

## Original Article

# A Study on Urinary Specific Gravity- in Detection of Proteinuria in Children with Nephrotic Syndrome

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**ABSTRACT**

**Introduction:** Nephrotic syndrome is a common renal disease that causes pathological proteinuria. Twenty-four hours of urinary protein excretion, which is a commonly accepted method for quantification of proteinuria is time-consuming and inconvenient. Spot urinary protein creatinine ratio (PCR) has been widely adopted as a practical alternative. Urinary specific gravity or relative density, which is influenced by proteinuria can be readily measured in the bedside dipstick test and might be used as a rapid screening test for proteinuria. The study aimed to analyze urinary specific gravity, in the detection of proteinuria in children with nephrotic syndrome. **Methods:** This cross-sectional study was conducted in the Department of Pediatric Nephrology (NIKDU), Dhaka, from October 2019 to June 2021, and a total of 153 patients with nephrotic syndrome were enrolled after taking written consent. A urinary heat coagulation test was done. Urine samples were collected for both 24 hours and spot for estimation of urinary protein, urinary creatinine, dipstick protein, and specific gravity by dipstick method. Spot urinary PCR and 24 hours urinary protein were also estimated. **Result:** Maximum study subjects (44.4%) were 2-5 years old with males (61.4%) predominant. Twenty-four hours UTP was  $7.52 \pm 7.65$  gm/m<sup>2</sup>/24 hours, 24 hours urinary specific gravity was  $1.02 \pm 0.02$ , spot urinary PCR

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was  $21.87 \pm 18.24$  and specific gravity was  $1.02 \pm 0.01$ . Area Under Curve (AUC) of 24 hours urinary specific gravity was 0.551 and spot urinary specific gravity (0.520) was low in prediction of proteinuria (heat coagulation test >++) in children with nephrotic syndrome. But good value of AUC for 24 hours urinary specific gravity (0.789) in prediction of proteinuria (24 hours proteinuria >1000mg/m<sup>2</sup>/day) and spot urinary specific gravity (0.872) in prediction of proteinuria (spot urinary PCR >2mg/mg) was observed. Area under curve (AUC) of spot urinary specific gravity was (0.719) in prediction of proteinuria (spot dipstick protein >++) and 24 hours urinary specific gravity (0.734) in prediction of proteinuria (24 hours dipstick protein >++) in children with nephrotic syndrome were not poor also. Best sensitivity, specificity, PPV and NPV of 24 hours urinary specific gravity and spot urinary specific gravity were at a cut off value of 1.020. Sensitivity and specificity were poor for both 24 hours urinary specific gravity (64% and 41%) and spot urinary specific gravity (64% and 39%) in predicting proteinuria defined by heat coagulation test >++ in children with nephrotic syndrome. Sensitivity and specificity of spot urinary specific gravity were 65.5% and 100% as a marker in predicting proteinuria (spot urinary protein creatinine ratio >2 mg/mg) in children with nephrotic syndrome with 100% Positive predictive value and 13.8% negative predictive value. As a marker in predicting proteinuria defined by spot dipstick protein >++, sensitivity and specificity of spot urinary specific gravity were 57.6% and 85.7% with 95% positive predictive value and 30% negative predictive value. In predicting proteinuria (24hrs dipstick protein >++) in children with nephrotic syndrome, sensitivity was 65.7% and specificity was 80% with good positive predictive value 95.8% and 25% negative predictive value. Sensitivity is and specificity is of 24hrs urinary specific gravity were 63.7% and 85.7% respectively as a marker in predicting 24 hours proteinuria (>1000mg/m<sup>2</sup>/day) in children with nephrotic syndrome with 98.9% positive predictive value and 10.2% negative predictive value. Specificity and sensitivity of urinary specific gravity were significant to detect proteinuria. **Conclusion:** According to this study's findings 24 hours of urinary specific gravity can be used as a diagnostic test to detect proteinuria in children with nephrotic syndrome.

