

Integrating Viral Burden, Immune Dysregulation, and Tissue Injury for Predicting 28-Day Mortality in Severe Fever With Thrombocytopenia Syndrome: Development and External Validation of Interpretable Models

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Abstract

Background

Severe fever with thrombocytopenia syndrome (SFTS) is a life-threatening viral disease in which fatal progression is associated with interactions between viral replication and dysregulated host immune responses. Whether markers representing these complementary biological processes can be integrated into an interpretable framework for mortality risk stratification remains unclear. We therefore developed and externally validated biologically informed prediction models incorporating viral, immune, inflammatory, and tissue-injury markers.

Methods

This multicenter retrospective cohort included 530 patients with laboratory-confirmed SFTS, comprising 372 patients in the training cohort and 158 patients from an independent center for external validation. Five biologically relevant predictors were selected: DBV RNA, IL-10, Hs-CRP, CD4/CD8 ratio, and CK. Logistic regression and XGBoost models were developed using the same predictor set and evaluated for discrimination, calibration, prediction error, clinical utility, and interpretability.

Results

Non-survivors showed higher DBV RNA, IL-10, Hs-CRP, and CK levels and lower circulating T-cell counts and CD4/CD8 ratios, indicating concurrent virological, inflammatory, and cellular immune abnormalities. In external validation, logistic regression and XGBoost achieved AUCs of 0.815 (95% CI, 0.730–0.900) and 0.848 (95% CI, 0.765–0.931), respectively. Logistic regression showed better calibration, with a lower Brier score than XGBoost (0.116 vs. 0.154), while both models provided clinical net benefit.

Conclusion

Integrating markers of viral burden, immune dysregulation, systemic inflammation, and tissue injury enabled reproducible mortality risk stratification across independent SFTS cohorts. These findings support a biologically informed framework for clinically interpretable risk assessment, while prospective studies with longitudinal immune profiling are needed to further validate this approach.

1 Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne infectious disease caused by *Banavirus dabieense* (DBV), which was first reported in China in 2009 [1]. The disease is characterized by acute onset, rapid progression, and a high case-fatality rate. Previous studies have shown that the mortality rate of SFTS ranges from 5% to 30%, and may exceed 40% in severe cases [2]. Although viral replication is essential for disease initiation, accumulating evidence suggests that clinical deterioration cannot be explained by viral burden alone [3, 4]. Instead, the outcome of SFTS appears to reflect a dynamic interaction between viral replication and the host immune response, in which

ineffective viral control, dysregulated cytokine responses, perturbation of cellular immunity, and immune-associated tissue injury may collectively contribute to fatal progression [5–7].

Among these host immune abnormalities, cytokine dysregulation and impaired cellular immunity appear particularly relevant to severe SFTS. Increased concentrations of immunoregulatory and proinflammatory cytokines, including IL-10 and IL-6, have been associated with disease severity and fatal outcomes [4, 8]. IL-10 is of particular interest because its immunoregulatory role may reflect an important counter-regulatory component of the dysregulated antiviral response, potentially linking excessive immune activation with impaired antiviral effector function [9]. In parallel, marked alterations in lymphocyte subsets have been reported in severe SFTS, including depletion of CD4 + and CD8 + T cells together with phenotypic features of T-cell activation, apoptosis, and exhaustion [7, 10]. The CD4/CD8 ratio may therefore provide a complementary measure of the relative distribution of major T-cell compartments, alongside the absolute abundance of individual lymphocyte subsets [11].

Viral burden, immune dysregulation, systemic inflammation, and tissue injury have each been associated with SFTS severity, but these processes are often evaluated separately. Existing prognostic models have rarely integrated virological and host immune markers within a unified biological framework [12–14]. Whether these complementary components can be integrated to provide clinically interpretable mortality risk stratification remains unclear.

In this study, we sought to translate a biologically informed framework of SFTS progression into clinically interpretable tools for early mortality risk stratification. We selected representative markers of viral burden (DBV RNA), cytokine-mediated immune dysregulation (IL-10), cellular immune imbalance (CD4/CD8 ratio), systemic inflammatory activation (Hs-CRP), and tissue injury (CK), and integrated them using two complementary modeling strategies: logistic regression and explainable XGBoost. By externally validating these models in an independent center, we aimed to determine whether this multidimensional framework could provide reproducible prognostic information across heterogeneous clinical populations.

2 Methods

2.1 Study design and participants

This multicenter retrospective cohort study included adult patients with laboratory-confirmed Severe Fever with Thrombocytopenia Syndrome (SFTS) who were hospitalized at Yantai Qishan Hospital and Qingdao No. 6 People's Hospital between January 2024 and December 2025. Patients were screened consecutively according to predefined eligibility criteria. The Yantai Qishan Hospital cohort was used as the training cohort, and the Qingdao No. 6 People's Hospital cohort was used as the external validation cohort. The inclusion criteria were: (1) age ≥ 18 years; (2) laboratory-confirmed SFTS, defined by at least one of the following criteria: detection of SFTSV RNA by reverse transcription-polymerase chain reaction (RT-PCR), presence of SFTSV-specific IgM antibodies, a ≥ 4 -fold increase in SFTSV-specific IgG antibody

titers between acute and convalescent serum samples, or isolation of SFTSV from clinical specimens. The exclusion criteria were: (1) severe acute conditions unrelated to SFTS that could independently affect short-term mortality assessment, including active malignancy, end-stage organ failure, or other life-threatening non-SFTS conditions; (2) concurrent acute infections caused by other pathogens at admission; (3) missing essential predictor information required for model development.

Patients with missing essential predictors were excluded because the primary analysis required complete predictor information for model development and external validation. All predictor variables included in the final models, including quantitative DBV RNA, IL-10, and lymphocyte subset measurements, were available for all patients included in the final analysis. Exclusion decisions were made based on baseline clinical information and laboratory availability before outcome assessment and were independent of subsequent survival status.

2.2 Data collection

All data were extracted from the hospitals' electronic medical record systems and independently cross-checked by two trained investigators. Blood samples used for laboratory measurements were collected within 24 hours after hospital admission and before initiation of disease-specific treatment or organ-support interventions whenever possible. Laboratory variables included routine hematological parameters, biochemical markers, inflammatory cytokines, viral load, and lymphocyte subsets. These data include demographics (age, gender, medical history and outcome), clinical symptoms and signs, and laboratory data (white blood cell [WBC], neutrophils, lymphocytes, hemoglobin [HGB], platelet [PLT], albumin [ALB], creatine phosphokinase [CK], lactate dehydrogenase [LDH], prothrombin time [PT], activated partial thromboplastin time [APTT], high-sensitivity C-reactive protein [Hs-CRP], procalcitonin [PCT], IL-6, interleukin-10 [IL-10], Dabie bandavirus RNA [DBV RNA], CD3 + T cells, CD4 + T cells, CD8 + T cells, and CD4/CD8 ratio).

2.3 Diagnosis and Definition

Neurological signs were defined as the presence of at least one of the following abnormalities: altered consciousness, involuntary limb movements, abnormal reflexes or muscle tone. Hemorrhage was defined as the presence of one or more of the following manifestations: skin ecchymosis or petechiae, oral or gingival bleeding, hemoptysis, hematemesis, hematuria, hematochezia, or melena. The primary outcome was 28-day all-cause mortality after hospital admission. Patients were categorized into two groups according to their vital status at 28 days after admission: the survival group and the non-survival group. The non-survival group included patients who died from any cause within 28 days after hospital admission. The survival group included patients who were alive at 28 days after admission, regardless of whether they had been discharged or remained hospitalized. Vital status was obtained from hospital medical records and, when necessary, confirmed through telephone follow-up after discharge. For patients discharged before day 28, follow-up was conducted to ascertain survival status up to 28 days after admission.

