

1 **Full title:** Causes of death among hospitalized adults with dengue fever
2 in Tainan, 2015: emphasis on cardiac events and bacterial infections

3
4 **Short title:** Causes of death among hospitalized adults with dengue fever

5
6 Jen-Chieh Lee¹, Cong-Tat Cia¹, Nan-Yao Lee^{1,2}, Nai-Ying Ko^{4,5,6}, Po-Lin Chen^{1,2,3,7*},
7 Wen-Chien Ko^{1,2,3*}

8
9 ¹ Department of Internal Medicine, National Cheng Kung University Hospital,
10 College of Medicine, National Cheng Kung University, Tainan, Taiwan

11 ² Center for Infection Control, National Cheng Kung University Medical College and
12 Hospital, Tainan, Taiwan

13 ³ Department of Internal Medicine, College of Medicine, National Cheng Kung
14 University, Tainan, Taiwan

15 ⁴ Institute of Allied Health Sciences, Collage of Medicine, National Cheng Kung
16 University, Tainan, Taiwan

17 ⁵ Department of Public Health, Collage of Medicine, National Cheng Kung
18 University, Tainan, Taiwan

19 ⁶ Department of Nursing, College of Medicine, National Cheng Kung University,
20 Tainan, Taiwan

21 ⁷ Department of Microbiology and Immunology, College of Medicine, National
22 Cheng Kung University

23
24 *Corresponding author:

25 E-mail address: winston3415@gmail.com (WCK); cplin@mail.ncku.edu.tw (PLC)

26

27 **Keyword:** dengue fever, fatality, mortality, bacterial infection, bacteremia, cardiac

28 arrest, Taiwan

Abstract

Introduction. The 2015 dengue outbreak in southern Taiwan caused substantial mortality rates in the elderly. We analyzed here the causes of death among adults with dengue.

Methods. The retrospective study was conducted at a medical center in Tainan from the 1st of August to 31th of December in the year 2015. The detection of the dengue NS1 antigen IgM or viral RNA in patients' blood were used to diagnose dengue. Clinical courses and causes of death were retrieved from chart reviews by two intensivists.

Results. There were 4,488 cases of dengue diagnosed in the study hospital, and these cases had an in-hospital case fatality rate of 1.34% (60 cases). Of these, the mean age was 73 years and gender did not predict outcome. Twenty-eight (46.7%) cases died of severe dengue, and 29 (48.3%) deaths were possibly caused by dengue-related complications, which were mostly secondary infections (24 cases). Most of the families of fatal case (70%) signed do-not-resuscitate (DNR) orders prior to the patients' death. When the dengue epidemic peaked, 13 cardiac arrest events, including out-of-hospital (5 events) and in-hospital (8) cardiac arrests at the emergency department, occurred within four weeks of the dengue epidemic. Notably, in half (7) of these cases, the patients did not search for medical aid prior to experiencing cardiac arrest. Of the 40 cases that had early death (occurring within one week after hospitalization), 60% died of severe dengue. In contrast, 50% of the 20 deaths that occurred later than one week after hospitalization were related to hospital-acquired infections, mainly pneumonia.

Conclusion. The elderly that experience dengue fever may die of severe dengue early

53 or die of secondary infections later. Cardiac arrests can also occur unpredictably at the
54 first aids, which highlight the need of professional and patient education regarding the
55 danger signs that are related to severe dengue in an epidemic setting.

56 **Author summary**

57 The 2015 dengue outbreak in Tainan City caused substantial deaths among the
58 elderly. The main causes of death were severe dengue and its complications. We here
59 highlight the deaths caused by heart complications of dengue that the elderly has
60 underlying cardiovascular comorbidities is more prone to be involved. The
61 presentations of heart complications vary, ranging from arrhythmia to myocarditis and
62 to unexpected cardiac arrest. Clinicians should carefully evaluate and monitor the
63 heart function of patients with severe dengue and provide timing intervention.
64 Secondary infections or healthcare-associated infections may occur throughout the
65 whole hospitalized course. They were also the leading causes of death during the late
66 or recovery phase of dengue in the study. Judicious application of antimicrobial
67 agents and early elimination of infection source may be beneficial. Overall, the
68 substantial deaths during this outbreak may be related to low public awareness of
69 dengue, emergency department overclouding, and lack of clinical experience.
70 Professional and public education regarding the danger signs that are related to severe
71 dengue is necessary in an epidemic setting.

Introduction

Dengue is a mosquito-borne viral disease that affects humans and is emerging as a major threat to public health throughout the tropics and subtropics [1, 2]. Dengue affects children primarily in hyper-endemic areas [3] where epidemiological studies have shown the susceptible age group moved toward older children and adults [4]. Taiwan is not a hyperendemic area, but dengue outbreaks develop almost every year [5, 6]. Dengue predominantly affects adults in Taiwan. The highest prevalence rate is among people in their sixties [6]. During 2015, a large-scale dengue outbreak, which was caused by the dengue virus serotype 2, occurred in Tainan City [7] and a total of 22,777 dengue cases were confirmed [8]. Among these, 2%-3% had severe diseases or complications that required intensive care [9, 10]. However, with the increased utilization of intensive care units, the hospital stays for severe dengue patients were prolonged and more invasive devices were used. Healthcare-associated infections thus became unavoidable during the recovery phase.

