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ORIGINAL ARTICLE

Evaluation of Urinary Monocyte Chemotactic Protein 1 as a Predictive Marker of Steroid Responsiveness in Children with Idiopathic Nephrotic Syndrome

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ABSTRACT

Background: Nephrotic syndrome is a common pediatric kidney condition t. It happens in young children and adolescents. The goal of this research was to investigate the diagnostic value of urinary MCP-1 in pediatric patients with idiopathic nephrotic syndrome. **Methods:** At the pediatric nephrology outpatient clinic and the pediatric nephrology unit, this case-control study was carried out at Zagazig University hospitals on children attending at pediatric inpatient and outpatient clinics. They were divided into three groups: group A, which consisted of 27 nephrotic patients in remission; group B, which consisted of 27 nephrotic patients who were active and experiencing either their first attack or relapses; and group C, which consisted of 27 sex- and age-matched healthy children who were present at a general pediatric clinic. **Results:** There is a statistically significant difference in urinary monocyte chemotactic Protein 1. The best cutoff of urinary monocyte chemotactic protein 1 in the diagnosis of nephrotic syndrome is ≥79 with the area under curve 1, sensitivity 100%, specificity 96.3%, positive predictive value 98.2%, negative predictive value 100%, and overall accuracy 98.8%. The best cutoff steroid-resistant nephrotic syndrome by using urine monocyte chemotactic protein 1 as a diagnostic marker is ≥512 with area under curve 0.992, sensitivity 96.3%, specificity 88.9%, positive predictive value 89.7%, negative predictive value 96%, and overall accuracy 92.6%. **Conclusions:** The findings imply that urine MCP-1 levels can differentiate between patients with active disease and those who are in remission, as well as between cases of steroid-resistant nephrotic syndrome and cases of steroid-sensitive nephrotic syndrome.

Keywords: Idiopathic Nephrotic Syndrome - Urinary Monocyte Chemotactic Protein 1 - Steroid Responsiveness.

INTRODUCTION

One of the most prevalent kidney conditions in children is idiopathic nephrotic syndrome (NS). The symptoms of nephrotic syndrome (NS) include hypercholesterolemia, edema, and severe proteinuria. The majority of idiopathic NS cases are steroid responsive, although some instances develop steroid resistance throughout the course of their clinical course [1].

The immune system, including lymphocyte activation, is said to have a significant role in the pathogenesis and pathophysiology of idiopathic NS, despite the lack of clarity on these factors. Numerous cytokines and chemokines have been linked to idiopathic NS, according to reports [2].

Idiopathic NS may also exhibit T-cell functional abnormalities and dysregulated cytokines, although it is still managed with GCs and other immunosuppressive medications, according to a number of clinical and experimental data [3].

However, GCs have a number of negative side effects, and 50% of adults and 10% to 20% of children with NS have steroid resistance or are developing it [4].

Sadly, no proven biomarker has been found to be able to predict steroid resistance in NS, and it is still unknown what molecular processes control GC resistance [5].

Therefore, even though GC is the primary therapy for the majority of NS patients, a sizeable portion of them may eventually by the time they encounter severe side effects from ongoing GC exposure and go on to develop SRNS and may have seen disease progression despite getting an ineffectual medication [4].

In an effort to more accurately pinpoint patients who are highly unlikely to react to GC and help them avoid its unneeded harm, a few studies have looked for urine and plasma biomarkers for SRNS in children [5].

As a result, recently T lymphocytes expressing inflammatory cytokines and macrophage migration inhibitory factor in plasma, and Monocyte chemoattractant protein-1(MCP-1 (in urine have been implicated in persistent proteinuria and SRNS in childhood NS [6].

Monocyte chemoattractant protein-1belongs has 76 amino acids, is encoded on chromosome 17, and belongs to the CC-chemokine family. It is created in the kidney by mesangial, tubular, epithelial, and smooth muscle cells. Monocytes, activated macrophages, T cells, and NK cells are the main cell types that express it [7].

MCP-1 plays a significant role in the glomerular inflammation by inducing the recruitment and retention of monocytes as well as the transformation of fibroblasts in the glomeruli [8].

Macrophages may be crucial in the pathogenesis of steroid-resistant NS known as focal segmental glomerulosclerosis, according to histological findings. Additionally, we have previously stated that macrophages have a role in the pathophysiology of pediatric NS that is refractory [9].

The goals of this study were to determine the diagnostic utility of urine MCP-1 in children who had idiopathic nephrotic syndrome.

