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Clinical utility of urinary soluble CD163 in evaluation of lupus nephritis patients

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ABSTRACT

Aim of the work: To assess urinary soluble CD163 (sCD136) in systemic lupus erythematosus (SLE) patients compared to healthy controls. In addition to determine its association with different SLE clinical features, laboratory investigations and pathological indices focusing on those suggest renal disease activity.

Patients and methods: The study included 58 SLE patients and 30 controls. SLE disease activity index (SLEDAI) was assessed and patients subdivided into active lupus nephritis (ALN) (renal SLEDAI $\geq$ 4) and no-renal activity (NRA) SLE patients (renal SLEDAI = 0). Urinary sCD163 was measured by Enzyme-Linked Immunosorbent Assay (ELISA). Urine values were normalized to urinary creatinine excretion. Renal biopsies were performed in 21 ALN patients.

Results: They were 54 females and 4 males with a mean age 31.8 ± 9.1 years and disease duration 6.2 ± 4.8 years. They were 31 with ALN and 27 NRA SLE patients. Urinary sCD163 level was significantly higher in SLE patients (1.85 ± 0.3) than controls (0.5 ± 0.36, $p < 0.001$). In ALN, it was significantly higher (2.91 ± 2.52) compared to NRA SLE patients (0.64 ± 0.38) and controls ($p < 0.001$ in both). The optimum cut-off value above which normalized urinary sCD136 can predict renal activity was > 0.82 with sensitivity of 90.3%, specificity of 88.89%, $p < 0.001$. Urinary sCD163 significantly correlated with renal ($r = 0.75$, $p < 0.001$) but not with extra-renal SLEDAI. It correlated with activity index of renal biopsy ($r = 0.46$, $p = 0.038$).

Conclusion: Urinary sCD163 is a potential biomarker for LN activity. Its level is associated with clinical features, laboratory investigations and pathological indices that indicate renal disease activity.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by production of autoantibodies and involvement of multiple organ systems [1]. Lupus nephritis (LN) is occurring in up to 60% of SLE patients with varying degrees of renal involvement [2]. Approximately 10–17% of LN patients will progress to end-stage renal disease (ESRD) [1]. Early recognition of renal involvement in SLE patients is very necessary as it is an important factor of long term outcome [2].

Although renal biopsy is the current gold standard for the diagnosis and classification of LN, it is invasive and cannot be done repeatedly to assess response to treatment. Moreover, the limited tissue obtained each time may not accurately reflect the complete spectrum of renal lesions. In contrast, urine samples can be easily obtained and are ideal for frequent monitoring. Non-invasive urinary biomarkers may emerge as an alternative method for LN assessment [3]. Proteinuria and active sediments are the traditional urinary biomarkers of renal involvement but they have a number of limitations [4]. Patients with renal damage can be presented with proteinuria while presence of leucocytes in urine can be seen with urinary tract infection and interstitial inflammation [5].

Autoantibodies production and complement activation are the major mechanisms in initiating the inflammatory response in LN while cellular immune mechanisms mediated through infiltrating mononuclear cells including macrophages have an important role in amplification and progression of renal injury in SLE. Macrophages are involved in apoptotic cells clearance which is inefficient in SLE patients, resulting in the presence of antigens that

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trigger autoantibody production [6]. Macrophages are classified into M1 and M2 macrophages based on their phenotype as well as function [7]. M2 macrophages express CD163 and are predominantly anti-inflammatory in activity as compared with M1 macrophages. Their major functions are resolution of inflammation, tissue remodeling and fibrosis promotion [8].

CD163 is a type I trans-membrane protein has been discovered on the membrane of mononuclear-phagocytes and belonging to the cysteine-rich scavenger receptor superfamily type B that acts as a scavenger receptor for the haemoglobin–haptoglobin complex. CD163 regulates the expression of anti-inflammatory molecules, such as interleukin10 and hemeoxygenase-1 [9]. It is actively released from the plasma membrane by metalloproteinases in response to certain inflammatory stimuli and diffuses to inflammatory tissues or enters the circulation in its soluble form (sCD163) [10]. After cleavage, the sCD163 is shed into the urine where it can be detected in active kidney diseases such as anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and LN [11,12].

