Machine learning–based construction of a clinical prediction model for hypercapnia during one-lung ventilation for lung surgery

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Article

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Abstract

In this study, we developed a clinical prediction model for hypercapnia during one-lung ventilation for lung surgery by machine learning. We analyzed the cases and intraoperative blood gases of 348 patients who had undergone lung surgery at Jiangxi Cancer Hospital from November 2019 to June 2021. We analyzed the factors that independently influence hypercapnia during one-lung ventilation for lung surgery by selecting the best variables through a combination of random forest and logistic regression stepwise selection (Step AIC). Thereafter, we used these factors to construct logistic regression models and a nomogram. Receiver operating characteristic curves were used to measure the predictive accuracy of the nomogram and its component variables, and the predictive probabilities of the nomogram were compared and calibrated by calibration curves. We used bootstrap to verify the internal validation method to judge the reliability of the model, and we employed decision curve analysis (DCA) for clinical decision analysis. The independent influencing factors for hypercapnia during one-lung ventilation for lung surgery were age, gender, and one-lung ventilation position. We established the hypercapnia during one-lung ventilation for lung surgery logistic regression model: −5.421 + 0.047 × age + 1.8 × gender (=1) + 0.625 × one-lung ventilation position (=1). The prediction accuracy probability of the nomogram is 0.7457 (95% confidence interval [0.6916, 0.7998]). The prediction model showed good agreement between the calibration curve and the ideal predicted value, and bootstrap internal validation showed the area under the curve was 0.745 and the C-index was 0.742. DCA indicated that the model has some clinical value. In this study, three independent influences on hypercapnia during one-lung ventilation were established. We constructed an individualized model for predicting hypercapnia during one-lung ventilation for pulmonary surgery, as well as the first internally validated predictive model and nomogram for hypercapnia during one-lung ventilation for pulmonary surgery, both of which have good predictive and calibration properties and can provide some clinical guidance value.

Introduction

Lung cancer is the leading cause of cancer-related deaths in North America and other developed countries[1]. Lung cancer deaths account for the highest number of cancer-related deaths in the United States, with an average five-year survival rate of 15%[2]. Surgical resection plays a very important role in the treatment of lung cancer[3]. To enable surgical resection, it is necessary to cause the affected lung to atrophy, but unilateral lung atrophy cannot be achieved without the technical support of one-lung ventilation. One-lung ventilation techniques are widely used in thoracic surgery, including lung surgery, esophageal surgery, and mediastinal surgery [4]. As the advantages of one-lung ventilation became apparent, the technique started to be widely used in areas other than thoracic surgery[5]. However, some side effects are inevitable with the use of one-lung ventilation. When switching from two-lung to one-lung ventilation, intrapulmonary shunts increase and oxygenation decreases, which can raise the probability of hypoxemia[6]. A retensioned and atrophied lung at the end of one-lung ventilation can lead to ischemia–reperfusion injury, causing additional damage to the lung[7]. One-lung ventilation is also more likely to elevate CO_2 and more likely to lead to the development of hypercapnia. In a retrospective cohort study, hypercapnia was found to occur in 50% of children during one-lung ventilation[8]. Hypercapnia has a protective effect on the lungs. In a study by Lee et al., hypercapnia was found to improve PaO_2 and O_2 carriage and oxygenation during one-lung ventilation[9]. Animal experiments revealed that hypercapnia may achieve a reduction in ventilator-associated lung injury by attenuating inflammatory responses and biochemical mechanisms of injury[10]. One study found that hypercapnia achieved lung protection by inhibiting the NF-κB pathway in a variety of lung injury models[11]. However, hypercapnia also has certain detrimental effects. Hypercapnia may impair alveolar epithelial cell function through a pH non-dependent mechanism involving Na,K-ATPase endocytosis, thereby impairing the regression of pulmonary edema[12]. It has been shown that persistent hypercapnia adversely affects patients with acute exacerbations of chronic obstructive pulmonary disease[13].

This suggests that hypercapnia has some clinical significance and research value. However, a predictive model for hypercapnia during one-lung ventilation in pulmonary surgery has not been constructed, so our research team chose to conduct an exploratory study on this topic. The aim of this study was to develop a predictive model for hypercapnia during one-lung ventilation for pulmonary surgery, which will provide some clinical guidance.

Methods

Data source

This study was a clinical review and analysis of 348 patients who had undergone lung surgery at Jiangxi Cancer Hospital from November 2019 to June 2021. The surgical indications were as follows: patients with occupying lesions in the lung, suspected malignant tumors, and in whom conservative treatment was ineffective. The surgical procedures were performed by our senior surgeons, and the anesthetic procedures were performed by our senior anesthesiologists. This study was conducted in accordance with the Declaration of Helsinki. All data were anonymous and retrospective.This study was conducted in accordance with relevant guidelines and regulations and was approved by the Medical Ethics Committee of Jiangxi Cancer Hospital. Due to the retrospective nature of the study, the Medical Ethics Committee of Jiangxi Cancer Hospital approved a waiver of the requirement for informed consent.

Inclusion and discharge criteria

Inclusion criteria were as follows: (1) greater than 18 years of age and less than 85 years of age. (2) Patients with ASA classifications I–III. (3) Patients undergoing lung surgery.

