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Original Article

# Causes of death among dengue patients causes of death among hospitalized adults with dengue fever in Tainan, 2015: Emphasis on cardiac events and bacterial infections

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Received 13 November 2020; received in revised form 28 February 2021; accepted 19 March 2021  
Available online 9 April 2021

## KEYWORDS

Dengue fever;  
Fatality;  
Mortality;  
Bacterial infection;  
Cardiac arrest;  
Taiwan

**Abstract** *Introduction:* The 2015 dengue outbreak in southern Taiwan caused substantial mortality. We analyzed the causes of death among these patients.

*Materials and methods:* This retrospective study was conducted at a medical center in Tainan from August 2015 to December 2015. Dengue was diagnosed based on the detection of serum dengue NS1 antigen, IgM, or viral RNA in the blood. Causes of death were retrieved from chart reviews by three clinicians.

*Results:* There were 4488 cases of dengue in the study hospital, with an in-hospital fatality rate of 1.3% (60 cases). The mean age of the 60 fatal cases was 73 years, among whom 90% were aged  $\geq 65$  years. Twenty-eight (46.7%) patients died of severe dengue, and 29 (48.3%)

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deaths were possibly related to dengue. Of the latter, 24 (40%) died of secondary infections. Thirteen cardiac arrest events, including out-of-hospital (5 events) and in-hospital (8) cardiac arrests in the emergency department, occurred during the dengue epidemic. Seven (53.8%) patients did not receive medical aid before the event. Of the 40 deaths that occurred within one week after hospitalization, 60% died of severe dengue. In contrast, 50% of 20 deaths that occurred one week after hospitalization were related to hospital-acquired infections, mainly pneumonia.

**Conclusion:** Of 60 fatal cases, with a predominance of elderly patients, deaths were related to severe dengue within the first week after admission and secondary infections thereafter. The absence of medical care before cardiac arrest events highlights the importance of health education for warning signs of dengue.

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## Introduction

Dengue is a mosquito-borne viral disease that affects humans and is an emerging major threat to public health throughout the tropics and subtropics.<sup>1,2</sup> Although dengue affects children primarily in hyperendemic areas,<sup>3</sup> some epidemiological studies have reported that susceptible age groups tend toward older children and adults.<sup>4</sup> Although Taiwan is not a hyperendemic area, dengue outbreaks develop virtually every year.<sup>5–7</sup> Dengue predominantly affects adults in Taiwan. The highest prevalence rate was among individuals in their seventh decade of life (i.e., 60s).<sup>6</sup> In 2015, a large-scale dengue outbreak caused by the dengue virus serotype 2 occurred in Tainan City<sup>8</sup> and 22,777 dengue cases<sup>9</sup> were confirmed. Among these, 2%–3% experienced severe disease(s) or complications that required intensive care.<sup>10,11</sup> Patients with severe dengue tend to receive critical care and undergo invasive procedures, which contribute to prolonged length of hospital stay. Thus, patients may be predisposed to healthcare-associated infections during the recovery phase.

A substantial proportion of elderly dengue patients do not exhibit typical features of dengue infection, such as fever and thrombocytopenia only,<sup>12</sup> which makes early diagnosis difficult. With multiple comorbidities complicating the clinical course of dengue, the elderly exhibited more severe presentations and a higher mortality rate than children and young adults during this outbreak.<sup>13</sup> Ascertaining their causes of death may alarm clinicians to the early symptoms and signs of life-threatening conditions. However, this information is limited to the literature. The present study aimed to analyze the causes of death among dengue patients who were cared for at a medical center in Taiwan in 2015.

## Materials and methods

### Case inclusion

The present study was conducted at the National Cheng Kung University Hospital (NCKUH), a medical center located in southern Taiwan, between August 1 and December 31,

2015. Cases of dengue were identified from dengue notifications in the Infection Control Center, NCKUH. The diagnosis of dengue fever was established by documentation of dengue NS1 antigen (Bioline Dengue NS1 Ag kit, Standard Diagnostics Inc., Korea), dengue immunoglobulin (Ig) M (Bioline Dengue Duo kit, Standard Diagnostics Inc., Korea), or dengue virus RNA (TIB Molbiol, Lightmix kit, Roche Applied Science, Berlin, Germany) in the sera or blood of the patients. The study was approved by the Institutional Review Board at NCKUH (A-ER-104-386), and requirements for informed consent were waived.

