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# Investigation of the relationship between proteinuria and urine protein/creatinine ratio and the severity of paediatric dengue fever

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### Abstract

**Aim:** The study was undertaken to establish early predictors of disease severity *viz.*, urine protein creatinine ratio (UPCR) and proteinuria in children with dengue.

**Methods:** A prospective study was conducted in the Department of Paediatrics in collaboration with pathology department for a period of 18 months, after taking the approval of the protocol review committee and institutional ethics committee. A total of 200 children were included in this study.

**Results:** Out of the total, 41 were neonates, 57 were between the ages of 1 and 8 and 102 were children beyond the age of 8. This study included 140 Males and 60 Female children. An evident correlation was seen between elevated UPCR levels and the occurrence of bleeding symptoms, with statistical significance. An analysis revealed a statistically significant correlation between the use of inotropes and increased UPCR levels in the studied instances. The relationship between elevated UPCR levels and death demonstrated a substantial positive connection. Within our series, there were a total of 9 fatalities attributed to dengue fever. Among these cases, 5 children had proteinuria levels below 100 mg/dl, whereas 4 children had proteinuria levels beyond 100 mg/dl. The correlation was statistically significant.

**Conclusion:** This study showed that UPCR is a reliable indicator for predicting the severity of the illness, the loss of fluid in the third space, bleeding symptoms, the need for inotropes, and unfavorable outcomes in children with dengue fever. Proteinuria of considerable magnitude was determined to be a valuable indicator for forecasting unfavorable consequences.

**Keywords:** Pediatric dengue fever, urine protein creatinine ratio, proteinuria, prognostic indicators, predictor tools

### Introduction

Dengue is a significant and growing viral disease that affects people worldwide, causing illness and death. Currently, the illness is prevalent on all continents with the exception of Europe [1]. Dengue mostly impacts the paediatric population, and death from dengue is caused by increased capillary permeability, hemostasis problems, and in extreme instances, dengue shock syndrome [2]. Commencing administration of treatment after the onset of shock or hemorrhage leads to an increased death rate. The risk factors associated with the development of severe illness are not well-defined, leading to frequent hospitalization of simple cases for surveillance during the crucial period of capillary leakage syndrome. This, in turn, results in increased financial burden for patients. Hence, there is a pressing need for advancements in the early detection and forecasting of severe illness, particularly in terms of identifying uncomplicated clinical and or laboratory markers that are feasible and cost-effective for implementation in low-resource nations.

The cause of death in dengue is attributed to anomalous capillary permeability, disturbances in hemostasis, and in extreme instances, dengue shock syndrome. The yearly occurrence rate of dengue is 49.5 cases per 1000 child years in children who have fever for more than 3 days [3]. The risk factors for severe disease progression are not well defined, resulting in frequent hospitalisation of simple cases for monitoring during the crucial period of capillary leakage syndrome. This condition becomes burdensome for both patients and treating physicians.

Hence, there is an urgent want for advancements in the early detection and forecasting of serious illness. This would provide timely and suitable action. Optimally, the test should possess the qualities of being cost-effective, rapid, simple to execute, very sensitive, and highly specific [4].

Microalbuminuria has been suggested as a possible indicator of increased risk for severe dengue [5, 6]. However, there is little data on the extent, timing, and progression of urine protein excretion throughout the illness. Furthermore, doing 24-hour urine albumin measurements is a laborious and time-consuming process. Both spot urine protein estimation and urine protein to creatinine ratio are less burdensome and more practical methods. The use of spot urine protein to creatinine ratio is a more convenient and hence acceptable way of measurement [7].

The spot PCR is calculated by dividing the urine protein excretion (measured using either a 24-hour urine sample or a spot urine sample) by the creatinine excretion, and is given as mg/mmol or mg/mmol. Spot PCR offers a convenient substitute for the 24-hour urine collection method since it is more easily obtained and not affected by fluctuations in water consumption or urine production [7].

The research aimed to identify early indicators of illness severity, namely the urine protein creatinine ratio (UPCR) and proteinuria, in children with dengue.

**Materials and Methods**

A Hospital based prospective study was conducted in the Department of Paediatrics in collaboration with pathology department for a period of 18 months, after taking the approval of the protocol review committee and institutional ethics committee. A total of 200 children included in this study.

**Inclusion Criteria**

1. Children aged less than 14 years.
2. Presented with clinical warning signs of dengue or severe dengue.
3. Testing positive serology (NS1, IgM).

**Exclusion criteria**

Dengue without warning signs.

**Methodology**

Upon admission, fundamental characteristics like age, gender, weight, and history data were documented. A comprehensive and systematic assessment was conducted. The clinical characteristics of dengue fever were observed and patients were treated based on the illness severity recommendations provided by the World Health Organization (WHO). After a

patient met the criteria for dengue fever, they were assigned to one of three groups (A, B, or C) for case management. The laboratory tests for all the patients were documented. These tests include using a quick solid phase immunochromographic method to quantitatively detect dengue NS1 antigen and differentiate between IgM and IgG antibodies. Furthermore, the following diagnostic tests were conducted: haemoglobin assessment, packed cell volume measurement, platelet count analysis, ultrasound examination of the belly, and chest x-ray imaging. A urine protein creatinine ratio test, using the pyrogallol red technique to test for urine protein and the modified Jaffe's method to test for creatinine, was conducted to confirm the diagnosis of dengue fever. The protein content in urine was determined by measuring the absorbance at a wavelength of 600 nm. Coagulation profile, renal and liver function tests, and serum electrolytes were examined in accordance with the patient's clinical state. Further investigations were conducted in cases where the first findings were aberrant or if there was a decline in the patient's clinical condition. If the first report was abnormal, therapy was initiated and completed within a 24-hour timeframe. All enrolled children were assigned according to urine protein creatinine ratio into 4 groups viz., < 0.5, 0.5-1, 1-3, 3.

