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Prevalence, Characteristics, and Factors Associated with Acute Kidney Injury among Adult Dengue Patients in Vietnam

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Abstract. Acute kidney injury (AKI) is a serious and potentially lethal complication of dengue disease; however, the actual incidence in dengue patients in Vietnam is unknown. This study aimed to determine the prevalence, clinical and laboratory characteristics, and risk factors for AKI in adults with dengue. This is a multicenter, cross-sectional study conducted between January and December 2017 in 2,417 adult patients with dengue. Indicators of demographic, clinical, and laboratory findings were evaluated. The prevalence of dengue disease–associated AKI was 2.7% (64/2,417), and dengue patients with AKI had a higher mortality rate than patients without AKI (12.5% versus 0.6%; $P < 0.01$). Characteristics of AKI were more common in male gender (male: female was 6.1:1), a history of hypertension (7.8% versus 2.3%; $P < 0.02$), the situations of hemoconcentration (hematocrit > 44%; $P < 0.008$), hypovolemic shock (21.9% versus 6.8%; $P < 0.01$), organ failure (42.3% versus 2.3%; $P < 0.01$), or manifestations of myocarditis (20.3% versus 6.6%; $P < 0.01$), hyperbilirubinemia (28.7 ± 7.6 versus 12.0 ± 0.9; $P < 0.01$), elevated enzymes such as alanine aminotransferase (ALT) (407 ± 151 versus 113 ± 6; $P < 0.01$) and aspartate aminotransferase (AST) (891 ± 475 versus 172 ± 11; $P < 0.01$), and prolonged PT Prothrombin Time (s) (13.9 ± 4.6 versus 12.3 ± 1.5; $P < 0.01$). Independent risk factors for AKI by multivariate analysis were male gender (odds ratio [OR]: *43.6*; 95% CI: *2.4–810*), severe dengue classification (OR: *25.7*; 95% CI: 2–*333*), and creatine kinase > 190 U/L (OR: *11.7*; 95% CI: *1.1–122.4*). The study results indicate a need to continue studying the association between AKI and mortality in dengue disease and the need for improved management of AKI with dengue.

INTRODUCTION

The incidence of dengue has been reported worldwide and is increasing rapidly in recent decades. With the geographical spread of dengue illness, clinical manifestations of the disease have also been reported to be more complicated and unpredictable.[1] In addition to shock and severe bleeding that have been reported as the main causes of death from the disease, several unusual manifestations, including neurological, hepatic, and renal, have also been reported in relation to severity and mortality.[2] Acute kidney injury (AKI) is considered infrequent complication of dengue patients; however, that increases the mortality of the disease.[1,3,4] In the Southeast Asian countries where dengue has become a public health problem, there have been some reports about the risk of AKI in patients with dengue. This is also a problem that is recommended for more systematic study and more accurate clinical evaluation for proper management.[2,5]

In Vietnam, dengue has been recognized as endemic localized illness and tends to increase in recent years. The disease is common all year round and at any age. Because of the importance of the disease, since 1997, the Ministry of Health of Vietnam has developed active surveillance programs for dengue fever.[6,7] There have also been many studies on dengue in Vietnam such as virology, epidemiology, clinical features, and treatment solutions to improve mortality.[8–12] However studies on kidney damage in dengue disease are still limited, especially AKI is unclear. Kidney involvement is underrecognized and often only reported when microscopic hematuria, proteinuria, electrolyte imbalance are concerned.[13] Along with the development of tourism in Vietnam and the trend of globalization, the accurate assessment of the status of AKI will help clinicians appropriate treatment and limit the risk of severe and mortality in dengue patients.[2,3,14] The purpose of this study was to determine the prevalence, clinical characteristics, and factors associated with AKI in adults with dengue.

METHODS

Study design. *Multicenter cross-sectional study.* Sample size. We used the following sample calculation formula for a descriptive study:

$$n = \frac{z^2_{1-\alpha/2}\ (1-P)}{P\varepsilon^2},$$

where ε is the relative error, and we choose ε = 18% (15–20%); z 1 − α/2 is the reliability factor, with 95% confidence, z 1 − α/2 = 1.96; and P is the rate of AKI in dengue patients estimated as 5%[14,15] to 14.2%,[16] and a minimum sample size of 2,252 patients was sufficient for this study.

