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Original Article

Urinary Tumor Necrosis Factor-like Weak Inducer of Apoptosis as a Biomarker for Lupus Nephritis: A Meta-analysis

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Objective. This study evaluates serum or urinary tumor necrosis factor-like weak inducer of apoptosis (TWEAK) as a biomarker for lupus nephritis (LN). **Methods.** We conducted a meta-analysis examining serum or urinary TWEAK levels in patients with systemic lupus erythematosus (SLE), patients with LN (active or inactive), and healthy controls. We tabulated correlation coefficients between urinary TWEAK level and total or renal SLE Disease Activity Index (tSLEDAI or rSLEDAI). **Results.** Eight studies were included in this meta-analysis. The meta-analysis revealed that serum TWEAK levels tended to be higher in patients with SLE than in controls (standard mean difference [SMD] = 0.850, 95% confidence interval [CI] = −0.067 ~ 1.767, p = 0.069). Urinary TWEAK was significantly higher in patients with active LN than in those with inactive LN (SMD = 2.865, 95% CI = −0.831 ~ 4.898, p = 0.006). In addition, urinary TWEAK was positively associated with tSLEDAI and rSLEDAI (correlation coefficient = 0.436, 95% CI = 0.204 ~ 0.622, $p = 4.3 \times 10^{-4}$; correlation coefficient = 0.483, 95% CI = 0.108 ~ 0.738, p = 0.014). Pooled sensitivity and specificity of urinary TWEAK for diagnosis of LN were 81.3% (95% CI, 73.3 ~ 87.8) and 76.0% (95% CI, 66.3 ~ 84.2), indicating good diagnostic accuracy. **Conclusion.** The meta-analysis demonstrated that urinary TWEAK was significantly higher in patients with active LN than in those with inactive LN, and that urinary TWEAK levels were positively correlated with renal disease activity. **(J Rheum Dis 2017;24:85-92)**

Key Words. Urinary TWEAK, Lupus nephritis, Biomarker

INTRODUCTION

Renal involvement occurs in up to 60% of patients with systemic lupus erythematosus (SLE), and lupus nephritis (LN) remains the predominant cause of morbidity and mortality in SLE [1]. The pathogenesis of LN involves autoantibody deposition in the glomeruli, activation of complement and macrophages, cell proliferation, and production of extracellular matrix proteins, proinflammatory cytokines, and chemokines, leading to glomerular damage, tubulointerstitial inflammation, and fibrosis [2].

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a proinflammatory cytokine that induces the activation of several intracellular signal transduction cascades, including the nuclear factor kappa B and mitogen-activated protein kinase pathways [3], thus controlling many cellular activities including proliferation, migration, differentiation, apoptosis, angiogenesis, and inflammation [4]. TWEAK induces apoptosis of glomerular mesangial cells and tubular epithelial cells with induction of proinflammatory cytokines and chemokines [5]. TWEAK may also contribute to kidney injury through enhanced permeability, which increases the extravasation of immunoglobulin G (IgG) and subsequent glomerular IgG deposition, thereby increasing immune complex-mediated activation, which may play an important role in the pathogenesis of LN [6]. TWEAK is

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mainly produced by cells of the innate immune system, such as monocytes, dendritic cells, and natural killer cells [7]. TWEAK is abundant in most tissues, but levels are lower in the kidneys [8]. Monocytes and T lymphocytes infiltrating the kidneys may be the potential sources of TWEAK in the kidneys of patients with LN [9].