In LN patients, CD163 cells have been found in cellular crescents, proliferative glomerular and acute tubulointerstitial lesions [7,13]. CD163 gene expression is increased in glomeruli from patients with active LN compared with healthy kidney donors [14]. This has been confirmed by a single-cell transcriptomic study revealed that M2c macrophages expressing the CD163 receptor infiltrate kidney tissue and represent the most abundant cells detected in urine from LN patients [15].

Based on these findings, we hypothesized that urinary soluble CD163 level may be a potential biomarker of renal disease activity in SLE patients. The aim of this study was to assess urinary soluble CD163 in SLE patients compared to healthy controls. In addition to determine its association with different SLE clinical features, laboratory investigations and pathological indices focusing on those suggest renal disease activity. Subsequently, to investigate its ability to act as an alternative non-invasive method to identify and evaluate patients with LN.

2. Patients and methods

This comparative cross sectional study was carried out on 58 adult SLE patients diagnosed according to systemic lupus international collaborating clinics (SLICC) classification criteria [16]. Patients recruited from the Rheumatology and Rehabilitation Department, Faculty of Medicine, Assiut University. Patients who were pregnant, those with active infection or any other autoimmune disease were excluded. Thirty age and gender matched healthy individuals were enrolled as a control group. The study was approved by the ethics committee of the Faculty of Medicine, Assiut University, Egypt. Informed consent was obtained from all participants after explanation of the study aims and procedures.

The socio-demographic data, detailed medical history and thorough clinical examination were assessed for all patients. Therapeutic history and radiographic findings were recorded. Disease activity was assessed using SLE Disease Activity Index (SLEDAI) [17]. Renal SLEDAI was used to assess kidney disease activity; the score consists of the four kidney related parameters: hematuria, pyuria, proteinuria and urinary casts, each of them has a score of 4. Based on results of renal SLEDAI, the patients were classified into active LN patients (ALN) if renal SLEDAI score of $\geq$4 and no-renal activity (NRA) SLE patients those had inactive renal disease (renal SLEDAI = 0) at the time of their clinic visit [17].

The SLICC/American College of Rheumatology Damage Index (SLICC/ACR-DI) [18] was assessed to measure irreversible damage resulting from SLE disease activity and its treatment.

Renal biopsies were done for 21 patients with ALN, the remaining 10 in this group either refused to perform it or had previously undergone this procedure. Renal biopsies were classified according to the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) 2003 classification of LN [19] and scored by the National Institutes of Health (NIH) activity and chronicity indices [20]. The maximum score was 24 points for the activity index (AI) and 12 for the chronicity index (CI). Biopsy interpretation was done before the availability of the biomarker results in all cases.

Laboratory investigations: venous blood samples were collected from all patients under complete aseptic conditions to perform complete blood count (CBC), erythrocyte sedimentation rate (ESR), *liver function tests*: serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), *kidney function tests*: blood urea nitrogen (BUN), serum creatinine, creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). In addition to immunological profile that included: antinuclear antibodies (ANA), anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA antibody) by immunofluorescence and complement C3 and C4.

24-hour urine was collected to estimate 24-hour urinary protein and creatinine clearance. Mid-stream urine samples were collected from patients and controls in sterile containers. Urine analysis was done. Urine was centrifuged at 2000–3000 rpm for 20 min, supernatant was removed, aliquoted and stored at −20 to −80C° for further assessment of sCD163.

Urinary sCD163 determination: Quantitative determination of human sCD163 in urine was done using SinoGeneClon Biotech Co., Ltd Enzyme-Linked Immunosorbent Assay (ELISA) Kit, China, Catalog no., SG-10585. Urinary creatinine (mg/dl) was determined. Urinary sCD163 levels were normalized to urinary creatinine (U/ml)/(mg/dl) before further analysis.

