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ORIGINAL RESEARCH

# Increased cTnI Predicts Early Death in Patients with Severe Fever with Thrombocytopenia: A Multicenter Study in North China

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**Background:** Myocardial injury is common in severe fever with thrombocytopenia syndrome (SFTS) patients. Currently, research on the prognostic value of cardiac troponin I (cTnI) for predicting the mortality of SFTS patients, especially death within 7 days is limited.

**Methods:** Between May 2011 and October 2022, clinical and laboratory data on admission of consecutive SFTS cases were collected from six medical centres in China. The clinical endpoint was in-hospital all-cause death within seven days. Risk factors of myocardial injury and death were analysed using multivariable regression models. Prognostic models were established using Cox regression and performance of indicators was evaluated in terms of calibration, discrimination.

**Results:** A total of 1379 laboratory-confirmed patients were enrolled, in which 686 subjects were included for analysis. The median age was 66 years, with 48.1% of male. Eighty-seven patients died within seven days and 396 patients diagnosed with myocardial injury during hospitalization. Non-survivors had significant higher levels of cardiac indices than survivors, including cTnI, aspartic transaminase (AST) and lactate dehydrogenase (LDH). Elevated levels of cTnI (HR = 1.058, 95% CI:1.032–1.085), AST (HR = 1.191, 95% CI:1.150–1.234) and LDH (HR = 1.019, 95% CI:1.009–1.029) predicted risk of early in-hospital mortality. cTnI model performed best, with area under curve of 0.850 (0.774–0.926) and concordance index of 0.842, respectively. Statistical differences were found between high and low levels of cTnI for mortality ($P$<0.001) using 0.35 ng/mL as the optimal cut-off.

**Conclusion:** The risk of early in-hospital death can be predicted by cTnI. Clinical doctors should remind vigilant concerning the elevation of cardiac enzyme as soon as possible.

**Keywords:** severe fever with thrombocytopenia syndrome, cardiac troponin I, early death, mortality, risk

## Background

Severe fever with thrombocytopenia syndrome (SFTS) caused by the SFTS virus (SFTSV) remains a pandemic with significant morbidity and mortality.[1] SFTS was initially reported in China in 2009,[2] and later reported in Korea and Japan in 2012.[3,4] To date, SFTS outbreaks have been reported in over twenty provinces of China and other regions in Asia.[5–8] Since there are currently no vaccines or specific antiviral drugs available for prevention and treatment,[9] SFTS has become one of the most important infectious diseases posing a threat to public health. In fact, it was listed by the World Health Organization as one of the top ten priority infectious diseases in the 2018 annual review of the Blueprint list.[10] Typical clinical presentations in SFTS patients encompass

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acute fever, gastrointestinal symptoms, hemorrhagic manifestations, central nervous system manifestations, thrombocytopenia, and leucopenia.[11]

SFTS is sepsis-like condition that the host response overwhelms infection, finally shock and multiple organ failure, with death recorded in 12–50% of the patients who were hospitalized.[12] Due to the high mortality associated with in-hospital SFTS, identifying patients at a high risk of early death can be instrumental in designing personalized treatments crucial for improving patient survival. While numerous models exist for predicting the risk of death in SFTS patients, none have specifically investigated in-hospital mortality within the initial seven days of SFTS onset. This underscores the necessity for a predictive model specifically tailored to early mortality in these patients.

Multiorgan involvement is common in hospitalized patients with SFTS, as documented in previous studies,[13,14] and myocardial injury is no exception. Fulminant myocarditis has been previously reported as a complication of SFTS.[15] Moreover, several preceding studies have emphasized that biomarkers indicative of cardiac injury, such as lactate dehydrogenase (LDH), creatine kinase (CK), creatinine kinase-myocardial band (CK-MB), and aspartic transaminase (AST) levels, exhibited significant elevations in the death group compared to those in the recovery group. These biomarkers have demonstrated the capability to forecast fatal outcomes in SFTS.[16–18] However, detailed information regarding the incidence and risk factors of myocardial injury in SFTS patients is currently lacking. Furthermore, the role of cardiac troponin (cTn), primarily an index of myocardial function, is less well-defined in the context of adverse outcomes in SFTS.

Given the reported findings of altered myocardial enzyme indices, characterization of myocardial injury in SFTS patients and the investigation of their relationship with in-hospital early death is a key imperative. To address this knowledge gap, based on a nationwide multicenter cooperative network across north China, the primary aim of this study was to determine the predictive value of myocardial indicators, especially cTnI, on in-hospital death within seven days. Secondary aims were to describe the features and potential causes of myocardial injury in this understudied population.

# Methods

## 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: (1) Beijing Ditan Hospital Capital Medical University, (2) Dandong Infectious Disease Hospital, (3) Qingdao No. 6 People's Hospital, (4) Tai'an City Central Hospital, (5) Yantai City Hospital for Infectious Disease, (6) Public Health Clinical Center of Dalian.

A prospective observational cohort study of patients with SFTS admitted to the hospital was conducted across these sites from May 2011 to October 2022. All these patients should follow these diagnostic criteria: (1) epidemiological history; (2) acute fever (temperature > 37.5°C for over 24 h) with thrombocytopenia (platelet count < $100 \times 10^9$/L); (3) laboratory-confirmed SFTSV infection by the detection of viral RNA. Exclusion criteria included were as follows: (1) previous leukemia, idiopathic thrombocytopenic purpura, and other hemopathies; (2) previous acute and chronic viral hepatitis, alcoholic liver disease, and other hepatopathies; (3) previous autoimmune diseases; and (4) missing myocardial enzyme assays; and (5) out-patients. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Ethics Committee of the Beijing Ditan Hospital, Capital Medical University (No. DTEC-KY2022-022-03). All subjects in the study signed an informed consent.

