estimate of the inflammatory state with easy availability and low cost. The previous literature data also suggest that few subtypes specific for leucocytes have high predictive values for assessing cardiovascular risk and poor prognosis in various disorders compared to WBC counts. NLR marks the poor prognosis for various disorders including myocardial infarction, chronic kidney disease, and/or malignancies. Also, PLR is linked to poor prognosis in various disorders including breast cancer and acute coronary syndrome. Previous literature data established both PLR and NLR as inflammatory markers in subjects with ESRD.[4]

CRP (C-reactive protein) and ESR (Erythrocyte sedimentation rate) are the acute phase reactants that signify inflammation and are used to assess disease activity in subjects with crescentic GN with a limited role in prognosis or disease extent prediction. The present study was conducted to assess the relationship between pathological findings of renal biopsy, prognostic factors, PLR (platelet-to-lymphocyte ratio), and NLR (neutrophil-to-lymphocyte ratio) in subjects with RPGN (Rapidly progressive glomerulonephritis).

MATERIALS AND METHODS

The present study was conducted to assess the relationship between pathological findings of renal biopsy, prognostic factors, PLR (platelet-to-lymphocyte ratio), and NLR (neutrophil-to-lymphocyte ratio) in subjects with RPGN (Rapidly progressive glomerulonephritis). The study was conducted after obtaining clearance from the concerned Ethical committee. The study population was comprised of the subjects visiting the Outpatient Departments of the Institute. The control group for the present study was subjected to comparable age and gender with blood pressure within the normal limits who visited the Medicine Department of the Institute with no kidney disease or inflammatory disease.

Reports of the renal biopsy were assessed for all the 289 subjects with the confirmed diagnosis on biopsy. The inclusion criteria for the study were the presence of a minimum of one fibrocellular or cellular crescent. Renal biopsies were conventionally processed using immunofluorescence and microscopy. Clinicopathologic correlation helped in confirming the diagnosis. The clinical data and medical records were assessed for all the subjects including management, laboratory findings, clinical features, demographic data, and follow-up records.

Clinical outcomes and treatment details including mortality, inflammatory markers, dialysis status, proteinuria, and renal function were assessed at admission, at 1 month, 3 months, and 6 months. The calculation of eGFR (estimated glomerular filtration rate) was done with Modification of Diet in Renal Disease Study equation.[5] Reduced GFR was defined by GFR of <60 ml/min/1.73 m2. Along with inflammation, the nutritional status of the study subjects was assessed to assess the disease activity. For this, apart from CRP and albumin individually, their ratio was also assessed.

The collected data were subjected to the statistical evaluation using SPSS software version 21 (Chicago, IL, USA) for results formulation. The data were expressed in percentage and number. The level of significance was kept at $p<0.05$.

RESULTS

The present study was conducted to assess the relationship between pathological findings of renal biopsy, prognostic factors, PLR (platelet-to-lymphocyte ratio), and NLR (neutrophil-to-lymphocyte ratio) in subjects with RPGN (Rapidly progressive glomerulonephritis). The study included 52 subjects and 42 controls. The demographic and disease characteristics of the study subjects are listed in Table 1. It was seen that the mean age of controls and patients was 49.18±2.10 and 48.94±2.71 years respectively. Hematuria, proteinuria, and ferritin were seen in the subjects only with respective values of 185.74±50.69/HPF, 4327.31±682.04 mg/gun, and 375.14±64.63 ng/ml. Significantly lower values were seen in subjects for MDRD-GFR, Albumin, hematocrit, hemoglobin, and lymphocytes with respective values of 34.37±4.07, 2.78±0.08, 30.05±0.73, 10.06±0.26, and 1401.46±91.22 against 103.53±4.31, 4.26±0.78, 42.11±0.94, 13.94±0.38, and 2466.82±127.94 for controls. The values significantly higher in subjects were CRP/albumin ratio, CRP, creatinine, BUN, NLR, platelet, neutrophils, and WBC with respective values of 24.24±5.96, 61.99±14.37, 4.07±0.34, 50.72±3.07, 277962.94±13749.64, 7420.95±395.17, and 9720.16±587.72 respectively (Table 1).

