

The outcomes of patients with severe dengue admitted to intensive care units

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Abstract

Outcomes of adult patients with dengue infections requiring intensive care unit (ICU) admissions remain unclear. We assessed the clinical manifestations and prognostic factors of patients critically ill with severe dengue.

This retrospective study was done in a tertiary referral hospital with 96 adult ICU beds. All of the patients with laboratory-confirmed severe dengue infections and admitted to the ICU were enrolled between July 31 and November 31, 2015, during the large outbreak period. The medical records of all the recruited patients were reviewed for the following information: age, gender, clinical manifestations, disease severity scores, underlying conditions, laboratory examinations, and outcomes. The primary endpoint was to find the predictors of ICU mortality.

During the study period, 4787 patients with dengue infections required ICU admission. One hundred forty-three (2.99%) were critically ill (mean age: 69.7 years). Hypertension (n=90, 62.9%) and diabetes mellitus (n=70, 49.0%) were the 2 most common underlying diseases. Eighty critically ill patients (55.9%) had cobacterial infections, and 33 had cobacteremia. The hematologic system failed most often, followed by thoracic and cardiovascular systems. Fever was the most common presentation (n=112; 78.3%), followed by anorexia (n=47; 32.9%) and abdominal pain (n=46; 32.2%). Overall, 33 patients died (mortality rate: 23.1%). Multivariate analysis showed that ICU mortality was significantly associated with lower Glasgow Coma Scale (GCS) scores, lower platelet counts before ICU discharge, and more organ failures.

The number of severe dengue patients who require ICU admission remains high. The mortality rate was associated with lower GCS scores, lower platelet counts, and more organ failures. In addition, more than half of the critically ill dengue patients had comorbid bacterial infections.

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, CRRT = continuous renal replacement therapy, ICU = intensive care unit, TISS = Therapeutic Intervention Scoring System.

Keywords: dengue, intensive care unit, outcome

1. Introduction

Dengue has become the most common mosquito-borne viral disease worldwide.^[1,2] According to estimates by the World Health Organization (WHO), the global incidence of dengue infections ranges between 50 million and 200 million every

year.^[1] However, the real disease burden of dengue may be underestimated because of inadequate disease surveillance, misdiagnosis, and low levels of reporting. The clinical manifestations range from asymptomatic infections to severe and fatal forms.^[2,3] One recent study,^[4] based on 1780 country-years of mortality data from 130 countries and 1636 country-years of dengue case reports from 76 countries, estimated an average of 9221 dengue deaths per year between 1990 and 2013. Overall, global mortality greater than 1% rates have been reported.^[5,6]

Taiwan is no exception, and several dengue infection outbreaks have recently been reported here.^[7-10] In 2015, a large outbreak of dengue infections caused by dengue serotype 2 developed in Tainan, Taiwan, and a significant portion of patients with severe dengue infections required intensive care unit (ICU) admission. Because the outcomes of adult patients with dengue infections requiring ICU admissions have rarely been investigated,^[11-17] we did this retrospective study to assess the clinical manifestations and the prognostic factors of patients critically ill with severe dengue infections.

2. Methods

2.1. Patients and hospital setting

This study was done at Chi Mei Medical Center, a tertiary referral hospital with 96 adult ICU beds. In this retrospective study, all of the patients with laboratory-confirmed severe dengue

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CCL and CMC designed the study, interpreted the data, and drafted and revised the article. KSC, WLY, KCC, HCC, and CYY contributed to data collection.

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infections and admitted to the ICU were enrolled between July 31 and November 31, 2015, during the large outbreak period. The data were routinely collected and the analyses were done retrospectively. Therefore, the study was approved by the Institutional Review Board of Chi Mei Medical Center (IRB10503-005), and informed consent was waived.

