Identification of Susceptible and High-Risk Population for Postoperative Systemic Inflammatory Response Syndrome in Elderly Patients: A Machine Learning-Based Approach

Haiyan Mai, Yaxin Lu, Yu Fu, Tongsen Luo, Xiaoyue Li, Yihan Zhang, Zifeng Liu, Yuenong Zhang, Shaoli Zhou, Chaojin Chen

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Table of Contents

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Haiyan Mai[1*]; Yaxin Lu[2*]; Yu Fu[1*]; Tongsen Luo[3]; Xiaoyue Li[3]; Yihan Zhang[3]; Zifeng Liu[2]; Yuenong Zhang[4]; Shaoli Zhou[3]; Chaojin Chen[3, 2]

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Abstract

Background: Systemic inflammatory response syndrome (SIRS) is a serious postoperative complication among geriatric surgical patients which frequently develops into sepsis or even death. Notably, the incidence of SIRS and sepsis steadily increased with age.

Objective: We aimed to develop and validate an individualized predictive model to identify susceptible and high-risk population of SIRS in elderly patients.

Methods: Data of surgical patients aged ? 65years from September 2015 to September 2020 in three independent medical centers were retrieved and analyzed. The eligible patient cohort in the Third Affiliated Hospital of Sun Yat-sen University was separated into an 80% training set and a 20% internal validation set randomly. Four machine learning (ML) models were developed to predict postoperative SIRS. Area under receiver-operating curve (AUC), F1 score, Brier score, and calibration curve were used to evaluate the model performance. Model with the best performance was further validated in the other two independent datasets involving 844 and 307 cases respectively.

Results: The incidence of SIRS in the three medical centers was 24.3%, 29.6% and 6.5%, respectively. 15 predictors were selected and applied in four ML models to predict postoperative SIRS. The Random Forest Classifier (RF) model showed the best overall performance to predict postoperative SIRS, with an AUC of 0.751, sensitivity of 0.682, specificity of 0.681 as well as F1 score of 0.508 in the internal validation set, and higher AUCs in external validation-1 set (0.759) and external validation-2 set (0.804).

Conclusions: We developed and validated a generalizable RF model for prediction of postoperative SIRS in elderly patients, that enables clinicians to screen susceptible and high-risk patients and implement early individualized intervention.

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Abstract

Background: Systemic inflammatory response syndrome (SIRS) is a serious postoperative complication among geriatric surgical patients which frequently develops into sepsis or even death. Notably, the incidence of SIRS and sepsis steadily increased with age.
Objective: We aimed to develop and validate an individualized predictive model to identify susceptible and high-risk population of SIRS in elderly patients.
Methods: Data of surgical patients aged ≥ 65years from September 2015 to September 2020 in three independent medical centers were retrieved and analyzed. The eligible patient cohort in the Third Affiliated Hospital of Sun Yat-sen University was separated into an 80% training set and a 20% internal validation set randomly. Four machine learning (ML) models were developed to predict postoperative SIRS. Area under receiver-operating curve (AUC), F1 score, Brier score, and calibration curve were used to evaluate the model performance. Model with the best performance was further validated in the other two independent datasets involving 844 and 307 cases respectively.
Results: The incidence of SIRS in the three medical centers was 24.3%, 29.6% and 6.5%, respectively. 15 predictors were selected and applied in four ML models to predict postoperative SIRS. The Random Forest Classifier (RF) model showed the best overall performance to predict postoperative SIRS, with an AUC of 0.751, sensitivity of 0.682, specificity of 0.681 as well as F1 score of 0.508 in the internal validation set, and higher AUCs in external validation-1 set (0.759) and external validation-2 set (0.804).
Conclusions: We developed and validated a generalizable RF model for prediction of postoperative SIRS in elderly patients, that enables clinicians to screen susceptible and high-risk patients and

implement early individualized intervention.

Keywords: Elderly patients; Machine learning; Postoperative SIRS; Prediction model

Introduction

Systemic inflammatory response syndrome (SIRS) is a non-homeostatic, self-destructive and uncontrollable inflammatory response of the whole body triggered by infection, trauma, or major operations [1]. Recognizing SIRS has been a prerequisite of suspecting potential sepsis and implementing decisions such as sample culturing for the source of infection, escalating antibiotic regimens and the level of patient monitor and care [2,3]. It has been reported that the incidence of postoperative SIRS could be as high as 89% [4] in patients undergoing abdominal surgery, which frequently developed into sepsis and even multiple organ dysfunction syndrome (MODS) [5]. A 13-fold increase in mortality was reported in patients with postoperative SIRS compared with those without SIRS [6]. Notably, the incidence of SIRS and sepsis steadily increased with age, and octogenarians were almost twice more likely to develop sepsis than those aged less than 50 years [7,8]. Although standardized preoperative antibiotic prophylaxis has been recommended and clinically applied for geriatric populations with high risk of postoperative infection and SIRS, there were still nearly a quarter of elderly patients developed SIRS within 3 days after surgery [9]. Thus, it's important to identify the risk of postoperative SIRS for elderly patients at a sufficiently early stage, which would allow preemptive individualized enhanced therapy to be conducted to improve the prognosis of elderly patients.

Compared with traditional biostatistical methods, machine learning (ML) methods hold the advantages of flexibility, scalability and the ability of analyzing diverse data types, which can be deployed for many tasks, such as risk stratification, diagnosis and classification, and survival predictions [10]. In recent years, there have been many ML models used to predict sepsis [11-17], the majority of which were developed in similar populations such as ICU patients [18]. However, only a few have focused on elderly surgical patients, and ML model for predicting postoperative SIRS has been rarely reported.

The goal of our study was using ML methods to develop an individualized predictive model for the elderly surgical patients to screen susceptible and high-risk population of SIRS, so as to instruct appropriate early intervention. Meanwhile, the generalizability of the model was validated with the data sets of other two medical centers.

Methods

Setting, dates and population

The study protocol was in accordance with the principles of the Declaration of Helsinki, approved by the Institutional Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University on 27 July, 2022 (No. [2019]02-609-04). The requirement for informed consent and clinical trial registration were waived by the committee.

The study was performed based on the Electronic Health Record (EHR) systems of three medical centers including the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China), Lingnan Hospital of Sun Yat-sen University and Yuedong Hospital of Sun Yat-sen University, using data of surgical patients aged ≥65 years.

During the retrospective enrollment, the inclusion criteria included: (1) aged ≥65 years old; (2) patients who underwent general anesthetic with endotracheal intubation or laryngeal mask. (3) patients who had preoperative antimicrobial prophylaxis. The patients were excluded if their total intraoperative infusion volumes, fluid loss or ASA classifications was not recorded.

Data sources

The EHR system of our hospital was established by extracting medical records from the hospital information system (HIS), the laboratory information system (LIS), the picture archiving and communication system (PACS) and the Docare Anesthesia System (2005-2020 Medical system Co., Ltd. Suzhou, China), which enabled access to comprehensive data collected during hospital admission, inpatient stay, and post-hospital follow-up visit, including demographic characteristics, daily documentation, laboratory tests, imaging results, anesthesia records, etc.

Outcome

SIRS was diagnosed according to the American College of Chest Physicians [19]: It was defined when 2 or more of the following criteria were present: (1) temperature < 36°C or ≥ 38°C, (2) heart rate ≥ 90 bpm, (3) respiratory rate ≥ 20 bpm or arterial carbon dioxide tension < 32 mmHg, and (4) WBC count < 4×109/L, ≥ 12×109/L, or > 10% immature forms. The incidence of SIRS within 3 postoperative days was recorded in the study.

Dataset

Datasets of the three medical centers were created separately, which included: (1) patient demographics such as age, gender, smoking history; (2) preoperative complications, including diabetes, hypertension and fever; (3) anesthesia records, including ASA, administration of ulinastatin, dexamethasone, methylprednisolone and dexmedetomidine; (4) liquid management including volume of fluid loss, blood loss and colloid input; duration of surgery; (5) laboratory parameters, including alanine aminotransferase(ALT), white blood cell count (WBC), hemoglobin (HGB), creatinine, albumin, high sensitivity C-reactive protein (hs-CRP), activated partial thromboplastin time (APTT), glucose (GLU), low density lipoprotein (LDL), high density lipoprotein (HDL), blood urea nitrogen (BUN), fibrinogen (FIB), thrombin time (TT), lymphocyte (LYM), red blood cell count (RBC), indirect bilirubin (IBILI). These variables were selected based on EHR availability and their relevance to SIRS risk according to literature and clinical experience [20].

For the purpose of developing and validating the ML models for risk prediction, the cohort of eligible patients of the Third Affiliated Hospital of Sun Yat-sen University was divided into an 80% training set and a 20% internal validation set randomly. In addition, two validation datasets were created with the eligible patients of the Lingnan Hospital and Yuedong Hospital for external validation.

Statistical analysis and ML model training

Four ML algorithms were trained on the training set, including Random Forest (RF), XGBoost, Logistic Regression (LR) and Multilayer Perceptron (MLP). They were chosen for their ability to effectively incorporate many variables into the model. Grid search was applied to find the optimal hyperparameters for each algorithm. A comparison between the optimal model and the nomogram we established before [21] was also conducted in the internal validation set.

The statistical analyses were all done by Python 3.7 [22-25] and R-3.6.2 [26]. All results were considered statistically significant at $p < 0.05$.