Atypical presentations of dengue in the elderly are not uncommon [11] and make early diagnoses difficult. With multiple comorbidities complicating the clinical course of dengue, the elderly has more severe presentations and a higher mortality rate than children and young adults during this outbreak [12]. To know their cause of deaths may alarm early symptoms and signs of life-threatening conditions to clinicians. However, this information was limited in the literature. A two-year review in Malaysia has discussed deaths that were directly caused by dengue [13]. The causes of death stratified by the pathophysiology of dengue fever include dengue shock syndrome, severe bleeding, and severe organ involvement. Two case series that include seven and ten cases, respectively, mention deaths that were related to the complications other than dengue [14, 15]. Other studies that have paramedical points

97 of view, discuss how these factors involve clinicians, patients, and the medical
98 system, will lead to dengue death [16, 17]. The present study aimed to analyze the
99 causes of death among dengue patients that were cared at a medical center in 2015.

Methods

Case inclusion

The study was conducted at the National Cheng Kung University Hospital (NCKUH), a medical center in southern Taiwan, between August 1st and December 31th in the year 2015. Cases of dengue were identified from the dengue notification in the Infection Control Center, NCKUH. The diagnosis of dengue fever was established by the documentation of dengue NS1 antigen (Bioline Dengue NS1 Ag kit, Standard Diagnostics Inc., Korea), dengue IgM (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 protocol was approved by the Institutional Review Board at NCKUH (A-ER-104-386) and informed consents were waived. The study was funded by Ministry of Health and Welfare, Taiwan, with award number: MOHW107-TDU-B-211-123003. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Definitions

Cardiac arrest events at the emergency department (ED) included out-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). The weekly mortality rate was determined as the ratio of fatal case number and the number of newly diagnosed cases of dengue fever during the indicated week. Typical presentations of dengue fever included fever with two of the following symptoms or signs: nausea/vomiting, rash, aches/pains, positive tourniquet test, leucopenia, or any of warning signs [18]. If the initial manifestations of dengue did not fulfil the above criteria of the typical presentations, these cases were considered to be atypical. The

severity of dengue fever was graded using the WHO guidelines issued in 2009 [18]. Group A includes those without warning signs, Group B those with warning signs, co-existing complicated conditions, or special social circumstances, and Group C includes those with the signs of severe plasma leakage, severe hemorrhages, or severe organ impairment. Plasma leakage was supported by a hematocrit change of more than 20% or the presence of pleural effusion or ascites. Unstable vital signs indicate the presence of hypotension (systolic pressure less than 90 mmHg or mean pressure less than 65 mmHg), impending respiratory failure, or altered mental status. The age-modified Charlson's index was used to evaluate comorbidity status [19]. Days of hospitalization here were included days of ED stay.

Organ failure associated with dengue fever was defined as the dysfunction of the cardiovascular system, respiratory system, nervous system, liver, or kidney after dengue onset. Cardiovascular failure was defined as the patients having a mean blood pressure of less than 65 mmHg, the need of inotropic agents to maintain blood pressure, or low cardiac output signs. Respiratory failure was defined as a $\text{PaO}_2/\text{FiO}_2$ ratio of less than 300 [20] or PaCO_2 more than 50 mmHg [21], with or without increased breathing effort. Nervous system failure was characterized as the patient having a Glasgow Coma scale score of less than 8 [22]. Serum bilirubin level of more than 2 mg/dl was regarded as liver failure [20]. The KDIGO criteria were applied to define renal failure, *i.e.*, an increase of serum creatinine levels of more than twice the baseline level or more than 4 mg/dl, urine output of less than 0.3 ml/kg/hour over 24 hours, or anuria for 12 hours [23]. Multiorgan failure was defined as the presence of failure of more than two organ systems.

Causes of death

Cause of death in the cases of dengue fever was evaluated by two intensivists with complete training in infectious diseases. The causes of death were categorized into three groups. Death was considered to be related to “severe dengue” if the patient died of severe plasma leakage, major bleeding, or organ failures. If the patient died of organ failures but we were unable to attribute this death solely to severe dengue, the death was classified as “possibly dengue related”. If there were other clinical diseases that inevitably lead to death, the cause of death was classified as “other”.

Data acquisition

All parameters including demographic information, underlying disease, status of organ system dysfunction, date and cause of death, dengue onset, date of hospital visiting, and timing of the do-not-resuscitation (DNR) order, were obtained and calculated from electronic medical records.

Statistical methods

To analyze the causes of death, patients were further stratified into deaths within one week of hospitalization and deaths after one week. Chi-squared or Fisher exact tests were used to compare categorical variables between groups. Continuous variables were compared using a Student’s t-test. All data were processed using SPSS (20th edition, IBM). A *P* value of less than 0.05 is denoted as significant.