### Definitions

Patients >65 years of age were defined as elderly. Fatal cardiac events, including ventricular tachycardia and ventricular fibrillation (VT/VF), refractory heart failure, and peri-myocarditis, can cause death. These cardiac events were confirmed based on electrocardiography findings, hemodynamic parameters, lactate, cardiac enzyme levels, and/or chest film. Cardiac arrests that occurred in the emergency department (ED) were categorized as out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) according to the location of occurrence. Although cardiac events may cause cardiac arrest, cardiac arrest is not exclusively caused by cardiac events. Typical presentations of dengue fever included fever with two of the following signs or symptoms: nausea/vomiting, rash, aches/pains, positive tourniquet test, leucopenia, or any of the typical warning signs.<sup>14</sup> If the initial manifestations of dengue did not fulfill the above criteria of the typical presentations, these cases were considered atypical.<sup>12</sup> The severity of dengue fever was graded according to guidelines issued by the World Health Organization (WHO) in 2009.<sup>14</sup> Group A includes those without warning signs, group B includes those with warning signs, coexisting complicated conditions, or special social circumstances, and group C includes those with signs of severe plasma leakage, severe hemorrhage(s), or severe organ impairment. Plasma leakage was supported by a change in hematocrit >20% or the presence of bilateral pleural effusion or ascites. Unstable vital signs indicate the presence of hypotension (systolic blood pressure < 90 mmHg or mean

pressure < 65 mmHg), impending respiratory failure (desaturation requiring application of high-flow oxygenation device or poor respiratory pattern noted), or altered mental status in which patients cannot respond well to stimulation. The age-adjusted Charlson's Comorbidity Index (ACCI) was used to evaluate comorbidity status.<sup>15</sup> Days of hospitalization included the period of ED stay.

Organ failure associated with dengue fever was defined as dysfunction of the cardiovascular system, respiratory system, nervous system, liver, or kidney after dengue onset. Cardiovascular failure was defined in patients with a mean blood pressure <65 mmHg, the need for inotropic agents to maintain blood pressure, or signs of low cardiac output. Respiratory failure was defined as a partial pressure of oxygen (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) ratio of <300 or a partial pressure of carbon dioxide (PaCO<sub>2</sub>) > 50 mmHg,<sup>16,17</sup> with or without increased breathing effort. Severe coma indicating nervous system failure was characterized by a Glasgow Coma scale score <8,<sup>18</sup> while serum bilirubin level >2 mg/dL was regarded as liver failure.<sup>16</sup> The Kidney Disease Improving Global Outcome criteria were applied to define renal failure; more specifically, an increase in serum creatinine levels of more than twice the baseline level or >4 mg/dL, urine output <0.3 mL/kg/h over 24 h, or anuria for 12 h.<sup>19</sup> Multiorgan failure was defined as the presence of failure of >2 organ systems.

### Causes of death

Causes of death in the present study were evaluated by two intensivists with subspecialist training in infectious diseases and an infectious disease specialist. Cause of death was based on the consensus of these individuals, which was categorized into one of the following three groups. First, death was related to severe dengue if the patient died of severe plasma leakage, major bleeding, or organ failure in the critical phase.<sup>14</sup> Second, some deaths were arbitrarily defined as being possibly related to dengue, according to the following three criteria: the patient survived the critical phase of dengue; the death could not be attributed to severe dengue; or the fatal event ensued during hospitalization due to dengue. Third, in those with dengue, if there were other diseases unrelated to dengue, the cause of death was classified as "other". Do not resuscitate (DNR) orders before death were ascertained using chart reviews. All causes of death, with and without DNR, were analyzed.

### Data acquisition

All parameters, including demographic information, underlying disease, organ system dysfunction status, date and cause of death, dengue onset, date of hospital visit, and timing of the DNR order, were obtained and determined from electronic medical records.

### Statistical methods

To analyze the causes of death, patients were further stratified according to death within and after one week of

hospitalization. The chi-square test or Fisher's exact test was used to compare categorical variables between the groups. Continuous variables were compared using Student's *t* test. All data were processed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA); differences with *p* < 0.05 were considered significant.

## Results

During the study period, 4488 patients with serologically documented dengue were hospitalized at the NCKUH, Tainan. Among these patients, 60 died, corresponding to a crude in-hospital mortality rate of 1.34%, and 40 (66.7%) died within seven days of hospitalization. The mean age of those who died was 73 years, and 90% (54/60) were ≥65 years of age. The major underlying medical illnesses were hypertension (*n* = 32 [53.3%]), diabetes mellitus (*n* = 30 [50%]), and chronic kidney disease (*n* = 20 [33.3%]), as summarized in Table 1. Of the 60 fatal cases, the timing of dengue diagnosis varied, with 44 (73.3%) diagnosed with dengue at the first hospital visit either to outpatient clinics or the ED, three (5%) at the second visit to the ED, and five (8.3%) after admission with initial clinical suspicions other than dengue. Eight (13.3%) patients were diagnosed at other hospitals and were referred to the study hospital.

Regarding causes of death, 46.7% (*n* = 28) died of severe dengue and 48.3% (*n* = 29) of deaths were possibly related to dengue (Table 2). A substantial proportion (40% [*n* = 24]) died due to secondary infections. Two (3.3%) deaths were related to complications of acute renal failure (pulmonary edema), while hemodialysis was not applied, and two (3.3%) died of respiratory failure without advanced airway management. A patient refused invasive procedures to stop bleeding and was believed to have died of massive gastrointestinal bleeding, which occurred while the patient

