Evaluation of Interleukin -17 (Il-17) As Urinary Immune-Related Biomarker in the Diagnosis of Lupus Nephritis

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Abstract

Background: Kidney involvement is a key problem in systemic lupus erythematosus (SLE), affecting about 50% of patients and responsible for a large amount of morbidity and mortality. Early identification and treatment can significantly alter the course of renal illness and enhance long-term survival. This study aimed to evaluate the diagnostic value Interleukin-17 as urinary immune-related biomarker for the diagnosis of lupus nephritis in patients of SLE. Methods: A cross sectional study on 78 patients with SLE (72 females and 6 males) was conducted from September 2021 to March 2022. Renal involvement was determined using the renal SLEDAI, which incorporates the SLEDAI-2k kidney-related parameters: "hematuria, pyuria, proteinuria, and urinary casts." Results: Urinary IL- 17 levels were statistically higher in the LN group than those without LN (p value <0.000). Levels of urinary IL-17 were not significantly associated with renal SLEDAI. Conclusions: This study concluded that urinary IL-17 had a high accuracy and can be considered as good predictors for diagnosis of active LN in SLE patients.

Keywords: u Interleukin 17, urinary biomarker, lupus nephritis biomarker.

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disease associates with the production of a variety of autoantibodies directed against native DNA and other cellular constituents. It is a prototypic disease with heterogeneous clinical manifestations that may involve many different organs and systems [1].

Most patients with SLE develop kidney disease (nephritis). Lupus nephritis (LN) is an important cause of morbidity and even mortality in patients with SLE. Lupus nephritis has diverse morphologic manifestations with varying clinical presentations and consequences. The pathogeneses involve immune complexes, which can deposit anywhere in the kidney [2].

Current laboratory markers for LN such as "proteinuria, urinary protein-to-creatinine ratio, creatinine clearance, anti-dsDNA, and complement" levels are unsatisfactory. They lack sensitivity and specificity for differentiating renal activity and damage in LN. Significant kidney damage can occur before renal function is impaired and first detected by laboratory parameters. Renal biopsy is the gold standard for providing information on the histological classes of LN and the relative degree of activity and chronicity in the glomeruli. However, it is invasive and serial biopsies that are impractical in the monitoring of LN. Thus, novel biomarkers that are able to discriminate lupus renal activity and its severity, predict renal flares, and monitor treatment response and disease progress are clearly necessary [3].

Unlike other "biological specimen sources," such as tissue or serum, urine samples are noninvasive, allow for regular monitoring, and self-administered collection, transportation, and storage. In addition, urine biomarkers seem to be more helpful in assessing LN than serum markers. As they are derived from urinary system tissues and can thus reflect its current clinical condition. Consequently, urine is a valuable source for identifying possible biomarkers in the investigation of LN [4].

Interleukin 17 (IL-17) is a potent pro-inflammatory cytokine produced by activated T cells, with Th17 cells being the most notable producer. It stimulates the production of several "chemoattractants for

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monocytes and neutrophils in the target organ, as exemplified by MCP-1" [5]. Interleukin 17-producing cells are present in the inflamed kidney tissues from patients with lupus nephritis. Urinary IL-17 associates with renal tissue damage, though its precise role in the pathogenesis of LN remains unclear [6].

This study aimed to evaluate the diagnostic value of IL-17 as urinary immune-related biomarker for diagnosis of nephritis in SLE patients.

2. Methods

A cross sectional study on 78 patients with SLE (72 females and 6 males) was conducted from September 2021 to March 2022. All the patients were recruited from AL-Seder teaching medical city in the province of Najaf, Iraq. The age range of patients was between 12 to 53 years.

Inclusion Criteria

Each patient should have at least 4 scores of "American college of rheumatology" of SLE to be enrolled in this study as a SLE patient.

