ORIGINAL ARTICLE

Assessment of Urinary TNF-like Weak Inducer of Apoptosis as a Marker of Lupus Nephritis

[1]Rasha M. Elnagar*, [2]Hifaa G. Al-Noman, [3]Hanan E. Al-Rashidi, [4]Mohamed M. Elzayady, [5]Elshimaa S. Eleraky, [6]Safaa M. EL-Ageery, [7]Nawal S. Gouda, [8]Mariam Selim, [9]Sofanah A. Alahmadi, [10]Rania Talaat

[1]Medical Microbiology and Immunology Department, Faculty of Medicine, Mansoura University, Mansoura 35516, Egypt; Basic Medical Sciences Department, College of Medicine, AlMaarefa University, Riyadh, 11597 Saudi Arabia
[2]Nogoud Medical Center, Almadinah Almonawarah, Ministry of Health, Saudi Arabia
[3]Medical Laboratory Technology Department, Faculty of Applied Medical Sciences, Taibah University, Saudi Arabia
[4]Internal Medicine Department, Faculty of Medicine, Mansoura University
[5]Internal Medicine Department, Faculty of Medicine, Horus University, Egypt
[6]Medical Microbiology and Immunology Department, Faculty of Medicine, Mansoura University, Egypt
[7]Microbiology Department, Faculty of Medicine, Northern Border University, Ar·ar, Saudi Arabia
[8]Mansoura Manchester Medical Program, Faculty of Medicine, Mansoura University, Egypt
[9]Al-Rayan College of Medicine, Almadinah Almonawarah, Saudi Arabia
[10]Medical Microbiology and Immunology Department, Faculty of Medicine, Helwan University

Key words:
Lupus, nephritis, urinary, TWEAK

Corresponding Author:
Rasha M. Elnagar
Department of Medical Microbiology and Immunology, Faculty of Medicine, Mansoura University, Mansoura 35516, Egypt; Department of Basic Medical Sciences, College of Medicine, AlMaarefa University, P.O.Box 71666, Riyadh, 11597 Saudi Arabia
drrasha_m@mans.edu.eg
https://orcid.org/0000-0002-5661-850X

ABSTRACT

Background: *TNF-related weak inducer of apoptosis (TWEAK) is a proinflammatory cytokine that may play a major role in the pathophysiology of lupus nephritis (LN).* ***Aim:*** *We investigated the correlation between LN and urinary TWEAK and its use as a biomarker in LN.* ***Methodology:*** *This study comprised 56 females with systemic lupus erythematosus (SLE) and 56 age-matched healthy female controls. Patients were grouped into 27 patients with non-renal SLE and 29 with LN. The LN group was also categorized into patients with active renal disease (n=19) and inactive renal disease (n=10). Urinary TWEAK was measured in all participants using ELISA.* ***Results:*** *The LN group had markedly elevated urinary TWEAK levels compared to non-renal SLE, inactive LN, and normal controls. Significant positive associations were observed between urinary TWEAK and tSLEDAI (P< 0.001), as well as rSLEDAI (P< 0.001). Negative associations were identified between urinary TWEAK and C3 and C4 (P< 0.001). Urinary TWEAK levels exhibited a positive correlation with elevated kidney biopsy grades (P< 0.001). The threshold values for urinary TWEAK were >2.06 for SLE, >5.91 for LN, and >6.5 for active LN, with corresponding sensitivity rates of 100%, 75.86%, and 84.21%, respectively. The specificity rates were 94.74%, 88.89%, and 70%, respectively. The positive and negative predictive values augmented the importance of urine TWEAK. The accuracy rates were 97.3% for SLE, 82.1% for LN, and 79.3% for active LN.* ***Conclusion:*** *Urinary TWEAK demonstrated a positive correlation with the activity parameters of LN, indicating its potential role as a marker for monitoring renal involvement and disease activity.*

INTRODUCTION

One of the most prevalent clinical manifestations of SLE is LN, characterized by inflammation due to immune complex deposition, renal microvascular damage, hematuria, proteinuria, and eventually progressive renal impairment[1,2]. About 60% of SLE cases have LN, which is a major contributor to patient morbidity and mortality[3,4]. About 22% of patients with LN may progress to end-stage renal disease within 15 years, with the largest risk occurring in the first 5 years. Therefore, it is crucial to recognize and intervene early to maintain renal function[5].

The most reliable way to diagnose LN and determine the course of disease is a percutaneous renal biopsy[6]. But this is an invasive maneuver, therefore it might not be the best choice in every situation[7]. It is quite difficult to early detect and follow up LN because of its unexpected nature and gradual onset[8].

Proteinuria, creatinine clearance, levels of complement components, anti-double stranded DNA antibodies (anti dsDNA Abs), and other biochemical markers can be used to assess LN activity in a clinical

setting. The reliability of these markers as indicators of disease activity and outcome predictions remains controversial, and their association with LN is still debatable[9]. When it comes to differentiating between renal activity and damage in LN, these indicators aren't sensitive or specific. Before these biomarkers were firstly detected, significant kidney damage may have already occurred[10].

Urine biomarkers surpass serum biomarkers in efficacy due to their ease of acquisition and their ability to accurately reflect the current renal condition, as they are precisely the direct result of inflammatory activity in the kidneys. Therefore, urine biomarkers offer a convenient, noninvasive, and accurate method for clinicians to reliably track renal impairment in SLE and perhaps anticipate LN sequences[11].