Results

Study cohorts and characteristics

Among the 14357 patients aged ≥ 65 years accessed from the EHR system, only 3602 patients meeting the inclusion criteria were included in the development cohort with 876 (24.3%) postoperative SIRS events. The development cohort was then randomly separated into the training set and the internal validation set, which comprised of 2882 and 720 patients, respectively. Meanwhile, 844 and 307 patients were finally included in the external validation-1 set (Lingnan Hospital and the external validation-2 set (Yuedong Hospital), respectively (*Figure 1*).

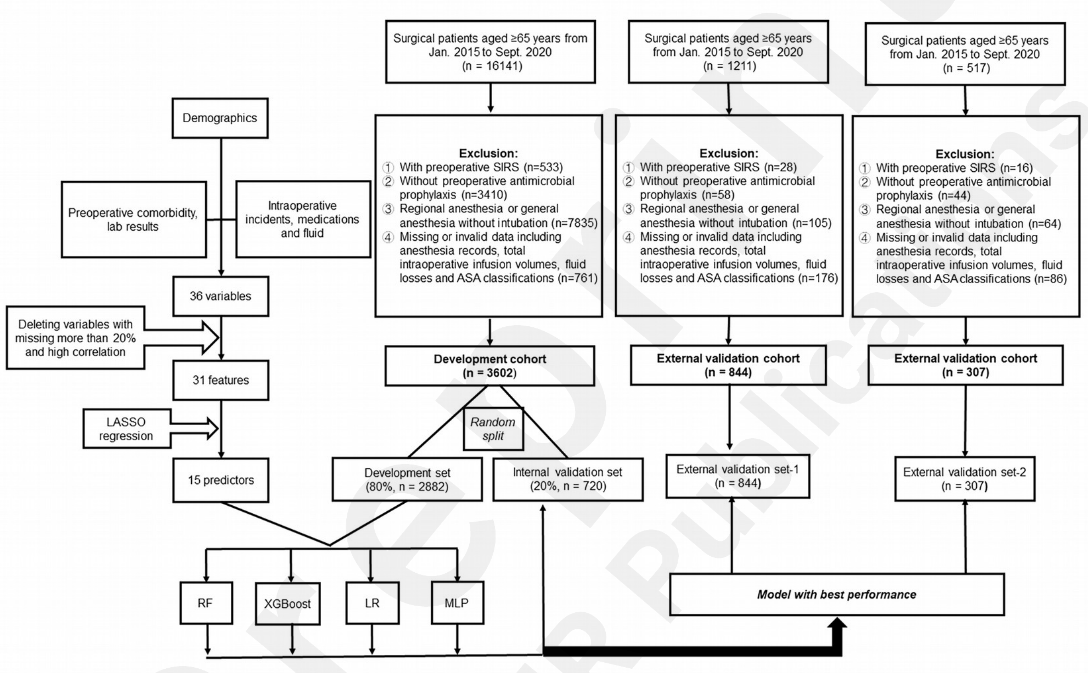


Figure 1. Study design and flowchart.

Characteristics of the three cohorts from different medical centers are shown in *Table 1*. The incidence rate of postoperative SIRS in the three medical centers was 24.3%, 29.6% and 6.5%, respectively. Among the 3602 patients of the development cohort with mean age of 70.0 years old, 2144 (59.5%) were females, 2152 (59.7%) were comorbid with hypertension, 1140 (31.6%) were comorbid with diabetes, and 437 (12.1%) were smokers. In addition, 420 (11.7%) patients had preoperative fever and 1330 (36.9%) were assessed as ASA III/IV/V preoperatively.

Table 1. Baseline characteristics of patients.

Characteristics	**Development cohort n=3602**	**External validation-1 n=844**	**External validation-2 n=307**
Postoperative SIRS [n (%)]			
No	2726(75.7%)	594(70.4%)	287(93.5%)
Yes	876(24.3%)	250(29.6%)	20(6.5%)
Demographics			
Age, [y; median (IQR)]	70.0 [67.0;75.0]	70.0[67.0;76.0]	72.0 [67.2;78.8]
Gender [n (%)]			

Female	2144 (59.5%)	468 (55.5%)	169 (55.0%)
Male	1458 (40.5%)	376 (44.5%)	138 (45.0%)
Hypertension [n (%)]			
No	1450 (40.3%)	313 (37.1%)	173 (56.4%)
Yes	2152 (59.7%)	531 (62.9%)	134 (43.6%)
Diabetes [n (%)]			
No	2462 (68.4%)	526 (62.3%)	51 (54.8%)
Yes	1140 (31.6%)	318 (37.7%)	42 (45.2%)
History of smoking [n (%)]			
No	3165 (87.9%)	755 (89.5%)	257 (86.2%)
Yes	437 (12.1%)	89 (10.5%)	41 (13.8%)
Preoperative fever [n (%)]			
No	3182 (88.3%)	642 (76.1%)	290 (94.5%)
Yes	420 (11.7%)	202 (23.9%)	17 (5.54%)
ASA classification [n (%)]			
I/II	2272 (63.1%)	509 (60.3%)	236 (76.9%)
III/IV/V	1330 (36.9%)	335 (39.7%)	71 (23.1%)
Preoperative variables[a]			
WBC [10^9 L^{-1}; median (IQR)]	6.41 [5.15;8.11]	6.57 [5.38;8.66]	6.69 [5.57;8.53]
LYM [10^9 L^{-1}; median (IQR)]	1.60 [1.20;2.05]	1.50 [1.09;1.96]	1.73 [1.32;2.19]
RBC [10^12 L^{-1}; median (IQR)]	4.27 [3.85;4.66]	4.15 [3.74;4.62]	4.29 [3.91;4.72]
HGB [g L^{-1}; median (IQR)]	127 [113;138]	124 [111;137]	125 [111;136]
RDW-CV [%; median (IQR)]	0.13 [0.13;0.14]	0.13 [0.12;0.14]	13.5 [12.9;14.4]
hs-CRP [mg L^{-1}; median (IQR)]	6.41 [5.10;8.20]	6.56 [5.30;8.66]	10.0 [4.17;34.9]
Albumin [g L^{-1}; median (IQR)]	39.6 [36.2;42.7]	39.0 [36.0;41.7]	37.8 [34.3;40.8]
ALT [U L^{-1}; median (IQR)]	17.0 [13.0;26.0]	18.0 [13.0;28.0]	19.0 [13.0;28.0]
TBILI [umol L^{-1}; median (IQR)]	9.80 [7.00;13.9]	10.3 [7.30;14.7]	14.6 [11.2;19.5]
DBILI [umol L^{-1}; median (IQR)]	3.10 [2.10;4.90]	3.51 [2.30;5.55]	3.40 [2.60;4.85]
IBILI [umol L^{-1}; median (IQR)]	6.50 [4.50;9.10]	6.50 [4.60;9.20]	10.8 [8.15;14.4]
GLU [mmol L^{-1}; median (IQR)]	5.42 [4.87;6.48]	5.52 [4.83;6.69]	5.43 [4.92;6.48]
Creatinine [umol L^{-1}; median (IQR)]	75.0 [61.0;90.0]	79.0 [64.0;96.0]	74.0 [62.4;89.4]
BUN [mmol L^{-1}; median (IQR)]	5.67 [4.60;7.02]	5.83 [4.70;7.58]	5.66 [4.50;6.82]
LDL [mmol L^{-1}; median (IQR)]	2.90 [2.24;3.59]	2.87 [2.24;3.53]	2.55 [2.06;2.99]
HDL [mmol L^{-1}; median (IQR)]	1.05 [0.86;1.26]	1.11 [0.92;1.33]	1.21 [0.98;1.56]
PT [sec; median (IQR)]	13.2 [12.8;13.9]	13.1 [12.5;13.8]	11.1 [10.6;11.6]
APTT [sec; median (IQR)]	37.4 [34.9;40.0]	36.3 [33.5;39.1]	31.1 [29.2;33.7]
FIB [g L^{-1}; median (IQR)]	3.65 [3.08;4.52]	3.67 [3.08;4.58]	3.23 [2.83;3.92]
TT [sec; median (IQR)]	17.5 [17.5;17.5]	17.0 [17.0;17.0]	15.7 [14.9;16.4]
PTINR [median (IQR)]	1.00 [0.96;1.06]	0.99 [0.94;1.07]	1.01 [0.96;1.05]
Intraoperative variables			
Ulinastatin [n (%)]			
No	2817 (78.2%)	627 (74.3%)	305 (99.3%)
Yes	785 (21.8%)	217 (25.7%)	2 (0.65%)
Dexamethasone [n (%)]			
No	3222 (89.5%)	762 (90.3%)	303 (98.7%)
Yes	380 (10.5%)	82 (9.72%)	4 (1.30%)
Dexmedetomidine [n (%)]			
No	2270 (63.0%)	566 (67.1%)	110 (35.8%)
Yes	1332 (37.0%)	278 (32.9%)	197 (64.2%)

Methylprednisolone [mg; median (IQR)]	0.00 [0.00;0.00]	0.00 [0.00;40.0]	0.00 [0.00;40.0]
Total volume of fluid loss [mL; median (IQR)]	500 [220;900]	505 [250;900]	420 [220;808]
Volume of blood loss [mL; median (IQR)]	50.0 [20.0;150]	100 [30.0;200]	20.0 [10.0;80.0]
Intraoperative colloid [mL; median (IQR)]	500 [500;500]	500 [500;500]	500 [500;500]
Duration of surgery [min; median (IQR)]	163 [95.0;250]	170 [105;253]	140 [87.8;210]

