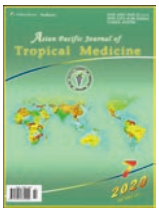

Original Article

Asian Pacific Journal of Tropical Medicine

journal homepage: www.apjtm.org

doi: 10.4103/1995−7645.285829

Impact Factor: 1.77

A cohort study of hospitalized adult dengue patients with fatality in Taiwan: The elderly and febrile characteristics matter for prognosis

Tsung−Hang Kuo[1,2], Chia−Chang Chuang[2], Chin−Chung Tseng[3], Ming−Yuan Hong[2], Sheng−Hsiang Lin[1,4,5,✉]

[1]*Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan 70403*

[2]*Department of emergency, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan 70403*

[3]*Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan 70403*

[4]*Biostatistics Consulting Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan 70403*

[5]*Department of Public Health, College of Medicine, National Cheng Kung University, Tainan 70403*

ABSTRACT

Objective: To identify the febrile characteristics and clinical presentations associated with fatality in hospitalized adult patients with dengue virus (DENV) infections.

Methods: A total of 289 adult hospitalized patients with laboratory-confirmed DENV infections were examined, of which 22 were fatal and 267 were non-fatal. A comparison of the clinical and laboratory characteristics was retrospectively conducted of the deceased and surviving individuals. Multivariate logistic regression and receiver operating characteristic curve analysis were performed to identify predictors of fatality.

Results: Fatal patients exhibited significantly more comorbidities, particularly renal and cardiac comorbidities, and they were, in general, older than control individuals (P<0.000 1). The results of logistic regression analysis showed that febrile duration of less than four days before arriving in the Emergency Department (*OR*=5.34; 95% *CI:* 1.39–20.6), episode of hypotension in the Emergency Department (*OR*=6.95; 95% *CI:* 2.40–20.1), and comorbidity with congestive heart failure (*OR*=11.26; 95% *CI:* 2.31–54.79) were all significantly associated with inpatient fatality due to DENV infection. The ROC curve analysis indicated that the final prognostic model yielded an area under the curve of 0.87 (95% *CI:* 0.79–0.97) for fatality.

Conclusions: The aforementioned clinical findings may help clinicians predict fatality among adult inpatients with DENV infection.

KEYWORDS: Dengue; Hospitalized patient; Adult; Fatality; Febrile duration; Hypotension

1. Introduction

The substantial increase in global dengue fever (DF) cases in recent decades has made it the most rapidly spreading arthropod-borne viral disease worldwide[1]. The World Health Organization (WHO) estimated that approximately 50 million dengue virus (DENV) infections occur annually, with 2.5 billion people living in dengue-endemic countries. Most DF cases have been reported from tropical and sub-tropical countries across Asia, Africa, and America[1]. In Tainan City, southern Taiwan, DENV infection was once sporadic, and in the decade preceding 2015, only a few hundred cases were reported annually, and most of these were imported from southeastern Asian countries. In 2015, however, Taiwan experienced the worst DENV outbreak in recent 10 years, with a high DF death rate (5.15%) and 43 784 notified cases, of which 22 777 (52%) occurred in Tainan[2]. This outbreak, caused by DENV2, was the most severe epidemic in Tainan's history.

Clinically, DENV infection ranges from asymptomatic, mild DF to dengue shock syndrome (DSS), a potentially fatal complication with a fatality rate ranging from <1% to 10%[3–5]. According to the latest WHO classification, DENV infections are classified into

✉To whom correspondence may be addressed. E-mail: shlin922@mail.ncku.edu.tw

How to cite this article: Kuo TH, Chuang CC, Tseng CC, Hong MY, Lin SH. A cohort study of hospitalized adult dengue patients with fatality in Taiwan: The elderly and febrile characteristics matter for prognosis. Asian Pac J Trop Med 2020; 13(7): 301-307.

Article history: Received 3 May 2020 Revision 27 May 2020
Accepted 28 May 2020 Available online 17 June 2020

severe dengue and non-severe dengue, with the former potentially associated with lethal complications caused by plasma leakage, fluid accumulation, severe bleeding, respiratory distress, or organ impairment.

The clinical phases of DENV infection can be broadly classified into three stages: febrility, defervescence, and recovery. The majority of patients with DENV infection normally recover after 2-5 days of acute febrile illness. However, in a small proportion of patients, the acute febrile stage may be followed by thrombocytopenia, plasma leakage, and major hemorrhage, indicating severe dengue during defervescence. Defervescence is thus considered as a critical phase. Therefore, the stage of the disease during which a patient is diagnosed is critical in determining the accuracy with which physicians can predict the possibility of progression to severe dengue and death.