The proinflammatory cytokine TNF-related weak inducer of apoptosis (TWEAK), is one new member of the TNF ligand superfamily. Innate immune cells, including monocytes, dendritic cells, and natural killer cells, are responsible for producing the vast majority of TWEAK[12]. Moreover, renal TWEAK can originate from intrarenal monocytes, tubular epithelial cells, mesangial cells, and T-cells[13]. Physiological tissue regeneration and repair following acute damage is now believed to be aided by TWEAK. On the other hand, dysregulated TWEAK expression causes further inflammation and cell death in chronic inflammatory diseases[14,15]. TWEAK regulates its activity via binding to fibroblast growth factor-inducible 14 (Fn14), leading to the recruitment of TRAF2 and TRAF5 and the activation of intracellular signaling pathways. The binding consequence of TWEAK/Fn14 and the resulting activated signaling pathways are dependent upon cell types, cell states, and microenvironment[16]. Notably, the exact renal response to TWEAK is modified by the cell microenvironment. Renal tubular cells apoptosis could not be stimulated by TWEAK alone but could occur through co-stimulation with TNFα and interferon γ present in injured kidney[17].

.Recently, there has been an interest in using urine TWEAK as a biomarker for LN. Increased TWEAK levels are associated with worsening renal illness in patients with active LN as compared to those without LN[18]. So, this study aimed to determine the value of urinary TWEAK as a biomarker in LN and its correlation with disease activity.

METHODOLOGY

Study design

This prospective cohort study was conducted in the Immunology Unit of Medical Microbiology and Immunology Department, Mansoura University and Nephrology Unit of the Internal Medicine Department of Mansoura University Hospital over a period of 6 months. The study comprised 56 females who had been diagnosed with SLE using the criteria set by the American College of Rheumatology[19]. Patients were divided into two groups: one group had non-renal SLE, which included 27 participants with normal serum creatinine and urine sediment levels, and no significant renal symptoms related to SLE. The other group had LN, which included 29 patients diagnosed with LN based on kidney biopsy results and/or significant renal symptoms related to SLE, like increased serum creatinine and proteinuria. Considering the renal SLE disease activity index (rSLEDAI) score, the LN group was further divided into two groups: active renal disease (n =19) and inactive renal disease (n =10). The study also incorporated a control group of 56 randomly selected age matched females.

Exclusion criteria

Patients with essential hypertension, diabetes mellitus, urinary tract infections, urinary stones, acute renal failure, other urological problems, neoplasms, and other autoimmune diseases were excluded from the research.

Clinical and laboratory assessment

All cases underwent comprehensive medical history assessment and general physical examination. The assessment of SLE disease activity was conducted using the SLE Disease Activity Index (SLEDAI)[20]. The SLEDAI has a theoretical range of 0 to 105, where 0 indicates the absence of disease activity[21]. A four-parameter rSLEDAI including pyuria, hematuria, proteinuria, and urine casts, was used to evaluate LN activity; the score can range from 0 (showing non-active kidney disease) to 16 (maximum score)[22]. A rSLEDAI score of 4 or above was suggestive of active LN, whereas a score of 8 or higher indicated considerable kidney disease activity, as stated by Schwartz et al[23] and Zhu et al[24]. Patients with active lupus nephritis were further examined by ultrasound-guided kidney biopsy, unless contraindicated. All biopsies were evaluated according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of LN[25]. Class I refers to very little changes, class II to mesangial modifications, class III to localized proliferative, class IV to diffuse proliferative, and class V to membrane glomerulonephritis, according to the World Health Organization's (WHO) criteria for renal biopsy specimens[26].

Serum creatinine, blood urea nitrogen, serum albumin, serum complement components C3 and C4, anti-dsDNA, erythrocyte sedimentation rate (ESR), urinalysis, complete blood count, and protein quantification in 24-hour urine samples were among the laboratory tests performed for each patient.

Early morning, freshly voided urine samples were collected from all participants. Urine samples were kept at 4°C and then quickly transferred to the laboratory, where they were centrifuged to remove debris, then preserved at -80°C for further examination. The Human TWEAK Instant ELISA kits purchased from Thermo Fisher Scientific; USA were used to measure the levels of TWEAK in the urine. To standardize the urinary TWEAK levels, the concentrations of creatinine in the urine were determined at the same spot urine test and expressed as pg/mg creatinine.

Ethical approval

The Institutional Review Board of the Faculty of Medicine, Mansoura University, Egypt, granted ethical approval for this study (code number: R.25.03.3106), in compliance with the Declaration of Helsinki.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 25.0, developed by IBM, was used to tabulate and analyze the data. For two-group comparisons and non-parametric variable significance testing, the Mann Whitney test was used; for comparisons involving three or more groups, the Kruskal-Wallis test was applied. By utilizing a chi-square test, the correlation between two qualitative variables was investigated. To determine the strength of the association between two numerical variables, we applied Spearman's correlation. The receiver operating characteristic (ROC) curve was a useful tool for evaluating sensitivity and specificity for quantitative diagnostic tests that categorize patients into two categories. The optimal cutoff value was found by optimizing the area under the curve (AUC). With a 95% confidence interval, a *P*-value below 0.05 was deemed significant.

RESULTS

Of the 56 SLE patients who were studied, 27 individuals without renal involvement, 19 with active LN, and 10 with inactive renal disease. Blood pressure (systolic and diastolic), serum creatinine and urea, ESR and serum albumin, 24-hour urine protein, tSLEDAI, rSLEDAI, C3, and C4 were among the variables that showed statistically significant differences among the three groups. Comprehensive comparisons among the three groups are presented in table 1.

Compared to non-renal SLE patients, inactive LN, and normal controls, the LN group had significantly higher urinary TWEAK levels. Table 2 and figure 1 show the urine TWEAK levels for all groups.

Regarding the relationship between urine TWEAK and clinical and laboratory indicators of SLE, there were significant positive correlations between urinary TWEAK and systolic blood pressure (mmHg) (P <0.001), diastolic blood pressure (mmHg) (P <0.001), hematuria (P <0.001), pyuria (P <0.017), urinary casts (P <0.001), 24-hour urinary proteins (P <0.001), tSLEDAI (P <0.001), and rSLEDAI (P <0.001). Inverse correlations were seen between urine TWEAK and C3 and C4 (P <0.001). No correlations were reported between urinary TWEAK levels and serum creatinine or blood urea as illustrated in table 3 and figure 2.

