

Urine Protein Creatinine Ratio as a Predictor of Disease Severity in Dengue Fever in a Tertiary Hospital in South Tamil Nadu

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Abstract

Introduction: Dengue mainly affects the pediatric age group and causes high mortality initiating management after the occurrence of shock or hemorrhage results in a higher mortality rate. The need for the hour is a simple and valuable clinical or biochemical tool to predict the severity in dengue patients. This study was undertaken to establish urine spot protein creatinine ratio as an early predictor of disease severity.

Materials and Methods: This is a hospital-based prospective study with a sample size of eighty cases that were categorized based on the severity of the WHO guidelines. Urine spot protein creatinine ratio was done daily since the day of admission and the values were compared with the clinical parameters and blood indices.

Results and Conclusions: Out of 80 dengue cases, 28 (35%) belonged to Category A, 32 (40%) belonged to Category B, and 20 (25%) belonged to Category C. Urinary protein creatinine ratio was significantly raised in severe cases of dengue (Category C). Increased level of peak urine creatinine ratio has a positive correlation with clinical severity, severe thrombocytopenia, rising hematocrit, and low blood pressure levels. Urine spot protein creatinine ratio can be an accurate marker in predicting disease severity, bleeding manifestations, need for inotropes, and adverse outcome in children with dengue fever.

Key words: Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome, Severe dengue, Urine spot protein creatinine ratio

INTRODUCTION

Dengue is one of the most important emerging viral disease of humans in the world afflicting humanity in terms of morbidity and mortality. At present, the disease is endemic in all continents except Europe.^[1]Dengue mainly affects the pediatric age group and mortality due to dengue is due to capillary permeability, abnormalities of hemostasis, and in severe cases, dengue shock syndrome.^[2]

Initiating management after the occurrence of shock or hemorrhage results in a higher mortality rate. The risk

factors for the development of severe disease are poorly characterized, and consequently, uncomplicated cases are frequently hospitalized for observation during the critical phase for capillary leakage syndrome, thereby increasing the financial cost to patients. Therefore, improvements in early diagnosis and risk prediction for severe disease are urgently needed, particularly with respect to the identification of simple clinical and/or laboratory indicators that are practical and affordable for use in resource-poor countries. This would enable appropriate and early intervention. Ideally, the test should be cheap, fast, easy to perform, highly sensitive, and specific. This study was undertaken to establish urine spot protein creatinine ratio as an early predictor of disease severity.

Aim

To assess, whether urine protein creatinine ratio could be used as a predictor of disease severity in children diagnosed with dengue.

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MATERIALS AND METHODS

This study was a prospective study done over a period of 1 year between May 2018 and April 2019 in the Institute of Paediatrics, Government Rajaji Hospital, Madurai. An informed oral consent was obtained from the parent/guardian of the child during enrolment into the study. The study was approved by the Institute Ethical Committee.

Patients diagnosed as dengue using nonstructural protein 1 (NS1) antigen or IgM antibody depending on the day of admission were followed up from the day of admission during the acute period and subsequent days. Demographic and epidemiological data were collected at enrolment. Detailed clinical examination, biochemical analysis, and imaging studies were done as per standard treatment protocol.

The patients were categorized into three categories based on the WHO guidelines. Symptoms and signs were recorded each day. Complete blood count and spot urine collection were done every day. Urine protein is detected and quantified by pyrogallol red method and creatinine by modified Jaffes method.

In children with age <2 years, a urine protein creatinine ratio (UPCR) value of <0.5 and in subjects with age more than 2 years a value <0.2 was considered as normal. Values lower than this range were considered insignificant.

Peak value of urine protein creatinine ratio in patient with dengue with no warning signs, dengue with warning signs, and severe dengue was compared.

Statistical Analysis

Data obtained were analyzed using SPSS software – version 19. Outcomes were tested using the Chi-square test. $P < 0.05$ was considered significant.

RESULTS AND ANALYSIS

A total of 80 dengue cases were enrolled in the study and were grouped into three categories based on the WHO guidelines. Of the total 80 cases, 28 cases belonged to Category A, 32 belonged to Category B, and 20 cases belonged to Category C.

Majority of the children were male, but gender distribution has no correlation with dengue severity. Majority of cases are admitted during the 4th or 5th day of illness in all categories [Figure 1].

Of the total 80 participants, 25% ($n = 5$) of cases with severe dengue (category 3) had very high protein creatinine

ratio (PCR) on admission which is found to be statistically significant. ($P < 0.001$) [Table 1].

Majority of cases had peak UPCR on day 5 which is the critical phase [Figure 2].

In all the six cases, for whom the UPCR value was more than 1.5, thrombocytopenia (platelet below 50000/cu.mm) was seen, which was statistically significant [Table 2].

