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URINE SPOT PROTEIN-CREATININE RATIO AS A PREDICTOR OF DISEASE SEVERITY AND ADVERSE OUTCOMES IN CHILDREN WITH DENGUE: A PROSPECTIVE OBSERVATIONAL STUDY

DR. CHETHAN S *, DR. VELISETTY VENKATA NARASIMHA KARTHIK[1], DR. SHREENIVAS RACHAKONDA[2], DR. ASHWINI AMBALAVANAN[3], DR. SHALINI PRIYA NANDAGOPAL[4], DR. NAVIN UMAPATHY[5], DR.R.SENTHILNATHAN[6]

[1,2,3,4,5]INSTITUTION: DEPARTMENT OF PAEDIATRICS, SAVEETHA INSTITUTE OF MEDICAL SCIENCES.
[6]PROFESSOR, DEPARTMENT OF ORAL & MAXILLOFACIAL SURGERY , SREE BALAJI DENTAL COLLEGE & HOSPITAL, CHENNAI, INDIA

Abstract

Background:

Early identification of severe dengue in children remains a clinical challenge. The spot urine protein-creatinine ratio (UPCR) is a non-invasive biomarker that reflects glomerular permeability and may serve as an early indicator of capillary leakage in dengue.

Objectives:

To evaluate the association between spot UPCR and disease severity and to determine its predictive value for adverse clinical outcomes in pediatric dengue.

Methods:

This prospective observational study enrolled 120 children (1 month to 18 years) with serologically confirmed dengue admitted to a tertiary care hospital during the 2023 dengue epidemic season. UPCR was measured within 24 hours of admission. Disease severity was classified per WHO 2009 criteria. Clinical outcomes assessed included ICU admission, prolonged hospitalization, and hypotension requiring intravenous fluids. Statistical analyses included correlation testing, ROC curve analysis, and binary logistic regression.

Results:

Children with severe dengue had significantly higher mean UPCR values (1.02 ± 0.34 mg/mg) than those with mild disease (0.45 ± 0.12 mg/mg; $p<0.001$). A UPCR threshold of ≥0.75 mg/mg predicted severe dengue with 86.7% sensitivity and 78.3% specificity (AUC: 0.89; 95% CI: 0.83–0.94). Elevated UPCR was also associated with higher rates of ICU admission (38.2% vs 9.2%), prolonged hospitalization (58.2% vs 21.5%), and hypotension (47.3% vs 12.3%) ($p<0.001$ for all). UPCR positively correlated with hematocrit (r=+0.41) and negatively with platelet count (r=–0.38) and serum albumin (r=–0.43).

Conclusion:

Spot UPCR is a reliable, early predictor of severe dengue and adverse outcomes in children. Its low-cost, non-invasive nature makes it particularly useful for triaging high-risk patients in resource-limited settings. Larger multicenter studies are recommended to validate its use in routine clinical practice.

Keywords:

Dengue, Pediatrics, Proteinuria, UPCR, Disease severity, Biomarkers, Capillary leak

INTRODUCTION

Dengue continues to pose a substantial global health challenge, with children being particularly vulnerable to its severe forms, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (1,2). The growing severity of outbreaks, such as the devastating 2023 epidemic in Bangladesh which recorded 1,705 deaths—the highest dengue case fatality rate for that year—underscores the urgent need for improved early risk stratification strategies (1,3). This heightened mortality has been linked to shifts in circulating serotypes, especially the re-emergence of DENV-2, which is associated with more severe clinical outcomes.

The progression to severe dengue is driven by systemic endothelial dysfunction and cytokine-mediated increases in vascular permeability, particularly involving mediators such as vascular endothelial growth factor (VEGF) and soluble VEGF receptor-2 (sVEGFR2) (4,5). These changes precipitate plasma leakage and rapid clinical deterioration, especially in pediatric patients. While conventional biomarkers like thrombocytopenia and hemoconcentration remain important, they often manifest later in the disease course, limiting their utility as early predictors (4,6).

