The role of peritubular capillaritis in severity of lupus nephritis

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Abstract

Background & Objective: Presence of lupus nephritis is associated with a shorter time to death in systemic lupus erythematosus. The aim of this study was to determine the frequency of peritubular capillaritis (ptc) and its relationship with both active and chronic lesions in lupus nephritis.

Material-Methods: Specimens from 57 patients were re-evaluated. The degree of inflammation within the peritubular capillaries in each biopsy was assessed according to the Banff classification, and ptc scoring was performed. Additionally, patients were grouped based on high/low activity and chronicity index scores.

Results: Forty-five (78.9%) of the patients were female, with a mean age of 27.43 years. Ptc was identified in 45 (78.9%) patients, with ptc scores of 1, 2, and 3 observed in 20 (35.08%), 20 (35.08%), and 5 (8.7%) patients, respectively. Severe ptc (scores 2 or 3) was more commonly detected in patients with elevated serum creatinine (>1.20 mg/dL) compared to those with normal creatinine levels (92.3% vs 29.5%, p < 0.001). The severity of ptc was higher in Class 4 patients than in Class 3 patients (68.2% vs 21.7%, p = 0.005). The rate of high ptc scores was greater in patients with an activity index of 6 or above compared to those with an activity index below 6 (62.5% vs 30.3%, p = 0.032). No significant correlation was found between the chronicity index and ptc.

Conclusions: The findings of this study suggest that ptc is a frequently observed pathological feature in patients with lupus nephritis. Furthermore, the severity of ptc appears to be positively associated with elevated serum creatinine levels, and higher ptc scores are more commonly detected in cases with a high activity index.

Keywords

Lupus nephritis, peritubular capillaritis, banff classification, activity index, renal outcome

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystemic autoimmune disease that can affect any organ in the body, including the kidneys. The kidneys are the most frequently affected visceral organs in SLE. Lupus nephritis (LN) is a type of glomerulonephritis that occurs in patients with SLE, affecting approximately 20%–65% of these patients during the course of the disease. Leading cause of morbidity and mortality in SLE patients. Despite advancements in therapeutic modalities, around 10% of patients with LN progress to end-stage renal disease (ESRD). Moreover, SLE patients with LN have a shorter life expectancy compared to those without LN. The stage of the disease of the disease

The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification is the most widely used system for categorizing glomerular lesions in LN

based on the location of immune complex deposition. In 2018, the ISN/RPS revised the classification for LN, clarifying certain definitions and proposing a modified National Institutes of Health (NIH) scoring system for all classes based on activity and chronicity indices. This revision

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replaced the earlier definitions for Class 3/4 lesions. According to this updated classification, LN is divided into non-proliferative (Classes 1, 2, and 5), proliferative (Classes 3 and 4), and advanced sclerotic LN (Class 6), based on glomerular pathology.⁹

The Banff Classification is an internationally recognized standard for the histopathological evaluation of kidney transplants. It includes criteria for T cell-mediated rejection (TCMR), antibody-mediated rejection (AMR), and borderline changes. Histopathological findings in AMR include ptc, glomerulitis, and thrombotic microangiopathy (TMA). ^{10–12}

Ptc is associated with endothelial injury and is an important feature in the evaluation of rejection in transplant kidney biopsies. However, it is not exclusive to transplant cases and has also been detected in native kidney biopsies. Despite this, there remains insufficient research on the significance and frequency of ptc in native kidney disease. In this cross-sectional study, we re-examined renal biopsies from patients with LN to determine the frequency of ptc using the Banff scoring system. Additionally, we explored the association between the severity of ptc and various demographic, clinical, and histological characteristics of LN.

Materials and methods

Biopsy sections from 57 patients diagnosed with LN between 2015 and 2023 at our institution were obtained from the pathology department archive. The demographic and clinical characteristics at the time of renal biopsy were retrieved from the patients' electronic health records. This study was approved by the Non-invasive Clinical Research Ethics Committee of Eskişehir Osmangazi University (E-25403353-050.99-2400052898).

Histopathologic evaluation

All biopsies were initially evaluated by light microscopy (H&E, Masson trichrome, Periodic acid–Schiff, Methenamine silver, and Congo red) and immunofluorescence microscopy (IgG, IgA, IgM, C3, C1q, κ , and λ). Pathological lesions in renal biopsies diagnosed with LN were redefined and reclassified according to the revised 2018 ISN/RPS classification.

