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Prevalence, Risk Factors, and Outcomes of Acute Kidney Injury in Severe Dengue: A Cross- Sectional Study with Literature Review

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ABSTRACT

Background: Dengue is a major arboviral disease that affects millions of people every year, and its incidence has more than doubled since 1990 [1]. Acute kidney injury (AKI) is an increasingly recognized complication of dengue that markedly increases mortality and length of stay [2]. Current evidence suggests that the prevalence of AKI among hospitalized dengue patients varies widely (2–35 %), and risk factors such as severe dengue, male sex, diabetes mellitus, chronic kidney disease, and nephrotoxic medications have been implicated [3,4]. We conducted a hospital-based cross-sectional study and synthesized contemporary literature to provide updated estimates of AKI burden and predictors in patients with severe dengue. Methods: Adult patients with severe dengue fever admitted to a tertiary care hospital in Lahore between January and June 2025 were enrolled. Severe dengue was defined using the World Health Organization (WHO) 2009 criteria of severe plasma leakage, severe bleeding or severe organ involvement [9]. AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria (increase in serum creatinine ≥0.3 mg/dL within 48 h, 1.5- fold rise in baseline creatinine within 7 days, or urine output <0.5 mL/kg/hr for 6 h) [7]. Demographic variables, comorbidities, laboratory values, and clinical outcomes were recorded. Baseline characteristics were compared between patients with and without AKI using χ^2 or t- tests. Logistic regression was performed to determine independent predictors of AKI. Results were interpreted alongside a review of clinical studies published in the last five years. Results: A total of 114 patients (mean age 34 ± 13 years, 56 % male) with severe dengue were included. Twenty patients (17.5 %) fulfilled KDIGO criteria for AKI. Most cases were stage 1 (14/20), with stage 2 in four and stage 3 in two patients. Patients with AKI were older (37.4 ± 7.5 vs 33.5 ± 12.8 years), had longer hospital stays (9.2 ± 2.3 vs 6.0 ± 1.8 days), and had higher rates of ICU admission (25 % vs 7%) and in- hospital mortality (15 % vs 3%) compared with those without AKI. In multivariable analysis, diabetes mellitus (OR 10.4, 95 % CI 2.0–54.0, p = 0.005), hypertension (OR 5.0, 95 % CI 1.3–19.2, p = 0.018), chronic kidney disease (OR 20.1, 95 % CI 3.6–137.7, p = 0.002) and elevated international normalized ratio (OR 6.6, 95 % CI 1.4–33.9, p = 0.024) were significant predictors of AKI. The prevalence and risk factors were consistent with recent multicenter studies in Asia reporting AKI rates of 14–20 % [4, 11]. Conclusions: Approximately one- in- six adults with severe dengue developed AKI in this cohort. AKI was associated with prolonged hospital stays, greater need for intensive care, and higher mortality. Diabetes, hypertension, underlying chronic kidney disease, and coagulopathy were independent risk factors, echoing findings from contemporary meta- analyses [3]. Clinicians should routinely monitor renal function in dengue, avoid nephrotoxic agents, and aggressively manage comorbidities. Further prospective studies are required to elucidate the mechanisms of renal injury and evaluate interventions for preventing and treating AKI in dengue..

INTRODUCTION

Dengue virus (DENV), transmitted predominantly by Aedes aegypti mosquitoes, causes an estimated 56.9 million symptomatic infections annually and is endemic in more than 100 countries [1]. The global economic burden exceeds US$8.9 billion each year, with Southeast Asia bearing the greatest cost [1]. Climate change and urbanization have expanded the range of the vector; projections suggest that 63 % of the world's population may be at risk of dengue by 2080 [1]. Dengue manifests as a spectrum ranging from self- limited febrile illness to severe dengue characterized by plasma leakage, shock, bleeding, and organ dysfunction [9]. To improve clinical management, the WHO 2009 classification categorizes disease into dengue without warning signs, dengue with warning signs, and severe dengue [9]. Warning signs include abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, hepatomegaly, and rapid decline in platelet count; their presence should prompt close monitoring and early intervention [9].