170 Result

171 During the study period, there were 4,488 hospitalized cases of serologically
172 documented dengue in NCKUH, Tainan. Among these patients, 60 died with a crude
173 in-hospital mortality rate of 1.34%, and 40 (66.7%) died within seven days of
174 hospitalization. The mortality rate reached a peak of 1.57% during the 40th week and
175 the case number reached its peak in the 36th week of 2015.

176 The mean age of patients in fatal cases was 73 years and the major underlying
177 medical illnesses were hypertension (32 cases, 53.3%), diabetes mellitus (30, 50%),
178 and chronic kidney disease (20, 33.3%), as shown in Table 1.

179

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

Parameters	Case No. (%)
Age (mean $\pm$ standard deviation), years	73.4 $\pm$ 12.4
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.

180

181 As for the causes of death, 46.7% (28 cases) died of severe dengue, and 65%
 182 (39) of the deaths were possibly related to dengue (Table 2). Of the later, a substantial
 183 proportion (40%, 24 cases) died of secondary infections. Two (3.3%) deaths were
 184 related to acute renal failure, and two (3.3%) died of respiratory failure without
 185 advanced airway management. A patient that refused interventional procedures died
 186 of massive gastrointestinal bleeding, which occurred while the patient had a platelet
 187 count of $94 \times 10^9/L$ during the 22nd day of hospitalization. Three patients died from a
 188 brain tumor, medication suffocation, and a traffic accident that caused a skull bone
 189 fracture and intracranial hemorrhage and were coincident with dengue fever,
 190 respectively.

191

Table 2. Clinical characteristics of the deaths of adults with dengue fever occurring ≤ 1 week and >1 week after their hospitalization.

Variables	Death after hospitalization		<i>P</i> value
	≤ 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	5 (12.5)	0 (0)	0.16
Possibly dengue-related	14 (35)	15 (75)	0.003
Secondary infections	14 (35)	10 (50)	0.58
Bacteremia	6 (15)	0 (0)	0.17
Candidemia	2 (5)	1 (5)	1
Pneumonia	5 (12.5)	8 (40)	0.02
Pneumonia and bacteremia	1 (2.5)	0 (0)	1
Necrotizing fasciitis	0 (0)	1 (5)	0.33
Renal failure and its complication	0 (0)	2 (10)	0.11
Respiratory failure	0 (0)	2 (10)	0.11
Lower gastrointestinal bleeding	0 (0)	1 (5)	0.33
Others	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

ED, emergency department

192

193 The death causes were compared between those dying within one week and those
194 after one week of hospitalization (Table 2). For the former, the primary causes of
195 death were severe dengue (24 cases, 60%) and secondary infection (14, 35%). Of the
196 24 deaths caused by severe dengue, five (12.5%) died from cardiac events that

included fatal arrhythmia, myocarditis, and refractory heart failure. Among those that died after one week of hospitalization, the major causes of death were secondary infections (10 cases, 50%), renal failure (2, 10%), and respiratory failure (2, 10%). There were four (20%) cases in which the patients died from severe dengue. Of these, three (15%) died from intracranial hemorrhage, which developed during the critical phase of dengue. Candidemia can occur either early (within one week, two cases) or late (after one week, one case) during hospitalization. In contrast, among the seven fatal cases in which death was caused by bacteremia, all of these deaths occurred during the first week.

The mortality rate and the number of new cases and cardiac arrest events at the ED by week are shown in Figure 1. Of note, 13 cardiac arrest events occurred between the 36th and 39th week of 2015, also when the dengue outbreak peaked. Among the cases that had cardiac arrest, five occurred out-of-hospital cardiac arrest (OHCA) and eight had in-hospital cardiac arrest (IHCA) while staying at the ED (Table 3).

Figure 1. Weekly notified dengue cases in the study hospital and early mortality rates. The case number of newly diagnosed dengue patients came to peak in the Week 36 while the early mortality rate (*i.e.*, death within the first week of hospitalization). peaked in the Week 40. Cardiac arrest events occurred mainly in Week 36-39 when the outbreak was in full swing. An asterisk (*) indicates a cardiac arrest event at the emergency department.

Table 3. Characteristics of 13 cardiac arrest events at the emergency department.

Serial No.	OHCA					IHCA							
	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													
Charlson's comorbidity index	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	ND	4	ND	6	0	6	1	3	0	2	5	0	5

CPR, cardiopulmonary resuscitation; ED, emergency department; IHCA, in-hospital cardiac arrest at the ED; ND: no data; OHCA, out-of-hospital cardiac arrest; OPD, outpatient department.

