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Original Article

In-hospital mortality predictors among hospitalized adults and those with chronic kidney disease with dengue

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Abstract *Background:* Accurately identifying risk factors that predict fatality in dengue is crucial for patient triage and clinical management. Our objective was to identify predictors of death associated with dengue and investigate the clinical characteristics and risk factors among patients with chronic kidney disease (CKD) who died from dengue.
Methods: A multicenter longitudinal observation study conducted from 2008 to 2019.
Results: A total of 1272 patients (113 who died and 1186 who recovered) diagnosed with

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dengue were included. Old age, CKD, and an elevated white blood cell count at hospital presentation were identified as independent predictors of in-hospital mortality among individuals infected with the dengue virus. In a subgroup analysis of 138 patients with CKD infected with dengue virus, 64 (46.3%) patients died, with 46 (33.3%) patients dying within 7 days after symptom onset. Among 64 fatal dengue patients with CKD, 34.4% were in stages 2 and 3 of kidney disease, 51.5% were in stages 4 and 5, and 14.1% had end stage renal disease as per the classification by Kidney Disease Improving Global Outcomes. Multivariate analysis revealed that initial altered consciousness, pulmonary edema, and leukocytosis during hospitalization were independently associated with in-hospital mortality in CKD patients infected with the dengue virus. Leukocytosis during hospitalization and severe hepatitis were independent risk factors for death within 7 days after dengue illness onset in CKD patients.

Conclusions: This study offers valuable insights into predictors linked to fatality in dengue and reinforces the importance of optimizing patient triage to improve the quality of care.

Introduction

Dengue is a mosquito-borne illness that occurs in tropical and subtropical parts of the world. The World Health Organization (WHO) estimated that >3.9 billion people living in tropical and subtropical areas are at risk of dengue infection. Approximately 100—400 million dengue infection cases develop annually.[1,2] The clinical manifestations of dengue vary greatly, ranging from asymptomatic, self-limiting febrile illness, to being life-threatening.[3] The cornerstone of management and prevention of dengue-related mortality is early recognition of severe-form dengue and prompt management. In 2009, the WHO guidelines classified dengue into those with and without warning signs, and severe dengue.[3] These warning signs included abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement >2 cm, and an increase in hematocrit concurrent with a rapid decrease in platelets. Nevertheless, the sensitivity of each warning sign in predicting severe dengue is extremely low, and therefore, has limited clinical value.[4]

Secondary infection by a dengue virus serotype which differs from that responsible for the prior dengue episode increases the risk of developing severe dengue.[5] However, it is difficult for frontline physicians to distinguish primary from secondary dengue infection at the early stage without a serology test, particularly in dengue endemic areas of countries with limited medical resources. Besides secondary infections, pre-existing comorbidity is another predictor of severe dengue.[6,7] Macias et al. revealed the fatality rate of dengue increases with comorbidities independently of age and/or disease severity.[7] Earlier studies found that co-morbidities, such as diabetes mellitus, hypertension, coronary artery disease, and chronic obstructive airway disease/bronchial asthma, were more common among patients with dengue shock syndrome.[8—10] A systematic review of 243 studies described that in addition to diabetes and hypertension, renal insufficiency also was a significant risk factor associated with increased severity and fatal outcomes.[11] Atypical clinical presentations and worsening renal function with poor clinical outcomes were reported in patients with chronic kidney disease (CKD) who suffered from dengue.[12—14] To date, existing studies that examined the influence of CKD on the clinical outcome of dengue have mostly been single-centered and involved only a small number of cases. Elucidating the association between CKD and dengue outcomes can aid frontline physicians to identify the vulnerable subpopulations for intensive monitoring and early intervention. In this study, we comprehensively performed a multicenter longitudinal observation study of adult patients with dengue, and investigated the predictors associated with the clinical outcomes. Further, we examined the clinical course and laboratory features of patients with CKD and infected with the dengue virus, and explored the independent risk factors associated with death. The results of this analysis could provide insight into early prognostic factors associated with dengue mortality and support the optimization of patient triage to improve the quality of care.

Methods

Ethics statement

The Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (document no. 202201241B0) approved this study. Informed consent was not required because of the retrospective design and the data were de-identified prior to analysis.

Study population and data retrieval

The study population comprised 1272 consecutive adult hospitalized patients (aged 20 years or older) with dengue who received treatment at the Kaohsiung Chang Gung Memorial Hospital (2500 beds), Kaohsiung Medical University Hospital (1700 beds), and the National Cheng Kung University Hospital (1342 beds), between 2008 and 2019. These hospitals serve as primary care and tertiary referral centers in Taiwan.