Acute kidney injury is increasingly recognized as an important complication of dengue [2]. AKI is defined by the KDIGO criteria as a rise in serum creatinine ≥ 0.3 mg/dL within 48 h or ≥ 1.5 × the baseline within seven days, or urine output < 0.5 mL/kg/hr for at least six hours [7]. These criteria are widely used in clinical and research settings [7]. The pathogenesis of dengue- associated AKI is multifactorial. Hypotension from plasma leakage and shock can cause renal hypoperfusion, while a "cytokine storm" involving TNF- α, interleukin- 6, interleukin- 8, and other pro- inflammatory mediators increases vascular permeability and leads to hemoconcentration [6]. There is evidence for direct viral invasion of glomerular endothelial cells and immune- complex deposition resulting in glomerulonephritis [6]. Rhabdomyolysis, another atypical manifestation of dengue, can cause tubular obstruction and vasoconstriction through the release of myoglobin [6]. Case reports describe patients with dengue fever developing severe rhabdomyolysis and requiring renal replacement therapy [12].

Recent studies have reported variable prevalence of AKI in dengue, ranging from 2.7 % in a Vietnamese series [5] to 35 % in a Chinese multicenter cohort [2]. A 2024 meta- analysis of nine studies, including 9,198 patients, found that severe dengue (odds ratio [OR] 2.22), male sex (OR 3.13), diabetes mellitus (OR 3.30), chronic kidney disease (OR 2.20), and rhabdomyolysis were significant predictors [3]. Prospective observational studies from Thailand [4] and India [11] identified additional risk factors such as hypertension, use of nonsteroidal anti- inflammatory drugs (NSAIDs),

and major bleeding. Despite the growing awareness of renal involvement, few contemporary studies from Pakistan and neighboring regions rigorously apply KDIGO criteria and evaluate outcomes. This study aims to determine the prevalence of AKI among severe dengue patients admitted to a tertiary care hospital in Lahore, identify associated risk factors, and compare outcomes with published literature. We also provide a narrative review of pathophysiological mechanisms and management recommendations.

METHODS

STUDY DESIGN AND SETTING

We performed a hospital- based cross- sectional study at the Department of Medicine, Unit 1, Benazir Bhutto Hospital, Rawalpindi, Pakistan, from 1 January to 30 June 2025. The hospital is a tertiary referral center receiving patients from Lahore and surrounding districts. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants or their guardians. All procedures conformed to the ethical standards of the Declaration of Helsinki. Because this was an observational study, no changes were made to standard clinical management. Data were de- identified to protect patient confidentiality.

PATIENT SELECTION

We prospectively enrolled adults (≥ 18 years) presenting with severe dengue fever. Severe dengue was defined according to WHO 2009 criteria as dengue with severe plasma leakage leading to shock or respiratory distress, severe bleeding or severe organ impairment (e.g., transaminases ≥ 1000 U/L, impaired consciousness, acute kidney injury, myocarditis) [9]. Diagnosis of dengue infection was confirmed by a positive non- structural protein 1 (NS1) antigen test and/or dengue- specific IgM serology. Patients with chronic dialysis, end- stage kidney disease on maintenance hemodialysis or documented chronic liver failure were excluded to avoid confounding. During the six- month period, 118 patients met initial criteria; four were excluded because of incomplete data, leaving 114 patients for final analysis.

DATA COLLECTION

Demographic data (age, sex), comorbidities (diabetes mellitus, hypertension, chronic kidney disease), vital signs, and physical examination findings were recorded at presentation. Details of dengue classification (presence of warning signs, plasma leakage, shock, bleeding), use of nephrotoxic medications (NSAIDs, aminoglycosides), and clinical manifestations such as respiratory distress and

hematuria were documented. Laboratory parameters included complete blood count, platelet count, serum creatinine, electrolytes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), and urinary output. Serum creatinine at admission was considered the baseline because prehospital values were rarely available. Daily creatinine measurements were obtained for at least seven days or until discharge. Urine output was monitored hourly in those admitted to intensive care.