Biomarkers are potentially useful in the context of disease diagnosis and management. Serum or urinary TWEAK levels have been reported to be markedly elevated in patients with LN, and elevation of TWEAK levels in urine reflects renal expression. Thus, serum or urinary TWEAK has been considered a potential biomarker for LN because it plays a major role in the pathogenesis of LN. However, studies examining the association of serum or urinary TWEAK levels with renal involvement in SLE have shown mixed results, mainly because of the small number of trials conducted and the small sample sizes. Therefore, in order to overcome the limitations of individual studies, we performed a meta-analysis to investigate whether serum or urinary TWEAK could serve as a biomarker for LN.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a literature search for studies that examined serum or urinary TWEAK concentrations in patients with SLE, patients with LN, and healthy controls. PubMed, Embase, and Cochrane databases were searched to identify all available past articles (until October 2016). The keywords and subject terms used in the search were "TWEAK," "systemic lupus erythematosus," and "SLE." All references cited were also reviewed to identify additional studies not covered by the abovementioned electronic databases. Studies were considered eligible if: (1) they were case-control or cohort studies; (2) they included cases of SLE or LN; (3) they provided data on serum or urinary TWEAK levels in cases and controls; (4) they provided data on the association between TWEAK levels and SLE or renal activity based on the total or renal SLE Disease Activity Index (t- or rSLEDAI); or (5) they included sufficient data to calculate the sensitivity and specificity of urinary TWEAK for diagnosis of LN. No language or race restrictions were applied. Studies were excluded if: (1) they contained overlapping or insufficient data; (2) they included fewer than 5 subjects in the case or control groups; or (3) they were reviews or case reports. Data on methods and results were extracted from original studies by two independent reviewers. Discrepancies in findings between the reviewers were resolved by consensus. The meta-analysis was conducted in accordance with PRISMA guidelines [10]. The following information was extracted from each study: primary author, year of publication, country, number of participants, mean and standard deviation (SD) of TWEAK levels, and correlation coefficients between the urinary TWEAK level and disease activity. Raw data on TWEAK levels were extracted from primary studies to fill 4 cell values (true positive, false positive, true negative, and false negative) in a diagnostic 2×2 table. When the data given were medians, interquartile ranges, or ranges, the mean and SD values were obtained using previously described formulae [11,12].

Evaluation of statistical associations

We performed a meta-analysis examining serum or urinary TWEAK levels in patients with SLE, patients with LN (active or inactive), and healthy controls; correlation coefficients between the urinary TWEAK level and tSLEDAI or rSLEDAI; and the diagnostic accuracy of urinary TWEAK in patients with LN. For continuity of data, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). Odds ratios (ORs) and 95% CIs were calculated for dichotomous data. We assessed within-study and between-study variations and heterogeneities using Cochran's Q test [13]. The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When the significant Q statistic ($p<0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis [14]. When the significant Q statistic ($p<0.10$) did not indicate heterogeneity across studies, the fixed-effects model was used. The model assumed that all studies estimated the same underlying effect, and it considered within-study variations only [13]. We quantified the effect of heterogeneity using $I^2=100\%\times(Q-df)/Q$ [15], where I^2 measured the degree of inconsistency between studies and determined whether the percentage of total variation across studies was due to heterogeneity rather than chance. I^2 ranged from 0% to 100%; I^2 values of 25%, 50%, and 75% were referred to as low, moderate, and high estimates, respectively [15]. We combined sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR, respectively), and diagnostic odds ratio (DOR) estimates and analyzed sum-

mary receiver operating characteristic (SROC) curves for diagnosing LN. Area under the curve (AUC) (in this case, area under the SROC curve) provides an overall summary of test performance and shows the trade-off between sensitivity and specificity [16]. Q* index is another useful global estimate of test accuracy for comparing SROC curves [16]. In the present meta-analysis, statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA) and Meta-DiSc version 1.4 (Hospital Universitario Ramón y Cajal, Madrid, Spain) [17].

Evaluation of publication bias

Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and their interpretation involves subjective judgment. Therefore, we assessed the publication bias using Egger's linear regression test [18], which measured funnel plot asymmetry using a natural logarithm scale of ORs.

RESULTS

Studies included in the meta-analysis

We identified 191 studies using electronic and manual search methods. Twelve of the studies were selected for full-text review on the basis of titles and abstracts. Four of these were excluded because they contained groups with