**Keywords:** Nephrotic Syndrome, Urinary Specific Gravity, Proteinuria, Protein Creatinine Ratio (PCR)

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## INTRODUCTION

Nephrotic syndrome is a common disease of the glomerulus in children. The incidence of nephrotic syndrome is 1.15 to 16.9 per 100,000 children [1]. The clinical and biochemical features of nephrotic syndrome result from heavy proteinuria (>40mg/m<sup>2</sup>/hour; 1gm/m<sup>2</sup>/24 hour) followed by hypoalbuminemia, hypercholesterolemia, and edema [2]. In

nephrotic syndrome, quantitative measurement of protein in a 24-hour urine collection is the gold standard. Spot urinary protein creatinine ratio is another reliable method of screening for proteinuria that would be more acceptable as it is less time-consuming [3][4]. Recent studies have shown that the correlation between spot urinary protein/creatinine ratio (UPr: UCr), urinary dipstick, and 24 hours urinary

total protein (UTP) estimation is statistically highly significant for all levels of proteinuria. Though 24 hours UTP is the gold standard test for the assessment of proteinuria it is time-consuming, and cumbersome, since it is difficult to collect a complete 24-hour urine sample accurately [5][6]. To obviate these difficulties short timed urine collection has been advocated as protein excretion is nearly constant throughout the day. The ratio of urine protein concentration to urine creatinine concentration has been widely adopted as a practical alternative since it correlates closely with urine albumin excretion rate [7]. In the presence of stable GFR (Glomerular Filtration Rate) excretion of urinary creatinine is fairly constant in a given individual; this principle is applied behind the use of protein creatinine ratio in quantifying 24 hours proteinuria [8]. In diluted urine, as indicated by a low urine specific gravity, the urinary protein creatinine ratio (UPCR) is more likely to overestimate the actual daily urine protein excretion. On the contrary, UPCR of concentrated urine is more likely to result in an underestimation [9]. The spot urinary PCR must be measured in a laboratory and the delay in resulting makes the PCR impractical. Recently, more rapid screening methods like dipstick tests have been developed for estimating urinary protein concentration. But variation in the rate of diuresis may substantially alter the concentration of protein concentration in the urine without changing the rate of protein excretion which makes dipstick measurement of protein concentration less predictive. It may give a false-

positive result in concentrated urine and a false-negative result in dilute urine [10]. The gold standard for estimating urinary concentration is the measurement of its osmolality but this procedure is not readily available to the practicing physician. Therefore urine concentration is usually determined by measurement of its specific gravity (SG), which provides a fair estimation of urine osmolality. The SG of urine is the density of urine divided by the density of pure water at a constant temperature. The SG is impacted by the particles' molecular mass (molar mass) in addition to their number. Therefore, the presence of heavy molecules like radiocontrast agents and abnormal concentrations of glucose and protein in the urine causes a disproportionate increase in SG as compared to its osmolality. Specific gravity, measured by refractometry is influenced by proteinuria, such that for each 10g/l protein the SG increases by 0.003 [11]. Urine-specific gravity or relative density, which values changes with urinary protein excretion can be readily measured in the clinic and also at the bedside by dipstick and might be used as sensitive, specific, and rapid screening tests for proteinuria. thereby measurement of proteinuria-specific gravity can be a good guide to assessing proteinuria in nephrotic syndrome. This study aimed to establish urine-specific gravity (Usg) as a diagnostic test for the detection of urinary protein excretion.

## **OBJECTIVE**

### **General Objective**

- To evaluate urinary specific gravity as a

diagnostic test for detection of proteinuria in children with nephrotic syndrome.

### Specific Objectives

- To estimate spot urinary specific gravity for diagnosis of proteinuria in children with nephrotic syndrome
- To correlate urinary specific gravity with bedside urine albumin.
- To compare urinary specific gravity with 24-hour urinary total protein
- To see the relation of urinary specific gravity with spot protein creatinine ratio
- To compare dipstick urinary specific gravity with dipstick protein

### METHODS

This cross-sectional study was conducted in the Department of Pediatric Nephrology (NIKDU), Dhaka, from October 2019 to June 2021, and a total of 153 patients with nephrotic syndrome were enrolled after taking written consent. A urinary heat coagulation test was done. Urine samples were collected for both 24 hours and spot for estimation of urinary protein, urinary creatinine, dipstick protein, and specific gravity by dipstick method. Spot urinary PCR and 24 hours urinary protein were also estimated. Informed written consent was taken from the parents. The questionnaire had been developed using the selected variables according to the specific objectives. Data

was collected by using a pre-designed data collection sheet. Statistical analysis was done by using SPSS version 22.0 for Windows. Numerical variables were presented as mean with standard deviation and categorical variables were expressed as proportions. Spearman ranks correlation test was done for correlation. A value of  $p < 0.05$  was considered statistically significant for all tests. Laboratory investigations were done in the Biochemistry lab of Dhaka Shishu Hospital (DSH) after taking written permission from the Director of DSH. Before the commencement of this study, the research protocol was approved by the "Ethical Committee" of NIKDU, Dhaka.

