The Association Between Elevated Myocardial Injury-Related Biomarker (TnI) and Increased Mortality in Patients With Severe Fever With Thrombocytopenia Syndrome

OBJECTIVES: The objective of this study was to investigate the dynamic profiles of myocardial injury biomarkers and their association with mortality in patients with severe fever with thrombocytopenia syndrome (SFTS).

DESIGN: A retrospective cohort study.

SETTINGS: Union Hospital in Wuhan, China.

PATIENTS: A total of 580 patients with SFTS, observed between May 2014 and December 2021, were included in the final analysis.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: In total, 580 patients with SFTS were enrolled in the study, comprised of 469 survivors and 111 nonsurvivors, with a 21-day fatality rate of 19.1%. The elevation of troponin I (TnI) was observed in 61.6% patients (357/580) with SFTS upon admission, and 68.4% patients (397/580) developed an abnormal TnI level during hospitalization. Multivariate logistic regression identified age, viral load, platelet count, creatinine level, and TnI level as potential risk factors for mortality in patients with SFTS. The results of restricted cubic splines revealed that when the TnI level (baseline TnI: 1.55 [lg (ng/L+1)], peak value: TnI 1.90 [lg (ng/L+1)]) exceeded a certain threshold, the predicted mortality of patients with SFTS increased alongside the rise in TnI levels. Mortality rate surpassed 40% among patients with SFTS with TnI greater than or equal to 10 times the upper limit of normal at admission (43.8%) or during hospitalization (41.7%). Older age, a history of cardiovascular disease, and higher D-dimer levels were potential risk factors for elevated TnI levels in patients with SFTS.

CONCLUSIONS: Elevated TnI levels were prevalent among patients with SFTS and were strongly associated with an increased risk of mortality.

KEYWORDS: mortality; risk factor; severe fever with thrombocytopenia syndrome; troponin I

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Severe fever with thrombocytopenia syndrome (SFTS) emerged as an infectious disease first reported in 2009, subsequently appearing in more than 19 provinces in China and other countries, including Japan, Korea, the United States, and the United Arab Emirates (1). The causative agent, Dabie Bandavirus (DBV), also known as SFTSV, is a novel virus belonging to the genus Bandavirus in the family Phenuiviridae (2). Patients with SFTS typically manifest a range of symptoms, including acute fever, thrombocytopenia, gastrointestinal issues, and CNS symptoms. However, severe cases progressed rapidly to multiple organ failure, with high mortality ranging from 12% to 30% (3, 4).

In recent years, myocardial injury in noncardiotropic viral infections (such as severe acute respiratory syndrome coronavirus 2, influenza virus, etc.) drew

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KEY POINTS

Question: What is the dynamic profiles of myocardial injury-related serum biomarkers and their association with mortality risk in patients with severe fever with thrombocytopenia syndrome (SFTS) ?

Findings: The elevation of troponin I (TnI) was observed in 61.6% patients (357/580) with SFTS upon admission, and 68.4% patients (397/580) developed abnormal TnI levels during hospitalization. Multivariate logistic regression identified age, viral load, platelet count, creatinine level, and TnI level as potential risk factors for mortality in patients with SFTS. The results of restricted cubic splines showed that when the level of TnI exceeded a certain threshold, the predicted mortality of patients with SFTS increased with the rise in TnI levels. Mortality exceeded 40% among SFTS patients with TnI levels greater than or equal to 10 times the upper limit of normal at admission (43.8%) or during hospitalization (41.7%). Older age, a history of cardiovascular disease (CVD), and higher D-dimer levels were potential risk factors for elevated TnI levels in SFTS patients.

Meaning: Elevated TnI levels were prevalent in patients with SFTS and are closely associated with a higher risk of mortality. Clinicians are advised to closely monitor older patients with elevated TnI levels, higher D-dimer levels, and a history of CVD.

significant attention, as indicated by elevated serum cardiac troponin I (cTnI) (5–8). Elevated serum TnI levels were observed in patients with SFTS, along with transient diffuse left ventricular motion reduction and wall thickening noted in echocardiography, and diffuse ST segment elevation on electrocardiography, which excluded other heart diseases and indicated fulminant myocarditis (9). An autopsy finding of a deceased patient with SFTS revealed structural disorders, vacuolar degeneration, and lipofuscin dispersion in myocardial cells (10). Furthermore, several other serum enzymes related to myocardial injury, such as aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), and CK-myocardial band (CK-MB) isoenzymes, were elevated in patients infected with SFTSV, as reported (10, 11). Shock and arrhythmia were identified as risk factors for mortality in patients with SFTS (11). These studies indicated that patients with SFTS may have experienced cardiac dysfunction or injury. However, current reports lack a systematic description of biomarkers related to myocardial injury, particularly TnI, and the risk factors for elevated TnI levels remain unclear.

In this retrospective cohort study, we studied the dynamic profile of myocardial injury-related biomarkers (TnI) and performed an analysis of the potential risk factors in hospitalized patients with SFTS. This study aimed to assist clinicians in the early diagnosis of patients with SFTS exhibiting elevated TnI levels.