Table 1. Characteristics of individual studies included in the meta-analysis

Author	Country	Number		Age, yr		Disease duration	Main findings
		SLE	Control	SLE	Control		
Salem, 2016 [19]	Egypt	14*	24†	25.6±10.7*	27.3±9.0†	2.2±2.1*	The uTWEAK levels were significantly higher in patients with SLE with active LN compared to those without or with inactive renal disease and normal healthy subjects.
Choe, 2016 [20]	Korea	70	61	40.4±11.2	4.6±9.1	6.4±4.4	sTWEAK might be a serologic biomarker candidate that reflects disease activity and renal involvement in patients with SLE.
Xuejing, 2012 [21]	China	34*	12†	14~53*	14~53†	12.7±3.4*	uTWEAK levels were correlated with all active indexes of LN, suggesting its potential role as a novel biomarker of active lupus nephritis.
Wang, 2012 [22]	China	62	15	34.1±10.0	36.6±11.6	NA	Patients with SLE express low levels of TWEAK mRNA but high levels of sTWEAK. Additionally, sTWEAK level was associated with several clinical manifestations of SLE, indicating that TWEAK may play a complex role in SLE.
El-shehaby, 2011 [23]	Egypt	50*	23†	29.1±7.9*	29.7±8.8†	6.1±4.2*	Urinary levels of TWEAK positively correlate with renal involvement as assessed by rSLEDAI with reasonable sensitivity, specificity, and predictive values to detect LN.
Schwartz, 2009 [24]	USA	30‡	61	40.4±11.2†	4.6±9.1	6.4±4.4	High uTWEAK levels are indicative of LN, as opposed to non-LN SLE and other healthy and disease control populations, and reflect renal disease activity in longitudinal follow-up.
ElGendi, 2009 [25]	Egypt	47	20	25.3±7.2	NA	25.7±3.1	sTWEAK may be used as a serum biomarker for the assessment of disease activity and development of LN.
Schwartz, 2006 [26]	USA	83	NA	35	NA	NA	Urinary TWEAK levels may be useful as a novel biomarker in LN.

Values are presented as number and mean±standard deviation. SLE: systemic lupus erythematosus, TWEAK: tumor necrosis factor-like weak inducer of apoptosis, uTWEAK: urinary TWEAK, LN: lupus nephritis, sTWEAK: serum TWEAK, NA: not available, rSLEDAI: renal SLE disease activity index. Definition of Active LN in this analysis: rSLEDAI score ≥4. *Active LN, †non-LN SLE, ‡LN.

subject number less than 5, or were reviews. Thus, 8 articles met the inclusion criteria [19-26] (Table 1). There were 4 studies on serum in SLE or LN, 3 on urinary TWEAK levels, 4 on correlation coefficients between urinary TWEAK level and SLE and renal activity, and 3 on the diagnosis of LN (Table 1). The characteristic features of the studies included in the meta-analysis are summarized in Table 1.

Meta-analysis of serum or urinary TWEAK level in SLE and LN

The meta-analysis revealed that the serum TWEAK level tended to be higher in patients with SLE than in controls (SMD=0.850, 95% CI=−0.067∼1.767, p=0.069) (Table 2, Figure 1). However, the meta-analysis showed no significant difference in serum TWEAK level between the LN group and the control group, or between the active-LN group and the inactive-LN group (Table 2). The meta-analysis indicated that the urinary TWEAK level tended to be higher in patients with LN than in controls (SMD=1.655, 95% CI=−0.289∼3.600, p=0.095) (Table 2). However, the meta-analysis also showed that the urinary TWEAK level was significantly higher in the active-LN group than in the inactive-LN group (SMD=2.865, 95% CI=−0.831∼4.898, p=0.006) (Table 2, Figure 1).

Meta-analysis of the relationship between urinary TWEAK level and SLE, renal disease activity

The meta-analysis identified that urinary TWEAK was positively associated with SLE activity based on tSLEDAI

Table 2. Meta-analysis of serum and urinary TWEAK levels in lupus nephritis

Comparison	Population	Number of study	Test of association			Test of heterogeneity			Publication bias p-value
			SMD	95% CI	p-value	Model	p-value	I^2	
Serum TWEAK									
SLE vs. Control	Overall	4	0.850	−0.067∼1.767	0.069	R	0.000	92.5	0.823
LN vs. Control	Overall	3	1.326	−0.695∼3.347	0.198	R	0.000	95.9	0.244
LN vs. Non-LN	Overall	3	0.997	−0.513∼2.506	0.196	R	0.000	94.8	0.025
Urinary TWEAK									
LN vs. Control	Overall	2	1.655	−0.289∼3.600	0.095	R	0.000	93.2	NA
Active LN vs. Inactive LN	Overall	3	2.865	0.831∼4.898	0.006	R	0.000	92.5	0.441

TWEAK: tumor necrosis factor-like weak inducer of apoptosis, SMD: standard mean difference, CI: confidence interval, SLE: systemic lupus erythematosus, LN: lupus nephritis, R: random effects model, NA: not available.

