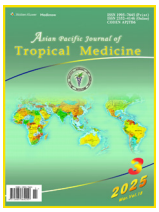

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Diagnosis delays associated with mortality among patients with haemorrhagic fever in Upper Southern Thailand: A hospital-based case control study

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ABSTRACT

Objective: To investigate the association between diagnosis delays and mortality in patients with haemorrhagic fever in Upper Southern Thailand.

Methods: A hospital-based case control study was conducted between December 2019 and January 2020. Cases were defined as patients who had been diagnosed with haemorrhagic fever and died during hospitalization, while controls were patients with similar conditions who survived. Medical records were retrospectively reviewed, with the primary variable being a diagnosis delay of more than three days after the onset of illness. The outcome of interest was mortality during hospitalization. Data analysis involved descriptive statistics and multiple logistic regression.

Results: A total of 38 815 haemorrhagic fever cases were reported from 2014 to 2019. The case-to-control ratio was 1:3, comprising 66 cases and 198 controls. Among 66 cases and 198 controls, the median (IQR) time from illness onset to diagnosis was 4 (4) days in cases *vs.* 1 (0) day in controls. Diagnosis delays significantly increased mortality risk [adjusted *OR* (a*OR*) 5.60, 95% *CI* 2.74-11.46]. Other risk factors for mortality included age ⩽5 years (a*OR* 16.15, 95% *CI* 3.70-70.42) and overweight status (a*OR* 3.43, 95% *CI* 1.57-7.52).

Conclusions: Delayed diagnosis in patients with haemorrhagic fever was strongly associated with higher mortality rates. These findings highlight the critical importance of early diagnosis to reduce mortality in haemorrhagic fever cases.

KEYWORDS: Diagnosis delays; Mortality; Haemorrhagic fever; Dengue haemorrhagic fever; Dengue shock syndrome

1. Introduction

Haemorrhagic fever is an increasingly prevalent disease and continues to pose a significant public health challenge. It imposes a substantial annual burden in terms of disease morbidity and healthcare costs[1]. Outbreaks predominantly occur in tropical and subtropical regions[2]. Haemorrhagic fever is a vector-borne disease caused by the dengue virus, with the primary vector being the *Aedes aegypti* mosquito[3]. Infections are classified into three clinical forms: dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS), and are caused by four distinct serotypes: DEN-1, DEN-2, DEN-3, and DEN-4[4]. While infection with one serotype confers long-term immunity against that particular

Summary

Question: Dose a delayed diagnosis increase mortality risk in haemorrhagic fever patients?

Findings: This hospital-based case-control study found that patients diagnosed more than three days after illness onset had a significantly higher mortality risk (a*OR* 5.60, 95% *CI* 2.74-11.46).

Meaning: Early diagnosis of haemorrhagic fever is critical for reducing mortality, emphasizing the need for timely intervention.

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strain[5], severe clinical symptoms often occur with secondary infections by a different serotype[6,7].

Globally, the number of individuals infected with haemorrhagic fever is steadily increasing, with the highest numbers reported in Asia[1], particularly in Southeast Asia[8]. In Thailand, the morbidity rate from 2013 to 2017 fluctuated, showing a decline overall (241.03, 63.25, 222.58, 97.71, and 81.68 per 100 000 population, respectively). Meanwhile, the mortality rate saw a slight increase (0.09, 0.12, 0.10, 0.10, and 0.13 per 100 000 population, respectively[9]. In upper southern Thailand, the morbidity and mortality rates for haemorrhagic fever have also shown fluctuations. Urban areas tend to have higher rates compared to rural regions, with morbidity rates of 320.74, 149.73, 147.66, 106.23, and 144.48 and mortality rates of 0.15, 0.20, 0.12, 0.04, and 0.19 per 100 000 population during 2013 and 2017[10]. The region's tropical rainforests, high humidity, and significant annual rainfall create favorable environmental conditions for mosquito breeding, contributing to outbreaks of haemorrhagic fever[11].