MATERIALS AND METHODS

Patients and Data Collection

The electronic medical record system of Wuhan Union Hospital was searched for SFTS cases spanning from May 2014 to December 2021, resulting in the retrieval of 1412 records. All patient information, including clinical history, physical examination findings, and laboratory results, was collected from medical records by two trained physicians. **Supplementary Figure S1** (http://links.lww.com/CCM/H564) illustrates the workflow of participant enrollment in this study. Participants were laboratory-confirmed through a real-time reverse transcriptase-polymerase chain reaction of DBV RNA, with 551 patients testing negative for DBV being excluded. Patients with incomplete medical histories (97 patients), lacking records of TnI (154 patients), or being admitted to the hospital more than 2 weeks after disease onset were excluded. All patients were admitted to the hospital within 2 weeks after disease onset. Additionally, patients coinfected with Epstein-Barr virus, cytomegalovirus, HIV, hepatitis E virus, or other acute pathogens (24 patients), and diagnosed with tumors, autoimmune diseases, or other malignant illnesses (6 patients), were excluded. Ultimately, 580 patients, comprised of 111 nonsurvivors and 469 survivors, were enrolled in this study. The ethical committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, approved the study (approval no. 2023-0432; title: "A retrospective study on the severe characteristics and clinical diagnosis and treatment of severe fever with thrombocytopenia syndrome") on June 5, 2023. The study procedures adhered to the requirements of the Declaration of Helsinki. The requirement for written

informed consent was waived due to the retrospective nature of the study.

Definition of Troponin I and Other Cardiac Biomarker Elevations

According to the Fourth Universal Definition of Myocardial Infarction (2018), TnI elevation was defined as serum levels of cardiac biomarkers (TnI) exceeding the 99th percentile in a healthy reference population (26.2 ng/L) (12). Serum troponin I (TnI) levels collected within 21 days of disease onset were used to assess myocardial health. Additionally, serum enzymes associated with myocardial injury, including CK-MB, CK, and α-Hydroxybutyrate dehydrogenase (α-HBDH), were analyzed. The upper limit of normal (ULN) references for cardiac enzymes in the serum are: CK-MB equals to 6.6 ng/mL, CK equals to 140 U/L, and α-HBDH equals to 182 U/L.

Statistical Analysis

Continuous variables were presented as mean ± SD or median (interquartile range). Significant differences between the two groups were assessed using Student *t* test or the nonparametric two-tailed Mann-Whitney *U* test. Differences among multiple groups were determined using one-way analysis of variance or the Kruskal-Wallis test. Categorical variables were expressed as frequencies and proportions and analyzed using the chi-square or Fisher exact test. Risk factors for mortality of SFTS and elevated TnI levels were determined using univariate or multivariate logistic regression analyses. The propensity matching score (PSM) was used to mitigate the confounding bias stemming from the age, viral load, and platelet count in the examination of the association between TnI levels and mortality. One-to-one greedy matching was conducted with a caliper width set at 0.30 times the pooled SD of the logit of the propensity score to identify matched patients within the groups. We used a restricted cubic splines (RCS) model with five knots to further investigate the association between TnI and SFTS mortality. The dynamic profiles of myocardial injury-related biomarkers, tracked from days 1 to 21 after illness onset, were depicted using locally weighted scatterplot smoothing (LOESS). Kernel density estimation (KDE) plots were used to determine the distribution of myocardial injury-related biomarkers in survivors and nonsurvivors. **p* less than 0.05, ***p* less than 0.01, and ****p* less than 0.001 were considered statistically significant. All statistical analyses were conducted using SPSS (version 25.0; SPSS, Armonk, NY) and R (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Additionally, R (version 4.0.2.) and GraphPad Prism 9 (GraphPad Software, La Jolla, CA) were used to generate the figures.

RESULTS

Baseline Characteristics and Laboratory Results of Patients With SFTS

A total of 580 laboratory-confirmed patients with SFTS, including 338 (58.3%) females, were enrolled in this study, with a median age of 61 years (53–68). Among the 580 patients with SFTS, 175 (30.2%) had underlying cardiovascular disease (CVD), including hypertension, coronary atherosclerotic heart disease, and other structural heart diseases. The patients were categorized into two groups based on their outcomes: 469 survivors (80.9%) and 111 nonsurvivors (19.1%), resulting in a 21-day fatality rate of 19.1% (111/580). **Table 1** displays the baseline characteristics and laboratory parameters of patients with SFTS. The median age of patients in the nonsurviving group was significantly higher than that in the surviving group (65 vs. 59 yr, $p < 0.001$). No significant differences in days from symptom onset to admission, sex distribution, or prevalence of underlying CVD (28.8% vs. 36.0%, $p = 0.134$) were observed between the survivors and nonsurvivors. Patients in the nonsurvivor group exhibited lower percentages of lymphocytes and monocytes, as well as lower lymphocyte count, monocyte count, and platelet count compared with patients in the survivor group (all $p < 0.05$). However, nonsurvivors had higher levels of viral load, neutrophil percentage, liver function biomarkers (total bilirubin, direct bilirubin, alanine aminotransferase [ALT], AST, alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]), renal function biomarkers (creatinine [Cr], blood urea nitrogen), myocardial injury-related biomarkers (LDH, CK, CK-MB, TnI, α-HBDH), and D-dimer (all $p < 0.05$). Furthermore, nonsurvivors showed significantly prolonged prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) compared with survivors (all $p < 0.05$).