On assessing the demographic and disease characteristics in the primary crescentic and secondary crescentic subjects significantly higher values in primary crescentic subjects were seen for ferritin, CRP/albumin ratio, CRP, albumin, creatinine, neutrophils, and WBC with respective values of 453.56±79.52ng/ml, 28.43±6.73, 72.87±16.07 mg/dl, 2.87±±0.13 g/dl, 4.47±0.42 mg/dl, 7919.52±620.06 10^3/ul, and 10337.52±652.76 10^3/ul, whereas, significantly lower values in primary crescentic were seen compared to secondary crescentic for MDRD-GFR with values for primary and secondary crescentic was 26.64±4.03 and 56.62±8.25 respectively as shown in Table 2. Hematuria, proteinuria, BUN, PLR, NLR, hematocrit, hemoglobin, platelet count, and lymphocytes showed statistically non-significant differences between primary crescentic and secondary crescentic groups with 39 and 13 subjects respectively (Table 2).

Concerning the correlation between dialysis dependency and histopathologic renal biopsy findings in the study subjects at the time of admission, it was seen that for fibrinoid necrosis mean values of 19.54±6.08 and 10.47±3.56 for dialysis dependency and non-dependency. Fibrous crescent had 3.19±1.61 and 4.27±1.84 values for dialysis dependency and non-dependency and cellular crescent had respective values of 39.37±6.67 and 16.72±3.34 for dialysis dependency and non-dependency. These values were statistically non-significant for fibrinoid crescent, fibrous crescent, and cellular crescent with $p>0.05$. Fibrocellular crescent had respective values of 19.19±5.47 and 10.53±2.47 for dialysis dependency and non-dependency and for sclerotic glomeruli, these values were 3.32±1.34 and 1.63±0.36 respectively. A significant correlation was seen for dialysis dependency in fibrocellular crescent and sclerotic glomeruli with a p-value of <0.05 as depicted in Table 3.

DISCUSSION

The present study was conducted to assess the relationship between pathological findings of renal biopsy, prognostic factors, PLR (platelet-to-lymphocyte ratio), and NLR (neutrophil-to-lymphocyte ratio) in subjects with RPGN (Rapidly progressive glomerulonephritis). The study included 52 subjects and 42 controls. It was seen that the mean age of controls and patients was 49.18±2.10 and 48.94±2.71 years respectively. Hematuria, proteinuria, and ferritin were seen in the subjects only with respective values of 185.74±50.69/HPF, 4327.31±682.04 mg/gun, and 375.14±64.63 ng/ml. Significantly lower values were seen in subjects for MDRD-GFR, Albumin, hematocrit, hemoglobin, and lymphocytes with respective values of 34.37±4.07, 2.78±0.08, 30.05±0.73, 10.06±0.26, and 1401.46±91.22 against 103.53±4.31, 4.26±0.78, 42.11±0.94, 13.94±0.38, and 2466.82±127.94 for controls. The values significantly higher in subjects were CRP/albumin ratio, CRP, creatinine, BUN, NLR, platelet, neutrophils, and WBC with respective values of 24.24±5.96, 61.99±14.37, 4.07±0.34, 50.72±3.07, 277962.94±13749.64, 7420.95±395.17, and 9720.16±587.72 respectively. These demographics and disease characteristics were comparable to the studies of Yaprak M et al[6] in 2016 and Maraj M et al[7] in 2018 where authors assessed subjects with comparable demographics as in the present study.

Concerning the assessment of the demographic and disease characteristics in the primary crescentic and secondary crescentic subjects significantly higher values in primary crescentic subjects were seen for ferritin, CRP/albumin ratio, CRP, albumin, creatinine, neutrophils, and WBC with respective values of 453.56±79.52ng/ml, 28.43±6.73, 72.87±16.07 mg/dl, 2.87±±0.13 g/dl, 4.47±0.42 mg/dl, 7919.52±620.06 10^3/ul, and 10337.52±652.76 10^3/ul, whereas, significantly lower values in primary crescentic were seen compared to secondary crescentic for MDRD-GFR with values for primary and secondary crescentic was 26.64±4.03 and 56.62±8.25 respectively. Hematuria, proteinuria, BUN, PLR, NLR, hematocrit, hemoglobin, platelet count, and lymphocytes showed statistically non-significant differences between primary crescentic and secondary crescentic groups with 39 and 13 subjects respectively. These results were consistent with the results of Turkmen K et al[8] in 2014 and Ozcicek A et al[9] in 2017 where authors reported the results as of the present study for the difference in demographic and disease characteristics of the primary crescent and secondary crescent subjects.