The following histologic features were recorded: endocapillary hypercellularity, neutrophils/karyorrhexis, fibrinoid necrosis, wire loop lesions/hyaline deposits, cellular/fibrocellular crescents, interstitial inflammation, global and/or segmental sclerosis, fibrous crescents, tubular atrophy, interstitial fibrosis, and ptc.

Evaluation of btc

The degree of inflammation within the peritubular capillaries in each biopsy was evaluated according to the Banff

Classification and ptc scoring was performed.¹² Areas affected by acute pyelonephritis or necrosis, subcapsular cortex with nonspecific inflammation, inflammatory cells within veins and medullary capillaries (vasa recta), and longitudinally cut peritubulary capillaries were excluded from scoring. The scoring was as follows:

- ptc 0—Maximum number of leukocytes <3.
- ptc 1—At least 1 leukocyte cell in ≥10% of cortical peritubular capillaries, with 3-4 leukocytes in the most severely involved peritubulary capillaries.
- ptc 2—At least 1 leukocyte in ≥10% of cortical peritubular capillaries, with 5-10 leukocytes in the most severely involved peritubulary capillaries.
- ptc 3—At least 1 leukocyte in ≥10% of cortical peritubular capillaries, with >10 leukocytes in the most severely involved peritubulary capillaries.

Activity and chronicity assessment

The NIH activity and chronicity scoring system was applied to determine the activity and chronicity scores of biopsies. This system is a modified version of the NIH activity and chronicity index in LN, based on the study by Austin et al (Table 1).

Clinical evaluation

At the time of the biopsy and after the treatment, serum creatinine levels, serum albumin levels, the presence of hematuria (macroscopic and microscopic), quantitative value of proteinuria, and the presence of nephrotic syndrome were documented for all patients. Patients with serum creatinine levels greater than 1.20 mg/dL were categorized as having high creatinine, with clinically significant elevation. ¹⁴ Patients with ≥ 3 erythrocytes per highpower field (HPF) on urine microscopy analysis were considered to have microscopic hematuria. 15 Patients with visible blood in their urine were considered to have macroscopic hematuria. Patients with protein levels greater than 500 mg in a 24-h urine collection were considered to have proteinuria. 16 Additionally, post-biopsy treatment information, renal outcomes, and follow-up periods were recorded.

Statistical analysis

The normality of continuous variables was assessed using the Shapiro-Wilk normality test. Intergroup comparisons of continuous variables were performed using the Mann-Whitney U test and the Kruskal-Wallis test. Pearson's chi-square, Yates' chi-square, and Fisher's exact tests were used to compare categorical variables between groups. A *p*-value of <0.05 was considered statistically significant. All

Table 1. The modified NIH activity and chronicity scoring system.

Modified NIH activity index	lified NIH activity index Definition			
Endocapillary hypercellularity	illary hypercellularity Endocapillary hypercellularity in <25% (1+), 25%-50%, or >50% (3+) of glomeruli			
Neutrophils/karyorrhexis	Neutrophils and/or karyorrhexis in <25% (1+), 25%-50%, or >50% (3+) of glomeruli			
Fibrinoid necrosis	Fibrinoid necrosis in <25% (1+), 25%-50%, or >50% (3+) of glomeruli			
Hyaline deposits	Wire loop lesions and/or hyaline thrombi in <25% (1+), 25%-50%, or >50% (3+) of glomeruli			
Cellular/fibrocellular crescents	Cellular and/or fibrocellular crescents in <25% (1+), 25%-50%, or >50% (3+) of glomeruli			
Interstitial inflammation	Interstitial leukocytes in <25% (1+), 25%-50%, or >50% (3+) of the cortex	0-3		
Total		0-24		
Modified NIH chronicity index	C Definition	Score		
Total glomerulosclerosis score	Global and/or segmental sclerosis in <25% (1+), 25%-50%, or >50% (3+) of glomeruli	0-3		
Fibrous crescents	Fibrous crescents in <25% (1+), 25%-50%, or >50% (3+) of glomeruli	0-3		
Tubular atrophy	Tubular atrophy in <25% (1+), 25%-50%, or >50% (3+) of the cortical tubules	0-3		
Interstitial fibrosis	Interstitial fibrosis in <25% (1+), 25%-50%, or >50% (3+) of the cortex	0-3		
Total		0-12		

statistical analyses were conducted using IBM SPSS Statistics Version 25.