.In accordance with the WHO classification for grading renal biopsies in LN, 4 patients were classified as class II, 8 patients as class III, 15 patients as class IV and 2 patients as class V. Urinary TWEAK levels showed ascending levels associated with increased renal biopsy grades (p <0.001), as shown in table 4 and figure 3.

The ROC curve was performed to demonstrate the efficacy of urine TWEAK as a biomarker for distinguishing between different clinical groups. The area under the curve (AUC) findings shown remarkable discriminating capability, particularly in the SLE vs control group (AUC =0.981), signifying that urine TWEAK is highly effective in identifying SLE patients. The threshold values for urine TWEAK are >2.06 for SLE, >5.91 for LN, and >6.5 for active lupus nephritis, with corresponding sensitivity rates of 100%, 75.86%, and 84.21% respectively. The specificity rates are 94.74%, 88.89%, and 70%, respectively. The positive and negative predictive values enhanced the significance of urine TWEAK. The accuracy rates were 97.3% for SLE, 82.1% for LN, and 79.3% for active LN (table 5 and figure 4).

Table 1: Clinical and laboratory characteristics of the studied patients

Parameter (mean±SD)	Non-renal SLE (*n* =27)	Active LN (*n* =19)	Inactive LN (*n* =10)	*P* value
Age (years)	38.7±5	36.3±9	37.7±3	NS
SLE Disease duration (years)	3.7±2.6	4.2±1.8	5.7±2.9	NS
Systolic blood pressure (mmHg)	118.3±3.2	138.1±19.2	122.7±18.5	0.002
Diastolic blood pressure (mmHg)	70.3±9.3	85.1±8.9	75.2±9.6	0.002
Total SLEDAI	7.4±3.5	14.6±9.2	6.8±6.3	0.001
Renal SLEDAI	0.0±0.0	9±3	0.0±0.0	0.001
ESR (mm/1st h)	62.5±27.7	87.3± 58.1	39.4 ±20.7	0.010
Hemoglobin (g/dl)	11.57±1.12	11.24±1.69	11.18±1.83	NS
Total WBC (10^3/µL)	7.87±3.15	6.41±2.81	7.54±2.84	NS
Platelet count (10^3/µL)	272.62±95.61	282.71±94.93	262.41±88.84	NS
Serum creatinine (mg/dl)	0.8±0.2	2.3±1.4	1.1±0.9	0.011
Blood urea (mmol/l)	25.12 ±8.92	94.65 ± 56.45	47.65±94.38	0.021
Serum albumin (g/dl)	3.5±11	2.2 ±.13	3.9±35	0.002
24- h urinary proteins (g/24h)	88.3±98.32	2125.34±2247.18	189.46±98.78	0.003
C3 (u/ml)	1.54±0.42	0.503±0.31	1.63±0.12	<0.001
C4 (u/ml)	0.24±0.21	0.11±0.12	0.22±0.42	0.004
Anti-ds DNA (IU/ml)	428.84±589.81	532.41±598.52	527.83±541.92	NS

NS: non-significant, p <0.05 is considered significant.

Table 2: Urinary TWEAK Levels in the cases and control groups

Urinary TWEAK (pg/mg creatinine)	Healthy control (*n* =56)	Total SLE (*n* =56)	Non-renal SLE (*n* =27)	Total LN (*n* =29)	Active LN (*n* =19)	Inactive LN (*n* =10)	*P1*	*P2*	*P3*
Mean±SD	1.76±0.69	9.24±9.24	5.13±5.25	13.07±10.51	16.67±11.41	16.67±11.41	<0.001	<0.001	0.005
Median (min-max)	1.64 (1.2-5.75)	4.9 (2.41-39.75)	3.53 (2.41-26.03)	9 (3.5-39.75)	9.25 (4.25-39.75)	9.25 (4.25-39.75)			

p1: comparison between SLE and control groups, *p2*: comparison between SLE with and without LN, *p3*: comparison between inactive and active LN, p <0.05 is considered significant.

