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**Original Research Article**

# Renal function in dengue fever and its correlation with disease severity - A Retrospective observational study in a Tertiary Centre

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## Abstract

**Background:** The renal manifestations of dengue are less understood and often ignored. Limited data is available from our geographical location to estimate the prevalence of renal dysfunction & its impact on duration of hospitalization and mortality among dengue patients with varied severity. We intend to address this lacuna.
**Methods:** Retrospective observational cross-sectional study including 120 patients with confirmed dengue serology admitted in Medicine Department of Father Muller Medical College and Hospital during November 2018-December 2019. We compared data including Renal function test, Liver function test, urinalysis, duration of hospital stay and condition at discharge among patients with Acute Kidney Injury (AKI) group and non-AKI group.
**Results:** Acute kidney injury was significantly higher in severe dengue (SDG) patients (41.7%) compared to patients with dengue without warning signs (DWWS) and dengue with warning signs (DWS). Dengue warning signs such as reduced urine output, fluid accumulation, respiratory distress due to fluid accumulation, shock, Acute respiratory distress syndrome (ARDS), other organ failure, impaired consciousness and elevated Serum glutamic oxaloacetic transaminase (SGOT)/Serum glutamic pyruvic transaminase (SGPT) >1000 were all significantly higher in the Acute Kidney Injury (AKI) group compared to non-AKI group. Moderate hyponatremia was seen in 10.6%, 14.3% and 25% patients with DWWS, DWS and SDG respectively. Severe hypokalemia was seen in 10.6%, 4.7% and 20% patients with DWWS, DWS and SDG respectively. Proteinuria and hematuria were significantly high in SDG. Patients with AKI had persistent thrombocytopenia (35.7%) and poor outcome with 7.1% mortality.
**Conclusion:** Prevalence of AKI in our study was 11.7%. Renal dysfunction in dengue varies from asymptomatic urinary abnormalities to AKI, later is more commonly seen in severe dengue. Hepatic involvement in the form of with elevated transaminases and bilirubin were commonly seen in our patients with AKI. Dengue patients with AKI had persistent thrombocytopenia and poor outcomes with higher mortality rate.
**Keywords:** Dengue, Acute Kidney Injury, Proteinuria, Hyponatremia.

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## 1. Introduction

Dengue virus, the most important arthropod- borne disease is transmitted to humans by female mosquitos of the *Aedes* family.[1] Four dengue virus serotypes can cause the disease which can present as a mild self-limiting illness, dengue fever, or as the more severe forms of the disease, dengue hemorrhagic fever or dengue shock syndrome.[2] The modified categorization of WHO in 2009 classifies the disease into dengue with or without warning signs or severe dengue.[3]

Dengue fever has emerged as one of the most important viral disease in the world. In India, dengue is endemic in almost all states and is the leading cause of hospitalization. The disease had a predominant urban

distribution a few decades earlier but is now also reported from peri-urban as well as rural areas.[4-5] During 2019, the National Vector Borne Disease Control Program reported more than 1.5 lakh laboratory confirmed cases of dengue.[6] It is therefore possible that dengue disease burden is grossly under-estimated in India.

Dengue infection is associated with multiple organ dysfunction involving the liver, muscles, heart, brain and kidneys. The renal manifestations seen in dengue are varied, ranging from mild electrolyte imbalance and tubular injury to acute kidney injury (AKI) requiring dialysis.[7] The incidence of these manifestations vary from 17% to 62% in patients with dengue.[8] Yet very few studies have been conducted in our geographic location regarding the renal manifestations of dengue, and its impact on the morbidity and mortality. Studies assessing renal involvement using the newer WHO 2009 dengue classification are also scarce. We hope to address these issues in our study.

## 2. Materials and methods

This was a retrospective observational cross-sectional study including 120 patients with confirmed dengue serology admitted in Medicine Department of Father Muller Medical College and Hospital during November 2018 - December 2019. Patients above 18 years of age with confirmed dengue serology (IgM positive by spot) were included in the study. Patients with Chronic Kidney Disease of any etiology as evident by clinical, radiological and biochemical parameters; history of long-term intake of nephrotoxic drugs; concurrent infections causing renal dysfunction- such as but not limited to leptospirosis, malaria, secondary sepsis; patients with past history of proteinuria of any etiology with preserved renal function and patients on ACE/ ARB and diuretics for any indication were excluded.

