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Serum Level of Interleukin-2 and Renal Involvement in Lupus Erythematosus Patients

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is an autoimmune condition with potential multiorgan involvement. Defective interleukin-2 (IL-2) production contributes to immunological dysregulation in SLE. IL-2 insufficiency impacts T-cell activity and immunological tolerance.

Objective: The current work aimed to assess the connection between renal involvement and serum IL-2 levels in patients with SLE.

Patients and Methods: Sixty adult SLE patients were divided into two groups: those with active lupus nephritis and those without. Clinical data, including medical history, physical examination, and laboratory investigations were collected. Disease activity and serum IL-2 levels were measured. Statistical analyses, non-parametric tests, correlation analyses, and logistic regression were performed.

Results: Predominance in females. Patients with nephritis had considerably lower median serum IL-2 levels compared to those without. A statistically significant negative association was observed between serum IL-2 levels and both serum creatinine and the protein/creatinine ratio, indicating an association between lower IL-2 levels and worse renal function. No statistically significant association was found between total SLE disease activity and serum IL-2 levels, though a trend towards greater IL-2 levels was seen in patients with milder disease activity.

Multivariate logistic regression identified elevated serum creatinine and decreased serum IL-2 levels as independent predictors of lupus nephritis in SLE patients.

Conclusion: This study demonstrates a significant association between reduced serum IL-2 levels and lupus nephritis in SLE patients. The negative correlations between IL-2, renal dysfunction markers, and the independent predictive value of IL-2 for nephritis, suggest that IL-2 may be a valuable biomarker for identifying and potentially predicting renal involvement in SLE.

Keywords: Systemic lupus erythematosus, Autoimmune diseases, Lupus nephritis, Interleukin-2

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disorder characterized by damage to immune tolerance, leading to a dysregulated immune response and widespread damage across various organ systems. This loss of tolerance is pivotal in the pathogenesis of SLE, resulting in the production of autoantibodies that target host tissues and contribute to the hallmark clinical manifestations of the disease. The complex interplay of genetic, environmental, and hormonal factors further exacerbates the aberrant immune activation seen in SLE. Consequently, patients often experience a heterogeneous array of symptoms, including skin rashes, joint pain, and hematological abnormalities, reflecting the disorder's systemic nature and the involvement of multiple interrelated pathways in its etiology [1].

Among the myriad manifestations of SLE, lupus nephritis (LN) stands out as one of the most severe and clinically significant complications. It affects a substantial majority of individuals with SLE, impacting their prognosis and quality of life. LN is characterized by the deposition of immune complexes within the glomeruli, which triggers a cascade of inflammatory responses involving the recruitment of various immune cells, including T lymphocytes and macrophages. The combination of immune complex formation, cell infiltration, and elevated levels of pro-inflammatory cytokines can lead to significant and often irreversible damage to renal tissue. This immune-mediated injury results in glomerular inflammation, impaired renal function, and, in advanced cases, end-stage renal disease. Therefore, understanding the underlying mechanisms driving LN is crucial for developing effective therapeutic strategies to preserve renal function in patients suffering from this life-threatening complication of SLE [2].

The 15.5 kDa α-helical cytokine interleukin-2 (IL-2) is essential for controlling immunological responses. Natural killer (NK) cells, dendritic cells, macrophages, and activated CD4+ and CD8+ T lymphocytes are the main producers of it. For T cells, IL-2 is a crucial growth factor that especially affects the survival and multiplication of regulatory T cells (Tregs). Tregs are crucial for preserving tolerance and immunological homeostasis in the body. As part of the body's intrinsic response to infection, IL-2 also plays a crucial role in distinguishing between foreign antigens ("non-self") and self-antigens. This process is

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vital for preventing autoimmune responses, as IL-2 orchestrates the activation and differentiation of various immune cell subsets through its interaction with IL-2 receptors expressed by lymphocytes, thereby promoting a balanced immune response [3].

Interleukin-2 (IL-2) exhibits pleiotropic effects, meaning it has diverse biological functions. This versatility stems from its ability to activate multiple signaling pathways within cells: the JAK-STAT pathway, the PI3K/AKT/mTOR pathway, and the MAPK/ERK pathway. Each of these pathways has a unique function in mediating the effects of IL-2, influencing cellular processes such as survival, proliferation, and differentiation [4].