[a]WBC, White blood cell count; LYM, Lymphocyte; RBC, Red blood cell count; HGB, Hemoglobin; RDW-CV, Red blood cell distribution width- coefficient of variation; hs-CRP, high sensitivity C-reactive protein; ALT, Alanine aminotransferase; TBILI, Total bilirubin; DBILI, Direct bilirubin; IBILI, Indirect bilirubin; GLU, Glucose; BUN, Blood urea nitrogen; LDL, Low density lipoprotein; HDL, High density lipoprotein; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, Fibrinogen; TT, Thrombin time; PTINR, international normalized ratio of prothrombin time

The characteristics of patients with/without postoperative SIRS in the development cohort is shown in *Table 2*. Patients that ended up with SIRS (SIRS group) were mainly female (65.4% *vs.* 57.6%, $p < 0.001$), and more likely to have been diagnosed with diabetes (38.1% *vs.* 29.6%, $p < 0.001$) and assessed as ASA III/IV/V preoperatively (53.9% *vs.* 31.5%, $p < 0.001$). With evident incidence of preoperative fever (20.8% *vs.* 8.7%, $p < 0.001$), the total volume of fluid loss, volume of blood loss and duration of surgery also increased significantly in SIRS group (700 [330;1200] *vs.* 430 [200;800], 100 [50.0;200] *vs.* 50 [20.0;100], 207 [133;310] *vs.* 150 [90;232], all $p < 0.001$). Additionally, laboratory indicators including hs-CRP, BUN, DBILI and PT were higher in SIRS patients than in non-SIRS patients whereas ALB were lower in SIRS patients (all $p < 0.001$) (*Table 2*).

Table 2. Characteristics of Non-SIRS and SIRS groups in development cohort.

Characteristics	**Development cohort**			
	Total n=3602	**Non-SIRS n=2726**	**SIRS n=876**	***p* value**
Demographics				
Age [y; median (IQR)]	70.0 [67.0;75.0]	70.0 [67.0;75.0]	71.0 [67.0;76.2]	<0.001
Gender [n (%)]				<0.001
Female	2144 (59.5%)	1571 (57.6%)	573 (65.4%)	
Male	1458 (40.5%)	1155 (42.4%)	303 (34.6%)	
Hypertension [n (%)]				0.760
No	1450 (40.3%)	1093 (40.1%)	357 (40.8%)	
Yes	2152 (59.7%)	1633 (59.9%)	519 (59.2%)	
Diabetes [n (%)]				<0.001
No	2462 (68.4%)	1920 (70.4%)	542 (61.9%)	
Yes	1140 (31.6%)	806 (29.6%)	334 (38.1%)	
History of smoking [n (%)]				0.001
No	3165 (87.9%)	2423 (88.9%)	742 (84.7%)	
Yes	437 (12.1%)	303 (11.1%)	134 (15.3%)	
Preoperative fever [n (%)]				<0.001
No	3182 (88.3%)	2488 (91.3%)	694 (79.2%)	
Yes	420 (11.7%)	238 (8.73%)	182 (20.8%)	
ASA classification [n (%)]				<0.001
I/II	2272 (63.1%)	1868 (68.5%)	404 (46.1%)	
III/IV/V	1330 (36.9%)	858 (31.5%)	472 (53.9%)	

Preoperative variables				
WBC [10^9 L^{-1}; median (IQR)]	6.41 [5.15;8.11]	6.32 [5.07;7.88]	6.80 [5.44;8.94]	<0.001
LYM [10^9 L^{-1}; median (IQR)]	1.60 [1.20;2.05]	1.63 [1.23;2.05]	1.54 [1.12;2.05]	0.007
RBC [10^12 L^{-1}; median (IQR)]	4.27 [3.85;4.66]	4.28 [3.88;4.66]	4.22 [3.73;4.65]	0.006
HGB [g L^{-1}; median (IQR)]	127 [113;138]	127 [115;138]	126 [110;139]	0.044
RDW-CV [%; median (IQR)]	0.13 [0.13;0.14]	0.13 [0.12;0.14]	0.13 [0.13;0.14]	<0.001
hs-CRP [mg L^{-1}; median (IQR)]	6.41 [5.10;8.20]	6.31 [5.03;7.93]	6.83 [5.46;9.20]	<0.001
Albumin [g L^{-1}; median (IQR)]	39.6 [36.2;42.7]	40.0 [36.6;42.9]	38.2 [35.0;41.7]	<0.001
ALT [U L^{-1}; median (IQR)]	17.0 [13.0;26.0]	17.0 [12.0;25.0]	19.0 [14.0;32.0]	<0.001
TBILI [umol L^{-1}; median (IQR)]	9.80 [7.00;13.9]	9.70 [6.90;13.5]	10.2 [7.30;15.2]	<0.001
DBILI [umol L^{-1}; median (IQR)]	3.10 [2.10;4.90]	3.00 [2.10;4.70]	3.50 [2.30;5.50]	<0.001
IBILI [umol L^{-1}; median (IQR)]	6.50 [4.50;9.10]	6.40 [4.60;8.90]	6.60 [4.50;9.50]	0.158
GLU [mmol L^{-1}; median (IQR)]	5.42 [4.87;6.48]	5.41 [4.87;6.41]	5.43 [4.88;6.75]	0.308
Creatinine [umol L^{-1}; median (IQR)]	75.0 [61.0;90.0]	73.0 [60.0;88.0]	78.0 [63.0;96.0]	<0.001
BUN [mmol L^{-1}; median (IQR)]	5.67 [4.60;7.02]	5.59 [4.56;6.90]	5.96 [4.69;7.42]	<0.001
LDL [mmol L^{-1}; median (IQR)]	2.90 [2.24;3.59]	2.92 [2.26;3.59]	2.81 [2.19;3.58]	0.055
HDL [mmol L^{-1}; median (IQR)]	1.05 [0.86;1.26]	1.07 [0.88;1.28]	1.02 [0.81;1.24]	<0.001
PT [sec; median (IQR)]	13.2 [12.8;13.9]	13.2 [12.7;13.8]	13.4 [12.9;14.2]	<0.001
APTT [sec; median (IQR)]	37.4 [34.9;40.0]	37.2 [34.9;39.9]	38.0 [35.0;41.3]	0.001
FIB [g L^{-1}; median (IQR)]	3.65 [3.08;4.52]	3.63 [3.09;4.44]	3.77 [3.05;4.75]	0.033
TT [sec; median (IQR)]	17.5 [17.5;17.5]	17.5 [17.5;17.5]	17.5 [17.5;17.5]	0.055
PTINR [median (IQR)]	1.00 [0.96;1.06]	1.00 [0.96;1.06]	1.02 [0.97;1.09]	<0.001
Intraoperative variables				
Ulinastatin [n (%)]				<0.001
No	2817 (78.2%)	2214 (81.2%)	603 (68.8%)	
Yes	785 (21.8%)	512 (18.8%)	273 (31.2%)	
Dexamethasone [n (%)]				0.809
No	3222 (89.5%)	2436 (89.4%)	786 (89.7%)	
Yes	380 (10.5%)	290 (10.6%)	90 (10.3%)	
Dexmedetomidine [n (%)]				0.014
No	2270 (63.0%)	1749 (64.2%)	521 (59.5%)	
Yes	1332 (37.0%)	977 (35.8%)	355 (40.5%)	
Methylprednisolone [mg; median (IQR)]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	0.00 [0.00;0.00]	<0.001
Total volume of fluid loss [Ml; median (IQR)]	500 [220;900]	430 [200;800]	700 [330;1200]	<0.001
Volume of blood loss [mL; median (IQR)]	50.0 [20.0;150]	50.0 [20.0;100]	100 [50.0;200]	<0.001
Intraoperative colloid [mL; median (IQR)]	500 [500;500]	500 [500;500]	500 [500;1000]	<0.001
Duration of surgery [min; median (IQR)]	163 [95.0;250]	150 [90.0;232]	207 [133;310]	<0.001

The prognosis of Non-SIRS and SIRS groups in the development cohort is shown in *Table 3*. Compared with the Non-SIRS group, patients in the SIRS group were significantly more likely to develop postoperative complications that included hemorrhage (50.9% *vs.* 34.4%, $p < 0.001$), ARDS (1.6% *vs.* 0.1%, $p < 0.001$), cardiac arrest (1.1% *vs.* 0.2%, $p < 0.001$), agitation and delirium (7.4% *vs.* 1.2%, $p < 0.001$), coma (6.8% *vs.* 0.3%, $p < 0.001$), and acute kidney injury (9.2% *vs.* 2.0%, $p < 0.001$). Furthermore, SIRS patients also had a longer postoperative hospitalization (12.0 [8.0;19.0] *vs.* 7.0 [5.0;10.0] days, $p < 0.001$), higher cost (91.8 [61.7;135.5] *vs.* 56.5 [34.3;77.0] thousand RMB, $p < 0.001$), higher risk of postoperative ICU admission (37.1% *vs.* 3.3%, $p < 0.001$) as well as higher in-hospital mortality (2.4% *vs.* 0.4%, $p < 0.001$).

Table3. Prognosis of Non-SIRS and SIRS groups in development cohort.

