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ORIGINAL RESEARCH

Association and Predictive Ability between Inflammatory Burden Index and Fever Following Endobronchial Forceps Biopsy in Lung Cancer Patients

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Introduction: Fever is a very common complication during endobronchial forceps biopsy (EBFB). Inflammatory burden index (IBI) are prognostic indicators for a multitude of inflammation and cancers, and our study focuses on evaluating the prognostic significance of the IBI on fever post-EBFB in lung cancer patients.

Methods: 501 patients with primary lung cancer undergone EBFB were enrolled in this study. The connection between the IBI and the risk of fever was studied using logistic regression analysis, restricted cubic spline (RCS) was employed to assess the association's form. Then, the most influential factors were selected through the application of Boruta algorithm and LASSO regression method and nomogram model was developed using multivariate logistic regression. Internal validation was performed using bootstrapping. Model performance was evaluated using the area under the curve (AUC), calibration curves, and decision curve analysis (DCA).

Results: With an upwards shift in IBI vertices, the rate of fever post-EBFB steadily rose. The RCS analysis indicated J-shaped associations. Inflection points occurred at IBI=8.615 for fever post-EBFB. Patients in the highest IBI quartile had a significantly higher risk of fever post-EBFB compared to those in the lowest quartile. Sensitivity subgroup analyses also verified this association (all HRs > 1.0). Finally, the integration of Boruta and LASSO methodologies identified neutrophil percentage, C-reactive protein, examination time, nausea or vomiting, bleeding as significant predictors. We applied these predictors (model 1) separately and combined them with IBI (model 2) to develop two predictive models. The AUC of model 1 was 0.956 (95% CI, 0.936–0.972), and it was 0.958 (95% CI, 0.941–0.972) in model 2. The predictive model was well calibrated and DCA indicated its potential clinical usefulness. The predictive performance of Model 2 is better than that of Model 1.

Discussion: IBI can serve as effective indicators for predicting the fever post-EBFB in lung cancer patients.

Keywords: fever, endobronchial forceps biopsy, lung cancer, IBI, prediction nomogram

Introduction

Endobronchial biopsy (EBB) is a crucial diagnostic method for lung cancer.[1] Various biopsy techniques are used in EBB, including forceps biopsies, cryobiopsies, bronchial brushing, and needle aspiration biopsies, with forceps biopsy being the most commonly applied in clinical practice.[2,3] Postoperative fever is a frequent complication following bronchoscopy, particularly after forceps biopsies in lung cancer patients.[4–6] Endobronchial forceps biopsy (EBFB) often results in symptoms such as fever, headache, fatigue, loss of appetite, and general discomfort.[7] Patients experiencing high fever may require non-steroidal anti-inflammatory drugs and antibiotics, which can prolong hospital stays and increase medical costs. Additionally, fever can exacerbate the psychological burden on lung cancer patients and impact their subsequent treatment.

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Currently, the fever after EBFB prediction and treatment decisions of patients depend on the traditional medical testing methods such as white blood cell (WBC) and C-reactive protein (CRP), But its accuracy and reliability are still unsatisfactory. Moreover, there is currently a lack of a comprehensive and reliable indicator to identify high-risk patients for postoperative fever early on, which poses a challenge for clinical decision-making. Therefore, more indicators are needed to further improve its application. Currently, a new blood indicator, IBI, which is defined as C-reactive protein × neutrophils/lymphocytes, has been proven to play a significant predictive role in multiple studies.[8–10] This study aims to elucidate the relationship and predictive capacity of IBI in identifying the high-risk fever patients after EBFB. Therefore, early implementation of relevant psychological guidance, preoperative communication, and therapeutic interventions can be carried out.

Material and Methods

Data Source

This retrospective, single-center study utilized clinical records of lung cancer patients diagnosed via EBFB from the Department of Respiratory and Critical Care Medicine at the 8th Medical Centre, Chinese PLA General Hospital, between January 2021 and September 2024. The study adhered to the ethical standards of the institution/national research committee and the 1964 helsinki Declaration and its amendments. It was approved by the hospital's ethics committee (No. 202400207), and written informed consent was obtained from all participants prior to inclusion.

Participants

We included lung cancer patients diagnosed via EBFB who required hospitalization. Exclusion criteria were as follows: (1) severe pleural reactions or pneumothorax postoperatively; (2) severe bleeding (>100 mL) during surgery; (3) combined use of other biopsy methods (eg, cryobiopsy or needle aspiration biopsy) during surgery; (4) presence of other diseases (eg, tuberculosis, fungal infections); (5) incomplete medical records. Patients were divided into fever (axillary temperature >37.2°C) and non-fever groups. Collected variables included: patient demographics (gender, age, smoking history, Chronic obstructive pulmonary disease COPD history); preoperative Nonsteroidal Anti-Inflammatory Drugs NSAIDs/antibiotics use; laboratory tests (white blood cell count WBC, neutrophil percentage, C-reactive protein CRP); surgical and cancer features (lesion location, histological type, stage [early: I–II; advanced: III–IV], anesthesia type, nausea/vomiting during surgery/recovery, bleeding requiring treatment [4°C saline/diluted adrenaline], examination time, biopsy count, postoperative oxygen supplementation).

Surgical Technique

EBFB is a minimally invasive procedure widely used for lung cancer diagnosis. The operation was conducted using fiberoptic bronchoscopy (Olympus BF-1TQ29) with patients under general or local anesthesia in a supine position. Biopsies were typically taken at the lesion site using rigid endoscopic forceps. For significant bleeding after EBFB, intrabronchial instillation of 4°C saline and/or diluted adrenaline (1:10000) was the initial hemostatic measure, repeated as necessary.

Statistical Analysis

The variance inflation factor (VIF) was calculated to assess multicollinearity among variables, with a threshold of 5 to exclude variables and mitigate collinearity. VIF quantifies the extent to which multicollinearity inflates the variance of regression coefficients. Univariate (Model 1) and multivariate logistics proportional models were constructed to evaluate IBI's association with clinical outcomes, considering IBI as categorical variable. Models were partly (models 2) or fully (model 3) adjusted for Age, Sex, WBC, Neutrophil, Use of antibiotics, Examination time, Anesthesia, Nausea or vomiting, Bleeding, Lesion location, Cancer stage, Number of biopsies, Oxygen supplement after surgery. The median value of the quartiles was employed as a quasi-continuous variable in the models to determine trends' p-values.

