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ORIGINAL STUDY

Role of Monocyte Chemoattractant Protein-1 in Assessment and Diagnosis of Lupus Nephritis in Children

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Abstract

Objectives: **To investigate the value of urinary monocyte chemoattractant protein-1 (MCP-1) as a biomarker for lupus nephritis (LN) activity.**

Background: **There is a correlation between LN and increased mortality and morbidity rates, and it is more common and severe in pediatric patients.**

Patients and methods: **A case−controlled study was carried out involving 30 patients with systemic lupus erythematosus (SLE) who met the 2012 revised classification criteria, along with 30 healthy controls matched for age and sex. Both groups underwent a comprehensive assessment, including detailed medical history, clinical exams, routine laboratory tests, MCP-1 level measurement, and, for patients with active LN, renal biopsy.**

Results: **Comparing SLE patients with active LN to those without or with inactive renal disease, as well as to healthy individuals, revealed substantially higher levels of MCP-1.**

Conclusion: **Measuring MCP-1 in urine appears to be a helpful noninvasive urine biomarker for identifying the degree of renal involvement in SLE. For children with SLE, checking urinary MCP-1 levels can help evaluate disease activity and assess kidney involvement.**

Keywords: Lupus nephritis, Monocyte chemoattractant protein-1, Systemic lupus erythematosus, Urinary

1. Introduction

Systemic lupus erythematosus (SLE) is a long-term autoimmune disorder. It is characterized by heterogeneity, multiple organ system involvement, autoantibody production, and unknown etiology. Up to 60% of patients experience kidney problems, with monocyte chemoattractant protein-1 (MCP-1) being a key indicator of both complications and overall risk. Early diagnosis is vital to prevent the increased kidney failure risk and chronic disease of end-stage kidney that can arise from delayed treatment [1].

Lupus nephritis (LN) is an SLE serious manifestation marked by immune complexes deposition either beneath the endothelial or epithelial layers of the kidney. If not treated, LN can lead to significant acute kidney injury, loss of nephrons, and long-term, irreversible damage that impairs kidney function. The prevalence of LN ranges from 35 to 60%, relying on factors like the age of the patient at onset, ethnicity, and sex [2].

Twenty percent of LN patients still have a chance of developing end-stage renal disease during their illness first decade, even though the frequency has dropped over the past several decades. Predicting

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the long-term renal prognosis at an early stage of the disease is therefore crucial. To enhance patient monitoring and treatment, several studies have focused on identifying early clinical signs, laboratory tests, and molecular pathways linked to poor renal prognosis. Managing LN involves two main objectives: short-term goals of preventing flare-ups and long-term goals of preserving kidney function. Recent research highlights the importance of identifying two molecular markers related to disease activity, damage, treatment response, and renal prognosis, in addition to traditional clinical and histological indicators [3].

Numerous urine indicators in LN patients have already been identified and studied. Their levels can be raised by inflammatory, fibrotic, or renal ischemia urine sediment gene expression biomarkers, among other conditions. They are frequently not exclusive to SLE but rather represent cellular activities that range at the level of the glomerulus or tubules [4].

An essential component of inflammatory reactions is MCP-1, a class of chemokines produced by white blood cells. Blocking MCP-1 has been demonstrated to reduce kidney damage in LN animal models. LN activity was correlated with urinary MCP-1 in several single-center trials, and treatment nonresponders had consistently high urinary MCP-1 levels [5].

Our study aimed to investigate the value of urinary MCP-1 as LN activity biomarker.

2. Patients and methods

This case−control study was carried out on 60 children divided into two groups:

Patient group (group 1): consisted of 30 patients diagnosed with SLE recruited from pediatric nephrology outpatient clinics and Pediatric Department inpatient wards. This group is further subdivided into patients who had LN (group 1a) and patients without LN (group 1b).

Control group (group 2) consisted of 30 healthy age and sex matched controls.

Written informative consents were taken from the parents or guardians of children during a period between January 2022 and to end of January 2024; in addition to, accepted by the Committee of Human Rights in Research at Menoufia University was obtained from every participant before the initiation of study − record no.1/2022 pedi42.