	Total cohort (N=3602)	Non-SIRS (N=2726)	SIRS (N=876)	*p* value
Postoperative complications[a]				
Hemorrhage	1385 (38.5%)	939 (34.4%)	446 (50.9%)	<0.001
ARDS	16 (0.4%)	2 (0.1%)	14 (1.6%)	<0.001
Cardiac arrest	15 (0.4%)	5 (0.2%)	10 (1.1%)	<0.001
Agitation and delirium	97 (2.7%)	32 (1.2%)	65 (7.4%)	<0.001
Coma	67 (1.9%)	7 (0.3%)	60 (6.8%)	<0.001
Acute kidney injury	136 (3.8%)	55 (2.0%)	81 (9.2%)	<0.001
Postoperative ICU Admission[a]	352 (11.4%)	79 (3.3%)	273 (37.1%)	<0.001
In-hospital death[a]	31 (0.9%)	10 (0.4%)	21 (2.4%)	<0.001
Postoperative hospital stay[b]	8.0 [5.0;12.0]	7.0 [5.0;10.0]	12.0 [8.0;19.0]	<0.001
Total hospital stay[b]	16.0 [11.0;22.0]	15.0 [10.0;20.0]	21.5 [15.0;32.0]	<0.001
Total cost[b]	62434 [39886;87937]	56542 [34273;76956]	91846 [61675;135548]	<0.001

[a]expressed as n (%); [b]expressed as median [Q1, Q3].

Variable selection

Among the 36 variables selected according to literature and our clinical experience, 31 variables were finally retained after deleting variables with missing rate over 20% (*Figure 2*) and deleting high correlation variables with correlation index above 0.7 to avoid colinearity (*Figure 3*).

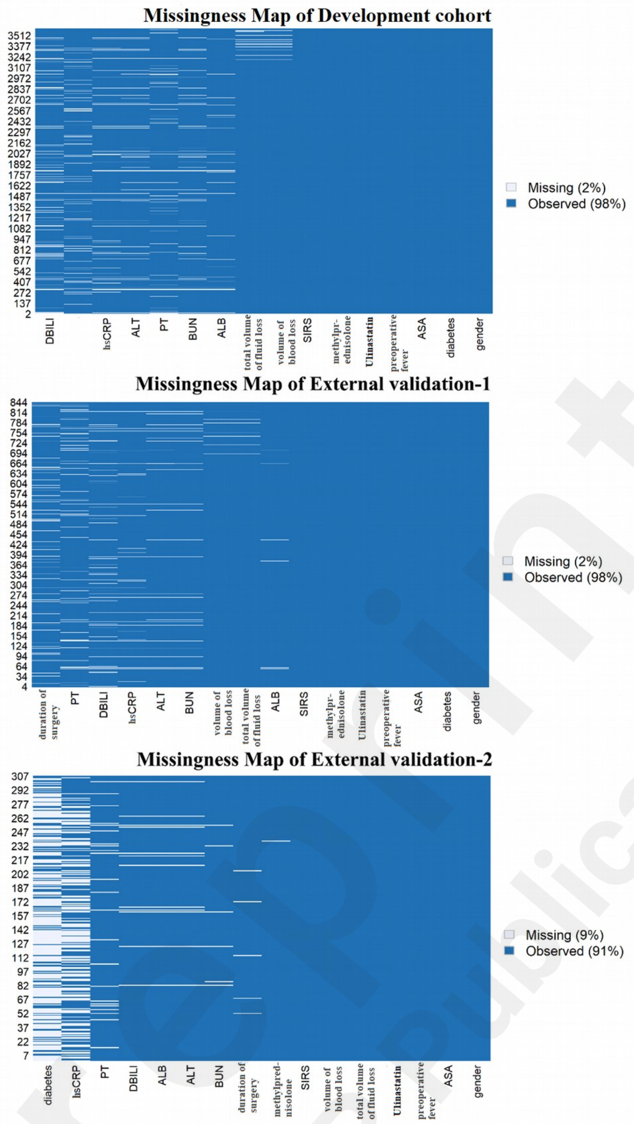


Figure 2. Missing map of the three cohorts in the study.

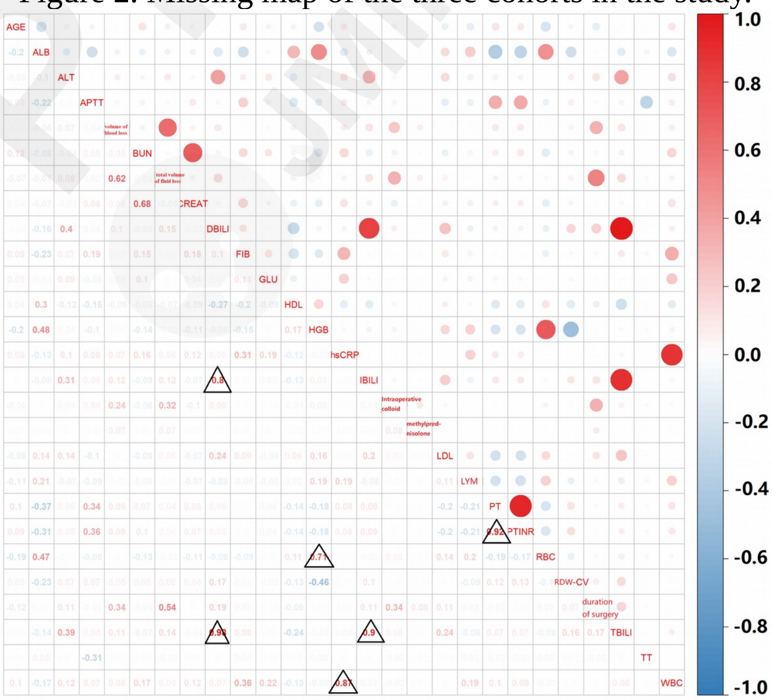
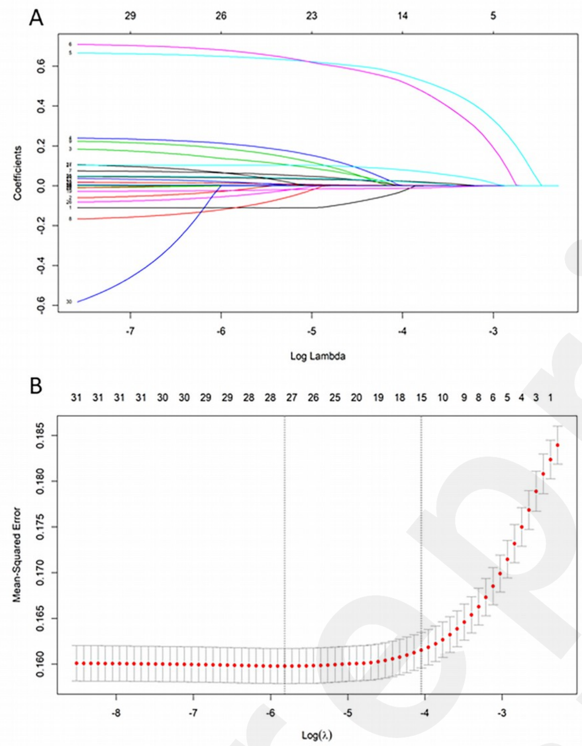


Figure 3. Colinearity analysis among the variables in the study.

Since partially relevant or less important features may negatively affect the performance of ML models, feature selection was performed using least absolute shrinkage and selection operator (LASSO) regression methods. As shown in *Figure 4*, the dimensionality was reduced to 15 features after LASSO, including preoperative fever, ASA, PT, hsCRP, BUN, diabetes, duration of surgery, ulinastatin, methylprednisolone, ALT, total volume of fluid loss, volume of blood loss, DBILI, ALB, and gender. Except that ALB and gender were negatively associated with postoperative SIRS, all other features were positively associated with postoperative SIRS in elderly patients (*Figure 4*).



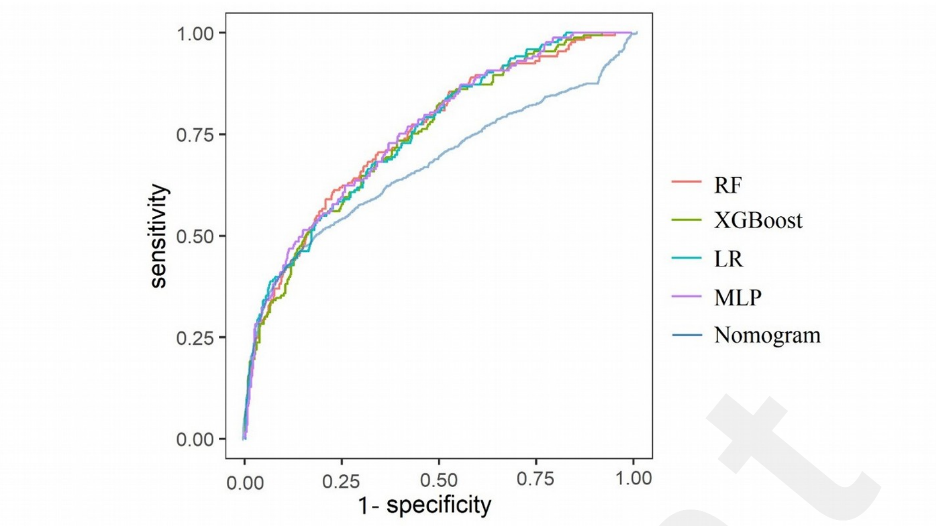
Characteristics	Coef
Preoperative fever	0.104
ASA classification	0.101
PT	0.016
hs-CRP	0.005
BUN	0.004
Diabetes mellitus	0.001
Duration of surgery	<0.001
Ulinastatin	<0.001
Methylprednisolone	<0.001
ALT	<0.001
Total volume of fluid loss	<0.001
Volume of blood loss	<0.001
DBILI	<0.001
ALB	-0.002
Gender	-0.005

PT, prothrombin time; hs-CRP, high sensitivity C-reactive protein; BUN, Blood urea nitrogen; ALT, Alanine aminotransferase; DBILI, Direct bilirubin

Figure 4. Feature selection using LASSO regression.