219
 220 The intervals between ED arrival and the IHCA event varied, ranging between
 221 one and 46 hours. The estimated interval between dengue onset and death ranged
 222 between 0 and 6 days. Ages in these cases ranged between 41 and 83 years and the
 223 Charlson's index ranged between 1 and 9. Of these 13 cases, 7 cases did not search
 224 for medical aid prior to the events, and 12 cases presented to the ED with severe
 225 dengue (WHO Grade B or C). The exception was a case of WHO Grade A disease
 226 that died soon after the onset of upper back pain with diffuse ST-T elevation (Figure
 227 2) in electrocardiography records at the ED. This is shown as case 13 in Table 3.

228
 229 **Figure 2. Electrocardiography record from a patient with dengue fever that was**
 230 **dying of myocarditis.** The diagnosis of myocarditis was suggested by the diffuse ST-
 231 T elevation (case 13 in Table 3).

232
 233 Of the 60 fatal cases, 70% (42) signed do-not-resuscitate (DNR) orders prior to
 234 their death (Table 4), and two thirds (28 cases) of DNR decisions were made within
 235 one week after their hospital arrival. Of note, DNR was requested in six cases without
 236 organ failure, twelve with failure of one organ system, and eight with failure of two
 237 organ systems

Table 4. Number of organ failures in the 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)

238 Discussion

239 The 2015 dengue outbreak in southern Taiwan came to its peak in early
240 September. The mortality rate of patients included in this study reached its peak
241 during Week 40. Of note, the majority of the sudden death events, including OHCA
242 and IHCA at the ED, occurred within the first four weeks of the dengue outbreak.
243 This is likely related to the following: first, public awareness of dengue was low
244 during the early phase of the epidemic and less than one half (6) of the 13 patients that
245 experienced cardiac arrest sought medical care before their death. Early medical care
246 could be life-saving before dengue deteriorated [13-15]. Second, ED overclouding
247 may be associated with increased mortality rates and morbidity [24, 25], and the role
248 of patient diversion [24, 26] and the short stay ward at the ED [27] during large
249 outbreaks of infectious diseases is mentioned. With the implementation of a patient
250 diversion program in Tainan, and dengue rapid screening clinics in the study hospital,
251 the ED patient burden was correspondingly decreased, which may facilitate optimal
252 initial care for the elderly that have severe dengue. Third, a lack of clinical experience
253 in the ED professional staff may delay the timely diagnosis and appropriate care for
254 severe diseases. A recent study found that case management training can improve
255 dengue outcomes [28] and protocolized care may accelerate the transformation of
256 knowledge [29] and help inexperienced healthcare providers.

257 Dengue in Taiwan often involves the elderly [6], for which the diagnosis of
258 dengue may be challenging because of atypical presentations [5, 30]. The febrile
259 elderly with leucopenia has been referred to as a trigger for diagnostic laboratory tests
260 for dengue fever [31]. The clinical symptoms and signs that are presumably linked to
261 underlying comorbidities in the elderly can further delay the diagnosis of dengue.
262 More than half of our patients had atypical presentation during their initial medical

visits, and the diagnosis of infection with the dengue virus was delayed in eight cases. Thus, to achieve the goal of early diagnosis, clinical suspicion of dengue should not be limited to the typical dengue fever “criteria” in endemic settings.

In our series, five OHCA and eight IHCA cases that had atypical presentation at the ED had a fulminant course. Not all fatal dengue cases received optimal intensive care in the ED before their death. Thrombocytopenia was not observed in five cases, and five had no evidence of plasma leakage, contradictory to severe manifestations of dengue fever [18]. Closely laboratory test and vital sign monitoring may be necessary in patients really needed intensive care. Another potentially fatal complication of dengue fever is pericardiomycocarditis, which is illustrated by sudden collapse, diffuse ST-T elevation in electrocardiograms (Figure 2), and elevated serum cardiac enzymes, but without thrombocytopenia or plasma leakage.

The overall mortality rate of hospitalized patients with dengue fever in the study hospital was 1.3%. Multiple factors, such as increased age or epidemic serotype 2 dengue virus, may contribute 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. Through advances in organ support, those with severe dengue may have a greater chance to survive, but DNR orders precludes the intensive care provided by healthcare workers. In Taiwan, old age is the main factor in signing DNR orders in critically ill patients [32, 33]. A study in Taiwan revealed that patients with renal failure had the highest percentage of signed DNR orders [34]. Furthermore, aspects of Taiwanese culture caused many to refuse tracheostomy [35]. We observed that dengue patients with DNR orders and without organ failure were older than those with organ failures, although the difference was not significant. However, their prognosis may remain poor even without a DNR order under advanced medical

support.

To further analyze the causes of death, more than half of the early deaths (*i.e.*, deaths within one week of hospitalization) were related to severe dengue with either plasma leakage or major bleeding. However, there were three cases in which the patients experienced rapid organ failure without evidence of plasma leakage and major bleeding. In contrast, the two main causes of death that occurred after one week of hospitalization were healthcare-associated bacterial infections and organ dysfunction that was related to severe dengue. Identifying secondary infections among hospitalized dengue patients is critical during dengue epidemics. The primary pathogens that caused bacteremia in dengue patients were *Staphylococcus aureus*, *Streptococcus* species, and *Enterobacteriaceae* [36]. Old age, comorbidities, severe disease with gastrointestinal bleeding, prolonged activated prothrombin time, and acute renal failure were recognized as risk factors for concurrent bacteremia [37-39]. Laboratory parameters, such as leukocyte count [38], serum C-reactive protein [39], and procalcitonin [40], may be useful to differentiate those with concurrent bloodstream infections from those that had only dengue virus infection alone.

