The Egyptian Journal of Hospital Medicine (October 2025) Vol. 101, Page 5459-5468

The Association of Recurrent Urinary Tract Infections and Matrix Metalloproteinase 7 Levels as Predictors of Lupus Nephritis Flares in Systemic Lupus Erythematosus

Shimaa E. T. Atwa*[1], Youmna Amer[2], Somia Hafez[3], Nagwa Ibrahim[1]
Departments of [1]Medical Microbiology and Immunology, [2]Rheumatology and Rehabilitation and [3]Clinical Pathology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author: Shimaa E. T. Atwa**, **Mobile:** (+20) 01097979227, **E-mail:** atwashimaa@gmail.com

ABSTRACT

Background: Systemic lupus erythematosus **(**SLE) is an autoimmune multisystemic disorder characterized by chronic inflammatory response. SLE frequently manifests as urinary tract disease. The most characteristic is renal involvement and consequently secondary lupus nephritis.

Objectives: To assess the possible impact of urinary matrix metalloproteinase 7 (MMP7) as an early predictor of lupus nephritis (LN) flares in SLE also to detect urinary tract infections (UTIs) and most common organisms in LN flares in SLE cases, and to associate between recurrent urinary tract infections and matrix metalloproteinase 7 levels in SLE cases.

Subjects and methods: This case-control study was subjected to 180 participants, Group I (SLE group): included 60 cases with SLE without nephritis. Group II (LN group): included 60 patients with LN. Group III (control group): included 60 normal participants. All cases were subjected to clinical examination and laboratory tests including CBC, urine analysis, Kidney function tests, 24-hour proteinuria, C3, C4, ANA, and Anti-DNA antibodies. Urinary MMP7 level were detected by ELISA. Microbiological detection of bacterial urinary tract infections was done by conventional methods and VITEK system.

Results: Regarding the isolated microorganisms, there was remarkable variation between the strains and both urinary and serum MMP7 ($p<0.001$). At cut-off point (1.628 ng/ml) the capability of serum MMP7 to differentiate between SLE cases with LN and without LN was with 65% of sensitivity and 35% of specificity. At cut-off point (3.135 ng/ml) the ability of urinary MMP7 to differentiate between SLE cases with nephritis and without LN had (75%) sensitivity and (45%) specificity.

Conclusion: Both urinary and serum MMP7 have potential ability to predict lupus nephritis with distinction of urinary MMP7. Bacterial infection is a prevalent infection in SLE cases, and its diagnosis is critical for proper treatment of those individuals.

Keywords: MMP7, Urinary tract, Lupus nephritis, Systemic lupus erythematosus, Infection.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune illness defined by a decline of self-tolerance and the development of autoantibodies targeted towards nuclear and cytoplasmic antigens, causing the accumulation of immune complexes and inflammation across numerous organ systems. Its etiology is multifactorial, involving genetic predisposition, hormonal influence, and environmental factors, which together induce aberrant activation of both types of immunity [1].

Renal involvement, or lupus nephritis (LN), is one of the most severe and prognostically important outcomes of SLE. Nearly 40–60% of cases develop LN through the progression of the condition, and its recurrent flares are strongly associated with progressive glomerulosclerosis, tubulointerstitial fibrosis, and eventual renal failure [2]. Early detection of renal activity and differentiation between inflammatory flares and infection-related exacerbations are critical to prevent irreversible renal injury. However, traditional biomarkers such as serum creatinine, proteinuria, and complement levels often lack sensitivity and specificity for predicting renal flares at an early stage [3].

From a microbiological perspective, infections represent a major etiology of morbidity and death in SLE. Both condition-related immune dysfunction and immunosuppressive therapy contribute to increased susceptibility to bacterial infections, particularly urinary tract infections (UTIs) [3].

UTIs in SLE are frequently recurrent, with *Escherichia coli* and *Klebsiella pneumoniae* being the predominant pathogens. Recurrent infections may exacerbate renal inflammation and complicate the clinical interpretation of disease activity [4]. Therefore, biomarkers that can discriminate between infection-induced renal dysfunction and immune-mediated nephritis are urgently needed.

Matrix metalloproteinases (MMPs) control extracellular matrix turnover and tissue remodeling. Among them, MMP-7, or matrilysin-1, is generated by tubular epithelial cells and activated macrophages during inflammation. Beyond its structural role, MMP-7 influences immune regulation by modulating cytokine release, cleaving cell-surface molecules such as Fas ligand, and facilitating immune cell infiltration. Elevated urinary MMP-7 (uMMP-7) levels have been reported in several renal pathologies, including diabetic nephropathy and lupus nephritis, and may reflect active tubular injury and local fibrotic remodeling [5].