With careful treatment, the fatality rate of DSS can be reduced to <0.2%[6]. Therefore, early identification of risk factors associated with disease progression from mild to severe dengue and death is essential in determining subsequent management. Previous studies have reported various risk factors associated with fatality in patients with DENV infection[7-11]. Significant risk factors associated with fatality reported were profound thrombocytopenia and leucocytosis[7], tachycardia on admission[12], hematemesis and melena[13], and absence of myalgia and leukocytosis[8]. A Brazilian study reported that patients exhibiting gastrointestinal bleeding, ascites, pericardial pleural effusion, hepatomegaly, hypotension, and shock, were at a higher risk of progression to death[14]. Another study in India showed that APACHE II scores alone could predict fatality among dengue patients admitted to the intensive care unit[15]. However, few studies have investigated the association between risk factors for fatality and febrile duration before arrival at the Emergency Department.

In this study, we retrospectively compared the clinical and laboratory characteristics of hospitalized adults with DENV infection to determine possible association with fatality and identify clinical and laboratory predictors for fatality.

2. Materials and methods

2.1. Data collection

We reviewed the medical records of hospitalized adult patients (aged >20 years) with laboratory-confirmed DENV infection between July 1, 2015 and December 31, 2015 at National Cheng Kung University Hospital in southern Taiwan, along with the data extracted from the hospital database. DENV infections were considered confirmed when at least one of the following criteria was met: (1) DENV-specific nonstructural glycoprotein-1 (NS1) antigen (SD BIOLINE Dengue Duo Dengue NS1 Ag+Ab Combo, Standard Diagnostics Inc., Republic of Korea) was detected in acute-phase serum; (2) DENV-specific reverse transcription-polymerase chain reaction (RT-PCR) (LightMix Kit Dengue Virus EC, TIB MOLBIOL GmbH, Berlin, Germany) was positive; or (3) enzyme-linked immunosorbent assay was positive for a specific DENV immunoglobulin M antibody (SD BIOLINE Dengue Duo Dengue NS1 Ag+Ab Combo, Standard Diagnostics Inc., Republic of Korea) in acute-phase[16,17].

2.2. Ethical approval

This study was approved by the ethics committee/institutional review board of the National Cheng Kung University Hospital (IRB number: A-ER-104-243).

2.3. Disease severity classification

Disease severity was defined according to the 2009 WHO guidelines, and was categorized into severe dengue, dengue with warning signs and dengue without warning signs. Warning signs included severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, fatigue, restlessness and blood in vomit. Severe dengue cases were defined as patients with shock (systolic blood pressure <90 mmHg), fluid accumulation with respiratory distress, severe plasma leakage (hematocrit elevation >20%), severe bleeding, or organ impairment[18].

A manual search was conducted and data were mainly retrieved from the hospital's electronic medical records. The data collected included demographic characteristics, laboratory test results, radiography/ultrasound examination results, the presence or absence of signs and symptoms, and reported morbidity at the time of Emergency Department admission. The time from the onset of fever to arrival in the Emergency Department (febrile duration before arriving in the Emergency Department) of each patient was also recorded. Fever was defined as a tympanic temperature >38.3 ℃. From chest radiography and ultrasonography scans, clinical fluid accumulation was defined as detection of pleural effusion or ascites. Leukocytosis was defined as a peripheral white blood cell (WBC) count of >10 000 cells/μL[19]. Acute kidney injury (AKI) was defined as an absolute increase in serum creatinine of ⩾0.3 mg/dL or a ⩾50% increase in serum creatinine within 48 hours[20]. Episodes of hypotension in the Emergency Department was defined as SBP <90 mmHg in the Emergency Department.

2.4. Data analysis

To identify early predictors of fatality due to DENV infection, clinical records from the time of arrival in the Emergency Department were analyzed. The demographic, clinical, and laboratory characteristics of hospitalized adult patients with or without fatality due to DENV infection were compared. *Chi*-square or Fisher's exact tests and Wilcoxon rank sum tests were used to

determine statistical significance for categorical and continuous variables, respectively. Differences with $P<0.05$ were considered significant. Multivariable logistic regression was performed using significant variables ($P<0.05$) from the univariate logistic regression to identify independent predictors of fatality. Firth's penalized-likelihood logistic regression was used to alleviate the small numbers of case diagnoses[21]. The interaction between hypotension and febrile duration before arriving in the Emergency Department was also determined, where febrile duration before arriving in the Emergency Department was treated as a binary variable (fever duration <4 days or ≥4 days). All statistical analyses were performed using the SAS 9.4 statistical software package (SAS Institute, Cary, NC).

