STUDY EVALUATION OF URINE PROTEIN/URINE CREATININE RATIO FOR QUANTIFICATION OF PROTEINURIA IN RAPID AND RELIABLE DIAGNOSIS OF NEPHROTIC SYNDROME

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ABSTRACT

BACKGROUND

Nephrotic syndrome is a common renal disease in 2-6-year-old children characterised by proteinuria, hypoalbuminemia, oedema and hypercholesterolemia. Incidence is 2-3 /1 lakh children per year. Without treatment, nephrotic syndrome in children is associated with significant morbidity and mortality.

Aim of the study is to evaluate the usefulness of urine protein/urine creatinine ratio of (UP/UC) in a random and reliable test for the quantification of proteinuria.

MATERIALS AND METHODS

This is a prospective case control study for a period of one year i.e., from 1st July 2013 to 30th June 2014 carried out in the paediatric wards of King George Hospital, Visakhapatnam, Andhra Pradesh. A case group of 40 children suffering from nephrotic syndrome and a control group of 40 children with proteinuria due to causes other than nephrotic syndrome who fulfilled the inclusion criteria were included in the study.

RESULTS

A case group of 40 children between the ages of 2-12 years who were admitted with nephrotic syndrome during the study period. Males were 24(60%) and 16(40%) females. 24(60%) children presented with first episode and 16(40%) children with relapse at the time of admission. All cases presented with anasarca. 21(52.5%) children also had scrotal oedema. Oliguria was present in 39(97.5%) cases and UTI in 22 (55%) children.

Regarding lab investigations, urine albumin was found to be 4+ in 36 children. Mean values of serum creatine was 0.603 mg//dl. Urine spot protein to urine creatine ratio was 6.16 in study group, whereas it was 1.01 in control group and the p value was statistically significant (0.0001). Applying tests of significance and kappa statistics, the UP/UC test in comparison with 24-hour urine protein ratio values were found to have a sensitivity of 95%, positive predictive value of 95%, specificity of 95%, positive predictive value of 95% and correlation coefficient r=0.802 and p <0.0001 on linear regression method.

CONCLUSION

In the present study, the UP/UC test is highly reliable and rapid test for quantification of proteinuria, and UP/UC ratio of >3 with normal renal function represents nephrotic range proteinuria.

KEYWORDS

Nephrotic Syndrome, Proteinuria, UP/UC Ratio, Renal Function.

HOW TO CITE THIS ARTICLE: Chakravarthy BS, Prathima Devi S. Study evaluation of urine protein/urine creatinine ratio for quantification of proteinuria in rapid and reliable diagnosis of nephrotic syndrome. J. Evid. Based Med. Healthc. 2018; 5(47), 3282-3287. DOI: 10.18410/jebmh/2018/667

BACKGROUND

Nephrotic syndrome is a common renal disease all over the world and characterized by heavy proteinuria (>40 mg/m^2/hour or 3+/4+), hypoalbuminemia (≤2.5 gm/dl), oedema and hyperlipidaemia (cholesterol >200 mg/dl). Its incidence is reported to be 2-3/1 lakh children per year.[1] In approximately 90% of children the cause of nephrotic syndrome is idiopathic and in 3-5% cases it is secondary to a systemic disorder. The onset of minimal change nephrotic syndrome, which is the commonest form in children is usually between 2-6 years of age and with male preponderance. 80% cases respond to corticosteroid therapy. Untreated nephrotic syndrome in children is associated with high risk morbidity and mortality, particularly due to infections. The most commonly used definitive method for quantitative estimation is 24-hour urinary protein. Nephrotic range of proteinuria is defined as proteinuria >3.5 gm/24-hours or urine protein: creatinine ratio >2.