2.1. Inclusion criteria

SLE was diagnosed in patients related to the standards established by the Systemic Lupus International Collaborating Clinics (SLICC) [6]. Red blood cell casts present in the patient's urine, a ratio of urine protein-to-creatinine of 0.5 or higher, or a 24-h urinary protein level of 500 mg or more were the criteria that were used to identify persons with LN. The patients' ages ranged from 6 to 18 at the time of diagnosis.

2.2. Exclusion criteria

Patients with systemic autoimmune diseases causing proteinuria other than SLE. Patients who were suffering from diseases causing palate, buccal, tongue, or nasal ulcers such as vasculitis and Behçet's disease.

2.3. Methodology

All patients and controls were subjected to the following:

Full detailed history taking including sex and age. Onset of symptoms, course, duration. History of red urine. History of any previous skin rashes, ulcers, or oral ulcers. Having a history of two or more joints being swollen or tenderness and stiffness for at least 30 min first thing in the morning. Previous hospital admission. Family history.

Detailed clinical examination for each patient, including:

General examination includes anthropometric measurement (weight/kg − height/cm). Vital signs (blood pressure/mmHg − temperature/degree − heart rate/min). Skin examination for different types of rashes. Mouth, tongue, and nasal examination. Joint examination.

2.3.1. Systemic examination, including chest examination

Inspection (scar, veins, etc.), palpation (tenderness), auscultation (type of breathing, adventitious sounds). Cardiac examination: inspection and palpation (bulge and scar), auscultation (normal heart sounds, murmurs). Abdominal, including genital examinations. Neurological examination with emphasis on psychosis and seizures.

Laboratory investigations of LN including complete blood count [hemoglobin (g/dl), platelet count (10^3), total leukocytic count (10^3), 24-h urinary proteins]. Blood urea ($N = 20$−40 mg/dl), serum creatinine ($N = 0.2$−0.7 mg/dl), and complete urine analysis.

2.3.2. Investigations to confirm systemic lupus erythematosus

Antibodies of antinuclear (ANA level), anti-dsDNA antibody level, antiphospholipid antibodies, levels of C3, C4.

Urinary markers of MCP-1.

2.4. Sample collection and storage

Urine samples were collected using sterile pee tubes. Using centrifugation for 10 min, the particles were extracted. The temperature of the samples was −20 °C. Minimize the use of freeze−thaw cycles.

2.5. Assay procedure

It is advisable to place all standards and samples in triplicate on the micro ELISA strip plate. Prior to the commencement of the test, 50 μl of the standard solution was introduced into the designated wells for the standard. Preparation of all reagents was completed. Prior to adding 40 μl of sample diluent, the testing sample wells were filled with 10 μl of the sample. After that, each well was supplemented with 100 μl of HRP-conjugate reagent. Incubation at 37 °C for 60 min followed the placement of an adhesive strip to the plate. Afterward, we used the automatic washer to suction and wash each well five times, each time with 400 μl of wash solution. To achieve maximum efficiency, ensure that all fluids are fully removed at every stage. After finishing the last wash, we inverted the plate and used new paper towels to dry it thoroughly, ensuring the removal of any residual liquid.

Each well was then treated independently with 50 μl of chromogen solution A and 50 μl of chromogen solution B. After being shielded from light, the plates were placed in an incubator set at 37 °C for 15−30 min. Careful mixing of the materials was carried out. With the change from blue to yellow hue occurring during incubation, 50 μl of Stop solution was administered to each well. The optical density was measured at 450 nm using a microtiter plate reader within 15 min of the experiment starting.

2.5.1. Calculation of result

Standard curves are useful for determining the concentration of unknown samples; they are made by graphing the average optical densities at 450 nm for six standard concentrations on the Y-axis and the corresponding concentrations on the X-axis. The test can detect concentrations between 2.5 and 100 ng/ml, with 0.5 ng/ml sensitivity.

