Review Article

Predictors and Outcomes of Dengue-Associated Acute Kidney Injury

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Abstract. Dengue viral infections present with a wide clinical spectrum ranging from asymptomatic to severe manifestations with organ involvement. The term “expanded dengue syndrome” has been commonly used to illustrate the unusual or atypical manifestations; acute kidney injury (AKI) is one of the atypical manifestations of this syndrome. The use of heterogeneous criteria to determine the presence of AKI in dengue patients due to the vast diversity in populations led to difficulties in assessing the true incidence of dengue-associated AKI. This review presents a variable, but often high, frequency of dengue-associated AKI among vastly diverse populations with various disease severities. Dengue-associated AKI is not an uncommon complication, and its importance has often been neglected during the management of dengue patients. The risk factors and certain clinical and laboratory findings commonly reported among dengue patients with AKI should be considered to support a timely diagnosis and case management. This review highlights the need for clinicians to be aware of dengue-associated AKI to reduce the morbidity and mortality associated with this common and important tropical disease.

INTRODUCTION

Although dengue infection is one of the most important mosquito-borne diseases in tropical regions, it is challenging to determine its true incidence because the disease presents with a wide clinical spectrum ranging from asymptomatic condition to more severe manifestations.^{1,2} Overlap between clinical presentations has been observed in dengue patients grouped using earlier classification of dengue infection by the WHO: dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).³ The 2009 WHO reclassification of dengue infection into dengue without warning signs, dengue with warning signs, and severe dengue was intended for better recognition of patients presented with atypical manifestations or organ involvement that did not fall into any of the disease group in the 1997 WHO dengue classification.^{3,4} The WHO also included the organ involvement in dengue into another disease group called the expanded dengue syndrome to illustrate these atypical manifestations.¹ Acute kidney injury (AKI) is one of the unusual manifestations of dengue that fits in both severe dengue and in expanded dengue syndrome, which may be underreported or go unrecognized.^{1,5} Therefore, proper clinical assessment is essential for the appropriate management of this condition.

Current data show that AKI is present in 0.9% to 69.4% of dengue patients with variations based on the population studied and the criteria for the diagnosis of AKI adopted.^{6–9} The most widely used laboratory parameters include serum creatinine (SCr) levels, changes in urine output, and glomerular filtration rate.^{10–12} On the basis of these measured values, several classifications, such as the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification, Acute Kidney Injury Network (AKIN) classification, and Kidney Disease Improving Global Outcomes (KDIGO) criteria, have been used to determine the status of AKI.^{13–15} Although an increase in SCr is known to be associated with increased

mortality,¹⁶ the development of AKI in patients with dengue infection remains poorly understood and explored. This review intends to enlighten readers about dengue-associated AKI with emphasis on the variances in the risk factors and disease outcomes in this particular population, hence leading to better recognition of the importance of dengue-associated AKI. The search strategy used in this study is described in Figure 1.

INCIDENCE OF DENGUE-ASSOCIATED AKI

The incidence of dengue-associated AKI varies depending on the population, underlying disease, disease spectrum, and the AKI criteria used in each study. Published data from both prospective and retrospective studies show that the incidence of dengue-associated AKI ranged from 0.9% to 69.4% (Table 1). Two studies conducted in Taiwan and one study conducted in Thailand used elevated SCr levels (up to > 2 mg/dL) as an AKI criterion and reported a incidence of 3.3%, 10.2%, and 0.9%, respectively.^{7,17,18} The differences in the incidence of AKI might be attributed to the different populations examined in the study because the studies conducted in Taiwan included adults and geriatric populations, whereas the study performed in Thailand involved pediatric patients. These results show that similar SCr-level cutoffs for adults should not be used in pediatric patients. Alternatively, the RIFLE criteria used by Kuo et al. and Basu et al. yielded an AKI incidence of 4.0% and 35.7%, respectively.^{6,19} Both studies were conducted in similar disease spectrums. The reason for the large difference in the proportion of patients with AKI is not clear.

