Incidence, Risk Factors and Outcomes of Renal Involvement in Patients with Dengue Viral Infection

Abstract

Background: Kidney involvement has been reported frequently in people with Dengue virus infection (DVI). We evaluated the patterns of renal involvement in DVI and its effect on morbidity and mortality. **Materials and Methods:** This study was conducted on 170 patients hospitalized with dengue fever in a tertiary care hospital between July 2022 and September 2023. Patients were tested for clinical and laboratory parameters, including urine routine and microscopy, spot urine protein/creatinine ratio, and ultrasonography. Patients with renal involvement were followed up for four and 12 weeks. **Results:** Of 170 patients, 51 (30%) had renal involvement, and 36 (21.17%) had acute kidney injury (AKI). Ten patients developed Kidney Disease Improving Global Outcome Stage 3 AKI, of which seven required kidney replacement therapy, and 27.6% of patients developed urinary abnormalities. Patients with renal involvement had higher mortality (p-value <0.001). Among those who survived, renal abnormalities resolved in all except one who progressed to chronic kidney disease. Three patients showed cast nephropathy in their renal biopsies. **Conclusion:** This study links renal involvement to higher mortality of patients with DVI, underscoring its importance in management and prognostication.

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

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Introduction

Dengue is the most prevalent arthropod-borne viral disease worldwide, with ~400 million annual infections, of which ~100 million (25%) cause clinical illness.[1] Dengue viral infection (DVI) has numerous presentations, including undifferentiated fever, multiple end-organ damage, and life-threatening symptoms. The literature evaluating the epidemiology of renal involvement in dengue fever and its forms is relatively scarce. The mechanisms causing acute kidney injury (AKI) need to be understood.

Studies suggest that the incidence of renal manifestations in dengue is widely variable (0.9% to 69.4%) and AKI is an infrequent complication of dengue, with an incidence of ~014%.[2-4] AKI in dengue has been associated with increased morbidity and mortality.[5] Dengue's association with AKI is primarily observed through retrospective data from various regions. Literature on dengue's association with AKI is primarily retrospective data from scattered areas. Specific prospective data are unavailable; therefore, this study is important. We assessed the renal involvement incidence and its correlation with morbidity and mortality in DVI.

Materials and Methods

We performed this prospective, observational, single-center study in 170 patients >12 years of age admitted to the emergency medical services of the Post Graduate Institute of Medical Education and Research, Chandigarh, between July 2022 and September 2023. Our primary objective was to assess renal involvement incidence in DVI. Secondary objectives included correlating renal involvement in DVI with morbidity and mortality and detecting the proportion of dengue-related AKI patients progressing to CKD. Patients with severe dengue or dengue with warning signs were included.[6] Dengue was defined as per the World Health Organization (WHO) diagnostic criteria.[7] Patients who did not consent; those with underlying CKD (as per clinical judgment), obstructive uropathy, underlying decompensated chronic liver disease, congestive cardiac

failure, and advanced malignancy; and those with a tropical fever, either diagnosed with a specific tropical illness or not satisfying the WHO diagnostic criteria for DVI[7], were excluded from the study. The Institute Ethics Committee approved the study protocol (No: INT/IEC/2022/SPL1743). The study was conducted by the ethical principles in the Declaration of Helsinki, and in accordance with the International Conference on Harmonization's Good Clinical Practice Guidelines. All participants provided written and informed consent.

We obtained the following: (a) clinical history and examination details; (b) investigations and patient management details, including the need for kidney replacement therapy (KRT); (c) urine routine, microscopy, and protein creatinine ratio; (d) follow-up with renal function tests until discharge; (e) biopsy for patients whose renal function did not resolve at four weeks. All patients with AKI or urinary abnormalities were followed up at four and 12 weeks with urine microscopy, protein creatinine ratio, and serum creatinine testing to assess the percentage who progressed to CKD.