Statistical analysis: Data analysis was undertaken using statistical package for social sciences (SPSS) version 25 SPSS. Data were presented as frequencies and percentages or mean and standard deviation. After testing data normality, non-parametric tests were performed. Mann Whitney U test (if 2 groups) and Kruskal Wallis test (if > 2 groups) were used for comparison. Spearman's correlation was considered. Receiver operating characteristic (ROC) curve analysis was done to identify diagnostic ability of urinary sCD163 to predict renal disease activity among SLE patients. Multivariate linear regression analysis was used to identify factors predicting increase in urinary sCD163 among SLE patients. p values <0.05 were considered significant.

3. Results

The study included 58 SLE patients; 54 females and 4 males, with a mean age of 31.8 ± 9.1 (19–54) years and disease duration 6.2 ± 4.8 (0.5–20) years. There were 31 with active lupus nephritis (ALN) and 27 with no-renal activity (NRA). The controls were 30 matched for gender: 27 (90%) females and 3 (10%) males and age (31 ± 9.5; 19–52 years) (p = 0.69, p = 0.58 respectively). Characteristics of the patients and those with ALN and NRA are presented in Table 1 and laboratory investigations in Table 2.

Association of normalized urinary sCD163 levels with pathological classification of renal biopsy done in 21 ALN patients are presented in Table 3. The means of their activity and chronicity indices were 6.48 ± 0.77 (2–14), 1.38 ± 0.35 (0–5) respectively.

The mean of urinary sCD163 level in patients (1.85 ± 0.3; 0.16–11.21) was significantly higher than in control (0.5 ± 0.36; 0.15–1.52), p < 0.001. It was significantly higher in patients with ALN (2.91 ± 2.52; 0.44–11.21) than NRA patients (0.64 ± 0.38; 0.16–2.1) and controls (0.5 ± 0.36; 0.15–1.52); p < 0.001 in both. While levels were similar between NRA patients and controls (p = 0.06) (Fig. 1). Non-significant relation was found between urinary

Table 1
Demographic data, clinical characteristics and therapeutic history of systemic lupus erythematosus patients with and without active renal disease.

Parameter mean ± SD/n (%)	All SLE (n = 58)	ALN (n = 31)	NRA (n = 27)	p
Age (years)	31.8 ± 9.1	31.2 ± 9	32.6 ± 9.4	0.58
Female:Male	54:4	28:3	26:1	0.61
Disease duration (years)	6.2 ± 4.8	5.3 ± 4.3	7.2 ± 5.2	0.14
Constitutional	58 (100)	31 (100)	27 (100)	–
Musculoskeletal	54 (93.1)	27 (87.1)	27 (100)	0.12
Mucocutaneous	55 (94.8)	29 (93.5)	26 (96.3)	1
Vascular	15 (25.9)	9 (29)	6 (22.2)	0.44
Serositis	13 (22.4)	7 (22.6)	6 (22.2)	0.97
Neuropsychiatric	32 (55.2)	15 (48.4)	17 (63.0)	0.53
Ocular	18 (31)	7 (22.6)	11 (40.7)	0.14
Nephritis	41 (70.7)	31 (100)	10 (37)	**<0.001**
Medications				
Methotrexate	13 (22.4)	5 (16.1)	8 (29.6)	0.22
Leflunomide	2 (3.4)	1 (3.2)	1 (3.7)	0.92
HCQ	58 (100)	31 (100)	27 (100)	–
Azathioprine	32 (55.2)	16 (51.6)	16 (59.3)	0.56
CYC	24 (41.4)	12 (38.7)	12 (44.4)	0.66
MMF	11 (19)	5 (16.1)	6 (22.2)	0.55
Steroids	53 (91.4)	29 (93.5)	24 (88.9)	0.66
SLEDAI total	15.2 ± 9.5	18.1 ± 8.7	12 ± 9.6	**0.004**
renal	4.5 ± 4.7	8.3 ± 3.3	–	–
extra-renal	10.8 ± 8.9	9.8 ± 1.7	11.9 ± 3.9	0.34
SLICC/DI	3.9 ± 1.8	3.9 ± 1.9	4 ± 1.7	0.63