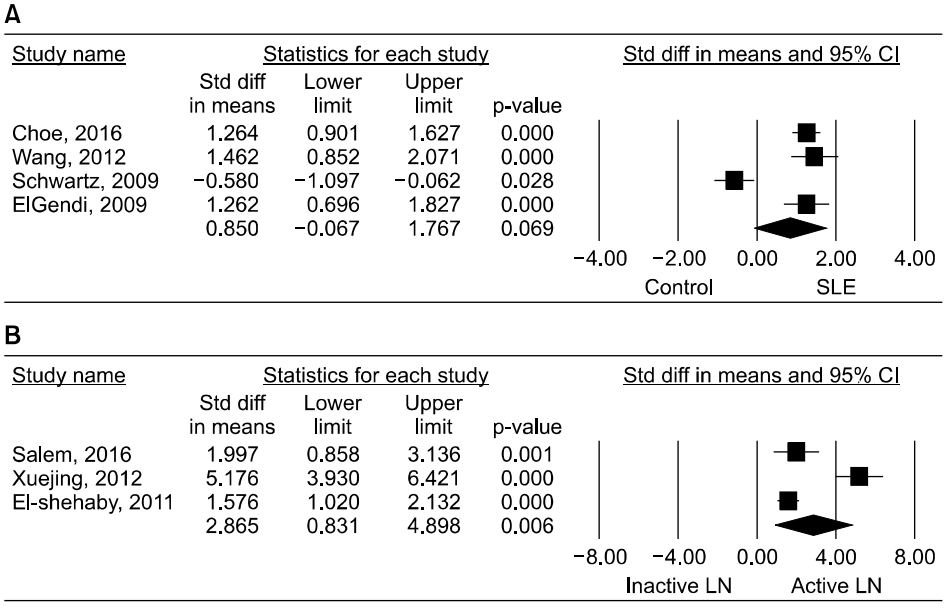

Figure 1. Meta-analysis of the relationship between serum TWEAK level and SLE compared with control (A), and between urinary TWEAK level and active LN compared with inactive LN (B). TWEAK: tumor necrosis factor-like weak inducer of apoptosis, SLE: systemic lupus erythematosus, LN: lupus nephritis, CI: confidence interval, Std diff: standardized difference.

Table 3. Meta-analysis of the correlation coefficient between urinary TWEAK level and SLE and renal activity, and the diagnosis of LN

A. Correlation between uTWEAK and SLE or renal activity

Comparison	Number		Test of association			Test of heterogeneity			Publication bias p-value
	Study	Patient	Correlation coefficient	95% CI	p-value	Model	p-value	I^2	
tSLEDAI	4	212	0.436	0.204～0.622	4.3×10^{-4}	R	0.002	79.7	0.949
rSLEDAI	4	289	0.483	0.108～0.738	0.014	R	0.000	92.0	0.705

TWEAK: tumor necrosis factor-like weak inducer of apoptosis, SLE: systemic lupus erythematosus, LN: lupus nephritis, uTWEAK: urinary TWEAK, CI: confidence interval, tSLEDAI: total SLE disease activity index, rSLEDAI: renal SLE disease activity index, R: random effects model.

B. Diagnosis of LN

Population	Study No.	Number		Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (SE)	Q* (SE)
		LN	Non-LN							
Overall	3	123	96	0.813 (0.733～0.878)	0.760 (0.663～0.842)	2.723 (1.774～4.180)	0.248 (0.073～0.843)	11.28 (5.128～24.82)	0.836 (0.038)	0.768 (0.035)

LN: lupus nephritis, PLR: positive likelihood ratio, NLR: negative likelihood ratio, DOR: diagnostic odds ratio, AUC: area under the curve, CI: confidence interval, SE: standard error.