All sera from reported or suspected cases of dengue undergo examination at either the Taiwan Centers for Disease Control (CDC) or a CDC-certified dengue diagnosis laboratory center. The diagnostic methods for dengue include molecular analysis using dengue virus-specific real-time reverse transcriptase-polymerase chain reaction (RT-PCR), serological analysis using captured IgM/IgG enzyme-linked immunosorbent assay, and virus isolation through cell culture. Since 2008, the nonstructural glycoprotein-1 antigen specific to the dengue virus has been employed as one of the diagnostic tools for outbreak surveillance. The dengue serotype was determined using serotype-specific RT-PCR, with the primer sequences for detecting and serotyping the dengue virus described elsewhere.[15]

The dengue virus-specific RT-PCR was conducted using QuantiTect SYBR Green (Qiagen, Hilden, Germany), while dengue virus-specific nonstructural glycoprotein-1 antigens from Bio-Rad Laboratories (France), AsiaGen Corp (Taiwan), or SD BIOLINE (Korea) were used to confirm the diagnosis in plasma samples obtained during the acute phase of the disease. Patients were classified as having laboratory-confirmed dengue if the real-time RT-PCR or nonstructural glycoprotein-1 antigen yielded positive results in the acute phase serum, or if there was a fourfold increase in immunoglobulin G antibody levels between paired specimens.

A standardized form was designed for the collection of clinical data. Clinical variables were obtained from electronic medical records and supplemented by a secondary manual search. The variables collected encompassed demographic characteristics, presence of comorbidities (diabetes, hypertension, ischemic heart disease, and CKD), reported outcomes, symptoms/signs upon arrival, and laboratory test results at the time of hospital presentation and during hospitalization. In addition to the nadir platelet count, the highest value of each available laboratory data during hospitalization was utilized for analysis. The endpoint was in-hospital mortality among all patients with dengue. Information regarding in-hospital mortality and mortality within 7 days after illness onset in patients with CKD was retrieved for further analysis.

Definitions

The international guidelines provided by Kidney Disease Improving Global Outcomes (KDIGO) present the classification of kidney disease, which consists of five stages. Stage 1 is characterized by a normal or increased estimated Glomerular Filtration Rate (eGFR) ($>$90 mL/min/1.73 m^2). Stage 2 involves a mild reduction in eGFR (60—89 mL/min/1.73 m^2). Stage 3 indicates a moderate reduction in eGFR (59-30 mL/min/1.73 m^2). Stage 4 signifies a severe reduction in eGFR (15—29 mL/min/1.73 m^2). Finally, Stage 5 denotes kidney failure (eGFR $<$15 mL/min/1.73 m^2 or dialysis). The definition of CKD includes individuals who fall under KDIGO Stage 2—5 classification.[16]

Diabetes was defined as being on antihyperglycemic medications. Hypertension was defined as being on antihypertensive medications. Ischemic heart disease was defined as a medical history of coronary artery disease diagnosed through coronary angiography or myocardial perfusion scan, or individuals who had undergone coronary artery bypass graft surgery. Pulmonary edema was defined as the abnormal accumulation of extravascular fluid in the lung parenchyma, which can be caused by either cardiogenic or non-cardiogenic factors. Altered consciousness refers to various changes in cognitive function, such as confusion, disorientation, decreased alertness, or loss of consciousness. Leukocytosis was defined as a peripheral white blood cell count equal to or exceeding 12.0×10^9 cells/L. Severe hepatitis was defined as the presence of markedly elevated liver enzymes, specifically alanine aminotransferase levels equal to or greater than 1000 U/L.

Statistical analysis

A comparison was conducted between (1) survivors and non-survivors and (2) patients with fatal CKD and non-fatal CKD infected by the dengue virus. Fisher's exact test was used for categorical variables, while the Mann—Whitney U test was used for continuous variables. A significance level of $P < 0.05$ was employed to determine statistical significance. Variables found to be significant with a P value < 0.05 in the univariate analyses were included in the multivariate logistic regression model with stepwise selection to identify independent factors associated with death. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 17.0; SPSS Inc., Chicago, IL).

