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ORIGINAL ARTICLE

The influence of Epigenetic Dysregulation and hyperprolactinemia on risk and disease activity Of systemic lupus erythematosus

Nearmeen M. Rashad*[1], Lobna. I Kotb [2], Nahawand A. El-Deeb 1, Mai M .El-Daly[3], Rehab M. Atef[4], Lamiaa Goda Mohammad [5] , Ahmed El-Sayed Hassan[5,7] , Amira M. Elsayed[6]

1 Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.
2 Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.
3 Medical Biochemistry and molecular biology department, Faculty of Medicine, Zagazig University,Egypt
4 Clinical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig,Egypt
5 Medical Physiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
6 Internal Medicine Department, Faculty of Medicine, Benha University, Beha, Egypt
7 Department of Basic Medical Sciences, College of Medicine, Sulaiman Al-Rajhi University, Bukayriah, Saudi Arabia.

.***Corresponding author**:
Nearmeen M. Rashad

Email:
nrashad78@yahoo.com
n.rashad@zu.edu.eg

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ABSTRACT

Background: Prolactin, a hormone with established endocrine functions, has increasingly been recognized for its immunomodulatory properties. This study aimed to explore the association between serum prolactin levels, its gene expression, and clinical as well as laboratory indicators of disease activity in patients with systemic lupus erythematosus (SLE).

Methods: A cross-sectional study was conducted involving 40 individuals diagnosed with SLE. Participants were grouped according to disease activity based on the SLE Disease Activity Index (SLEDAI). Serum prolactin concentrations were measured via immunoassay, and prolactin mRNA expression was assessed using real-time PCR. Correlations with disease activity, organ involvement, and immunological parameters were analyzed..

Results: Both circulating prolactin and its mRNA expression were significantly elevated in SLE patients compared to healthy individuals, with the highest values observed in patients with severe disease activity. A strong positive correlation was found between prolactin levels and SLEDAI scores, especially in those with renal, neurological, thrombotic, and pulmonary manifestations. Higher prolactin activity was also associated with complement consumption, positive antiphospholipid antibodies, hematologic abnormalities, and renal impairment. Notably, elevated prolactin levels persisted despite immunosuppressive treatment. Multivariate analysis indicated that ANA positivity predicted serum prolactin levels, while SLEDAI and anti-dsDNA levels independently predicted prolactin mRNA expression..

Conclusion: : Elevated prolactin levels and gene expression are closely linked to disease activity and immune dysfunction in SLE. These findings suggest that prolactin may contribute to lupus pathogenesis and could serve as both a biomarker for disease monitoring and a potential therapeutic target.

Keywords: Systemic lupus erythematosus; SLEDAI; mRNA; Prolactin

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic prototypic autoimmune disease [1]. Emerging evidence demonstrated that immunological, genetic, epigenetic, environmental, and hormonal factors have important pathogenic role in SLE [2]. A line of evidence has confirmed that SLE is more common in women, and more interestingly, SLE flares is associated with pregnancy [3] and with estrogen replacement therapy. This association could be due to hormonal influences such as estrogen and prolactin (PRL) [4].

Several lines of evidence indicate that PRL has pleiotropic functions, influencing metabolic homeostasis and immune system [5]. Interesting studies have illustrated that hyperprolactinemia in SLE potentially contributing to many factors such as lymphocytes in active SLE patients may produce higher amounts of prolactin [6], proinflammatory cytokines stimulate anterior cells to secrete more PRL and more important player is genetic factor [7].

Omics-based research has shown that prolactin (PRL) receptors are present on various immune cells, including T-cells, B-cells, monocytes, and natural killer (NK) cells. Therefore, differences in extra-pituitary PRL expression may contribute to the development or modulation of immune-related diseases [8].

Biomarkers play an essential role in the diagnosis, prognosis, monitoring, and therapeutic guidance of a wide range of diseases, including SLE, diabetes, cardiovascular conditions, and cancer [9]. An ideal biomarker should be disease-specific, easily measurable, sensitive to changes in disease activity, suitable for regular monitoring, and cost-effective. However, the diagnostic process for SLE remains challenging due to its complex pathophysiology and overlapping features with other autoimmune disorders. Hence, the discovery and validation of reliable biomarkers, along with a deeper understanding of their underlying mechanisms, are vital for enhancing diagnostic accuracy and improving treatment outcomes in SLE [10].

