**Title Page**

**Incidence, Risk Factors and Outcome of Renal Involvement in Patients of Dengue Viral Infection Admitted to a Tertiary Care Hospital in North-Western India: A single center, prospective observational study.**

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**Shortened title: Renal Involvement in Patients of Dengue**

**Abstract:**

Dengue Viral Infection (DVI) has emerged as one of tropical belts' most common mosquito-borne diseases worldwide. This study was an attempt to evaluate the patterns of renal involvement in DVI and its effect on morbidity and mortality arising from the illness. This study was conducted on 170 patients hospitalized with the diagnosis of Dengue fever in the Emergency department of the Post Graduate Institute of Medical Education and Research, Chandigarh, from July 2022 to September 2023. All clinical and laboratory parameters of the patient were recorded. To evaluate patterns of renal involvement, patients underwent urine dipstick, urine routine and microscopy, spot urine protein/creatinine ratio, creatinine and ultrasonography. Patients with renal involvement were followed up for four weeks and 12 weeks. The median age was 36 years, with 60% male patients. A total of 51 patients (30%) had renal involvement, and 36 (21.17%) had Acute Kidney injury. Ten patients developed KDIGO Stage 3 AKI, of which 7 required renal replacement therapy. Forty-seven (27.6%) patients developed urinary abnormalities (which included proteinuria, hematuria, and active sediments in urine). Patients with renal involvement had significantly higher mortality (p-value <0.001). Among the patients who survived, renal abnormalities resolved in all except one, who progressed to chronic kidney disease. Renal biopsy was done in three patients, and cast nephropathy was seen in all. This study establishes that renal involvement accompanies higher mortality in patients with DVI, thereby underscoring the importance of its evaluation for the management and prognostication of patients.

**Keywords: Dengue, DVI, Renal Involvement, AKI**

**1 Introduction**

Dengue is probably the most prevalent arthropod-borne viral disease worldwide, with ~400 million infections occurring annually, of which ~100 million (25%) cause clinical illness 1. Dengue Viral Infection (DVI) has numerous presentations ranging from undifferentiated fever to cases with multiple end-organ damage and life-threatening diseases. The literature and studies evaluating the epidemiology of renal involvement in Dengue fever and its forms are relatively scarce. Also, the mechanisms leading to Acute Kidney Injury (AKI) in Dengue infection still need to be understood.

AKI is considered an infrequent complication of Dengue, but various studies keep the incidence of renal manifestations in Dengue widely variable, ranging from as low as 0.9% to 69.4%. The incidence of AKI is around 14% in various studies2-4. AKI in cases of Dengue fever has been associated with increased morbidity and mortality5; hence, early recognition of Dengue patients with AKI may reduce these parameters. Literature on Dengue and its association with AKI is primarily retrospective data from scattered areas. Specific prospective data is yet to be provided, hence the importance of this study. This prospective study was planned to assess renal involvement in DVI and correlate it with morbidity and mortality.

**2 Methods**

***2.1 Study setting and design***

This was a prospective, observational, single-centre study carried out in 170 patients above 12 years of age who visited the Emergency Medical Services of Post Graduate Institute of Medical Education and Research, Chandigarh, from July 2022 to September 2023.

***2.2 Study Participants***

All patients older than 12 years who were admitted to the emergency department with the symptomatology of tropical fever illness and satisfied the clinical definition of Dengue fever under World Health Organisation(WHO) diagnostic criteria were enrolled6. The admission criteria, under guidelines of the National Vector Borne Disease Control Programme (NVBDCP), were: DVI with warning signs (recurrent vomiting, abdominal pain/tenderness, lethargy/ restlessness, pleural effusion/ascites, hepatomegaly, increased haematocrit of more than 20%); patients with persistent high-grade fever; bleeding from any site; signs of hypotension; rapid fall of platelet count; patients with evidence of organ involvement7. Exclusion criteria included patients who did not give consent; patients with underlying CKD (per clinical judgment), obstructive uropathy, underlying decompensated chronic liver disease, congestive cardiac failure, and advanced malignancy; and patients with coexisting alternate diagnoses presenting with a tropical fever were either diagnosed with a specific tropical illness or did not satisfy the WHO Diagnostic criteria for DVI6.

***2.3 Objectives***

The primary objective of this study was to assess the incidence of renal involvement in DVI. The secondary objectives included the determination of the correlation of renal involvement in DVI with morbidity and mortality and the detection of the proportion of Dengue-related AKI patients progressing to chronic kidney disease (CKD) at three months.