To explore potential nonlinear associations between IBI and patient outcomes, restricted cubic spline (RCS) analyses were performed, using four knots (at the 5th, 35th, 65th, and 95th percentiles). If a nonlinear relationship between the IBI

and fever risk was revealed by the RCS, we further calculated the inflection point and analyzed the relationship on either side of this point.

For selection of variables for analysis, the Boruta algorithm and LASSO regression performed feature screening to identify the features most associated with the risk of fever post-EBFB. Multivariable logistic regression analysis using backward stepwise procedure and the likelihood ratio test were used to develop the predictive model. Model performance was assessed based on three dimensions: discrimination, calibration, and clinical usefulness. Discrimination was measured using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve and internal validation was performed using bootstrapping (resampling = 500). Calibration was evaluated using calibration curves and unreliability tests. The clinical utility of the model was assessed using decision curve analysis (DCA) by quantifying the standardized net benefit at different threshold probabilities. Nomogram was constructed to predict the risk of fever post-EBFB.

Concerning baseline characteristics, continuous variables were reported as mean±standard deviation (SD), and categorical variables as counts (percentage), while those deviating from normal distribution were represented as median (quartiles). For group comparisons, appropriate statistical tests-unpaired t-tests or Kruskal–Wallis tests, and Pearson chi-squared or Fisher's exact tests were applied. Statistical analysis was done using R software (version 4.2.1, http://www.r-project.org/), and P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

We screened 734 hospitalized patients primarily diagnosed as lung cancer by EBFB. 233 patients were excluded for the following reasons: 35 patients with pleural reactions and pneumothorax after surgery; 43 patients with severe bleeding (>100mL) during surgery; 105 patients combined use of other biopsy methods during surgery; 37 patients diagnosed with lung cancer combined with other diseases (tuberculosis, aspergillus and mucormycosis infections); 13 patients insufficient information. The flow chart shows the strategy to identify the participants of the lung cancer patients diagnosed with EBFB cohort (Figure S1). The demographic and clinical characteristics of patients with and without fever were summarized in Table 1. Table 1 showed that fever group had a significant difference with non-fever in terms of 12 factors, including IBI,

Table 1 Clinical Characteristics of Patients With and Without Fever

Characteristic		Total (n=501)	No-Fever (n=323)	Fever (n=178)	P
Anesthesia, n(%)	General	86(17.166)	67(20.743)	19(10.674)	0.004
	Local	415(82.834)	256(79.257)	159(89.326)	
Nausea or vomiting, n(%)	Yes	92(18.363)	42(13.003)	50(28.090)	<0.001
	No	409(81.637)	281(86.997)	128(71.910)	
Bleeding, n(%)	Yes	295(58.882)	161(49.845)	134(75.281)	<0.001
	2	206(41.118)	162(50.155)	44(24.719)	
Histological type, n(%)	Adenocarcinoma	161(32.136)	110(34.056)	51(28.652)	0.645
	Squamous cell carcinoma	170(33.932)	105(32.508)	65(36.517)	
	Small cell lung cancer	86(17.166)	55(17.028)	31(17.416)	
	Others	84(16.766)	53(16.409)	31(17.416)	
Lesion location, n(%)	Left main bronchus	56(11.178)	41(12.693)	15(8.427)	0.030
	Left upper lobar bronchi	72(14.371)	43(13.313)	29(16.292)	
	Left lower lobar bronchi	25(4.990)	12(3.715)	13(7.303)	
	Right main bronchus	83(16.567)	59(18.266)	24(13.483)	
	Right upper lobar bronchi	82(16.367)	50(15.480)	32(17.978)	
	Right middle bronchus	66(13.174)	47(14.551)	19(10.674)	
	Right middle lobar bronchi	42(8.383)	24(7.430)	18(10.112)	
	Right lower lobar bronchi	31(6.188)	14(4.334)	17(9.551)	
	The trachea	44(8.782)	33(10.217)	11(6.180)	

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Table 1 (Continued).

Characteristic		Total (n=501)	No-Fever (n=323)	Fever (n=178)	P
Cancer stage, n(%)	Advanced	312(62.275)	211(65.325)	101(56.742)	0.058
	Early	189(37.725)	112(34.675)	77(43.258)	
Number of biopsies, n(%)	≥5	220(43.912)	120(37.152)	100(56.180)	<0.001
	<5	281(56.088)	203(62.848)	78(43.820)	
Oxygen supplement after surgery, n(%)	Yes	276(55.090)	203(62.848)	73(41.011)	<0.001
	No	225(44.910)	120(37.152)	105(58.989)	
Use of NSAIDs,n(%)	Yes	71(14.172)	51(15.789)	20(11.236)	0.162
	No	430(85.828)	272(84.211)	158(88.764)	
Use of antibiotics, n(%)	Yes	127(25.349)	94(29.102)	33(18.539)	0.009
	No	374(74.651)	229(70.898)	145(81.461)	
COPD,n(%)	Yes	126(25.150)	84(26.006)	42(23.596)	0.552
	No	375(74.850)	239(73.994)	136(76.404)	
Smoking, n(%)	Yes	174(34.731)	114(35.294)	60(33.708)	0.721
	No	327(65.269)	209(64.706)	118(66.292)	
Gender, n(%)	Male	327(65.269)	208(64.396)	119(66.854)	0.580
	Female	174(34.731)	115(35.604)	59(33.146)	
Examination time, median[IQR]		31.200[25.150,37.000]	27.800[23.470,32.010]	37.683[33.776,42.280]	<0.001
WBC, mean (±SD)		6.332±1.682	6.106±1.623	6.741±1.709	<0.001
Neutrophil, mean (±SD)		66.294±5.289	64.648±4.839	69.281±4.732	<0.001
CRP, median[IQR]		8.425[5.744,11.897]	6.855[5.012,8.924]	13.339[10.011,17.846]	<0.001
Age, mean (±SD)		58.544±11.621	58.823±12.232	58.037±10.400	0.449
IBI, median[IQR]		21.799[13.389,33.770]	16.197[11.606,23.589]	39.327[27.842,55.456]	<0.001

Abbreviation: IQR, Interquartile Range.

preoperative WBC, preoperative neutrophil percentage, preoperative CRP, cancer stage, lesion location, anesthesia type, whether nausea or vomiting, bleeding, examination time, number of biopsies, whether oxygen supplement after surgery.