3. Results

A total of 519 hospitalized patients with laboratory-confirmed DENV infection were identified during the six-month study period. Of these, 230 patients with no fever or unknown febrile duration. Thus, the analysis was conducted on 289 (55.60%) hospitalized patients with laboratory-confirmed DENV infection, of which 22 were fatal and 267 were non-fatal. We compared demographic, clinical and laboratory variables between 289 included patients and 230 excluded patients. The results showed that most variables were not significantly different (Supplementary Table 1).

The mean age of the 22 fatal cases was (77.4±8.04) years (range, 57-91 years; Table 1), and 45.45% of these patients were male. Upon arriving in the Emergency Department, 9 (40.91%) of these fatality patients were identified as having a DENV infection with mucosal bleeding, and severe dengue was identified in the other 13 (59.09%). The most common comorbidities were hypertension (72.73%), diabetes (40.91%), and chronic kidney disease (40.91%). Fourteen (63.64%) patients were diagnosed with acute kidney injury (AKI) according to the Kidney Disease: Improving Global Outcomes criteria[22], and 12 (54.55%) required ventilator support during the Emergency Department admission.

Compared with non-fatal patients, fatal patients exhibited a shorter febrile duration before arriving in the Emergency Department. No significant difference was observed in the sex distribution between non-fatal and fatal patients. Fatal patients had a higher rate of AKI, as well as a higher initial WBC count than non-fatal patients. Thrombocytopenia (Platelet count<100 000 cells/μL) and elevated serum transaminase levels (>40 unit per liter of serum) were common laboratory findings in both groups (Table 1).

In the univariate logistic model, older age, febrile duration before arriving in the Emergency Department (<4 days), presence of AKI upon arriving in the Emergency Department, presence of episodes of hypotension in the Emergency Department, WBC >10 000 cells/μL, and comorbidities of congestive heart failure and chronic kidney

Table 1. Demographic, clinical and laboratory variables of dengue patients with fatality and without fatality.

Variables	Without fatality (n=267)	With fatality (n=22)	P value
Age (years)[#]	72 (57-78)	76 (73-85)	<0.001
Male	142 (53.18)	10 (45.45)	0.634
Febrile duration before arriving in the ED[#]	3 (2-5)	2 (1-3)	0.001
Acute kidney injury	83 (31.09)	14 (63.64)	0.004
Hepatitis	168 (62.92)	16 (72.73)	0.491
Episode of hypotension in the ED	46 (17.23)	13 (59.09)	<0.001
Severe dengue in the ED	20 (7.49)	13 (59.09)	<0.001
Mechanical ventilation	2 (0.75)	12 (54.55)	<0.001
Warning signs			
Mucosal bleeding	100 (37.45)	9 (40.91)	0.926
Clinical fluid accumulation	61 (22.85)	5 (22.73)	1.000
Laboratory features			
WBC (cells/μL)[#]	4 200 (2 900-6 000)	7 750 (5 400-9 000)	0.011
WBC>10 000 cells/μL	15 (5.62)	4 (18.18)	0.046
Platelet (cells/μL)[#]	53 000 (18000-119 000)	35 500 (11 000-81 000)	0.050
Platelet<100 000 cells/μL	178 (66.67)	16 (81.82)	0.220
ALT (U/L)[#]	50 (18-94)	77 (130-44)	0.183
ALT>100 U/L	50 (22.96)	878.5 (53.134)	0.301
Comorbid condition			
Hypertension	140 (52.43)	16 (72.73)	0.107
Diabetes	71 (26.59)	9 (40.91)	0.232
Dementia	5 (1.87)	0 (0.00)	1.000
Ischemic heart disease	38 (14.23)	4 (18.18)	0.540
Cerebral vascular disease	21 (7.87)	4 (18.18)	0.109
Congestive heart failure	6 (2.25)	4 (18.18)	0.004
Chronic kidney disease	34 (12.73)	9 (40.91)	0.002
Malignancy	36 (13.48)	4 (18.18)	0.522

[#]Data are expressed as median range. Categorical variables are shown as the number and percentage of patients. Continuous variables are shown as the median and interquartile range. ED: Emergency Department; WBC: white cell count; ALT: alanine aminotransferase.

Table 2. Analysis of demographic, clinical and laboratory variables associated with fatality in dengue patients by logistic regression.