The intricate nature of interleukin-2 (IL-2) signaling elucidates its fundamental role in regulating normal immune function, as well as in the pathogenesis of autoimmune diseases. The growth, survival, and differentiation of T cells depend on IL-2, especially when it comes to regulatory T cells (Tregs), which are vital for preserving immunological homeostasis and averting autoimmunity. Dysregulation of IL-2 production, whether due to genetic predisposition, environmental factors, or other physiological perturbations, can severely impact the immune system's functionality. In the context of autoimmune disorders, such as systemic lupus erythematosus (SLE) or psoriasis, aberrant IL-2 signaling has been recognized as a key factor that compromises Treg activity. This impairment can result in a diminished capacity to suppress autoreactive T cells, leading to a failure of immune tolerance and facilitating the development and evolution of autoimmune pathologies [5].

Research has consistently demonstrated that in various autoimmune conditions, including SLE, there is often a significant reduction in IL-2 responsiveness, which contributes to the dysfunction of Tregs. This phenomenon has been substantiated by both murine models and clinical studies, providing compelling evidence that supports the critical involvement of IL-2 in the maintenance of immune balance. In SLE, for instance, patients exhibit characteristics of altered IL-2 signaling, with diminished Treg function correlating with disease activity and severity. These findings underscore the importance of IL-2 as not only a growth factor for T cells but also as a pivotal regulator of immune tolerance and self-reactivity [6]. Moreover, the relationship between IL-2 dysregulation and autoimmune disease progression suggests potential therapeutic implications. By targeting the IL-2 signaling pathway, it may be possible to restore Treg function and enhance the immune system's ability to preserve tolerance. Strategies such as low-dose IL-2 therapy have emerged as promising avenues for research, aimed at boosting Treg activity and mitigating autoimmune responses. Understanding the multifaceted roles of IL-2 in immune regulation will be instrumental in developing novel treatment strategies that can potentially provide effective management for patients suffering from autoimmune diseases [4, 5, 6].

Research by **Lykhopiy *et al.*** [7] has elucidated the multifaceted function of IL-2 in restoring CD4+ Treg homeostasis, highlighting its potential therapeutic application in autoimmune diseases at low doses. By selectively inducing Tregs, low-dose IL-2 therapy has become a viable tactic to re-establish immune tolerance and mitigate autoimmunity. Studies suggest that this approach may improve the functional capacity of Tregs, thereby enhancing their ability to control aberrant immune responses characteristic of autoimmune conditions, including SLE. Given this rationale, ongoing investigations are focused on characterizing the optimal dosing regimens and patient populations that may benefit from IL-2 therapy, further supporting its inclusion in the therapeutic arsenal against autoimmune disorders.

In the present study, we aimed to thoroughly assess the connection between renal involvement and serum interleukin-2 (IL-2) levels in patients with systemic lupus erythematosus (SLE). By analyzing serum IL-2 concentrations in the context of renal function and pathology, we seek to elucidate the potential role of this cytokine in influencing the severity of lupus nephritis. The outcomes of this investigation may provide critical insights into the mechanisms underpinning renal complications in SLE and establish a foundation for further research into targeted IL-2-based therapeutic interventions for managing LN. This study ultimately aspires to contribute to the understanding of how modulation of the immune response via IL-2 can impact clinical outcomes in patients suffering from this debilitating autoimmune disease.

PATIENTS AND METHODS

This study included a total of sixty adult patients diagnosed with systemic lupus erythematosus (SLE), attending the Departments of Rheumatology Outpatient Clinic and the Internal Medicine and Rheumatology Inpatient, Ain Shams University Hospitals.

The included subjects were evenly divided into two groups; **Group 1** included 30 patients with active lupus nephritis, and **Group 2** included 30 patients with SLE without current evidence of nephritis.

The diagnosis of SLE was confirmed based on the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [8]. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [9]. Disease activity was categorized into five levels: inactive (SLEDAI = 0), mild (SLEDAI = 1-5), moderate (SLEDAI = 6-10), severe (SLEDAI = 11-19), and very high (SLEDAI > 20).

Laboratory investigations:

These included blood urea nitrogen (BUN), serum creatinine, quantitative C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and a complete blood count (CBC). Urinalysis and urine protein-to-creatinine ratio (P/C) were also performed.