### Inclusion Criteria

- Patients with nephrotic syndrome.
- Patients with both initial episode and relapse cases.
- Both male and female patients.
- The age of patients was  $>2$  to  $\leq 18$  years.

### Exclusion Criteria

- Patients having proteinuria other than nephrotic syndrome.
- Patients who were unable to answer the criteria question.

### RESULTS

Among 152 study subjects maximum (44.4%) were 2 – 5 years old followed by 58 (37.9%) who were 5-10 years and 27 (17.6%) were  $>10$  years old. Boys (61.4%) were more predominant than girls (38.6%). **[Table 1]** Mean 24hrs urinary volume was  $1097.78 \pm 662.63$

ml, 24hrs urinary creatinine was  $32.17 \pm 23.70$  mg/dl, 24hrs urinary total protein was  $851.42 \pm 123.68$  mg/dl, 24hrs UTP was  $7.52 \pm 7.65$  gm/m<sup>2</sup>/24hrs, 24hrs urinary specific gravity  $1.02 \pm 0.02$ , Spot urinary protein  $989.49 \pm 1136.73$  mg/dl, Spot urinary creatinine  $46.09 \pm 43.73$  mg/dl, Spot urinary PCR  $21.87 \pm 18.24$  and Spot urinary specific gravity was  $1.02 \pm 0.01$  [Table 2]. It was found that at a cut-off value of 1.020 poor sensitivity and specificity of both 24hrs urinary specific gravity (64% and 41%) and spot urinary specific gravity (64% and 39%) as a marker in predicting proteinuria (Heat coagulation test >++) in children with nephrotic syndrome [Table 3]. At a cut-off value of 1.020 sensitivity and specificity of spot urinary specific gravity are 65.5% and 100% as a marker in predicting proteinuria (spot urinary PCR >2 mg/mg) in children with nephrotic syndrome. The positive predictive value is 100% but the negative predictive value is very poor (13.8%). [Table 4] At a cut-off value of 1.020 of 24hrs urinary specific gravity, sensitivity is 63.7% and specificity is 85.7% as a marker in predicting 24 hours proteinuria (>1000mg/m<sup>2</sup>/day) in children with nephrotic syndrome, the positive predictive value is 98.9% but the negative predictive value is very poor, 10.2%. [Table 5] It was seen that predicting proteinuria (24hrs dipstick protein >++) in children with nephrotic syndrome, the sensitivity of 24hrs urinary specific gravity was 65.7% and specificity was 80% at cut off value of 1.020 with good positive predictive value 95.8% and poor negative predictive value 25%. [Table 6] 57.6% sensitivity and 85.7% specificity of spot

urinary specific gravity with high positive predictive value (95%) and low negative predictive value (30%) as a marker in predicting proteinuria (spot dipstick protein >++) in children with nephrotic syndrome. [Table 7] Area under the curve (AUC) of 24 hours urinary specific gravity was 0.551 and spot urinary specific gravity was 0.520 in the prediction of proteinuria (heat coagulation test >++) in children with nephrotic syndrome. Spot urinary specific gravity and 24 hours urinary specific gravity diagnosed proteinuria >++ defined by heat coagulation test correctly of total subjects respectively 52% and 55.1% only. [Figure 1] Area under the curve (AUC) of spot urinary specific gravity was 0.872 in the prediction of proteinuria (spot urinary PCR >2 mg/mg) in children with nephrotic syndrome. It indicated that 87.2% of the total subjects had been diagnosed with proteinuria correctly defined as spot urinary PCR >2 mg/mg by spot urinary specific gravity [Figure 2] Area under the curve (AUC) of 24hrs urinary specific gravity was 0.789 in the prediction of proteinuria (>1000mg/m<sup>2</sup>/day) in children with nephrotic syndrome. It indicated that 78.9% of the total subjects had been diagnosed with proteinuria correctly defined as 24 hours of proteinuria (>1000mg/m<sup>2</sup>/day) by 24 hours of urinary specific gravity [Figure 3] Scatter diagram showed the area under the curve (AUC) of 24hrs urinary specific gravity was 0.734. So, 24 hours of urinary specific gravity diagnosed proteinuria (24hrs dipstick protein >++) in 73.4% of the study population correctly. [Figure 4] Area under the

curve (AUC) of spot urinary specific gravity was 0.719. So, spot urinary specific gravity diagnosed proteinuria (spot dipstick protein >++) in 71.9% of the study population correctly. [Figure 5]

