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A new parameter predicting steroid response in idiopathic IgA nephropathy: a pilot study of pan-immune inflammation value

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Abstract. – OBJECTIVE: In this pilot study, we aimed at investigating the predictive power of pan-immune inflammation value (PIV) on response rates at 6 months in idiopathic IgA nephropathy (IgAN) patients who started steroids.

PATIENTS AND METHODS: The study was conducted with patients diagnosed with idiopathic IgAN and treated with 3-6 months of conservative treatment and steroid therapy started because proteinuria was above 1 g/day. Patients with proteinuria lower than 0.3 g/day, no macroscopic hematuria, and no hematuria detected in 3 consecutive urinalyses for 6 months were considered to be patients in remission. PIV was calculated by [neutrophil count (10^3 µL)*platelet count (10^3 µL)*monocyte count (10^3 µL)]/[lymphocyte count (10^3 µL)]. Patients were compared according to their remission status in terms of PIV.

RESULTS: The mean PIV was significantly higher in patients in the non-remission group than in patients in the remission group (1,869.2±1,781.9 to 574.1±364.5, respectively). The best cut-off for PIV was 752.6 to predict non-remission with a 75% sensitivity and 71.4% specificity.

CONCLUSIONS: Our study showed that PIV is a reliable marker for predicting steroid response at the 6th month in patients with idiopathic IgAN.

Key Words:
IgA nephropathy (IgAN), Pan-immune inflammation value (PIV), Steroids, Treatment.

Introduction

IgA nephropathy (IgAN) is an autoimmune kidney disease characterized by IgA deposits in the mesangial areas of the glomeruli[1]. IgAN is one of the most common causes of primary glomerulonephritis in the world[2-4]. The Oxford classification of IgAN (also known as MEST-C scoring) is a pathological scoring system developed by the International IgAN Network and used to predict renal outcomes in IgAN patients[5]. The International IgAN Prediction Tool was developed because the Oxford classification only includes pathological features and does not include some parameters that have been clinically proven to be associated with poor kidney outcomes[6,7]. However, it is known that the International IgAN Prediction Tool can be used to inform patients about prognosis, not to determine the possible effect of any particular treatment regimen. There is a need for parameters that may determine response rates to immunosuppressive treatments initiated in IgAN.

Pan-immune inflammation value (PIV) is a new marker calculated with neutrophil, lymphocyte, platelet, and monocyte counts in the peripheral blood circulation and thought to reflect the total immune response[8]. PIV was first studied by Fucà et al[9] as a prognostic marker in patients with metastatic colorectal cancer and was found to be a strong predictor of survival outcomes. It is thought that the detection of PIV as such a strong marker is because it includes four main cell groups that contribute to the complex interactions between the cancer-immunity-inflammation triad. IgAN is a glomerular disease closely related to immunity and inflammation[10-13]. In our literature search, we could not find any study investigating the predictive power of PIV on steroid response in idiopathic IgAN patients.

In this pilot study, we aimed at investigating the predictive power of PIV on response rates at 6 months in steroid-initiated idiopathic IgAN patients.

Patients and Methods

Patients

All patients diagnosed with IgAN between June 2015 and June 2021 were retrospectively evalu-

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ated. Patients with secondary IgA nephropathy, crescentic IgA nephropathy, acute infection during PIV calculation, hematological or oncological cancer, use of drugs that may affect complete blood count parameters, and patients who did not have sufficient file data were excluded from the study. The study was conducted on patients diagnosed with idiopathic IgA nephropathy and treated with 3-6 months of conservative treatment and steroid therapy started because proteinuria was above 1 g/day. Patients whose proteinuria decreased below 1 g/day with conservative treatments were also excluded from the study. Figure 1 shows the patients and study design. All patients included in the study were receiving optimized supportive care consisting of the maximum tolerated dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy. Smokers were advised to quit smoking, and patients were also counseled by a dietitian for salt- and protein-restricted diet and weight control.