Chemically measuring the protein in a timed collection of urine, typically over 24-hours, is a more precise way of determining protein excretion but is difficult in young children. The urine protein to creatinine ratio can be used to

Financial or Other, Competing Interest: None.
Submission 30-10-2018, Peer Review 01-11-2018,
Acceptance 17-11-2018, Published 19-11-2018.
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DOI: 10.18410/jebmh/2018/667

screen for abnormal protein excretion without the necessity of an accurately timed collection and is especially useful for following children with Proteinuria in whom repetitive 24-hour urine collections are cumbersome and this study helps in children.[2]

MATERIALS AND METHODS

The present study was conducted out on children admitted to paediatric wards of King George hospital, Andhra medical college, Visakhapatnam, Andhra Pradesh during the period of 1st July 2013 to 30th June 2014. This is a prospective case control study comprising of two groups selected by purposive sampling technique.

Group 1 (case group): Number of cases of nephrotic syndrome-40.

Group 2 (control group): Number of patients who are admitted for evaluation of proteinuria secondary to causes other than nephrotic syndrome like acute nephritic syndrome, urinary tract infection-40.

Inclusion Criteria

All cases of nephrotic syndrome in whom steroid therapy is not yet started. All cases satisfied the following criteria:

1. Massive proteinuria >40 mg/m^2/hour
2. Hypoalbuminemia <2.5 gm/dl
3. Generalised oedema
4. Hypercholesterolemia >200 mg/dl

Exclusion Criteria

Abnormality of renal function as evidenced by the presence of abnormal biochemical parameters, i.e.

1. Blood urea
2. Serum creatinine

Exclusion criteria was considered as a necessity for this study since the ratio of urine protein and creatinine in a random sample reflects the protein excretion only in presence of a stable glomerular filtration rate.

Cases noted down into the proforma with respect to history, examination and investigation.

Following parameters are noted on entry into study as per the proforma.

1. History
2. Examination
3. Investigation

All patients were asked to carefully collect a 24-hour urine protein sample which is measured using Esbach's Albuminometer.

A random urine sample was obtained, and urine protein/creatinine ratio was calculated. Urine protein was estimated by Biuret method and creatinine is measured by Jaffe's reaction. The random urine, protein-creatinine ratio was calculated mg/mg.

Comparison of cases and controls was done with respect to a single pertinent variable, i.e. proteinuria.

Statistical Analysis

Data was analysed by linear regression and by calculating the correlation coefficient between urinary protein/creatinine ratio and 24-hour urinary protein. The validity of this test was assessed by sensitivity, specificity and positive predictive value. Also, chi-square test was applied for non-parametric data.

RESULTS

Present study was conducted in the department of paediatrics, King George hospital from July 2013 to June 2014. A total of 40 children with nephrotic syndrome who fulfilled the inclusion criteria were included in the study.

Age (Years)	Male		Female		Total	
	No.	%	No.	%	No.	%
0-1	0	0%	0	0%	0	0%
2-5	13	61.9%	8	38.1%	21	100%
6-12	11	57.9%	8	42.1%	19	100%
>12	0	0%	0	0%	0	0%
Total	**24**	**60%**	**16**	**40%**	**40**	**100%**

Table 1. Age and Sex Distribution of Cases (n=40)

	Number	Percentage
First attack	24	60%
Relapse	16	40%
Total	40	100%

Table 2. Mode of Presentation in Cases (n=40)

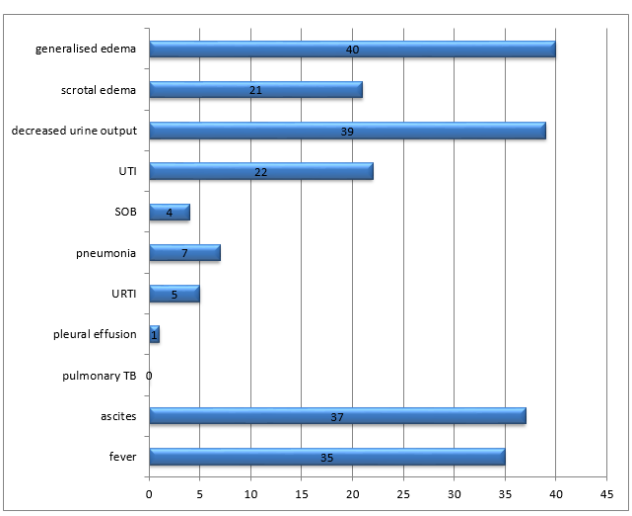

Figure 1. Distribution of Symptoms and Complications among Cases (n=40)

Urine Albumin	Cases	Controls	Total
1+	0	26	26
2+	0	14	14
3+	4	0	4
4+	36	0	36
Total	**40**	**40**	**80**

Table 3. Distribution of Urine Albumin Levels among Cases and Controls

Chi square value=80.000, df=3, P value=0.0001 (significant).

