

Original Research Article

EVALUATING PROTEINURIA'S PROGNOSTIC VALUE IN CHILDHOOD DENGUE INFECTIONS IN A TERTIARY CARE HOSPITAL

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Received : 28/01/2026
Received in revised form : 20/03/2026
Accepted : 03/04/2026

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DOI: 10.70034/ijmedph.2026.2.68

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (2); 411-416

ABSTRACT

Background: Dengue is a major public health problem in tropical countries, with children being particularly vulnerable to severe forms of the disease. Early identification of prognostic markers is essential in tertiary care settings to reduce morbidity and mortality. Proteinuria, resulting from endothelial dysfunction and plasma leakage, has emerged as a potential indicator of disease severity in dengue infection. **Objectives:** To correlate urine protein creatinine ratio (UPCR) with severity of illness in children diagnosed with dengue fever. To assess whether proteinuria can serve as a predictor of progression to severe dengue.

Materials and Methods: A hospital-based prospective observational study was conducted in the Department of Pediatrics over a period of one year. A total of 140 children aged 1 month to 12 years with laboratory-confirmed dengue infection were included. Daily early morning urine samples were collected from day 3 to day 9 of fever or until discharge. Proteinuria was assessed using urine dipstick and quantified by urine protein creatinine ratio (UPCR). Patients were categorized as probable dengue, dengue with warning signs, and severe dengue as per WHO criteria. Data were analyzed using SPSS version 19.0. Pearson Chi-square test and ANOVA were applied; $p < 0.05$ was considered statistically significant.

Results: Of 140 children, 55% had probable dengue, 24.2% had dengue with warning signs, and 20.7% had severe dengue. Severe dengue accounted for 38% mortality within its group. Both dipstick proteinuria and UPCR values were significantly higher in severe dengue compared to other groups ($p < 0.05$). Proteinuria peaked between days 5–6 of illness and declined during recovery. Expired patients demonstrated markedly elevated UPCR and dipstick values compared to survivors. No significant association was observed between platelet count and UPCR.

Conclusion: Proteinuria, particularly quantified by UPCR, shows significant correlation with dengue severity in children. Serial monitoring of UPCR may serve as a useful prognostic marker for early identification of severe disease and guide clinical management in tertiary care settings.

Keywords: Dengue; Proteinuria; Urine Protein Creatinine Ratio; Pediatric Dengue; Severe Dengue; Prognostic Marker; Renal Involvement.

INTRODUCTION

Dengue virus infection, transmitted primarily by *Aedes aegypti* mosquitoes, remains one of the most important arthropod-borne viral diseases globally, with an estimated 390 million infections annually and

a substantial burden among children in endemic regions.^[1] The clinical spectrum of dengue ranges from asymptomatic infection and uncomplicated dengue fever (DF) to severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which are associated with

significant morbidity and mortality.^[2] Children are particularly vulnerable to rapid deterioration during the critical phase of illness, making early identification of predictors of severity crucial in tertiary care settings.^[3]

The pathophysiology of severe dengue is characterized by increased vascular permeability, plasma leakage, thrombocytopenia, and coagulopathy.^[4] While hematocrit rise, platelet count decline, and warning signs recommended by the World Health Organization (WHO) are routinely used for monitoring disease progression, these parameters may not always reliably predict severity in the early stages of illness.^[3] Therefore, there is an ongoing search for simple, cost-effective, and early prognostic markers that can aid in risk stratification, particularly in pediatric populations.

Renal involvement in dengue infection has gained increasing attention in recent years. The spectrum of renal manifestations ranges from transient proteinuria and hematuria to acute kidney injury in severe cases.^[6] Proteinuria, in particular, is thought to result from increased glomerular permeability secondary to systemic endothelial dysfunction—a hallmark of severe dengue⁶. Since endothelial damage and capillary leakage are central mechanisms in dengue pathogenesis, urinary protein excretion may reflect the severity of plasma leakage and disease progression.