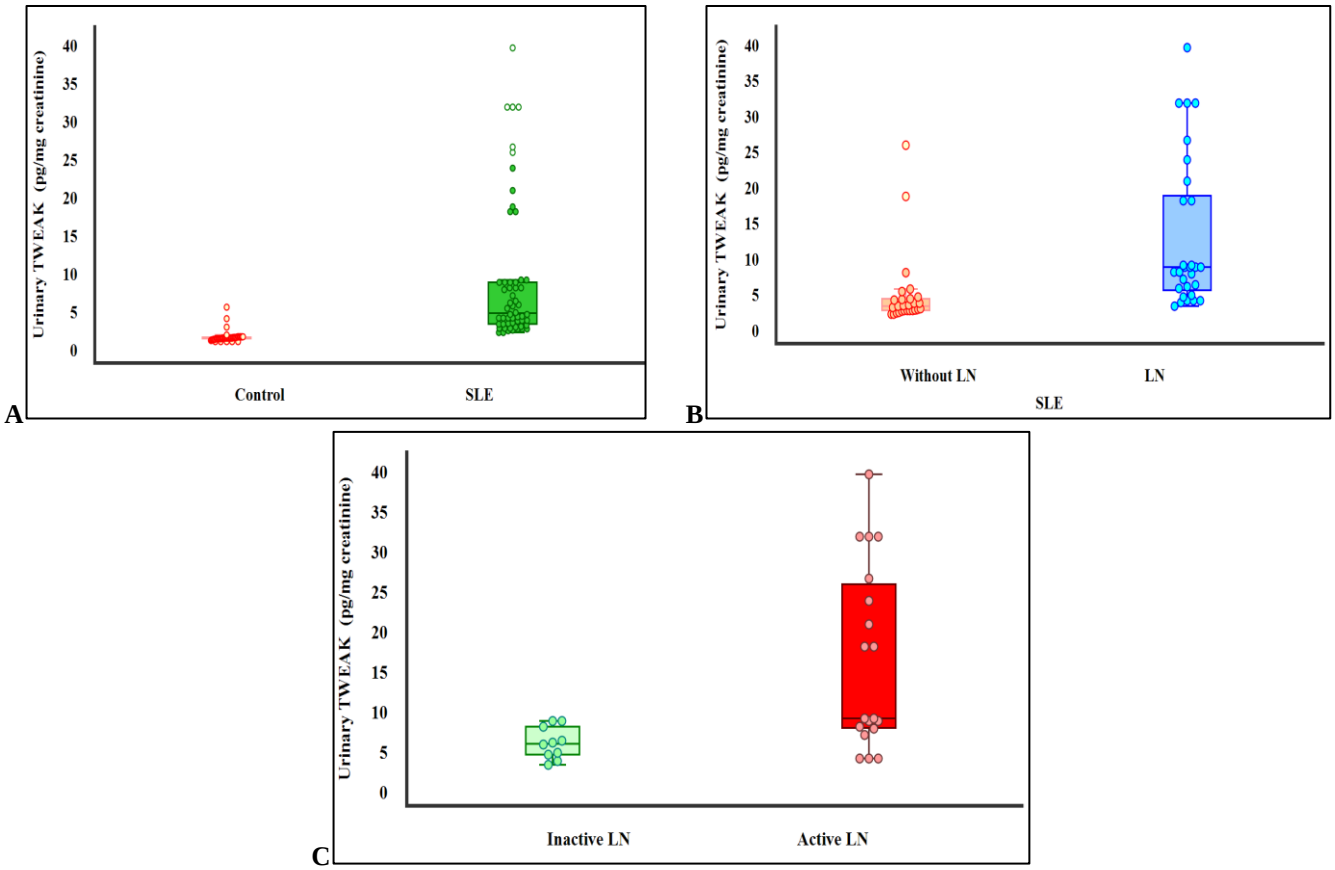

Fig. 1. Concentrations of urinary TWEAK according to the study groups
The expression levels of urinary TWEAK in (A) SLE and control groups; p <0.001, (B) LN and non-renal SLE groups; p <0.001, and (C) inactive and active LN groups; p =0.005.

Table 3: The correlations between urinary TWEAK levels and other clinical and laboratory variables

Variable	Urinary TWEAK (pg/mg creatinine)	
	Rs	***P* value**
Systolic blood pressure (mmHg)	0.419	0.001
Diastolic blood pressure (mmHg)	0.423	0.001
Creatinine (mg/dl)	0.214	NS
Blood urea (mmol/l)	0.223	NS
Hematuria	0.621	<0.001
Pyuria	0.318	0.017
Urinary casts	0.586	<0.001
24-h urinary proteins	0.561	<0.001
tSLEDAI	0.730	<0.001
rSLEDAI	0.695	<0.001
C3 (u/ml)	-0.538	<0.001
C4 (u/ml)	-0.440	<0.001

Rs, Spearman's correlation coefficient, NS: non-significant, p <0.05 is considered significant.