TABLE 1.
Baseline Characteristics and Laboratory Parameters in Patients With Severe Fever With Thrombocytopenia Syndrome

Characteristic	Total (*n* = 580)	Troponin I		
		Survivor (*n* = 469)	Nonsurvivor (*n* = 111)	*p*
Age (yr)	61 (53–68)	59 (52–67)	65 (59–70)	< 0.001
Sex, female (%)	338 (58.3)	59 (53.2)	279 (59.5)	0.134
History of cardiovascular disease	175 (30.2)	135 (28.8)	40 (36.0)	0.134
Days after onset	6 (5–7)	6 (5–7)	6 (5–7)	0.303
Viral load (Log10)	3.81 (2.94–4.84)	3.57 (2.81–4.39)	5.13 (4.36–6.14)	< 0.001
RBC (× 10^{12}/L)	4.31 (3.96–4.70)	4.28 (3.94–4.69)	4.44 (4.07–4.76)	0.111
Hemoglobin (g/dL)	129 (118–142)	129 (118–142)	131 (119–143)	0.366
WBC (× 10^9/L)	2.24 (1.47–3.68)	2.23 (1.46–3.78)	2.27 (1.49–3.33)	0.808
Neutrophil (%)	70.00 (55.70–81.10)	67.90 (52.70–80.55)	76.30 (62.40–82.10)	0.001
Lymphocyte (%)	23.60 (15.10–34.80)	24.95 (15.23–36.90)	18.80 (14.50–26.70)	< 0.001
Monocyte (%)	4.40 (2.20–8.03)	4.80 (2.40–8.20)	2.64 (1.68–6.15)	< 0.001
Neutrophil (× 10^9/L)	1.44 (0.87–2.60)	1.41 (0.84–2.60)	1.59 (1.02–2.60)	0.263
Lymphocyte (× 10^9/L)	0.50 (0.34–0.80)	0.52 (0.36–0.82)	0.40 (0.28–0.65)	0.001
Monocyte (× 10^9/L)	0.09 (0.05–0.18)	0.10 (0.05–0.19)	0.06 (0.03–0.15)	< 0.001
Platelet (× 10^9/L)	48 (33–62)	50 (35–65)	37 (24–52)	< 0.001
Total bilirubin (μmol/L)	9.4 (7.2–12.4)	9.3 (7.0–12.3)	10.0 (8.0–14.3)	0.006
Direct bilirubin (μmol/L)	4.5 (3.6–6.3)	4.4 (3.5–5.9)	5.8 (4.2–9.0)	< 0.001
Alanine aminotransferase (U/L)	70 (44–118)	68 (43–112)	93 (55–172)	< 0.001
Aspartate aminotransferase (U/L)	195 (100–372)	174 (93–327)	288 (172–594)	< 0.001
Alkaline phosphatase (U/L)	65 (53–85)	63 (53–83)	72 (56–100)	0.006
γ-Glutamyl transpeptidase (U/L)	30 (19–57)	29 (19–52)	39 (22–84)	0.004
Creatinine (μmol/L)	73.5 (61.3–94.0)	71.1 (60.4–89.6)	89.1 (68.9–129.0)	< 0.001
Blood urea nitrogen (μmol/L)	5.16 (3.70–7.32)	4.86 (3.52–6.65)	6.10 (4.92–10.81)	< 0.001
Lactic dehydrogenase (U/L)	758 (481–1239)	718 (463–1097)	1186 (637–1922)	< 0.001
Creatine kinase (U/L)	577 (264–1252)	504 (244–1014)	991 (457–2181)	< 0.001
Creatine kinase isoenzymes (ng/mL)	2.7 (1.2–5.9)	2.5 (1.1–4.9)	5.2 (1.8–10.6)	< 0.001
Troponin I (ng/L)	41.5 (12.2–97.8)	35.8 (10.0–82.8)	77.2 (23.2–249.2)	< 0.001
Brain natriuretic peptide (ng/L)	34.5 (15.9–89.9)	32.4 (14.4–78.2)	46.0 (20.8–124.6)	0.037
α-Hydroxybutyrate dehydrogenase (U/L)	489 (351–775)	461 (338–653)	904 (495–1329)	< 0.001
D-dimer (mg/L)	3.57 (2.01–7.28)	3.28 (1.86–5.73)	6.26 (3.53–11.75)	< 0.001
Prothrombin time (s)	13.2 (12.5–13.9)	13.1 (12.4–13.9)	13.6 (12.8–14.3)	< 0.001
International normalized ratio	1.02 (0.95–1.09)	1.01 (0.94–1.08)	1.06 (0.98–1.13)	< 0.001
Activated partial thromboplastin time (s)	54.1 (47.8–64.1)	52.5 (46.2–60.4)	64.6 (53.0–78.0)	< 0.001
Fibrinogen (g/L)	2.58 (2.24–2.93)	2.59 (2.27–2.96)	2.46 (2.04–2.80)	0.007
Thrombin time (s)	25.4 (21.5–34.9)	24.5 (21.0–31.0)	32.8 (24.4–50.8)	< 0.001

Mann-Whitney *U* analysis or Fisher exact test was performed. $p < 0.05$ was considered statistically significant.

Potential Risk Factors for Mortality of SFTS

The above results suggested that patients with SFTS were complicated by multiple organ injury, including liver, kidney, heart, coagulation function, and hematologic system, and more obvious in the nonsurvivors group. To explore the risk factors associated with mortality in patients with SFTS, several variables (age, viral load, neutrophil percentage, platelet count, ALT, Cr, TnI, D-dimer, PT) were included in a multivariate logistic regression analysis for further analysis. The "Forward: LR" method was used to screen these variables, revealing that older age (odds ratio [OR] 1.056; 95% CI, 1.009–1.106; $p = 0.019$), higher viral load (OR 2.340; 95% CI, 1.636–3.349; $p < 0.0001$), lower platelet count (OR 0.996; 95% CI, 0.944–0.989; $p = 0.004$), higher Cr level (OR 1.010; 95% CI, 1.004–1.016; $p = 0.002$), and higher TnI level (OR 1.001; 95% CI, 1.000–1.002; $p = 0.020$) were critical risk factors for fatal outcomes (**Table S1**, http://links.lww.com/CCM/H564).

