Original Article

Serum Prolactin: A Diagnostic and Disease Activity Marker for Lupus Nephritis

Md. Saif Bin Mizan[1], Mohammed Mejbahuddin Mia[2], Samia Hoque[3], Sumaya Afroze[4], Md. Juber Alam[5], Syed Imtiaz Ahmed[6], Bepasha Naznin[7], Sheikh Anisul Haque[8]

Abstract

Background: *Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE), affecting all renal compartments. Despite advances, existing noninvasive markers for LN lack the needed sensitivity and specificity.*

Objective: *This study aimed to assess serum prolactin as a diagnostic and disease activity indicator for LN.*

Materials and Methods: *Conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from September 2016 to August 2017, the cross-sectional study diagnosed Systemic Lupus Erythematosus (SLE) patients based on ACR 1997 criteria. Group A, with suspected lupus nephritis, underwent renal biopsy, while Group B included active SLE patients without renal involvement. Serum prolactin, C3, C4, and anti-dsDNA levels were measured. Renal histology followed International Society of Nephrology/ Renal Pathology Society (ISN/RPS 2004) criteria, and disease activity was assessed using Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) and Renal-SLEDAI scores.*

Results: *In Group A, where 80% displayed severe disease activity (mean renal score: 11 ± 3.47), serum prolactin levels were significantly higher (41.51 ± 16.79 ng/ml) than in Group B (14.92 ± 6.71 ng/ml). A positive correlation existed between serum prolactin and LN renal activity scores, while negative correlations occurred with C3 and C4 levels. Notably, patients with Class III and IV LN exhibited higher prolactin levels than those with Class II and V.*

Conclusions: *The study suggests serum prolactin's potential as a valuable serological biomarker for diagnosing lupus nephritis and monitoring disease activity. Elevated prolactin levels were associated with severe renal involvement, emphasizing its diagnostic utility. This research contributes to the ongoing quest for more reliable LN markers, offering promising insights for improved diagnostic and prognostic approaches in lupus nephritis management.*

Key words: *Lupus Nephritis (LN), Systemic Lupus Erythematosus (SLE), SELENA, SLEDAI.*

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Introduction

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease characterized by a broad spectrum of clinical manifestations and the production of a variety of autoantibodies. These manifestations can range from relatively mild symptoms, such as joint and skin involvement, to severe and life-threatening multi-organ complications. The diagnosis of SLE is challenging and relies on the expertise of experienced clinicians who must recognize a constellation of characteristic clinical and laboratory features while excluding other potential diagnoses.[1]

Lupus nephritis (LN) is recognized as one of the most severe complications of SLE, affecting all four renal compartments: glomeruli, tubules, interstitium, and blood vessels. Histopathological evaluation of renal biopsies according to the ISN/RPS 2004 classification is widely employed to categorize LN cases into specific classes based on observed renal lesions. However, even within a single class, there may be significant variation in the degree of renal involvement, and glomerular lesions can evolve from one class to another over time.[2]

Notably, up to 25% of LN patients may progress to end-stage renal disease (ESRD) within a decade of their renal involvement.[3] Furthermore, when LN occurs early in the course of SLE,

1. Associate Professor and Head, Department of Nephrology, Dr. Sirajul Islam Medical College, Dhaka, Bangladesh
2. Assistant Professor, Department of Transfusion Medicine, Khwaja Yunus Ali Medical College and Hospital, Sirajganj, Bangladesh
3. Assistant Professor, Department of Transfusion Medicine, Khwaja Yunus Ali Medical College and Hospital, Sirajganj, Bangladesh
4. Lecturer, Department of Forensic Medicine and Toxicology, Shahabuddin Medical College and Hospital, Dhaka, Bangladesh
5. Assistant Professor, Department of Cardiology, Dhaka Community Medical College and Hospital, Dhaka, Bangladesh
6. Assistant Registrar, Department of Nephrology, National Institute of Kidney Diseases and Urology, Dhaka, Bangladesh
7. Associate Consultant, Department of Transfusion Medicine, Asgar Ali Hospital, Dhaka, Bangladesh
8. Associate Professor, Department of Transfusion Medicine, Khwaja Yunus Ali Medical College & Hospital, Sirajganj, Bangladesh