On assessing the correlation between dialysis dependency and histopathologic renal biopsy findings in the study subjects at the time of admission, it was seen that for fibrinoid necrosis mean values of 19.54±6.08 and 10.47±3.56 for dialysis dependency and non-dependency. Fibrous crescent had 3.19±1.61 and 4.27±1.84 values for dialysis dependency and non-dependency and cellular crescent had respective values of 39.37±6.67 and 16.72±3.34 for dialysis dependency and non-dependency. These values were statistically non-significant for fibrinoid crescent, fibrous crescent, and cellular crescent with $p>0.05$. Fibrocellular crescent had respective values of 19.19±5.47 and 10.53±2.47 for dialysis dependency and non-dependency and for sclerotic glomeruli, these values were 3.32±1.34 and 1.63±0.36 respectively. A significant correlation was seen for dialysis dependency in fibrocellular crescent and sclerotic glomeruli with a p-value of <0.05. These findings were in agreement

with the findings by Emiroglu N et al[10] in 2017 and Quin G et al[12] in 2016 where fibrocellular crescent and sclerotic glomeruli showed significant dialysis dependency.

CONCLUSION

Within its limitations, the present study concludes that mortality in subjects with RPGN (Rapidly progressive glomerulonephritis) can be accurately predicted with NLR with the correlation of systemic inflammation. A negative correlation was seen with fibrocellular crescents percentage and can be considered as a measure for glomerular inflammatory condition. Also, PLR (platelet-to-lymphocyte ratio) can be taken as an indicator for assessing disease severity in the acute phase of crescentic glomerulonephritis. However, the present study had a few limitations including a smaller sample size, geographical area biases, recall bias, and single-institution nature. Hence, more longitudinal and prospective studies with larger sample sizes, and longer monitoring periods are needed to reach a definitive conclusion.

REFERENCES

1. Kocyigit I, Eroglu E, Unal A, Sipahioglu MH, Tokgoz B, Oymak O, *et al*. Role of neutrophil/lymphocyte ratio in prediction of disease progression in patients with stage-4 chronic kidney disease. *J Nephrol* 2013;*26*:358-65.
2. Ayça B, Akin F, Çelik Ö, Yüksel Y, Öztürk D, Tekiner F, *et al.* Platelet to lymphocyte ratio as a prognostic marker in primary percutaneous coronary intervention. *Platelets.* 2015;*26*:638-44.
3. Krenn-Pilko S, Langsenlehner U, Thurner EM, Stojakovic T, Pichler M, Gerger A, *et al.* The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. *Br J Cancer.* 2014;*110*:2524-30.
4. Kaplan M, Ates I, Akpinar MY, Yuksel M, Kuzu UB, Kacar S, *et al.* Predictive value of C-reactive protein/albumin ratio in acute pancreatitis. *Hepatobiliary Pancreat Dis Int.* 2017;*16*:424-30.
5. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;*150*:604-12.
6. Yaprak M, Turan MN, Dayanan R, Akın S, Değirmen E, Yıldırım M, *et al.* Platelet-to-lymphocyte ratio predicts mortality better than neutrophil-to-lymphocyte ratio in hemodialysis patients. *Int Urol Nephrol* 2016;*48*:1343-8.
7. Maraj M, Kuśnierz-Cabala B, Dumnicka P, Gala-Błądzińska A, Gawlik K, Pawlica-Gosiewska D, *et al*. Malnutrition, inflammation, atherosclerosis syndrome (mia) and diet recommendations among end-stage renal disease patients treated with maintenance hemodialysis. *Nutrients.* 2018;*10*:pii.E69.
8. Turkmen K, Ozcicek F, Ozcicek A, Akbas EM, Erdur FM, Tonbul HZ. The relationship between neutrophil-to-lymphocyte ratio and vascular calcification in end-stage renal disease patients. *Hemodial Int* 2014;*18*:47-53.
9. Ozcicek A, Ozcicek F, Yildiz G, Timuroglu A, Demirtas L, Buyuklu M, *et al.* Neutrophil-to-lymphocyte ratio as a possible indicator of epicardial adipose tissue in patients undergoing hemodialysis. *Arch Med Sci* 2017;*13*:118-23.