Previous studies have identified several factors associated with mortality among patients with haemorrhagic fever, including demographic characteristics[12-14], clinical signs and symptoms[15,16], and the quality of health service systems[17-20]. Early diagnosis and the time from illness onset to diagnosis play a critical role in improving treatment outcomes and increasing survival rates. Delayed diagnosis is linked to higher mortality due to the advanced progression of the disease. The clinical manifestations of haemorrhagic fever are typically evident within the first three days of infection, and mortality risk increases when the diagnosis is delayed. Due to the similarity of clinical signs and symptoms between viral infections, differentiating them can be challenging. Haemorrhagic fever also progresses rapidly, with severe complications if not promptly diagnosed.

The association between diagnosis delays and mortality among patients with haemorrhagic fever remains poorly understood. Previous studies have reported conflicting and uncertain findings regarding this relationship. Some studies suggest that diagnosis delays may increase mortality risk[19], while others report only a minimal risk[17]. In contrast, a recent study even suggested a slight protective effect of diagnosis delays on mortality[18]. However, none of these studies yielded statistically significant results[17,18]. Therefore, the aim of this study was to determine whether an association exists between diagnosis delays and mortality among patients with haemorrhagic fever. This investigation seeks to enhance the current understanding of diagnosis delays, highlight the importance of early detection, and improve patient outcomes through timely intensive care, ultimately reducing mortality in haemorrhagic fever cases.

2. Methods

2.1. Study design

This hospital-based case-control study was conducted between December 2019 and January 2020. Data were obtained from the haemorrhagic fever surveillance system, routinely reported through the electronic database of the epidemiological surveillance report registry. The data were monitored by the Office of Disease Prevention and Control 11, located in Nakhon Sri Thammarat, Thailand. In addition, we retrospectively reviewed the medical records of patients with haemorrhagic fever who were hospitalized in public secondary and tertiary hospitals across seven provinces in upper southern Thailand: Chumphon, Ranong, Surat Thani, Phang-Nga, Nakhon Si Thammarat, Phuket, and Krabi. A map of the study locations in the Upper Southern region as shown in Figure 1.

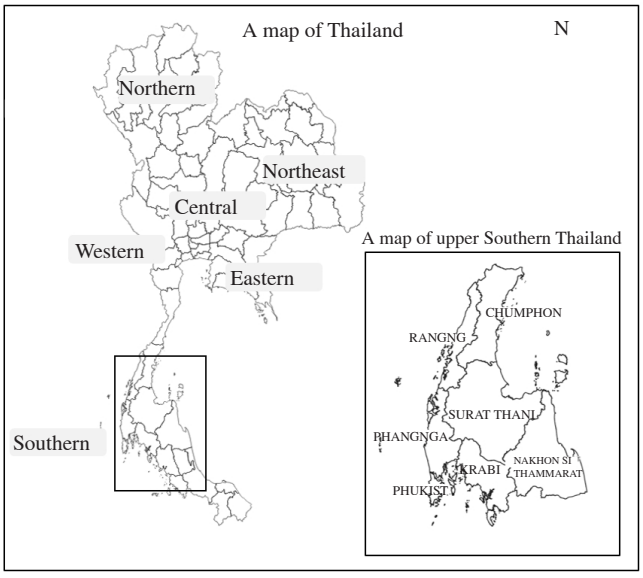

Figure 1. Map of Thailand highlighting the study locations in the Upper Southern region.

2.2. Study subjects

The subjects of this study were patients diagnosed with haemorrhagic fever between January 1, 2014, and December 31, 2019. Eligibility criteria included: 1) a confirmed diagnosis of haemorrhagic fever as either dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS), 2) admission to public secondary or tertiary hospitals in upper southern Thailand, 3) Thai citizenship, and 4) consent to include their medical records as part of the case-control data set in each hospital. DHF and DSS were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), with the following codes: A97.0 and A97.1 for DHF, and A97.2 for DSS.

Cases were defined as patients diagnosed with haemorrhagic fever

who died during hospitalization within the study period. Controls were patients with the similar diagnosis who survived. Additionally, controls were randomly selected from the same hospitals and admission periods, using identification numbers obtained from the epidemiological surveillance report registry.