Results

Characteristics between survivors and non-survivors (Table 1)

The 1272 patients with dengue included 86 patients who had died and 1186 patients who had survived. As shown in Table 1, the median age of the deceased patients was 73.9 years (interquartile range 62.0—77.0 years), which was significantly older than survived patients (53.5 years, interquartile range 37—64 years). Type 2 diabetes mellitus, hypertension, ischemic heart disease, and CKD were significantly more frequent among the deceased patients (45.3%, 62.8%, 17.4%, and 74.4%, respectively) than those who survived (16.6%, 26.2%, 13%, and 6.2%, respectively). Fever, bone pain, rash, headache, petechiae, and vomiting were significantly less common in the deceased patients (77.9%, 20.9%, 5.8%, 20.9%, 10.5%, and 16.3%, respectively) than in those who survived (92.3%, 39.1%, 33.6%, 37.9%, 21%, and 27%, respectively). Gastrointestinal bleeding was significantly more common in the deceased patients (52.3%) than that in survived patients (10.9%). The deceased patients had significantly lower concentrations of hemoglobin and platelet at the time of hospital presentation than those who survived. Moreover, the deceased patients exhibited a significantly higher white blood cell count and serum creatinine at the time of hospital presentation. A significantly elevated white blood cell count, alanine aminotransferase and aspartate aminotransferase levels, and lower platelet count during hospitalization were found in the deceased patients. Results of the multivariate analysis

Table 1 Patient characteristics.

Variable	Overall (n = 1272)	Non-survivor (n = 86)	Survivor (n = 1186)	P[a]	Adjusted odds ratio	95% Confidence interval	P[b]
Demographic							
Median age (IQR), years	54.5 (38–66)	73.9 (62.7–78)	53.5 (37–64)	<0.001	1.049	1.016–1.082	0.003
Male	618 (48.6)	44 (51.2)	574 (48.4)	0.656			
Type 2 diabetes mellitus	236 (18.6)	39 (45.3)	197 (16.6)	<0.001			
Hypertension	365 (28.7)	54 (62.8)	311 (26.2)	<0.001			
Ischemic heart disease	51 (4)	15 (17.4)	36 (3)	<0.001			
Chronic kidney disease	138 (10.8)	64 (74.4)	74 (6.2)	<0.001	3.907	1.785–8.552	0.001
Dengue virus serotype				0.003			
Serotype 1	18 (6.8)	3 (3.5)	15 (1.3)				
Serotype 2	854 (67.1)	82 (95.3)	772 (65.1)				
Serotype 3	94 (7.4)	1 (1.2)	93 (7.8)				
Serotype 4	1 (0.1)	0	1 (0.1)	–			
Un-typing	305 (24)	0	305 (25.7)	–			
Median time from illness onset to presentation (IQR), day	3 (2–5)	2 (1–3)	3 (2–5)	<0.001			
Symptoms and signs observed at the time of presentation							
Fever	1162 (91.4)	67 (77.9)	1095 (92.3)	<0.001			
Myalgia	418 (32.9)	21 (24.4)	397 (33.5)	0.096			
Bone pain	489 (38.4)	18 (20.9)	471 (39.1)	0.001			
Rash	404 (31.8)	5 (5.8)	399 (33.6)	<0.001			
Headache	468 (36.8)	18 (20.9)	450 (37.9)	0.002			
Petechiae	258 (20.3)	9 (10.5)	249 (21)	0.018			
Abdomen pain	249 (19.6)	16 (18.6)	233 (19.6)	0.889			
Vomiting	334 (26.3)	14 (16.3)	320 (27)	0.031			
Gum bleeding	97 (7.6)	3 (3.5)	94 (7.9)	0.202			
Gastrointestinal bleeding	174 (13.7)	45 (52.3)	129 (10.9)	<0.001			
Laboratory data obtained at the time of hospital presentation							
Median WBC (IQR), $\times 10^9$ cells/L	4 (2.8–5.9)	7.3 (4.8–10.3)	3.9 (2.7–5.6)	<0.001	1.061	1.001–1.124	0.047
Median hemoglobin (IQR), g/dL	13.4 (12.2–14.7)	12.8 (10.7–14.27)	13.4 (12.2–14.7)	<0.001			
Median platelet count (IQR), $\times 10^9$ cells/L	97 (44–137) (n = 1237)	80 (12–148) (n = 85)	98 (46–137) (n = 1152)	0.017			
Median creatinine (IQR), mg/dl	0.7 (0.6–0.9) (n = 790)	2.4 (1.9–4.6)	0.7 (0.6–0.8) (n = 707)	<0.001			

(*continued on next page*)

Table 1 (*continued*)

Variable	Overall (n = 1272)	Non-survivor (n = 86)	Survivor (n = 1186)	P[a]	Adjusted odds ratio	95% Confidence interval	P[b]
Laboratory data collected during the hospitalization[c]							
Median WBC (IQR), × 109 cells/L	4.7 (2.811.6) (n = 716)	13.9 (10.7–20) (n = 82)	4.2 (2.7–9.3) (n = 634)	<0.001			
Median platelet count (IQR), × 10^9 cells/L	47 (16–99)	13 (9–37)	52 (18–101)	<0.001			
Median AST (IQR), IU/L (reference <40 U/L)	109 (60–216) (n = 587)	2206 (119–8201) (n = 73)	99.5 (56–167.2) (n = 514)	<0.001			
Median ALT (IQR), IU/L (reference <40 U/L)	79 (43–167) (n = 595)	945.5 (97.2–2381) (n = 70)	73 (41–134) (n = 525)	<0.001			

