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ORIGINAL RESEARCH

To Study the Renal Involvement in Hospitalized Children with Dengue Fever in A Tertiary Care Center

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ABSTRACT

Background: Dengue was one of the top 10 probable health concerns to the world in 2019 according to the World Health Organization. Dengue fever has been associated with various types of renal manifestations such as proteinuria, hematuria, glomerulonephritis, and acute kidney injury (AKI). Hence, this prospective cross-sectional observational study was designed to analyze the frequency, characteristics, and clinical outcome of dengue fever in children with renal manifestations.

Materials & Methods: This was a cross sectional observational study done on 225 cases of children with dengue fever in the Department of pediatrics, SPMCHI hospital Sawai Man Singh Medical College, Jaipur. Data regarding the need for fluid resuscitation, colloid infusion, inotrope support, ventilatory requirement were collected. Creatinine values and urine output were noted and 'Kidney Disease Improving Global Outcome 2012 (KDIGO)' guideline was used to stage the acute kidney injury. Various renal manifestations of dengue will be studied and compared between the severity of dengue fever. Continuous variables were summarized as mean and standard deviation and were analyzed using independent sample t test for comparison between 2 groups and ANOVA test was used for comparison between multiple groups (>2 groups).

Results: Our study showed that Mean age of 225 children with dengue in present study was 7.98 ± 4.21 years. Male to female ratio was 1.06:1. Renal involvement was highest in patients with dengue shock syndrome (28.6%), followed by those with dengue hemorrhagic fever (18.4%) and was least in those with dengue fever (4.7%). This difference in incidence of renal involvement in relation to severity of dengue was found to best artistically significant (p<0.001). The duration of hospital stay was highest in patients with Failure p RIFLE criteria (11.5 ± 4.95 days), followed by injury category (7

± 1.41 days) and was least in risk category (5± 0.89 days), and this difference was found to best artistically significant (p=0.019).

Conclusion: We concluded that renal involvement was more common in dengue shock syndrome. Transient proteinuria and hematuria have been detected in most patients with dengue fever. So a clinician who is dealing with dengue patients should have closed watched on renal functions so kidney injury can be avoid to some extent as well as the mortality in dengue.

Keywords: Dengue Fever, Renal Involvement, KDIGO, AKI.

INTRODUCTION

Dengue was one of the top 10 probable health concerns to the world in 2019 according to the World Health Organization. Dengue was predicted to have a 104 million (95% CI 64 to 159) case global burden in 2017[1], with South Asia having the highest burden at 3546.9 instances (95% Uncertainty interval 2128.5 to 5429.5) per 100,000 people.[1]Clinically apparent dengue can afflict people of any age, however it is most frequently seen in people between the ages of 5 and 15 around the world, with children under the age of five having the greatest mortality rates.[2]In India, during last two decades, large and frequent dengue outbreaks and urban to rural spread with increasing proportion of severe cases, along with hyper endemicity in urban areas are reported.[3]In 2017, National Vector Borne Disease Control Program (NVBDCP) reported 188,401 laboratory confirmed cases of dengue and 325 deaths through its network of 646 sentinel surveillance hospitals.[4,5]

The World Health Organization views Dengue, a mosquito-borne viral disease that is very widespread in the tropics and subtropics, as a serious threat to world health.[6,7]Aedes aegypti, the yellow fever mosquito, primarily of A. aegypti species, and to a lesser extent A. albopictus (commonly known as the "tiger mosquito" because of its striking black and white stripes), transmit the dengue virus, an RNA virus from the genus Flavivirus.[6,7]Additionally, Zika, Chikungunya, and yellow fever are also spread by this insect.