Exclusion Criteria

Any patient with other connective tissue diseases such as rheumatoid arthritis or scleroderma, diabetes mellitus, any disease that can affect urinary biomarker such as immunodeficiency disease, autoimmune disease, malignancy, and chronic infection, urinary tract infections, LN but undergoing hemodialysis or has a history of renal transplantation and LN but with renal insufficiency from non–lupus-related causes.

Patients Groups

Renal involvement in SLE patient was assessed with the renal SLEDAI, which consists of the 4 "kidney-related parameters of the SLEDAI-2K: hematuria, pyuria, proteinuria, and urinary casts. Each item in the renal SLEDAI is assigned 4 points. Thus, scores for the renal SLEDAI can range from 0 (inactive renal disease) to a maximum of 16."

Therefore, patients at the time of their clinic visit were randomly selected and classified into:

1-Group of patients without LN.

2-Group of patients with LN.

For the purposes of the present study, the group of patients without LN was prospectively defined as those having a renal SLEDAI score of 0 or 4 (one abnormal result for renal parameters, when hematuria, pyuria, or urinary casts but not proteinuria was the renal-related criterion. While "the LN group was prospectively defined as those having a renal SLEDAI score of ≥8 (i.e., at least 2 abnormal results for renal parameters) or, when proteinuria was the renal-related criterion, a renal SLEDAI score of 4." The latter limit was used in order to select those patients who had already displayed changes in glomerular permeability [7].

The samples (blood and urine) were collected from the SLE patients. Afterwards, aliquots of fresh urine samples from each patient were frozen at -40°C for later analysis. The Human Interleukin 17 was measured using ELISA Kit (E0142Hu, bioassay technology laboratory®, China; Sensitivity 1.06ng/L).

3. Statistical Analysis

Data of both studied groups were entered and analyzed using the statistical package for social sciences (SPSS) (version.25 Inc., Chicago, USA) and GraphPad Prism software, version 9.3.1 (La Jolla, CA, USA). Descriptive statistics presented as "median with interquartile range (IQR)" frequencies and proportions. Comparison between groups was calculated using "Mann-Whitney U test. Multiple comparisons were done using the Kruskal-Walli's test". "Pearson's Chi-square and Fisher's" exact (when proportions were too small) tests used alternatively to compare frequencies. Level of significance of ≤ 0.05 was considered as significant difference or correlation. "The receiver operating characteristic curve (ROC)" analytical curve has been used to estimate the diagnostic efficiency of IL-17 as clinically viable by assay the ratio of area under the curve (AUC).

4. Results

According to renal SLEDAI score, 46 (59%) SLE patients were with LN and 32 (41%) SLE patients were without LN as shown in table (1)

There was a significant difference (P = 0.003), between the mean age of SLE patients with LN [28 year (± 9.03)] and SLE patients without LN [35.1 (± 10.7)], and there was an insignificant difference regarding the distribution of both groups according to gender (P = 0.187). The group of SLE patients with LN included 2 males and 44 females, accounting for 4.3 % and 95.7%, respectively, whereas SLE patients without LN included 4 males and 28 females, accounting for 12.5 % and 87.5 %, respectively, as shown in table (1).

Table 1: Demographic Characteristics and Medications of SLE Patients with and without LN

Characteristic	Patients with LN n = 46	Patients without LN n = 32	P- value
Age, mean (± SD) years	28 (± 9.03)	35.1 (± 10.7)	0.003*
Adult patients; no. (%)	37 (80.4 %)	30 (93.8 %)	0.097
Adolescent patients; no. (%)	9 (19.6 %)	2 (6.2 %)	
Gender: male no. (%) Female: no. (%)	2 (4.3%)	4 (12.5%)	0.187
	44 (95.7%)	28 (87.5%)	