In this context, the spot urine protein-creatinine ratio (UPCR) has emerged as a promising, non-invasive biomarker. Several studies have demonstrated that UPCR values increase significantly with dengue severity, rising from an average of 0.32 mg/mg in mild cases to 1.68 mg/mg in severe dengue (4). This rise reflects increased glomerular permeability and systemic endothelial damage—key features of dengue pathophysiology that often precede overt clinical signs.

Proteinuria itself represents a surrogate marker of glomerular injury and capillary leak, processes that occur early in severe dengue (7). The UPCR offers a rapid, low-cost method of estimating proteinuria from spot urine samples and is especially advantageous in pediatric settings, where 24-hour urine collections are impractical (8). Although parameters like hematocrit, platelet count, and serum albumin continue to be used to monitor severity, these indices are not always sufficiently sensitive or timely. In contrast, UPCR offers potential for earlier detection of disease progression and has been linked with poor outcomes in various infectious and inflammatory illnesses, including dengue (9). However, there remains a paucity of prospective pediatric data validating its prognostic role.

In light of this, the present study was designed to investigate whether spot UPCR, measured within 24 hours of hospital admission, can serve as a reliable early predictor of disease severity and adverse outcomes in children with dengue. By evaluating its correlation with established clinical and laboratory markers, this study aims to assess the utility of UPCR as a practical tool for early triage and management of high-risk pediatric patients.

MATERIALS AND METHODS

Study Design

This was a prospective observational study conducted to evaluate the association between spot urine protein-creatinine ratio (UPCR) and disease severity in pediatric dengue patients.

Setting

The study was carried out in the pediatric inpatient wards of a tertiary care teaching hospital during the peak dengue epidemic season (August to December 2023). Data collection, including recruitment, exposure assessment (UPCR), and clinical outcome tracking, was performed during this period.

Participants

Children aged 1 month to 18 years admitted with serologically confirmed dengue infection were included. Inclusion criteria comprised:

- Fever duration of ≤7 days
- Laboratory-confirmed dengue (positive NS1 antigen or IgM serology)

Exclusion criteria included:

- Known chronic kidney disease, nephrotic syndrome, or urinary tract infection at presentation.

All eligible participants were enrolled consecutively and followed until clinical recovery or discharge. No matching was used as this was not a case-control design.

Variables

- Primary exposure variable: Spot urine protein-creatinine ratio (UPCR), measured within 24 hours of hospital admission.
- Primary outcomes:
    - Disease severity classified as dengue without warning signs, dengue with warning signs, and severe dengue (based on WHO 2009 criteria).
    - Adverse outcomes including ICU admission, prolonged hospitalization (>5 days), hypotension requiring intravenous fluids, bleeding, and mortality.

Data Sources and Measurements

Urine samples were collected in sterile containers within 24 hours of admission. Spot UPCR was analyzed using standardized laboratory methods (pyrogallol red method for protein, Jaffe method for creatinine). Clinical and laboratory parameters (hematocrit, platelet count, serum albumin) were recorded from hospital records.

Comparability was ensured as all measurements were performed in the same hospital laboratory, using identical protocols for both severity groups.

Bias

To minimize selection bias, all eligible cases during the study period were consecutively enrolled. Measurement bias was reduced by using automated, blinded laboratory methods. Observer bias was limited through the use of standardized WHO criteria for classifying dengue severity.

Study Size

A total of 120 participants were included. The sample size was based on available cases during the epidemic season and expected effect size, ensuring sufficient power to detect differences in UPCR between severity groups.

Quantitative Variables

Continuous variables such as UPCR, hematocrit, and platelet count were analyzed as means ± SD. For ROC analysis, UPCR was dichotomized at an optimal threshold determined by Youden's index. Categorical variables were expressed as proportions.