## Data Collection

The demographic characteristics including age and gender, clinical data including comorbidities, treatments, complications, and outcomes, laboratory test results (hematological and biochemical data) and results of myocardial enzymes for participants during hospitalization were extracted from electronic medical records. All the data entered into an electronic data collection system by a group of trained study members. Patients who discontinued therapy or were discharged from the hospital for adverse clinical progression or other reasons were followed up until 28 days from the start of admission to determine their final outcome (death or survival).

Myocardial injury was defined as blood levels of cardiac biomarkers cardiac troponin I (cTnI) increased above the 99th percentile upper reference limit.[19] The normal reference range of cTnI is 0–0.04 ng/mL; the normal reference range

of AST, LDH, CK-MB and CK are 15–40 U/L, 120–250 U/L, 0–25 U/L and 50–310 U/L, respectively. The date of disease onset was defined as the day fever was noticed (self-reported). The clinical endpoint was rate of in-hospital all-cause death within seven days.

### Statistical Analysis

We summarized continuous variables as mean (standard deviation) or median (interquartile range, IQR). Categorical variables were expressed as frequencies and proportions. We used the Mann–Whitney *U*-test and Chi-square test for the comparison of continuous and categorical variables, respectively. Logistics regression analysis with odds ratio (OR) was performed to determine the predictors of myocardial injury. Sankey and contour plots were used to descript the association between early in-hospital death with myocardial indicators and age. Cox regression models were utilized to determining the risk myocardial indicators for early in-hospital death.

Data was randomly split into training (70%) and test (30%) sets. In the training set, six different prognostic models (cTnI, AST, LDH, CK, CK-MB and combination of indicators) were established using Cox regression. The performance of indicators was evaluated by brier score, calibration curve, concordance index, and receiver operating characteristic (ROC) curve. The optimal cut-offs for myocardial enzyme indexes were calculated using maximally selected rank statistics. Participants were classified into low and high groups according to cut-off values. Survival differences between the two groups were assessed using Log rank test.

A two-sided $P < 0.05$ was considered significant. All statistical analyses were conducted using SAS software (version 9.4) and R software (version 4.2.2). Contour plots were generated using Surfer (version 8).

## Results

### Patient Characteristics

Figure 1 depicts the flowchart of this study. Between May 2011 and October 2022, a total of 1379 laboratory-confirmed SFTS patients were enrolled, in which 686 subjects were included for analysis. The median age was 66 years (IQR, 58–73 years), with 48.1% of male. There were 119 (17.3%) patients died in hospital, and 87 (73.1%) of them were early in-hospital death. The most common comorbidity was chronic liver disease (25.2%), followed by hypertension (23.0%) and diabetes (15.7%), Table 1.

### Comparison of Baseline Clinical Characteristics Between Patients with and without Myocardial Injury

In all, 396 (57.7%) patients diagnosed with myocardial injury during hospitalization. As shown in Table 1, patients with myocardial injury had older age, higher mortality, and more prevalence of hypertensives and diabetes ($P < 0.05$). As expected, the levels of all cardiac indices (cTnI, AST, LDH, CK and CK-MB) in myocardial injury patients were significantly higher than those in non-myocardial injury patients (all $P < 0.001$). Myocardial injury patients also presented abnormal laboratory Results, such as elevated blood urea nitrogen, creatinine, uric acid, alanine aminotransferase, direct bilirubin, globulin, γ-glutamyl transferase, total bile acid, alkaline phosphatase, adenosine deaminase, white blood cell counts and neutrophil counts, and decreased total protein, albumin, cholinesterase and platelet counts (all $P < 0.05$).

### Predictors of Myocardial Injury

In univariable logistic regression analysis, senior age, hypertension, diabetes, blood urea nitrogen, creatinine, uric acid, alanine aminotransferase, direct bilirubin, globulin, γ-glutamyl transferase, adenosine deaminase and platelet counts were risk factors for myocardial injury; while total protein was protective factor (Table 2). In multivariable logistic regression analysis, senior age (OR = 1.048, 95% CI: 1.028–1.069), alanine aminotransferase (OR = 1.004, 95% CI: 1.001–1.007), globulin (OR = 1.108, 95% CI: 1.042–1.178), adenosine deaminase (OR = 1.037, 95% CI: 1.019–1.055) and total protein (OR = 0.947, 95% CI: 0.912–0.984) were still predictors (Table 2).