Regarding these data, the current study designed to assess the possible impact of urinary MMP-7 as an early non-invasive biomarker for LN flares in cases with SLE. In addition, we aimed to identify the

Received: 05/06/2025
Accepted: 07/08/2025

incidence and microbiological spectrum of UTIs in LN cases and to explore the potential association between recurrent UTIs and urinary MMP-7 levels.

SUBJECTS AND METHODS

Patients:

This case–control study was conducted at the Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University Hospitals. Patients with systemic lupus erythematosus (SLE) with and without lupus nephritis (LN) were recruited from outpatient and inpatient clinics, while age- and sex-matched healthy subjects served as controls.

Ethical approval:

All participants signed informed consent after a full explanation of procedures. The protocol was approved by the Institutional Review Board of Zagazig University and followed the principles of the Declaration of Helsinki.

Participants and diagnostic criteria:

SLE diagnosis was based on the 2019 EULAR/ACR classification criteria. Patients fulfilling the entry criterion of ANA ≥ 1:80 and a total weighted score ≥ 10, or those with biopsy-proven class III/IV LN and ANA positivity, were included. LN was defined as biopsy-proven nephritis and/or persistent proteinuria > 500 mg/day with active urinary sediments. Disease activity was assessed by the SLE Disease Activity Index 2000 (SLEDAI-2K) [1].

180 participants were categorized into 3 equal groups as:

- **Group I:** SLE without nephritis meeting ACR/SLICC criteria [5];
- **Group II:** Clinically or biopsy-proven LN fulfilling ACR criteria;
- **Group III:** Healthy controls of similar age and sex.

Exclusion Criteria:

Patients with other autoimmune diseases, diabetes mellitus, chronic kidney disease unrelated to SLE, or current pregnancy were excluded. Subjects who had received antibiotics, corticosteroid pulses, or immunosuppressive therapy within four weeks before sampling were also excluded to avoid biomarker interference.

Clinical and laboratory assessment:

A complete history and physical examination were performed, including articular and extra-articular manifestations. Disease activity was scored using SLEDAI [6-8]. Laboratory investigations included: ESR by the Westergren method [9]; CBC (Cell Dyn Ruby analyzer); CRP by nephelometry (BN Prospect, Siemens; normal 1–6 mg/dL) [10]; renal profile (BUN and serum creatinine, Cobas 8000 analyzer, Roche Germany); 24-hour urinary protein and urinalysis for RBCs, WBCs, casts, and proteinuria. Autoantibodies were measured by immunofluorescence for ANA [11], and ELISA for anti-dsDNA; complement C3 and C4 were quantified by immunenephelometry (BN ProSpec, Dade Behring, USA).

Sample collection and biomarker estimation:

Morning venous blood (5 mL) and midstream urine (10 mL) were obtained aseptically before medication or antibiotic intake. Serum was separated by centrifugation at 3000 rpm for 10 min and stored at −80 °C. Urine was centrifuged at 1500 rpm for 5 min; the supernatant was frozen at −80 °C. MMP-7 levels in serum and urine were measured by ELISA (Human MMP-7 ELISA, R&D Systems, Minneapolis, USA) according to the manufacturer's protocol. The assay sensitivity was 0.05 ng/mL, with intra- and inter-assay CVs of 4.8 % and 6.3 %. All samples were analyzed in triplicate; mean values were used for analysis.

Urine culture and susceptibility testing:

Midstream urine was examined microscopically for cells and bacteria, then cultured quantitatively using a 0.001-mL calibrated loop on CLED and MacConkey agar, incubated at 35–37 °C for 18–24 h. Counts ≥ 10^5 CFU/mL were considered significant. Isolates were identified by standard biochemical tests and VITEK. Antimicrobial susceptibility was determined by disk diffusion following CLSI M100 (35^{th} ed., 2025) [8].

Statistical analysis:

Data were analyzed using SPSS v23.0 (IBM Corp., Armonk, NY, USA). Quantitative data were expressed as mean ± SD, range, and median and compared using Student's t-test or one-way ANOVA with Tukey's post-hoc test. Categorical variables were expressed as frequency and percentage and were analyzed with Chi-square or Fisher's exact test. Correlations were assessed by Pearson's r. Receiver operating characteristic (ROC) curves determined optimal cut-off values. A p-value < 0.05 denoted statistical significance.

RESULTS

A total of 180 participants were enrolled: 60 patients with active LN, 60 SLE cases without LN, and 60 normal controls. Disease activity was remarkably greater in the LN group compared to non-LN SLE (Table 1).