**Table 1** Clinical characteristics of 60 fatal cases of dengue fever.

| Parameters                                      | Case No. (%) |
|---|--------------|
| Age (mean ± standard deviation), years          | 73.4 ± 12.4  |
| Male sex  | 30 (50.0)    |
| Underlying disease                              |              |
| Hypertension                                    | 32 (53.3)    |
| Diabetes mellitus                               | 30 (50.0)    |
| Chronic kidney disease                          | 20 (33.3)    |
| Cancer  | 16 (26.7)    |
| Coronary arterial disease                       | 15 (25.0)    |
| Neurological disease                            | 12 (20.0)    |
| Rheumatic disease                               | 8 (13.3)     |
| Congestive heart failure                        | 7 (11.7)     |
| Chronic hepatitis                               | 7 (11.7)     |
| Liver cirrhosis                                 | 4 (6.7)      |
| Chronic obstructive pulmonary disease or asthma | 4 (6.7)      |
| Chronic renal replacement therapy               | 2 (3.3)      |
| Recent chemotherapy                             | 2 (3.3)      |

Neurological disease indicates one or more of old stroke, dementia, parkinsonism, or multiple sclerosis.

**Table 2** Clinical characteristics of the deaths occurring  $\leq 1$  week and  $>1$  week after admission among adults with dengue fever.

| Variables                                  | Death after admission, case No. (%) |                   | P value |
|--|-------------------------------------|-------------------|---------|
|  | $\leq 1$ week, n = 40               | $>1$ week, n = 20 |         |
| Age (mean $\pm$ standard deviation), years | 73.1 $\pm$ 13.4                     | 75.2 $\pm$ 10.5   | 0.52    |
| Male gender                                | 17 (42.5)                           | 13 (65)           | 0.17    |
| Causes of death                            |                                     |                   |         |
| Severe dengue                              | 24 (60)                             | 4 (20)            | 0.03    |
| Intracranial hemorrhage                    | 2 (5)                               | 3 (15)            | 0.32    |
| Cardiac events <sup>a</sup>                | 5 (12.5)                            | 0 (0)             | 0.16    |
| Causes possibly related to dengue          | 14 (35)                             | 15 (75)           | 0.003   |
| Secondary infections                       | 14 (35)                             | 10 (50)           | 0.58    |
| Bacteremia                                 | 6 (15)                              | 0 (0)             | 0.17    |
| Pneumonia                                  | 5 (12.5)                            | 8 (40)            | 0.02    |
| Candidemia                                 | 2 (5)                               | 1 (5)             | 1       |
| Pneumonia and bacteremia                   | 1 (2.5)                             | 0 (0)             | 1       |
| Necrotizing fasciitis                      | 0 (0)                               | 1 (5)             | 0.33    |
| Renal failure                              | 0 (0)                               | 2 (10)            | 0.11    |
| Respiratory failure                        | 0 (0)                               | 2 (10)            | 0.11    |
| Lower gastrointestinal bleeding            | 0 (0)                               | 1 (5)             | 0.33    |
| Others <sup>b</sup>                        | 2 (5)                               | 1 (5)             | 1       |
| Do-not-resuscitate                         | 24 (60)                             | 18 (90)           | 0.02    |
| Cardiac arrest events at ED                | 13 (32.5)                           | 0 (0)             | 0.03    |

<sup>a</sup> Include ventricular tachycardia/fibrillation, refractory heart failure, and myocarditis.

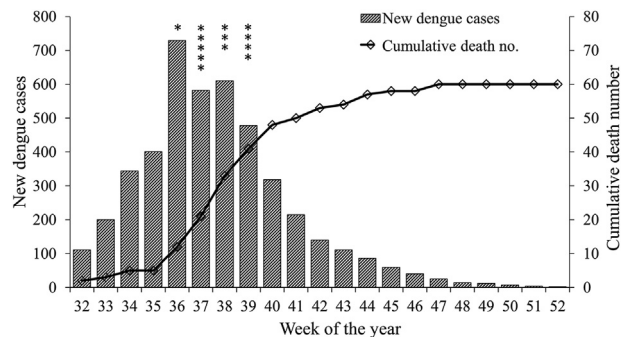
<sup>b</sup> Brain tumor, suffocation while taking medicine, or traffic accident with skull bone fracture. ED, emergency department.

had a platelet count of  $94 \times 10^9/L$  on day 22 of hospitalization. Three patients died of a brain tumor, suffocation while taking medicine, and a traffic accident that caused a skull fracture and intracranial hemorrhage (ICH), all of which were coincident with dengue fever.

The causes of death were compared between those who died within one week and those after one week of hospitalization (Table 2). For the former, the primary causes of death were severe dengue (n = 24 [60%]) and secondary infections (n = 14 [35%]). Of the 24 deaths caused by severe dengue, five (12.5%) died of cardiac events including VT/VF, myocarditis, and refractory heart failure. Among the 20 patients who died after one week of hospitalization, the major causes of death were secondary infections (n = 10 [50%]), renal failure (n = 2 [10%]), and respiratory failure (n = 2 [10%]). Four (20%) patients died of severe dengue. Of these, three (15%) died of ICH, which developed during the critical phase of dengue, but death occurred after one week of hospitalization. The cause of death was categorized as severe dengue because death can be expected while ICH occurred. The other died of renal and hepatic failure with multiple-site bleeding. According to the manifestation of thrombocytopenia, this patient is still in the critical phase of dengue. Candidemia can occur either early (within one week [n = 2]) or late (after one week [n = 1]) during hospitalization. Patients with candidemia in this case series all had hepatic dysfunction (two had acute hepatic failure and one had hypovolemic shock with subsequent ischemic hepatitis). In contrast, among the seven fatal cases in which death was caused by bacteremia, all deaths occurred during the first week.