It is well established that maintaining disease stability in SLE is critical to minimizing the risk of irreversible organ damage and reducing mortality. Therefore, identifying noninvasive biomarkers that can reflect disease activity and predict flares is essential for effective long-term management. In this context, our study aimed to evaluate serum and mRNA levels of PRL in patients with SLE to explore their potential roles in disease susceptibility and, more importantly, in assessing disease activity.

2 Methods

A cross-sectional case-control study involved 80 subjects. 40 healthy subjects and 50 patients diagnosed with SLE according to 2009 SLICC revision of ACR classification criteria of SLE [11]. Only female patients were included to minimize gender-related variations in serum prolactin levels. All patients were subjected to full history taking, clinical examination, assessment of severity of SLE by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [12].

We excluded, those with other causes of hepatic diseases, arthritis or autoimmune diseases, pregnancy, thyroid and parathyroid disorders, certain antipsychotics, and patients on PPI, H2 blockers, antiemetics, hormonal contraception and drugs that influences PRL.

Laboratory tests for serum PRL were performed using prolactin ELISA kits. Blood samples for serum prolactin assessment were obtained in the early morning (8:00–10:00 a.m.) following an overnight fast. Participants remained seated and relaxed for about 20 minutes before sampling to reduce stress-related fluctuations. They were also advised to abstain from breast or nipple stimulation, sexual activity, strenuous exercise, and emotional stress for the preceding 24 hours. None of the participants were acutely ill or on medications known to alter prolactin secretion.

Ethical consideration

The current study adheres to the principles outlined in the Declaration of Helsinki, with signed informed consent acquired from all participants prior to their involvement in the research. This research has received approval from the Research Ethics Committee of Zagazig University Faculty of Medicine, Egypt (IRB≠, 414/4- June 2024).

DNA Extraction

Genomic DNA was extracted from EDTA whole blood using a spin-column method according to the protocol

Quantitative (qPCR) PCR: Isolation of total RNA from blood using Trizol Reagent (Invitrogen, CA, USA) following the manufacturer's manual. The gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method. GAPDH was used as an endogenous control. The PRL mRNA primers sequences were: Forward primer :5′-GAG-ACA-CCA-AGA-AGA-AGA-AGA-ATC-GGA-3, and reverse

primer: 5-ATG-ATT-CGG-CAC-TTC-AGG-AGC-3.

Statistical analysis

The data collected were organized and entered on Excel sheet and statistically analyzed using SPSS software statistical computer package for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). The significance level was set at $P < 0.05$.

Results

Demographic and Clinical Characteristics

The study included 40 patients with systemic lupus erythematosus (SLE), categorized according to disease activity into four groups: no activity (n=16), mild (n=14), moderate (n=7), and severe (n=3). There were no statistically significant differences among the groups regarding age (p=0.323) or disease duration (p=0.781). As expected, the SLE Disease Activity Index (SLEDAI) scores significantly increased across groups with disease severity (p<0.001).

Concerning clinical features of SLE; hypertension, nephritis, cardiac, CNS, thrombotic, and pulmonary involvement presented with an increasing prevalence in relation to disease activity. Additionally, the prevalence of nephritis, cardiac involvement, CNS manifestations, thrombosis, and pulmonary findings were significantly more frequent in active disease groups compared to the inactive group (p<0.001), while hypertension did not reach statistical significance (p=0.152), table 1.

Regarding Laboratory Parameters

There were significant differences in several laboratory markers across disease activity levels. Hemoglobin, total leukocyte count (TLC), and platelet count progressively declined with disease severity (all p<0.001). Serum creatinine and proteinuria increased significantly with higher disease activity (p<0.001). The erythrocyte sedimentation rate (ESR) also showed a marked elevation with increasing activity (p<0.001).

Complement consumption varied between groups: C4 consumption was significantly higher in more active disease (p=0.005), while C3 consumption showed higher prevalence but without reaching statistical significance (p=0.065). Regarding anticardiolipin IgG and lupus anticoagulant antibodies, were significantly more prevalent in active disease groups (p<0.05). However, anti-dsDNA and ANA there were non-significant differences (p=0.837 and 0.870, respectively), table 1.

Concerning Medications used in different groups of SLE

Use of steroids, azathioprine, and mycophenolate mofetil was significantly more common among patients with higher disease activity (p=0.016, <0.05, and <0.05, respectively). Cyclophosphamide and cyclosporine also showed increased usage in moderate-to-severe cases, though not all reached statistical significance, table 1

Comparison of prolactin serum and mRNA relative expression in studied groups

The interesting result of the existing research is that prolactin serum and mRNA relative expression values were overexpressed in the SLE group (22.68±7.2, 2.84±1.3, respectively) in comparison to control group (11.5±1.89,0.82, ±0.16, respectively), figure 1a, P <0.001).