Table (1): The distribution of the demographic characteristics, duration of disease, and isolated organisms among studied groups					
Demographic characteristics		**Groups**			**P**
		Lupus without nephritis Group	**Lupus with nephritis group**	**Control group**	
		N=60	**N=60**	**N=60**	
Sex	**Female**	55(91.7%)	58 (96.7 %)	58 (96.7 %)	0.89
	Male	5(8.3%)	2(3.3 %)	2(3.3 %)	
Age (years)	**Mean ± SD**	37.25±10.3	35.7±9.9	36.7±10.4	0.85
	Range	20 – 60	20 – 58	19-59	
Disease duration (years)	**Mean ± SD**	8.5±5.7	5.9±3.9	-	0.03*
	Range	1 – 20	1 -15	-	
	Median	8	7	-	
Isolated organisms	**Acineto**	8(13.3)	0(0.0)	0(0.0)	<0.01*
	E. coli	14 (23.3)	0(0.0)	0(0.0)	
	Klebsiella	8(13.3)	0(0.0)	0(0.0)	
	Negative	15 (25.0)	54 (90.0)	56 (93.3)	
	Pseudomonas	4 (6.7)	0(0.0)	0(0.0)	
	Staphylococcus aureus	11 (18.3)	6 (10.0)	4(6.7)	

Both serum and urinary MMP-7 values were remarkably elevated among SLE cases compared with controls ($p < 0.001$). Urinary MMP-7 was also substantially greater in LN compared with non-LN SLE ($p < 0.001$), reflecting its potential association with renal involvement (Figure 1).

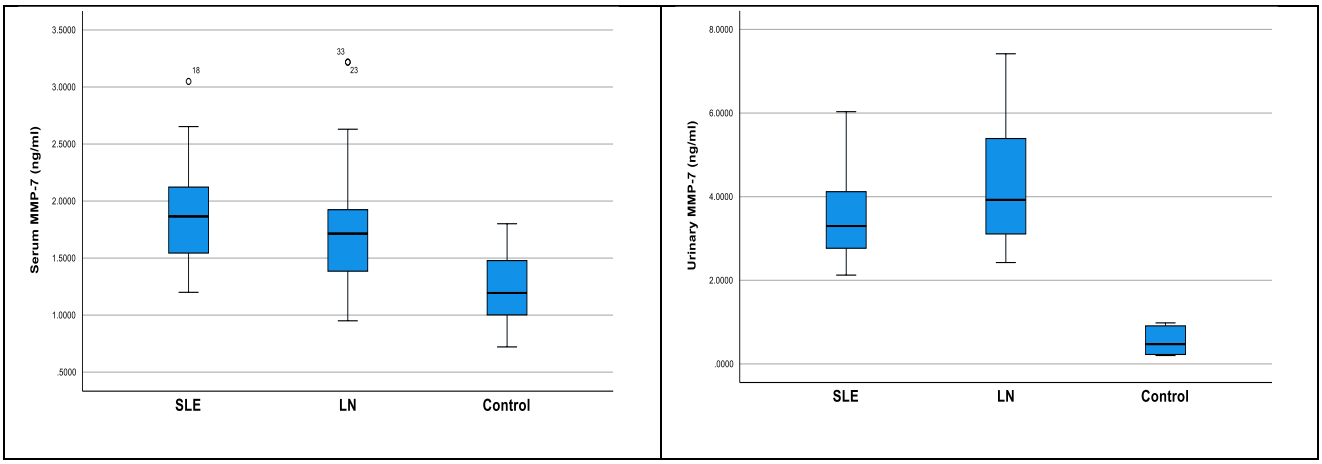

Figure (1): Comparison of serum and urinary MMP7 between three groups.

One-Way ANOVA is used to analyze the difference between the groups.

Correlation analysis determined that serum MMP-7 was associated with hemoglobin levels in non-LN SLE ($r = 0.517$) and with C3 in LN ($r = 0.362$) (Table 2).

Table (2): Correlation of serum MMP7 with demographic data, disease activity index (SLEDAI), and laboratory data					
		Serum MMP7			
		Lupus without nephritis		Lupus with nephritis	
		R	P	R	P
Age		0.055	0.735	-0.252	0.117
Duration of disease		0.089	0.709	-0.220	0.350
SLEDAI		0.407	0.649	0.033	0.841
CBC	**Hemoglobin**	0.517	<0.001	-0.195	0.227
	TLC	0.12	0.943	-0.248	0.123
	PLTs	-0.296	0.063	-0.087	0.592
Acute phase reactant	**CRP**	0.177	0.273	-0.066	0.686
	ESR	0.313	0.050	0.089	0.587
KFTs (kidney function tests)	**S. creatinine**	-0.152	0.348	-0.002	0.991
	BUN	0.058	0.724	-0.227	0.159
	24h protein in urine	0.041	0.865	-0.285	0.074
Urine analysis	**Hematuria**	0.366	0.113	-0.228	0.335
	Pyuria	0.107	0.664	-0.093	0.695
Immunologic data	**C3**	0.52	0.752	0.362	0.002
	C4	0.199	0.219	0.291	0.069
Correlation between Serum MMP7 and variables is analyzed using **Pearson correlation coefficient**. P <0.05 was defined as statistically significant.					