Model construction, internal validation and horizontal comparison

Finally, the 15 selected predictors were applied in the four ML models to predict postoperative SIRS, including RF, XGBoost, LR and MLP, the performance of different ML algorithms in the internal validation set are shown in *Figure 5* and the calibration curves are presented in *Figure 6*. The area under the receiver operating characteristics curve (AUC) of RF model was 0.751 (95% CI, 0.709, 0.793) with highest sensitivity of 0.682 and specificity of 0.681. The F1 score of RF model (0.508) was the highest among the four ML models and the Brier score (0.153) was also relatively higher. As a result, upon general consideration of AUC, F1 score, Brier score, calibration curve and the ability of subsequent cross-center promotion and application, we thought that the RF model demonstrated the best performance. Additionally, the performance of RF model in the internal validation set was compared with the nomogram [21] we once established to predict postoperative SIRS in older patients (*Fig.3*). The results showed that RF model had significantly higher AUC (AUC=0.751) than the nomogram (AUC=0.671) in the internal validation set , which further proved the generalizability of the RF model.



Metrics	RF	XGBoost	LR	MLP	Nomogram
AUC	0.751 (0.709, 0.793)	0.744 (0.702, 0.786)	0.752 (0.711, 0.793)	0.756 (0.715, 0.797)	0.671 (0.648, 0.694)
Cutoff	0.237	0.226	0.230	0.216	0.276
Sensitivity	0.682	0.665	0.671	0.665	0.626
Specificity	0.681	0.667	0.672	0.665	0.625
Accuracy	0.682	0.666	0.672	0.665	0.626
F1 score	0.508	0.489	0.496	0.488	0.448
PPV	0.404	0.387	0.393	0.386	0.349
NPV	0.871	0.863	0.866	0.862	0.839
Brier score	0.153	0.153	0.151	0.154	0.174

Figure 5. Performance of different ML algorithms in the internal validation set.

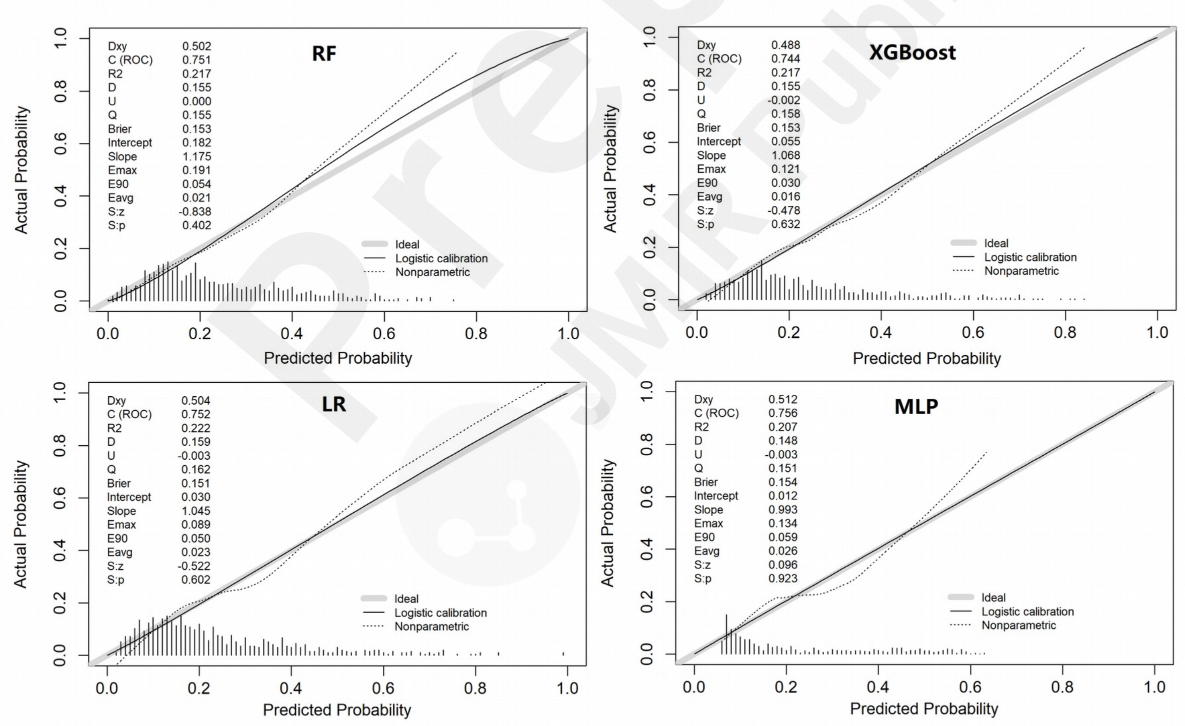


Figure 6. The calibration curves in the internal validation set.

External validation performance

The external validation of the the developed RF algorithm was conducted with the eligible data of patients of the Lingnan Hospital (External validation-1) and Yuedong Hospital (External validation-2), respectively. As shown in Table 4, the RF model achieved relatively higher AUCs for external validation-1 (0.759, 0.723-0.795) and external validation-2 sets (0.804, 0.746-0.863). Moreover, the external validation-2 set demonstrated much higher sensitivity (lower false-negative rate) compared to that of the internal validation set (0.800 *vs.* 0.682), and the specificity of the model was improved in both external validation sets.

Table 4. External validation performance of RF model.

Metrics	**Internal validation**	**External validation-1**	**External validation-2**
AUC	0.751 (0.709, 0.793)	0.759 (0.723, 0.795)	0.804 (0.746, 0.863)
Cutoff[a]	0.237	0.237	0.237
Sensitivity	0.682	0.680	0.800
Specificity	0.681	0.689	0.690
Accuracy	0.682	0.686	0.697
F1 score	0.508	0.562	0.256
PPV	0.404	0.479	0.152
NPV	0.871	0.836	0.980

[a]We chose a balanced cutoff between sensitivity and specificity.

Feature importance weight

The feature importance permutation was used to rank the levels of feature importance, which is defined to be the decrease in a model score when a single feature value is randomly shuffled (*Figure 7*). The results showed that the total volume of fluid loss, duration of surgery, ASA and volume of blood loss have significant impact on the outcome with higher importance weight value of 0.121, 0.119, 0.118 and 0.101, respectively (*Table 5*).

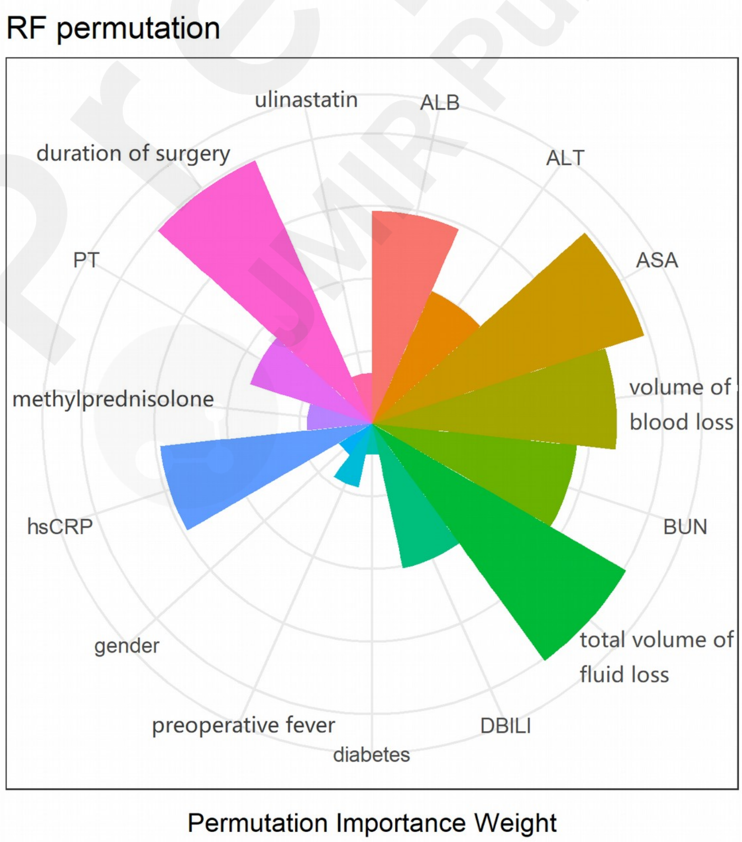


Figure 7. Feature importance weight of the RF algorithm.

Table 5. Feature importance weight of the RF algorithm.