Interestingly, among the SLE subgroups, serum prolactin levels increased progressively with higher disease activity. The mean ± SD serum prolactin level was 17.38 ± 8.19 ng/mL in patients with no disease activity (n = 16), 23.40 ± 4.50 ng/mL in those with mild activity (n = 14), 23.62 ± 7.83 ng/mL in the moderate activity group (n = 7), and 22.23 ± 11.51 ng/mL in patients with severe activity (n = 3).The overall mean for all patients (n = 40) was 20.94 ± 7.59 ng/mL, with values ranging from 1.00 to 44.00 ng/Ml. Median prolactin levels were 13.0, 11.0, 11.0, and 11.0 ng/mL for the no, mild, moderate, and severe activity groups, respectively. Although variation among groups was observed, higher prolactin concentrations tended to be associated with increased disease activity, figure 1b.

Regarding PRL mRNA, A similar upward trend was noted for prolactin mRNA expression. The mean ± SD expression values were 1.78 ± 0.40 for patients without disease activity, 2.51 ± 0.46 for mild, 3.82 ± 1.25 for moderate, and 4.00 ± 2.65 for severe activity groups. Median values followed the same

pattern, rising from 1.0 in inactive diseases to 4.0 in severe cases. These findings indicate that both serum prolactin levels and prolactin mRNA expression increase in parallel with SLE disease activity, Figure 1c

Correlations of prolactin serum and mRNA relative expression with studied variables among patients with SLE.

Serum prolactin levels and relative expression of prolactin mRNA showed significant positive correlations with SLEDAI (r=0.463 and r=0.393, respectively; both p<0.001). Prolactin mRNA expression was also significantly correlated with hypertension (r=0.316, p=0.047), nephritis (r=0.362, p=0.022), anti-dsDNA (r=0.422, p<0.001), ANA (r=0.407, p<0.001), serum creatinine (r=0.365, p<0.001), and consumed C4 (r=0.353, p=0.026) as shown in table 2.

Linear Regression Analysis

Linear regression analysis identified ANA positivity as a significant independent predictor of serum prolactin levels (β=0.552, p<0.001). Regarding prolactin mRNA expression, SLEDAI (β=-0.869, p<0.001) and anti-dsDNA (β=-0.518, p<0.001) were significant negative predictors, suggesting that increased disease activity and dsDNA levels are independently associated with higher prolactin mRNA expression table 3.

The diagnostic performance of PRL serum and mRNA relative expression in distinguishing SLE and control

To assess the diagnostic performance of serum PRL and PRL mRNA relative expression in distinguishing SLE patients from healthy controls, receiver operating characteristic (ROC) curve analysis was performed. The area under the curve (AUC) for serum prolactin was 0.824 (95% CI: 0.720–0.927, p < 0.001), indicating good diagnostic accuracy. Similarly, prolactin mRNA expression demonstrated a slightly higher AUC of 0.832 (95% CI: 0.732–0.931, p < 0.001), also reflecting strong diagnostic potential, figure 2a.

Optimal cutoff values were identified using coordinate points of the ROC curve. For serum PRL, a threshold of 12.7 µg/L yielded a sensitivity of 82.5% and specificity of 77.5%. For PRL mRNA, a cutoff of 1.07 (relative expression) provided a sensitivity of 82.5% and specificity of 77.5% as well. Both markers maintained a balance between high sensitivity and acceptable specificity.

The diagnostic performance of PRL serum and mRNA relative expression in differentiating mild SLE from Inactive Disease

To assess whether prolactin levels could discriminate against mild disease activity from remission. Serum PRL had an AUC of 0.831 (95% CI: 0.659–1.000; *p* = 0.010). PRL mRNA showed a superior AUC of 0.919 (95% CI: 0.784–1.000; *p* = 0.001). At a cutoff of **1.20** for PRL mRNA, sensitivity was 90%, and specificity was 83.3%, suggesting strong discriminative power, particularly for the mRNA marker, figure 2b.

The diagnostic performance of PRL serum and mRNA relative expression in distinguishing moderate from mild activity SLE

Serum PRL had an AUC of 0.806 (95% CI: 0.633–0.979; p = 0.002). PRL mRNA had an AUC of 0.824 (95% CI: 0.667–0.981; p = 0.001). Both markers were able to distinguish moderate from mild activity. For PRL mRNA, a cutoff of 1.75 maintained high sensitivity (86.4%) with reduced specificity (60%). the diagnostic performance of PRL serum and mRNA relative expression in distinguishing severe from moderate activity SLE, figure 2c.