AKI[8] and CKD[9] were defined as per Kidney Disease Improving Global Outcome. Hematuria was defined as >3 RBCs/high power field (HPF) on three urine analyses, >100 RBCs/HPF on a single occasion, or gross hematuria.[10] Proteinuria was defined as moderately increased albuminuria (30-300 mg albumin or albumin/g of creatinine, in 24-hour or morning spot urine samples, respectively); severely increased albuminuria: (300-3500 mg albumin or albumin/g of creatinine, in 24-hour or morning spot urine samples, respectively); and nephrotic range (>3500 mg albumin or albumin/g of creatinine, in 24-hour or morning spot urine samples, respectively).[10]

We used SPSS 25.0 (IBM SPSS Inc., Armonk NY, US). Categorical variables were summarized as a proportion or percentage, and quantitative variables were summarized as mean ± 95% confidence intervals or median ± interquartile range according to the normalcy of the data. Differences between qualitative and quantitative variables were compared using the Chi-square and Student-T tests, respectively. Univariate analysis and multivariate analysis were done where applicable. A p-value of <0.05 was considered statistically significant.

Results

As per information from the Central Records Department of the Institute, 230 patients with dengue were admitted to the Emergency Department between July 2022 and September 2023. Due to inclusion criteria, time constraints, loss to follow-up and incomplete data, only 170 patients were recruited [Figure 1]. The median age was 36 years, and 60% were males. Around 80% of the population were previously healthy, and the rest had comorbidities [Table 1]. Equal halves of the study population belonged to urban
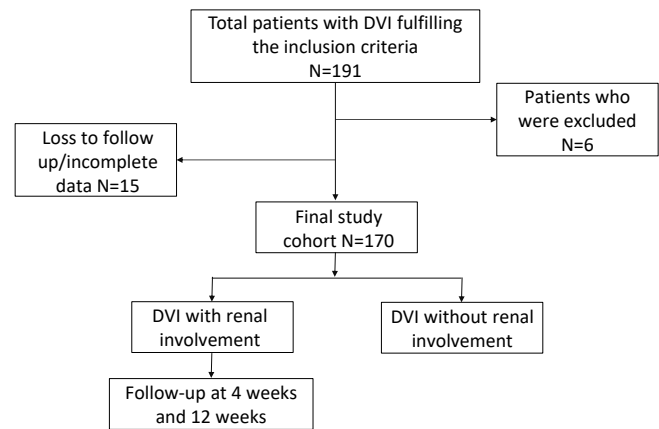

Figure 1: Flow diagram for participants included in the primary analysis. DVI: Dengue viral infection.

and rural residential areas. However, among patients with renal involvement (51), 62.74% (32) and 37.3% (19) belonged to rural and urban areas, respectively. There was a statistical association between rural residence and the incidence of renal involvement in patients with DVI [Table 1]. Fifty-five patients (32.4%) of the cohort had severe dengue, while 115 (67.6%) had dengue with warning signs. In patients with severe dengue, 141 had dengue Fever (DF), 10 had dengue hemorrhagic fever (DHF), and 19 were diagnosed with dengue shock syndrome (DSS), according to the WHO definitions. All patients with DVI had fever, and chills, myalgia, nausea, and vomiting were the most common symptoms (around 50% each). Almost 40% of patients had abdominal pain, and 17.1% presented with altered sensorium, both associated with renal involvement, the latter significantly so (p value-0.001).

Outcome data and main results
Hematuria and oliguria were found in 2.9% and 7.1% of patients, respectively [Table 1]. The details of the investigations and their association with renal involvement have been described in Table 2. A total of 17 expired due to the illness (10%), of which 14 had renal involvement. Thus, univariable analysis established an increased risk of mortality in patients of DVI with renal involvement (p value-0.0001) [Table 2]. Of the study population, 51 patients (30%) had renal involvement in the form of abnormalities, either asymptomatic or with AKI. There were 47 patients with urine microscopic abnormalities. Twenty-one had proteinuria (12.35%), of whom 14 had severely increased, one had nephrotic range and six had moderately increased proteinuria. Twelve of them also had AKI. Thirteen had hematuria (7.6%), seven of whom had AKI. Nine had granular casts (5.29%). Four (2.3%) had pyuria, of which three had AKI. Of the 36 patients who developed AKI, 10 had stage 3, seven of which required KRT, and only two survived. Stage 1 and 2 were seen in 26 patients, of whom five expired.

Table 1: Baseline characteristics of the study participants with and without renal involvement

	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

CAD: Coronary artery disease, CVA: Cerebrovascular accident. The values are presented as mean (95% confidence interval) or numbers (percentage). Bold values indicates that the comparison between the two study groups are statistically significant.