Results

A total of 57 newly diagnosed, biopsy-proven lupus nephritis (LN) cases were included in the study. The mean age of the participants was 29.4 years (range: 8–71). Nine (15.7%) patients were younger than 18 years of age. Forty-five patients (78.9%) were female and 12 (21.05%) were male. The median serum creatinine was 0.69 mg/dL (interquartile range [IQR]: 0.26–6.2 mg/dL). Thirteen patients (22.8%) had clinically significant elevated serum creatinine levels. Proteinuria was present in all patients, with a median value of 1619 mg/24h (range: 517–10,104 mg/24h). The median serum albumin level was 3.48 mg/dL (IQR: 1.70–4.50 mg/dL). Clinical manifestations consistent with nephrotic syndrome were observed in 15 (26.3%) patients. Hematuria was detected in 28 patients (49.1%).

Class 3 was the most common form of LN, accounting for 40.4% of cases, followed by Class 4 (38.6%), Class 5 (10.5%), and Class 2 (5.3%). Conversely, Classes 6 and 1 were the least frequently diagnosed, representing 1.7% and 3.5% of cases, respectively.

The median activity index score was 4.5 (range: 0-15), and the median chronicity index score was 2.2 (range: 0-9). Based on the activity index scores, patients were divided into low (0-5) and high (6-24) activity groups. Similarly, based on chronicity index scores, patients were categorized into low (0-2) and high (3-12) chronicity groups. A high activity index was identified in 42.1% (n=24) of the biopsies, while 40.4% (n=23) of the patients had a high chronicity index.

Ptc was detected in 45 (78.9%) patients, with ptc scores of 1, 2, and 3 observed in 20 (35.1%), 20 (35.1%), and 5 (8.8%) patients, respectively (Figures 1–3). The highest frequency of ptc was observed in Class 4 among proliferative LNs. Ptc was identified in 21 (96%) of the 22 patients with Class 4 LN. Of these, 6 (27%) had ptc score 1, 12 (55%) had ptc score 2, and 3 (14%) had ptc score 3. Conversely, ptc score 0 was found in 9 (39%) of the 23 patients with Class 3 LN. In total, ptc was observed in 14 (69%) Class 3 patients, including 9 patients with ptc score 1 and 5 patients with ptc score 2. No patients in Class 3 exhibited ptc score 3. Ptc score 1 was identified in all 3 biopsies diagnosed as Class 2.

Among non-proliferative LN biopsies, ptc was observed in 5 (83.3%) of 6 Class 5 patients. Of these, 1 patient (16.6%) had ptc score 1, 3 patients (50%) had ptc score 2, and 1 patient (16.6%) had ptc score 3. Only 2 biopsy samples were diagnosed with Class 1 LN, with ptc scores of 0 and 1, respectively. The single biopsy classified as Class 6 had a ptc score of 3 (Figure 4).

In this study, biopsies with ptc scores of 0 and 1 were categorized as low severity, while biopsies with ptc scores of 2 and 3 were categorized as high severity. Statistical analysis revealed a higher prevalence of ptc in Class 4 patients compared to Class 3 patients. High-severity ptc (scores 2-3) was observed in 68.2% (n = 15/22) of Class 4 biopsies, significantly higher than the 21.7% (n = 5/23) found in Class 3 biopsies (p = .005).

The detection rate of high-severity ptc (scores 2-3) was significantly higher in biopsy specimens with a high activity index compared to those with a low activity index (p = 0.032). Ptc scores 2-3 were recorded in 62.5% of cases with an activity index of 6 or greater, whereas only 30.3% of cases with a low activity index had ptc scores 2-3.

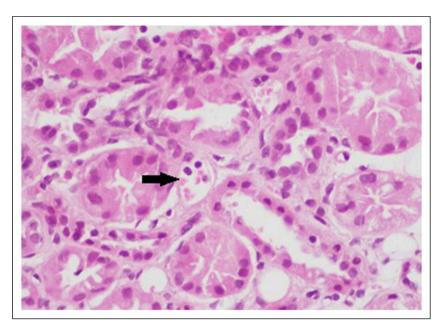


Figure 1. Ptc with a score of 1 (indicated by the arrow). Representative ptc lesions are shown (H&E, ×400).

