



2023

Section: Internal Medicine

## Clinical significance of urinary tumor necrosis factor-like weak inducer of apoptosis in lupus nephritis

Elsayed Mohamed Rashed

*Department of Internal Medicine and Nephrology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt*

Hani Ismail Hamed

*Department of Internal Medicine and Nephrology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt*

Abdelsalam Fathy Abdelsalam

*Department of Clinical Pathology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.*

Amr Atef Ali Aref

*Department of Internal Medicine and Nephrology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt, amatar@gmail.com*

Follow this and additional works at: <https://aimj.researchcommons.org/journal>



Part of the [Medical Sciences Commons](#), [Obstetrics and Gynecology Commons](#), and the [Surgery Commons](#)

### How to Cite This Article

Rashed, Elsayed Mohamed; Hamed, Hani Ismail; Abdelsalam, Abdelsalam Fathy; and Aref, Amr Atef Ali (2023) "Clinical significance of urinary tumor necrosis factor-like weak inducer of apoptosis in lupus nephritis," *Al-Azhar International Medical Journal*. Vol. 4: Iss. 12, Article 21.

DOI: <https://doi.org/10.58675/2682-339X.2160>

This Original Article is brought to you for free and open access by Al-Azhar International Medical Journal. It has been accepted for inclusion in Al-Azhar International Medical Journal by an authorized editor of Al-Azhar International Medical Journal. For more information, please contact [dryasserhelmy@gmail.com](mailto:dryasserhelmy@gmail.com).

# Clinical Significance of Urinary Tumor Necrosis Factor-like Weak Inducer of Apoptosis in Lupus Nephritis

Elsayed Mohamed Rashed <sup>a</sup>, Hani Ismail Hamed <sup>a</sup>, Abdelsalam Fathy Abdelsalam <sup>b</sup>, Amr Atef Ali Aref <sup>a,\*</sup>

<sup>a</sup> Department of Internal Medicine and Nephrology, Cairo, Egypt

<sup>b</sup> Department of Clinical Pathology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

## Abstract

**Background:** TWEAK is a cytokine that is both pleiotropic and multifunctional. It is a member of the tumor necrosis factor superfamily, which regulates the pathways that lead to inflammation. TWEAK is a critical component in the development of lupus nephritis (LN) because it is responsible for the death of renal mesangial cells and tubular epithelial cells. This death occurs as a result of several intracellular signal transduction cascades.

**Aim and objectives:** To better understand how TWEAK is related to LN, and to look at whether or not TWEAK levels may be used as a marker of LN existence and activity.

**Patients and methods:** The case–control study was done on 40 cases with biopsy-proven LN at the Nephrology Department of Al Hussein University Hospital among April and September of 2022.

**Results:** All the cases showed positive ANA and anti-dsDNA antibodies regarding laboratory data. The urinary level of TWEAK was statistically significantly higher in the LN cases matched to the control group. A statistically significant positive relationship among urinary TWEAK with serum creatinine and albumin/creatinine ratio a statistically significant negative correlation between urinary TWEAK with C3. The best cutoff point of urinary TWEAK to identify cases with LN was more than 6.83 pg/ml.

**Conclusion:** In cases when the diagnosis of a flare is uncertain, urinary TWEAK may be a useful biological tool. The treatment requirements and prognosis of individuals with LN can be better determined if this can be refined for routine clinical usage.

**Keywords:** Apoptosis, Lupus nephritis, Urinary tumor necrosis factor-like

## 1. Introduction

Immune complex deposition, renal microvascular lesions, inflammation, proteinuria, hematuria, and increasing renal impairment are hallmarks of lupus nephritis (LN), a typical clinical symptom of systemic lupus erythematosus (SLE).<sup>1</sup>

LN is a major source of illness and mortality, since around 60 % of those who have SLE will acquire it at some point. It has been projected that 22 % of persons with LN will proceed to end-stage renal disease within 15 years, with the largest risk happening in the first 5 years of the progression of the illness.<sup>2</sup>

The percutaneous renal biopsy is the most accurate way for identifying LN and collecting helpful information for the purpose of risk assessment and the planning of therapy. In order to track the progression of LN, routine monitoring of levels of complement, anti-dsDNA, serial creatinine, the urine protein/creatinine ratio, and urinalysis are able to be performed.<sup>3</sup>

Current biomarkers for gauging LN activity, however, fall short on both the sensitivity and specificity fronts. There is not always a perfect relationship between these markers and renal function or injury. On top of that, monitoring LN

Accepted 6 August 2023.