Immunological assessments included the measurement of antinuclear antibodies (ANA) titer and anti-double-stranded DNA (anti-dsDNA) antibodies using enzyme-linked immunosorbent assays (ELISA). Serum levels of complement components C3 and C4 were also measured. Serum interleukin-2 (IL-2) concentrations were quantified using a commercially available **human IL-2 ELISA kit.** This kit utilizes a double-antibody sandwich ELISA technique to measure human IL-2 in serum samples.

Ethical approval: This study received ethical approval from the Ethical Committee of Ain Shams University (IRB number 000017585). All participants provided an informed consent prior to enrollment. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, ensuring the protection of human subjects involved in research.

Statistical Analysis:

IBM SPSS Statistics software, version 20 (IBM Corp., Armonk, NY, USA), was used to perform statistical analyses. The data was compiled using descriptive statistics. For data with a normal distribution, continuous variables were displayed as means ± standard deviations; for data with a skewed distribution, they were displayed as medians (interquartile ranges). Frequencies and percentages were used to display categorical variables.

The following statistical tests were employed to assess relationships between variables:

- **Comparison of categorical variables:** The chi-square (χ^2) test was leveraged to compare categorical variables. Fisher's exact test was used as an alternative to the chi-square test when the expected cell count in any cell was less than 5, ensuring the validity of the statistical analysis in cases of small sample sizes within categories.
- **Comparison of continuous variables between two groups:** The Mann-Whitney U test (a non-parametric test) was used to compare continuous variables between two independent groups when the data did not meet the assumptions of normality. The independent samples t-test (a parametric test) was used when the data met the assumptions of normality and equal variances.
- **Comparison of continuous variables among more than two groups:** One-way analysis of variance (ANOVA) was used to compare means of continuous variables among three or more independent groups. Post-hoc tests were performed as needed to determine which specific groups differed significantly from each other.
- **Correlation analysis:** Spearman's rank correlation coefficient (ρ) was used to assess the monotonic relationship between two continuous variables, especially when the data were not normally distributed.
- **Diagnostic accuracy:** Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of specific biomarkers or clinical parameters in distinguishing between groups.
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- **Predictive modeling:** Logistic regression analysis was used to identify independent predictors of a binary outcome variable (e.g., presence or absence of nephritis).

For all statistical tests, a two-sided p-value of less than 0.05 was considered statistically significant. Specifically, the following significance levels were defined:

- $p > 0.05$: Not statistically significant
- $p < 0.05$: Statistically significant
- $p < 0.01$: Highly statistically significant

The confidence interval was set at 95%, corresponding to a margin of error of 5%.

RESULTS

Sixty patients with SLE, 56 women (93.3%) and 4 men (6.7%) were studied. Their age ranged from 19 to 58 years with mean age of 31.25 (±9.41). The median disease duration was 4 (0.25-24years). Table (1) shows demographic features, laboratory investigations and medications used among two groups. Serum creatinine and protein /creatinine ratio were significantly higher in Group 1 compared to Group 2. As regard medications used by the studied groups, in Group 1, more patients received cyclophosphamide whereas in Group 2 more patients received azathioprine.

Table (1): Demographic features, laboratory investigations and medications used in the two studied groups:

Sociodemographic data	Total (n=60)	Group1 (n=30)	Group2 (n=30)	Test of significance (p value)
Age (years)				t=1.65
Mean ± SD.	31.25±9.41	29.27±7.97	33.23±10.41	P=0.103
Min-Max	19-58	19-52	19-58	
Sex				FET
Male	4 (6.7%)	3 (10.0%)	1 (3.3%)	p=0.301
Female	56 (93.3%)	27 (90.0%)	29 (96.7%)	
Disease Duration (years) Median (min-max)	4	4.5	4	Z =0.089
	(0.25-24)	(0.33-24)	(0.25-23)	p=0.929
Lab parameter				
Hb (g/dl)	11.11± 2.11	10.86± 2.45	11.37± 1.71	t=0.928
Mean ± SD				p=0.357
PLT (10^3/µL)	235.5	240	209.5	Z=0.747
Median (Min-Max)	(8-435)	(30-435)	(8-363)	p=0.455
TLC (10^3/µL)	5.80 (2.4-13.4)	5.65	6	Z=0.163
Median (Min-Max)		(2.8-13.4)	(2.4-13.3)	p=0.871
ESR (mm/hr.)	35	35	35 (6-140)	Z=0.348
Median (Min-Max)	(6-140)	(10-130)		p=0.728
CRP (mg/dL)	5	5	5	Z=0.777
Median (Min-Max)	(1.2-48)	(1.2-48)	(1.6-38)	p=0.437
BUN (mg/dl)	22	24	18.5	Z=1.88
Median (Min-Max)	(5-87)	(6-87)	(5-54)	p=0.059
Serum creatinine (mg/dl)	0.8	1.15	0.7	Z=4.85
Mean ± SD	(0.1-3.7)	(0.5-3.7)	(0.1-0.9)	p≤0.001**
P/C ratio	0.23	1.1	0.11	Z=6.66
Median (Min-Max)	(0.04-8.6)	(0.27-8.6)	(0.04-0.19)	p≤0.001**
ANA				FET
Positive	58 96.7%)	29 96.7%)	29 (96.7%)	p=1.0
Negative	2 (3.3%)	1 (3.3%)	1 (3.3%)	
Anti-ds DNA				χ^2 =0.287
Positive	38 63.3%)	20(66.7%)	18(60.0%)	p=0.592
Negative	22(36.7%)	10 (33.3%)	12 (40.0%)	
Variables	**Frequency (%)**		**Test of significance**	**P value**
	Group1 (n=30)	**Group2 (n=30)**		
Steroids	28(93%)	30(100%)	FET	0.492
Immunosuppressive drug	30 (100%)	18 (60%)		
Azathioprine	9 (30%)	13(43%)	χ^2 =15	≤0.001*
			χ^2 =1.15	0.283
Mycophenolate Mofetil	4 (13%)	3 (10%)	χ^2 =0.16	0.687
Cyclophosphamide	17(57%)	2(7%)	χ^2 =17.33	≤0.001*
HCQ (hydroxychloroquine)	28(93%)	24(80%)	FET	0.254
NSAIDs	4(13%)	6(20%)	χ^2 =0.48	0.488

NSAID: non-steroidal anti-inflammatory drug

FET: Fischer exact test, $\chi^{2:}$ Chi square test, Z: Mann Whitney test, **highly significant p≤0.001

t: student t- test, $\chi^{2:}$ Chi square test, Z: Mann Whitney test, **highly significant p≤0.001. Hb: hemoglobin, PLT: platelets, TLC: total leucocytic count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BUN: blood urea nitrogen, P/C ratio: protein creatinine ratio.

Table (2): The SLEDAI and parameters of disease activity among the studied groups

Activity	Total (n=60)	Group1 (n=30)	Group2 (n=30)	Test of significance (p value)
SLEDAI Median (Min-Max)	12 (2-27)	12 (6-27)	10.5 (2-23)	Z=1.18 p=0.238
Activity: Mild	4 (6.7%)	0 (0%)	4 (13.3%)	
Moderate	23(38.3%)	12 (40%)	11(36.7%)	MC
High	26 (43.3%)	15 (50%)	11 (36.7%)	p=0.198
Very high	7 (11.7%)	3 (10%)	4 (13.3%)	
Variables	**Frequency (%)**		**Test of significance**	**P value**
	Group1 (n=30)	**Group2 (n=30)**		
Seizure	1 (3.3%)	0(0%)	FET	1.0
Psychosis	1(3.3%)	0(0%)	FET	1.0
Organic brain syndrome	0(0%)	0(0%)	-	-
Visual	0(0%)	0(0%)	-	-
Cranial nerve disorder	1(3.3%)	2(6.7%)	FET	1.0
Lupus headache	1(3.3%)	0(0%)	FET	1.0
Cerebrovascular accident(s)	6(20%)	3(10%)	FET	0.472
Vasculitis	2(6.7%)	5(16.7%)	FET	0.424
Arthritis	18(60%)	15(50%)	χ^2 =0.606	0.436
Myositis	1(3.3%)	1(3.3%)	FET	1.0
Urinary casts	1(3.3%)	0(0%)	FET	1.0
Hematuria	4(13.3%)	3(10%)	FET	1.0
Proteinuria	30(100%)	0(0%)	χ^2 =60	≤0.001*
Pyuria	9(30%)	5(16.7%)	χ^2 =1.49	0.222
Rash	2(6.7%)	4(13.3%)	FET	0.671
Alopecia	12(40%)	10(33.3%)	χ^2 =0.287	0.592
Mucosal ulcers	9(30%)	11(36.7%)	χ^2 =0.300	0.584
Pleurisy	1(3.3%)	1(3.3%)	FET	1.0
Pericarditis	2(6.7%)	2(6.7%)	FET	1.0

Z: Mann Whitney test, MC: Monte Carlo test.