The exclusion criteria were as follows: (1) Patients with ASA grade IV. (2) Patients with severe heart failure. (3) Patients who are unable to breathe on their own, and patients on ventilator maintenance therapy. (4) Patients in preoperative coma. (5) Patients with severe preoperative electrolyte imbalance and acid-base imbalance.

Hypercapnia

Hypercapnia is defined as meeting at least one of the following criteria: a partial pressure of carbon dioxide ($PaCO_2$) of ≥ 45 mmHg on ambulatory blood pressure monitoring, or a mean $PaCO_2$ of ≥ 47 mmHg at night[14]. $PaCO_2$ > 45 mmHg can be defined as hypercapnia[15,16].

Data collection and study covariates

The following information were collected in this study as study variables and baseline information: (1) age, (2) gender, (3) weight, (4) one-lung ventilation position, (5) one-lung ventilation time, (6) lung function, (7) minute ventilation, and (8) $PaCO_2$.

Screening of variables

Initially, variable screening was performed using random forest, an integrated approach that provides estimates of predictive models and variable importance[17]. Random forest algorithms have been widely used in various fields of medicine, playing roles in facilitating cardiovascular research[18–20]and also in the field of cancer[21]. The best variables were then selected using logistic regression stepwise selection (Step AIC)[22].

Logistic regression model establishment and construction of nomogram

Multivariate logistic regression was used to filter and compare variables, and the most important variables were selected by comprehensive random forest variable screening, from which the logistic regression model and the nomogram were constructed. The nomogram was developed by integrating the selected significant variables using the final logistic regression model. The nomogram can be fitted to the probability of clinical events by combining key variables[23].

ROC curves, calibration curves, and internal validation of models

The receiver operating characteristic (ROC) curve was used to measure the recognition ability of the nomogram. Calibration plots were generated to check the predictive agreement between the probabilities predicted by the nomogram and the actual results, and 1,200 bootstrap resamples were used in the calibration curve. In the internal validation, bootstrap provided stable estimates with low bias and was effective in predicting the internal validity of logistic regression[24]. It has also been used in clinical model building; for example, bootstrapping served as an internal validation in a study on acquired premature ejaculation[25].

Clinical decision curve building

Subsequently, DCA was used to assess the clinical utility of the model. Clinical decision analysis can be helpful in clinical settings to determine the pros and cons of decisions by predictive models[26]. DCA is widely used in the medical field. For example, one study showed that in urology, DCA curves can serve as a good judge of predictive models for decision making[27].

Statistical analysis

Nonparametric tests (Mann–Whitney *U* test or Kruskal–Wallis test) were used to analyze data with non-normal distributions or heterogeneous variances. Categorical data were compared using Pearson's chi-squared tests. The statistical software used for data analysis and model construction was R for Windows, version 4.131, and SPSS 25.

Ethics approval and consent to participate

This study was conducted in accordance with relevant guidelines and regulations and was approved by the Medical Ethics Committee of Jiangxi Cancer Hospital. Due to the retrospective nature of the study, the Medical Ethics Committee of Jiangxi Cancer Hospital approved a waiver of the requirement for informed consent.

Results

Study enrollment analysis process

The flowchart for the enrollment of this study is shown in Fig. 1. In total, 400 patients underwent lung surgery from November 2019 to June 2021, but 52 were unsuitable for this study due to severe electrolyte imbalance ($n = 3$), severe acid–base imbalance ($n = 3$), severe heart failure ($n = 1$), and intraoperative blood gas analysis not being performed ($n = 45$). The remaining 348 patients were included in the experimental study, among whom 96 had hypercapnia and 252 had non-hypercapnia.

Table analysis of clinical baseline characteristics

Between the two patient groups, the differences in the following variables were statistically significant: age ($p = 0.001$), weight ($p = 0.01$), gender ($p = 0.001$), one lung ventilation time (min) ($p = 0.409$), and pulmonary function ($p = 0.047$) (Table 1).

Comprehensive variable screening and construction of logistic regression models

Random forest and preliminary variable screening were applied first. The results are shown in Fig. 2. A larger value of MeanDecreaseAccuracy or MeanDecreaseGini reflects the higher importance of the variable. MeanDecreaseAccuracy indicated that gender, age, one-lung ventilation position, minute ventilation, one-lung ventilation time, weight, and pulmonary function had progressively decreasing importance. MeanDecreaseGini indicated that age, weight, one-lung ventilation time, minute ventilation, gender, one-lung ventilation position, and pulmonary function had progressively decreasing importance.

Through further analysis of variable selection using logistic regression analysis and stepwise (stepAIC) selection, the best variables selected by stepwise (stepAIC) selection were gender, age, and one-lung ventilation position. The first three quantities of MeanDecreaseAccuracy in random forest variable selection were consistent. The logistic regression model constructed with gender, age, and one-lung ventilation position had an AIC of 363. The logistic regression model constructed with age, weight, and one-lung ventilation time had an AIC of 393. The smaller the AIC value, the closer the estimated probability distribution is to the true distribution, the more stable the model is, and the better the prediction effect is. Therefore, the logistic regression model constructed with gender, age, and one-lung ventilation position was the most stable model and had the best prediction effect.

