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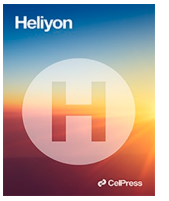

Research article

Activated partial thromboplastin time predicts mortality in patients with severe fever with thrombocytopenia syndrome: A multicenter study in north China

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ABSTRACT

Background: Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease with high lethality. This study aimed to determine whether prolonged activated partial thromboplastin time (APTT) predicted SFTS mortality.

Methods: SFTS patients were enrolled from 6 hospitals in the north China. Subjects were divided into training cohort and 5 externally validation cohorts. The least absolute shrinkage and selection operator Cox regression model was performed to screen potential prognostic factors. Risk factors were analyzed using multivariable regression models. Prognostic models were established by Cox regression and random survival forest (RSF) methods, and evaluated regarding discrimination, validity and clinical benefit. Time-dependent receiver operating characteristic (ROC) curve was used to evaluate the predictive effectiveness of variables.

Results: 1332 SFTS cases were included, in which 211 patients died. Six potential prognostic factors were screened, and pulse, breath, APTT and aspartic transaminase (AST) were independently associated with mortality in both training cohort (Yantai, N = 791) and external validation cohort (N = 541). APTT was steadily correlated with the fatality (HR: 1.039–1.144; all $P < 0.01$) in each five sub-validation cohorts (Dandong, Dalian, Tai'an, Qingdao and Beijing). RSF model with variables of APTT, AST, pulse and breath had considerable prognostic effectiveness, which APTT showed the highest prognostic ability with the area under the curve of 0.848 and 0.787 for

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7-day and 14-day survival, respectively. Survival differences were found between high and low levels of APTT for mortality using 50s as the optimal cut-off.
Conclusions: SFTS patients have prolonged APTT, which is an independent risk factor for fatality. APTT≥50s was recommended as a biomarker to remind physicians to monitor and treat patients more aggressively to improve clinical prognosis.

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by a novel bunya virus, which mainly transmitted by contact with ticks, or, in rare cases, by immediate contact with the infected tissues and animal's/human fluids [1–3]. It was first proposed in China in 2009 [4], and subsequently reported in Japan [5], South Korea [6], Vietnam [7] and other Asian countries. According to the Chinese Disease Prevention and Control Information System, incidence was highly spatially clustering, with 99.23 % of cases concentrated in seven provinces, including Anhui, Henan, Shandong, Hubei, Jiangsu, Zhejiang, and Liaoning. Recently, more than 15 provinces in China have reported SFTS cases [8].

Patients with mild SFTS typically manifest with hyperthermia and thrombocytopenia, accompanied by leukopenia, gastrointestinal symptoms and multiple-organ failure including encephalopathy, cardiac failure, acute respiratory distress syndrome, severe acute pancreatitis, acute kidney injury and disseminated intravascular coagulation (DIC), with a mortality rate of more than 10 % [9,10]. Due to high lethality, SFTS was listed as one of the top ten priority infectious diseases in the 2018 annual review of the Blueprint list by World Health Organization in 2018. Even worse there are no specific antiviral drugs available that have been developed to date. Hence, early identification of risk factors associated with the severity of disease is crucial to mitigate the number of fatal cases.

According to previous studies, one of the characteristics and indicators of severe disease in SFTS patients is a prolonged activated partial thromboplastin time (APTT) [11–13]. Case reports and case series indicate that APTT could also impact outcomes. Studies suggested that SFTS patients with APTT prolongation of 60 s or more face a four-fold higher mortality risk compared to those with less marked prolongation [14]. Even though some studies have begun to explore the predictive capacity of APTT for mortality risk, most of them were limited by small sample sizes or lack external validation. Moreover, the mechanisms underlying the prolongation of the APTT in SFTS patients remain poorly understood. Therefore, the predictive value of APTT for mortality risk in SFTS is still uncertain. Larger population cohort studies are warranted to confirm its predictive ability.

In this study, our objective was to assess whether prolonged APTT is linked to mortality in a cohort of 1332 SFTS patients across six hospitals in northern China. Additionally, we aimed to establish a threshold value of APTT indicative of mortality risk and develop a prognostic model for predicting death events in SFTS patients, which we validated externally. Through this study, we wish to provide a relatively reliable conclusion regarding the association between APTT and mortality risk based on a substantial sample size and offer a valuable clinical tool for early identification and management of SFTS.

2. Methods

2.1. Study design and population

This analysis is a retrospective observational cohort study. Eligible patients with SFTS were recruited from six independent infectious disease departments in the north China from May 2011 to October 2022. In the current study, we split the subjects from these six centers into two cohort.

(1) Training cohort (n = 791): SFTS patients enrolled from Yantai City Hospital for Infectious Disease.
(2) Validation cohort (n = 541): patients with SFTS were included from Dandong Infectious Disease Hospital (n = 194), Public Health Clinical Center of Dalian (n = 166), Tai'an City Central Hospital (n = 70), Qing Dao No. 6 People's Hospital (n = 63) and Beijing Ditan Hospital Capital Medical University (n = 58).

According to the Expert Consensus on Diagnosis and Treatment of Severe Fever with Thrombocytopenia Syndrome with Integrated Traditional Chinese and Western Medicine [15], the diagnostic criteria for SFTS were as follows: (1) epidemiological history (working, living, or traveling in endemic areas during the epidemic season; contact history to SFTS cases; and recent tick bite history); (2) acute fever (temperature>37.5 °C for over 24 h); (3) thrombocytopenia (platelet count$<100 \times 10^9$/L); and (4) laboratory-confirmed SFTSV infection (positive-serum nucleic acid test, tice positive-serum IgG and/or IgM antibody for SFTSV, or SFTSV isolated from specimens). The inclusion criteria included subjects who met the diagnostic criteria and were admitted to the hospital within 7 days from disease onset.