Available online 25 January 2024

\* Corresponding author at: Department of Internal Medicine, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt.  
E-mail address: [amatar@gmail.com](mailto:amatar@gmail.com) (A.A.A. Aref).

<https://doi.org/10.58675/2682-339X.2160>

2682-339X/© 2023 The author. Published by Al-Azhar University, Faculty of Medicine. This is an open access article under the CC BY-SA 4.0 license (<https://creativecommons.org/licenses/by-sa/4.0/>).

flares serially through renal biopsy is impracticable due to the intrusive nature of the technique.<sup>4</sup>

One of the ligands that belong to the tumor necrosis factor superfamily is called TWEAK, and it is a multifunctional cytokine. It is known as fibroblast fibronectin-inducible protein of 14 kDa (FN14), and it interacts with its receptor by binding to it. TWEAK is highly expressed in natural killer cells, macrophages, and dendritic cells. These cell types are all part of the innate immune system and are thought to play a key role in the regulation of immunological processes. TWEAK is robustly expressed in all three of these cell types.<sup>5</sup>

TWEAK is a critical factor in the pathophysiology of LN because it induces apoptosis in glomerular mesangial cells and tubular epithelial cells. This occurs as a result of many intracellular signal transduction cascades.<sup>6</sup>

The use of urine TWEAK (uTWEAK) as a biomarker of LN has gained attention in recent years. Patients with SLE and active LN had greater uTWEAK levels than those without LN, and these levels corresponded with the severity of their renal illness over time.<sup>7</sup>

The study's goal was to determine whether or the presence of TWEAK in the urine may be used as an indicator of the existence and activity of LN.

## 2. Patients and methods

In April 2022, the Nephrology Department at Al Hussein University Hospital began a 6-month

case–control study. Forty biopsy-proven LN patients and 20 age/sex/ethnic-matched healthy volunteers were studied as a control group. The Al Hussein University Hospital Nephrology Department recruited and screened the study groups.

Inclusion criteria: all chosen patients met at least four of the American College of Rheumatology's criteria for the diagnosis of SLE, and their ages had to be between 18 and 60.

Exclusion criteria: this study excludes dialysis patients and those with renal affection-causing illnesses such urinary tract infections, essential hypertension, diabetes, etc.

Participants were separated into two groups depending on the inclusion and exclusion criteria, and these groups were: 40 individuals with SLE who also met the criteria for LN as established by the American College of Rheumatology had kidney biopsies. Fig. 1 shows the 2019 ACR Classification Criteria for SLE and a comparison group of 20 healthy volunteers who were matched on age, sex, and ethnicity.

Committee on the Ethics of Research: all operations were approved by the Al-Azhar University ethics committee, and all patients provided written consents before participation. Patients were informed of the study's goals and any potential risks involved, and their privacy was protected.

### 2.1. Methods

Full medical histories and laboratory evaluations were performed on all patients.