Blood and Urinary Parameters of SLE Patient Groups

The outcomes of blood and urinary parameters results in the two patient groups are shown in tables (2) and (3). Patients with LN had significantly higher levels of blood urea and serum creatinine [35 mg/dl (27.0-58.2) and 0.8 (0.66-1.35), respectively]

compared to that of patients without LN [22 mg/dl (17.5-28.0) and 0.7 mg/dl (0.6-0.7), respectively] (P - < 0.01) and there was a significant difference in glomerular filtration rate, (P- <0.05) between patients with LN [99.5 mL/min (53.5-122.5)] and patients without LN [114.5 mL/min (104-124)], While the hematological parameters (hemoglobin, WBC and platelets) showed an insignificant difference between patient with LN [11.2 mg/dl (10.3-11.7), 6.3 x 10^9/liter (4.1-9.5) and 232 x 10^9/liter (196-301), respectively] and patients without LN [11.5 mg/dl (10.4-12.9), 5.5 x 10^9/liter (4.5-7.5) and 243 x 10^9/liter (200-296), respectively] as revealed in table (2).

Table 2: Blood Biochemical and Hematological Parameters of SLE Patient Groups

Characteristic	Patients with LN	Patients without LN	P- value
Blood urea (mg/dl)	35 (27.0-58.2)	22 (17.5-28.0)	<0.0001**
Serum creatinine (mg/dl)	0.8 (0.66-1.35)	0.7 (0.6-0.7)	0.003*
Glomerular Filtration Rate (EPI) (mL/min/1.73m2)	99.5 (53.5-122.5)	114.5 (104-124)	0.050*
Hemoglobin (mg/dl)	11.2 (10.3-11.7)	11.5 (10.4-12.9)	0.374
WBC (x 109/liter)	6.3 (4.1-9.5)	5.5 (4.5-7.5)	0.384
Platelets (× 109/liter)	232 (196-301)	243 (200-296)	0.872

There were a highly significant differences (P- <0.0001) in spot urinary protein, and spot protein to creatinine ratio between patients with LN [105.4 mg/dl (24.1-225.0) and 917.9 mg/g (344.6-3159.7), respectively] and patients without LN [14.0 mg/dl (6.5-20.0)and 109.3 mg/g (52-222.5), respectively] , while there was no significant difference in urinary creatinine between patients with LN [70.7 mg/dl (33.8-143.2)] and patients without LN [107.3 mg/dl (66.0-175.6)].

Table 3: Urinary Biochemical Parameters in SLE Patient Groups

Characteristic	Patients with LN	Patients without LN	P- value
Urinary protein (mg/dl)	105.4 (24.1-225.0)	14.0 (6.5-20.0)	<0.0001**
Urinary creatinine (mg/dl)	70.7 (33.8-143.2)	107.3 (66.0-175.6)	0.076
Protein to creatinine ratio (mg/g)	917.9 (344.6-3159.7)	109.3 (52-222.5)	<0.0001**

Urinary Interleukin 17 in SLE Patients with and without LN

The urinary IL-17 levels was corrected with urinary creatinine, to evaluate whether urinary interleukin 17 is related to lupus renal disease and compared between lupus patients with and without LN. Urinary IL-17 levels were statistically higher (P = 0.022) in the LN group (median 0.09 ng/mg creatinine, IQR 0.04-0.31; n = 46) compared to those without LN (median 0.04 ng/mg creatinine, IQR 0.024-0.109; n = 32) as shown in figure (1).

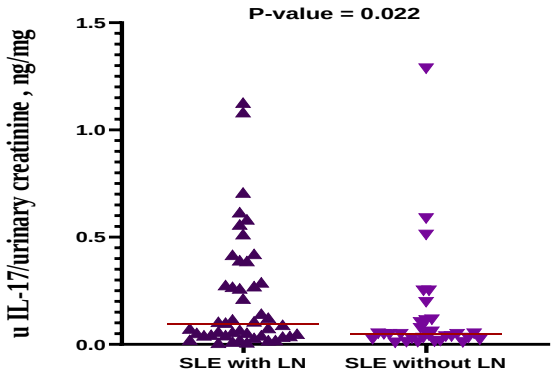

Figure 1: Urinary Levels of IL-17 in SLE Patients with and without Nephritis.