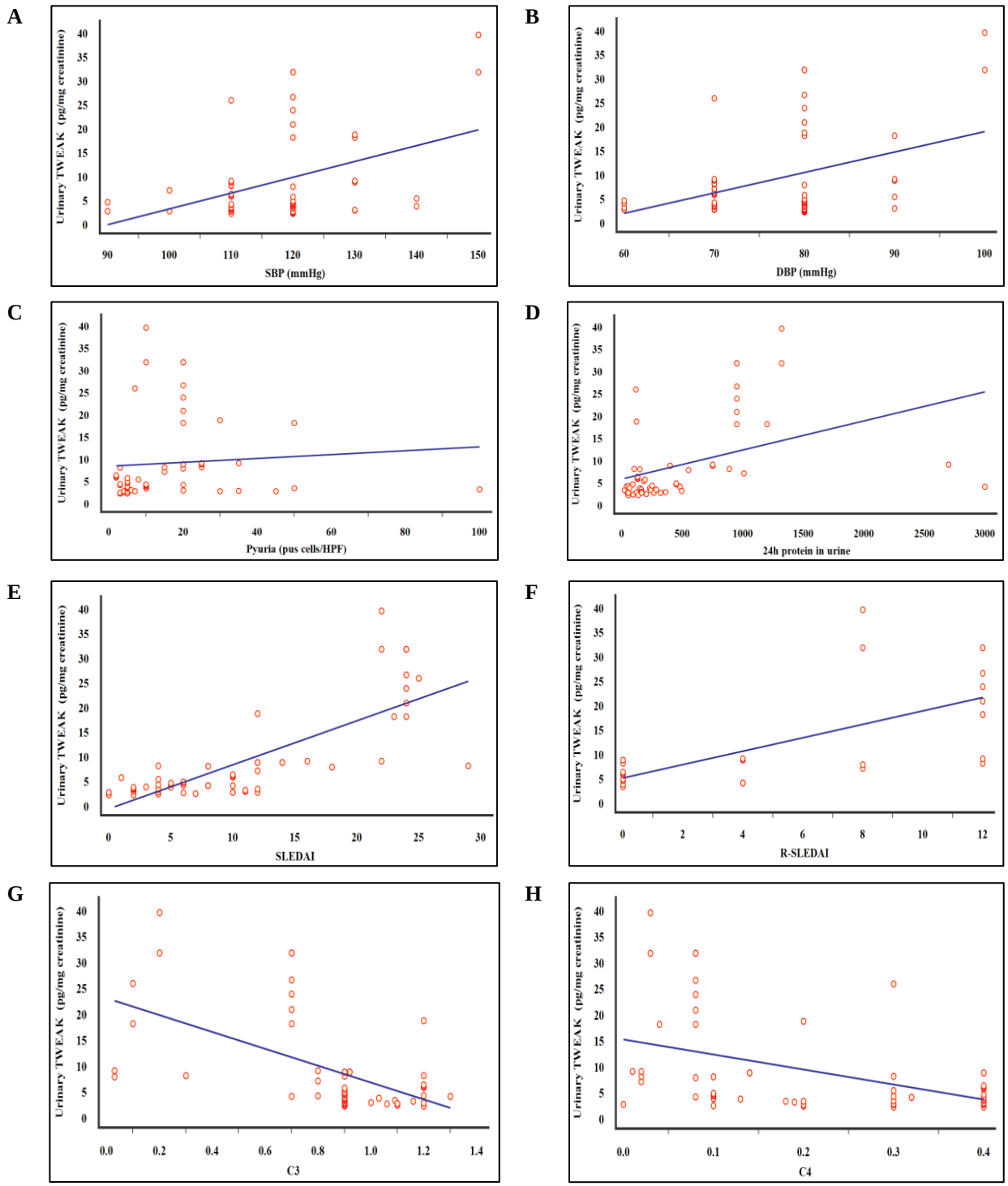

Fig. 2. The correlations between urinary TWEAK versus clinical and laboratory parameters

Positive correlation between (A) urinary TWEAK vs. systolic blood pressure, (B) urinary TWEAK vs. diastolic blood pressure, (C) urinary TWEAK vs. pyuria, (D) urinary TWEAK vs. 24-h urinary protein, (E) urinary TWEAK vs. SLEAI, and urinary TWEAK vs. rSLEAI. Negative correlation between: (G) urinary TWEAK vs. C3, (H) urinary TWEAK vs. C4.

Table 4: Concentrations of urinary TWEAK according to renal biopsy grades

Urinary TWEAK (pg/mg creatinine)	Renal biopsy grades				
	II *n* =4	III *n* =8	IV *n* =15	V *n* =2	*P value*
Mean± SD	4.19±0.12	6.5±1.28	15.9±9.37	35.88±5.48	<0.001
Median (min-max)	4.25 (4-4.25)	6.38 (4.75-8.25)	9.25 (3.5-32)	35.88 (32-39.75)	

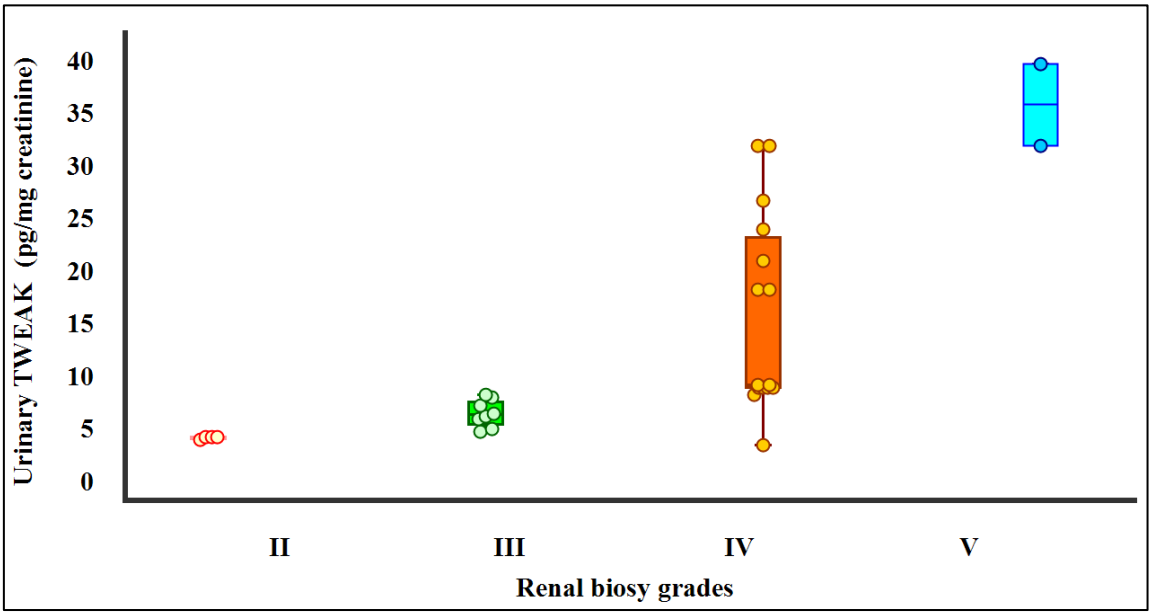

Fig. 3. Urinary TWEAK levels according to renal biopsy grades

Urinary TWEAK showed ascending levels associated with increased renal biopsy grades, p <0.001.

Table 5: Validity of urinary TWEAK for discrimination between studied groups

Urinary TWEAK (pg/mg creatinine)	SLE vs. controls	LN vs. non-renal SLE	Active LN vs. inactive LN
AUC	0.981	0.875	0.818
95% CI	0.936 to 0.997	0.759 to 0.948	0.632 to 0.936
P value	<0.001	<0.001	<0.001
Cut off	>2.06	>5.91	>6.5
Sensitivity (%)	100	75.86	84.21
Specificity (%)	94.74	88.89	70.0
Positive predictive value (%)	94.9	88.0	84.2
Negative predictive value (%)	100.0	77.4	70.0
Accuracy (%)	97.3	82.1	79.3