Variables	Univariate regression		Multivariate regression	
	OR (95% *CI*)	*P* value	*OR* (95% *CI*)	*P* value
Age (years)	2.57 (1.52-4.38)	<0.001	1.89 (1.05-3.44)	0.035
Male (*vs.* women)	0.73 (0.31-1.76)	0.487	-	
Febrile duration before arriving in the ED (<4 days *vs.* ≥4 days)	7.01 (1.61-30.58)	0.009	5.34 (1.39-20.6)	0.015
Acute kidney injury (yes *vs.* no)	3.88 (1.57-9.60)	0.003	1.23(0.41-3.72)	0.711
Hepatitis (yes *vs.* no)	1.57 (0.60-4.15)	0.361	-	
Episode of hypotension in the ED (yes *vs.* no)	6.94 (2.80-17.19)	<0.001	6.95 (2.40-20.1)	<0.00
Mucosal bleeding (yes *vs.* no)	1.16 (0.48-2.80)	0.748	-	
Clinical fluid accumulation (yes *vs.* no)	0.99 (0.35-2.80)	0.990	-	
WBC (>10 000 cells/μL *vs.* ≤10 000 cells/μL)	3.73 (1.12-12.42)	0.032	2.84 (0.71-11.36)	0.140
Platelet (<100 000 cells/μL *vs.* ≥100 000 cells/μL)	2.25 (0.74-6.85)	0.153	-	
ALT (>100 U/L *vs.* ≤100 U/L)	1.81 (0.73-4.52)	0.201	-	
Hypertension (yes *vs.* no)	2.41 (0.92-6.37)	0.074	-	
Diabetes (yes *vs.* no)	1.91 (0.78-4.66)	0.155	-	
Ischemic heart disease (yes *vs.* no)	1.34 (0.43-4.17)	0.614	-	
Cerebral vascular disease (yes *vs.* no)	2.60 (0.81-8.40)	0.109	-	
Congestive heart failure (yes *vs.* no)	9.67 (2.50-37.38)	0.001	11.26 (2.31-54.79)	0.003
Chronic kidney disease (yes *vs.* no)	4.74 (1.89-11.94)	0.001	2.05 (0.64-6.55)	0.227
Malignancy (yes *vs.* no)	1.43 (0.46-4.45)	0.541	-	

Age as ordinal variables: 0-65, 65-75, 75-85, ≥85; *OR*: odds ratio; *CI*: confidence interval; ED: Emergency Department; WBC: white cell count; ALT: alanine aminotransferase.

Table 3. Odds ratios of the development of fatality in dengue patients by the presence of hypotension episode and febrile duration before arriving in the ED <4 days.

Mortality	Patients without hypotension episode and more fever days (*n*=86)	Patients without hypotension episode and less fever days (*n*=144)	Patients with hypotension episode and more fever days (*n*=26)	Patients with hypotension episode and less fever days (*n*=33)
Yes [*n* (%)]	1 (1.16)	8 (5.56)	1 (3.85)	12 (36.36)
No [*n* (%)]	85 (98.84)	136 (94.44)	25 (96.15)	21 (63.64)
Crude *OR* (95% *CI*)	1	3.55 (0.61-20.76)	3.35 (0.33-34.63)	33.14 (5.64-194.8)*
Adjusted *OR*[a] (95% *CI*)	1	3.62 (0.60-21.91)	4.55 (0.42-48.94)	26.66 (4.11-172.8)#

[a]adjustment for age and congestive heart failure. *OR*: odds ratio; *CI*: confidence interval; ED: Emergency Department. *P=0.000 1; #P=0.000 6.