SLE: systemic lupus erythematosus, ALN: active lupus nephritis, NRA: no-renal activity, HCQ: hydroxychloroquine, CYC: cyclophosphamide, MMF: mycophenolatemofetil, SLEDAI: SLE disease activity index, SLICC DI: systemic lupus international collaborating clinics damage index. Bold values are significant at $p < 0.05$.

Table 2
Laboratory investigations of systemic lupus erythematosus patients with and without active renal disease.

Parameter mean ± SD/n (%)	All SLE (n = 58)	ALN (n = 31)	NRA (n = 27)	p
WBCs ($\times 10^3$/ul)	6.2 ± 0.4	6.8 ± 0.06	5.6 ± 0.5	0.14
Hb (g/dl)	11.1 ± 2.1	11 ± 2.1	11.2 ± 2.1	0.74
Platelets ($\times 10^3$/ul)	288.9 ± 106	281.7 ± 94.6	297.4 ± 120.8	0.58
ESR (mm/1st h)	65.3 ± 4.5	66.3 ± 6.5	64.2 ± 7.6	0.84
BUN (mmol/L)	5.4 ± 3	6.1 ± 3.3	4.7 ± 2.5	**0.03**
Serum Cr. (umol/l)	67.8 ± 27.8	76.45 ± 32.8	58.2 ± 16.8	**0.01**
Serum albumin (g/L)	38 ± 6.7	36 ± 6.8	39 ± 9.2	**0.002**
AST (U/L)	29.9 ± 4.4	33.4 ± 8.5	26.1 ± 2.5	0.34
ALT (U/L)	22.2 ± 2.6	24.6 ± 4.6	19.4 ± 2.4	0.51
CPK (U/L)	76.3 ± 6.6	67.7 ± 9.8	86 ± 9.2	**0.01**
LDH (U/L)	235.7 ± 83.5	220.6 ± 81.7	253 ± 83.7	0.09
Proteinuria (g/24 h)	0.91 ± 0.09	1.5 ± 0.3	0.2 ± 0.02	**<0.001**
Cr. Cl. (mL/min)	92.3 ± 5.7	86.9 ± 8.2	98.4 ± 7.1	0.19
Ur. Cr. (mg/dl)	99.4 ± 10.7	51.8 ± 8.1	153.9 ± 15.3	**<0.001**
+ve ANA	40 (69)	22 (71)	18 (66.7)	0.78
+ve anti ds-DNA	18 (31)	14 (45.2)	4 (14.8)	**0.02**
C3(g/L)	1.2 ± 0.4	1.1 ± 0.4	1.3 ± 0.3	0.11
Low C3	13 (22.4)	9 (29)	4 (14.8)	0.23
C4 (g/L)	0.2 ± 0.09	0.2 ± 0.1	0.2 ± 0.08	0.62
Low C4	6 (10.3)	4 (12.9)	2 (7.4)	0.68

SLE: systemic lupus erythematosus, ALN: active lupus nephritis, NRA: no-renal activity, WBCs: white blood cells, RBCs: red blood cells, ESR: erythrocyte sedimentation rate, BUN: blood urea nitrogen, Cr.: creatinine, AST: aspartate amino transaminase, ALT: alanine amino transaminase, CPK: creatine phosphokinase, LDH: lactate dehydrogenase, Cr.Cl.: creatinine clearance, Ur. Cr.: urinary creatinine, ANA: antinuclear antibodies, Anti-dsDNA antibody: anti-double stranded deoxyribonucleic acid antibody, C: complement. Bold values are significant at $p < 0.05$.