Population. Patients > 18 years, hospitalized for the first 3 days of illness, and diagnosed with dengue were enrolled in this study. The study was conducted in the two largest infectious disease centers in Vietnam (National Hospital of Tropical Diseases [NHTD]) in the north and Hospital for Tropical Diseases [HTD] in south). The study period is from January 1 to December 31, 2017. At each study site, the number of patients was randomly selected proportional to the number of hospitalized patients per month in the year. Study patients were assessed clinically for at least 7–10 days from the date of illness. Laboratory findings, including kidney function tests (serum creatinine [SCr] and urea), were carried out at three times: the acute phase, the critical phase, and the recovery phase (or if the disease gets worse). All patient`s study data were recorded by using a structured case report form.

Case definition, clinical classification, and abnormal manifestations were based on the WHO criteria.[1,2] The suspected

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cases of dengue admitted to hospital were evaluated clinical history and examination compatible, confirmed by positive for the SD Bioline Dengue Duo NS1 or IgM/IgG (Standard Diagnostic, Yongin, Korea) or PCR method to detect dengue virus serotype. The PCR can detect dengue virus serotyping using specific primers and probe for each dengue serotypes from 1 to 4.

To determine the AKI, we compared SCr data on individual patients. Values with lowest SCr at any time in a laboratory test were identified as the baseline values of the patient. Acute kidney injury is also determined based on one of the two following situations: an increase in SCr from 0.3 mg/dL or more within 48 hours or an SCr increase to 1.5 times the baseline in the last 7 days. Stage 1 AKI is defined as an increase in SCr > 26.5 μmol/L or a 1.5–2-fold increase from the baseline. Stage 2 AKI is defined as an increase in SCr of > 2- to 3-fold from the baseline. Stage 3 AKI is defined as an increase in SCr of ≥ 3-fold from baseline or an absolute SCr of > 354 μmol/L.[17,18] The baseline SCr was also estimated using the Modification of Diet in Renal Disease equation by assuming a glomerular filtration rate of 75 mL/minute/1.73 m^2, for patients with only a single SCr result.[19] Patients with chronic kidney disease and patients with incomplete information on demographics, physical examination, and laboratory findings (especially SCr levels) for analysis were excluded from the study.

Patients in the study all agreed to participate in the study and signed a consent form. The study was approved by the Ethics Committee in Biomedical Research at the NHTD.

Statistical analysis. Study patients were divided into two groups: dengue patients with AKI (study group) and those without AKI (control group). All statistical analyses were performed using the SPSS statistical version 17.0. Comparisons between the two groups of patients were performed using Student's *t* test, Fisher's exact test, and the chi-square test, where appropriate. To determine the independent risk factors for development of AKI in dengue patients, independent variables were selected based on univariate analyses and thorough literature reviews. The significant variables in univariate analysis were included in the multivariate logistic regression model for further analysis. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

In total 2,922 dengue patients have been enrolled in the study, including 1,738 (59.5%) patients in the NHTD site and 1,184 (40.5%) patients in the HTD site. Eleven patients with chronic renal disease and 505 patients without the adequate creatinine test to evaluate were excluded. Finally, 2,417 patients were enrolled and eligible for analysis. The clinical classification of study patients was as follows: no warning sign/warning sign/severe dengue were 1,341 (55.5%)/803 (33.2%)/273 (11.3%), respectively. Of a total of 2,417 patients studied, 639 (26.4%) were classified by SCr estimates with only a single SCr result.

Prevalence and clinical and laboratory characteristics of dengue patients with AKI. Of the 2,417 patients studied, 64 patients achieved full diagnostic criteria for AKI. The prevalence of AKI was 2.7%, including 34 (53.1%) patients as stage 1 AKI, 18 (28.1%) as stage 2 AKI, and 12 (18.8%) as stage 3 AKI.

AKI has been observed in different clinical classifications of dengue patients. Out of 64 dengue patients with AKI, 21 among them were diagnosed AKI during the first 3 days of illness. Tables 1 and 2 presents comparative analysis of the characteristics of patients included demographic, clinical and laboratory among dengue patients with and without AKI. We found significant differences in sex ($P < 0.01$), dengue classification (special shock and severe organ failure) ($P < 0.01$), history of hypertension ($P < 0.02$) and myocarditis ($P < 0.01$). Similarly, the mortality rate in patients with dengue group AKI was also statistically higher ($P < 0.01$). However, the study results also showed no difference in age groups, such as those > 60 years old ($P < 0.11$) (Table 1). We also found the development of AKI among dengue patients is significantly associated with higher levels of red blood cells ($P < 0.007$), hemoglobin ($P < 0.002$), hematocrit ($P = 0.008$) serum total bilirubin ($P < 0.01$), enzyme ALT, AST ($P < 0.01$), and prothrombin time ($P < 0.01$), when compared with those patients who did not develop AKI (Table 2).