Characteristics	Permutation Importance Scores	Feature Importance Weight
Total volume of fluid loss	0.047 ± 0.002	0.121
Duration of surgery	0.047 ± 0.001	0.119
ASA	0.046 ± 0.003	0.118
Volume of blood loss	0.039 ± 0.001	0.101
hs-CRP	0.035 ± 0.002	0.088
Albumin	0.034 ± 0.002	0.088
BUN	0.033 ± 0.000	0.085
DBILI	0.024 ± 0.001	0.061
ALT	0.023 ± 0.001	0.060
PT	0.021 ± 0.001	0.053
Methylprednisolone	0.011 ± 0.001	0.027
Preoperative fever	0.011 ± 0.001	0.027
Ulinastatin	0.008 ± 0.001	0.021
Gender	0.006 ± 0.000	0.016
Diabetes mellitus	0.005 ± 0.000	0.013

Online Application

An online risk calculator [27] to make the RF model accessible to anesthesiologists and peers around the world was developed with the fifteen variables enrolled in our model which can be routinely obtained during the perioperative period to calculate the risk of postoperative SIRS in the elderly patients conveniently.

Discussion

Principal Results

In this study, we evaluated the ability of four ML algorithms including RF, XGBoost, LR and MLP to predict postoperative SIRS in the elderly patients based on the eligible data from the EHR systems, and concluded that RF model has moderately better performance than other ML algorithms, with the AUC value of 0.751, highest sensitivity of 0.682 and specificity of 0.681. The RF model also exhibited better performance in the internal validation set than the nomogram we once established to predict postoperative SIRS in older patients. Furthermore, the applicability of the RF model was proved by external validation in other two independent medical centers with relatively higher AUC value of 0.759 and 0.804, indicating good reproducibility and generalizability of the model in elderly patients. Finally, an online risk calculator was developed to improve clinical usability and make our model accessible to anesthesiologists and peers around the world.

Currently, given more severe mortality and adverse prognosis, most studies adopted sepsis as a clinical endpoint[2]. In our study, we used SIRS as the primary outcome because it has been an acknowledged criterion which is easily to identify and can help physicians notice the possibility of sepsis and prescribe tests to examine whether infection truly exists. Although there is a tendency to apply criteria including SOFA score or quick SOFA score to identify the possibility of sepsis [28], SIRS criteria has demonstrated higher sensitivity compared to qSOFA score [3], and it has served as both useful inclusion criteria and therapeutic target of trails aiming to treat sepsis [29]. Identifying patients who would develop postoperative SIRS early may enable clinicians to provide timely interventions to prevent sepsis and improve outcomes.

As the population ages, the surgical population is also ageing faster than the general population, with higher morbidity and mortality rates [30]. Notably, the elderly are predisposed to postoperative infection, SIRS and even sepsis due to preexisting comorbidities, repeated and prolonged hospitalizations, immune dysregulation, and functional limitations [31]. Although preoperative antimicrobial prophylaxis has been routinely used for elderly patients in multiple specialized operations, the persistent high incidence of postoperative SIRS indicated that it cannot be prevented effectively in this way [9]. In fact, for the older patients undergoing different types of surgery, there is still a lack of effective tools to identify high-risk patients with postoperative SIRS and assist decision making on the need of individualized intervention.

In this study, we utilized ML method to analyze diverse data types [10] due to its advantage of flexibility and scalability as well as the ability. A predictive model based on RF algorithm was developed to identify the elderly patients with high risk of postoperative SIRS. Internal validation and two external validations confirmed that the established model could predict postoperative SIRS with high accuracy and specificity. The results might be important derivatives and supplements to the current perioperative prevention and management programs, which enable the surgeons and anesthesiologists to identify the elderly patients who are suspected to postoperative SIRS. In addition to screening high-risk groups, this model can also help prevent and treat postoperative SIRS in elderly patients more accurately and timely by using various of drug or non-drug means under the guideline of enhanced recovery after surgery (ERAS), so as to promote the short-term and long-term prognosis of patients [32].

Comparison with Prior Work

Distinguished from previous investigations which mainly focus on a single indicator or a single surgery, we fully utilized the perioperative data of patients and constructed optimal combination of risk factors to predict postoperative SIRS in elderly patients. In this study, 15 variables were identified significantly associated with postoperative SIRS, including preoperative fever, ASA [33], PT, hsCRP, BUN, diabetes [34], duration of surgery [35], ulinastatin, methylprednisolone, ALT, total volume of fluid loss, volume of blood loss, DBILI [36], ALB, and gender [37]. These variables have also been reported to be associated with postoperative SIRS and sepsis in earlier studies, adding clinical credibility to our model. Meanwhile, all the variables were routinely recorded and widely used in clinical practice, which makes the model more feasible and can be widely used in different hospitals.

It is also found that methylprednisolone and ulinastatin were associated with postoperative SIRS, which may be attributed to the fact that both medicines are widely used among high-risk surgical patients with postoperative infection according to the anesthesiologists' clinical experience [38-40]. Additionally, intraoperative fluid loss ranks first in the feature importance weight of RF model, which indicates that fluid management such as intraoperative intravenous infusion should be given higher priority during perioperative period to prevent postoperative SIRS, and this was consistent with the consensus on early management of sepsis [41].

Limitations

Notably, several limitations must be noted here. Firstly, this is a retrospective cohort study with collection and entry bias, as well as possible residual confounding, which requires future prospective studies to validate the model. Secondly, we selected 36 variables based on the availability of EHR, correlation with SIRS risk and predictive potential, but it should be noted that we may miss other indicators with more predictive performance in postoperative SIRS due to the limitation of our data.

Finally, it should be emphasized that estimates in our model are predictive and should not be interpreted as causal [42], such as the association of intraoperative use of methylprednisolone and ulinastatin with higher SIRS incidence rate. Intraoperative use of such drugs is likely a marker of risk stratification with low risk of infection patients less likely to use these drugs than those with high risk.

Conclusions

We enrolled three independent cohorts to develop and validate a generalizable RF model, for prediction of postoperative SIRS in elderly patients, that enables surgeons and anesthesiologists to screen susceptible and high-risk population of SIRS in elderly surgical patients and implement early individualized intervention based on existing prevention and management programs.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Abbreviations

EHR: Electronic Health Record
HIS: hospital information system
ICU: intensive care unit
LASSO: least absolute shrinkage and selection operator
LIS: laboratory information system
LR: Logistic Regression
ML: machine learning
MLP: Multilayer Perceptron
PACS: picture archiving and communication system
RF: RandomForest
SIRS: Systemic inflammatory response syndrome
XGB: XGBoost