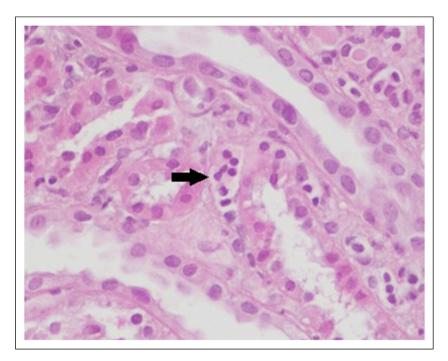


Figure 2. Ptc with a score of 2 (indicated by the arrow). Representative ptc lesions are shown (H&E, ×400).

There was no significant difference between the severity of ptc in groups with low and high chronicity indices (p = 0.442).

A significantly higher incidence of ptc was observed in patients with clinically significant elevated serum creatinine levels compared to those with serum creatinine levels within the normal range (p < 0.001). High-severity ptc (scores 2-3)

was found in 92.3% of patients with elevated serum creatinine levels.

Hematuria (either macroscopic or microscopic) was present in 28 patients (49.1%). High-severity ptc was observed in 41.4% of patients without hematuria and 46.4% of those with hematuria, with no significant difference between the two groups (p = 0.907).

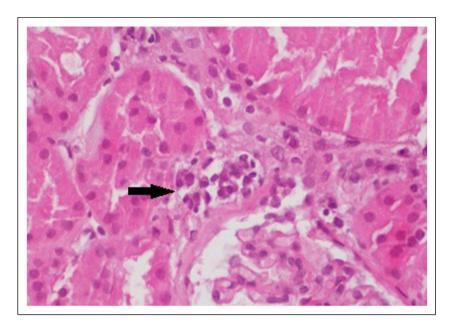


Figure 3. Ptc with a score of 3 (indicated by the arrow). Representative ptc lesions are shown (H&E, ×400).

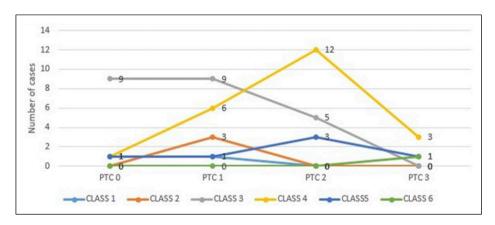


Figure 4. Distribution of the ptc scores according to the classes of the LN.

The relationship between ptc severity and certain clinical and histopathological features is summarized in Table 2.

Clinical follow-up data were not available for 3 patients. The median follow-up period for the remaining 54 patients was 47.6 months (range: 4–105 months). In addition to steroids, combination therapies including cyclophosphamide, azathioprine, rituximab, and mycophenolate mofetil were administered to all patients. During the follow-up period, remission was achieved in 72.2% (39 of 54 patients) of patients, while partial remission and/or resistance occurred in 18.5% (10 of 54 patients). Chronic renal failure developed in 9.3% (5 of 54 patients) of patients, and 1 (1.8%) patient died. One patient underwent a renal transplant.

Proteinuria decreased in 76.4% of cases after treatment. This rate was 80.6% in patients with low ptc scores, while it was slightly lower in patients with high ptc scores (70.8%),

though this difference was not statistically significant (p = 0.597). The median proteinuria level in patients with low ptc scores was 185 mg/24h (range: 53–5731 mg/24h), whereas it was 230 mg/24h (range: 67–4600 mg/24h) in patients with high ptc scores (p = 0.396). Serum creatinine levels decreased to below 1.2 mg/dL in 85.5% of cases. This rate was 90.3% in patients with low ptc scores, compared to 79.2% in patients with high ptc scores (p = 0.597). The median serum creatinine level in patients with low ptc scores was 0.63 mg/dL (range: 0.41–7.19 mg/dL), while it was 0.81 mg/dL (range: 0.37–7.16 mg/dL) in those with high ptc scores (p = 0.069).

During follow-up, remission was achieved in 80% (24 of 30 patients) of patients in the low ptc group, with partial remission and/or resistance in 20% (6 of 30 patients). No patients in the low ptc group progressed to chronic renal

failure. In contrast, 62.5% (15 of 24 patients) of patients with high ptc scores achieved remission, 16.7% (4 of 24 patients) had partial remission and/or resistance, and 20.8% (5 of 24 patients) progressed to chronic renal failure (p = 0.032). The relationship between ptc group and renal outcomes is summarized in Table 3.