Table 2 shows the OR values, 95% confidence intervals (CIs), and p-values for each variable in the logistic regression model, where $p < 0.05$ is statistically significant. Figure 3(A) shows the visualization of the forest plot for each variable. The following variables were independently predicted in the hypercapnia risk model:

1. age ($p = 0.002$, OR = 1.047, 95% CI [1.016, 1.078]);
2. Gender = 1 ($p < 0.001$, OR = 5.693, 95% CI [2.844, 11.394]);
3. one-lung ventilation position = 1 ($p = 0.019$, OR = 1.888, 95% CI [1.111, 3.209]).

Hence, we constructed logistic regression models for these three variables. The OR values, 95% CIs, and p-values of the screening variables in the final logistic, also shown in Table 3, were as follows:

1. age ($p = 0.001$, OR = 1.048, 95% CI [1.02, 1.078]);
2. gender = 1 ($p < 0.001$, OR = 6.051, 95% CI [3.209, 11.41]);
3. one-lung ventilation position = 1 ($p = 0.019$, OR = 1.868, 95% CI [1.106, 3.154]).

Figure 3(B) shows the visualization of the forest plot for the screening variables.

Combined with Table 4, the result of the Hosmer–Lemeshaw test of significance was > 0.05, indicating a stable and well-fitting model.

The final established model is as follows: $-5.421 + 0.047\text{age} + 1.8\times\text{gender}\ (= 1) + 0.625\times\text{one-lung ventilation position}\ (= 1)$.

Construction of nomogram

The nomogram was constructed based on the final established logistic regression model. As shown in Fig. 4, the nomogram contains all independent factors that can significantly affect hypercapnia from the logistic regression model. A valid intuitive scoring scale was established based on the dominance ratio (OR) values of the risk factors. By summing the scores associated with each variable, the probability of hypercapnia can be predicted.

Results of the ROC curve and calibration curve

As shown in Table 5 and Fig. 5, the prediction of our constructed nomogram was 0.7457 (95% CI [0.6916, 0.7998]), which was higher than the prediction of any single factor in the nomogram (i.e., age, gender, and one-lung ventilation position), reflecting the good prediction of our nomogram. Furthermore, as shown in Fig. 6, calibration curves indicated good agreement between the nomogram and the actual situation.

Internal validation

Bootstrap was used as the internal validation method. The number of iterations was 1000, the average AUC was 0.745, and the average C-index was 0.742, showing that the model has good internal validation results with good predictability and stability.

Clinical decision curve results

DCA was conducted for the nomogram including age, gender, and one-lung ventilation position, and the results, shown in Fig. 7, indicate that the nomogram has some clinical benefit.

Discussion

Hypercapnia is often present in one-lung ventilation and has both pros and cons. Moderate hypercapnia may be a favorable condition in some specific cases and may play a role in improving blood flow in circulatory shock[28]. In patients with acute respiratory distress syndrome, low tidal volume ventilation with permissive hypercapnia can play a role in reducing mortality[29]. It has been shown that hypercapnia can affect the neuroelectrical activity of the brain[30]. In a clinical trial, hypercapnia was found to increase myocardial blood flow to some extent[31]. There is also a negative side to hypercapnia, with some clinical studies illustrating that in patients with acute respiratory distress syndrome, severe hypercapnia is an independent risk factor and more likely to lead to death[32]. Mild hypercapnia has also been found to impair microvascular function[33]. Elevated carbon dioxide levels can impair alveolar epithelial cell function[34]. Therefore, it is important to screen the independent influencing factors affecting hypercapnia and to construct a predictive model for hypercapnia during one-lung ventilation so that clinical guidance on appropriate preventive measures can be developed.

In this study, the best variables were selected by random forest and logistic regression stepwise selection (Step AIC), and the OR values of the variables were visualized by forest plots. Forest plots are widely used in the field of meta-analysis since they allow data to be effectively visualized. For example, forest plots have been utilized in studies on the risk of malaria infection and endemic Burkitt's lymphoma[35], bladder cancer[36], and rheumatoid arthritis[37]. Next, logistic regression models were constructed by screening the best variables. The final model was $-5.421 + 0.047\text{age} + 1.8 \times \text{gender} (= 1) + 0.625 \times$ one-lung ventilation position (= 1).