The Correlation of the IBI with Fever Post-EBFB

When SHR was categorized into quartiles, it emerged as a significant risk factor for fever post-EBFB across three models: the unadjusted Model 1, the partially adjusted Model 2, and the fully adjusted Model 3 (Table 2). Patients in the highest IBI quartile (quartile 4) also had a significantly higher risk of fever post-EBFB compared to those in the lowest quartile. The RCS analysis of fever (Figure 1A and B) further revealed J-shaped associations between the IBI and fever risk, with inflection points occurring at 8.615. In addition, multivariable stratified analysis was performed for subgroups of patients (Table 3). Multivariable stratified analyses verified the association of IBI with risk of fever post-EBFB almost in all subgroups. In summary, these findings highlighted the importance of IBI as a predictor for fever post-EBFB.

Table 2 Multivariate Regression Analyses for the Correlation Between IBI and Fever Post-EBFB

Variables	N	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P
IBI		Model1		Model2		Model3	
Quartile1	126						
Quartile2	125	1.009(0.421,2.420)	0.984	0.997(0.415,2.3940	0.994	0.844(0.257,2.773)	0.780
Quartile3	125	6.517(3.185,13.335)	<0.001	6.378(3.113,13.067)	<0.001	4.405(1.608,12.071)	0.004
Quartile4	125	66.417(29.766,148.199)	<0.001	67.069(29.980,150.039)	<0.001	48.061(13.638,169.371)	<0.001

Notes: Model 1: unadjusted; Model 2: adjusted for Age, Sex; Model 3: adjusted for Age, Sex, WBC, Neutrophil, Use of antibiotics, Examination time, Anesthesia, Nausea or vomiting, Bleeding, Lesion location, Cancer stage, Number of biopsies, Oxygen supplement after surgery.

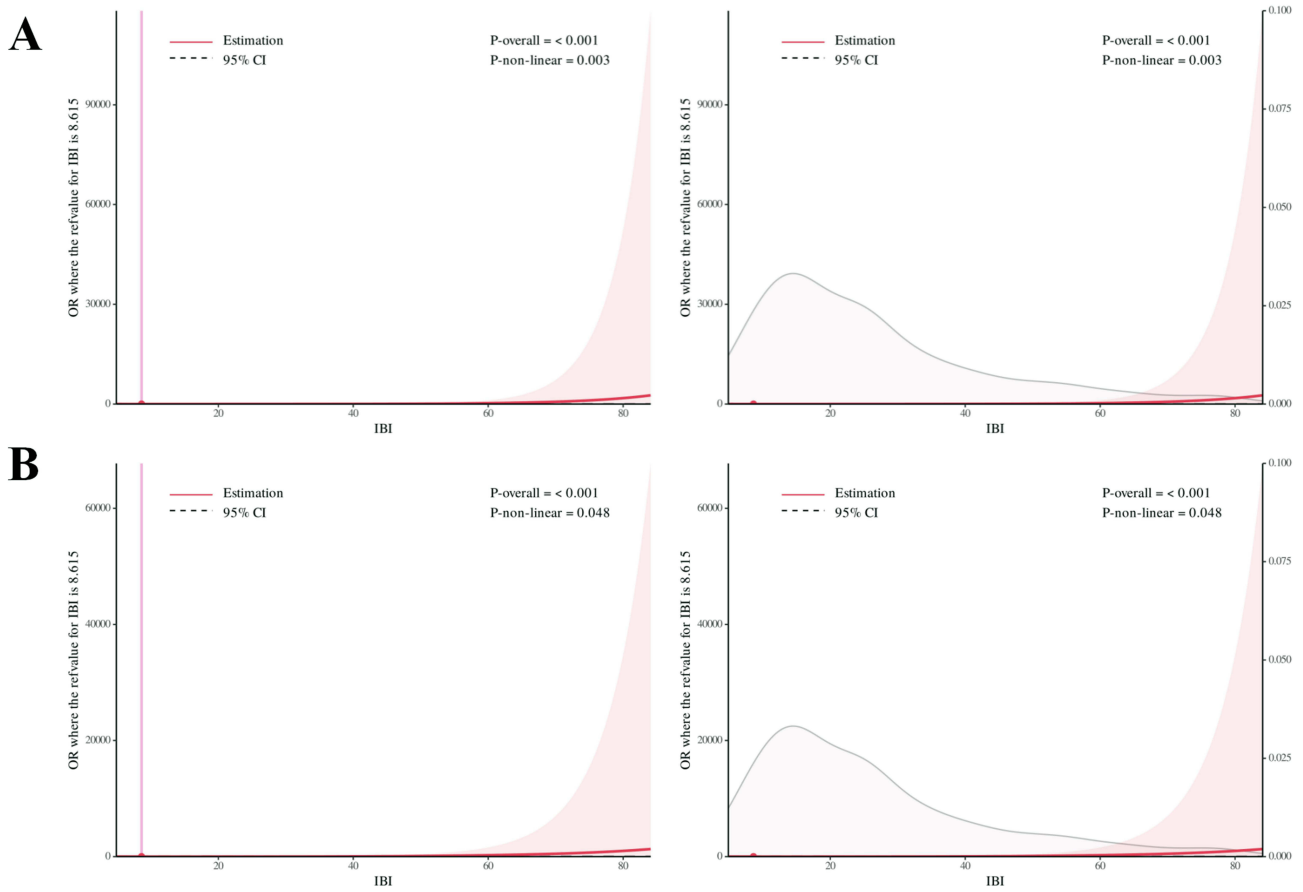

Figure 1 Restricted cubic spline curves showing the association between IBI and fever post-EBFB. (**A**) Unadjusted analysis of fever. (**B**) Adjusted analysis of fever. Adjustments were made for Age, Sex, WBC, Neutrophil, Use of antibiotics, Examination time, Anesthesia, Nausea or vomiting, Bleeding, Lesion location, Cancer stage, Number of biopsies, Oxygen supplement after surgery.