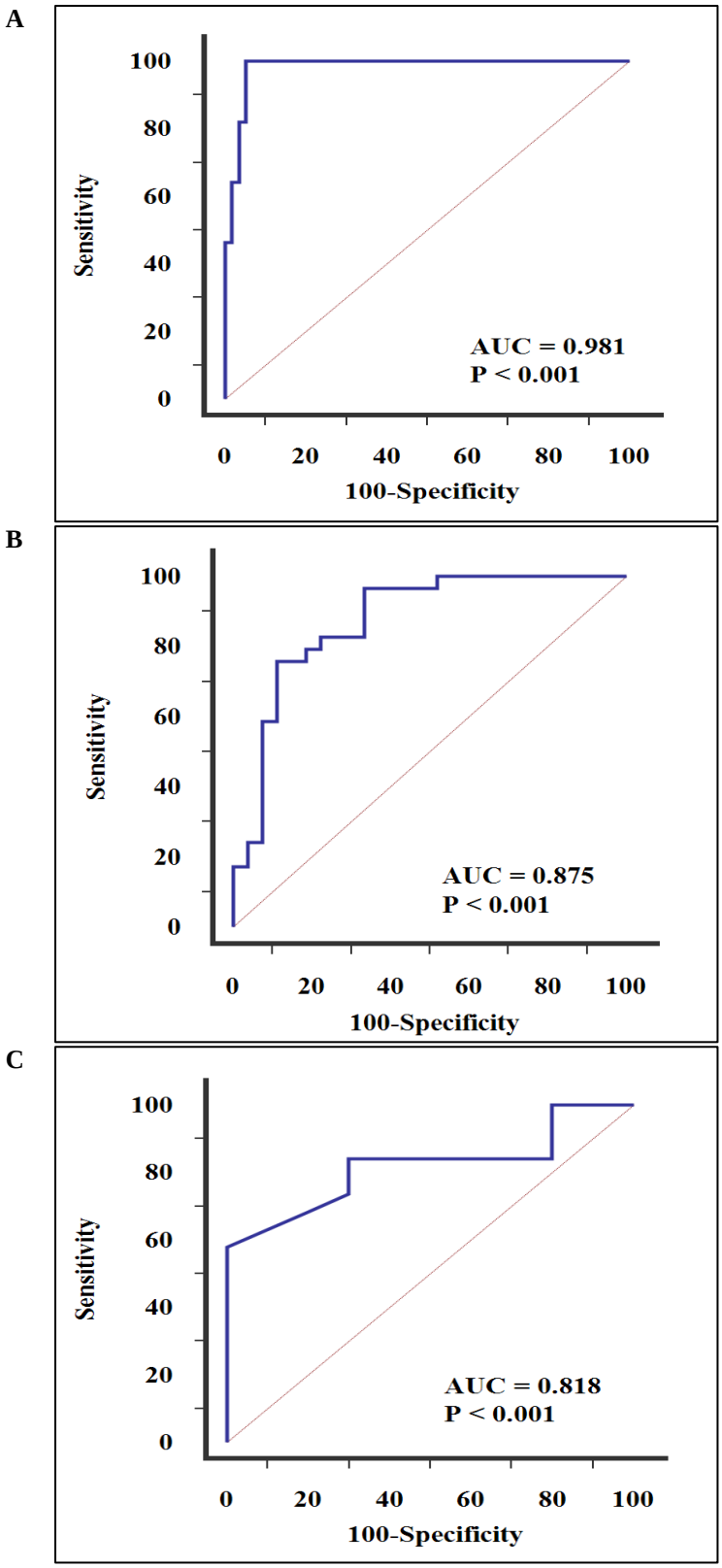

Fig. 4. Analysis of ROC curves for urinary TWEAK SLE vs. control, (B) LN vs. non-renal SLE, and (C) inactive LN vs. active LN groups.

DISCUSSION

LN is a common complication for people with SLE. Therapy timing is critical for prognosis, as studies on LN have shown that delay in therapy could result in poorer outcomes[27]. Many novel LN biomarkers have been developed, however so far none of them have shown to be fully relevant in large-scale longitudinal case cohorts. To improve the predictive power of renal flares and LN prognosis, researchers have proposed combining new biomarkers with traditional clinical indicators in the future[28].

A crucial factor in the pathogenesis of SLE is the dysregulation of cell death mediated by TWEAK[29]. TWEAK/Fn14 may significantly influence LN pathophysiology by causing apoptosis in tubular epithelial and glomerular mesangial cells, thus promoting the generation of proinflammatory cytokines and resulting in damage to the tubules and glomeruli[30,31]. Consequently, the purpose of this research was to quantify urinary TWEAK and establish its correlation with disease activity in LN.

This analysis revealed a significant disparity in urinary TWEAK levels. Specifically, we observed that the LN group had significantly elevated levels of urinary TWEAK in comparison to non-renal SLE patients, inactive LN, and normal controls. Like our findings, El-Shehaby et al demonstrated that non renal SLE or inactive LN cases had lower urinary TWEAK levels than active LN cases (P <0.0), suggesting that greater urinary TWEAK levels could indicate active LN[32]. Furthermore, Schwartz et al discovered that urinary TWEAK had superior efficacy in differentiating between non-renal SLE and LN patients compared to anti-dsDNA antibodies or complement component levels. Additionally, they found that urinary TWEAK level of both biopsy-based LN cases and clinically diagnosed LN was not different but was significantly higher than non-renal SLE cases, proving that high urinary TWEAK level could support LN diagnosis with possibly replacement of the need to invasive renal biopsy in SLE patients. They also found that high urinary TWEAK level in SLE cases was associated with 7- fold increased odds of LN[23]. Urinary TWEAK levels were considerably higher in LN cases than in non-lupus glomerulopathy patients, according to an investigation done on Mexican patients. However, compared to healthy volunteers and non-renal SLE patients, individuals with non-lupus glomerulopathy had noticeably higher urine TWEAK levels[33].

