Section: Pediatrics

Original Research Article

TO PREDICT THE SEVERITY OF DENGUE FEVER IN HOSPITALISED CHILDREN BY ESTIMATING PROTEINURIA AND URINARY PROTEIN TO CREATININE REATIO

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ABSTRACT

Background: Dengue is the most prevalent mosquito-borne viral disease worldwide, majority of the infections are asymptomatic or result in a mild febrile illness, but the dengue virus (DENV) is also capable of producing a life-threatening disease. The objective is to investigate the presence of proteinuria during dengue disease in children by simple urinalysis strip and by urine protein creatinine ratio and whether it could be used to indicate which patient with dengue fever would progress to DHF or DSS.

Materials and Methods: Total of 60 dengue patients admitted to department of Paediatrics in SS Institute of medical sciences and hospital, Davangere in span of 2 years from January 2021 to September 2022 were included in the study who fulfilled the inclusion criteria. Urine samples were collected and subjected to urine dip stick and UPCR.

Results: In our study it was found that prognostic markers of dengue like platelet count, hemoconcentration, bleeding, hypotension correlated well with urinary excretion of protein which was estimated by UPCR and UDS with significant statistical correlation.

Conclusion: This study showed that by estimation of protein excretion in urine, it was possible to predict the cases going into complication. UPCR and UDS showed good correlation with some of the already existing dengue parameters which are used for prognosticating.

Keywords: Dengue, UPCR, UDS

INTRODUCTION

Dengue fever is a benign syndrome caused by arthropod-borne viruses and is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia & lymphadenopathy. Dengue hemorrhagic fever is a severe often fatal, febrile disease caused by one of four dengue viruses, which is characterized by increased capillary permeability and abnormalities of hemostasis. In severe cases it can manifest has a protein-losing shock syndrome called dengue shock syndrome.[1]

Dengue is one of the disease noted under World Health Organization (WHO) 2021- 2030 road map against neglected tropical diseases.[2]

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years incidence has increased 30-fold with increasing geographic expansion to new countries and in the present decade shifted from urban to rural settings, an estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries.[3]

The first evidence of occurrence of dengue fever in the country was reported in 1956 from Vellore district in Tamil Nadu. 4,5 The first dengue hemorrhagic fever (DHF) outbreak occurred in Calcutta (West Bengal) in 1963. The national dengue day was observed on 16 may 2016. It is endemic in 18 out of 35 states.[2]The incidence of dengue is increasing in the last few years. In 2019,157315 cases

were reported, it increased to 193245 in 2021 and data for the year 2022 till 31st October reported 110473.The case fatality ratio (CFR– deaths per 100 cases) has declined from 3.3% in 1996 to 0.4% in 2010 after the national guidelines on clinical management of Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), Dengue Shock Syndrome (DSS) were developed and circulated in 2007. This further declined to 0.3% in 2013.[2] Every year, during the period July–November, a upsurge in cases of DF, DHF, DSS has been observed. The disease has a seasonal pattern; the cases peak after the monsoons and are not uniformly distributed throughout the year. However, the states in the southern and western parts of the country report perennial transmission.[6]

The incidence of severe dengue and mortality is comparatively high in paediatric age group when compared to adult population. This fact warranted an investigation which would pick up progression to severe form, before it reaches a peak severity. Dengue is a disease which when acted upon at the appropriate time reduces complications and gives better outcome. Hence, this study was undertaken to see the application of urine dip stick and urine protein to creatinine ratio for detecting progression to severe form. Main form of severe dengue is characterised by plasma leakage and increased vascular permeability which may lead to circulatory collapse, severe manifestations occur during the critical phase. Early clinical management based on fluid replacement therapy reduces the morbidity and mortality associated with severe dengue. The major obstacle for an effective clinical management of dengue is inability to accurately predict at an early stage which patient are likely to develop severe form of disease. Increased urinary excretion of protein in patients infected by dengue virus is thought to be a hall mark of vascular endothelial cells defect and plasma leakage associated with complicated forms of dengue and is considered possible prognostic marker.[7] Proteinuria has been reported in up to 74% of patients with dengue haemorrhagic fever (DHF).[8] The mechanism underlying the hypothesis of increased protein excretion in urine is that during dengue viral illness the glycocalyx of the endothelial cells is disrupted either by direct action of the virus or by the NS1 antigen,[7,9,10] causing plasma leakage. At the kidney level, alteration of the glycocalyx layer that coats the glomerular endothelial cells enables the passage of macromolecules in the primary urine. In normal conditions, this passage is restricted in order to maintain the intravascular albumin concentration. As macromolecules cannot be reabsorbed by tubules, a glomerular proteinuria mainly characterised by the presence of albumin in the final urine occurs. The presence of micro-albuminuria has been postulated as potential risk predictor for severe dengue, but there is little information on the magnitude, timing of onset or evolution of urinary protein excretion during infection. Moreover, 24 hour urinary albumin measurements are cumbersome and time consuming to perform. But measurement of spot urine protein estimation as well as urine protein to creatinine ratio is a more practical and therefore readily acceptable alternative11.Hence, we studied 60 cases of dengue which met the inclusion criteria, we measured urinary dip stick and urine protein to creatinine ratio from day of admission till recovery phase or minimum of three readings were taken. Cases were categorised according to WHO severity classification.