The present study found factors associated with the occurrence of hypercapnia during one-lung ventilation for lung surgery, which included age, gender, and one-lung ventilation position. The probability of hypercapnia occurring during one-lung ventilation was positively correlated with age. In a study of chronic obstructive pulmonary disease and hypercapnia, chronic obstructive pulmonary disease was found to occur at a greater age in the hypercapnia group[38]. It has been shown that the cerebral vasodilatory response to hypercapnia decreases with increasing age, along with a decrease in prefrontal cortex oxyhemoglobin[39]. Therefore, when dealing with older patients undergoing pulmonary surgery, we need to consider some of the side effects of hypercapnia so that appropriate intraoperative management and intraoperative ventilation measures can be taken to reduce the adverse effects of hypercapnia. Gender is also an independent influencing factor in the occurrence of hypercapnia during one-lung ventilation for lung surgery. It has been shown that young women have increased muscle sympathetic activity during hypercapnia but an attenuated increase in ventilation per minute[40]. This suggests that gender influences the effects of hypercapnia on sympathetic and chemoreceptors. In the current study, it was found that male patients had a higher probability of hypercapnia during pulmonary surgery on a single lung. The probability of hypercapnia was also found to be affected differently in the current study when the left and right lungs were ventilated with one-lung ventilation. The probability of hypercapnia was approximately 1.86 times higher in the left lung than in the right lung when one-lung ventilation was performed. Few international studies have investigated the effect of one-lung ventilation in the left and right lungs on the occurrence of hypercapnia, which is a new finding in the present study. We will further elucidate the possible mechanism of the effect of one-lung ventilation position on the occurrence of hypercapnia in a follow-up study.

We constructed a nomogram based on the key variables of the composite screening. The nomogram can show the proportion of variables in the prediction model and the probability of the prediction model through score visualization. Nomograms have been widely used in various fields of medicine, such as colorectal cancer[41], liver cancer[42], lung cancer[43], endometrial sarcoma[44], and breast cancer[45]. The prediction of our nomogram was 0.7457 (95% CI [0.6916, 0.7998]), reflecting a good predictive property. The calibration curve plots indicated the constructed model was in good agreement with the actual situation. We validated the model by internal validation using the bootstrap method; the number of iterations was 1000, the average AUC was 0.745, and the average C-index was 0.742, showing that the model had good internal validation results, with good predictive outcome and stability. Finally, we plotted the DCA, which showed that the model had some clinical benefit. There were some limitations in this experiment, and only internal validation of the model was performed, not external validation.

In conclusion, this study identified three independent influencing factors on the occurrence of hypercapnia during one-lung ventilation for lung surgery, namely, age, gender, and one-lung ventilation position. This study was the first to analyze the effect of left and right position of one-lung ventilation on hypercapnia, finding that the left lung was more prone to hypercapnia during one-lung ventilation. The nomogram of the prediction model was also established and shown to have good prediction and calibration. In addition, DCA and clinical decision analysis were conducted. It is hoped that our predictive model can assist with clinical decision making in the future.

Declarations

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Huaping Xiao planned and supervised the research .Yiwei Fan,He contributed to conception and design,data acquisition,and manuscript drafting.Ting Ye and Tingting Huan collected data.All authors drafted the final manuscript.All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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Tables

Table 1: Patient Baseline Characteristics Table

Variables	Hypercapnia patients=1 (N=96)	Non-hypercapnia patients=0 (N=252)	p
age,(years)	63(56-68)	59(50-66)	0.001
weight	61.5(53-68.5)	57(52-65)	0.01
One.lung.ventilation.time(min)	172.5(120-210)	152(120-200)	0.409
minute ventilation ml/min	6000(5600-7162.5)	6000(5237.5-7125)	0.232
gender,n(%)			
female=0	14(14.6)	124(49.2)	<0.001
male=1	82(85.4)	128(50.8)	
Pulmonary.function			
abnormal=1	25(26)	42(16.7)	0.047
normal=0	71(74)	210(83.3)	
one.lung.ventilation.position			
right=0	35 36.5	117 46.4	0.094
left=1	61 63.5	135 53.6	

Table 2: Variables in logistic regression analysis

Variables	OR (95% CI)	P value
age	1.047(1.016-1.078)	0.002
gender(male:1 vs female:0)	5.693(2.844-11.394)	<0.001
one.lung.ventilation.position (left:1 vs right:0)	1.888(1.111-3.209)	0.019
weight	1.025(0.995-1.055)	0.104
Pulmonary.function (abnormal:1 vs normal:0)	1.271(0..658-2.455)	0.476
One.lung.ventilation.time	1.001(0.998-1.004)	0..437
minute.ventilation	1.000(1.000-1.000)	0.253

Table 3: Screening variables in the final logistic regression analysis

Variables	OR (95% CI)	P value
age	1.048(1.020-1.078)	0.001
gender(male:1 vs female:0)	6.051(3.209-11.410)	<0.001
one.lung.ventilation.position (left:1 vs right:0)	1.868(1.106-3.154)	0.019

Table 4: Hosmer-Lameshaw test

Hosmer-Lameshaw test			
1	5.245	8	.731

Table 5: The discriminative ability of the prediction model

Constituted variables	AUC	95%CI
Age+gender+one.lung.ventilation.position	0.7457	0.6916-0.7998
age	0.612	0.551-0.673
gender	0.673	0.614-0.733
one.lung.ventilation.position	0.55	0.483-0.617