Renal Histopathology Characteristics of LN Patients

A Twenty-six of the 46 LN patients who were selected for the study had a kidney biopsy. According to the "World Health Organization's system" for classifying diseases [8], 5 of these patients had type II glomerulonephritis (GN), 14 had type III GN, 6 had type IV GN, and 1 had type V glomerulopathy as shown in figure (2).

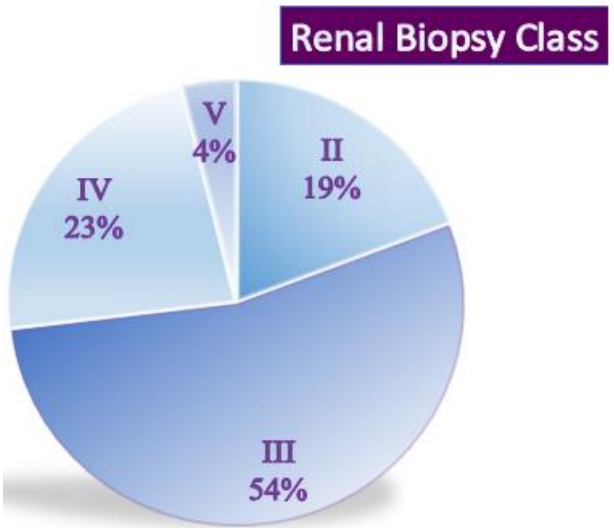

Figure 2: Renal Histopathology Characteristics of Lupus Nephritis Patients

Diagnostic Performance of Urinary Interleukin 17

A receiver operating characteristic (ROC) curve was used to quantify the diagnostic utility of urinary interleukin 17 by ELISA between LN patients proven by biopsy (the current gold standard) and SLE patients without renal involvement. The results were shown in figures (3) and table (4). Indeed, the cutoff values obtained for urinary interleukin 17, were good predictors because of an area under the curve of more than 0.8 and significant P values (*P* <0.05), as shown in table (4). The levels of accuracy were more than 70%.

At a cutoff value of urinary interleukin 17 (0.051 ng/mg creatinine), the sensitivity of urinary interleukin 17 levels for the diagnosis of LN was 60%, with a specificity of 92%.

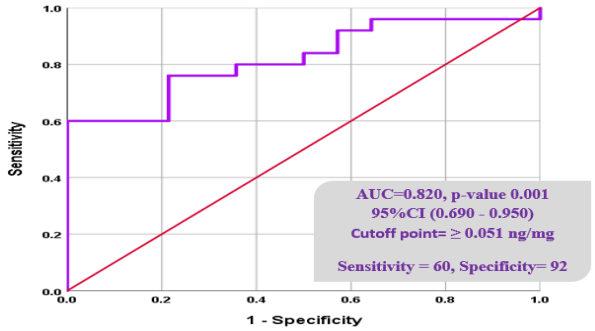

Figure 3: Receiver Operator Characteristic (ROC) Curve Analysis to Find the Best Urinary Interleukin 17/ Urinary Creatinine Cutoff Value that Can Predict Lupus Nephritis in Systemic Lupus Patients.

Table 4: Characteristics of Receiver Operator Characteristic (ROC) Curve in LN Patients	
Characteristic	**u IL-17/u creatinine**
AUC	0.820
SE	0.066
Sig.	0.001
95% Confidence Interval	0.690 – 0.950
Cut off point	≥ 0.051 ng/mg
Sensitivity (%)	60
Specificity (%)	92
PPV (%)	93.7
NPV (%)	56.5
Diagnostic effectiveness (accuracy)	71.7 %
Youden's index	0.52

AUC, Area under the Curve; SE, stander error, Optimal Cut-Point Value, PPV (Positive Predictive Value), NPV, (Negative Predictive Value); Youden's index is a measure for evaluating the biomarker effectiveness.