PATIENTS AND METHODS

This case-control study was conducted at Pediatrics nephrology unit, pediatric nephrology outpatient clinic at Zagazig university Hospital on children attending at pediatric inpatient and outpatient clinic. They categorized as belonging to group A: There were 27 nephrotic patients in this group who had undergone considerable proteinuric remission. to < 4 mg/m^2/hr or urine albumin dipstick of 0 to trace for 3 days in a row along with edema relief) **[10],** group B: This group included 27 nephrotic patients in activity either with 1st attack or relapsers (severe proteinuria > 40 mg/m^2/hr or urine albumin dipstick ++ or more on 3 successive days, often with association or recurrence of edema) after withdrawal of steroid therapy **[2]** and the control group: This sample contained 27 healthy children attending a general pediatric clinic who were age and sex-matched. Written informed consent was obtained from all participant's parents.

Patients with idiopathic nephrotic syndrome, include both sexes and at age between two and sixteen were included in the study.

Patients with any signs or symptoms of a systemic disease, patients with secondary nephrotic syndrome, and < 2 years or > 16 years were excluded from the study.

All patients underwent a thorough history-taking process that included questions about their current symptoms, response to steroid therapy, frequency of relapses, complications from steroid therapy, and medications they had taken. They also underwent a thorough general and physical examination, as well as a full round of laboratory tests, including the full blood count (CBC), C-reactive protein (CRP), serum creatinine, blood urea, serum albumin, serum total cholesterol, full urine analysis, and urine protein/creatinine are some of the tests that are commonly performed. Plasma and urinary monocyte chemotactic protein-1 (MCP-1) were done by ELISA technique.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS) by IBM (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp.) was used to analyze the data. The tests used were as follows: chi-square analysis - Analysis of variance (ANOVA or F test), Kruskal-Wallis test, post Hoc tests and ROC Curve (receiver operating characteristic).

Results

There is a statistically non-significant difference between the studied groups regrading age, age of onset, disease duration, or gender (Table 1).

There is a statistically significant difference between the studied nephrotic patients regarding the incidence of edema (0% within steroid-sensitive versus 92.6% within steroid-resistant groups had edema). There is a statistically non-significant difference between the studied nephrotic patients regarding incidence of hematuria, high blood pressure (Table 2).

There is a statistically significant difference between the studied groups regarding Urinary Monocyte Chemotactic Protein 1. There is a statistically non-significant difference between the studied groups regarding plasma Monocyte Chemotactic Protein 1 (Table 3).

The best cutoff of urinary monocyte chemotactic protein 1 in the diagnosis of nephrotic syndrome is ≥79 with area under curve 1, sensitivity 100%, specificity 96.3%, positive predictive value 98.2%, negative predictive value 100%, and overall accuracy 98.8% (Table 4).

The best cutoff of urinary monocyte chemotactic protein 1 in diagnosis of steroid-resistant nephrotic syndrome is ≥512 with area under curve 0.992, sensitivity 96.3%, specificity 88.9%, positive predictive value 89.7%, negative predictive value 96%, and overall accuracy 92.6% (Table 5).

There is a statistically significant positive correlation between urinary monocyte chemotactic protein 1 among patients with nephrotic syndrome and all of depths of proteinuria, Protein creatinine ratio, duration of steroid use, and serum cholesterol. There is a statistically significant negative correlation between urinary monocyte chemotactic protein 1 among patients with nephrotic syndrome and serum albumin. On the other hand, there is a non-significant correlation between urinary monocyte chemotactic protein 1 among patients with NS and either age, age of disease onset, disease duration, WBCs, hemoglobin, platelet, urea, creatinine (Table 6) and (Figure 1-4).

Table (1): Comparison between the studied groups regarding demographic data and presentation of the disease

	Group A N=27 (%)	**Group B N=27 (%)**	**Group C N=27 (%)**	**χ^2**	**p**
Sex: **Female** **Male**	 15 (55.6%) 12 (44.4%)	 12 (44.4%) 15 (55.6%)	 12 (44.4%) 15 (55.6%)	0.89	0.641
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**p**
Age (year)	7.27 ± 1.81	7.54 ± 1.65	6.74 ± 1.81	1.435	0.244
	Median (IQR)	**Median (IQR)**		**Z**	**p**
Age of onset (year)	3.6(2.7 – 4.1)	4.1(3.4 – 4.5)		-1.923	0.055
Disease duration (year)	4.15(2.58 – 4.95)	3.85(2.63 – 4.93)		-0.412	0.68