Corticosteroid Regimen

All patients received a standardized corticosteroid regimen[14]. They started with methylprednisolone at a dose of 0.6-0.8 mg/kg in the first 2 months of treatment, with a maximum of 80 mg/day. For the following 4 months, the dose was reduced by 8 mg per month, and steroid cessation was planned for a total of 6 months. A proton pump inhibitor and calcium-cholecalciferol supplementation were also given. All patients completed the steroid regimen without experiencing any side effects that required discontinuation of the drug. All patients were monthly examined by a nephrologist in the outpatient clinic.

Definition of Remission

Patients with proteinuria less than 0.3 g/day, no macroscopic hematuria, and no hematuria detected in 3 consecutive urinalyses for 6 months were considered to be patients in remission. Patients with proteinuria above 0.3 g/day after the steroid protocol, macroscopic hematuria, or those who were found to have microscopic hematuria in their 6-month follow-up after the steroid was discontinued were considered patients who were not in remission.

Pan-Immune Inflammation Value

The last complete blood count parameters before steroid initiation were used to calculate PIV. All complete blood counts of patients were analyzed with an automatic analyzer (Cobas 6000, Roche Diagnostics International AG, Rotkreuz, Switzerland). PIV was calculated by [neutrophil count (10^3 μL)*platelet count (10^3 μL)*monocyte count (10^3 μL)]/lymphocyte count (10^3 μL)].

Statistical Analysis

Categorical variables were expressed as frequencies and percentages. The Chi-square test

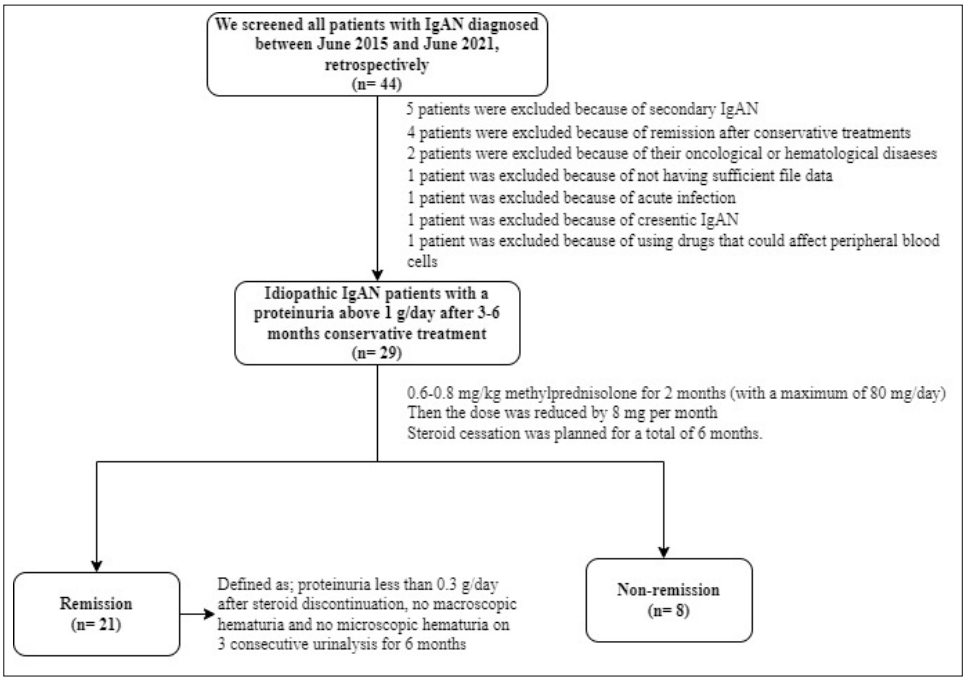

Figure 1. Study design.

was used to compare categorical variables between remission and non-remission groups. Conformity of continuous variables to normal distribution was checked with visual histograms and the Shapiro-Wilk test. Continuous variables with normal distribution were presented as mean and standard deviation, and continuous variables without normal distribution as median and interquartile (range: 25-75). In the comparison of continuous variables between groups, an independent sample *t*-test was used for parameters with normal distribution, and the Mann-Whitney U test was used for parameters without normal distribution. The predictive power of PIV for non-remission status was investigated by ROC curves. The Youden index was used to select the best cut-off value. A *p*-value lower than 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 26.0 package program (version 26.0, IBM Corp., Armonk, NY, USA).