One unique finding in the present study is that cardiac events were associated with dengue virus infection. Before their death, five patients suffered 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 and ranged from subclinical functional myocardial impairment to fulminant myocarditis [41, 42]. Fluid resuscitation may predispose patients with impaired cardiac function to pulmonary edema, and arrhythmias may be induced when plasma leakage or renal function impairment was ongoing. Patients with risk factors, such as old age, underlying cardiovascular disease,

313 abnormal electrocardiogram findings, elevated cardiac enzymes, and shock
 314 unresponsive to fluid resuscitation, warrant further evaluation by cardiac specialists
 315 [43].

316 Our study has several limitations. First, this study was conducted at a single
 317 medical center in southern Taiwan, which provided care for more than half of the
 318 critical patients from Tainan City during the 2015 dengue epidemic. Second, the data
 319 were collected retrospectively, and certain important parameters, such as the time of
 320 disease onset and detailed symptoms and signs, cannot be obtained from medical
 321 records. Third, the causes of death were clinically categorized and cannot be verified
 322 by autopsy. However, the study results were recorded by two experienced intensivists
 323 who had the Taiwan board of infection disease specialization.

324 In conclusion, elderly patients with severe dengue are at risk of fatal cardiac
 325 events and secondary infections. Absence of medical care among one half of adults
 326 with cardiac arrest reveals the importance of health education for the public during
 327 dengue epidemics.

328 **Acknowledgement**

329 We thank Chih-Cheng Hsieh and Wei-Chieh Lin for their help in
330 conceptualization of the study and preparing the manuscript.

References

1. Gibbons RV, Vaughn DW. Dengue: an escalating problem. *Brit Med J*. 2002;324: 1563-6.
2. Halstead SB. Dengue. *Lancet*. 2007;370:1644-52.
3. Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev*. 1998;11:480-96.
4. Lin RJ, Lee TH, Leo YS. Dengue in the elderly: a review. *Expert Rev Anti Infect Ther*. 2017;15:729-35.
5. 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.
6. Hsu JC, Hsieh CL, Lu CY. Trend and geographic analysis of the prevalence of dengue in Taiwan, 2010-2015. *Int J Infect Dis*. 2017;54:43-49
7. Wang SF, Chang K, Loh EW, Wang WH, Tseng SP, Lu PL, Chen YH4, Chen YA. Consecutive large dengue outbreaks in Taiwan in 2014-2015. *Emerg Microbes Infect*. 2016;5:e123.
8. Center of Disease Control, Taiwan. National Infectious Disease Statistics system. https://nidss.cdc.gov.tw/ch/NIDSS_DiseaseMap.aspx?dc=1&dt=2&disease=061
9. Hsieh CC, Cia CT, Lee JC, Sung JM, Lee NY, Chen PL, Kuo TH, Chao JY, Ko WC. A cohort study of adult patients with severe dengue in Taiwanese intensive care units: the elderly and APTT prolongation matter for prognosis. *PLoS Negl Trop Dis*. 2017;11:e0005270.
10. Chen CM, Chan KS, Yu WL, Cheng KC, Chao HC, Yeh CY, Lai CC. The outcomes of patients with severe dengue admitted to intensive care units. *Medicine (Baltimore)*. 2016;95:e4376.
11. Lee CC, Hsu HC, Chang CM, Hong MY, Ko WC. Atypical presentations of

356 dengue disease in the elderly visiting the ED. *Am J Emerg Med*. 2013;31:783-7.

357 12. Yeh CY, Chen PL, Chuang KT, Shu YC, Chien YW, Perng GC, Ko WC, Ko
358 NY. Symptoms associated with adverse dengue fever prognoses at the time of
359 reporting in the 2015 dengue outbreak in Taiwan. *PLoS Negl Trop Dis*.
360 2017;11:e0006091.

361 13. Woon YL, Hor CP, Hussin N, Zakaria A, Goh PP, Cheah WK. A two-year
362 review on epidemiology and clinical characteristics of dengue deaths in
363 Malaysia, 2013-2014. *PLoS Negl Trop Dis*. 2016;10:e0004575.

364 14. Ong A, Sandar M, Chen MI, Sin LY. Fatal dengue hemorrhagic fever in adults
365 during a dengue epidemic in Singapore. *Int J Infect Dis*. 2007;11:263-7.

366 15. Sam SS, Omar SF, Teoh BT, Abd-Jamil J, AbuBakar S. Review of dengue
367 hemorrhagic fever fatal cases seen among adults: a retrospective study. *PLoS*
368 *Negl Trop Dis*. 2013;7:e2194.