Figures

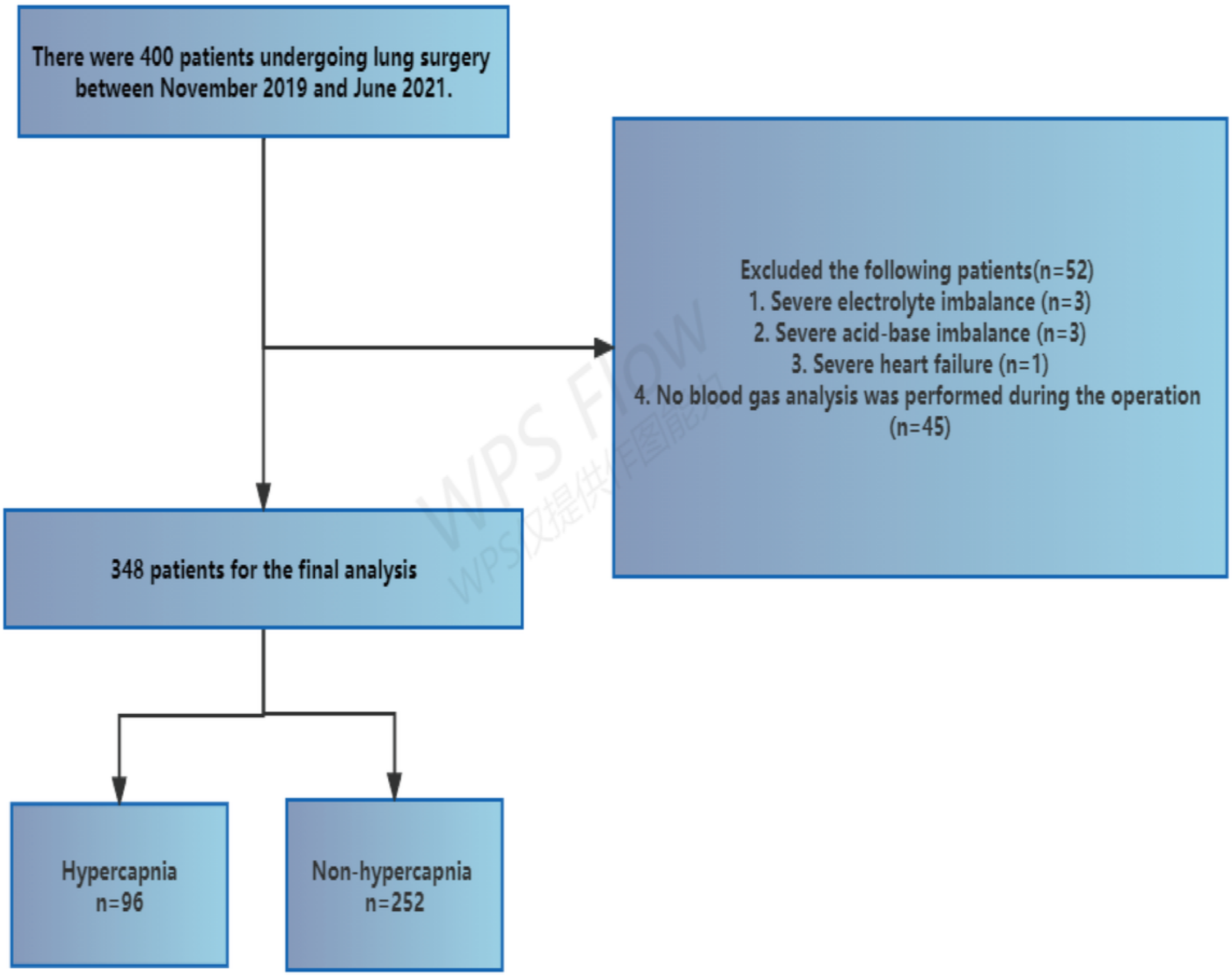

Figure 1 Study design and flow chart of the enrollment process

Figure 1

See image above for figure legend.