Table 2 presents the distribution of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores among the studied groups, revealing an average score that ranged from 2 to 27, with a median score of 12. Within Group 1, which comprised patients diagnosed with lupus nephritis, the disease activity profile indicated that no patients exhibited mild activity (0%), while 40% demonstrated moderate activity, 50% presented with severe activity, and 10% had very high activity. In contrast, Group 2, which consisted of patients without renal involvement, displayed a different distribution of disease activity, with 13.3% of patients experiencing mild activity, 36.7% exhibiting moderate activity, 36.7% classified as severe, and an additional 13.3% showing very high activity. When examining specific parameters of disease activity, a significant association was noted regarding the presence of proteinuria. It was found that proteinuria was present in 100% of patients within Group 1, in stark contrast to Group 2, where it was absent in all cases, yielding a statistically significant result ($p \leq 0.001$), as highlighted in Table 2. This finding underscores the critical role of proteinuria as a clinical marker for renal involvement in SLE and differentiates patients with lupus nephritis from those without it. Despite the significant differences observed in proteinuria between the two groups, no other clinically relevant differences were established regarding additional clinical manifestations associated with SLE. This indicates that while renal involvement distinctly correlates with disease activity as indicated by SLEDAI scores, the overall presence and severity of other systemic manifestations may be comparable across groups. Further investigation into renal pathology was conducted through renal biopsy in Group (1). The histopathological findings classified the patients into several classes, with 17 patients (56.6%) identified as class II, suggesting mesangial proliferative lupus nephritis. Meanwhile, 8 patients (26.7%) were classified as class III, indicative of focal proliferative lupus nephritis. Additionally, 3 patients (10%) fell into class IV, correlating with diffuse proliferative nephritis, and only 2 patients (6.7%) were classified as class V, which often corresponds to membranous lupus nephritis. These results illustrate the varied renal manifestations in patients suffering from lupus nephritis and emphasize the necessity for tailored therapeutic strategies based on the classification of renal biopsy findings.

Table (3): Serum Interleukin-2 among the studied groups and its correlation with SLE disease activity and other variables

Serum IL-2 (ng/L) Median (Min-Max)	**Total (n=60)**	**Group1 (n=30)**	**Group2 (n=30)**	**Test of significance (p value)**
	39.8 (5-165)	25.5 (5-90)	53.5 (29-165)	Z=4.69 p≤0.001**

Variables	**Serum IL-2**	
	R	**P value**
Age (years)	0.107	0.416
Hb (g/dl)	0.109	0.408
PLT (10^3/µL)	-0.027	0.840
TLC (10^3/µL)	-0.187	0.153
ESR (mm/hr.)	0.090	0.496
CRP (mg/dL)	-0.074	0.575
BUN (mg/dL)	-0.176	0.178
s. creatinine (mg/dL)	-0.494	≤0.001**
P/C ratio	-0.512	≤0.001**
SLEDAI	-0.108	0.411
C3(Group1) (mg/dL)	-0.169	0.563
C4(Group1) (mg/dL)	-0.172	0.557

s.IL-2 (ng/L)	**Mild**	**Moderate**	**High& very high**	**Test of significance (p value)**
Serum IL-2 Median (Min-Max)	52.5 (45-60)	40 (15-135)	31 (5-165)	KW =1.36 P= 0.508
P value mild versus moderate	P=0.148			
P value mild versus high activity	P=0.378			
P value moderate versus high activity	P=0.967			

KW: Kruskil Wallis test

Table 3 demonstrates a significant difference in serum Interleukin-2 (IL-2) levels between the two study groups. The median IL-2 levels in Group (1), comprising patients with active lupus nephritis, was significantly lower at 25.5 ng/L (range: 5-90 ng/L) compared to Group (2), consisting of SLE patients without nephritis, where the median IL-2 level was 53.5 ng/L (range: 29-165 ng/L) ($p \leq 0.001$). Furthermore, a statistically significant negative correlation was observed between serum IL-2 levels and both serum creatinine levels ($r = -0.494$, $p \leq 0.001$) and the urine protein-to-creatinine ratio ($r = -0.512$, $p \leq 0.001$), suggesting an inverse relationship between IL-2 levels and markers of renal dysfunction.

