

Spot Urine Protein: Creatinine Ratio as Risk Factor in Relapsing Nephrotic Syndrome

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Abstract

Background: Nephrotic Syndrome is a common childhood illness. Major problem with this disease is frequent relapse. So, it is important to identify the children at risk for relapses to treat and further follow up.

Aim & Objective: Aim of present study was to determine Spot PCR is a strong indicator of relapse in Nephrotic Syndrome. The primary objective of study was to determine the correlation between acute phase Spot PCR and subsequent relapses in Nephrotic Syndrome.

Material and Method of study: Fifty five children having Nephrotic Syndrome were included in this prospective cohort study at Rajendra Institute of Medical Sciences, Ranchi, Jharkhand. Spot urine protein:creatinine ratio was estimated at the acute phase of disease before starting steroid therapy. These cases were followed up for six months from the time of remission to look for further relapse. Follow up was done every 2 weeks.

Results: In our study Spot PCR level for Relapsers was 10.18 ± 8.20 mg/mg and for non-relapsers was 4.1 ± 2.0 mg/mg. High level of Spot PCR at acute phase of Nephrotic syndrome was a risk factor for relapse with adjusted OR = 1.64, significance = 0.001.

Conclusion: Significantly elevated level of Spot PCR at acute phase of disease is a predictor of further relapses in Nephrotic syndrome.

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I. Introduction

Nephrotic syndrome is the clinical manifestation of glomerular disease associated with heavy proteinuria (nephrotic range). Nephrotic syndrome is characterised by proteinuria >40 mg/m²/hr, hypoalbuminemia <2.5 mg/dl, edema, and hypercholesterolemia >200 mg/dl. The proteinuria is relatively selective, primarily constitute albumin¹.

In Developed countries, the incidence of nephrotic syndrome is reported to be 20-40 per million population while in the Indian subcontinent it is estimated at 90-100 per million population².

More than 90% of childhood nephrotic syndrome is primary (idiopathic) and 10% is secondary³. Primary nephrotic syndrome is either congenital (Finnish type), minimal change disease ($>80\%$) or due to focal segmental glomerulosclerosis, mesangial proliferation and membranoproliferative glomerulonephritis. Secondary nephrotic syndrome occurs in systemic lupus erythematosus, anaphylactoid purpura, sickle cell disease, Hodgekins lymphoma, diabetes mellitus, amyloidosis, malaria, intrauterine infections (syphilis, toxoplasmosis, cytomegalovirus infection) and other infections like HIV, parvovirus B19 and hepatitis B and C viruses.

Glucocorticoid therapy is the standard therapy for nephrotic syndrome. Based on steroid responsiveness the idiopathic nephrotic syndrome may be classified into- 1) steroid responsive nephrotic syndrome, in which proteinuria rapidly resolves after starting steroid therapy, and 2) steroid-resistant nephrotic syndrome, in which steroids do not induce remission⁴. 80% of children with nephrotic syndrome respond to corticosteroid therapy.

Without treatment, nephrotic syndrome in children is associated with a high risk of death, most commonly from infections. Steroid sensitive nephrotic syndrome has a satisfactory long term outcome. In contrast, the steroid resistant form has a less satisfactory course and significant proportion progress to chronic renal failure⁵.

Quantitative measurement of proteinuria by a 24 hour urine collection has been the accepted method of evaluation, but it is associated with many errors including incomplete collection, incorrect timing, incomplete bladder voiding and bacterial growth.

An alternative approach has been advocated by some researchers avoiding 24 hours collection. This is the measurement of protein:creatinine ratio in a random urine sample. This approach is based on the fact that in the presence of a stable glomerular filtration rate, urinary creatinine excretion has been reported to be fairly

constant in a given individual⁶. Random urine collection is simple and can be done at any time of the day preferably in the morning. A test for quantification of urinary protein excretion in term of protein:creatinine ratio can be performed to predict accurately the level of proteinuria and relevant to assess the prognosis and treatment of renal disease .

Hence we have performed a study to assess prognosis and relapses of nephrotic syndrome by assessing spot protein: creatinine ratio.

II. Materials And Methods

It is a prospective cohort study, which includes children diagnosed as having Nephrotic syndrome at Rajendra Institute of Medical Sciences, Ranchi, Jharkhand from June 2017 to May 2019.