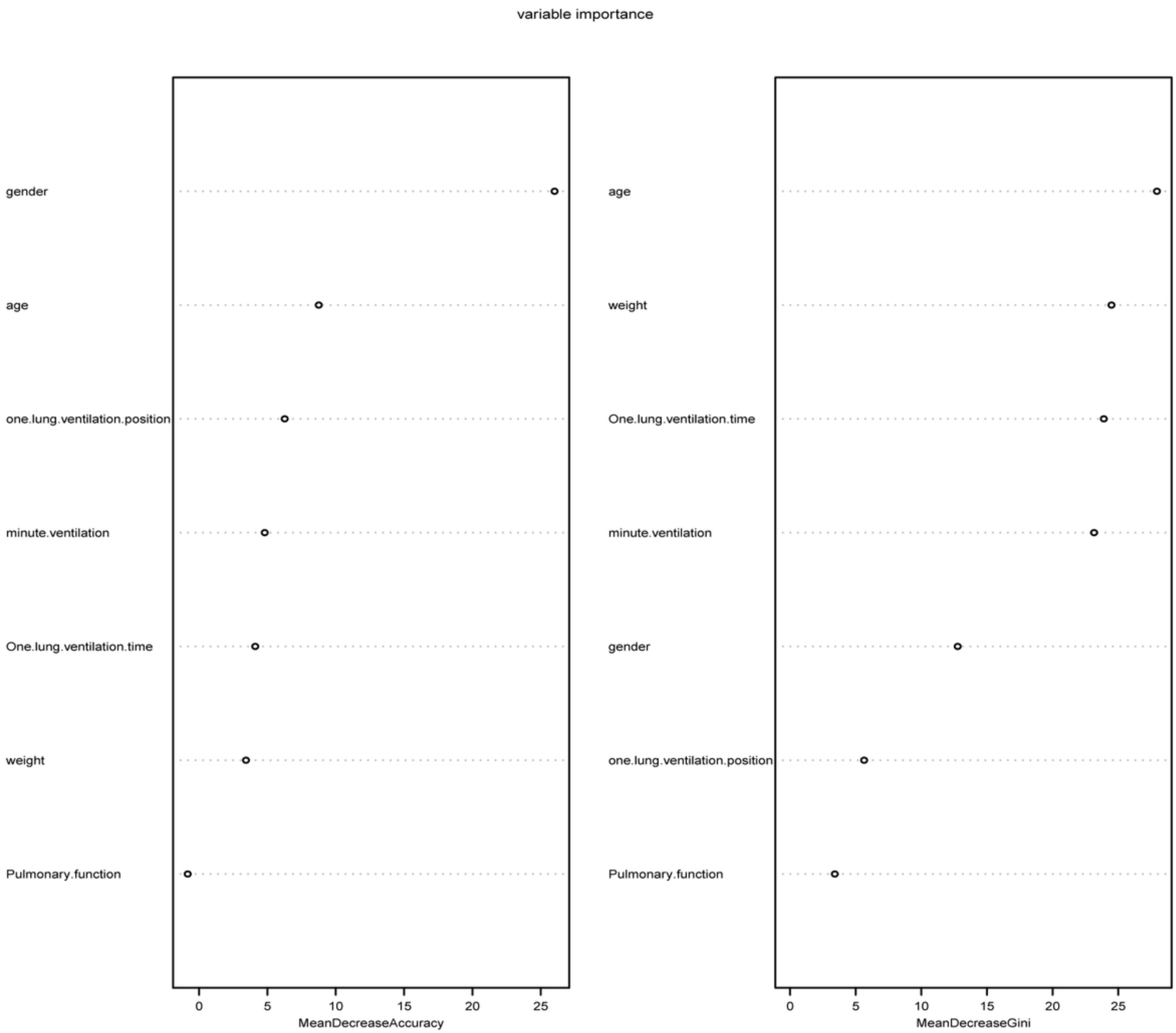

Figure 2 Mean Decrease Accuracy : The value of a variable becomes a random number, and the degree to which the accuracy of random forest predictions is reduced. The larger the value, the more important the variable is. Mean Decrease Gini : Compare the importance of variables by calculating the effect of each variable on the heterogeneity of observations at each node of the classification tree. The larger the value, the more important the variable is.

Figure 2

See image above for figure legend.