According to Mok's research, a good LN biomarker should be highly correlated with proteinuria or urine sediment levels, which are indicators of renal impairment[28]. In our study, urinary TWEAK level had a significant positive correlation with parameters of rSLEDAI; hematuria (p <0.001), pyuria (p =0.017), urinary casts (p <0.001) and 24-h urinary proteins (p <0.001). Similar results were reported by El-Shehaby et al, as the presence of these parameters could reflect renal inflammation[32]. Therefore, urinary TWEAK is a biomarker of LN activity, as shown by this significant positive association. Meanwhile, current LN laboratory biomarkers such pyuria, proteinuria, and hematuria are insufficient. They can't tell the difference between normal kidney function and damage in LN due to their low sensitivity and specificity. Major renal damage can occur before changes of these laboratory parameters. Persistent proteinuria is not necessarily an indicator of ongoing kidney inflammation and may reflect a preexisting chronic lesion or a recent renal damage throughout the disease course. In addition, there may be no obvious or recent rise in proteinuria when nephritis flares up[34]. Prior research has indicated that compared to non-renal SLE patients, LN patients had elevated blood levels of TWEAK, soluble CD40L, and anti-C1q. They may be utilized as indicators to monitor renal involvement and disease activity, since high levels of these serum markers were favorably linked with conventional disease activity criteria. However, elevated serum TWEAK level showed the greatest sensitivity for LN development[35].

Our analysis revealed a negative correlation between urinary TWEAK and both C3 and C4 (P <0.001, for each). Previous studies have demonstrated analogous results[32,34]. This finding has substantial clinical implications. That is because C3 and C4 complement components are known to be consumed not only in SLE patients with LN but also in SLE other immune complex mediated lesions, such as vasculitis, with a stable renal function. So, urinary TWEAK is considered a more specific biomarker due to its potential diagnostic and prognostic applications in assessing LN [36].

Based on our research, there was no evidence that urinary TWEAK levels were correlated with serum creatinine levels. It was suggested that high urinary TWEAK levels have stronger correlation with acute disease activity than with the degree of renal insufficiency. Several investigations have come to the same conclusion[25,34].

Our investigation into the correlation between urinary TWEAK levels and renal histology revealed that elevated urinary TWEAK levels were associated with increased renal biopsy grades (P <0.001). Similarly, Rashed et al identified a significant connection between urine TWEAK levels and the histological renal activity index (P =0.001) but found no association with the renal chronicity index (P =0.278). Based on these findings, it appears that renal disease activity rather than renal insufficiency degrees is the strongest predictor of increased urinary TWEAK levels[37].

Some investigations found no statistically significant correlation between urine TWEAK levels and various

types of renal biopsy, which contrasts with the current findings. So, detection of urine TWEAK could not fully substitute renal biopsy in the diagnosis of LN, according to these investigations[24,25,32]. This could be due to absence of a clear method to evaluate tissue levels of inflammatory disease activity, inherent sample difficulties with renal biopsies, and a small number of patients evaluated with further splitting into many histological groups[38].

Renal biopsy is the gold standard for studying the histological classifications of LN with varying degrees of glomerular activity or chronicity. Nonetheless, it is invasive, and monitoring LN by successive biopsies is impractical[28]. Based on our findings, the urinary TWEAK threshold values were >2.06 for SLE, >5.91 for LN, and >6.5 for active LN, with corresponding sensitivity rates of 100%, 75.86%, and 84.21%, respectively. Also, the specificity rates were as high as 94.74%, 88.89% and 70% respectively. The importance of urinary TWEAK was enhanced by positive and negative predictive values. The elevated accuracy rates (97.3% for SLE, 82.1% for LN, and 79.3% for active LN) highlighted the promise of urinary TWEAK as an effective diagnostic marker of LN. In a different study, urinary TWEAK demonstrated 89% sensitivity and 56% specificity[32]. Hence, urinary TWEAK is useful for predicting renal flares, measuring treatment efficacy, and tracking disease progression[34].

CONCLUSIONS

To sum up, urinary TWEAK stands out as a biomarker in LN, showing more sensitivity and specificity than other laboratory tests that have been used before. High level of urinary TWEAK is positively correlated with conventional activity parameters of LN and so, it can be used as an indicator to monitor renal involvement and disease activity. Implementation of novel therapeutic approaches such as the monoclonal antibody antagonizing the effect of some inflammatory cytokine; TWEAK could be the lost thread for treatment of cytokine dependent LN.

Conflicts of interest

The authors declare that they have no financial conflicts of interest related to the work done in the manuscript.

Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.

This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

REFERENCES

1. Ding Y, Tan Y, Qu Z, Yu F. Renal microvascular lesions in lupus nephritis. Ren Fail. 2019; 42(1):19-29.
2. Kwok SK, Tsokos GC. New insights into the role of renal resident cells in the pathogenesis of lupus nephritis. Korean J Intern Med. 2018; 33(2): 284–9.
3. Monroy Trujillo JM, Fine DM. Fine Management of proliferative lupus nephritis. Panminerva Med. 2016; 58(4): 286–93.
4. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017; 12(5): 825–35.
5. Tektonidou MG, Dasgupta A, Ward MM. Risk of end stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and Bayesian meta-analysis. Arthritis Rheumatol. 2016; 68(6): 1432–41.
6. Goilav B, Putterman C, Rubinstein TB. Biomarkers for kidney involvement in pediatric lupus. Biomark Med. 2015; 9(6): 529–43.
7. Rahman A, Isenber D. Systemic lupus erythematosus. N Engl J Med. 2008; 358: 929–39.
8. Schwartz N, Michaelson JS, Putterman C. Lipocalin-2, TWEAK, and other cytokines as urinary biomarkers for lupus nephritis. Ann NY Acad Sci. 2007; 1109: 265–74.
9. Illei GG, Tackey E, Lapteva L, Lipsky PE. Biomarkers in systemic lupus erythematosus: II. Markers of disease activity. Arthritis Rheum. 2004; 50: 2048–65.
10. Bruschi M, Angeletti A, Prunotto M, Meroni PL, Ghiggeri GM, Zeus consortium, et al. A critical view on autoantibodies in lupus nephritis: Concrete knowledge based on evidence. Autoimmun Rev. 2024; 23(5):103535.
11. Maecker H, Varfolomeev E, Kischkel F, Lawrence D, Le Blanc H, Lee W, et al. TWEAK attenuates the transition from innate to adaptive immunity. Cell. 2005; 123: 931–44.
12. Munoz-Garcia B, Martin-Ventura JL, Martinez E, Sanchez S, Hernandez G, Ortega L, et al. Fn14 is upregulated in cytokine-stimulated vascular smooth muscle cells and is expressed in human carotid atherosclerotic plaques modulation by atorvastatin. Stroke. 2006; 37(8): 2044–53.
13. Sanz AB, Santamaria B, Ruiz Ortega M, Egido J,Ortiz A. Mechanisms of renal apoptosis in health and disease. J Am Soc Nephrol. 2008; 19(9): 695–703.
14. Burkly LC, Michaelson JS, Hahm K, Zheng TS. TWEAKing tissue remodeling by a multifunctional cytokine: Role of TWEAK/Fn14 pathway in health and disease. Cytokine. 2007; 40(1): 1–16.