Several studies have documented the occurrence of proteinuria during the febrile and critical phases of dengue infection. Andries et al. demonstrated that proteinuria is common in children with dengue and that urine protein excretion peaks around the critical phase of illness.^[1] Their study showed that quantitative measures such as the urine protein-to-creatinine ratio (UPCR) correlated better with disease severity compared to qualitative dipstick testing¹. Similarly, Vasanwala et al. reported that peak proteinuria levels were significantly higher in patients who developed DHF or DSS compared to those with uncomplicated DF, suggesting that proteinuria may serve as a predictor of severe disease.^[6]

Dipstick proteinuria testing is inexpensive, rapid, and feasible even in resource-limited settings. However, its sensitivity in early detection of severe dengue has been reported to be suboptimal.^[2] Studies have shown that while dipstick proteinuria of $\geq 1+$ may have reasonable specificity for severe dengue, it lacks adequate sensitivity to function as a standalone screening tool.^[2] In contrast, quantitative methods such as UPCR provide a more accurate estimation of urinary protein excretion and have demonstrated stronger associations with warning signs, bleeding manifestations, and requirement for intensive care support.^[7]

Research conducted in tertiary care hospitals has highlighted that elevated UPCR values are significantly associated with complications such as shock, severe thrombocytopenia, and prolonged hospitalization.^[7] Nanjundappa et al. found that

proteinuria, when combined with other clinical and laboratory parameters, improved the predictive accuracy for severe dengue in children.^[4] Additionally, renal involvement has been shown to correlate with adverse outcomes, emphasizing the importance of monitoring urinary abnormalities during hospitalization.^[5]

Despite growing evidence, proteinuria has not yet been universally adopted as a prognostic marker in routine dengue management protocols. Variations in study design, timing of urine sampling, severity classification criteria, and methods of protein quantification have contributed to inconsistent findings across studies.^[1,6] Furthermore, most available data are derived from mixed adult and pediatric populations, with relatively fewer studies exclusively evaluating children in tertiary care settings.

Given that tertiary care hospitals manage complicated dengue cases and serve as referral centers, identifying early and reliable prognostic indicators is particularly important. Proteinuria assessment offers several advantages: it is non-invasive, repeatable, inexpensive, and easily integrated into routine clinical practice. If validated as a prognostic marker, it could aid clinicians in early risk stratification, closer monitoring of high-risk patients, timely fluid management, and optimal allocation of intensive care resources.

In endemic countries such as India and other South-East Asian regions, where dengue outbreaks impose significant strain on healthcare systems, a simple urinary biomarker could significantly enhance clinical decision-making. Therefore, evaluating the prognostic value of proteinuria in childhood dengue infections within a tertiary care hospital setting is both clinically relevant and operationally feasible.

The present study aims to assess the association between proteinuria—measured qualitatively by dipstick and quantitatively by urine protein-to-creatinine ratio—and disease severity in children with confirmed dengue infection. By examining its correlation with warning signs, complications, and clinical outcomes, this study seeks to determine whether proteinuria can serve as an early and reliable prognostic marker in pediatric dengue.

Objectives

1. To correlate urine protein creatinine ratio with severity of illness in children diagnosed to have dengue fever.
2. To assess whether proteinuria could be used as a predictor of disease progression to severe illness.

MATERIALS AND METHODS

Study Design: Hospital based prospective observational study.

Study area: The study was carried out in the Department of Pediatrics.

Study Period: 1 year.

Study population: Children of age group 1 month to 12 years diagnosed to have dengue infection admitted within the study period.

Sample size: The study consisted of a total of 140 subjects.

Sampling Technique: Convenient sampling method.

Inclusion Criteria: Children of age group 1 month to 12 years diagnosed to have dengue infection admitted within the study period.

Exclusion Criteria

1. Age < 1 month.
2. Children with pre-existing renal disease
3. Children whose parents have not given consent.

Ethical Consideration: Institutional Ethical committee permission was taken before the commencement of the study.

Study tools and Data collection procedure

A total of 140 patients who were admitted in the hospital, who showed signs and symptoms of dengue

fever and were also positive for Ns1Ag and or dengue IgM in the blood were included. At the time of admission basic data regarding age, sex and pre-existing disease were documented. Day of onset of fever was noted. Daily early morning urine samples were collected and serial measurements of urine dip stick and urine protein creatinine ratio was sent. Daily platelet counts were measured. Samples were collected from day 3 of fever to day 9 or discharge whichever comes earlier. Patients were categorized into severe dengue, dengue with warning signs and probable dengue as per WHO criteria.

Urine dip stick for proteins was done using strip method which uses the principle of the protein error of indicators to produce a visible colorimetric reaction. Indicator used is 3,4,5,6 tetrabromosulphthalin which appears yellow in the absence the proteins. As the protein concentration increases, the colour progresses to various shades of green and finally to blue.

Trace	<15 mg/dl
1+	30 mg/dl
2+	100 mg/dl
3+	300 mg/dl
4+	>1000mg/dl

Urine protein creatinine ratio is measured by QuantiChrom protein creatinine ratio assay kit in which urinary creatinine and urinary protein is calculated and their ratio is taken.