Results

The study was conducted on 29 patients with idiopathic IgAN. The median age of the patients was 52 years (Q1-Q3=35-65 years). 20 (69%) patients were male and 9 (31%) were female. After 6 months of steroid treatment, 21 (72.4%) of the patients were in the remission group, while 8 were in the non-remission group. All patients in the non-remission group were male and gender distribution was found to be significantly different between groups ($p<0.05$). Table I shows the comparison of the groups in terms of demographical and pathological characteristics.

While serum albumin was found to be lower in patients in the non-remission group than in the patients in the remission group, serum creatinine, daily proteinuria and albuminuria were higher. Table II shows the comparison of laboratory tests between groups ($p<0.05$).

Mean PIV was significantly higher in patients in a non-remission group than in patients in the remission group (1,869.2±1,781.9 to 574.1±364.5, respectively). Figure 2 shows the comparison of PIVs of the group. ROC curve showed that PIV can predict non-remission with an AUC of 0.714 (95% CI=0.460-0.969, $p= 0.05$). The best cut-off for PIV was 752.6 to predict non-remission, with a 75% sensitivity and 71.4% specificity. Figure 3 shows the ROC curve for PIV to predict non-remission.

After that, we divided patients into two groups in terms of the best cut-off value of PIV. Remission rates were found to be statistically significantly higher in patients with low PIV than in those with high PIV. Figure 4 shows remission rates in terms of PIV groups.

Table I. Comparisons of demographical and pathological characteristics of the groups.

Characteristic	Total (n = 29)	Remission (n = 21)	Non-remission (n = 8)	p
Age, median (Q1/Q3)	52 (35/65)	49 (32/66)	56 (39/66)	0.238
Male gender, n (%)	20 (72.4)	12 (57.1)	8 (100)	0.033
Diabetes mellitus, n (%)	7 (24.1)	5 (23.8)	2 (25)	NS
Hypertension, n (%)	10 (34.5)	7 (33.3)	3 (37.5)	NS
Edema, n (%)	19 (65.5)	14 (66.7)	5 (62.5)	NS
Macroscopic hematuria, n (%)	13 (44.8)	7 (33.3)	6 (75)	0.092
Mesangial hypercellularity				0.154
M0, n (%)	17 (58.6)	14 (66.7)	3 (37.5)	
M1, n (%)	12 (41.4)	7 (33.3)	5 (62.5)	
Endocapillary hypercellularity				0.305
E0, n (%)	23 (79.3)	18 (85.7)	5 (62.5)	
E1, n (%)	6 (20.7)	3 (14.3)	3 (37.5)	
Segmental glomerulosclerosis				NS
S0, n (%)	18 (62.1)	13 (61.9)	5 (62.5)	
S1, n (%)	11 (37.9)	8 (38.1)	3 (37.5)	
Tubular atrophy/interstitial fibrosis				0.055
T0, n (%)	17 (58.6)	14 (66.7)	3 (37.5)	
T1, n (%)	6 (20.7)	5 (23.8)	1 (12.5)	
T2, n (%)	6 (20.7)	2 (9.5)	4 (50)	
Crescent				0.176
C0, n (%)	26 (89.7)	20 (95.2)	6 (75)	
C1, n (%)	3 (10.3)	1 (4.8)	2 (25)	

Table II. Comparison of laboratory tests between groups.