Table 3
Association of normalized urinary sCD163 levels with pathological classification of renal biopsy inactive lupus nephritis patients.

Renal biopsy LN class in 21 ALN patients	Urinary sCD163 mean ± SD (range)	p
MPGN class II (n = 3)	0.86 ± 0.37 (0.42–1.59)	0.77
FPGN class IIIA (n = 2)	1.35 ± 0.65 (0.7–2)	
DPGN class IV (n = 13)	2.08 ± 0.44 (0.44–5.21)	
MGN class V (n = 3)	2.07 ± 1.4 (0.53–4.86)	

LN: lupus nephritis, ALN: active LN, MPGN: mesangeoproliferative glomerulonephritis, FPGN: focal proliferative GN, DPGN: diffuse proliferative GN, MGN: membranous GN.

sCD163 level and different clinical characteristics of patients throughout the disease course except with LN. Urinary sCD163 was significantly higher in patients with LN (2.3 ± 2.4; 0.2–11.2) than those without (0.7 ± 0.4; 0.2–2.1) (p < 0.001). The level was significantly higher in those with positive anti ds-DNA (2.26 ± 0. 48) than those negative (1.66 ± 0.35; p = 0.03). Non-significant relations were found between urinary sCD163 levels with the consumed complement or receiving any medications.

Correlations of urinary sCD163 with some demographic, clinical, laboratory and pathological variables among SLE patients presented in Table 4. The diagnostic ability of urinary sCD163 for differentiation between patients with ALN and NRA is presented

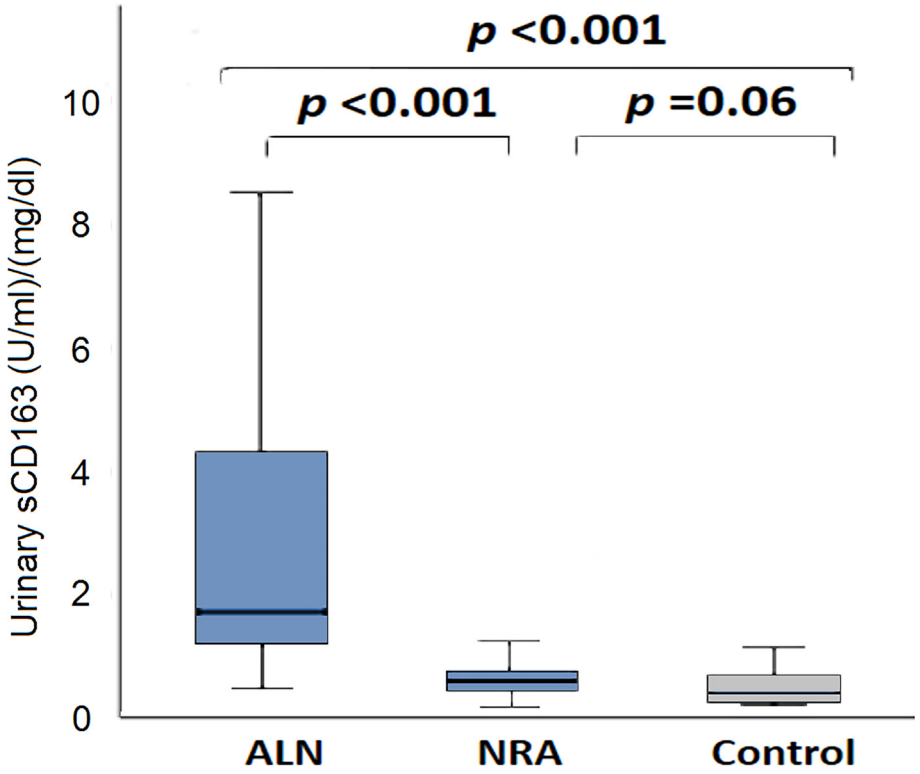

Fig. 1. Box plot for normalized urinary sCD163 levels in systemic lupus erythematosus patients and controls. ALN: active lupus nephritis, NRA: no-renal activity.