2.4 Statistical analysis

Continuous variables with normal distribution were expressed as mean $\pm$ standard deviation and compared using the independent-samples t-test, whereas non-normally distributed variables were presented as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables were summarized as n (%) and analyzed using the chi-square test or Fisher's exact test. DBV RNA and creatine kinase (CK) were log₁₀-transformed to reduce skewness.

Predictor selection was based primarily on biological plausibility, clinical relevance, prior evidence, and multicollinearity assessment using the variance inflation factor (VIF), with univariable logistic regression used only as exploratory support. The final logistic regression model included five predictors: DBV RNA, IL-10, Hs-CRP, CD4/CD8 ratio and CK. The number of events per variable exceeded 10, supporting the adequacy of the sample size for this parsimonious multivariable model.

A separate extreme gradient boosting (XGBoost) model was developed using the same set of five predictors. Hyperparameter tuning of the XGBoost model was performed using a nested cross-validation (nested CV) framework within the training cohort to prevent data leakage and ensure that the external validation cohort remained completely isolated throughout the optimization process. The outer loop used a 5-fold cross-validation scheme to partition the training data, while the inner loop combined 5-fold cross-validation with a randomized search strategy for hyperparameter optimization. The primary optimization objective was to maximize the mean area under the receiver operating characteristic curve (AUC) across the inner validation folds. The predefined search space included max_depth (1–6), n_estimators (20–300), learning_rate (0.01–0.2), min_child_weight (1–5), subsample (0.6–0.9), colsample_bytree (0.6–0.9), gamma (0–5), and reg_lambda (0.5–5). To minimize the risk of overfitting, log-loss was simultaneously monitored during model training, and early stopping was implemented with a patience of 10 rounds. Given the class imbalance in the cohort (approximately 23% mortality), scale_pos_weight was set to 3.48, corresponding to the ratio of negative to positive cases, to increase the penalty for misclassification of the minority class. However, because class weighting can systematically distort the predicted probability distribution and compromise clinical calibration, a training-only sigmoid (Platt) calibration sensitivity analysis for XGBoost was additionally performed. This recalibrated analysis was considered exploratory because it adds a second modeling layer and would require prospective confirmation before clinical implementation. Under stringent regularization constraints designed to reduce overfitting in a moderate-sized clinical dataset, the optimization procedure ultimately favored a conservative model architecture characterized by shallow decision trees. The final XGBoost model was subsequently retrained on the entire training cohort using this optimized parameter set and independently evaluated in the external validation cohort.

Model performance was evaluated in terms of discrimination, calibration, overall prediction error, and clinical utility. Discrimination was assessed using receiver operating characteristic curves and the area under the curve (AUC) with bootstrap 95% confidence intervals. Overall prediction error was quantified using the Brier score. In the training cohort, internal calibration was examined using bootstrap bias-corrected calibration curves and Brier scores. In the external validation cohort, calibration was assessed using calibration intercept, calibration slope, and Brier scores. Decision curve analysis was used to

assess clinical utility, and SHAP values were calculated to interpret predictor contributions in the final XGBoost model.

Because the primary logistic regression model was not class-weighted whereas XGBoost used class-imbalance handling during tuning, a class-weighted logistic regression sensitivity analysis was performed. Then, because the Youden-index cutoff gives equal weight to sensitivity and specificity, a sensitivity-prioritized cutoff was explored to illustrate the trade-off between missed high-risk cases and false-positive alerts. A two-sided $P < 0.05$ was considered statistically significant. Analyses were conducted using SPSS 30.0, R 4.5.3, and Python 3.13.

3 Results

3.1 Clinical characteristics of patients with SFTS

A total of 530 patients with confirmed SFTS were finally enrolled, including 372 hospitalized at Yantai Qishan Hospital from January 2024 to December 2025 in the training cohort, and 158 patients hospitalized at Qingdao No. 6 People's Hospital from January 2024 to December 2025 in the validation cohort (Figure 1) (Supplementary Table 1). The median age of all cohorts at admission was 67 years (IQR, 60-74 years), and 239 (45.09%) patients were male (Supplementary Table 2). The training cohort comprised 372 patients with SFTS, including 289 (77.69%) survivors and 83 (22.31%) non-survivors. The median age was 68 years, with non-survivors being older than survivors (72 vs 67 years). The study population included 173 males (46.51%), with no significant difference in sex distribution between the survivor and non-survivor groups. Compared with survivors, non-survivors had a higher incidence of hemorrhage and neurological signs (all $P < 0.05$). In addition, levels of neutrophils, CK, LDH, APTT, Hs-CRP, PCT, IL-6, IL-10 and DBV RNA were significantly higher in non-survivors than in survivors (all $P < 0.05$). Conversely, levels of lymphocytes, ALB, CD3⁺ T cells, CD4⁺ T cells, CD8⁺ T cells, and CD4/CD8 ratio were significantly lower in the non-survivor group (all $P < 0.05$) (Table 1). Similar differences between non-survivors and survivors were observed in the validation cohort (Supplementary Table 3).

The external validation cohort had a similar 28-day mortality rate to the training cohort (25.32% vs. 22.31%, $P = 0.454$), but showed evidence of baseline case-mix differences. Compared with the training cohort, the external validation cohort had higher DBV RNA (median 4.12 vs. 3.25 log₁₀ TCID₅₀/mL, $P < 0.001$), Hs-CRP (4.26 vs. 3.31 mg/L, $P = 0.031$), LDH (672.00 vs. 500.50 U/L, $P < 0.001$), and CK (2.62 vs. 2.51 log₁₀ U/L, $P = 0.019$), and lower IL-10 (11.10 vs. 14.87 pg/ml, $P < 0.026$), ALB (31.90 vs. 33.50 g/L, $P < 0.001$) and CD4/CD8 ratio (0.94 vs. 1.09, $P = 0.045$) (Supplementary Table 2). These findings indicate that the external cohort was not an identical population distribution and that model transportability should be interpreted in the context of cross-center case-mix heterogeneity.

Figure 1. Flow diagram of patient selection and cohort allocation. All eligible patients diagnosed with SFTS during the study period were consecutively screened according to predefined criteria. Patients with missing essential predictor information were excluded before model development.

Table 1. Clinical and laboratory characteristics of survivors and non-survivors in the training cohort of SFTS patients