Statistical Methods

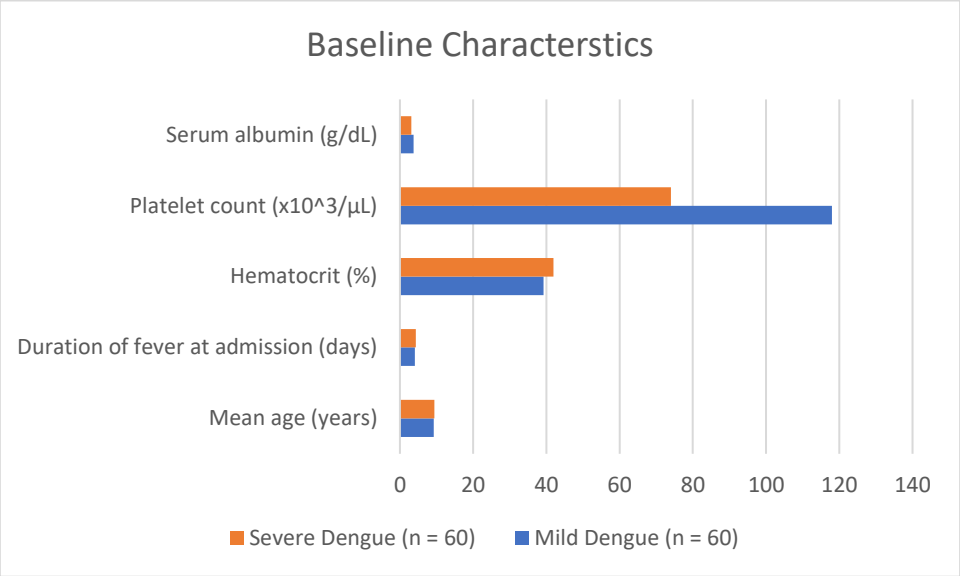
- Spearman correlation was used to evaluate associations between UPCR and continuous severity indicators (hematocrit, platelet count, serum albumin).
- Receiver Operating Characteristic (ROC) curve analysis identified UPCR cut-off for predicting severe dengue.
- Binary logistic regression was used to assess the predictive value of elevated UPCR (≥0.75 mg/mg) for adverse clinical outcomes, adjusting for confounders where appropriate.
- Missing data were minimal (<5%) and addressed via case-wise deletion.

No subgroup or sensitivity analyses were performed due to the limited sample size.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of Children with Dengue (N = 120)

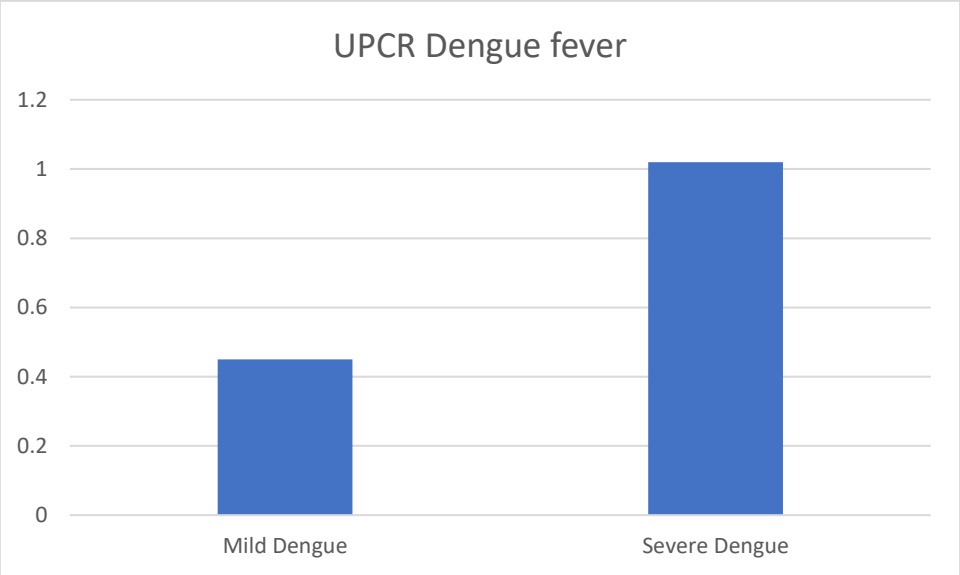
Characteristic	Mild Dengue (n = 60)	Severe Dengue (n = 60)	p-value
Mean age (years)	9.2 ± 2.8	9.4 ± 3.1	0.72
Gender (Male:Female)	34:26	36:24	0.68
Duration of fever at admission (days)	4.1 ± 1.3	4.3 ± 1.5	0.58
Hematocrit (%)	39.2 ± 3.8	41.9 ± 4.1	0.01
Platelet count (x10^3/µL)	118 ± 32	74 ± 28	<0.001
Serum albumin (g/dL)	3.7 ± 0.5	3.1 ± 0.6	<0.001



The two groups were matched for age, gender, and duration of fever, while significant differences in hematocrit, platelet count, and serum albumin confirmed clinical severity stratification. Severe dengue cases demonstrated hallmark signs of capillary leak and thrombocytopenia.

