ORIGINAL ARTICLE

CONTENTS

Evaluation of serum and urine levels of matrix metalloproteinase (MMP-2) in children with nephrotic syndrome

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ABSTRACT

Aim: To evaluate the serum and urine levels of MMP-2 in children with nephrotic syndrome.

Materials and Methods: This study was conducted at Pediatric Nephrology consultation Clinic in Al Imamain Kadhimain Medical City, Ibn Balady Children and Maternity Hospital, Child Central Teaching Hospital, Baghdad, Iraq and Children Welfare Teaching Hospital/Medical City Complex from 1st of November 2021 to 31th of March 2022 and included 60 Patients who are children with NS , and 60 healthy children age and sex matched as a control group Patients with NS were admitted to pediatric ward or attending the pediatric Nephrology clinic.

Results: found there was no significant difference in age and gender between the three groups, healthy controls, SSNS and SRNS However, SRNS had significantly higher mean SBP and DBP (123.0±15.79 mmHg and 79.97±12.44mmHg, respectively) than either SSNS patients (109.58±13.08 mmHg and 73.5±11.31mmHg, respectively) or controls (99.75±9.23 mmHg and 65.58±5.83 mmHg, respectively).

Conclusions: there was no significant difference in age and gender between the three groups, healthy controls, SSNS and SRNS However, SRNS had significantly higher mean SBP and DBP, However , ACE, cyclosporine and MMF were more common among patients with SRNS For MMP-2 the results found serum MMP-2 and urine MMP-2 was significantly higher in SSNS patients SRNS patients.

KEY WORDS: serum MMP-2 and urine MMP-2, SRNS, SSNS

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INTRODUCTION

Collagenases and stromelysins, which make up the majority of the huge family of zinc-containing matrix-degrading MMPs, According to Kontogiorgis et al. [1], the matrix metalloproteinases (MMPs) , a family of calcium- and/or zinc-dependent endopeptidases that are normally involved in the breakdown of extracellular matrix and tissue remodeling. However, under normal circumstances, their activity is extremely low and is tightly controlled by natural tissue inhibitors (TIMPs). Four structurally similar proteins known as the TIMPS (TIMP-1, 2, 3, and 4) exercise dual control over the MMPs by blocking both their activation and their active forms [2]. TGF-b1, among other inflammatory cytokines, stimulates MMP production. Matrix metalloproteinases (MMPs) are a class of zinc-dependent proteinases that are among the MMPs produced in the kidney and whose activities are focused on the breakdown and renewal of extracellular matrix (ECM) proteins. To far, around 30 metalloproteinases have been identified. They are separated into many classes according to their structure andfunction. [3] However A prevalent kind of kidney illness in children is nephrotic syndrome [4] According to estimates, corticosteroid therapy will help roughly 80% of kids with idiopathic nephrotic syndrome completely resolve their proteinuria and edema. This group of people who respond to steroids has a varied clinical outcome, with up to 60% experiencing repeated relapses or becoming reliant on steroid medication to keep their condition in remission. [5] Increased MMPs glomerular expression is strongly correlated with the degree of glomerular damage and the course of kidney disease, according to experimental data and clinical research [6] Higher blood levels and/or urine excretions of MMPs and TIMPs may serve as biomarkers for an early stage of nephrotic syndrome, according to recent research in patients with diabetic nephropathy, chronic kidney disease (CKD) following kidney transplantation. [7]

AIM

To evaluate the serum and urine levels of MMP-2 in children with nephrotic syndrome.

MATERIALS AND METHODS

SUBJECT

This study was conducted at Pediatric Nephrology consultation Clinic in Al Imamain Kadhimain Medical City, Ibn Balady Children andMaternity Hospital, Child Central Teaching Hospital, Baghdad, Iraq andChildren Welfare Teaching Hospital/ Medical City Complex from 1st ofNovember 2021 to 31th of March 2022. The practical part was conducted atdepartment of chemistry and biochemistry, College of Medicine, Al-Nahrain University and the biochemical laboratory at Ibn Balady Children and Maternity Hospital included 60 Patients who are children with NS, and 60 healthy children age and sex matched as a control group Patients with NS were admitted to pediatric ward or attending the pediatric Nephrology clinic. Diagnosis of NS was made depending on to criteria such as : heavy proteinuria >40 mg/h/m2 or >50 mg/kg/day Albustix ≥+++,hypo-albuminemia <2.5 g/dL, edema and hyperlipidemia[8].

