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# BIOMARKER-DRIVEN EARLY DETECTION AND PROGNOSTIC MODELING OF RENAL INJURY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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*Systemic lupus erythematosus (SLE) is frequently accompanied by renal involvement, termed lupus nephritis (LN), which continues to be a leading contributor to morbidity and mortality among affected patients. While renal biopsy remains the diagnostic gold standard, its invasive nature restricts widespread and repeated use in clinical practice. This underscores the urgent need for accurate and non-invasive biomarkers. The present study aims to assess the diagnostic and prognostic utility of serum vascular cell adhesion molecule-1 (VCAM-1) and vascular endothelial growth factor (VEGF) in differentiating SLE patients with and without renal involvement.*

***Keywords:*** *systemic lupus erythematosus, lupus nephritis, VCAM-1, VEGF, biomarker, non-invasive biomarkers, microalbuminuria, proteinuria*

**Introduction:** Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disorder of unclear etiology, characterized by the overproduction of organ-specific and non-specific autoantibodies directed against various nuclear and cytoplasmic components. These immunological abnormalities lead to immune-complex–mediated inflammation and subsequent damage to tissues and internal organs. The annual incidence of SLE is estimated at 50–70 new cases per 1 million population, whereas its global prevalence reaches approximately 40–50 per 100,000 individuals [1].

Renal involvement represents one of the most frequent and devastating complications of SLE and is clinically classified as lupus nephritis (LN). Despite significant progress in understanding LN pathophysiology and improvements in therapeutic approaches, complete remission is achieved in only 50–70% of patients.

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Consequently, LN remains a major contributor to morbidity, disability, and mortality in individuals with SLE.

In recent years, vascular cell adhesion molecule-1 (VCAM-1) and vascular endothelial growth factor (VEGF) have gained considerable attention as promising molecular biomarkers for assessing renal involvement in SLE. Previous studies have demonstrated that VCAM-1 levels exhibit a strong association with renal biopsy activity indices, with elevated concentrations corresponding to higher nephritic activity [5]. Furthermore, urinary VCAM-1 has been proposed as a sensitive predictor of significant renal function decline (≥25% reduction), demonstrating a sensitivity of 91% and specificity of 76% [2].

Similarly, VEGF has been reported to be increased in both serum and urine samples of patients with active LN, and its levels correlate with renal tissue fibrosis, angiogenesis, and repair mechanisms [4]. This suggests that VEGF may serve not only as a marker of active nephritis but also as an indicator of ongoing structural remodeling within the kidneys.

VCAM-1, a key adhesion molecule belonging to the integrin and immunoglobulin superfamily, is upregulated on endothelial cells in response to various pro-inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-1 (IL-1). Through its interaction with leukocyte integrins, VCAM-1 facilitates the recruitment and transmigration of inflammatory cells into renal tissue. Numerous studies report that urinary VCAM-1 concentrations are significantly elevated in patients with SLE compared with healthy controls, and higher levels have been associated with an increased risk of long-term renal function decline [3]. VCAM-1 (CD106) is abundantly expressed in peripheral circulation, particularly on endothelial cells and parietal epithelial cells lining the Bowman's capsule. Elevated serum and urinary levels of VCAM-1 have consistently been linked to both the activity and severity of lupus nephritis. Several investigations also demonstrate its association with proliferative LN classes and its marked reduction following effective immunosuppressive therapy [4].

Vascular endothelial growth factor (VEGF), in contrast, functions as a serum biomarker reflecting LN activity. VEGF is a potent endothelial cell–specific growth factor that promotes endothelial proliferation, differentiation, and survival. Additionally, VEGF contributes to endothelium-dependent vasodilation, enhances microvascular permeability, and plays an essential role in extracellular matrix remodeling and tissue repair processes [5].

