1 **Full title:** Causes of death among hospitalized adults with dengue fever

2 in Tainan, 2015: emphasis on cardiac events and bacterial infections

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

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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.

Author summary

56

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 arrythmia 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

72

73   Dengue is a mosquito-borne viral disease that affects humans and is emerging as

74 a major threat to public health throughout the tropics and subtropics [1, 2]. Dengue

75 affects children primarily in hyper-endemic areas [3] where epidemiological studies

76 have shown the susceptible age group moved toward older children and adults [4].

77 Taiwan is not a hyperendemic area, but dengue outbreaks develop almost every year

78 [5, 6]. Dengue predominantly affects adults in Taiwan. The highest prevalence rate is

79 among people in their sixties [6]. During 2015, a large-scale dengue outbreak, which

80 was caused by the dengue virus serotype 2, occurred in Tainan City [7] and a total of

81 22,777 dengue cases were confirmed [8]. Among these, 2%-3% had severe diseases

82 or complications that required intensive care [9, 10]. However, with the increased

83 utilization of intensive care units, the hospital stays for severe dengue patients were

84 prolonged and more invasive devices were used. Healthcare-associated infections thus

85 became unavoidable during the recovery phase.

86   Atypical presentations of dengue in the elderly are not uncommon [11] and make

87 early diagnoses difficult. With multiple comorbidities complicating the clinical course

88 of dengue, the elderly has more severe presentations and a higher mortality rate than

89 children and young adults during this outbreak [12]. To know their cause of deaths

90 may alarm early symptoms and signs of life-threatening conditions to clinicians.

91 However, this information was limited in the literature. A two-year review in

92 Malaysia has discussed deaths that were directly caused by dengue [13]. The causes

93 of death stratified by the pathophysiology of dengue fever include dengue shock

94 syndrome, severe bleeding, and severe organ involvement. Two case series that

95 include seven and ten cases, respectively, mention deaths that were related to the

96 complications other than dengue [14, 15]. Other studies that have paramedical points

6

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.

7

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

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125   severity of dengue fever was graded using the WHO guidelines issued in 2009 [18].

126   Group A includes those without warning signs, Group B those with warning signs, co-

127   existing complicated conditions, or special social circumstances, and Group C

128   includes those with the signs of severe plasma leakage, severe hemorrhages, or severe

129   organ impairment. Plasma leakage was supported by a hematocrit change of more

130   than 20% or the presence of pleural effusion or ascites. Unstable vital signs indicate

131   the presence of hypotension (systolic pressure less than 90 mmHg or mean pressure

132   less than 65 mmHg), impending respiratory failure, or altered mental status. The age-

133   modified Charlson's index was used to evaluate comorbidity status [19]. Days of

134   hospitalization here were included days of ED stay.

135   Organ failure associated with dengue fever was defined as the dysfunction of the

136   cardiovascular system, respiratory system, nervous system, liver, or kidney after

137   dengue onset. Cardiovascular failure was defined as the patients having a mean blood

138   pressure of less than 65 mmHg, the need of inotropic agents to maintain blood

139   pressure, or low cardiac output signs. Respiratory failure was defined as a PaO_2/FiO_2

140   ratio of less than 300 [20] or $PaCO_2$ more than 50 mmHg [21], with or without

141   increased breathing effort. Nervous system failure was characterized as the patient

142   having a Glasgow Coma scale score of less than 8 [22]. Serum bilirubin level of more

143   than 2 mg/dl was regarded as liver failure [20]. The KDIGO criteria were applied to

144   define renal failure, *i.e.,* an increase of serum creatinine levels of more than twice the

145   baseline level or more than 4 mg/dl, urine output of less than 0.3 ml/kg/hour over 24

146   hours, or anuria for 12 hours [23]. Multiorgan failure was defined as the presence of

147   failure of more than two organ systems.

148

149   **Causes of death**

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150   Cause of death in the cases of dengue fever was evaluated by two intensivists

151   with complete training in infectious diseases. The causes of death were categorized

152   into three groups. Death was considered to be related to "severe dengue" if the patient

153   died of severe plasma leakage, major bleeding, or organ failures. If the patient died of

154   organ failures but we were unable to attribute this death solely to severe dengue, the

155   death was classified as "possibly dengue related". If there were other clinical diseases

156   that inevitably lead to death, the cause of death was classified as "other".

157

Data acquisition

159   All parameters including demographic information, underlying disease, status of

160   organ system dysfunction, date and cause of death, dengue onset, date of hospital

161   visiting, and timing of the do-not-resuscitation (DNR) order, were obtained and

162   calculated from electronic medical records.