Urinary Interleukin 17 and Renal Activity

Patients with LN showed an insignificant association between urinary IL-17/urinary creatinine and the renal SLEDAI score (r=0.166, P=0.146) as shown in figure (4).

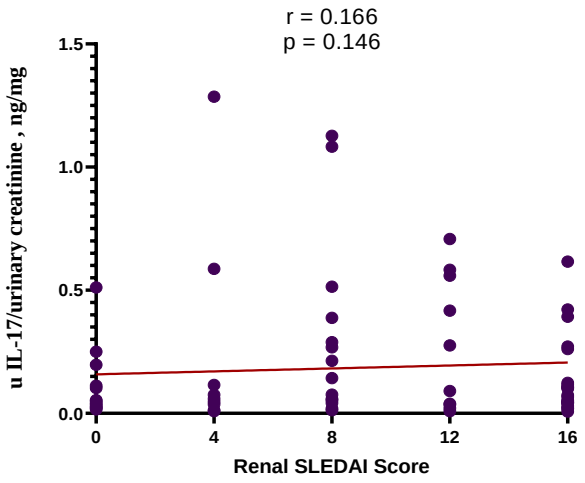

Figure 4: Correlation Between Urinary Interleukin 17 Levels in SLE Patients and Indices of Renal Activity.

5. Discussion

Interleukin 17 is a proinflammatory cytokine produced by a subtype of T cells and may play a role in the pathogenesis of LN. Interleukin 17 has strong proinflammatory effects, induces other cytokines, promotes recruitment of inflammatory cells such as neutrophils, macrophages, and lymphocytes, and facilitates T-cell infiltration [5]. Interleukin 17 increase in patients with SLE. Interleukin 17 producing cells are present in the inflamed kidney tissues of patients with lupus nephritis [9].

In the present study, the level of IL-17/creatinine in the urine was significantly different between the LN and non-LN groups. This agrees with several studies performed by Kwan et al [10], Chen et al [11], Susianti et al [12] and Saber et al [13].

In disagreement with the current findings, Doreau et al [14] and Wang et al [15] reported a statistically significant correlation between IL-17 and disease activity (renal SLEDAI). In the current study, although IL-17 did not show a significant correlation with disease activity (rSLEDAI) (r = 0.166, P = 0.146) which agrees with Saber et al [13], but there is an increasing in the urinary IL-17 with the increase in the disease activity score (renal SLDAI) in patients with LN. Therefore, in the present study, this increasing in the urinary IL-17 beside the previous result which indicates the significant difference in the level of urinary IL-17/creatinine between the LN and non-LN groups suggests this cytokine may be involved in the inflammatory process of renal disease during the acute phase of SLE patients. This suggestion is supported by Dong et al [16], who found that IL-17 play a key role in the pathogenesis of LN through the induction of IgG and anti-dsDNA overproduction.

In the current study, there is no significant correlation between the immune-related biomarker (interleukin 17) and the age or the gender of the LN patients. These findings demonstrate ideal features of interleukin 17 as a biomarker for LN when this biomarker is not affected by age or gender [17].

In the present study, there is no significant correlation of the blood biochemical parameters (blood urea, serum creatinine and GFR) with urinary IL-17 in LN patients because this marker reflect the renal inflammatory state rather than the renal insufficiency, where abnormal eGFR decline or increase in serum creatinine occurs in stage 4 chronic kidney disease (CKD) [17] which indicate severe renal insufficiency.

Patients with LN did not exhibit a significant connection between hemoglobin and urinary IL-17. This finding may indicate the lack of an important effect of this biomarker on the renal production of erythropoietin in LN patients of this study.

In addition, there was no apparent correlation between WBC and IL-17 in the urine of patients with LN.

Although thrombocytopenia is known as one of the hematological criteria of SLE, according to the American College of Rheumatology (ACR)

classification criteria. Patients diagnosed with LN did not demonstrate a significant correlation between platelets and IL-17 in urine, which may indicate that this biomarker doesn't have an important role in the development of thrombocytopenia in LN patients.