Variable Selection in the Cohort

LASSO regression serves as a compression estimation method that accomplishes variable selection and complexity adjustment through the formulation of an optimization objective function incorporating penalty terms. In this study, LASSO

Table 3 Subgroup Analyses for IBI With Risk of Fever Post-EBFB

Variables	n (%)	OR (95% CI)	*P*
All patients	501 (100.00)	1.13 (1.10 ~ 1.15)	<0.001
Gender			
Male	327 (65.27)	1.11 (1.08 ~ 1.14)	<0.001
Female	174 (34.73)	1.17 (1.12 ~ 1.23)	<0.001
Smoking			
Yes	174 (34.73)	1.10 (1.07 ~ 1.14)	<0.001
No	327 (65.27)	1.15 (1.11 ~ 1.19)	<0.001
COPD			
Yes	126 (25.15)	1.10 (1.06 ~ 1.15)	<0.001
No	375 (74.85)	1.14 (1.11 ~ 1.17)	<0.001
Use of antibiotics			
Yes	127 (25.35)	1.12 (1.07 ~ 1.17)	<0.001
No	374 (74.65)	1.13 (1.10 ~ 1.16)	<0.001

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Table 3 (Continued).

Variables	n (%)	OR (95% CI)	*P*
Use of NSAIDs			
Yes	71 (14.17)	1.14 (1.06 ~ 1.22)	<0.001
No	430 (85.83)	1.13 (1.10 ~ 1.15)	<0.001
Anesthesia			
General	86 (17.17)	1.24 (1.12 ~ 1.38)	<0.001
Local	415 (82.83)	1.12 (1.09 ~ 1.14)	<0.001
Nausea or vomiting			
Yes	92 (18.36)	1.14 (1.08 ~ 1.21)	<0.001
No	409 (81.64)	1.13 (1.10 ~ 1.15)	<0.001
Bleeding			
Yes	295 (58.88)	1.12 (1.09 ~ 1.15)	<0.001
No	206 (41.12)	1.15 (1.10 ~ 1.20)	<0.001
Histological type			
Adenocarcinoma	161 (32.14)	1.12 (1.08 ~ 1.16)	<0.001
Squamous cell carcinoma	170 (33.93)	1.14 (1.10 ~ 1.19)	<0.001
Small cell lung cancer	86 (17.17)	1.09 (1.04 ~ 1.14)	<0.001
Others	84 (16.77)	1.21 (1.11 ~ 1.33)	<0.001
Lesion location			
Left main bronchus	56 (11.18)	1.15 (1.06 ~ 1.24)	<0.001
Left upper lobar bronchi	72 (14.37)	1.10 (1.04 ~ 1.15)	<0.001
Left lower lobar bronchi	25 (4.99)	1.21 (1.03 ~ 1.42)	0.021
Right main bronchus	83 (16.57)	1.12 (1.06 ~ 1.18)	<0.001
Right upper lobar bronchi	82 (16.37)	1.11 (1.06 ~ 1.16)	<0.001
Right middle bronchus	66 (13.17)	1.19 (1.09 ~ 1.31)	<0.001
Right middle lobar bronchi	42 (8.38)	1.15 (1.05 ~ 1.27)	0.003
Right lower lobar bronchi	31 (6.19)	1.13 (1.04 ~ 1.23)	0.003
The trachea	44 (8.78)	1.15 (1.05 ~ 1.25)	0.002
Cancer stage			
Advanced	312 (62.28)	1.11 (1.08 ~ 1.14)	<0.001
Early	189 (37.72)	1.17 (1.12 ~ 1.23)	<0.001
Number of biopsies			
≥5	220 (43.91)	1.16 (1.11 ~ 1.21)	<0.001
<5	281 (56.09)	1.11 (1.08 ~ 1.14)	<0.001
Oxygen supplement after surgery			
Yes	276 (55.09)	1.13 (1.09 ~ 1.16)	<0.001
No	225 (44.91)	1.13 (1.10 ~ 1.17)	<0.001
Age quartile			
1	125 (24.95)	1.14 (1.08 ~ 1.20)	<0.001
2	125 (24.95)	1.11 (1.07 ~ 1.15)	<0.001
3	125 (24.95)	1.12 (1.08 ~ 1.17)	<0.001
4	126 (25.15)	1.16 (1.09 ~ 1.23)	<0.001
WBC quartile			
1	125 (24.95)	1.13 (1.07 ~ 1.18)	<0.001
2	125 (24.95)	1.17 (1.11 ~ 1.24)	<0.001
3	125 (24.95)	1.11 (1.07 ~ 1.15)	<0.001
4	126 (25.15)	1.12 (1.08 ~ 1.17)	<0.001
Neutrophil quartile			
1	125 (24.95)	1.13 (1.04 ~ 1.23)	0.004
2	125 (24.95)	1.24 (1.14 ~ 1.35)	<0.001
3	125 (24.95)	1.11 (1.06 ~ 1.15)	<0.001
4	126 (25.15)	1.09 (1.06 ~ 1.13)	<0.001

(*Continued*)

Table 3 (Continued).

Variables	n (%)	OR (95% CI)	*P*
CRP quantile			
1	125 (24.95)	1.03 (0.90 ~ 1.18)	0.676
2	125 (24.95)	1.22 (1.11 ~ 1.34)	<0.001
3	125 (24.95)	1.09 (1.02 ~ 1.16)	0.014
4	126 (25.15)	1.12 (1.05 ~ 1.19)	<0.001
Examination time quartile			
1	125 (24.95)	1.07 (0.99 ~ 1.16)	0.081
2	125 (24.95)	1.13 (1.07 ~ 1.19)	<0.001
3	125 (24.95)	1.12 (1.08 ~ 1.17)	<0.001
4	126 (25.15)	1.14 (1.08 ~ 1.20)	<0.001

regression was utilized to identify characteristic factors (Figure 2A and B) including Neutrophil, CRP, Examination time, Nausea or vomiting, Bleeding, Number of biopsies, Oxygen supplement after surgery. In contrast, utilizing the Boruta algorithm, an extension of the RF algorithm, enabled the identification of the actual feature set by accurately estimating the importance of each feature. The Boruta algorithm identified 7 key factors (Figure 2C), including WBC, Neutrophil, CRP, Examination time, Anesthesia, Nausea or vomiting, Bleeding. Subsequently, utilizing Venn diagrams, a comprehensive analysis led to the identification of 5 variables (Neutrophil, CRP, Examination time, Nausea or vomiting, Bleeding, Figure 2D) for the construction of the model.