2.6. Statistical analysis

Software for Social Science Statistics (IBM Corp., 2017). This data was reviewed, coded, and organized using IBM Corp., Armonk, New York, USA.

Two types of statistics were done:

Descriptive statistics is comprised of the following examinations: the quantitative data was shown as the mean ± SD for descriptive statistics, while the qualitative data was shown as frequency and percentage. When all the observations are added together and then partitioned by the observation's total number, the resulting average is called the mean. One way to look at the dispersion of individual values from the mean is by calculating their SD.

Analytical statistics includes the following test: χ^2 test: this test is employed to compare the distribution of a single qualitative variable across two or more groups. Student's t test: this test was used to compare two groups with respect to normally distributed (parametric) quantitative data. Mann−Whitney U test: this nonparametric test serves as an alternative to the Student's t test. It is used to determine if there are substantial differences among two groups for a quantitative variable that is not normally distributed. One-way analysis of variance (F): this test is used to assess whether there are substantial differences among several groups with respect to a normally distributed quantitative variable. It evaluates the overall variance between the groups in a single analysis. Kruskal−Wallis test (K): this nonparametric test serves as an alternative to analysis of variance. It is used to determine if there are significant differences among several groups for a quantitative variable that is not normally distributed. Pearson correlation: this test was used to measure the relationship between two continuous variables that are normally distributed. The receiver operating characteristic curves: this procedure assesses the effectiveness of classification systems based on a variable with two categories used to categorize subjects. It involves constructing performance measures by calculating the sensitivities and specificities of the variable.

3. Results

As regards demographic data, we found that females were the most frequent among patients (83.3%) and controls (83.3%), their ages from 10 to 18 years. No significant difference among the groups of study regarding age and sex (Table 1).

Our study found that 24 h urinary protein and serum urea and creatinine were significantly higher among patients than control ($P < 0.001$). While C3 level and C4 level were significantly lower among patients than control ($P < 0.001$). As well as, hemoglobin, total leukocyte count, and platelet count

Table 1. Demographic data among patients and control groups.

Demographic data	Patients ($N = 30$) [n (%)]	Control ($N = 30$) [n (%)]	Test of significance	P value
Sex				
Male	5 (16.7)	5 (16.7)	$\chi^2 = 0.000$	1.000
Female	25 (83.3)	25 (83.3)		
Age (years)				
Minimum–maximum	10.00–18.00	10.00–17.00	$t = 1.323$	0.191
Mean ± SD	13.57 ± 2.42	12.80 ± 2.06		
Median (IQR)	13.00 (12.0–16.0)	13.0 (11.0–15.0)		

χ^2, χ^2 test; IQR, interquartile range; t, Student t test.

were significantly lower among patients than control ($P < 0.05$) (Table 2).

In our study, we found that urinary MCP-1 was significantly higher among the patients' group (29.10 ± 2.15 ng/dl) than control (25.53 ± 0.98 ng/dl) (Fig. 1).

In addition, we reported that urinary MCP-1 in patients with renal involvement (30.53 ± 2.01 ng/dl), especially those with renal involvement class 4 (32.27 ± 1.29 ng/dl) was significantly higher than those with renal involvement class 3 (30.68 ± 1.76 ng/dl), than patients without renal involvement (27.67 ± 1.09 ng/dl) (Table 3).

In evaluating the diagnostic performance of urinary MCP-1 for detecting renal involvement (LN) in patients, our study found that a cutoff level of more than 28.12 ng/ml was indicative of renal involvement. At this level, the urine MCP-1 showed a sensitivity of 86.67% and a specificity of 80.0%, with an area under the curve (AUC) of 0.891 (Fig. 2).

In examining the association between urinary MCP-1 and various parameters in patient groups, we noticed a substantial positive association between urinary MCP-1 and 24-h urinary protein as well as creatinine levels. However, no substantial

Table 2. Laboratory investigations among the two studied groups.