***2.4 Study procedure***

Patients who fulfilled the inclusion criteria and gave full and informed consent to participate were enrolled. Clinical history and examination were done in all study participants. All investigations, including complete blood count, renal function tests, liver function tests, coagulation profile, chest radiograph, and ultrasound examination, were done at the time of hospital admission. All the patients underwent a urine routine, urine microscopy, and urine protein creatinine ratio in addition to the above investigations. Patients were followed daily with renal function tests till the end of their hospital stay. Patients who did not have a resolution of renal function at four weeks of illness underwent kidney biopsy as per the department’s protocol. All patients with AKI or urinary abnormalities were followed up at 4 and 12 weeks with serum creatinine and urine protein creatinine ratio to assess the percentage of patients who progressed to CKD.

***2.5 Renal Parameters assessed***

The renal parameters which were assessed were: (a) Serum Urea: 3ml of serum (derived from whole blood collected in a plain vial) was sent to the Biochemistry lab and was subjected to the quantitative determination of urea on the Roche Cobas C® system, which utilized the principle of kinetic test with urease and glutamate dehydrogenase enzymes; (b) Serum Creatinine: 3ml of serum (derived from whole blood collected in a plain vial) was sent to the Biochemistry lab, which was analyzed by Roche Cobas C® system using Jaffè's colorimetric assay for creatinine; (c)Urine dipstick: The Mission® urine reagent strips were used- the test for protein is based on the phenomenon of 'protein error' of pH indicators where proteins act as anions, the test for blood in urine is based on the principle that hemoglobin catalyzes the reaction of diisopropyl benzene dihydroperoxide and 3, 3`, 5, 5`-tetramethylbenzidine which yields color change; (d)Urine routine examination microscopy for albumin, pus cells, casts, and active sediments: The urine sample was sent to the Renal lab in the Department of Nephrology, where it was centrifuged, and sediment was examined under the microscope; (e) Urinary protein/Creatinine ratio: The spot urine sample was analyzed using the turbidimetric method for urine protein and creatinine; (f) Kidney morphology on Ultrasonography.

***2.6 Statistical analysis***

IBM Statistical Package for Social Sciences (SPSS) Version 25 was used for data analysis. The categorical variables were summarized as a proportion or percentage. The quantitative variables were summarized as mean ± 95% Confidence Intervals (CI) or median ± interquartile range (IQR) according to the normalcy of the data. Differences between qualitative and quantitative variables were compared using the Chi-square test and Student-T test, respectively. Univariate analysis and multivariate analysis were done where applicable. A p-value of <0.05 was considered statistically significant.