Classification of dengue

Probable Dengue	Dengue with Warning Signs	Severe Dengue
<ul style="list-style-type: none"> • live in or travel to dengue endemic area. fever and any of following criteria: • Nausea, vomiting Rash • Aches and pain Tourniquet test positive Leukopenia • Any warning sign • Lab confirmed dengue 	<ul style="list-style-type: none"> • abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • lethargy/restlessness 6. hepatomegaly>2 cm • increase in hct with decrease in platelets 	<ul style="list-style-type: none"> • Severe plasma leakage leading to shock or RDS • Severe bleeding • severe organ involvement: • Liver-AST/ALT>1000 • CNS- impaired consciousness • Heart and other organs.

Data Analysis: SPSS 19.0 version was used to analyze the data. Associations between different variables were studied using Pearson Chi Square

test& ANNOVA test. P value of <0.05 was considered as existence of statistically significant difference.

RESULTS

Table 1: Depicts age wise distribution

Age in years	Incidence
0-4	40 (28.5%)
5-9	71 (50.7%)
10-14	29 (20.7%)

Maximum number of cases were seen in the age group of 5 to 9 years of age.

Table 2: Showing age wise distribution of dengue cases based on severity

Age (Years)	Probable Dengue N=77	Dengue with warning signs N=34	Severe Dengue N=29
0-4	26 (33.7%)	7 (20%)	7 (24.1%)
5-9	33 (42.8%)	24 (70.5%)	14 (48.2%)
10-14	18 (23.3%)	3 (8%)	8 (27.5%)

Children are at higher risk of severe dengue. Severe dengue is primarily a disease of infants and children, although adults may be afflicted with severe disease. In the present study, the mean age of presentation of

probable dengue is 6.43 years, dengue with warning signs is 6.56 years, severe dengue is 6.79 years. In the present study ,62% are males and 38 % are females. The incidence of severe dengue is slightly

more in males compared to females, which was not of statistical significance.

Table 3: Clinical classification of cases and their outcome

Group	Discharged	Death	Total
Severe Dengue	18 (62%)	11 (38%)	29 (20.7%)
Dengue with warning signs	34	0	34 (24.2%)
Probable Dengue	77	0	77 (55%)
Total	129 (92.2%)	11 (7.8%)	140

In our study, the incidence of severe dengue is 20.7% .7.8% of total cases died which accounts for 38% of severe dengue cases.

Table 4: Showing the mean dipstick values for proteins from day 3 to day 9 of fever in dengue cases

Urine dip sticks mean values	Probable dengue	SD	Dengue with warning signs	SD	Severe Dengue	SD	P value
Day 3	0.32	0.02	1.41	0.32	2.11	0.62	<.05
Day 4	1.24	0.16	1.80	0.33	2.77	0.73	<.05
Day 5	1.15	0.12	2.2	0.23	3.29	1.0	<.05
Day 6	1.02	0.09	2.2	0.43	3.38	1.13	<.05
Day 7	1.00	0.03	1.62	0.12	2.52	0.98	<.05
Day 8	0.87	0.37	1.33	0.09	1.82	0.74	<.05
Day 9	0.60	0.22	1.04	0.32	1.5	0.46	<.05

The mean urine dipstick values for proteins showed higher values in severe dengue compared to other groups with statistically significant p value of <.05. The mean urine dip stick for proteins showed an increasing trend till day 5,6 followed by decreasing trends.

Table 5: Showing the mean urine protein creatinine values from day 3 to day 9 of fever in dengue cases

Urine protein creatinine ratio	Probable dengue	SD	Dengue with warning signs	SD	Severe Dengue	SD	P value
Day 3	0.14	0.03	0.58	0.06	1.22	0.43	<.05
Day 4	0.21	0.02	1.09	0.33	2.6	0.73	<.05
Day 5	0.24	0.05	1.75	0.43	3.7	1.0	<.05
Day 6	0.24	0.08	1.97	0.41	3.95	1.13	<.05
Day 7	0.21	0.03	1.60	0.24	2.83	0.98	<.05
Day 8	0.15	0.01	1.11	0.07	1.87	0.74	<.05
Day 9	0.10	0.001	0.85	0.04	1.25	0.46	<.05

The mean urine protein creatinine ratio values showed higher values in severe dengue compared to other groups with statistically significant p value of

<.05. It showed increasing trends till day 5,6 of fever followed by decreasing trends.