	Patients ($N = 30$)	Control ($N = 30$)	Test of significance	P value
24 h urinary protein (g/24 h)				
Minimum–maximum	0.0–6.30	0.0–0.15	$t = 5.412$*	<0.001*
Mean ± SD	1.71 ± 1.67	0.05 ± 0.06		
Median (IQR)	1.10 (0.30–3.0)	0.0 (0.0–0.10)		
Creatinine (mg/dl)				
Minimum–maximum	0.40–1.60	0.40–0.80	$U = 159.000$*	<0.001*
Mean ± SD	0.96 ± 0.32	0.62 ± 0.12		
Median (IQR)	0.96 (0.70–1.10)	0.60 (0.50–0.70)		
Urea (mg/dl)				
Minimum–maximum	20.0–65.0	15.0–35.0	$t = 8.167$*	<0.001*
Mean ± SD	44.40 ± 12.38	24.07 ± 5.72		
Median (IQR)	45.0 (40.0–55.0)	25.0 (20.0–30.0)		
C3 level (mg/dl)				
Minimum–maximum	20.0–177.4	78.0–170.0	$U = 104.500$*	<0.001*
Mean ± SD	53.55 ± 40.28	110.6 ± 22.02		
Median (IQR)	36.0 (25.0–70.0)	107.5 (95.0–120.0)		
C4 level (mg/dl)				
Minimum–maximum	3.0–94.90	15.0–35.0	$U = 97.000$*	<0.001*
Mean ± SD	12.26 ± 17.18	23.70 ± 5.58		
Median (IQR)	7.80 (6.50–10.0)	24.50 (18.0–28.0)		
Hemoglobin (g/dl)				
Minimum–maximum	5.50–15.0	10.80–15.20	$t = 5.780$*	<0.001*
Mean ± SD	10.45 ± 2.10	13.01 ± 1.22		
Median (IQR)	10.75 (9.0–12.0)	13.0 (12.0–14.0)		
Total leukocytic count (10^3/Ul)				
Minimum–maximum	1.07–13.70	10.0–20.0	$t = 9.149$*	<0.001*
Mean ± SD	6.45 ± 3.04	12.81 ± 2.29		
Median (IQR)	6.0 (5.0–7.90)	12.80 (11.0–14.0)		
Platelet (10^3/Ul)				
Minimum–maximum	35.0–402.0	27.0–510.0	$t = 2.575$*	0.013*
Mean ± SD	215.7 ± 86.92	275.1 ± 91.88		
Median (IQR)	234.0 (158.0–255.0)	275.5 (220.0–312.0)		

IQR, interquartile range; t, Student t test; U, Mann–Whitney test.
*Statistically significant at P value less than or equal to 0.05.

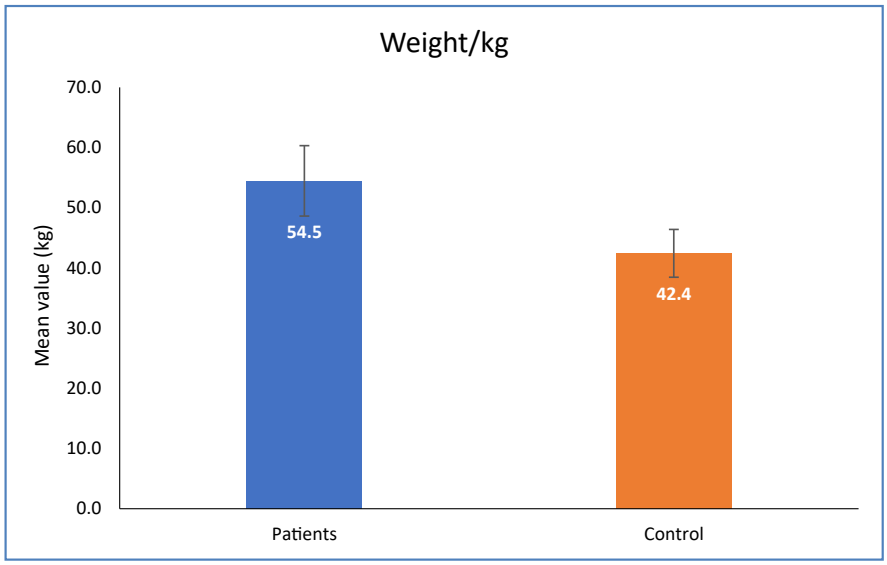

Fig. 1. Urinary MCP-1 distribution among the studied groups. MCP-1, monocyte chemoattractant protein-1.