The sample size was calculated using continuity correction to fit the case-control study design with a dichotomous outcome[21-24]. We set the alpha (α) at 0.05 and the beta (β) at 0.20. The area under the normal curve for $Z_{1-\alpha/2}$ (0.975) was 1.96, and for $Z_{1-\beta}$ (0.80) was 0.84. The ratio between cases and controls (r) was 3. Based on a previous study, the proportion of mortality among cases and controls was 0.72 and 0.89, respectively[18], resulting in a sample size of 60 cases and 180 controls. A case-to-control ratio of 1:3 was employed in this study.

A total of 38 815 patients were diagnosed with haemorrhagic fever between January 1, 2014, and December 31, 2019. Data for the haemorrhagic fever investigation were routinely reported electronically through the epidemiological surveillance report registry, managed by the Office of Disease Prevention and Control 11, Nakhon Sri Thammarat. Of these, 25 150 patients were excluded as they were diagnosed with dengue fever (DF). Among the remaining 13 665 patients, 77 died during hospitalization, comprising three cases of dengue haemorrhagic fever (DHF) and 74 cases of dengue shock syndrome (DSS). Eleven cases were excluded due to incomplete medical records regarding the date of illness onset and diagnosis. Thus, 66 cases were included in the study, consisting of two DHF and 64 DSS cases. For the control group, 198 patients were selected using systematic random sampling methods as shown in Figure 2.

2.3. Data collection

The data were collected by researchers and research assistants responsible for epidemiological surveillance and disease control between December 2019 and January 2020. They were trained to extract data from medical records using a case report form specifically developed for the study. The form was reviewed and validated by three experts in epidemiological surveillance and disease control, achieving a content validity index (CVI) of 0.89. Data accuracy was ensured using the double data entry method before analysis.

The variables of interest in this study included demographic

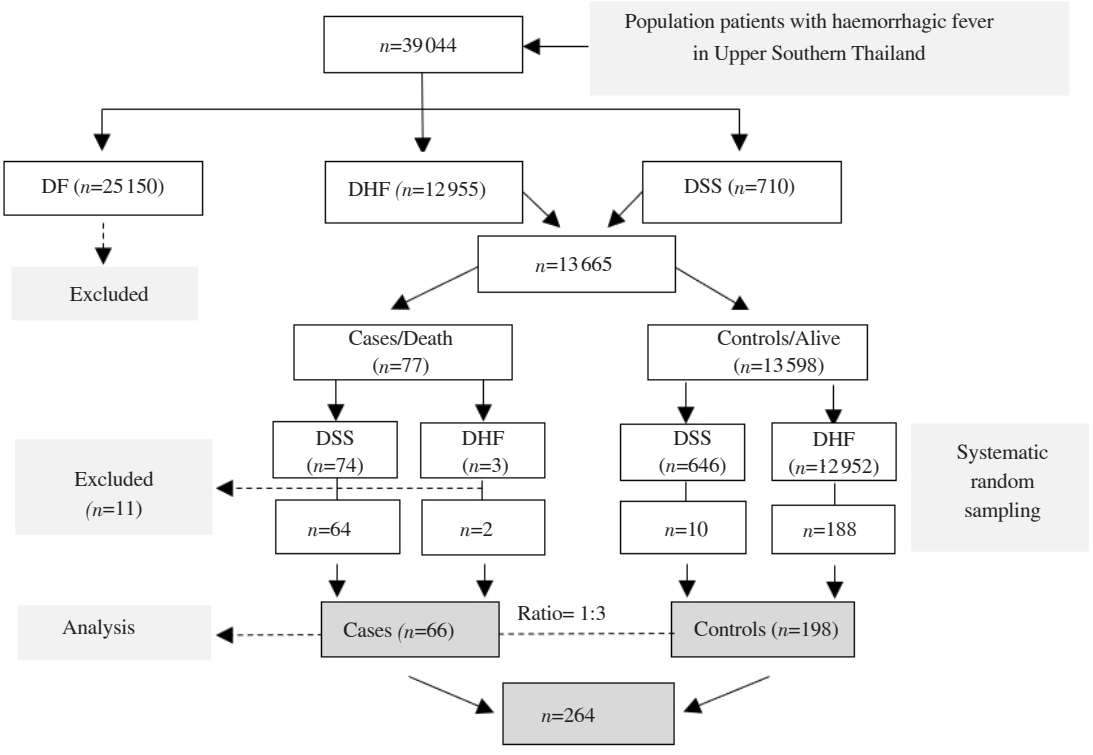

Figure 2. Flowchart depicting the selection process of the study samples.