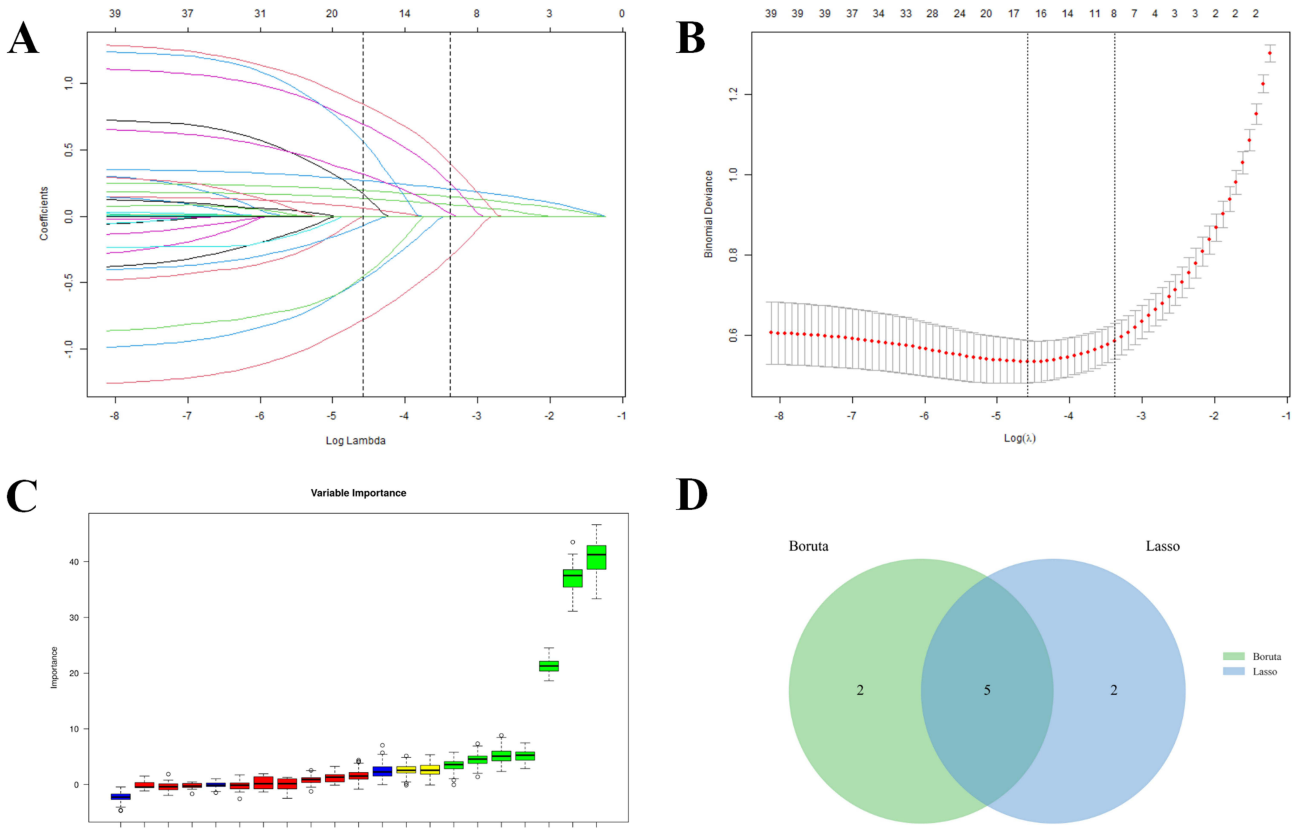

Figure 2 Predictor screening results. (**A**) LASSO regression model screening variable trajectories; (**B**) Factor screening based on the LASSO regression model, with the left dashed line indicating the best lambda value for the evaluation metrics (lambda. min) and the right dashed line indicating the lambda value for the model where the evaluation metrics are in the range of the best value by one standard error (lambda.1se); (**C**) Boruta. The horizontal axis shows the name of each variable, and the vertical axis represents the Z-score for each variable. The box plot illustrates the Z-score distribution of each variable during model computation. Green boxes represent important variables identified by the model, while red boxes indicate unimportant variables; (**D**) Venn analysis of the results of the above two algorithms.

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Development and Validation of a Nomogram for Fever Post-EBFB

We applied 5 selected clinical features (Neutrophil, CRP, Examination time, Nausea or vomiting, Bleeding; model 1) separately and combined them with IBI (model 2) to develop two predictive models. For the prediction model, the area under the ROC curve for the model 1 was 0.956 (95% CI, 0.937–0.974), and it was 0.956 (95% CI, 0.936–0.972) in the internal validation using bootstrapping (resampling times = 500), indicating moderate performance (Figure 3A and B). The area under the ROC curve for the model 2 was 0.958 (95% CI, 0.942–0.974), and it was 0.958 (95% CI, 0.941–0.972) in the internal validation using bootstrapping (resampling times = 500) (Figure 4A and B), The calibration curves of the models also showed good consistency (Figure 5A and B). Decision curves (Figure 6) showed that the fever post-EBFB were more accurately predicted using these models. In conclusion, the models have good predictive ability and the predictive performance of Model 2 is better than that of Model 1. Finally, the nomogram was generated based on the contributed weights of factors in model 2 (Figure 7). In the nomogram, each factor has a related score for its contribution to diagnostic success.