Table 3. Relation between renal involvement and urinary monocyte chemoattractant protein-1 and urinary monocyte chemoattractant protein-1 (ng/ml) among different classes in different biopsy.

Relation between renal involvement and urinary MCP-1					
	Renal involvement (lupus nephritis)			*t*	*P* value
	No (*N* = 15)	Yes (*N* = 15)			
Urinary MCP-1 (ng/ml)					
Mean ± SD	27.67 ± 1.09	30.53 ± 2.01		4.840*	<0.001*
Median (minimum–maximum)	27.50 (26.20–29.80)	30.62 (26.70–33.99)			
Urinary MCP-1 (ng/ml) among the different classes in different biopsy					
	Renal involvement			*F*	*P* value
	Class 2 (*N* = 4)	Class 3 (*N* = 7)	Class 4 (*N* = 4)		
Urinary MCP-1 (ng/ml)					
Mean ± SD	28.53 ± 1.25	30.68 ± 1.76	32.27 ± 1.29	5.988*	0.016*
Median (minimum–maximum)	28.96 (26.70–29.50)	30.62 (27.92–33.79)	31.95 (31.18–33.99)		

F, *F* for one-way analysis of variance test; MCP-1, monocyte chemoattractant protein-1; *t*, Student *t* test.
*Statistically significant at *P* value less than or equal to 0.05.

association between urinary MCP-1 and the levels of C4 and C3 was found (Table 4).

The results of our study revealed a notable and favorable association between the levels of MCP-1 in urine and the activity index. However, there was no notable association found between urine MCP-1 and the chronicity index (Table 5).

4. Discussion

SLE, an autoimmune illness, has the potential to impact all organs in the body. About 75% of individuals develop renal involvement that is clinically evident; most of the other patients, however, have subclinical illness that would be detectable with renal biopsy. Periodic urine analyses and glomerular filtration rate estimation are useful tools for early detection of renal involvement, which typically appears in the initial years of illness [7].

Since LN contributes significantly to mortality and morbidity in SLE patients, it is essential to find noninvasive and reliable techniques for routinely evaluating kidney health in these individuals [8].

In the present study, among patients, 15 (50.0%) had renal involvement; the most common was class 3 was found in seven (46.7%), then class 2 and class 4 found in four (26.7%).

Similar to our study, Kim et al. [9], in which a study was done on 104 control and 80 SLE patients, reported that clinical evidence of renal involvement is present in 40–85% of SLE patients. This finding is smaller compared to the study by Gigante et al. [10],

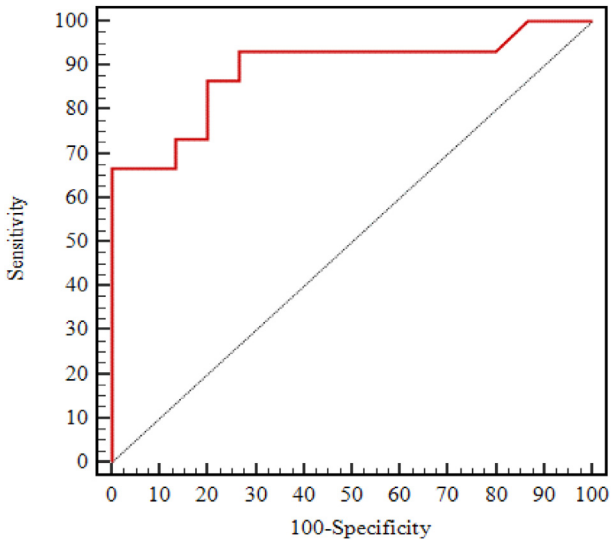

Fig. 2. ROC curve for Urinary MCP-1 to defect renal involvement (lupus nephritis) patients. MCP-1, monocyte chemoattractant protein-1; ROC, receiver operating characteristic.