**Relevance:** Renal involvement in SLE represents one of the most serious and clinically challenging complications, frequently progressing to chronic kidney disease or end-stage renal failure. Although renal biopsy remains the diagnostic "gold standard," its invasive nature and potential risk of complications restrict its widespread and repeated application in clinical practice. This underscores the need for accurate, practical, and non-invasive biomarkers. Among emerging candidates, serum biomarkers such as VCAM-1 and VEGF have shown considerable promise for the early detection and prognostic evaluation of renal injury in patients with SLE.

**Materials and Methods:** The study was carried out between 2023 and 2025 at the multidisciplinary clinic of Tashkent State Medical University, specifically within the departments of rheumatology and nephrology. The investigation included both inpatient and outpatient individuals diagnosed with SLE, with and without lupus nephritis (LN), as well as a control group consisting of 20 practically healthy subjects. In total, 90 participants were enrolled. They were stratified into two principal groups:

- **Group 1 (SLE/LN–):** 40 patients with SLE without renal involvement. The group included 4 males (8%) and 36 females (92%), with a mean age of 33.59 ± 10.65 years.
- **Group 2 (SLE/LN+):** 50 patients with SLE and confirmed renal involvement. The group included 4 males (8%) and 46 females (92%), with a mean age of 31.56 ± 8.97 years.
- **Control group:** 20 age- and sex-matched healthy individuals (medical staff and students).

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The mean age of the study participants was 32 ± 2.7 years, and more than 90% of them were female. The diagnosis of SLE was established in accordance with the 2012 SLICC (Systemic Lupus International Collaborating Clinics) classification criteria, while renal involvement was confirmed based on the 1997 ACR (American College of Rheumatology) criteria (Appendix 2) and the 2019 EULAR/ACR recommendations. Renal disease activity in SLE patients was evaluated using the rBILAG (renal British Isles Lupus Assessment Group, 2004) index (Appendix 3), and overall disease activity was assessed using the SLEDAI-2K index (Appendix 1). Patients with comorbid conditions that could independently affect renal function—such as diabetic nephropathy, other nephrological disorders, or concomitant autoimmune diseases—as well as individuals who had recently received immunosuppressive therapy, were excluded from the study.

**Results:** Autoantibody production and the formation of immune complexes are hallmark immunological features of SLE and are widely recognized in international literature as key contributors to organ injury, including the development of lupus nephritis (LN) [6].

In the present study, renal function parameters—including urinary microalbuminuria (MAU), serum biochemical markers (urea, creatinine), glomerular filtration rate (GFR), and renal Doppler ultrasound findings—were evaluated in patients from Groups 1 and 2. The analysis revealed a marked difference in urinary MAU levels between the groups. Specifically, MAU concentrations were significantly elevated in Group 2 compared with Group 1. In Group 1, the mean MAU value was 28.79 ± 0.23 μg/min, whereas in Group 2 this parameter increased more than tenfold, reaching 287.46 ± 2.01 μg/min (Table 1).

**Table 1.** Clinical and laboratory parameters in SLE patients with/without LN

| **Parameter** | **Group 1 (SLE/LN–)** | **Group 2 (SLE/LN+)** |
|---|---|---|
| **Age (years)** | 33.59 ± 10.65 | 31.56 ± 8.97 |
| **Disease duration (years)** | 7.2 ± 2.3 | 3.0 ± 2.5 |
| **SLEDAI-2K score (2000)** | 7.0 ± 5.3 | 9.3 ± 6.7 |

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| | | |
|---|---|---|
| **SLICC/ACR index (2012)** | 0 [0;1] | 2 [1;2] |
| **ACR criteria (1997), score** | 3.6 ± 1.0 | 5.3 ± 1.2* |
| **rBILAG renal index (2004), score** | 4.2 ± 2.6 | 9.1 ± 4.8* |
| **MAU (mg/L)** | 28.79 ± 0.23 | 287.46 ± 2.01* |
| **Proteinuria (g/L)** | 0.1 ± 0.05 | 1.5 ± 0.4* |
| **Urea (mmol/L)** | 5.44 ± 0.18 | 11.54 ± 0.51* |
| **Creatinine (µmol/L)** | 81 ± 11 | 129 ± 17* |
| **GFR (ml/min)** | 97 ± 8 | 61 ± 12* |
| **Renal ultrasound abnormalities, %** | 10% | 68%* |
| **ANA positive, %** | 85% | 96% |
| **Anti-dsDNA positive, %** | 68% | 84%* |
| **C3 (g/L)** | 0.97 ± 0.14 | 0.62 ± 0.11* |
| **C4 (g/L)** | 0.21 ± 0.06 | 0.14 ± 0.03* |

*Significant compared with Group 1 ($p<0.05$).