Distribution of Elevated TnI Levels in Patients With SFTS at Baseline and During Hospitalization

We analyzed the distribution of elevated TnI levels in patients with SFTS, as presented in **Table 2**. The elevation of TnI was observed in 61.6% patients (357/580) with SFTS upon admission, and 68.4% patients (397/580) developed abnormal TnI levels during hospitalization in this study. Nonsurvivors exhibited a higher percentage of elevated TnI compared with survivors (baseline 72.1% vs. 59.1%, $p = 0.011$; in-hospital 87.4% vs. 64.0%, $p < 0.001$). Eleven percent patients (64/580) had remarkably high levels of TnI (≥ 10 ULN) at admission, and 29% patients (168/580) developed TnI levels greater than 10 ULN during hospitalization. Furthermore, survivors experienced less severity of elevated TnI than nonsurvivors ($p < 0.001$). Among nonsurvivors, 63.1% (70/111) were found to have increased TnI levels higher than 10 ULN during hospitalization, while only 20.9% (98/469) of SFTS survivors experienced increased TnI levels higher than 10 ULN (Table 2).

Kinetic Analysis of Myocardial Injury Biomarkers in Surviving and Nonsurviving Patients With SFTS

KDE was used to describe the distributions of TnI and other cardiac biomarkers (CK-MB, CK, and α-HBDH) in the survivors and nonsurvivors

TABLE 2.
Distribution of Elevated Troponin I Levels in Patients With Severe Fever With Thrombocytopenia Syndrome

Characteristic	Total ($n = 580$)	Survivor ($n = 469$)	Nonsurvivor ($n = 111$)	p
Elevation of TnI (n (%))				
Baseline	357 (61.6)	277 (59.1)	80 (72.1)	0.011
In-hospital	397 (68.4)	300 (64.0)	97 (87.4)	< 0.001
Distribution of elevated TnI levels (n, %)				
Baseline				< 0.001
Normal	223 (38.4)	192 (40.9)	31 (27.9)	
1–5 ULN	244 (42.1)	202 (43.1)	42 (37.8)	
5–10 ULN	49 (8.4)	39 (8.3)	10 (9.0)	
≥ 10 ULN	64 (11.0)	36 (7.7)	28 (25.2)	
In-hospital				< 0.001
Normal	183 (31.5)	169 (36.0)	14 (12.6)	
1–5 ULN	179 (30.9)	159 (33.9)	20 (18.0)	
5–10 ULN	50 (8.6)	43 (9.2)	7 (6.3)	
≥ 10 ULN	168 (29.0)	98 (20.9)	70 (63.1)	

TnI = troponin I, ULN = upper limit of normal.

Nonparametric two-tailed Mann-Whitney U test, chi-square test, or Fisher exact test was performed. $p < 0.05$ was considered statistically significant.

(**Supplementary Figs S2** and **S3**, http://links.lww.com/CCM/H564). The overall distribution of TnI and other biomarkers related to myocardial injury was wider in nonsurviving patients than in surviving patients. The distribution of TnI, CK-MB, CK, and α-HBDH in the nonsurvivors was more dispersed compared with that in survivors, especially the peak values during hospitalization.

To determine the dynamic distribution and trajectory of myocardial injury-related parameters in patients with SFTS, we continuously collected data on TnI and other cardiac biomarkers (CK-MB, CK, and α-HBDH) during hospitalization (**Fig. 1**; and **Supplementary Fig. S4**, http://links.lww.com/CCM/H564). The dynamic differences in myocardial injury-related parameters between the surviving and nonsurviving groups are shown in Figure 1. TnI levels between the two groups significantly diverged at days 7–9 following disease onset, while levels of CK-MB, CK, and α-HBDH began to diverge at days 4–6 postdisease onset. The nonsurviving group showed a more pronounced increase in TnI and other myocardial injury-related biomarkers than the surviving group during the second week of SFTS (Fig. 1).

Meanwhile, LOESS models were used to describe the trajectories of TnI, CK-MB, CK, and α-HBDH levels in SFTS patients (Supplementary Fig. S4, http://links.lww.com/CCM/H564). Following the onset of SFTS, TnI levels increased rapidly, peaked at days 10–12, and gradually decreased but remained above the normal upper limit for more than 20 days. CK-MB, CK, and α-HBDH levels in surviving SFTS patients peaked around 1-week postdisease onset and decreased during the second week. Conversely, in nonsurviving patients, these levels increased significantly and remained at a relatively high level during the second week.

Association Between Elevated TnI and Mortality Rate in Patients With SFTS

To investigate the correlation between troponin I levels and mortality among patients with SFTS, PSM was used to control for confounding variables such as age, viral load, and platelet count. PSM identified 84 pairs