The virus that causes sickness (DENV1, DENV2, DENV3, and DENV4) has four different serotypes. In 2013, a fifth serotype was identified.[8]Following recovery from an infection caused by a certain serotype, lifelong immunity against that specific serotype is provided. However, when exposed to various serotypes of infection, there is only a limited and imperfect cross-immunity. The initial or primary serotype infection is typical of the majority of viral infections and is frequently self-limiting. However, the chance of getting severe Dengue is greatly increased by successive secondary infections with a different serotype (SD).[9]

Incubation period of dengue virus infection is 3–14 days with a variety of clinical manifestation including asymptomatic infection, undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), and life-threatening dengue shock syndrome (DSS).[10] Similar to other tropical infections, dengue infection is associated with multiple organ dysfunction involving liver, muscles, heart, brain, and kidneys.[11,12] Dengue fever has been associated with various types of renal manifestations such as proteinuria, hematuria, glomerulonephritis, and acute kidney injury (AKI). Positive incidence of these renal manifestations varies between 17% and 62% in patients with dengue fever.[13] Such complications impose a heavy burden on the country not only in terms of morbidity and mortality but also impact the economic growth of the country. Currently, there is relatively sparse data from Bangladesh on the renal manifestations of dengue fever and their outcomes. Hence, this cross-sectional observational study was designed to analyze the frequency, characteristics, and clinical outcome of dengue fever in children with renal manifestations.

MATERIALS & METHODS

This was a cross sectional observational study done on 225 cases of children with dengue fever in the Department of pediatrics, SPMCHI hospital Sawai Man Singh Medical College, Jaipur. This study was started after approval of the Research Review Board and extended from October 2021 to October 2022.

INCLUSION CRITERIA

All the pediatrics dengue patients admitted to the JK loan hospital after taking consent.

EXCLUSION CRITERIA

1. Children those parents don't give consent.
2. Children with known or established chronic/metabolic diseases.

METHODOLOGY

Study was started after approval from Institutional Ethics Committee. All admitted patients who were diagnosed as dengue fever according to WHO 2012 guideline were enrolled after taking written informed consent from parents. Data regarding the need for fluid resuscitation, colloid infusion, inotrope support, ventilatory requirement were collected. Creatinine values and urine output were noted, and 'Kidney Disease Improving Global Outcome 2012 (KDIGO)' guideline was used to stage the acute kidney injury. Various renal manifestations of dengue will studied and compared between the severity of dengue fever.

Other tests like urinalysis, complete blood count, serum electrolytes, liver function test, and coagulation parameters were also noted.

WHO GUIDELINE 2012 FOR DENGUE

Clinical feature plus either NS 1 Positive or dengue IgM Positive or both Dengue IgM and IgG Positive was considered as dengue in present study. Proteinuria was defined as urinary protein ≥1+ (30 mg/dl) by dipstick test and microscopic hematuria was defined as >5 red blood cells/high power field.

Kidney Disease Improving Global Outcome 2012 (KDIGO)' guideline was used to stage the acute kidney injury.

Stage	Serum creatinine	Urine output
Stage 1	1.5-1.9 Times of baseline Or >/=0.3mg/dl increase	< 0.5ml/kg per hour for 6-12 hours
Stage 2	2.0-2.9 times baseline	<0.5ml/kg per hour for ≥12h
Stage 3	3.0 time baseline Or Increase in s. creatinine to ≥4.0mg/dl (≥353.6 umol/l) Or Initiation of renal replacement therapy or in patients <18 yr, Decrease in eGFR to <35 ml/min per 1.73 m2	<.3ml/kg/hfor≥24 hour Or Anuria for ≥ 12 hours

The Pediatric RIFLE (pRIFLE) criteria adapted for defining the stage of AKI in children with dengue fever[14]

Stage	Serum creatinine	Urine output
Risk	Increased creatinine 1.5 times from baseline or eGFR decreased by 25%	< 0.5ml/ kg/ hour for 8 hours
Injury	Increasedcreatinine2timesfrom baseline or eGFR decreased by >50%	< 0.5ml/ kg/ hour for 16 hours
	Increasedcreatinine3timesfrom baseline or eGFR decreased by >75%	<.3ml/ kg/ h for 24 hour Or Anuria for ≥ 12 hours
Loss	Persistent failure >4 weeks	
End stage	Persistent failure >3 months	

STATISTICALANALYSES

Continuous variables were summarized as mean and standard deviation and were analyzed using independent sample t test for comparison between 2 groups and ANOVA test was used for comparison between multiple groups (>2 groups). Ap value≤0.05was taken as statistically significant. All statistical analyses were done by using Epi info version 7.2.1.0 statistical software.