The newly diagnosed cases reached a peak in week 36 of 2015. The curve for the cumulative number of deaths had two inflection points—at weeks 35 and 40—and reached the ceiling at week 47 (Fig. 1). Of note, 13 cardiac arrest events occurred between weeks 36 and 39 of 2015, which was the second month of the dengue outbreak. Among the patients experiencing cardiac arrest, five were out-of-hospital cardiac arrest (OHCA) and eight in-hospital cardiac arrests (IHCA) while staying in the ED (Table 3). Of the five patients with OCHA, three were discharged from the ED or outpatient clinic and experienced arrest at home.

The intervals between ED arrival and the IHCA event varied, ranging from 1 h to 46 h. The estimated interval between dengue onset and death ranged from  $<1$  day to 6 days. The ages of these 13 cases ranged from 41 to 83 years,



**Figure 1.** Weekly notified dengue cases in the study hospital and cumulative fatal cases. An asterisk (\*) indicates a cardiac arrest event at the emergency department.

**Table 3** Characteristics of 13 cardiac arrest events at the emergency department (ED).

| Serial No.                         | Out-of-hospital cardiac arrest |     |     |     |    | In-hospital cardiac arrest at ED |    |    |    |    |     |     |     |
|------------------------------------|--------------------------------|-----|-----|-----|----|----------------------------------|----|----|----|----|-----|-----|-----|
|                                    | 1                              | 2   | 3   | 4   | 5  | 6                                | 7  | 8  | 9  | 10 | 11  | 12  | 13  |
| Age                                | 62                             | 80  | 62  | 55  | 69 | 83                               | 76 | 74 | 76 | 70 | 78  | 45  | 41  |
| Gender                             | M                              | F   | M   | F   | F  | F                                | F  | F  | M  | M  | F   | M   | F   |
| Latest ED arrival to CPR, hours    |                                |     |     |     |    | 46                               | 14 | 22 | 4  | 7  | 20  | 1   | 39  |
| Prior ED or OPD visits             | No                             | Yes | Yes | Yes | No | No                               | No | No | No | No | Yes | Yes | Yes |
| WHO grade on latest ED arrival     | C                              | C   | C   | C   | C  | B                                | B  | B  | B  | C  | B   | C   | A   |
| Underlying disease                 |                                |     |     |     |    |                                  |    |    |    |    |     |     |     |
| Age-adjusted CCI                   | 9                              | 8   | 6   | 5   | 3  | 9                                | 6  | 6  | 5  | 5  | 4   | 3   | 1   |
| Central nervous system disease     |                                |     | ●   |     |    |                                  |    |    |    | ●  |     |     |     |
| Coronary arterial disease          | ●                              | ●   | ●   |     |    | ●                                |    |    |    | ●  |     |     |     |
| Heart failure                      |                                | ●   |     |     |    |                                  |    |    |    |    |     |     |     |
| Hypertension                       |                                | ●   |     |     |    | ●                                | ●  | ●  | ●  | ●  |     |     |     |
| Liver disease                      |                                |     |     |     |    |                                  |    |    |    |    |     | ●   |     |
| Chronic kidney disease             | ●                              | ●   |     |     |    | ●                                | ●  | ●  |    | ●  |     |     |     |
| Diabetes mellitus                  | ●                              |     | ●   | ●   |    |                                  |    |    | ●  | ●  |     |     |     |
| Cancer                             |                                |     |     | ●   |    |                                  |    |    |    |    |     |     |     |
| Unstable vital signs at the triage | ●                              | ●   | ●   | ●   | ●  |                                  |    |    | ●  | ●  |     | ●   |     |
| Thrombocytopenia at ED             | ●                              |     |     |     | ●  | ●                                | ●  | ●  |    | ●  | ●   | ●   |     |
| Evidence of plasma leakage at ED   |                                | ●   |     | ●   |    | ●                                | ●  | ●  |    | ●  | ●   | ●   |     |
| Interval from onset to death, days | NA                             | 4   | ND  | 6   | 0  | 6                                | 1  | 3  | 0  | 2  | 5   | 0   | 5   |

Black circle: existence of the clinical characteristics; CCI: Charlson's comorbidity index; CPR, cardiopulmonary resuscitation; F, female; M, male; NA: not available; OPD, outpatient department.