**Statistical Analysis**

The collected data was consolidated and spread into a spreadsheet software programme (Microsoft Excel 2010) and then transferred to the data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included the calculation of percentages. The analysis used the chi-square test. The confidence interval and p-value were established at a 95% level of confidence and a significance level of 5%.

**Results**

**Table 1:** Age vs UPCR Distribution

Age/UPCR	UPCRR<0.5	0.5-1.0	1.0-3.0	>3.0	Total
<1year	5	6	10	20	41
1-8year	25	4	25	3	57
>8year	40	40	20	2	102
Total	70 (35)	50 (25)	55 (27.5)	25 (12.5)	200
Gender	N		%		
Male	140		70		
Female	60		30		

Of these 41 were infants, 57 between 1-8 years and 102 children were above 8 years of age.

The total children based on the sex difference is 140 were Males and 60 Females.

**Table 2:** Bleeding manifestations during course of illness

No. of children with bleeding manifestations	UPCRR <0.5	0.5-1.0	1.0-3.0	>3.0	Total
Yes	0	5	7	8	20
No	70	45	48	17	180

There was a statistically significant association between high UPCR and bleeding manifestations.

**Table 3:** UPCR vs. Inotrope Usage

Inotropes	UPCRR<0.5	0.5-1.0	1.0-3.0	>3.0	Total
Yes	6	5	15	15	41
No	64	45	40	10	159
Total	70	50	55	25	200

It was observed that cases that needed inotropes had higher UPCR and this association was statistically significant.

**Table 4:** UPCR vs. Outcome

Outcome	<0.5	0.5-1.0	1.0-3.0	>3	Total
Discharge	70	50	51	20	191
Death	0	0	4	5	9

The association of raised UPCR with mortality showed a positive correlation and was statistically significant.

**Table 5:** Significant Proteinuria vs Outcome

Proteinuria/ outcome	<100	100-300	>300	Total
Death	5	4	0	9
Discharge	190	6	5	191

In this study we observed, 9 deaths occurred due to dengue, among which 5 children had proteinuria < 100 mg/dl and 4 children had proteinuria >100 mg/dl. The association was statistically significant.

### Discussion

Dengue is a viral disease transmitted by arthropods, mostly affecting people, and is a significant worldwide public health concern. The prevalence of this issue is consistently rising, particularly in poorer nations where it has become an endemic concern [8]. Dengue mostly impacts the paediatric population and is linked to significant levels of illness and death [4]. Dengue sickness may be categorized into three primary phases: the febrile period, the critical phase, and the recovery phase. The critical phase, which typically starts 4-7 days following the beginning of fever, is characterized by severe clinical illness symptoms that typically continue for 48-72 hours. During the critical period, patients' status might exhibit rapid fluctuations, necessitating vigilant monitoring by care providers. Implementing fluid replacement treatment in the early stages of severe dengue significantly decreases the occurrence of illness and death [9]. Out of the total, 41 were infants (<1 year age), 57 were between 1-8 years old, and 102 were over 8 years old. The results of this study were similar with the findings of Yip WC, Vasanwala FF *et al.*, and Vasanwala FF *et al* [10, 12]. Who conducted a study on the Predictive Value of proteinuria in dengue patients? They concluded that proteinuria, as measured by a laboratory-based UPCR test, can be both sensitive and specific in predicting the prognosis of dengue patients. Upon admission, the urine protein creatinine ratio was assessed and classified in all of these children. The results of our investigation showed a statistically significant negative relationship between UPCR and age. Garcia *et al.* (1995) reported a proteinuria prevalence of 22% among individuals with dengue fever. Among those affected, 38% had proteinuria during the first 4 days after the beginning of constitutional symptoms [13].

Although bleeding symptoms are often seen in cases of dengue fever, there is currently no existing published research that demonstrates a connection between bleeding symptoms, coagulation disorders, and increased urine protein creatinine ratio in children [14, 16]. An evident and meaningful correlation was seen between elevated UPCR levels and the occurrence of bleeding symptoms. A statistically significant correlation was found between higher UPCR levels and the requirement for inotropes in observed instances. The connection between elevated UPCR levels and death demonstrated a strong positive correlation. Within our series, there were a total of 9 fatalities attributed to dengue fever. Among these cases, 4 children had proteinuria levels below 100 mg/dl, whereas 3 children had proteinuria levels beyond 100mg/dl. The correlation was statistically significant. We conducted an examination on the importance of proteinuria and its correlation with the severity of illness in paediatric patients with dengue fever. Although we did not see any notable link between proteinuria and the severity of the illness, we did identify a statistically significant positive relationship between severe proteinuria and mortality ( $p < 0.05$ ). Renal involvement and its consequences, especially in cases with dengue shock syndrome, have been shown in other research [17, 18].

### Conclusion

This research showed that UPCR is a reliable indicator for predicting the severity of the illness, the loss of fluid in the third space, bleeding symptoms, the use for inotropic medications, and unfavorable outcomes in children with dengue fever. Proteinuria of considerable magnitude has been identified as a valuable indicator for predicting unfavorable outcomes. Therefore, we suggest using both UPCR and proteinuria quantification in all children with dengue fever as a screening tool for hospitalization, care, and prognosis assessment.

### Acknowledgement

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### Conflict of Interest

None to be declared

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