in Fig. 2. The optimum cut-off value for urinary sCD136 to predict renal activity was >0.82 with sensitivity 90.3%, specificity 88.89%, positive predictive value (PPV) 90.35%, negative predictive value (NPV) 88.9%, area under the curve (AUC) 0.93, 95% confidence interval (CI) (0.83–0.98), p < 0.001. At the same value, it can differentiate patients from controls with sensitivity 53.43%, specificity 80.41%, PPV 83.43%, NPV 47.14%, AUC 0.81, 95% CI (0.71–0.88), p = 0.048.

Multivariate linear regression revealed that renal SLEDAI (ß = 0.12, p = 0.04, CI = 0.006–0.231), proteinuria/24 hr (ß = 0.296, p = 0.01, CI = 0–0.001) and decrease in urinary creatinine (ß = −0.26, p = 0.04, CI = −0.014–0.00) were significant predictors of increase in urinary sCD163 level among SLE patients.

Table 4
Correlations of urinary sCD163 with some demographic, clinical, laboratory and pathological variables among systemic lupus erythematosus patients.

Variable r (p)	Urinary sCD163 in SLE patients	
Age	0.08	(0.49)
Disease duration	0.07	(0.58)
SLEDAI total	0.54	**(<0.001)**
renal	0.7	**(<0.001)**
extra-renal	0.16	(0.22)
SLICC DI	0.08	(0.52)
Serum albumin	−0.46	**(<0.001)**
BUN	0.17	(0.21)
Serum creatinine	0.15	(0.25)
Proteinuria	0.51	**(<0.001)**
Urinary creatinine	−0.97	**(<0.001)**
C3	0.21	(0.11)
C4	0.13	(0.33)
Activity Index	0.46	**(0.038)**
Chronicity Index	0.03	(0.37)

SLE: systemic lupus erythematosus, SLEDAI: SLE disease activity index, SLICC DI: systemic lupus international collaborating clinics damage index, BUN: blood urea nitrogen, C: complement. Bold values are significant at $p < 0.05$.

4. Discussion

Lupus nephritis (LN) is a common and serious manifestation of SLE which associated with high morbidity and mortality [21]. For proper management of LN, it is important to recognize active nephritis from chronic kidney damage as both of them often manifest as proteinuria and impaired kidney function. Moreover, clinical and histologic findings are frequently inconsistent [22,23]. Currently used noninvasive biomarkers have insufficient sensitivity and specificity for detection of active renal inflammation [24]. Thus, search to recognize specific markers that can identify patients with active LN and predict its synchronous underlying pathology could be helpful method in guiding the management of LN. Serum biomarkers that reflect systemic activity may not be specific for nephritis. Therefore, the focus has recently shifted in various Egyptian studies with promising results for identifying new urinary biomarkers as it is noticeable that cells and micro particles are shed in urine during inflammation [25–27].

Macrophages comprise the largest number of cells in the urinary sediment which is a valuable information in terms of LN pathogenesis [7]. They have been implicated in LN pathogenesis with the spectrum of phenotypes activation ranging from classically activated inflammatory M1 to alternatively activated M2 macrophages [28,29]. CD163 has been known as a marker of M2 macrophages, especially M2c [13]. Soluble CD163 derives from the cleavage of the CD163 M2c macrophage receptor [30]. Several studies have shown that the macrophage infiltrate in LN kidneys is predominantly composed of CD163 cells [7,13–15]. Renal biopsy findings on LN patients that showed infiltration of CD163+ macrophages in tubulointerstitial and glomerular lesions supports their pathogenic role [12,31].