Characteristics	Total (n = 372)	Survivors (n=289)	Non-survivors (n=83)	P value
Age, year	68.00 (61.00, 74.00)	67.00 (60.00, 73.00)	72.00 (64.50, 77.00)	<0.001
Gender, (male), n (%)	173 (46.51)	129 (44.64)	44 (53.01)	0.178
Comorbidities, n (%)				
Hypertension	105 (28.23)	83 (28.72)	22 (26.51)	0.693
Diabetes	72 (19.35)	56 (19.38)	16 (19.28)	0.984
Cerebral diseases	27 (7.26)	18 (6.23)	9 (10.84)	0.153
Cardiac diseases	28 (7.53)	21 (7.27)	7 (8.43)	0.722
Symptoms, n (%)				
Fever	361 (97.04)	280 (96.89)	81 (97.59)	1.000
Shiver	159 (42.74)	124 (42.91)	35 (42.17)	0.905
Fatigue	338 (90.86)	267 (92.39)	71 (85.54)	0.056
Headache	48 (12.90)	37 (12.80)	11 (13.25)	0.914
Myalgia	145 (38.98)	120 (41.52)	25 (30.12)	0.060
Nausea	187 (50.27)	155 (53.63)	32 (38.55)	0.015
Vomiting	110 (29.57)	88 (30.45)	22 (26.51)	0.488
Abdominal pain	60 (16.13)	47 (16.26)	13 (15.66)	0.896
Diarrhea	155 (41.67)	121 (41.87)	34 (40.96)	0.883
Signs, n (%)				
Lymphadenectasis	133(35.75)	107 (37.02)	26 (31.33)	0.340
Neurological signs	181 (48.66)	126 (43.60)	55 (66.27)	<0.001
Hemorrhage	67 (18.01)	36 (12.46)	31 (37.35)	<0.001
Laboratory parameters				
WBC (10 ⁹ /L)	2.30 (1.64, 3.35)	2.29 (1.63, 3.34)	2.35 (1.69, 3.45)	0.760
Neutrophils (10 ⁹ /L)	1.43 (0.95, 2.13)	1.38 (0.91, 2.05)	1.69 (1.07, 2.60)	0.047
Lymphocytes (10 ⁹ /L)	0.46 (0.34, 0.76)	0.50 (0.34, 0.79)	0.38 (0.28, 0.55)	0.003

HGB (g/L)	140.00 (128.00, 151.00)	140.00 (128.00, 151.00)	142.00 (129.00, 154.00)	0.366
PLT (10 ⁹ /L)	65.00 (49.00, 86.00)	70.00 (52.00, 92.00)	52.00 (37.50, 69.50)	<0.001
ALB (g/L)	33.50 (30.25, 36.75)	34.00 (30.60, 37.00)	30.90 (28.20, 35.30)	<0.001
LDH (U/L)	500.50 (327.00, 839.00)	429.00 (307.00, 696.00)	772.00 (567.00, 1566.00)	<0.001
PT (sec)	13.20 (12.70, 13.80)	13.10 (12.70, 13.70)	13.40 (12.90, 14.10)	0.002
APTT (sec)	48.45 (41.90, 55.90)	46.90 (40.80, 53.80)	53.70 (47.85, 65.40)	<0.001
PCT (ng/ml)	0.18 (0.09, 0.64)	0.16 (0.09, 0.50)	0.44 (0.15, 0.99)	<0.001
Hs-CRP (mg/L)	3.31 (0.86, 9.22)	2.52 (0.69, 7.51)	6.85 (2.34, 19.66)	<0.001
IL-6 (pg/ml)	22.05 (8.35, 60.45)	16.70 (6.10, 36.80)	103.40 (28.15, 217.75)	<0.001
IL-10 (pg/ml)	14.87 (4.00, 45.90)	9.00 (3.40, 29.30)	59.10 (25.05, 102.45)	<0.001
CK (log10 U/L)	2.51 (2.19, 2.94)	2.41 (2.14, 2.85)	2.91 (2.50, 3.21)	<0.001
DBV RNA (log10 TCID50/mL)	3.25 (2.28, 4.34)	2.93 (2.12, 3.93)	4.49 (3.80, 5.38)	<0.001
CD3+ T cells (/μL)	346.50 (213.00, 633.02)	412.00 (251.00, 722.00)	221.00 (161.50, 319.50)	<0.001
CD4+ T cells (/μL)	163.00 (87.50, 295.57)	189.00 (108.00, 322.00)	77.00 (52.00, 149.50)	<0.001
CD8+ T cells (/μL)	157.50 (88.00, 286.00)	186.66 (98.00, 321.00)	104.00 (73.50, 168.50)	<0.001
CD4/CD8	1.09 (0.66, 1.58)	1.16 (0.74, 1.65)	0.83 (0.52, 1.17)	<0.001

Abbreviations: SFTS, severe fever with thrombocytopenia syndrome; DBV, Bandavirus dabiense; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; ALB, albumin; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; Hs-CRP, high-sensitivity C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; IL-10, interleukin-10; CK, creatine phosphokinase; CD3/CD4/CD8, cluster of differentiation; CD3+ T cells, CD3-positive T lymphocytes; CD4+ T cells, CD4-positive T lymphocytes; CD8+ T cells, CD8-positive T lymphocytes; CD4/CD8, ratio of CD4+ to CD8+ T cells. Continuous variable data are presented as median (interquartile ranges, IQR). Classified variable data are presented as n (%). *P* values indicate differences between survivors and non- survivors in the

training cohort. $P<0.05$ was considered statistically significant. Statistically significant values are shown in bold.

3.2 Selection of predictors for developing models

Univariable logistic regression identified age, nausea, neurological signs, hemorrhage, lymphocytes, PLT, ALB, LDH, APTT, Hs-CRP, IL-6, IL-10, CK, DBV RNA, CD3+ T cells, CD4+ T cells, CD8+ T cells, and CD4/CD8 ratio as factors associated with mortality (all $P < 0.05$) (Table 2). Candidate predictors were then reviewed according to clinical relevance, biological plausibility, prior evidence, event count, and VIF-based multicollinearity assessment rather than statistical significance alone (Supplementary Table 4).

Given that SFTS progression involves complex interactions between viral replication, immune dysregulation, systemic inflammation, and tissue injury, five biomarkers representing complementary pathophysiological domains were selected for model development: DBV RNA reflecting viral burden, IL-10 and CD4/CD8 ratio reflecting immune dysregulation, Hs-CRP reflecting systemic inflammatory activation, and CK reflecting tissue injury.

Table 2. Univariate analysis of factors related to the mortality of SFTS patients in the training cohort

Variables	Univariate analysis	P value
	OR (95% CI)	
Age	1.051 (1.022-1.081)	<0.001
Gender	0.715 (0.438-1.166)	0.179
Neurological signs	2.541 (1.524-4.236)	<0.001
Hemorrhage	4.190 (2.380-7.374)	<0.001
WBC	0.976 (0.867-1.079)	0.549
Neutrophils	0.992 (0.882-1.116)	0.894
Lymphocytes	0.385 (0.186-0.799)	0.010
HGB	1.009 (0.994-1.023)	0.245
PLT	0.974 (0.963-0.985)	<0.001
ALB	0.924 (0.879-0.971)	0.002
LDH	1.001 (1.001-1.002)	<0.001
PT	1.082 (0.967-1.210)	0.170
APTT	1.040 (1.023-1.057)	<0.001
Hs-CRP	1.018 (1.006-1.030)	0.004
PCT	1.061 (0.996-1.130)	0.064
IL-6	1.001 (1.000-1.002)	0.007
IL-10	1.018 (1.012-1.024)	<0.001
CK	2.629 (1.679-4.118)	<0.001
DBV RNA	2.198 (1.775-2.722)	<0.001
CD3+T cells	0.997 (0.996-0.998)	<0.001
CD4+T cells	0.993 (0.990-0.996)	<0.001
CD8+T cells	0.996 (0.993-0.998)	<0.001
CD4/CD8	0.453 (0.295-0.694)	<0.001

Abbreviations: SFTS, severe fever with thrombocytopenia syndrome; DBV, Bandavirus dabiense; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; ALB, albumin; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; Hs-CRP, high-sensitivity C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; IL-10, interleukin-10; CK, creatine phosphokinase;

CD3/CD4/CD8, cluster of differentiation; CD3+ T cells, CD3-positive T lymphocytes; CD4+ T cells, CD4-positive T lymphocytes; CD8+ T cells, CD8-positive T lymphocytes; CD4/CD8, ratio of CD4+ to CD8+ T cells. $P < 0.05$ was considered statistically significant. Statistically significant values are shown in bold.

