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Systemic immune inflammation index and pan-immune inflammation value as prognostic markers in patients with idiopathic low and moderate risk membranous nephropathy

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Abstract. – OBJECTIVE: We aimed to investigate the prognostic values of systemic immune inflammation index and pan-immune inflammation value in patients with idiopathic low and moderate risk membranous nephropathy.

PATIENTS AND METHODS: All membranous nephropathy patients diagnosed in the nephrology clinic between January 2015 and January 2022 were reviewed retrospectively. Patients with idiopathic membranous nephropathy were included. The patients were divided into two groups; the complete remission group: whose proteinuria decreased below 0.3 g/day and serum albumin level above 3.5 g/dL after 6 months of conservative treatment, and the non-remission group: all other patients. Groups were compared in terms of systemic immune inflammation index and pan-immune inflammation value.

RESULTS: Patients in the non-remission group had significantly higher systemic immune-inflammation index (SII) and pan-immune-inflammation value (PIV) than patients in the complete remission group ($p<0.05$). An SII of 1,056.2 was found to have 63.6% sensitivity and 100% specificity in predicting non-remission, and a PIV of 447.4 was found to have 100% sensitivity and 70.6% specificity in predicting non-remission.

CONCLUSIONS: SII and PIV are reliable markers for predicting non-remission in patients with low and moderate risk idiopathic MN.

Key Words:

Inflammation, Membranous nephropathy, Pan-immune inflammation value, Remission, Systemic immune inflammation index.

Introduction

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults[1]. MN is mainly a term used to express histopathological findings with thickening of the glomerular basement membrane without cellular infiltrates[2]. Many causes such as hepatitis B and C viruses, malignancies, drugs, and systemic lupus erythematosus can lead to the development of secondary MN[3-7]. In approximately 75% of MN cases, no underlying cause can be found, and these cases are defined as primary or idiopathic MN. Although it is known that gender, increased creatinine at the time of diagnosis, amount of proteinuria, presence of nephrotic syndrome, and poor histopathological features decrease complete remission rates in patients with idiopathic MN, there are not enough studies on this subject in low and moderate risk MN patients. Although urinary alpha-1 and beta-2 microglobulin levels were found to be prognostic markers in MN patients in the study of van den Brand et al[8], these two markers have not been widely used. Anti-phospholipase A2 receptor antibodies are the most frequently detected antibodies in the development of idiopathic MN[9]. Although it has been found that this antibody can also be used to predict remission, this marker is not widely available[10]. Therefore, more easily accessible prognostic markers are needed in patients with idiopathic MN.

The systemic immune-inflammation index (SII) and pan-immune-inflammation value (PIV) are two recently proposed scoring systems that include immune-inflammatory cells in the peripheral blood count[11,12]. These systems are believed to reflect the immune-inflammatory load in the patient. Although both scoring systems were first developed in cancer studies, they were later studied[13,14] in non-cancerous clinical conditions such as vasculitis or coronary artery disease.

In this study, we aimed to investigate the prognostic values of SII and PIV in patients with idiopathic low and moderate risk MN.

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Patients and Methods

Patients and Groups

The files of all MN patients diagnosed in the nephrology clinic between January 2015 and January 2022 were reviewed retrospectively. Patients with secondary MN, patients with a high and very high risk of progression at the time of diagnosis, patients using drugs that may affect the parameters in the complete blood count, patients who did not have sufficient file data for the study, and patients with acute infection were excluded from the study. MN diagnosis was done with kidney biopsy in all patients. Patients with positive anti-phospholipase A2 receptor (anti-PLA2R) antibody test results and no secondary cause revealed were considered idiopathic MN patients. The patients were divided into two groups; the complete remission group: whose proteinuria decreased below 0.3 g/day and serum albumin level above 3.5 g/dL after 6 months of conservative treatment, and the non-remission group: all other patients. Groups were compared in terms of demographical and laboratory measurements. The study design and groups are shown in Figure 1.

Definitions and Calculation of Markers

Low risk: proteinuria less than 4 g/day.

Moderate risk: proteinuria between 4-8 g/day.

High risk: proteinuria above 8 g/day.