2.2. Variables measured

The following information was collected: age, gender, and severity scores—the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Therapeutic Intervention Scoring System (TISS), and Glasgow Coma Scale (GCS) score. Underlying comorbidities included congestive heart failure, chronic lung diseases, end-stage renal disease, liver cirrhosis, diabetes mellitus, and cancer. We also measured immunocompromised conditions, associated infections and organisms, the number of multiorgan failures, the use of a mechanical ventilator and continuous renal replacement therapy (CRRT), associated laboratory data at or during admission, symptoms presented in the emergency room, and patient outcomes. The primary endpoint was to find the predictors of ICU mortality.

2.3. Definitions

Laboratory-confirmed dengue cases included those with at least one of the following positive laboratory results: nonstructural protein 1 antigen test, dengue immunoglobulin-M, dengue immunoglobulin-G, a dengue polymerase chain reaction, or viral isolation.

Thoracic failure was defined as the ratio of the partial pressure of oxygen in the patient's arterial blood to the fraction of oxygen in the inspired air less than 200. Cardiovascular failure was defined as a systolic blood pressure (SBP) of ≤ 90 mm Hg or a mean arterial pressure (MAP) ≤ 65 mm Hg for at least 1 hour despite adequate fluid resuscitation; or the need for vasoactive agents (dopamine ≥ 5 mg/kg/min) to maintain SBP ≥ 90 mm Hg or MAP ≥ 65 mm Hg. Metabolic acidosis was defined as a pH ≤ 7.30 or a base deficit ≥ 5.0 mEq/L and a plasma lactate level >3 mmol/L. Hematologic failure was considered a platelet count $<80,000/\text{mm}^3$ or a 50% decrease in the platelet count from the highest value recorded over the previous 3 days. Kidney failure was considered oliguria with an average urine output <0.5 mL/kg/h for 4 hours despite adequate fluid resuscitation or a creatinine level ≥ 2 mg/dL. Hepatic failure was defined as a markedly increased serum bilirubin level ≥ 4 mg/dL.

According to the WHO 2009 criteria, patients were classified as having dengue with warning signs if there were reports of abdominal pain or tenderness, vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, hepatomegaly, and a rise in hematocrit concurrent with a rapid drop in the platelet count. Severe dengue (group C) criteria included the following symptoms: severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, severe organ involvement, or transaminase levels >1000 IU/L.^[18,19] Those who were diagnosed with severe dengue by emergency physicians were admitted to the ICU and included in this study. The focus of bacterial infections was diagnosed on the basis of clinical, laboratory, and radiologic findings. Patients with bacteremia were divided into 2 subgroups: secondary bacteremia caused by another primary focus, such as a respiratory tract or urinary tract infection, and if no primary focus could be identified, the bacteremia was classified as primary.

2.4. Statistical analysis

Continuous variables are expressed as means \pm standard deviation. The differences between groups, and between survivors and nonsurvivors at hospital discharge, were examined using univariate analysis. Continuous data were compared using Student *t* test or the Wilcoxon rank-sum test. Categorical variables were analyzed using χ^2 or Fisher exact tests. Significance was set at $P < 0.05$. Patients significantly associated with in-hospital mortality in univariate analysis ($P < 0.05$) were tested for interaction with multiple logistic regression analysis. Odds ratios and 95% confidence intervals were also calculated. SPSS 19.0 for Windows (SPSS, Inc., Chicago, IL) was used for all data analysis.

3. Results

During the study period, there were 4787 patients with dengue infections, 143 (2.99%) of whom were critically ill and required ICU admission (mean age: 69.7 years; age range: 6–94 years) (Table 1). Thirty-three of these patients died (mortality rate:

Table 1
Demographic and clinical variables of the dengue groups at admission.