There was no remarkable variation in serum MMP-7 values across various clinical manifestations in either SLE group ($p > 0.05$). This suggests that serum MMP-7 elevation is more disease-related than feature-specific (Table 3, Figure 2).

Table (3): Correlation of serum MMP7 with clinical manifestations:							
Clinical manifestations		**Serum MMP7(ng/ml)**					
		Lupus without nephritis N=60			**Lupus with nephritis N=60**		
		Absent	**Present**	**P**	**Absent**	**Present**	**P**
Constitutional	**Fever**	1.86±0.51	2.20±0.48	0.379	-	-	-
Hematological	**Anemia**	2.12±0.61	1.75±0.66	0.104	1.55±0.94	1.87±0.48	0.318
	Leucopenia	1.92±0.49	1.36±0.00	0.282	1.79±0.61	-	-
	Thrombocyto-penia	1.89±0.5	-	-	1.79±0.61	-	-
Neurological	**Seizures**	1.94±0.5	1.65±0.51	0.365	-	-	-
	Headache	1.93±0.50	1.7±0.50	0.480	-	-	-
Vascular	**Vasculitis**	1.88±0.5	1.92±0.54	0.876	-	-	-
Musculoskeletal	**Arthritis**	1.87±0.33	1.9±0.53	0.936	1.32±0.18	1.87±0.62	0.154
	Myositis	1.9±0.50	1.9±0.54	0.948	1.81±0.64	1.64±0.22	0.314
Serositis	**Pleurisy**	1.9±0.52	1.87±0.50	0.907	1.54±0.52	1.93±0.63	0.186
Mucocutaneous	**Malar rash**	2.05±0.45	1.86±0.85	0.512	-	-	-
	Hair Loss	2.03±0.37	1.85±0.54	0.510	-	-	-
	Oral ulcers	2.01±0.51	1.73±0.46	0.227	1.67±0.41	2.02±0.87	0.341
Immunologic data	**Anti-dsDNA**	1.86±0.18	1.91±0.61	0.801	1.85±0.63	1.46±0.40	0.332
Student t test is used to analyze the difference between the two groups.							