Very high risk: life-threatening nephrotic syndrome or rapid decline of kidney function.

Complete remission: proteinuria decreased below 0.3 g/day and serum albumin level above 3.5 g/dL after 6 months of conservative treatment.

Non-remission: proteinuria above 0.3 g/day and/or serum albumin level below 3.5 g/dL after 6 months of conservative treatment.

SII was calculated as (platelet count*neutrophil count)/lymphocyte count.

PIV was calculated as (platelet count*neutrophil count*monocyte count)/lymphocyte count.

Follow-Up

A standard conservative treatment approach was applied to all low and moderate risk patients.

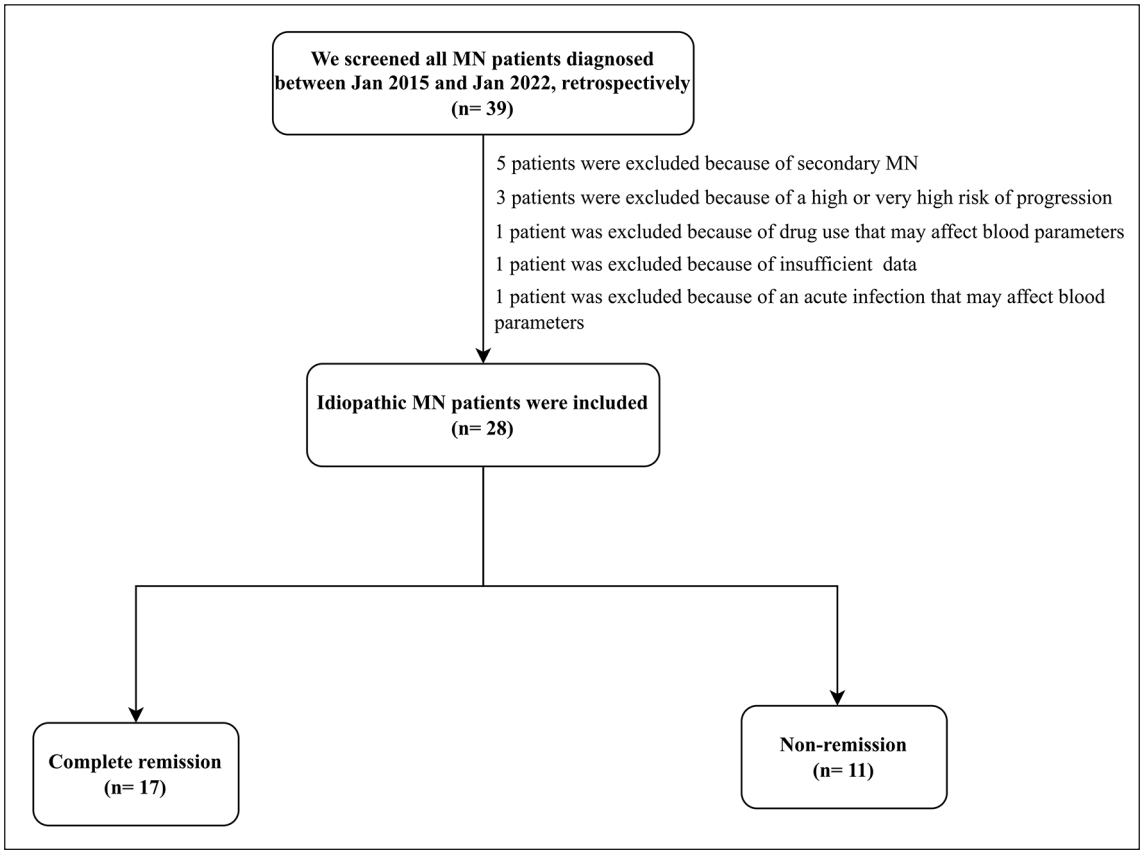

Figure 1. Study design and groups.