The present finding revealed that the urinary protein had no apparent correlation with immune-related biomarker (IL-17) in the urine of patients with LN. This is consistent with the findings of Mok et al [18], who reported no correlation between proteinuria and urinary IL-17. Lack of such correlation between of IL-117 and spot urinary protein in LN patient may be due to low sensitivity of spot urinary protein increase with the increase of the immune-biomarker, since the spot measurement of protein in urine may vary depending upon the hydration status of the patient and on renal function. In addition, this immune related biomarker may reflect the inflammatory status of the kidney rather than the loss of protein in urine because persistent proteinuria may not necessarily indicate ongoing inflammation in the kidneys and may be contributed by pre-existing chronic lesions or recent damage in the kidneys during the course of the disease [3].

This limitation of spot urinary protein can be overcome by the use of spot ur inary protein to creatinine ratio by normalization of spot urinary protein with urinary creatinine.

Spot urinary protein/creatinine ratio has been increasingly widely adopted as a simpler method than 24-hour timed urine collections to estimate the degree of proteinuria. The numeric ratio of protein and creatinine concentrations approximates the number of grams per day of proteinuria [19]. In addition, American College of Rheumatology (ACR) renal disease subcommittee recommends measuring protein-to-creatinine ratio in a morning void urine sample or even a spot urine sample [17].

The protein to creatinine ratio has proven to be more beneficial for glomerular disorders in general and lupus nephritis in particular due to its simplicity and convenience [20].

The current finding showed that the urinary creatinine had a strong negative correlation with IL-17 in the urine of LN patients. In spite of this strong correlation, most of the results of urinary creatinine of LN patients were within the normal range. These findings may imply that the level of biomarker rise with a relative decrease in creatinine clearance but without an abnormal decline in renal efficiency because this biomarker reflect the renal inflammatory state rather than the renal insufficiency.

Regarding urinary IL-17/creatinine level, there was a significant correlation with the protein to creatinine ratio in the group of patients with LN ($r = 0.296$, $P = 0.018$). This agrees with Saber et al. [13], who found a correlation in the patient group with LN. As mentioned above, the limitations of spot urinary protein were overcome by the use of spot PCR. So, the spot PCR rather than the spot urinary protein correlates with the severity of the renal inflammation, which was indicated by the increase in the level of the urinary biomarker (IL-17).

The receiver operating characteristic (ROC) curve analysis was constructed to quantify the utility of urinary Interleukin 17 in the diagnosis of LN in SLE patients with nephritis proven by biopsy (the current gold standard) and SLE patients without renal involvement. At a cutoff value of ≥ 0.051 ng/mg creatinine, urinary IL 17 was considered as a good predictor for LN because the area under the curve was more than 0.7 (AUC = 0.820 with a 95% confidence interval of 0.690 – 0.950) and a significant P value ($P < 0.001$). The level of accuracy was 71.7%, with a high specificity (92%) but relatively low sensitivity (60%). Urinary IL-17 may play an essential role in the inflammatory process of renal disease during the acute phase of SLE patients. Consequently, the current findings suggest that they could be evaluated as novel biomarkers for diagnosing LN. Additionally, it is an inexpensive and readily available biomarker.

6. Conclusions

Based on this study, the following conclusions could be made:

1. Urinary interleukin 17 levels were statistically higher in the LN group than those without LN.
2. Urinary IL-17 was not significantly associated with rSLEDAI.
3. Urinary IL-17 measurements may be an ideal non-invasive measure, which could reduce the need for renal biopsy.

Recommendations

1. A study of IL-17 on early diagnosed LN patients is highly recommended to minimize the effects of immunosuppressant drugs on disease development.
2. Measure the urinary biomarker (IL-17) in 24-hour urine collections instead of spot urine collection, which is more sensitive.
3. Measure the serum biomarker (IL-17) in LN patients to identify if the production of this biomarker is local (renal) or systemic.

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