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Personal predictive model based on systemic inflammation markers for estimation of postoperative pancreatic fistula following pancreaticoduodenectomy

Long ZD *et al*. Machine learning for predicting pancreatic fistula

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Abstract

BACKGROUND

Postoperative pancreatic fistula (PF) is a serious life-threatening complication after pancreaticoduodenectomy (PCDT). Our research aimed to develop a machine learning (ML) aided model for PF risk stratification.

AIM

To develop a machine learning (ML) aided model for PF risk stratification.

METHODS

We retrospectively collected 618 patients who underwent PCDT from two tertiary medical centers between January 2012 and August 2021. We used ML algorithm to build prediction models, and use subject prediction index, that is, decision curve analysis (DCA), area under operating characteristic curve (AUC) and clinical impact curve (CIC) to assess the prediction efficiency of each model.

RESULTS

Finally, a total of 29 variables were used to build the ML prediction model. Among them, the best prediction model was random forest classifier, the AUC was [0.897, 95% confidence interval (CI): 0.370-1.424], while the AUC of the artificial neural network (ANN), eXtreme gradient boosting (XGBoost), support vector machine (SVM), and

decision tree (DT) were between 0.726 (95%CI: 0.191-1.261) and 0.882 (95%CI: 0.321-1.443).

CONCLUSION

Fluctuating serological inflammatory markers and prognostic nutritional index (PNI) can be detected in the early postoperative period, which has been clinically proved to predict postoperative PF; In particular, RFC performed best, which can guide optimal treatment, clinical management, and prevent or mitigate adverse consequences.

Key Words: Pancreatoduodenectomy; Pancreatic fistula; Machine learning algorithm; Systemic inflammatory biomarker; Risk prediction

Core Tip: Our research is based on machine learning algorithm and integrates the correlation between serum inflammatory factors and high risk of postoperative pancreatic fistula, and constructs early warning models that can predict postoperative pancreatic fistula, and the predictive efficiency of these machine learning-based models may be at the population-based level. In the future, we expect these findings to expand external research to strengthen valuable supporting information and guide treatment decisions.

INTRODUCTION

Pancreaticoduodenectomy (PCDT), also known as a Whipple procedure, is one of the most difficult and complex surgeries that carries a high rate of major complications[1]. Post-operative pancreatic fistula (PF), as one of the most difficult complications after PCDT, can seriously endanger the lives of patients, so it has become a field of continuous concern for pancreatic surgeons[1,2]. Although the safety of PCDT has improved significantly in the past three decades[3,4]. Alarmingly, previous prospective studies have reported that postoperative PF occupied an incidence of more than 10%[5-7].

In recent years, people have studied different styles of surgery and perioperative attempts to reduce the incidence of post-operative PF. However, regardless of the type of surgery, PF is still the most common fatal complication after pancreatectomy. Herein, understanding the potential complications and early warning of these complications is very important for the care of these severe patients.

Previous studies have utilized preoperative radiology and clinical variables combinedwith specific intraoperative factors to predict the risk of post-operative PF[8-11]. Undoubtedly, despite advancements in prediction platforms for post-operative PF that haveundergone a constantly changing approach. However, because of its unsatisfactory prediction performance, an improved delivery system is deemed necessary. Therefore, exploring an optimal risk score range model may contribute to eliminating potential life-threatening, and stratifying patients with post-operative PF risk, which can be better applied to clinical management.

Nowadays, a series of serum markers suggest that detecting systemic inflammation may be associated with the risk of benign and malignant disease progression[12-14]. At the same time, the systemic reaction stimulated by local inflammation is closely related to the complications after gastrointestinal surgery[15,16]. In addition, machine learning (ML) algorithm has been widely used in the field of medicine. These unceasing new algorithms and iterative analyses might be useful for prognostication in cases and optimize individual treatment decisions[17]. Collectively, this combination has facilitated elevated predictive performance while minimizing the prediction error.

Given this situation, we groped for the help of inflammatory factors and ML-based algorithms to optimize the predicted accuracy of post-operative PF. In this study, we tried to identify alternative predictors independently related to postoperative PF and develop an optimal risk stratification model that can accurately identify high-risk patients with postoperative PF.