Discussion

One of the Banff lesion scores, ptc, assesses the degree of inflammation within the peritubular capillaries. Along with glomerulitis, ptc represents a form of microvascular inflammation characteristic of both acute AMR and chronic

active AMR.¹⁷ While ptc is commonly observed in transplant kidney biopsies, it can also be found in native kidney biopsies and has been documented in a variety of underlying kidney disease, including pauci-immune glomerulone-phritis, ¹⁸ LN, ¹⁹ cryoglobulinemia, ^{20,21} and viral infections. ²² It has also been observed in numerous other native kidney diseases. ^{23,24}

The most comprehensive study on the frequency of ptc in non-transplant kidney biopsies in the English literature was conducted by Sarioğlu et al., who analyzed 169 native kidney biopsies and found ptc in 53.3% of cases. Among the 15 LN biopsies included in their study, ptc was present in 4%. ²³ In contrast, the prevalence of ptc in our study was

Table 2. General characteristics of patient groups with ptc 0-1 (low score) and ptc 2-3 (high score).

	ptc 0-1 (n:32)	ptc 2-3 (n:25)	p value
Gender (F/M), n	24/8	21/4	0.617
Age, mean ± SD	27.72 ± 1.78	31.64 ± 2.93	0.741
Hematuria, n (%)	17 (58.6)	12 (41.4)	0.907
Absent present	15 (53.6)	13 (46.4)	
Serum albumin value (mg/dl) mean ± SD	3.53 ± 0.11	3.08 ± 0.13	0.008
Serum creatinine value (mg/dl) mean ± SD	0.65 ± 0.37	1.55 ± 0.26	0.001
Serum creatinine level, n (%)			<0.001
>I.2 mg/dl	I (7.7)	12 (92.3)	
≤I.2 mg/dl	31 (70.5)	13 (29.5)	
Proteinuria value (mg/24h) mean ± SD	2266.4 ± 423.9	3509.9 ± 576.8	0.045
Nephrotic syndrome, n (%)	26 (61.9)	16 (38.1)	0.244
Absent present	6 (40)	9 (60)	
Classes of lupus nephritis n (%)	` ,	` ,	
Class I	2 (100)	0 (0)	0.005
Class 2	3 (100)	0 (0)	
Class 3	18 (78.3)	5 (21.7)	
Class 4	7 (31.8)	15 (68.2)	
Class 5	2 (33.3)	4 (66.7)	
Class 6	0 (0)	I (100)	
Activity index, mean ± SD	4.09 ± 0.61	6.96 ± 0.81	0.005
Activity index, n (%)			0.032
≥6	9 (37.5)	15 (62.5)	
<6	23 (69.7)	10 (30.3)	
Chronicity index, mean ± SD	2.18 ± 0.29	3.04 ± 0.46	0.213
Chronicity index (≥3), n (%)			0.442
>2	11 (47.8)	12 (52.2)	
≤2	21 (61.8)	13 (38.2)	

Table 3. Clinical follow-up of patient groups with ptc 0-1 (low score) and ptc 2-3 (high score).

	ptc 0-1 (n:30)	ptc 2-3 (n:24)	Total (n:54)	p value
Renal outcome, n (%)				
Remission	24 (80)	15 (62.5)	39 (72.2)	0.032
Partial remission/Resistant	6 (20)	4 (16.7)	10 (18.5)	
ESRD	0 (0)	5 (20.8)	5 (9.3)	

significantly higher, at 78.9%. Notably, 44% of LN patients exhibited high ptc severity.

In our study, no significant correlation was found between age, gender, hematuria, or nephrotic syndrome and the severity of ptc. However, high ptc severity was observed in 68% of Class 4 LN biopsies, while only 22% of Class 3 biopsies exhibited high ptc severity. The presence of proliferation in LN histopathology is widely accepted as a poor prognostic indicator, warranting more aggressive treatment for patients with Class 3 and 4 LN. ^{25–27} Our results align with this notion, as ptc severity was significantly higher in Class 4 compared to Class 3 patients, suggesting that ptc may serve as an additional marker of disease severity.