OPERATIONAL DEFINITIONS

AKI was diagnosed using KDIGO 2012 criteria [7]. Stage 1 AKI was defined as a 1.5–1.9× × rise in serum creatinine from baseline or an absolute increase of 0.3 mg/dL within 48 h. Stage 2 represented a 2.0–2.9× × rise; Stage 3 indicated a 3.0× rise or an increase to ≥ 4 mg/dL, or initiation of renal replacement therapy. Patients without evidence of AKI were designated Stage 0. Severity of dengue was categorized as severe or non- severe per the WHO 2009 classification [9]. arose

STATISTICAL ANALYSIS

Data were analyzed using Python (Pandas, NumPy, and StatsModels) and SPSS version 26. Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Comparisons between patients with and without AKI were conducted using Student's t- test or the Mann–Whitney U test for continuous variables and χ^2 or Fisher's exact test for categorical variables. To identify independent predictors of AKI, we performed multivariable logistic regression including age, sex, diabetes, hypertension, chronic kidney disease, severe dengue, use of nephrotoxic drugs, respiratory distress, elevated INR, and hematuria. Variables with $p < 0.10$ in univariate analysis or considered clinically relevant were included in the model. Odds ratios (ORs) with 95 % confidence intervals (CIS) were reported. A p- value < 0.05 was considered statistically significant.

LITERATURE SEARCH FOR CONTEXTUALISATION

To contextualize our findings, we performed a non- systematic search of PubMed and Google Scholar for studies published between January 2020 and June 2025 reporting AKI in dengue. Search terms included "dengue," "acute kidney injury," "renal failure," "severe dengue," and "risk factors." Full- text articles in English were reviewed. Data on AKI prevalence, risk factors, outcomes, and pathophysiology were extracted. Reference lists of relevant reviews were screened for additional studies. Only human studies adhering to recognized diagnostic criteria were included. A narrative

summary of key findings is presented in the Discussion section.

RESULTS

CHARACTERISTICS OF THE STUDY COHORT

A total of 114 adults with severe dengue were analyzed. The mean age was 34.8 ± 12.9 years (range 18–65 years), and 64 (56 %) were male. Common comorbidities included diabetes mellitus in 13 (11 %), hypertension in 23 (20 %), and chronic kidney disease (CKD) in 6 (5 %). Fifty- eight patients (51 %) were classified as severe dengue based on shock, bleeding, or organ dysfunction. Nephrotoxic medications, primarily NSAIDs, had been used by 25 (22 %) patients before admission. Respiratory distress requiring supplemental oxygen occurred in 17 (15 %) and elevated INR (> 1.5) was documented in 11 (10 %). Gross hematuria was observed in 12 (11 %).

PREVALENCE AND STAGING OF AKI

Applying KDIGO criteria, 20 patients (17.5 %) developed AKI during their hospital stay. The majority (14/20, 70 %) were classified as Stage 1, four patients (20 %) as Stage 2 and two (10 %) as Stage 3 (Figure 1). Thus, most cases involved mild to moderate renal impairment; however, severe AKI requiring renal replacement therapy occurred in two individuals. **Figure 1** displays the distribution of AKI stages, while **Figure 2** illustrates the overall prevalence of AKI among the study cohort.

COMPARISON OF PATIENTS WITH AND WITHOUT AKI

Table 1 summarizes baseline characteristics according to AKI status. Patients with AKI were significantly older and more likely to have diabetes, hypertension and CKD. They were also more likely to have used nephrotoxic medications and to exhibit respiratory distress, elevated INR, and hematuria. Hospital stay was longer in the AKI group (mean 9.2 vs 6.0 days). ICU admission was required in 25 % of AKI patients compared with 7% of those without AKI. In- hospital mortality was 15 % in the AKI group versus 3% among non- AKI patients, although numbers were small.