MATERIALS AND METHODS

Patients selection

Patients who underwent PCDT to treat various periampullary tumors from two tertiary medical centers (Jingzhou Hospital and Lu'an Hospital of Anhui Medical University) between January 2012 and August 2021 were retrospectively collected. The inclusion criteria were as follows: (1) The resected tumor specimens were confirmed to be malignant by pathological examination; (2) blood routine examination andliver function examination results were found within 3 d before operation; and (3) the patient had complete case data and relevant indicators of imaging, pathology and laboratory examination. The exclusion criteria were as follows: (1) Patients receiving preoperative treatment, such as thermal ablation, neoadjuvant chemotherapy or radiotherapy; (2) the patients had severe respiratory and circulatory diseases; (3) patients with severe acute cholangitis or infection in other parts of the body before operation; (4) patients with metastasis from other parts of the primary tumor or direct invasion of adjacent organs from the primary tumor; and (5) patients with parathyroid diseases or other factors interfering with abnormal changes of procalcitonin (PCT) were diagnosed. This study was a retrospective cohort study, which has been approved by the ethics committee of Jingzhou Central Hospital (Reference: 2021-JH005) and conforms to the declaration of Helsinki. Because this study adopts anonymous follow-up, the patient's personal privacy information is strictly confidential. The detailed research flow chart is shown in Figure 1.

Diagnostic criteria for post-operative PF

According to the standards defined and graded by the international PF research group in 2016 (ISGPF,2016), that is, the drainage flow is greater than 30 mL 72 h or more after an operation, and the amylase content of drainage fluid is measured. If it exceeds 3 times or more of the upper limit of normal blood amylase and has a certain clinical impact (such as abdominal pain, fever, *etc.*), it is judged that PF occurs if it needs active clinical treatment. The grade of PF updated by ISGPS in 2016 removes the diagnosis of grade a PF. The increase of amylase in asymptomatic drainage fluid is considered biochemical leakage, *i.e.*, non real PF. The occurrence of significant clinical symptoms

based on biochemical leakage and the change of treatment strategy (such as puncture and drainage, interventional hemostasis, indwelling abdominal drainage tube for more than 3 wk, infection, *etc.*) is defined as grade B PF. If grade B PF needs surgical treatment, or is complicated with organ failure or even death, the grade of PF will rise to grade C. Therefore, grade B PF and grade C PF are also known as clinical post-operative PF[18,19].

Blood sample collection

We chose to collect about 3-5 mL blood samples from each patient on an empty stomach in the morning of 3 d before operation, and included the latest blood routine and liver function tests in this study. Meanwhile, peripheral venous blood was taken in the morning of the 1st, 3rd, and 5th d after the operation, and the changes in C-reactive protein (CRP), serum PCT, and white blood cell were continuously observed.

Data collection and quality assessment

We obtained population baseline data and clinical pathological data from the patient's medical records. For instance, the pancreatictexture is evaluated by the surgeon during the operation (soft is 1, hard is 0), and the diameter of the main pancreatic duct is obtained by computed tomography (CT) or magnetic resonance imaging (MRI) images before the operation. In addition, we also collected routine laboratory measurement results, and when the missing value is greater than 10% or more of the bias of the total variable, the variable will be directly discarded and not included in the final model variable screening[20]. Finally, a total of 29 variables that met the inclusion criteria are used to build ML-based models.

Construction and verification of ML-based models

At the beginning of building the model, we randomly divided the population data into two parts, namely, the training queue and the verification queue. Among them, the training queue was used to build the development of the prediction model, and the

validation queue was used as the internal validation of the model to evaluate the robustness of the model. In addition, when screening candidate variables, we adopt the "two-step segmentation evaluation", that is, the principle of random sorting to obtain the intersection[21]. In short, by sorting the intersection of variable sets, the optimal subset modeling was obtained. Finally, these models are evaluated through inspection, discrimination and calibration.