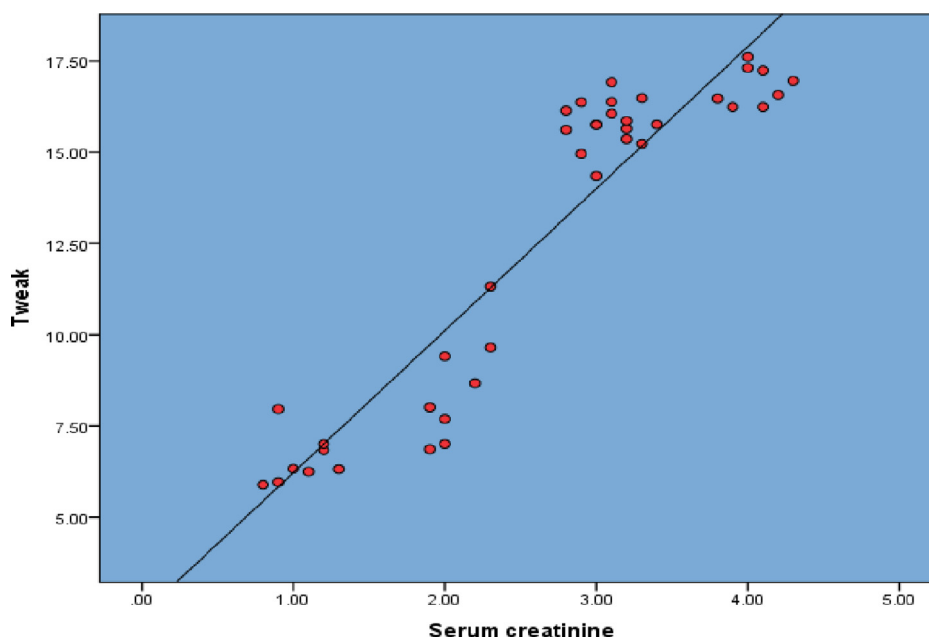


Fig. 1. Relationship among urinary TWEAK and serum creatinine.

Different criteria were used to compare the two groups; these included: laboratory data from the LN group; comparative study of case and control TWEAK levels in urine (pg/ml), predictive utility of urine TWEAK (pg/ml) in detecting instances of LN and its correlation with laboratory data in the LN group.

The use of statistics: SPSS 22.0 (IBM/SPSS Inc., Chicago, Illinois, USA) was utilized to conduct statistical analysis of the data. There were two distinct statistical analyses performed.

## 2.2. Descriptive statistics

Mean, SD, median, and range estimations were provided for the continuous data. Quantitative information was presented using a frequency with percentage (%) distribution.

The Mann–Whitney *U* test, also known as the *Z* test, was utilized to continuous data in order to look for a statistically significant difference between two separate groups that had nonparametric data. The Shapiro–Wilk test and the Levine test were used, respectively, to verify the assumptions of normality in each group as well as the homogeneity of the variances.

Table 1. Results from the laboratory for the cases group.

Lupus nephritis cases (N = 40)	
Serum creatinine (mg/dl)	
Mean ± SD	2.67 ± 1.05
Median (range)	2.95 (0.8–4.30)
Albumin/creatinine ratio	
Mean ± SD	2476.33 ± 2272.30
Median (range)	1195 (28–6854)
Urinary TWEAK (pg/ml)	
Mean ± SD	12.71 ± 4.39
Median (range)	15.485 (5.89–17.61)
C3 (mg/dl)	
Mean ± SD	50.08 ± 35.30
Median (range)	68.5 (8–95)
C4 (mg/dl)	
Mean ± SD	11.83 ± 5.76
Median (range)	15 (4–21)
ANA [n (%)]	
Negative	0
Positive	40 (100)
Anti-dsDNA [n (%)]	
Negative	0
Positive	40 (100)

Table 2. Urine TWEAK concentrations (pg/ml) were compared between the study's cases and control groups.

Urinary TWEAK (pg/ml)	Lupus nephritis cases (N = 40)	Control group (N = 20)	Test of significance	P value
Mean ± SD	12.71 ± 4.39	5 ± 2.44	Z = -5.316	<0.001 <sup>a</sup>
Median (range)	15.485 (5.89–17.61)	4.985 (1.27–9.26)		

Z, Mann–Whitney test.

<sup>a</sup> Statistically significant (P < 0.05).

Spearman's correlation was applied to nonparametric quantitative data in order to assess the hypothesis of a possible relationship between two variables.

## 3. Results

### Table 1.

Data from the laboratory tests performed on the cases may be seen below. Positive results for ANA and anti-dsDNA antibodies were seen in every case (Table 2).