[a] Univariate analyses.
[b] Multivariable analyses.
[c] The nadir platelet count and the highest value of each available laboratory data were retrieved for analysis.
Data are no (%) unless otherwise indicated. Interquartile range, IQR; white blood cell, WBC.

demonstrated that old age (adjusted odds ratio [aOR]: 1.049; 95% confidence interval [CI]: 1.016–1.082), CKD (aOR: 3.907; 95% CI: 1.785–8.552), and elevated white blood cell count at presentation (aOR: 1.061; 95%: 1.001–1.124), were the independent risk factors for in-hospital mortality in patients with dengue (Table 1).

Characteristics of CKD patients with dengue

Table 2 shows the characteristics of the 138 dengue patients with CKD. A total of 64 (46.3%) patients died of dengue. Moreover, 46 (33.3%) of these patients died ≤7 days after the onset of the infection. Of the 64 fatal dengue patients with CKD, the median age was 74 years (interquartile range 64.5–79.5 years), 71.9% had hypertension, and 50% had type 2 diabetes mellitus. The CKD stage of these 64 fatal patients was as follows. A total of 22 (34.4%) were stages 2 and 3, 33 (51.5%) were stages 4 and 5, and 9 (4.1%) were end stage renal disease on dialysis. The 3 most common signs and symptoms were fever (76.6%), myalgia (26.6%), and altered consciousness (23.4%). Among the 64 fatal dengue patients with CKD, 36% (56.3%) had gastrointestinal bleeding, 26 (40.6%) had severe hepatitis, 16 (25%) had pneumonia, 8 (12.5%) had pulmonary edema, and 6 (9.4%) had bacteremia. The median time from symptom onset to death was 6 days (interquartile range 3–9.3 days).

Of the 46 CKD patients who died within 7 days after the onset of dengue illness, the median age was 75.4 years. The median duration of hospital stay was 3 days (interquartile range, 2–5 days). Among them, 24 (52.2%) had stage 4–5 CKD, and 7 (15.2%) had end-stage renal disease. Out of the 46 CKD patients, 17 (37%) died within 3 days after the onset of symptoms. The main signs and symptoms observed upon arrival in these 46 CKD patients were fever (76%), myalgia (26.1%), abdominal pain, and vomiting (each 21.7%). Altered consciousness was observed in 6 (13%) patients upon arrival. Five (10.8%) patients presented with constitutional symptoms (fever in 5 patients and diarrhea in 2 patients) at the time of hospital presentation but rapidly progressed within 5 days after hospitalization.

Of the 74 (53.6%) non-fatal dengue patients with CKD, the median age was 73.5 years (interquartile range 66–78.3 years), 85.1% had hypertension, and 50% had type 2 diabetes mellitus. Among them, 35 (47.3%) patients with CKD were in stages 2 and 3, 25 (33.7%) in CKD stages 4 and 5, and 14 (18.9%) had end stage renal disease requiring dialysis. The most common symptoms were fever (75.7%), myalgia (18.9%), and abdominal pain (17.6%). The leading dengue-associated complications were gastrointestinal bleeding (39.2%), pneumonia (18.9%), bacteremia (6.8%), and severe hepatitis (5.4%).

Comparison between fatal (n = 64) and non-fatal (n = 74) patients with CKD infected by the dengue virus (Tables 2 and 3)

For patients with CKD, the median length from the onset of illness to hospital presentation was significantly shorter among those with fatal than those who survived. Fatal patients with CKD had a significantly higher frequency of altered consciousness than those who survived.

Table 2 Characteristics of the 138 patients with CKD infected by the dengue virus.