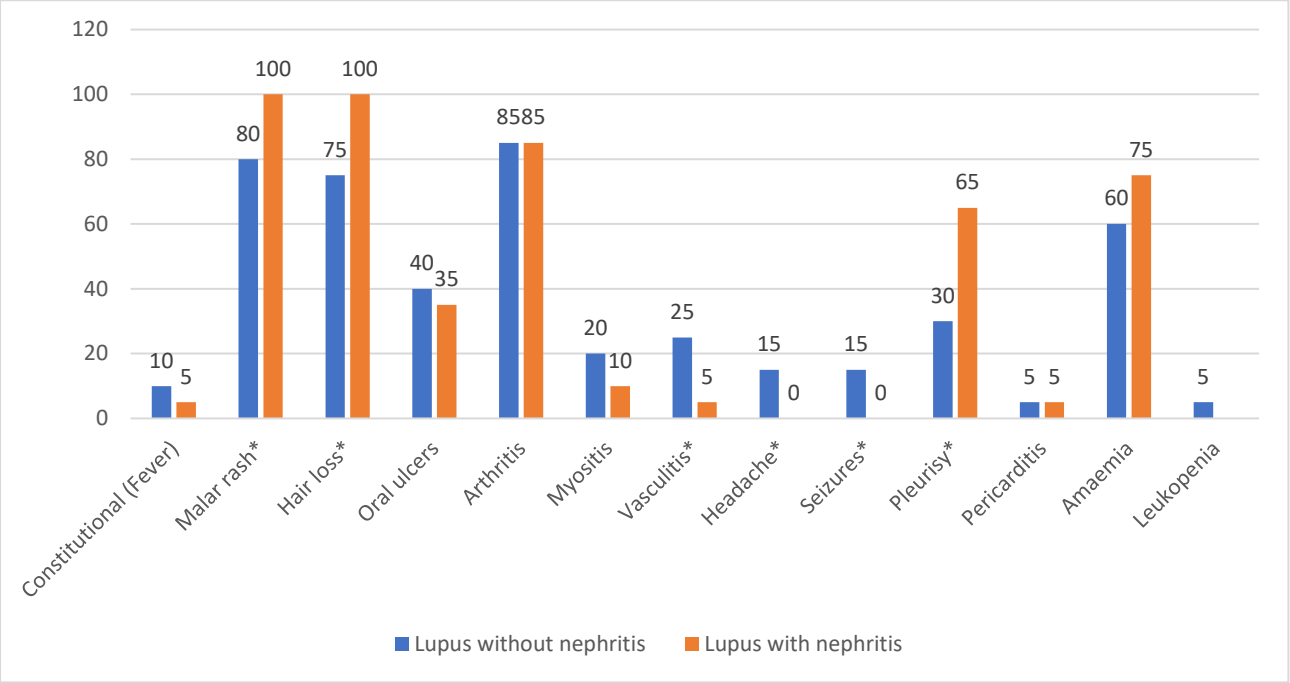

Figure (2): Distribution of the studied patients according to clinical manifestation

Urinary MMP-7 correlated positively with 24-hour proteinuria in both SLE without nephritis (r = 0.447) and LN patients (r = 0.622), and with hemoglobin in LN (r = 0.510) (Table 4).

Table (4): Correlation of urinary MMP7 with demographic data and SLE disease activity index (SLEDAI):

		Urinary MMP7			
		Lupus without nephritis		Lupus with nephritis	
		R	P	r	P
Age		0.288	0.219	-0.076	0.749
Duration of disease		0.165	0.486	-0.033	0.889
SLEDAI		0.102	0.668	-0.397	0.083
CBC	**Hemoglobin**	0.019	0.935	0.510	<0.001
	TLC	0.161	0.320	0.242	0.304
	PLTs	-0.122	0.452	0.084	0.607
Acute phase reactant	**CRP**	-0.185	0.253	-0.169	0.296
	ESR	0.155	0.340	-0.474	0.112
KFTs (kidney function tests)	**S. creatinine**	-0.370	0.119	-0.192	0.235
	BUN	0.298	0.202	0.300	0.060
	24h protein in urine	0.447	0.048	0.622	<0.001
Urine analysis	**Hematuria**	0.139	0.559	-0.049	0.838
	Pyuria	-0.060	0.801	-0.006	0.980
Immunologic data	**C3**	0.081	0.620	-0.261	0.104
	C4	-0.015	0.924	-0.142	0.382

Correlation between urinary MMP7 and variables is analyzed using **Pearson correlation coefficient**. P <0.05 was defined as statistically significant.

Clinically, urinary MMP-7 was remarkably higher among non-LN SLE cases presenting with myositis (p = 0.012), and in LN cases with positive anti-dsDNA antibodies (p = 0.026). (Table 5)

Table (5): Correlation of urinary MMP7 with clinical manifestations:

Clinical manifestations		**Urinary MMP7 (ng/ml)**					
		Lupus without nephritis N=60			**Lupus with nephritis N=60**		
		Absent	**Present**	**P**	**Absent**	**Present**	**P**
Constitutional	**Fever**	3.52±1.03	3.18±1.50	0.676	-	-	-
Hematological	**Anemia**	3.47±1.1	3.5±1.05	0.953	5.33±2.15	3.98±1.11	0.081
	Leucopenia	3.42±1.03	4.7±0.00	0.241	4.38±1.51	3.19±0.00	0.453
	Thrombocy-topenia	3.49±1.04	-	-	4.32±1.49	-	-
Neurological	**Seizures**	3.57±1.11	3.01±0.17	0.065	-	-	-
	Headache	3.54±1.11	3.17±0.46	0.523	-	-	-
Vascular	**Vasculitis**	3.85±1.15	3.2±0.36	0.277	-	-	-
Musculoskeletal	**Arthritis**	3.2±0.25	3.5±1.12	0.290	5.14±0.85	4.17±1.55	0.314
	Myositis	3.2±0.85	4.6±1.08	0.012	4.28±1.54	4.65±1.35	0.753
Serositis	**Pleurisy**	3.4±1.16	3.69±0.74	0.589	4.86±1.96	4.03±1.16	0.332
Mucocutaneous	**Malar rash**	3.57±1.05	3.47±1.07	0.862	-	-	-
	Hair Loss	3.71±0.57	3.41±1.16	0.593	-	-	-
	Oral ulcers	3.59±1.07	3.34±1.04	0.622	4.42±0.96	4.12±2.27	0.748
Immunologic data	**Anti-dsDNA**	4.09±1.08	3.16±0.90	0.540	4.03±1.12	5.94±2.56	0.026

Student t test is used to analyze the difference between the two groups. P <0.05 was defined as statistically significant

Microbiological assessment revealed significant variation in isolated pathogens among groups (p < 0.001). *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter*, and *Staphylococcus aureus* were the most frequent isolates in SLE, predominantly within the LN subgroup. Both serum and urinary MMP-7 values varied significantly according to the type of isolated microorganism (p < 0.001), highlighting a possible infection-related modulation of MMP-7 expression (Table 6).