AKIN criteria was the most commonly used in studies to determine dengue-associated AKI. Two similar studies conducted in Pakistan²⁰ and Malaysia⁸ reported incidence of AKI as 13.3% and 14.2%, respectively. However, a study by Huang et al. in Taiwan recruited a much larger number of patients from a population in which dengue was not endemic and reported an incidence of 1.4%.²¹ The most updated AKI criteria, the KDIGO criteria, were used to determine the AKI status among dengue patients in several studies, including those conducted by Nair et al. and Diptyanusa et al.^{9,22} The former study included only 85 patients, among whom the incidence of dengue-associated AKI was 69.4%.⁹ The latter

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In generating relevant articles of dengue-associated acute kidney injury for the review, we searched the PubMed database for following strings for each section and other relevant articles were sought using article citations and the PubMed 'Similar articles' feature.

- Dengue-associated acute kidney injury: acute AND (kidney OR renal) AND (injury OR complicat* OR fail* OR involvement) AND dengue [MeSH Terms]
- Prevalence and incidence: (dengue AND (prevalen* OR inciden*) AND (kidney OR renal) AND (injury OR complicat* OR fail* OR involvement))
- Pathophysiology: (dengue AND (kidney OR renal) AND (injury OR complicat* OR fail* OR involvement) AND (diagnosi* OR definition*))
- Clinical manifestations: (dengue AND (kidney OR renal) AND (injury OR complicat* OR fail* OR involvement) AND (physic* OR clinic* OR manifest* OR finding*))
- Laboratory findings: (dengue AND (kidney OR renal) AND (injury OR complicat* OR fail* OR involvement) AND (manifest* OR finding* OR lab* OR laborator* OR test*))
- Risk factors: (dengue AND (kidney OR renal) AND (injury OR complicat* OR fail* OR involvement) AND (risk* OR predict*))
- Outcomes: (dengue AND (kidney OR renal) AND (injury OR complicat* OR fail* OR involvement) AND (outcome* OR mortal* OR fatal* OR death*))

FIGURE 1. Review search strategy.

study included 1,484 participants belonging to a similar age group and yielded an AKI incidence of 4.8%.²² Additionally, Nair et al. did not mention the severity of dengue in their study, which could affect the incidence of AKI.⁹

The use of heterogeneous criteria in determining AKI among dengue patients has resulted in difficulties in determining the true incidence of dengue-associated AKI. Solely using elevated levels of SCr (> 2 mg/dL) to determine AKI might lead to an underestimation of the true incidence of AKI because the progression of AKI itself is rapid with the ever-changing levels of SCr.^{7,17,23} Moreover, this SCr cutoff level is likely to be applied in adult patients. AKI in pediatric dengue patients should be carefully addressed because creatinine levels in children are highly affected by the lesser muscle mass and nutritional status.²⁴ Therefore, the use of pediatric KDIGO or neonatal modified KDIGO criteria in this population is more

appropriate.²⁵ Dengue-associated AKI has been commonly reported to occur during the earlier stages,^{6,8,22,26} and thus more dynamic and sensitive criteria are preferred to allow for a more accurate diagnosis of AKI among dengue patients. Furthermore, dengue-associated AKI patients, the incidence of renal replacement therapy (RRT) varied. In non-intensive care unit (ICU) settings, the proportion of adult dengue patients with AKI requiring RRT ranged from 1.2% to 44.7%.^{6,9,17,19,22,27,28} Meanwhile, the proportion of pediatric AKI patients requiring RRT ranged from 44.0% to 61.5%.^{7,29}

CLINICAL AND LABORATORY MANIFESTATIONS

AKI is a manifestation of dengue that may be underreported and underrecognized; therefore, the clinical and laboratory characteristics must be identified for the early diagnosis and