In this study, the mean SLEDAI-2K (2000) score was 7.0 ± 5.3 in Group 1 and 9.3 ± 6.7 in Group 2 ($p < 0.05$), indicating significantly greater overall disease activity among patients with lupus nephritis. A positive correlation was observed between SLEDAI scores and the degree of proteinuria ($r = +0.65$), demonstrating that higher systemic disease activity was associated with increased renal involvement.

The SLICC/ACR Damage Index (2012) further reflected this difference: median values were 0 [0;1] in Group 1 and 2 [1;2] in Group 2 ($p < 0.05$), signifying more pronounced cumulative organ damage—including renal impairment—in LN patients. To evaluate renal involvement, urinary protein levels, microalbuminuria (MAU), serum urea and creatinine concentrations, and renal ultrasound (US) findings were comprehensively assessed. Between-group comparisons revealed significant deterioration of both renal filtration capacity and structural integrity in LN patients (Table 1). All observed differences reached statistical significance ($p < 0.05$), confirming more advanced glomerular and parenchymal injury in Group 2.

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Notably, pronounced elevations in proteinuria and MAU indicated disruption of the glomerular filtration barrier due to SLE-related immune-inflammatory injury. Moreover, proteinuria and MAU showed a strong positive correlation ($r = 0.72$; $p < 0.05$), suggesting that increases in global urinary protein loss were accompanied by parallel rises in microalbuminuria. A significant positive association was also identified between renal ultrasound abnormalities and proteinuria, supporting the relationship between structural renal alterations (such as glomerular fibrosis and parenchymal consolidation) and the extent of protein loss.

Serum urea levels averaged $5.44 \pm 0.18$ mmol/L in Group 1 and increased to $11.54 \pm 0.51$ mmol/L in Group 2 ($p < 0.05$), indicating impaired clearance of nitrogenous waste products in LN patients. Serum creatinine was $74.40 \pm 1.06$ μmol/L in Group 1 compared with $153.17 \pm 3.62$ μmol/L in Group 2 ($p < 0.05$), reflecting substantially reduced glomerular filtration. Correspondingly, GFR values declined sharply from $89.53 \pm 0.64$ ml/min in Group 1 to $43.53 \pm 1.47$ ml/min in Group 2 ($p < 0.05$).

Collectively, these findings demonstrate that progression to lupus nephritis is accompanied by notable worsening of renal function parameters. Increased urea and creatinine levels, together with decreased GFR, underscore the progressive deterioration of both filtration capacity and structural integrity of the kidneys in patients with LN.

Correlation analysis:

- Urea ↔ Creatinine: $r = +0.60$ (moderate positive correlation), $p<0.05$
- Urea ↔ GFR: $r = –0.57$ (negative correlation), $p<0.05$
- Creatinine ↔ GFR: $r = –0.78$ (strong negative correlation), $p<0.05$

These correlations indicate that renal dysfunction is directly associated with the accumulation of nitrogenous metabolites (urea, creatinine) and a decline in filtration rate. The findings confirm that elevated urea and creatinine, together with reduced GFR, reliably reflect the progression of renal insufficiency in SLE patients with nephritis.

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During the study, the serum levels of VCAM-1 and VEGF biomarkers were evaluated in patients diagnosed with systemic lupus erythematosus. Table 6 below presents the mean values (± SD) across the three groups: SLE/LN(+), SLE/LN(–), and healthy controls (Table 6).