Laboratory test	Total (n = 29)	Remission (n = 21)	Non-remission (n = 8)	p
Leukocyte (*10³/µL)	8.23 ± 2.9	7.94 ± 1.9	8.98 ± 4.7	0.404
Neutrophil (*10³/µL)	5.55 ± 2.9	5.01 ± 1.7	6.95 ± 4.7	0.108
Lymphocyte (*10³/µL)	1.77 ± 0.9	2.01 ± 0.9	1.13 ± 0.5	**0.011**
Monocyte (*10³/µL)	0.81 ± 0.3	0.82 ± 0.3	0.81 ± 0.4	0.915
Hemoglobin (g/dL)	13.34 ± 1.8	13.4 ± 1.7	13.53 ± 1.9	0.730
Platelets (*10³/µL)	240.6 ± 61.5	237.14 ± 58.9	249.8 ± 71.4	0.630
Urea (mg/dL)	54.23 ± 31.4	45.09 ± 21.5	73.75 ± 43.8	0.134
Creatinine (mg/dL)	1.19 ± 0.5	1.06 ± 0.4	1.62 ± 0.5	**0.002**
Albumin (g/dL)	3.36 ± 0.9	3.58 ± 0.8	2.78 ± 1.3	**0.045**
Alanin-aminotransferase (U/L)	15.83 ± 6.8	16.86 ± 7.5	13.62 ± 4.5	0.286
C-reactive protein (mg/dL)	2.32 ± 2.8	2.05 ± 2.5	2.98 ± 3.6	0.440
Proteinuria (g/day)	3.34 ± 0.7	3.18 ± 0.5	3.76 ± 0.9	**0.039**
Albuminuria (g/day)	1.96 ± 0.7	1.79 ± 0.6	2.35 ± 0.9	**0.065**

Discussion

Our study showed that PIV is a reliable marker for predicting steroid response at the 6th month in patients with idiopathic IgAN. The triggering event in the pathogenesis of IgAN is the initiation of IgA deposits in the mesangial area[15]. IgA deposits in the mesangial area mainly consist of polymeric IgA1. This polymeric IgA1 leads to the release of numerous proinflammatory cytokines. It has been shown in a rat study[16] that polymeric IgA1 binding to renal mesangial cells increases the secretion of interleukin-6 (IL-6). IL-6 is produced by monocytes/macrophages, activated immune cells, lymphocytes, endothelial cells, fibroblasts, and hepatocytes[17]. We designed this study by considering the role of peripheral blood cells in inflammatory processes and thinking that PIV formed with these cell counts may be an indicator of the total inflammatory response in the patient. According to the results of our study, PIV can be used as an inflammation marker that can be used to evaluate the response to steroids in IgAN patients.

According to the findings of our study, one might suggest that the main reason for the PIV being lower in the remission group is the significantly higher lymphocyte count in this group. Nomoto et al[18] found high levels of IgA-producing lymphocytes in the peripheral blood of patients with IgA nephropathy. Our study shows that patients with lower PIV benefit better from

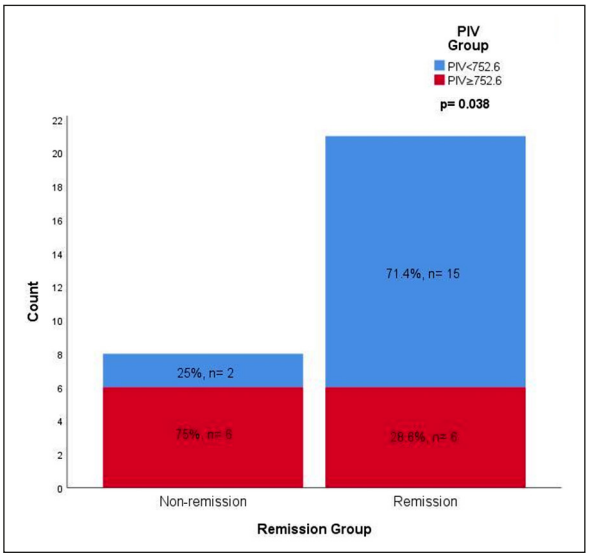

Figure 2. Remission rates in terms of PIV groups.