The exclusion criteria included were as follows: (1) age under 18 years old; (2) previous leukemia, idiopathic thrombocytopenic purpura, and other hemopathies; (3) previous acute and chronic viral hepatitis, alcoholic liver disease, and other hepatopathies; (4) previous autoimmune diseases; and (5) missing clinical data.

This study was approved by the local Ethics Committee of the Beijing Ditan Hospital, Capital Medical University (No. DTEC-KY2022-022-03). All subjects in the study signed an informed consent.

2.2. Data collection and definitions

The demographic characteristics (age and gender), anthropometric data (breath, blood pressure and pulse rate), clinical data (comorbidities, complications and outcomes), and first laboratory parameters (blood routine index, myocardial enzymes, infection indicators, coagulation function index and biochemical indicators) for participants during hospitalization were extracted from electronic medical records. Data collection occurred within two weeks of the onset of illness. Pulse rate, measured in beats per minute (bpm), was recorded over one full minute. Seated blood pressure and pulse rate were measured after at least 5 min of rest using an automatic sphygmomanometer. Breath rate, measured in breaths per minute over one full minute, was obtained via the electrocardiogram monitor. Patients who ceased therapy or were discharged from the hospital were followed up until 28 days from the beginning of admission to ascertain their outcome (death or survival).

The date of disease onset was defined as the day fever was noticed (self-reported). The primary clinical endpoint was in-hospital all-cause death, and the time of death was defined as the period from admission to in-hospital death occurred. The secondary outcome was the development of complications, including myocardial injury, liver injury, renal injury, central nervous system lesion, pulmonary infection, and multiple organ dysfunction syndrome (MODS), categorized based on the number of complications (0, 1–2, and 3–6). All data were entered into an electronic data collection system (EDC) by a team of trained study members.

2.3. Statistical analysis

2.3.1. Data preprocessing

Missing data brings challenges for data analysis and model fitting, which is common in epidemiological and clinical research. Multiple imputation by chained equations (MICE) involves a series of imputation models, where each variable containing missing data is regressed on all other variables, including previously imputed missing variables [16,17]. We retained variables with missing rate<30 % for data imputation. To evaluate the effectivity of data imputation [18], we established univariate binary logistic regression with fatal outcome (death or survival) of SFTS patients as dependent variable in the original data and filled data, respectively; then, the relative error of regression coefficient (θ) was calculated by the following formula:

$$\theta = (\beta - \beta_0) / \beta_0 \times 100\%$$

where β_0 and β are regression coefficients in original data and filled data, respectively.

The ratings for θ are excellent ($|\theta| \leq 10$ %), good (10 % $< |\theta| \leq 20$ %), medium (20 % $< |\theta| \leq 50$ %), and poor ($|\theta| > 50$ %). Finally, we retained the variables with $|\theta| \leq 20$ %.

2.3.2. Statistic description

The categorical variables were represented by percentages (n, %) and comparisons analyzed by χ^2 test. We carried Shapiro-Wilk test for normality of continuous data. Normally distributed variables were expressed as mean (standard deviation), and comparisons analyzed by independent samples *t*-test between groups. Non-normally distributed variables were expressed as median (interquartile range, IQR), and comparisons analyzed by Mann-Whitney *U* test between groups. All correlations were analyzed using rank correlation test except for ordinal variables where Mantel-Haenszel χ^2 test was implemented.

2.3.3. Variables selection

Based on the training set, the least absolute shrinkage and selection operator (LASSO) Cox regression model [19,20] to screen potential prognostic factors for fatal outcome of patients with SFTS. Subsequently, the Cox's proportional hazard regression analysis and ordinal logistic regression analysis were utilized to analyze the associations between selected variables and outcomes (death and complications).

2.3.4. Model establishment and validation

We established six different prognostic models using Cox regression method and random survival forest (RSF) method in the training set. The performance of all six prognostic models was evaluated in both training and external validation sets in terms of discrimination, validity and clinical benefit. Evaluation metrics included the concordance index (C-index), brier score and decision curve analyses (DCA). Additionally, predictive effectiveness was assessed using time-dependent receiver operating characteristic (ROC) curves at 7 and 14 days. Random survival forest analysis was employed to assess the importance of variables in the model. The optimal cut-off for APTT was calculated using maximally selected rank statistics for time to occurrence of fatal outcomes of SFTS. Participants in the training and validation sets were then classified into low- and high-APTT groups based on this value. Differences between low- and high-APTT groups were assessed using log-rank tests and Kaplan-Meier (K-M) analysis.

2.3.5. Statistical tools

All statistical analyses were conducted by R software (version 4.2.2). A two-sided $P < 0.05$ was considered significant. "MICE" package was employed for data imputation; "glmnet" for Lasso-Cox analysis; "survival" for Cox proportional hazard regression analysis; "MASS" for ordinal logistic regression analysis; "rms" for Cox regression model construction; "randomForestSRC" for random survival forest model analysis; "pec" for model validation; "timeROC" for time-dependent ROC curves construction; "Maxstat" for maximally selected rank statistics; "survival" and "survminer" for Kaplan Meier curves and log-rank statistic calculation.

3. Results

3.1. Study population

Fig. 1 depicted the study flow. In data processing, 70 variables with a missing rate less than 30 % underwent data imputation, resulting in 53 variables being retained (Table S1). The training cohort comprised 791 patients (49.6 % males; median 66 years), with 151 (19.1 %) fatalities recorded. Patient characteristics from this cohort are summarized in Table 1. The prevalence of comorbidities was similar between survivors and non-survivors. Deceased patients were elder and exhibited higher breath and pulse rate compared to survivors (all $P < 0.001$). Abnormal laboratory indicators were observed in non-survivors, including indicators of blood routine, myocardial enzyme, coagulation and biochemical. Additionally, Table S2 described the patient characteristics in the validation cohort, which included 541 patients, with 60 (11.1 %) deaths occurring in hospital. The median age was 62 years (IQR, 55–70 years), and 275 (50.8 %) cases were male.