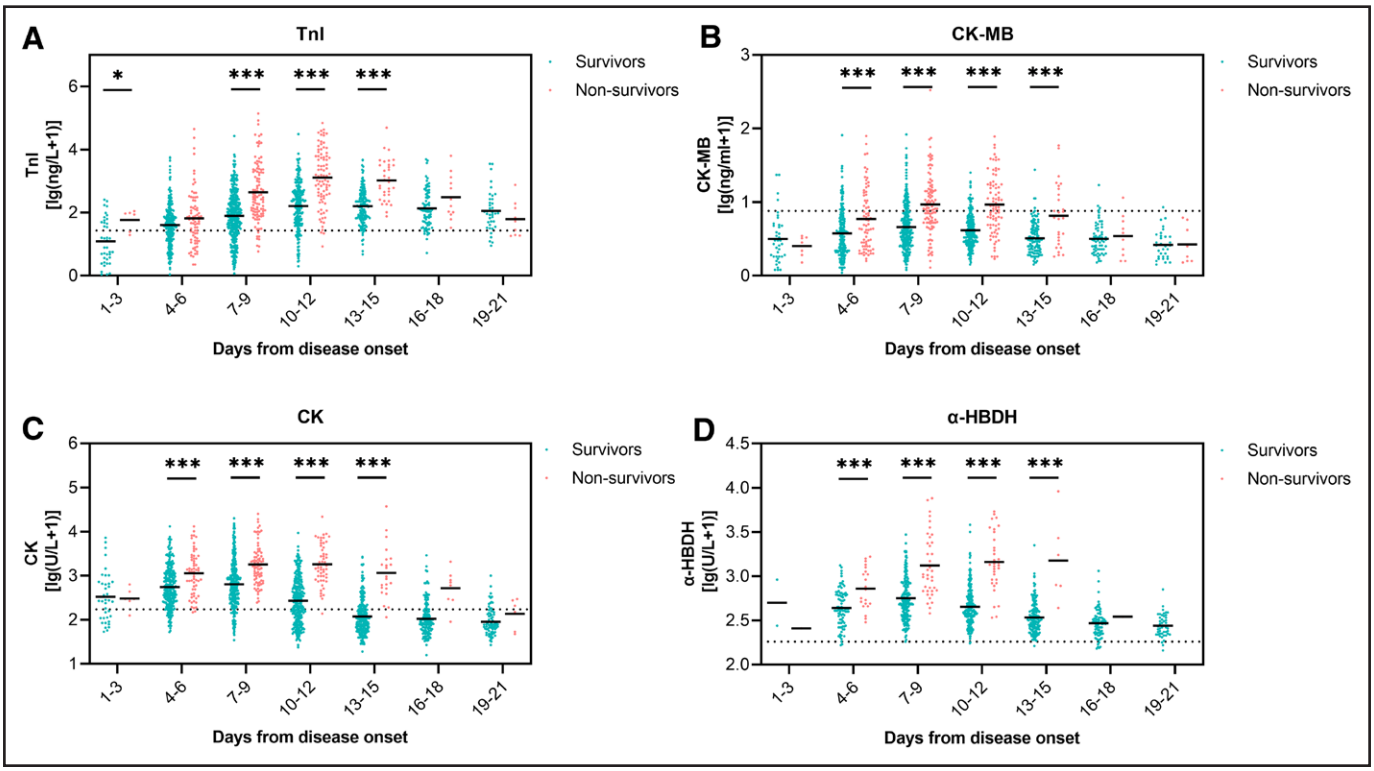

Figure 1. Kinetic analysis of myocardial injury-related biomarkers in both surviving and nonsurviving patients with severe fever with thrombocytopenia syndrome (SFTS). All parameters were analyzed at different time intervals for the entire hospital stay. The *dashed line* represents the upper normal limit of each parameter. $p < 0.05$ was considered statistically significant. $p < 0.05$ was considered statistically significant. CK = creatine kinase, CK-MB = creatine kinase isoenzymes, TnI = troponin I, α-HBDH = α-hydroxybutyrate dehydrogenase;.

of patients (**Table S2**, http://links.lww.com/CCM/H564). The association between TnI levels (baseline or peak in-hospital value) and the mortality rate of SFTS was evaluated on a continuous scale using RCS curves based on a logistic regression model. As depicted in **Figure 2*A***, the risk of mortality remained relatively flat until approximately 1.55 [lg (ng/L+1)] of the predicted baseline TnI, after which it began to increase rapidly. Above 1.55 [lg (ng/L+1)], the OR per SD of a higher predicted TnI was 1.021 (1.007–1.036). Additionally, a significant linear relationship was observed between baseline TnI and mortality (*p* value for nonlinearity = 0.10). Similarly, we analyzed the relationship between peak TnI level and mortality during hospitalization using RCS based on a logistic regression model. The results mirrored those previously obtained: the risk of mortality remained relatively flat until around 1.90 [lg (ng/L+1)] of the predicted peak TnI level, after which it sharply increased. Additionally, there was also a linear relationship between peak TnI level and mortality (*p* value for nonlinearity = 0.40) (**Fig. 2*B***).

We also presented the distribution of mortality across various levels of TnI within the entire cohort. As depicted in **Supplementary Figure S5*A*** (http://links.lww.com/CCM/H564), patients with SFTS exhibiting elevated TnI (> ULN) demonstrated higher mortality rates either at baseline (22.4% vs. 13.9%, $p = 0.01$) or during hospitalization (24.4% vs. 7.7%, $p < 0.001$) compared with patients with a normal level of TnI. When patients were stratified into four groups based on TnI levels, as suggested by a previous study (13): less than the ULN (26.2 ng/L, $n = 223$), 1–5 ULN (26.2–131 ng/L, $n = 244$), 5–10 ULN (131–262 ng/L, $n = 49$), and greater than or equal to 10 ULN (262 ng/L, $n = 64$), the highest mortality was observed in the group with TnI greater than or equal to 10 ULN (**Supplementary Fig. S5*B***, http://links.lww.com/CCM/H564). The mortality rate exceeded 40% among patients with SFTS with TnI greater than or equal to 10 ULN at admission (43.8%) or during hospitalization (41.7%). In summary, higher TnI levels in patients with SFTS were associated with a worse prognosis.