Variable	All patients (n=143)	Died (n=33)	Survived (n=110)	P*
Age, y	69.7 \pm 16.1	72.8 \pm 10.8	68.8 \pm 17.3	0.212
Male patients	70.0 (49.0)	15.0 (45.5)	55.0 (50.0)	0.647
APACHE II score	17.9 \pm 9.6	28.0 \pm 10.4	14.8 \pm 6.8	<0.001
TISS	22.8 \pm 11.2	33.5 \pm 11.6	19.5 \pm 8.7	<0.001
Glasgow Coma Scale	12.0 \pm 4.2	7.1 \pm 4.7	13.6 \pm 2.5	<0.001
Comorbidity				
Hypertension	90 (62.9)	26 (78.8)	64 (58.2)	0.032
Diabetes	70 (49.0)	20 (60.6)	50 (45.5)	0.127
Coronary artery disease	27 (18.9)	9 (27.3)	18 (16.4)	0.160
Cancer	17 (11.9)	5 (15.2)	12 (10.9)	0.509
Stroke	16 (11.2)	2 (6.1)	14 (12.7)	0.287
End-stage renal disease	12 (8.4)	5 (15.2)	7 (6.4)	0.110
COPD	9 (6.3)	2 (6.1)	7 (6.4)	0.857
Autoimmune disease	3 (2.1)	1 (3.0)	2 (1.8)	0.670
Alcohol	2 (1.4)	1 (3.0)	1 (0.9)	0.363
Liver cirrhosis	1 (0.7)	1 (3.0)	0 (0)	0.068
Associated infections				
Bacterial infections	80 (55.9)	23 (69.7)	57 (51.8)	0.070
Pneumonia	40 (28.2)	15 (45.5)	25 (22.7)	0.016
Urinary tract infection	33 (23.2)	4 (12.1)	29 (26.4)	0.084
Bacteremia	33 (23.2)	13 (39.4)	20 (18.2)	0.018
Primary	11 (7.7)	7 (21.2)	4 (3.6)	0.001
Secondary	22 (15.4)	6 (18.2)	16 (14.5)	0.612
Other infection foci	12 (8.4)	1 (3.0)	11 (7.7)	0.205
Influenza infection	3 (2.1)	1 (3.0)	2 (1.9%)	0.681
Multiorgan failures (n \pm SD)	1.9 \pm 1.6	4.0 \pm 1.5	1.3 \pm 0.9	<0.001
Multiple organ failures	59 (41.3%)	31 (93.9%)	28 (25.5%)	<0.001
Hematologic	113 (79.0)	30 (90.9)	83 (75.5)	0.056
Thoracic	46 (32.2)	24 (72.7)	22 (20.0)	<0.001
Cardiovascular	43 (30.1)	24 (72.7)	19 (17.3)	<0.001
Kidney	31 (21.7)	21 (63.6)	10 (9.1)	<0.001
Metabolic acidosis	30 (21.1)	23 (69.7)	7 (6.4)	<0.001
Hepatic	14 (9.8)	10 (30.3)	4 (3.6)	<0.001
Mechanical ventilation used	50 (35.0)	27 (81.8)	23 (20.9)	<0.001
CRRT used	20 (14.0)	15 (45.5)	5 (4.5)	<0.001

Expressed as mean \pm SD or n (%). APACHE II = Acute Physiology and Chronic Health Evaluation II, COPD = chronic obstructive pulmonary disease, CRRT = continuous renal replacement therapy, SD = standard deviation, TISS = Therapeutic Intervention Scoring System.

* Comparison between survivors and patients who died.

Table 2
Laboratory data of dengue groups at admission.