163

Statistical methods

165   To analyze the causes of death, patients were further stratified into deaths within

166   one week of hospitalization and deaths after one week. Chi-squared or Fisher exact

167   tests were used to compare categorical variables between groups. Continuous

168   variables were compared using a Student's t-test. All data were processed using SPSS

169   (20th edition, IBM). A P value of less than 0.05 is denoted as significant.

Result

170

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 ± standard deviation), years	73.4 ± 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)

11

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

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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 94×10^9/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		*P* value
	≤1week, n=40	>1week, n=20	
Age (mean ± standard deviation), years	73.1 ± 13.4	75.2 ± 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

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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

197   included fatal arrhythmia, myocarditis, and refractory heart failure. Among those that

198   died after one week of hospitalization, the major causes of death were secondary

199   infections (10 cases, 50%), renal failure (2, 10%), and respiratory failure (2, 10%).

200   There were four (20%) cases in which the patients died from severe dengue. Of these,

201   three (15%) died from intracranial hemorrhage, which developed during the critical

202   phase of dengue. Candidemia can occur either early (within one week, two cases) or

203   late (after one week, one case) during hospitalization. In contrast, among the seven

204   fatal cases in which death was caused by bacteremia, all of these deaths occurred

205   during the first week.

206   The mortality rate and the number of new cases and cardiac arrest events at the

207   ED by week are shown in Figure 1. Of note, 13 cardiac arrest events occurred

208   between the 36th and 39th week of 2015, also when the dengue outbreak peaked.

209   Among the cases that had cardiac arrest, five occurred out-of-hospital cardiac arrest

210   (OHCA) and eight had in-hospital cardiac arrest (IHCA) while staying at the ED

211   (Table 3).

212

213   **Figure 1. Weekly notified dengue cases in the study hospital and early mortality**

214   **rates.** The case number of newly diagnosed dengue patients came to peak in the

215   Week 36 while the early mortality rate (*i.e.*, death within the first week of

216   hospitalization). peaked in the Week 40. Cardiac arrest events occurred mainly in

217   Week 36-39 when the outbreak was in full swing. An asterisk (*) indicates a cardiac

218   arrest event at the emergency department.

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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.

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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)

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Discussion

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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

263   visits, and the diagnosis of infection with the dengue virus was delayed in eight cases.

264   Thus, to achieve the goal of early diagnosis, clinical suspicion of dengue should not

265   be limited to the typical dengue fever "criteria" in endemic settings.

266   In our series, five OHCA and eight IHCA cases that had atypical presentation at

267   the ED had a fulminant course. Not all fatal dengue cases received optimal intensive

268   care in the ED before their death. Thrombocytopenia was not observed in five cases,

269   and five had no evidence of plasma leakage, contradictory to severe manifestations of

270   dengue fever [18]. Closely laboratory test and vital sign monitoring may be necessary

271   in patients really needed intensive care. Another potentially fatal complication of

272   dengue fever is pericardiomyocarditis, which is illustrated by sudden collapse, diffuse

273   ST-T elevation in electrocardiograms (Figure 2), and elevated serum cardiac enzymes,

274   but without thrombocytopenia or plasma leakage.

275   The overall mortality rate of hospitalized patients with dengue fever in the study

276   hospital was 1.3%. Multiple factors, such as increased age or epidemic serotype 2

277   dengue virus, may contribute to the substantial mortality rate in our study. One

278   potential contributing sociocultural factor is the DNR signature during hospitalization

279   in up to 70% of fatal cases. Through advances in organ support, those with severe

280   dengue may have a greater chance to survive, but DNR orders precludes the intensive

281   care provided by healthcare workers. In Taiwan, old age is the main factor in signing

282   DNR orders in critically ill patients [32, 33]. A study in Taiwan revealed that patients

283   with renal failure had the highest percentage of signed DNR orders [34]. Furthermore,

284   aspects of Taiwanese culture caused many to refuse tracheostomy [35]. We observed

285   that dengue patients with DNR orders and without organ failure were older than those

286   with organ failures, although the difference was not significant. However, their

287   prognosis may remain poor even without a DNR order under advanced medical

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288   support.