The patients were categorized based on the modified WHO classification of 2009 into dengue with or without the warning signs and severe dengue. Following data was retrospectively collected from the hospital medical records - patient demographics, severity of dengue, duration of hospital stay and laboratory parameters – complete blood count, liver function test, serum creatinine, urea, electrolytes and urinalysis. The peak values of creatinine were considered if the values were repeated serially for any patient. The baseline creatinine for all the patients was calculated using the simplified Modification of Diet in Renal Disease formula.[9] Acute kidney injury (AKI) was defined by the AKIN criteria and all patients with a creatinine ≥ 1.5 times the estimated baseline creatinine were classified into the "AKI" group while the remaining patients constituted the "Non-AKI" group.[10] The normal range of serum sodium was considered to be 135-145 mEq/L and hyponatremia was classified into mild (125-135 mEq/L), moderate (120-125 mEq/L) and severe (less than 120 mEq/L). The normal range of serum potassium was considered to be 3.5-5 mEq/L, while hypokalemia was classified into mild (3-3.5 mEq/L), moderate (2.5-3 mEq/L) and severe (<2.5 mE/L).[11-12] However, none of our patients had hypernatremia/ hyperkalemia. Urinary abnormalities included proteinuria and hematuria (measured by dipstick). Study endpoints were categorized into complete recovery, recovering from illness and fatal outcome.

Estimated minimal sample size for this study was 120 cases of Dengue infection. Data analysis was done using the Statistical Package for the Social Science (SPSS) Version 20. Statistical methods employed for data analysis are Chi-Square test for categorical outcomes and unpaired t-test for comparison of means. Comparison of multiple means was done using One Way-ANOVA with post hoc analysis using Least Significant Difference (LSD). A two tailed probability value of <0.05 was accepted as the level of statistical significance.

## 3. Results

Out of 120 patients, 66 patients (55%) had DWWS, 42 patients (35%) had DWS and 12 patients (10%) had SDG. Mean age of the patients was 34.8±15.1 years. Male to female (M:F) ratio was 1.6:1. Acute kidney injury was seen in 7 (10.6%), 2 (4.8%) and 5 (41.7%) patients among DWWS, DWS and SDG respectively. Proteinuria was seen in 1(1.5%), 6 (14.3%) and 10 (83.3%) patients among DWWS, DWS and SDG respectively. Hematuria was seen in 1(1.5%), 1(1.5%) and 3 (25%) patients with DWWS, DWS and SDG respectively as shown in **Table 1**.

**Table 1: AKI and urinary abnormalities in dengue patients**

| | Dengue Classification | | | | | | P Value |
|---|---|---|---|---|---|---|---|
| | DWWS (n=66) | | DWS (n=42) | | SDG (n=12) | | |
| | N | N % | N | N % | N | N % | |
| AKI | 7 | 10.6% | 2 | 4.8% | 5 | 41.7% | 0.002 |
| Proteinuria | 1 | 1.5% | 6 | 14.3% | 10 | 83.3 | <0.0001 |
| Hematuria | 1 | 1.5% | 5 | 11.9% | 3 | 25% | 0.007 |

In our study, we did not find significant difference in mean age, hemoglobin, hematocrit, WBC count, and platelet count among patients with AKI and non-AKI. Mean SGOT, SGPT, Alkaline phosphatase (ALP), total bilirubin and direct bilirubin levels were significantly elevated in patients with AKI as compared to patients with non-AKI [SGOT 445.4 ±539.2 vs. 208.2 ±548.6 IU/L: P=0.01 respectively; SGPT 212.2 ±246.9 Vs. 100.2 ± 181.0 IU/L: P=0.04 respectively; ALP 124.2 ±113.2 Vs. 82.3 ±54.2 IU/L: P=0.02 respectively; total bilirubin 1.1 ± 1.3 Vs. 0.6 ±0.5 IU/L: P=0.007 respectively; and direct bilirubin 0.8 ±1.3 Vs. 0.3 ±0.4 IU/L: P=0.002 respectively] as shown in **Table 2**.