Potential Factors Associated With Elevated TnI in Patients With SFTS

To further explore the characteristics of patients with SFTS with increased TnI, we categorized them into two groups: those with a normal TnI level (< ULN) and those with an abnormal TnI level (> ULN) based on the baseline TnI level. Notably, patients with elevated TnI levels were older and exhibited a higher prevalence of preexisting CVD (all $p < 0.05$). Furthermore, patients with abnormal TnI (> ULN) had lower platelet counts and higher levels of monocyte counts, liver biomarkers (e.g., ALT, AST, GGT), and other cardiac-related biomarkers (e.g., CK-MB, BNP, α-HBDH), or coagulation biomarkers (e.g., D-dimer, APTT, TT) (all $p < 0.05$) (**Table 3**).

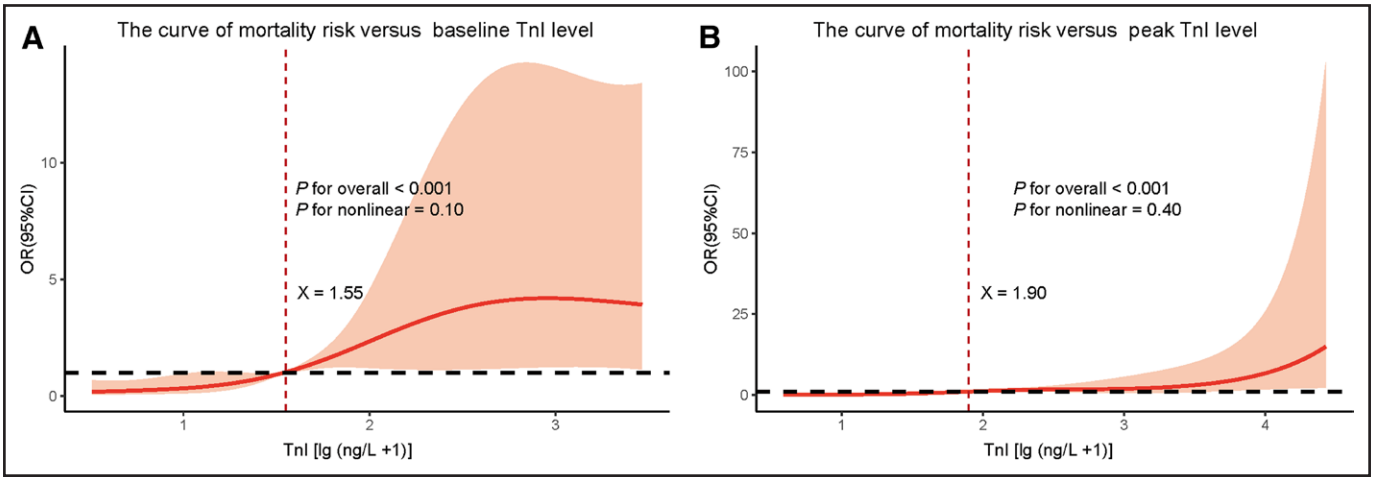

Figure 2. Restricted cubic spline models depicting the relationship between troponin I (TnI) levels and mortality risk in severe fever with thrombocytopenia syndrome (SFTS). The association between TnI levels (**A**, baseline; **B**, peak value during hospitalization) and SFTS mortality was assessed using the restricted cubic splines (RCS) model. The 95% CIs of the adjusted odds ratios (ORs) are represented by the *red-shaded* areas. TnI knot locations were based on Harrell's recommended percentiles (P5, P27.5, P50, P72.5, and P95). The *dotted line in black* on the *y*-axis represents an OR of 1. The *red-dotted line* on the *x*-axis represents the inflection point of TnI.

TABLE 3.

Baseline Characteristics and Laboratory Parameters in Severe Fever With Thrombocytopenia Syndrome Patients With or Without Troponin I Elevation

