

Clinical characteristic and risk factors of acute kidney injury among adults with dengue viral infections at a tertiary care center

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Abstract

Background: Several mechanisms have been proposed for DF-induced acute kidney injury (AKI), including direct action by the virus, hemodynamic instability, rhabdomyolysis, and acute glomerular injury. Previous studies have shown great disparity in the incidence of dengue induced AKI ranging from 0.83% to 13.3%. We conducted this study to assess clinical characteristic and risk factors of acute kidney injury among adult patients with dengue viral infection. **Material and Methods:** Present study was prospective, observational type conducted in Department of Medicine, in patients with age more than 18 years and admitted with primary confirmed diagnosis of dengue viral fever. **Results:** Incidence of acute kidney injury in present study was 19%. 19-40 years age was most common in total patients (58 %) and in patients without kidney injury (64 %). In AKI group all age-groups had similar contribution. But as age increases incidence of AKI is increasing significantly. With 37 total patients in age group >60 years, 30 patients developed AKI. Male patients had more incidence of AKI (73 %) as compared to female (27 %). Male to female ratio with AKI in present study was 2.7:1. We noted 70%, 25 % and 5 % patients with dengue fever, dengue hemorrhagic fever and dengue shock syndrome. In patients with AKI incidence of dengue fever, dengue hemorrhagic fever and dengue shock syndrome was 15%, 63%, 23%. Mean duration of hospitalization was 5.49±1.16 days in patients with AKI, as compared to days in patients without AKI. Proteinuria and Hematuria was statistically significant in patients with AKI when compared with patients without AKI. Overall 40%, 34% and 26 % incidence noted in grade I, II and III respectively. We noted 66 % patients had complete recovery, while 15 % patient had partial recovery. Total 26 % patients required Renal replacement therapy. 19 % mortality was noted in present study. **Conclusion:** With rising incidence of dengue in general population, more patients are diagnosed with dengue associated AKI. Elderly patients, male, associated co-morbid condition like diabetes, hypertension and presence of proteinuria are few predictors of AKI.

Key Words: acute kidney injury; dengue viral infection; mortality; predictors for AKI.

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INTRODUCTION

Dengue is the most rapidly spreading mosquito-borne, arboviral disease of mankind, with a 30- fold increase in global incidence over the last five decades. It is a major

public health concern throughout the tropical and subtropical regions of the world¹. According to the World Health Organization, the incidence of dengue globally has shot up 30-fold in the past 50 years. More than 1.25 billion people reside in India; hence, a huge population is at risk and there is a high cumulative dengue disease burden². Dengue fever is an acute febrile disease characterized by sudden onset of fever of 3-5 days, intense headache, myalgia, retro-orbital pain, anorexia, gastrointestinal disturbances and rash. Several mechanisms have been proposed for DF-induced acute kidney injury (AKI), including direct action by the virus, hemodynamic instability, rhabdomyolysis, and acute glomerular injury. Previous studies have shown great disparity in the incidence of dengue induced AKI ranging

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from 0.83% to 13.3%^{3,4,5}. Successful efforts to improve early recognition have clearly demonstrated benefit, especially by reducing some of the more dreaded consequences such as cortical necrosis⁶. Specific treatment for dengue is not available, but early detection and fluid replacement therapy and use of analgesics and antipyretics with good nursing care ensures marked reduction of the mortality rates 20% to less than 1% due to severe cases⁷. We conducted this study to investigate clinical and laboratory profile of dengue fever patients at our tertiary health care center

MATERIAL AND METHODS

Present study was prospective, observational study conducted in Department of Medicine, NIMS Medical Collage Jaipur, during the period from January 2018 to September 2019. Permission from institutional ethical committee was taken.

All patients with age more than 18 years, who were admitted with primary diagnosis of dengue viral fever were included in the present study.

primary diagnosis of dengue viral fever was done using at least one of the following criteria:

1. Positive reverse transcriptase–polymerase chain reaction result
2. Presence of dengue immunoglobulin M and G antibodies in acute phase serum by enzyme-linked immunosorbent assay. Primary dengue infection was distinguished from

secondary infection using IgM/IgG ratio where dengue infection was defined as primary if ratio was >1.2 and as secondary if <1.2.

3. Positive NS1 antigen test.
4. At least 4-fold increase in dengue-specific hemagglutination inhibition titers in convalescent serum when compared with acute phase serum.

