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# Predicting Study by some New Serum and Urinary Biomarkers for The Diagnosis of Lupus Nephritis in SLE Patients in Kerbela Province

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***Abstract***

***Background:*** *As a common side effect of SLE, lupus nephritis is an immunological complex glomerular nephritis (GN). Its pathogenesis involves a number of pathogenic pathways. The increased incidence of ESRD emphasizes the significance of early diagnosis in this challenging to control disease with unpredictable course that is caused by multiple combinations of genetic variants that compromise those mechanisms normally assuring immune tolerance to nuclear auto antigens.* ***Aim of study****: This study aimed to Measuring Level Urinary Epidermal Growth Factor (UEGF) in urine, Neutrophil gelatinase-associated Lipocaline (NG- AL) and measuring the level of complement (C1q, C3, C4) in serum for Lupus Nephritis patients by using ELISA method, this research included eighty female patients with SLE.* ***Methodology:*** *A cross section study of patients with Systemic lupus erythematosus was conducted. Imam AL Hasan Al Mujtaba Hospital in Karbala city during period from November 2022 to March 2023.* ***Results:*** *The findings of the present investigation have demonstrated a considerable reduction of UEGF concentration in Sever Lupus nephritis group, compeer with Moderate Lupus nephritis and other organ SLE group, the mean of UEGF was (145.97±45.55 ng/L) (195.78±60.38 ng/L) (339.15±85.59ng/L) respectively. The findings of this study have demonstrated a considerable rise in NGAL concentration in Sever Lupus nephritis group, compeer with Moderate Lupus nephritis and other organ SLE group, the mean of NGAL was (1027.53± 259.01 ng/ml) (768.82± 228.8) (715.89± 173.9 ng/ml**)** respectively. The findings of the current investigation showed a negligible decline in C1q in Sever Lupus nephritis group, compeer with Moderate Lupus nephritis and other organ SLE group, the mean of C1q was (8.04± 8.93 µg/ml) (8.44± 1.46 µg/ml) (9.43± 2.52 µg/ml) respectively. The result of C3 show un-Significant reduction in the concentration in the Sever Lupus Nephritis Patients compeer with Moderate Lupus nephritis and other organ SLE, The Mean concentration of C3 (0.79± 0.36 g/l) (0.85± 0.47g/l) (1.04± 0.35g/l) respectively. And the mean concentration of C4 as show un-Significant reduction in the concentration in the Sever Lupus Nephritis Patients compeer with Moderate Lupus nephritis and other organ SLE, The Mean concentration of C4 (0.14± 0.1g/l) (0.31± 0.17g/l) (0.38± 0.2g/l) respectively.* ***Conclusions:*** *Decrease both the level of UEGF expression and urinary excretion after kidney injury and the level of the complement system is a major factor in lupus nephritis-related kidney damage and Increase Neutrophil gelatinase-associated Lipocaline (NGAL) can serve as an early indicator for the diagnosis of acute renal damage.*



**Keywords:** *Urinary Epidermal Growth Factor , Neutrophil Gelatinase Associated Lipocaline , complement 1q, Complement 3, Complement 4 , Glomerular Nephritis, End Stage Renal Disease.*

## 1. Introduction

A well-known function of C1q is the binding and subsequent expulsion of immune complexes from tissue deposits or the circulation. The idea of C1q taking on a new role in the clearance of apoptotic cell debris in the absence of antibodies has also been suggested by recent research, which is interesting to note (Korb & Ahearn, 1997). The glomeruli of C1q deficient animals, which develop an SLE-like illness with a high incidence of nephritis, displayed many apoptotic bodies. This provides more evidence that apoptosis contributes to the development of nephritis. (Bao et al.,2011).

Systemic lupus' extra renal genesis is based on a variety of genetic variant combinations that undermine the immune tolerance systems that ordinarily ensure tolerance to nuclear autoantigens. One of the effects of SLE, an autoimmune illness marked by excessive antibody production to self-antigens, which are mostly derived from cell components like the nucleus, cytoplasm, ribosomes, and cell membranes, is lupus nephritis. Clinically noticeable antinuclear antibodies make this loss of tolerance (Yu et al., 2010).

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## 2. Materials And Methods

### Study design and setting

This study (cross sectional) for patients with Systemic lupus erythematosus was taken from Imam AL Hasan Al Mujtaba Hospital in Karbala city during period from November 2022 to March 2023. eighty female patients (80) In this cross-sectional study, participants were divided into three groups based on clinical diagnosis; patients were those with Severe Lupus Nephritis. was taken /30] Female patient, the second group Moderate Lupus Nephritis include [20] female patient and the third group was other organ SLE [30] Female patient.