The data in this table demonstrate: in the cases group, the average TWEAK concentration in the urine was 12.71 4.39 pg/ml (range: 5.89–17.61 pg/ml). The mean TWEAK concentration in the placebo group was 2.44 1.26 pg/ml (range, 1.27–9.26 pg/ml). In instances with LN, the concentration of TWEAK in the urine was substantially greater than in the healthy controls (Table 3).

The data in this table demonstrate: serum creatinine ( $r = 0.902$ ,  $P < 0.001$ ) and the albumin to creatinine ratio ( $r = 0.714$ ,  $P < 0.001$ ) are positively correlated with urinary TWEAK. There is a substantial inverse relationship between C3 ( $r = -0.402$ ,  $P = 0.010$ ) and C4 ( $r = -0.501$ ,  $P = 0.001$ ) and urine TWEAK (Table 4, Fig. 2).

This table shows the best cutoff point of urinary TWEAK to identify cases with LN was more than 6.83 pg/ml. This point showed high sensitivity (82.5 %) with high specificity (80 %) with a statistically significant value ( $P < 0.001$ ) and area under the curve (AUC) (0.924) (Fig. 3).

ROC analysis, which stands for 'receiver operating characteristic,' it is a graph showing how different cutoffs affect the sensitivity versus specificity (false + ve rate). Youden index J, the point on the ROC curve furthest from the line of equality [maximum (sensitivity + specificity)–1] was used to find the best cutoff value. Total area under ROC curve (AUC or AUROC) is a statistic used to evaluate a test's precision. A higher AUC indicates that a test is more reliably able to distinguish between healthy and ill individuals. The ROC curve was utilized to assess the optimal cutoff value, the AUC, the SE, and the P value of the test. Estimates such as sensitivity, specificity, positive predictive value,

Table 3. The relationship among laboratory data and urine TWEAK (pg/ml) in a cohort with lupus nephritis.

		Urinary TWEAK (pg/ml)
Serum creatinine (mg/dl)	<i>r</i>	0.902
	<i>P</i>	<0.001*
Albumin/creatinine ratio	<i>r</i>	0.714
	<i>P</i>	<0.001*
C3 (mg/dl)	<i>r</i>	-0.402
	<i>P</i>	0.010*
C4 (mg/dl)	<i>r</i>	-0.501
	<i>P</i>	0.001*

\*: Statistically significant ( $P < 0.05$ ).

Table 4. Predictive value of urinary TWEAK (pg/ml) in identifying cases with lupus nephritis.

Diagnostic criteria	Urinary TWEAK (pg/ml)
AUC	0.924
Cut off point	>6.83
<i>P</i>	<0.001*
Sensitivity	82.5 %
Specificity	80 %
PPV	84.5 %
NPV	86.4 %
Accuracy	85.2 %

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

negative predictive value, and accuracy were also determined at the ideal threshold to evaluate the test's performance.

#### 4. Discussion

SLE, a chronic autoimmune disease, affects several organ systems and has a high death and

morbidity rate. SLE is defined by autoantibodies that are directed against nuclear antigens. LN, is a common predictor of a bad prognosis and is therefore one of the most significant SLE-related outcomes.<sup>8</sup>

Proteinuria, hypocomplementemia, and strong anti-dsDNA titers still diagnosis renal flares, although they have limitations. Chronic glomerular injury may cause proteinuria. Low C3, C4, and anti-dsDNA are also unreliable indications of LN severity, particularly renal flare and response.<sup>9</sup>

The current research revealed that the mean serum creatinine of the patients group was  $2.67 \pm 1.05$  mg/dl. There was an average ratio of  $2476.33 \pm 2272.30$  between albumin and creatinine. C4 was  $11.83 \pm 5.76$  mg/dl and C3 was  $50.08 \pm 35.30$  mg/dl on average. In this research, we found that ANA and anti-dsDNA positivity occurred in every single patient.

Low C3 levels indicate LN due to alternate complement system activation, according to Kwon et al.<sup>10</sup> anti-dsDNA antibodies predict LN at SLE diagnosis.

Consistent with the present results, Liu et al.<sup>11</sup> found that elevated serum creatinine, decreased complement C4 and positive anti-dsDNA are all independent hazards of active SLE.