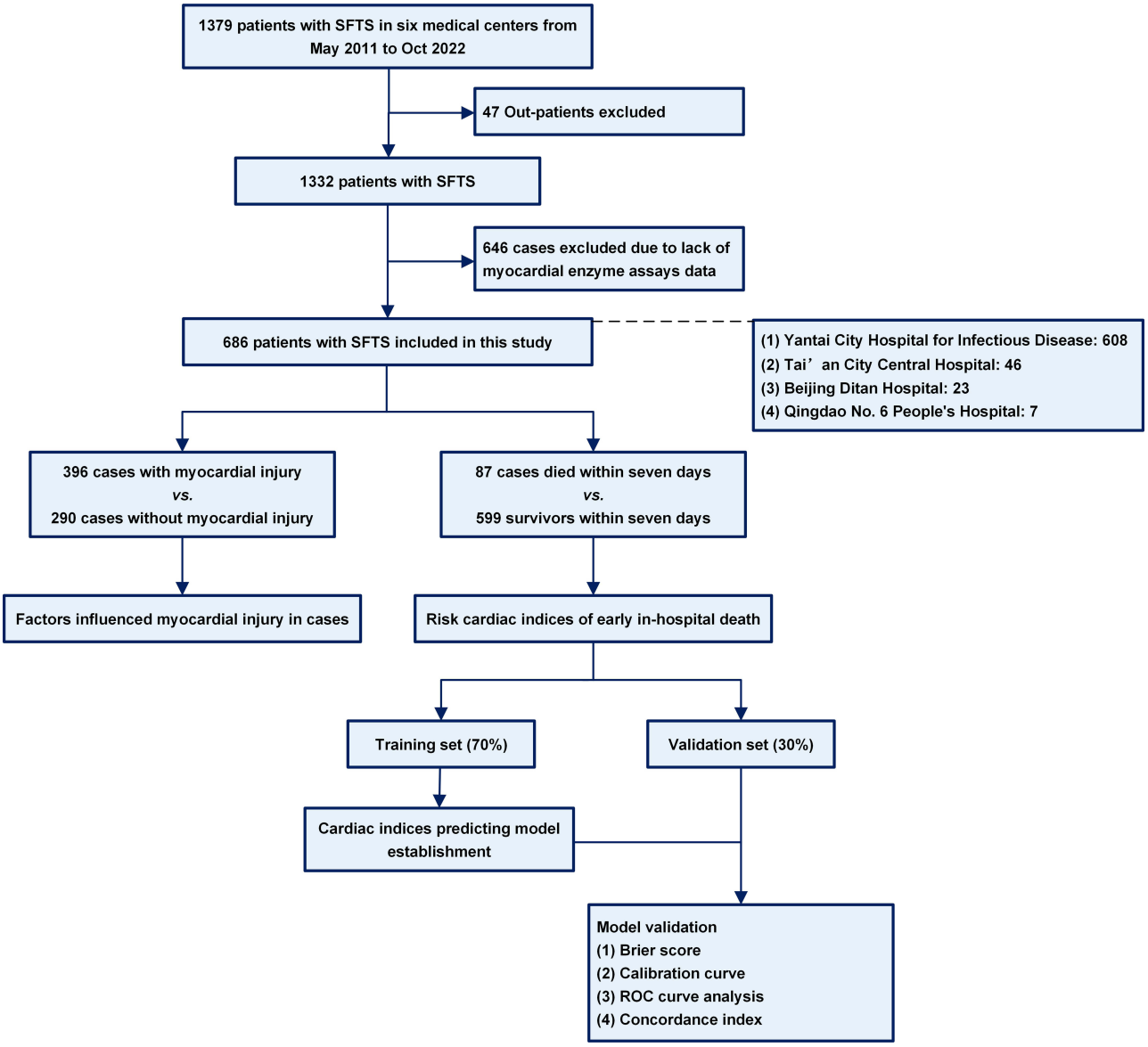


**Figure 1** Flow chart of study.
**Abbreviations**: SFTS, severe fever with thrombocytopenia syndrome.

## Comparison of Baseline Clinical Characteristics Between Survivors and Non-Survivors

In Table S1, we found that compared with survivors, died patients had older age, lower prevalence of chronic liver disease and cerebrovascular disease, and more frequencies of complications, including myocardial injury, liver injury, renal injury, central nervous system lesion, bleeding, multiple organ dysfunction syndrome and acid–base imbalance (all $P < 0.01$). As expected, non-survivors also displayed abnormal laboratory results, such as elevated cardiac indices and decreased platelet counts ($P < 0.001$).

Though days from onset of illness to admission were similar between the two groups, the hospital stays, and days from onset to end of observation were lower in dead group than those in the survival group ($P < 0.001$, Table S1). In Table S2, we summarized the distribution of days from onset to end of observation in all patients, and found that in dead group, most (68.9%) patients died during the second week from onset of illness; and in survival group, most (65.6%) patients discharged during the third and fourth weeks.