TABLE 1
Summary of studies on incidence of dengue-associated AKI

Reference	Year	Country	Population age (years)	Study size	Dengue spectrum	AKI criteria used	Incidence (%)
Khan et al. ³⁵	2008	Saudi Arabia	6–94	91	DHF	Not specified	2.2
Kuo et al. ⁶	2008	Taiwan	All ages	519	DF/DHF/DSS	RIFLE	4.0
Lee et al. ¹⁷	2009	Taiwan	> 18	304	DHF/DSS	SCr > 2 mg/dL	3.3
Laoprasopwattana et al. ⁷	2010	Thailand	< 15	2,893	DF/DHF/DSS	SCr > 2 mg/dL	0.9
Basu et al. ¹⁹	2011	India	≥ 18	28	DF/DHF/DSS	RIFLE	35.7
Khalil et al. ²⁰	2012	Pakistan	> 14	532	DF/DHF/DSS	AKIN	13.3
Lee et al. ⁶⁷	2012	Taiwan	> 18	309	DF/DHF/DSS	SCr increase ≥ 0.5 mg/dL	4.5
Mehra et al. ²⁶	2012	India	All ages	223	DF/DHF	AKIN	10.8
Huang et al. ²¹	2015	Taiwan	≥ 18	1,076	DF/DHF/DSS	AKIN	1.4
Mallhi et al. ⁸	2015	Malaysia	≥ 12	667	DF/DHF/DSS	AKIN	14.2
Nair et al. ⁹	2016	India	> 18	85	Not specified	KDIGO	69.4
Huang et al. ¹⁸	2017	Taiwan	≥ 65	627	DF	SCr > 2 mg/dL	10.2
Vakrani et al. ³⁹	2017	India	All ages	101	DF/DHF/DSS	SCr > 1.2 mg/dL	15.8
Basu and Roy ²⁹	2018	India	< 14	97	DF/DHF/DSS	eGFR < 60 mL/min/1.73 m ²	13.4
Lee et al. ⁴⁵	2018	Taiwan	≥ 18	1,068	DF/DHF/DSS	KDIGO	3.8
Mallhi et al. ⁵	2018	Malaysia	≥ 12	526	DF/DHF/DSS	AKIN	13.7
Mehta et al. ²⁸	2018	India	≥ 18	230	Not specified	AKIN	16.5
Diptyanusa et al. ²²	2019	Thailand	≥ 18	1,484	DF/DHF/DSS	KDIGO	4.8
Padyanaet al. ⁶¹	2019	India	All age	96	DHF/DSS	Not specified	35.4
Patel et al. ⁴⁹	2019	India	> 14	620	DF/DHF/DSS	AKIN	16.4

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease Improving Global Outcomes; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; SCr = serum creatinine.

management of this disease. However, the pathophysiology of dengue-associated AKI is complex. The mechanisms of kidney injury involve glomerular or tubular damage, or both, leading to AKI. The alterations in renal tubular function might be due to hemodynamic fluctuation and hypotension,³⁰ direct viral invasion of the kidney,³¹ cytokine production,³² hemolysis, and rhabdomyolysis.³³ Immune complex deposition with glomerular damage was evidenced by the finding of immunoglobulin (Ig)G, IgM, and C3 deposition in the glomeruli of dengue-infected patients.^{31,34} It is also noteworthy that AKI can be more pronounced in dengue patients with underlying diseases, including diabetes mellitus and chronic kidney disease.^{6,8} The pathophysiology of dengue-associated AKI is depicted in Figure 2. As summarized in Table 2, a range of manifestations, such as spontaneous bleeding, hypotension, dyspnea, and hypoalbuminemia, along with the presence of fluid in body cavities, impaired liver function, and abnormal findings in urine sediments have been reported in patients with dengue-associated AKI. Further, because AKI secondary to dengue infection was more commonly observed in severe dengue cases, the aforementioned symptoms may have resulted from severe dengue rather than AKI itself. Bleeding tendencies in severe dengue may be due to the presence of severe thrombocytopenia, along with coagulopathy and vasculopathy.^{7,29,35,36} Details of patients with dengue-associated AKI presenting with pleural effusion or ascites have been reported^{17,21,37} and supported by laboratory findings of hypoalbuminemia.^{21,22} Massive bleeding and plasma leakage into body cavities contribute to the development of hypovolemia and shock-induced AKI.^{22,26,38,39}

Several dengue patients with AKI have been reported to develop dyspnea, and some progress to respiratory distress concurrent with metabolic acidosis.^{18,26,37} Another electrolyte imbalance commonly found in patients with dengue-associated AKI is hyponatremia.^{6,8,29} Hyponatremia in dengue patients commonly caused by plasma leakage results in intravascular volume depletion especially in severe dengue cases.^{40,41} Other factors including low salt intake, diarrhea, vomiting, hypotonic saline therapy, and transient secretion of inappropriate antidiuretic hormone may contribute to develop