3.3 Development and demonstration of logistic regression and XGBoost models for predicting mortality in patients with SFTS

By integrating DBV RNA, IL-10, CD4/CD8 ratio, Hs-CRP and CK, a logistic regression model was constructed to predict mortality in patients with SFTS and was visualized using a nomogram (Supplementary Table 5) (Figure 2). In parallel, an XGBoost model was developed using the same set of five predictors. The XGBoost hyperparameters and search space are provided in Supplementary Table 6. To enhance interpretability, SHAP analysis was performed on the XGBoost model to estimate the contribution of each predictor to model output (Supplementary Figure 1).

The nomogram visually highlighted the contribution of viral burden and dysregulated host immune responses to mortality prediction in SFTS. DBV RNA and IL-10 accounted for the greatest proportion of the predictive score, supporting the importance of viral replication and hyperinflammatory responses in disease progression. The inverse contribution of CD4/CD8 further suggested that impaired cellular immune balance was associated with increased mortality risk. CK was incorporated into the model as an additional biomarker, but its contribution to the total nomogram score was relatively limited compared with the other predictors (Figure 2).

In the SHAP summary plot, features were ranked according to their mean absolute SHAP values, with DBV RNA showing the greatest contribution to the XGBoost model, followed by IL-10, CK, CD4/CD8 ratio, and Hs-CRP. Each point represents an individual patient, and the x-axis indicates the SHAP value, reflecting the direction and magnitude of each predictor's contribution to the model output on the log-odds scale. Higher DBV RNA, IL-10, and CK values generally contributed to increased predicted mortality risk, whereas higher CD4/CD8 ratios were associated with a lower predicted mortality risk. Hs-CRP showed a relatively smaller but directionally consistent contribution, with higher values tending to increase the predicted risk of mortality (Supplementary Figure 1).

Figure 2. Nomogram predicting the mortality of patients based on logistic regression analysis in the training cohort. Abbreviations: DBV, Dabie bandavirus; CK, creatine phosphokinase; Hs-CRP, high-sensitivity C-reactive protein; IL-10, interleukin-10; CD4/CD8, ratio of CD4+ T cells to CD8+ T cells.

3.4 Performance of logistic regression and XGBoost models in predicting mortality in patients with SFTS in the training cohort

In the training cohort, the predictive performance of individual predictors was first evaluated, followed by assessment of model performance. As shown in Figure 3 and Table 3, the logistic regression model had an AUC of 0.836 (95% CI: 0.779-0.892), whereas the tuned XGBoost model had an apparent AUC of 0.863 (95% CI: 0.811-0.916). The optimal cutoff values determined by the Youden index in the training

cohort were 0.313 for logistic regression and 0.244 for tuned XGBoost, yielding sensitivities of 67.47% and 75.9% and specificities of 86.51% and 84.08%, respectively.

The linear specification of the five continuous predictors in the logistic regression model was further examined using restricted cubic splines in the training cohort(Supplementary Table 7). No significant nonlinear associations with the logit of 28-day mortality were observed for CK, Hs-CRP, IL-10, DBV RNA, or CD4/CD8 ratio (nonlinearity P = 0.370, 0.623, 0.297, 0.792, and 0.533, respectively). Therefore, these predictors were retained as linear terms in the final logistic regression model.

Bootstrap bias-corrected internal calibration showed that logistic regression maintained closer agreement between predicted and observed mortality probabilities across most of the predicted risk range. The Brier score was lower for logistic regression than for tuned XGBoost in the training cohort (0.121 vs. 0.132), indicating better overall probabilistic accuracy (Supplementary Figure 2).

Decision curve analysis in the training cohort showed that both models provided greater net benefit than the treat-all or treat-none strategies over clinically relevant threshold ranges. However, the logistic regression model showed more consistent net benefit across a broader range of threshold probabilities, whereas tuned XGBoost yielded a narrower range of positive clinical utility (Supplementary Figure 3).

Figure 3. ROC curve analysis of logistic regression and tuned XGBoost models for predicting mortality in patients with SFTS in the training cohort. Abbreviations: ROC, receiver operating characteristic; SFTS, severe fever with thrombocytopenia syndrome; AUC, area under the curve.

Table 3. Predictive value of prognostic indicators, logistic regression and XGBoost models for mortality in patients with SFTS in the training cohort

Parameters	Cutoff	AUC (95%CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IL-10	27.2	0.788 (0.726-0.850)	74.7	71.97	43.36	90.83
Hs-CRP	7.62	0.665 (0.595-0.735)	48.19	76.12	36.7	83.65
CD4/CD8	0.97	0.652 (0.582-0.722)	62.65	64.36	33.55	85.71
DBV RNA	4.17	0.793 (0.732-0.854)	68.67	81.66	51.82	90.08
CK	2.47	0.687 (0.618-0.756)	80.72	54.67	33.84	90.8
Logistic model	0.313	0.836 (0.779-0.892)	67.47	86.51	58.95	90.25
XGBoost model	0.244	0.863 (0.811-0.916)	75.9	84.08	57.8	92.4

Abbreviations: AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; DBV, Dabie bandavirus; CK, creatine phosphokinase; Hs-CRP, high-sensitivity C-reactive protein; IL-10, interleukin-10; CD4/CD8, ratio of CD4⁺ T cells to CD8⁺ T cells.

3.5 External validation, cutoff performance, and sensitivity analyses

In the external validation cohort, the logistic regression model achieved an AUC of 0.815 (95% CI: 0.730–0.900), while the XGBoost model achieved an AUC of 0.848 (95% CI: 0.765–0.931). (Figure 4 and Table 4).

Calibration assessment in the external cohort showed that the logistic regression model had a calibration intercept of 0.125 and a slope of 0.951, whereas the XGBoost model had a calibration intercept of 0.452 and a slope of 0.584. The Brier score was 0.116 for logistic regression and 0.154 for XGBoost, supporting better external probabilistic accuracy and calibration stability for logistic regression (Figure 5 and Table 4).

As exploratory sensitivity analyses, a Platt-calibrated XGBoost model was assessed, yielding a Brier score of 0.145, and calibration intercept and slope of 0.213 and 0.822, respectively. This sensitivity analysis suggested that post hoc probability calibration influenced model performance but did not materially alter the overall external validation results (Supplementary Tables 8 and 9).

When the training-derived Youden cutoff of 0.313 was fixed in the external validation cohort, the logistic regression model achieved a sensitivity of 75.00%, specificity of 77.12%, positive predictive value (PPV) of 52.63%, and negative predictive value (NPV) of 90.10%. These results indicate that the model had strong rule-out value for 28-day mortality but only moderate rule-in value at the Youden threshold. In the class-weighted logistic regression sensitivity analysis, the external AUC remained essentially unchanged (AUC = 0.815), and the same external classification counts were obtained at the training-derived Youden cutoff, although the Brier score increased to 0.163. This suggests that class weighting did not improve probability calibration in this dataset. When a sensitivity-prioritized threshold of 0.048 was used, external sensitivity increased to 97.59%, but specificity decreased to 29.76% and PPV decreased to 28.52%, illustrating the expected trade-off between minimizing missed deaths and increasing false-positive high-risk alerts (Supplementary Table 10).

Decision curve analysis showed that both models achieved positive net benefit across low-to-moderate threshold probabilities, but logistic regression produced a higher and more sustained net benefit over a wider range of clinically plausible thresholds in the external validation cohort (Supplementary Figure 4).

Figure 4. ROC curve analysis of logistic regression and tuned XGBoost models for predicting mortality in patients with SFTS in the external validation cohort. Abbreviations: ROC, receiver operating characteristic; SFTS, severe fever with thrombocytopenia syndrome; AUC, area under the curve.