289   To further analyze the causes of death, more than half of the early deaths (*i.e.,*

290   deaths within one week of hospitalization) were related to severe dengue with either

291   plasma leakage or major bleeding. However, there were three cases in which the

292   patients experienced rapid organ failure without evidence of plasma leakage and

293   major bleeding. In contrast, the two main causes of death that occurred after one week

294   of hospitalization were healthcare-associated bacterial infections and organ

295   dysfunction that was related to severe dengue. Identifying secondary infections

296   among hospitalized dengue patients is critical during dengue epidemics. The primary

297   pathogens that caused bacteremia in dengue patients were *Staphylococcus aureus*,

298   *Streptococcus* species, and *Enterobacteriaceae* [36]. Old age, comorbidities, severe

299   disease with gastrointestinal bleeding, prolonged activated prothrombin time, and

300   acute renal failure were recognized as risk factors for concurrent bacteremia [37-39].

301   Laboratory parameters, such as leukocyte count [38], serum C-reactive protein [39],

302   and procalcitonin [40], may be useful to differentiate those with concurrent

303   bloodstream infections from those that had only dengue virus infection alone.

304   One unique finding in the present study is that cardiac events were associated

305   with dengue virus infection. Before their death, five patients suffered cardiac events,

306   including heart failure with cardiogenic shock or pulmonary edema, fatal arrhythmia,

307   and fulminant myocarditis. In the literature, the disease spectrum for cardiac

308   involvement in dengue patients was wide and ranged from subclinical functional

309   myocardial impairment to fulminant myocarditis [41, 42]. Fluid resuscitation may

310   predispose patients with impaired cardiac function to pulmonary edema, and

311   arrhythmias may be induced when plasma leakage or renal function impairment was

312   ongoing. Patients with risk factors, such as old age, underling cardiovascular disease,

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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.