### Ethical consideration

The research adhered to the protocols established by the Department of Clinical Laboratories at the College of Applied Medical Sciences at the University of Karbala for handling biological material and potentially harmful bacteria. The samples for this inquiry were collected from patients at the Imam AL Hasan Al Mujtaba Hospital in Karbala city after obtaining the required authorization from the hospital administration and patients.

### Statistical analysis:

The quantitative values are expressed using the mean and standard deviation. The student t-test was used to compare these data between patients who were eligible for home discharge and those who needed to be admitted to the intensive care unit. The frequency percentages of the binomial data were examined using chi square analysis. A receiver operating characteristic (ROC) curve was used to evaluate the predictive value for all markers that substantially differed between the two groups at admission in predicting ICU admission. All data were analyzed using SPSS for Windows, v.25.0; IBM Corp., Armonk, New York, USA.

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## 3. Results and Discussion

**Table (1) Novel Test for patients with Lupus Nephritis and other organ**

| Marker | Sever LN | Moderate LN | Other organ SLE | Normal Range |
|---|---|---|---|---|
| UEGF Mean ±SD | 145.97±45.55 | 195.78±60.38 | 339.15± 85.59 | (216-740) ng/L |
| NGAL Mean ±SD | 1027.53± 259.01 | 768.82± 228.8 | 15.89± 173.9 | (283-990) ng/ml |

The findings of this investigation have demonstrated a notable difference of UEGF between the three groups which Sever Lupus nephritis group and Moderate Lupus nephritis and other organ SLE group, the mean of UEGF was (145.97±45.55 ng/L) (195.78±60.38 ng/L) (339.15±85.59ng/L) respectively as shown in Table (1).

The findings of the present investigation showed a substantial difference of NGAL between the three groups which Sever Lupus nephritis group and Moderate Lupus nephritis and other organ SLE group, the mean of NGAL was (1027.53± 259.01 ng/ml) (768.82± 228.8) (715.89± 173.9 ng/ml) respectively in table (1).

**Table (2) The Tradional complement test for patients with Lupus Nephritis and other organ**

| Markers | Sever LN | Moderate LN | Other organ SLE | Normal range |
|---|---|---|---|---|
| C1q Mean ±SD | 8.04± 8.93 | 8.44± 1.46 | 9.43± 2.52 | (2.5-9.5) µg/ml |
| C3 Mean ±SD | 0.79± 0.36 | 0.85± 0.47 | 1.04± 0.35 | (0.9-1.8) g/L |
| C4 Mean ±SD | 0.14± 0.1 | 0.31± 0.17 | 0.38± 0.2 | (0.15-0.45) g/L |

The findings of the current investigation showed no statistically significant difference between C1q in the three groups which Sever Lupus nephritis group and Moderate Lupus nephritis and other organ SLE group, the mean of C1q was (8.04± 8.93 µg/ml) (8.44± 1.46 µg/ml) (9.43± 2.52 µg/ml) respectively in table (2)

The result of C3 show un-Significant reduction in the concentration in the Sever Lupus Nephritis patients and Moderate Lupus nephritis compare to the Other organ SLE, The Mean concentration of C3 (0.79± 0.36g/l) (0.85± 0.47g/l) (1.04± 0.35g/l) respectively in table (2).

The result of C4 show un significant reduction in the concentration in sever lupus nephritis group and moderate lupus nephritis and other organ SLE (0.14± 0.1g/l) (0.31± 0.17g/l) (0.38± 0.2g/l) respectively in table (2).

The current work is in line with a study by Isaka (2016) that demonstrates the EGF has received interest as a biomarker of renal disease due to its decreased urinary excretion being shown in practically all human kidney disorders, including diabetic nephropathy, IgA nephropathy, and lupus nephritis. According to research by Lechner et al. (2007), urinary epidermal growth factor may speed up kidney recovery by promoting tubular cell regeneration and reducing apoptosis and fibrogenic damage responses. (Lechner *et al.*,.2007).

The current investigation supports Ju's (2015) findings that kidney damage reduces urine excretion and tissue expression of EGF (Ju et al., 2015). Immune complex deposition causes proteinuria and injury to glomerular visceral epithelial cells (podocytes) in proliferative LN. EGF has recently been demonstrated to support podocyte proliferation and differentiation markers' re-expression following exposure to high glucose concentrations (Sun et al., 2021). EGF's capacity to repair podocytes enables it to improve glomerular function, which in turn lowers proteinuria in LN. Since the kidneys are the only organs that can produce EGF, urine EGF levels may be a good indicator of local renal production. As a result, LN patients who responded to therapy and had higher levels of EGF in their urine may have experienced less acute kidney damage and had more ability to tolerate ( Ngamjanyaporn *et al.*,.2022).