Study design: prospective cohort study

Study location: Rajendra Institute of Medical Sciences, Ranchi, Jharkhand

Study duration: from June 2017 to May 2019

Sample size :55 cases of nephrotic syndrome in whom steroid therapy is not yet started.

Inclusion criteria: All cases of nephrotic syndrome in whom steroid is not yet started

- Massive proteinuria >40mg/m²/hour
- Hypoalbuminaemia <2.5g/dl
- Generalised edema
- Hypercholesterolemia >250mg/dl
- Spot urine protein:creatinine ratio >2

Exclusion Criteria

- Patients with abnormal renal function and hematuria which is suggestive of nephritic syndrome.
- Nephrotic syndrome due to secondary causes such as systemic lupus erythematosus(SLE), Henoch Schonlein purpura(HSP) ,Amyloidosis, Hepatitis B,HIV etc as in this study patients with only primary or idiopathic nephrotic syndrome will be included.
- Age <1 year and >12 year

Procedure Methodology

The cases of nephrotic syndrome were followed up for six months from the time of remission to determine the further relapse. Follow up was done in every 2 weeks. All cases of nephrotic syndrome in whom steroid is not yet started were included in the study. Cases of secondary nephrotic syndrome were excluded from the study. Parental consent and ethical committee approval were obtained. Detailed clinical history was elicited and a thorough clinical examination was performed. Baseline blood investigations, Spot Protein : creatinine ratio, serum albumin, lipid profile ,urine albumin, urine culture and sensitivity, chest X ray & TB screening were performed.

Spot urine protein: creatinine ratio estimation:

Early morning urine sample was obtained before starting steroid therapy and urinary protein was estimated by Biuret method and creatinine is measured by Jaffes reaction . Spot protein : creatinine ratio will be calculated by mg/mg. The cut off value of spot pcr was >2 in children having nephrotic syndrome.

Data analysis:

Data was analysed using SPSS 21.00 Software version. The association between spot protein : creatinine ratio and relapses was analysed using chi-square test and t-test.

III. Results

In the present study, 56.4% of the cases belonged to 6-12 years age group followed by 1-5 years age group, which accounted for 43.6% of the nephrotic syndrome patients. The mean age was 6.85. There was a male preponderance in this study, 76% of cases were male while 24% of cases were female (M:F::3:1). While only 47.3% of patients presented for the first time, about 52.7% of patients had one or more relapse at the time of admission.

All patients presented with puffiness of face and swelling of limbs. The least common denominator was genital edema which was seen in only about 25.5% of cases.

A significant history, i.e. history of decreased frequency and volume of micturition was obtained in 81.8%. History of burning micturition was seen in 25.5% of cases.

63% of patients presented with massive edema while 36% of patients presented with mild edema. Hepatomegaly was present in 7.3% of cases.

In the present study UTI was the commonest (27.3%) infection associated with nephrotic syndrome. Peritonitis (1.8%), tuberculosis (3.6%) and pneumonia (1.8%) were also observed.

The mean haemoglobin level observed was 11.18g/dl.

The mean serum albumin level observed was 1.89 g/dl.

The mean serum cholesterol observed was 344.300 mg/dl.

The mean serum creatinine observed was 0.57mg/dl.

The mean blood urea observed was 30.85mg/dl.

The mean spot urine protein: creatinine ratio observed was 7.54.

Table 1: Comparison of baseline characteristics between the Relapsers and Non- relapsers

Characteristic	Relapser	Non Relapser	Chi square	P value
Age	6.48±2.63	7.3±3.09	7.652	0.5
Serum urea	31.48±14.54	29.87±12.27	29.927	0.4
Serum creatinine	0.57±0.23	0.57±0.24	0.014	0.9
Serum Albumin	1.92±0.47	1.91±0.48	0.018	0.8
Serum Cholesterol	413.9±132.4	415.3±115.6	41.447	0.5
Spot PCR	10.18±8.20	4.12±2.02	32.115	0.004

p<0.05 was considered to be statistically significant

Table 1 shows the comparison of baseline characteristics between the Relapsers and Non-relapsers which were comparable. Spot Protein:Creatinine Ratio was significantly different between Relapsers and Non-relapsers.

Table 2: Significance of Spot Protein : Creatinine Ratio

Predictors	Adjusted OR	SE	Significance	95% CI of OR
Spot PCR	1.64	0.153	0.001	1.218, 2.218

Table 2 shows further, on performing logistic regression analysis, spot PCR (adjusted OR= 1.64, p=0.001) was found to be statistically significant. So, during acute phase Spot PCR was a good predictor of relapses in Nephrotic Syndrome children.