STUDY DESIGN

This study included three groups as following

Group 1: consist of 30 children with SSNS ,blood samples and urine were collected from them during relapse, **Group 2** : consist of 30 children with SRNS, blood samples and urine werecollected from them during relapse, **Group 3 (Control)** : consist of 60 healthy children , who are matched withages and sex , recruited from outpatient clinic with normal kidney function.

INCLUSION CRITERIA

Children with nephrotic syndrome aged(1-15)years matched with healthy control.

EXCLUSION CRITERIA

1. Secondary nephrotic syndrome.
2. Congenital Nephrotic Syndrome.
3. Children with thyroid disease.
4. Liver disease.
5. Children with cancer.
6. Children with birth diabetic.
7. Presence of any other medical or surgical illness.

SAMPLE COLLECTION

BLOOD SAMPLES

Five (5) ml of venous blood will be drawn from both patients and controls to collect samples, which will then be placed in a plane tube (without anticoagulant). Blood is allowed to stand for 30 minutes before being centrifuged for 15 minutes at 2000 RPM. Transfer serum to a fresh tube and store at -20 C.

URINE SAMPLES

Patients and healthy kids provided ten milliliter urine samples in the morning, which were later collected in the aircraft. For the following measurement of urinary MMP2, which was determined using an ELISA approach and urinary, the urine sample was centrifuged to remove any foreign objects before being separated into simple tubes and kept at -40Co.

DETERMINATION OF SERUM AND URINE MMP-2

Determination serum and urine MMP-2 was achieved by sandwich ELISA assay according to Kit instructor (Mybiosource/USA) and the concentration was obtained depending on the standard curve in fig. 1.

STATISTICAL ANALYSIS

The data that obtain could be analyzed using SPSS Numeric data were expressed as mean ± SD. ANOVA and Student's t test will be used to calculate individual p-value between normal and patient. Correlation between nephrotic syndrome and other variable will be considered using Pearson correlation test. P value < 0.05 was considered significant.

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

The study included 60 children diagnosed with nephrotic syndrome (30 SSNS, 30 SRNS) and 60 age- and sex-matched healthy controls. There were no significant differences in age and gender among the three groups ($p > 0.05$). However, SRNS patients had significantly higher mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to SSNS and control groups ($p < 0.001$) (Table 1).

Regarding clinical characteristics, steroid therapy was the first-line treatment for all patients, but 90% of SRNS patients required additional immunosuppressive therapy, including angiotensin-converting enzyme (ACE) inhibitors, cyclosporine, and mycophenolate mofetil (MMF).

Analysis of dietary patterns revealed that 20% of SRNS patients had a high-sodium diet, compared to 10% in SSNS and 5% in controls. Hydration status was adequate in all groups, as assessed by urine specific gravity and serum osmolality.