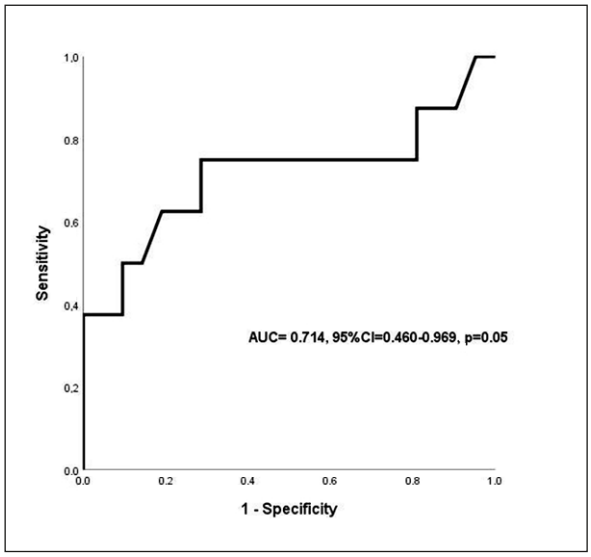

Figure 3. ROC curve of PIV to predict non-remission.

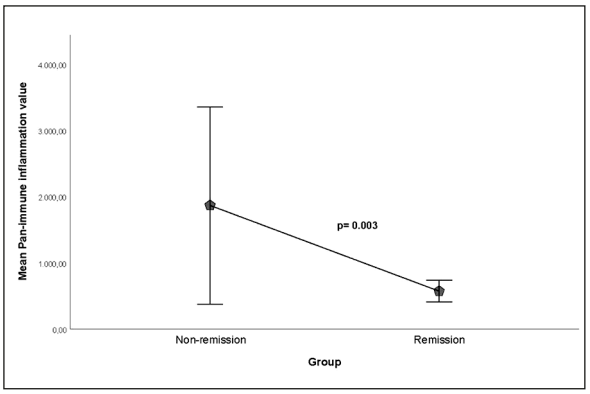

Figure 4. Comparison of the groups in terms of PIV.

steroid therapy than patients with high PIV. We think that the better response to steroids in patients with low PIV, that is, high lymphocyte count, is due to the decrease in steroid-induced lymphocyte counts. On the other hand, it cannot be said that PIV is affected by lymphocyte count alone. As the PIV name suggests, it contains many cell types in the peripheral blood that are the basis of immunity and inflammation. Apeland et al[19] revealed in their study that factors associated with circulating inflammation are increased in IgAN patients. We also found that PIV was associated with systemic inflammation in these patients, and high PIV was associated with poor steroid response.

Limitations

There are several limitations in our study. Firstly, it has a retrospective design and therefore we cannot establish a cause-effect relationship. Secondly, it is a single-center study. The third and perhaps the biggest limitation of our study is that it was conducted with a very limited number of patients. We think that this is because it was a single-center study, aiming at evaluating the response to steroids in patients with idiopathic IgAN. Moreover, 15 IgAN patients were not included in the analysis for various reasons.

However, despite these limitations, this is the first study investigating the predictive power of PIV on steroid response in patients with idiopathic IgAN.

Conclusions

Our study investigating PIV as a systemic inflammation marker to predict steroid response in idiopathic IgAN was designed as a pilot study. PIV is an inexpensive and easily accessible parameter and found as a reliable predictive marker for steroid response in patients with idiopathic IgAN. Because this was a pilot study, prospective, multicenter, and larger studies may provide more precise information on this issue.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study protocol complied with the Declaration of Helsinki and was approved by the Local Ethics Committee. (Afyonkarahisar Health Sciences University Clinical Research Ethics Committee, meeting date: 02/09/2022, meeting number: 2022-11, decision no: 440, ethics committee code: 2011-KAEK-2).

Consent to Participate

Not applicable because of the retrospective design.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Funding

None.

Authors' Contribution

Tunca O. and Kazan Dizen E. contributed to the design, and implementation of the research, and the writing of the manuscript. Statistical analysis was done by Tunca O.

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