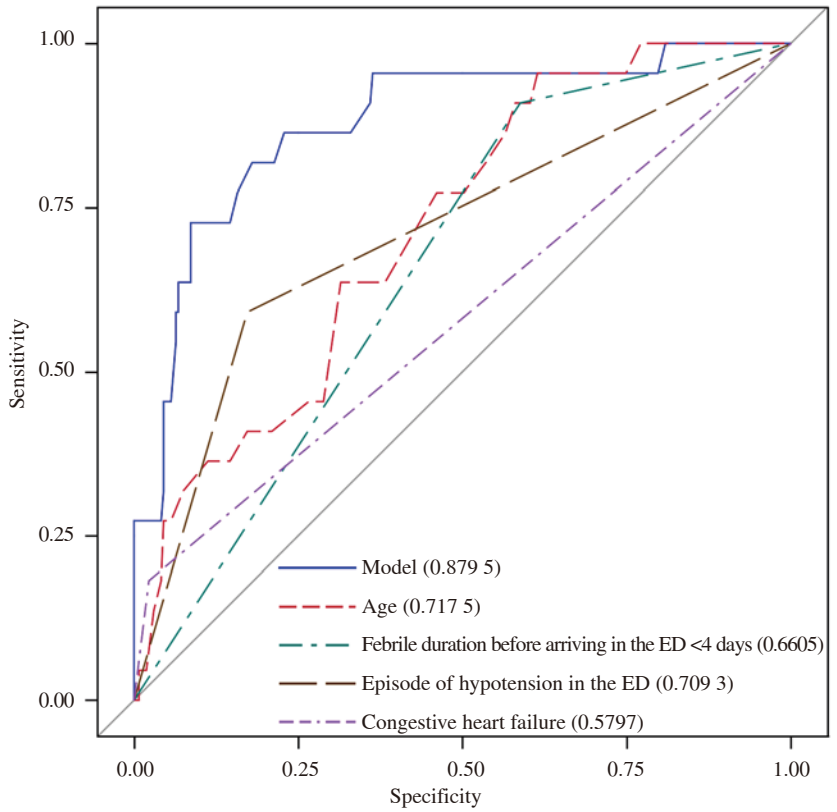

Figure 1. Receiver-operating characteristic curve for predictors of fatality in patients with dengue virus infection. ED: Emergency Department.

disease were significantly associated with in-hospital fatality. In the multivariate analysis, older age [*OR*=1.89; 95% *CI:* 1.05-3.44], febrile duration before arriving in the Emergency Department of <4 days (*OR*=5.34; 95% *CI:* 1.39-20.6), episodes of hypotension during Emergency Department admission (*OR*=6.95; 95% *CI:* 2.40-20.10), comorbidity with congestive heart failure (*OR*=11.26; 95% *CI:* 2.31-54.79) were independent predictive factors for in-hospital fatality after adjusting for age, febrile duration before arriving in the Emergency Department, AKI upon arriving in the Emergency Department, episodes of hypotension in the Emergency Department, WBC >1 000, and comorbidity with congestive heart failure and chronic kidney disease (Table 2). Patients with a febrile duration before arriving in the Emergency Department of <4 days had a significantly higher risk of fatality if they also had an episode of hypotension in the Emergency Department (adjusted *OR*=26.66; 95% *CI:* 4.11-172.80; Table 3) .

The area under the ROC curve (AUC) for age was 0.71 (95% *CI:* 0.61-0.82) and for febrile duration before arriving in the Emergency Department of <4 days was 0.66 (95% *CI:* 0.59-0.70) (Figure 1). For episodes of hypotension in the Emergency Department, the AUC was 0.71 (95% *CI:* 0.60-0.82), and for comorbidity with congestive heart failure it was 0.58 (95% *CI:* 0.50-0.66). The mean AUC was 0.87 (95% *CI:* 0.79-0.97).

4. Discussion

To the best of our knowledge, this is the first study to investigate the association between febrile duration before arriving in the Emergency Department and fatality in patients with DENV infection. Moreover, this is one of the few studies that has both reported the association between fatality due to DENV infection and clinical variables at Emergency Department admission, and identified febrile duration before arriving in the Emergency Department, episodes of hypotension in the Emergency Department, and comorbidity with congestive heart failure as independent predictive factors for in-hospital fatality.

Early identification of a high risk of fatality due to DENV infection based on initial signs and symptoms is a major clinical challenge that requires laboratory support and detailed clinical monitoring of vital signs. A recent study in Taiwan showed that organ failure and activated partial thromboplastin time prolongation may be prognostic factors for identifying critically ill adults with DENV infection[23]. In our study, the acute kidney injury was found to be 33.56% in the overall patient and 63.64% patient with fatality. Multifactorial causes may lead to acute kidney injury in patient with DENV infection[24, 25]. Shock with kidney hypoperfusion due to plasma leakage in severe dengue may provoke AKI in patient with DENV infection, especially in elderly host[24]. Besides, hepatic failure is also one of organ failure in patients with DENV infection. However, in our current study, ALT was not useful in predicting fatal outcomes. This reflects the inability of liver enzyme to discriminate severe dengue cases reported in several study from Singapore and Taiwan[8,26].

A previous study showed shock to be the most common cause of death, followed by organ impairment, including AKI, severe hepatitis, and impaired consciousness[27]. A case control study from Brazil found that patients with hypotension and shock are at a greater risk of progression to death[14]. A Puerto Rican study suggested that the presentation with shock should alert clinicians of the risk of severe dengue[28]. In the present study, an episode of hypotension in the Emergency Department was also a significant risk factor for fatality due to DENV infection.