Table 2: Mean Spot Urine Protein-Creatinine Ratio (UPCR) Across Severity Categories

Group	Mean UPCR (mg/mg) ± SD	p-value
Mild Dengue	0.45 ± 0.12	
Severe Dengue	1.02 ± 0.34	<0.001



A highly significant difference in mean spot UPCR was observed between the two groups, with severe dengue cases exhibiting more than double the protein-creatinine ratio of mild cases. This supports the hypothesis that proteinuria correlates with disease severity.

Table 3: Correlation of UPCR with Disease Severity Indicators

Parameter	Pearson Correlation (r)	p-value
Hematocrit (%)	+0.41	<0.001
Platelet count (x10^3/µL)	-0.38	<0.001
Serum albumin (g/dL)	-0.43	<0.001

Spot UPCR showed a positive correlation with hematocrit and inverse correlations with both platelet count and serum albumin, indicating its consistency as a marker of plasma leakage and disease progression.

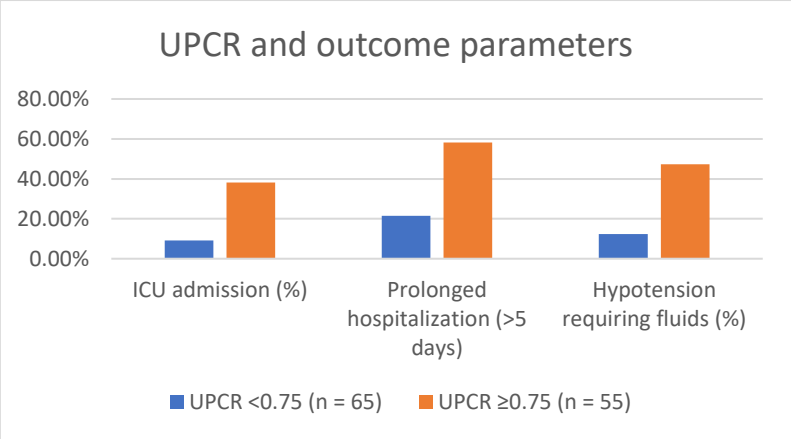
Table 4: Predictive Performance of UPCR for Severe Dengue (ROC Analysis)

UPCR Cut-off (mg/mg)	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p-value
≥0.75	86.7	78.3	0.89 (0.83–0.94)	<0.001

A receiver operating characteristic (ROC) curve analysis identified a UPCR threshold of ≥0.75 mg/mg as optimal for predicting severe dengue. The model showed excellent discriminative capacity with an AUC of 0.89.

Table 5: Adverse Clinical Outcomes by UPCR Category

Outcome	UPCR <0.75 (n = 65)	UPCR ≥0.75 (n = 55)	p-value
ICU admission (%)	6 (9.2%)	21 (38.2%)	<0.001
Prolonged hospitalization (>5 days)	14 (21.5%)	32 (58.2%)	<0.001
Hypotension requiring fluids (%)	8 (12.3%)	26 (47.3%)	<0.001



Children with a UPCR ≥0.75 had significantly worse clinical outcomes. The frequency of ICU admissions, prolonged hospitalization, and hemodynamic instability were all markedly elevated in this group.