The diagnostic performance of PRL serum and mRNA relative expression in differentiating severe from moderate SLE Activity.

Interestingly, the diagnostic performance differed markedly between the two biomarkers. Serum PRL had a poor AUC of 0.310 (95% CI: 0.000–0.811; *p* = 0.362), suggesting no significant discriminative ability. In contrast, PRL mRNA achieved an excellent AUC of 0.952 (95% CI: 0.817–1.000; *p* = 0.030), indicating very strong diagnostic performance. At a cutoff of 2.75, PRL mRNA achieved 100% sensitivity and 57.1% specificity, demonstrating potential as a powerful marker for detecting severe disease. Thus, across all comparisons, PRL mRNA

outperformed serum PRL in discriminating between disease states. Its ability to distinguish between both activity levels and health controls suggests that PRL mRNA may serve as a more sensitive and robust biomarker for assessing SLE disease activity. figure 2c.

Table1: Demographic and clinical characteristics, and laboratory parameters of the SLE groups.

Variables	No activity, n=16	Mild, n=14	Moderate, n=7	Severe, n=3	P value
Age	**29.6±4.8**	**32.8±7.8**	**35.1±5.5**	**29.8±4.5**	**0.323**
Disease duration (years)	**6.3±0.87**	**6.5±1.9**	**5.4±4.1**	**6. 3±0.34**	**0.781**
SLEDAI	**2.3±0.8**	**5.3±2.46**	**7.3±3.46**	**13.9±4.08**	**<0.001***
Hypertension N (%)	**9(56.3%)**	**12(85.6%)**	**6(85.7%)**	**3(100%)**	**0.152**
Nephritis, N (%)	**2(12.5%)**	**11(78.6%)**	**6(85.7%)**	**3(100%)**	**<0.001***
Mucocutaneous, N (%)	**14(87.5%)**	**12(85.7%)**	**7(100%)**	**3(100%)**	**0.680**
Musculoskeletal, N (%)	**15(93.8%)**	**12(85.7%)**	**7(100%)**	**2(66.7%)**	**0.372**
Cardiac, N (%)	**0(0%)**	**4(28.4%)**	**5(71.4%)**	**3(100%)**	**<0.001***
CNS, N (%)	**0(0%)**	**3(21.4%)**	**4(57.1%)**	**2(66.7%)**	**<0.001***
Venous/arterial thrombosis	**0(0%)**	**9(64.3%)**	**5(71.4%)**	**2(66.7%)**	**<0.001***
Pulmonary (%)	**0(0%)**	**9(64.3%)**	**5(71.4%)**	**2(66.7%)**	**<0.001***
Hemoglobin (g/dl)	**10.3±0.56**	**10.7±1.35**	**8.8±0.10**	**8.7±0.06**	**<0.001***
TLC ($\times10^3$/mm3)	**6.3±0.56**	**6.76±1.35**	**4.8±0.12**	**4.7±0.06**	**<0.001***
Platelets ($\times10^3$/mm3)	**198.5±15.2**	**204.4±25.7**	**167.6±2.1**	**166.7±1.3**	**<0.001***
Serum creatinine (mg/dL)	**0.74±0.13**	**0.82±0.06**	**0.99±0.02**	**0.79±0.14**	**<0.001***
Proteinuria (g/d)	**0.028±0.06**	**0.82±0.06**	**0.99±0.02**	**1.64±0.14**	**<0.001***
ESR (mm/hr)	**15.82±0.06**	**62.76±2.62**	**78.25±5.29**	**116.35±4.83**	**<0.001***
C3 (consumed)	**1(6.3%)**	**5(35.7%)**	**4(57.1%)**	**1(33.3%)**	**0.065**
C4 (consumed)	**2(12.5%)**	**8(57.1%)**	**6(85.7%)**	**2(66.7%)**	**0.005**
Positive dsDNA, N (%)	**13(81.3%)**	**11(78.6%)**	**6(85.7%)**	**3(100%)**	**0.837**
Positive ANA, N (%)	**15(93.8%)**	**13 (92.9%)**	**7(100%)**	**3(100%)**	**0.870**
Positive Anticardiolipin IgG	**2(12.5%)**	**9(64.3%)**	**5(71.4%)**	**2(66.7%)**	**<0.05***
Positive Lupus anticoagulant	**3(18.8%)**	**9(64.3%)**	**5(71.4%)**	**2(66.7%)**	**<0.05***
Medications					
Steroids, N (%)	**6(37.5%)**	**9(64.3%)**	**7(100%)**	**3(100%)**	**0.016**
Hydroxychloroquine, N (%)	**11(68.8%)**	**13(92.9%)**	**5(71.4%)**	**2(66.7%)**	**0.400**
Azathioprine, N (%)	**2(12.5%)**	**5(35.7%)**	**3(42.5%)**	**3(100%)**	**<0.05***
Cyclophosphamide, N (%)	**2(12.5%)**	**6(42.9%)**	**4(57.1%)**	**2(66.7%)**	**0.080**
Cyclosporine, N (%)	**0(100%)**	**0(100%)**	**1(14.3%)**	**2(66.7%)**	**<0.05***
Mycophenolate mofetil, N (%)	**2(12.5%)**	**11(78.6%)**	**6(85.7%)**	**3(100%)**	