Statistical analysis

As for descriptive variables (*i.e.* continuous variables or classified variables), the median (interquartile range) or frequency (percentage) were used for statistics in this study. Chi-square test or Mann-Whitney test was used to calculate the variables between groups to evaluate whether there was a statistical difference. Stepwise regression based on the minimum value of the Akaike information standard was used to select the variables. All data analysis was completed with the help of R language software (version 4.0.4, http://www.r-project.org/). All *P* values were double tailed, $P < 0.05$ was statistically significant.

RESULTS

Clinicopathological baseline characteristics of patients

In this study, all patients were randomly divided into a training set (n = 432, 70%) and validation set (n = 186, 30%) *via* the caret package. Seventy-eight (18.06%) and 20 (10.75%) patients developed postoperative PF in the training and validation group, respectively, as shown in Table 1. Among these PF cases, grades B and C were 76 (12.3%) and 22 (3.6%) respectively. One patient died of multiple organ failure due to drug-resistant bacterial infection; 5 cases underwent operation again because of continuous blood drainage by drainage tube, which was confirmed to be abdominal bleeding caused by PF during operation; 2 cases were transferred to intensive care.

Selection of candidate variables

Feature selection is a universal problem in ML[22]. Here, we performed an iterative analysis of 29 potential candidate variables, and the correlation matrix showed that there was a significant correlation between postoperative PF and inflammatory factors and some clinical variables (Figure 2A), including CRP, PCT, neutrophil to LR (NLR), platelet to LR (PLR), and HALP. As shown in Figure 2B, HALP, PCT, neutrophil-to-albumin ratio (NAR), PLR, and PNI. Meanwhile, the seven top-ranked predictors were HALP, remnant texture, PCT, NAR, PLR, PNI, and body mass index (BMI).

Construction of PF prediction model based on ML algorithm

In the training queue, each patient can use positive or negative training and output the final judgment results. For example, a random forest classifier (RFC) algorithm can be used to effectively navigate the free parameter space to obtain a robust model (Figure 3A). The variable Gini index in the RFC model was shown in supplementary Table 1. In addition, data mining through the decision tree (DT) model was very useful, as shown in Figure 3B, among the candidate variables related to inflammatory factors, PCT and BMI also played an important role in DT as "branch weight", which can be used as an important predictorof postoperative PF. At the same time, the artificial neural network (ANN) model also showed relatively robust prediction performance, but slightly lower than RFC (Figure 4). We also constructed nomographs, which depended on the parameters obtained by LR, as shown in Supplementary Table 2. In general, compared with traditional prediction models, inflammatory factors also accounted for an important proportion.

Comparison between ML-based models

To explore the effectiveness of five supervised learning models for postoperative pf evaluation, we used decision curve analysis (DCA) for evaluation, which was consistent with the results of the included candidate variables. Even if different prediction models included the samevariables, there were certain differences in their prediction effectiveness, as shown in Figure 5. In addition, as shown in Table 2, the prediction

efficiency of RFC was the best [0.897, 95% confidence interval (95%CI): 0.370-1.424] compared with the other four prediction models, followed by ANN (0.882, 95%CI: 0.321-1.443), DT (0.807, 95%CI: 0.250-1.364), extreme gradient boosting (XGboost) (0.793, 95%CI: 0.270-1.316), and support vector machine (SVM) (0.726, 95%CI: 0.191-1.261). In conclusion, the iterative algorithm analysis using supervised learning, RFC and ANN, as well as DT (ML aided decision support) models were properly used to guide postoperative PF prediction.

Internal validation of the optimal post-operative PF predictive model

In this study, we evaluated the clinical prediction efficiency of the optimal prediction model (RFC), as shown in Supplementary Figure 1. RFC can be used to achieve accurate stratification of patients' postoperative PF *via* clinical impact curve (CIC). In general, RFC performed best in the construction of prediction models by fusing inflammatory markers.

DISCUSSION

Our study revealed two major findings. First, accurate risk stratification of post-operative PF in patients who received PCDT, which mainly depended on the added value of systemic inflammation markers. Second, the ML based prediction model is better than the traditional prediction algorithm model, which is very suitable for identifying whether patients have postoperative PF.