Discussion

Postoperative fever is a frequent complication following bronchoscopy, with an incidence rate reported to be approximately 10–20% according to relevant studies. However, surgical procedures and interventions performed via bronchoscopy can notably elevate the risk of postoperative fever.[11,12] Endobronchial forceps biopsy (EBFB) is a crucial diagnostic tool for lung cancer, yet patients who undergo this procedure often experience varying degrees of fever.[13,14] This fever can impose additional psychological stress on lung cancer patients and may impact their subsequent cancer treatment. Our focus is on identifying accurate and comprehensive fever post-EBFB related factors, using the simplest and most accessible indicators, and developing appropriate personalized treatment plans based on these predictive factors to improve and extend therapeutic interventions.

IBI are recently highlighted inflammatory indicators, which is defined as C-reactive protein × neutrophils/lymphocytes. C-reactive protein (CRP) is a key biomarker of systemic inflammation, widely used and readily accessible in clinical practice.[15–17] Elevated CRP levels are often associated with fever and inflammation. Neutrophils and lymphocytes are crucial components of blood inflammatory cells. Neutrophils, the predominant type of white blood cells, produce various cancer-

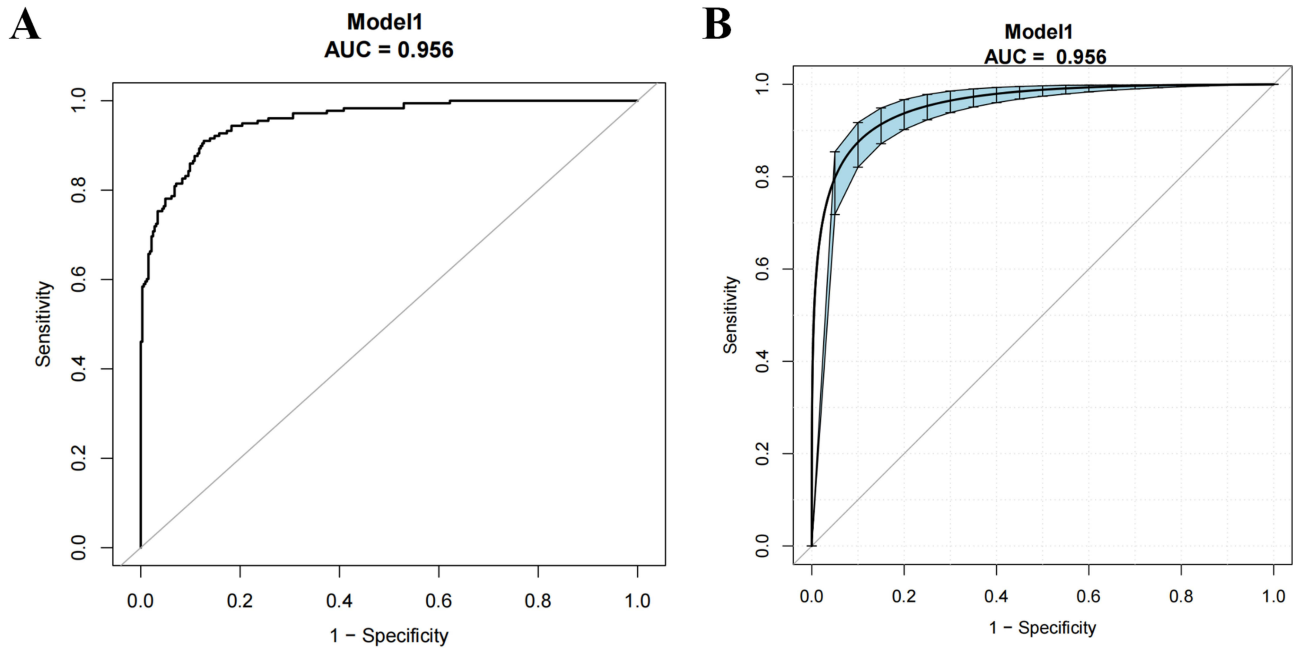

Figure 3 ROC validation of the model 1 prediction of the fever post-EBFB. The y-axis represents the rate of true positives for the risk prediction. The x-axis represents false positives for the risk prediction. The area under the curve represents the performance rate of the model. (**A**) shows AUC 0.956 (95% CI, 0.937–0.974) of the predictive model and (**B**) shows AUC 0.956 (95% CI, 0.936–0.972) of the internal validation with the bootstrap method (resampling times = 500). The dotted vertical lines represent 95% confidence interval.