**Table 1** Baseline Characteristics in SFTS Patients with and without Myocardial Injury

| Characteristics | Normal Range | Total (n=686) | Myocardial Injury (n=396) | Without Myocardial Injury (n=290) | *P*-value |
|---|---|---|---|---|---|
| Hospital death[&] | – | 119 (17.3) | 104 (26.3) | 15 (5.2) | <0.001 |
| Early hospital death[&] | – | 87 (12.7) | 81 (20.5) | 6 (2.1) | <0.001 |
| Age (years) [†] | – | 66 (58–73) | 68 (61–75) | 62 (55–69) | <0.001 |
| Gender (male) [&] | – | 329 (48.10) | 184 (46.6) | 145 (50.2) | 0.353 |
| Hypertension[&] | – | 158 (23.0) | 102 (25.8) | 56 (19.3) | 0.048 |
| Diabetes[&] | – | 108 (15.7) | 78 (19.7) | 30 (10.3) | <0.001 |
| Coronary artery disease[&] | – | 52 (7.6) | 30 (7.6) | 22 (7.6) | 0.996 |
| Chronic liver disease[&] | – | 173 (25.2) | 98 (24.7) | 75 (25.9) | 0.739 |
| Cerebrovascular disease[&] | – | 58 (8.5) | 36 (9.1) | 22 (7.6) | 0.484 |
| Chronic lung disease[&] | – | 88 (12.8) | 49 (12.4) | 39 (13.4) | 0.678 |
| Cancer[&] | – | 20 (2.9) | 13 (3.3) | 7 (2.4) | 0.504 |
| Cardiac troponin I[†] | 0–0.04 ng/mL | 0.051 (0.020–0.139) | 0.110 (0.070–0.279) | 0.020 (0.010–0.030) | <0.001 |
| Aspartic transaminase[†] | 15–40 U/L | 142 (70–298) | 207 (119–438) | 83 (50–164) | <0.001 |
| Lactate dehydrogenase[†] | 120–250 U/L | 637 (382–900) | 859 (569–900) | 403 (305–648) | <0.001 |
| Creatine kinase[†] | 50–310 U/L | 465 (200–1194) | 670 (256–1707) | 280 (138–655) | <0.001 |
| CK-MB[†] | 0–25 U/L | 19.0 (12.0–32.0) | 22.0 (15.0–40.0) | 14.0 (9.0–24.0) | <0.001 |
| Blood urea nitrogen[†] | 3.1–8.0 mmol/L | 5.8 (4.2–8.2) | 6.5 (4.5–9.4) | 5.1 (3.9–6.7) | <0.001 |
| Creatinine[†] | 57–97 μmol/L | 66.0 (54.6–83.0) | 68.0 (54.6–91.0) | 63.9 (54.6–74.5) | 0.001 |
| Uric acid[†] | 202–416 μmol/L | 254 (191–334) | 265 (190–355) | 244 (196–310) | 0.029 |
| Alanine aminotransferase[†] | 9–50 U/L | 71.0 (41.3–135.5) | 92.1 (52.4–168.5) | 48.8 (30.7–85.3) | <0.001 |
| Total bilirubin[†] | 0–18.8 μmol/L | 10.1 (7.5–13.4) | 10.3 (7.8–13.9) | 9.9 (7.2–13.0) | 0.095 |
| Direct bilirubin[†] | 0–6.8 μmol/L | 4.5 (3.4–6.4) | 4.6 (3.5–7.1) | 4.2 (3.2–5.7) | 0.003 |
| Total protein[†] | 65–85 g/L | 56.9 (52.8–61.0) | 55.9 (52.0–60.0) | 58.2 (54.4–62.7) | <0.001 |
| Albumin[†] | 40–55 g/L | 31.5 (28.5–34.2) | 30.1 (27.6–32.8) | 33.4 (30.1–36.1) | <0.001 |
| Globulin[†] | 20–40 g/L | 25.5 (22.6–28.3) | 25.8 (23.0–28.8) | 25.0 (22.4–27.7) | 0.021 |
| γ-glutamyl transferase[†] | 11–49 U/L | 33.0 (21.0–68.1) | 41.0 (23.0–88.3) | 28.9 (19.0–49.5) | <0.001 |
| Total bile acid[†] | 0–15 μmol/L | 6.4 (3.4–12.3) | 7.4 (3.5–15.0) | 5.3 (3.2–9.7) | <0.001 |
| Alkaline phosphatase[†] | 40–150 U/L | 63.0 (51.0–82.3) | 65.4 (51.5–93.9) | 61.0 (51.0–77.0) | 0.005 |
| Adenosine deaminase[†] | 4–18 U/L | 29.2 (21.2–41.3) | 35.0 (25.5–50.9) | 23.3 (17.6–31.2) | <0.001 |
| Cholinesterase[†] | 4000–11,000 U/L | 5978 (4861–7016) | 5654 (4609–6638) | 6375 (5314–7652) | <0.001 |
| White blood cell[†] | 3.5–9.5 $\times10^9$/L | 2.18 (1.45–3.80) | 2.31 (1.55–4.18) | 2.00 (1.38–3.25) | 0.002 |
| Neutrophil[†] | 1.8–6.3 $\times10^9$/L | 1.31 (0.82–2.46) | 1.47 (0.88–2.67) | 1.18 (0.75–1.98) | 0.001 |
| Lymphocyte[†] | 1.1–3.2 $\times10^9$/L | 0.52 (0.33–0.90) | 0.53 (0.33–0.92) | 0.52 (0.33–0.85) | 0.812 |
| Monocyte[†] | 0.1–0.6 $\times10^9$/L | 0.15 (0.08–0.35) | 0.16 (0.08–0.43) | 0.14 (0.08–0.28) | 0.149 |
| Red blood cell[†] | 4.3–5.8 $\times10^{12}$/L | 4.5 (4.2–4.9) | 4.5 (4.2–4.9) | 4.5 (4.2–4.9) | 0.926 |
| Hemoglobin[†] | 130–175 g/L | 137 (126–150) | 137 (126–149) | 138 (126–150) | 0.876 |
| Hematocrit[†] | 40–50% | 39.9 (37.0–43.5) | 39.9 (37.0–43.6) | 40.0 (37.1–43.5) | 0.993 |
| Platelet[†] | 125–350 $\times10^9$/L | 59.0 (42.5–76.0) | 52 (38–71) | 67 (50–85) | <0.001 |

**Notes**: Continuous variables are presented as median (interquartile range); categorical variables are presented as frequencies (percent). [&], Statistical testing by $\chi^2$ test. [†], Statistical testing by Mann–Whitney *U*-test.
**Abbreviations**: SFTS, server fever with thrombocytopenia syndrome; CK-MB, creatinine kinase-myocardial band.

## Cardiac Indices Were Risk Factors for Early in-Hospital Death

We drew Sankey and contour plots to determine the relationship between levels of cardiac biomarkers, age and mortality. The results showed that the higher mortality was consistently associated with the higher initial levels of cTnI, AST, LDH, CK and CK-MB. Similarly, this phenomenon also occurred in mortality and age (Figure 2).

We calculated the associations between cardiac biomarkers and early in-hospital mortality (Table 3), in univariable Cox regression analysis, cTnI [hazard ratio (HR) = 1.052, 95% CI: 1.028–1.077], AST (HR = 1.203, 95% CI: 1.169–