**Table 2: Distribution of demographics and laboratory parameters among AKI and non-AKI**

| | Non-AKI (N=106) | AKI (N=14) | **P Value** |
|---|---|---|---|
| | N(N%) | N(N%) | |
| Gender (M/F) | 65(61.3%)/41(38.7%) | 10(71.4%)/4(28.6%) | 0.4 |
| | Mean ± SD | Mean ± SD | |
| Age (Years) | 34.2 ± 14.7 | 41.3 ± 15.3 | 0.09 |
| Hb (g/dl) | 14.1 ± 2.2 | 14.4 ± 2.9 | 0.6 |
| HCT (%) | 41.8 ± 6.5 | 42.2 ± 8.4 | 0.8 |
| Platelet count (cu.mm) | 101,537 ± 63,918 | 74,000 ± 50,883 | 0.1 |
| WBC (cu.mm) | 4,278.3 ± 2,107.4 | 5,207.1 ± 3,051.7 | 0.1 |
| SGOT/AST (IU/L) | 208.2 ± 548.6 | 445.4 ± 539.2 | 0.01 |
| SGPT/ALT (IU/L) | 100.2 ± 181.0 | 212.2 ± 246.9 | 0.04 |
| Alkaline phosphatase IU/L) | 82.3 ± 54.2 | 124.2 ± 113.2 | 0.02 |
| TOTAL BILIRUBIN (mg/dl) | 0.6 ± 0.5 | 1.1 ± 1.3 | 0.007 |
| DIRECT BILIRUBIN (mg/dl) | 0.3 ± 0.4 | 0.8 ± 1.3 | 0.002 |

On evaluation of dengue warning signs, we found reduced urine output was seen in one patient (7.1%) with AKI. Fluid accumulation was seen in 28.6% and 5.7% patients with AKI and non-AKI respectively. Shock was seen in 14.3% and 2.8% patients with AKI and non-AKI respectively. Fluid accumulation causing respiratory distress was seen in 14.3% and 1.9% patients with AKI and non-AKI respectively. ARDS was seen in 21.4 % and 0.9% patients with AKI and non-AKI respectively. SGOT or SGPT>1000 IU/L was seen in 21.4 % and 3.8% patients with AKI and non-AKI respectively. Organ failure was seen in 21.4 % and 1.9% patients with AKI and non-AKI respectively. Impaired consciousness was seen in 14.3 % and 0.9% patients with AKI and non-AKI respectively as shown in **Table 3**.

**Table 3: Distribution of dengue warning signs among AKI and non-AKI**

| **Dengue Warning signs** | **Non-AKI (N=106)** | | **AKI (N=14)** | | |
|---|---|---|---|---|---|
| | **N** | **N %** | **N** | **N %** | **P value** |
| Reduced urine output | 0 | 0.0% | 1 | 7.1% | 0.006 |
| Fluid accumulation | 6 | 5.7% | 4 | 28.6% | 0.004 |
| Shock | 3 | 2.8% | 2 | 14.3% | 0.04 |
| Fluid accumulation causing Respiratory Distress | 2 | 1.9% | 2 | 14.3% | 0.01 |
| ARDS | 1 | 0.9% | 3 | 21.4% | <0.001 |
| AST or ALT >1000 IU/L | 4 | 3.8% | 3 | 21.4% | 0.008 |
| Organ failure | 2 | 1.9% | 3 | 21.4% | 0.001 |
| Impaired consciousness | 1 | 0.9% | 2 | 14.3% | 0.003 |