Figure 5. Calibration curves of logistic regression and tuned XGBoost models in the external validation cohort. The dashed line represents perfect calibration. Calibration intercept, calibration slope, and Brier

scores are shown in the figure legend.

Table 4. Discrimination, calibration, and prediction-error performance of logistic regression and tuned XGBoost models

Cohort	Model	AUC (95%CI)	Brier score	Calibration intercept	Calibration slope
Training cohort	Logistic regression	0.836 (0.779- 0.892)	0.121	–	–
Training cohort	Tuned XGBoost	0.863 (0.811- 0.916)	0.132	–	–
External validation cohort	Logistic regression	0.815 (0.730- 0.900)	0.116	0.125	0.951
External validation cohort	Tuned XGBoost	0.848 (0.765- 0.931)	0.154	0.452	0.584

Abbreviations: AUC, area under the curve; 95% CI, 95% confidence interval. Calibration intercept and slope were calculated in the external validation cohort. Empty cells indicate that these recalibration parameters were not used as the primary internal validation metrics, where bootstrap bias-corrected calibration curves and Brier scores were reported.

4 Discussion

In this multicenter study, fatal SFTS was associated with a coordinated pattern of virological and host immune abnormalities, characterized by higher viral burden, increased IL-10 and systemic inflammatory activation, disturbed T-cell composition, and greater tissue injury. Rather than considering these abnormalities as isolated prognostic markers, we integrated them within a unified biological framework. The resulting models retained prognostic performance in an independent external cohort despite substantial differences in baseline biomarker profiles, suggesting that these complementary biological dimensions may capture reproducible features associated with fatal SFTS. Among the two modeling strategies, XGBoost showed numerically higher discrimination, whereas logistic regression provided more stable probability calibration and clinical net benefit.

The concurrent contributions of DBV RNA and IL-10 are biologically noteworthy because they may reflect two closely interconnected aspects of SFTS progression: viral burden and dysregulated host immune regulation. High viral load has consistently been associated with fatal SFTS, inadequate control of viral

replication activates macrophages and monocytes to trigger excessive inflammatory response and induce cytokine storms [15,16]. IL-10 is of particular interest in this context. Although IL-10 normally acts as an immunoregulatory cytokine that restrains excessive inflammation and limits immune-mediated tissue damage [17,18], excessive or sustained IL-10 signaling during SFTSV infection may also impair effective antiviral immune responses [19,20]. Kang et al. reported that IL-10 and IL-6 levels were markedly elevated in patients with fatal SFTS, with the increase in IL-10 preceding that of IL-6. Moreover, inhibition of IL-10 signaling reduced IL-6 production while increasing TGF- β levels [21]. In an animal study, Choi et al. demonstrated that the SFTSV nonstructural protein (NSs) interacts with the TPL2-ABIN2-p105 complex and activates TPL2 signaling, thereby inducing IL-10 expression. Whereas wild mice exhibited rapid weight loss and mortality following SFTSV infection, *Tpl2*^{-/-} and *Il10*^{-/-} mice survived [9]. These findings suggest that IL-10 may not merely serve as a biomarker associated with disease severity but may also participate in the immunopathogenesis of SFTS.

Disturbances in cellular immunity represent another important component of the host response to SFTSV infection. In our cohort, non-survivors exhibited marked reductions in CD3⁺, CD4⁺, and CD8⁺ T-cell counts, together with a lower CD4/CD8 ratio, indicating broad perturbation of the peripheral T-cell compartment. Previous studies have similarly documented substantial T-cell abnormalities in SFTS [22,23]. Huang et al. reported reductions in CD3⁺, CD4⁺, and CD8⁺ T cells accompanied by highly activated and exhaustion-associated phenotypes [7], whereas Zong et al. demonstrated pronounced activation of CD8⁺ T cells, with increased expression of activation and inhibitory receptors and enhanced antiviral effector responses [6]. CD4⁺ T-cell disturbance may also be particularly relevant to disease progression, as depletion of CD4⁺ T cells and alterations in Th-cell subset composition have been associated with SFTS severity [10]. Within this context, the CD4/CD8 ratio in our model should not be interpreted as a direct marker of T-cell exhaustion or dysfunction, but rather as a complementary measure of the relative distribution of the major T-cell compartments. Notably, previous studies have not consistently demonstrated an association between the CD4/CD8 ratio itself and SFTS severity, suggesting that its prognostic relevance may depend on the broader immunological context. In our study, its contribution alongside DBV RNA and IL-10 suggests that information on cellular immune composition may complement measures of viral burden and cytokine dysregulation when characterizing the host response associated with fatal SFTS.

Systemic inflammation and tissue injury may represent downstream manifestations of the dysregulated host response in severe SFTS. Hs-CRP is an acute-phase reactant that reflects systemic inflammatory activity, and elevated CRP levels have been associated with adverse outcomes in SFTS [24,25]. CK, in contrast, provides complementary information on tissue injury and has repeatedly been reported to increase in fatal SFTS [26-28]. Previous studies have shown that CK levels are substantially higher in fatal cases and may remain persistently elevated during disease progression, while meta-analytic evidence has confirmed a significant association between elevated CK and SFTS mortality [27]. Within our framework, Hs-CRP and CK were therefore not intended to represent direct mediators of antiviral immunity, but rather to capture systemic inflammatory activation and downstream tissue injury accompanying severe disease.

An important implication of these findings is that no single biomarker appeared to encompass the biological complexity associated with fatal SFTS. Therefore, we developed two models based on these biomarkers which support a multidimensional interpretation of fatal SFTS.

Both models retained good discrimination in the external validation cohort, supporting the prognostic relevance of the biologically informed predictor set across different clinical settings. XGBoost showed numerically higher discrimination, whereas logistic regression demonstrated better calibration and more consistent clinical net benefit. These findings highlight the complementary strengths of the two approaches rather than the superiority of either model. The favorable calibration and transparent structure of logistic regression may facilitate individualized risk estimation and bedside interpretation, whereas XGBoost may provide additional flexibility for risk ranking. Notably, restricted cubic spline analyses did not identify significant nonlinear associations for the five continuous predictors, which may partly explain why the greater flexibility of XGBoost did not translate into a clear overall advantage.

Sensitivity analyses further supported the robustness of these findings. Platt recalibration of XGBoost preserved discrimination while improving the Brier score and calibration parameters, suggesting that its main limitation was probability estimation rather than risk ranking. Conversely, class weighting of logistic regression did not improve discrimination and resulted in a higher Brier score. These findings highlight that discrimination and probability accuracy are distinct aspects of model performance and that good calibration remains essential for individualized risk estimation. Because recalibration introduces an additional modeling layer requiring independent validation, the Platt-calibrated XGBoost model was retained as an exploratory analysis.

The external validation cohort differed substantially from the training cohort, with higher DBV RNA, Hs-CRP, LDH, and CK levels and lower IL-10, albumin, and CD4/CD8 ratios, indicating meaningful differences in case mix and biomarker distributions. The preservation of predictive performance despite these differences strengthens evidence for model transportability and suggests that the selected predictors capture biological processes relevant across heterogeneous SFTS populations. Nevertheless, such population differences may affect calibration and absolute risk estimates, underscoring the need for prospective validation in broader geographic and clinical settings. Clinically, the models should therefore be regarded as tools for early risk stratification rather than automatic triggers for invasive or resource-intensive interventions. At the training-derived cutoff, the logistic regression model achieved a PPV of 52.63% in external validation, indicating that its current value may lie primarily in supporting closer monitoring and early clinical reassessment rather than directly determining treatment escalation. Threshold selection should ultimately be tailored to the intended clinical context and the relative consequences of false-positive and false-negative classifications.