characteristics such as gender, age, overweight status, underlying diseases, and occupation, as well as patient delays and diagnosis delays. Overweight status was defined as a body mass index (BMI) ≥23 kg/m^2 for adults aged ≥20 years[25] and a BMI-for-age ≥95th percentile for children aged 2-20 years[26]. Patient delays were defined as a duration from the onset of illness to hospitalization exceeding three days[27]. Diagnosis delays were defined as a duration from the onset of illness to diagnosis exceeding three days[16]. For patient delays, subjects with haemorrhagic fever who were diagnosed on their first hospital visit within 24 hours of admission were classified as having no delay. A diagnosis made after 24 hours of hospitalization was considered a diagnosis delay.

Diagnosis delays were categorized as a dichotomous variable: diagnosis delay (Yes) and no diagnosis delay (No). Vital signs of subjects with haemorrhagic fever were routinely reported through the epidemiological surveillance report registry and were confirmed by reviewing medical records at each hospital.

2.4. Statistical methods

Descriptive statistics were used to analyze demographic characteristics, patient delays, and diagnostic delays. The primary outcome of interest was in-hospital mortality, defined as a binary variable: death (Yes) or survival (No). Multiple logistic regression was performed to examine the association between diagnostic delays and mortality among patients with haemorrhagic fever. Logistic regression analysis was initially conducted to evaluate potential factors influencing mortality. A separate model was constructed for each variable of interest. Continuous variables, such as patient age, were categorized, and polytomous variables, including age and occupation, were converted into dummy variables before being included in the models. Factors with a *P* value for Wald's test ≤0.25 were entered into the initial model. Through backward elimination, factors with a *P* value for Wald's test ≥0.05 were removed. The model's fit was assessed using the partial likelihood ratio test. The final model incorporated all relevant factors and was adjusted for confounding variables, including age, BMI, underlying diseases, and patient delays. In the final model, the goodness of fit of the logistic regression was assessed using the Hosmer-Lemeshow test, which indicated an adequate fit to the data (*Chi*-square statistic=1.41, *P*-value=0.998). Additionally, we calculated the study's power using continuity correction for the case-control design. The proportions of diagnosis delays were 0.60 for cases and 0.12 for controls. With an alpha (α) of 0.05 and *Z* (0.975) of 1.96, the study's power was determined to be 100% (1- β)[21-24].

The results were presented as odds ratios (*OR*) with a 95 percent confidence interval (95% *CI*). A risk association between diagnosis delays and mortality was indicated by an *OR*>1, while a protective association was indicated by an *OR*<1. If there was no association between diagnosis delays and mortality, the *OR* would include 1 within its confidence interval.

2.5. Ethical consideration

Permission to use the epidemiological surveillance report registry database of haemorrhagic fever was granted by the Office of Disease Prevention and Control 11, Nakhon Sri Thammarat. The data in the medical records were approved by the directors of the hospitals in upper southern Thailand. Additionally, this study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Ethics Committee on Human Rights Related to Human Experimentation, Thaksin University, Thailand, under COA No. TSU 2019-008 (28 August 2019) and COA No. TSU 2019-038, REC No. 086 (6 December 2019).

3. Results

3.1. Demographic characteristics among subjects

A summary of the demographic characteristics of the study subjects is provided in Table 1. The study comprised 66 cases and 198 controls. Among the cases, 63.64% were female, compared to 55.56% of the controls. The median age (IQR) was 15.68 (17.13) years for cases and 26.53 (21.72) years for controls. Overweight individuals accounted for 39.39% of cases and 24.75% of controls. Children represented 46.97% of cases and 40.91% of controls. Additionally, 24.24% of cases and 8.59% of controls had underlying diseases. Common conditions among cases included hypertension (40.74%), diabetes mellitus (29.63%), and dyslipidaemia (18.52%). In the control group, hypertension (48.15%) and diabetes mellitus (18.52%) were prevalent. Other underlying diseases in both groups, such as thalassemia, cirrhosis, heart disease, cancer, and thyroid abnormalities, are not detailed in the table.