While a statistically significant correlation between SLE disease activity, as assessed by the SLEDAI, and serum IL-2 levels was not observed in this study, a trend was evident. Notably, the highest median IL-2 levels were observed in patients with mild SLE disease activity (45-60 ng/L), followed by those with moderate disease activity (15-135 ng/L), with the lowest levels detected in patients with high disease activity (5-165 ng/L). This observation suggests a potential, albeit non-significant, association between declining IL-2 levels and increasing SLE disease activity."

Table (4): Receiver operating characteristics (ROC) curve for prediction of nephritis by serum IL-2

	AUC	**95% CI**	**Cutoff**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
s.IL-2	0.852	0.75-0.95	< **38.8**	76.7%	80%	79.3	77.4	78.3%

Occurrence of nephritis in the SLE patients can be predicted by measuring the serum level of IL-2 at a cutoff point of **< 38.8 ng/L** by using the ROC-curve: with total accuracy of 78.3%, sensitivity 76.7%, and specificity 80%. AUC was (0.852) with 95% CI (0.75-0.95),

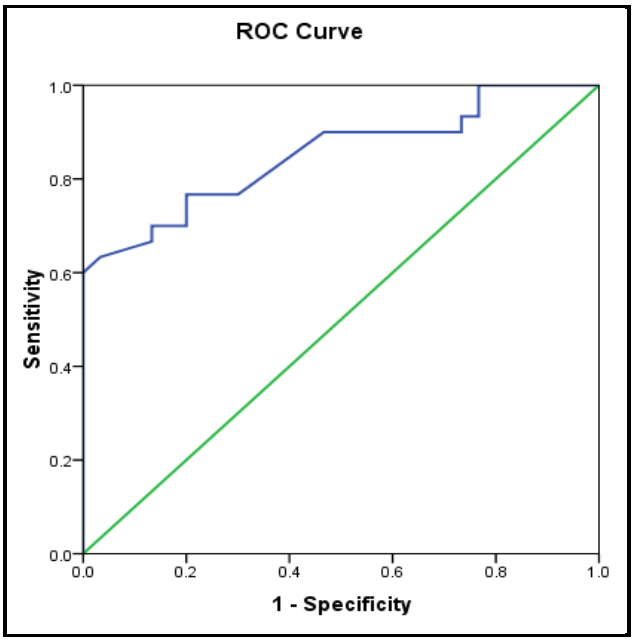

Figure (1): ROC curve for prediction of nephritis by serum IL-2.

Table (5): Regression analysis for independent predictors of nephritis:

	P value	OR	95% CI
Serum creatinine > 0.7	0.002	12.25	2.5-60.9
Serum IL-2 < 53.5	0.007	5.68	1.6-20.3

Multiple regression analysis, as presented in Table 5, revealed that both elevated serum creatinine levels and decreased serum IL-2 levels were independently associated with a significantly increased probability of developing nephritis in SLE patients ($p < 0.01$).

DISCUSSION

Systemic lupus erythematosus (SLE) represents a complex and chronic autoimmune disease that has the possibility to influence nearly any organ system in the body. The clinical manifestations of this disorder exhibit considerable variability, which can range from mild and indolent presentations to more severe and fulminant forms. This variability complicates both diagnosis and management, necessitating a nuanced understanding of the disease [10]. It is estimated that SLE affects predominantly women, illustrating a significant gender disparity in prevalence, with the female-to-male ratio often exceeding 9:1. In the current study, we found that only 4 patients (6.7%) were male, while the overwhelming majority, 56 patients (93.3%), were female, thus corroborating findings from previous investigations that also highlighted this striking gender difference [11].