Corresponding author: Mohammed Mejbahuddin Mia, Assistant Professor, Department of Transfusion Medicine, Khwaja Yunus Ali Medical College & Hospital, Sirajganj, Bangladesh. **Cell**: +8801775511111, **E-mail:** drmejbah2013@gmail.com

it is a major predictor of poor prognosis.[4] Currently, the diagnosis and assessment of LN activity rely on a combination of clinical and laboratory parameters, including proteinuria, urine protein creatinine ratio, creatinine clearance, anti-double-stranded DNA (anti-dsDNA) antibody levels, and complement component (C3 and C4) levels. However, these markers may lack the specificity and sensitivity needed for accurate diagnosis in challenging cases.[5]

Thus, there is a critical need to explore and evaluate novel biomarkers that can detect renal flare with higher specificity and sensitivity, especially in diverse patient populations.[3] Prolactin (PRL), a polypeptide hormone produced by lactotropes in the anterior lobe of the pituitary, has gained attention as a potential biomarker for LN. Prolactin levels can be influenced by various factors, including pregnancy, stress, elevated temperature, specific diseases (e.g., prolactinoma, primary hypothyroidism, polycystic ovarian syndrome), and certain medications (e.g., dopamine antagonists, dopamine-depleting drugs, oral contraceptives).[6] Importantly, lymphocytes can synthesize and secrete a biologically active PRL-like protein that serves as an autocrine growth factor for lymphoproliferation, suggesting a connection between PRL and the immune system.[7,8]

Studies have shown that SLE patients, specifically those with lupus nephritis, exhibit significantly elevated levels of PRL.[9] Additionally, experimental models involving mice with autoimmune predisposition have demonstrated lupus nephritis-like features after PRL injections, supporting the hypothesis that lymphocytic PRL might play a role in SLE pathogenesis, particularly in lupus nephritis flares. Some studies have also suggested a relationship between elevated PRL levels, anti-ds DNA antibodies, and lupus nephritis flares.[10] Elevated serum PRL levels have been associated with severe lupus nephritis, and these levels correlate positively with anti-ds DNA titers while negatively correlating with serum C3 and C4 levels. PRL levels also align with disease activity, and the reduction of serum PRL levels has been observed following treatment for lupus nephritis. These findings suggest that serum PRL might serve as a novel marker for diagnosing lupus nephritis and assessing its activity, providing a valuable addition to the diagnostic and monitoring tools for this complex and serious condition.[11]

Diagnosis and assessment of lupus nephritis remain clinical challenges, and the need for improved diagnostic and monitoring biomarkers is evident. Serum prolactin, given its associations with disease severity and activity, offers promise as a novel and valuable marker for lupus nephritis, potentially enhancing our ability to diagnose and manage this condition more effectively.

Materials and Methods

This study utilized a cross-sectional design. The research was conducted in the Department of Nephrology and Department of Transfusion Medicine at Bangabandhu Sheikh Mujib Medical University in Dhaka, Bangladesh. Data was collected from September 2016 to August 2017. The study focused on patients with active Systemic Lupus Erythematosus (SLE) with or without renal involvement. Convenient purposive sampling was employed to select participants. The study was conducted according to the ethical guidelines of the 2013 Declaration of Helsinki (The Code of Ethics of the World Medical Association) and received approval from the Institutional Review Board of the Bangabandhu Sheikh Mujib Medical University (No. BSMMU/2017/681). All patients in the study signed the informed consent.

The inclusion criteria was set to be patients who gave informed written consent and of both genders diagnosed as a case of SLE with or without renal involvement. Exclusion criteria was set to be pregnant and lactating females. Also patients with other co-morbidities were not considered. However, due to constraints related to budget and time, the sample size was ultimately set at 80 participants. This approach was employed to ensure that the study had sufficient power to detect meaningful differences and correlations while optimizing the utilization of available resources.

Statistical Analysis

The statistical analysis was conducted using computer-based techniques and systems. Data were meticulously recorded in preformatted data collection forms. Quantitative data were presented as mean and standard deviation, while qualitative data were expressed as frequency distribution and percentage.

The statistical analyses were performed using IBM SPSS Statistics software version 23 (Armonk, NY: IBM Corp), GrapHPad Prism 8 running on a Windows-based computer. Associations between categorical variables were assessed using chi-square tests, and for continuous variables, t-tests were employed. A significance level of $p < 0.05$ was considered statistically significant for all statistical tests.