Several risk factors leading to such complications have been reported in the relevant literature, including pancreas texture, BMI, intraoperative blood loss, blood transfusion, and operative time[9,23,24]. We summarized updated literature on predicting postoperative PF, in combination with various candidate predictive markers in Supplementary Table 3. Guo *et al*[25] reported that the texture of pancreas, the size of main pancreatic duct, portal vein invasion and confirmed pathology are the risk factors of postoperative PF. Tajima *et al*[26] summarized that preoperative imaging evaluation of pancreatic pathologies would be also beneficial for stratifying. Not surprisingly,

systemic inflammatory markers such as neutrophils, lymphocytes, platelets, CRP, albumin, and biomarkers may help predict postoperative PF. The systemic response to postoperative local inflammatory stimulation is tightly related to the complications after gastrointestinal surgery[27]. Gasteiger *et al*[15] reported that postoperative pancreatitis and inflammatory reaction are the main determinants of postoperative PF[15]. Intriguingly, our calculated risk factors for post-operative PF and inflammatory factors accounted for an irreplaceable weight in the prediction model.

In this study, an attempt was made to improve early-postoperative risk stratification by combining local pancreatic residual inflammatory status and systemic response, we found that abnormal HALP, PCT, NAR, PLR, and PNI showed reliable predictivevalue for postoperative PF. Previous studies have confirmed that neutrophils, as thesource of vascular endothelial growth factor and tissue inhibitor protease, can promote tumor infiltration and distant metastasis[28-30]. Additionally, the number of lymphocytes in cancer patients changes frequently, which seriously affects the prognosis and survival rate [31,32]. As noted above, it appears apparent that inflammatory factors were highly related to the presence of post-operative PF. Combined with these findings, our analysis showed that systemic inflammatory markers are of great value in predicting postoperative PF.

Our ML-based model was based on clinical parameters and laboratory test results, which were consistent with previous research results. Clinical indicators including preoperative serum albumin, lipase level, and amount of intraoperative fluid infusion were independent risk factors of post-operative PF[23,24,33]. Therefore, we further analyzed the accuracy of the prediction model constructed between clinical parameters and systemic inflammatory markers based on an ML-based algorithm. Not surprisingly, we found that systemic inflammatory markers accounted for a high weight in each model. Among these predictive models, the RFC allowed the calculation of risk level based on candidate variables, so the best prediction efficiency was obtained. It's not surprising that RFC adopted the re-sampling technique of bootstrap to repeatedly focus on the "bagging" procedure[34]. To detect the discrimination of the ML-based model, the

DCA and CIC methods were used to evaluate the predictive performance, and the results are consistent with the expected goal. Taken together, our model may apply to patients who intended to receive PCDT, especially to help surgeons decide whether to prevent post-operative PF after surgery.

Despite several strengths, there are some noteworthy limitations to this study. First, the inclusion of patients from two tertiary referral hospitals, which cannot capture the most changes owing to a selection bias. Second, although we have established a perfect prediction model through ML-based algorithm, our prediction model still needs to be further confirmed in other hospital settings. Although we had adopted internal data cross-validation, which still needed more external data to verify its feasibility in the future. Third, we only adopted simple data obtained from classification, missing clinical data were not considered throughout the study. Hence, incorporating specific new technologies suchas immunodiagnostic biomarkers may help to improve the accuracy of predictive models.

CONCLUSION

In conclusion, our results provide new insights into candidate predictive markers associated with high risk of PF. With the help of halt, NAR, CRP, PCT and PLR, we have developed ML-based prediction models, and the prediction performance of these unsupervised integrated models is very superior to the traditional prediction models. We expect these findings to expand external research to strengthen valuable clinical decision-making and guide treatment.

ARTICLE HIGHLIGHTS

Research background

We provide insights into the candidate predictive markers associated with a high risk of post-operative pancreatic fistula (PF) *via* serum inflammatory secretion. With the help of halt, NAR, CRP, PCT, and PLR, we develop ML-based prediction models, and the prediction performance of these unsupervised integrated models is very superior to the

traditional prediction models. We expect these findings to expand external research to strengthen valuable clinical decision-making and guide treatment.

Research motivation

Integrating undulate serological inflammation markers and prognostic nutritional index (PNI) are detectable early post-operatively, clinically well established to predict post-operative PF; in particular, random forest classifier (RFC) performed best, which can guide optimal treatment, clinical management and prevent or mitigate adverse consequences.