Variable	All patients (n = 143)	Died (n = 33)	Survived (n = 110)	P*
Procalcitonin, ng/mL	12.3±34.7	9.9±18.0	13.2±39.1	0.668
C-reactive protein, mg/L	49.0±72.8	66.9±72.1	43.4±72.4	0.111
NT-proBNP, pg/mL	4788.5±7492.8	7019.9±9631.9	3763.2±6163.2	0.214
APTT, s	47.7±31.4	65.9±49.8	41.8±19.6	0.011
BUN, mg/dL	35.6±29.9	40.3±23.9	34.2±31.5	0.311
Creatinine, mg/dL	2.5±3.2	3.2±3.2	2.3±3.2	0.172
Sodium, mmol/L	134.0±5.5	134.7±5.8	133.8±5.5	0.440
Potassium, mmol/L	3.9±1.0	4.3±1.5	3.8±0.7	0.144
Lactate, mmol/L	3.4±4.1	6.2±6.7	2.4±1.9	0.003
Albumin, g/dL	3.0±0.6	2.8±0.6	3.1±0.5	0.015
Hemoglobin, g/dL	12.3±3.1	11.1±2.6	12.6±3.2	0.010
Hematocrit, %	35.5±8.5	32.3±7.1	36.4±8.7	0.015
Platelet on admission, 10 ³ /mm ³	9.8±8.5	10.9±9.3	9.4±8.2	0.372
Lowest platelet, 10 ³ /mm ³	3.5±4.3	2.3±1.7	3.9±4.8	0.003
Last platelet before ICU discharge, 10 ³ /mm ³	15.1±10.7	7.2±6.6	17.3±10.6	<0.001
Leukocyte counts, 10 ³ /mm ³	6.8±5.8	7.8±4.3	6.5±6.1	0.259
Highest AST/GOT, IU/L	1126.4±2488.5	3444.4±4191.9	226.4±357.6	<0.001
Highest ALT/GPT, IU/L	395.7±739.8	959.9±1251.5	226.4±357.6	0.002

Expressed as mean±SD. ALT/GPT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST/GOT = aspartate aminotransferase, BUN = blood urea nitrogen, ICU = intensive care unit, NT-proBNP = N-terminal of the prohormone brain natriuretic peptide.

* Comparison between survivors and patients who died.

23.1% for ICU patients and 0.7% for all hospital patients). The average APACHE II, TISS, and GCS scores were 17.9, 22.8, and 12.0, respectively. Hypertension (n=90; 62.9%) and diabetes mellitus (n=70; 49.0%) were the 2 most common comorbidities. Eighty patients had cobacterial infections: the lungs (pneumonia) (n=40) and the urinary tract (n=33) were the most common sites. Thirty-three of the 80 patients had cobacteremia: 11 primary bacteremia cases and 22 secondary bacteremia cases; 59 (41.3%) had multiorgan failure: the hematologic system failed most frequently, followed by thoracic and cardiovascular systems. Overall, there were 50 (35.0%) patients who required mechanical ventilation and 20 (14.0%) who required CRRT. The patients who died in hospital had significantly higher APACHE II, TISS, and GCS scores, and more hypertension, bacteremia, pneumonia, and organ failure (cardiovascular, thoracic, metabolic, renal and hepatic failures, and multiorgan failure) and needed more mechanical ventilation and CRRT than did survivors.

The levels of procalcitonin and C-reactive protein (CRP) were 12.3 (±34.7) µg/L and 49.0 (±72.8) mg/L, respectively (Table 2). The mean levels of the N-terminal prohormone brain natriuretic peptide and of lactate were 4788.5 (±7492.8) and 3.4 (±4.1), respectively. The lowest platelet count was 35,000 (±43,000)/mm³, and it recovered to 151,000 (±107,000)/mm³ before the patients were discharged from the ICU. The highest levels of aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) were 1126.4 (±2488.5) IU/L and 395.7 (±739.8) IU/L, respectively. The patients who died had significantly higher activated partial thromboplastin time, lactate, AST/GOT, and ALT/GPT levels than did survivors. The patients who died, however, had significantly lower albumin, hemoglobin, and hematocrit, and lower platelet counts in the trough and recovery stage before they were discharged from the ICU than did survivors.

At ICU admission, fever was the most common presentation symptom (n=112; 78.3%), followed by anorexia (n=47; 32.9%) and abdominal pain (n=46; 32.2%) (Table 3). The

gastrointestinal tract (n=45; 31.5%), the genitourinary tract (n=26; 18.2%), and the gums (n=3; 2.1%) were the most common sites, in that order, for bleeding. There were no significant differences in the symptoms, the overall ICU 7.8 (±10.3) and hospital-stay 14.7 (±16.1) days, or hospital costs between survivors and patients who died.