**Table 6. Comparative analysis of VCAM-1 and VEGF levels across clinical groups**

| Group | VCAM-1 (ng/ml) ± SD | VEGF (pg/ml) ± SD |
|---|---|---|
| Control | 1.47 ± 0.37 | 123.42 ± 22.96 |
| SLE/LN(+) | 5.64 ± 0.64* | 413.29 ± 37.18* |
| SLE/LN(–) | 3.09 ± 0.80* | 259.42 ± 39.09* |

According to the analysis, serum VCAM-1 and VEGF levels were significantly higher in the SLE/LN(+) group, indicating enhanced endothelial inflammation and angiogenesis in patients with nephritis. Statistical evaluation (t-test) confirmed that these differences between groups were significant at $p < 0.05$ (Figure 1).

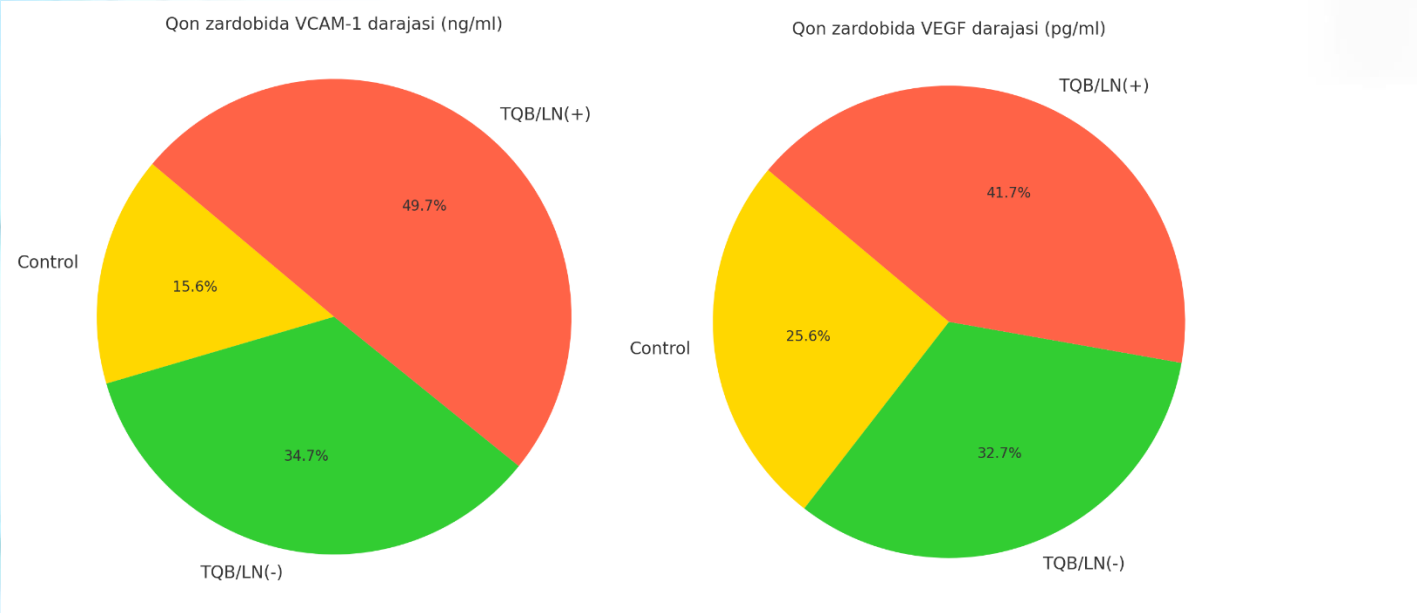


**Figure 1. Analysis of the significance level of VCAM-1 and VEGF indicators between SLE/LN(+) and SLE/LN(–) groups.**

Values are presented as mean ± SD. Differences between groups were statistically significant at $p < 0.05$.