In this study, the urinary sCD163 level was significantly higher in active LN than no-renal activity patients and controls. This is consistent with findings of other studies who observed that uri-

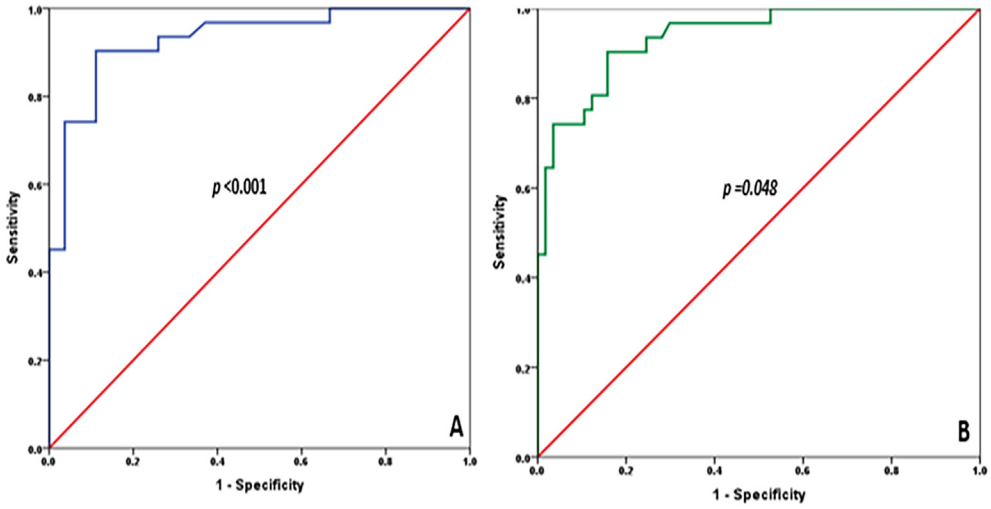

Fig. 2. Receiver operating characteristic (ROC) curves for prediction active lupus nephritis (A) and systemic lupus erythematosus (B) by normalized urinary sCD163 level.

nary sCD163 was significantly higher in active nephritis patients as compared with inactive disease, active non-renal disease and controls [5,32]. In the same context, another study found that urinary sCD163 levels were significantly higher in patients with active LN than controls, patients with in active SLE and patients with active extra-renal SLE [33].These observations suggest that, in LN, there is local activation of M2 macrophages in the kidneys leading to sCD163 production by proteolysis that is reflected in the urine. This may suggest a role for M2 macrophages in LN pathogenesis [12,31].

In this work, the diagnostic ability urinary sCD163 for differentiation between patients with active LN than no-renal activity patients showed that the optimum cut-off value which normalized urinary sCD136 can significantly predict renal activity was >0.82 (U/ml/mg/dl) with sensitivity of 90.3%, specificity of 88.89%. At the same cut-off value, urinary sCD136 can significantly differentiate SLE patients than controls but with less sensitivity (53.4%) and specificity (80.41%). These findings were compatible with *Gupta and his colleagues* study which found urinary sCD163 differentiate between active nephritis and active non renal [5] and with *Mejia-Vilet et al.* work which reported urinary sCD163 at a cutoff >130 ng/mmol had 97% sensitivity and 94% specificity to distinguish between patients with active and inactive LN [33]. The role of macrophages as well as CD163 cells in LN has not been fully explained. In several mouse LN models, systemic depletion of macrophages or inhibition of macrophage recruitment improved nephritis [29], while in others, depletion of macrophages slowed resolution and promoted fibrosis [34,35]. M2c macrophages are considered to have remodeling or anti-inflammatory roles [7]. Polarization of macrophages to a M2c-like phenotype is essential for efficient clearance of apoptotic cells, which when defective participate in SLE initiation and immortalization [36,37]. However, the increased infiltration of CD163 macrophages in active crescents, proliferative LN and acute tubulointerstitial lesions, it has also suggested that CD163 macrophages are involved in progression of kidney injury [31].