**3 Results**



**Flow diagram for participants included in the primary analysis**

Abbreviations: DVI, Dengue Viral Infection

***3.1 Baseline features and outcomes of the study participants***

3.1.1 Demographic Characters

The median age for the study population was 36 years (interquartile range, 23-46) and almost 60% were males. Almost 80% of the population were previously healthy, while the rest had comorbidities like diabetes, hypertension, coronary artery disease, and hypothyroidism (Table 1). Among the study population, equal halves belonged to urban and rural residential areas. However, among patients with renal involvement, 62.74% (32 out of 51) belonged to rural areas, while 37.3% belonged to urban areas. With a p-value of 0.03, there was a statistical significance between rural residence and the incidence of renal involvement in patients with DVI (Table 1).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| , | **Total**  **(n=170)** | **Dengue with renal involvement**  **(n=51)** | **Dengue without renal involvement**  **(n=119)** | **2-tail sig**  **or**  **p-value** |
| Age in years | 36 (23-46) | 39 (28-50) | 34 (22-43) | 0.30 |
| Male | 101 (59) | 32 (62.7) | 69 (58) | 0.56 |
| **Address** |  |  |  |  |
| Urban | 85 (50) | 19 (37.3) | 66 (55.5) | **0.03** |
| **Comorbidities** |  |  |  |  |
| Diabetes | 15 (8.8) | 4 (7.8) | 11 (9.2) | 0.76 |
| Hypertension | 11 (6.5) | 4 (7.8) | 7 (5.9) | 0.63 |
| CAD | 2 (1.2) | 1 (2) | 1 (0.8) | 0.53 |
| CVA | 2 (1.2) | 1 (2) | 1 (0.8) | 0.53 |
| Hypothyroidism | 2 (1.2) | 0 | 2 (1.7) | 0.35 |
| Charlson comorbidity index | 0 (0-0) | 0 (0-0.5) | 0 (0-0) | 0.61 |
| **Presentation** |  |  |  |  |
| Fever | 169 (99.4) | 51 (100) | 118 (99.2) | 0.51 |
| Chills | 93 (54.7) | 32 (62.7) | 61 (51.3) | 0.16 |
| Myalgia | 96 (56.5) | 30 (58.8) | 66 (55.5) | 0.68 |
| Joint pain | 23 (13.5) | 8 (15.7) | 15 (12.6) | 0.59 |
| Rashes | 9 (5.3) | 2 (3.9) | 7 (5.9) | 0.60 |
| Headache | 51 (30) | 15 (29.4) | 36 (30.3) | 0.91 |
| Retro orbital pain | 7 (4.1) | 2 (3.9) | 5 (4.2) | 0.93 |
| Nausea/Vomiting | 89 (52.4) | 23 (45.1) | 66 (55.5) | 0.21 |
| Bleeding manifestations | 43 (25.3) | 10 (19.6) | 33 (27.7) | 0.26 |
| Hematuria | 5 (2.9) | 5 (9.8) | 0 | **0.001** |
| Oliguria | 12 (7.1) | 9 (17.6) | 3 (2.5) | **0.000** |
| Altered sensorium | 29 (17.1) | 17 (33.3) | 12(10.1) | **0.000** |
| Abdominal pain | 66 (38.8) | 13 (25.5) | 53 (44.5) | **0.02** |
| **Physical Examination** |  |  |  |  |
| Heart rate, per minute | 98 (86-110) | 102 (86-112) | 96 (86-110) | 0.06 |
| Systolic blood pressure, mm of Hg | 110 (100-122) | 108 (90-128) | 111 (100-122) | 0.30 |
| Diastolic blood pressure, mm of Hg | 71 (60-80) | 69 (60-84) | 71 (60-80) | 0.49 |
| Respiratory Rate per minute | 22 (20-24) | 22 (20-24) | 22 (20-22) | 0.83 |
| Pallor | 20 (11.8) | 8 (15.7) | 12 (10.1) | 0.29 |
| Icterus | 10 (5.9) | 6 (11.8) | 4 (3.4) | **0.03** |
| Edema | 33 (19.4) | 19 (37.3) | 14 (11.8) | **0.000** |
| Lymphadenopathy | 1 (0.6) | 0 | 1 (0.8) | 0.51 |

**Table no 1 Baseline Characteristics of the study participants with and without Renal involvement**

Abbreviation: CAD, Coronary Artery Disease

CVA, Cerebrovascular Accident

The values are presented as mean (95% confidence interval) or numbers (percentage).