**Table 4** Number of organ failures in 42 fatal cases of dengue fever at the time of the do-not-resuscitate (DNR) signature.

| Parameters  | Case No. (%) |
|---|--------------|
| No organ failure                                  | 6 (14.3)     |
| Failure of one organ system                       | 12 (28.6)    |
| Respiratory failure                               | 5 (11.9)     |
| Renal failure requiring renal replacement therapy | 4 (9.5)      |
| Cardiovascular failure                            | 2 (4.8)      |
| Central nervous system (CNS) failure              | 1 (2.4)      |
| Failure of two organ systems                      | 8 (19.0)     |
| Renal and respiratory failure                     | 3 (7.1)      |
| CNS and respiratory failure                       | 3 (7.1)      |
| Cardiovascular and respiratory failure            | 1 (2.4)      |
| CNS and renal failure                             | 1 (2.4)      |
| Multiorgan failure                                | 16 (38.1)    |
| DNR signature within 7 days after admission       | 28 (66.7)    |

and the ACCI ranged from 1 to 9. Of the 13 patients who experienced cardiac arrest, seven did not receive medical aid before the events, and 12 presented to the ED with severe dengue (WHO grade B or C) (Table 3). Notably, seven patients had an ACCI <6, indicative of lower complexity in terms of comorbidities. The exception was a patient with WHO grade A disease, who died soon after the onset of upper back pain with diffuse ST-T elevation on electrocardiography at the ED (Case 13 in Table 3).

Of the 60 fatal cases, 70% (n = 42) signed DNR orders before their death (Table 4), and two-thirds (n = 28) of

DNR decisions were made within one week after hospital arrival. Of note, DNR was requested in six cases without organ failure, 12 with failure of one organ system, and eight with failure of two organ systems.

## Discussion

The 2015 dengue outbreak in southern Taiwan began in August and peaked in early September. The number of fatal cases increased dramatically between week 35 and week 40 and reached a ceiling at week 47. Of note, all the sudden death events, including OHCA and IHCA in the ED, occurred within the second month of dengue epidemic. This was likely due to the following reasons. First, local residents were not aware of the diverse severity of dengue in the beginning of the endemic, because only six of 13 patients experiencing cardiac arrest ever sought medical care before their death, which could have been prevented by early medical intervention(s).<sup>20–22</sup> Second, ED overcrowding, as noted in the surge of dengue cases, may have been associated with increased mortality and morbidity.<sup>23,24</sup> Contingency plans for patient diversion<sup>23,25</sup> and short-stay wards in the ED during large outbreaks of infectious diseases<sup>26</sup> could be practical solutions. With the implementation of a patient diversion program by the Public Health Bureau of Tainan City Government in early September, patient burden in the ED of the study hospital decreased, which facilitated optimal first medical care for those with severe dengue.

Dengue in Taiwan often affects the elderly,<sup>6</sup> for which a diagnosis of dengue may be challenging because these individuals often lack characteristic dengue symptoms.<sup>5,27</sup> In fact, the 2009 WHO criteria for the clinical diagnosis of

dengue in adults has been questioned for its sensitivity and specificity.<sup>28</sup> Before the problem arises, febrile elderly individuals with leucopenia had been referred to as a trigger for diagnostic laboratory tests for dengue fever.<sup>29</sup> More than one-half of our patients did not exhibit typical dengue features when they initially sought medical help, and the diagnosis of infection with the dengue virus was delayed in eight cases. Clinical signs and symptoms that are presumably linked to underlying comorbidities (e.g., cancer pain) in the elderly can further delay a diagnosis of dengue. Because Tainan is not an area hyperendemic for dengue, most populations may be naïve to dengue infection. Primary dengue infection is usually asymptomatic or is associated only with mild flu-like symptoms, and most patients may not seek medical attention. To increase the detection rate, clinical suspicion of dengue should not be limited to typical dengue fever “criteria” in an endemic period.

In our series, five OHCA and eight IHCA cases presented to the ED with fulminant courses. Thrombocytopenia was not observed in five cases, indicating that fatal events occurred in the early phase of dengue infection.<sup>14</sup> Another potentially fatal complication of dengue fever is pericardiomycarditis, which manifests as sudden collapse, diffuse ST-T elevation on electrocardiography, and elevated serum cardiac enzyme levels, but without thrombocytopenia or signs of plasma leakage. On the other hand, more than one-half of the 13 patients ( $n = 7$ ) who experienced unexpected cardiac arrest in the ED had an ACCI  $< 6$ . The presentation and underlying comorbidities may not accurately predict the miserable outcomes of these patients. Therefore, optimization of healthcare resources is of significant importance in the outbreak of infectious diseases. For example, the relocation of patients to temporary dengue wards in conjunction with regular laboratory tests and vital signs monitoring, and education of medical staff with a rapid discharge plan for class A patients will preserve more healthcare resources in the ED for class B or C patients who tend to develop severe complications.