MATERIALS AND METHODS

This is a hospital based prospective study conducted in department of pediatrics, S.S Institute of medical science & research center, Davangere, Karnataka with a study period of 2 years (2020 – 2022). Study was conducted after receiving approval from institute ethical board, prior to sample collection informed consent of parents or guardians was taken.

Dengue cases meeting the inclusion criteria were taken up evaluated from day of admission till recovery phase. Clinical parameters, demographic data and serial lab investigations like complete blood count and urinary parameters were collected Cases were divided according to WHO guidelines

Detection of dengue virus: Dengue was detected via serodiagnosis which involved detection of NS1 antigen, detection of IgM and/or IgG. If dengue was strongly clinically suspected but the above investigation showed no positive result, then viral PCR was sent for detection of viral genome sequence.

Inclusion Criteria

A confirmed dengue case is defined by the detection:

- Detection of the NS1 protein and/or viral RNA by PCR
- IgM seroconversion
- Normal serum urea/creatinine ratio

Exclusion Criteria

- Patient having underlying comorbidities (cardiac, pulmonary, liver)
- Pre-existing chronic kidney disease/ nephrotic syndrome/nephritic syndrome
- Female patient during menstrual cycle
- Urinary tract infections

Methods for measuring urinary proteins:

1. Urine dip stick method:

This method relies on the principle that presence of protein in a buffer solution causes a change in the pH of the solution which is proportional to the concentration of the protein. The dipstick contains a pH indicator dye and a buffer. The indicator colour changes ranging from pale green to green to blue when stick is dipped in urine containing the proteins. The test is more sensitive to albumin and less sensitive to immunoglobulin light chains and other globulins. The test is very sensitive enough to detect even 20mg/dl of protein in urine. But it does not take into account the volume of urine. When urine volume is high and the urine is very much dilute, a relatively large amount of protein can even go undetected. If a total protein excretion approaching approximately 1 g/day may not be detected if urine output is as high as

10L/day as the concentration of urine protein falls below 20mg/dl.

The dipstick reports are interpreted as follows:

1. Negative <30mg %
2. 1+ 30-10mg/dl
3. 2+ 100-300mg/dl
4. 3+ 300-1000mg/dl
5. 4+ >1000 mg/dl

Patient bedside urine sample was collected following all the sterile procedures, sample was collected in a clean container. A dip stick was taken holding the thick gripping surface at the end of the dip stick. The dip stick is then submerged all the way making sure all test square is submerged. Once saturated the strip is removed, allowed to react with reagent for 2 minutes and then the readings are compared against the colorimeter, it is a simple bed side test and was done by the principal investigator. Minimum of three readings were taken.

2. Urine protein to creatinine ratio:

UPCR is obtained by the ratio between urine protein excretion (measured by spot urine sample) and creatinine excretion, expressed as mg/mg or mg/mmol. UPCR represents a practical alternative to the 24-hour urine collection because it is easier to obtain and is not influenced by variations in water intake or diuresis. And the same sample can also be used for investigations under microscope. A close correlation between the UPCR in a random urine sample and the 24-hour protein excretion has been demonstrated in a wide range of patients, including those with different types of glomerulonephritis (GN) evaluated longitudinally during treatment.

UPCR was estimated by colorimetric method, 2ml of urine sample was sent, had a turn around time of 2 hours, readings were taken for 3 days.