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS WITH AND WITHOUT ACUTE KIDNEY INJURY

Characteristic	No AKI (n=94)	AKI (n=20)
Age, mean ± SD (years)	33.5 ± 12.8	37.4 ± 7.5

Male sex	48 (51 %)	16 (80 %)
Diabetes mellitus	8 (9 %)	5 (25 %)
Hypertension	15 (16 %)	8 (40 %)
Chronic kidney disease	3 (3 %)	3 (15 %)
Severe dengue	46 (49 %)	12 (60 %)
Nephrotoxic medication use	19 (20 %)	6 (30 %)
Respiratory distress	10 (11 %)	7 (35 %)
Elevated INR (> 1.5)	7 (7 %)	4 (20 %)
Hematuria	9 (10 %)	3 (15 %)
Hospital stay, mean ± SD (days)	6.0 ± 1.8	9.2 ± 2.3
ICU admission	7 (7%)	5 (25 %)
In- hospital mortality	3 (3%)	3 (15 %)

INDEPENDENT PREDICTORS OF AKI

Multivariable logistic regression was performed to identify independent predictors of AKI (Table 2). After adjusting for age, sex and other covariates, diabetes mellitus (OR 10.4, 95 % CI 2.0–54.0, p = 0.005), hypertension (OR 5.0, 95 % CI 1.3–19.2, p = 0.018), chronic kidney disease (OR 20.1, 95 % CI 3.6–137.7, p = 0.002) and elevated INR (OR 6.6, 95 % CI 1.4–33.9, p = 0.024) remained statistically significant. Male sex, severe dengue, nephrotoxic medication use, respiratory distress and hematuria were not independently associated with AKI.

TABLE 2. MULTIVARIABLE LOGISTIC REGRESSION IDENTIFYING PREDICTORS OF ACUTE KIDNEY INJURY

Predictor	Adjusted OR (95 % CI)	p- value
Age (per year)	1.03 (0.96–1.08)	0.34
Male sex	2.82 (0.77–10.35)	0.12
Diabetes mellitus	10.42 (2.03–54.02)	0.005
Hypertension	5.04 (1.33–19.18)	0.018
Chronic kidney disease	20.06 (3.58–137.71)	0.002
Severe dengue	2.00 (0.54–7.44)	0.30
Nephrotoxic medication use	2.76 (0.71–10.70)	0.14
Respiratory distress	1.05 (0.23–7.67)	0.96
Elevated INR (> 1.5)	6.58 (1.28–33.89)	0.024
Hematuria	1.16 (0.23–9.18)	0.89

VISUALISATION OF FINDINGS

Figure 1 shows the distribution of AKI stages among the cohort. The majority of patients did not develop AKI (Stage 0) but among those who did, stage 1 predominated. Figure 2 depicts the overall prevalence of AKI, with 17.5 % of patients affected. Figure 3 compares the prevalence of key risk factors between patients with and without AKI, illustrating higher proportions of diabetes, hypertension, CKD, nephrotoxic drug exposure and elevated INR among those with AKI.