Research objectives

Finally, a total of 29 variables were used to build the ML prediction model. Among them, the best prediction model was random forest classifier, the AUC was [0.897, 95% confidence interval (CI): 0.370-1.424], while the AUC of the artificial neural network(ANN), eXtreme gradient boosting (XGBoost), support vector machine(SVM), and decision tree (DT) were between 0.726 (95%CI: 0.191-1.261) and 0.882 (95%CI: 0.321-1.443).

Research methods

As for descriptive variables (*i.e.* continuous variables or classified variables), the median (interquartile range) or frequency (percentage) were used for statistics in this study. Chi-square test or Mann-Whitney test was used to calculate the variables between groups to evaluate whether there was a statistical difference. Stepwise regression based on the minimum value of the Akaike information standard was used to select the variables. All data analysis was completed with the help of R language software (version 4.0.4, http://www.r-project.org/). All P values were double tailed, $P < 0.05$ was statistically significant.

Research results

Finally, a total of 29 variables were used to build the ML prediction model. Among them, the best prediction model was random forest classifier, the AUC was [0.897, 95% confidence interval (CI): 0.370-1.424], while the AUC of the artificial neural network(ANN), eXtreme gradient boosting (XGBoost), support vector machine(SVM),and decision tree (DT) were between 0.726 (95%CI: 0.191-1.261) and 0.882 (95%CI: 0.321-1.443).

Research conclusions

Fluctuating serological inflammatory markers and prognostic nutritional index (PNI) can be detected in the early postoperative period, which has been clinically proved to predict postoperative PF; In particular, RFC performed best, which can guide optimal treatment, clinical management, and prevent or mitigate adverse consequences.

Research perspectives

PCDT, also known as a Whipple procedure, is one of the most difficult and complex surgeries that carries a high rate of major complications. Pancreatic fistula (post-operative PF), as one of the most difficult complications after PCDT, can seriously endanger the lives of patients, so it has become a field of continuous concern for pancreatic surgeons. Although the safety of PCDT has improved significantly in the past three decades. Alarmingly, previous prospective studies have reported that post-operative PF occupied an incidence of more than 10%. Herein, understanding the potential complications and early warning of these complications is very important for the care of these severe patients.

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Figure Legends

Figure 1 The flow chart. PCDT: Pancreatoduodenectomy.

Figure 2 Variable filtering and weight allocation. A: Correlation matrix analysis; B: The weight distribution of the candidate variables.

Figure 3 Visualization of prediction model based on machine learning algorithm. A: Random forest classifier model; B: Decision tree (DT) model. The candidate factors associated with postoperative pancreatic fistula were ordered *via* RFC algorithm (A) and (B) prediction node and weight were allocated *via* DT algorithm.

Figure 4 Visualization of prediction model based on artificial neural network algorithm A: Artificial neural network model; B: Variable importance using connection weight.

Figure 5 Efficiency evaluation of machine learning-based prediction model A: Decision curve analysis (DCA) of training set; B: DCA of testing set.