This study revealed that urinary sCD163 had significant correlations with total and renal SLEDAI scores but not with extrarenal SLEDAI, which suggests that urinary sCD163 level in SLE patients is not a marker of systemic inflammation but specifically represents the renal inflammation. This is consistent with findings of other studies that showed significant correlations of sCD163 with total and renal SLEDAI [5,32]. M2 macrophages predominance which are "anti-inflammatory" and pro-fibrotic in nature on renal biopsies in LN makes a questionable issue about their role in an "inflammatory" active LN [37]. This can be explained by the pro-inflammatory subtypes of macrophages are the early players (subclinical phase of LN) in LN pathogenesis which set the stage for the adaptive immune system to take over the inflammation and perpetuate the damage. Later, these are replaced by anti-inflammatory subtypes of macrophages by the time the clinical disease sets in. Another explanation could be that the drugs used in LN treatment are known to increase the CD163 expression and thereby M2 phenotype in macrophages [7].

In this work, urinary sCD163 had significant correlation with 24-hour protein in urine and significant negative correlation with urinary creatinine. This is in agreement with the study of *Gupta and his colleagues* that demonstrated correlation of urinary sCD163 with proteinuria [5] and with *Zhang et al* study that found urinary sCD163 significantly correlated with urine protein to creatinine ratio [32].

This study revealed that urinary sCD163 was significantly higher in patients with positive anti ds-DNA antibodies than those with negative results which is compatible with the work of *Zhang and his co-workers* that found significant correlation between urinary sCD163 and anti ds-DNA [32]. In this work, no significant correlation was found between urinary sCD163 and serum C3 unlike the study of *Zhang et al.* which observed that urinary sCD163 correlated with C3 [32]. This may be explained by the number of patients in this study who had positive anti ds-DNA antibodies was significantly higher in patients with active LN than no-renal activity SLE patients.

Urinary CD163 behaves as a histologic biomarker that correlates with the number of CD163 cells infiltrating the glomeruli. This correlation may allow urinary CD163 to differentiate between LN histologic classes with a high degree of macrophage infiltration and less inflammatory classes [33]. Among active LN patients of this study who had performed renal biopsy, the level of urinary sCD163 varied by pathological class of LN, but this variation was not significant. This finding is consistent with *Gupta et al* study that revealed urinary sCD163 values were not different in patients with proliferative LN as compared with memberanous nephropathy among the patients of active nephritis group [5]. At variance *Zhang and his colleagues* study found that urinary sCD163 was significantly elevated in patients with proliferative LN, especially in class IV LN [32]. In this work, urinary sCD163 had significant correlation with activity index of renal biopsy but not with chronicity index.

These findings were compatible with those of other studies [12,32,33].

CD163 expression on macrophages has been described to be influenced by many medications including glucocorticoids, mycophenolate mofetil, rituximab and cyclophosphamide [7,38–40]. This work revealed that urinary sCD163 levels hadn't significant relation with the use of steroids or any type of medication received. This finding was harmonic with the study of *Zhang and co-workers* [32]. Thus, the elevation in urinary sCD163 in active LN patients could not be attributed to medications.

This study is limited by a relatively small sample size and its cross sectional design. Longitudinal studies with larger sample size are required to assess if urinary sCD163 can predict renal flares and to analyze treatment effects on its level.

In conclusion, urinary sCD163 is a potential marker of renal disease activity in SLE patients. It can differentiate between patients with active LN and no-renal activity patients. Its level is associated with SLE clinical features, conventional laboratory investigations and pathological indices that indicate renal disease activity. Thus, it is a promising marker for lupus nephritis activity.

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CRediT authorship contribution statement

Nada M. Gamal: Conceptualization the research idea, Methodology, Data curation, Software, Writing, Reviewing, Editing and Revision of the manuscript. **Eman R. Badawy:** Conceptualization the research idea, Methodology and Laboratory investigations. **Esraa A Talaat:** Conceptualization the research idea, Methodology, Data curation and Software. **Hamdy M. Ibrahim:** Conceptualization the research idea, Radiological investigations. **Mona H. Abd Elsamea:** Conceptualization the research idea, Methodology, Writing the original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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