Results

In this study, a total of 80 patients were enrolled. Group A, consisting of patients with lupus nephritis, included 40 individuals, while the remaining 40 patients were in Group B, representing those with systemic lupus erythematosus (SLE) but without renal involvement. The age distribution of the patients, reveals that the majority (37.50%, n=30) of patients fell within the 21–30 years' age group. Patients aged 31–40 years and 11–20 years accounted for 30% (n=24) and 21% (n=17), respectively. Consequently, most patients (58.5%, n=47) were in their second and third decades of life. The gender distribution among the two groups. Females were predominant in both Group A (lupus nephritis) and Group B (SLE without renal involvement), with 85% and 90%, respectively. The male-to-female ratio was approximately 1:8.5 in Group A and 1:9 in Group B. Importantly, the difference in gender distribution between the two groups was not statistically significant (p=0.737).

Table I: Frequency of clinical parameters among patients (n=80)

History/Examination	Group A n (%)	Group B n (%)	P value
Anemia			
• Mild	24 (60.0)	24 (60.0)	
• Moderate	4 (10.0)	16 (40.0)	0.001 #
• Severe	5(12.5)	0 (0)	
ACR criteria for SLE			
• Malar rash	11 (27.5)	37 (92.5)	0.001 #
• Discoid rash	0 (0)	12 (30.0)	0.001 #
• Photosensitivity	9 (22.5)	28 (70.0)	0.001 #
• Oral ulcers	23 (57.5)	31 (77.5)	0.094 #
• Arthritis	25 (62.9)	21 (52.5)	0.498 #
• Serositis	18 (45.0)	14 (35.0)	0.494 #
Blood pressure	Mean ±SD	Mean ± SD	
• Systolic BP (mmHg)	133 ± 14	113 ± 9	0.015 ##
• Diastolic BP (mmHg)	80 ± 10	72 ± 5	0.236 ##

#Chi-square test was done to measure the level of significance. ##Unpaired t test was done to measure the level of significance. SD: Standard deviation, BP: Blood Pressure.

Table I provides an overview of the frequency of clinical parameters among patients in both groups. Mild anemia was prevalent in both groups, with 60% in each. However, moderate anemia was more common in Group B (SLE without renal involvement) at 40%, compared to only 10% in Group A (lupus nephritis). Severe anemia was exclusively observed in 12.5% of patients in Group A. The difference in anemia prevalence between the two groups was statistically significant (p=0.001).

Various clinical manifestations were evaluated, including oral ulcers, arthritis, serositis, and neurological and hematologic disorders, with no statistically significant differences observed between the groups.

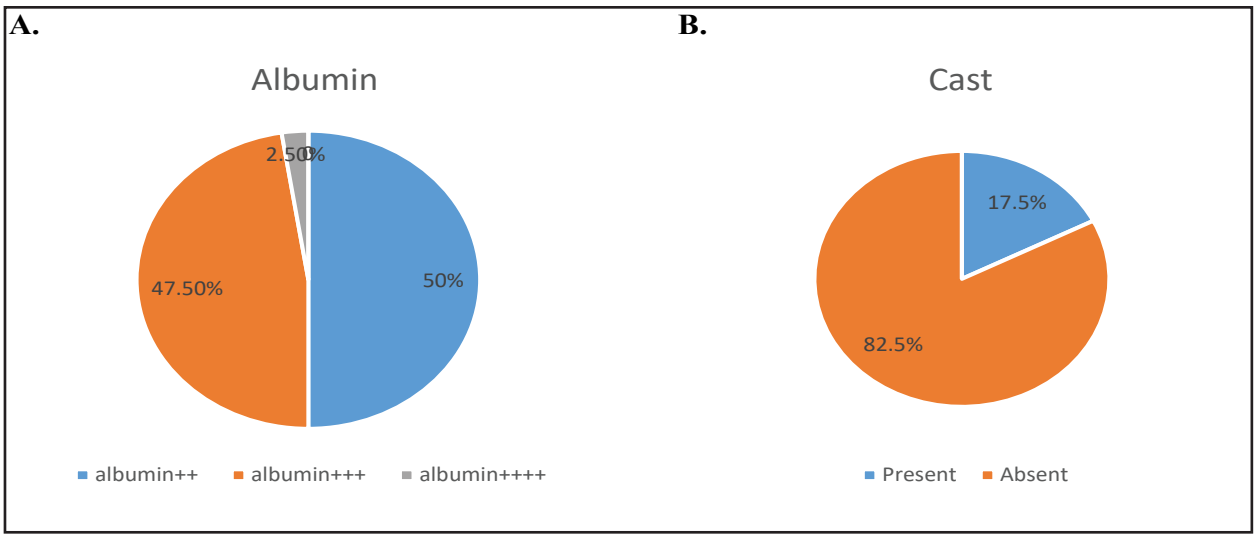

Figure 1: Describes the urine routine microscopic examination (RME) findings of patients in Group A (lupus nephritis). Fig 1A The examination revealed that 50% had two plus albumin in their urine. Additionally, Fig1B 17.5% of patients had casts present.