Low urine EGF has been demonstrated to be a risk factor for renal advancement in non-diabetic kidney disorders (Ju et al., 2015), and urinary EGF levels have been shown to correlate with the severity of tubulointerstitial fibrosis in primary glomerulonephritis (Worawichawong et al., 2016).

The findings of the present study concur with those of Nakhjavani (2019), who discovered that people with SLE had considerably increased urinary NGAL levels. In addition, NGAL was considerably higher in SLE patients with LN than in those without nephritis. Additionally, specific sera biomarkers were linked to histologic LN findings, particularly those that indicated LN activity (Nakhjavani *et al.,* 2019).

The current study is in line with the findings of Parikh's (2011) study, which indicates that NGAL has been the subject of the most research in the field of acute renal injury and has been shown to have excellent diagnostic performance. Previous research has revealed that NGAL concentrations in urine serve as sensitive, specific, and highly prognostic biomarkers for acute renal injury following cardiac surgery (Parikh et al., 2011).

The current study supports Xiang and Bolignano's (2012) findings regarding increased levels of NGAL in patients with chronic kidney disease (CKD), such as in cases of polycystic kidney disease, IgA nephropathy, dysplasia, obstruction, lupus nephritis, and glomerulonephritis.

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The results of the present study are consistent with those from Tang's work from 2005, which demonstrated that the complement classical route is a major cause of renal damage in LN. Immune complexes cause tissue damage by activating the complement cascade through the traditional mechanism. Patients with LN invariably have sub-endothelial and sub-epithelial deposits of Ig and complement classical pathway elements such C4 and C1q (Tang et al., 2005).

Low levels of C1q were found to be the best predictor of the subsequent occurrence of a renal flare when compared to levels of other complement components (Jonsson et al., 1995). Low levels of C1q have also been associated with current renal illness. Depending on the severity of the disease, the complementary elements of the classical route change.

A well-known function of C1q is the binding and subsequent expulsion of immune complexes from tissue deposits or the circulation. The idea of C1q taking on a new role in the clearance of apoptotic cell debris in the absence of antibodies has also been suggested by recent research, which is interesting to note (Korb & Ahearn, 1997). The glomeruli of C1q deficient animals, which develop an SLE-like illness with a high incidence of nephritis, displayed many apoptotic bodies. This provides more evidence that apoptosis contributes to the development of nephritis (Botto *et al.,* 1998).

The pathophysiology of SLE is characterized by immunological dysfunction. The creation of autoantibodies, the formation of immune complexes, and the defect of autoimmune tolerance are all primarily caused by immunological disorders, which in turn result in injury to several organs (Yap & Lai, 2015).

It has been established that the complement system is essential for removing immune complexes and autoantigens produced as a result of cell death and for preventing autoimmune-related tissue and organ damage (Elkon & Santer ,2012).

Due to the complement system's opsonizing function in the physiological clearance of autoantigens and apoptotic bodies, a dysfunctional complement system may result in a failure to correctly identify and promptly remove cell debris and autoantigens, which in turn activates immune response and produces autoantibodies. Sequentially binding autoantibodies to complement fragments results in tissue damage,

particularly to the kidneys (Dragon-Durey et al., 2013).These findings concur with those of Li et al. (2015), who discovered decreased complement C3 and C4 serum levels in Chinese SLE patients.

The results of the present investigation are consistent with those of Julkunen et al. (2012), who hypothesized that complement C3 and C4 serum levels are correlated with disease activity and that patients with active lupus nephritis had considerably lower levels of C3 and C4 than patients with inactive lupus nephritis.

The findings of the cuttent study concur with those of Birmingham et al. (2010), who demonstrate that C4 is particularly important for initiating a renal flare and that C3 activation is associated with actual tissue damage. Furthermore, Ho et al. (2001) discovered that declines in complement levels in the serum were not only associated with contemporaneous increases in renal and hematologic SLE activity but also were not always linked to SLE flares.

## 4. Conclusion

Decrease the concentration of Human epidermal growth factor (urinary EGF) and increase the concentration of NGAL especially in Lupus nephritis patients make them good markers for predecting the renal failure at early stage, while reduced the concentration of (C1q, C3 and C4) As a result, we can infer that the criterion and a disease flare-up are related.

## Conflict of Interest

The authors say they have no competing interests.

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