3.2. Patient delays and diagnosis delays among subjects with haemorrhagic fever

Table 2 presents data on patient delays and diagnosis delays among cases and controls. Over half of the cases (57.58%) experienced diagnosis delays, compared to 12.63% of the controls. The median (IQR) duration from the onset of illness to hospitalization was 3 (1, 4) days for cases and 3 (1, 5) days for controls. The median (IQR) duration from the onset of illness to diagnosis was 4 (1, 5) days for cases and 1 (1, 1) day for controls. Additionally, a quarter of the cases (25.76%) and nearly half of the controls (49.49%) experienced patient delays.

Table 1. Characteristics of subjects with haemorrhagic fever.

Demographic characteristics	Cases (*n*=66)	Controls (*n*=198)
Sex		
Male	24 (36.36)	88 (44.44)
Female	42 (63.64)	110 (55.56)
Age, years		
≤5	11 (16.67)	5 (2.53)
6-21	33 (50.00)	96 (48.48)
≥22	22 (33.33)	97 (48.99)
Overweight		
No	40 (60.61)	149 (75.25)
Yes	26 (39.39)	49 (24.75)
Occupation		
Agriculture workers and employees	18 (27.27)	82 (41.41)
Students	11 (16.67)	10 (5.05)
Children under five years	31 (46.97)	81 (40.91)
Others	6 (9.09)	25 (12.63)
Underlying diseases		
No	50 (75.76)	181 (91.41)
Yes	16 (24.24)	17 (8.59)
Hypertension	11 (40.74)	13 (48.15)
Diabetes mellitus	8 (29.63)	5 (18.52)
Dyslipidaemia	5 (18.52)	2 (7.41)
Thalassemia	2 (7.41)	3 (11.12)
Cirrhosis	1 (3.71)	0 (0.00)
Heart diseases	0 (0.00)	2 (7.41)
Cancer	0 (0.00)	1 (3.71)
Thyroid abnormality	0 (0.00)	1 (3.71)

Table 2. The data of the patient delays and diagnosis delays among subjects with haemorrhagic fever.

Type of delays	Cases (*n*=66)	Controls (*n*=198)
Patient delays		
No	49 (74.24)	100 (50.51)
Yes	17 (25.76)	98 (49.49)
Duration of time from the onset of illness to hospitalisation (days)		
≤3	49 (74.24)	100 (50.51)
4	10 (15.15)	47 (23.74)
≥5	7 (10.61)	51 (25.76)
Diagnosis delays		
No	28 (42.42)	173 (87.37)
Yes	38 (57.58)	25 (12.63)
Duration of from the onset of illness to diagnosis (days)		
≤3	28 (42.42)	173 (87.37)
4	21 (31.82)	16 (8.08)
≥5	17 (25.76)	9 (4.55)

3.3. Bivariate analysis of the factors associated with mortality among subjects

As shown in Table 3, bivariate analysis identified several factors significantly associated with mortality among subjects with haemorrhagic fever. Subjects aged ≤5 years were nearly 10 times more likely to die (*OR* 9.70, 95% *CI* 3.09-30.76) compared to those aged ≥22 years. Overweight individuals had almost twice the likelihood of mortality (*OR* 1.98, 95% *CI* 1.10-3.57) compared to those with normal weight. The presence of underlying diseases increased the odds of death by four times (*OR* 3.41, 95% *CI* 1.61 -7.22). Students had a fivefold higher risk of dying (*OR* 5.01, 95% *CI* 1.85-13.58) compared to agriculturists or employees.