Advantages of spot PCR include:

- Not cumbersome
- Not affected by diuretics or variation in water intake
- The sample can be used for microbial analysis

Statistical analysis: Data collected was analysed using Jamovi software tool. Chi-square test was used for testing the outcome. Significant p value was taken as <0.05

RESULTS

60 cases were enrolled in this study, which met the required inclusion criteria. Majority of the cases in the study were males Most of the admission happened on day 4 and 5 of illness.

Table 1: Age vs UPCR Distribution

Age/Peak value of UPCR	<0.5	0.5-1.0	1.0-1.5	1.5-2.0	Total
1	9	3	2	0	14
2	19	21	2	4	46
Total	28	24	4	4	60

-Majority of the cases were above 2 years

Table 2: UPCR vs Dengue severity

UPCR on Admission				
Dengue classification	**<0.5**	**0.5-1.0**	**1.0-1.5**	**Total**
Category A	12	9	0	21
Category B	16	6	1	23
Category C	7	7	2	16
Total	35	22	3	60

This association had no significant association (P: 0.278)

Table 3: HCT vs Peak UPCR

PEAK_VALUE_OF_UPCR						
HCT		**<0.5**	**0.5-1.0**	**1.0-1.5**	**1.5-2.0**	**Total**
20-30	Observed	2	3	2	0	7
	% of total	3.3 %	5.0 %	3.3 %	0.0 %	11.7 %
30-40	Observed	26	11	2	1	40
	% of total	43.3 %	18.3 %	3.3 %	1.7 %	66.7 %
>40	Observed	4	5	1	3	13
	% of total	6.7 %	8.3 %	1.7 %	5.0 %	21.7 %
Total	Observed	32	19	5	4	60
	% of total	53.3 %	31.7 %	8.3 %	6.7 %	100.0 %

- Patients with high HCT had comparatively high peak UPCR

Table 4: AGE vs Peak value of UDS

PEAK_VALUE_OF_UDS						
AGE		**Nil**	**1+**	**2+**	**3+**	**Total**
<2 years	Observed	9	2	3	0	14
	% of total	15.0 %	3.3 %	5.0 %	0.0 %	23.3 %
>2years	Observed	26	13	6	1	46
	% of total	43.3 %	21.7 %	10.0 %	1.7 %	76.7 %
Total	Observed	35	15	9	1	60
	% of total	58.3 %	25.0 %	15.0 %	1.7 %	100.0 %

Age did not correlate with UDS values at admission

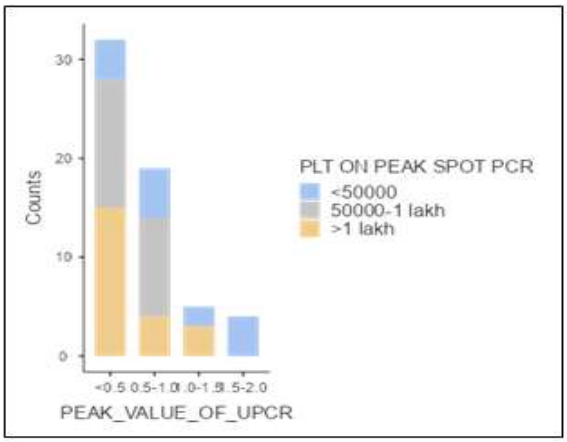

Figure 1: Platelet vs peak spot PCR

-Decrease in platelet count was associated with comparative increase in UPCR values

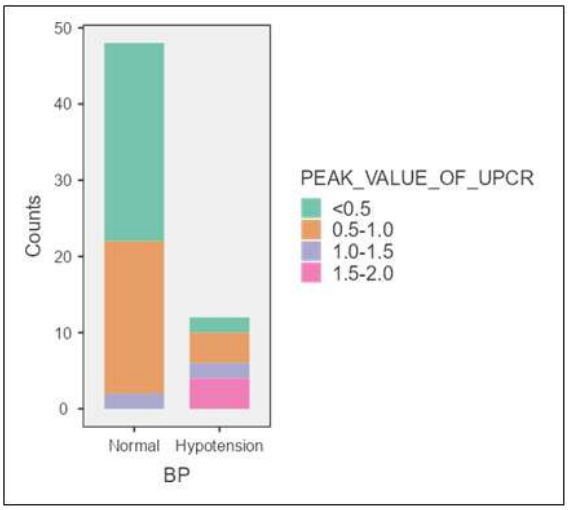

Figure 2: Blood pressure vs peak value of UPCR

- The association of blood pressure and peak value of UPCR was studied and was found to be statistically significant.

