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A Cross-Sectional Study of Assessment of Urine Spot Protein Creatinine Ratio as an Indicator of Disease Severity and Adverse Outcomes in Pediatric Dengue

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Abstract

Introduction : Dengue, a viral infection with diverse presentations, necessitates the ability to predict disease severity upon admission to appropriately monitor patients requiring close observation. Severe dengue is characterized by increased urinary protein clearance due to heightened systemic vascular permeability. Utilizing a simple urine protein excretion screening test could aid in triaging and monitoring patients suspected of dengue infection. **Objective:** To assess the Urine Spot Protein Creatinine Ratio (UPCR) as a tool for predicting disease severity and adverse outcomes in children with dengue. **Methods:** This cross-sectional study was conducted at Vinayaka Missions Medical College , Karaikal . Children aged 1 month to 12 years presenting with fever and thrombocytopenia (platelet count less than 150,000 /μL) with or without dengue NS1/ Immunoglobulin M Enzyme Linked Immunosorbent Assay (ELISA) positivity were included. Study parameters encompassed demographic factors, severity of dengue classification according to National Vector Borne Disease Control Programme (NVBDCP) guidelines, and urine spot PCR. UPCR was compared between dengue-positive and -negative cases, as well as within different categories of dengue severity. Chi-square tests were employed for comparing results. **Results:** Out of 100 enrolled children, 72 (72%) tested positive for dengue, while 28 (28%) were negative. The most prevalent age group was 4-6 years, followed by 7-9years. Among children with dengue, 53 (73.6%) exhibited high UPCR, while only 3 (10.7%) non-dengue cases had high UPCR, a statistically

significant difference (p<0.0001). Mean spot UPCR was 0.31+/-0.14 in mild dengue, 0.69+/-0.5 in moderate dengue, and in 1.72+/-1.4 severe dengue, demonstrating statistically significant differences (p<0.0001). Children with severe dengue displayed higher PCR values compared to those with mild and moderate dengue. **Conclusion:** A significant association was observed between urine spot PCR and the severity of dengue, suggesting the potential utility of this test for triaging and monitoring children suspected of having dengue.

Keywords : viral infection , fever , thrombocytopenia , UPCR = urine protein creative ratio.

Introduction

Dengue poses a significant global public health challenge, with its incidence steadily rising, particularly in developing countries where it has become endemic [5]. Primarily affecting the pediatric population, dengue is associated with substantial morbidity and mortality [8]. Mortality in dengue is attributed to abnormal capillary permeability, hemostatic abnormalities, and, in severe cases, dengue shock syndrome. The annual incidence rate of dengue is reported to be 49.5 per 1000 child years among children with fever lasting more than three days [11]. The risk factors for severe disease development remain poorly characterised, resulting in frequent hospitalisation of uncomplicated cases for observation during the critical capillary leakage phase, posing challenges for patients and healthcare providers alike. Therefore, there is an urgent need for improved early diagnosis and risk prediction for severe disease to enable timely intervention. Ideally, such a test should be cost-effective, rapid, easy to perform, and highly sensitive and specific [8].

Microalbuminuria has been proposed as a potential predictor of severe dengue [15,2], yet there is limited information regarding its magnitude, onset timing, or evolution of urinary protein excretion during infection. Moreover, 24-hour urinary albumin measurements are labor-intensive. Both spot urine protein estimation and urine protein-to-creatinine ratio offer less cumbersome and more practical alternatives. Measurement of spot urine protein-to-creatinine ratio is particularly favoured due to its simplicity and acceptability [5]. Spot PCR is derived from the ratio between urine protein excretion (measured by 24-hour collection or spot urine sample) and creatinine excretion, expressed as mg/mmol or mg/mmol. Spot PCR presents a convenient alternative to 24-hour urine collection as it is easier to obtain and remains unaffected by variations in water intake or diuresis [1]. While it has been investigated in adult dengue cases [5], its utility as a predictive tool in the pediatric population remains insufficiently explored. Therefore, the present study emphasises the simple laboratory investigation of UPCR as a predictor of disease severity in children with dengue infection, which is crucial for monitoring and managing at-risk children, especially during dengue epidemics. Consequently, this study was designed to

assess the UPCR as a tool for predicting disease severity and adverse outcomes in children with dengue.

Methods :

The current cross-sectional study took place at the Vinayaka Missions Medical College , Karaikal , Puducherry , India , spanning from October 2022 to December 2023. The study commenced following approval from the Institutional Ethical Committee (IEC) and after obtaining written informed consent from the parents or legal guardians of the participants.