This study has several limitations. First, the relatively limited sample size and number of death events may affect model stability and precision. Second, only admission measurements were available, without longitudinal assessment of viral load, inflammatory markers, immune-cell subsets, or organ dysfunction. The absence of information on symptom onset and time to death further limited assessment of disease-

stage effects and precluded time-to-event analyses. Third, post-admission treatments and center-specific management practices were not captured and may have contributed to differences in outcomes and external model performance. Fourth, although the selected biomarkers were interpreted within a biologically informed virus–host framework, the observational design cannot establish causal relationships among viral burden, immune dysregulation, inflammation, tissue injury, and mortality. Finally, IL-10 and lymphocyte-subset testing may not be routinely available in resource-limited settings, potentially restricting model applicability. Future prospective multicenter studies incorporating standardized sampling, longitudinal immune profiling, treatment data, and survival time are needed to validate the models and further clarify the biological processes underlying SFTS progression.

5 Conclusion

In this multicenter study, fatal SFTS was associated with coordinated abnormalities involving viral burden, immune dysregulation, systemic inflammation, and tissue injury. Integrating DBV RNA, IL-10, CD4/CD8 ratio, Hs-CRP, and CK within this biologically informed framework yielded interpretable models with reproducible prognostic performance in an independent external cohort. These findings support the potential value of integrating complementary virological and host-response markers for early mortality risk stratification in SFTS. Further prospective studies incorporating longitudinal immune profiling are needed to validate this framework and clarify the biological mechanisms underlying fatal disease progression.

Declarations

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Data availability statement

The data underlying this study contain sensitive patient information and are not publicly available due to ethical restrictions. De-identified data may be made available upon reasonable request and with approval from the Ethics Committee of Beijing Ditan Hospital, Capital Medical University (approval No. DTEC-KY2022-022-03). Requests for data access should be directed to the Ethics Committee Office, Beijing Ditan Hospital, Capital Medical University, No. 8 Jingshun East Street, Chaoyang District, Beijing 100015, China; email: bjdytll@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University (approval No. DTEC-KY2022-022-03), which served as the leading ethics committee for this multicenter study. The approval covered the participating study

centers, including Yantai Qishan Hospital and Qingdao No. 6 People's Hospital, as well as the use of eligible patient data collected during the study period from January 2024 to December 2025. The study was conducted in accordance with the Declaration of Helsinki, applicable local regulations, and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MXL: Conceptualization, Methodology, Writing-original draft, Writing-review and editing, Project administration. WP: Data curation, Methodology, Writing-original draft, Writing-review and editing. JXW: Formal analysis, Resources, Writing-original draft, Writing-review and editing. RRW: Resources, Writing-review and editing. LL: Resources. JPD: Resources. ZHC: Supervision, Funding acquisition. All authors contributed to the manuscript revision.

Conflict of interest

The authors declare no conflict of interest.

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Figures

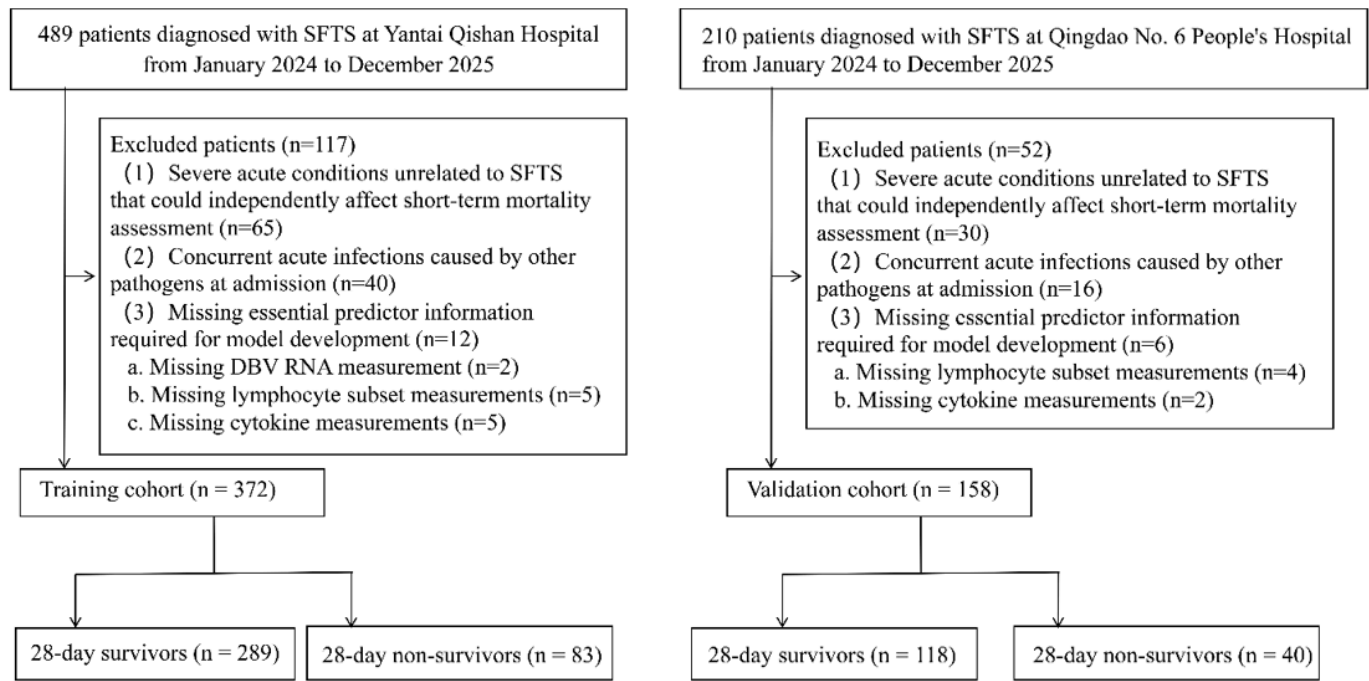


Figure 1

Flow diagram of patient selection and cohort allocation. All eligible patients diagnosed with SFTS during the study period were consecutively screened according to predefined criteria. Patients with missing essential predictor information were excluded before model development.