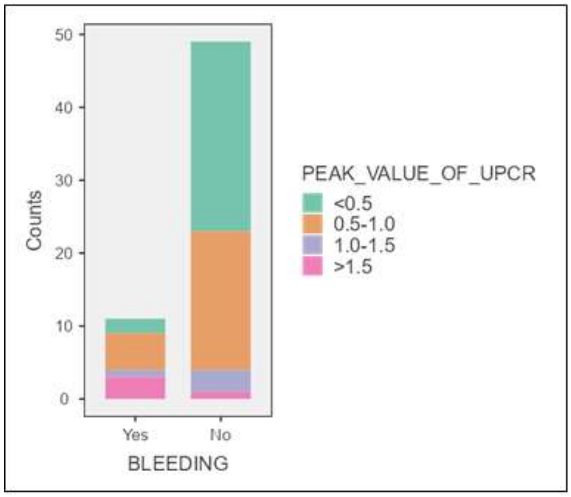

Figure 3: Bleeding vs peak value of UPCR

Correlation of bleeding and peak UPCR was done and was found to be significant.

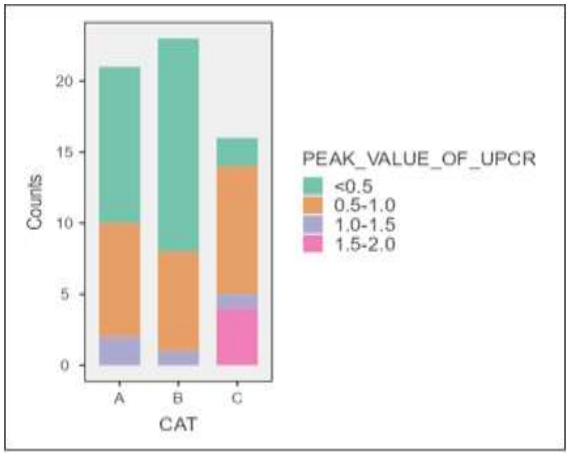

Figure 4. Categories vs peak value of UPCR

-It is observed that patients falling into category-C have comparatively higher UPCR levels.
Alternate hypothesis is true. Mean peak value of UPCR between the categories are different with F statistic of 7.99 and p<0.001