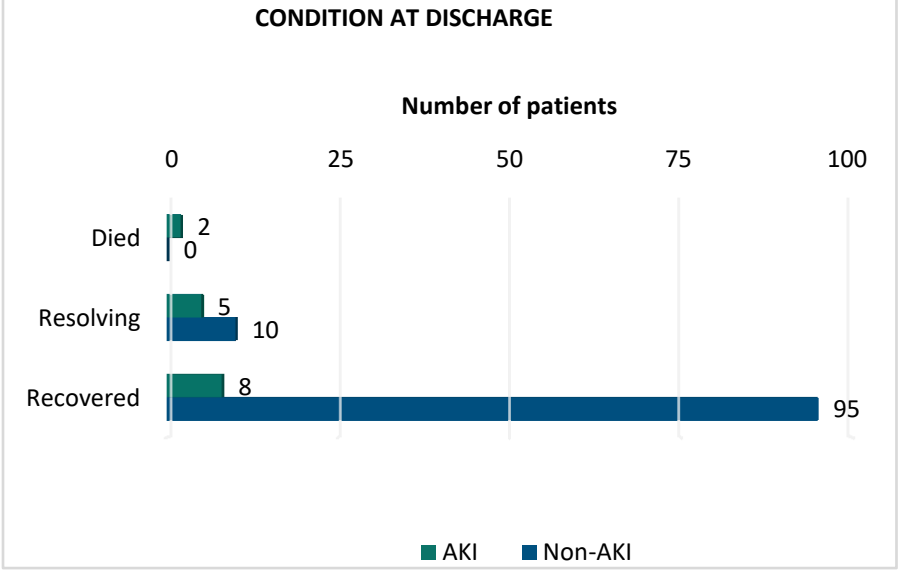
Among DWWS, 10.6%, 18.2% and 71.2% patient had moderate hyponatremia, mild hyponatremia and eunatremia respectively. Among DWS, 14.3%, 21.4% and 64.3% patient had moderate hyponatremia, mild hyponatremia and eunatremia respectively. Among SDG, 25%, 33.3% and 41.7% patient had moderate hyponatremia, mild hyponatremia and eunatremia respectively. Among DWWS, 16.9% and 83.1% patient had mild hypokalemia and eukalemia respectively. Among DWS, 5% and 95% patient had mild hypokalemia and eukalemia respectively. Among SDG, 20%, 20% and 60% patient had severe hypokalemia, mild hypokalemia and eukalemia respectively as shown in **Table 4**.

**Table 4: Serum electrolytes abnormalities among dengue patients**

| Serum Electrolytes | | Dengue Classification | | | | | |
|---|---|---|---|---|---|---|---|
| | | DWWS (n=66) | | DWS (n=42) | | SDG (n=12) | |
| | | N | N % | N | N % | N | N % |
| S Sodium | Moderate Hyponatremia | 7 | 10.6% | 6 | 14.3% | 3 | 25.0% |
| | Mild Hyponatremia | 12 | 18.2% | 9 | 21.4% | 4 | 33.3% |
| | Eunatremia | 47 | 71.2% | 27 | 64.3% | 5 | 41.7% |
| S Potassium | Severe Hypokalemia | 7 | 10.6% | 2 | 4.7% | 2 | 20.0% |
| | Mild Hypokalemia | 10 | 15.1% | 2 | 4.7% | 2 | 20.0% |
| | Eukalemia | 49 | 74.2% | 38 | 90.6 % | 8 | 60.0% |

Based on condition at discharge, In non-AKI group; 89.6% patients showed complete recovery, 9.4% patients were recovering from illness and 0.9% patient had a fatal outcome. In AKI group; 57.1% patients showed complete recovery, 35.7% patients were recovering from illness and 14.2% patients had a fatal outcome as shown in **Figure 1**.

**Figure 1: Condition at discharge among patients with AKI and Non-AKI**




## 4. Discussion

The demographics of our study revealed a male predominance with a M:F ratio of 1.6:1. Several Asian studies have all reported a male predominance, which might be due to the lower self-reporting among women in the economically backward countries.[7,13-14] Interestingly, data collected from 82 studies by Guerra-Silveira *et al*[15] showed a female predominance in the reproductive age group (20-59 years) with a M:F ratio of 0.73 for severe dengue.

Several plausible mechanisms have been proposed for the etiopathogenesis of the renal impairment in dengue such as direct cytopathic effects of viral proteins or circulating immune complexes on glomerular and tubular cells, hemodynamic instability, rhabdomyolysis (by intra renal vasoconstriction, direct tubular injury or tubular obstruction), and hemolysis.[16-17] In our study, 14 patients had AKI (11.67%) which appears to be higher than those reported by various other authors.[7,18] AKI was commonly seen in SDG patients(41.7%). The mean age of the patients with AKI in our study was higher, however not statistically significant compared to non-AKI group. Yet, age related structural and functional changes in elderly kidney are known to make them highly susceptible to hypo perfusion induced ATN.[19] Prior knowledge of the expected clinical profile and predictors of AKI would help us in identifying the patients at a higher risk. Dengue warning signs such as reduced urine output, fluid accumulation, respiratory distress due to fluid accumulation, shock, ARDS, other organ failure, impaired consciousness and elevated SGOT/SGPT >1000 were significantly higher in the AKI group compared to non-AKI group.