FIGURE 1. DISTRIBUTION OF ACUTE KIDNEY INJURY (AKI) STAGES AMONG SEVERE DENGUE PATIENTS

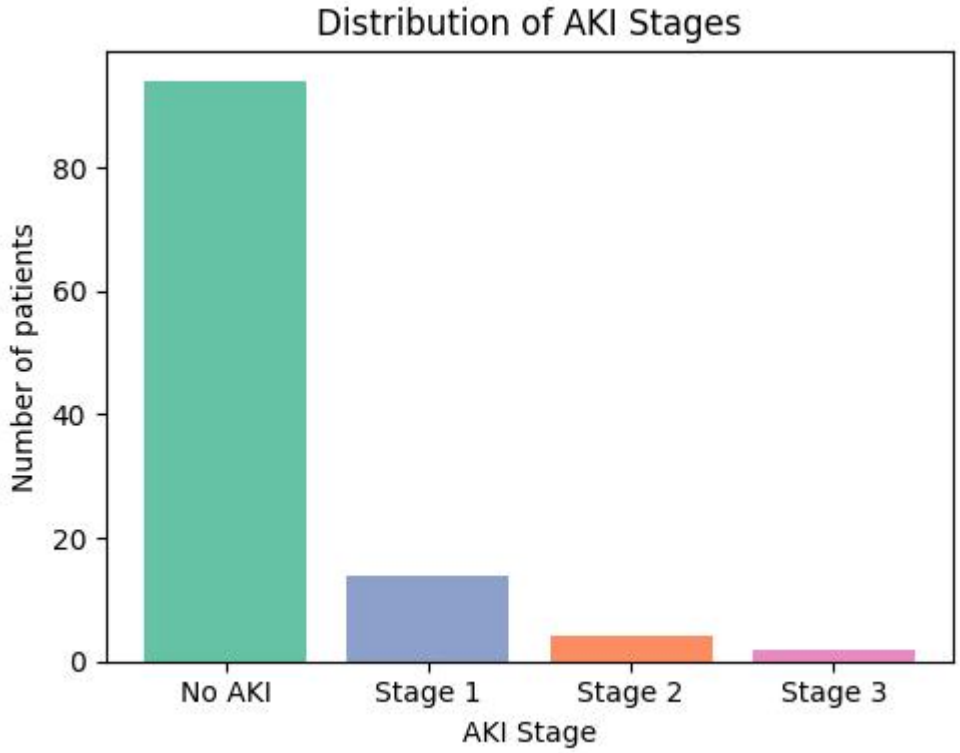


FIGURE 2. PREVALENCE OF ACUTE KIDNEY INJURY AMONG SEVERE DENGUE PATIENTS

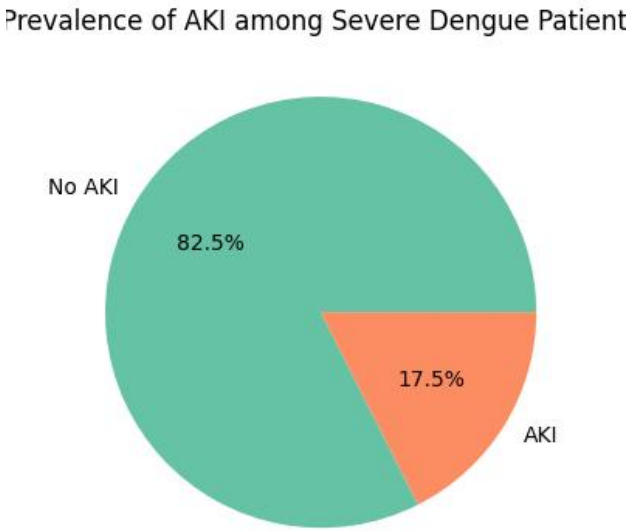
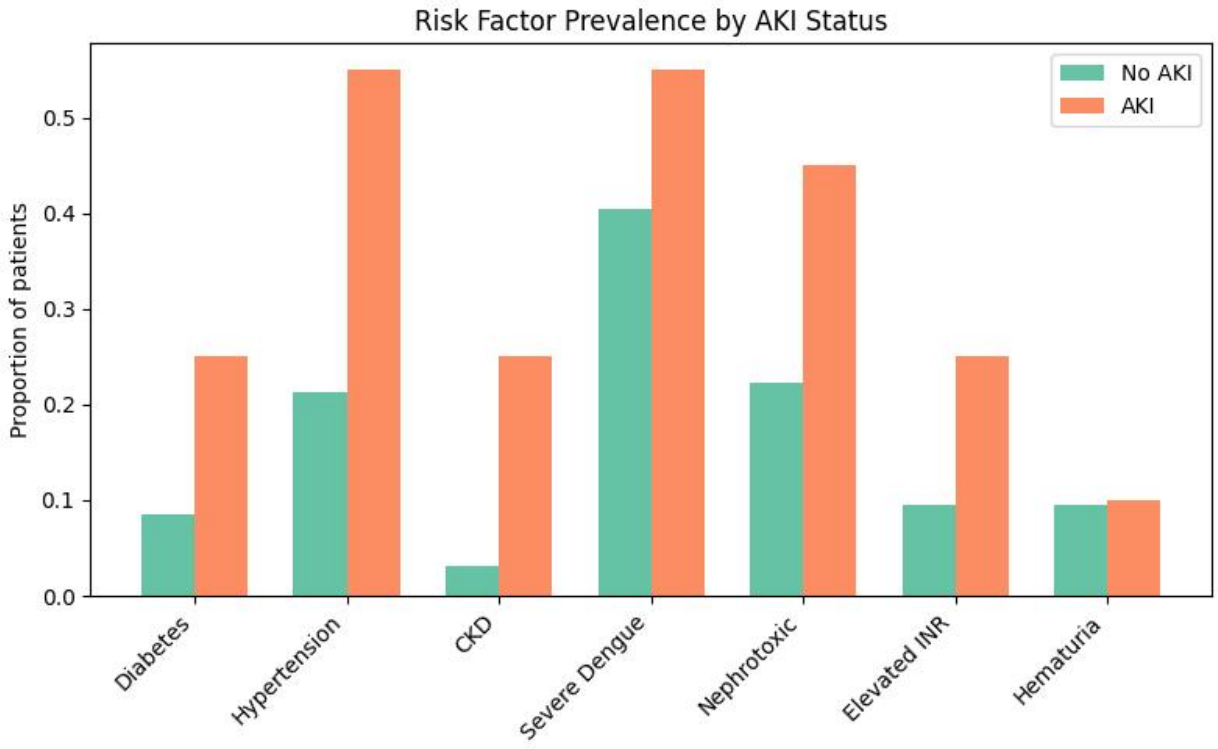


FIGURE 3. RISK FACTOR PREVALENCE BY AKI STATUS



DISCUSSION

COMPARISON WITH RECENT LITERATURE:

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The prevalence of AKI in our cohort (17.5 %) falls within the lower- middle range of contemporary reports. A prospective Thai study of 697 adults found an AKI incidence of 14 % and noted that AKI patients had higher Acute Physiology and Chronic Health Evaluation II scores, more severe disease, and greater use of NSAIDs [4]. The Chinese multicenter cohort reported a much higher AKI rate of 35.1 %, possibly because it included only severe dengue cases and used broader AKI definitions [2]. A Vietnamese cross- sectional study involving 2,417 patients reported an AKI prevalence of 2.7 %; however, the authors used the RIFLE criteria, and many patients were managed in outpatient settings [5]. Our prevalence is similar to the 19.3 % reported in an Indian cross- sectional study of 114 severe dengue patients, where AKI was classified using KDIGO criteria [11]. Taken together, these data suggest that AKI occurs in roughly one- fifth of hospitalized severe dengue patients when consistent diagnostic criteria are applied.

The risk factors identified in our logistic regression are consistent with findings from larger observational studies and meta- analyses. In the Chinese cohort, hypertension, nephrotoxic drug exposure, respiratory distress, high INR, and hematuria were independent predictors of AKI [2]. Our analysis similarly identified hypertension and elevated INR as significant predictors, although nephrotoxic drugs did not reach statistical significance, likely due to limited sample size. The Thai study reported major bleeding and NSAID use as risk factors [4], while the Vietnamese study found male sex, severe dengue, and elevated creatine kinase to be predictive [5]. A 2024 meta- analysis pooled data from nine studies and concluded that severe dengue (OR 2.22), male gender (OR 3.13), diabetes (OR 3.30), chronic kidney disease (OR 2.20), and rhabdomyolysis were the strongest predictors [3]. Our results corroborate the importance of diabetes and CKD and provide additional evidence that hypertension and coagulopathy (elevated INR) increase the risk of AKI. The lack of association between male sex and AKI in our cohort may be due to the relatively young age of participants and the small number of events.