Table 4. Correlation between urinary monocyte chemoattractant protein-1 and different parameters in patients' group (N = 30).

	Urinary MCP-1 (ng/ml)	
	r	*P* value
24 h urinary protein (g/24 h)	0.564	0.001*
Creatinine (mg/dl)	0.417	0.022*
C4 level (mg/dl)	0.166	0.381
C3 level (mg/dl)	0.163	0.389

MCP-1, monocyte chemoattractant protein-1; *r*, Pearson coefficient.
*Statistically significant at *P* value less than or equal to 0.05.

Table 5. Correlation between urinary monocyte chemoattractant protein-1 with activity index and chronicity index in patients' group (N = 11).

	Urinary MCP-1 (ng/ml)	
	r	*P* value
Activity index	0.666	0.025*
Chronicity index	−0.284	0.398

MCP-1, monocyte chemoattractant protein-1; *r*, Pearson coefficient.
*Statistically significant at *P* value less than or equal to 0.05.

who reported renal involvement in ~60% of their patients. Similarly, Sinico et al. [11] observed that 50% of 60 patients had LN.

Also, Ramadan et al. [12] discovered that 80% of SLE patients had renal involvement, as evaluated both clinically and histopathologically. This greater rate may be explained by the fact that renal biopsy findings are used to diagnose LN.

Another study by Mahajan et al. [13] observed that class 4 nephritis, also known as diffuse proliferative glomerulonephritis, was the most often reported categorization of LN. Conversely, cases of nephritis in class 1 and class 6 were the least commonly recorded.

Our study found that urinary MCP-1 was substantially higher among the patients' group (29.10 ± 2.15 ng/dl) than control (25.53 ± 0.98 ng/dl) in addition to urinary MCP-1 was significantly higher among patients having renal involvement (30.53 ± 2.01 ng/dl) than patients without renal involvement (27.67 ± 1.09 ng/dl).

In the same line, Wada et al. [14], who studied 31 patients with SLE who were diagnosed as having silent LN, showed that urine MCP-1 in patients with LN was significantly higher than in patient without LN. Also, Tucci et al. [15] investigated how a functional MCP-1 polymorphism affects LN and SLE. They demonstrated that patients with LN had considerably higher U MCP-1 values. Additionally, Rovin et al. [16] discovered that the mean urinary MCP-1 values in renal flares were notably greater than those in nonrenal flares. Additionally, when compared to a control group of healthy volunteers and other renal involvement causes, these levels were greater.

Another study by Ramadan et al. [12] revealed that while there was no significant difference in urine MCP-1 levels between the control group and those without LN, there was a substantial increase in these levels in their SLE patients and nephritis patients compared to the controls. This suggests the presence of LN in patients was the main cause of the difference between all SLE patients and controls.

In the same line, Singh et al. [17] found that urine MCP-1 successfully distinguished between patients with active LN, inactive renal disease, and stable SLE in a 20 patients longitudinal study.

Also, Alharazy et al. [18] revealed that levels of urine MCP-1 were considerably greater in individuals with active LN compared to those with inactive kidney disease. Furthermore, urinary MCP-1 levels were higher in individuals with active renal illness, according to recent research by Watson et al. [19] on LN patients with juvenile-onset of SLE.

Consistent with our study, Marks et al. [20] found that LN patients had much greater MCP-1 levels in their urine than healthy controls. Patients with LN also had significantly higher levels of urinary MCP-1 than children without LN.

Additionally, Rosa et al. [21] discovered that the group suffering from active LN exhibited noticeably high levels of urinary MCP-1.

Our study revealed that renal involvement may be detected when the urine MCP-1 level exceeds 28.12 ng/ml. This indicator was able to acquire an

AUC of 0.891, with a sensitivity of 86.67% and specificity of 80.0%.