3.1.2 Clinical Presentation and Investigations

In patients with DVI, fever was present in all patients, while chills, myalgia, nausea, and vomiting were the following most common symptoms (around 50% each). Almost 40% of patients had pain in the abdomen, and it was significantly associated with renal involvement. Around one-fourth of the patients had bleeding manifestations. 17.1% of the patients presented with altered sensorium, and there was a significant relation between the presence of altered sensorium in patients of DVI and renal involvement (p value-0.001). Haematuria was found in 2.9%, and oliguria was reported in 7.1% (Table 1). The details of investigations and their association with the renal involvement group is described in Table 2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total**  **(n=170)** | **Dengue with renal involvement**  **(n=51)** | **Dengue without renal involvement**  **(n=119)** | **2-tail sig**  **or**  **p-value** |
| Haemoglobin (g/L) | 12.19 (11.72-12.65) | 11.78 (10.81-12.75) | 12.4 (11.8-12.9) | 0.25 |
| Total Leucocyte Count x 103 (cells/)\* | 6.9 (4.75-11.02) | 9.6 (6.3-13.5) | 6.1 (4.3-9.5) | **0.005** |
| Platelet count x 103 cells/\* | 34 (16-65) | 47 (18-78) | 29 (14-58) | **0.043** |
| Hematocrit | 38 (36-39) | 37 (34-39.9) | 38 (37-40) | 0.489 |
| Sodium (meq/l) | 136.70 (135.95-137.46) | 135.92 (134.33-137.51) | 137.03 (136.19-137.89) | 0.182 |
| Potassium (meq/l) | 4.26 (4.14-4.38) | 4.51 (4.22-4.80) | 4.15 (4.03-4.26) | **0.006** |
| Chloride (meq/l) | 101.33 (99.06-103.6) | 103.26 (101.6-104.93) | 100.5 (97.33-103.67) | 0.272 |
| Calcium (mg/dl) | 8.27 (8.1-8.4) | 8.0 (7.7-8.4) | 8.3 (8.2-8.4) | 0.058 |
| Phosphorous (mg/dl)\* | 2.96 (2.41-3.5) | 3.4 (2.4-4) | 2.84 (2.41-3.26) | **0.000** |
| Magnesium (mg/dl) | 2.84 (1.22-4.74) | 2.16 (2.0-2.31) | 3.12 (0.88-5.41) | 0.599 |
| Urea (mg/dl)\* | 25 (17-48) | 65 (25-89) | 21 (15-32) | **0.00** |
| Creatinine (mg/dl)\* | 0.8 (0.63-1) | 1.7 (0.96-2.47) | 0.73 (0.57-0.9) | **0.00** |
| Total Bilirubin (mg/dl)\* | 0.7 (0.5-1.6) | 1.3 (0.7-2.67) | 0.7 (0.43-1.3) | 0.117 |
| Total Protein (mg/dl) | 5.9 (5.7-6.0) | 5.7 (5.35-6.04) | 5.96 (5.81-6.12) | 0.103 |
| Albumin (mg/dl) | 4.5 (1.7-7.3) | 2.88 (2.68-3.08) | 5.2 (1.19-9.21) | 0.456 |
| Aspartate Transaminase (IU/L)\* | 181 (97-450) | 224 (133-1279) | 160 (92-342) | 0.015 |
| Alanine Transaminase (IU/L)\* | 96 (54-277) | 126 (74-755) | 91 (49-198) | 0.008 |
| Alkaline phosphatase (IU/L)\* | 123 (91-187) | 133 (93-333) | 120 (90-165) | **0.000** |
| pH | 7.39 (7.38-7.48) | 7.35 (7.32-7.40) | 7.41 (7.40-7.42) | **0.001** |
| Bicarbonate | 21.0 (20.23-21.77) | 17.7 (16.19-19.280) | 22.41 (21.64-23.17) | **0.000** |
| Lactate\* | 1.5 (1.0-2.39) | 1.95 (1.2-4.7) | 1.4 (1-2) | **0.000** |
| NS1 Ag Positive | 81 (47.6) | 22 (43.1) | 59 (49.6) | 0.13 |
| Anti-Dengue IgM Positive | 111 (65.3) | 36 (70.6) | 75 (63) |  |
| ECG Abnormality | 46 (27.1) | 13 (25.5) | 33 (27.7) | 0.76 |
| Chest Xray Abnormality | 78 (45.9) | 35 (68.6) | 43 (36.1) | **0.00** |
| * Pleural Effusion | 50 (29.4) | 17 (33.3) | 33 (27.7) | **0.01** |
| * Pulmonary Edema | 28 (16.5) | 18 (35.3) | 10 (8.4) | **<0.001** |
| Ultrasound Abnormal | 117 (68.8) | 40 (78.4) | 77 (64.7) | 0.07 |
| **Outcome** |  |  |  |  |
| Death | 17 (10) | 14 (27.5) | 3 (2.5) | **0.00** |
| Duration of hospital stay in  Days\* | 4 (2-6) | 4 (2-8) | 4 (2-5) | 0.102 |

**Table 2 Baseline investigations and outcomes of the study participants with and without renal involvement**

\*Represents variables where data is skewed and hence median is used. In such cases, Parenthesis indicates interquartile range.

In all other variables, wherever applicable, values have been represented as mean (95% confidence limits) and numbers (percentage).

3.1.3 Outcome

The mean duration of hospital stay was four days in the total study population (95% confidence interval, 2-6 days), with no statistical difference between patients with and without renal involvement. A total of 17 out of 170 patients expired during the illness (10%), with 14 of these deaths occurring in patients with renal involvement, thus establishing an increased risk of mortality in patients of DVI with renal involvement on univariable analysis (p value-0.0001) (Table 2).

Fifty-one patients had renal involvement, either AKI or asymptomatic abnormalities, out of the total population of patients with DVI (30%). Urine microscopic abnormalities included proteinuria, haematuria, or other active sediments like granular casts in urine detected in these patients. Forty-seven patients had one or more of these abnormalities (27.64%). Twenty-one patients had proteinuria (12.3%), of which twelve had AKI, while nine did not. 14 out of the 21 patients with proteinuria had severely increased proteinuria, and 1 had nephrotic range proteinuria. In comparison, the rest had moderately increased proteinuria. 13 patients had haematuria (7.6%), seven of which had AKI. Granular casts were found in 9 patients (5.29%), while pyuria was found in 4 patients (2.3%), of which 3 had AKI. (Table 3).

A multivariable analysis was done on factors significantly associated with renal involvement in DVI, where residence, altered sensorium, platelet count, and lactate levels were compared since they were found significant on univariate analysis. It was located on logistic regression that altered sensorium and lactate were independently associated with, and hence, significant predictors of renal involvement (Table 4).