The current study showed that the urine TWEAK level was substantially higher in LN patients than in the control group ( $5 \pm 2.44$  vs.  $12.71 \pm 4.39$ ,  $P < 0.001$ ).

SLE + LN exhibited higher urine TWEAK levels than the other groups:  $12.88 \pm 8.33$  pg/mg Cr; SLE

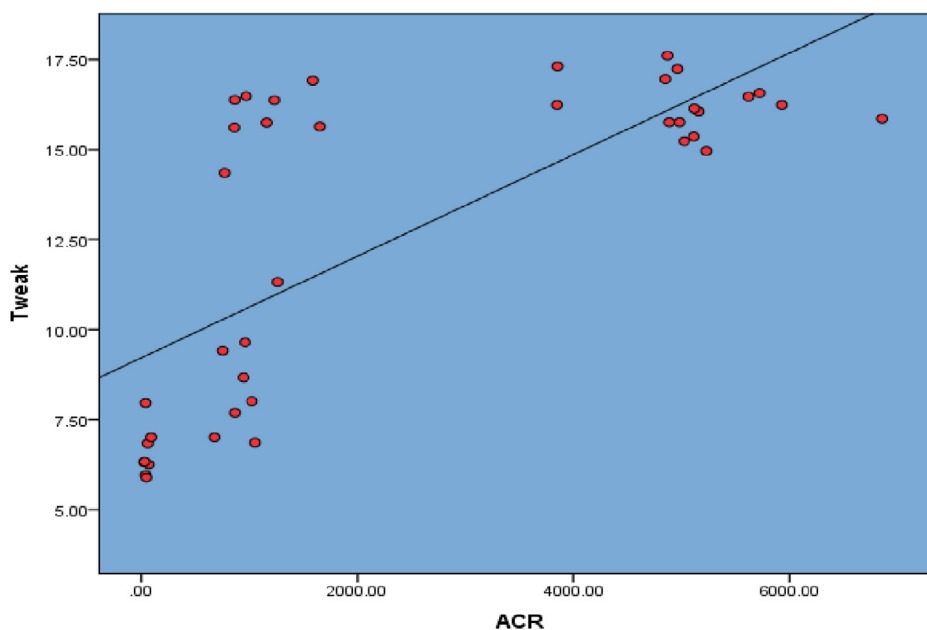


Fig. 2. Relationship among urinary TWEAK and albumin/creatinine ratio.