Inclusion Criteria:

All children aged between 1 month and 12 years, presenting with symptoms of fever and thrombocytopenia (<1,50,000/μL), with or without dengue NS1/IgM positivity, were eligible for inclusion in the study.

Exclusion Criteria:

Children who developed fever >48 hours after admission or following surgery were excluded from participation.

Initially, 72 children tested positive for dengue based on dengue NS1/IgM ELISA positivity, while 28 were dengue negative. Positivity or negativity was determined solely based on dengue NS1/IgM reports.

Sample Size:

A total of 100 children presenting with fever to the hospital during the study period from October 2022 to December 2023 were enrolled in the study using purposive sampling.

Methods and Materials

Demographic factors including age and sex, as well as laboratory parameters such as urine protein and creatinine, were evaluated. Urine spot protein was detected and quantified using the pyrogallol red method, while creatinine was assessed using the modified Jaffe's method. The urine spot protein-to-creatinine ratio (UPCR) was calculated by dividing the level of protein (mg/dL) in a spot urine by the creatinine level (mg/dL). UPCR values were obtained after admission.

For children aged <2 years, a UPCR value of <0.5 was considered normal, while for those aged ≥2 years, a value <0.2 was deemed normal. A small amount of protein in the urine was considered acceptable, with proteinuria defined as protein excretion greater than 100 mg/m2 per day or a urine protein/creatinine ratio (UPCR) >0.2 on a single spot urine collection. In neonates and infants, a higher amount of protein excretion, up to 300 mg/m2, was permissible.

Urine creatinine (24-hour urine collection) values ranged from 500 to 2000 mg/day.

Comparison of UPCR: UPCR was compared between dengue-positive and dengue-negative cases based on dengue NS1/IgM positivity. Subsequently, UPCR was assessed in mild, moderate, and severe categories of dengue cases following dengue NS1/IgM positivity. The severity of dengue classification was based on the NVBDCP guidelines and the World Health Organization (WHO) 1997 classification scheme, which includes Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS), categorized based on clinical signs to determine the degree of disease severity.

The statistical analyses were conducted utilizing Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc, Chicago, IL). Data is expressed as mean ± standard deviation or percentages. Chi-square tests were employed to compare proportions, with a p-value of <0.05 indicating statistical significance.

Results

Table 1 : Demographic Parameters

SNO	Categories	Variables	Dengue positive(n=72)	Dengue negative (n=28)	p value
1	Sex	Male	41	18	0.282
		Female	31	10	
2	Age group (years)	</= 1	4(5.5%)	2 (7.14%)	0.349
		>1 - 3	12(16.6%)	5 (17.8%)	
		4-6	27(37.5%)	7 (25%)	
		7-9	23(31.9%)	9 (32.1%)	
		10-12	6(8.3%)	5 (17.8%)	
3	Urine protein	Mean+/- SD	33.6 +/- 1.2	11.2 +/- 0.4	0.0298
4	Creatinine	Mean+/- SD	71.5 +/- 1.5	29 +/- 0.5	0.0002
5	UPCR	Mean	0.43	0.28	0.32

Table 2 : Urine Spot protein creatinine ratio in dengue and non dengue children

Dengue	Urine spot PCR		Chi-square test	p-value
	Normal Age(<2 years) <0.5 Age(>or=2years)<0.2	High Age(<2 years) >0.5 Age(>or=2years)>0.2		
Yes (72)	19(26.3%)	53(73.6%)	3.752	<0.0001
No (28)	25(89.3%)	3(10.7%)		

Table 3:Comparison between Urine protein creatinine ratio and severity of dengue

SNO	Type of dengue	N(%)	Mean UPCR	Chi square test	p value
1	Mild dengue - Dengue fever	46 (64%)	0.31+/- 0.14	12.857	0.0019
2	Moderate dengue - Dengue hemorrhagic fever	19 (27%)	0.69+/- 0.5		
3	Severe dengue - Dengue shock syndrome	7 (9%)	1.72+/- 1.4		

Table 4 : Urine spot protein creatinine ratio in dengue positive children among various age groups

Age group	Urine spot PCR		Chi-square test	p-value
	Normal Age(<2 years) <0.5 Age(>or=2years)<0.2	High Age(<2 years) >0.5 Age(>or=2years)>0.2		
< 2 years	8(62%)	5(38%)	16.98	0.00012
>= 2 years	16(27.1%)	43(73%)		