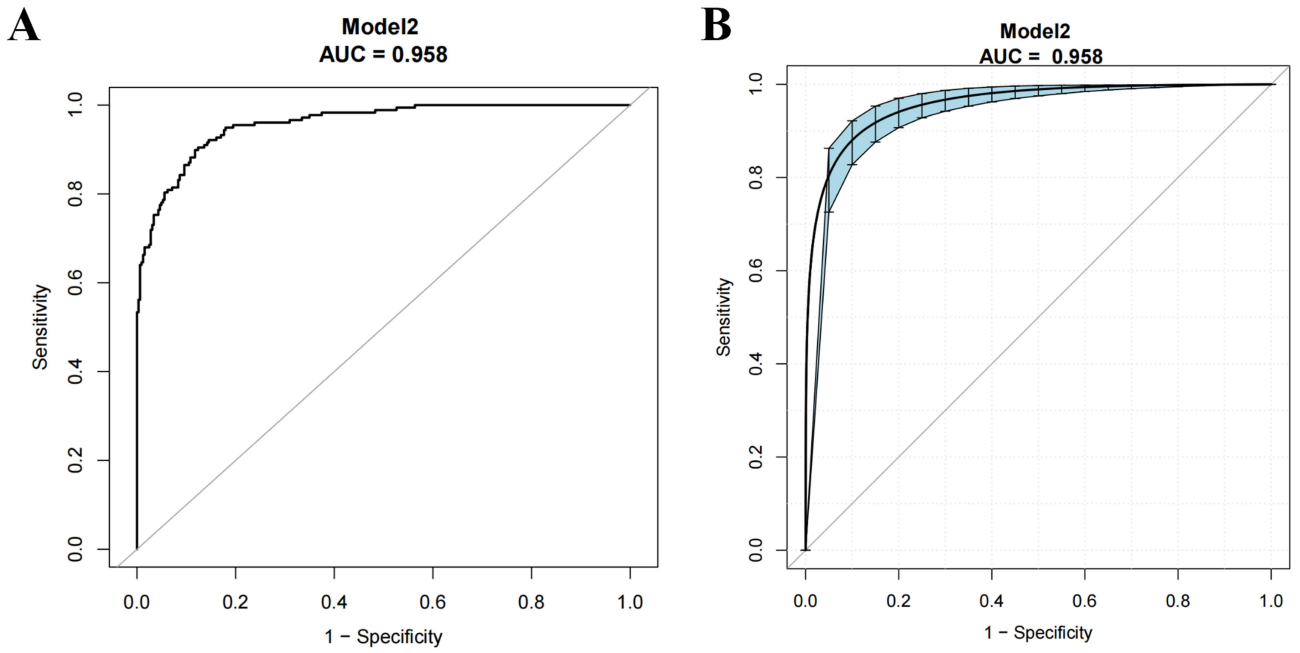

Figure 4 ROC validation of the model 2. (**A**) shows AUC 0.958 (95% CI, 0.942–0.974) of the predictive model and (**B**) shows AUC 0.958 (95% CI, 0.941–0.972) of the internal validation with the bootstrap method (resampling times = 500). The dotted vertical lines represent 95% confidence interval.

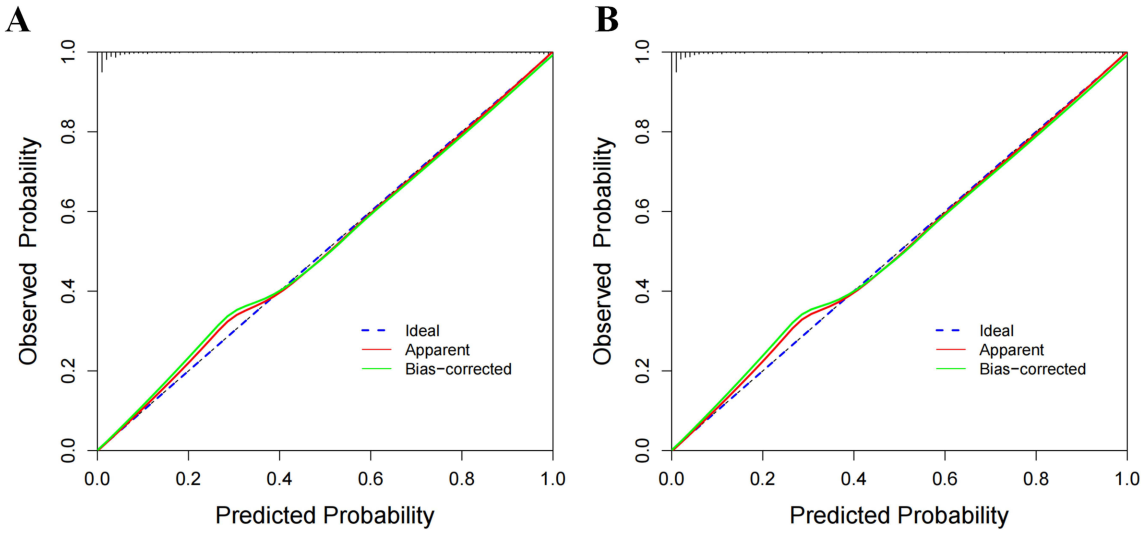

Figure 5 Calibration curves of the risk model prediction of the fever post-EBFB. The y-axis meant the actual diagnostic success. The x-axis meant the predicted diagnostic success. The blue line represents an ideal predictive model, and the solid red line shows the actual performance of the model 1 (**A**) and model 2 (**B**). The green line represents a bias-corrected performance.

promoting factors such as neutrophil elastase, matrix metalloproteinase 9 (MMP9), and vascular endothelial growth factor (VEGF). Activated by inflammatory stimuli, neutrophils contribute to chemotaxis, phagocytosis, intracellular killing, and adaptive immune regulation. Lymphocytes, on the other hand, play a vital role in tumor immune surveillance by inducing cytotoxic cell death and inhibiting tumor cell proliferation and growth, serving as the first line of defense against cancer. Numerous studies have shown that neutrophil/lymphocyte ratios are strongly linked to adverse outcomes in cancer patients. By integrating CRP, neutrophils, and lymphocytes, the Inflammatory-Based Index (IBI) leverages the strengths of these parameters to provide a comprehensive assessment of the body's inflammatory and immune status.[18–20] In our study, The results showed that IBI significantly impacted the occurrence of fever post-EBFB, and patients in the highest IBI quartile also