**Table 2** Risk Indicators of Myocardial Injury in Patients with Fever with Thrombocytopenia Syndrome

| Characteristics | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P*-value | OR | 95% CI | *P*-value |
| Age (years) | 1.055 | 1.037–1.072 | <0.001 | 1.048 | 1.028–1.069 | <0.001 |
| Hypertension | 1.556 | 1.028–2.354 | 0.037 | 1.135 | 0.692–1.862 | 0.628 |
| Diabetes | 1.951 | 1.194–3.188 | 0.008 | 1.425 | 0.792–2.562 | 0.237 |
| Blood urea nitrogen (mmol/L) | 1.095 | 1.045–1.148 | <0.001 | 1.022 | 0.975–1.071 | 0.366 |
| Creatinine (μmol/L) | 1.008 | 1.003–1.014 | 0.002 | 1.003 | 0.998–1.009 | 0.260 |
| Uric acid (μmol/L) | 1.003 | 1.001–1.004 | <0.001 | 1.001 | 0.999–1.003 | 0.459 |
| Alanine aminotransferase (U/L) | 1.007 | 1.005–1.010 | <0.001 | 1.004 | 1.001–1.007 | 0.004 |
| Direct bilirubin (μmol/L) | 1.096 | 1.037–1.159 | 0.001 | 1.021 | 0.979–1.065 | 0.331 |
| Total protein (g/L) | 0.960 | 0.935–0.985 | 0.002 | 0.947 | 0.912–0.984 | 0.006 |
| Albumin (g/L) | 1.001 | 0.999–1.003 | 0.600 | 1.001 | 0.997–1.005 | 0.637 |
| Globulin (g/L) | 1.063 | 1.022–1.106 | 0.002 | 1.108 | 1.042–1.178 | 0.001 |
| γ-glutamyl transferase (U/L) | 1.003 | 1.001–1.005 | 0.005 | 1.001 | 0.999–1.003 | 0.538 |
| Total bile acid (μmol/L) | 1.014 | 0.999–1.029 | 0.062 | 1.002 | 0.988–1.016 | 0.774 |
| Alkaline phosphatase (U/L) | 1.000 | 0.999–1.001 | 0.558 | 0.996 | 0.991–1.002 | 0.175 |
| Adenosine deaminase (U/L) | 1.058 | 1.042–1.073 | <0.001 | 1.037 | 1.019–1.055 | <0.001 |
| Cholinesterase (0.001×U/L) | 1.001 | 0.998–1.004 | 0.612 | 1.001 | 0.996–1.006 | 0.651 |
| White blood cell ($\times 10^9$/L) | 1.052 | 0.980–1.130 | 0.158 | 0.970 | 0.886–1.063 | 0.515 |
| Platelet ($\times 10^9$/L) | 0.988 | 0.982–0.994 | <0.001 | 1.000 | 0.994–1.007 | 0.911 |

**Notes**: Statistical testing by logistic regression model.
**Abbreviations**: OR, odds ratio; CI, confidence interval.

1.239), LDH (HR = 1.036, 95% CI: 1.028–1.045), CK (HR = 1.009, 95% CI: 1.004–1.014) and CK-MB (HR = 1.406, 95% CI: 1.232–1.606) were risk factors for early in-hospital fatality. In multivariable Cox regression analysis, cTnI (HR = 1.058, 95% CI: 1.032–1.085), AST (HR = 1.191, 95% CI: 1.150–1.234) and LDH (HR = 1.019, 95% CI: 1.009–1.029) were still risk factors.

## Establishing and Evaluating Predictive Model of Cardiac Indicators for Early in-Hospital Mortality

As shown in Table S3, the difference of baseline characteristics between training set and test set were all non-significant, except for central nervous system lesion ($P = 0.013$), blood urea nitrogen ($P = 0.001$), creatinine ($P = 0.002$) and red blood cell ($P = 0.019$). Cox regression models were developed in the training set and evaluated in the test set. The integrated Brier score and calibration curve showed that cardiac indicators performed effectively to predict early fatal outcome (Figure 3). As shown in Table 4, the Cox regression model with variable of cTnI has the best performance, with the concordance index of 0.842 and AUC value of 0.850 (0.774–0.926). Therefore, we identified cTnI as a predicting biomarker for the SFTS fatal outcome within seven days.

## Identifying Optimal Cut-Offs of Cardiac Biomarkers for Early in-Hospital Death

Maximally selected rank statistics determined cTnI = 0.35 ng/mL as the optimal cut-off to predict early fatality (Figure 4A). By Kaplan–Meier analysis (Figure 4B), cTnI > 0.35 ng/mL was markedly associated with higher early hospitalized death [42/82 (51.2%) vs 45/604 (7.5%), $P < 0.001$].

In Figures S1–S4, we also calculated the optimal cut-offs of other cardiac indexes, in which AST = 353 U/L, LDH = 894 U/L, CK = 1364 U/L and CK-MB = 42 U/L, respectively. Moreover, cardiac indicators above these cut-offs were associated with higher hospitalized morality [AST: 54/139 (38.8%) vs 33/547 (6.0%), $P < 0.001$; LDH: 66/224 (29.5%) vs 21/462 (4.5%), $P < 0.001$; CK: 46/145 (31.7%) vs 41/541 (7.6%), $P < 0.001$; CK-MB: 39/112 (34.8%) vs 48/574 (8.4%), $P < 0.001$].

