Medical Science and Discovery
ISSN: 2148-6832

Pan-immune-inflammation value (PIIV) in Lupus Nephritis

Firdevs Ulutaş[1]*, Veli Çobankara[1]

1 Pamukkale University, Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Denizli, TR

*** Corresponding Author**: Firdevs Ulutaş **E-mail:** firdevsulutas1014@gmail.com

ABSTRACT

Objective: Pan-immune-inflammation value (PIIV) is a newly defined marker that has been validated to predict the prognosis of several oncological diseases. We investigated whether PIIV at diagnosis could predict a reduced glomerular filtration rate (GFR) during follow-up in patients with lupus nephritis (LN).

Material and Methods: We included 45 patients with biopsy-proven LN in this case-control study. PIIV at the diagnosis was calculated for each patient before starting any immunomodulatory and/or immune-suppressive drugs. The study group was classified into two subgroups: patients with a minimum 10 % decreased glomerular filtration rate (GFR) from baseline or preserved GFR. LN-specific indices, inflammation-related laboratory results at diagnosis, medications and developing comorbidities at the follow-up were also noted. Chi-Square Test was used to compare the subgroups. Associated factors were analyzed by logistic regression analysis. Statistically, the significance level was accepted as $p<0.05$.

Results: 77.8 % of all patients (n=35) were female, whereas 22.2 % were male. The mean age of the study group was 33.0 ± 13.4 years. The median follow-up period was 36 months (range: 4-108 months). A vast majority of patients (n=32, 71.1%) had class IV LN. GFR reduction was observed in eleven patients (n=11). The mean age at diagnosis, presence of developing hypertension, mean PIIV value, and PIIV >75% were significantly higher in patients with decreased GFR than the patients with preserved GFR (p=0.019, p=0.044, p=0.015, and p=0.011, respectively). In addition, the presence of developing HT and PIIV >75% were found to be statistically significant factors in the multivariate model (p=0.029 and p=0.022).

Conclusion: An increased PIIV at baseline was independently associated with a reduction in GFR in LN patients. A high PIIV might become a new biomarker for the risk of GFR reduction and the need for improved/intensive treatment of these patients.

Keywords: Pan-immune-inflammation value, systemic lupus erythematous, inflammation

INTRODUCTION

Pan-immune-inflammation value (PIIV) is a newly-defined marker calculated from the complete blood count. PIIV is derived from four blood cell counts, including neutrophils, platelets, monocytes, and lymphocytes, and shows the severity of an inflammation [1].

It has a growing interest in predictive scores of variable oncological malignancies. The PIIV is validated as a strong predictor of survival in patients with metastatic diseases [2]. Recently, there have been investigations into the use of PIIV in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) [3]. The authors showed lower survival rate in AAV patients with highest baseline PIIV values.

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by variable clinical presentations. Lupus nephritis (LN) is a life-threatening and frequent major organ involvement of SLE. [4]. It is seen in approximately 30-45% of the patients. A recent meta-analysis revealed multiple variable factors that affect the renal prognosis of the patients. For instance, renal response can be evaluated using anti-C1q and anti-ds DNA antibodies, while renal histological findings, including class type (IV or V), tubulointerstitial or vascular lesions, and chronicity index, can help predict the development of chronic kidney disease (CKD). Age, smoking, and vascular lesions are important factors to consider when evaluating mortality rates [5].

Research Article

Received 17-03-2023

Accepted 15-04-2023

Available Online: 17-04-2023

Published 30-04-2023

Distributed under
Creative Commons CC-BY-NC 4.0

OPEN ACCESS

http://dx.doi.org/10.36472/msd.v10i4.918

Despite these heterogeneous predictors, researchers are still making an effort to find a new useful biomarker. Recently, several urine biomarkers, including urinary adiponectin, urinary monocyte chemoattractant protein, and urinary vascular cell adhesion protein 1, have been investigated as potential diagnostic and prognostic tools for patients, with promising results. Despite the availability of new biomarkers, kidney biopsy remains the gold standard for diagnosis and renal prognosis in daily clinical practice [6]. Approximately 10-25% of patients develop chronic kidney disease (CKD), and a mortality rate of 10-20% at ten years has been reported [5]. Also, the probability of achieving complete or partial remission does not exceed 60-70% in LN [7]. Unfortunately, the literature lacks of good prognostic factors in LN. Using optimal and practical urine/blood biomarkers may provide a way to classify patients according to their risk categories and guide their initial therapeutic options of LN therapy [8].