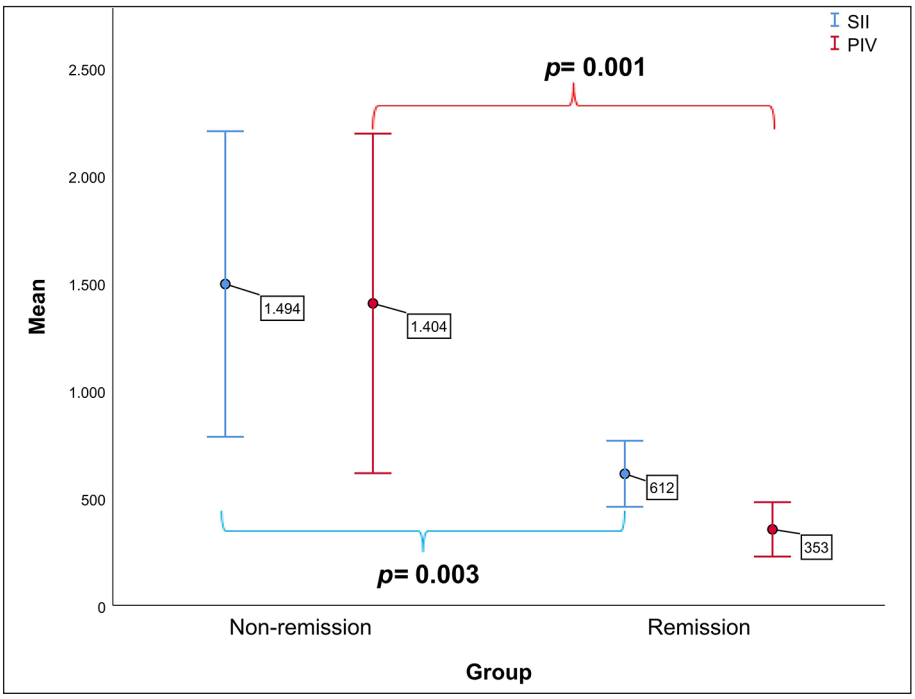

Figure 2. Comparison of SII and PIV between groups. SII: Systemic immune-inflammation index; PIV: Pan-immune inflammation value.

All patients were referred to a dietitian to have a salt and protein-restricted diet. Patients were started on renin-angiotensin-aldosterone inhibitors at the maximum tolerated dose for blood pressure control. Anticoagulation prophylaxis was started in patients with serum albumin levels below 2.8 g/dL. Furosemide tablets were started as diuretic therapy in patients with grade 2 or higher edema. Proteinuria was evaluated at the time of diagnosis and during follow-up, by protein and albumin excretion in 24-hour urine. The patients were called for monthly controls during the 6-month follow-up period.

Ethics Approval

Ethics approval was obtained by Ethics Committee of Afyonkarahisar Health Sciences University in date 02.09.2022 (code of Ethics Committee: 2011-KAEK-2, meeting number: 2022/11, decision number: 441).

Statistical Analysis

Qualitative variables were presented as frequency and percentages. The Chi-square test or Fisher's exact test was used to compare qualitative variables between groups. Continuous variables were checked for normal distribution with the Shapiro-Wilk's test. Normally distributed continuous variables were presented as mean±standard deviation (SD). Non-normally distributed continuous variables were presented as median and interquartile range-1 and interquartile range-3 (Q1-Q3). Independent samples *t*-test was used to compare normally distributed continuous variables between groups. Mann-Whitney U test was used to compare non-normally distributed continuous variables between groups. ROC curves were used to determine the sensitivity and specificity of SIV and PIV to predict complete remission. The Youden index was used to determine the best cut-off values. Statistical analyses were performed with SPSS 26.0 (IBM Corp., Armonk, NY, USA) package program. All *p*-values presented were bidirectional and the values less than 0.05 were expressed as statistically significant.