Three of the patients underwent renal biopsy, out of which two were post-mortem. The first patient had persistent AKI and continued to be dialysis-dependent for more than 12 weeks. Her renal biopsy revealed Hemoglobin cast nephropathy. She finally improved and is currently off hemodialysis. By definition, she progressed to CKD. The other two patients presented with multi-organ damage, including AKI, for which they needed intermittent hemodialysis. Post-mortem renal biopsy in both these cases revealed acute tubular injury with cast nephropathy. (Figure 1)

**Table 3 Urine microscopic abnormalities in patients with renal involvement**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| Urinary microscopic abnormality | Total Patients | With AKI | Without AKI |
|  |  |  |  |
| Proteinuria\* | 21 | 12 | 9 |
| Moderately increased proteinuria | 6 | 1 | 2 |
| Severely Increased proteinuria | 14 | 9 | 5 |
| Nephrotic range proteinuria | 1 | 1 | 0 |
| Haematuria | 13 | 7 | 6 |
| Granular casts | 9 | 9 | 0 |
| Pyuria | 4 | 3 | 1 |

Abbreviation: AKI, Acute Kidney Injury

\*included epithelial cell casts and granular casts in our patients

The values are presented as numbers (percentage)

**Table 4 Multivariable analysis in Renal v/s No Renal Involvement**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Renal Involvement | No Renal Involvement | Odd’s Ratio (95% Confidence Intervals) | p-value |
| Address (Urban and Rural) | 19/51 (37.3) | 66/119 (55.5) | 1.48 (0.03-0.2) | 0.140 |
| Altered sensorium | 17/51 (33.3) | 12/119 (10.1) | 3.19 (0.1-0.4) | 0.002 |
| Platelet Count x 103 cells/ | 47 (18-78) | 29 (14-58) | 1.025 (0.001-0.002) | 0.307 |
| Lactate | 1.95 (1.2-4.7) | 1.4 (1-2) | 4.16 (0.03-0.1) | 0.000 |

|  |  |
| --- | --- |
| **A** | **B** |
| **C** | **D** |

**Figure 1 Renal Biopsy:** Imagesshow **A** low power view and **B** high power view ofkidney biopsy showing PAS stain showing 1 glomerulus with mesangial hypercellularity and tubules showing presence of pigment casts, that were further positive for hemoglobin immuno stain. Images **C** and **D** show low power view (20X) of kidney biopsy with PAS staining showing severe acute tubular injury with pigmented red cell casts in tubules with Glomerulus being unremarkable.

***3.2 Comparison among survivors and non-survivors with renal involvement***

The survivor population was compared with non-survivors across baseline characteristics. Oliguria, altered sensorium, and oxygen requirement, each with a p-value of less than 0.01, were significantly associated with the non-survival factor. A total of 7 patients required hemodialysis, out of which five expired (29.4% in the non-survivor group). The association of various laboratory findings with non-survivorship was also seen (Table 5).

14 out of 17 non-survivors had renal involvement in the form of AKI, which was significantly higher (p-value 0.0001) than the survivor group, where 37 out of 153 had AKI (Table 5).

A multivariable analysis was done among renal involvement and oxygen requirement (both were significantly associated with mortality on the univariable analysis), and the association withstood (Table 6).