Hepatitis, other organ failure and shock were identified by Mehra *et al*[20] as predictors of AKI in dengue. Several other studies have also validated the presence of transaminitis to be an independent risk factor.[21] Thus, the presence of these findings during the initial presentation itself should forewarn the treating physician and guide fluid management. Hepatic

involvement in the form of elevated transaminases and bilirubin were commonly seen in our patients with AKI. We did not found statistical significant difference in platelet counts among AKI and non-AKI group, thus mirroring the recent reports of occurrence of AKI even in the absence of thrombocytopenia and bleeding manifestations, which has been attributed to the direct cytopathic effect of the virus.In our study mortality was significantly higher (14.2%) in the AKI group, with similar results being reported by various other authors.[7,22-23]

We found hyponatremia in 34.2% of our patients. This was lower in comparison to the results by Vinay *et al*[13] (59.91%) and Unnikrishnan *et al*[24] (50.90%) and was closer to the values reported by Jain *et al* (38%) and Naqvi R(35%).[25-26] We also found that hypokalemia (20.8%) is not as common as hyponatremia, and similar results have been reported by other authors.[13,27-28] Serum electrolyte abnormalities in dengue seem to be transient due to functional impairment rather than due to structural renal impairment.

Immune complex mediated injury to the glomerulus has been considered responsible for the usually observed urinary abnormalities in dengue. Proteinuria was the most common abnormality in our study (14.17%) followed by hematuria (7.50%), both of which were related significantly to the disease severity. Proteinuria was seen in only 9% of the patients in the study by Eswarappa *et al*[7], which was closer to our results. There is a wide variability in the overall incidence of proteinuria, as low as 3.89%, seen in the study by Sultana *et al*[29], to as high as 74% in the study by Horvath *et al*.[30] As in our study, proteinuria without an associated AKI seemed to have no impact on the duration of hospitalization and final outcomes. Nonetheless, there have been case reports of dengue associated lupus nephritis and transient IgA nephropathy, where proteinuria accompanied the renal dysfunction, and such possibilities should always be mulled over.[17,31] The incidence of hematuria was 4% in the study by Nayak *et al*.[14] The combination of proteinuria and hematuria was seen in three of our SDG patients, all of who had other bleeding manifestations (melena and mucosal bleed), and a longer hospital stay (mean duration of 8 days as compared to the overall mean duration of 5.22 days).

Final outcomes were better in the non- AKI group. We encountered 2 deaths in the AKI group. Large scale studies about the clinical impact of urinary abnormalities in dengue patients are lacking, and more research is warranted.

## 5. Strengths of the study

**1)** First study among adults conducted to estimate the prevalence of renal dysfunction in dengue patients based on 2009 modified dengue categorization of WHO.

**2)** Study sample included only IgM positive dengue patients and AKI due to other tropical infections were excluded.

**3)** Our study was comprehensive and included urinary abnormalities along with the serum values of creatinine and electrolytes.

## 6. Limitations of the study

**1)** The patients were selected from a tertiary care center which usually tends to see a clustering of more severe cases as the less severe ones may be treated on out-patient basis. Hence the results of the study may not be an accurate representation of the entire population.

**2)** Since this was a retrospective study, we could not assess the repeat urinalysis, to look for the reversibility of these changes.

**3)** We did not study the trends of serum creatinine and electrolytes but only assessed the highest value during the admission.

**4)** Renal biopsy was not done in any of the patients for the histopathological confirmation.

## 7. Conclusion

In our study, prevalence of AKI was 11.7%. Renal dysfunction in dengue varies from asymptomatic urinary abnormalities to AKI and is more commonly seen in severe dengue. Hepatic involvement in the form of with elevated transaminases and bilirubin were commonly seen in our patients with AKI. Proteinuria and hematuria are the most commonly seen urinary abnormality and were determinant of prolonged hospital stay. Dengue patients with AKI had persistent thrombocytopenia and poor outcomes with higher mortality rate.

**Conflict of interests:** None

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