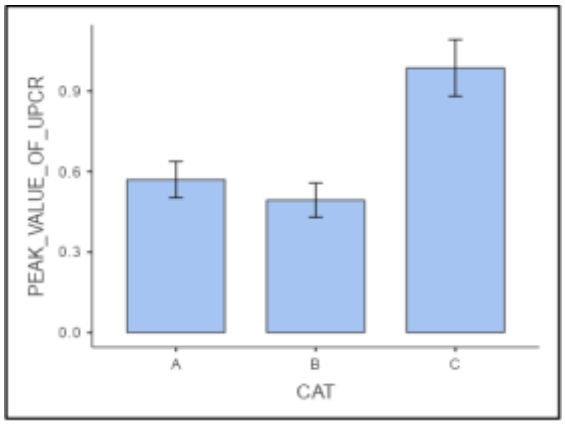

Figure 5: Mean Peak value of UPCR versus categories

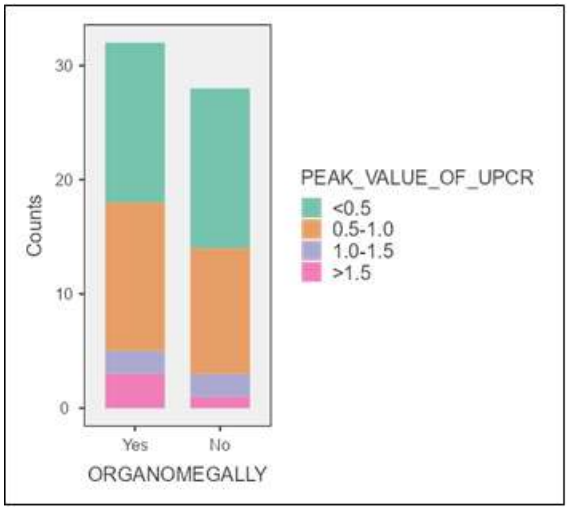

Figure 6: Organomegaly versus peak value of UPCR

-The above association is not statistically significant

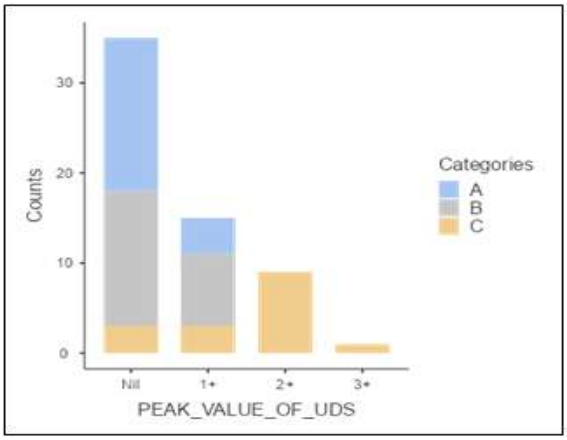

Figure 7: Categories vs Peak value of UDS

-It is observed that patients falling into category B and C have comparatively higher protein excretion.
-Majority with normal BP had relatively NIL excretion, those with low BP had higher values.
-Correlation of bleeding and peak UDS was done and was found to be significant

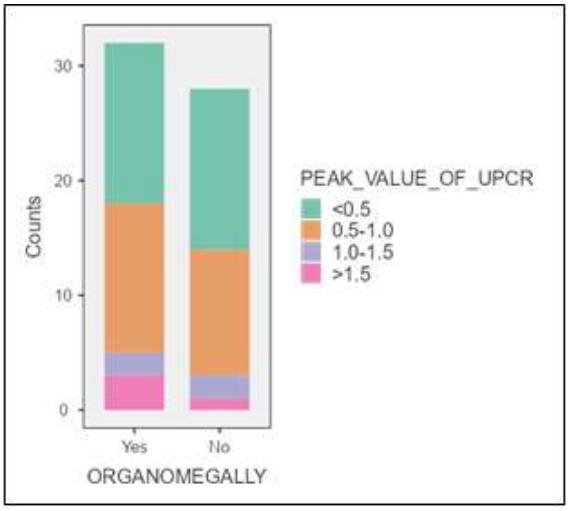

Figure 8: Organomegaly vs peak value of UDS

-The above comparison did not reach levels of statistical significance
95% of category A, 86% of category B and 37% of category C patients had NIL value, Category C showed that 62% of patients had values more than NIL.
There was no correlation between the two variables (Haematocrit on peak UDS vs peak value of UDS) and was statistically insignificant.
- Decrease in platelet count and UDS values did not correlate in statistical significant levels.

DISCUSSION

Out of 60 cases, 21 cases belonged to category A (35%), 23 belonged to category B (38%) and 16 belonged to category C (27%). Children were divided into < 2 year and >2 year age group. 14(23%) cases belonged to < 2 year age group and 46 (77%) cases belonged to > 2 year age group. Out of 60 cases 38(63%) were male and 22(37%) were female. There was no statistical significance related to gender distribution. 6(10%) cases were admitted on day-3 of illness, 13(21%) cases were admitted on day 4 of illness, 27(46%) cases were admitted on day 5 of illness and 14(23%) cases were admitted on day 6 of illness. In the above study out of 60 patients 12(20%) cases were found to be hypotensive and 11(18%) cases had bleeding manifestations.
All cases were subjected to UPCR estimation from admission till recovery phase. An average of minimum 3 readings were taken. Values were divided has <0.5, 0.5 – 1, 1 – 1.5 and >1.5. They were then compared against various variables.
AGE vs UPCR: Age group were taken has less than 2 years and more than 2 years, majority of the cases falling into the later group. When age was compared with UPCR it was found to be statistically insignificant (P - 0.133).
Admission UPCR vs Category: 57% of category-A cases, 69% of category-B cases and 43% of category C patients had UPCR < 0.5, cases were compared against admission UPCR, this association did not reach statistical significance. (P – 0.278).
Haematocrit vs PEAK UPCR: 21.7% of cases had HCT>40, out of this group it was found that 69% of cases had UPCR >0.5, this association reached statistical significance (P: 0.0025).
Platelet vs PEAK UPCR: Out of 60 cases,63% of cases had platelet value less than 1 lakh. It was found that UPCR increased proportionally to decrease in platelet count, 31% of cases in >1lakh group, 76 % of cases in 50000 – 1 lakh group and 73% of cases in <50000 had UPCR > 0.5. This association was statistically significant (P: 0.002).
UPCR vs Blood Pressure: 83 % of the cases in hypotensive group had UPCR >0.5, which was statistically significant (P< 0.001).
PEAK UPCR vs Bleeding: 11(18%) cases had bleeding manifestations, out of 11 cases 81% had UPCR >0.5. Peak value of UPCR in category C showed 87% of cases had UPCR > 0.5, which was statistically significant (P : 0.011).
PEAK UPCR vs Category: 47% cases of category A, 34% cases of category B and 87% of category C patients had peak UPCR > 0.5, which reached levels of statistical significance (P: 0.004)
MEAN UPCR vs CATEGORY: Mean UPCR of category A was 0.57, category B was 0.493 and category C had 0.987. This association was statistically significant (P: 0.001)
Organomegaly vs PEAK UPCR: 54% of cases had organomegaly, this association was found to be insignificant (P: 0.824).
All cases were subjected to urine dip stick estimation of proteinuria from admission till recovery phase. An average of minimum 3 readings were taken. Values were divided has NIL, 1(+), 2(+), 3(+) and 4(+). They were then compared against various variables.
AGE vs UDS: 56% of less than 2 year age group and 57% of more than 2 year age group had NIL values.