Variable	Fatal CKD cases		Non-fatal CKD cases (n = 74)	P[a]	P[b]
	Total (n = 64)	Died ≤7 days (n = 46)			
Demographic and outcomes					
Median age (IQR), years	74 (64.5–79.5)	75.4 (68.7–81.5)	73.5 (66–78.3)	0.671	0.211
Male	36 (56.3)	22 (47.8)	51 (68.9)	0.157	0.034
Type 2 diabetes mellitus	32 (50)	25 (54.3)	37 (50)	>0.99	0.709
Hypertension	46 (71.9)	35 (76.1)	63 (85.1)	0.063	0.233
Ischemic heart disease	10 (15.6)	7 (15.2)	16 (21.6)	0.392	0.478
Chronic kidney disease staging					
Stage 2–3	22 (34.4)	15 (32.6)	35 (47.3)	Ref	Ref
Stage 4–5	33 (51.5)	24 (52.2)	25 (33.7)	0.063	0.057
End stage renal disease on dialysis	9 (14.1)	7 (15.2)	14 (18.9)	0.498	0.805
Multi-comorbidities ≧2	51 (79.6)	40 (86.9)	66 (89.1)	0.155	0.774
Dengue virus serotype					
Serotype 1	3 (4.7)	1 (2.2)	2 (2.7)	–	–
Serotype 2	60 (93.8)	45 (97.8)	70 (94.6)	>0.99	0.648
Serotype 3	1 (1.6)	0	2 (2.7)	–	–
Serotype 4	0	0	0	–	–
Median time from illness onset to presentation (IQR), day	2 (1–3)	1 (1–3)	3 (2–5)	0.007	<0.001
Median time from illness onset to death (IQR), day	6 (3–9.3)	4.5 (3–6)	–	–	–
Symptoms and signs observed at the time of presentation					
Fever	49 (76.6)	35 (76.1)	56 (75.7)	>0.99	>0.99
Myalgia	17 (26.6)	12 (26.1)	14 (18.9)	0.312	0.371
Bone pain	12 (18.8)	6 (13)	10 (13.5)	0.486	>0.99
Rash	4 (6.3)	2 (4.3)	11 (14.9)	0.169	0.128
Headache	12 (18.8)	9 (19.6)	6 (8.1)	0.078	0.089
Petechiae	8 (12.5)	4 (8.7)	8 (10.8)	0.795	0.766
Abdomen pain	14 (21.9)	10 (21.7)	13 (17.6)	0.668	0.636
Vomiting	12 (18.8)	10 (21.7)	10 (13.5)	0.486	0.314
Gum bleeding	3 (4.7)	1 (2.2)	3 (4.1)	>0.99	>0.99
Altered consciousness	15 (23.4)	6 (13)	3 (4.1)	0.001	0.084
Laboratory data obtained at the time of hospital presentation					
Median WBC (IQR), $\times 10^9$ cells/L	7.9 (5.3–10.9)	8.1 (6–11)	6 (4.5–8.5)	0.008	0.002
Median hemoglobin (IQR), g/dL	12.9 (10.7–14.4)	12.8 (11–14.5)	12 (9.9–13.7)	0.057	0.053
Median hematocrit (IQR), %	38.1 (32.3–43.5)	38.3 (34.3–43.5)	34.7 (30.5–40.3)	0.081	0.027
Median platelet count (IQR), $\times 10^9$ cells/L	51 (12–137.7)	75.5 (12–152.5)	52 (17–122.5)	0.430	0.972
Median AST (IQR), IU/L (reference <40 U/L)	346 (59–6457) (n = 55)	699 (68.2–7373) (n = 40)	151 (63–303) (n = 63)	0.028	0.004
Median ALT (IQR), IU/L (reference <40 U/L)	160 (39–1346) (n = 55)	318 (47.5–1587.2) (n = 42)	82 (34–146.5) (n = 65)	0.013	0.003
Median creatinine (IQR), mg/dL	2.2 (0.9–4.6)	2.4 (1.6–4.6)	2.5 (1.9–3.2)	0.818	0.862
Laboratory data collected during the hospitalization[c]					
Median WBC (IQR), $\times 10^9$ cells/L	15.4 (12.7–21.5) (n = 61)	15.5 (12.7–21.5) (n = 45)	11.7 (10.1–15) (n = 62)	<0.001	<0.001
Leukocytosis, n/N (%) (WBC≧12.0 $\times 10^9$ cells/L)	53/61 (86.8)	38/45 (84.4)	26/62 (41.9)	<0.001	<0.001
Median hematocrit (IQR), g/dL	40.1 (35.5–44.3)	40.1 (36.2–44.7)	37.6 (31.8–42.2)	0.085	0.053
Median platelet count (IQR), $\times 10^9$ cells/L	12 (9–19.5)	12 (9–17.7)	15 (10–37.5)	0.047	0.076
Median AST (IQR), U/L (reference <40 U/L)	3718 (265–10890) (n = 59)	5425 (682–11520) (n = 43)	125 (57–294) (n = 61)	<0.001	<0.001
Median ALT (IQR), U/L (reference <40 U/L)	1337.5 (307–2630.7) (n = 56)	1408 (359.2–3106.5) (n = 44)	95 (38–181) (n = 61)	<0.001	<0.001
Median creatinine (IQR), mg/dL	3.5 (2.2–5.8)	3.4 (2.2–5.1)	2.4 (2–3.2)	0.003	0.012