χ^2Chi square test F One way ANOVA test Z Mann Whitney test

Table (2): Comparison between the studied groups regarding symptoms

	Group A N=27 (%)	**Group B N=27 (%)**	**χ^2**	**p**
Edema **Absent** **Present**	 27 (100%) 0 (0%)	 2 (7.4%) 25 (92.6%)	46.552	<0.001**
Blood pressure: **Normal** **High**	 24 (88.9%) 3 (11.1%)	 23 (85.2%) 4 (14.8%)	Fisher	>0.999

Hematuria **Absent** **Present**	 25 (92.6%) 2 (7.4%)	 24 (88.9%) 3 (11.1%)	Fisher	>0.999

**p≤0.001 is statistically highly significant χ^2Chi square test

Table (3): Comparison between the studied groups regarding Urinary and plasma Monocyte Chemotactic Protein 1

Monocyte Chemotactic Protein 1(pg/ml)	Group A N=27 (%)	Group B N=27 (%)	Group C N=27 (%)	F	p
	Mean ± SD	Mean ± SD	Mean ± SD		
Plasma level	60.96 ± 17.97	62.07 ± 15.44	68.7 ± 17.21	1.655	0.198
Urinary level	401.59 ± 83.53	785.37 ± 110.95	56.93 ± 11.7	553.699	<0.001**
LSD	**P_1 <0.001****	**P_2 <0.001****	**P_3 <0.001****		

F One way ANOVA test LSD Fisher least significant difference **p≤0.001 is statistically highly significant *p<0.05 is statistically significant p1 difference between groups A and B p2 difference between groups B and C p3 difference between groups A and C

Table (4): Performance of Urinary Monocyte Chemotactic Protein 1 in diagnosis of nephrotic syndrome

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P
≥79	1	100%	96.3%	98.2%	100%	98.8%	<0.001**

**p≤0.001 is statistically highly significant PPV positive predictive value NPV negative predictive value AUC area under the curve

Table (5): Performance of Urinary Monocyte Chemotactic Protein 1 in diagnosis of steroid-resistant nephrotic syndrome

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥512	0.992	96.3%	88.9%	89.7%	96%	92.6%	<0.001**

**p≤0.001 is statistically highly significant PPV positive predictive value NPV negative predictive value AUC area under curve

Table (6): Correlation between urinary monocyte chemotactic protein 1 and the studied parameters among patients with nephrotic syndrome

	R	P
Age (year)	0.128	0.358
Age at onset (year)	0.214	0.12
Disease duration (year)	-0.001	0.997
Proteinuria	0.793	**<0.001****
Creatinine (mg/dl)	0.085	0.541
Protein/creatinine ratio	0.789	**<0.001****
Urea (mg/dl)	-0.054	0.635
Albumin (g/dl)	-0.441	**<0.001****
Cholesterol (mg/dl)	0.733	**<0.001****
Platelet (10^3/mm^3)	-0.117	0.4
WBCs (10^3/mm^3)	0.096	0.49
Hemoglobin (g/dl)	0.028	0.838
Relapse	0.12	0.388
Steroid duration	0.758	**<0.001****

r Pearson correlation coefficient §Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