BMI: body mass index, SLEDAI; systemic lupus erythematosus disease activity index, ESR; erythrocyte sedimentation rate, dsDNA: double-stranded DNA, ANA: antinuclear antibodies C3; complement 3, C4: complement 4.* Statistically significant ($P < 0.05$).

£ Significant P values ($P < 0.05$) when compared with no activity group.

$ Significant P values ($P < 0.05$) when compared with mild group.

Significant P values ($P < 0.05$) when compared with moderate group.

* Statistically significant ($P < 0.05$)

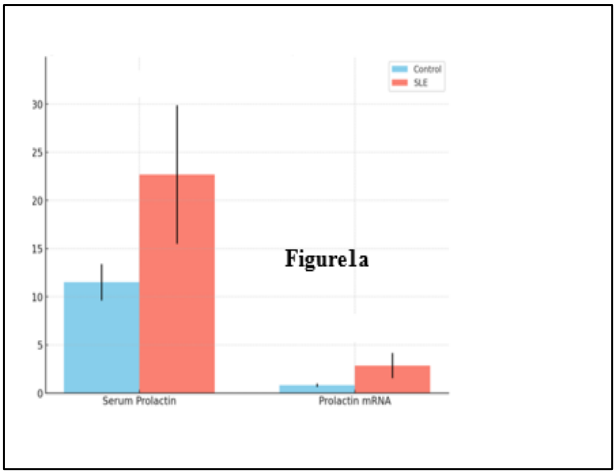
Table 2: Correlation between serum and relative expression of prolactin mRNA and clinical as well as laboratory variables among patients with SLE (N=40)

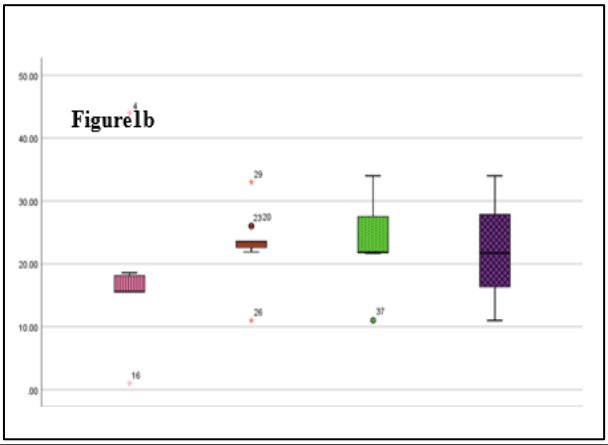
	Prolactin		Prolactin mRNA	
	r	p	r	p
Age	-0.131	0.420	-0.047	0.773
Disease duration (years)	-0.186	0.251	-0.250	0.120
SLEDAI	0.463	<0.001*	0.393	<0.001*
Hypertension N (%)	0.140	0.389	0.316	0.047
Nephritis, N (%)	0.189	0.243	0.362	0.022
dsDNA	0.333	<0.001*	0.422	<0.001*
ANA	0.405	<0.001*	0.407	<0.001*
Serum creatinine (mg/dL)	0.453	<0.001*	0.365	<0.001*
Proteinuria (g/d)	0.273	0.089	0.268	0.094
ESR (mm/hr)	0.077	0.639	0.251	0.119
C3 (consumed)	-0.046	0.777	0.071	0.661
C4 (consumed)	0.208	0.198	0.353	0.026

SLE; systemic lupus erythematosus, SLEDAI; systemic lupus erythematosus activity index ESR; erythrocyte sedimentation rate, dsDNA: double-stranded DNA C3; complement 3, C4; complement 4.* Statistically significant (P < 0.05)