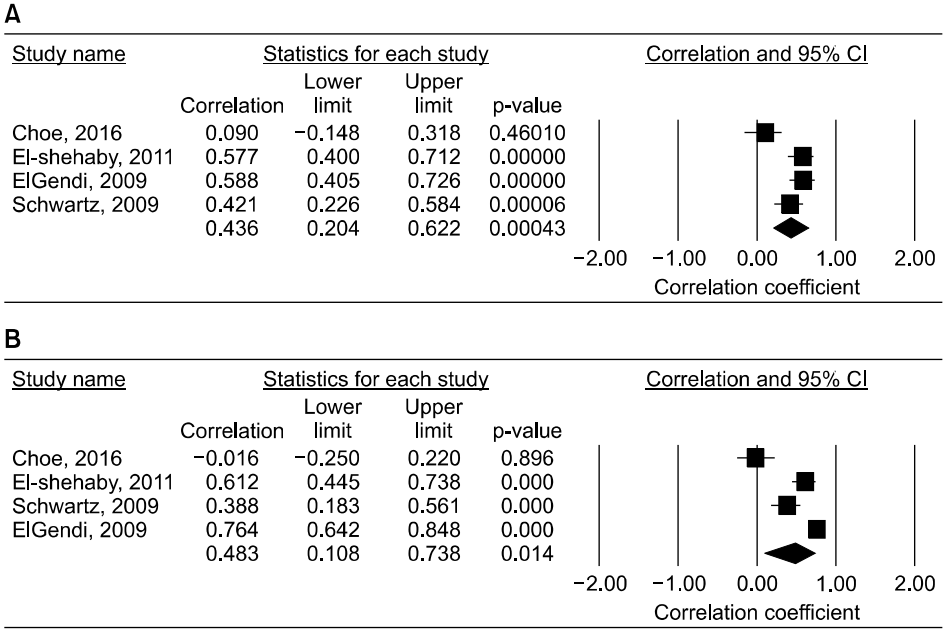

Figure 2. Meta-analysis of the correlation coefficient between urinary TWEAK and total SLEDAI (A) and renal SLEDAI (B). TWEAK: tumor necrosis factor-like weak inducer of apoptosis, SLEDAI: systemic lupus erythematosus disease activity index, CI: confidence interval.

(correlation coefficient=0.436, 95% CI=0.204～0.622, $p=4.3\times10^{-4}$) (Table 3, Figure 2). Urinary TWEAK was also positively associated with renal disease activity based on rSLEDAI (correlation coefficient=0.483, 95% CI=0.108～0.738, p=0.014) (Table 3, Figure 2).

Diagnostic accuracy of urinary TWEAK level in LN

The pooled sensitivity and specificity of urinary TWEAK were 81.3% (95% CI, 73.3～87.8) and 76.0% (95% CI, 66.3～84.2), respectively (Table 3). The PLR, NLR, and DOR of urinary TWEAK were 2.723 (95% CI, 1.774～4.180), 0.248 (95% CI, 0.073～0.843), and 11.28 (95% CI, 5.128～24.82), respectively (Table 3). Figure 3 shows the performance of the urinary TWEAK test in the form of SROC curves. The AUC and Q* index of urinary TWEAK were 0.836 and 0.768, respectively (Table 3, Figure 3).

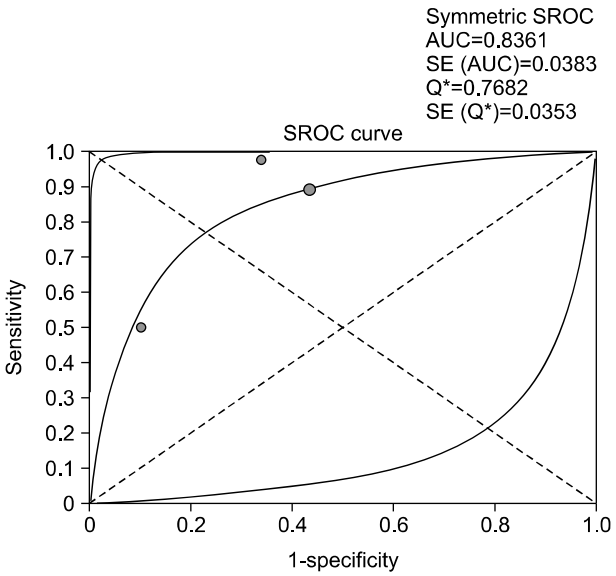

Figure 3. Summary receiver-operating characteristic curves for urinary TWEAK for the diagnosis of LN. Solid circles represent individual studies included in this meta-analysis. The curve shown is a regression line that summarizes the overall diagnostic accuracy. TWEAK: tumor necrosis factor-like weak inducer of apoptosis, LN: lupus nephritis, SROC: summary receiver operating characteristic, SE (AUC): standard error of the area under the curve, Q*: an index defined by the point on the SROC curve where the sensitivity and specificity are equal; and SE (Q*): Q* index standard error.