Table (6): The association between the types of isolated organisms and serum and urinary MMP7 among the studied groups

	Urinary MMP7	**Serum MMP7**
Acineto	3.06 (3.06 ±0.42)	1.91(1.91±0.092)
E. coli	3.20 (3.35 ±0.79)	1.71(1.79±0.42)
Klebsiella	4.40 (4.40 ±0.51)	1.99(1.99±0.01)
Staphylococcus aureus	4.70 (3.95 ±1.95) (0-6)	1.91(1.91±0.59) (1-3)
Pseudomonas	2.87 (2.87 ±0.5)	1.20 (1.20±0.3)
P	<0.01*	<0.01*

The Chi square test is used to analyze the difference between the two groups. *P<0.05 was defined *as statistically significant

Antibiotic susceptibility profiles of isolated pathogens are summarized in the supplementary dataset. At the optimal diagnostic threshold, serum MMP-7 ≥ 1.628 ng/mL differentiated LN from non-LN SLE with 65% sensitivity and 35% specificity (AUC = 0.418; p = 0.223). In contrast, urinary MMP-7 ≥ 3.135 ng/mL achieved superior diagnostic performance with 75% sensitivity, 45% specificity, and AUC = 0.660 (p = 0.008) (Tables 7, 8).

Table (7): The sensitivity and resistance of different isolated organisms			
	Total	**Sensitivity**	**Resistance**
AMC			
E. coli	14	8	6
Staphylococcus aureus	10	0(0.0)	10(100.0)
klebsiella	8	0(0.0)	8(100.0)
SAM			
E. coli	14	6	8
Acineto	4	0(0.0)	4(100.0)
klebsiella	8	0(0.0)	8(100.0)
TPZ			
E. coli	14	14(100.0)	0(0.0)
Acineto	4	4(100.0)	0(0.0)
Klebsiella	8	8(100.0)	0(0.0)
Pseudomonas	4	4(100.0)	0(0.0)
Staphylococcus aureus	10	????	???
FEP			
E. coli	14	6	8
Acineto	4	0(0.0)	4(100.0)
Klebsiella	8	0(0.0)	8(100.0)
Pseudomonas	4	0(0.0)	4(100.0)
Staphylococcus aureus	10	10(100.0)	0(0.0)
CN			
E. coli	14	10(	4
Acineto	4	4(100.0)	0(0.0)
Klebsiella	8	8(100.0)	0(0.0)
Pseudomonas	4	4(100.0)	0(0.0)
Staphylococcus aureus	10	0(0.0)	10(100.0)
GEN			
Staphylococcus aureus	10	10(100.0)	0(0.0)
CFX			
Staphylococcus aureus	10	10(100.0)	0(0.0)
LEV			
E. coli	14	0(0.0)	14(100.0)
Acineto	4	0(0.0)	4(100.0)
Klebsiella	8	0(0.0)	8(100.0)
Pseudomonas	4	0(0.0)	4(100.0)
Staphylococcus aureus	10	0(0.0)	10(100.0)
DOR			
E. coli	14	0(0.0)	14(100.0)
Acineto	4	0(0.0)	4(100.0)
Klebsiella	8	0(0.0)	8(100.0)
Pseudomonas	4	0(0.0)	4(100.0)

Table (8): Performance of MMP7 in prediction of lupus nephritis patients among the studied patients:									
	Cut-off (ng/ml)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR	P
Serum	1.628	**0.418**	**65**	**35**	**50**	**50**	**1.00**	**1.00**	**0.223**
Urinary	3.135	**0.660**	**75**	**45**	**57.62**	**64.29**	**1.36**	**0.56**	**0.008**

AUC; area under the curve, **PPV:** positive predictive value, **NPV:** negative predictive value, **+LR:** positive likelihood ration, **-LR:** negative likelihood ratio. **P**<0.05 is significant.