Table 6: Showing the mean platelet count values from day 3 to day 9 of fever in dengue cases

Urine protein creatinine ratio	Probable dengue Mean	SD	Dengue with warning signs	SD	Severe Dengue	SD	P value
Day 3	84000	0.03	82000	0.06	68000	0.43	0.10
Day 4	76000	0.02	70000	0.33	43000	0.73	0.52
Day 5	50000	0.05	44000	0.43	34000	1.0	1.1
Day 6	48000	0.08	32000	0.41	42000	1.13	2.1
Day 7	64000	0.03	68000	0.24	68000	0.98	0.43
Day 8	78000	0.01	78000	0.07	56000	0.74	0.33
Day 9	98000	0.001	92000	0.04	88000	0.46	1.12

The mean platelet counts values showed increasing trend till day 5 and day 6 of fever followed by changing patterns, which was statistically insignificant.

Table 7: Showing the mean dipstick and urine protein creatinine ratio in expired dengue patients

Day of fever	Urine dipstick Mean	SD	Urine protein creatinine ratio	SD
Day 3	2.50	0.98	1.5	0.65
Day 4	3.10	1.12	3.5	1.22
Day 5	3.70	1.00	4.78	1.43
Day 6	3.77	0.87	5.6	1.08
Day 7	3.5	1.2	5.2	1.56

The mean dipstick and urine protein creatinine ratio showed higher values in expired patients when compared to patients who recovered, with statistically significant p value of <0.05.

DISCUSSION

Age group from 1 month to 12 years of age group was taken in our study. The mean age of the study population was 6.59. The mean age of presentation of probable dengue is 6.43 years in our study, which is less compared to the study done by Andries et al,^[1] in which mean age is 7 years. The mean age of dengue with warning signs is 6.56 years in our study as compared to Andries et al¹ study which is 8.5 years. The mean age of presentation of severe dengue is 6.79 years in our study. In Andries et al,^[1] study it is 9 years. In our study there is no significant age difference between all three groups of dengue fever. In our study, 28.5% were <5 years, 50.7% were between 6-10 years, 20.7% were between 11-12 years, compared to study done by Priyanka Datla et al⁷, in which 23.7% were infants, 13.1% in 1-5 years age group and 63.2% were over 5 years. Both studies showed more children in >5 years of age.

Of 140 cases of our study, 87(62%) were males and 53(38%) were females. The incidence of dengue among males is more than females in our study which is similar to Priyanka et al,^[7] in which 45 (59%) were males and 31 (41%) were females. In our study, in probable dengue group 67.5% were males which is similar to Andries et al,^[1] study where it is 62.5%. In dengue with warning signs group 58.8% were males which is almost same as that of Andries et al¹ study where it was 60%. In severe dengue group males accounted for 51.7% which is similar to other two studies.

In our study severe dengue cases accounted for 20.7% of cases (29). Dengue with warning signs were 24.2% cases (34). Probable dengue were 55% cases (77). The comparison between the groups is statistically significant with p value <0.05. In Priyanka Datla et al,^[7] study severe dengue was 38.2% (29), dengue with warning signs were 36.8% (28), probable dengue was 25% (19). There were a greater number of probable dengue cases in our study because we included cases admitted in the ward as well as in PICU. The incidence of severe dengue and dengue with warning signs is higher in our study compared to national incidence probably due to our hospital being a tertiary care hospital and the prime referral centre in our state.

In our study, daily early morning urine sample was collected and urine dipstick for proteins was done. The values were compared between day 3 to day 9 of fever. In probable dengue, the mean urine dipstick protein value on day 3 of fever was 0.32, then showing an increasing trend with highest value on day 4 (mean value=1.24) followed by a decreasing trend from day 5 to day 9. In dengue with warning signs, the mean value on day 3 was 1.41, which is higher

than in probable dengue, followed by increasing trend with highest value on day 5 & 6 (mean values of 2.2 & 2.2 respectively), then showing a decreasing trend. In severe dengue, the mean value on day 3 was 2.11, with highest value on day 6 (mean value=3.38). It was statistically significant with p value between the groups less than 0.05. The mean urine dipstick for protein value in death patients was highest on day 6 (mean value=3.77). In dengue infection, severe disease is due to vascular leakage. Increase in urine dipstick for proteins can be explained by loss of proteins in urine due to vascular leakage as severity of dengue increases. Andries et al,^[1] observed proteinuria in 75% of severe dengue infection patients, in which urine dipstick for proteins was positive in 52% of dengue with warning signs patients and 38% of dengue without warning signs. In study conducted by Priyanka et al,^[7] probable dengue patients showed proteinuria less than 100 mg/dL. 7% with moderate dengue and 7% with severe dengue showed significant proteinuria. However, the values were not statistically significant. In both the studies quantification for urine dipstick for proteins was not done.