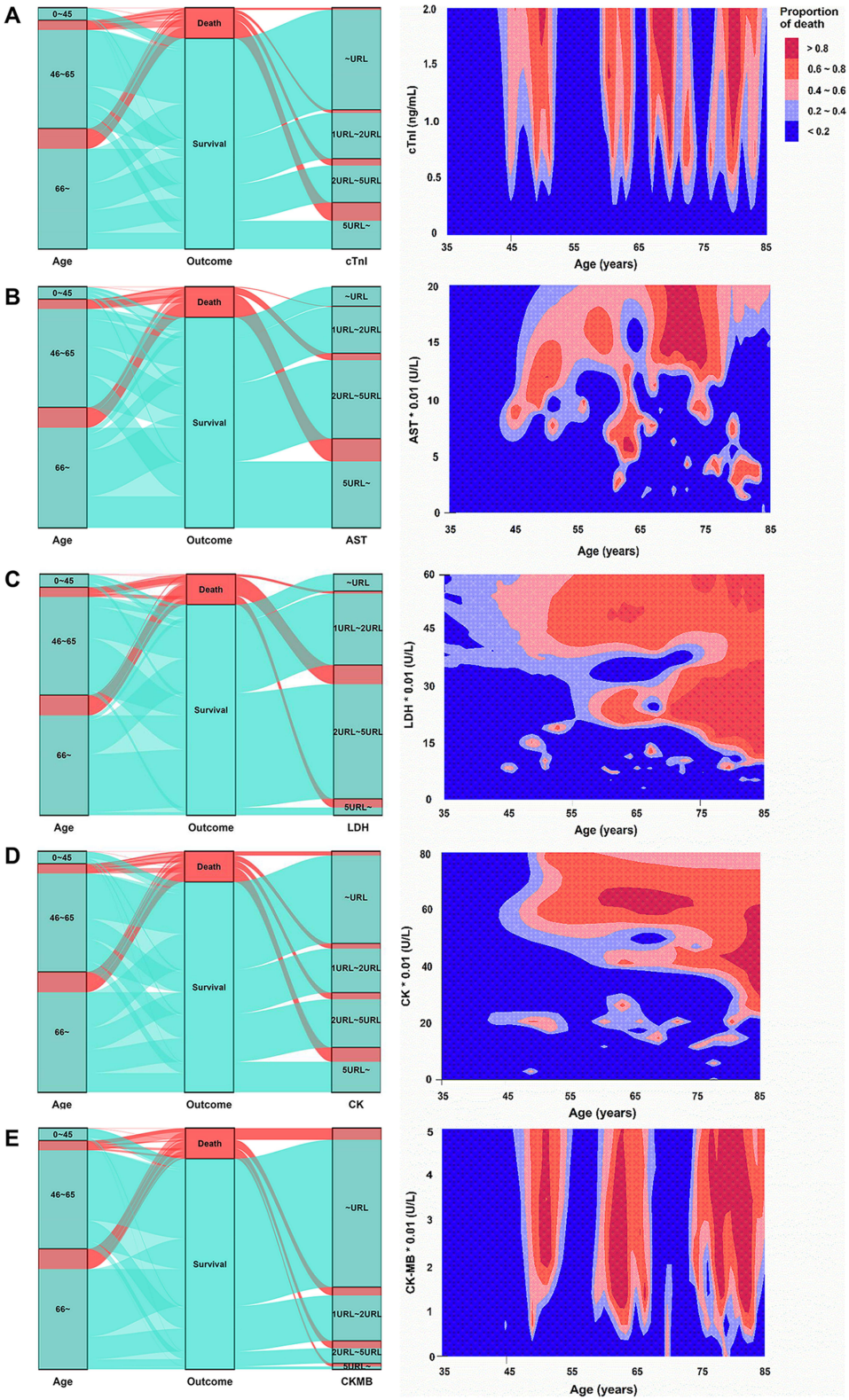


**Figure 2** Relationship between levels of cardiac biomarkers, age and early in-hospital mortality. (**A**) cTnI; (**B**) AST; (**C**) LDH; (**D**) CK; (**E**) CK-MB.
**Abbreviations**: URL, upper reference limit; cTnI, cardiac troponin I; AST, aspartic transaminase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatinine kinase-myocardial band.

**Table 3** Risk Myocardial Indicators of Early in-Hospital Mortality in Patients with SFTS

| Characteristics | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Cardiac troponin I (ng/mL) | 1.052 | 1.028–1.077 | <0.001 | 1.058 | 1.032–1.085 | <0.001 |
| Aspartic transaminase (0.01*U/L) | 1.203 | 1.169–1.239 | <0.001 | 1.191 | 1.150–1.234 | <0.001 |
| Lactate dehydrogenase (0.01*U/L) | 1.036 | 1.028–1.045 | <0.001 | 1.019 | 1.009–1.029 | <0.001 |
| Creatine kinase (0.01*U/L) | 1.009 | 1.004–1.014 | <0.001 | 1.004 | 0.998–1.009 | 0.186 |
| Creatinine kinase-myocardial band (0.01*U/L) | 1.406 | 1.232–1.606 | <0.001 | 1.103 | 0.929–1.339 | 0.321 |

**Notes**: Statistical testing by Cox regression model.
**Abbreviations**: SFTS, server fever with thrombocytopenia syndrome; HR, hazard ratio; CI, confidence interval.

## Discussion

The major findings of the present study are as follows: (i) the majority (73.1%) of dead patients with SFTS were early in-hospital deaths; (ii) myocardial injury is common (57.7%) among patients with SFTS, especially in those who die; (iii) elevated levels of cTnI, AST and LDH predicted risk for early in-hospital death, which suggested that SFTS patients with myocardial damage are more likely to develop quick fatality; and (iv) cTnI performed the best predictive effectiveness for the SFTS fatal outcome within seven days, and cTnI = 0.35 ng/mL was determined as the optimal cut-off.