15. Winkles JA. The TWEAK-Fn14 cytokine receptor axis: discovery, biology and therapeutic targeting. Nat Rev Drug Discov. 2008; 7(5): 411–25.
16. Sanz A, Izquierdo M, Sanchez-Nin˜ o M, Ucero A, Egido J, Ruiz-Ortega M, et al. TWEAK and the progression of renal disease: clinical translation. Nephrol Dial Transplant. 2014; 29(1): 54-62.
17. Justo P, Sanz AB, Sanchez-Nin˜ o. Cytokine cooperation in renal tubular cell injury: the role of TWEAK. Kidney Int. 2006; 70: 1750–8.
18. Suttichet TB, Kittanamongkolchai W, Phromjeen C, Anutrakulchai S, Panaput T, Ingsathit A, et al. Urine TWEAK level as a biomarker for early response to treatment in active lupus nephritis: a prospective multicentre study. Lupus Sci Med. 2019; 6: e000298.
19. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40(9): 1725.
20. Isenberg DA, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology (Oxford). 2005; 44(7): 902-6.
21. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of SLEDAI: a disease activity index for lupus patients. Arthritis Rheum. 1992; 35: 630–40.
22. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosis disease activity index 2000. J Rheumatol. 2002; 29: 288–91.
23. Schwartz N, Rubinstein T, Burkly LC, Collins CE, BlancoI, SuL, et al. Urinary TWEAK as a biomarker of lupus nephritis: a multicenter cohort study. Arthritis Res Ther. 2009; 11(5): R143.
24. ZhuX, Tan J, Li J, Xu X, Yuan S, Liu F. Urinary TWEAK level as a marker of lupus nephritis activity in 46 cases. J Biomed Biotechnol. 2012; 2012: 359647.
25. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004; 65(2): 521-30.
26. Kodama M, Uchida K, Karasawa K, Moriyama T, Nitta K. Long-term outcome of 102 cases of lupus nephritis: A single-center cohort study in Japan. Int J Clin Med. 2017; 8(12): 668-79.
27. Korbet SM, Lewis EJ, Schwaartz MM, Reichlin M,Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Lupus Collaborative Study Group. AJKD. 2000; 35(5): 904-14.
28. Mok CC. Biomarkers for lupus nephritis: a critical appraisal. J Biomed Biotechnol. 2010; 2010: 638413.
29. Marchini M, Antonioli R, Lleò A, Barili M, Caronni M, Origgi L, et al. HLA class II antigens associated with lupus nephritis in Italian SLE patients. Hum Immunol. 2003; 64(4): 462–8.
30. Harley JB, Alarcon-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL et al. Genome wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet. 2008; 40: 204–10.
31. Lee YH, Woo JH, Choi SJ, Ji JD, Song G. Association of programmed cell death 1 polymorphisms and systemic lupus erythematosus: a meta-analysis. Lupus. 2009; 18(1): 9-15.
32. El-Shehaby A, Darweesh H, El-Khatib M, Momtaz M, Marzouk S, El-Shaarawy N, Emad Y. Correlations of urinary biomarkers, TNF-like weak inducer of apoptosis (TWEAK), osteoprotegerin (OPG), monocyte chemoattractant protein-1 (MCP-1), and IL-8 with lupus nephritis. J Clin Immunol. 2011; 31(5): 848-56.
33. Reyes-Martínez F, Pérez-Navarro M, Rodríguez-Matías A, Soto-Abraham V, Gutierrez Reyes G, Medina-Avila Z, Valdez-Ortiz R. Assessment of urinary TWEAK levels in Mexican patients with untreated lupus nephritis: An exploratory study. Nefrologia (Engl Ed). 2018; 38(2): 152-60.
34. Salem MN, Taha HA, Abd El-Fattah El-Feqi M, Eesa NN, Mohamed RA. Urinary TNF-like weak inducer of apoptosis (TWEAK) as a biomarker of lupus nephrits. Z Rheumatol. 2018; 77(1): 71-7.
35. El Gendi SS, El-Sherif WT. Anti-C1q antibodies, sCD40L, TWEAK and CD4/CD8 ratio in systemic lupus erythematosus and their relations to disease activity and renal involvement. Egyptian J Immunol. 2009; 16(1): 135-48.
36. Vasilev V, Artero MR, Petkova M, Mihaylova G, Dragon-Durey MA, Radanova M, Roumenina LT. Clinical Relevance of Anti-C3 and Anti-C4 Autoantibodies in Lupus Nephritis. Kidney Int Rep. 2024; 9(5): 1429-40.
37. Rashed EM, Hamed HI, Abdelsalam A F, Aref AA. Clinical significance of urinary tumor necrosis factor-like weak inducer of apoptosis in lupus nephritis. AIMJ. 2023; 4(12): 147-52.
38. Lu J, Tam LS, Lai FM, Kwan BC, Choi PC, Li EK, Chow KM, Li PK, Szeto CC. Repeat renal biopsy in lupus nephritis: a change in histological pattern is common. Am J Nephrol. 2011; 34(3): 220-5.