Range	2-60
Mean	10.625
Standard deviation (SD)	9.6813
Standard error (SE)	1.5307
Table 4. Pus Cells (n=40)	

Range	12-33 mg/dl
Mean	22.988 mg/dl
Standard deviation (SD)	4.6306 mg/dl
Standard error (SE)	0.7322 mg/dl
Table 5. Blood Urea	

Range	0.4-0.8 mg/dl
Mean	0.603 mg/dl
Standard deviation (SD)	0.1405 mg/dl
Standard error (SE)	0.0222 mg/dl
Table 6. Serum Creatinine (n=40)	

Range	1.6-2.6 gm/dl
Mean	2.0110 gm/dl
Standard deviation (SD)	0.25915 gm/dl
Standard error (SE)	0.04097 gm/dl
Table 7. Serum Albumin (n=40)	

Range	246-804 mg/dl
Mean	352.375mg/dl
Standard deviation (SD)	103.1277 mg/dl
Standard error (SE)	16.3059 mg/dl
Table 8. Serum Cholesterol (n=40)	

Range	2.54-18.30
Mean	6.16
Standard deviation (SD)	3.85
Standard error (SE)	0.60
Table 9. Urine Spot Protein to Creatinine Ratio in Cases (n=40)	

Range	0.32-3.89
Mean	1.01
Standard deviation (SD)	0.66
Standard error (SE)	0.10
Table 10. Urine Spot Protein to Creatinine Ratio in Controls (n=40)	

On unpaired t test, the difference of means between the two groups was found to be statistically significant. (t=8.317, df=78, P value=0.0001).

Range	3.11-3.98
Mean	3.3298
Standard deviation (SD)	0.24730
Standard error (SE)	0.03910
Table 11. 24 Hour Urinary Protein in Cases (n=40)	

Range	0.14-2.85
Mean	0.3730
Standard deviation (SD)	0.49286
Standard error (SE)	0.07793
Table 12. 24 Hour Urinary Protein in Controls (n=40)	

On unpaired t test, the difference of means between the two groups was found to be statistically significant. (t=33.913, df=78, P value=0.001).

Urine Protein/Creatinine Ratio	**Proteinuria (24 Hour) >3gm/day**	**Proteinuria (24 Hour) <3gm/day**
>3.0	38(a)	2(b)
<3.0	2(c)	38(d)
Table 13. Validity Indicators of Urine Protein/Creatinine		

On applying the tests of significance, chi square value was found to be 64.800, with df=1 and P value of 0.001, which is statistically highly significant. Further analysis was done by applying kappa statistics, to see the percentage of agreement between urine protein/creatinine ratio and 24-hour proteinuria and it was found that kappa value was 0.9 which shows a strong agreement between the two tests.

- Sensitivity= a/a+c*100=95%
- Specificity=d/b+d*100=95%
- Positive predictive value=a/a+b*100=95%
- Negative predictive value=d/c+d*100=95%
- Percentage of false negative=c/a+c*100=5%
- Percentage of false positive=b/b+d*100=5%

In the present study, out of 40 cases, 21 cases were in the age group of 2-5 years and 19 cases were in the age group of 6-12 years. None of the nephrotic syndrome patients were below 2 years and above 12 years. There was male preponderance in this study. 24 (60%) were males and 16 (40%) were females in the present study. While 60% of the patients presented for the first time, about 40% of the patients had relapse at the time of admission. All the cases presented with generalised oedema. About half of the cases i.e., 52.5% had presented with scrotal oedema. A significant history i.e., history of decreased frequency and volume of urine output was observed in 39 (97.5%) cases. Respiratory complications were reported in few cases. Shortness of breath was reported in four (10%) of cases. Seven (17.5%) cases had pneumonia. Five (12.5%) cases had upper respiratory tract infection. One case (2.5%) developed pleural effusion. None of the cases developed pulmonary tuberculosis. Ascites was observed in 37(92.5%) of the cases. Whereas fever was observed in 35(87.5%) of the cases. Most of the cases had 3+, 4+ urine albumin levels whereas most of the controls had 1+, 2+ levels of urine albumin. This difference was found to be statistically significant.