Patients less than 18 years age, pre-existing substantial chronic liver, kidney or heart disease, with history of hematological disorders, no laboratory evidence of dengue viral fever or single positive dengue IgG were excluded from present study. A detailed history (demographic, symptoms) was taken and careful clinical examination was performed. Routine investigations such as hemoglobin, total leucocyte count (TLC) and differential leucocyte count (DLC), platelet count, peripheral blood smear for malarial parasite, hematocrit (HCT), liver function tests (LFT), blood urea, and serum creatinine were done. Other investigations like malarial antigen, IgM antibodies and Widal test for typhoid, and X-ray chest and ultrasonography (USG) of abdomen were also done according to the clinical conditions of the patients. All subjects were classified according to WHO guidelines as shown in Table 18. Warning signs were defined as presence of at least one of the following: abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy/restlessness, liver enlargement >2 cm, and concurrent increase in hematocrit with thrombocytopenia.

Table 1: classification of dengue viral infection

DF/DHF	Grade	Signs and symptoms	Laboratory
DF	With / without haemorrhagic manifestations	Fever with two of the following: (i) Headache. (ii) Retro-orbital pain. (iii) Myalgia. (iv) Arthralgia /bone pain. (v) Rash. (vi) Haemorrhagic manifestations. (vii) No evidence of plasma leakage.	Leucopenia (WBC ≤5000 cells/mm ³). (i) Thrombocytopenia (platelet count <150 000 cells/mm ³). (ii) Rising haematocrit (5%–10%). (iii) No evidence of plasma loss.
DHF	I	Fever and haemorrhagic manifestation (positive tourniquet test) and evidence of plasma leakage.	Thrombocytopenia - <100 000 cells/mm ³ ; HCT rise ≥20%.
DHF	II	As in Grade I plus spontaneous bleeding.	Thrombocytopenia - <100 000 cells/mm ³ ; HCT rise ≥20%.
DHF	III	As in Grade I or II plus circulatory failure (weak pulse, narrow pulse pressure (≤20 mmHg), hypotension, restlessness).	Thrombocytopenia - <100 000 cells/mm ³ ; HCT rise ≥20%.
DHF	IV	As in Grade III plus profound shock with undetectable BP and pulse.	Thrombocytopenia < 100 000 cells/mm ³ ; HCT rise ≥20%.
Dengue Shock Syndrome (DSS):		All the above criteria for DHF with evidence of circulatory failure manifested by rapid and weak pulse and narrow pulse pressure (mmHg) or hypotension for age, cold and clammy skin and restlessness	

AKI was defined as per Acute Kidney Injury Network (AKIN) classification (mild AKI as AKIN-I; severe AKI as AKIN-II or AKIN-III) 9. Renal outcome was defined according to Acute Dialysis Quality Initiative consensus guidelines. Complete renal recovery was defined as a return to baseline creatinine and a partial recovery as an improvement in RIFLE status of a patient free of dialysis¹⁰. The patients were divided into two cohorts (those with and without AKI) to determine independent predictors of AKI. The criterion of significance was set at p < 0.05. All details collected in a proforma and analysed with appropriate statistical method.

Table 2: AKIN grading¹¹

AKIN stage	Serum creatinine criteria	Urinary Output Change
1	≥ 1.5-fold increase of serum creatinine or increase of ≥ 0.3 mg/dL	< 0.5 mL/kg/hr for 6–12 hr
2	≥ 2.0-fold increase of serum creatinine	< 0.5 mL/kg/hr for ≥ 12 hr
3	≥ 3.0-fold increase of serum creatinine or serum creatinine ≥ 4.0 mg/dL with acute increase of ≥ 0.5 mg/dL or Renal Replacement Therapy	< 0.3 mL/kg/hr for ≥ 24 hr or anuria for ≥ 12 hr

RESULTS

After applying inclusion and exclusion criteria, total 460 patients were studied. Incidence of acute kidney injury in present study was 19%. 19-40 years age was most common in total patients (58 %) and in patients without kidney injury (64 %). In AKI group all age-groups had similar contribution. But as age increases incidence of AKI is increasing significantly. With 37 total patients in age group >60 years, 30 patients developed AKI. Male patients had more incidence of AKI (73 %) as compared to female (27 %). Male to female ratio with AKI in present study was 2.7:1. We have classified dengue disease as per WHO guidelines. (Table-1). We noted 70%, 25 % and 5 % patients with dengue fever, dengue hemorrhagic fever and dengue shock syndrome. In patients with AKI incidence of dengue fever, dengue hemorrhagic fever and dengue shock syndrome was 15%, 63%, 23%. Co-morbid conditions like diabetes, hypertension and ischemic heart disease were significantly related with AKI in dengue viral fever. While congestive heart failure was not related with AKI in dengue viral fever. Total 221 patients required hospitalization for more than 3 days, all patients diagnosed with AKI required Hospitalization for more than 3 days. Mean duration of hospitalization was 5.49±1.16 days in patients with AKI, as compared to days in patients without AKI. Both parameters (i.e. hospitalization >3 days and mean duration of hospitalization) were statistically significant in patients with AKI. Proteinuria and Hematuria was statistically significant in patients with AKI when compared with patients without AKI.