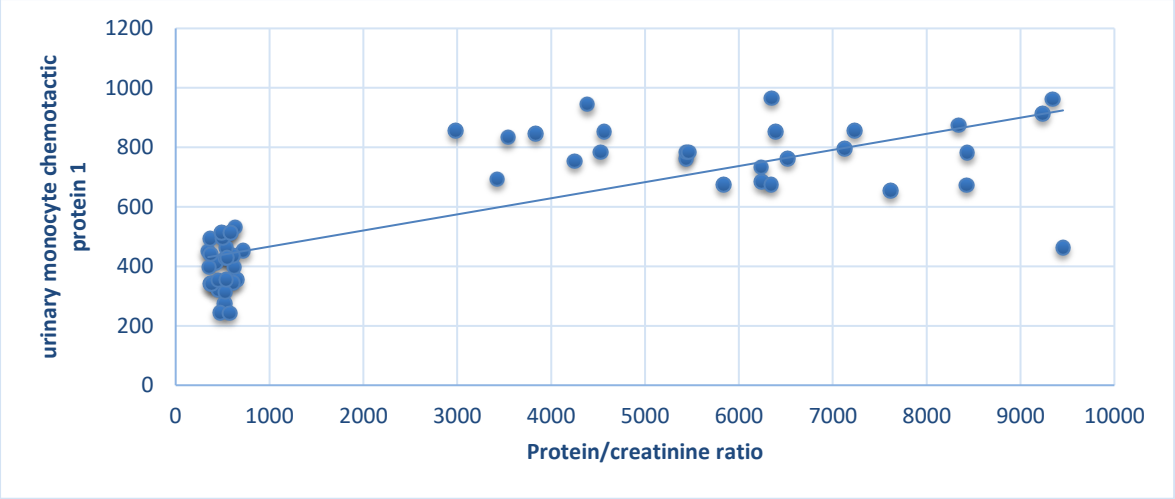

Figure (1): Scatter dot graph showing a significant positive correlation between urinary monocyte chemotactic protein 1 and PCR among patients with NS

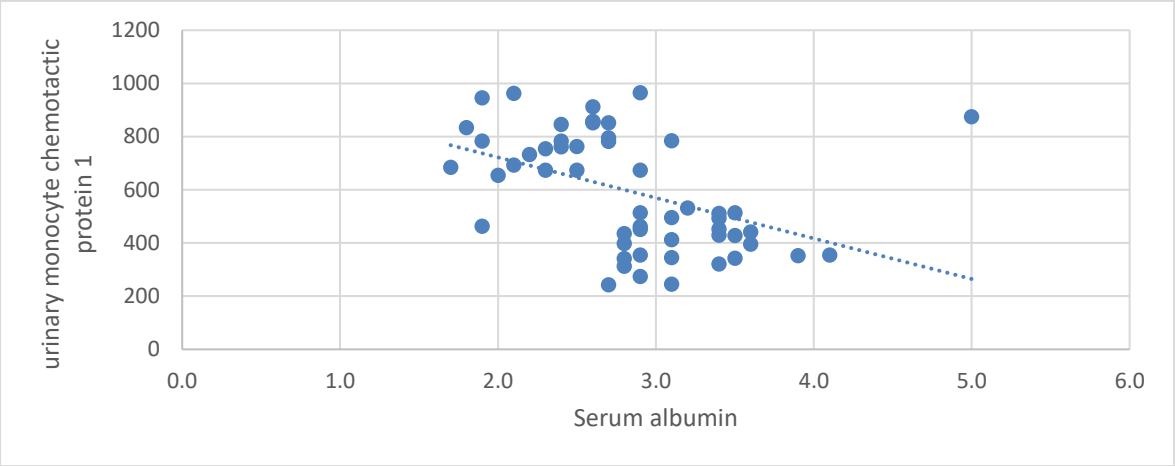

Figure (2): Scatter dot graph showing a significant negative correlation between urinary monocyte chemotactic protein 1 and albumin among patients with NS

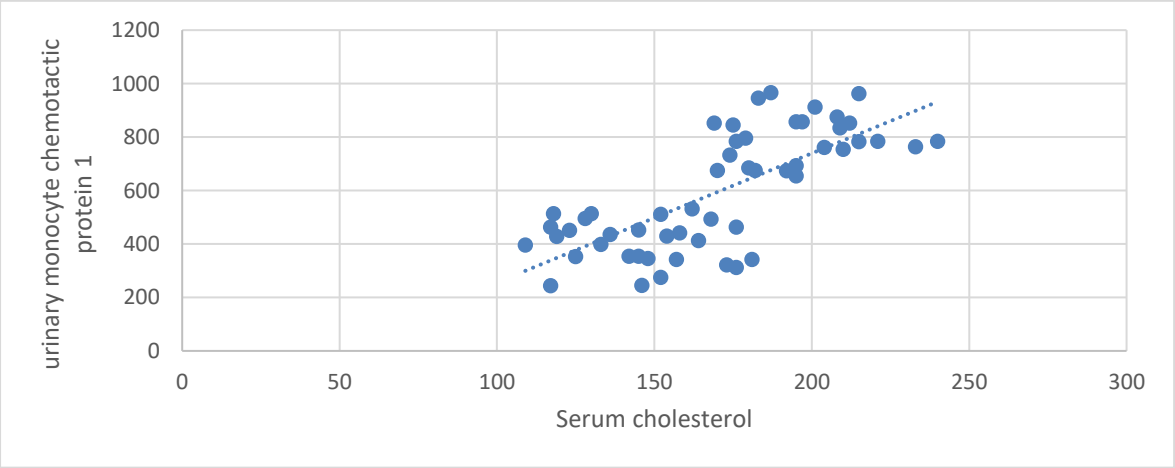

Figure (3): Scatter dot graph showing a significant positive correlation between urinary monocyte chemotactic protein 1 and cholesterol among patients with NS