We calculated PIIV as a simple and cheap tool derived from commonly performed blood cell counts as a possible prognostic tool in these patients. We investigated whether PIIV at diagnosis could predict the reduction of glomerular filtration rate (GFR) and/or mortality during follow-up in patients with LN.

MATERIAL and METHODs

This study was conducted in accordance with the Declaration of Helsinki and local Ethical Commitee approval (Ethical Review Board date/number, 2020/512). In this case-control study patients‘ medical records were retrospectively evaluated by hospital data system, so informed consent was not obtained from all patients.

All of the patients were initially classified as having LN in our health center between June 2010 and June 2020 following the current SLE guidelines [9]. All of them had LN confirmed by kidney biopsy, and the kidney biopsy classification system. We included all of the patients with LN who are on regular follows-up defined as at least three times in a year. The follow-up period was calculated for each patient and defined as the time from the diagnosis of LN to the date of their last regular visit or to the time of death for deceased patients. It is described as months.The patients who had concurrent medical conditions, such as malignancies, chronic/acute infectious diseases, or hematologic disorders were excluded.

PIIV, LN-specific indices (anti-nuclear antibody, extractable nuclear antigens, and serum levels of complements), inflammation-related laboratory results (erythrocyte sedimentation rate, C-reactive protein and serum albumin) at diagnosis were calculated and noted for each patient before starting immunosuppressive/modulatory drugs. The PIIV at diagnosis was calculated as follows: the neutrophil count (multiplied by 1000/m^3) multiplied by the monocyte count (multiplied by 1000/m^3) multiplied by the platelet count (multiplied by 1000/mm^3), divided by the lymphocyte count (multiplied by 1000/m^3) [2]. Their medications, comorbidities developing in the follow-up, and final labaratory panels at the last visit were also noted. During the follow-up, the development of comorbidities related to atherosclerosis, including hypertension, hyperlipidemia, diabetes mellitus, cardiovascular diseases, and cerebrovascular diseases, were noted and each of them was defined according to diagnostic criteria. 24-hour protein excretion at the initial and final visits was also noted for each patient. Cockroft and Gault formula was used to determine the baseline and the following GFR. The study group was classified into two subgroups, including patients with decreased glomerul filtration rate (GFR) or preserved GFR compared with baseline values. GFR reduction was determined as 10% reduction compared to baseline.

In 42 patients, remission induction therapy was performed using a combination of azathioprine, cyclophosphamide, and mycophenolate mofetil (MMF) with varying degrees of corticosteroids. All of the patients used renin angiotensin aldosterone system (RAAS) blockers with different dosages for proteinuria. Intravenous pulses of glucocorticoids were used only for remission induction. The patients were also on different maintenance therapy modalities (including rituximab plus the above-mentioned ones).

Statistical analysis: The SPSS 15.0 program was used for statistical analysis. Descriptive statistics are given as numbers and percentages for categorical variables, whereas given as mean +- standard deviation, minimum, maximum, and median for numerical variables. Chi-Square Test was used to compare the groups. Comparisons of numerical variables between two independent groups were made using the Student t-Test when the normal distribution condition was met and the Mann-Whitney U test when the situation was not met. Chi-Square Test was used to compare the groups. Associated factors were analyzed by logistic regression analysis. Mean values for normally distributed variables and median values for non-normal variables were given. Statistically, the significance level was accepted as $p<0.05$.

RESULTs

We included 45 patients diagnosed with biopsy-proven LN consisting of 35 females and 10 males. The mean age of the study group was 33.0±13,4 years. The median follow-up period was 36 months (4-108 months). Out of the total number of patients, 32 (71.1%) were found to have class IV LN.. GFR reduction was seen in eleven patients (n=11). Only one patient developed end-stage renal disease (ESRD), and ultimately died. All demographic data and clinical features of the study group were summarized in Table 1.