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In this study, the diagnostic and prognostic relevance of serum VCAM-1 and VEGF concentrations was assessed in SLE patients with and without lupus nephritis. Our results demonstrated that both biomarkers were significantly elevated in the LN(+) group compared with the LN(–) and control groups, supporting their involvement in endothelial inflammation, immune activation, and angiogenic processes accompanying renal injury.

VCAM-1 exhibited moderate negative correlations with GFR (r = –0.40) and ANA (r = –0.53), indicating that higher VCAM-1 levels were associated with reduced renal filtration capacity and alterations in autoantibody activity. Although VCAM-1 showed weak or non-significant associations with serum creatinine and urea, its positive correlation with complement C3 (r = +0.43) underscores its role in complement activation and inflammatory pathways. These findings align with previous studies reporting that VCAM-1 mirrors renal disease activity and decreases following effective therapeutic intervention.

VEGF, in contrast, demonstrated strong positive correlations with proteinuria (r = +0.64) and serum creatinine (r = +0.66), along with a strong negative correlation with GFR (r = –0.62). These relationships indicate that VEGF may contribute to enhanced glomerular permeability, progressive renal dysfunction, and impaired filtration characteristic of active LN. Additionally, its moderate-to-strong correlation with complement C3 (r = +0.54) suggests a mechanistic link between VEGF-mediated angiogenesis and immune-driven renal tissue injury.

Taken together, these findings suggest that VCAM-1 is a more specific biomarker for disease activity and renal injury in SLE, while VEGF is more closely associated with the severity of renal dysfunction and proteinuria. This distinction highlights the complementary roles of these biomarkers: VCAM-1 as a marker of active endothelial inflammation, and VEGF as a marker of glomerular permeability and progression of renal impairment.

Within the scope of the study, the associations of VCAM-1 and VEGF biomarkers with renal function and immunological parameters in the SLE/LN(+) group were determined using Pearson correlation analysis. The results demonstrated

that these biomarkers were statistically correlated not only with renal injury indicators (proteinuria, creatinine, GFR) but also with immuno-inflammatory markers (ANA, ds-DNA, C3, C4). These correlations varied in strength, with some being strong, others moderate or weak, thereby reflecting their clinical significance at different stages of the disease (Figure 2).