**Table 1: Demographic profile of the study subjects (N=153)**

Features	N	%
<b>Age (years)</b>		
2 – 5	68	44.4
5 – 10	58	37.9
>10	27	17.6
<b>Gender</b>		
Boy	94	61.4
Girl	59	38.6

**Table 2: Laboratory urine findings of the study subjects (N=153)**

Laboratory parameters	Mean SD	Min-Max
24hrs urinary volume (ml)	1097.78 ± 662.63	200.00 - 3400.00
24hrs urinary creatinine(mg/dl)	32.17 ± 23.70	3.24 – 155.69
24hrs urinary total protein (mg/dl)	851.42 ± 123.68	8.00 - 11046.00
24hrs UTP (gm/m <sup>2</sup> /24hrs)	7.52 ± 7.65	0.10 - 67.00
24hrs urinary specific gravity	1.02 ± 0.02	1.00 - 1.025
Spot urinary protein (mg/dl)	989.49 ± 1136.73	0.70 - 6147.30
Spot urinary creatinine (mg/dl)	46.09±43.73	0.87-306.79
Spot urinary PCR	21.87 ± 18.24	0.14 - 148.06
Spot urinary specific gravity	1.02 ± 0.01	1.00 - 1.030

**Table 3: Effectiveness of urinary specific gravity in the prediction of proteinuria (heat coagulation test >++) in children with nephrotic syndrome (N=153)**

Laboratory parameter	Cut off	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
24hrs urinary specific gravity	1.020	0.640	0.410	0.511	0.542
Spot urinary specific gravity	1.020	0.640	0.397	0.505	0.534

**Table 4: Effectiveness of spot urinary specific gravity in the prediction of spot urinary PCR (>2 mg/mg) in children with nephrotic syndrome (N=153)**

Laboratory parameter	Cut-off	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
Spot urinary specific gravity	1.020	0.655	1.000	1.000	0.138

**Table 5: Effectiveness of 24hrs urinary specific gravity in the prediction of proteinuria (>1000mg/m<sup>2</sup>/day) in children with nephrotic syndrome (N=153)**

Laboratory parameter	Cut-off	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
24-hour urinary specific gravity	1.020	0.637	0.857	0.989	0.102

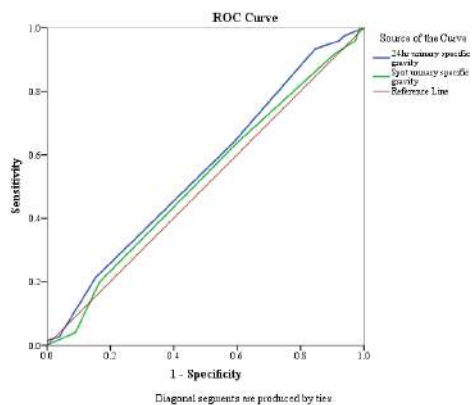
**Table 6: Effectiveness of 24hrs urinary specific gravity in the prediction of 24hrs dipstick protein (>++) in children with nephrotic syndrome (N=153)**

Laboratory parameter	Cut-off	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
24-hour urinary specific gravity	1.020	0.657	0.800	0.958	0.250

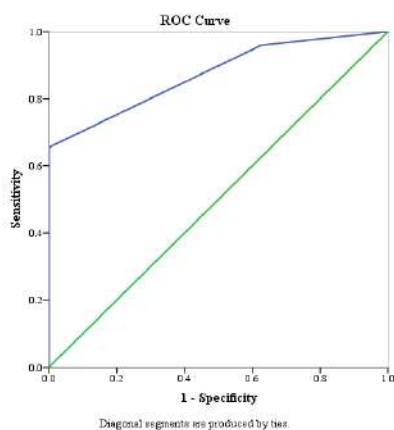
**Table 7: Effectiveness of spot urinary specific gravity in the prediction of spot dipstick protein (>++) in children with nephrotic syndrome (N=153)**