A high serum creatinine level is a common finding in disorders affecting renal endothelial function. The patients diagnosed with LN, the baseline serum creatinine level was an effective predictor of the eventual outcome. 28,29 Patients with high serum creatinine levels have a low remission rate, a poor overall long-term prognosis and an increased incidence of ESRD and mortality. Austin et al. reported that patients with a baseline serum creatinine level of ≥1.4 mg/dL had more than a 3.5-fold increased risk of progressing to ESRD over an eight-year follow-up period compared to patients with a serum creatinine level of <1.4 mg/dL.³⁰ Korbet et al. indicated that patients with an initial serum creatinine level of 1.0 mg/dL or lower had the most favorable prognosis.²⁸ In our study, we found that high ptc severity was significantly associated with elevated serum creatinine levels (>1.2 mg/dL), indicating a potential link between ptc and unfavorable renal outcomes in LN.

We conducted a retrospective study to evaluate the modified NIH activity and chronicity scores in patients with LN. The modified NIH scoring system provides more detailed information compared to the shorthand A, C, and A/C parameters previously used. ^{9,13} In our study, we did not find an association between low (0-2) and high (3-12) chronicity index scores and the severity of ptc. Many studies have linked a higher chronicity index to poor renal outcomes. ^{18,31–33} Increased glomerular and interstitial fibrosis may contribute to higher ptc severity. The limited number of Class 5 and Class 6 biopsies in the current study may have influenced the statistical results.

The results of previous studies have consistently shown a correlation between the activity index, its components, and renal outcomes. Austin et al. reported that the composite activity index, cellular crescents, and fibrinoid necrosis were highly predictive of renal failure and outcomes. ¹³ Rijnink et al. found that fibrinoid necrosis was associated with a higher risk for ESRD. ³⁴ In their prediction tool for the development of ESRD in LN patients, Tang et al. identified cellular crescents and an activity index greater than 20 as significant factors. ³⁵ Singh et al. also found a correlation

between a higher activity index and a lower complete response to treatment. In our study, a high activity index was identified in 42.1% of biopsy samples. This finding was not unexpected, given the relatively high incidence of Class and 4 biopsies in the cohort. Additionally, the severity of ptc was statistically significantly higher in biopsy samples with an activity index of 6 or above.

Our study also found significant relationships between high ptc severity and elevated serum creatinine levels, higher proteinuria, and lower serum albumin levels (p = 0.001, p = 0.045, and p = 0.008, respectively). During follow-up, patients with high ptc scores had a lower remission rate (62.5% vs 80%) and a higher incidence of chronic renal insufficiency (20% vs 0%) compared to those with low ptc scores. These findings suggest that ptc severity may be a valuable prognostic marker in LN.

While there are few studies investigating ptc in native kidney biopsies, and even fewer that explore its prognostic significance, this study represents one of the first to address this issue. However, there are limitations. We were unable to compare pre- and post-treatment biopsy scores, as biopsies are typically not conducted immediately following treatment. Additionally, the follow-up period in our study was relatively short, limiting our ability to assess late-stage renal failure or long-term renal outcomes. Since biopsies were primarily conducted during disease flare-ups, the majority of patients in our study were classified as Class 3 and 4, limiting the ability to evaluate ptc in other classes. Furthermore, as a singlecenter study with a relatively small sample size, larger multi-center studies with longer follow-up are needed to validate these findings.

Conclusion

Despite recent advancements in treatment, LN remains a challenging condition, with approximately 10% of patients progressing to ESRD despite appropriate treatment. The modified NIH scoring system has proven prognostic value in predicting complete renal response, though the lesions comprising the system may evolve over time. In our study, we found a significant correlation between high ptc severity, elevated creatinine levels, and high activity index scores. These findings suggest that ptc severity may be an important marker of disease activity and severity in LN, potentially adding value to the NIH scoring system. Further studies with larger patient cohorts and longer follow-up are required to confirm the prognostic significance of ptc in LN. 37-41

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical statement

Ethical approval

This study was approved by the Non-invasive Clinical Research Ethics Committee of Eskişehir Osmangazi University (E–25403353-050.99-2400052898) on February 27, 2024.

Informed consent

This is an retrospective study, patient consent was not required. Patient data will not be shared with third parties.

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Data availability statement

Available to only corresponding author.

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