A few scoring systems have been developed to identify adult patients with worse predicted outcomes, such as DSS and severe dengue. The simple clinical risk score for the early prediction of severe dengue in adult patients described by Lee *et al*. suggests that an age of $\geqslant$65 years, the presence of minor gastrointestinal bleeding, a platelet count of $\geqslant 100\times10^9$ cells/L, and leukocytosis (WBC $>10\times10^9$ cells/L) are independent risk factors that can distinguish severe dengue from non- severe dengue for models of dengue illness with a duration 4 days[19]. These studies defined severe dengue according to the 2009 WHO criteria. However, not all severe dengue cases progressed to death, and not all non- severe dengue cases survived. Indeed, in the present study, 40% of severe dengue cases survived and 7.5% of non- severe dengue cases eventually died. Therefore, the establishment of a simple yet precise scoring system for DENV infection is crucial.

Clinically, patients with DENV infection are often hospitalized for close monitoring due to a lack of simple and reliable clinical tools for predicting the risk of fatality. This large cohort of adult patients hospitalized for DENV infection included 22 fatal cases. Clinical data upon Emergency Department admission were analyzed, and because DENV infection is a dynamic disease that can result in various clinical manifestations, the febrile duration before arriving in the Emergency Department was also taken into consideration. We identified four significant independent predictors of fatality: old age, febrile duration before arriving in the Emergency Department, episode of hypotension in the Emergency Department, and comorbidity with congestive heart failure. By rounding the regression coefficients into integers, we developed a simple mortality-risk model for hospitalized patients with DENV infection, which was highly predictive for the risk of fatality (AUC=0.870).

There have been many previous reports from Singapore regarding adult DENV fatalities[12,27,29,30]. Our study included many fatal cases, who had a median age of 76 years. The median age of the fatal cases in our study was higher than reported previously, indicating a possible shift of severe disease toward the elderly population. Aging is also generally associated with atypical symptoms and higher rates of illness and fatality due to increased susceptibility to infections, which may be related to many factors, such as environmental conditions, presence of comorbidities, and physiological or immunological changes.

During the course of DENV infection, some patient's acute febrile stage may be followed by a plasma leakage, thrombocytopenia, or major hemorrhage, indicating the severe form of dengue hemorrhagic fever or DSS. Therefore, febrile duration before arriving in the Emergency Department should be considered as an important factor for predicting the outcomes of DENV infection. In addition, fever is an easily recognizable indicator of illness onset, so the reliability of this variable should be relatively high. Previously, Thein *et al*. reported leukocytosis and the absence of myalgia upon admission as independent predictors of fatality[8]. Furthermore, a cross-sectional study in Pakistan found that an SGPT >300 mg/dL, bleeding, an altered mental status and shock at presentation were all significantly associated with mortality in patients with dengue virus infection[9]. In 2017, a study in Taiwan showed elderly, hypotension, hemoptysis and DM were independent mortality predictors and developed dengue fever mortality score[31]. However, these studies did not consider febrile duration before arriving in the Emergency Department. A study in Taiwan in 2018 developed risk scoring models and emphasizing factors associated with death ≤7 days after illness onset. Another study in North India in 2017 found presentation to the hospital (≥5 days after disease onset) was an independent predictor of dengue severity[32]. However, the illness onset and disease onset were not clearly defined in this study. We think that defining illness onset as fever onset is easier[33].

A study from Brazil reported gastrointestinal bleeding was associated with higher risk of death[14]. Another study from Mexico reported risk factors associated with fatality were hematemesis and melena[13]. However, a matched case-control study in Singapore reported fatal cases had similar hemorrhagic manifestations as controls[8]. In our study, hemorrhagic manifestations were also not useful in predicting fatal outcomes. This is consistent with another study in Taiwan in 2008[34].

Our study has two principal strengths. First, it presents the first prediction model for mortality from DENV infection that considers febrile duration before arriving in the Emergency Department. Second, all DENV infections were confirmed by RT-PCR or NS1 detection. In contrast, most previous reports on fatal DENV infections rely on serology only. There are also a few limitations to our study. First, it was conducted at a single medical center, so the patients included may reflect a bias toward more serious cases. Second, the lack of a standardized protocol for the management of DENV infection may have affected the clinical outcomes of the patients included in this retrospective analysis. Third, information regarding primary versus secondary DENV infections were not complete. In our study, IgG data of 46 subjects were not examined. After analyzing 243 subjects remained, we found that secondary infection of the patients did not affect the mortality of recent dengue virus infection (P=0.76). This result was not consistent with the previous finding, which reported secondary dengue infection and virulence of the circulating dengue strain were risk factors for development of dengue shock syndrome[35]. It may be due to incomplete data and this may have a bearing on illness severity.