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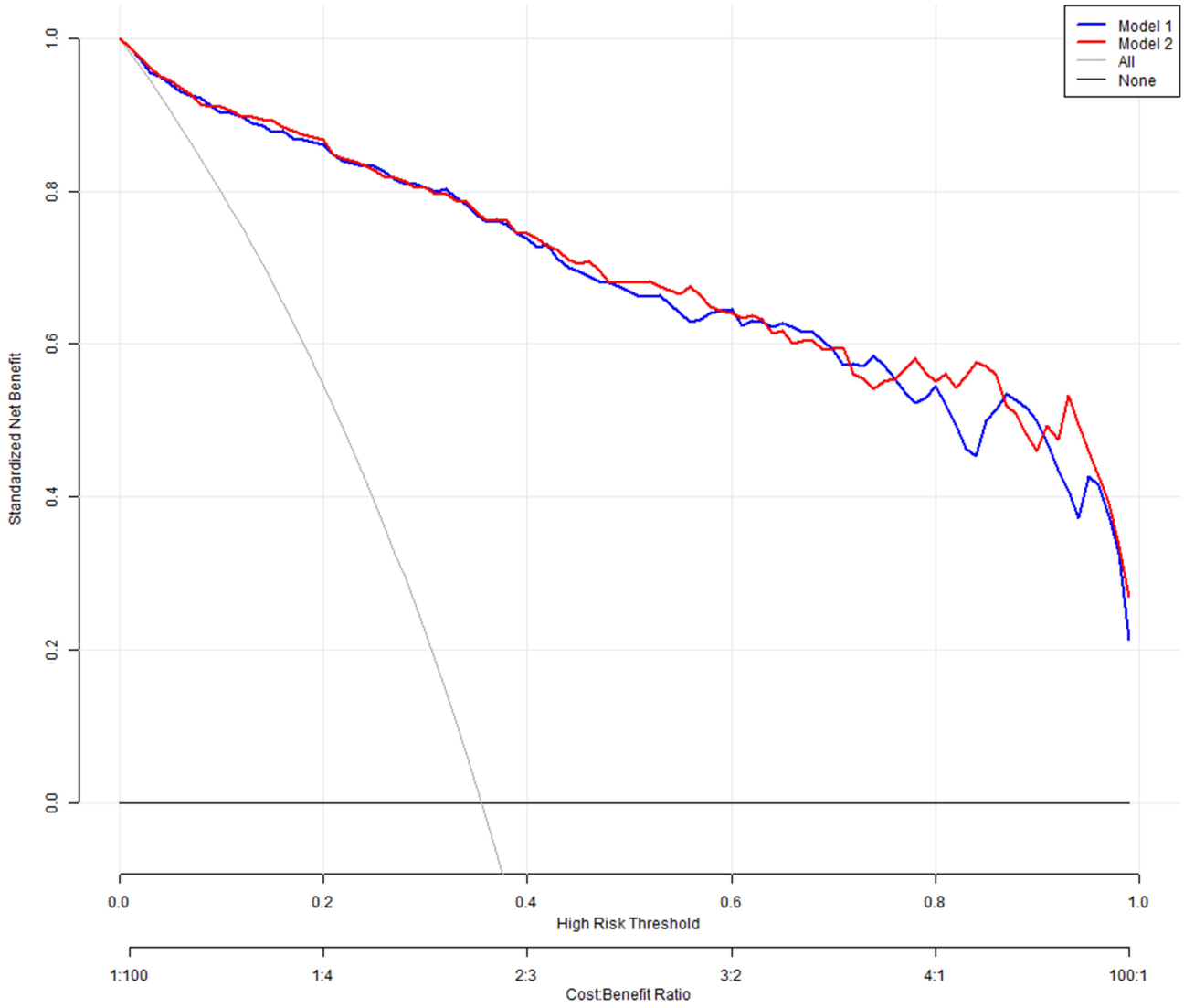

Figure 6 Decision curve of 2 predictive model. Net benefit was produced against the high risk threshold.

had a significantly higher risk of fever post-EBFB compared to those in the lowest quartile. We also observed a J-shaped relationship between IBI and fever post-EBFB. Specifically, when IBI exceeded 8.615, fever risk rose significantly. In addition, multivariable stratified analyses verified the association of IBI with risk of fever post-EBFB almost in all subgroups.

To verify the predictive performance of IBI and construct a simple and concise predictive model for fever post-EBFB, we developed two predictive models (5 clinical features selected by LASSO and Boruta separately and combined them with IBI). Both the two prediction model showed good discrimination ability and calibration. The decision curve based on this model revealed that the model to predict diagnostic rate would benefit when compared to either treat-all or treat-none strategies. We also compared the AUC of two models and the AUC of Model 2 is better than that of Model 1. In summary, these findings highlighted the importance of IBI as a predictor for fever post-EBFB. Finally, the nomogram including IBI was also constructed to facilitate the application of the model.

This study also has several limitations. Firstly, these models was constructed based on a single-center retrospective study, which inevitably suffered from confounding bias;. Secondly, an independent validation is very important for determining the clinical usefulness of a predictive model; therefore, whether the proposed model is applicable to other endoscopic centers needs further validation. Future studies should involve larger sample sizes, multicenter prospective studies, or randomized controlled trials (RCTs).

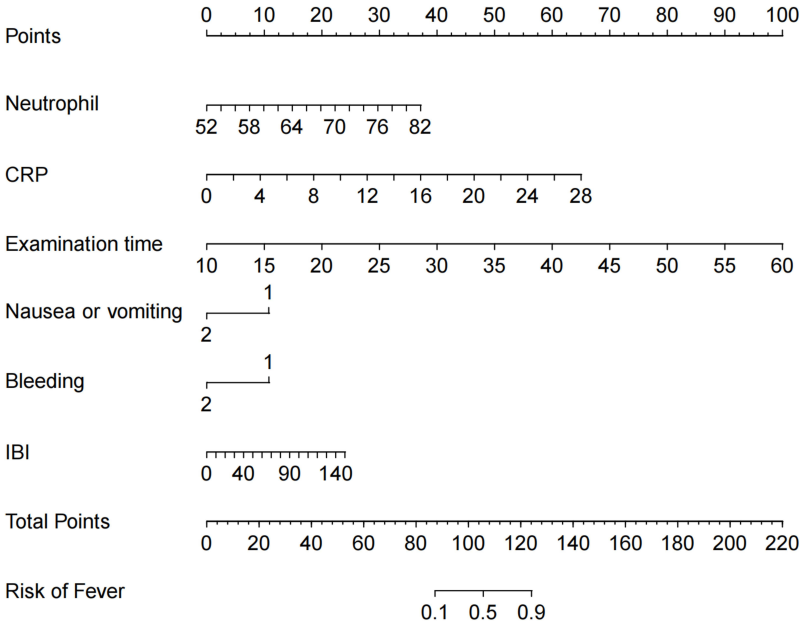

Figure 7 The nomogram for predicting diagnostic rate of the fever post-EBFB. (Nausea or vomiting 1 Yes, 2 No; Bleeding 1 Yes, 2 No).

Conclusion

In conclusion, the study verified the association of IBI with risk of fever post-EBFB. And explored the predictive performance of IBI. Finally a simple and concise nomogram including IBI was constructed to predict the fever post-EBFB. The robust performance of the model suggests its potential clinical utility in guiding treatment decisions and improving outcomes for patients. Further validation and refinement of the model could contribute to its integration into clinical practice for personalized care.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author (Minlong Zhang).

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the institutional ethics committee of the hospital (The Ethics Committee of 8th Medical Centre, Chinese PLA General Hospital, Beijing, China No. 202400207). Written informed consent was obtained from all participants before inclusion.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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