Table II: Proteinuria of group A (lupus nephritis) patients (n=40)

Proteinuria (24 hour UTP)	**n (%)**	
500mg/day– 1gm/day	8 (20)	
> 1gm/day– 2.9 gm/day	20 (50)	
>3 gm/day	12 (30)	
Laboratory findings	**Mean ± SD**	**Min – Max**
S. Creatinine (mg/dl)	**1.13 ± 0.34**	**0.52 – 1.60**
S. Albumin (g/L)	**28.22 ± 7.42**	**12 – 47**
ESR (mm in 1st hour)	**58.90 ± 31.56**	**8 – 124**

UTP: Urinary total protein SD: Standard deviation, ESR: Erythrocyte sedimentation rate.

Table II provides an overview of proteinuria in Group A (lupus nephritis) patients. Most of the patients (50%) exhibited proteinuria ranging from >1gm/day to 2.9 gm/day, followed by 30% with proteinuria exceeding 3 gm/day. The mean serum creatinine level was found to be 1.13 ± 0.34 mg/dl, with a range of 0.52 to 1.60 mg/dl. The mean serum albumin level was 28.22 ± 7.47 g/L, ranging from 12 to 47 g/L. The mean erythrocyte sedimentation rate (ESR) was 58.90 ± 31.56 mm in the first hour.

Table III: Distribution of patients according to disease activity of SLE measure and renal activity score (SELENA-SLEDAI) among the groups (n=80)

Parameters	**Group**		**p value**
	A n(%)	**B n(%)**	
Disease activity score			
• Mild to moderate	8 (20)	36 (90)	0.001
• Severe	32 (80)	4 (10)	
Renal activity score (SLEDAI)	11 ± 3.47		

Chi-square test was done to measure the level of significance. Group A: Lupus nephritis patients, Group B: SLE without renal involvement.

Table III examines the disease activity in SLE patients, as measured by the SELENA-SLEDAI score. In Group A (lupus nephritis), 80% of patients exhibited severe disease activity, with a mean renal activity score of 10.11 ± 4.43. On the other hand, the majority of Group B patients (90%) had mild to moderate disease activity. The difference in SLE disease activity between the two groups was statistically significant (p=0.001).

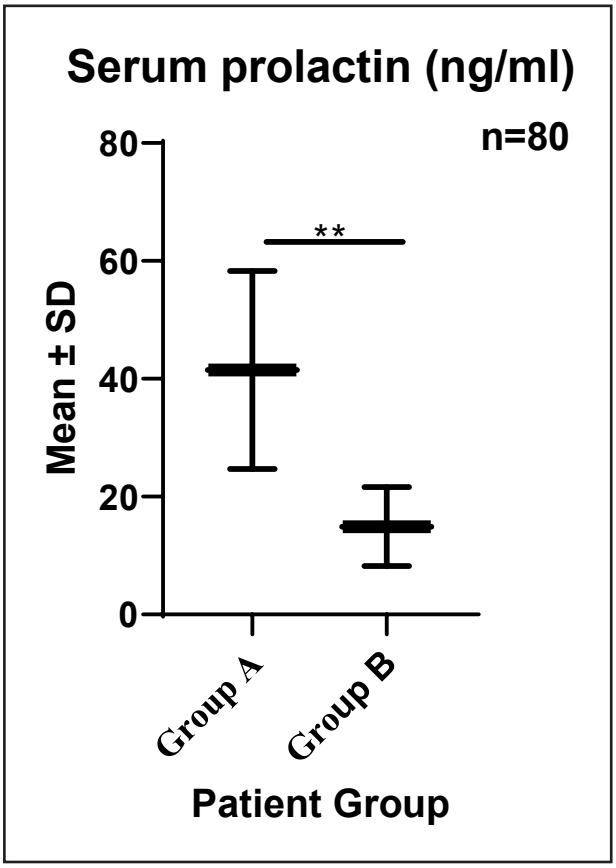

Figure 2: Serum prolactin level in study subjects (n=80). [p value * <0.05, ** <0.005, *** <0.0005, **** <0.0001] Unpaired t-test was done to measure the level of significance. SD: Standard deviation. Group A: Lupus nephritis patients, Group B: SLE without renal involvement.