The mean age at diagnosis, mean baseline PIIV value, and PIIV>75% were significantly higher in patients with decreased GFR than in patients with preserved GFR (p=0.019, p=0.044, p=0.015, p=0.011) (Table 2).

There was no statistical difference between the subgroups in terms of biopsy findings and treatment modalities. In the univariable analy¬sis, the presence of developing hypertension (OR: 5.60, p=0.022) and PIIV (PIIV>75%) (OR: 6.96, p=0.012) at diagnosis were signifi¬cantly associated with GFR reduction. In the multivariable analysis, the presence of hypertension (OR: 9.44, p=0.029) and PIIV (OR: 10.81, p=0.022) were identified as significant and independent risk factors for GFR reduction (Table 3).

http://dx.doi.org/10.36472/msd.v10i4.918

Table 1: Demographic and descriptive data of all study subjects.

Gender (%)	Male	10 (22.2)
	Female	35 (77.8)
Age		33.0±13,4 / 16-74 (27)
Age at diagnosis		28.8±12.9 / 8-64 (26)
Developing comorbidities n (%)	DM	3 (6.7)
	HT	12 (26.7)
	HL	2 (4.4)
	CVD	4 (8.9)
PIIV		243.7±206.7 / 13-1032 (201)
Biopsy findings n (%)	Class 2	2 (4.4)
	Class 3	3 (6.7)
	Class IV	32 (71.1)
	Class V	8 (17.8)
Remission Induction n (%)	AZA	2 (4.4)
	CyP	27 (60.0)
	MMF	13 (28.9)
Maintenance Therapy n (%)	AZA	1 (2.2)
	CsA	2 (4.4)
	GCs (only)	4 (8.9)
	HCQ (only)	1 (2.2)
	MMF	29 (64.4)
	RTK	2 (4.4)
	RTK, AZA	1 (2.2)
	RTK, MMF	4 (8.9)
	TAC	1 (2.2)
Follow-up period (months)		4-108
Mortality n (%)		1 (2.2)
Reduction of GFR n (%)	Absent	34 (75.6)
(**10** % from baseline)	Present	11 (24.4)

All data are given as n (%, number and percent) or mean ± SD / min-max (median). DM. Diabetes mellitus, HT: hypertension, HL: hyperlipidemia, CVD: cardiovascular disease, PIIV: pan-immune inflammation value, AZA: azatiopurine, CyP: cyclophosphamide, MMF: mycophenolate mofetil, CsA; cyclosporine, GCs: glucocorticoids, HCQ: hydroxichlorokine, RTK: rituximab, TAC: tacrolimus, GFR: glomerul filtration rate.

Table 2: Comparison of subgroups

		Reduction of GFR (10 % from baseline)		
		Absent (n=34)	**Present (n=11)**	
Gender n (%)	Male	8 (23.5%)	2 (18.2%)	1.000
	Female	26 (76.5%)	9 (81.8%)	
Age		30.6±11.3 17-60 (26)	40.4±16.9 16-74 (40)	0.068
Age at diagnosis		26.1±10.8 8-52 (23.5)	37.1±15.6 14-64 (32)	0.019
PIIV		213.6±206.4 13-1032 (156)	336.7±186.5 101-665 (403)	0.015
PIIV IQR n (%)	<%25 (78,5)	11 (32.4%)	0 (0.0%)	0.011
	%25-75	18 (52.9%)	5 (45.5%)	
	>%75 (361)	5 (14.7%)	6 (54.5%)	
Anti-ds DNA n (%)		18 (52.9%)	6 (54.5%)	1.000
C3 (mg/dL)		65.5±39.1 0.3-164 (53.5)	79.6±48.9 25-157 (67)	0.570
C4 (mg/dL)		9.8±8.2 0.04-35 (8.5)	12.2±11.3 3-36 (6)	0.672
Albumin (g/dL)		3.09±0.81 1.5-4.8 (3.1)	2.85±0.90 1.6-4.3 (2.7)	0.443
Biopsy findings n (%)	Class 2	2 (5.9%)	0 (0.0%)	1.000
	Class 3	2 (5.9%)	1 (9.1%)	
	Class IV	24 (70.6%)	8 (72.7%)	
	Class V	6 (17.6%)	2 (18.2%)	
Remission Induction n (%)	CyP	20 (58.8%)	7 (63.6%)	1.000
	MMF	12 (35.3%)	1 (9.1%)	0.136
	AZA	1 (2.9%)	1 (9.1%)	0.433
	GCs	1 (2.9%)	2 (18.2%)	0.143
Maintenance Therapy n (%)	MMF	24 (70.6%)	5 (45.5%)	0.372
	AZA	1 (2.9%)	0 (0.0%)	
	CSA	1 (2.9%)	1 (9.1%)	
	GCs	2 (5.9%)	2 (18.2%)	
	HCQ	1 (2.9%)	0 (0.0%)	
	RTK	1 (2.9%)	1 (9.1%)	
	RTK, AZA	1 (2.9%)	0 (0.0%)	
	RTK, MMF	2 (5.9%)	2 (18.2%)	
	TAC	1 (2.9%)	0 (0.0%)	