Table 3: linear regression analyses to test the influence of the main independent variables against serum and relative expression of prolactin mRNA (dependent variable) in patients with SLE
SLE; systemic lpus erythems, SLEDAI; systemic lupus erythematosus disease activity index * Statistically significant (P < 0.05)

Model		Unstandardized Coefficients		Standardized Coefficients	t	p	95% C.I.	
		B	SE	Beta			Lower Bound	Upper Bound
Prolactin	(Constant)	0.187	0.646		.289	.774	-1.123	1.497
	SLEDAI	0.012	0.008	0.215	1.564	.127	-0.004	0.028
	dsDNA	-0.079	0.426	-0.025	-.185	.855	-0.942	0.785
	ANA	0.087	0.021	0.552	4.148	.000	0.044	0.130
Relative expression of Prolactin mRNA	(Constant)	89.153	4.775		18.66	<0.001*	79.671	98.635
	SLEDAI	-2.703	0.769	-0.848	-3.517	<0.001*	-4.229	-1.177
	dsDNA	-0.061	0.015	-0.518	-4.000	<0.001*	-0.091	-0.031
	ANA	-0.040	0.192	-0.023	0-.207	0.836	-0.421	0.341





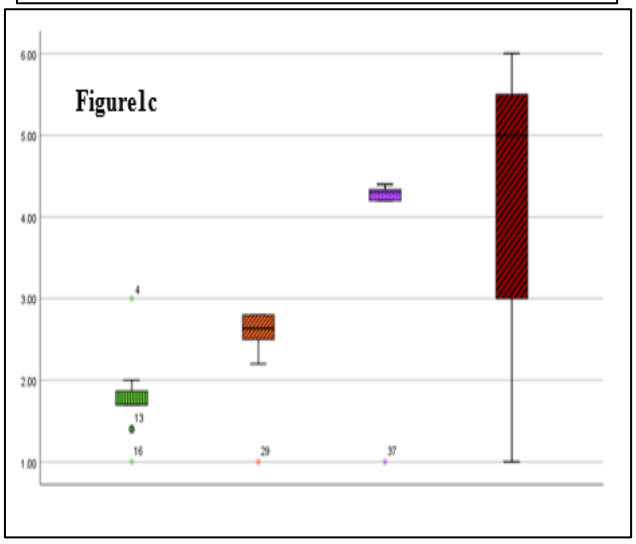


Figure1a: Comparison of prolactin serum and mRNA relative expression in SLE vs control group. Figure 1b, comparison of serum prolactin level in SLE subgroups. Figure 1c, comparison of prolactin mRNA relative expression in SLE subgroups