In terms of bleeding manifestations, patients presented with bleeding had high UPCR values, which were statistically significant ($P = 0.006$) [Table 3].

The presence of third space fluid was compared to the peak UPCR, which was found to be statistically not significant [Table 4]. Out of 13 patients who had hypotension during the hospital stay ten cases had peak

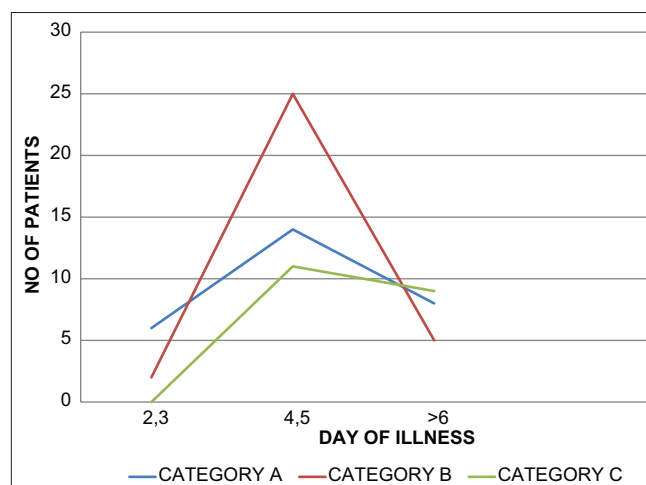


Figure 1: Day of illness on admission versus severity categories

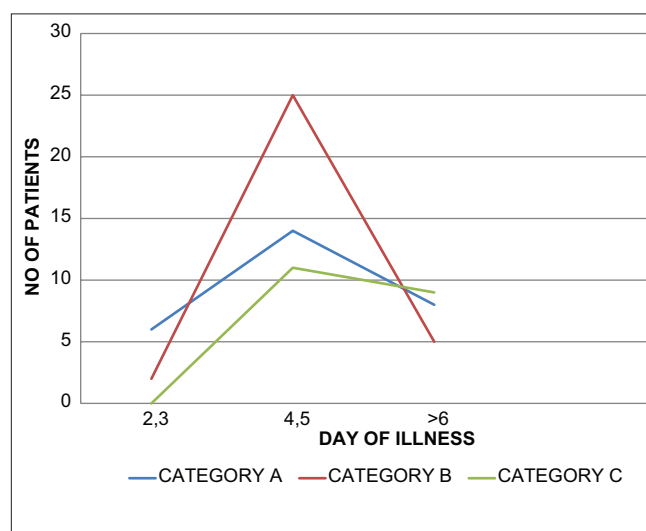


Figure 2: Peak UPCR versus Day of illness

Table 1: Spot PCR on day of admission

Spot PCR on admission	Category A	Category B	Category C	Total
<0.5	16	20	3	39
0.5–1.0	10	10	11	31
1.0–1.5	2	2	1	5
>1.5	0	0	5	5
Total	28	32	20	80
Chi-square	23.298			
p value	<0.001 Significant			

PCR: Protein creatinine ratio

Table 2: Platelet count versus peak urine protein creatinine ratio

PLT on peak spot PCR	Peak value				Total
	<0.5	0.5–1.0	1.0–1.5	>1.5	
<50000	5	6	3	6	20
50000–1 lakh	16	14	1	0	31
>1 lakh	20	5	4	0	29
Total	41	25	8	6	80
Chi-square	28.556				
p value	<0.001 Significant				

PCR: Protein creatinine ratio

Table 3: Bleeding manifestations versus peak urine protein creatinine ratio

Bleeding	Peak value				Total
	<0.5	0.5–1.0	1.0–1.5	>1.5	
Yes	3	5	4	3	15
No	38	20	4	3	65
Total	41	25	8	6	80
Chi square	12.518				
p value	0.006 Significant				

Table 4: Third space fluid versus peak urine protein creatinine ratio

3 rd space collection	Peak value				Total
	<0.5	0.5–1.0	1.0–1.5	>1.5	
Yes	5	7	3	3	18
No	36	18	5	3	62
Total	41	25	8	6	80
Chi-square	6.565				
p value	0.087 Not significant				

UPCR more than 1, which was statistically significant ($P = 0.00001$) [Table 5].

Peak urine PCR was compared with the hematocrit levels and it was found that variability in hematocrit is statistically significant with rise in UPCR [Table 6].

Mean urine protein creatinine ratio was calculated, and it was found that mean UPCR was higher in Category C which is statistically significant [Table 7].