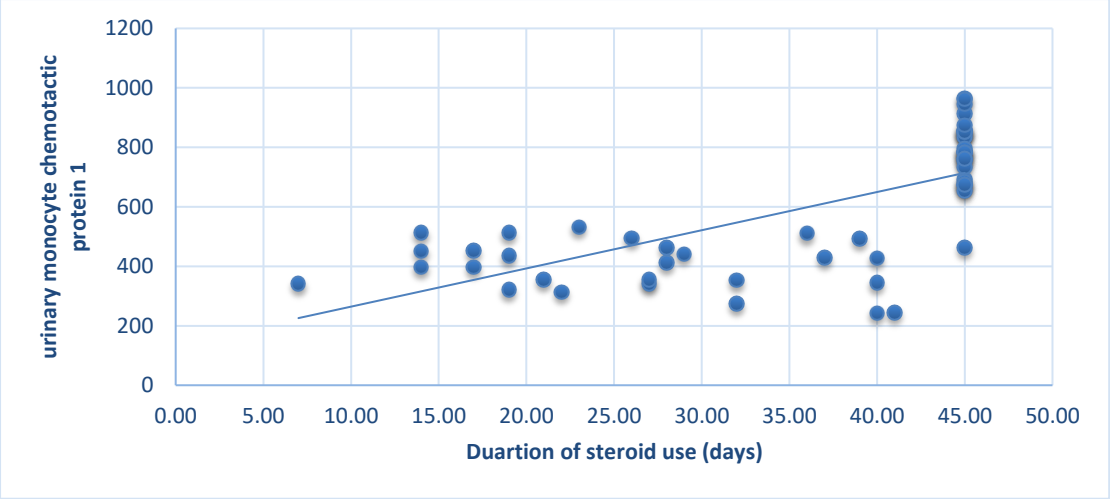

Figure (4): Scatter dot graph showing significant positive correlation between urinary monocyte chemotactic protein 1 and duration of steroid use among patients with NS

DISCUSSION

In our study, the mean age in group A is 7.27 years, while in group B, the mean age is 7.54 years, and in group C, the mean age is 6.74 years with a statistically non-significant difference.

This is consistent with Moon et al. [11] who studied how glucocorticoids affected bone geometry and BMD in kids with NS, and they discovered the mean age was 10.7±3.1 years.

This is in disagreement with Rhuma et al. [12] who stated that the disease's greatest occurrence occurred between the ages of 2-3 years in pre-school-aged youngsters.

Saraswathi et al. [13] found that NS in children can happen at any age, although it is most prevalent between the ages of 1 12, and 5 years, according to reports.They noticed that the frequency of the illness distribution depends significantly on the age at initial presentation, with 70% younger than five years of age, and 20–30% of teenage nephrotic patients with MCNS.

In this study, in group A, 15 participants (55.6%) are female, and 12 participants (44.4%) are male. In group B, 12 participants (44.4%) are female, and 15 participants (55.6%) are male. In group C, 12 participants (44.4%) are female, and 15 participants (55.6%) are male with a statistically non-significant difference.

Our results were supported by Rhuma et al. [12] and Ephraim et al. [14] as they stated that more men than women were impacted by INS.

This agreed with Hassan et al. [15] who sought to learn more about the histology, clinic-laboratory, and various patterns of nephrotic syndrome, as well as the connection between its clinical features and prognosis. They reported that there was a slight male preponderance,

Abd Elaziz et al. [16] reported that Approximately 76.7% of patients were male. Regarding sex, The cases and controls did not differ statistically significantly from one another ($p>0.05$).

On the other hand, El hamshary et al. [17] who aimed the association between steroid sensitivity and the urine individuals with idiopathic nephrotic syndrome had elevated levels of monocyte chemotactic protein-1 (uMCP-1). There were 54% more women in their research than men.

In the current investigation, there is a statistically significant difference between the investigated nephrotic patients relating incidence of edema (0% within steroid sensitive versus 92.6% within steroid resistant groups had edema).

This is in agreement with Ray et al. [18] who reported that edema is one of the clinical hallmarks of nephrotic syndrome.