Patients with AKI were followed up at 4 and 12 weeks. Renal function resolved by four weeks in all survivors except one. This one patient had stage 3 AKI with RRT requirement, which eventually progressed to CKD.

Multivariable and subgroup analysis

A multivariable analysis was done on residence, altered sensorium, and lactate levels as univariate analysis found them to be significantly associated factors. Altered sensorium and lactate were found independently associated with renal involvement, making them significant predictors [Table 3].

There were 17 non-survivors and 153 survivors. The survivors and non-survivors were compared across baseline characteristics. Oliguria, altered sensorium, and oxygen requirement were significantly associated with the non-survival (p-value < 0.01). Of the 37 patients on oxygen support, 12 needed mechanical ventilation. Seven patients required hemodialysis, of whom five expired (29.4% in the non-survivor group). Various laboratory findings were associated with mortality was also seen. Thirteen non-survivors (76.5%) and 46 survivors (30.1%) had raised lactate levels. Nine non-survivors (52.9%) and 46 survivors (30.1%) had raised bilirubin. Five non-survivors (29.4%) and nine survivors (5.9%) had raised phosphorous levels. Hence, more non-survivors than survivors had raised phosphorous, lactate, and bilirubin levels.

Fourteen non-survivors had renal involvement in the form of AKI and asymptomatic urinary abnormalities (13 with

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

	Total (n=170)	Dengue with renal involvement (n=51)	Dengue without renal involvement (n=119)	2-tail sig or p-value
Hemoglobin (g/L)	12.2 (11.7-12.6)	11.8 (10.8-12.8)	12.4 (11.8-12.9)	0.25
Total leucocyte count x 10^3 (cells/μL)*	6.9 (4.7-11)	9.6 (6.3-13.5)	6.1 (4.3-9.5)	**0.005**
Platelet count x 10^3 cells/μL*	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)	137 (136-138)	136 (134-138)	137 (136-138)	0.182
Potassium (mEq/L)	4.3 (4.1-4.4)	4.5 (4.2-4.8)	4.2 (4.0-4.3)	0.006
Chloride (mEq/L)	101 (99-104)	103 (101-105)	101 (97-104)	0.272
Calcium (mg/dl)	8.3 (8.1-8.4)	8.0 (7.7-8.4)	8.3 (8.2-8.4)	0.058
Phosphorous (mg/dL)*	3.0 (2.4-3.5)	3.4 (2.4-4)	2.8 (2.4-3.3)	**0.000**
Magnesium (mg/dL)	2.8 (1.2-4.7)	2.2 (2.0-2.3)	3.1 (0.9-5.4)	0.599
Urea (mg/dL)*	25 (17-48)	65 (25-89)	21 (15-32)	**0.00**
Creatinine (mg/dL)*	0.8 (0.6-1)	1.7 (1.0-2.5)	0.7 (0.6-0.9)	**0.00**
Total bilirubin (mg/dL)*	0.7 (0.5-1.6)	1.3 (0.7-2.7)	0.7 (0.4-1.3)	0.117
Total protein (mg/dL)	5.9 (5.7-6.0)	5.7 (5.4-6)	6.0 (5.8-6.1)	0.103
Albumin (mg/dL)	4.5 (1.7-7.3)	2.9 (2.7-3.1)	5.2 (1.1-9.2)	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 (20.2-21.8)	17.7 (16.2-19.3)	22.4 (21.6-23.2)	**0.000**
Lactate*	1.5 (1.0-2.4)	2.0 (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

*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). Bold values indicates that the comparison between the two study groups are statistically significant, NS: Non-structural, IgM: Immunoglobulin M, ECG: Electrocardiography.

Table 3: Multivariable analysis in renal v/s no renal involvement among the study participants

Variable	Renal involvement	No renal involvement	Odd's ratio (95% CIs)	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
Lactate	1.95 (1.2-4.7)	1.4 (1-2)	4.16 (0.03-0.1)	**0.000**

CI: Confidence intervals. Bold values indicates that the comparison between the two study groups are statistically significant.

AKI, and 1 with proteinuria in the absence of AKI), which was significantly higher (p-value 0.0001) than the survivor group, where 37 had renal involvement (23 had AKI and 14 had asymptomatic urinary abnormalities). The association between renal involvement and oxygen requirement (both were significantly associated with mortality on univariate analysis) withstood a multivariate analysis.