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328

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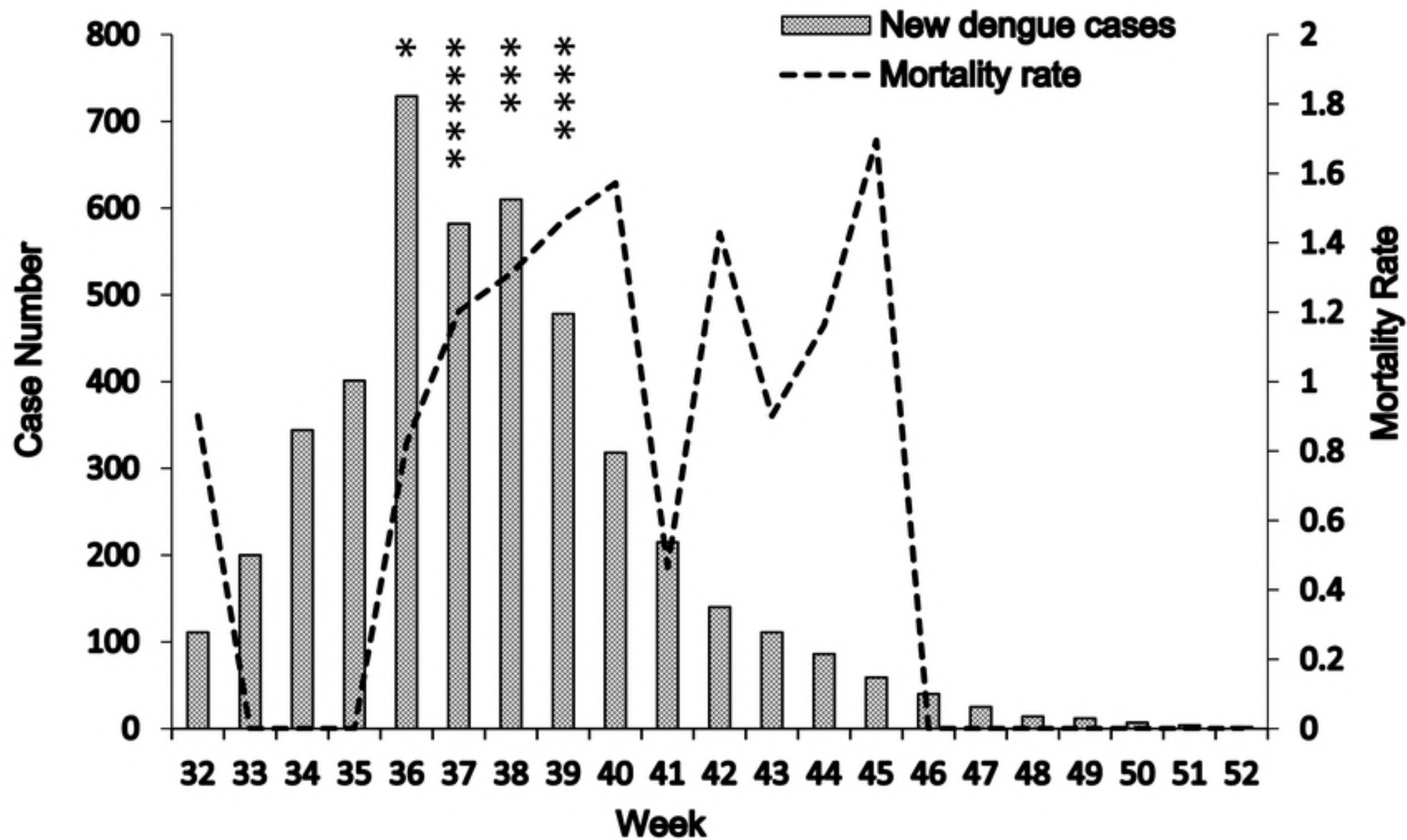
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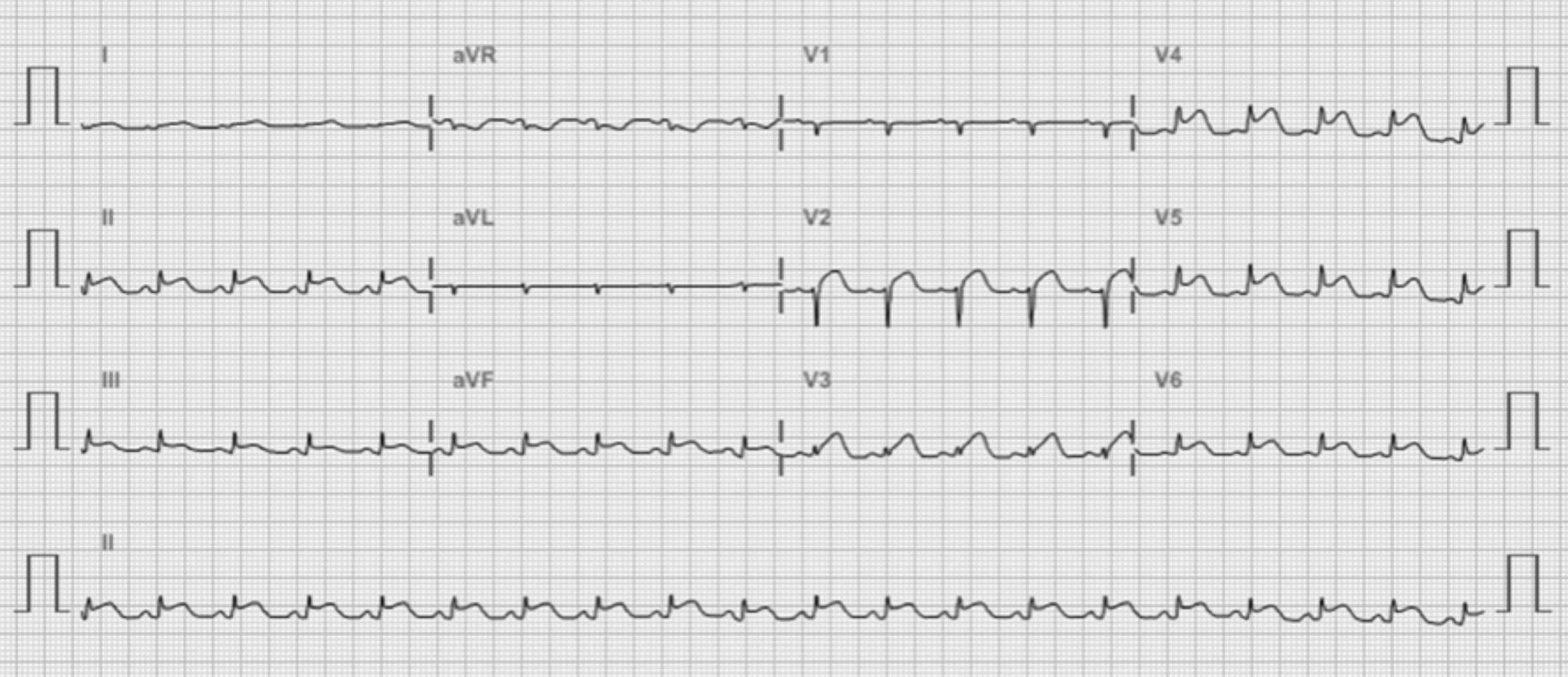
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455 **Supporting information**

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

457 **S1 Checklist. STROBE Checklist**

Figure

Figure