DISCUSSION

Biomarkers have become indispensable tools in the management of autoimmune diseases, offering insights into diagnosis, activity monitoring, and prediction of organ-specific complications. In systemic lupus erythematosus (SLE), however, the heterogeneity of immunopathogenic mechanisms and the frequent influence of infections make it difficult for a single biomarker to demonstrate sufficient sensitivity and specificity. Consequently, combining multiple markers that reflect diverse immunologic and microbial pathways may enhance disease assessment and help identify patients at increased risk of severe manifestations such as lupus nephritis (LN) [12].

Among the matrix metalloproteinase (MMP) family, **MMP-7 (matrilysin-1)** is one of the smallest but biologically potent enzymes. It can activate other MMPs and contribute to extracellular matrix remodeling, inflammation, and tissue injury [13]. In renal pathology, MMP-7 is expressed in tubular epithelial cells and secreted into the tubular lumen, where it can be detected in urine. Elevated urinary MMP-7 (uMMP-7) levels have been documented in various renal diseases, suggesting its potential as a non-invasive biomarker of renal inflammation and fibrosis [13].

The present study assessed urinary and serum MMP-7 levels as early indicators of LN flares in Egyptian patients with SLE. To our knowledge, this is among the limited number of studies evaluating MMP-7 in the Egyptian population, linking its role to both renal involvement and infectious burden.

Demographic and Clinical Characteristics

In this cohort, 90% of SLE cases were females, aligning with the established female predominance in SLE and consistent with **Abd Elazeem *et al.*** [14] who attributed this to hormonal and X-chromosome–related factors influencing immune regulation. Our analysis revealed no significant differences between patient groups regarding gender or disease duration, similar to the findings of **Vira *et al.*** [15]. However, patients with LN were significantly younger, which may reflect the earlier onset of severe renal disease in susceptible individuals.

Mucocutaneous manifestations such as malar rash and alopecia were significantly more common among LN patients, a finding parallel to that of **Elsayed and Mohafez** [16] who noted similar trends in Egyptian SLE cohorts. Meanwhile, pleurisy and neurological manifestations, including headache and seizures, were also higher in the LN group, possibly reflecting systemic immune activation and secondary endothelial dysfunction.

Microbial Spectrum and Infection Burden

Infections represent a major cause of morbidity and mortality in SLE, often complicating disease flares. In our study, Gram-negative organisms predominated, with *Escherichia coli* and *Klebsiella pneumoniae* being the most frequently isolated pathogens among LN cases. This agrees with previous Egyptian and international reports highlighting the predominance of Gram-negative bacilli in SLE-associated infections [17–19]. **Abd El-Raouf *et al.*** [17] observed that urinary tract infections (UTIs) were the most frequent bacterial infections in SLE (55%), with *E. coli* accounting for approximately one-quarter of isolates. Similarly, **Mohamed *et al.*** [18] **and Chen *et al.*** [19] demonstrated that *E. coli* was the leading pathogen, emphasizing its ubiquitous role in SLE-related UTIs. Other Gram-negative organisms, including *Pseudomonas aeruginosa* and *Klebsiella species*, were also common, corroborating earlier findings by **Yu *et al.*** [20] **and Chen *et al.*** [21].

While infections were once primarily attributed to immunosuppressive therapy, emerging evidence indicates that intrinsic immune dysregulation in SLE contributes independently to infection susceptibility [22,23]. Indeed, **Rúa-Figueroa *et al.*** [24] reported that nearly one-quarter of severe infections in SLE occurred even without recent immunosuppressant use, implicating both disease activity and complement dysfunction as underlying factors.

Serum and Urinary MMP-7 Findings

Our results revealed significantly elevated serum and urinary MMP-7 levels in SLE patients compared with controls, with urinary MMP-7 particularly increased among those with LN. This observation is consistent with **Vira *et al.*** [15] who reported markedly higher serum MMP-7 concentrations in SLE than controls, and with **Wang *et al.*** [4]**,** who demonstrated that urinary MMP-7 was elevated in LN and correlated with renal flare incidence.

The localization of MMP-7 within tubular epithelium and its secretion into urine support its role as a marker of tubular injury. **Zhou *et al.*** [13] **and Yang *et al.*** [25] both showed that uMMP-7 reflects tubular damage and correlates with the degree of renal fibrosis and inflammatory activity. In addition, experimental data indicate that MMP-7 facilitates Fas ligand shedding in renal cells, promoting apoptosis and local inflammation [26-28]. Thus, elevated urinary MMP-7 likely mirrors both structural damage and active immune-mediated renal injury.

In our cohort, serum MMP-7 correlated positively with complement C3 levels but not with anti-dsDNA or proteinuria. This finding is in partial agreement with **Goletti *et al.*** [29] who noted that serum MMP-7 and CXCL12 were both associated with lupus nephritis but might not directly mirror dsDNA titers. The absence of association with disease activity indices in our study suggests that serum MMP-7 may serve

more as a general inflammatory marker rather than a specific indicator of renal or systemic flare.