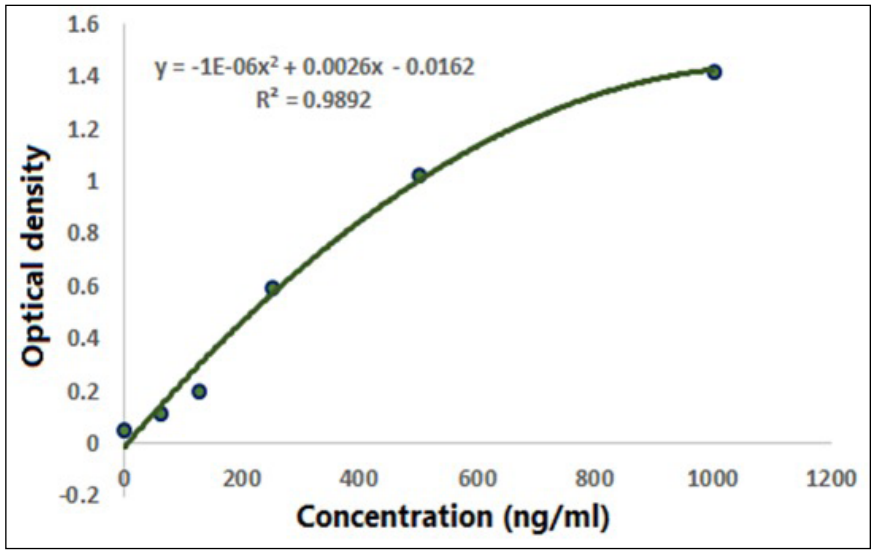

Fig. 1. Calibration curve of MMP-2

There were no significant difference in age between the three groups, healthy controls, SSNS and SRNS as showed in table (3-1) these findings agreed with studies as [9] and agreed[10] , in Iraq also these findings agreed with [11 ; 12] However These earlier investigations discovered substantial differences between the SS and SR groups in terms of age and gender. Additionally, the current study revealed a predominance of male over female patients, and the outcome was consistent with other studies [13] To avoid issues with age differences, the groups in the research were chosen for ages that were near together.

In contrast, our study found that SRNS had significantly higher mean SBP and DBP than either SSNS patients or controls, which was consistent with Roy's study from 2011 [14] and his colleague's study from Bangladesh that found more hypertension events in the SRNS group than SSNS ($p > 0.05$). However, our data disagreed with a study from Indonesia from 2016 that found that blood pressure in the SSNS group was higher than the SRNS group [15], A recent research discovered There were cyclical variations in the systolic blood pressure readings between the two groups, with the SSNS group having a higher systolic median than the SRNS group. In the diastolic blood pressure data, there was no statistically significant difference between the two groups [16].

About 20% of children who develop hypertension have renal problems [17]. Due to steroid toxicity, hypertension can occur in both illness-related conditions and during NS disease progression [18]. By decreasing the retention of salt and water in the kidneys, corticosteroids can lead to hypertension by expanding plasma volume, which in turn raises blood pressure [16] . According to the theory, the major cause of sodium retention in NS is a decreased circulation volume brought on by fluid shifting from intravascular to interstitial compartments as a result of hypoalbuminemia's decreased plasma oncotic pressure. The kidneys' ability to retain water and salt is activated by this shift. While the overfill theory contends that salt retention demonstrates the lack of inherent kidney handling abnormalities, which results in volume growth, [18] , as well as this may associated the long term medication that increase the hypertension[19].

CLINICAL CHARACTERISTICS OF THE PATIENTS

The median duration of illness did not differ significantly between patients with SSNS and SRNS (52.0 months versus 58.0 months). All patients in both groups were on steroid therapy. Beside steroid, 8 patients (26.67%) in SSNS use additional medications compared with 90% in SRNS who used these additional medications with a highly significant difference. In particular, ACE, cyclosporine and MMF were more common among patients with SRNS (43.33%, 46.67% and 26.67%, respectively) than SSNS (16.67%, 6.67% and 3.33%, respectively with significant differences Table 2.

The obtained findings in table (3-2) was agreed with who found the duration of disease 24 (16–38) months and While [21] found. The median duration of NS was 12 months this difference between the studies could be due to a referral bias of difficult cases.

From the other side, the combined high-dose of angiotensin II receptor blocker and high-dose angiotensin-converting enzyme inhibitor treatment is safe and efficient in lowering proteinuria in childhood SRNS, especially ACE, cyclosporine, and MMF were more prevalent among patients with SRNS than SSNS [22] For individuals with primary (idiopathic) nephrotic syndrome, ACE inhibitors are frequently used to control high blood pressure brought on by faulty kidneys that result in fluid retention or overload [23].