Table 5: e

Dengue	Sex	Urine spot PCR		Chi-square test	p-value
		Normal Age(<2 years) <0.5 Age(>or=2years)<0.2	High Age(<2 years) >0.5 Age(>or=2years)>0.2		
Yes (72)	Female	2	2	2.427	0.113
	Male	6	3		
No (28)	Female	4	17	0.612	0.354
	Male	12	26		

Out of 100 children hospitalized with fever and thrombocytopenia, 72 (72%) tested positive for dengue serology, while 28 (28%) were negative for dengue. In the dengue-positive group, the majority of patients (37.7%) were aged between 4 and 6 years, followed by 31.9% in the 7-9 years age group, and 16.6% in the 1-3 years age group. Conversely, in the dengue-negative group, the highest proportion (32.1%) of children fell within the 7-9 years age range, with 25% in the 4-6 years age group. Among the dengue-positive group, 56.9% were male and 43.1% were female, while in the dengue-negative group, 64.2% were male and 35.7% were female [Table-1].

Out of the 72 children diagnosed with dengue, 73.6% exhibited high urine PCR levels, compared to only 10.7% of the 28 non-dengue children, which was statistically significant ($p<0.0001$) [Table-2].

Among the 72 children with dengue, those with mild dengue (64%) had a mean spot PCR of 0.31+/-0.14, while those with moderate dengue (27%) had a mean spot PCR of 0.69+/-0.5, and those with severe dengue (9%) had a mean urine spot PCR of 1.72+/-1.4, indicating statistical significance (p-value=0.0019) [Table-3].

Discussion

Dengue fever has become widely prevalent, manifesting with a range of presentations and its own mortality rate. Mortality in dengue is attributed to abnormal capillary permeability, hemostatic abnormalities, and in severe cases, dengue shock syndrome. In the pediatric population, particularly in cases of severe dengue, patient outcomes rely heavily on maintaining a high level of suspicion and vigilant monitoring for complications. The assessment of UPCR is a simple and inexpensive test that showed a significant association with dengue severity, making it a useful tool for triaging and monitoring children suspected of having dengue. This study aimed to investigate the significance of Urine Protein Creatinine Ratio (UPCR) as an early predictor of illness severity in children with

dengue fever. Our findings indicated a statistically significant increase in proteinuria among children with dengue compared to those with non-dengue thrombocytopenia, consistent with observations by Graham RR et al. [16]. Additionally, we found that among children with dengue, proteinuria was significantly higher in severe cases compared to mild and moderate cases ($p<0.001$), indicating a positive association between the degree of proteinuria and disease severity. These results align with a study by Vasanwalla FF et al., where patients with Dengue Hemorrhagic Fever (DHF) exhibited significantly higher median peak proteinuria levels compared to those with dengue fever [4]. Our study suggests that a higher UPCR serves as a non-invasive marker for predicting dengue severity in children with dengue fever, potentially aiding in screening and managing disease severity upon admission. Notably, our study revealed a significantly higher UPCR value in children older than 2 years compared to infants ($p<0.0001$), indicating that older children may manifest more severe dengue illness. Furthermore, gender did not show a significant association with the degree of proteinuria in our study, suggesting that dengue severity does not exhibit a gender predisposition, consistent with findings by Datla P et al. [6]. While our study had no recorded mortality among the 72 children with dengue, we cannot draw conclusions regarding the association of proteinuria with adverse outcomes such as mortality. However, Datla P et al. found a positive correlation between elevated UPCR and mortality [6]. Overall, our study underscores the importance of utilizing a simple laboratory investigation such as urine spot PCR as a predictor of dengue severity in children, particularly during dengue epidemics, to facilitate effective monitoring and management of at-risk children.

Conclusion :

With the rise in dengue fever cases among children and the accompanying complications, the importance of early predictors of disease severity cannot be overstated for efficient and effective monitoring of at-risk children. Assessing the urine spot protein creatinine ratio is a simple and cost-effective test. Our study revealed a statistically significant correlation between urine spot PCR and the severity of dengue, indicating its potential usefulness in triaging and monitoring children suspected of having dengue. Higher urine spot protein creatinine ratios were identified as a non-invasive marker for predicting the severity of dengue in children with dengue fever. Therefore, urine spot protein creatinine ratio assessment in children with dengue fever could serve as a valuable screening tool for predicting disease severity upon admission.

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