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Research Article

SPOT URINE PROTEIN-TO-CREATININE RATIO AS AN EARLY PREDICTOR OF DENGUE HAEMORRHAGIC FEVER AND DENGUE SHOCK SYNDROME: A PROSPECTIVE OBSERVATIONAL STUDY

Dr.Manjunath S Hiremani[1*], Dr.ShravankumarPotkar[2], Dr.Gavishiddesh Vishwanath Ronad[3]

[1*]Assistant Professor, Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore.
[2]Assistant Professor, Department of General Medicine, BLDE (DU) Shri B M Patil Medical College, Hospital and Research Centre, Vijayapura-586103 Karnataka.
[3]Assistant Professor, Department of General Medicine, KIMS, Koppal.
Corresponding Author: Dr.Manjunath S Hiremani
Assistant Professor, Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore.
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Abstract

Background: Dengue produces a wide clinical spectrum, from self-limiting dengue fever (DF) to life-threatening dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). A simple, rapid and inexpensive marker of severe disease would improve triage. Transient proteinuria reflects the capillary and glomerular leak of severe dengue and can be quantified rapidly by the spot urine protein-to-creatinine ratio (UPCR).

Objectives: To describe the clinical profile of adults admitted with dengue and to assess spot UPCR as a marker for early risk prediction of DHF/DSS.

Methods: In this prospective observational study, 109 adults with serologically confirmed dengue admitted to a tertiary-care centre (2018–2021) were enrolled. Patients with pre-existing renal disease, hypertension or diabetes mellitus were excluded. Spot UPCR was measured and disease classified per WHO criteria. Non-parametric tests and diagnostic performance metrics were used; $p<0.05$ was significant.

Results: Mean age was 30.0 ± 10.2 years; 58.7% were men. DF occurred in 68.8%, DHF in 24.8% and DSS in 6.4%. Median UPCR rose steeply with severity: DF 236, DHF 970 and DSS 2160 mg/g ($p<0.001$). UPCR was higher in patients with bleeding (1268 vs 236 mg/g) and needing transfusion (1300 vs 233 mg/g) (both $p<0.001$) and was unrelated to age or sex. A spot UPCR >600 mg/g predicted DHF/DSS with sensitivity 88.2%, specificity 98.7%, positive predictive value 96.8% and negative predictive value 94.9%. Case fatality was 0.9%.

Conclusion: Spot UPCR is a cheap, rapid, non-invasive marker that reliably identifies dengue patients progressing to DHF/DSS. A value >600 mg/g should prompt intensive monitoring.

Keywords: Dengue; Urine protein-creatinine ratio; Proteinuria; Dengue haemorrhagic fever; Plasma leakage.

INTRODUCTION

Dengue is the most rapidly spreading mosquito-borne viral infection in the world and the most prevalent arboviral disease in South and South-East Asia.[1] It is caused by four antigenically distinct serotypes (DENV-1 to DENV-4) of the genus Flavivirus and is transmitted principally by Aedes aegypti.[2] Over the past three decades the global incidence has risen many-fold, and an estimated 2.5 billion people now live in areas at risk.[3] India carries a substantial share of this burden, with wide regional variation in seroprevalence and case distribution.[4],[5]

The clinical spectrum ranges from an undifferentiated febrile illness (DF) to severe forms DHF and DSS defined by plasma leakage, haemorrhage and circulatory failure. The pathological hallmark of severe dengue is a transient, generalised increase in vascular permeability driven by endothelial dysfunction and immune-mediated injury.[6] Because progression can be abrupt and typically occurs around defervescence, early identification of at-risk patients is central to reducing mortality.[7]

The same capillary leak that produces effusions, ascites and haemoconcentration also affects the glomerular filtration barrier, and dengue virus NS1 protein directly disrupts endothelial and glomerular integrity, resulting in transient, non-selective proteinuria.[8],[9],[10] Proteinuria has therefore been proposed as an accessible surrogate for the severity of vascular leak. Although 24-hour urinary protein estimation is the reference standard, it is cumbersome in acutely ill patients; the spot UPCR provides a rapid, inexpensive, single-sample estimate that correlates well with 24-hour excretion.[11],[12]

We hypothesised that the degree of proteinuria, measured as spot UPCR, would parallel dengue severity and could serve as an early bedside predictor of DHF/DSS.

MATERIAL AND METHODS

Study design, setting and participants

This prospective observational study was conducted in the Department of General Medicine of a tertiary-care teaching hospital between 2018 and 2021. Consecutive adults (>18 years) admitted with serologically confirmed dengue who met the eligibility criteria and gave written informed consent were enrolled. Patients with pre-existing renal disease, systemic hypertension or diabetes mellitus were excluded, as these independently cause proteinuria and would confound the primary exposure.