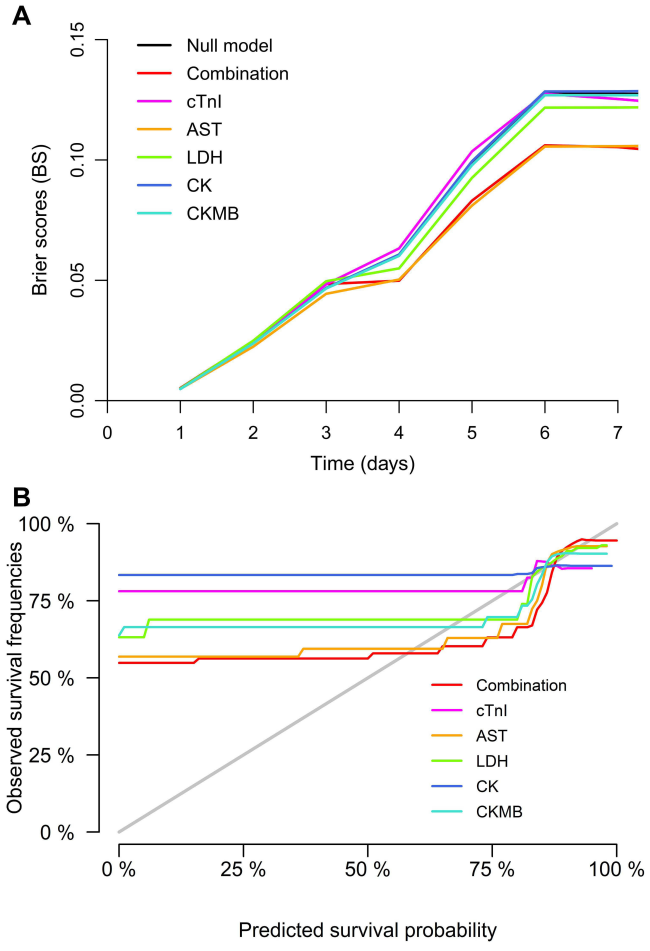


**Figure 3** The evaluation of the cardiac indicator predictive models for early in-hospital mortality. (**A**) Integrated Brier score to evaluate model performance to predict mortality; (**B**) Time-dependent receiver operating characteristic (ROC) curve for predicting mortality at seven days.
**Abbreviations**: cTnI, cardiac troponin I; AST, aspartic transaminase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatinine kinase-myocardial band.

**Table 4** Evaluation Results of Cox Regression Model Performance in the Test Set

| Indicators | C-index | AUC (95% CI) | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| cTnI | 0.842 | 0.850 (0.774–0.926) | 89.29% | 70.22% | 0.317 | 0.976 |
| AST | 0.774 | 0.680 (0.546–0.815) | 60.71% | 83.15% | 0.362 | 0.931 |
| LDH | 0.786 | 0.780 (0.661–0.899) | 78.57% | 70.79% | 0.297 | 0.955 |
| CK | 0.683 | 0.667 (0.531–0.804) | 64.29% | 64.61% | 0.222 | 0.920 |
| CK-MB | 0.727 | 0.724 (0.593–0.855) | 71.43% | 64.04% | 0.238 | 0.934 |
| Combination | 0.805 | 0.846 (0.730–0.902) | 71.43% | 84.27% | 0.417 | 0.949 |

**Abbreviations**: cTnI, cardiac troponin I; AST, aspartic transaminase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatinine kinase-myocardial band; C-index, concordance index; AUC, area under the ROC curve; ROC, receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value.

As a complicated multi-system disease, SFTS has characteristics of rapid disease progression and high mortality. The natural course of SFTS is divided into three distinct stages after the onset of illness: fever stage, multiple-organ dysfunction (MOD) stage and convalescent stage.[20] In general, from the onset of illness, the fever stage persists for approximately seven days, the MOD stage develops rapidly at 7–13 days, and the two periods may overlap.[21] The clinical progress in MOD phase is key to predicting the disease outcome. The overall mortality of SFTS was about 12–30%, and the vast majority of patients died in MOD stage.[2,16] Our study presented consistent results with this phenomenon, in the current study, among the 119 (17.3%) hospitalized deaths, 87 of them died within seven days from admission, with a high proportion of 73.1%. Furthermore, we found 68.9% patients died during the second week from onset of illness, which means that they died during the MOD stage of this disease.

Cytokine storm-mediated immune activation and mechanisms of impairment of innate immune responses could justify the main pathogenesis of SFTS in recent research.[22,23] Firstly, virus transmission to humans commonly occurs from virus-carrying-tick-bite. And then, virus goes to the circulation system, in response to viremia, immune cells are over-stimulated causing the cytokine storm.[23] Furthermore, cytokine storm induces the disseminated intravascular coagulation and endothelial damage and lead to multi-organ impairments, including heart, liver and kidney and so on, reflected by the dramatic elevation of cardiac, liver and kidney serum markers.[24]

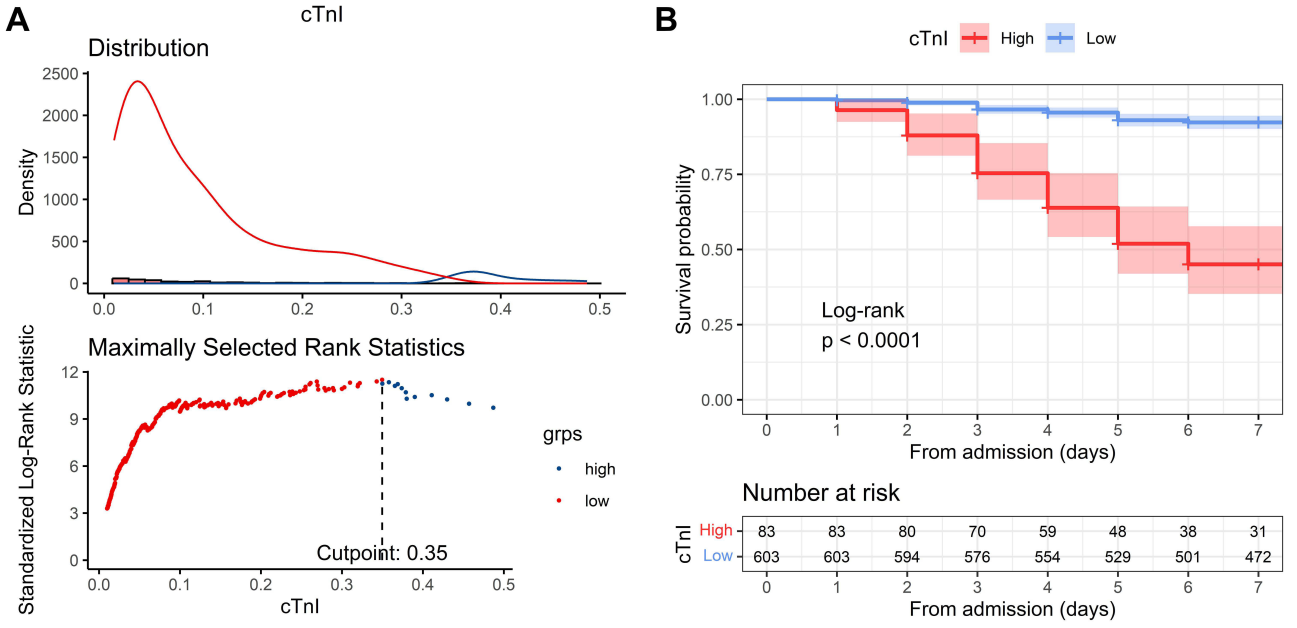


**Figure 4** Identification of optimal cTnI cut-off for early hospitalized death in SFTS cases. (**A**) Maximally selected rank statistics determined cTnI = 0.35 ng/mL as the optimal cut-off to predict early death; (**B**) Kaplan-Meier analysis with Log rank test using the cTnI optimal cut-off demonstrated significant differences in predicting early mortality. cTnI, cardiac troponin I.