Heterogeneity and publication bias

Between-study heterogeneity was identified during the meta-analyses of serum and urinary TWEAK in patients with SLE or LN (Tables 2 and 3). However, most of the studies showed the same direction of the effect size. Publication bias results in a disproportionate number of positive studies, and poses a problem for meta-analyses. However, we found no evidence of publication bias for the meta-analyses (Egger's regression test p-values >0.1), except for the analysis of serum TWEAK in patients with LN versus non-LN (Tables 2 and 3).

DISCUSSION

In this meta-analysis, we combined the evidence of serum and urinary TWEAK levels as a biomarker in patients with LN. This meta-analysis showed no significant difference in serum TWEAK levels between patients with LN and controls, or between the active-LN group and the inactive-LN group. In contrast, the urinary TWEAK level was significantly higher in patients with active LN than in patients with inactive LN. In addition, urinary TWEAK was positively associated with SLE and LN activity based on the tSLEDAI and rSLEDAI. The pooled sensitivity and specificity of urinary TWEAK for diagnosis of LN were 81.3% and 76.0%, respectively, and the AUC of urinary TWEAK was 0.836, indicating good diagnostic performance. These meta-analysis data suggest that urinary TWEAK may be a useful potential biomarker for assessing LN activity and diagnosing LN, and for differentiating between active and inactive LN in patients who have SLE with renal involvement.

TWEAK also contributes to the renal inflammatory process and damage in LN. TWEAK induces apoptosis of glomerular mesangial cells and tubular epithelial cells with induction of proinflammatory cytokines and chemokines, thus causing glomerular and tubular injury, which plays a major role in the pathogenesis of LN [6]. TWEAK, like monocyte chemoattractant protein-1 (MCP-1), is a potent mediator of renal involvement and renal disease activity in SLE [27]. Our results suggest that urinary TWEAK levels reflect LN activity because urinary TWEAK levels correlated with rSLEDAI scores, and were increased significantly in the active-LN group compared to the inactive-LN group.

There has been a need for biomarkers for LN, because biomarkers provide a method to noninvasively evaluate the extent and activity of LN [28]. Biomarkers should be pathophysiologically relevant and simple to utilize in routine practice [29]. It will be valuable to identify a reliable, noninvasive assessment method that reflects the activity of LN. Urine biomarkers appear to be more promising than serum biomarkers in the assessment of renal involvement in SLE, because urine biomarkers are the direct products or consequences of kidney inflammation and may most accurately reflect renal status [28]. In addition, urine biomarkers are easily obtained. Among several biomarkers, urinary TWEAK has been considered a sensitive and specific biomarker for LN [30]. Urinary TWEAK levels are correlated with their local production in the kidneys with LN because TWEAK produced in the kidneys shows elevated levels in the urine [30]. Our meta-analysis revealed that urinary but not serum TWEAK levels were increased significantly in the active-LN group compared to the inactive-LN group. Thus, measurement of urinary TWEAK may be a useful noninvasive method for evaluating renal involvement in SLE, allowing possible differentiation of patients with active LN from those with inactive LN on the basis of levels of this urinary biomarker.

The present study has certain shortcomings that should be considered. First, a small number of studies were included in this meta-analysis, and most of the included studies had small sample sizes. Thus, the meta-analysis may be underpowered. Second, the studies included in the meta-analysis were heterogeneous in demographic characteristics and clinical features. The heterogeneity and confounding factors in clinical status and disease activity in the included populations may have affected our results. However, the small number of studies did not permit further subgroup meta-analyses. Nevertheless, this meta-analysis also has its strengths: First, to the best of our knowledge, our meta-analysis is the first study that provides combined evidence regarding serum or urinary TWEAK levels in SLE and LN according to the activity. Second, compared with individual studies, our study should provide more reliable data on the relationship between urinary TWEAK level and LN by increasing the level of statistical power and resolution through the pooling of the results of independent analyses.

CONCLUSION

Our meta-analysis demonstrated that the urinary TWEAK level was significantly higher in patients with active LN than in patients with inactive LN. Moreover, urinary TWEAK was positively associated with renal disease activity in patients with SLE, and showed good diagnostic accuracy. Our meta-analysis suggests that urinary TWEAK may be a useful potential biomarker for evaluating LN activity and differentiating between LN and non-LN. Further studies are necessary to elucidate whether urinary TWEAK can serve as a biomarker for diagnosing LN and monitoring LN activity in practice.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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