DISCUSSION

This study on evaluating the utility of random urine protein/creatinine ratio was conducted between 1st July 2013 to 30th June 2014 on the cases of nephrotic syndrome admitted in the paediatric wards of king George hospital, Andhra medical college, Visakhapatnam.

Age Distribution

In the present study the age distribution of cases ranged from 2 years to 12 years. The mean age in the present study was 6.02 years.

Similar observations were made by Chahar OP et al.[3] and Shastri NG et al.[4]

Study	N	Range	Mean
Present study	40	2-12 years	6.02 years
Chahar OP et al.[3]	30	2.5-14 years	6.7 years
Shastri NJ et al.[4]	79	1.5-12 years	7.3 years

Table 14

Eventhough commonly nephrotic syndrome is seen in pre-school children, in our study the mean age was 6.02 years as majority of cases (60%) were first attacks.

Study	N	Males	Females	M:F ratio
Present study	40	24	16	3: 2
Siegel NJ et al.[5]	61	47	14	3.35: 1

Table 15

Mode of Presentation

In the present study, 60% of cases who had nephrotic syndrome for the first time and 40% got admitted with relapse.

Duration of Symptoms Prior to Presentation

In the present study, the duration of symptoms prior to the presentation ranged from 3 days to 20 days.

Symptomatology

Oedema

Present study showed face and limbs as the commonest site to be involved i.e. in 100% whereas oedema involving genital area was least i.e. in 52.5% cases. Only 5 patients presented with respiratory distress due to massive oedema. (pleural effusion and massive ascites).

Micturition

All most all cases i.e. 97.5% presented with history of decreased frequency and volume of micturition. 55% of cases had burning micturition and all of them had UTI.

Other Symptoms

87.5% of cases had fever.

Other Signs

Oedema

Pitting type of oedema was noticed in all patients in the present study. Ascites was present in 92.5% of cases.

Infections and/or Complications Associated with Nephrotic Syndrome

Present study (n=40) showed UTI and pneumonia to be present in 55% and 17.5% of cases respectively.

Gorensek MJ et al.[6] (n=214) in a 20-year retrospective study observed 17.3% cases of peritonitis.

Study	Number	Percentage of Case
Present study	40	0
Gorensek MJ et al.[6]	214	17.3

Table 16

No cases were observed in our study because of small number of sample size and short duration of study whereas Gorensek et al.[6] studied for a period of 20 years.

Investigative Parameters

1. Haemoglobin (HB gm/dl): in the present study (n=40), 75% of cases showed presence of anaemia. The value of Hb ranged from 8 gm/dl to 13 gm/dl.
2. Total leucocyte count (TLC): in the present study (n=40), the total leucocyte count ranged from 3500-14,500 cells/mm^3.
3. Blood urea: in the present study the value of blood urea ranged from 12-33 mg/dl. The mean value of blood urea was noted to be 22.98 mg/dl.
4. Serum creatinine: in the present study the value of serum creatinine ranged from 0.4-0.8 mg/dl. The mean value of serum creatinine observed was 0.603 mg/dl.
5. Serum albumin: in the present study, serum albumin ranged from 1.6 gm to 2.4 gm/dl. The mean serum albumin level observed was 2.01 gm/dl. Similar observations were made by Hiraoka et al.[7]

Study	Serum Albumin
Present study	2.01 g/dl
Hiraoka et al.[7]	1.8 g/dl

Table 17

Serum Cholesterol

The range of serum cholesterol in the present study was 246-804 mg/dl and the mean serum cholesterol was noted to be 352 mg/dl. Similar observations were made by Appeal GB et al.[7]

Study	No.	Mean (mg/dl)
Present study	40	352
Appeal GB et al.[8]	20	302

Table 18

Urine Analysis

Urine Culture: UTI was noted in 55% of cases in the present study. E. coli, proteus, klebsiella were the organisms grown in 50%, 8%, 41% of cases respectively.