Laboratory parameter	Cut-off	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
Spot urinary specific gravity	1.020	0.576	0.857	0.950	0.300

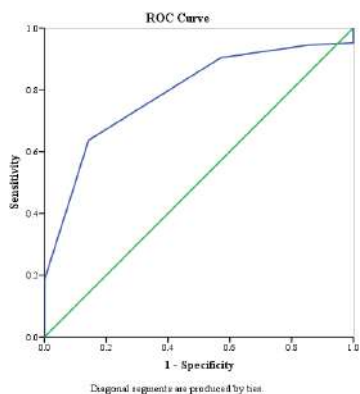
**Figure 1: ROC curve of 24 hours urinary specific gravity and spot urinary specific gravity in the prediction of proteinuria (heat coagulation test >+).**



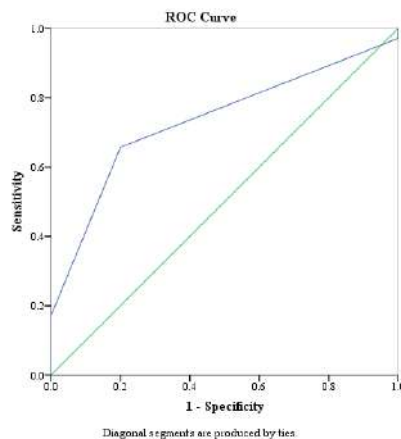
**Figure 2: ROC curve of spot urinary specific gravity in the prediction of proteinuria (spot urinary PCR >2 mg/mg)**



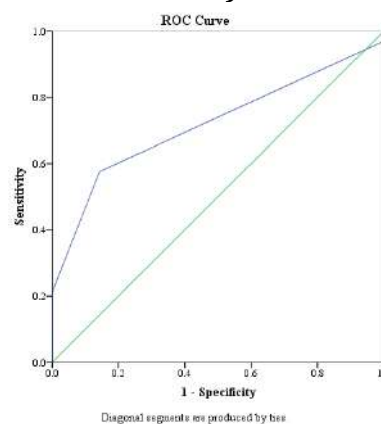
**Figure 3: ROC curve of 24hrs urinary specific gravity in the prediction of 24 hours proteinuria (>1000mg/m<sup>2</sup>/day).**



**Figure 4: ROC curve of 24 hours urinary specific gravity in the prediction of proteinuria (24hrs dipstick protein >+).**



**Figure 5: ROC curve of spot urinary specific gravity in the prediction of proteinuria (spot dipstick protein >+)**



**DISCUSSION**

Maximum study subjects (44.4%) were 2 – 5 years old followed by 58 (37.9%) were 5-10 years and 27 (17.6%) were >10 years old. In a study, the majority of the patients belonged to the 1-5 years age group i.e. 45% between 0-5 years and 42.5% between 6-10 years, and only 12.5% of cases belonged to >10 years of age which was similar to this study. [12] Male predominance was observed in a study, where males were 62.0% and females were 38.0%. A similar observation was also made by another