Predictors of AKI in dengue infection. To determine the factors independently associated with AKI in dengue patients, we developed a series of logistic regression analysis. The independent risk factors for AKI in univariate analysis and multivariate analysis are presented in Table 3. By multiple logistic regression analyses, after adjusting the parameters of demographics, clinical characteristics and laboratory characteristics, the risk for developing AKI in male patients with dengue was 43.6 times (95% confidence interval [CI] 2.4–810) that of female patients, and in severe dengue patients it was 25.7 times (95% CI 2.0–333) that of non-severe dengue patients. The risk of AKI in dengue patients with CK > 190 U/L was also significantly higher with an odds ratio of 11.7 (95% CI 1.1–122.4).

DISCUSSION

To identify AKI in dengue patients, we conducted a cross-sectional study of 2,417 dengue patients at two central hospitals in Vietnam: the NHTD in the north and the HTD in the south. The results showed that the frequency of AKI was 2.7% (64/2,417). The low rate of AKI in dengue patients also explained the reason this problem has not been interested yet in previous studies in Vietnam. This ratio was similar to the results of AKI studies related to dengue[15,20,21] and was expected to range from 2 to 5%.[14] However, some studies also showed that the rate of AKI in dengue patients ranges from 13.3%[22] to 13.7%,[23] even 20.7%.[24] Some studies have suggested using the patients' SCr on admission as the baseline for the determination of AKI. However, in our study results, SCr increased in the first 3 days of illness among 24/64 (37.5%) dengue patients with AKI. In general, the SCr in all study patients improved within 2 weeks, in the recovery phase.[4,21,25] Therefore, we choose the lowest SCr as the patients' baseline SCr. In our opinion, the difference in the prevalence of AKI in dengue patients between studies related to a number of factors, such as the study population (e.g., gender, male and female, and patients with chronic kidney disease),[17] dengue classification (no warning sign/warning sign/severe dengue),[5,15,20] sample size and sample selection, or diagnostic criteria of acute renal failure.[26]

Comparison between two groups of dengue patients with AKI and without AKI, in terms of demographics, although we did not find a difference by age-group, but AKI was more common in men and people with a history of hypertension.

TABLE 1
Demographics and clinical characteristics among dengue patients with and without AKI

Parameter	Non-AKI group, *N* = 2,353	AKI group, *N* = 64	*P*-value
Mean age (range)	33.4 ± 12.7	35.4 ± 16.7	< 0.21*
Age-group (years)			
18–40	1782 (75.7)	46 (71.9)	0.11†
41–60	476 (20.2)	12 (18.8)	
> 60	95 (4.0)	6 (9.4)	
Gender			
Male	*1,115* (*47.4*)	*55* (*85.9*)	*< 0.01*†
Female	*1,238* (*52.6*)	*9* (*14.1*)	
Pregnant women	124 (5.3)	0 (0)	N/A
Underlying disease			
Liver disease	40 (1.7)	2 (3.1)	0.31‡
Renal disease	4 (0.2)	0 (0)	N/A
Pulmonary diseases	8 (0.3)	0 (0)	N/A
Hypertension	*55* (*2.3*)	*5* (*7.8*)	*0.02*†
Diabetes mellitus	40 (1.7)	2 (3.1)	0.3‡
Other disease	88 (3.7)	3 (4.7)	0.73‡
Clinical classification			
No Warning sign	*1,326* (*56.4*)	*15* (*23.4*)	*< 0.01*†
Warning sign	*795* (*33.8*)	*8* (*12.5*)	
Severe dengue	*232* (*9.9*)	*41* (*64.1*)	
Complications and unusual manifestations			
Shock	*159* (*6.8*)	*14* (*21.9*)	< 0.01‡
Severe bleeding	20 (0.8)	0 (0)	N/A
Severe organ impairment	*53* (*2.3*)	*27* (*42.3*)	< 0.01‡
Myocarditis	*156* (*6.6*)	*13* (*20.3*)	*< 0.01*‡
Neurological	12 (0.5)	2 (3.1)	0.051‡
Hepatic	786 (34.4)	20 (33.3)	0.87†
Respiratory	137 (5.8)	7 (10.9)	0.1‡
Death	14 (0.6)	8 (12.5)	< 0.01‡

AKI = acute kidney injury; N/A = not available.
* *T*-test.
† Pearson chi-square.
‡ Fisher's exact test.