In our study daily urine protein ratio was measured and compared between the 3 groups over a period of 7 days. In probable dengue group, on day 3 of fever mean value was 0.14. Then showed increasing trend on day 5 (mean value=0.24) followed by decreasing values till day 9 of fever (mean value=0.10). In dengue with warning signs group, the mean value on day 3 was 0.58 followed by highest value on day 6, mean value of 1.97 followed by decreasing trend till day 9. In severe dengue group, the mean values compared to other two groups were higher on all days with highest mean value of 3.95 on day 6 of illness. Similar results were seen in studies done by Garesa et al⁸, which showed that 27.6% in severe dengue group showed urine protein creatinine ratio >3. The values between the groups were compared by ANNOVA test which was statistically significant with p value less than 0.05. In Priyanka et al⁷ study, 27.6% patients showed urine protein creatinine ratio greater than 3 in severe dengue group and 34.5% patients showed urine protein creatinine ratio between 1-3. In probable dengue group, urine protein creatinine ratio was less than 3 in all the patients. In Andries et al,^[1] study, 50% of severe dengue had urine protein creatinine ratio > 45mg/mmol. And the median day of illness where urine protein creatinine ratio was high was on day 6 of illness. Quantification of urine protein creatinine ratio on different day of illness was not done in the above studies, only spot UPCr values were taken into consideration.

In our study daily platelet count was measured and compared in different groups and also with urine protein creatinine ratio. There was no significant association with platelet count and urine protein creatinine ratio. This may be due to platelet transfusions given to the patients in dengue which was not taken into account in the present study. Increased urinary excretion of proteins in patients

with dengue infection is thought to be the hallmark of vascular endothelial defect and plasma leakage associated with complicated forms of dengue and is considered a possible prognostic marker. Proteinuria has been reported in 74% of patients of dengue hemorrhagic fever and cases of self-limiting nephrotic range proteinuria in patients with DHF presenting no manifestations of renal damage have been described. The mechanism underlying the hypothesis of increased protein excretion in urine is that during dengue virus infection the glycocalyx of the endothelial cells is disrupted either by direct action of the virus or by NS1 antigen causing plasma leakage. At the kidney level, the alteration of the glycocalyx layer that coats the glomerular endothelial cells enables the passage of macromolecules in the primary urine in normal conditions. As macromolecules cannot be reabsorbed in the tubules, a glomerular proteinuria, mainly characterised by the presence of the albumin in urine occurs. Increased clearance of proteins in urine due to disruption of glycocalyx has been described during diabetes mellitus, nephritis syndrome and meningococcal septicaemia.

We first investigated the presence of proteinuria by using dipstick, one of the cheapest methods for the detection of proteins in urine. Then it was compared with urine protein creatinine ratio which showed significant values as severity of dengue increased. The urine protein creatinine ratio is a better tool to assess the proteinuria than simple dipstick as it intends to adjust for the fluctuations in fluid intake and hydration status.

The gold standard to determine the proteinuria is provided by the measurement of total proteins or albumin in urine over 24 hr period. However, this method is time consuming and cumbersome. Measurement of urine albumin creatinine or protein creatinine ratio has been demonstrated to be an acceptable alternative to 24 hr urine protein samples. Our multivariate analysis of urine protein creatinine ratio during the course of the disease indicated that this ratio was significantly higher six to seven days after the onset of fever which is in agreement with the study conducted by Andries et al.^[1] Rather than being a marker that could be used for patient triage at the time of first medical consultation, as done in other studies, urine protein creatinine ratio measurement seems to be more useful for monitoring patients during the course of the disease. Indeed, the peak UPCR occurred at the end of the critical phase of the disease and decrease in ratio seemed to correspond with the beginning of the recovery phase.

CONCLUSION

Our study demonstrates a significant association between proteinuria—measured via urine dipstick

and urine protein-creatinine ratio (UPCR)—and dengue severity in children, with elevated levels peaking on days 5-6 during the critical phase across all groups, followed by a decreasing trend in recovery. Higher values in severe dengue enable prognostication, patient triaging at admission, and monitoring in PICU, where declining trends alongside clinical and hematological parameters signal safe transfer or discharge, easing ICU burden. Urine dipstick, being simple and accessible, holds promise for peripheral setups like PHCs for early referral. Further studies are needed to standardize these markers.

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