study which was quite similar to this study. [13][14] In a study, mean urinary protein was found to be  $1.85 \pm 0.94$  (gm/L) or  $185 \pm 94$  mg/dl which is lower than this study, creatinine  $38.08 \pm 14.34$  (mg/dl) is near to this study, and the ratio is  $5.32 \pm 3.08$  when spot urine investigations were done at the first week that is lower compared to this study [12] In this study, spot urinary protein creatinine ratio was  $21.87 \pm 18.24$ . According to the study of an author, the ratio was found to be 5.55, a study done by the other two authors also showed a lower ratio of 3.28 and 2.52 respectively. Before taking a sample of 2<sup>nd</sup>-morning urine for spot urinary protein creatinine ratio most of the study patients got I/V diuretics routinely for treatment purposes as a result creatinine concentration became low in the sample. It may be the reason for getting a higher value of spot PCR in this study than in others. [15][16][17] In this study 24hrs urinary specific gravity was  $1.02 \pm 0.02$  and spot urinary specific gravity was  $1.02 \pm 0.01$ . A study showed that the urine specific gravity (mean  $\pm$  SD) with dipstick test results of proteinuria -,  $\pm$ , 1+,  $\geq$ 2+ were  $1.011 \pm 0.007$ ,  $1.020 \pm 0.006$ ,  $1.024 \pm 0.007$ , and  $1.020 \pm 0.008$ , respectively. [18] In this study Area Under Curve (AUC) of 24 hours urinary specific gravity was 0.551 and spot urinary specific gravity (0.520) was low in prediction of proteinuria (heat coagulation test >++) in children with nephrotic syndrome. But good value of AUC for 24 hours urinary specific gravity (0.789) in prediction of proteinuria (24 hours proteinuria >1000mg/m<sup>2</sup>/day) and spot urinary specific gravity (0.872) in prediction of proteinuria (spot urinary PCR >2mg/mg) was observed. Area under curve (AUC) of spot urinary specific gravity was (0.719) in prediction of proteinuria (spot dipstick protein >++) and 24 hours urinary specific gravity (0.734) in prediction of

proteinuria (24 hours dipstick protein >++) in children with nephrotic syndrome were not poor also. Best sensitivity, specificity, PPV and NPV of 24 hours urinary specific gravity and spot urinary specific gravity were at a cut off value of 1.020. Sensitivity and specificity were poor for both 24 hours urinary specific gravity (64% and 41%) and spot urinary specific gravity (64% and 39%) in predicting proteinuria defined by heat coagulation test >++ in children with nephrotic syndrome. Sensitivity and specificity of spot urinary specific gravity were 65.5% and 100% as a marker in predicting proteinuria (spot urinary protein creatinine ratio >2 mg/mg) in children with nephrotic syndrome with 100% Positive predictive value and 13.8% negative predictive value. As a marker in predicting proteinuria defined by spot dipstick protein >+, sensitivity and specificity of spot urinary specific gravity were 57.6% and 85.7% with 95% positive predictive value and 30% negative predictive value. In predicting proteinuria (24hrs dipstick protein >++) in children with nephrotic syndrome, sensitivity was 65.7% and specificity was 80% with good positive predictive value 95.8% and 25% negative predictive value. Sensitivity is and specificity is of 24hrs urinary specific gravity were 63.7% and 85.7% respectively as a marker in predicting 24 hours proteinuria (>1000mg/m<sup>2</sup>/day) in children with nephrotic syndrome with 98.9% positive predictive value and 10.2% negative predictive value. A study showed the diagnostic accuracy of urine dipstick for proteinuria. When PCR  $\geq$ 0.5 g/g was set as standard, the AUC of the ROC curve was 0.968 (95% CI, 0.964–0.971) and the 1+ cut-off was closest to the ideal test point. When the positive dipstick result was set as a trace or more, they obtained 98.6% sensitivity, 75.6% specificity, and 56.8% PPV. At cut-off value for the dipstick resulted in 1+ or

greater 95.6% sensitivity, 86.9% specificity, and 70.4% PPV observed. [19]

### Limitations of The Study

The study was conducted in a single hospital with a small sample size for a short duration. It was not possible to collect a large number of sample due to pandemic situation of COVID 19. So, the results may not represent the whole community. Urinary specific gravity is influenced by several factors and hydration status is most important among them. Children with nephrotic syndrome usually have low effective blood volume. Moreover the patients of this study got diuretics daily 12 hourly that aggravated dehydration status more. During sample collection hydration status was not estimated properly. It was not possible to overcome this confounding factor.

### CONCLUSION

In this study, it was revealed that both 24 hours urinary specific gravity and spot urinary specific gravity had significant specificity and sensitivity for predicting proteinuria defined as 24 hours UTP (>1000mg/m<sup>2</sup>/day) and spot PCR >2 mg/mg respectively at cut off value of 1.020. According to this study finding it can be concluded that 24 hours and spot urinary specific gravity can be considered as a diagnostic test to detect urinary protein excretion in patients with nephrotic syndrome

### RECOMMENDATION

Urinary specific gravity may be used in detection of proteinuria in children with nephrotic syndrome so that it can guide the physicians in early detection of relapse of nephrotic syndrome.

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**Conflict of interest:** None declared

**Ethical approval:** The study was approved by the Institutional Ethics Committee

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