Table 1 Baseline demographic and clinicopathological characteristics of patients

Variables	Training set				Testing set			
	Overall (*n* = 432)	Non-POPF (*n* = 354)	POPF (*n* = 78)	*P* value	Overall (*n* = 186)	Non-POPF (*n* = 166)	POPF (*n* = 20)	*P* value
Age, median [IQR]	55.00 [49.00, 61.00]	55.00 [49.00, 61.00]	53.00 [47.25, 61.00]	0.147	55.00 [50.00, 60.00]	55.00 [50.00, 60.00]	51.50 [45.75, 59.50]	0.182
BMI, median [IQR]	23.10 [21.80, 24.60]	22.80 [21.50, 24.20]	25.00 [23.33, 26.92]	< 0.001	22.85 [21.72, 24.30]	22.70 [21.52, 23.98]	24.35 [22.88, 26.13]	< 0.001
Gender (%)								
Male	283 (65.5)	227 (64.1)	56 (71.8)	0.247	127 (68.3)	110 (66.3)	17 (85.0)	0.148
Female	149 (34.5)	127 (35.9)	22 (28.2)		59 (31.7)	56 (33.7)	3 (15.0)	
Smoking (%)								
Yes	198 (45.8)	143 (40.4)	55 (70.5)	< 0.001	89 (47.8)	76 (45.8)	13 (65.0)	0.165
No	234 (54.2)	211 (59.6)	23 (29.5)		97 (52.2)	90 (54.2)	7 (35.0)	
Drinking history (%)								
Yes	129 (29.9)	78 (22.0)	51 (65.4)	< 0.001	54 (29.0)	40 (24.1)	14 (70.0)	< 0.001
No	303 (70.1)	276 (78.0)	27 (34.6)		132 (71.0)	126 (75.9)	6 (30.0)	
Diabetes (%)								
Yes	110 (25.5)	49 (13.8)	61 (78.2)	< 0.001	44 (23.7)	30 (18.1)	14 (70.0)	< 0.001
No	322 (74.5)	305 (86.2)	17 (21.8)		142 (76.3)	136 (81.9)	6 (30.0)	
Hypertension (%)								
Yes	164 (38.0)	129 (36.4)	35 (44.9)	0.208	59 (31.7)	49 (29.5)	10 (50.0)	0.108
No	268 (62.0)	225 (63.6)	43 (55.1)		127 (68.3)	117 (70.5)	10 (50.0)	
Abdominal operation (%)								
Yes	130 (30.1)	103 (29.1)	27 (34.6)	0.409	53 (28.5)	47 (28.3)	6 (30.0)	1
No	302 (69.9)	251 (70.9)	51 (65.4)		133 (71.5)	119 (71.7)	14 (70.0)	
Remnant texture (%)								
Soft	121 (28.0)	62 (17.5)	59 (75.6)	< 0.001	44 (23.7)	27 (16.3)	17 (85.0)	< 0.001
Hard	311 (72.0)	292 (82.5)	19 (24.4)		142 (76.3)	139 (83.7)	3 (15.0)	
Blood transfusion (%)								
Yes	232 (53.7)	188 (53.1)	44 (56.4)	0.686	96 (51.6)	84 (50.6)	12 (60.0)	0.577
No	200 (46.3)	166 (46.9)	34 (43.6)		90 (48.4)	82 (49.4)	8 (40.0)	