Of the three patients that underwent kidney biopsy, the first one (at 4 weeks) revealed hemoglobin cast nephropathy. The patient progressed to CKD at three months with a serum creatinine of 4 mg/dL. The other two patients presented with multi-organ damage, including AKI, for which they needed intermittent hemodialysis. Post-mortem renal biopsy in both cases revealed acute tubular injury with pigment-cast nephropathy [Figure 2]. Creatine phosphokinase (CPK) levels were 1403 IU/mL and 704 IU/mL in patients with acute tubular necrosis (ATN) due to pigment cast nephropathy and they were 498 IU/mL in the patient with hemoglobin cast nephropathy.
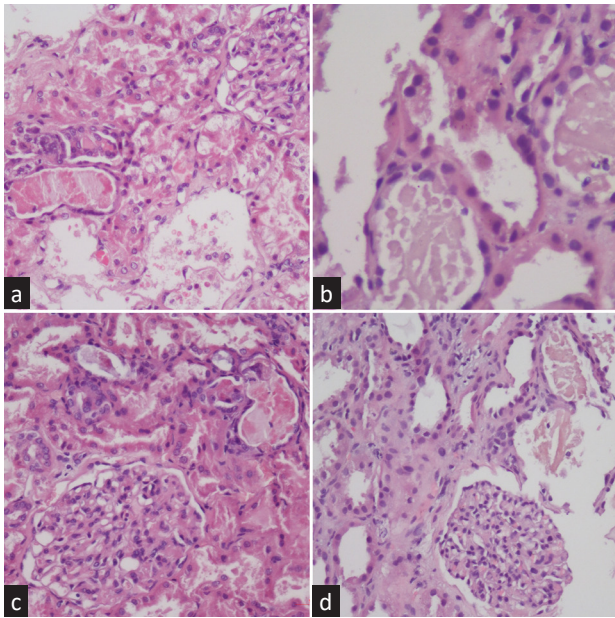
Figure 2: Renal biopsy images depicting (a) granular pigment casts in tubules with acute tubular injury and mild mesangial expansion in the glomerulus (H&E, 100x), (b) granular pigment casts in tubules (H&E, 400x), (c) mild mesangial expansion and pigment casts in tubules (H&E, 200x), (d) red, granular pigment casts in tubules (H&E, 200x). H&E: Hematoxylin and Eosin.

Four patients had very high levels of CPK (Laboratory upper limit: 382 IU/mL), ranging from 4457 IU/mL to 36605 IU/mL. However, renal biopsy was not done in these cases. For those who underwent biopsy, patients with ATN due to pigment cast nephropathy and hemoglobin cast nephropathy had CPK levels of 1403 IU/mL and 704 IU/mL, and 498 IU/mL, respectively.

Discussion

AKI, proteinuria, hematuria, and asymptomatic urinary abnormalities were seen in 30% of patients. AKI was found in 21.17% of patients, and one patient (0.5%) progressed to CKD. Overall mortality was 10%, while mortality in patients with AKI was 36.1%. AKI and mortality were significantly associated according to univariable and multivariable analyses.

Mallhi *et al.* studied 667 cases of dengue irrespective of severity, and found 14.2% cases.[11] Khalil *et al.* studied 532 patients, and of AKI 13.3% of dengue patients developed AKI.[12] Both of these studies included cases of all severities. The proportion of AKI in DVI has been variable, ranging from 3.4% to 20.5%.[13,14] The index study saw a higher proportion of AKI (21.17%) compared to previous studies; possible explanation being the

Table 4: Comparison of AKI, mortality, and risk factors for AKI in severe DVI across various studies in the last ten years