This is in accordance with El hamshary et al. [17] who reported that, Regarding the existence of edema, there was a extremely significant statistical difference between the control group and the patients ($p < 0.001$). On the other hand, none of the patients in the control group or group A who were in remission displayed any signs of edema, while 76% of patients in the exercise group (group B) did.

Ejaz et al. [19] According to their study, face and L.L. edema were present in 65% of cases of active nephrotic syndrome, which is consistent with our findings. The current study's findings show that there is no statistically significant difference between the examined nephrotic patients and patients regarding incidence of hematuria, high blood pressure.

Similarly, El hamshary et al. [17] demonstrated that there was no obvious difference in blood pressure between the patients and the control group.

This is consistent with the research conducted by Filha et al. [20] study observed no appreciable difference in blood pressure between the control group and INS patients. Clinicians caring for children with steroid sensitive and steroid resistant nephrotic syndrome frequently face arterial hypertension.

There is a statistically significant difference between the analyzed groups in our study with regards to Urinary Monocyte Chemotactic Protein 1 (on doing posthoc test, the difference is significant between each two individual groups).

This is in accordance with Abdel Haie et al. [21] who discovered that children with INS had greater urine MCP-1 levels, suggesting that immune cells have a role in the creation of NS. MCP-1 levels in the urine were noticeably higher after relapse than during remission. By triggering monocyte migration and retention as well as fibroblast change in the glomeruli, MCP-1 strongly contributes to glomerular inflammation.

Similarly, Filha et al. [20] uMCP-1 levels The study's findings revealed that post proteinuria regression, relapse rates were considerably greater in children with minimal change disease (MCD) than in the MCD group and controls.

Additionally, our result is consistent with earlier research that discovered When compared to the control group and at the time of onset, MCP-1 levels in the urine of INS children were considerably greater [20,21].

Moreover, El hamshary et al. [17] comparing the patients' and control group's uMCP-l levels, there was an extremely significant statistical difference ($p < 0.001$).

Additionally, this study concurred with the research conducted by Wasilewska et al. [22] who demonstrated that uMCP-1 in children with minimal change disease in relapse (IA) was significantly higher than in group IB (MCD after proteinuria reduction) and controls. ($p < 0.05$).

The best cutoff of urinary monocyte chemotactic protein 1 in diagnosis of nephrotic syndrome is ≥79 98.8% overall accuracy, 100% sensitivity, 100% specificity, 98.2% positive predictive value, 100% negative predictive value, and area under curve 1 (AUC1).

Wasilewska et al. [22] reported that, Children with a first or second INS attack and children who had many relapses had the same level of uMCP-1/cr. ($p > 0.05$).

The optimum cutoff for detecting steroid-resistant nephrotic syndrome using urinary monocyte chemotactic protein 1 is ≥512 with area under curve 0.992, sensitivity 96.3%, specificity 88.9%, positive predictive value 89.7%, negative predictive value 96%, and overall accuracy 92.6%.

In another study, Khatibi et al. [23] found that uMCP-1 can predict glucocorticoid resistance since SRNS patients had greater levels of uMCP-1 than SSNS patients did.

Additionally, our findings supported those of Agrawal et al. [3] who discovered that uMCP-1 may separate kids with SRNS from kids with SSNS when the condition first manifests.

Moreover, Angela [24] noticed that SRNS patients exhibited greater MCP-1 levels in their urine than SSNS patients did. ($p < 0.001$).

In our study, there is a statistically significant positive link between urine monocyte chemotactic protein 1 and all levels of proteinuria, protein creatinine ratio, steroid use duration, and serum cholesterol in individuals with neuropathy syndrome (NS). In patients with NS, there is a statistically significant inverse relationship between serum albumin and urine monocyte chemotactic protein 1.

This agrees with Abdel Haie et al. [21] who discovered substantial positive associations between uMCP and urinary protein creatinine ratio, serum cholesterol, and urinary protein creatinine ratio, as well as significant negative correlations between uMCP and serum albumin, suggesting that uMCP may be regarded a sensitive biomarker of disease activity.

Furthermore, numerous investigations found that individuals with active idiopathic nephrotic syndrome excreted significantly more MCP-1 in their urine than did patients in remission or controls Angela [24] and Mariani et al. [25].

Conclusion:

This study highlights the potential diagnostic value of urine MCP-1 in pediatric patients with idiopathic nephrotic syndrome. The findings imply that urine MCP-1 levels can differentiate between patients with active disease and those who are in remission, as well as between cases of steroid-resistant nephrotic syndrome and cases of steroid-sensitive nephrotic syndrome.

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