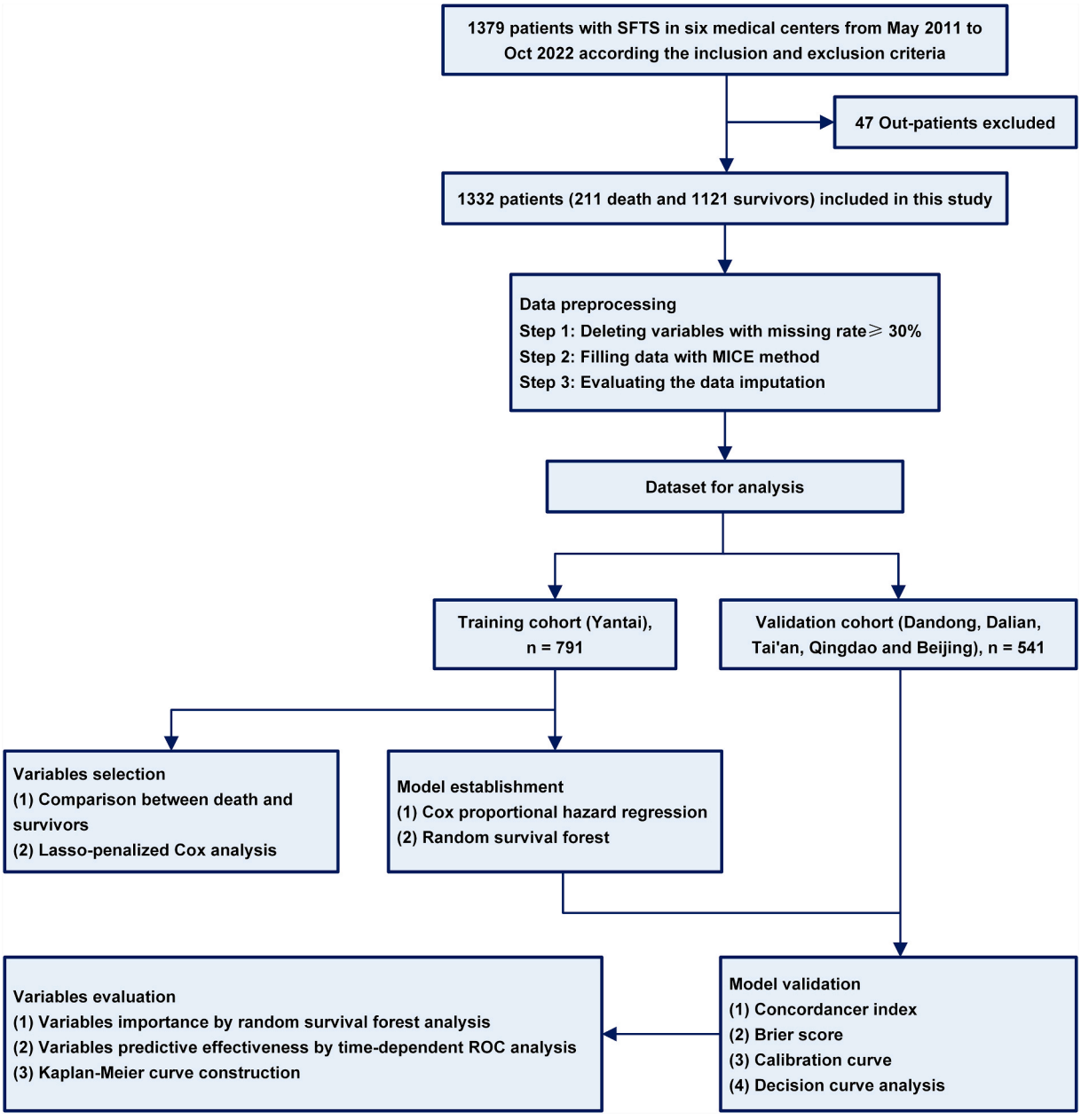

Fig. 1. Flow diagram of study profile. SFTS, severe fever with thrombocytopenia syndrome; MICE, multiple imputation by chained equations; Lasso, least absolute shrinkage and selection operator; ROC, receiver operating characteristic.

Table 1
Description of patient characteristics at admission between survivor and death groups in the training cohort.