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Table 2 (*continued*)

Variable	Fatal CKD cases		Non-fatal CKD cases (n = 74)	P[a]	P[b]
	Total (n = 64)	Died ≤7 days (n = 46)			
Complications					
Gastrointestinal bleeding	36 (56.3)	23 (50)	29 (39.2)	0.060	0.262
Severe hepatitis (ALT ≥1000 U/L)	26 (40.6)	22 (47.8)	4 (5.4)	<0.001	<0.001
Pneumonia	16 (25)	10 (21.7)	14 (18.9)	0.414	0.815
Bacteremia	6 (9.4)	2 (4.3)	5 (6.8)	0.754	0.706
Pulmonary edema	8 (12.5)	3 (6.5)	1 (1.4)	0.012	0.157

[a] Comparison between total fatal CKD patients and non-fatal CKD patients.
[b] Comparison between CKD patients who died ≤7 days after illness onset and non-fatal CKD patients.
[c] The nadir platelet count and the highest value of each available laboratory data were retrieved for analysis.
Data are number (%) unless otherwise indicated. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; IQR, Interquartile range; WBC, white blood cell.

Significantly elevated white blood cell count, alanine aminotransferase and aspartate aminotransferase levels in the laboratory tests performed at presentation were observed in fatal patients with CKD than in those who survived (Table 2). Moreover, fatal CKD patients exhibited significantly elevated white blood cell count, alanine aminotransferase, aspartate aminotransferase, and creatinine levels, as well as a lower platelet count, along with the presence of leukocytosis, in comparison to nonfatal CKD patients during their hospitalization (Table 2). Although elevated serum creatinine levels were observed in 64 fatal CKD patients after hospitalization, there was no significant difference observed in the change of serum creatinine levels between the time of hospital presentation (median creatinine 2.2 mg/dL) and during hospitalization (median creatinine 3.5 mg/dL) (P = 0.082). Additionally, fatal patients with CKD had significantly higher frequencies of severe hepatitis and pulmonary edema than non-fatal patients with CKD (Table 2). Results from the multivariate analysis revealed that altered consciousness at presentation (aOR: 23.008; 95% CI 2.226–237.843), pulmonary edema (aOR: 13.525; 95% CI: 1.348–135.663), and leukocytosis during hospitalization (aOR: 1.131; 95% CI: 1.023–1.250) were independently correlated to in-hospital mortality in patient with CKD who were infected by the dengue virus (Table 3).

Comparison between CKD dengue patients who died ≤7 days after illness onset (n = 46) and non-fatal (n = 74) CKD dengue patients (Tables 2 and 4)

A significantly shorter time from illness onset to hospitalization was noted in patients with CKD who died ≤7 days after symptom onset, compared with non-fatal patients with CKD. The female sex predominated among patients with CKD who died ≤7 days after illness onset than in non-fatal patients with CKD. Compared to the non-fatal patients with CKD, those with CKD who died ≤7 days after dengue illness onset had a significantly elevated white blood cell count, hematocrit, as well as alanine aminotransferase and aspartate aminotransferase levels at presentation (Table 2). During hospitalization, an association was observed between elevated white blood cell count, alanine aminotransferase, aspartate aminotransferase, and creatinine levels, as well as the presence of leukocytosis and severe hepatitis, with an increased mortality rate within 7 days after the onset of dengue symptoms (Table 2). Results from the multivariate analysis showed that leukocytosis during hospitalization (aOR: 1.117; 95% CI: 1.002–1.246) and severe hepatitis (aOR: 6.281; 95% CI: 1.348–29.265) were independent risk factors of death ≤7 days after the onset of dengue in patients with CKD (Table 4).

Discussion

Dengue has become a major global public health concern and poses a large financial burden on the world, particularly in developing countries.[1,2] In this study, we identified that old age, CKD, and elevated white blood cell count at presentation were mortality risk factors for acutely ill adult patients with dengue admitted to the hospital. This study

Table 3 Multivariate analysis between fatal and non-fatal patients with CKD infected by the dengue virus.

	Fatal patients with CKD (n = 64) versus non-fatal patients with CKD (n = 74)		
	aOR	95% CI	P
Altered consciousness upon arrival	23.008	2.226–237.843	0.009
Pulmonary edema	13.525	1.348–135.663	0.027
Leukocytosis (WBC≧12.0 × 10^9 cells/L) during hospitalization	1.131	1.023–1.250	0.016

aOR, adjusted odd ratio; CKD, chronic kidney disease; CI, confidence interval.

also confirmed that pre-existing CKD exacerbated the course of acute dengue virus infection, resulting in higher fatality risk. These results highlighted the role of host factors, prominently, advanced age and pre-existing CKD, the most important predictors associated with poor clinical outcomes at the time of admission for dengue illness.