Systemic lupus erythematosus (SLE) is a multifaceted and chronic autoimmune disorder characterized by its propensity to impact various organ systems within the body. The clinical manifestations of SLE are notoriously heterogeneous, ranging from mild, indolent presentations that may go unnoticed to more aggressive, fulminant forms that can result in significant morbidity and mortality. This considerable variability in disease expression presents considerable challenges for healthcare providers in both diagnosing and managing the condition effectively. A thorough understanding of SLE's diverse and dynamic nature is essential for clinicians, as it influences treatment strategies and prognostic assessments. The complexity of SLE is further compounded by its involvement of a wide array of tissues, leading to manifestations such as cutaneous rashes, arthralgia, hematological abnormalities, renal impairment, and neurological symptoms. Each of these manifestations requires tailored treatment approaches that consider the patient's specific clinical presentation and disease manifestations [10,11].

The pathogenesis of SLE is multifaceted and involves an interplay of genetic predisposition, environmental factors, and dysregulation of the immune system. Among the key contributors to immune dysregulation in SLE is interleukin-2 (IL-2), a vital cytokine for maintaining immune homeostasis. Studies indicate that levels of IL-2 are notably deficient in individuals with SLE, which may contribute to the diminished function of T cells and the regulatory T cell subset, further perpetuating autoimmunity. Accordingly, this deficiency might act as a key part in the disease's immunopathology, affecting both the disease course and the clinical presentation [12,13].

In examining parameters of disease activity among our cohort, we noted that proteinuria was universally present in all patients classified within the lupus nephritis (LN) group, with its absence confirmed in all patients of the non-nephritis group. This clear distinction underscores the importance of monitoring renal involvement in the context of SLE, as kidney damage is a common and severe complication of lupus. While our findings indicated no significant differences in other clinical manifestations between the two groups, these results are consistent with prior studies emphasizing proteinuria as a hallmark of renal involvement in SLE [14].

When analyzing laboratory results, we observed that both mean serum creatinine levels and protein-to-creatinine ratios were significantly higher in the lupus nephritis group equated to the non-nephritis group, further validating the presence of renal compromise in these patients. However, we did not find statistically significant variances between the two groups concerning hemoglobin concentration, platelet counts, total leukocyte counts, erythrocyte sedimentation rates, C-reactive protein levels, or blood urea nitrogen levels. This aligns with existing literature that often highlights renal function markers as more sensitive indicators of lupus nephritis severity compared to other hematological parameters [14]. The role of autoantibodies,

such as antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) is well-documented in SLE diagnosis, yet our study revealed insignificant differences between the nephritis and non-nephritis groups. This finding was in concordance with **Bruschi *et al.*** [15] who reported that the association between anti-dsDNA IgG and lupus nephritis is not supported by recent studies. And anti-dsDNA's specificity is unknown because it binds several proteins that are structural elements of the glomerular basement membrane.

In our analysis, renal biopsies performed on the lupus nephritis group revealed variances in the classification of renal pathologies: class II (56.6%), class III (26.7%), class IV (10.0%), and class V (6.7%). These findings differ from those reported by **Habas *et al.*** [16], who noted a higher prevalence of class IV lesions, reinforcing the variability in renal histopathology observed across different studies. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores obtained for patients in this study showed no statistically substantial changes between the nephritis and non-nephritis groups. This is in line with the findings of **Shao *et al.*** [12], although it deviates from the results of **Sedighi *et al.*** [13], highlighting potential discrepancies that may arise from variations in study design and sample sizes.

Our investigations revealed a non-significant trend towards higher serum interleukin-2 (IL-2) levels in patients with mild to moderate systemic lupus erythematosus (SLE) disease activity compared to those with high disease activity. This observation contrasted with the findings of **Sedighi *et al.*** [13], who reported a statistically significant correlation between IL-2 serum levels and the SLE Disease Activity Index. And with **Humrich *et al.*** [17] who concluded that low-dose IL-2 is beneficial in active SLE.