Age and urine proteinuria showed no significant relation (P: 0.624).

Category vs PEAK UDS: 19% of category A patient, 34% of category B and 81% of category C had values above NIL, it was seen that increasing severity was found to have more proteinuria. This was statistically significant (P: 0.001).

BP vs PEAK UDS: 29% of normal BP group had values more than NIL, this when compared to hypotensive group, showed that 91% of the cases had values more than NIL. Hence, showing possible correlation between the two, they reached levels of statistical significance (P: 0.001).

Bleeding vs PEAK UDS: 11 cases out of 60 had bleeding manifestations associated with them. 65 % of the cases which had no bleeding manifestations had NIL value.Where as all cases associated with bleeding had protein detected, this association was statistically significant (P : <0.001).

Organomegaly vs PEAK UDS: The association between the two did not reach levels of significance (P: 0.759).

Category vs UDS on admission: It was found that 95% of category A, 86% of category B and 37% of category C patients had NIL value. Category C showed that 62% of patients had values more than NIL. Hence, a urine dipstick at admission can help in prognosticating. The association was significant (P: 0.001)

Haematocrit vs PEAK UDS: Has majority of the cases did not show any traces of protein, only 24(40%) cases could be taken up, the association did not reach any level of significance.(P : 0.688).

Platelet vs PEAK UDS: Having the same drawback has the above comparison. This too did not reach levels of significance.(P : 0.616)

The above study results was comparable with other similar studies done by, Anne-Claire Andries et al,[12] A positive dipstick result was observed for 38.1% and 32% of the patients admitted at hospital for a dengue WS- and WS+, respectively. Proteins were detected in the urine sample of 75% of the patients which presented with a severe dengue. The UPCR was tested at admission in 52 patients and proteinuria was detected in 23.1% of the cases. None of the WS-dengue cases had proteinuria compared with 16.1% in WS+ cases and 50% in patients experiencing severe dengue.

Priyanka Datla et al,[13] in this study, it was observed that UPCR values were found to be directly proportional to increasing severity of disease. This association was statistically significant (p = 0.024). Among children that had bleeding manifestations during course of illness, 55.6% had UPCR >3. There was a statistically significant association between high UPCR and bleeding manifestations (p<0.05)19 children with mild disease did not have significant proteinuria (<100mg/dl). 7% of children with moderate disease severity had significant proteinuria. In severe disease, 7% had significant proteinuria.

Farhad F.Vasanwala et al,[14] observed that the peak UPCR could distinguish patients likely to develop DHF from those who did not and that peak UPCR occurred at day 7of the illness. A significant increase in proteinuria was seen one day before defervescence which corresponded to one day before the development of DHF. Patients with uncomplicated DF had significantly lower proteinuria than patients with impending DHF and DSS.

CONCLUSION

This study showed that by estimation of protein excretion in urine, it was possible to predict the cases going into complication. UPCR and UDS showed good correlation with some of the already existing dengue parameters which are used for prognosticating. UPCR correlated well with hemoconcentration, thrombocytopenia, bleeding and hypotension. UDS was also having similar correlation, and it offered additional benefit of helping in prognosis at the time of admission. This study recommends the use of UPCR and UDS in the management of dengue cases.

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