Characteristics	Total (n = 791)	Survivors (n = 640)	Death (n = 151)	*P*
Age (years), median (IQR) [b]	66 (58–74)	65 (56–73)	70 (64–76)	<0.001
Gender (male), *n* (%) [a]	392 (49.6)	308 (48.1)	84 (55.6)	0.097
Breath (breaths/min) [b]	19 (18–20)	19 (18–20)	20 (18–22)	<0.001
Pulse rate (beats/min) [b]	78 (70–87)	76 (69–85)	84 (76–98)	<0.001
Comorbidities, *n* (%) [a]				
Hypertension	172 (21.7)	134 (20.9)	38 (25.2)	0.257
Diabetes	116 (14.7)	90 (14.1)	26 (17.2)	0.324
Coronary artery disease	63 (8.0)	53 (8.3)	10 (6.6)	0.498
Cerebrovascular disease	66 (8.3)	57 (8.9)	9 (6.0)	0.239
Cancer	22 (2.8)	16 (2.5)	6 (4.0)	0.322
Blood routine index, median (IQR) [b]				
Neutrophil rate (%)	66.4 (50.8–77.5)	64.7 (49.5–76.0)	71.9 (61.0–80.3)	<0.001
Neutrophil count (10^9/L)	1.41 (0.88–2.67)	1.35 (0.86–2.55)	1.79 (0.96–3.39)	0.020
Lymphocyte rate (%)	23.9 (16.2–34.7)	25.3 (17.0–36.1)	18.1 (13.4–26.9)	<0.001
Lymphocyte count (10^9/L)	0.57 (0.35–0.96)	0.61 (0.36–1.00)	0.45 (0.31–0.76)	<0.001
Monocyte rate (%)	7.3 (3.9–12.0)	7.7 (4.5–12.7)	5.5 (2.3–9.9)	<0.001
Monocyte count (10^9/L)	0.16 (0.08–0.41)	0.18 (0.10–0.42)	0.11 (0.05–0.35)	<0.001
Hemoglobin (g/L)	137 (126–150)	137 (126–149)	142 (126–155)	0.009
Hematocrit (%)	40.3 (37.3–43.7)	40.1 (37.2–43.5)	41.4 (37.6–44.9)	0.038
Platelet count (10^9/L)	59.0 (43.0–77.0)	62.0 (46.0–80.0)	48.0 (34.0–65.0)	<0.001
Myocardial enzyme indicators, median (IQR) [b]				
Lactate dehydrogenase (U/L)	623 (382–900)	555 (358–900)	900 (649–918)	<0.001
Creatine kinase (U/L)	444 (194–1213)	383 (172–954)	1199 (340–2000)	<0.001
Creatinine kinase-myocardial band (U/L)	19.0 (12.0–32.0)	17.0 (11.0–27.0)	32.0 (17.0–61.0)	<0.001
Coagulation function index, median (IQR) [b]				
Prothrombin time (s)	12.1 (11.3–12.9)	12.0 (11.3–12.7)	12.5 (11.5–13.6)	<0.001
Prothrombin activity (%)	112 (99–127)	115 (101–129)	103 (85–116)	<0.001
Activated partial thromboplastin time (s)	43.5 (36.2–52.4)	41.6 (34.9–49.0)	55.7 (44.6–71.2)	<0.001
Internationally standardized ratio	0.94 (0.87–1.01)	0.93 (0.87–1.00)	0.98 (0.91–1.09)	<0.001
Thrombin time (s)	20.4 (16.2–24.7)	20.1 (16.0–23.9)	22.1 (18.1–30.0)	<0.001
Biochemical indicators, median (IQR) [b]				
C-reactive protein (mg/L)	4.4 (1.5–13.3)	3.5 (1.3–12.4)	7.6 (2.7–21.3)	<0.001
Blood urea nitrogen (mmol/L)	5.8 (4.2–8.4)	5.4 (3.9–7.7)	7.8 (6.0–12.2)	<0.001
Creatinine (μmol/L)	66.0 (54.5–84.0)	64.0 (53.0–80.0)	79.0 (65.0–126.0)	<0.001
Uric acid (μmol/L)	261 (194–340)	247 (188–318)	333 (242–457)	<0.001
Alanine aminotransferase (U/L)	70.5 (41.9–138.1)	66.0 (39.0–117.5)	109.8 (57.9–232.0)	<0.001
Aspartic transaminase (U/L)	140 (70–294)	119 (62–242)	353 (162–838)	<0.001
Total bilirubin (μmol/L)	10.4 (7.9–14.2)	10.2 (7.7–13.6)	11.6 (8.7–16.8)	<0.001
Direct bilirubin (μmol/L)	4.64 (3.39–6.80)	4.38 (3.30–6.31)	6.20 (4.38–10.4)	<0.001
Total protein (g/L)	57.0 (52.9–61.1)	57.2 (53.1–61.6)	55.4 (51.7–60.0)	0.004
Albumin (g/L)	31.5 (28.4–34.0)	31.8 (28.9–34.4)	29.5 (27.0–32.8)	<0.001
γ-glutamyl transferase (U/L)	34.0 (21.0–69.0)	32.0 (20.6–63.9)	48.5 (28.3–141.2)	<0.001
Alkaline phosphatase (U/L)	63.0 (51.0–83.0)	61.9 (50.3–78.0)	75.0 (53.0–149.0)	<0.001
Cholinesterase (U/L)	6013 (4903–7092)	6086 (5006–7163)	5582 (4626–6616)	0.001
Total bile acid (μmol/L)	6.4 (3.4–12.6)	5.5 (3.0–10.8)	12.1 (5.1–26.6)	<0.001
Adenosine deaminase (U/L)	29.4 (20.8–42.3)	27.0 (20.0–37.1)	47.6 (30.7–70.4)	<0.001

IQR, interquartile range.
[a] Statistical testing by χ^2 test.
[b] Statistical testing by Mann-Whitney *U* test.

3.2. The potential prognostic factors for mortality in different population with SFTS

According to the lasso results (Fig. S1), six potential prognostic factors for SFTS fatal outcome were identified from 37 variables, including pulse rate, breath, creatinine, APTT, aspartic transaminase (AST) and adenosine deaminase (ADA). As shown in Table 2, in the derivation cohort, all six factors were significantly associated with high mortality. The hazard ratio (HR) (95%CI) for pulse rate, breath, creatinine, APTT, AST and ADA were 1.024 (1.012–1.036), 1.142 (1.001–1.084), 1.003 (1.001–1.005), 1.014 (1.005–1.022), 1.178 (1.135–1.124) and 1.009 (1.003–1.015), respectively. In the validation cohort, pulse rate (HR = 1.036, 95%CI: 1.017–1.055), breath (HR = 1.162, 95%CI: 1.009–1.118), APTT (HR = 1.036, 95%CI: 1.024–1.048) and AST (HR = 1.078, 95%CI: 1.021–1.138) were independently associated with mortality. Furthermore, we found that only APTT was consistently correlated with the fatality (HR: 1.039–1.144; all $P < 0.01$, Table S3) in each sub-validation cohort (Dandong, Dalian, Tai'an, Qingdao and Beijing).