Results

The files of 39 patients with MN were scanned for the study. The study was conducted with 28 idiopathic MN patients (Figure 1). Idiopathic MN was diagnosed because of a positive anti-PLA2R antibody in 57.1% (n=16) of the patients and be-

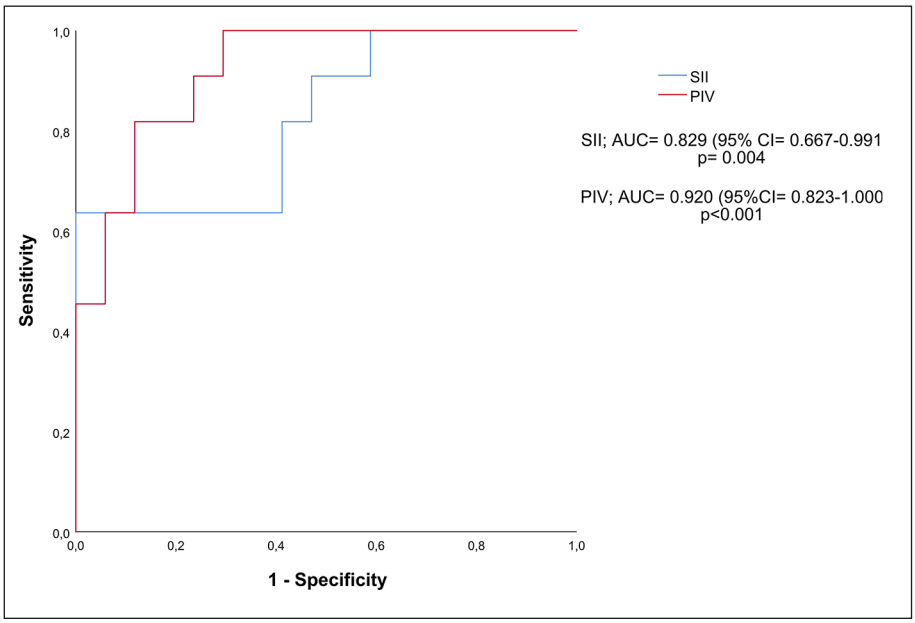

Figure 3. ROC curve of SII and PIV for predicting non-remission. SII: Systemic immune-inflammation index; PIV: Pan-immune inflammation value; AUC: Area under curve; CI: Confidence interval.

cause no secondary cause could be found in 42.9% (n=12) of the patients. Of the patients, the 78.6% (n=22) were men. The median age of the patients was 60 years (IQR1-3=52-66.8). Of the patients, the 75% (n=21) had edema and 21.6% (n=6) started diuretics. The anti-coagulant requirement was also present in 21.4% (n=6) of the patients. Hypertension was present in 46.4% (n=13) and diabetes mellitus in 32.1% (n=9) of the patients.

At the end of the 6-month follow-up period with conservative treatments, 60.7% (n=17) of the patients were in the complete remission group and 39.3% (n=11) in the non-remission group. Patients in the non-remission group had significantly higher edema rates than patients in the complete remission group (p<0.005). Table I shows the comparison of the groups in terms of general characteristics.

Patients in the non-remission group had significantly higher monocyte count, albuminuria, proteinuria, and lower serum albumin than patients in the complete remission group (p<0.005). Table II shows the comparison of the groups in terms of laboratory measurements.

Patients in the non-remission group had significantly higher SII and PIV than patients in the complete remission group (p<0.05). Figure 2 shows the comparison of SII and PIV between groups.

An SII of 1,056.2 was found to have 63.6% sensitivity and 100% specificity in predicting non-remission, and a PIV of 447.4 was found to have 100% sensitivity and 70.6% specificity in predicting non-remission. Figure 3 shows the ROC curve of SII and PIV for predicting non-remission.

Table I. Comparison of general characteristics of groups.

Characteristic	Complete remission (n=17)	Non-remission (n=11)	*p*
Male gender, %-n	70.6-12	90.9-10	0.355
Age, median/Q1-Q3	59/52-63.5	62/51-71	0.488
Edema, %-n	58.8-10	100-11	**0.023**
Diuretics, %-n	11.8-2	36.4-4	0.174
Anti-coagulant, %-n	11.8-2	36.4-4	0.174
Diabetes mellitus, %-n	17.6-3	54.5-6	0.095
Hypertension, %-n	41.2-7	54.5-6	0.700

Table II. Comparison of the groups in terms of laboratory measurements.