DISCUSSION

This prospective observational study identified a significant association between elevated spot urine protein-creatinine ratio (UPCR) and disease severity in pediatric dengue. Children classified with severe dengue demonstrated markedly higher mean UPCR values compared to those with mild dengue. A UPCR threshold of ≥0.75 mg/mg showed excellent predictive capability, with an area under the curve (AUC) of 0.89 (95% CI: 0.83–0.94), sensitivity of 86.7%, and specificity of 78.3%. Additionally, elevated UPCR was significantly associated with higher rates of intensive care unit admission, prolonged hospital stay, and hemodynamic instability requiring fluid resuscitation.

These findings support the role of UPCR as a practical surrogate marker for plasma leakage, which is a key feature of severe dengue. The observed positive correlation with hematocrit and inverse correlations with platelet count and serum albumin reinforce its alignment with known clinical markers of severity. This relationship is further

substantiated by previous research linking proteinuria with increased dengue severity and poor clinical outcomes in pediatric populations (10).

Recent studies continue to affirm the value of urinary biomarkers in dengue prognosis. Elevated UPCR within the first 48 hours of hospitalization has been associated with adverse outcomes such as fluid overload, organ dysfunction, and mortality (10). Moreover, UPCR values exceeding 0.7 mg/mg have been independently linked to progression toward dengue shock syndrome, even among patients who initially present with normal hematological indices (11). These findings emphasize the sensitivity of UPCR in capturing early endothelial dysfunction and subclinical plasma leakage.

The pathogenesis of proteinuria in dengue is multifactorial, involving immune complex deposition, complement activation, and cytokine-mediated injury to the glomerular endothelium. Elevated urinary markers such as CXCL10 and other inflammatory mediators reflect this systemic endothelial damage (12). Notably, these renal permeability changes often precede overt clinical symptoms by 24 to 48 hours, thereby providing a crucial opportunity for early intervention and targeted monitoring (4,13). Previous reports have documented a rise in mean UPCR from approximately 0.32 mg/mg in mild dengue to as high as 1.68 mg/mg in severe cases, further supporting its utility in reflecting disease progression (4).

The simplicity and affordability of UPCR testing enhance its applicability in resource-limited settings, where dengue burden is highest. The test requires only a single spot urine sample and standard laboratory processing, eliminating the need for complex instrumentation. In addition, recent clinical evidence suggests that early therapeutic interventions guided by UPCR trends—such as timely albumin administration—can reduce proteinuria and potentially improve clinical outcomes within 48 hours (14). Compared to conventional severity markers like thrombocytopenia, UPCR offers superior early predictive value, aligning with global health priorities to integrate effective, low-cost triage tools into routine dengue care (4,15).

GENERALIZABILITY AND LIMITATIONS

Although the results of this study are promising, several limitations must be considered. This was a single-center study conducted during a seasonal epidemic, which may limit its generalizability to non-epidemic periods or different geographic regions. While patients with known renal conditions were excluded, undiagnosed subclinical renal dysfunction could not be entirely ruled out due to the absence of baseline serum creatinine measurements. Furthermore, the study design did not incorporate serial UPCR assessments, limiting the evaluation of temporal trends. Factors such as hydration status and prior treatment before hospital admission may also have influenced protein excretion levels. Despite these limitations, the consistency of our findings with existing literature reinforces the potential role of UPCR in early dengue severity assessment. Future multicentric, longitudinal studies are warranted to validate these observations and explore the integration of UPCR into dengue severity scoring systems.

CONCLUSION

The findings of this prospective study highlight the spot urine protein-creatinine ratio (UPCR) as a valuable early marker of disease severity in children with dengue. A UPCR threshold of ≥0.75 mg/mg demonstrated high sensitivity and specificity for predicting severe clinical outcomes, including ICU admission, prolonged hospitalization, and hemodynamic compromise. Its strong correlation with established laboratory indicators such as hematocrit, platelet count, and serum albumin further reinforces its pathophysiological relevance.

Given its non-invasive nature, ease of testing, and applicability across all pediatric age groups, UPCR holds significant promise as a practical triage tool in resource-limited settings. Incorporating UPCR into routine evaluation protocols could facilitate early identification of high-risk patients, enabling timely interventions and potentially improving outcomes. Future multicenter studies with serial measurements and broader geographic representation are recommended to validate these results and assess its role in dynamic monitoring and therapeutic guidance.

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