The mean serum prolactin level was significantly higher in Group A (lupus nephritis) compared to Group B (SLE patients without renal involvement). The mean serum prolactin level in Group A was 41.51 ± 16.79 ng/ml, ranging from 11.60 to 77.00 ng/ml. In Group B, the mean serum prolactin level was 14.92 ± 6.71 ng/ml, with a range of 3.70 to 29.50 ng/ml. The p value was less than 0.001, signifying a statistically significant difference.

Table IV presents a comparison of immunological findings, including anti-dsDNA, serum C3, and C4 levels, along with serum prolactin levels between Group A (lupus nephritis) and Group B (SLE without renal disorder) at the time of renal biopsy. The analysis showed that serum prolactin was elevated in 75% of Group A patients and 7.5% of Group B patients, a statistically significant difference (p=0.001). In contrast, anti-ds DNA positivity, serum C3 and C4 levels, while varying between the groups, did not reach statistical significance.

Table IV: Immunological findings and serum prolactin among groups (n=80)

Lab parameters	Group A n (%)	Group B n (%)	p value
Serum prolactin			
• Elevated	30 (75.0)	3(7.50)	0.001
• Normal	10 (25.0)	37 (92.5)	
Anti-ds DNA			
• Positive	22 (55.0)	26 (65.0)	0.494
• Negative	18 (45.0)	14 (35.0)	
Serum C3			
• Low	27 (67.5)	12 (30.0)	0.002
• Normal	13 (32.5)	28 (70.0)	
Serum C4			
• Low	22 (55.0)	10 (25.0)	0.012
• Normal	18 (45.0)	30 (75.0)	

Unpaired t-test was done to measure the level of significance. C3: Complement 3, C4: Complement 4. Group A: Lupus nephritis patients, Group B: SLE without renal involvement.

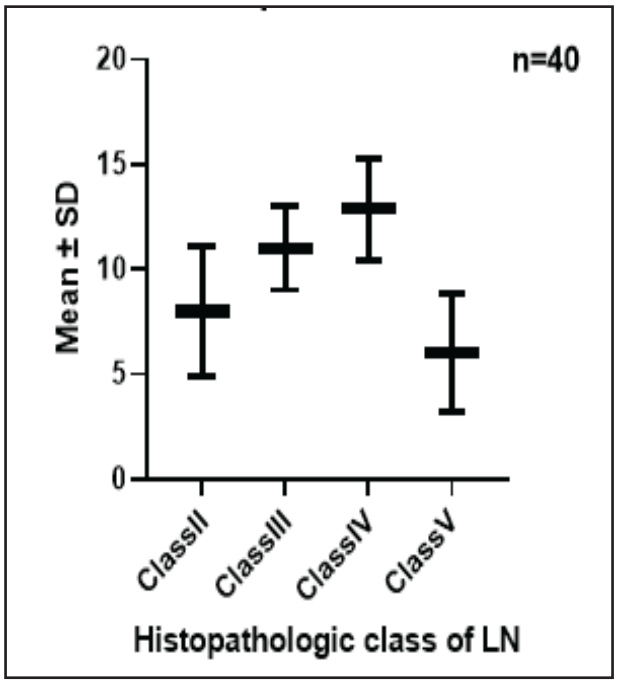

Figure 3: Renal activity score (Renal SLEDAI) in different classes of lupus nephritis patients (n=40)

The renal activity score (Renal SLEDAI) in different histopathologic classes of lupus nephritis patients in Group A. Class IV lupus nephritis patients displayed the highest disease activity with a mean value of 12.87 ± 2.39, followed by Class III, II, and V patients.

Table V: Serum prolactin level in different classes of lupus nephritis patient (n=40)

Histopathologic class of LN	n (%)	Serum prolactin		p value
		Mean ± SD	Range (Min - Max)	
Class II	11 (27.5)	20.64 ± 5.70	11.60 - 30.00	
Class III	04 (10.0)	37.25 ± 3.86	33.00 - 41.00	0.001
Class IV	23 (57.5)	53.54± 9.44	39.00 - 77.00	
Class V	02 (5.0)	26.50 ± 4.94	23.00 -30.00	

One-way ANOVA was done to measure the level of significance. LN: Lupus nephritis, SD: Standard deviation.

Table V shows serum prolactin levels in different histopathologic classes of lupus nephritis patients. The serum prolactin level was highest in Class IV (53.54 ± 9.44), followed by Class III, Class V, and Class II. The differences in serum prolactin levels among the different classes of lupus nephritis patients were statistically significant (p=0.001).