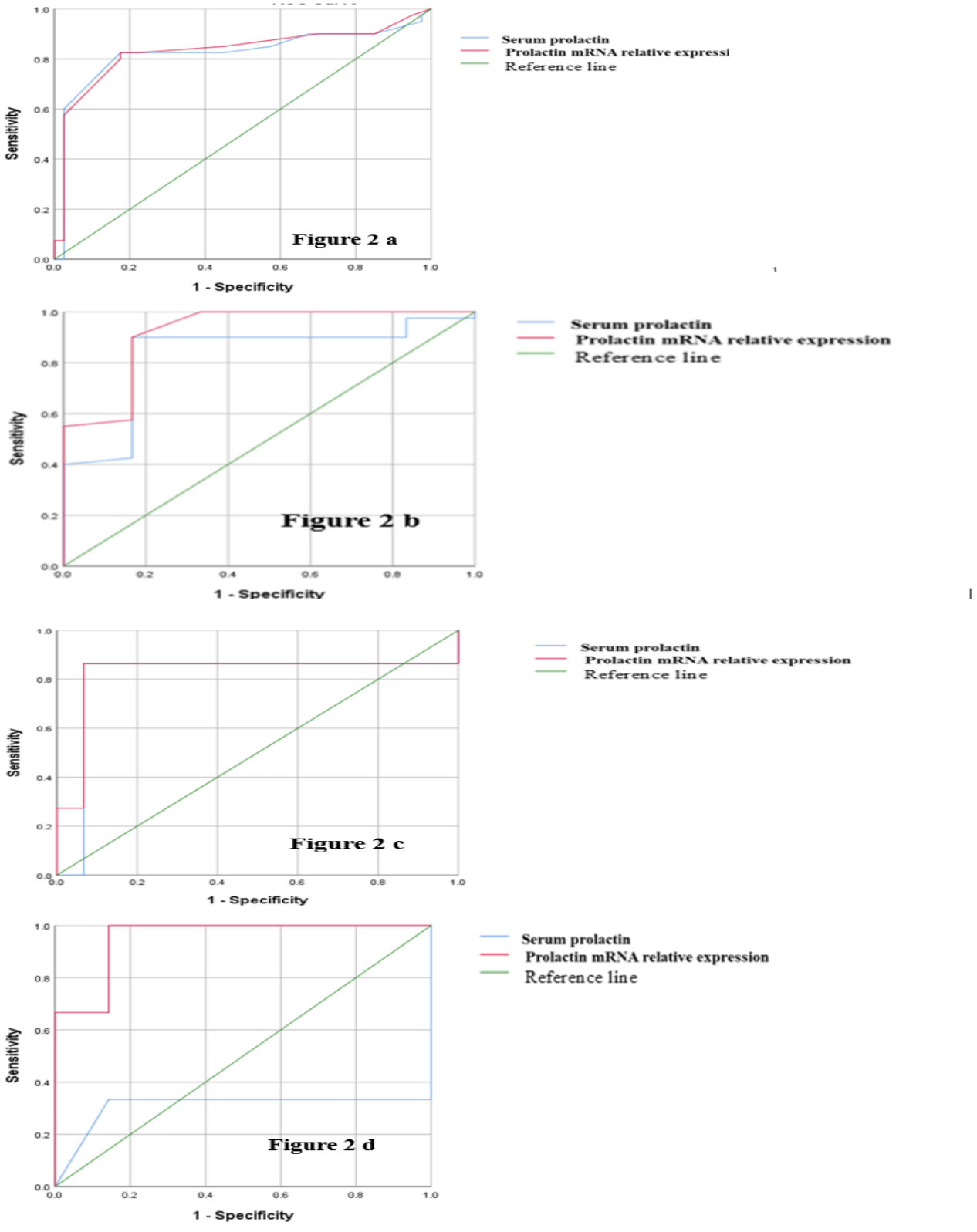


Figure 2: The diagnostic performance of PRL serum and mRNA relative expression in distinguishing SLE and control 2a. The diagnostic performance of PRL serum and mRNA relative expression in differentiating mild SLE from Inactive Disease 2b. The diagnostic performance of prolactin serum and mRNA relative expression in distinguishing moderate from mild activity SLE 2c. The diagnostic performance of PRL serum and mRNA relative expression in differentiating severe from moderate SLE Activity 2d

DISCUSSION

This study explored the connection between serum prolactin concentrations, its mRNA expression, and the clinical and laboratory characteristics of systemic lupus erythematosus (SLE) across different activity levels of the disease. The results provide compelling evidence of a strong relationship between elevated prolactin (PRL) levels and increased disease activity, suggesting a potential immunoregulatory function of prolactin in SLE pathogenesis.

Both circulating prolactin and its mRNA expression were markedly higher in patients with SLE than in healthy individuals, particularly among those with active disease compared to those in remission. The most pronounced elevations were noted in the severe activity group, with a significant positive correlation between prolactin levels and SLEDAI scores, reinforcing its potential as a disease activity marker.

These observations align with earlier research that reported hyperprolactinemia in active SLE, likely due to prolactin's known roles in enhancing B-cell survival, stimulating autoantibody production, and influencing T-cell behavior [13,14].

In this study, higher disease activity was associated with more frequent organ involvement—including renal, neuropsychiatric, cardiac, thrombotic, and pulmonary manifestations. These clinical features also correlated significantly with increased PRL mRNA expression. This finding is supported by prior studies linking elevated prolactin levels with lupus nephritis and neuropsychiatric lupus, potentially through its effects on cytokine production and inflammatory tissue damage [15].

It has been proposed that prolactin contributes to the regulation of both innate and adaptive immunity, raising the possibility of its involvement in the pathogenesis of autoimmune disorders [16,17]. Consistent with previous findings [18,19], our data revealed associations between elevated prolactin levels and multiple clinical features of lupus, including neuropsychiatric, renal, cutaneous, and joint involvement, as well as serological abnormalities such as anti-dsDNA positivity and higher disease activity indices [20,21].

Patients with increased prolactin expression also showed higher frequencies of complement depletion particularly C4 and positivity for antiphospholipid antibodies (e.g., anticardiolipin IgG, lupus anticoagulant), implying a potential role for prolactin in humoral immune dysregulation and prothrombotic states in lupus.