369 16. Tomashek KM, Gregory CJ, Rivera Sánchez A, Bartek MA, Garcia Rivera EJ,
370 Hunsperger E, Muñoz-Jordán JL, Sun W. Dengue deaths in Puerto Rico: lessons
371 learned from the 2007 epidemic. *PLoS Negl Trop Dis*. 2012;6:e1614.

372 17. Carabali M, Hernandez LM, Arauz MJ, Villar LA, Ridde V. Why are people
373 with dengue dying? A scoping review of determinants for dengue mortality.
374 *BMC Infect Dis*. 2015;15:301.

375 18. World Health Organization (2009) Dengue: guidelines for diagnosis, treatment,
376 prevention and control. Geneva: World Health Organization

377 19. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined
378 comorbidity index. *J Clin Epidemiol*. 1994;47:1245-51.

379 20. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM,
380 Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the

- 381 incidence of organ dysfunction/failure in intensive care units: results of a
382 multicenter, prospective study. Working group on "sepsis-related problems" of
383 the European Society of Intensive Care Medicine. *Crit Care Med.* 1998;26:1793-
384 800.
- 385 21. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, Church
386 AC, Creagh-Brown B, Dodd JW, Felton T, Foëx B, Mansfield L, McDonnell L,
387 Parker R, Patterson CM, Sovani M, Thomas L; BTS Standards of Care
388 Committee Member, British Thoracic Society/Intensive Care Society Acute
389 Hypercapnic Respiratory Failure Guideline Development Group, On behalf of
390 the British Thoracic Society Standards of Care Committee. BTS/ICS guideline
391 for the ventilatory management of acute hypercapnic respiratory failure in adults.
392 *Thorax.* 2016;71 Suppl 2:ii1-35.
- 393 22. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A
394 practical scale. *Lancet.* 1974;2:81-4.
- 395 23. Section 2: AKI Definition. *Kidney Int Suppl* (2011). 2012;2:19-36.
- 396 24. Shapiro JS, Genes N, Kuperman G, Chason K; Clinical Adenguesory Committee
397 H1N1 Working Group, New York Clinical Information Exchange, Richardson
398 LD. Health information exchange, biosurveillance efforts, and emergency
399 department crowding during the spring 2009 H1N1 outbreak in New York City.
400 *Ann Emerg Med.* 2010;55:274-9.
- 401 25. Cowan RM, Trzeciak S. Clinical review: Emergency department overcrowding
402 and the potential impact on the critically ill. *Crit Care.* 2005;9:291-5.
- 403 26. Schull MJ, Mamdani MM, Fang J. Community influenza outbreaks and
404 emergency department ambulance diversion. *Ann Emerg Med.* 2004;44:61-7.
- 405 27. Nasarudin NM, Mohd Saiboon I, Ismail AK. The role of an emergency