Table 1. Demographic characteristics of the study population

Variable	Controls (n=60)	SSNS (n= 30)	SRNS (n=30)	p-value
Age, years				
Mean±SD	8.86±4.09	8.67±4.27	9.62±3.92	0.620
Range	1.4-15.0	1.3-15.0	1.7-15.0	
Gender				
Males	45(75%)	24(80%)	21(70%)	0.670
Females	15(25%)	6(20%)	9(30%)	
SBP, mmHg				
Mean±SD	99.75±9.23	109.58±13.08	123.0±15.79	<0.001
Range	90-120	80-140.5	90-150	
DBP, mmHg				
Mean±SD	65.58±5.83	73.5±11.31	79.97±12.44	<0.001
Range	60-80	40-90	60-100	

SSNS = steroid-sensitive nephrotic syndrome; SRNS = steroid-resistant nephrotic syndrome

Table 2. Clinical characteristics of patients with nephrotic syndrome

Variable	SSNS (n=30)	SRNS (n=30)	p-value
Disease duration, month			
Mean±SD	61.43±43.9	59.37±41.5	0.852
Median	52.0	58.0	
Range	6-140	8-132	
Medication beside steroid			
No medication	22(73.33%)	3(10%)	<0.001
ACE	5(16.67%)	13(43.33%)	0.024
Cyclosporine	2(6.67%)	14(46.67%)	<0.001
MMF	1(3.33%)	8(26.67%)	0.013
Tacrom	1(3.33%)	3(10%)	0.605

SSNS = steroid-sensitive nephrotic syndrome; SRNS = steroid-resistant nephrotic syndrome; ACE = angiotensin converting enzyme

Table 3. Median serum and urine level of MMP-2 and serum levels of TIMP-1 in SSNS, SRNS patients and controls

Variable	Controls(n=60)	SSNS(n= 30)	SRNS(n=30)	p-value
SMMP-2, ng/ml				
Mean±SD	186.14±24.35	322.55±97.28	246.91±89.68	<0.001
Median	193.3	288.05	223.52	
Range	121.6-221	152.6-578.5	148.1-496.1	
UMMP-2, ng/ml				
Mean±SD	177.73±20.69	276.34±62.24	200.12±19.21	<0.001
Median	183.0	272.5	198.7	
Range	124.28-203.1	182.86-427.3	168.7-261.23	

Moreover the results were consistent with [24] who studied 35 patients with SRNS and gave cyclosporine to every patient. using cyclosporine Cyclosporine was originally proposed as a potential therapy for steroid-resistant nephrotic syndrome in 1984. Cyclosporin is a calcineurin inhibitor that reduces the transcription of many cytokine genes to decrease immune response. There have been several studies undertaken up to this point to identify doses, lengths of therapy, and adverse effects [25], which noted the Following the administration of immunosuppressive regimens containing cyclosporin, blood pressure rises quickly. Renal and systemic vasoconstriction are caused by characteristic vascular alterations [19].

However, a prior study discovered that steroid-resistant nephrotic syndrome affected 2 of 18 patients who underwent MMF treatment. The remaining patients (10 patients) all met the requirements for SD [26] The first management of SSNSin children has not yet been studied with MMF. However, it makes sense to take use of MMF's decreased toxicity when compared to glucocorticoids and exploit its efficacy for maintaining remission in the first therapy of SSNS [27].

Last but not least, it was proposed by [28] that TAC is a useful treatment approach for SRNS, including the

Table 4. Diagnostic value of SMMP-2, UMMP-2 in the context of discrimination between SSNS and controls

Markers	AUC	Sensitivity	Specificity	Cut off value
SMMP-2	0.97	97%	100%	221.82 ng/ml
UMMP-2	0.959	93%	78%	195.3 ng/ml

Table 5. Diagnostic value of SMMP-2, UMMP-2 in the context of discrimination between SRNS and controls

Markers	AUC	Sensitivity	Specificity	Cut off value
SMMP-2	0.663	73%	32%	181.19 ng/ml
UMMP-2	0.785	73%	65%	190.41 ng/ml

Table 6. Diagnostic value of SMMP-2, UMMP-2 in the context of discrimination between SSNS and SRNS

Markers	AUC	Sensitivity	Specificity	Cut off value
SMMP-2	0.732	93%	60%	244.05 ng/ml
UMMP-2	0.887	83%	73%	213.55 ng/ml

subset of kids who are unresponsive to the existing therapeutic approaches like cyclophosphamide and cyclosporine. When high-dose steroids are used as the initial line of therapy for adults with minimal change nephrotic syndrome, adverse effects, steroid resistance, and recurrence are frequent problems. Tacrolimus is a steroid-free immunosuppressant that is used to lessen the side effects of prolonged or repeated steroid therapy [29].