Table 3: Comparison of patients between non-AKI and AKI group with DVI

Parameters	Total	Non-AKI group	AKI group	P VALUE
Patients	460	372 (81%)	88(19%)	
Age group				
19-40 years	265 (58%)	239 (64%)	26 (30%)	
41-60 years	158 (34%)	126 (34%)	32 (36%)	
>60 years	37 (8%)	7 (2%)	30 (34%)	
Gender				
Male	274 (60%)	210 (56%)	64 (73%)	
Female	186 (40%)	162 (44%)	24 (27%)	
Diagnosis				
Dengue fever	322 (70%)	309 (83%)	13 (15%)	
Dengue hemorrhagic fever	113 (25%)	58 (16%)	55 (63%)	
Dengue shock syndrome	25 (5%)	5 (1%)	20 (23%)	
Presence of Co-morbid conditions				
Diabetes	31 (7%)	12 (3%)	19 (22%)	Significant
Hypertension	40 (9%)	14 (4%)	26 (30%)	Significant
Ischemic heart disease	11 (2%)	3 (1%)	8 (9%)	Significant
Congestive heart failure	3 (1%)	0	3 (3%)	Not significant
Duration of Hospitalization				
Hospitalization >3 days	221 (48%)	133 (36%)	88 (100%)	Significant
Mean duration of hospitalization	4.12±0.83	2.92±0.94	5.49±1.16	Significant
Urine examination				
Proteinuria	59 (13%)	21 (6%)	38 (43%)	Significant
Hematuria	11 (2%)	3 (1%)	8 (9%)	Significant

Patients with AKI were divided in 3 grades as per Table-2. Overall 40%, 34% and 26 % incidence noted in grade I, II and III respectively. Grade -1 AKI was common in dengue fever, while grade 3 AKI was common in dengue shock syndrome. Severity of dengue infection can be correlated with higher grades of AKI.

Table 4: Frequency and severity of AKI in dengue viral infection

Stage of AKI (Acute kidney injury)	AKI at presentation			AKI during hospital stay	Total
	Dengue fever	Dengue hemorrhagic fever	Dengue shock syndrome		
Grade I	17 (19%)	8 (9%)	6 (7%)	4 (5%)	35 (40%)
Grade II	5 (6%)	11 (13%)	10 (11%)	4 (5%)	30 (34%)
Grade III	1 (1%)	10 (11%)	11 (13%)	1 (1%)	23 (26%)
Total	23 (26%)	29 (33%)	27 (31%)	9 (10%)	88

We noted 66 % patients had complete recovery, while 15 % patient had partial recovery. Total 26 % patients required Renal replacement therapy. 19 % mortality was noted in present study.

Table 5: Patients' Renal outcome at discharge

Outcome	Number of patients (Percentage)
Complete recovery	58 (66%)
Partial recovery	13 (15%)
Mortality	17 (19%)
TOTAL	88
Renal replacement therapy required	23 (26%)

DISCUSSION

Dengue is one of the most important and fastest growing, mosquito-borne viral diseases affecting tropical and subtropical regions in the world, particularly the Asia Pacific region¹². Dengue Fever (DF) and its severe forms – Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) – have become major international public health concerns. Spectrum of dengue associated renal involvements varies from mild glomerulonephritis, urinary sedimentations to severe hemolytic-uremic syndrome and Acute Kidney Injury (AKI)¹³. Dengue infection has been associated with a variety of renal manifestations such as proteinuria, hematuria, glomerulonephritis, and acute kidney injury (AKI), which have been reported during or shortly after acute dengue infection. The incidence of the above renal manifestations varies between 17% and 62% in patients with DVI¹³. Mehra *et al.*⁵ reported an incidence of 10.8% using the AKIN definition while Hamid SA *et al.*¹⁴ in 2017 and Mallhi TH *et al.*¹⁵ in 2018 using the Acute Kidney Injury Network (AKIN) criteria found much different AKI prevalence of 20.7% and 13.7%, respectively. In present study we noted 19% incidence of AKI. Mallhi *et al.*¹⁶ compared five studies which used the conventional definition (SCr >2 mg/dL) and AKIN criteria. They found that when using AKIN criteria, the incidence of AKI was higher. This can be explained because AKIN criteria classify AKI as a 1.5-times increase in SCr from baseline within 7 days (compared to conventional SCr >2 mg/dL), or as increased SCr >26.2 μmol/L from baseline within 48 hours. In present study Male to female ratio with AKI was 2.7:1. Christopher Thiam *et al.*¹⁷ noted that, male sex was found to be an independent predictor for developing dengue infection associated AKI with an odds ratio of 2:1.34 In another retrospective study of 304 patients, DHF and being over the age of 30 were identified as risk