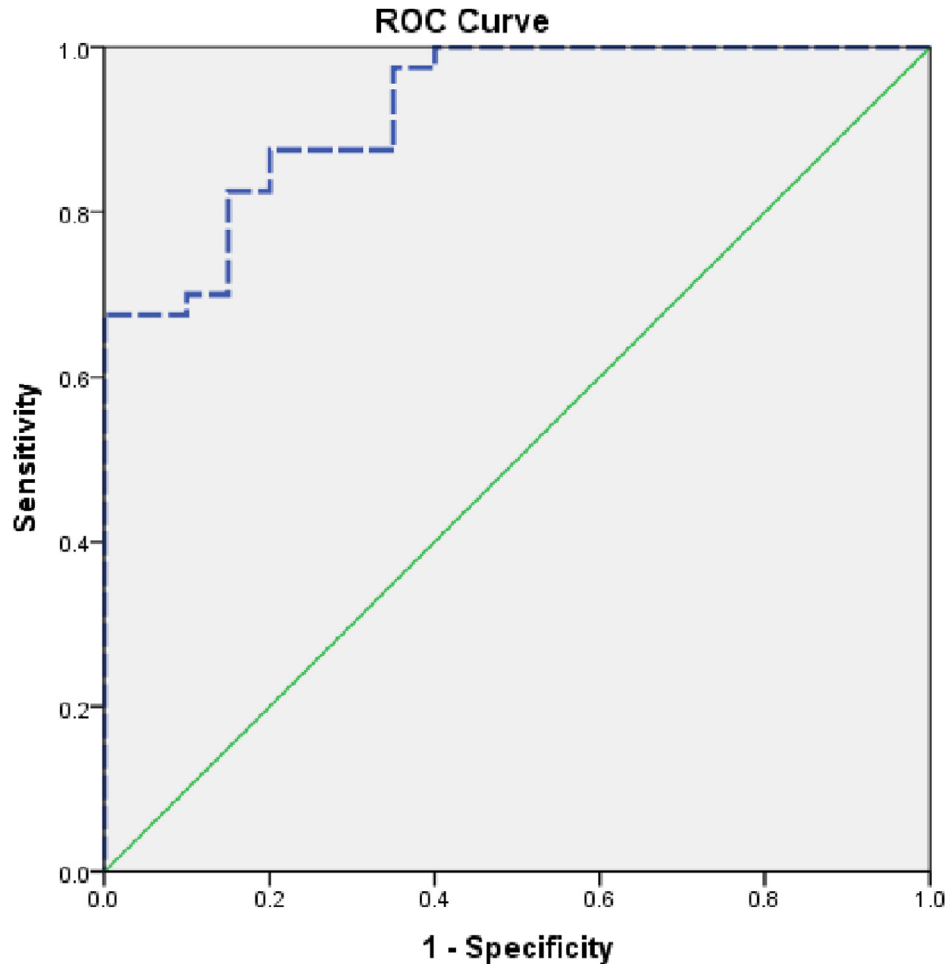


Fig. 3. Reciprocal area under the curve for urine TWEAK (pg/ml) in detecting lupus nephritis.

without LN,  $3.12 \pm 2.31$ ; patients with glomerulonephritis,  $4.36 \pm 2.31$ ; and controls,  $2.41 \pm 1.94$ .<sup>12</sup>

According to a meta-analysis of eight studies conducted by Lee and Song,<sup>13</sup> levels of TWEAK in the urine are positively connected with the severity of renal illness and are considerably greater in cases with active LN matched to those with inactive LN.

The current study reported a positive relationship among urinary TWEAK (pg/ml) and both serum creatinine ( $r = 0.902$ ,  $P < 0.001$ ) and albumin/creatinine ratio ( $r = 0.714$ ,  $P = 0.001$ ) in the LN group. In addition, there was an inverse relationship between urinary TWEAK and both C3 ( $r = -0.402$ ,  $P = 0.01$ ) and C4 ( $r = -0.501$ ,  $P = 0.001$ ), which makes sense given that low levels of these complement proteins are linked to LN activity.

The results are consistent with those found by Elsaid and colleagues, who evaluated the function of urine TWEAK in lupus patients and discovered a positive link with blood urea, serum creatinine, eGFR, proteinuria, anti-dsDNA, SLE disease activity

index (SLEDAI), and renal-SLE disease activity index a negative correlation with C3 and C4.<sup>9</sup>

In patients with immunoglobulin A nephropathy, Kim and Jeong<sup>14</sup> found a strong correlation among urinary TWEAK and serum albumin, urine protein excretion, and histological categorization.

Elsaid et al.<sup>9</sup> examined the potential role of urinary TWEAK in lupus cases and found that ROC curves analysis of urinary TWEAK in detecting SLE disease, SLE activity, LN, and LN activity showed an AUC of 1.00, 0.76, 1.00, and 1.00, respectively, with sensitivity of 100, 80.43, 100, and 100 % and specificity of 100, 50, 100, and 100 %, respectively.

In addition, the AUC was found to be 0.8640, and the diagnostic odds ratio was 14.89, in a recent meta-analysis research based on seven studies by Wang and colleagues. The pooled sensitivity for LN diagnosis was 0.55, specificity was 0.92, and the diagnostic odds ratio was 16.54. The diagnostic odds ratio, sensitivity, and specificity pooled to 0.91, 0.70, and 18.45, respectively, for evaluating LN activity.<sup>15</sup>



Elsayed et al.<sup>16</sup> also reported that a ROC curve was developed to assess how effectively urine TWEAK separates SLE cases with and without nephritis, and that the marker's sensitivity and specificity were 80 and 75 %, respectively, with an AUC of 0.872.