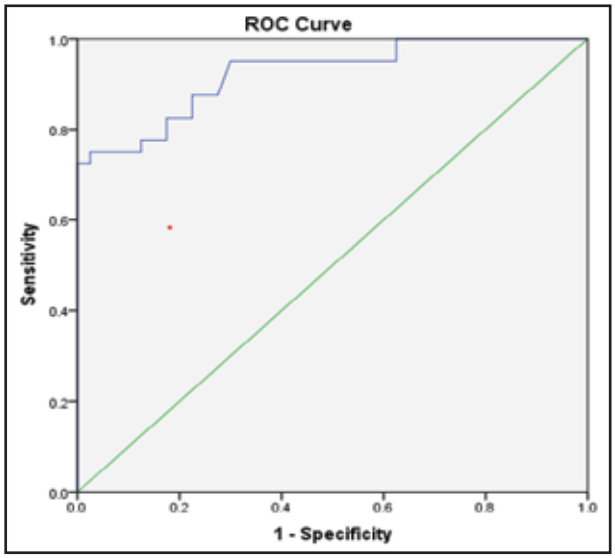

Figure 4: ROC curve of serum prolactin.

Figure 4 illustrates the ROC curve of serum prolactin. The area under the curve (AUC) for serum prolactin was 0.923 (95% CI 0.865 – 0.905), indicating strong diagnostic potential.

Discussion

Systemic Lupus Erythematosus (SLE) is a complex connective tissue disease with diverse manifestations and a course marked by relapses and remissions. Clinical nephritis, occurring in approximately 50% of SLE patients, is a critical risk factor for mortality.[12] Thus, the identification and monitoring of nephritis in SLE patients is of paramount importance. However, the lack of specificity in the currently available markers for renal exacerbations has necessitated the search for more reliable indicators of lupus nephritis detection and assessment of disease activity.[5]

Prolactin (PRL), a polypeptide hormone produced primarily by the anterior pituitary, is also synthesized in various parts of the brain and certain peripheral blood elements, including immune cells.[10] Notably, blood mononuclear cells from SLE patients secrete significantly higher levels of prolactin.[9] Several studies have linked elevated serum prolactin levels to the activity of lupus nephritis.[13]

In this cross-sectional study involving 80 patients, Group A comprised lupus nephritis patients, while Group B included SLE patients without laboratory evidence of nephritis. A majority (80%) of patients in Group A exhibited severe SLE disease activity, with a mean renal activity score of 10.11 ± 4.43. In contrast, most patients in Group B (90%) showed mild to moderate disease activity. Importantly, serum prolactin levels were significantly higher in Group A (lupus nephritis) compared to Group B (SLE patients without renal disorder). These results were consistent with previous findings by Abdo et al.[11] and Miranda et al.[14]

In this study, 75% of lupus nephritis patients (Group A) exhibited elevated serum prolactin, compared to only 7.5% of SLE patients without renal involvement (Group B). This disparity was statistically significant (p=0.001). The higher number of lupus nephritis patients with elevated serum prolactin in this study can be attributed to both the larger sample size and the higher disease activity of lupus nephritis patients in comparison to the Abdo et al. study.[11]

In contrast, other commonly used markers, such as Anti-ds DNA, C3, and C4, did not exhibit significant differences between the two groups in this study. These results were in agreement with a study by Farid et al.[15] for Anti-ds DNA and Birmingham et al.[16] for C3 and C4. The study also found that serum prolactin levels correlated positively with the renal activity score in lupus nephritis patients, making it a valuable tool for assessing disease activity. This correlation was consistent with the study conducted by Abdo et al.[11] and findings by Jara et al.[17] and Miranda et al.[14]

Additionally, serum prolactin levels varied significantly among different histopathologic classes of lupus nephritis patients, with Class IV patients showing the highest levels. This was attributed to their higher renal activity scores (renal-SLEDAI).

In summary, this study demonstrates that serum prolactin levels can effectively identify lupus nephritis patients with modest sensitivity but high specificity (75%, 92.5%). These results align with those of Abdo et al.[11] and underscore the potential of serum prolactin as a reliable biomarker for lupus nephritis detection and disease activity monitoring.

Conclusion

The findings of this study indicate that serum prolactin levels are notably elevated in SLE patients with nephritis compared to those without renal involvement. In contrast, the conventional markers of lupus activity fail to distinguish between renal and systemic disease. Therefore, serum prolactin emerges as a promising serological biomarker for identifying kidney involvement and, importantly, for closely monitoring the disease activity associated with lupus nephritis.

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