In summary, our data reveal differences in febrile characteristics, clinical manifestations, and comorbidities between fatal and non-fatal adult patients due to DENV infection. Our simple mortality-prediction model can assist clinicians to identify DENV infection patients with a higher risk of fatality. Further validation of the model is needed before it is used in routine practice.

Conflict of interest statement

We declare that there is no conflict of interest.

Acknowledgements

We are grateful to Wan-Ni Chen at the Biostatistics Consulting Center, National Cheng Kung University Hospital for the statistical consulting services.

Funding

The present study was supported by National Cheng Kung University Hospital (NCKUH-10505033).

Authors' contributions

T-H Kuo supervised this project and was involved in study conception and design, data collection, analysis and interpretation, writing manuscript and critical revision. C-C Chuang and C-C Tseng supported the study through critical comments and took part in data compilation. M-Y Hong was involved in data collection and performed statistical analysis. S-H Lin contributed on reviewing the manuscript, verified the analytical methods, critical revision for intellectual content and final approval of the version to be published.

References

[1] World Health Organization. *Dengue and severe dengue.* [Online]Available at: http://www.who.int/mediacentre/factsheets/fs117/en/ [Accessed on 27 May 2020].

[2] Wang WH, Lin CY, Chang K, Urbina AN, Assavalapsakul W, Thitithanyanont A, et al. A clinical and epidemiological survey of the largest dengue outbreak in Southern Taiwan in 2015. *Int J Infect Dis* 2019; **88**: 88-99.

[3] Bunnag T, Kalayanarooj S. Dengue shock syndrome at the emergency room of Queen Sirikit National Institute of Child Health, Bangkok, Thailand. *J Med Assoc Thai* 2011; **94**(Suppl 3): S57-S63.

[4] Ranjit S, Kissoon N, Jayakumar I. Aggressive management of dengue shock syndrome may decrease mortality rate: A suggested protocol. *Pediatr Crit Care Med* 2005; **6**: 412-419.

[5] Harapan H, Michie A, Mudatsir M, Sasmono RT, Imrie A. Epidemiology of dengue hemorrhagic fever in Indonesia: Analysis of five decades data from the National Disease Surveillance. *BMC Res Notes* 2019; **12**: 350.

[6] Wills BA, Nguyen MD, Ha TL, Dong TH, Tran TN, Le TT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005; **353**: 877-889.

[7] Lee IK, Liu JW, Yang KD. Fatal dengue hemorrhagic fever in adults: Emphasizing the evolutionary pre-fatal clinical and laboratory manifestations. *PLoS Negl Trop Dis* 2012; **6**: e1532.

[8] Thein TL, Leo YS, Fisher DA, Low JG, Oh HM, Gan VC, et al. Risk factors for fatality among confirmed adult dengue inpatients in Singapore: A matched case-control study. *PLoS One* 2013; **8**: e81060.

[9] Almas A, Parkash O, Akhter J. Clinical factors associated with mortality in dengue infection at a tertiary care center. *Southeast Asian J Trop Med Public Health* 2010; **41**: 333-340.

[10]Medagama A, Dalugama C, Meiyalakan G, Lakmali D. Risk factors associated with fatal dengue hemorrhagic fever in adults: A case control study. *Can J Infect Dis Med Microbiol* 2020; **2020**: 1042976.

[11]Mamun MA, Misti JM, Griffiths MD, Gozal D. The dengue epidemic in Bangladesh: Risk factors and actionable items. *Lancet* 2019; **394**: 2149-2150.

[12]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**: 263-267.

[13]Navarrete-Espinosa J, Gomez-Dantes H, Celis-Quintal JG, Vazquez-Martinez JL. Clinical profile of dengue hemorrhagic fever cases in Mexico. *Salud Publica Mex* 2005; **47**: 193-200.

[14]Cavalcanti LP, Coelho IC, Vilar DC, Holanda SG, Escossia KN, Souza-Santos R. Clinical and epidemiological characterization of dengue hemorrhagic fever cases in northeastern, Brazil. *Rev Soc Bras Med Trop* 2010; **43**: 355-358.

[15]Juneja D, Nasa P, Singh O, Javeri Y, Uniyal B, Dang R. Clinical profile, intensive care unit course, and outcome of patients admitted in intensive care unit with dengue. *J Crit Care* 2011; **26**: 449-52.