MATRIX METALLOPROTEINASE-2

Serum MMP-2 was significantly higher in SSNS patients (median= 288.05 ng/ml, range= 152.6-578.5 ng/ml) than either SRNS patients (median= 223.52 ng/ml, range= 148.1-496.1 ng/ml) or controls (median= 193.3 ng/ml, range= 121.6-221 ng/ml) as shown in table 3 and fig. 2.

Serum MMP-2 levels were significantly higher in SSNS patients (median = 288.05 ng/ml) compared to SRNS patients (median = 223.52 ng/ml) and controls (median = 193.3 ng/ml) ($p < 0.001$).

Similarly, urine MMP-2 levels were significantly elevated in SSNS patients (median = 272.5 ng/ml) compared to SRNS patients (median = 198.7 ng/ml) and controls (median = 183 ng/ml) ($p < 0.001$).

Similarly, urine level of MMP-2 was significantly higher in SSNS patients (median= 272.5 ng/ml, range= 182.8-427.3 ng/ml) than either SRNS patients (median= 198.7 ng/ml, range= 168.7-261.23 ng/ml) or controls (median= 183 ng/ml, range= 124.28-203.1 ng/ml) as shown in fig. 3.

The findings supported [30] whoever discovered MMP-2. It appears to be a possible marker to distinguish steroid sensitivity from resistance since the relative active form of MMP-2 was dramatically raised in SSNS post-treatment. Matrix metalloproteinases have been linked to the development of neuropathy in a few studies. According to Wasilewska and Zoch-Zwierz [31], MMP-2 has both an active and a proenzyme form. Our investigations suggested that, rather than absolute levels, relative ratios of both forms may be more useful in identifying SSNS from SRNS((Tsai et al., 2016). Increases in this ratio may be advantageous for the clinical response to steroids, according to molecular weight forms associated with larger active/proenzyme ratios in SSNS compared to SRNS post-treatment [32].

Wasilewska & Zoch-zwierz, [31] recorded the MMP2/TIMP2 ratio in urine sample in NS children treated with CyA was significantly lower in comparison with healthy controls this due to the cyclosporine, tacrolimusdecrease expression of MMP2 [33] as mentioned in previous most of SRNS patients was in mediction CyA and tacrolimus less than SSNS Patients ,Cyclosporine inhibits the expression of TIMP-1 in and it may further reduce the activation of MMP-2 [34]. In contrast, control group showed higher level of TIMP-1 (median= 2.36 ng/ml, range= 1.62-2.78 ng/ml) than SSNS patients (median= 1.29 ng/ml, range=0.43-1.71 ng/ml) with a significant difference, and SRNS (median= 1.8 ng/ml, range= 1.4-4.5 ng/ml) with no significant difference. Of note, the SRNS differs significantly from SSNS in this regard

The results were comparable to those reported in [35] There were no discernible variations in the median levels of serum TIMPs , MMPs and MMPs/TIMPs ratios between nephrotic patients and controls, while TIMP levels were rising in the control group. The findings were consistent with [35] which found a link between the urine MMP-2/TIMP-1 ratio value in SRSS and the median urinary MMP-2/Cr ratio (P =.01) and urinary TIMP-1/Cr ratio (P =.02) values in children with SRNS.