RESULTS

Our study showed that Mean age of 225 children with dengue in present study was 7.98 ± 4.21 years. Male to female ratio was 1.06:1. Most of patients (65.8%) had dengue fever, while 49 (21.8%) patients had Dengue hemorrhagic fever and 28 (12.4%) had Dengue shock syndrome. 24 (10.7%) patients had renal involvement. In our study, 10(4.3%) had AKI,11(4.8%) had proteinuria and 3 (1.3%) had hematuria (table 1).

Table 1: Demographic and clinical profile of patients

Demographic & Clinical variables	N (225)	Percentage
Age (yrs)		
Mean ± SD	7.98 ± 4.21 years	
Gender		
Male	116	51.6%
Female	109	48.4%
Dengue severity		
Dengue fever	148	65.8%
DHF	49	21.8%
DSS	28	12.4%
Renal involvement		
Yes	24	10.7%
No	201	89.3%
Type of renal involvement		
AKI	10	4.3%
Proteinuria	11	4.8%
Hematuria	3	1.3%
No involvement	201	89.3%

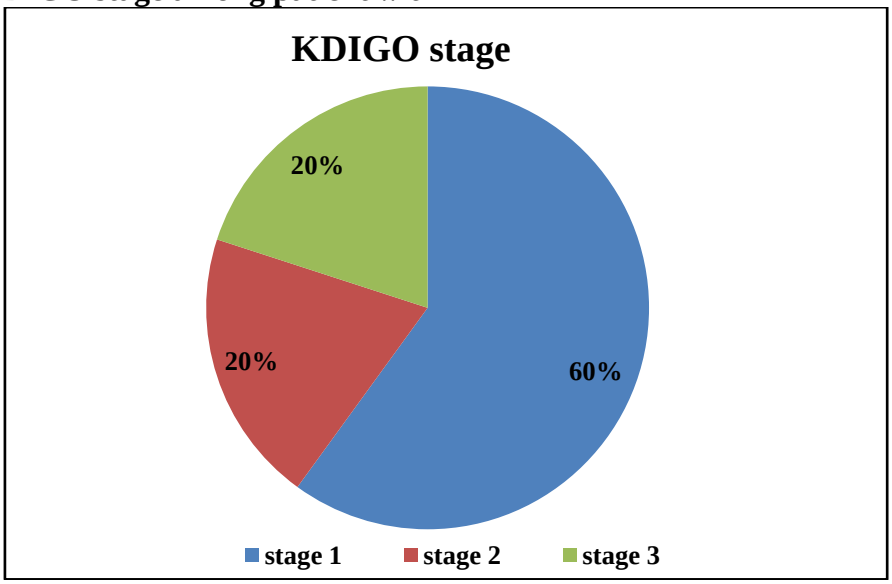
Among the 11 patients with proteinuria, most 6 (54.5%) had mild proteinuria, while 2 (18.2%) had moderate proteinuria, 2 (18.2%) had severe proteinuria and only1(9.1%) had nephritic range proteinuria (table 2).