Anemia (%)								
Yes	218 (50.5)	179 (50.6)	39 (50.0)	1	84 (45.2)	69 (41.6)	15 (75.0)	0.009
No	214 (49.5)	175 (49.4)	39 (50.0)		102 (54.8)	97 (58.4)	5 (25.0)	
Lesion size (%), cm								
> 3	182 (42.1)	125 (35.3)	57 (73.1)	< 0.001	67 (36.0)	54 (32.5)	13 (65.0)	0.009
≤ 3	250 (57.9)	229 (64.7)	21 (26.9)		119 (64.0)	112 (67.5)	7 (35.0)	
Pancreatic duct diameter (%), mm								
< 3	154 (35.6)	93 (26.3)	61 (78.2)	< 0.001	63 (33.9)	49 (29.5)	14 (70.0)	0.001
≥ 3	278 (64.4)	261 (73.7)	17 (21.8)		123 (66.1)	117 (70.5)	6 (30.0)	
ASA classification (%)								
I + II	231 (53.5)	188 (53.1)	43 (55.1)	0.843	85 (45.7)	78 (47.0)	7 (35.0)	0.436
III + IV	201 (46.5)	166 (46.9)	35 (44.9)		101 (54.3)	88 (53.0)	13 (65.0)	
CRP, median [IQR], mg/L	32.00 [22.00, 44.00]	29.00 [21.00, 38.00]	88.50 [56.00, 120.00]	< 0.001	30.00 [22.00, 40.00]	29.00 [21.00, 38.00]	84.50 [42.25, 109.25]	< 0.001
WBC (median [IQR]), 10^9	5.70 [5.30, 6.30]	5.70 [5.20, 6.20]	6.00 [5.60, 6.60]	< 0.001	5.70 [5.20, 6.30]	5.60 [5.20, 6.20]	6.40 [5.52, 6.82]	0.002
PCT, median [IQR], μg/L	0.54 [0.37, 0.68]	0.49 [0.34, 0.61]	1.06 [0.78, 1.21]	< 0.001	0.52 [0.37, 0.67]	0.49 [0.35, 0.63]	0.84 [0.68, 1.09]	< 0.001
AGR, median [IQR]	1.50 [1.30, 1.60]	1.50 [1.40, 1.60]	1.35 [1.20, 1.40]	< 0.001	1.50 [1.30, 1.60]	1.50 [1.40, 1.60]	1.35 [1.17, 1.52]	0.003
PNI, median [IQR]	49.60 [48.10, 51.23]	49.90 [48.32, 51.60]	48.60 [47.35, 49.60]	< 0.001	50.10 [48.40, 51.48]	50.30 [48.42, 51.60]	49.30 [46.85, 50.37]	0.02
Neutrophil count, median [IQR], 10^9	4.02 [3.49, 4.59]	4.18 [3.70, 4.68]	3.36 [3.03, 3.74]	< 0.001	3.94 [3.51, 4.54]	4.03 [3.57, 4.57]	3.46 [3.11, 3.76]	< 0.001
Lymphocyte count, median [IQR], 10^9	1.64 [1.51, 1.78]	1.63 [1.50, 1.76]	1.79 [1.60, 1.94]	< 0.001	1.64 [1.53, 1.76]	1.63 [1.52, 1.73]	1.83 [1.69, 1.98]	< 0.001
Platelet count, median [IQR], 10^9	230.00 [208.00, 252.00]	236.00 [213.00, 255.00]	206.00 [185.25, 229.75]	< 0.001	229.00 [206.00, 253.75]	232.00 [208.25, 257.75]	200.00 [182.50, 225.00]	< 0.001
Monocyte count, median [IQR], 10^9	0.52 [0.45, 0.60]	0.55 [0.47, 0.62]	0.44 [0.39, 0.49]	< 0.001	0.53 [0.46, 0.61]	0.54 [0.47, 0.62]	0.48 [0.42, 0.52]	0.003
Hemoglobin, median [IQR], g/L	132.00 [124.00, 139.00]	130.00 [121.25, 138.00]	138.00 [133.00, 142.75]	< 0.001	132.00 [126.00, 140.00]	132.00 [126.00, 139.75]	134.50 [130.00, 141.00]	0.026
NLR, median [IQR]	2.00 [1.70, 2.30]	1.90 [1.70, 2.20]	2.70 [2.22, 3.10]	< 0.001	2.00 [1.70, 2.30]	1.90 [1.60, 2.20]	2.80 [2.42, 3.05]	< 0.001
NAR, median [IQR]	0.08 [0.07, 0.09]	0.08 [0.07, 0.09]	0.60 [0.30, 0.88]	< 0.001	0.08 [0.07, 0.09]	0.08 [0.07, 0.09]	0.65 [0.38, 0.80]	< 0.001
PLR, median [IQR]	136.20 [116.68, 157.43]	143.85 [123.23, 161.70]	113.15 [102.58, 128.00]	< 0.001	136.45 [120.62, 155.80]	141.00 [121.22, 159.78]	120.15 [104.78, 128.57]	< 0.001
LMR, median [IQR]	3.40 [2.90, 3.80]	3.30 [2.80, 3.70]	3.90 [3.52, 4.70]	< 0.001	3.50 [3.00, 3.80]	3.40 [2.90, 3.70]	4.15 [3.75, 4.48]	< 0.001
HALP, median [IQR]	53.95 [51.08, 56.50]	52.90 [50.50, 55.20]	72.75 [69.32, 75.25]	< 0.001	52.45 [50.40, 55.18]	51.95 [50.10, 54.30]	70.10 [68.18, 72.62]	< 0.001

Table 2 The operating characteristic curve analyses for each machine learning-based model

	AUC		No. of candidate variables
Model	**Mean**	**95%CI**	
RFC	0.897	0.370-1.424	7
SVM	0.726	0.191-1.261	8
DT	0.807	0.250-1.364	8
ANN	0.882	0.321-1.443	7
XGboost	0.793	0.270-1.316	9

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