10. Emiroglu N, Cengiz FP, Bahalı AG, Ozkaya DB, Su O, Onsun N, *et al.* Red blood cell distribution width and neutrophil-to-lymphocyte ratio in patients with cutaneous vasculitis. *Ann Clin Lab Sci* 2017;*47*:162-5.
11. Qin G, Tu J, Liu L, Luo L, Wu J, Tao L, *et al.* Serum albumin and C-reactive protein/Albumin ratio are useful biomarkers of Crohn's disease activity. *Med Sci Monit* 2016;*22*:4393-400.

TABLES

Characteristics	Subjects (n=52)	Controls (n=42)
Mean age (years)	48.94±2.71	49.18±2.10
Haematuria (/HPF)	185.74±50.69	
Proteinuria (mg/gun)	4327.31±682.04	
Ferritin (ng/ml)	375.14±64.63	
MDRD-GFR	34.37±4.07	103.53±4.31
CRP/albumin ratio	24.24±5.96	0.66±0.62
CRP (mg/dl)	61.99±14.37	2.72±0.22
Albumin (g/dl)	2.78±0.08	4.26±0.78
Creatinine (mg/dl)	4.07±0.34	0.76±0.34
Blood urea nitrogen (mg/dl)	50.72±3.07	12.27±0.62
Glucose (mg/dl)	101.35±2.86	102.58±7.38
PLR	273.92±39.13	99.66±5.28
NLR	7.04±0.88	1.72±0.13
Hematocrit (%)	30.05±0.73	42.11±0.94
Hemoglobin (g/dl)	10.06±0.26	13.94±0.38
Platelet count (10^3/ul)	277962.94±13749.64	234920.02±10361.92
Lymphocytes (10^3/ul)	1401.46±91.22	2466.82±127.94
Neutrophils (10^3/ul)	7420.95±395.17	4050.85±218.16
WBC (10^3/ul)	9720.16±587.72	6455.62±310.17
Diastolic Blood pressure (mmHg)	79.18±1.49	77.18±1.78
Systolic Blood pressure (mmHg)	128.96±2.63	117.62±4.94

Table 1: Demographic and disease characteristics in the control and patients in the study

Characteristics	Primary crescentic (n=39)	Secondary crescentic (n=13)
Mean age (years)	52.24±2.81	36.62±5.74
Hematuria (/HPF)	165.74±68.86	157.52±32.03
Proteinuria (mg/gun)	4027.31±803.14	3912.34±1325.76
Ferritin (ng/ml)	453.56±79.52	131.02±31.18
MDRD-GFR	26.64±4.03	56.62±8.25
CRP/albumin ratio	28.43±6.73	2.26±1.67
CRP (mg/dl)	72.87±16.07	4.64±4.19

Albumin (g/dl)	2.87±±0.13	2.44±0.24
Creatinine (mg/dl)	4.47±0.42	2.95±0.74
Blood urea nitrogen (mg/dl)	53.24±3.44	43.66±6.36
PLR	244.19±23.56	358.82±136.33
NLR	6.75±0.68	7.72±2.71
Hematocrit (%)	29.55±0.74	31.51±1.83
Hemoglobin (g/dl)	9.87±0.27	10.47±0.62
Platelet count (10^3/ul)	268400.02±18012.22	253857.12±11474.24
Lymphocytes (10^3/ul)	1457.52±106.03	1241.44±178.36
Neutrophils (10^3/ul)	7919.52±620.06	5996.44±1027.69
WBC (10^3/ul)	10337.52±652.76	7957.16±1206.66

Table 2: Comparison of demographic and disease characteristics in the primary and secondary crescentic study subjects at baseline

Histopathologic features	Dependency on dialysis	Mean± S. D
Fibrinoid Necrosis	Dependent	19.54±6.08
	Non-dependent	10.47±3.56
Fibrous Crescent	Dependent	3.19±1.61
	Non-dependent	4.27±1.84
Fibrosellular crescent	Dependent	19.19±5.47
	Non-dependent	10.53±2.47
Cellular crescent	Dependent	39.37±6.67
	Non-dependent	16.72±3.34
Sclerotic Glomeruli	Dependent	3.32±1.34
	Non-dependent	1.63±0.36

Table 3: Correlation between dialysis dependency and histopathologic renal biopsy findings in the study subjects at the time of admission