Mortality was highest for 60- to 69-year-olds (8 died [36.4%]; 14 survived), 70- to 79-year-olds (16 died [24.2%]; 50 survived), and 80- to 89-year-olds (7 died [23.3%]; 23 survived) (Fig. 1). Multiple logistic regression analysis showed that ICU mortality was significantly positively associated with the following independent predictors: lower GCSs, lower platelet counts, and more organ failures before ICU discharge (Table 4).

4. Discussion

This is the first study that focuses on dengue patients in Taiwan who require ICU admission and is one of few studies^[11-13,17] that investigates this topic anywhere in the world.

Table 3
Symptoms at admission between dengue groups.

Items	All patients (n [%]) (n = 143)	Died (n [%]) (n = 33)	Survived (n [%]) (n = 110)	P*
Fever	112 (78.3)	27 (81.8)	85 (77.3)	0.578
Anorexia	47 (32.9)	11 (33.3)	36 (32.7)	0.948
Abdominal pain	46 (32.2)	11 (33.3)	35 (31.8)	0.870
Gastrointestinal bleeding	45 (31.5)	12 (36.4)	33 (30.0)	0.490
Myalgia	26 (18.2)	5 (15.2)	21 (19.1)	0.607
Hematuria	26 (18.2)	6 (18.2)	20 (18.2)	1.000
Diarrhea	14 (9.8)	5 (15.2)	9 (8.2)	0.237
Skin rashes	10 (7.0)	1 (3.0)	9 (8.2)	0.309
Gum bleeding	3 (2.1)	0 (0)	3 (2.7)	0.338

* Comparison between survivors and patients who died.

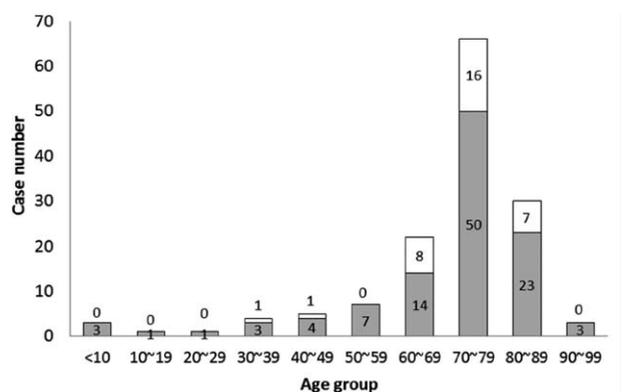


Figure 1. Survival and mortality by age group.

First, we found that the mortality of this specific group remains as high as 23.1%, which is higher than reported by other studies.^[11-13] In 1 study^[12] of 72 critically ill patients with dengue in northern India, 8 patients died (mortality: 11.1%). In another^[13] of 198 ICU patients with dengue in New Delhi, 12 patients died (mortality: 6.1%). In contrast, another multicenter study^[17] of 42 adults with dengue hemorrhagic fever or dengue shock syndrome admitted to ICU in India reported 8 in-ICU deaths (mortality: 19%). A study in Brazil^[11] of 97 adult patients with dengue admitted to the ICU reported in-ICU and in-hospital mortality rates of 18.6% and 19.6%, respectively. The differences between our study and others might be the differences in disease severity. In our study, the mean APACHE II score was 17.9 ± 9.6 , higher than the 7.5^[13] and the 11^[11] in 2 of the others. In addition, only group C (severe dengue patients with warning signs and organ failure) were enrolled in our study, which probably explains why the outcomes of our study were worse. In addition, the mean age of our enrolled patients was about 70 years, older than 2 of the other studies^[12,13]; age itself might also partially contribute to the higher mortality rate.

Second, univariate analysis showed that the patients who died had cases of dengue that were more severe, based on APACHE II, TISS, and GCS scores, than did survivors. This is similar with other reports^[11,13] that in-hospital mortality was associated with APACHE II scores and Sequential Organ Failure Assessment scores. In contrast, after multivariate analysis, only the association between lower GCS scores and in-hospital mortality remained significant in the present study. Our finding might indicate that GCS scores, in addition to other commonly used severity score systems, are good predictors of the outcomes of patients with severe dengue.