Interestingly, subjects who experienced patient delays were 65% less likely to die (*OR* 0.35, 95% *CI* 0.19-0.66) compared to those who did not. The duration from the onset of illness to hospitalization of 4 days or ≥5 days reduced mortality risk by 57% and 72%, respectively (*OR* 0.43, 95% *CI* 0.20-0.93; *OR* 0.28, 95% *CI* 0.12 -0.66), compared to those hospitalized ≤3 days. Conversely, diagnosis delays were associated with a significant increase in mortality risk, with affected individuals being nine times more likely to die (*OR* 9.39, 95% *CI* 4.93-17.87) compared to those without delays. Subjects with a delay in diagnosis of 4 days or >5 days had 8- and 11-fold higher odds of death (*OR* 8.11, 95% *CI* 3.78-17.40; *OR* 11.67, 95% *CI* 4.74-28.74), respectively.

3.4. Multivariate analysis of the factors associated with mortality among subjects

An adjusted multiple logistic regression analysis using the backward elimination method revealed that subjects who experienced diagnosis delays were six times more likely to die (a*OR* 5.60, 95% *CI* 2.74-11.46) compared to those who did not experience diagnosis delays. This association remained significant after accounting for confounding factors, including age, body mass index, underlying diseases, and patient delays, as shown in Table 4.

4. Discussion

Our study found that patients with haemorrhagic fever who experienced diagnosis delays had a significantly higher risk of mortality. Diagnosis delays were particularly detrimental because the critical period for dengue infection typically begins three days post-infection. Although the incubation period for dengue is approximately 5-8 days[28], clinical signs and symptoms often do not become apparent until after the first three days. Initially, symptoms may be nonspecific, such as high fever, headache, and myalgia[2], which are common to many viral infections[15]. During this early period, a tourniquet test may be positive, and a maculopapular rash may develop. Laboratory tests can reveal low white blood cell counts (<4000/mm^3), reduced polymorphonuclear neutrophils and platelets, and elevated lymphocyte levels[15,28].

The critical period of infection typically occurs 3-7 days post-onset of illness[29]. During this time, dominant clinical manifestations

Table 3. Bivariate analysis of an association between factors and mortality among subjects with haemorrhagic fever.

Factors	Death, *n* (%)	*OR*	95% *CI*	*P* values*
Sex				0.246
Male	24 (21.43)	Ref.		
Female	42 (27.63)	1.40	0.79-2.49	
Age, years				<0.001
≥22	22 (18.49)	Ref.		
6-21	33 (25.58)	1.52	0.82-2.79	
≤5	11 (68.75)	9.70	3.06-30.76	
Overweight				0.025
No	40 (21.16)	Ref.		
Yes	26 (34.67)	1.98	1.10-3.57	
Underlying diseases				0.002
No	50 (21.65)	Ref.		
Yes	16 (48.48)	3.41	1.61-7.22	
Occupations				0.012
Agriculture workers / employees	18 (18.00)	Ref.		
Students	11 (52.38)	5.01	1.85-13.58	
Children under five years	31 (27.68)	1.77	0.91-3.41	
Others	6 (19.35)	1.05	0.38-2.93	
Patient delays				0.001
No	49 (32.89)	Ref.		
Yes	17 (14.78)	0.35	0.19-0.66	
Duration from the onset of illness to hospitalisation, days				0.002
≤3	49 (32.89)	Ref.		
4	10 (17.54)	0.43	0.20-0.93	
≥5	7 (12.07)	0.28	0.12-0.66	
Diagnosis delays				<0.001
No	28 (13.93)	Ref.		
Yes	38 (60.32)	9.39	4.93-17.83	
Duration from the onset of illness to diagnosis, days				<0.001
≤3	28 (13.93)	Ref.		
4	21 (56.76)	8.11	3.78-17.40	
≥5	17 (65.38)	11.67	4.74-28.74	

**P*-values shown in this study are derived from Wald's test, which represents the overall *P*-value for each variable; *OR*: Odds ratios; 95% *CI*: 95% confidence interval; ref.: reference group.

Table 4. Multivariate analysis of an association between diagnosis delays and mortality among subjects with haemorrhagic fever.