The overall mortality rate of hospitalized patients with dengue fever in the study hospital was 1.3%. Multiple factors, such as older age or epidemic serotype 2 dengue virus, may have contributed to the substantial mortality rate in our study. One potential contributing sociocultural factor is the DNR signature during hospitalization in up to 70% of fatal cases. In Taiwan, healthcare workers do not routinely provide DNR advice for all admitted dengue patients unless requested on demand. In addition, patients rarely signed DNR in advance through advanced care planning because the law of patient advance directive came into force in January 2016, later than the 2015 dengue outbreak in Tainan. Through advances in organ support, individuals with severe dengue may have a greater chance for survival; however, DNR orders preclude intensive care provided by healthcare workers. In Taiwan, old age is the main factor in signing DNR orders in critically ill patients.<sup>30,31</sup> A study from Taiwan reported that patients with renal failure had the highest percentage of signed DNR orders.<sup>32</sup>

Furthermore, general misunderstanding has led the public to refuse tracheostomy for critically ill patients in Taiwan. This highlights the importance of shared decision-making between medical professionals and patients.<sup>33</sup> We observed that dengue patients with DNR orders and without

organ failure were older than those with organ failure, although the difference was not significant. However, their prognosis may remain poor even without a DNR order under advanced medical support. In this case series, DNR orders were signed for 18 (30%) patients when no or one organ failure occurred. Some of these patients may survive with minimal organ support. It may imply that our battle was fighting against not only the acute illness, but also the aging and comorbidity.

A review from Malaysia discussed deaths directly related to dengue.<sup>20</sup> The causes of death stratified according to the pathophysiology of dengue fever included dengue shock syndrome, severe bleeding, and severe organ involvement. In addition, two case series, including seven and 10 cases, respectively, reported the deaths related to complications other than dengue.<sup>21,22</sup> The failure of early recognition of warning signs of severe dengue—even in dengue endemic areas—has been noted in a retrospective study.<sup>34</sup> Moreover, several social determinants of health were proposed to be related to dengue-related death.<sup>35</sup> In this study, more than one-half of early deaths (*i.e.*, deaths within one week of hospitalization) were regarded to be related to either plasma leakage or major bleeding—the clinical manifestations of severe dengue. However, three patients experienced rapid organ failure, although there was no evidence of plasma leakage or major bleeding. No causes other than dengue could have contributed to the deaths based on clinical evaluation.

In contrast, the two main causes of deaths that occurred after one week of hospitalization were healthcare-associated infections and persistent organ dysfunction related to severe dengue. Coincidence of dengue with other infections is not rare, and identifying bacterial or fungal co-infections among hospitalized dengue patients is critical during the dengue endemic.<sup>36,37</sup> It is worth noting that the likelihood that concurrent bacteremia, mainly due to *Streptococcus* and/or *Escherichia coli*, could develop at the onset of dengue.<sup>38</sup> The potential pathophysiological mechanisms underlying concurrent bacterial infections include neutropenia related to bone marrow suppression by dengue virus, immune suppression by affecting immune system cells, cytokine signal transduction, and innate immunity pathway by dengue virus,<sup>36</sup> as well as microbial translocation in conjunction with intestinal mucosal injury.<sup>37</sup> Other common pathogens causing bacteremia in dengue patients include *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter* species.<sup>38,39</sup> Older age, comorbidities, severe disease with gastrointestinal bleeding, prolonged activated prothrombin time, and acute renal failure were recognized as risk factors for concurrent bacteremia.<sup>40–42</sup> Laboratory parameters, including leukocyte count,<sup>41</sup> serum C-reactive protein,<sup>42</sup> and procalcitonin,<sup>43</sup> may be useful in differentiating those with concurrent bloodstream infections from those who had only dengue virus infection alone. Candidemia is a rarely reported complication<sup>44</sup> that can occur either in the early or late stages of hospitalization. Hospital-acquired pneumonia was the most common secondary infection among those who survived dengue. In addition to the post-dengue immunity concern, deconditioning was an important

factor for airway compromise, and pneumonia occurred. Clinicians should carefully evaluate these conditions and provide timely antimicrobial therapy and suggestions for airway management.

Cardiac events associated with dengue fever tended to be underestimated and inadequately monitored. Before death, five patients experienced cardiac events, including heart failure with cardiogenic shock or pulmonary edema, fatal arrhythmia, and fulminant myocarditis. In the literature, the disease spectrum for cardiac involvement in dengue patients was wide, ranging from subclinical functional myocardial impairment to fulminant myocarditis.<sup>45,46</sup> Relative bradycardia was the most frequent finding associated with dengue.<sup>46,47</sup> Of 320 individuals from India with dengue fever, more than one-third (35% [n = 112]) exhibited cardiac involvement and, of 14 fatal cases, all had abnormal findings on electrocardiography, echocardiography, and serum cardiac markers indicative of cardiac injury.<sup>47</sup> Patients with risk factors, such as older age, underlying cardiovascular disease, abnormal electrocardiogram findings, elevated cardiac enzymes, and shock unresponsive to fluid resuscitation, warrant further evaluation by cardiac specialists.<sup>46</sup>

Our study had several limitations, the first of which was its single-center design (a medical center in southern Taiwan), which provided care for more than one-half of the critical patients from Tainan City during the 2015 dengue epidemic. Second, the data were collected retrospectively, and certain important parameters, such as the time of disease onset and detailed signs and symptoms, could not be obtained from medical records. Third, the causes of death were clinically categorized and could not be verified by autopsy. However, the study results were recorded by two experienced, intensivists certified by the Taiwan Board of Infection Disease Specialization.