Sample size

The sample size was calculated as $n = Z^2pq/d^2$, where p was the prevalence of dengue among admissions at the study centre (2.1%), $q = 1-p$ and d (absolute precision) = 0.03, yielding a minimum of 108; 109 patients were enrolled.

Investigations and case definitions

All patients underwent a structured history and examination and the following investigations: complete blood count and haemogram, dengue NS1 antigen and IgM antibody (ELISA), renal and liver function tests, HbA1c, chest radiography, ultrasonography of the abdomen and spot UPCR. Dengue was classified per WHO criteria as DF, DHF or DSS on the basis of plasma-leakage evidence (haemoconcentration, serous effusions), thrombocytopenia, haemorrhagic manifestations and circulatory failure.[13],[14] A spot UPCR of <30 mg/mmol (approximately <300 mg/g) was regarded as within the reference range.

Statistical analysis

Data were analysed with SPSS version 23 (IBM Corp.). Continuous variables were summarised as mean ± standard deviation and as median with interquartile range (IQR); categorical variables as frequencies and percentages. Normality was assessed with the Shapiro–Wilk test. As UPCR and most laboratory variables were non-normally distributed, group comparisons used the Mann–Whitney U test (two groups) and the Kruskal–Wallis test (three groups) with Dunn post-hoc testing and Šidák correction; correlation used the Spearman coefficient. Categorical associations used the chi-square or Fisher exact test. Sensitivity, specificity and predictive values of a spot UPCR threshold for DHF/DSS were calculated. A two-sided $p<0.05$ was significant.

Ethics

The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from every participant.

RESULTS

A total of 109 adults with confirmed dengue were studied. The mean age was 30.0 ± 10.2 years, and most patients (60.6%) were aged 21–30 years. There were 64 men (58.7%) and 45 women (41.3%), a male-to-female ratio of 1.4:1.

Fever was universal (100%). The commonest associated symptoms were myalgia (77.1%), headache (69.7%), arthralgia (39.4%), bleeding manifestations (33.0%), abdominal pain (28.4%) and vomiting (20.2%). On examination, facial flush (42%), conjunctival injection (39%) and lymphadenopathy (24%) were the most frequent signs. NS1 antigen was positive in 89.0% and IgM antibody in 30.3%. The clinical, serological and laboratory profile is shown in Table 1.

Thrombocytopenia was present in 95% of patients; the mean platelet count was 66,178 ± 34,947 /µL.[15] Transaminases were elevated (mean AST 98 U/L, ALT 72 U/L) and serum albumin was reduced (mean 2.9 g/dL), consistent with hepatic involvement and capillary leak. Evidence of plasma leakage was found in 29% overall (increased haematocrit 35.7%, ascites 20.2%, pleural effusion 11.9%, hypotension 6.4%). Blood-product transfusion was required in 37.6%.[16]

By WHO classification, 75 patients (68.8%) had DF, 27 (24.8%) had DHF and 7 (6.4%) had DSS. The overall median UPCR was 330 mg/g (IQR 160–860; range 90–2860).

UPCR increased markedly and monotonically with disease severity, from a median of 236 mg/g in DF to 970 mg/g in DHF and 2160 mg/g in DSS (Kruskal–Wallis $p<0.001$; Figure 1); pairwise comparisons were significant for DF versus DHF and DF versus DSS. When dichotomised, patients with DHF/DSS had a far higher median UPCR than those with DF (1310 vs 236 mg/g, $p<0.001$). UPCR was also significantly higher in patients with bleeding manifestations (1268 vs 236 mg/g) and in those requiring transfusion (1300 vs 233 mg/g) (both $p<0.001$; Figure 2). In contrast, UPCR showed no significant relationship with age (Spearman $\rho = -0.01$, $p=0.957$) or sex ($p=0.700$). These associations are summarised in Table 2.

Taking a spot UPCR threshold of >600 mg/g to predict progression to DHF/DSS yielded a sensitivity of 88.2%, specificity of 98.7%, positive predictive value of 96.8% and negative predictive value of 94.9% (Table 3). One patient (0.9%) died, giving a case-fatality rate of 0.91%.