Clinically, AKI was more common in dengue patients with hemoconcentration when the hematocrit increased by over 44% and patients with shock or organ failure. Moreover, AKI was also present in patients with manifestations of myocarditis, elevated serum total bilirubin, ALT, AST, prolonged PT time, and the death. According to the classification of the causes of acute renal failure: prerenal, intrinsic renal, and postrenal,[27] it is possible that our patients had prerenal lesions (hemoconcentration, shock, organ failure, and myocarditis) and intrinsic (hypertension and dengue infection). Although there were differences in the indicators studied and our research results, the studies also recognized dengue patients with AKI had the following characteristics: male predominance,[15,20] a history of hypertension,[15,28,29] severe dengue,[15,16,20,22,29] complications of

TABLE 2
Laboratory characteristics among dengue patients with and without AKI

	Non-AKI group		AKI group		
Parameter	*N*	Mean	*N*	Mean	*P*-value
WBC (×10^3/μL)	2,304	3.9 ± 2.5	62	4.1 ± 2.8	0.65*
Neutrophils (%)	2,304	48.3 ± 27.6	62	49.4 ± 13.6	0.75*
Lymphocytes (%)	2,304	35.1 ± 21.1	62	33.2 ± 10.9	0.49*
Red blood cell (×10^6/μL)	2,304	4.9 ± 0.7	62	5.1 ± 0.8	*0.007**
Hemoglobin (g/dL)	2,304	140.2 ± 17.7	62	147.2 ± 19.9	*0.002**
Hematocrit (%)	2,304	0.42 ± 0.05	62	0.44 ± 0.05	*0.008**
Platelet (×103/μL)	2,304	66.1 ± 47.4	62	70.2 ± 46.6	0.5*
Serum albumin (g/L)	416	39.5 ± 5.7	18	37.5 ± 9.9	0.16*
Serum total bilirubin (mg/dL)	217	12.0 ± 0.9	15	28.7 ± 7.6	*< 0.01**
AST (U/L)	2,312	172 ± 11	60	891 ± 475	*< 0.01**
ALT (U/L)	2,288	113 ± 6	60	407 ± 151	*< 0.01**
PT (%)	1,049	100.4 ± 21.5	38	94.4 ± 17.3	0.09*
PT (s)	1,110	12.3 ± 1.5	41	13.9 ± 4.6	*< 0.01**
INR	1,006	2.6 ± 1.3	36	1.6 ± 0.3	0.88*
aPTT (s)	1,078	39.1 ± 8.5	41	39.8 ± 9.2	0.58*
Fibrinogen (s)	1,078	2.4 ± 0.7	39	2.3 ± 0.8	0.22*
Creatine kinase (U/L)	149	170 ± 40	9	489 ± 169	0.06*

AKI = acute kidney injury; aPTT = activated partial thromboplastin time; INR = international normalized ratio; WBC = white blood cells.
* *T*-test.

TABLE 3
Prediction of AKI in adults with dengue

Parameter‡	Univariate analysis			Multivariate analysis	
	Non-AKI group	AKI group	*P*-value	OR (95% CI)	*P*-value
Age > 60 years	95 (4.0)	6 (9.4)	0.042	0.4 (0.0–5720,013)	0.91
Female	*1,238* (*52.6*)	*9* (*14.1*)	*< 0.01*	–	–
Male gender	*1,115* (*47.4*)	*55* (*85.9*)	*< 0.01*	*43.6* (*2.4–810*)	*0.011*
Underlying disease	235 (10.0)	9 (14.1)	*0.29*	–	–
Hypertension	*55* (*2.3*)	*5* (*7.8*)	*0.009*	0.05 (0.0–831,902.9)	0.73
Severe dengue	*232* (*9.9*)	*41* (*64.1*)	*< 0.01*	*25.7* (*2.0–333*)	*0.013*
Shock	*159* (*6.8*)	*14* (*21.9*)	*< 0.01*	–	–
Severe organ impairment	*53* (*2.3*)	*27* (*42.3*)	*< 0.01*	–	–
Unusual manifestations	1,345 (57.2)	33 (51.6)	*0.37*	–	–
Myocarditis	156 (6.6)	13 (20.3)	< 0.01	–	–
Hematocrit > 44%	*606* (*30.7*)	*28* (*50.0*)	*0.003*	–	–
Thrombocytopenia < 50.000	1,025 (44.4)	24 (38.7)	0.36	–	–
Hypoalbuminemia < 35 g/L	*66* (*16.1*)	*7* (*38.9*)	*0.02*	–	–
AST/ALT ≥ 1000 IU/L	*44* (*1.9*)	*8* (*13.3*)	*< 0.01*	*2.4* (*0.1–59.3*)	*0.58*
Serum total bilirubin > 15 (mg/dL)	*41* (*18.9*)	*7* (*46.7*)	*0.015*	–	–
Coagulopathy	660 (28.0)	24 (37.5)	0.10	–	–
PT (s) > 13 seconds	*259* (*23.3*)	*20* (*48.8*)	*< 0.01*	–	–
INR > 2	*14* (*1.4*)	*4* (*11.1*)	*< 0.01*	–	–
Creatine kinase > 190 U/L	*26* (*17.4*)	*5* (*55.6*)	*0.012*	*11.7* (*1.1–122.4*)	*0.04*