Consistent with other series, our analysis demonstrated that older patients have the highest risk of death from dengue. Advanced age has been previously reported to be a high mortality risk in dengue.[17,18] Age-related functional decline in both innate immunity and adaptive immunity rendered elderly adults at higher risk of infection-related mortality and morbidity, compared with the general population.[19,20] In addition to immunosenescence, aging can also result in physiologic changes that affect nearly every organ system, independently of existing co-morbidities.[21] Moreover, the high prevalence of co-morbidities in the elderly population can lead to worsening dengue virus infection.[8,22] This study reinforces the need for the implementation of standard clinical protocols for elderly patients with dengue so that timely management can be delivered as necessary.

The differences in the laboratory findings between the survivors and non-survivors were substantial as shown in the univariate analysis. However, only elevated white blood cell count (median, 7.3 × 10^9 cells/L) at initial presentation was a significant independent predictor of poor outcomes in the multivariable analysis. Leukopenia (<4000 × 10^9 cells/L) is a common laboratory finding in dengue.[23,24] In general, leukocytes reached a nadir at the 4th-6th day after symptom onset in those infected with the dengue virus.[23,24] Importantly, the time from the onset of symptoms to hospital presentation was shorter in patients who did not survive (median, 2 days). Furthermore, the majority of deceased patients subsequently developed leukocytosis (median 13.9 × 10^9 cells/L) during hospitalization, although it was not significantly associated with increased mortality risk in the multivariable analysis. Our study indicated that most deceased patients had been in a severe or critical condition on presentation. The unanticipated plasma leakage may have led to the elevated white blood cell count at initial presentation in the decreased patients. Thus, early vigilant monitoring along with high-quality supportive care is needed in patients who present with elevated white blood cell count in the initial phase of dengue virus infection.

In our study, patients with CKD and dengue virus infection had 3.9-fold greater odds of death. Chen et al. reported a high prevalence of severe dengue among patients with CKD.[14] Another study revealed that patients with advanced renal function impairments had a higher mortality rate.[12,13,25] Severe dengue is characterized by plasma leak manifested as the accumulation of fluid in the pleural and abdominal cavities and the hemoconcentration.[1] The pathogenesis of plasma leakage is related to endothelial dysfunction, leading to increased vascular permeability, mediated by a complex interplay between the dengue virus, cytokines, and endothelial cells.[26] In patients with CKD, circulating levels of interleukin-6, C-reactive protein, and tumor necrosis factor-α are generally elevated.[27,28] Furthermore, the production of adhesion molecules in patients with CKD, namely, E-selectin, ICAM-1, and VCAM-1, contributes to vascular endothelial dysfunction and suggests endothelial injury.[29–31] Endothelial dysfunction is evident in patients with CKD. The alteration is progressive and worsens as renal function progresses toward end stage kidney disease. Since endothelial dysfunction leading to increased vascular permeability is a hallmark of severe

Table 4 Multivariate analysis between CKD dengue patients who died ≤7 days after illness onset and non-fatal CKD dengue patients.

	CKD patients died ≤7 days after illness onset (n = 46) versus non-fatal CKD patients (n = 74)		
	aOR	95% CI	P
Severe hepatitis (ALT ≥1000 U/L)	6.281	1.348–29.265	0.019
Leukocytosis (WBC≧12.0 × 10^9 cells/L) during hospitalization	1.117	1.002–1.246	0.046

ALT, alanine aminotransferase; aOR, adjusted odd ratio; CKD, chronic kidney disease; CI, confidence interval.

dengue, patients with CKD and infected by the dengue virus were more susceptible to developing dengue-associated complications.

Initial altered consciousness, pulmonary edema, and leukocytosis during hospitalization were found to be independent risk factors of in-hospital mortality among patients with CKD and infected by the dengue virus. Altered consciousness in patients with dengue may be caused by a wide variety of etiologies, such as deranged electrolytes, hepatic encephalopathy, cerebral hypoperfusion due to shock, cerebral edema due to vascular leak, and direct neuronal injury due to the dengue virus.[32,33] Since metabolic disturbance is common in CKD, altered consciousness is not surprising in patients with CKD and infected by the dengue virus.