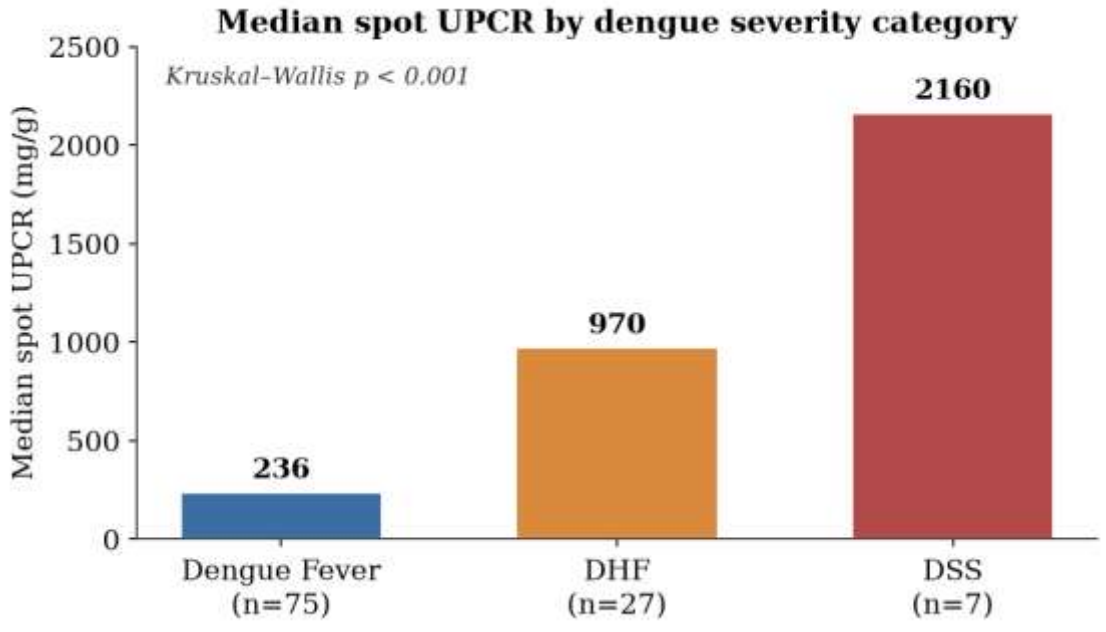

Figure 1. Median spot urine protein-to-creatinine ratio (UPCR) by dengue severity category. UPCR rose steeply across dengue fever, DHF and DSS (Kruskal–Wallis p<0.001).

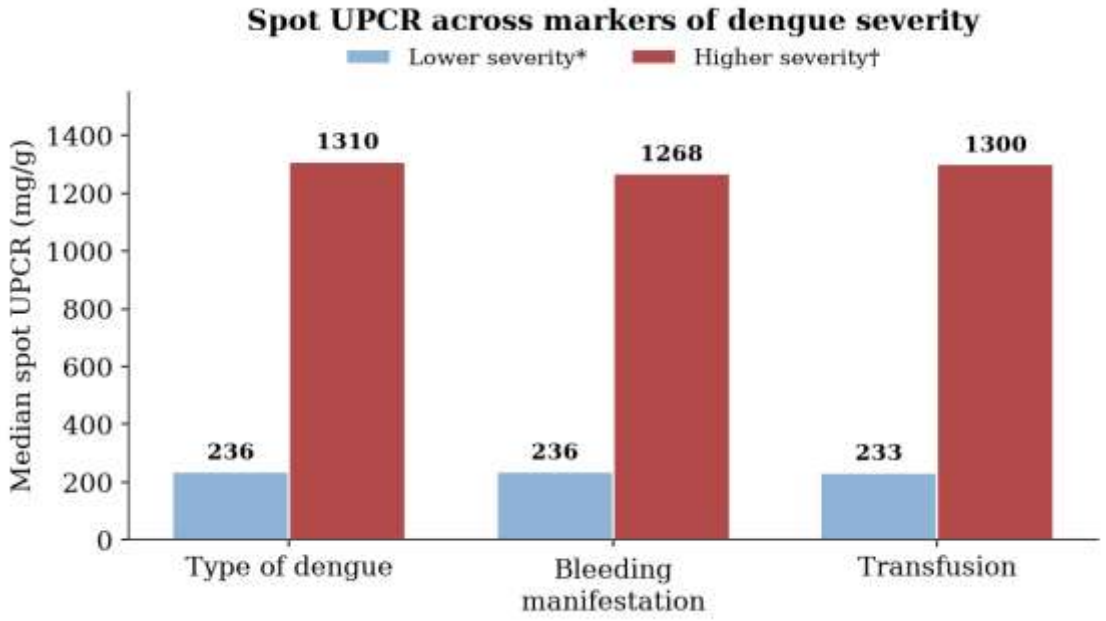

Figure 2. Median spot UPCR across markers of dengue severity. For each contrast the higher-severity group (DHF/DSS, bleeding present, transfusion required) had a markedly higher UPCR than the lower-severity group (dengue fever, bleeding absent, transfusion not required); all comparisons $p<0.001$.