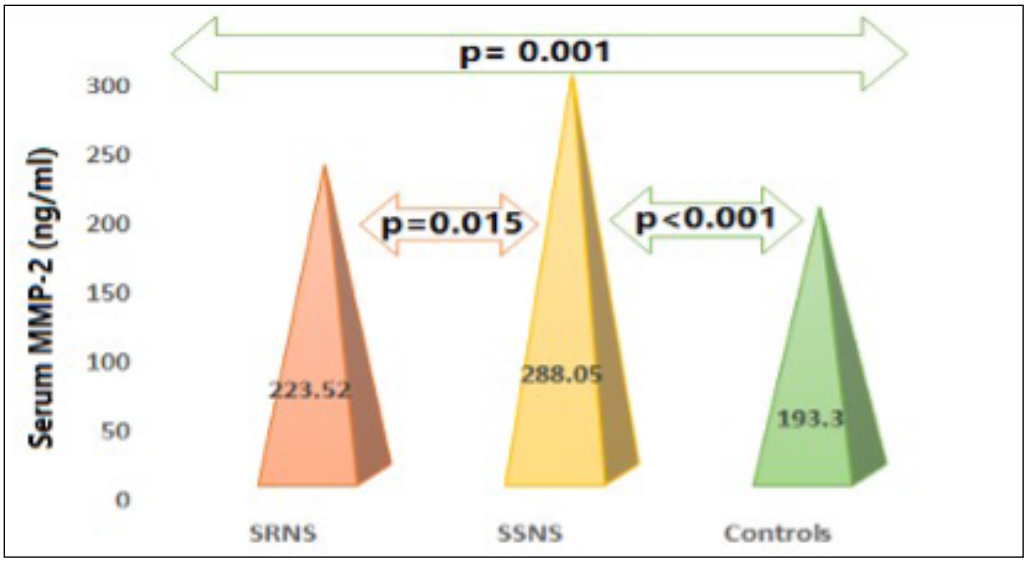

Fig. 2. Median serum level of MMP-2 in SSNS, SRNS patients and controls

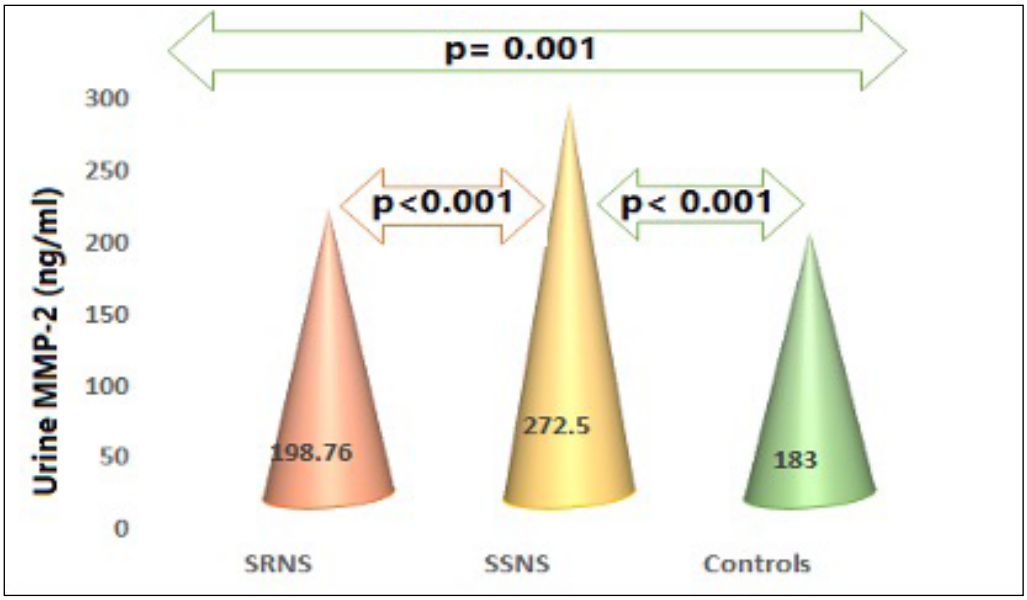

Fig. 3. Median urine level of MMP-2 in SSNS, SRNS patients and controls

DIAGNOSTIC VALUE OF MMP-2 AND ITS INHIBITOR

To assess the diagnostic value of MMP-2 and its inhibitor, the receiver operating characteristic (ROC) curve was used. In the context of discrimination between SSNS and controls, the area under the curve (AUC) for serum MMP-2 level was 0.97, 95% CI= 0.912-1.0, p <0.001. The test's sensitivity and specificity were 97% and 100%, respectively, at a cut-off value of serum MM-2 level = 221.82ng/mL. The AUC for urine MMP-2 level was 0.959, 95% CI= 0.913-1.0, p <0.001. The test's sensitivity and specificity were 93% and 78%, respectively, at a cut-off value of urine MMP-2 level = 195.31ng/ml.