In the present study, we identified a statistically significant difference in the median serum interleukin-2 (s.IL-2) levels between the two patient groups. Specifically, serum IL-2 concentrations were markedly lower in the lupus nephritis group, with a median of 25.5 ng/L (range 5-90 ng/L), in contrast to the non-nephritis group, which had a median of 53.5 ng/L (range 29-165 ng/L) ($p \leq 0.001$). This result was consistent with what **Shao *et al.*** [12] found, who also documented decreased serum IL-2 levels in SLE patients diagnosed with lupus nephritis. These reductions in IL-2 levels may reflect the underlying dysregulation of the immune response which arises in SLE, particularly in the context of renal involvement, demonstrating how IL-2 may serve as a gauge of the severity of a disease.

Contrarily, the findings of our study diverge from the results presented by **El-Shafey *et al*.** [18], who reported significantly elevated levels of soluble IL-2 receptor alpha (sIL-2Rα) in SLE patients when compared to control subjects, with even higher levels observed in patients experiencing active disease. Moreover, **Gomes and Khan** [19] concluded that sIL-2R alpha may be a useful serological biomarker for lupus nephritis diagnosis, prognosis, and therapy response monitoring.

This contrast may indicate that while total serum IL-2 levels may be reduced in the presence of lupus nephritis, other components of the IL-2 signaling pathway, such as sIL-2Rα, may be upregulated in an attempt to compensate for inadequate IL-2 availability. This discrepancy underscores the intricacies of cytokine biology in autoimmune diseases and the necessity for further exploration into the nuances of these signaling pathways.

Additionally, findings by **Alcocer-Varela *et al***. [20] corroborate our results, demonstrating that T cells derived from SLE patients exhibit diminished IL-2 production, particularly in those with active disease. This reduction in IL-2 output could potentiate a deleterious cycle of immune dysregulation, further exacerbating disease activity through insufficient modulation of T cell responses [21]. In our analysis, we observed a highly significant negative relationship between serum IL-2 levels and serum creatinine concentrations in patients with lupus nephritis. Similarly, there was a notable adverse relationship between IL-2 levels and the protein-to-creatinine ratio, suggesting that lower IL-2 levels are associated with more severe renal impairment. Nevertheless, no connection was identified between IL-2 and other clinical variables, indicating that its role may be specifically tied to renal involvement rather than the full spectrum of SLE manifestations.

Interestingly, prior literature, such as the study by **Sedighi *et al.*** [13], documented a strong association between serum IL-2 levels and patient age, suggesting that age may influence the bioavailability of IL-2 and its association with disease activity. In contrast, our findings imply that serum IL-2 function as a potential biomarker may be more specialized in relation to renal pathology rather than reflecting a general inflammatory status. Furthermore, the work by **Li *et al.*** [22] expanded upon the clinical relevance of IL-2 by demonstrating a robust relationship between serum IL-2 levels and various clinical and laboratory indicators of disease activity in both lupus and rheumatoid arthritis patients. These findings suggest that IL-2 may serve as a reliable serologic marker of disease activity in autoimmune inflammatory diseases, underscoring its potential utility in patient management.

In our investigation, we assessed the potential of serum IL-2 levels as a predictive marker for the occurrence of nephritis in SLE patients. Through the application of a receiver operating characteristic (ROC) curve analysis, we concluded that a serum IL-2 cutoff point of (< 38.8) ng/L could effectively predict the likelihood of nephritis, with a general accuracy of 78.3%, sensitivity of 76.7%, and specificity of 80%. The area under the curve (AUC) was calculated as 0.852, with a 95% confidence interval (CI) ranging from 0.75 to 0.95. Furthermore, utilizing logistic regression methods revealed that both a rise in serum creatinine and a decrease in serum IL-2 levels were independently linked to a heightened probability of lupus

nephritis occurrence, achieving high statistical significance ($p < 0.01$). Notably, this aspect of our findings is particularly unique, as existing literature has yet to extensively discuss the diagnostic performance of IL-2 in the context of nephritis within SLE, indicating a potential avenue for future research aimed at validating and expanding upon our results.

CONCLUSION

This study demonstrates a significant association between reduced serum IL-2 levels and lupus nephritis in SLE patients. These results indicate that measuring serum IL-2 levels in SLE patients could be valuable in predicting the risk of developing lupus nephritis. This could potentially aid in:

- **Early Intervention:** Identifying patients at higher risk allows for earlier and more aggressive treatment strategies to prevent or delay the onset of kidney damage.
- **Personalized Treatment:** Tailoring treatment plans based on individual risk factors could improve outcomes for SLE patients.
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