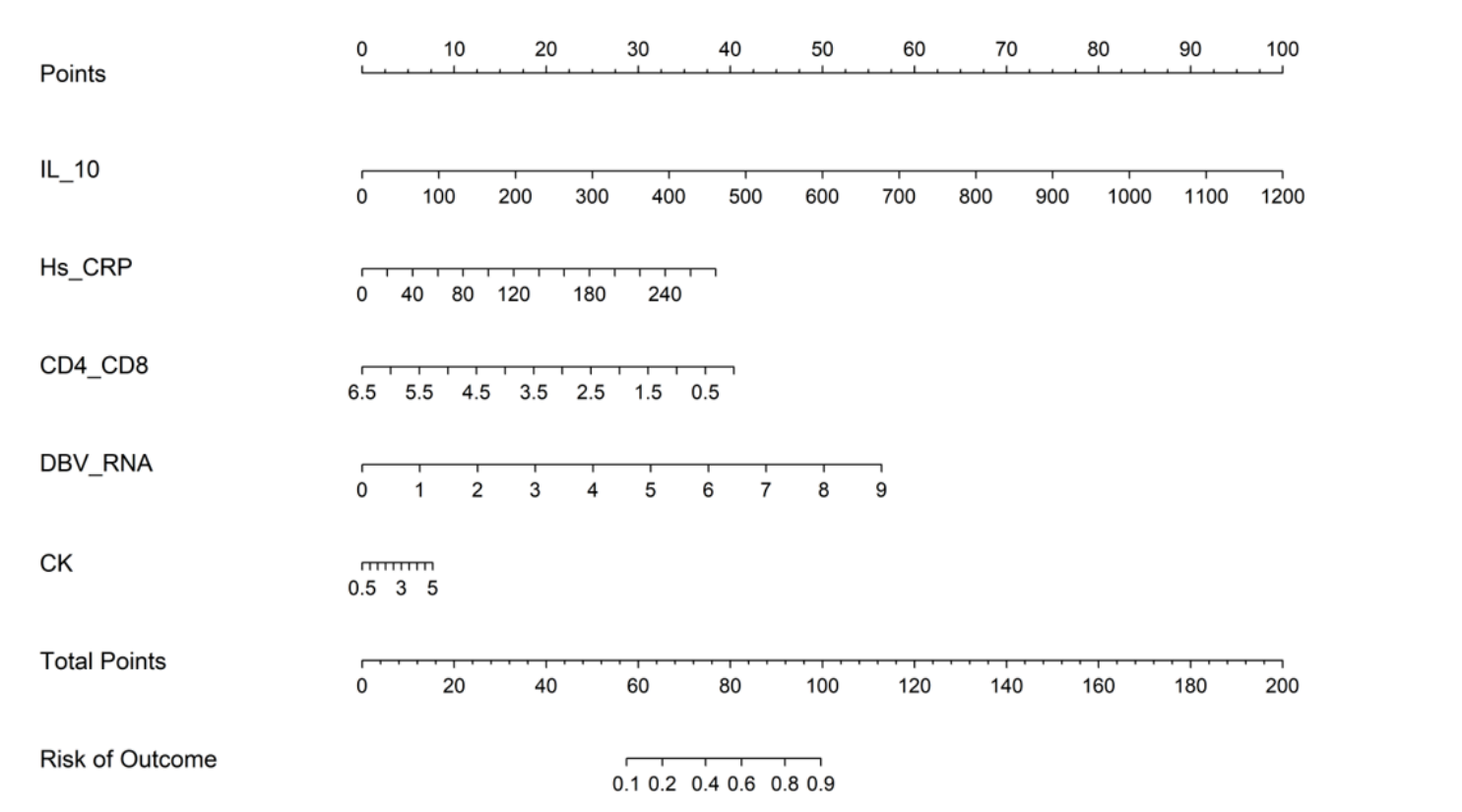


Figure 2

Nomogram predicting the mortality of patients based on logistic regression analysis in the training cohort. Abbreviations: DBV, Dabie bandavirus; CK, creatine phosphokinase; Hs-CRP, high-sensitivity C-reactive protein; IL-10, interleukin-10; CD4/CD8, ratio of CD4⁺ T cells to CD8⁺ T cells.

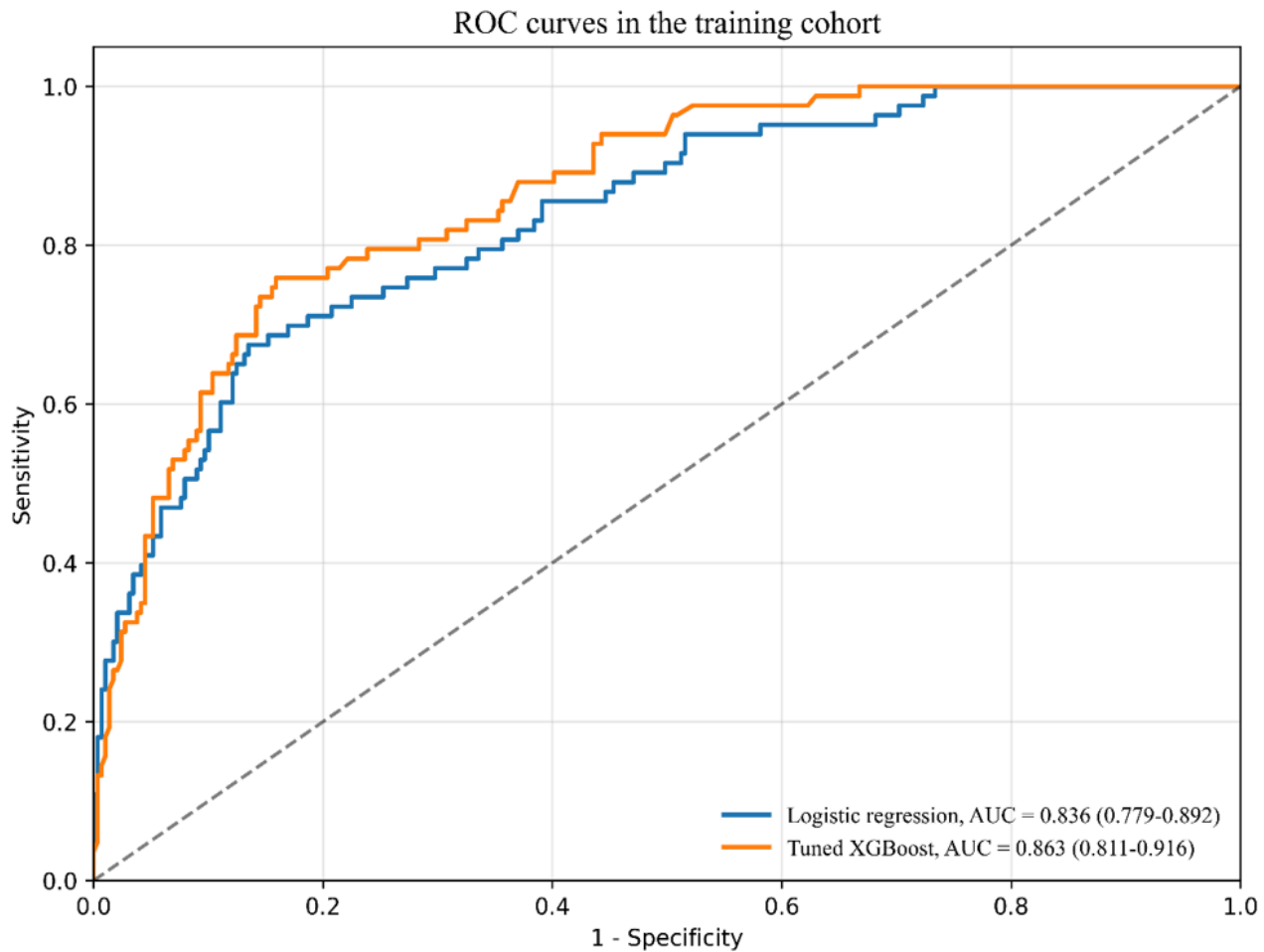


Figure 3

ROC curve analysis of logistic regression and tuned XGBoost models for predicting mortality in patients with SFTS in the training cohort. Abbreviations: ROC, receiver operating characteristic; SFTS, severe fever with thrombocytopenia syndrome; AUC, area under the curve.