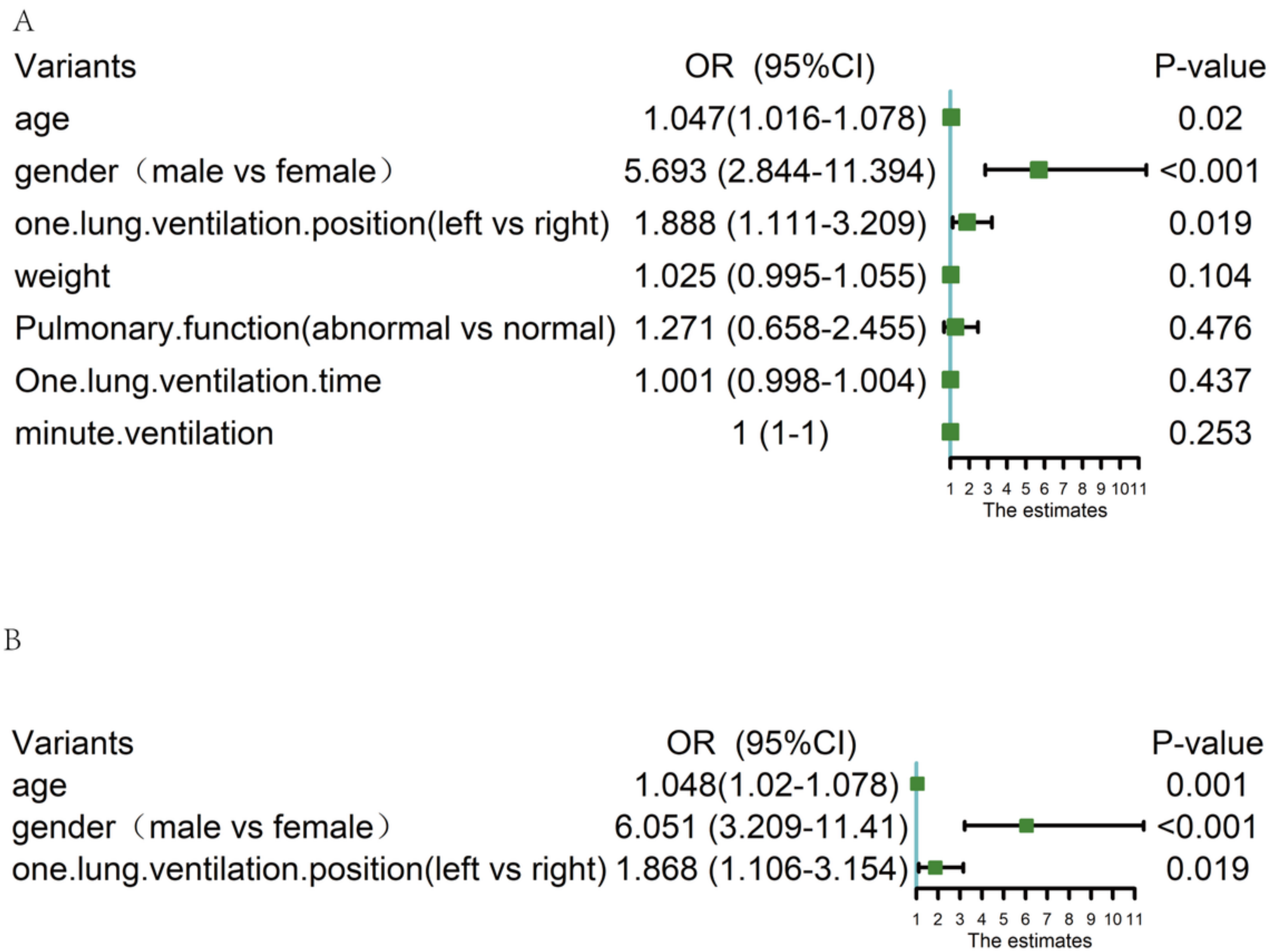

Figure 3（A）The OR, 95% CI, and p-values for age、gender、one.lung.ventilation.position、weight、Pulmonary.function、One.lung.ventilation.time、minute ventilation in a full-variable logistic regression model are shown as forest plots.（B)The OR, 95% CI, and p-value for age、gender、one.lung.ventilation.position are shown in a forest plot in the final logistic regression model.

Figure 3

See image above for figure legend.