IV. Discussion

The amount of protein excreted in urine has diagnostic and prognostic significance and it is also used to assess effectiveness of urinary creatinine excretion in the presence of a stable GFR. If GFR is fairly constant in a given patient, it can be reasoned that if the protein excretion rate were likewise fairly stable during a day, a simple ratio of the concentration of urinary protein and creatinine in a single voided urine sample, would reflect the cumulative protein excretion over a day as the ratio of two stable rates would cancel out time factor.⁷ Degree of proteinuria reflects the progression of renal disease which helps in assessing prognosis of renal disease which affecting the normal Renal functions (Caring for Australians with Renal impairment Guidelines, 2004). Estimation of protein in urine is used for not only monitoring prognosis but also for treatment purposes.

Traditionally, the assessment of proteinuria is done by collecting a 24-hours urine sample to measure the amount of protein excreted in mg per 24 hours. This method is fairly accurate but become unreliable due to the problem of 24-hours urinary samples which is never reliable. Also, the collection time is too long for the patient's patience.⁸ Protein: Creatinine ratio measurements on a single-voided specimen provide a convenient and reliable alternative method than 24-hours urine measurements.

In the present study the age distribution of cases ranged from 2 to 12 yrs. The mean age was 6.85 Yrs.

Similar observations were made by Sahana K.S et al⁹ where the mean age was 7.4.

Male: female ratio was noted to be 3.2:1.

In observation was made by Sahana K.S et al the ratio was 3.27:1.

In the present study 81.8% of cases presented to the hospital within 10 days of onset of symptoms whereas 18.2% of cases had duration of symptoms for more than 20 days before coming to the hospital.

All patients presented with puffiness of face and swelling of limbs (100%). The least common denominator was genital edema which was seen in only about 25.5% of cases.

History of decreased frequency and volume of micturition was obtained in 81.8%. History of burning micturition was seen in 25.5% of cases.

16.4% of cases had abdominal pain and 14.5% cases had fever.

Commonest infections observed was UTI in 25.5% of cases. E.Coli was commonest organism isolated.

In observation made by Tanuka Barua et al¹⁰ 30.8% cases presented with UTI.

Peritonitis was seen in 1.8% cases.

NerminUncu et al¹¹ observed 2.6% cases of peritonitis in nephrotic syndrome.

The value of Hb ranged from 6.5-14.8 and the mean Hb(g/dl) observed was 11.8.

In the present study, the value of serum creatinine ranged from 0.3mg/dl-1.2mg/dl. The mean serum creatinine observed was 0.57mg/dl. In observations were made by Navale et al⁶, mean serum creatinine observed was 0.8mg/dl.

In our study, the value of serum albumin ranged from 0.7g/dl-2.4g/dl. The mean serum albumin observed was 1.89g/dl. In observations made Krishnamurthy C et al¹² the mean serum albumin observed was 2.2g/dl.

The value of serum cholesterol ranged from 250mg/dl-778mg/d in our study. The mean observed was 414mg/dl. In observations made BhimsettiSrinivasa et al¹³ mean value was 352mg/dl.

In the present study, the value of Spot Urinary Protein:Creatinine ratio ranged from 2.2 - 41. The mean observed was 7.54.

In observations made Iyer RS et al¹⁴ mean value was 5.5.

Baseline characteristics like age, serum albumin, total cholesterol, blood urea and serum creatinine were compared between the relapsers and the non relapsers. There were no significant difference in the values of these parameters between the two groups. Spot urine protein: creatinine ratio was significantly different between Relapsers and Non-relapsers. Spot PCR level for Relapsers was 10.18±8.20 mg/mg and for non - relapsers was 4.1±2.0 mg/mg.

On performing logistic regression analysis, spot PCR (adjusted OR= 1.64, p=0.001) was found to be significant predictors of relapse.

Limitation

The present study had few limitations to be noted. Factors which affect creatinine excretion in urine like age, sex, muscle mass also affect the Spot PCR. Also the changes in Spot PCR response to therapy during follow up have to be studied further.

V. Conclusion

1. Spot PCR is a simple and convenient method for predicting relapse in children with Nephrotic syndrome.
2. Significantly elevated level of Spot PCR at acute phase of disease is a predictor of further relapses in Nephrotic syndrome.

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