Table 2: Distribution of study subjects according to grade of proteinuria

Grade of proteinuria	N	Percentage
Mild (+)	6	54.5
Moderate (++)	2	18.2
Severe (+++)	2	18.2
Nephritic	1	9.1
Total	11	100

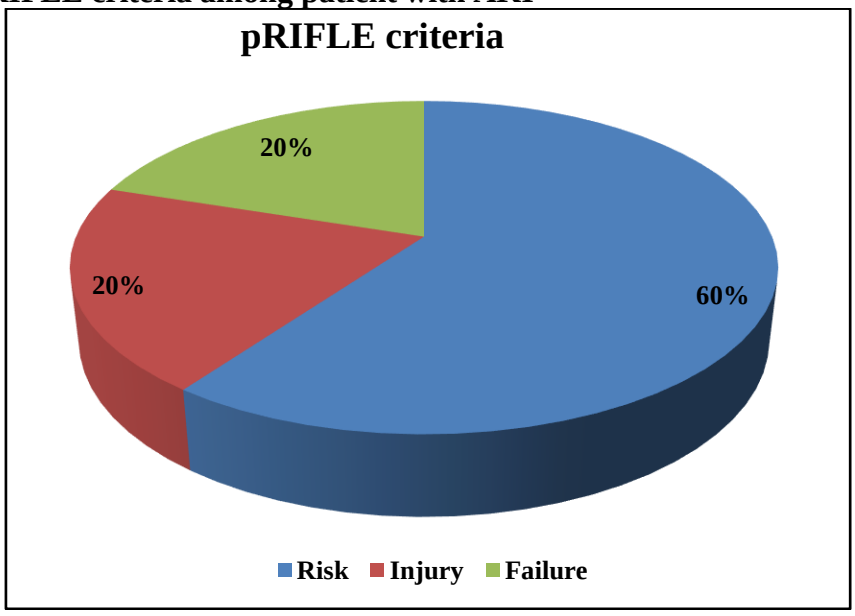
Patients with AKI were classified according to KDIGO staging. Among the 10 children with AKI in present study, 6 (60%) had stage 1AKI, 2 (20%) had stage 2 AKI, while 2 (20%) had stage 3 AKI (Graph 1).

Graph 1: KDIGO stage among patient with AKI



When the children with AKI were classified according to p RIFLE criteria, 6 (60%) were in risk criteria, 2(20%) were in Injury category, while 2(20%) were in failure category (Graph 2).

Graph 2: p RIFLE criteria among patient with AKI



Renal involvement was highest in patients with dengue shock syndrome (28.6%), followed by those with dengue hemorrhagic fever (18.4%)and was least in those with dengue fever (4.7%). This difference in incidence of renal involvement in relation to severity of dengue was found to best artistically significant (p<0.001) (table 3).

Table3: Renal involvement in relation to severity of dengue

Severity of dengue	Renal involvement		No Renal involvement		Total
	N	%	N	%	
Dengue fever	7	4.7	141	95.3	148
DHF	9	18.4	40	81.6	49
DSS	8	28.6	20	71.4	28
Total	24	10.67	201	89.33	100
Chi-square = 17.944 with 2 degrees of freedom; P < 0.001 (S)					

Hematocrait & total leucocyte count was higher in patients with renal involvement (41.38 ±6.74% & 8.96 ± 2.30 U/l) as compared to those without renal involvement (39.23±5.56% &7.94 ± 2.82 u/l), this difference was however not found to best artistically significant (p=0.083 & 0.087 respectively). Platelet count, serum sodium and potassium level were lower in patients with renal involvement as compared to those without renal involvement, this difference was however not found to best artistically significant (p=0.378, 0.472 & 0.651 respectively). Serum Creatinine level and urine output was statistically significant (P<0.001* & P=0.006*) when compared to patients with renal involvement and without renal involvement (table 4).

Table 4: Hematological profile of patients

Hematological profile	Patient with Renal involvement (N=24)	Patient without Renal involvement (N=201)	P-value
Hematocrait (%)	41.38 ± 6.74	39.23 ± 5.56	0.083
Platelet count (x109/L)	116.75 ± 55.52	125.69 ± 45.75	0.378
TLC (x106/L)	8.96 ± 2.30	7.94 ± 2.82	0.087
Serum creatinine level (mg/dl)	192.04 ± 67.68	79.61 ± 17.26	<0.001*
Urine output (ml/kg/hr)	0.92 ± 0.53	1.20 ± 0.46	0.006*
Serum sodium level (mmol/L)	135 ± 8.20	136.36 ± 8.81	0.472
Serum potassium level (mmol/L)	3.93 ± 0.73	3.86 ± 0.63	0.651

All the 3 deaths in children with dengue occurred in those who had renal involvement, and this difference was found to be statistically significant(p<0.001) (table 5).