Some published meta-analysis studies had emphasized the importance of SFTS-related organ damage on fatality of disease.[25–27] Notably, during the MOD phase, damage to the heart persisted.[28] In addition to the circulating inflammatory mediators, direct viral invasion of cardiomyocytes may lead to myocardial injury in SFTS. Immunohistochemistry of a SFTS patient revealed that SFTSV can directly infect multiple organs, including the heart,[29] which suggested that SFTSV can directly invade the cardiomyocytes. Due to present limited evidence, whether SFTSV can directly impair the heart remains to be further demonstrated. Myocardial injury is one of most common complications in SFTS patients and makes them more likely to develop critical or died cases.[30,31] Shao F et al illustrated more than half of SFTS patients had electrocardiograph (ECG) abnormalities with the characteristics of ST-T change, atrial fibrillation and sinus bradycardia, though these ECG changes were reversible as condition improved, the incidence of abnormal ECG in died patients was still at a high level.[30] In this study, the prevalence of myocardial injury in SFTS patients was up to 57.7%, and we further focused on determining the predictive value of myocardial indicators on in-hospital fatality.

Numerous studies have highlighted that elevated levels of LDH, CK, and CK-MB serve as risk factors for fatal SFTS.[31–33] Generally, preceding the clinical deterioration observed in SFTS, myocardial markers exhibit a sharp deviation from normal ranges.[34] Consistent with prior research, our findings indicate that patients who succumbed within seven days of admission displayed significantly higher levels of all cardiac indices (cTnI, AST, LDH, CK, and CK-MB) compared to survivors. Notably, cTnI, AST, and LDH were identified as associated with a higher risk of early in-hospital death due to SFTS.

Due to their absolute myocardial tissue specificity and high sensitivity, cTnI and cTnT are considered the preferred biomarkers for detecting myocardial damage.[35] As anticipated, our study revealed that cTnI is also the optimal predictor of early fatality among hospitalized patients with SFTS. To the best of our knowledge, this study is the first to assess the potential predictive value of cTnI in the rapid deterioration of SFTS.

Therefore, monitoring cTnI upon admission is crucial for facilitating timely treatment intervention and preventing early mortality.

In our study, we established a cut-off point of cTnI = 0.35 ng/mL to predict early fatal outcomes in SFTS. It is noteworthy that this singular threshold does not encompass individuals with normal cTnI levels upon admission. While it is premature to definitively conclude poor outcomes for these patients, the identified cut-off point serves as an early warning indicator for swift deterioration in SFTS when cTnI levels surpass the specified threshold.

Different from those models reported in existing literature predicting the morality in SFTS patients, the primary focus of this article is to investigate the predictive capacity of myocardial biomarkers, especially cTnI, in determining mortality, so the model in the present study only include the myocardial biomarkers, and there no additional indicators, although our AUC value is not as high as reported in the literature. Regardless, our findings provide valuable insights for clinical assessment of early mortality.

While this study represents the comprehensive exploration of in-hospital mortality rates within seven days among a substantial cohort of SFTS patients, certain limitations must be acknowledged. Firstly, the reliance on SFTS cases from sentinel hospitals introduces the potential for Berkson's bias. Secondly, the variations in detection Methods across the six hospitals may have impacted the comparability of laboratory results. Thirdly, the study's retrospective nature inherently weakens the argument for causality when compared to prospective cohort studies. Nevertheless, given the study's retrospective design, these limitations were inevitable.

Despite these constraints, our findings bring to light the significant predictive value of myocardial enzymes, particularly cTnI, in early SFTS mortality. Furthermore, we have established an optimal cutoff value for cTnI upon admission. While acknowledging these limitations, we posit that our discoveries could prove instrumental in mitigating rapid mortality rates by enabling accurate and timely identification of potential severe or fatal cases of SFTS.

## Conclusion

In individuals diagnosed with SFTS, the majority of fatalities occurred early during hospitalization, with myocardial injury emerging as a prevalent complication. Elevated levels of myocardial enzyme indices serve as significant risk factors for early in-hospital fatality. Among these indices, cTnI demonstrated the most reliable predictive effectiveness, and a cTnI level of 0.35 ng/mL was identified as the optimal cutoff value. This underscores the critical importance of vigilant monitoring of cTnI in the clinical management of SFTS patients.

## Data Sharing Statement

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

## Ethics Approval and Consent to Participate

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Ethics Committee of the Beijing Ditan Hospital, Capital Medical University (No. DTEC-KY2022-022-03). All subjects in the study signed an informed consent.

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## Author Contributions

Junnan Li, Ling Lin and Wenjuan Peng: Conception, design or planning of the study, acquisition of the data, analysis of the data, interpretation of the results, drafting of the manuscript. Wei Zhou, Ligang Zhang, Wenjuan Ji, Ziruo Ge, Jianming Lai and Wei Zhang: Acquisition of the data. Zhenghua Zhao, Jianping Duan and Zhihai Chen: Acquisition of the data, Conception, design or planning of the study. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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