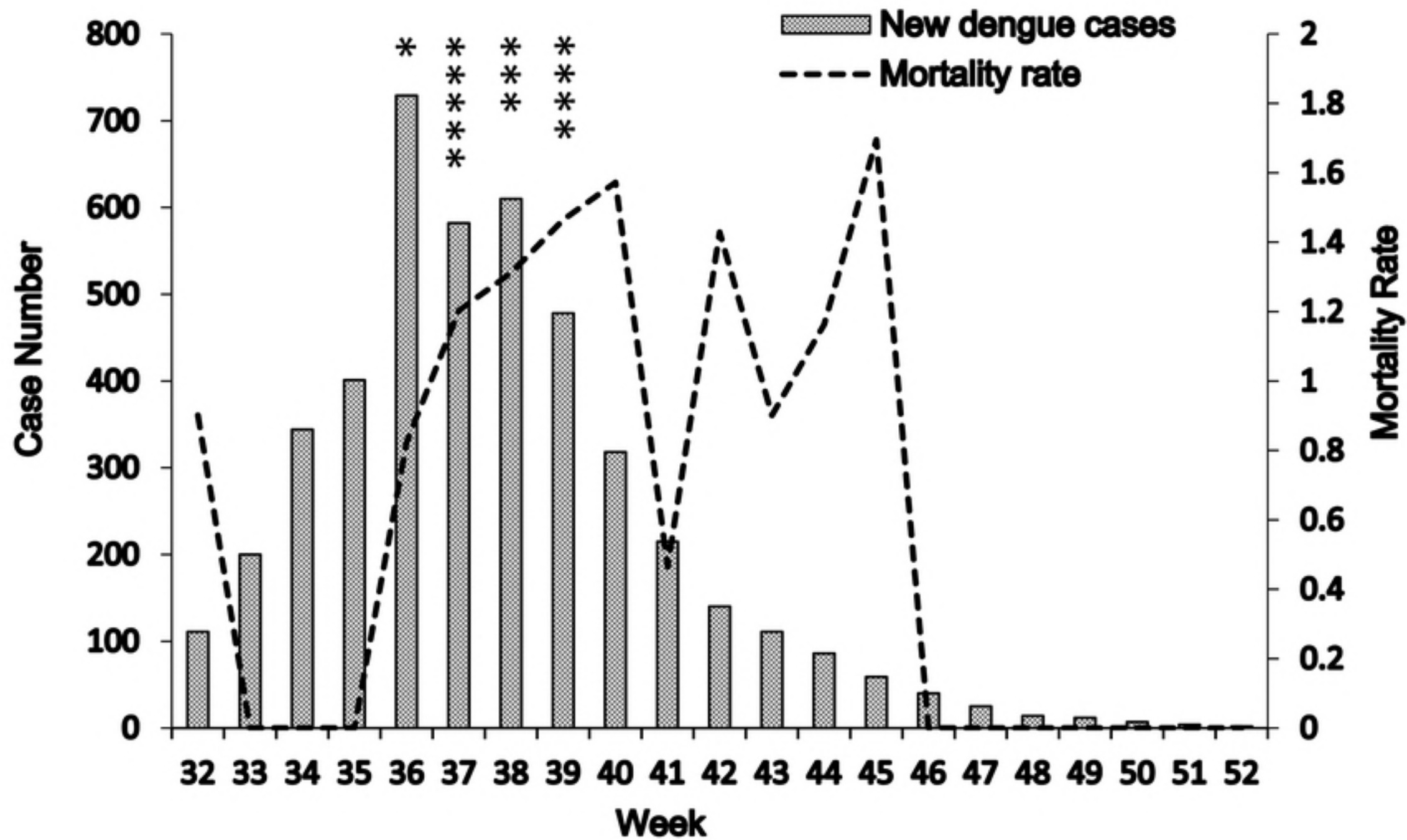
- 406 department short-stay ward in the management of dengue fever: a case-control
407 study in a university hospital. *Eurr J Emerg Med*. 2013;20:335-8.
- 408 28. Han GS, Gregory CJ, Biggerstaff BJ, Horiuchi K, Perez-Guerra C, Soto-Gomez
409 E, et al. Effect of a dengue clinical case management course on physician
410 practices in Puerto Rico. *Clin Infect Dis*. 2016;63:1297-303.
- 411 29. Rocha C, Silva S, Gordon A, Hammond SN, Elizondo D, Balmaseda A, et al.
412 Improvement in hospital indicators after changes in dengue case management in
413 Nicaragua. *Am J Trop Med Hyg*. 2009;81:287-92.
- 414 30. Rowe EK, Leo YS, Wong JG, Thein TL, Gan VC, Lee LK, et al. Challenges in
415 dengue fever in the elderly: atypical presentation and risk of severe dengue and
416 hospital-acquired infection. *PLoS Negl Trop Dis*. 2014;8:e2777.
- 417 31. Low JG, Ong A, Tan LK, Chaterji S, Chow A, Lim WY, et al. The early clinical
418 features of dengue in adults: challenges for early clinical diagnosis. *PLoS Negl
419 Trop Dis*. 2011;5:e1191.
- 420 32. Lin KH, Chen YS, Chou NK, Huang SJ, Wu CC, Chen YY. The associations
421 between the religious background, social supports, and do-not-resuscitate orders
422 in Taiwan: An observational study. *Medicine (Baltimore)*. 2016;95:e2571.
- 423 33. Huang CT, Chuang YC, Tsai YJ, Ko WJ, Yu CJ. High mortality in severe sepsis
424 and septic shock patients with do-not-resuscitate orders in East Asia. *PLoS One*.
425 2016;11:e0159501.
- 426 34. Chang HT, Lin MH, Chen CK, Chou P, Chen TJ, Hwang SJ. Trends of Do-Not-
427 Resuscitate consent and hospice care utilization among noncancer decedents in a
428 tertiary hospital in Taiwan between 2010 and 2014: A Hospital-based
429 observational study. *Medicine (Baltimore)*. 2016;95:e5394.
- 430 35. Yuan CR, Lan TY, Tang GJ. Can tracheostomy improve outcome and lower