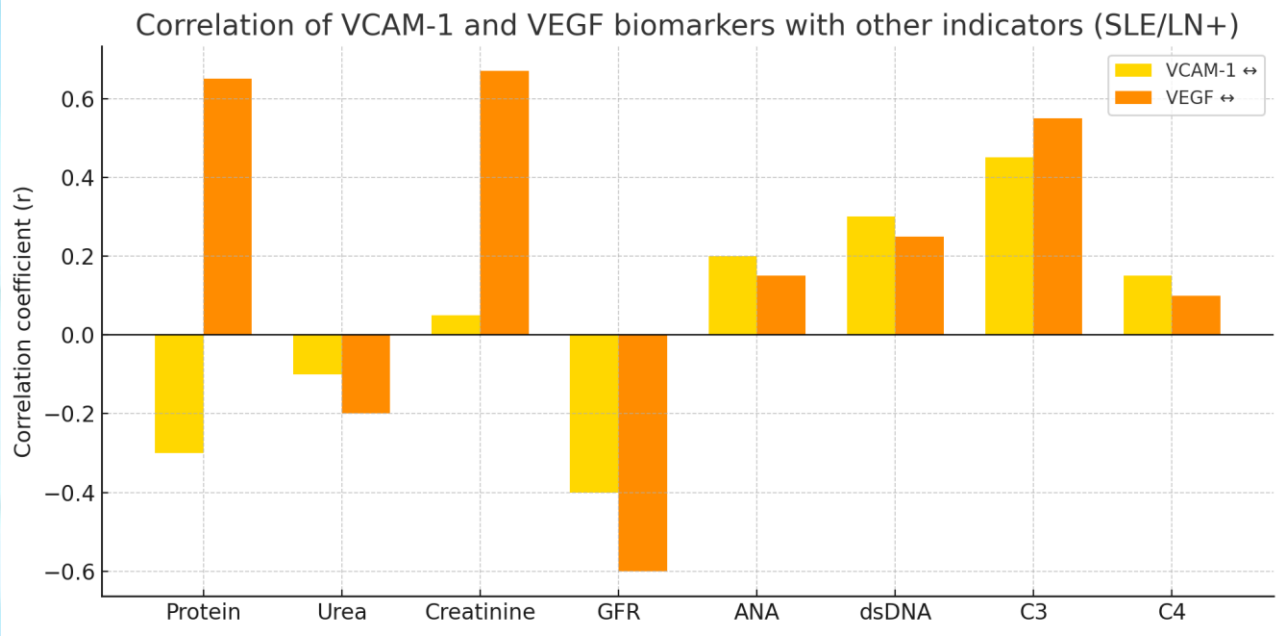


**Figure 2. Correlation of biomarkers with other indicators**

Pearson correlation analysis revealed that the VEGF biomarker showed strong positive associations with proteinuria ($r \approx +0.65$) and creatinine ($r \approx +0.67$), and a strong negative correlation with GFR ($r \approx -0.60$; $p<0.05$). These results confirm that VEGF is closely related to increased glomerular permeability and decreased renal filtration function. VCAM-1, on the other hand, demonstrated a negative correlation with GFR ($r \approx -0.40$) and ANA ($r \approx -0.53$), while showing a moderate positive association with complement C3 ($r \approx +0.43$). This indicates that VCAM-1 is more strongly linked to complement activation and immune-inflammatory pathways.

Overall, VCAM-1 was found to be primarily associated with endothelial injury and immunological activity, whereas VEGF correlated more closely with proteinuria and impaired renal function. These findings support the use of VCAM-1 as a non-invasive marker of disease activity and endothelial inflammation, and

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VEGF as a marker of disease severity and renal dysfunction in systemic lupus erythematosus.

Our results are consistent with international studies (Ikeda et al., 1998; Ghazali et al., 2017; Lai et al., 2025), confirming that VCAM-1 and VEGF have potential clinical utility as non-invasive biomarkers for the early detection and monitoring of lupus nephritis. Incorporating these biomarkers into clinical practice could improve diagnostic accuracy, enable earlier intervention, and ultimately contribute to better prognosis in SLE patients with renal involvement.

**Conclusion:** Our study demonstrated that the mean serum levels of VCAM-1 and VEGF were significantly elevated in SLE patients with renal involvement compared to those without nephritis ($p < 0.05$). These findings are consistent with the role of VCAM-1 in endothelial activation and immune-mediated inflammation, as well as the function of VEGF in vascular permeability and tissue remodeling.

Correlation analysis revealed significant associations between biomarker levels and key indicators of renal function (creatinine, urea, GFR, and proteinuria), immunological markers (ANA, anti-dsDNA, C3, C4), and disease activity indices (SLEDAI, SLICC/ACR, rBILAG). Specifically, VCAM-1 demonstrated a negative correlation with GFR, supporting its value as a marker of impaired filtration and inflammatory activity. In contrast, VEGF showed strong positive correlations with proteinuria and creatinine, and a negative correlation with GFR, highlighting its close link to renal dysfunction and glomerular barrier damage.

Taken together, these results confirm that VCAM-1 and VEGF can be considered reliable non-invasive biomarkers reflecting not only renal pathological processes and immune-inflammatory activity but also the overall severity of systemic lupus erythematosus. Their incorporation into clinical practice may facilitate earlier detection of lupus nephritis, improve monitoring of disease progression, and support individualized prognostic assessment and therapeutic decision-making.

VCAM-1 and VEGF are reliable non-invasive biomarkers for the early detection of renal involvement in systemic lupus erythematosus. VCAM-1 primarily

reflects endothelial injury and immune inflammation, while VEGF indicates vascular changes and tissue damage. Their use in clinical practice could improve early diagnosis, support timely intervention, and enhance prognosis in patients with lupus nephritis.

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