TABLE 2
Clinical manifestations and laboratory findings commonly reported in dengue patients with acute kidney injury (AKI) compared with those without AKI

Clinical manifestations	References
Spontaneous bleeding (petechiae, ecchymoses, gastrointestinal bleeding)	7,17,39
Hypotension to shock	22,26,37,39
Dyspnea to respiratory distress	7,18,26,37
Fluid in body cavities (pleural effusion, ascites)	17,21,37
Hypoalbuminemia	21,22,29
Transaminitis	6,8,17,20,22,29,35
Coagulopathy	7,20,22,29,35
Proteinuria (mild to moderate)	6,8,22,29,39
Microscopic hematuria	6,22,29,39
Pyuria	22
Hyponatremia	6,8,29
Oliguria	8
Rhabdomyolysis	8,21

hyponatremia in dengue patients.^{42,43} Studies have also reported abnormal findings in the urine sediments, such as the presence of proteinuria and hematuria in patients with dengue-associated AKI.^{6,29,39} The findings of urine sediment abnormalities concurrent with proteinuria may suggest acute glomerulonephritis; however, this diagnosis should be confirmed by the presence of red blood cell casts in the urine. Glomerular changes and acute glomerulonephritis due to immune complex deposition in dengue patients have been confirmed by histopathological studies.^{31,44} One study reported the presence of pyuria, which is an indication of tubular interstitial nephritis.²² However, none of the studies performed histopathological examinations to confirm these assumptions. Other features observed in patients with dengue-associated AKI, but not commonly reported, are drowsiness and oliguria.^{8,22,45} Because AKI progresses rapidly, a mild increase in SCr alone should warn the clinicians about the presence of AKI, especially in patients with DHF. Some other biomarkers for inflammation in AKI, such as neutrophil gelatinase-associated lipocalin and resistin, have been proposed to play a role in dengue-associated AKI.⁴⁶ These novel

FIGURE 2. Pathophysiology of dengue-associated acute kidney injury.

biomarkers are being studied in different clinical contexts in relation to the classic SCr and urine output.⁴⁷

RISK FACTORS OF DENGUE-ASSOCIATED AKI

Identification of the risk factors or predictors of AKI in dengue patients is essential. We reviewed the literature elaborating the risk factors or predictors of AKI in dengue-infected patients (Table 3). A large retrospective study conducted in pediatric dengue patients in Thailand reported a relatively low AKI incidence of 0.9% using the elevated SCr (> 2 mg/dL) criterion that is frequently used in adult population.⁷ The study identified dengue shock syndrome (odds ratio [OR] 16.9) and obesity (OR 6.3) as the major risk factors in the development of AKI in this population. Another study in 97 pediatric dengue patients conducted in India identified DHF or DSS as an independent risk factor for AKI, and < 5 years of age was associated with the development of AKI. However, details about the statistical methods used to determine the independent risk factor were not provided in these studies. Thus, the results of these two studies should be interpreted with caution.

A retrospective study by Lee et al. reviewed 304 hospitalized adult patients diagnosed with DHF and DSS and reported an AKI incidence of 3.3%.¹⁷ The study indicated that DSS was a strong, independent risk factor for the development of AKI in patients with DHF (OR 220). Mallhi et al. reported an AKI

incidence of 14.2% among 667 dengue patients aged older than 12 years.⁸ Male gender, DHF, rhabdomyolysis, multiple organ dysfunction syndrome (MODS), history of diabetes, late hospitalization, and use of nephrotoxic drugs were identified as the factors independently associated with the development of AKI among dengue patients in this study. An extended publication of the same study that compared the uses of different AKI criteria among dengue patients (AKIN, RIFLE, and conventional criteria) presented with different AKI predictors, with AKIN being the most sensitive of the three.⁴⁸