Urine protein by sulphosalicylic acid method (random sample): all cases showed urine protein to be > 3+ in the present study.

Urine Total Protein in a Timed 24-Hour Sample

In the present study, the range observed was 3.11-3.98 g/24-hours with a mean value of 3.32g/24-hour.

Iyer RS et al.[9] found the range of timed 24-hours urine protein to be 0.8-7 gm/24-hour and a mean value of 4.6g/24-hour was observed.

Study	No.	Range	Mean
Present study	40	3.11-3.98	3.32
Iyer RS et al.[9]	50	1.6-8.6	4.6±1.8

Table 19

Urine Protein/ Creatinine Ratio in a Random Sample of Cases: in the present study (n=40) the range of values observed was 2.54-18.30 with a mean of UP/UC 6.16.

The observed value for range and mean of UP/UC in various studies are given below.

Study	Number	Value of UP/UC in the Diagnosis of Nephrotic Syndrome	Range of Observed Values of UP/UC	Mean
Present Study	40	>2	2.54-18.3	6.16
Abitbol C et al.[10]	64	>3	*	*
Iyer RS et al.[9]	50	>3.5	1.7-9.6	5.5±2
Chahar OP et al.[3]	30	>3	1.25-6.22	2.52
Shastri NJ et al.[4]	79	>1**	*	*

Table 20

*details not mentioned; **log converted

Validity Indicators of Random Urine Protein/Creatinine Ratio in Cases of Nephrotic Syndrome

In the present study sensitivity of UP/UC ratio was 95% and specificity was 95%. The values obtained in this study was compared to various other studies, i.e. by Abitbol C et al.[10] Iyer RS et al.[9] Shastri NJ et al.[4] and were comparable to the values obtained by them.

The following table shows comparison of validity indicators of random urine protein/creatinine ratio in cases of nephrotic syndrome in various studies.

Study	Number	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Present study	40	95%	95%	95%	95%
Abitbol C et al[10]	64	95%	93%	93%	100%
Iyer RS et al[9]	50	97%	97%	95%	93%
Shastri NJ et al[4]	79	96%	96%	96%	98%

Table 21

Correlation Coefficient (r) between Values of 24-Hour Urine Protein and Random UP/UC Ratio

In the present study, correlation coefficient obtained in cases was 0.802, in control 0.891 and in the both groups combined value obtained was 0.753 and in all three groups value obtained was statistically significant ($p<0.001$).

The correlation coefficient obtained in the other studies is mentioned below and, in their studies, also values obtained were highly significant ($p<0.001$).

Studies	Correlation Coefficient
Present study	r=0.80
Abitbol [9]	r= 0.97
Shastri NJ et al.[4]	r=0.95

Table 22

CONCLUSION

Urine total protein in timed 24-hour sample of nephrotic syndrome patients was in the range of 3.11-3.98 gms with the mean value of 3.32 gms while as UP/UC ratio ranged from 2.54-18.30 with the mean value of 6.16.

Urine total protein in a 24-hour sample- proteinemia secondary to causes other than nephrotic syndrome (like AGN, UTI) was in the range of 0.14-2.85 gms with the mean value of 0.37 gms while as UP/UC ratio ranged from 0.32-3.89 with the mean value of 1.01.

A significant correlation was found between times 24-hour urinary protein and UP/UC ratio in both the groups, i.e. as timed 24-hour urinary protein increased UP/UC ratio also increased linearly.

Thus, we conclude that random urine protein-creatinine ratio is highly reliable and rapid test for qualification of proteinuria in children. It reflects the amount of protein in a 24-hour collection and UP/UC ratio >3 in patients with normal renal function which represents nephrotic range proteinuria. Thus, it avoids all the drawbacks which are associated with time collection method.

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