3.3. The associations between prognostic factors with complications in SFTS

In Table S4, we summarized the relationship of clinical characteristics with numbers of complications. Patients with more complications tended to be older and exhibited higher breath and pulse rates. Additionally, they had a higher prevalence of hypertension,

Table 2
Univariable and multivariable model for fatal outcome in the derivation and validation groups.

Characteristics	Univariate			Multivariate		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Derivation cohort (n = 791)						
Pulse rate (beats/min)	1.040	1.031-1.049	<0.001	1.024	1.012-1.036	<0.001
Breath (breaths/min)	1.151	1.117-1.186	<0.001	1.042	1.001-1.084	0.046
Creatinine (μmol/L)	1.007	1.006-1.008	<0.001	1.003	1.001-1.005	0.004
APTT (s)	1.033	1.028-1.038	<0.001	1.014	1.005-1.022	0.001
AST (100*U/L)	1.173	1.143-1.203	<0.001	1.078	1.034-1.124	<0.001
ADA (U/L)	1.022	1.019-1.025	<0.001	1.009	1.003-1.015	0.003
Validation cohort (n = 541)						
Pulse rate (beats/min)	1.044	1.029-1.061	<0.001	1.036	1.017-1.055	<0.001
Breath (breaths/min)	1.121	1.080-1.164	<0.001	1.062	1.009-1.118	0.022
Creatinine (μmol/L)	1.003	1.001-1.005	0.011	1.002	0.999-1.005	0.111
APTT (s)	1.046	1.037-1.055	<0.001	1.036	1.024-1.048	<0.001
AST (100*U/L)	1.151	1.109-1.194	<0.001	1.078	1.021-1.138	0.007
ADA (U/L)	1.007	1.002-1.011	0.003	0.998	0.992-1.004	0.590

Cox proportional hazard regression model was performed to identify factors independently associated with mortality.
HR, hazard ratio; CI, confidence interval; APTT, activated partial thromboplastin time; AST, aspartic transaminase; ADA, adenosine deaminase.

and elevated levels of neutrophils, myocardial enzyme indicators, APTT, thrombin time, blood urea nitrogen, creatinine, uric acid, alanine aminotransferase, AST, direct bilirubin, γ-glutamyl transferase, alkaline phosphatase, total bile acid and ADA. Conversely, patients with more complications had lower levels of lymphocytes, platelets, total protein, albumin and cholinesterase they were. Furthermore, we categorized the population into three groups based on the number of complications (0, 1–2 and 3–6), as shown in Table 3. The results of multiply ordinal logistic regression analyses indicated that pulse rate [odds ratio (OR) = 1.013, 95%CI: 1.002–1.025] and APTT (OR = 1.031, 95%CI: 1.019–1.043) were predictors of a higher probability of reporting more complications in the derivation cohort. However, no factors were associated with the number of complications in the validation cohort. In the five sub-validation cohorts, APTT was found to be related to the number of complications only in Dalian cohort (Table S5).

3.4. Prognostic models to predict mortality in SFTS

Cox regression models and RSF models were developed in the training cohort, and then the prognostic effectiveness of these models was evaluated in both training and external validation cohorts (Fig. 2). The integrated C-index revealed that the RSF model 3, which included variables of APTT, AST, pulse rate, breath, creatinine and ADA, performed best in predicting fatality. Following closely was RSF model 2, which reduced variables of creatinine and ADA (Fig. 2A and **B**). The integrated Brier score indicated that RSF model 2 was the most effective, while RSF model 3 demonstrated a prediction effect similar with that of RSF model 2. (Fig. 2C and **D**). The DCA demonstrated that RSF model 3 provided a higher net benefit than the other models in the internal validation (Fig. 2E); Conversely, in the external validation, cox model 2, incorporating variables of APTT, AST, pulse rate and breath, exhibited the highest net benefit, followed by RSF model 2 (Fig. 2F). The error rate for the selected model (RSF model 2) according to the number of trees and the estimate variable importance is described in Fig. S2. Variables that retained in the model, based on their importance in predicting

Table 3
Ordinal logistic regression on the probability of reporting more complications in the derivation and validation groups.

Characteristics	Univariate			Multivariate		
	OR	95%CI	*P*-value	OR	95%CI	*P*-value
Derivation cohort (n = 791)						
Pulse rate (beats/min)	1.020	1.011-1.030	<0.001	1.013	1.002-1.025	0.023
Breath (breaths/min)	1.077	1.032-1.126	<0.001	0.984	0.933-1.039	0.564
Creatinine (μmol/L)	1.007	1.004-1.010	<0.001	1.003	0.999-1.006	0.083
APTT (s)	1.043	1.033-1.055	<0.001	1.031	1.019-1.043	0.023
AST (100*U/L)	1.159	1.105-1.219	<0.001	1.013	0.951-1.082	0.564
ADA (U/L)	1.026	1.019-1.034	<0.001	1.011	1.002-1.021	0.083
Validation cohort (n = 541)						
Pulse rate (beats/min)	1.011	0.999-1.024	0.066	1.009	0.996-1.022	0.167
Breath (breaths/min)	1.079	1.026-1.138	0.004	1.037	0.982-1.096	0.194
Creatinine (μmol/L)	1.001	0.999-1.004	0.285	1.001	0.999-1.004	0.405
APTT (s)	1.022	1.010-1.033	<0.001	1.006	0.993-1.020	0.167
AST (100*U/L)	1.143	1.081-1.215	<0.001	1.094	1.028-1.169	0.194
ADA (U/L)	1.011	1.006-1.017	<0.001	1.007	1.002-1.013	0.405

Ordinal logistic regression model was performed to identify factors independently associated with complications. The complications were classified into three categories according to their numbers (0, 1–2 and 3–6).
OR, odds ratio; CI, confidence interval; APTT, activated partial thromboplastin time; AST, aspartic transaminase; ADA, adenosine deaminase.