A retrospective study conducted in Pakistan identified the following variables as predictors for AKI among dengue patients: male gender (OR 4.43), presence of DHF or DSS (OR 2.14), neurological involvement (OR 12.08), and prolonged activated partial thromboplastin time (OR 1.81).²⁰ The study also indicated AKI as a predictor for prolonged hospital stay among dengue patients. A more recent study in Thailand reviewed 1,484 adult dengue inpatients and reported that older age, male gender, diabetes mellitus, obesity, severe dengue, and coexisting bacterial infection were independent associated factors for AKI.²² A study conducted by Patel et al. revealed an AKI incidence of 16.4% among 620 hospitalized dengue patients of all spectrums older than 14 years.⁴⁹ Using multivariate logistic regression models, the study reported male gender (OR 2.9), DHF (OR 7.9), rhabdomyolysis (OR 8.2), MODS (OR 18.2), diabetes mellitus (OR 4.8), delayed hospitalization

TABLE 3
Summary of studies identifying risk factors or predictors of AKI among dengue patients

Reference	Population age (years)	AKI incidence N (%)	Risk factors/predictors	Adjusted OR	P value
Laoprasopwattana et al. ⁷	< 15	25/2,893 (0.9)	DSS	16.9 (4.2–68.5)	< 0.01
Basu and Roy ²⁹	< 14	13/97 (13.4)	Obesity	6.3 (1.4–28.8)	< 0.01
Lee et al. ¹⁷	> 18	10/304 (3.3)	DHF/DSS	–	–
Mehra et al. ²⁶	All ages	24/223 (10.8)	Age < 5 yo	–	–
			DSS	220.0 (19.80–2,443.89)	< 0.001
			Elevated ALT and ALP	–	–
			Hypoalbuminemia		
			Metabolic acidosis		
			Coexisting viral hepatitis		
			Sepsis		
			MODS		
			Inotropic drug use		
Mallhi et al. ⁸	≥ 12	95/667 (14.2)	Male	2.7 (1.25–5.99)	0.012
			DHF	8.0 (3.64–17.59)	< 0.001
			Rhabdomyolysis	7.9 (3.04–20.49)	< 0.001
			MODS	17.9 (9.14–35.12)	< 0.001
			Diabetes mellitus	4.7 (1.12–19.86)	0.034
			Late hospitalization	2.1 (1.06–4.13)	0.033
			Nephrotoxic drug use	2.9 (1.34–6.11)	0.006
Khalil et al. ²⁰	> 14	71/532 (13.3)	Male	4.43 (1.92–10.23)	< 0.001
			DHF/DSS	2.14 (1.06–4.32)	0.03
			Neurological involvement	12.08 (2.82–51.77)	0.001
			Prolonged aPTT	1.81 (1.00–3.26)	0.04
Diptyanusa et al. ²²	≥ 18	71/1,484 (4.8)	Older age	1.30 (1.03–1.64)	0.027
			Male	3.49 (1.75–6.95)	< 0.001
			Diabetes mellitus	2.89 (1.05–7.93)	0.039
			Obesity	1.94 (1.00–3.77)	0.049
			Severe dengue	5.45 (2.47–12.04)	< 0.001
			Coexisting bacterial infection	6.15 (2.57–14.74)	< 0.001
Patel et al. ⁴⁹	> 14	90/620 (16.4)	Male	2.9 (1.28–5.89)	0.015
			DHF	7.9 (3.69–18.60)	< 0.001
			Rhabdomyolysis	8.2 (3.14–21.52)	< 0.001
			MODS	18.2 (9.24–36.24)	< 0.001
			Diabetes mellitus	4.8 (1.15–18.97)	0.051
			Delayed hospitalization	2.2 (1.07–4.23)	0.032
			Nephrotoxic drug use	2.86 (1.36–6.22)	0.005

AKI = acute kidney injury; ALT = alanine aminotransferase; ALP = alkaline phosphatase; aPTT = activated partial thromboplastin time; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; MODS = multiple organ dysfunction syndrome; OR = odds ratio.

(OR 2.2), and nephrotoxic drug use (OR 2.86) as predictors of AKI in these patients.