Table 1. Clinical, serological and laboratory profile of the study population (n = 109)

Variable	Category / statistic	Value
Age (years)	Mean ± SD	30.0 ± 10.2
Sex	Male / Female	64 (58.7%) / 45 (41.3%)
Fever	Present	109 (100%)
Myalgia	Present	84 (77.1%)
Headache	Present	76 (69.7%)
Bleeding manifestations	Present	36 (33.0%)
Facial flush	Present	46 (42%)
NS1 antigen	Positive	97 (89.0%)
IgM antibody	Positive	33 (30.3%)
Haemoglobin (g/dL)	Mean ± SD	13.2 ± 2.2
Platelet count (/µL)	Mean ± SD	66,178 ± 34,947
Thrombocytopenia	Present	104 (95%)

Variable	Category / statistic	Value
AST / ALT (U/L)	Mean	98 / 72
Serum albumin (g/dL)	Mean ± SD	2.9 ± 0.4
Plasma-leakage evidence	Any	32 (29%)
Transfusion required	Yes	41 (37.6%)
Diagnosis	DF / DHF / DSS	75 / 27 / 7
Outcome	Recovered / Died	108 / 1

SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DF, dengue fever; DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome.

Table 2. Association of spot UPCR (mg/g) with dengue severity and clinical markers

Comparison	Median UPCR (mg/g)	Test	p value
DF vs DHF vs DSS	236 vs 970 vs 2160	Kruskal–Wallis	<0.001
DF vs DHF/DSS	236 vs 1310	Mann–Whitney	<0.001
DHF present vs absent	970 vs 236	Mann–Whitney	<0.001
DSS present vs absent	2160 vs 290	Mann–Whitney	<0.001
Bleeding present vs absent	1268 vs 236	Mann–Whitney	<0.001
Transfusion required vs not	1300 vs 233	Mann–Whitney	<0.001
Age (continuous)	$\rho = -0.01$	Spearman	0.957
Male vs Female	330 vs 290	Mann–Whitney	0.700

UPCR, urine protein-to-creatinine ratio; DF, dengue fever; DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome.

Table 3. Diagnostic performance of spot UPCR >600 mg/g for predicting DHF/DSS

Performance metric	Value
Sensitivity	88.2%
Specificity	98.7%
Positive predictive value	96.8%
Negative predictive value	94.9%

DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome.

DISCUSSION

In this prospective study of 109 adults with confirmed dengue, spot UPCR increased steeply and monotonically across the severity spectrum, from a median of 236 mg/g in DF to 970 mg/g in DHF and 2160 mg/g in DSS. A single spot UPCR >600 mg/g identified patients progressing to DHF/DSS with high specificity (98.7%) and predictive value, and the association held for other markers of severe disease bleeding and the need for transfusion while being independent of age and sex.

The result is biologically coherent. Proteinuria in dengue is transient and non-selective, reflecting the same systemic increase in vascular permeability that produces effusions, ascites and haemoconcentration; NS1-mediated glomerular endothelial injury and podocyte dysfunction allow protein to escape into the urine.[8],[9] Because permeability peaks around defervescence—the critical phase a rising UPCR signals that plasma leakage is under way, often before overt shock supervenes.[7]

Our findings are consistent with the growing literature on dengue proteinuria. Studies in children and adults have reported significantly higher peak proteinuria in DHF than DF, with UPCR correlating with third-space fluid loss, bleeding and adverse outcome.[18],[19]Vasanwala et al. found that patients with DHF had several-fold higher peak UPCR than those with DF and proposed UPCR as a sensitive and specific prognostic aid in adult dengue,[20],[21] and Andries et al. reported that patients with warning signs or severe dengue more often had proteinuria at admission.[22] The demographic and clinical profile of our cohort—young adults, male predominance, universal fever, high rates of myalgia and thrombocytopenia—mirrors other Indian and regional series.[23],[24],[25] Our diagnostic performance for a >600 mg/g threshold lies at the favourable end of the reported range, likely reflecting the exclusion of patients whose baseline proteinuria would otherwise dilute the signal.

The principal value of UPCR is as an inexpensive, rapid, non-invasive triage tool that requires only a single urine sample and is feasible in primary and secondary care, where dengue is most often first encountered. A high UPCR should prompt closer monitoring, judicious fluid management and early referral, complementing other bedside predictors of severe dengue; a low value is reassuring given the high negative predictive value.[26],[27]

Limitations

This was a single-centre study with a modest sample and included only adults, limiting generalisability. As a tertiary referral hospital, the case mix may over-represent complicated disease. Renal biopsy was not performed and proteinuria was not characterised by electrophoresis, so glomerular versus tubular contributions could not be distinguished. Finally, the >600 mg/g threshold was applied pragmatically; a formal receiver-operating-characteristic analysis with an internally derived cut-off and external validation would strengthen clinical adoption.

CONCLUSION

Spot UPCR is a cheap, rapid and non-invasive marker that reliably tracks dengue severity and predicts progression to DHF/DSS with high positive and negative predictive value. A spot UPCR >600 mg/g should prompt intensive monitoring and early supportive care and merits prospective, ROC-based validation as a routine triage test in dengue-endemic settings.

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