Characteristic	Total (*n* = 580)	Troponin I		*p*
		< ULN (*n* = 223)	> ULN (*n* = 357)	
Age (yr)	61 (53–68)	58 (51–64)	63 (55–69)	< 0.001
Sex, female (%)	338 (58.3)	125 (56.1)	213 (59.7)	0.436
History of cardiovascular disease	175 (30.2)	51 (22.9)	124 (34.7)	0.003
Viral load (Log10)	3.81 (2.94–4.84)	3.82 (2.94–4.91)	3.81 (2.39–4.80)	0.979
RBC (× 10^{12}/L)	4.31 (3.96–4.70)	4.30 (3.92–4.72)	4.32 (3.98–4.68)	0.754
Hemoglobin (g/dL)	129 (118–142)	131 (119–143)	129 (118–141)	0.296
WBC (× 10^9/L)	2.24 (1.47–3.68)	2.13 (1.45–3.26)	2.32 (1.49–3.87)	0.157
Neutrophil (%)	70.00 (55.70–81.10)	70.60 (58.20–81.30)	69.20 (53.00–81.05)	0.292
Lymphocyte (%)	23.60 (15.10–34.80)	23.15 (14.73–33.45)	23.60 (15.15–36.25)	0.543
Monocyte (%)	4.40 (2.20–8.03)	3.95 (1.98–7.30)	4.60 (2.30–8.28)	0.069
Neutrophil (× 10^9/L)	1.44 (0.87–2.60)	1.44 (0.91–2.30)	1.44 (0.85–2.78)	0.570
Lymphocyte (× 10^9/L)	0.50 (0.34–0.80)	0.48 (0.32–0.76)	0.52 (0.35–0.82)	0.078
Monocyte (× 10^9/L)	0.09 (0.05–0.18)	0.09 (0.04–0.16)	0.09 (0.05–0.22)	0.025
Platelet (× 10^9/L)	48 (33–62)	52 (37–69)	45 (31–59)	< 0.001
Total bilirubin (μmol/L)	9.4 (7.2–12.4)	9.7 (7.4–12.3)	9.10 (3.50–6.80)	0.333
Direct bilirubin (μmol/L)	4.5 (3.6–6.3)	4.5 (3.7–6.1)	4.60 (3.50–6.80)	0.441
Alanine aminotransferase (U/L)	70 (44–118)	60 (35–97)	79 (50–140)	< 0.001
Aspartate aminotransferase (U/L)	195 (100–372)	129 (68–257)	243 (127–430)	< 0.001
Alkaline phosphatase (U/L)	65 (53–85)	63 (54–80)	66 (53–88)	0.269
γ-Glutamyl transpeptidase (U/L)	30 (19–57)	29 (18–48)	33 (20–62)	0.023
Creatinine (μmol/L)	73.5 (61.3–94.0)	72.4 (62.8–89.9)	74.8 (60.75–97.20)	0.641
Blood urea nitrogen (μmol/L)	5.16 (3.70–7.32)	4.93 (3.60–6.57)	5.28 (3.70–7.52)	0.410
Lactic dehydrogenase (U/L)	758 (481–1239)	563 (348–887)	904.5 (575.75–1443.50)	< 0.001
Creatine kinase (U/L)	577 (264–1252)	367 (176–847)	736 (351–1610)	< 0.001
Creatine kinase isoenzymes (ng/mL)	2.7 (1.2–5.9)	1.6 (0.8–3.9)	3.2 (1.7–7.1)	< 0.001
Troponin I (ng/L)	41.5 (12.2–97.8)	7.5 (3.3–14.6)	78.0 (46.2–180.8)	< 0.001
Brain natriuretic peptide (ng/L)	34.5 (15.9–89.9)	18.8 (5.0–39.6)	41.3 (19.4–98.1)	0.001
α-Hydroxybutyrate dehydrogenase (U/L)	489 (351–775)	408 (303–576)	590 (394–887)	< 0.001
D-dimer (mg/L)	3.57 (2.01–7.28)	3.01 (1.71–6.17)	3.94 (2.38–7.67)	0.001
Prothrombin time (s)	13.2 (12.5–13.9)	13.3 (12.6–14.0)	13.15 (12.43–13.90)	0.164
International normalized ratio	1.02 (0.95–1.09)	1.03 (0.96–1.10)	1.02 (0.95–1.09)	0.183
Activated partial thromboplastin time (s)	54.1 (47.8–64.1)	51.0 (44.6–62.1)	56.0 (49.8–65.9)	< 0.001
Fibrinogen (g/L)	2.58 (2.24–2.93)	2.69 (2.25–3.04)	2.53 (2.32–2.88)	0.018
Thrombin time (s)	25.4 (21.5–34.9)	21.9 (19.8–26.3)	27.60 (23.23–40.95)	< 0.001

SFTSV = severe fever with thrombocytopenia syndrome virus, ULN = upper limit of normal.
Mann-Whitney *U* analysis or Fisher exact test was performed. $p < 0.05$ was considered statistically significant.

We further compared the characteristic differences among the four groups based on TnI level. Similarly, Table S2 (http://links.lww.com/CCM/H564) shows that age and preexisting CVD were correlated with higher TnI levels. Additionally, patients with higher TnI levels exhibited lower platelet counts and higher WBC and monocyte counts, liver injury biomarkers, coagulation biomarkers, and other cardiac-related biomarkers (all $p < 0.05$, Table S2, http://links.lww.com/CCM/H564). Interestingly, viral load was found to be higher in patients with higher TnI levels, particularly those with TnI greater than or equal to 10 ULN ($p = 0.001$).

Previous studies have suggested that inflammation-mediated damage, formation of microvascular thrombi, or direct viral invasion may lead to myocardial injury and subsequent troponin release in viral-infected diseases (14). Building upon previous results, we investigated the potential factors linked to elevated TnI during SFTS (**Table 4**). Multivariate regression analyses revealed that older age (OR 1.05; 95% CI, 1.03–1.07; $p < 0.001$), a history of CVD (OR 1.64; 95% CI, 1.00–2.68; $p = 0.049$), and higher D-dimer levels (OR 1.08; 95% CI, 1.03–1.13; $p = 0.003$) were potential risk factors for elevated TnI in patients with SFTS. Additionally, older age (OR 1.03; 95% CI, 1.01–1.06; $p = 0.003$), higher D-dimer levels (OR 1.06; 95% CI, 1.02–1.11; $p = 0.003$), and viral load (OR 1.19; 95% CI, 1.00–1.42; p = 0.049) were associated with high levels of TnI (≥ 10 ULN).

DISCUSSION

This study constituted an extensive retrospective analysis to explore myocardial injury-related biomarkers in patients diagnosed with SFTS. Our findings revealed a high prevalence of elevated TnI levels among patients with SFTS, consistently associated with an increased mortality risk.

cTnI is a component of the cardiomyocyte contractile apparatus, and it is predominantly expressed within cardiac tissue. Elevated serum TnI levels primarily arose from myocardial injury, exhibited in conditions such as angina pectoris, myocardial inflammation (without evident myocardial necrosis), myocardial hypertrophy, and myocardial toxicity induced by specific drugs or toxins (12, 15). However, TnI levels typically did not increase following noncardiac tissue injury (12). TnI was the preferred biomarker for assessing myocardial injury in clinical practice, offering superior sensitivity compared with other biomarkers such as CK, CK-MB, and α-HBDH (12).