In this concern, Taha et al. [22] reported that MCP-1 in urine had a specificity of 100%, a sensitivity of 97%, and an AUC of 0.99 for identifying active LN. Therefore, LN activity was identified with great sensitivity and specificity by urine MCP-1. Alharazy et al. [18] stated that the receiver operating characteristic curve for urinary MCP-1 outperformed serum C3, C4, anti-ds DNA Ab titer, and common biochemical indicators, indicating that it had a favorable diagnostic profile for early diagnosis of LN activity.

Partially with our study, Mirfeizi et al. [7] published the results showing that urinary MCP-1 showed a high degree of sensitivity in predicting LN in adult patients but a poor degree of specificity. Since urinary MCP-1 levels might rise in response to ischemia or toxic lesions in addition to other forms of renal injury, its nonspecificity may restrict its clinical value. Proteinuria in adults can also trigger the production of cytokines like MCP-1 by renal tubular epithelial cells, which can exacerbate proteinuria and chronic kidney disease. Nonetheless, the researchers did not discover any link between urinary MCP-1 and proteinuria.

In the present study, urine MCP-1 positively correlated with 24 h urine protein and creatinine. However it did not significantly correlate with C4 or C3 levels.

In the same line, Alharazy et al. [18] discovered no correlation between levels of urine MCP-1 and serum complement components of the third and fourth (C3, C4) or anti-dsDNA antibody titers. These findings agree with those informed by Watson et al. [19].

In the same concern, Ramadan et al. [12] noticed that levels of urinary MCP-1 correlated negatively with C3. This result was similar to those found by Kiani et al. [23] and Bauer et al. [24].

In the same line, Tucci et al. [15] have informed that there was a positive association among levels of urinary MCP-1 and serum creatinine. These findings were also instructed by Rovin et al. [16] in 89 patients with SLE longitudinal study. In contrast, Watson et al. [19] found no correlation between urine MCP-1 levels and serum creatinine.

In accordance with our study, Tucci et al. [15] found a favorable association between urine MCP-1 and 24-h protein excretion of urine. In another study, Kim et al. [9] found that proteinuria was positively correlated with MCP-1 excretion in the urine. Also, Kim and Tam [25] found that serum creatinine level and degree of proteinuria were linked with urine MCP-1.

In contrast to our study, Dai et al. [26] were unable to discover any association between urine MCP-1 and the level of urine protein excretion in LN patients. Also, Mirfeizi et al. [7] reported that: The mean value of UMCP-1 levels were 733.07 pg/ml ± 1282.54 and 144.16 pg/ml ± 137.90 in patients with and without LN respectively. The UMCP-1 level was significantly higher in group 2 than group 1. There was no significant correlation between UMCP-1 and 24-hour urine protein ($r = 0.031$, $P= 0.874$). The area under the ROC curve was 0.727 with a CI 95% of 0.597 to 0.857 ($P=0.002$). Using a cut-off value of 82 pg/ml, UMCP-1 had a sensitivity of 88.5% and a specificity of 46.3% for identifying LN.

On the other hand, El-Shehaby et al. [27] found an association between levels of urinary MCP-1 and serum complements C3 and C4.

Our study noticed a substantial positive association between urinary MCP-1 and activity index while no substantial association between urinary MCP-1 and chronicity index.

4.1. Limitations of the study

There are many limitations of our study, such as a small sample size of our patients thus, we recommend multicenter trials with longer follow-up periods and bigger samples to evaluate the LN activity of urine MCP-1. Confirmation and validation of our findings are dependent on this larger-scale investigation.

4.2. Conclusion

As a noninvasive urine biomarker, measuring MCP-1 in urine appears to be a helpful way to track the degree of renal involvement in SLE. Urinary MCP-1 measurement can be used to assess renal involvement and disease activity in pediatric SLE patients. Furthermore research is advised to understand MCP-1's function in the monitoring of LN. Urinary protein, urine microscopy, and serum creatinine are the primary methods used for clinical surveillance of LN. In order to diagnose active LN, urine MCP-1 in conjunction with the currently available detection markers and clinical symptoms may be more beneficial.

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Conflict of interest

There are no conflicts of interest.

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