**Table 5 Baseline characteristics of the study participants among survivors versus non-survivors**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total  N=170 | Survivors  N=153 | Non-Survivors  N=17 | P value/sig |
| Age | 36 (23-46) | 34 (32-37) | 35 (17-75) | 0.925 |
| Male | 101 (59) | 71 (60.2) | 9 (52.9) | 0.567 |
| **Presentation** |  |  |  |  |
| Oliguria | 12 (7.1) | 8 (5.2) | 4 (23.5) | 0.005 |
| Altered sensorium | 29 (17.1) | 17 (11.1) | 12 (70.6) | 0.000 |
| Oxygen requirement | 37 (21.8) | 25 (16.3) | 12 (70.6) | 0.000 |
| Pallor | 20 (11.8) | 13 (8.5) | 7 (41.2) | 0.000 |
| Edema | 33 (19.4) | 26 (17) | 7 (41.2) | 0.017 |
| Inotropic Requirement | 20 (11.76) | 15 (9.8) | 5 (29.4) | 0.03 |
| Hemodialysis requirement | 7 (4.1) | 2 (1.3) | 5 (29.4) | 0.000 |
| Chest Xray Abnormality | 78 (45.9) | 66 (43.1) | 12 (70.6) | 0.033 |
| Pottasium (meq/l) | 4.26 (4.14-4.38) | 4.19 (4.0-4.3) | 4.88 (4.35-5.42) | 0.000 |
| Phosphorous (mg/dl)\* | 2.96 (2.41-3.5) | 2.8 (2.3-3.4) | 3.65 (3.27-6.75) | 0.00 |
| Magnesium (mg/dl) | 2.84 (1.22-4.74) | 2.89 (1.12-4.66) | 2.33 (1.93-2.73) | 0.856 |
| Urea (mg/dl)\* | 25 (17-48) | 24 (17-43) | 81 (20-118) | 0.00 |
| Creatinine (mg/dl)\* | 0.8 (0.63-1) | 0.79 (0.61-1) | 2.03 (0.91-2.82) | 0.00 |
| Total Bilirubin (mg/dl)\* | 0.7 (0.5-1.6) | 0.7 (0.4-1.4) | 2.3 (0.74-4.95) | 0.00 |
| Aspartate Transaminase (IU/L)\* | 181 (97-450) | 174 (95-377) | 445 (147-2241) | 0.00 |
| Alanine Transaminase (IU/L)\* | 96 (54-277) | 94 (52-246) | 169 (85-2240) | 0.10 |
| Alkaline Phoshatase(IU/L)\* | 123 (91-187) | 122 (91-187) | 133 (82-280) | 0.150 |
| pH | 7.39 (7.38-7.48) | 7.41 (7.39-7.42) | 7.28 (7.20-7.36) | 0.00 |
| Bicarbonate | 21.0 (20.23-21.77) | 21.7 (21.01-22.46) | 14.4 (11.73-17.13) | 0.00 |
| Lactate\* | 1.5 (1.0-2.39) | 1.46 (1-2.1) | 4.24 (1.75-6.5) | 0.00 |
| Renal involvement | 51 (30) | 37 (24.2) | 14 (82.4) | 0.00 |
| with AKI | 36 (21.17) | 23 (15.03) | 13 (76.47) | 0.00 |
| Asymptomatic urinary  abnormalities | 15 (8.8) | 14 (9.2) | 1 (5.9) | 0.00 |

Abbreviation: AKI, Acute Kidney Injury. Age is represented as Mean (Range) \*Represents variables where data is skewed and hence median is used. In such cases, Parenthesis indicates interquartile range. In all other variables, wherever applicable, values have been represented as mean (95% confidence limits) and numbers (percentage).

**Table 6 Multivariable Analysis for factors among Survivor and Non survivor groups:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | Non-Survivors | Survivors | Odd’s Ratio (95% Confidence Intervals) | p-value |
| Renal Involvement | 14/17 (82.4) | 37/153 (24.2) | 3.85 (0.084-0.271) | 0.00 |
| Oxygen Requirement | 12/17 (70.6) | 25/153 (16.3) | 4.13 (0.10-0.31) | 0.00 |
| Inotropic Requirement | 5/17 (9.8) | 15/153 (29.4) | 1.50 (0.03-0.224) | 0.13 |

**4 Discussion**

***4.1 Key Results***

In this study, 30% of patients had renal involvement, including AKI, proteinuria, haematuria, and asymptomatic urinary abnormalities. 21.17% of patients in the total population developed AKI, and one patient (0.5%) progressed to CKD. 27.64% of patients were found to have urine abnormalities among the study participants. Patients residing in rural areas, patients presenting with altered sensorium, hyperkalemia, higher Phosphorous levels, higher AST, ALT and ALP levels, metabolic acidosis and higher lactate levels were identified as predictors of increased risk of renal involvement. Overall mortality was 10%, while mortality percentage in patients with AKI was 36.1%. The association of AKI with mortality was significant, each on univariable and multivariable analysis. Urine abnormalities resolved in all the patients on follow-up among those who survived.

***4.2 Interpretation***

Mallhi et al. studied 667 cases of Dengue irrespective of severity, and the proportion of AKI in their study was 14.2%8. Another study from Karachi by Khalil et al. included 532 patients, and 13.3% of all Dengue patients developed AKI in the survey 9. However, the proportion of AKI in various studies has been variable; for example, a study from Bengaluru by Eswarappa et al.in 2019 included 2416 patients where only 3.4% of patients developed AKI10, while another study by Rajan et al. from Chennai at around the same time reported the proportion of AKI as 20.5%11. A higher proportion of AKI in the study could be explained by the fact that the Chennai study included children admitted to Paediatric Intensive Care Unit (PICU) and hence were more severe cases. In contrast, the other studies comprised cases of all severities.

A higher proportion of AKI (21.17%) was seen in the index study compared to previous studies; possible explanations could be Berksonian bias, as patients with higher severity were admitted to the emergency department and were usually referred from peripheral centers. Delays in referral and inability to manage Dengue effectively could increase the chances of developing severe illness.