Among all patients diagnosed with SFTS, we observed elevated TnI levels in 68.4% of the patients during hospitalization, a rate consistent with reports of 63.2% in H7N9 (8) and it is significantly higher than rates reported in COVID-19 cases, ranging from 6.6% to 44% (14). Nonsurviving SFTS cases exhibited significantly higher TnI levels compared with survivors. Furthermore, myocardial injury-related enzymes such as CK-MB, CK, and α-HBDH were markedly elevated

TABLE 4.
Multivariate Logistic Regression Analysis on the Risk Factors Associated With Elevation of Troponin I

	TnI ≥ ULN		TnI ≥ 10 ULN	
Factors	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age (yr)	1.05 (1.03–1.07)	< 0.001	1.03 (1.01–1.06)	0.003
History of cardiovascular disease	1.64 (1.00–2.68)	0.049	1.34 (0.86–2.08)	0.191
Lymphocyte (× 10^9/L)	1.01 (0.58–1.76)	0.973	0.65 (0.38–1.13)	0.125
Monocyte (× 10^9/L)	0.92 (0.40–2.12)	0.846	1.68 (0.77–3.69)	0.194
Platelet (× 10^9/L)	0.99 (0.98–1.00)	0.087	1.00 (0.99–1.01)	0.466
D-dimer (mg/L)	1.08 (1.03–1.13)	0.003	1.06 (1.02–1.11)	0.003
Viral load (Log10)	0.88 (0.72–1.07)	0.187	1.19 (1.00–1.42)	0.049

OR = odds ratio, TnI = troponin I, ULN = upper limit of normal.

in the nonsurviving group, particularly after one week from disease onset.

The outcomes of our study have identified older age, higher viral load, lower platelet count, and elevated levels of creatinine and troponin I as significant risk factors for fatal outcomes. It is noteworthy that older age, high viral load, and low platelet count have consistently been identified as risk factors for mortality in previous research studies (16–18). Our study indicated that high TnI levels were associated with an increased risk of death in patients with SFTS. This underscores the importance of monitoring myocardial injury-related indicators, particularly TnI, dynamically and in conjunction with cardiac function and electrocardiogram assessments. Identifying patients at higher risk early in the disease course enables the timely implementation of supportive measures to protect cardiac health.

The mechanism causing the elevation of TnI levels due to DBV remains unclear. Traditionally, viral infections have been implicated in the development of viral myocardial injury. Viral replication within host myocardial cells can disrupt myocardial structure and function (19, 20). Factors such as viral infection dose, replication rate, and viral load persistence directly affect the onset and progression of viral myocarditis. During myocardial injury, cardiomyocytes release a large amount of troponin, leading to an increase in serum TnI levels (12). Our study discovered that DBV-infected patients had higher TnI levels, and a higher viral load increased the risk of elevated TnI levels (≥ 10 ULN), indicating a possible link between DBV and TnI elevation in patients with SFTS. Scientists have reported detectable DBV NP antigen or DBV RNA in cardiac tissue, albeit at lower levels compared with lymph nodes, spleen, kidneys, or liver (9, 10). However, a separate autopsy of a patient with SFTS from Japan showed no DBV antigens or RNA in cardiac tissue (21). This disparity may stem from variations in viral load and timing. DBV could be eliminated by macrophages in C57/BL6 mice with normal immune function (22).

Additionally, studies have considered myocardial injury as an immune-mediated process. Previous studies indicate that the infiltration of mononuclear cells (T cells, natural killer cells, macrophages, etc.) and subsequent immune damage are pivotal in viral myocarditis (14, 23, 24). Up-regulation of inflammatory cytokines is an important factor in the initiation and perpetuation of myocarditis (14, 23, 24). DBV infection has been shown to induce a robust cytokine storm and inflammation, potentially contributing to multiple organ damage, including cardiac injury (25, 26). Furthermore, older age and preexisting cardiovascular diseases were associated with elevated TnI levels in our study. Notably, older patients experienced more severe elevated TnI levels, which is consistent with findings in studies on other viral infections (8, 13). This may be related to the compromised cardiac status of elderly patients. We also observed significantly higher D-dimer levels in nonsurviving patients, suggesting a heightened risk of elevated TnI during DBV infection. This implies that microvascular thrombosis, hypercoagulability, and diffuse endothelial injury might be involved in elevated TnI levels. Nevertheless, the precise factors of elevated TnI levels in patients with SFTS warrant further investigation.

Our study was limited by its retrospective nature and the absence of sequential electrocardiography and echocardiography assessments, which prevented the evaluation of cardiac ventricular wall motion and function in patients with SFTS. Additionally, some patients were excluded due to a lack of quantitative DBV PCR results, potentially introducing selection bias. Future prospective studies are needed to explore whether DBV infection can lead to myocardial dysfunction and to elucidate the underlying mechanism of myocardial injury.

In conclusion, this study examined the dynamic characteristics of TnI in patients with SFTS and identified potential risk factors. The results of this study will improve the clinical management of patients with SFTS with increased risk for TnI elevation.

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Drs. Liang, Xu, and Li performed the study, data analysis, and wrote the article. Drs. Wang, Lu, Fan, Wang, Li, Zhu, Wang, Wang, and Peng contributed to patient enrollment and data collection. Drs. Shen and Zheng designed the study and revised the article.

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