AKI = acute kidney injury.

shock, organ failure, myocarditis,[15,16,28] elevated transaminases, hypoalbuminemia, prolonged PT,[15,20] and hyperbilirubinemia.[15] In addition, dengue patients with AKI also had a higher mortality rate than non-AKI patients.[15,28]

Acute kidney injury associated with dengue disease has been recognized by vast literature,[1,2] and documents[3,14]; however, the cause is unknown. These could be explained as complications of severe profound shock or associated with underlying host conditions/diseases,[1,2] and some studies suggested that it was related to acute tubular necrosis,[3] glomerulonephritis,[3,14] or directly due to dengue virus.[2,3]

To identify the independent factors related to the risk of AKI in dengue patients, we have developed a series of univariate and multivariate logistic analysis models. Univariate analysis results have shown that some demographic, clinical, and laboratory indicators were considered as candidates for predicting AKI risk. However, multivariate analysis results indicate that only three indicators have prognostic value, including severe dengue, male gender, and enzyme CK > 190 U/L (see Table 3). Previous studies have also suggested that the prognosis value of AKI in dengue patients should be based on the following indicators: severe dengue[15,20,22] and male gender,[15,16] without a threshold value of CK. Creatine kinase is an enzyme of around 82 kDa, consisting of two polypeptide subunits of around 42 kDa including muscle type (M) and brain type (B). These subunits result in the formation of three tissue-specific isoenzymes: cardiac muscle (CK-MB), skeletal muscle (CK-MM), and brain (CK-BB). Creatine kinase is found in the heart, brain, skeletal muscle, and other tissues. Any condition that causes muscle damage can cause an increase in CK in the blood. Although previous studies did not evaluate the CK value threshold in predicting AKI, rhabdomyolysis was also reported to be associated with AKI in dengue patients.[14–16]

In dengue patients with complications or unusual manifestations, we conducted close monitoring of vital indicators, including electrocardiogram, liver function, and kidney function. In all of our study patients, SCr status improved with infusion therapy and furosemid, with no patient requiring an indication of renal replacement therapy.[21,25] Some research results suggest that in dengue patients with AKI, it may be necessary to use this therapy. In the survivors, their kidney function recovered before discharge. In the AKI group, eight (12.5%) of the patients died from day 5 to 9 of the disease because of deep shock syndrome leading to disseminated intravascular coagulation and severe organ failure.[1]

Some limitations are in this study. First, this is a multicenter and cross-sectional study, so any bias cannot be avoided. Second, the relationship between AKI and primary or secondary infections in dengue patients has not been evaluated in this study. Third, the study was only evaluated in adults with dengue and not evaluated in children. Finally, in the context of an article, we have not been able to analyze the risk of mortality of AKI in dengue patients. To minimize bias in this study, we used a large sample size, presented standard protocols, and trained researchers before conducting the study.

CONCLUSION

The prevalence of AKI in adult patients with dengue in Vietnam was 2.7% (64/2,417), and dengue patients with AKI had a higher mortality rate than patients without AKI. Characteristics of AKI were more common in male gender, a history of hypertension, the situations of hemoconcentration (hematocrit > 44%), hypovolemic shock, organ failure, or manifestations of myocarditis, hyperbilirubinemia, elevated enzymes ALT and AST, and prolonged PT (s). The risk factors for AKI were severe dengue, male gender, and CK > 190 U/L. The study results indicate a need to continue studying the association between AKI and mortality in dengue disease and solutions of AKI management.

Data availability. The data used to support the findings of this study were supplied by the NHTD in the north and the HTD, Ho Chi Minh City, in the south of Vietnam and so cannot be made freely available. Requests for access to these data should be made to the corresponding author. Data are available for researchers who meet the criteria for access to confidential data.

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