Table5: Mortality in relation to platelet count in patients with renal involvement

Renal involvement	Died		Survived		Total
	N	%	N	%	
Yes	3	12.5	21	87.5	24
No	0	0	201	100	201
Total	3	12.5	222	87.5	24
Chi-square = 16.849 with 1 degree of freedom; P < 0.001 (S)					

The duration of hospital stay was highest in patients with Failure pRIFLE criteria (11.5 ± 4.95 days), followed by injury category (7 ± 1.41 days) and was least in risk category (5± 0.89 days), and this difference was found to be statistically significant(p=0.019) (table 6).

Table 6: Duration of hospital stay in relation to p RIFLE criteria of AKI

P RIFLE criteria	N	Duration of hospital stay (days) (Mean ± SD)	P value
Risk	6	5 ± 0.89	0.019 (S)
Injury	2	7 ± 1.41	
Failure	2	11.5 ± 4.95	

DISCUSSION

Dengue infection has been associated with a variety of renal disorders. This study had been carried out to know the profile of acute kidney injury in children with dengue who needed tertiary care hospital admission. Mean age of children with dengue in present study was 7.98 ± 4.21 years. Win Lai May et al (2015)[15] observed that patient's age ranged from 2 to 14 years and mean age was 7.34±2.88 years. Srinivasa K et al (2017)[16]observed that the mean age of presentation in this study was 8.2 years.

Among the 225 children with dengue in present study, 116 (51.6%) were males, while 109 (48.4%) were females, giving a male : female ratio of1.06 : 1. Srinivasa K et al (2017)[16] observed similarly that among the total of 185 children diagnosed to have dengue fever 122 were boys and 63 were girls with M: F ratio of 1.9:1. Sanjukta Poddar et al (2020)[17] contrarily observed the male-female ratio of 1:1.25. Mahalakshmi Rajan et al (2020)[18] however observed male majority similar to our study. Wajid Hussain et all (2021)[19] also observed that there were 71 (76.3%) male and 22 (23.7%) female children. Nikhil Batra et al (2022)[20] also observed the male majority though study was conducted among adults.

Mahalakshmi Rajan et al (2020)[18] observed that out of the 127 children, 6 (4.7%) were classified as dengue fever, 51 (40.1%) as dengue with warning signs and 70 (55.11%) as severe dengue. Nikhil Batra et al(2022)[20] found that majority of the patients (72.5%) had DF, 13.3% of the patients had dengue fever with warning signs and 14.2% of the patients had severe dengue, which consisted with our result.

In present study, 10 (4.3%) had AKI, 11 (4.8%) had proteinuria and 3 (1.3%) had hematuria. Muhammad A.M. Khalil et al (2012)[21] observed AKI among higher number (13.3%) of patients. Win Lai May et al (2015)[15] also found that 12.7% were classified as having AKI. Tauqeer Hussain Mallhi et al (2015)[22] observed that there were 14.2% patients who had AKI. Rubina Naqvi (2016)[23] revealed that about 1.21% developed AKI in association with dengue infection. Sanjukta Poddar et al (2020)[17] observed that out of 105 children with dengue, six (5.71%) cases developed AKI. Mahalakshmi Rajan et al (2020)[18] found that twenty six (20.5%) children developed acute kidney injury (AKI) and 23 (18%) of total had proteinuria. Azmeri Sultana et al (2020)[14] observed that among 316 dengue patients thirty-one patients (9.8%) had renal involvement. Among renal involvement, 14 patients (45.10%) had proteinuria, 13 (42%) had AKI, and 4 (12.90%) patients had hematuria. Nikhil Batra et al(2022)[20] observed the prevalence of AKI to be 27.5% in patients with dengue fever.