## Conclusion

Elderly individuals ( $\geq 65$  years of age) predominated among the fatal cases of dengue. Deaths were often related to severe dengue within the first week after admission and secondary infections thereafter. The absence of medical care among one-half of adults before cardiac arrest reveals the importance of health education for the public during dengue epidemics.

## Declaration of competing interest

The authors declare that they have no competing interests.

## Acknowledgments

The study was funded by the Ministry of Health and Welfare, Taiwan (award number: MOHW107-TDU-B-211-123003). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors thank Chih-Cheng Hsieh and Wei-Chieh Lin for their help in conceptualizing the study and drafting the manuscript.

## References

- Gibbons RV, Vaughn DW. Dengue: an escalating problem. *Br Med J* 2002;324:1563–6.
- Halstead SB. Dengue. *Lancet* 2007;370:1644–52.
- Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev* 1998;11:480–96.
- Lin RJ, Lee TH, Leo YS. Dengue in the elderly: a review. *Expert Rev Anti Infect Ther* 2017;15:729–35.
- Lin CC, Huang YH, Shu PY, Wu HS, Lin YS, Yeh TM, et al. Characteristic of dengue disease in Taiwan: 2002-2007. *Am J Trop Med Hyg* 2010;82:731–9.
- Hsu JC, Hsieh CL, Lu CY. Trend and geographic analysis of the prevalence of dengue in Taiwan, 2010-2015. *Int J Infect Dis* 2017;54:43–9.
- Pan CY, Liu WL, Su MP, Chang TP, Ho HP, Shu PY, et al. Epidemiological analysis of the Kaohsiung city strategy for dengue fever quarantine and epidemic prevention. *BMC Infect Dis* 2020;20:347.
- Wang SF, Chang K, Loh EW, Wang WH, Tseng SP, Lu PL, et al. Consecutive large dengue outbreaks in Taiwan in 2014-2015. *Emerg Microb Infect* 2016;5:e123.
- Center of Disease Control. *Taiwan. National infectious disease statistics system*. Available at: [https://nidss.cdc.gov.tw/ch/NIDSS\\_DiseaseMap.aspx?dc=1&dt=2&disease=061](https://nidss.cdc.gov.tw/ch/NIDSS_DiseaseMap.aspx?dc=1&dt=2&disease=061). [Accessed 13 September 2017].
- Hsieh CC, Cia CT, Lee JC, Sung JM, Lee NY, Chen PL, et al. A cohort study of adult patients with severe dengue in Taiwanese intensive care units: the elderly and APTT prolongation matter for prognosis. *PLoS Neglected Trop Dis* 2017;11:e0005270.
- Chen CM, Chan KS, Yu WL, Cheng KC, Chao HC, Yeh CY, et al. The outcomes of patients with severe dengue admitted to intensive care units. *Medicine (Baltimore)* 2016;95:e3476.
- Lee CC, Hsu HC, Chang CM, Hong MY, Ko WC. Atypical presentations of dengue disease in the elderly visiting the ED. *Am J Emerg Med* 2013;31:783–7.
- Yeh CY, Chen PL, Chuang KT, Shu YC, Chien YW, Perng GC, et al. Symptoms associated with adverse dengue fever prognoses at the time of reporting in the 2015 dengue outbreak in Taiwan. *PLoS Negl Trop Di* 2017;11:e0006091.
- World Health Organization. *Dengue: guidelines for diagnosis, treatment, prevention and control*. Geneva: World Health Organization; 2009.
- Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245–51.
- Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998;26:1793–800.
- Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. *Thorax* 2016;71:ii1–35.
- Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81–4.
- Section 2: AKI definition. *Kidney Int Suppl* 2011;2012(2):19–36.
- Woon YL, Hor CP, Hussin N, Zakaria A, Goh PP, Cheah WK. A two-year review on epidemiology and clinical characteristics of dengue deaths in Malaysia, 2013-2014. *PLoS Neglected Trop Dis* 2016;10:e0004575.
- Ong A, Sandar M, Chen MI, Sin LY. Fatal dengue hemorrhagic fever in adults during a dengue epidemic in Singapore. *Int J Infect Dis* 2007;11:263–7.