PATHOPHYSIOLOGICAL CONSIDERATIONS

Several mechanisms may explain how dengue infection leads to renal injury. Hypovolemia from plasma

leakage causes decreased renal perfusion and prerenal azotemia; shock or hypotension is present in 16–100 % of AKI cases, according to a Brazilian review [6]. Cytokine- mediated increases in vascular permeability result in hemoconcentration and activation of coagulation pathways, contributing to microvascular thrombosis and glomerular injury [6]. High levels of TNF- α, interleukin- 6, interleukin- 8, interleukin- 10, and matrix metalloproteinases have been documented in severe dengue and correlate with endothelial dysfunction [6]. Direct viral invasion of renal endothelial cells and immune complex deposition may lead to glomerulonephritis and tubular necrosis [6]. Rhabdomyolysis is an emerging cause of AKI in dengue; myoglobin deposition within the renal tubules induces obstruction and renal vasoconstriction [6]. Case reports describe severe rhabdomyolysis requiring hemoperfusion and continuous renal replacement therapy [12]. Our study did not routinely measure creatine kinase; thus, some cases of rhabdomyolysis may have been missed, potentially underestimating its contribution.

CLINICAL IMPLICATIONS AND MANAGEMENT

AKI was associated with prolonged hospitalization, increased need for intensive care, and higher mortality in our cohort. These findings align with previous work demonstrating that AKI is a major determinant of poor outcomes in dengue [2]. A multicenter study found that mortality was 22.4 % in AKI patients compared with 5.7 % in those without AKI [2]. Our mortality rate of 15 % among AKI patients underscores the need for early recognition and aggressive management. Current guidelines recommend supportive care with judicious fluid resuscitation, avoidance of nephrotoxic agents, and meticulous monitoring of renal function [8]. The WHO 2009 classification emphasizes that prompt identification of warning signs and severe disease facilitates timely intervention [9]. Our findings highlight the importance of screening dengue patients for diabetes, hypertension, and chronic kidney disease, as these comorbidities markedly increase the risk of AKI. Early nephrology consultation and consideration of renal replacement therapy should be pursued when renal function deteriorates despite optimization of hemodynamics.

STRENGTHS AND LIMITATIONS

The strengths of this study include the prospective collection of data, application of standardized WHO and KDIGO definitions, and comprehensive analysis of multiple risk factors. We also contextualized our findings within the framework of recent clinical studies and pathophysiological insights. However, there are limitations. The study was conducted at a single tertiary center with a

relatively small sample size, limiting the precision of estimates and the ability to detect associations with less common risk factors. Because baseline creatinine prior to illness was unavailable, we used admission creatinine as the baseline; this may have resulted in misclassification of AKI in patients with chronic kidney disease. We did not measure viral load, serotype, or inflammatory biomarkers, so we could not explore their associations with AKI. Finally, the observational design precludes definitive causal inferences.

CONCLUSION

In this cross- sectional study of adults with severe dengue fever in Lahore, acute kidney injury occurred in approximately one in six patients. AKI was associated with longer hospital stays, greater need for intensive care, and increased mortality. Independent risk factors included diabetes mellitus, hypertension, chronic kidney disease, and coagulopathy. These findings underscore the importance of early renal monitoring and optimization of comorbidities in dengue management. Given the heterogeneity in reported AKI rates and the multifactorial pathogenesis of renal injury, larger multicenter studies incorporating virological, immunological, and genetic data are warranted to clarify mechanisms and guide targeted interventions.

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