The study by Rajan et al.from Chennai reported the incidence of proteinuria as 18% while that of haematuria as 20.4% in patients of Dengue admitted to PICU11. Sultana et al. reported a proteinuria (45.1%) and haematuria (12.9%) 12. The study by Eswarappa et al.found the incidence of proteinuria to be 9.02% (where five patients developed nephrotic range proteinuria), which is close to the current study findings10. A study by Lumpapong et al. found a prevalence of haematuria at 18% in Dengue patients and 27% in DHF patients. Similarly, the prevalence of proteinuria was 15% and 27%, respectively13. The index study found the incidence of urinary abnormalities to be almost 28%. There has been a variable incidence of urine abnormalities in DVI across studies; however, an association of these findings with Dengue cannot be denied.

Various studies have identified numerous predictors of renal involvement in DVI, and their findings have been similar to the index study9-11, 14-20 (Table 7). These standard profiles of predictors also point to the possible pathophysiology and complications arising from renal involvement. For instance, these predictors suggest that pre-renal AKI due to circulatory disturbances and increased capillary permeability might be responsible for renal involvement in these cases. Coagulopathy and secondary hemophagocytic lymphohistiocytosis reflect the cytokine storm associated with DVI.

A retrospective analysis by Mallhi et al. found 1.2% mortality in 667 patients with Dengue8. Two more extensive studies reported similar figures: Vu Huy et al.- who studied 2417 patients, and Eswarappa et al.- who studied 2416 patients, reported 12.5% and 13.41% mortality in patients with AKI, respectively10, 15. Higher mortality (36% in the AKI cohort) in the present study may be attributed to Berkesonian bias as the study center receives more severe Dengue cases and delayed referrals from the primary and secondary center.

In the study by Dipyanusa et al., 0.7% of the patients had dialysis requirements, and most died (9 out of 10)14. Rajan et al.reported a hemodialysis requirement of 7% (9 out of 127 patients admitted to PICU). Six recovered and did not need dialysis at follow-up, while three succumbed to their illness11. A higher need for hemodialysis was seen in the index study and the study by Rajan et al., as more severe cases were included.

Scarce literature exists about renal pathology findings in patients with DVI, mainly as isolated case reports. Uthamalingam et al. reported Dengue myositis, where AKI occurred secondary to pigment cast nephropathy21. Repizo et al. reported a case of Dengue-related rhabdomyolysis led to biopsy-proven acute tubular necrosis22. Mesangial proliferation and immune complex deposition have been the other pathologies identified in patients with DVI23. The heterogeneity of the various pathological findings suggests the multiple possible mechanisms that lead to renal involvement in DVI, some of which are only postulated and not yet proven through histopathological correlation.

**Table 7 Comparison of AKI, mortality, and risk factors for AKI in DVI across various studies in the last ten years**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| S.No. | Study | Year | Study Population | Study location and size | Severity of Cases | Incidence of AKI | Risk factors for AKI identified | Mortality  AKI v/s Non-AKI |
| 1. | Mehra et al.17 | 2012 | Age not defined | Chennai, 223 | All | 10.8% | High ALT, ALP, Hypoalbuminemia, Metabolic acidosis, Hypoxia, Shock | All-cause mortality 9% |
| 2. | Khalil et al.9 | 2012 | >14 years | Karachi, 532 | All | 13.3% | Higher age group, Male gender, CNS involvement, Respiratory failure, prolonged aPTT | 11.3% v/s 0 |
| 3. | Mallhi et al.8 | 2015 | >12 years | Malaysia, 667 | All | 14.2% | Male gender, DHF, Rhabdomyolysis, MODS, DM, Use of nephrotoxic drugs | 1.2% v/s 0 |
| 4. | Diptyanusa et al.14 | 2018 | >18 years | Bangkok, 1484 | All | 4.8% | Lower age, Male gender, DM, Obesity, Severe Dengue, Severe thrombocytopenia, Hypoalbuminemia, Severe transaminitis, Coagulopathy, Shock, Metabolic acidosis, Rhabdomyolysis, Respiratory failure | 12.7% v/s 0 |
| 5. | Patel et al.18 | 2019 | >14 years | Lucknow, 620 | All | 14.51% | Lower Age, Male gender, Urban residence, Diabetes, 6.HTN, IHD, Severe Dengue, | 15.61% v/s 0 |
| 6. | Eswarappa et al.10 | 2019 | >15 years | Bengaluru, 2416 | All | 3.4% | Lower Age, Hypotension, MODS, Diabetes | 13.41% v/s 0.7% |
| 7. | Rajan et al.11 | 2020 | Children admitted to PICU | Chennai, 127 | Severe Dengue | 20.5% | Hypotension, Ventilatory requirement, Secondary HLH, Higher potassium levels, Higher AST and ALT, Coagulopathy | 11.53% v/s 0.9% |
| 8. | Surasombatpattana et al.19 | 2021 | >18 years | Songkla (Thailand), 120 | All | 14% | MODS, NSAID use | 12% v/s 1% |
| 9. | Bui Vu Huy et al.15 | 2021 | >18 years | Hanoi (Vietnam), 2417 | All | 2.7% | Male gender, HTN, Shock, MODS, Myocarditis | 12.5% v/s 0.9% |
| 10. | Wang C. et al.20 | 202320 | >18 years | Guangdong, China, 242 | Severe Dengue | 35.1% | HTN, Nephrotoxic drugs, Respiratory distress, Hematuria | 22.4% v/s 0 |
| 11. | Present Study (PGIMER, Chandigarh) | 2022-23 | >12 years | Chandigarh, 170 | All | 21.17% | Rural residence, Altered sensorium, Edema, Thrombocytopenia, Hyperkalaemia, Metabolic acidosis, Higher lactate levels | 7.64% v/s 0.005% |