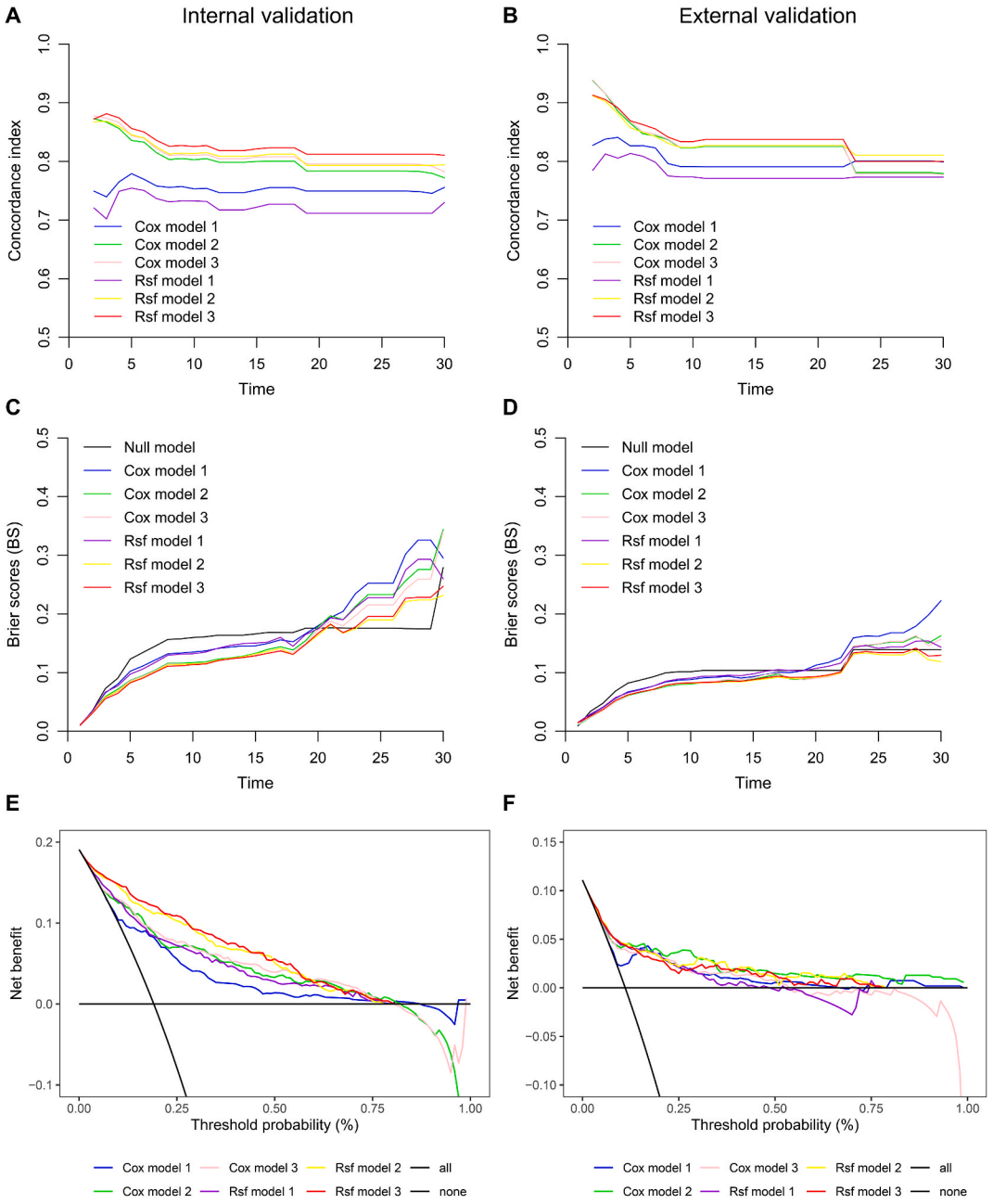

Fig. 2. The evaluations of model for SFTS in-hospital mortality. (A, B) Concordance index, (C, D) Brier score and (E, F) decision curve analyses to evaluate model performance for predicting mortality. Variables in Cox model and RSF model 1: APTT; Variables in Cox model and RSF model 2: APTT, AST, pulse rate and breath; Variables in Cox model and RSF model 3: APTT, AST, pulse rate, breath, creatinine and ADA. RSF, random survival forest; APTT, activated partial thromboplastin time; AST, aspartic transaminase; ADA, adenosine deaminase.

mortality, included APTT, breath, pulse rate and AST, with APTT identified as the single most important variable for predicting fatality in SFTS. In the validation cohort, the area under curve (AUC) for the combination of APTT, pulse rate, breath and AST were 0.849 for 7-day and 0.799 for and 14-day survival, respectively (Fig. 3).

3.5. *APTT as a prognostic biomarker for the prediction of mortality*

In Fig. 3, the AUC of APTT for 7-day survival was 0.848, which was higher than that of pulse rate (AUC = 0.669), breath (AUC = 0.665) and AST (AUC = 0.725). Similarly, for 14-day survival, the AUC of APTT was 0.787, still higher than that of pulse rate (AUC = 0.612), breath rate (AUC = 0.696), and AST (AUC = 0.654).