Factors	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)	*P* values*
Diagnosis delays			<0.001
No	Ref.	Ref.	
Yes	9.39 (4.93-17.87)	5.60 (2.74-11.46)	
Age, years			<0.001
≥22	Ref.	Ref.	
6-21	1.52 (0.82-2.79)	3.04 (1.28-7.23)	
≤5	9.70 (3.06-30.76)	16.15 (3.70-70.42)	
Overweight			0.002
No	Ref.	Ref.	
Yes	1.98 (1.10-3.57)	3.43 (1.57-7.52)	
Underlying diseases			0.024
No	Ref.	Ref.	
Yes	3.41 (1.61-7.22)	3.32 (1.17-9.41)	
Delays of the patients			0.034
No	Ref.	Ref.	
Yes	0.35 (0.19-0.66)	0.47 (0.23-0.96)	

**P* values calculated using partial likelihood ratio test; *OR*: Odds ratios; 95% *CI*: 95% confidence interval; ref.: reference group.

include right hypochondriac pain due to an enlarged liver, internal bleeding, and hypovolemic shock resulting from elevated haematocrit and plasma leakage[29]. Early diagnosis of haemorrhagic fever within the first three days is crucial for effective surveillance and intensive care, helping to prevent advanced disease progression and reduce mortality among infected patients. Approximately one-third of the subjects in this study were overweight (39.39%), and two-thirds were under 22 years of age (66.67%), which may be associated with mortality. Being overweight and young could influence the severity of dengue infections[30-32]. Increased white adipose tissue production leads to elevated levels of inflammation mediators among overweight or obese individuals[32]. This condition can also increase capillary permeability, resulting in progressive plasma leakage and a higher risk of mortality, particularly among obese children.

One-fifth of the cases in our study had underlying diseases (24.24%), including hypertension (40.74%), diabetes mellitus (29.63%), and dyslipidaemia (18.52%). Patients with haemorrhagic fever who have underlying conditions are at increased risk of mortality. Chronic conditions associated with cardiovascular diseases, such as hypertension and diabetes, can exacerbate the severity of haemorrhagic fever infections[33]. High prevalence of comorbidities among individuals with dengue infection includes obesity (BMI >25 kg/m^2, prevalence: 24.5%, 95% *CI* 18.6-31.6), hypertension (17.1%, 95% *CI* 13.3-21.8), and diabetes (13.3%, 95% *CI* 9.3-18.8)[33]. In our study, two-thirds of cases (60.00%) had comorbidities such as hypertension and diabetes mellitus[34]. Subjects with comorbidities like diabetes (a*OR* 1.78, 95% *CI* 1.06-2.97) and those with both diabetes and hypertension (a*OR* 2.16, 95% *CI* 1.18-3.96) were also more likely to be associated with dengue haemorrhagic fever infection[35].

This study aligns with the research conducted by Yatra *et al.*, who, in a 2015 case-control study in Indonesia, found that subjects with haemorrhagic fever who experienced diagnosis delays had a significantly higher risk of mortality (*OR* 8.23, 95% *CI* 2.03-23.96)[19]. In contrast, Nazish *et al.* found minimal risk associated with diagnosis delays in their 2008 case-control study in Pakistan, reporting no significant association (*OR* 1.33, 95% *CI* 0.89-1.96)[17]. Similarly, a retrospective study by Kaewnokkhoa and Areechokchai in Thailand in 2013 indicated a minimal protective effect of diagnosis delays on mortality among haemorrhagic fever patients, though the association was not statistically significant (*OR* 0.95, 95% *CI* 0.55-1.25)[18].

The findings of this study emphasize the critical need for early diagnosis in reducing mortality among haemorrhagic fever patients. Delays in diagnosis, particularly beyond the first three days of infection, significantly increase the risk of severe complications, including internal bleeding and hypovolemic shock. Therefore, healthcare systems in dengue-endemic areas must prioritize rapid identification of haemorrhagic fever, even when early symptoms are nonspecific. This study also highlights the need for targeted interventions for high-risk groups, particularly young and overweight individuals, and those with comorbidities such as hypertension and diabetes. These populations are more susceptible to severe outcomes, emphasizing the importance of routine screenings and prompt treatment in these vulnerable groups. Furthermore, the study's findings point to the need for healthcare infrastructure improvements, particularly in the area of medical record-keeping. The transition from manual to electronic records during the study period may have contributed to underreporting, suggesting that more reliable medical systems are necessary to avoid diagnostic delays in the future.