22. Sam SS, Omar SF, Teoh BT, Abd-Jamil J, AbuBakar S. Review of dengue hemorrhagic fever fatal cases seen among adults: a retrospective study. *PLoS Neglected Trop Dis* 2013;7:e2194.
23. Shapiro JS, Genes N, Kuperman G, Chason K, Clinical Adequacy Committee H1N1 Working Group. New York Clinical Information Exchange, et al. Health information exchange, biosurveillance efforts, and emergency department crowding during the spring 2009 H1N1 outbreak in New York City. *Ann Emerg Med* 2010;55:274–9.
24. Cowan RM, Trzeciak S. Clinical review: emergency department overcrowding and the potential impact on the critically ill. *Crit Care* 2005;9:291–5.
25. Schull MJ, Mamdani MM, Fang J. Community influenza outbreaks and emergency department ambulance diversion. *Ann Emerg Med* 2004;44:61–7.
26. Nasarudin NM, Mohd Saiboon I, Ismail AK. The role of an emergency department short-stay ward in the management of dengue fever: a case-control study in a university hospital. *Eur J Emerg Med* 2013;20:335–8.
27. Rowe EK, Leo YS, Wong JG, Thein TL, Gan VC, Lee LK, et al. Challenges in dengue fever in the elderly: atypical presentation and risk of severe dengue and hospital-acquired infection. *PLoS Neglected Trop Dis* 2014;8:e2777.
28. Bodinayake CK, Tillekeratne LG, Nagahawatte A, Devasiri V, Kodikara Arachchi W, Strouse JJ, et al. Evaluation of the WHO 2009 classification for diagnosis of acute dengue in a large cohort of adults and children in Sri Lanka during a dengue-1 epidemic. *PLoS Neglected Trop Dis* 2018;12:e0006258.
29. Low JG, Ong A, Tan LK, Chaterji S, Chow A, Lim WY, et al. The early clinical features of dengue in adults: challenges for early clinical diagnosis. *PLoS Neglected Trop Dis* 2011;5:e1191.
30. Lin KH, Chen YS, Chou NK, Huang SJ, Wu CC, Chen YY. The associations between the religious background, social supports, and do-not-resuscitate orders in Taiwan: an observational study. *Medicine (Baltim)* 2016;95:e2571.
31. Huang CT, Chuang YC, Tsai YJ, Ko WJ, Yu CJ. High mortality in severe sepsis and septic shock patients with do-not-resuscitate orders in East Asia. *PLoS One* 2016;11:e0159501.
32. Chang HT, Lin MH, Chen CK, Chou P, Chen TJ, Hwang SJ. Trends of Do-Not-Resuscitate consent and hospice care utilization among noncancer decedents in a tertiary hospital in Taiwan between 2010 and 2014: a Hospital-based observational study. *Medicine (Baltim)* 2016;95:e5394.
33. Huang CH, Chen IH. The Clinical application of the tracheostomy decision-making program in respiratory care center prolonged mechanical ventilation patients in Taiwan. *Int J Gen Med* 2020;13:1487–94.
34. Tomashek KM, Gregory CJ, Rivera Sánchez A, Bartek MA, Garcia Rivera EJ, Hunsperger E, et al. Dengue deaths in Puerto Rico: lessons learned from the 2007 epidemic. *PLoS Neglected Trop Dis* 2012;6:e1614.
35. Carabali M, Hernandez LM, Arauz MJ, Villar LA, Ridde V. Why are people with dengue dying? A scoping review of determinants for dengue mortality. *BMC Infect Dis* 2015;15:301.
36. Trunfio M, Savoldi A, Viganò O, Monforte AD. Bacterial coinfections in dengue virus disease: what we know and what is still obscure about an emerging concern. *Infection* 2017;45:1–10.
37. Syue LS, Tang HJ, Hung YP, Chen PL, Li CW, Li MC, et al. Bloodstream infections in hospitalized adults with dengue fever: clinical characteristics and recommended empirical therapy. *J Microbiol Immunol Infect* 2019;52:225–32.
38. Thein TL, Ng EL, Yeang MS, Leo YS, Lye DC. Risk factors for concurrent bacteremia in adult patients with dengue. *J Microbiol Immunol Infect* 2017;50:314–20.
39. Lee IK, Liu JW, Yang KD. Clinical characteristics and risk factors for concurrent bacteremia in adults with dengue hemorrhagic fever. *Am J Trop Med Hyg* 2005;72:221–6.
40. See KC, Phua J, Yip HS, Yeo LL, Lim TK. Identification of concurrent bacterial infection in adult patients with dengue. *Am J Trop Med Hyg* 2013;89:804–10.
41. Chen CM, Chan KS, Cheng KC, Chou W, Chao HC, Yeh CY, et al. The exploration of risk factors of concurrent bacteraemia in patients critically ill with severe dengue. *J Med Microbiol* 2016;65:1505–11.
42. Chen CM, Chan KS, Chao HC, Lai CC. Diagnostic performance of procalcitonin for bacteremia in patients with severe dengue infection in the intensive care unit. *J Infect* 2016;73:93–5.
43. Suzuki S, Kitazawa T, Ota Y, Okugawa S, Tsukada K, Nukui Y, et al. Dengue hemorrhagic shock and disseminated candidiasis. *Intern Med* 2007;46:1043–6.
44. Shivanthan MC, Navinan MR, Constantine GR, Rajapakse S. Cardiac involvement in dengue infection. *J Infect Dev Ctries* 2015;9:338–46.
45. Yacoub S, Griffiths A, Chau TT, Simmons CP, Wills B, Hien TT, et al. Cardiac function in Vietnamese patients with different dengue severity grades. *Crit Care Med* 2012;40:477–83.
46. Yacoub S, Wertheim H, Simmons CP, Screaton G, Wills B. Cardiovascular manifestations of the emerging dengue pandemic. *Nat Rev Cardiol* 2014;11:335–45.
47. Shah C, Vijayaraghavan G, Kartha CC. Spectrum of cardiac involvement in patients with dengue fever. *Int J Cardiol* 2021;324:180–5.