Hematologic abnormalities, including anemia, leukopenia, thrombocytopenia, elevated serum creatinine, and proteinuria, were more severe among patients with active diseases. These laboratory changes, especially those related to renal dysfunction, showed significant positive correlations with both serum prolactin and mRNA levels. This supports the hypothesis that prolactin may not only contribute to immune activation but may also be involved in end-organ damage—particularly renal impairment, a major determinant of SLE outcomes.

Although the use of immunosuppressive therapy (steroids, azathioprine, mycophenolate mofetil, cyclophosphamide) was more prevalent in patients with high disease activity, prolactin levels remained elevated, suggesting that conventional therapies may not directly influence prolactin pathways. This highlights the therapeutic potential of dopaminergic agents such as bromocriptine as adjunct treatments for SLE patients with hyperprolactinemia, a strategy that has shown promise in previous clinical trials [22].

Furthermore, multivariate regression analysis revealed that ANA positivity independently predicted serum prolactin levels, while prolactin mRNA expression was significantly associated with SLEDAI scores and anti-dsDNA levels. These findings imply that prolactin may be transcriptionally regulated in the context of active disease and could play a role in promoting the autoimmune response, particularly in seropositive individuals.

Recent clinical evidence and systematic reviews have consistently demonstrated that serum prolactin concentrations are elevated in

patients with systemic lupus erythematosus (SLE) and tend to rise in parallel with disease activity. A meta-analysis published in 2024 confirmed that hyperprolactinemia is more prevalent among SLE patients and that dopamine agonists such as bromocriptine may lower prolactin levels and modestly reduce disease activity scores. These findings support the current study's observation that prolactin secretion increases in relation to SLE activity and might serve as an auxiliary disease activity indicator [23].

Experimental studies provide mechanistic insights into these associations. Peripheral blood lymphocytes from SLE patients have been shown to express prolactin mRNA and synthesize the hormone locally, suggesting that prolactin acts in both endocrine and paracrine fashions. This immune-cell–derived prolactin can enhance B-cell survival, antibody production, and cytokine release. Such findings are consistent with the current study, which demonstrated that prolactin mRNA expression rises with greater disease activity, implying that immune dysregulation may stimulate extra-pituitary prolactin synthesis [24].

Data from lupus-prone murine models and human clinical trials lend further support to the immunomodulatory role of prolactin. Dopamine agonists such as bromocriptine have been observed to attenuate disease severity in experimental lupus by reducing prolactin secretion and downstream inflammatory responses. In small-scale human studies, the addition of bromocriptine to conventional immunosuppressive therapy resulted in improved SLEDAI scores and reduced antibody titters, although larger controlled trials are still needed. These results reinforce the possibility that modulating prolactin signaling could represent a complementary therapeutic approach for patients with refractory or hyperprolactinemic SLE [25].

Emerging evidence also suggests a potential epigenetic contribution to prolactin dysregulation in autoimmune diseases. Reviews focusing on lupus epigenetics have emphasized the influence of DNA methylation defects, histone modifications, and non-coding RNAs in altering immune gene expression. Since prolactin gene transcription in immune cells can be epigenetically regulated, these mechanisms may partly explain the increased prolactin mRNA expression observed in active SLE. Future research could investigate whether specific epigenetic marks at the prolactin promoter or enhancer regions are linked to disease severity and immune activation [26].

Despite substantial supporting data, inconsistencies still exist among published studies, possibly due to methodological variability in assay techniques, sampling times, or the inclusion of macroprolactin forms. A recent review recommended uniform sampling conditions, morning collection, and standardized analytical methods to ensure comparability across studies. In the present work, preanalytical precautions—such as collecting fasting morning samples after a resting period—were implemented to minimize these confounders, thereby strengthening the reliability of the results[27].

LIMITATIONS

This study is subject to certain limitations. The sample size, especially in the moderate and severe activity subgroups, was relatively small, which may impact on the generalizability of the results. Moreover, the cross-sectional design precludes conclusions about causality. Future longitudinal studies are warranted to determine whether prolactin levels can serve as predictive markers for disease flares or long-term organ damage. Additionally, while prolactin mRNA expression was assessed, the origin of this expression and its regulatory mechanisms warrant deeper investigation.

CONCLUSION

This study highlights a significant association between prolactin—both at the serum and mRNA expression levels—and SLE disease activity, immunological abnormalities, and multi-organ involvement. These findings support the concept that prolactin may actively contribute to the immunopathology of lupus and could serve as both a biomarker of disease

activity and a potential target for novel therapeutic interventions.

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