Fluid and hemodynamic management, in patients with CKD, represents a major challenge for frontline physicians. The consequences of dengue virus infection, particularly plasma leakage, resulting in fluid accumulation in the lung interstitium and pleural, which can aggravate already compromised renal function, and in turn, lead to pulmonary edema in patients with CKD. Besides, bacteremia was found in 9.4% and pneumonia in 25% of deceased CKD patients with dengue. Bacterial infection is the most common complication in patients receiving hemodialysis.[34,35] The detrimental interplay between the impaired immune status of patients with CKD and the development of secondary bacterial infection, in consistence with the finding of leukocytosis during the hospital course, is strongly associated with death. The study highlighted that timely detection and management of these conditions in patients with CKD may provide a window of opportunity to reduce the preventable mortality in dengue.

One of the goals of this study was to identify risks that may be associated with early mortality ($\leq$7 days) in patients with CKD on admission to the hospital. Notably, 72% of patients with CKD died $\leq$7 days after the onset of dengue illness. Early awareness of the potential risk factors may have enabled the physician to start treatment promptly and reduce mortality. Severe hepatitis and leukocytosis during hospitalization were identified as risk factors for mortality $\leq$7 days after the onset of dengue illness in patients with CKD. Results from the univariate analysis demonstrated that significantly more deceased patients with CKD than survivors presented with elevated alanine aminotransferase when they arrived. The evolution of hepatic failure in the first week of illness determined the clinical outcome of patients with CKD. As such, appropriate supportive therapy that protects important organs may be most beneficial.[36] Importantly, we cannot conclude from this study that patient with chronic hepatitis B (or C) virus is associated with a substantial risk of severe hepatitis; further investigation is needed.

Bacteremia was detected in 4.3% of patients with CKD who died within 7 days of illness onset. Most notably, 10 (21.7%) of 46 deceased patients with CKD developed pneumonia in the first 7 days after symptom onset. We believe that the developed leukocytosis in patients with CKD who died $\leq$7 days after illness onset could be attributed to secondary bacterial infection and organ damage including hepatic failure.[36,37] Multi-disciplinary management combining nephrology and hepatology care is a useful way of monitoring the severity and progression of complications, thereby, reducing the risk of death in patients with CKD and infected by the dengue virus.

In our series, pneumonia was found in 25% of 74 deceased CKD patients with dengue. Previous reports have highlighted lung involvement in dengue primarily due to increased vascular permeability, with pleural effusion being the most commonly observed chest imaging finding, often bilaterally.[38] Guzmán et al. reported that lung pathology was present in all fatal dengue cases, and the virus could be identified in the lungs of deceased individuals.[39] Pneumonia in dengue cases usually indicates a secondary bacterial infection, with *Staphylococcus aureus* being the most commonly reported pathogen.[40,41] Importantly, the involvement of the respiratory system indicates severe disease, emphasizing the vital need for early detection to save lives in the management of dengue patients. Moreover, the occurrence of bacteremia poses another critical challenge for frontline physicians when dealing with severe dengue patients. We have previously reported concurrent bacteremia in dengue patients, with the majority of isolated bacteria normally found in the intestinal tract, such as *Klebsiella pneumoniae*.[42] Another study conducted by Thein et al. revealed that the predominant bacteria were *S. aureus*.[43] In the present study, almost 10% of deceased CKD patients with dengue suffered from bacteremia. Although microbiology data was not available in our series, our findings underscore the importance of early diagnosis and timely antibiotic treatment for bacteremia in dengue patients. Collecting blood samples for cultures and administering empiric antibiotic therapy may be crucial for critically ill dengue patients.

Our study has several limitations. Firstly, the study population comprised adult patients; thus, the results cannot be generalized and applied to pediatric patients. Secondly, certain demographic data such as hepatitis B or C, stroke, dementia, or other cognitive diseases were not obtained, and laboratory tests such as blood culture were not available for all patients. The presence of missing data could potentially introduce bias in the evaluation of clinical characteristics. Thirdly, being a retrospective study, the clinical outcomes of patients with dengue may be biased by the lack of a standardized management protocol, particularly in patients with CKD. However, our study represents the largest series of patients from three medical centers in Taiwan. This improved the generalizability of our results to other regions.

Conclusions

In conclusion, we identified the mortality risk factors to assist with the prediction of the poor outcomes in hospitalized patients with dengue, namely, the elderly, patients with CKD, and those with elevated white blood cell count at baseline. Timely and intensive supportive care may be lifesaving. Altered consciousness at presentation, as well as pulmonary edema and leukocytosis during hospitalization, contribute to the critical illness state associated with mortality in patients with CKD and infected by the dengue virus. Certain CKD patients, such as those with severe hepatitis and leukocytosis, were particularly at risk of

progressing rapidly to death within one week of disease onset. The findings highlight the importance of close monitoring and intensive care in aging populations and patients with CKD. We also outlined the urgent actions required for developing a specific management protocol for these at-risk populations.

Declaration of competing interest

The authors declare that there are no competing interests.

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