Patients with AKI were classified according to KDIGO staging. Among the 10 children with AKI in present study, 6 (60%) had stage 1 AKI, 2 (20%) had stage 2 AKI, while 2 (20%) had stage 3 AKI. Similar results found by Tauqeer Hussain Mallhi et al (2015)[22] observed AKIN-I, AKIN-II and AKIN-III in 76.8%, 16.8% and 6.4% patients. Amit Kumar et al (2019)[24] also observed that majority (70.83%) fall under KDIGO I, while 20.83% constitute KDIGO II and remaining 8.33% categorized under KDIGO III.

Renal involvement was highest in patients with dengue shock syndrome (28.6%), followed by those with dengue hemorrhagic fever (18.4%) and was least in those with dengue fever (4.7%). This difference in incidence of renal involvement in relation to severity of dengue was found to be statistically significant. Muhammad A.M. Khalil et al (2012)[21] also found that presence of dengue hemorrhagic and dengue shock syndrome act as independent predictors for AKI. Tauqeer Hussain Mallhi et al (2015)[22]found that presence of dengue

hemorrhagic fever [OR (95% CI): 8.0 (3.64–17.59), P<0.001] was associated with AKI. Biswanath Basu et al (2018)[25] observed that in comparison to all children (100%) of RF cohort, only 32% children of non-RF cohort were suffering either from DHF or DSS. Amit Kumar et al (2019)[24] observed that 11% patients diagnosed with dengue fever developed AKI, while 16 patients (20%) developed AKI out of 80 patients diagnosed as dengue hemorrhagic fever. However, 100% of the patients developed AKI which was diagnosed as dengue shock syndrome. Almost similar to present study observations Mahalakshmi Rajan et al (2020)[18] found that no one in the dengue fever group had AKI. Six children out of 51 (11.8%) in dengue with warning signs group had AKI and 20 out of 70 (28.6%) in severe dengue group had AKI. Azmeri Sultana et al (2020)[14] also observed that in dengue fever, only 3 (1.4%) patients were found to have renal involvement, whereas dengue shock syndrome and dengue hemorrhagic fever had highest renal involvement 35.8% and (17.9%), respectively.

The hematological profile in our study was similar with Azmeri Sultana et al (2020)[14] also observed not significant difference between the two groups regarding platelet count, TLC, serum sodium & serum potassium but mean serum creatinine (micromole/L) is significantly higher in patients with dengue fever (185.17 ± 121.35) with renal involvement vs. patient without renal involvement (85.50 ± 16.99).

All the 3 deaths in children with dengue occurred in those who had renal involvement, and this difference was found to be statistically significant in our study. Biswanath Basu et al (2018)[25] also observed that majority of deaths were from RF cohort. Mahesh Eswarappa et al (2019)[26] observed that of all patients with DVI, 28 patients died, of which 11 had AKI (39.28%). The duration of hospital stay was found to be statistically significant in our study. Biswanath Basu et al (2018)[25]observed that duration of hospital stay was also longer among RF patients (median 6 days; range 4– 18 days) when compared to others (median 4 days; range 1–12 days) (mean 2 ± 1 vs. 4 ± 1 days, P < 0.001). Azmeri Sultana et al (2020)[14] in conformance to our study observed that duration of hospital stay in patients with AKI was 6 ± 2 days in risk group, 7 ± 5 days in injury, and 11 ± 2 days in patients with failure group.

CONCLUSION

We concluded that renal involvement was more common in dengue shock syndrome. Transient proteinuria and hematuria have been detected in most patients with dengue fever. So, a clinician who is dealing with dengue patients should have closed watched on renal functions so kidney injury can be avoid to some extent as well as the mortality in dengue.

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