#### 4.1. Conclusion

Urine TWEAK levels more than 6.83 pg/mg yielded a ROC curve AUC of 0.924, a sensitivity of 82.5 %, a specificity of 80 %, and an accuracy of 85.2 % for lupus-related renal activity. Urinary TWEAK may help diagnose flares. It will assist LN patients determine treatment and prognosis if it is routinely used.

#### Conflicts of interest

There are no conflicts of interest.

#### References

- Shi Z, Zhang YP, Hong D, et al. Anti-galectin-3 antibodies induce skin vascular inflammation via promoting local production of IL-1 $\beta$  in systemic lupus erythematosus. *Int Immunopharm.* 2022;112:109197.
- 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;68:1432–1441.
- Tunnicliffe DJ, Singh-Grewal D, Kim S, Craig JC, Tong A. Diagnosis, monitoring, and treatment of systemic lupus erythematosus: a systematic review of clinical practice guidelines. *Arthritis Care Res.* 2015;67:1440–1452.
- Koutsonikoli A, Trachana M, Farmaki E, et al. Novel biomarkers for the assessment of paediatric systemic lupus erythematosus nephritis. *Clin Exp Immunol.* 2017;188:79–85.
- Bekhit MR, Kamel NS, Mohammed MO, Abaza NM, Saad El Din SA. Role of tumor necrosis factor-like weak inducer of apoptosis/fibroblast growth factor-inducible molecule 14 pathway in lupus nephritis. *Egypt Rheumatol Rehabil.* 2018;45:182–187.
- Xu X, Zheng M, Liu B. Urinary TWEAK/Fn14 mRNA as a biomarker of lupus nephritis activity. *Int J Clin Exp Med.* 2016;9:11236–11243.
- Suttichet TB, Kittanamongkolchai W, Phromjeen C, 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.
- Yu C, Li P, Dang X, Zhang X, Mao Y, Chen X. Lupus nephritis: new progress in diagnosis and treatment. *J Autoimmun.* October 2022;132:102871.
- Elsaid DS, Noor RAA, Shalaby KA, Haroun RA-H. Urinary tumor necrosis factor-like weak inducer of apoptosis (uTWEAK) and urinary monocyte chemo-attractant protein-1 (uMCP-1): promising biomarkers of lupus nephritis activity? *Saudi J Kid Dis Transplant.* 2021;32:19–29.
- Kwon OC, Lee JS, Ghang B, et al. *Predicting Eventual Development of Lupus Nephritis at the Time of Diagnosis of Systemic Lupus Erythematosus.* Seoul, Republic of Korea: Elsevier; 2018:462–466.
- Liu X-R, Qi Y-Y, Zhao Y-F, Cui Y, Zhao Z-Z. Plasma soluble tumor necrosis factor receptor I as a biomarker of lupus nephritis and disease activity in systemic lupus erythematosus patients. *Ren Fail.* 2023;45:2174355.
- Reyes-Martínez F, Pérez-Navarro M, Rodríguez-Matías A, et al. Assessment of urinary TWEAK levels in Mexican patients with untreated lupus nephritis: an exploratory study. *Nefrologia.* 2018;38:152–160.
- Lee YH, Song GG. Urinary tumor necrosis factor-like weak inducer of apoptosis as a biomarker for lupus nephritis: a meta-analysis. *J Rheum Dis.* 2017;24:85–92.
- Kim JS, Jeong KH. Clinical significance of urinary tumor necrosis factor-like weak inducer of apoptosis (TWEAK) in immunoglobulin A nephropathy. *Clin Nephrol.* 2020;93:99.
- Wang Z-H, Dai Z-W, Dong Y-Y, et al. Urinary tumor necrosis factor-like weak inducer of apoptosis as a biomarker for diagnosis and evaluating activity in lupus nephritis: a meta-analysis. *J Clin Rheumatol.* 2021;27:272–277.
- Elsayed M, Elhefnawy KA, Qassem AA, Amr GE. Urinary tumor necrosis factor-like weak inducer of apoptosis (tweak) as a marker for lupus nephritis activity. *Int J Sci Res.* 2015;4:1615–1619.