In contrast, urinary MMP-7 exhibited significant correlations with both anti-dsDNA and 24-hour urinary protein excretion in LN cases, highlighting its closer link to renal involvement. These findings align with **Wang *et al.* [4] and Afkarian *et al.* [30]** who demonstrated that urinary MMP-7 increases with histologic activity and correlates with proteinuria and renal fibrosis markers. Collectively, these data suggest that urinary rather than serum MMP-7 is a more reliable biomarker for detecting renal activity in SLE.

Diagnostic Performance and Comparative Accuracy

Receiver operating characteristic (ROC) analysis in this study showed that urinary MMP-7 distinguished LN from non-LN SLE with moderate sensitivity (75%) and specificity (45%), outperforming serum MMP-7, which had weaker discriminatory capacity (65% sensitivity, 35% specificity). This modest accuracy is comparable to that reported by **Wang *et al.* [4]** who found that combining urinary MMP-7 with conventional markers improved predictive value for renal flare detection. The limited specificity may arise from MMP-7 elevation in non-lupus renal injuries and other inflammatory states [25,26].

Nevertheless, the ability of urinary MMP-7 to reflect renal pathology non-invasively is valuable, especially where renal biopsy is contraindicated or unavailable. As **Yu *et al.* [20]** emphasized, reliable urine biomarkers could reduce dependence on invasive procedures while allowing early intervention. Integrating uMMP-7 with traditional indices—such as anti-dsDNA, complement levels, and proteinuria—may enhance overall diagnostic precision.

Comparisons with Prior Literature and Mechanistic Implications

Our findings support the growing recognition of MMP-7 as an immunopathogenic mediator beyond its structural role. **Buhler *et al.* [31]** demonstrated that MMP-7 facilitates immune cell migration and reactivation in perivascular spaces, contributing to chronic neuroinflammation in autoimmune models. Analogously, **Vira *et al.* [15]** proposed that excessive MMP-7 expression may amplify tissue remodeling and inflammatory cell recruitment in SLE, representing a potential therapeutic target.

Furthermore, the observed increase of urinary MMP-7 during renal flares underscores its involvement in epithelial–mesenchymal transition (EMT) and fibrogenesis. **Zhou *et al.* [13]** showed that MMP-7 directly regulates E-cadherin degradation, promoting tubular cell detachment and fibrosis. Therefore, persistent MMP-7 activation may not only signal renal injury but also perpetuate it, explaining why elevated levels correlate with chronic damage indices.

Clinical Implications and Future Perspectives

The results of this study highlight the dual clinical relevance of MMP-7: first, as a **biomarker** capable of detecting renal involvement early, and second, as a **pathogenic mediator** potentially amenable to therapeutic modulation. The non-invasive nature of urinary measurement offers practical utility, especially in serial monitoring. Moreover, because urinary MMP-7 reflects tubular pathology, it may complement glomerular markers such as proteinuria or anti-dsDNA, providing a more comprehensive view of renal disease dynamics.

The concurrent analysis of urinary infections also provides clinically relevant insight. The predominance of Gram-negative uropathogens among LN cases reinforces the importance of vigilant infection surveillance, as UTIs may mimic or precipitate renal flares. Differentiating infection-induced renal dysfunction from immune-mediated LN remains a key diagnostic challenge, and biomarkers such as uMMP-7 could assist in resolving this ambiguity.

Nevertheless, certain limitations should be acknowledged. The relatively small sample size and single-center design limit generalizability. Additionally, histopathological correlation through renal biopsy was not uniformly available, precluding direct validation against histologic activity indices. Longitudinal studies are needed to evaluate uMMP-7 kinetics during flare and remission, and to explore its integration into composite predictive models alongside emerging markers such as NGAL, CXCL10, and urinary CD163.

CONCLUSION

In summary, this study demonstrates that urinary MMP-7 is significantly elevated in SLE patients, particularly in those with lupus nephritis, and correlates with key markers of renal activity. Its superiority over serum MMP-7 in reflecting renal involvement highlights its potential as a sensitive non-invasive biomarker. Furthermore, recurrent urinary infections were common among LN cases, emphasizing the need to consider microbial factors when interpreting biomarker fluctuations. Future multicenter studies are warranted to confirm the diagnostic and prognostic utility of MMP-7 and to explore whether its inhibition could offer therapeutic benefit in attenuating renal injury in lupus nephritis.

No funding.
No conflict of interest.

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