Table 5: Blood pressure versus peak urine protein creatinine ratio

BP	Peak value				Total
	<0.5	0.5–1.0	1.0–1.5	>1.5	
Normal	40	24	2	1	67
Hypotension	1	2	6	4	13
Total	41	26	8	5	80
Chi-square	42.3659				
p value	0.00,001 Significant				

Table 6: Hematocrit levels versus peak urine protein creatinine ratio

HCT	Peak value				Total
	<0.5	0.5–1.0	1.0–1.5	>1.5	
<20	1	3	1	2	7
20–30	2	4	3	1	10
30–40	36	15	3	1	55
>40	2	3	1	2	8
Total	41	25	8	6	80
Chi-square	25.281				
p value	<0.05 Significant				

HCT: Hematocrit

Table 7: PCR versus severity categories

Spot PCR	Category A	Category B	Category C
Mean	0.407	0.461	1.427
SD	0.302	0.285	1.413
p value	<0.001 Significant		

PCR: Protein creatinine ratio

DISCUSSION

Dengue hemorrhagic fever and dengue shock syndrome result in significant mortality in children.^[1] There are many studies available predicting the severity in adult patients, and only few are available in pediatric children. Hence, this study is undertaken to predict the severity of dengue, thereby improving the outcome. An increase in vascular permeability is the hallmark of dengue infection. This is due to the damage to the endothelial cells. Hypoalbuminemia and proteinuria are well recognized in dengue infection. This is due to altered filtration of the glycocalyx as dengue virus and NS1 are known to attach to heparan sulfate, which is part of the glycocalyx. Hence, we studied to estimate urine protein creatinine ratio from the day of admission.

Eighty children of our study were categorized based on the clinical findings and laboratory parameter into three categories. Out of 80, 28 (35%) belonged to Category A, 32 (40%) belonged to Category B, and 20 (25%) belonged to Category C.

Majority of admissions occurred on the 4th and 5th day of illness. The values of UPCR estimated on the

day of admission were increased in cases belonging to Category C.

We divided the age group of children into two groups as <2 years and more than 2 years based on the normal values of UPCR. Age does not show any correlation between UPCR which is similar to the study done by Datla *et al.*^[3]

Thirty percent of Category C had UPCR more than 1.5 which is similar to study by Vasanwala *et al.*^[4]

Third space collection was observed in 18 cases, of whom only three cases had UPCR >1.5, which is statistically insignificant ($P = 0.087$), but in a study by Datla *et al.*,^[3] 58% cases had third space collection who showed significant elevation of UPCR.

Thirteen (16%) children had hypotension, of whom 4 (30%) cases had UPCR value higher than 1.5. Most of the children had a peak value on days 4 and 5 of illness, which is the critical phase. This was similar to many other studies where elevated UPCR was observed before the shock.^[5-8]

When UPCR was compared with hematocrit, the majority of cases had hematocrit between 30 and 40, drastic fall and rise in hematocrit values were associated with an increase in UPCR which was significant and also the predictor of shock.^[6]

When platelet count was compared with UPCR, very low platelet count of <50,000 was associated with a significant rise in UPCR. Hence, low platelet and rise in UPCR indicated that the children can develop shock.^[7,8]

In our study, we calculated the mean UPCR with Categories A, B, and C. It was found to be significantly high in our study which was also similar to many other studies.^[8,9]

We observed that the peak UPCR could distinguish patients likely to develop dengue hemorrhagic fever (DHF) from those who did not and that peak UPCR occurred on day 4–7 of the illness. A significant increase in UPCR was seen on the day which corresponded to 1 day before the development of DHF. Patients with uncomplicated dengue fever had significantly lower UPCR than patients with impending DHF and dengue shock syndrome. Daily follow-up in this prospective study enabled a time-course analysis showing that the discriminatory value of UPCR was not evident in the early febrile period, but it is discriminatory between days 4 and 7, just before defervescence when maximal plasma leakage classically occurs.

Limitations

Our study had less number of patients with severe dengue. Another limitation is that no single diagnostic assay in isolation is adequately sensitive and specific enough to diagnose all acute cases of dengue. We used either reverse transcriptase (RT) PCR or NS1 structural protein to diagnose patients with dengue. RT-PCR is a robust test during the viremic febrile phase but is less sensitive during the time of the defervescence. NS1 rapid diagnostic tests have 49.4–98.9% sensitivity and 90.6–100% specificity in the detection of dengue ranging from 1 to 15 days of illness.

CONCLUSIONS

Increase occurrence of dengue fever and its associated complications necessitates the need for early predictors of disease severity. Such markers have not been well studied in the pediatric population. UPCR assessment is easy to perform and inexpensive. This study found UPCR to be an accurate marker in predicting disease severity, bleeding manifestations, need for inotropes, and adverse outcome in children with dengue fever.

We, therefore, recommend the usage of both UPCR estimation in all children afflicted with dengue fever as a screening device for hospitalization, management, and prognostication.

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