\*Enrolled severe Dengue cases only. All other studies had cases of varying severity

Abbreviation: AKI, Acute Kidney Injury; DVI, Dengue Viral Infection; ALT, Alanine aminotransferase; ALP, Alkaline Phosphatase; DHF, Dengue Haemorrhagic Fever; MODS, Multi-Organ Dysfunction Syndrome; DM, Diabetes Mellitus; CNS, Central Nervous System; HTN, Hypertension; IHD, Ischemic Heart Disease; AST, Aspartate aminotransferase; HLH, Hemophagocytic Lymphohistiocytosis; NSAID, Non-Steroidal Anti-inflammatory Drugs

***4.3 Implications of the study***

Renal involvement is an underreported complication of DVI, with a spectrum ranging from asymptomatic urine abnormalities to life-threatening organ dysfunction requiring renal replacement therapy.

Renal involvement may be predicted by various clinical and laboratory features in these patients, as highlighted in the current study and across studies on this topic.

AKI in Dengue is an independent factor associated with mortality in these patients. Although rare, renal involvement in DVI has the potential to progress to CKD; hence, early recognition and prompt management can go a long way in reducing the mortality burden of one of the most common tropical illnesses.

Though this study identified cast nephropathy as one of the etiologies for organ-threatening renal dysfunction, there is a need for more studies with histopathological correlates to comprehend knowledge about the pathophysiology of renal involvement in DVI and hence contribute to improved patient outcomes.

***4.4 Limitations***

This was a single-centre study in an apex tertiary care institute, with a potential for Berksonian bias. As cases admitted to the emergency were picked up, the sample size was relatively small compared to previous studies, which were largely retrospective and included data from patients visiting hospitals over several years. Moreover, a renal biopsy was performed on only three patients. More histopathological specimens would better elucidate the underlying mechanisms of renal involvement in DVI.

**5 Conclusion**

One third of the study cohort had renal involvement in the form of AKI or asymptomatic urinary abnormalities. The incidence of development of CKD was low in this study, as only one patient progressed to CKD out of the study population. This study establishes the association of AKI with mortality in patients with DVI, underscoring the importance of its evaluation in all patients who present to us with this disease.

**6 Other Information**

***6.1 Data availability Statement***

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical considerations.

***6.2 Funding***

This study was funded by the Post Graduate Institute of Medical Education and Research, Chandigarh.

***6.3 Conflict of Interest***

There were no conflicts of interest.

***6.4 Ethics Statement***

The Institute's Ethics Committee approved the study.

***6.5 Patient's Consent Statement***

All enrolled patients gave their signed informed consent for participation in the study.

***6.6 Author Contributions***

**Avichal Rajpal**: Data curation, writing-original draft, data analysis, patient management, writing-review and editing, patient management. **Mohan Kumar H**: Conceptualization, methodology, data curation, data analysis, writing-original draft, writing-review and editing, patient management. **Jasmine Sethi**: patient management, methodology, writing- original draft, writing-review and editing. **Radha Kanta Ratho**: Investigation, methodology, writing-review and editing. **Ashok Kumar Pannu**: Data curation, writing-original draft, methodology, data analysis, writing- review and editing, patient management. **Mani Rajendran**: Data curation, data analysis. **Ashish Behera**: patient management, writing-review and editing. **Saurabh Chandrabhan Sharda**: patient management, writing-review and editing. **Aravind Sekar**: Investigation, data curation, writing-review and editing. **Ritambhra Nada**: Investigation, data curation, writing-review and editing. **Navneet Sharma**: Patient management, methodology, writing-review and editing.

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