Laboratory	Complete remission (n=17)	Non-remission (n=11)	p
Leucocyte (*10^3/μL)	8.55±4.2	9.47±2.9	0.533
Neutrophil (*10^3/μL)	4.89±1.4	6.51±2.9	0.111
Lymphocyte (*10^3/μL)	2.93±3.7	1.85±0.9	0.350
Monocyte (*10^3/μL)	0.58±0.3	0.96±0.4	**0.003**
Hemoglobin (g/dL)	13.6±1.7	13.3±1.5	0.715
Platelets (*10^3/μL)	254.76±56.9	342.73±112.2	**0.011**
Urea (mg/dL)	35.6±6.8	39.4±7.1	0.174
Creatinin (mg/dL)	0.82±0.1	0.88±0.1	0.191
Glomerular filtration rate (ml/min/1.73 m^2)	77.2±7.6	74.1±6.1	0.269
C-reactive protein (mg/dL)	0.79±1.1	2.81±3.7	0.110
Sedimentation (mm/h)	25.69±12.8	25.64±8.3	0.990
Albumin (g/dL)	3.09±0.4	2.77±0.3	**0.019**
Proteinuria (g/day)	5.59±1.9	7.59±0.4	**0.002**
Albuminuria (g/day)	4.41±1.8	6.74±0.3	**<0.001**

Discussion

The present study showed that SII and PIV are reliable markers for predicting non-remission in patients with low and moderate risk idiopathic MN. In our literature search, this is the first study investigating SII and PIV on MN. Although the inflammation in MN patients is generally thought to be limited to the kidney, systemic inflammation is also found in these patients. Khalili et al[15] found that the highest urinary sC5b-9 levels were in MN patients in their study involving different types of autoimmune glomerulonephritis. Zhang et al[16] found that MN patients have higher T follicular helper cells and plasma cells in the peripheral blood, which may play a role in pathogenesis. These studies[15,16] are very important because they show that systemic inflammation is also present in MN patients. However, the use of the molecules in these studies, in clinical practice, has been very limited and there is a need for more easily accessible markers that can be used in this field. Our study found that SII and PIV were higher in low-moderate risk MN patients who did not achieve complete remission after 6 months of conservative treatments and follow-up.

Various cell types such as neutrophils, lymphocytes, platelets, and monocytes play a role in the complex relationship between immunity and inflammation in the pathogenesis of MN[17-20]. SII and PIV are two new markers that can be calculated with neutrophil, lymphocyte, thrombocyte, and monocyte counts in peripheral blood and are thought to reflect the total status of systemic inflammation. In our study, it was determined that although PIV, in which monocyte count was used in its formula, was found to be a more reliable marker compared to SII, both markers could significantly predict non-remission status. It has been shown[18,19,21] that both cellular and humoral immune mechanisms are important in the pathogenesis of MN, and monocytes play a role in both of these mechanisms. We think that the detection of PIV as a stronger marker than SII is because it also includes the monocyte count. When the cell types constituting SII and PIV were examined, it was determined that the platelet count and monocyte count were significantly different between the two groups. This made us think that the platelet count played a role in the different detection of SII between groups, and the platelet and monocyte counts played a role in the different detection of PIV between groups. In addition, in a recently published pilot study by Tunca and Dizen Kazan[22], it was shown that PIV can predict steroid response in idiopathic immunoglobulin A nephropathy, which is also a glomerular disease.

Limitations

The limitations of our study are that it was single-centered, included a small number of patients, and was retrospective. Despite these limitations, our study is important because it is the first to in-

vestigate the predictive power of SII and PIV for non-remission in MN patients.

Conclusions

Cell counts in peripheral blood and inflammation markers that can be formed with these numbers such as SII and PIV may be useful in predicting remission in patients with low-moderate risk idiopathic MN. Larger, prospective, multicenter studies on this subject may reveal this issue more clearly.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

There is no funding for the study.

Ethics Approval

Ethics approval was obtained by Ethics Committee of Afyonkarahisar Health Sciences University in date 02.09.2022 (code of Ethics Committee: 2011-KAEK-2, meeting number: 2022/11, decision number: 441).

Authors' Contributions

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

Availability of Data and Materials

The data supporting this study's findings are available on request from the corresponding author.

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