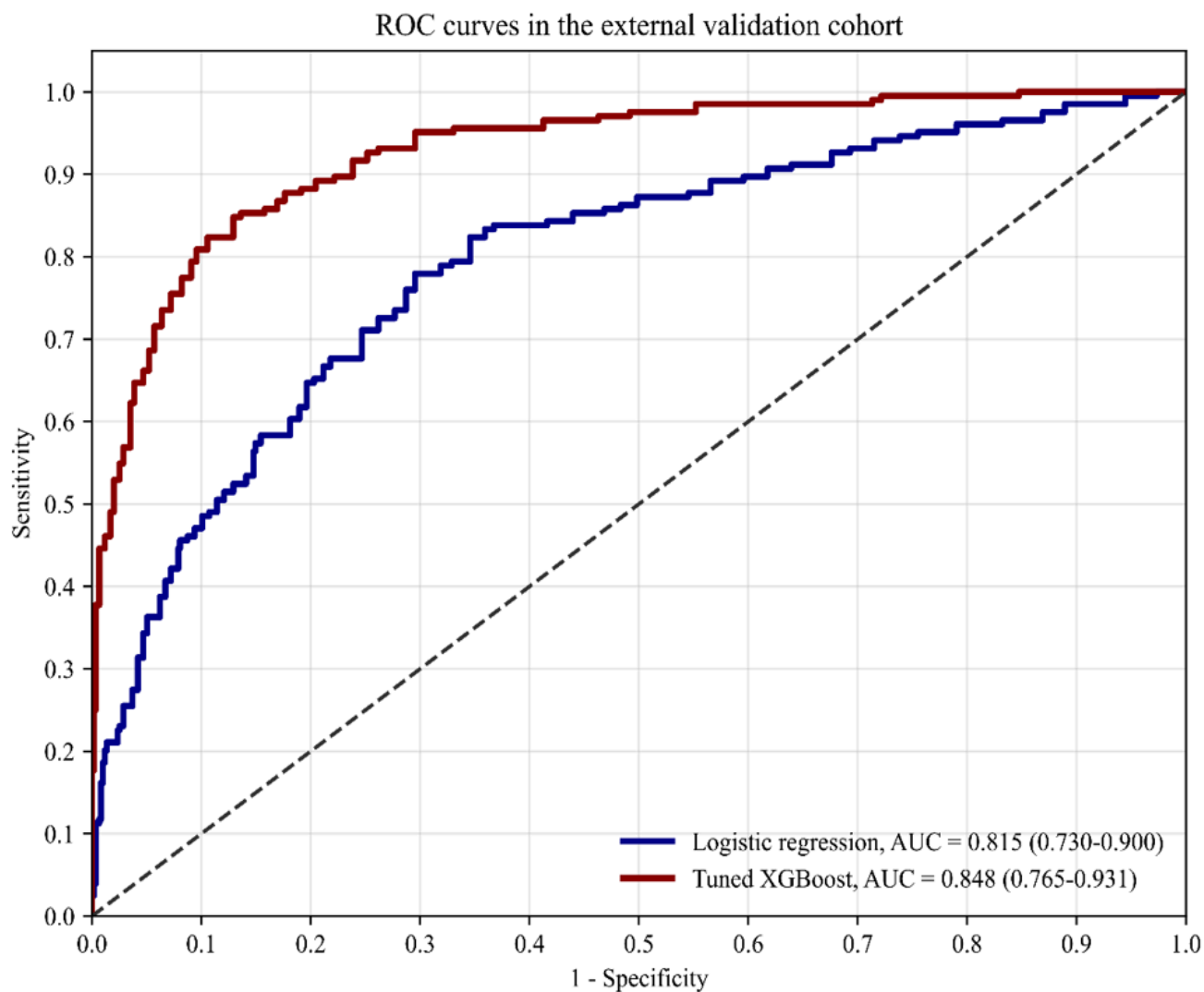


Figure 4

ROC curve analysis of logistic regression and tuned XGBoost models for predicting mortality in patients with SFTS in the external validation cohort. Abbreviations: ROC, receiver operating characteristic; SFTS, severe fever with thrombocytopenia syndrome; AUC, area under the curve.

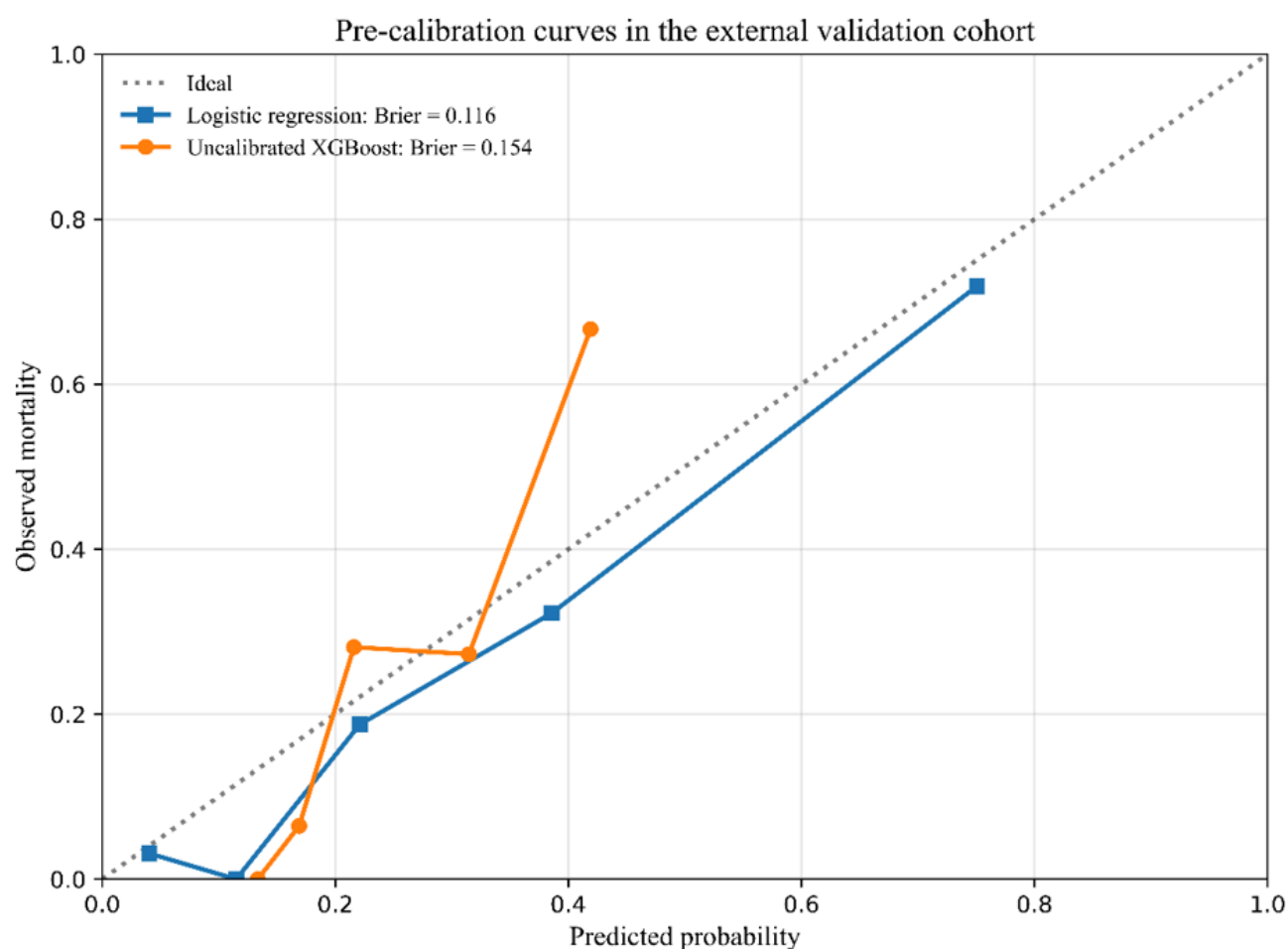


Figure 5

Calibration curves of logistic regression and tuned XGBoost models in the external validation cohort. The dashed line represents perfect calibration. Calibration intercept, calibration slope, and Brier scores are shown in the figure legend.

Supplementary Files

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