- 431 resource utilization for patients with prolonged mechanical ventilation? *Chin*
- 432 *Med J (Engl)*. 2015;128:2609-16.
- 433 36. Thein TL, Ng EL, Yeang MS, Leo YS, Lye DC. Risk factors for concurrent
- 434 bacteremia in adult patients with dengue. *J Microbiol Immunol Infect*.
- 435 2017;50:314-20
- 436 37. Lee IK, Liu JW, Yang KD. Clinical characteristics and risk factors for
- 437 concurrent bacteremia in adults with dengue hemorrhagic fever. *Am J Trop Med*
- 438 *Hyg*. 2005;72:221-6.
- 439 38. See KC, Phua J, Yip HS, Yeo LL, Lim TK. Identification of concurrent bacterial
- 440 infection in adult patients with dengue. *Am J Trop Med Hyg*. 2013;89:804-10.
- 441 39. Chen CM, Chan KS, Cheng KC, Chou W, Chao HC, Yeh CY, et al. The
- 442 exploration of risk factors of concurrent bacteraemia in patients critically ill with
- 443 severe dengue. *J Med Microbiol*. 2016;65:1505-11.
- 444 40. Chen CM, Chan KS, Chao HC, Lai CC. Diagnostic performance of procalcitonin
- 445 for bacteremia in patients with severe dengue infection in the intensive care unit.
- 446 *J Infect*. 2016;73:93-5.
- 447 41. Shivanthan MC, Navinan MR, Constantine GR, Rajapakse S. Cardiac
- 448 involvement in dengue infection. *J Infect Dev Ctries*. 2015;9:338-46.
- 449 42. Yacoub S, Griffiths A, Chau TT, Simmons CP, Wills B, Hien TT, et al. Cardiac
- 450 function in Vietnamese patients with different dengue severity grades. *Crit Care*
- 451 *Med*. 2012;40:477-83.
- 452 43. Yacoub S, Wertheim H, Simmons CP, Screaton G, Wills B. Cardiovascular
- 453 manifestations of the emerging dengue pandemic. *Nat Rev Cardiol*.
- 454 2014;11:335-45.

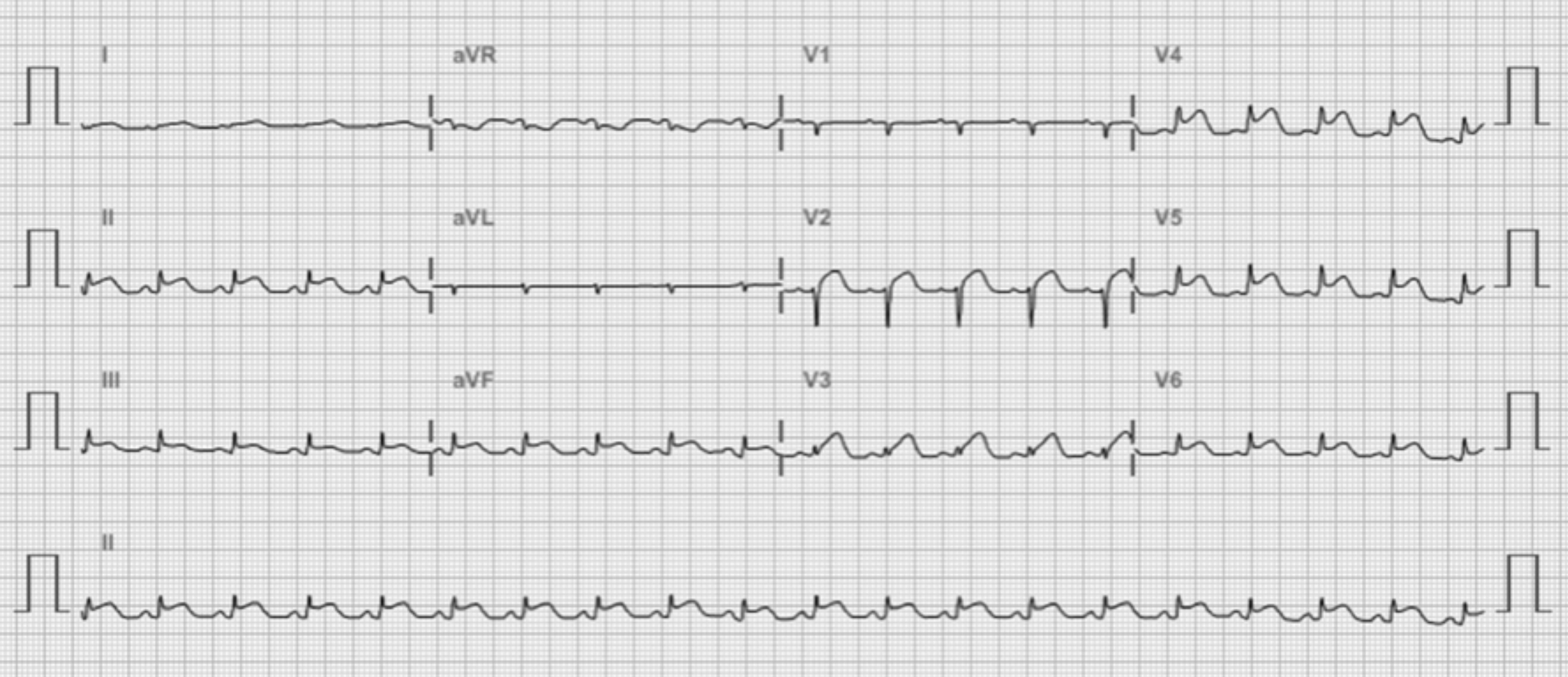
455 **Supporting information**

456 **S1 File. The data base of the 60 fatal cases in 2015 dengue outbreak in Tainan.**

457 **S1 Checklist. STROBE Checklist**



Figure



Figure