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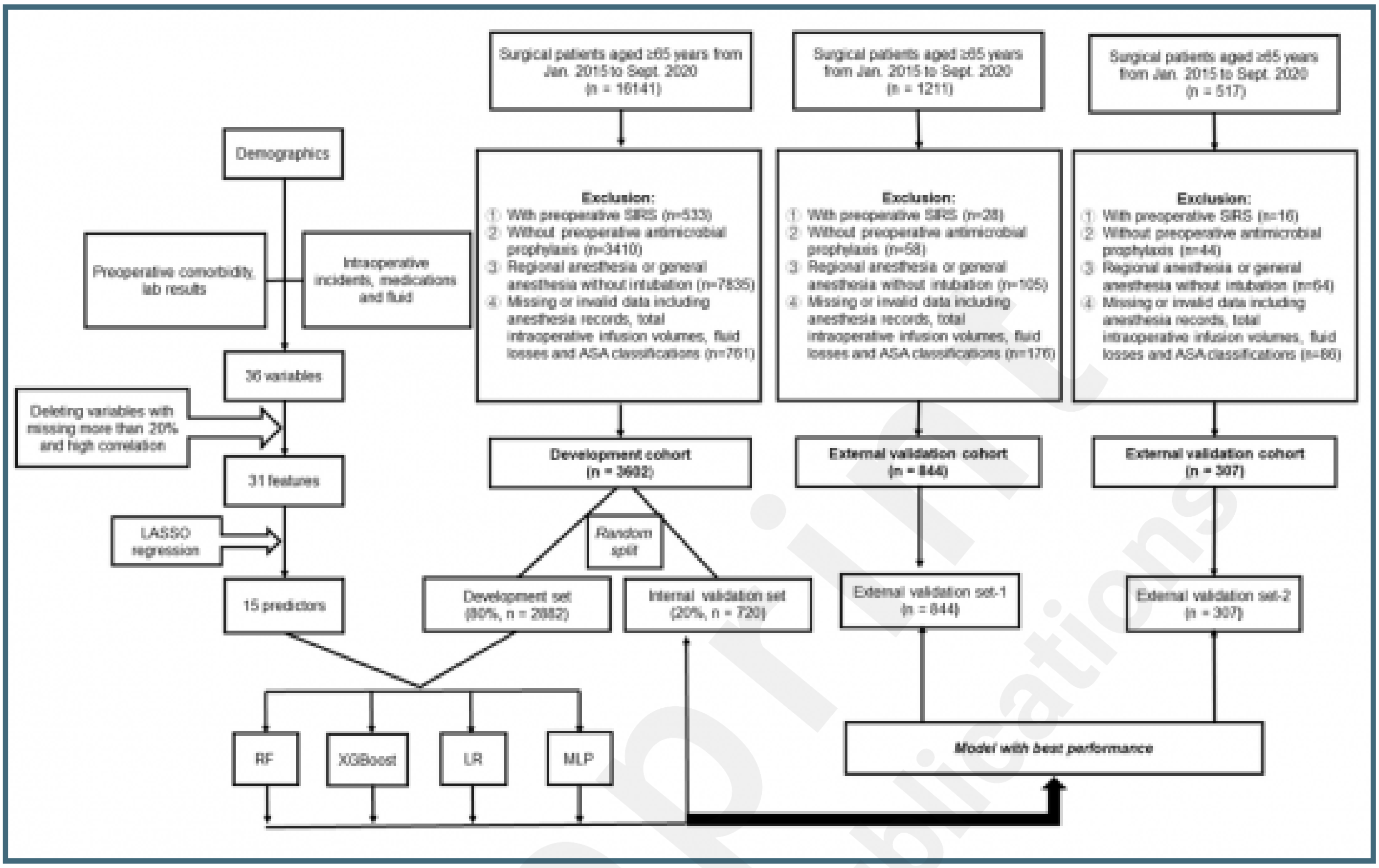
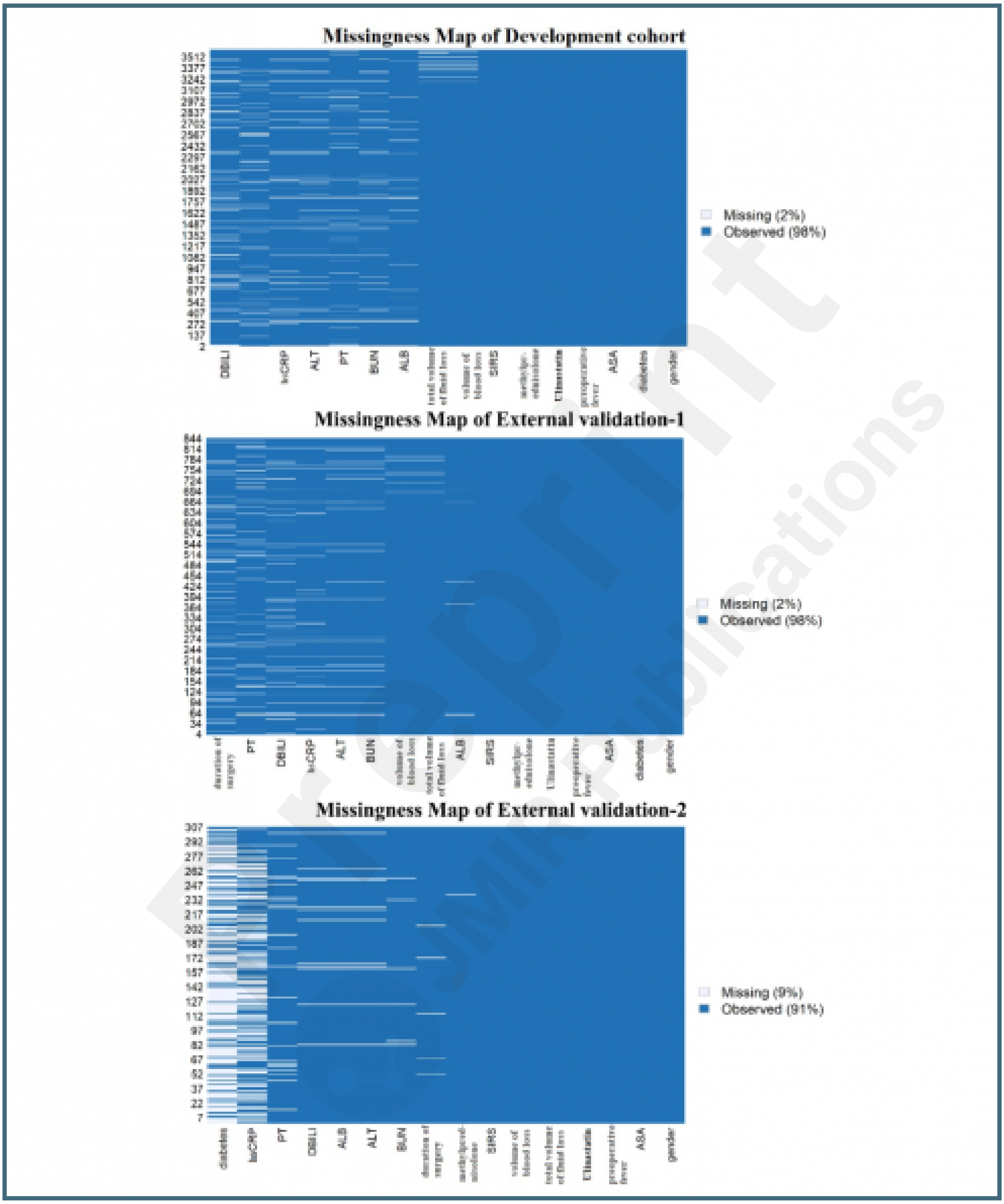
Supplementary Files

Figures

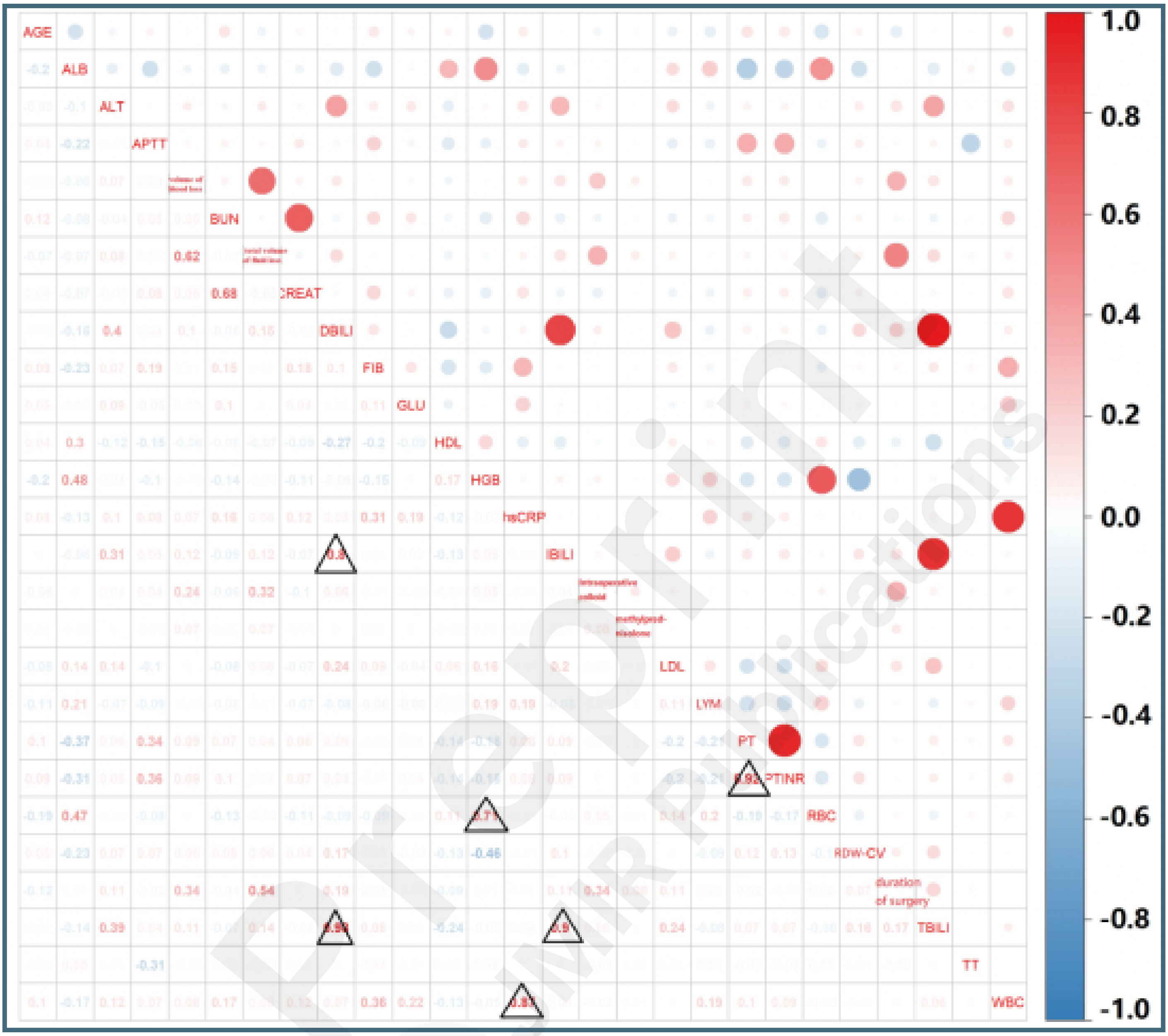
Study design and flowchart.