[16]Shu PY, Chang SF, Kuo YC, Yueh YY, Chien LJ, Sue CL, et al. Development of group- and serotype-specific one-step SYBR green I-based real-time reverse transcription-PCR assay for dengue virus. *J Clin Microbiol* 2003; **41**: 2408-2416.

[17]Shu PY, Yang CF, Kao JF, Su CL, Chang SF, Lin CC, et al. Application of the dengue virus NS1 antigen rapid test for on-site detection of imported dengue cases at airports. *Clin Vaccine Immunol* 2009; **16**: 589-591.

[18]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.

[19]Lee IK, Liu JW, Chen YH, Chen YC, Tsai CY, Huang SY, et al. Development of a simple clinical risk score for early prediction of severe dengue in adult patients. *PLoS One* 2016; **11**: e0154772.

[20]Liu Y, Chen KH, Chen SQ, Chen LL, Duan CY, Wang K, et al. Predictive value of post-procedural early (within 24 h) increase in cystatin C for contrast-induced acute kidney injury and mortality following coronary angiography or intervention. *Oncotarget* 2017; **8**: 109762-109771.

[21]Heinze G, Schemper M. A solution to the problem of separation in logistic regression. *Stat Med* 2002; **21**: 2409-2419.

[22]Acute Kidney Injury Work Group. KDIGO clinical practical guideline for acute kidney injury. *Kidney Intern* 2012; **2**(Suppl 1): 1-138. doi:10.1038/kisup.2012.2.

[23]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 Negl Trop Dis* 2017; **11**: e0005270.

[24]Kuo MC, Chang JM, Lu PL, Chiu YW, Chen HC, Hwang SJ. Difficulty in diagnosis and treatment of dengue hemorrhagic fever in patients with chronic renal failure: Report of three cases of mortality. *Am J Trop Med Hyg* 2007; **76**: 752-756.

[25]Eswarappa M, Reddy SB, John MM, Suryadevara S, Madhyashatha RP. Renal manifestations of dengue viral infection. *Saudi J Kidney Dis Transpl* 2019; **30**: 394-400.

[26]Lee LK, Gan VC, Lee VJ, Tan AS, Leo YS, Lye DC. Clinical relevance and discriminatory value of elevated liver aminotransferase levels for dengue severity. *PLoS Negl Trop Dis* 2012; **6**: e1676.

[27]Leo YS, Thein TL, Fisher DA, Low JG, Oh HM, Narayanan RL, et al. Confirmed adult dengue deaths in Singapore: 5-year multi-center retrospective study. *BMC Infect Dis* 2011; **11**: 123.

[28]Rigau-Perez JG, Laufer MK. Dengue-related deaths in Puerto Rico, 1992-1996: diagnosis and clinical alarm signals. *Clin Infect Dis* 2006; **42**: 1241-1246.

[29]Lahiri M, Fisher D, Tambyah PA. Dengue mortality: Reassessing the risks in transition countries. *Trans R Soc Trop Med Hyg* 2008; **102**: 1011-1016.

[30]Chan KP, Lau GK, Doraisingham S, Chan YC. Adult dengue deaths in Singapore. *Clin Diagn Virol* 1995; **4**: 213-222.

[31]Huang CC, Hsu CC, Guo HR, Su SB, Lin HJ. Dengue fever mortality score: A novel decision rule to predict death from dengue fever. *J Infect* 2017; **75**: 532-540.

[32]Jain S, Mittal A, Sharma SK, Upadhyay AD, Pandey RM, Sinha S, et al. Predictors of dengue-related mortality and disease severity in a tertiary care center in North India. *Open Forum Infect Dis* 2017; **4**: ofx056.

[33]Lee IK, Huang CH, Huang WC, Chen YC, Tsai CY, Chang K, et al. Prognostic factors in adult patients with dengue: Developing risk scoring models and emphasizing factors associated with death $\leqslant$7 days after illness onset and $\leqslant$3 days after presentation. *J Clin Med* 2018; **7**(11): 396.

[34]Lee IK, Liu JW, Yang KD. Clinical and laboratory characteristics and risk factors for fatality in elderly patients with dengue hemorrhagic fever. *Am J Trop Med Hyg* 2008; **79**: 149-153.

[35]Scott RM, Nimmannitya S, Bancroft WH, Mansuwan P. Shock syndrome in primary dengue infections. *Am J Trop Med Hyg* 1976; **25**: 866-874.