Receiver Operating Characteristic (ROC) curve analysis revealed that serum MMP-2 had an area under the curve (AUC) of 0.97, with 97% sensitivity and 100% specificity for distinguishing SSNS from controls. Urine MMP-2 had an AUC of 0.96, with 93% sensitivity and 78% specificity.

For differentiating SSNS from SRNS, urine MMP-2 performed better (AUC = 0.89) than serum MMP-2 (AUC = 0.73). These findings suggest that urinary MMP-2 may serve as a useful biomarker for predicting steroid responsiveness in nephrotic syndrome (Table 4).

The AUC for serum MMP-2 was 0.663, 95% CI= 0.522-0.804, p = 0.012 in the context of discriminating between SRNS and controls. With a cut-off value of 181.19ng/mL for serum MMP-2, the test's sensitivity and specificity were 73% and 32%, respectively. The AUC for the urine MMP-2 level was 0.785, 95% CI = 0.685-0.885, and p 0.001. At a cut-off value of urine MMP-2 level = 190.41 ng/ml, as shown in table 5, the test's sensitivity and specificity were 73% and 65%, respectively.

The AUC for blood MMP-2 level in the context of differentiating between SSNS and SRNS was 0.732, 95% CI= 0.601-0.863, p = 0.002. At a cut-off value of serum MM-2 level = 244.05ng/mL, the test's sensitivity and specificity were 93% and 60%, respectively. The urine

MMP-2 level's AUC was 0.887, 95% confidence interval (CI): 0.798-0.975, and p 0.001. At a cut-off value of urine MMP-2 level = 213.55 ng/ml, the test's sensitivity and specificity were 83% and 73%, respectively (Table 6).

This Roc analysis result largely concurred with other research on renal diseases, such as those by Altetam et al. [36] who disclosed their findings when analyzing the urine matrix in their study. The optimum cutoff for MMP2 in the diagnosis of Chroinc kidney disease has an area under curve of 0.766, sensitivity of 77.8%, and specificity of 63.9%. Metalloproteinase activity in diabetic kidney disease. The area under the ROC curve for urine MMP activity was 77%. ROC analysis shows that estimating MMP activity is more accurate than predicting people with progressing renal disease.

DISCUSSION

Our findings confirm that SRNS patients exhibit significantly higher blood pressure levels than SSNS patients, consistent with prior studies that reported a higher prevalence of hypertension in SRNS due to increased sodium retention and chronic steroid exposure.

The significantly elevated MMP-2 levels in SSNS compared to SRNS suggest a possible role for MMP-2 in predicting steroid responsiveness. Previous studies have linked MMP-2 to extracellular matrix remodeling in glomerular diseases, but our study specifically highlights its potential in distinguishing SSNS from SRNS [9].

Several studies have shown that cyclosporine and tacrolimus suppress MMP-2 expression, which may explain why SRNS patients had lower MMP-2 levels despite having a more severe disease course [10,11]. This suggests that urinary MMP-2 levels could serve as a dynamic biomarker for treatment monitoring.

Clinical Implications of MMP-2 Assays [12-15].

Given the high sensitivity and specificity of urinary MMP-2, it could serve as an early predictor of steroid responsiveness [16,17], potentially reducing the time required to determine whether a patient should receive second-line immunosuppressants [18,19,20].

Additionally, monitoring MMP-2 levels could help assess disease progression and treatment response in nephrotic syndrome [21,22,23]. Patients who fail to show a decline in MMP-2 levels after initial steroid therapy may require earlier initiation of alternative immunosuppressive agents [24,25].

Future studies should explore whether serial MMP-2 measurements could guide treatment adjustments and improve patient outcomes [26].

CONCLUSIONS

Our study demonstrates that serum and urine mmp-2 levels are significantly elevated in ssns compared to srns and healthy controls. These findings highlight the potential clinical utility of mmp-2 assays in predicting steroid responsiveness in pediatric nephrotic syndrome.

Given the high sensitivity and specificity of urine mmp-2 in differentiating ssns from srns, it may serve as a non-invasive biomarker for early identification of steroid-resistant patients, thereby guiding treatment decisions and minimizing unnecessary steroid exposure.

Future research should explore longitudinal monitoring of mmp-2 levels to assess treatment response and predict relapses.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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