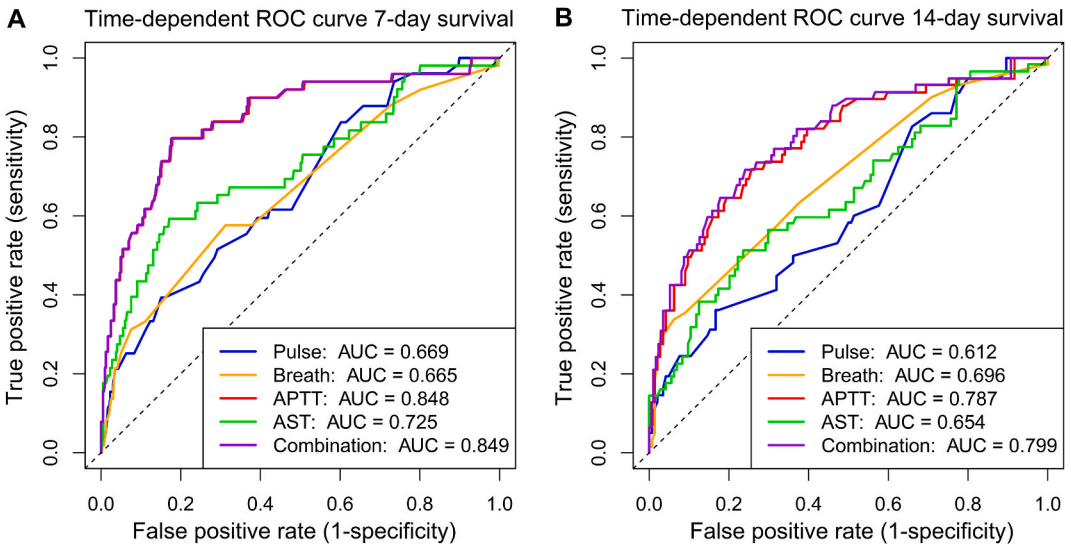

Fig. 3. Time-dependent receiver operating characteristic (ROC) curve for predicting mortality at 7 and 14 days in the external validation cohort (n = 541). APTT, activated partial thromboplastin time; AST, aspartic transaminase.

Taking economic applicability into consideration, we opted to utilize APTT as a predictive biomarker for SFTS fatal outcome. Maximally selected rank statistics determined APTT = 50 s as the optimal cut-off to predict fatality (Fig. 4A). According to Kaplan-Meier survival curve analysis (Fig. 4B), SFTS patients with higher APTT (≥50 s) had a lower survival probability compared to those with lower APTT (42/60 (70.0 %) *vs.* 91/481 (18.9 %), $P < 0.0001$).

4. Discussion

We present the first large-scale retrospective population-based study in China of investigating a variety of hematological variables and their association with the risk of poor prognosis. Our findings confirm that APTT, breath, pulse rate and AST are associated with increased risk of fatal outcome; independently of classical SFTS risk factors and of each other. Importantly, we highlight that APTT exhibits the strongest association with fatal risk, and SFTS patients with higher APTT (≥50 s) demonstrate lower survival probability than those with lower APTT levels.

SFTS is a potentially life-threatening disease, critical ill patients are frequently associated with lethal complications, such as multiple organ dysfunction syndrome and DIC accompanied by hemorrhage [21,22]. SFTSV can affect multiple organs in human, with infected cells detected in various tissues including the liver, adrenal gland, intestine, heart, lung, and kidney [23]. Hemorrhage is one of the most striking characteristics of SFTS. Xu et al. reported that high-dose SFTSV infection directly induces apoptosis, leading to the programmed cell death of human umbilical vein endothelial cells [24], which suggested that the virus-induced disruption of vascular endothelial integrity could be a critical contributor for hemorrhage.

Both thrombocytopenia and coagulation disorder contribute the hemorrhage. Thrombocytopenia occurs in almost all SFTS cases and is associated with heightened cytokine network activation, endothelial cell dysfunction, and disrupted coagulation response [25,26], as well as circulating platelet antibodies and phagocytosis in spleen [27,28]. Coagulation dysfunction is also common in SFTS patients [29] and bleeding symptom accounted for 35 % in patients [30]. In other viral hemorrhagic fevers such as dengue, coagulation dysfunction is caused by inflammation, which generally shifts the hemostatic mechanism toward thrombosis by upregulation of procoagulant factors, down-regulation of anticoagulants, and inhibit fibrinolytic activity [31]. SFTSV infection could result in remarkable damage of vascular endothelial cells and exposure of subcutaneous collagen fibers, promoting the platelet aggregation and cytokines activation, which initiates coagulation system, and further leads to abnormal coagulation function [32].

The coagulation dysfunction generally induced DIC through the damage to endothelial cells and DIC could further aggravate coagulation disorder. In this study, significantly differences were observed in coagulation markers between the non-survivors and survivors. Patients who succumbed to the disease showed pronounced prolongation of APTT, prothrombin time and thrombin time. Dengue virus similarly induces APTT prolongation, patients who died found APTT to be significantly prolonged [33]. Our study displayed that APTT (HR = 1.036, 95%CI: 1.017–1.055) was independently associated with mortality in SFTS, and this correlation was consistently observed in different SFTS sub-cohorts (HR: 1.039–1.144; all $P < 0.01$). Consistent result was reported in previous researches [32,34]. Indeed, numerous investigators have endeavored to elucidate the mechanism underlying the prolongation of APTT in SFTS, as well as strategies for its proper treatment and prevention.

APTT prolongation measurement could be a method to discriminate SFTS from Rickettsia, another tick-transmitted infection. When patients showed no significant difference in PT prolongation and APTT ≥35 s or longer, there is a high probability of SFTSV infection [35]. We identified APTT value of 50 s as the cut-off point for predicting the SFTS fatal outcome, which aligns with previous research.