Most studies have primarily described the severe disease spectrum of dengue as one of the risk factors or predictors of AKI among dengue patients.^{7,8,17,20,22,29,49} Patients with DHF may present with hypoalbuminemia, evidence of plasma leakage, and bleeding tendencies that contribute to the development of hypovolemia leading to DSS and shock-induced AKI.⁵⁰ Males are more likely to be affected by AKI,^{8,20,22,49} possibly because an enhanced inflammatory process is triggered by testosterone, causing intensified renal tubular cell inflammation and fibrosis, which have been evidenced in the animal models.^{51–53} Underlying diabetes mellitus in dengue patients was associated with the development of AKI,^{8,22,49} as persistent hyperglycemia causes interstitial inflammation and renal ischemia–reperfusion injury leading to AKI.^{54,55} Several studies identified impaired liver function to the extent of liver failure, respiratory distress due to metabolic acidosis, neurological involvement, or the presence of more than one organ failure to be associated with the development of AKI.^{8,20,26,49} Nephrotoxic drug use, as evidenced in some studies,^{8,20,49} could potentially act as a risk factor for AKI in dengue patients by triggering alterations in the intraglomerular hemodynamics, initiating inflammation, or inducing tubular cell toxicity.^{56,57} However, drug nephrotoxicity leading to AKI is more likely to occur if it presents along with other risk factors.⁵⁸

As summarized in Table 3, the majority of the included studies used the 1997 WHO classification in disease grouping of dengue patients, which reported either DHF or DSS as risk factors of AKI. This was not suitable because organ involvement was not noted in any of the disease groups in this classification. There was only one study, conducted by Diptyanusa et al., that included severe dengue patients in the statistical model of risk factors.²² Severe dengue has been known to be associated with the development of AKI and other renal disorder, such as glomerulonephritis.²⁰

OUTCOMES AND PROGNOSIS

The recovery of kidney function after dengue-associated AKI is an important determinant of morbidity because lack of recovery can lead to long-term consequences.⁵⁹ Table 4

summarizes mortality rates among inpatients with dengue-associated AKI, which range from 1.2% among the lower-risk groups to as high as 100% in ICU settings. Three studies comprising severe dengue patients admitted to the ICU and presenting with high mortality rates have been conducted.^{37,60,61} One study by Padyana et al. reported 19 deaths out of 34 patients with AKI who were admitted to the ICU (mortality rate 55.9%).⁶¹ The majority of deaths were reported to be observed among females aged 21 to 40 years.⁶¹ Goonasekera et al. included 54 DSS patients of all ages in their study, among which 10 (18.5%) had AKI and 80% of these patients underwent dialysis.³⁷ In this study, all DSS patients with AKI died despite administration of vasopressors and commencement of dialysis. Another study by Hsieh et al. reported an AKI incidence of 54.7% (41/75) among patients with severe dengue; dialysis was performed in 29.3% of patients with AKI.⁶⁰ The mortality rate was 56.1% in their study.

Other studies conducted in non-ICU populations demonstrated varying proportions of use of vasopressors, dialysis, and mortality rates.^{6–9,17,19,20,22,27–29,49} Many of these studies mentioned that several patients experienced persistent hypotension or refractory shock; however, they did not clearly mention the use of vasopressors among dengue patients with AKI. Vasopressors were given to 70% pediatric patients with dengue-associated AKI in one study,²⁹ whereas other studies in older populations reported the use of vasopressors in 7.0% and 12.7% of patients with AKI.^{20,22} The need for vasopressors has been associated with the development of AKI,¹⁵ although in these studies, the development of AKI might have preceded the initiation of the vasopressor therapy.

Most dengue patients who develop AKI have a relatively benign course.⁶² Nevertheless, dengue patients with AKI who require dialysis are possibly subjected to prolonged periods of hospitalization.^{6,20,22} On the contrary, no renal replacement therapy was required for the AKI patients in the studies conducted by Mallhi et al and Khalil et al.^{8,20} Encouragingly, other studies also reported recovery of renal function among survivors within 1 to 3 months of postdischarge,^{5,7} which was defined by the absence of the AKI criteria or the discontinuation of dialysis following AKI.⁶³ However, the impact of dengue-associated AKI on long-term survival and kidney functions requires further investigation.³⁶

TABLE 4

Summary of studies regarding use of vasopressors, initiation of dialysis and mortality rates among ICU and non-ICU patients with dengue-associated AKI