Table 4

The predictors of intensive care unit mortality using multiple logistic regression analysis.

Variable	Odds ratio	95% confidence interval	P
Glasgow coma scales	0.745	0.593–0.935	0.011
Last platelet before ICU discharge per $10^3/\mu\text{L}$	0.788	0.665–0.935	0.006
No. of multiorgan failures	3.195	1.613–6.135	<0.001

ICU = intensive care unit.

Third, a multivariate analysis showed that a higher number of organ failures was independently associated with mortality in the present study. Like another study^[20] which reported that some common etiologies of multiple organ dysfunction—dengue shock syndrome and multiple organ dysfunction syndrome—directly related to the organ failure index present a significant risk of mortality, we found that patients who died had more thoracic (72.2% vs 20.0%), cardiovascular (72.7% vs 17.3%), and multiorgan (93.9% vs 25.5%) failures than did survivors (both $P < 0.0001$). Other studies have reported that patients who die were more likely to have cardiovascular (100% vs 12%) or respiratory (88% vs 12%) failures than were survivors (both $P < 0.01$),^[17] that a dengue viral infection with an acute respiratory failure is a significant mortality risk,^[21] and that a lower platelet count before being discharged from the ICU was associated with higher in-hospital mortality.^[22]

Finally, we found that 80 (55.9%) of our patients developed bacterial infections in the ICU. Moreover, 15 (45.5%) of the 33 patients who died had pneumonia, and 13 (39.4%) had bacteremia. In another study,^[11] 45 (46.4%) patients had had been treated with antibiotics, and 7 (36.8%) of 19 deaths were presumably attributed to bacterial infections associated with dengue. In the present study, the most common pathogen in the 33 cases of confirmed bacteremia was *Escherichia coli*, followed by *Staphylococcus aureus* (*S aureus*), and *streptococcus* pp. Despite our finding that *S aureus* was the most commonly reported copathogen, different from that of other reports,^[23,24] the present study and other reports^[25,26] might indicate the clinical significance of bacterial infections in patients with severe dengue. It should at least emphasize the importance of an early diagnosis of cobacterial infections and prompt antibiotic treatment of patients critically ill with dengue.

In the present study, CRP levels were nonsignificantly higher in patients who died (66.9) than in survivors (43.4), which does not support the hypothesis that CRP is an early predictor of dengue severity in adult patients.^[27] The differences should be because of the different study populations. We enrolled only patients with severe dengue in the present study and found that CRP was a limited outcome predictor in patients with severe dengue. We also found that albumin levels were significantly lower (2.8 ± 0.6 vs 3.1 ± 0.5) and lactate significantly higher (6.2 ± 6.7 vs 2.4 ± 1.9) in patients who died than in survivors, which was consistent with other studies^[17,28] that low serum albumin levels on ICU admission were associated with worse outcomes. Although a multivariate analysis eliminated the significance in our study, it still indicates an association between albumin levels and the outcomes in patients with severe dengue.

Our study has some limitations. First, because it is a single-center study, the number of cases is limited. Therefore, our findings may not be generalizable to other hospitals. Second, because of the study design of a retrospective investigation, our data collection might have been inadequate. Third, we did not test the serotypes of dengue virus because our laboratory cannot do that type of examination. However, several studies^[28-31] have reported the association between dengue virus serotypes and the severity of dengue infection. Our findings should help clarify this association. In addition, the predictors of ICU mortality by multiple logistic regression analysis should be considered as the association with mortality but not the biological causes of death. Finally, despite several reports^[32-34] showed the association between different medications, such as *N*-acetyl cysteine, factor VII, diuretic, and fluid administration, and the outcome of dengue patients, we did not collect any information about this association.

In conclusion, the mortality of severe dengue patients admitted to the ICU remains high, and the mortality was associated with lower GCS scores, lower platelet count before being discharged from the ICU discharge, and more organ failures. In addition, a significant portion of patients with severe dengue who die in the ICU have bacterial infections.

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