This study investigated factors associated with mortality in haemorrhagic fever, focusing on patients treated in public secondary and tertiary hospitals across seven provinces in upper southern Thailand. The study utilized a robust dataset from epidemiological surveillance systems, providing a unique opportunity to analyze diagnostic delays and mortality determinants. Our findings highlight the critical impact of diagnosis delays and other risk factors on mortality outcomes. By presenting both confidence intervals and statistical significance, the study emphasizes the magnitude and precision of the observed effects, offering valuable insights into the relationship between diagnostic delays and mortality.

Despite its strengths, the study has several limitations. First, the scope was limited to upper southern Thailand, which may restrict generalizability to other regions. Future studies should include hospitals from diverse regions, such as primary care centers and private hospitals, to capture broader insights. Second, unmeasured variables, including the quality of care, staff experience, and healthcare resource availability, were not included due to the retrospective design and reliance on secondary data. These factors could influence outcomes and should be explored in future research through prospective designs or multi-level analyses.

The study is also subject to information bias due to the retrospective assessment of diagnosis delays from medical records. The transition from manual to electronic medical records during the study period may have led to an underestimation of diagnosis delays. Additionally, 14.29% of cases (11 cases) were excluded due to incomplete records, potentially resulting in an overestimation of the effect of diagnosis delays on mortality. Despite these challenges, the study demonstrated high precision and power, with 100% power using continuity correction in the case-control design. Wide confidence intervals for key predictors, such as age ≤5 years and diagnosis delays, indicate some uncertainty in the estimates. These intervals may reflect variability due to smaller sample sizes or the inclusion of rare events. While these findings are statistically significant, the wide confidence intervals highlight the need for larger cohorts in future studies to improve the precision of these estimates. Furthermore, a

goodness-of-fit test using the Hosmer-Lemeshow method confirmed the logistic regression model's adequacy, addressing potential concerns about overfitting and supporting the reliability of the findings.

These findings emphasize the need for prompt and thorough investigation of both symptomatic and asymptomatic patients to ensure early diagnosis. Early intervention is essential to prevent disease progression and improve outcomes. Factors influencing diagnostic delays and mortality may vary across regions with differing healthcare infrastructure, socioeconomic conditions, or endemicity of haemorrhagic fever. These findings provide critical insights for targeted interventions, particularly for high-risk groups such as young and overweight patients or those with comorbidities. The study highlights the need for actionable policy recommendations, including the implementation of early diagnostic protocols, enhanced training for healthcare professionals, and improved diagnostic tools in high-risk areas. Addressing these critical factors can substantially reduce mortality and improve survival rates in haemorrhagic fever patients.

In conclusion, this study provides critical insights into factors associated with mortality in haemorrhagic fever, offering a foundation for further research and policy development. While the findings are specific to the study region, they focus the importance of early diagnosis and targeted interventions to reduce mortality. Future research should include a broader range of healthcare facilities, such as primary care centers and private hospitals, to capture a more comprehensive understanding of diagnostic delays and mortality determinants. Incorporating hospital-level data, such as healthcare resource indices, staff training, and quality assurance measures, would better elucidate their impact on outcomes. Expanding the geographic scope and including larger cohorts could validate these findings and enhance their generalizability. Such studies would provide valuable comparative insights across diverse healthcare settings and strengthen the evidence base for targeted public health interventions.

Conflict of interest statement

The authors declare no conflicts of interest.

Authors' contributions

SC, BC, and SW conceptualized and designed the study. SC and SW collected the data and conducted the literature review, while SC and BC analyzed and interpreted the data. BC drafted the initial version of the manuscript, with input from SC and SW during the review and editing process. SW and BC supervised the project throughout. BC, as the guarantor, ensured the integrity of the work from its conception to the preparation of the manuscript. All authors have reviewed, approved, and endorsed the final version of the manuscript, affirming their confidence in the accuracy and integrity of the research.

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