factors for DAKI. The incidence of AKI was higher in those above the age of 65 years. Another study¹⁸ has demonstrated that endoplasmic reticulum stress plays a role in the development of AKI in both humans and animal models and that the kidneys of males are more susceptible to such endoplasmic reticulum stress, might be a cause of increased male susceptibility. Although clinical data are lacking, elderly patients are anticipated to be at a much higher risk of fluid overload from overzealous fluid therapy. This is further exacerbated by the increased risk of acute kidney injury and reduced myocardial function¹⁹. AKI has been described in all forms of dengue and the risk factors include elevated liver enzymes, low serum albumin, decreased serum bicarbonate, coexisting bacterial or viral infection, sepsis, multiple organs dysfunction, inotropic drugs, older age, obesity, severity of dengue infection, rhabdomyolysis, diabetes mellitus, late hospitalization and nephrotoxic drugs^{5,20}. Early recognition of AKI is essential to ensure prompt and appropriate management, and to avoid progression to deadlier stages of the disease. In the appropriate context, early detection requires a high degree of suspicion that AKI is occurring. Diagnosis requires a combination of a clinical history, a thorough physical examination, an accurate assessment of kidney function, appropriate imaging, and when indicated, a kidney biopsy. There are multiple proposed mechanisms for etiopathogenesis of renal impairment in DVI. Dengue causes capillary leakage and loss of fluid from the intravascular compartment leading to shock^{9, 10} which may lead to decreased kidney perfusion and acute tubular necrosis. Possible etiological factors for AKI in DF include hypotension with either hemolysis or rhabdomyolysis and shock. Successful efforts to improve early recognition have clearly demonstrated benefit, especially by reducing some of the more dreaded

consequences such as cortical necrosis²¹. Mallhi TH¹⁵ *et al* noted that the factors independently associated with AKI development were male gender (OR: 2.7), DHF (OR: 8), rhabdomyolysis (OR: 7.9), multiple organ dysfunction (OR: 17.9), diabetes mellitus (OR: 10.5), delayed hospital consultation (OR: 2.1) and use of nephrotoxic drugs (OR: 2.9). ROC curve analysis with AUC as 0.94 (P<0.001, 95%CI: 0.916–0.964) demonstrated that logistic model has excellent predictive ability for AKI. In a retrospective analysis²², authors described 667 dengue patients from 2008 to 2013. The patients were stratified into AKI and non-AKI groups by using AKIN criteria. Significant differences (P <0.05) in clinical and laboratory characteristics were observed between patients with and without AKI. The presence of DHF, rhabdomyolysis, multiple organ dysfunction syndrome (MODS), diabetes mellitus, and use of nephrotoxic drugs were associated with AKI. Kuo *et al*²³ retrospectively evaluated patients with DVI and divided them into renal failure and nonrenal failure groups. AKI was defined by RIFLE criteria and was seen in 4.2% of patients. A higher mortality rate (41.6%) was seen in the renal failure group than the nonrenal failure group (5.2%). Other factors influencing mortality were patients with late presentation, inadequate fluid administration, and comorbidities such as diabetes mellitus and hypertension. Severe degree of thrombocytopenia was associated with increased mortality among patients with renal manifestations. In present study we noted 19 % mortality. Diptyanusa A *et al*²⁴ noted that in patients with AKI, 14.1% (10/71) required dialysis, which is higher than the proportion of patients with dengue-associated AKI requiring dialysis reported in two other studies as “only” 1.2%²⁵ and 7.1%²⁶. In present study 26 % patients required RRT which is higher than all above studies. Elderly patients, presence of co-morbid conditions, severe forms of dengue infection predispose them for RRT. No specific preventive strategies are available for AKI apart from adequate fluid resuscitation, management of dengue-associated coagulopathies, and avoidance of nephrotoxic agents. Inotropic support is of benefit. Dialysis is certainly beneficial, although the exact role of dialysis remains controversial⁴.

CONCLUSION

With rising incidence of dengue in general population, more patients are diagnosed with dengue associated AKI. Elderly patients, male, associated co-morbid condition like diabetes, hypertension and presence of proteinuria are few predictors of AKI. Early recognition and prompt management can definitely help to reduce morbidity and mortality.

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