Table 3. Effects of variable factors on GFR

	Univariate			Multivariate		
	p	OR	95 % CI	p	OR	95% CI
Age	0.046	1.05	1.00-1.11			
Age at diagnosis	0.022	1.07	1.01-1.13			
HT (>120/80)	0.022	5.60	1.28-24.56	0.029	9.44	1.26-70.90
Other diseases (+)	0.077	4.29	0.86-21.48			
PIIV (Ref :≤ 75 % Persentil) > 75% Persentil	0.012	6.96	1.52-31.81	0.022	10.81	1.40-83.22

Hosmer and Lemeshow Test p= 0.697 Cox & Snell R Square: 0.365, HT: hypertension, PIIV: pan-immune inflammation value.

DISCUSSION

We believe that this study is an important contribution as it is the first of its kind to be conducted, and it provides valuable insights into the field.After a follow-up time of 4-108 months, increased PIIV at baseline was independently associated to a reduction in GFR in LN patients. Despite relatively small patient population and follow-up time, this study is suggesting this association. A high PIIV might become a new biomarker for the risk of GFR reduction and the need for improved/intensive treatment of these patients.

In rheumatic diseases, authors recently found an association between high PIIV values and poor prognosis in patients with AAV [3]. Lee LE et al. determined a cut-off value for PIIV in their study. The AAV patients with PIIV at diagnosis ≥1011.3 had a lower survival rate. In this study, we could not obtain the cut-off of PIIV using the ROC curve due to the small patient size. PIIV interquartile range (IQR) was arbitrarily defined as: < 25% (cut-off < 78.5), 25-75%, and > 75% (cut-off >361). Today, several blood cell calculations are also used to determine disease activity, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and mean platelet volume (MPV). The patients with nephritis had higher NLR and PLR levels than those without nephritis [10]. In addition, the systemic immune-inflammation index (SII) is another parameter that has been investigated through complete blood count analysis in SLE [11].Although it consists of neutrophil, platelet, and lymphocyte count similarly to PIIV, Taha SI et al. showed similar SII values in SLE patients and age-matched healthy controls. However, PIIV may provide more stable results using the counts of four types of blood cells, including monocytes as an extra. LN occurs as a result of autoantibody production and intrarenal immune complex formation. Besides, the accumulation and activation of monocytes are triggered by intracapillary immune complexes [12].

In new investigations, nocturnal hypertension and abnormal blood pressure patterns are common in LN patients. It may be related to degree of interstitial inflammation, salt sensitivity or advanced renal injury [13]. In our study, all patients were on antihypertensive drugs including angiotensin converting enzyme inhibitors or angiotensin receptor blockers from diagnosis of nephritis. A new developing hypertension was correlated with reduced GFR. We don't know whether this result is related to uncontrolled inflammation or chronic renal injury. However, hypertension is well-known as an additive cardiovascular risk factor in LN patients [14]. So, awareness of clinicians related to new developing hypertension in quite important.

The two most commonly used agents for remission induction were cyclophosphamide and MMF, whereas MMF was the most frequently used agent for maintenance treatment. The another point to emphasize is that patients with preserved GFR used MMF more frequently than those with reduced GFR despite not achieving statistical significance. The lack of significance may be attributed to the small number of patients included in the study, particularly those with reduced GFR. In addition, there was no association between biopsy classification groups and GFR reduction.