Reference	Population	Dengue spectrum	Age (years)	Study size	AKI N (%)	Use of vasopressors N (%)	Dialysis N (%)	Mortality N (%)
Basu and Roy ²⁹	Inpatients, non-ICU	DF/DHF/DSS	< 14	97	13 (13.4)	9 (70)	8 (61.5)	5 (38.0)
Basuet al. ¹⁹	Inpatients, non-ICU	DF/DHF/DSS	≥ 18	28	10 (35.7)	NS	2 (20.0)	6 (60.0)
Diptyanusa et al. ²²	Inpatients, non-ICU	DF/DHF/DSS	≥ 18	1,484	71 (4.8)	9 (12.7)	10 (14.1)	9 (12.7)
Goonasekera et al. ³⁷	ICU patients	DSS	All ages	54	10 (18.5)	10 (100)	8 (80.0)	10 (100)
Hsieh et al. ⁶⁰	ICU patients	Severe dengue	≥ 18	75	41 (54.7)	NS	12 (29.3)	23 (56.1)
Khalil et al. ²⁰	Inpatients, non-ICU	DF/DHF/DSS	> 14	532	71 (13.3)	5 (7.0)	0 (0)	8 (11.3)
Kuo et al. ⁶	Inpatients, non-ICU	DF/DHF/DSS	All ages	519	21 (4.0)	NS	7 (33.3)	6 (28.6)
Laoprasopwattana et al. ⁷	Inpatients, non-ICU	DF/DHF/DSS	< 15	2,893	25 (0.9)	NS	11 (44.0)	16 (25.0)
Lee et al. ¹⁷	Inpatients, non-ICU	DHF/DSS	> 18	304	10 (3.3)	NS	3 (30.0)	6 (60.0)
Mehta et al. ²⁸	Inpatients, non-ICU	Not specified	≥ 18	230	38 (16.5)	NS	17 (44.7)	9 (23.7)
Mallhi et al. ⁸	Inpatients, non-ICU	DF/DHF/DSS	≥ 12	667	95 (14.2)	NS	0 (0)	8 (8.4)
Nair et al. ⁹	Inpatients, non-ICU	Not specified	> 18	85	59 (69.4)	NS	1 (1.2)	1 (1.2)
Neeraja et al. ²⁷	Inpatients, non-ICU	DF/DHF/DSS	≥ 18	175	18 (10.0)	NS	8 (44.4)	4 (22.2)
Padyana et al. ⁶¹	ICU patients	DHF/DSS	All age	96	34 (35.4)	29 (85.3)	24 (70.6)	19 (55.9)
Patel et al. ⁴⁹	Inpatients, non-ICU	DF/DHF/DSS	> 14	620	90 (16.4)	NS	20 (22.3)	14 (15.6)

AKI = acute kidney injury; ICU = intensive care unit; DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; NS = not specified.

Mortality rates vary greatly depending on the population, underlying disease, and dengue spectrums; severe disease presentations with multiple organ failure will result in higher mortality rates.⁶⁴ Diverse proximate causes of death, including shock, septicemia, massive bleeding requiring blood transfusions, renal complications, MODS, and unsuccessful management of DHF/DSS, have been reported.^{6-9,17,27,29,49,60} It has been demonstrated that AKI is a significant risk factor for mortality,^{19,37,49,60,61} and the mortality rate increases as the AKI stage progresses.^{6,19,28} The high morbidity and mortality reported among patients with dengue-associated AKI make it essential for clinicians to be aware of this complication; hence, appropriate management must be initiated in a timely manner.⁶⁵

Clinicians should consider preventing dengue-associated AKI. We recommend closely monitoring kidney function, especially in high-risk groups, to detect AKI early and implement appropriate management. Adequate fluid replacement in those with hypovolemia and avoidance of nephrotoxic medications are essential for the prevention of AKI in dengue-infected patients.⁶⁶

CONCLUSION

The current review shows a variable, but often high, frequency of dengue-associated AKI among vastly diverse populations and disease severities. Dengue-associated AKI is not an uncommon complication, and the importance of AKI has often been neglected in the management of dengue patients. The risk factors and specific clinical and laboratory findings commonly reported among dengue patients with AKI should be considered for timely diagnosis and management of the cases. The burden of dengue-associated AKI is not limited to patient morbidity; it also influences mortality. This review highlights the need for clinicians to be aware of dengue-associated AKI to reduce the morbidity and mortality associated with this common and important tropical disease.

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