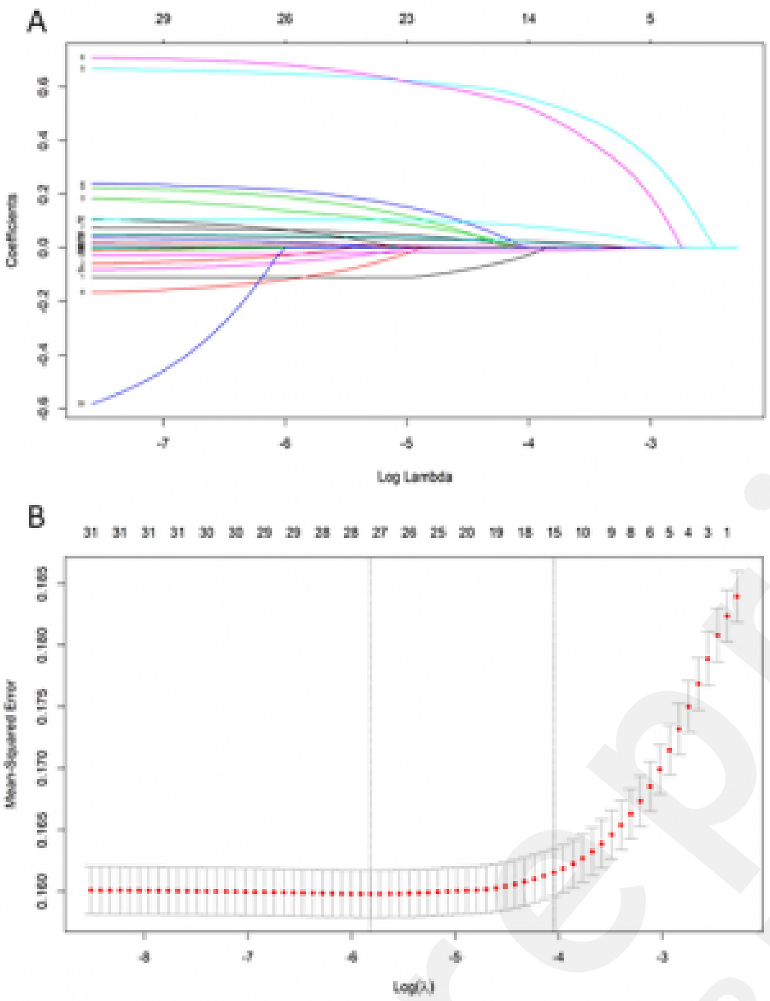
Missing map of the three cohorts in the study.



Colinearity analysis among the variables in the study.



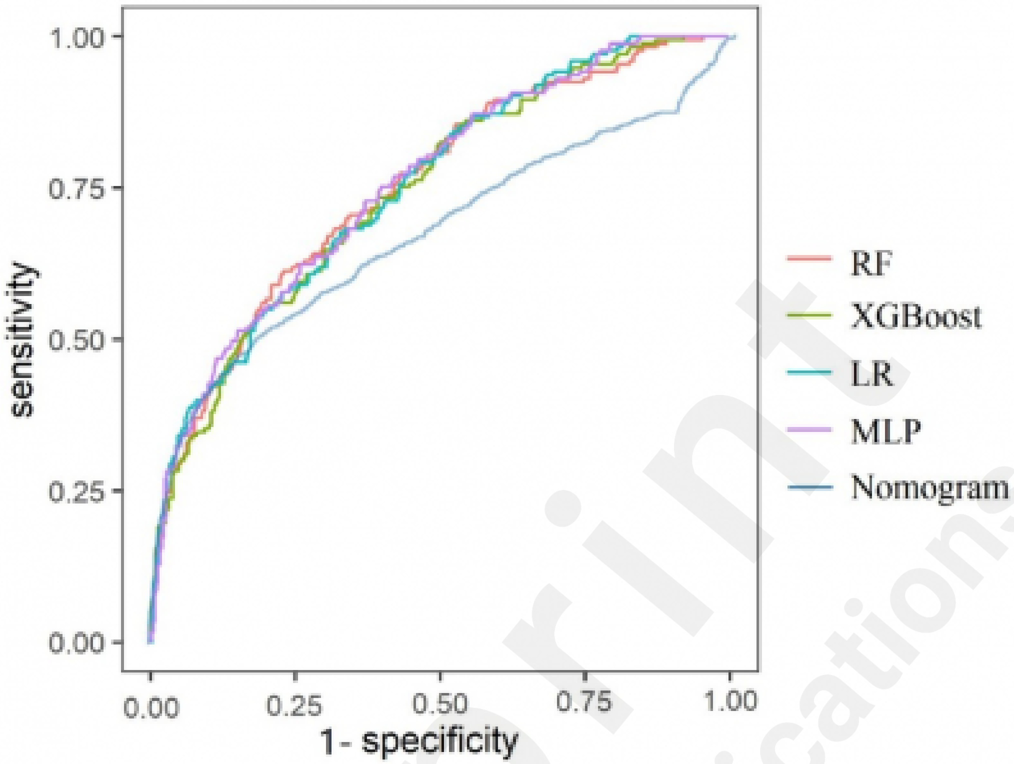
Feature selection using LASSO regression.



Characteristics	Coef
Preoperative fever	0.104
ASA classification	0.101
PT	0.016
hs-CRP	0.005
BUN	0.004
Diabetes mellitus	0.001
Duration of surgery	<0.001
Ulinastatin	<0.001
Methylprednisolone	<0.001
ALT	<0.001
Total volume of fluid loss	<0.001
Volume of blood loss	<0.001
DBILI	<0.001
ALB	-0.002
Gender	-0.005

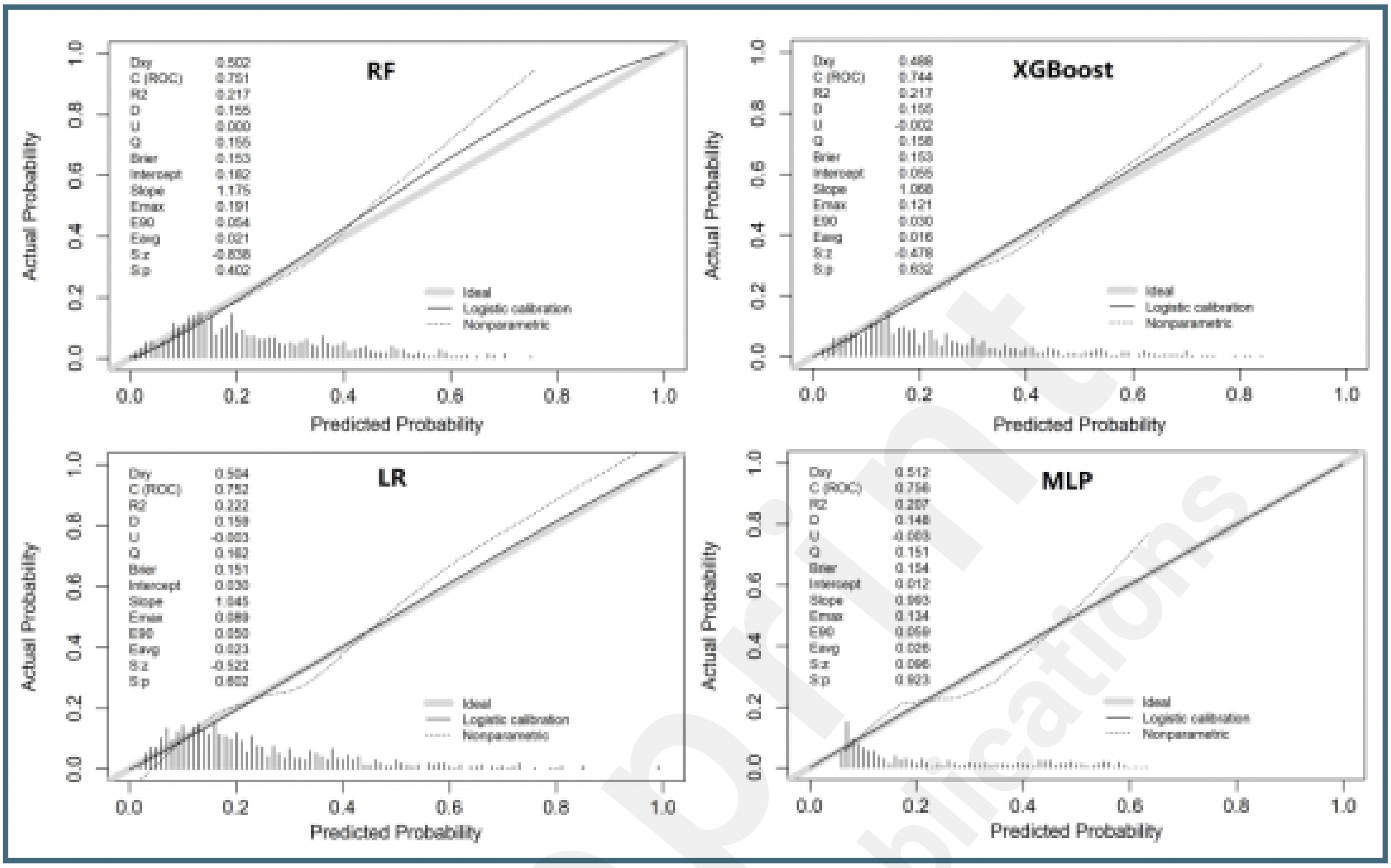
PT, prothrombin time; hs-CRP, high sensitivity C-reactive protein; BUN, Blood urea nitrogen; ALT, Alanine aminotransferase; DBILI, Direct bilirubin

Performance of different ML algorithms in the internal validation set.



Metrics	RF	XGBoost	LR	MLP	Nomogram
AUC	0.751 (0.709, 0.793)	0.744 (0.702, 0.786)	0.752 (0.711, 0.793)	0.756 (0.715, 0.797)	0.671 (0.648, 0.694)
Cutoff	0.237	0.226	0.230	0.216	0.276
Sensitivity	0.682	0.665	0.671	0.665	0.626
Specificity	0.681	0.667	0.672	0.665	0.625
Accuracy	0.682	0.666	0.672	0.665	0.626
F1 score	0.508	0.489	0.496	0.488	0.448
PPV	0.404	0.387	0.393	0.386	0.349
NPV	0.871	0.863	0.866	0.862	0.839
Brier score	0.153	0.153	0.151	0.154	0.174

The calibration curves in the internal validation set.



Feature importance weight of the RF algorithm.