This study is a single-center experience, and the relatively small size of the study group was a significant limitation. This study includes only SLE patients with nephritis and biopsy-proven patients. So it is difficult to generalize the results to all SLE patients. In addition, the study's retrospective nature limited us to obtaining the other comprehensive risk factors of ESRD, such as smoking history (or current smoker) and determination of the patients' body mass indexes at the follow-up. The cumulative corticosteroid doses were not calculated due to the not possible clear calculations.

CONCLUSION

PIIV at diagnosis could predict GFR reduction during follow-up in SLE patients with LN. Baseline PIIV may serve as a simple and cost-effective screening biomarker for LN.

Acknowledgments: None

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions: Study design, collecting data: **FU, VÇ,** Statically analysis: **FU, VÇ,** Writing: **FU, VÇ,** Literature search and review: **FU, VÇ.**

Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. (Ethical Review Board date/number, 2020/512).

REFERENCES

1. Guven DC, Sahin TK, Erul E, Kilickap S, Gambichler T, Aksoy S. The Association between the Pan-Immune-Inflammation Value and Cancer Prognosis: A Systematic Review and Meta-Analysis. Cancers (Basel). 2022(27);14(11):2675.

2. Fuca G, Guarini V, Antoniotti C, et al. The Pan-Immune-Inflammation Value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled analysis of the Valentino and TRIBE first-line trials. Br J Cancer 2020;123:403-9.

3. Lee LE, Ahn SS, Pyo JY, Song JJ, Park YB, Lee SW. Pan-immune-inflammation value at diagnosis predicts all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis. Clin Exp Rheumatol. 2021;39 Suppl 129(2):88-93.

4. Liu Y, Anders HJ. Lupus nephritis: from pathogenesis to targets for biologic treatment. Nephron Clin Pract. 2014;128(3-4):224-31.

5. Rodriguez-Almaraz E, Gutierrez-Solis E, Rabadan E, Rodriguez P, Carmona L, Morales E, et al. Something new about prognostic factors for lupus nephritis? A systematic review. Lupus. 2021;30(14):2256-2267.

6. Radin M, Miraglia P, Barinotti A, Fenoglio R, Roccatello D, Sciascia S. Prognostic and Diagnostic Values of Novel Serum and Urine Biomarkers in Lupus Nephritis: A Systematic Review. Am J Nephrol. 2021;52(7):559-571.

7. Morales E, Galindo M, Trujillo H, Praga M. Update on Lupus Nephritis: Looking for a New Vision. Nephron. 2021;145(1):1-13.

8. Caster DJ, Powell DW. Utilization of Biomarkers in Lupus Nephritis. Adv Chronic Kidney Dis. 2019;26(5):351-359.

9. Bajema IM, Wilhelmus S, Alpers CE, Brujin JA, Colvin RB, Cook HAT, et al. Revision oft he Internaitonal Society of nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int. 2018:93(4):789-796.

10. Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in the assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol. 2016;26(3):372-6.

11. Taha SI, Samaan SF, Ibrahim RA, Moustafa NM, Sehsah EM, Youssef MK. Can Complete Blood Count Picture Tell Us More About the Activity of Rheumatological Diseases? Clin Med Insights Arthritis Musculoskelet Disorders. 2022(22);15:11795441221089182.

12. Olaru F, Dobel T, Lonsdorf AS, Oehrl S, Maas M, Enk AH, et al. Intracapillary immune complexes recruit and activate slan-expressing CD16+ monocytes in human lupus nephritis. JCI Insight. 2018(7);3(11):e96492.

13. Mejia-Vilet JM, López-Hernández YJ, Trujeque-Matos M, Santander-Velez JI, Cano-Verduzco ML, Cruz C, et al. High frequency of nocturnal hypertension in lupus nephritis: should ABPM be implemented in usual practice? Clin Rheumatol. 2020;39(4):1147-1155.

14. Pogorevici A, Gluhovschi C, Gluhovschi G, Velciov SM, Trandafirescu V, Secrii RV. Hypertension in lupus nephritis. Rom J Intern Med. 2006;44(3):295-316.

Copyright © 2023 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), (CC BY NC) which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. International Journal of Medical Science and Discovery.