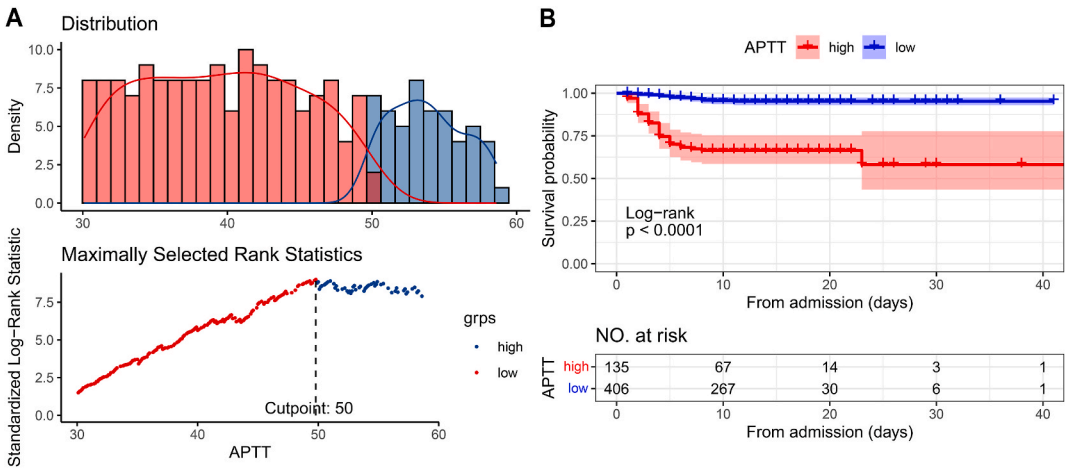

Fig. 4. Identification of optimal APTT cut-off for hospitalized death in SFTS cases. (A) Maximally selected rank statistics determined APTT = 50 s as the optimal cut-off to predict death; (B) Kaplan-Meier analysis with log-rank test using the APTT optimal cut-off demonstrated significant differences in predicting mortality. APTT, activated partial thromboplastin time; SFTS, severe fever with thrombocytopenia syndrome.

For instance, Jia et al. found that an APTT ≥51.9 s can predict death with 84.85 % sensitivity and 81.65 % specificity [36]. Although it is premature to conclude whether these patients are destined for poor outcomes, it plays a role as early warning for death in SFTS when APTT exceed the cut-off point.

Our study revealed RSF model 2 containing variables of APTT, AST, pulse rate and breath had considerable prognostic effectiveness and variables had comparatively high predictive values for mortality in SFTS patients. Elevated level of AST often indicates impairment of liver cells, which is a common phenomenon in SFTS patients [37]. Unlike acute disease caused by other RNA virus infection, SFTS is more prone to cause liver function derangement. Our result demonstrated AST was a predicator can be used to predict clinical outcome of SFTS, which agreed previous studies [14,38,39]. Notably, the significant associations between pulse rate (HR = 1.036, 95% CI: 1.017–1.055) and breath (HR = 1.162, 95%CI: 1.009–1.118) with SFTS fatality were firstly reported in this study.

This study has some limitations, (i) it may have Berkson's bias since all subjects were from sentinel hospitals, for instance, economic levels may affect patient admission rates an times, and potentially influencing the associations between APTT and fatality; (ii) it was a study with retrospective design, the strength of the argument for causality was not as robust as prospective cohort studies; (iii) several variables have been reported to be associated with SFTS mortality in previous studies, such as treatment medications, viral load and d-dimer, but this study didn't collect the relevant data; and (iv) there might be heterogeneity among patients and centers due to the inconsistence of treatment medications, laboratory testing instruments, equipment and reagents between medical institutions. Despite these limitations, our findings uncovered the predictive value of APTT for SFTS mortality, and determined an optimal cut-off value on admission.

5. Conclusion

In the current study, we confirmed the prolonged APTT was associated with unfavorable clinical outcome of SFTS within a large sample size. Prolonged APTT was demonstrated as an independent risk factor for death in patients with SFTS and serve as a significant predictive factor for adverse clinical outcome. Moreover, APTT exceeding 50 s were recommended as a biomarker to remind physicians to monitor and treat patients more aggressively to improve clinical prognosis in SFTS patients.

Ethics approval and consent to participate

This study was approved by the local Ethics Committee of the Beijing Ditan Hospital, Capital Medical University (No. DTEC-KY2022-022-03). All subjects in the study signed an informed consent.

Consent for publication

Not applicable.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Wenjuan Peng: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Junnan Li:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Hong Yu:** Writing – review & editing, Investigation. **Wei Zhou:** Writing – review & editing, Investigation. **Ling Lin:** Writing – review & editing, Investigation. **Ziruo Ge:** Writing – review & editing, Investigation. **Jianming Lai:** Writing – review & editing, Investigation. **Zhihai Chen:** Writing – review & editing, Investigation, Funding acquisition. **Liuluan Zhu:** Writing – review & editing, Investigation. **Zhenghua Zhao:** Writing – review & editing, Investigation. **Yi Shen:** Writing – review & editing, Investigation. **Ronghua Jin:** Writing – review & editing, Investigation. **Jianping Duan:** Writing – review & editing, Investigation. **Wei Zhang:** Writing – review & editing, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

SFTS	severe fever with thrombocytopenia syndrome
SFTSV	SFTS virus
DIC	disseminated intravascular coagulation
APTT	activated partial thromboplastin time
MICE	multiple imputation by chained equations
LASSO	least absolute shrinkage and selection operator
RSF	random survival forest
C-index	concordance index
DCA	decision curve analyses
ROC	receiver operating characteristic
K-M	Kaplan-Meier
AST	aspartic transaminase
ADA	adenosine deaminase
HR	hazard ratio
OR	odds ratio
AUC	area under curve

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31289.

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