Study, year, location	Study population and size	Incidence of AKI	Risk factors for AKI identified	Mortality AKI v/s Non-AKI
Mehra *et al.*, 2012, Chennai[20]	Age not defined, 223	10.8%	High ALT, ALP, hypoalbuminemia, metabolic acidosis, hypoxia, shock	All-cause mortality 9%
Khalil *et al.*, 2012, Karachi[12]	>14 years, 532	13.3%	Higher age group, Male gender, CNS involvement, respiratory failure, prolonged aPTT	11.3% v/s 0
Mallhi *et al.*, 2015, Malaysia[11]	>12 years, 667	14.2%	Male gender, DHF, rhabdomyolysis, MODS, DM, use of nephrotoxic drugs	1.2% v/s 0
Diptyanusa *et al.*, 2019, Bangkok[17]	>18 years, 1484	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
Patel *et al.*, 2019, Lucknow[21]	>14 years, 620	14.51%	Lower age, male gender, urban residence, diabetes, 6.HTN, IHD, Severe Dengue	15.61% v/s 0
Eswarappa *et al.*, 2019, Bengaluru[13]	>15 years, 2416	3.4%	Lower age, hypotension, MODS, diabetes	13.41% v/s 0.7%
Rajan *et al.*, 2020, Chennai[14]	Children in PICU, 127	20.5%	Hypotension, ventilatory requirement, secondary HLH, higher potassium levels, higher AST and ALT, coagulopathy	11.53% v/s 0.9%
Surasombatpattana *et al.*, 2021, Thailand[22]	>18 years, 120	14%	MODS, NSAID use	12% v/s 1%
Huy and Thuy 2020, Hanoi[18]	>18 years, 2417	2.7%	Male gender, HTN, shock, MODS, myocarditis	12.5% v/s 0.9%
Wang *et al.*, 2023, China[23]	>18 years, 242	35.1%	HTN, nephrotoxic drugs, respiratory distress, Hematuria	22.4% v/s 0
Our study, 2023, Chandigarh	>12 years, 170	21.17%	Rural residence, altered sensorium, edema, metabolic acidosis	7.64% v/s 0.005%

AKI: Acute kidney injury, DVI: Dengue viral infection, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, DHF: Dengue hemorrhagic 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 drug.

Berksonian bias. Delays in referral and inability to manage dengue effectively could increase the chances of developing severe illness.

The proteinuria incidence in patients with DVI ranges from 9.02%, as found by Eswarappa *et al*. (where five patients developed nephrotic range proteinuria),[13] to 45%, as in other studies.[14-16] Hematuria in DVI has been reported more consistently, with incidence ranging from 12.9% to 27%.[14-16] In our study, we found urinary abnormalities in 28% of patients. The incidence of urine abnormalities in DVI has varied across studies; however, an association with dengue cannot be denied.

Hypoxia, respiratory failure, hypoalbuminemia, deranged liver functions, hypotension, altered sensorium, and rhabdomyolysis have been identified as risk factors for renal involvement in DVI[12-14,17-23] [Table 4]. These standard profiles of predictors also point to possible pathophysiologies and complications arising from renal involvement.

A retrospective analysis by Mallhi *et al*. found 1.2% mortality in 667 patients with dengue.[11] Other studies report 11-15% mortality in patients of DVI with AKI[12,13,17,18,22] [Table 4]. Higher mortality (36% in the AKI cohort) in the present study may be attributed to Berksonian bias as our center receives more severe dengue cases and delayed referrals from the primary and secondary centers.

Diptyanusa *et al*., showed that of 0.7% of patients requiring KRTs, most died (9 out of 10).[17] Rajan *et al*. reported a 7% hemodialysis requirement (9 out of 127 patients admitted to PICU). Six recovered and did not need dialysis at follow-up, while three succumbed to their illness.[14] A higher need for hemodialysis was seen in the index study and the study by Rajan *et al*., as more severe cases were included.[14]

The heterogeneity of pathological findings in literature, such as rhabdomyolysis related pigment cast nephropathy and acute tubular necrosis,[24,25] mesangial proliferation, and immune complex deposition,[26] suggest multiple possible mechanisms leading to renal involvement in DVI. Some only postulated, not yet proven through histopathological correlation.

Our study was done at a single-tertiary care center, with a potential for Berksonian bias. Compared to previous retrospective studies, the sample size was smaller. Kidney biopsy was performed in limited patients. Electron microscopy was not done on the kidney biopsy specimens. More histopathological specimens would better elucidate the underlying mechanisms of renal involvement in DVI.

Our study establishes the association of AKI with mortality in patients with DVI in a prospective cohort, underscoring the importance of its evaluation in all patients who present to the emergency department.

Conflicts of interest: There are no conflicts of interest.

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