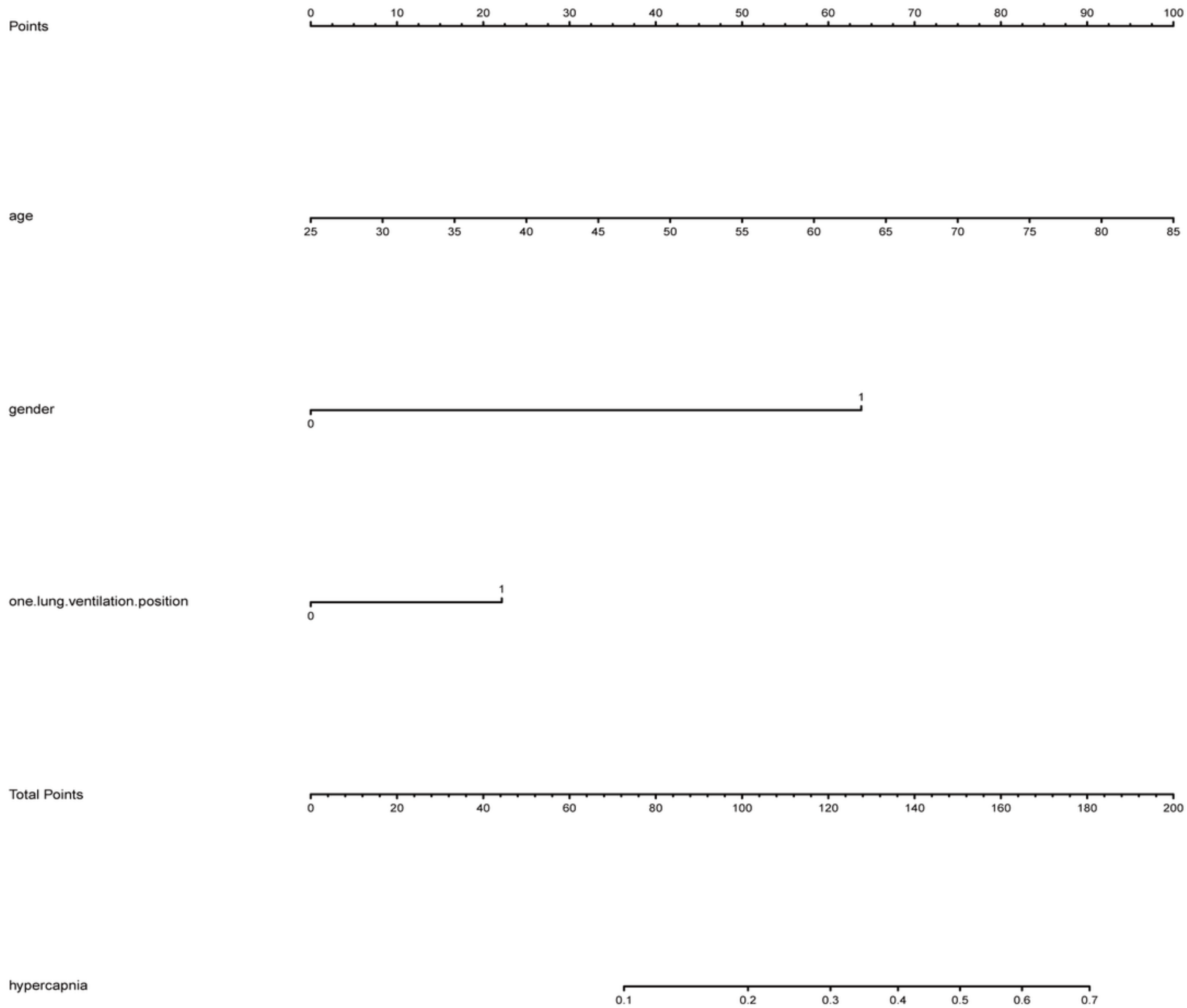

Figure 4 Plot of predicted probability of hypercapnia during one-lung ventilation during lung surgery.
To use this model, first determine the position of each variable on the corresponding axis. Second, draw a line on the point axis to represent the number of points, then add up the points for all variables. Third, a line was drawn from the total points axis at the lower line of the nomogram to determine the incidence of hypercapnia during one-lung ventilation for lung surgery.

Figure 4

See image above for figure legend.

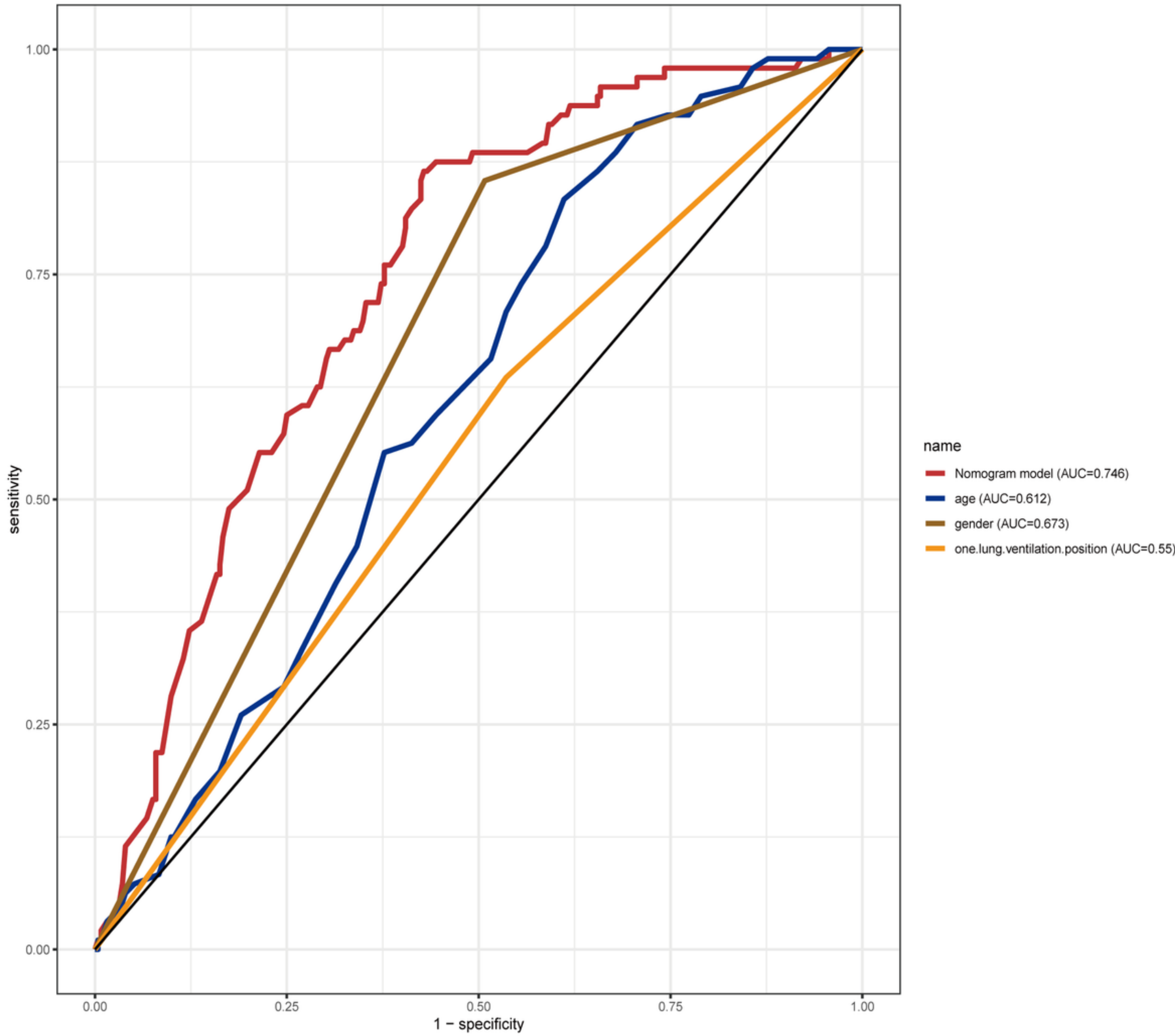

Figure 5 Red represents the ROC curve of the nomogram and its constituent variables, blue represents the ROC curve of age, brown represents the ROC curve of gender, and yellow represents the ROC curve of one.lung.ventilation.

Figure 5

See image above for figure legend.

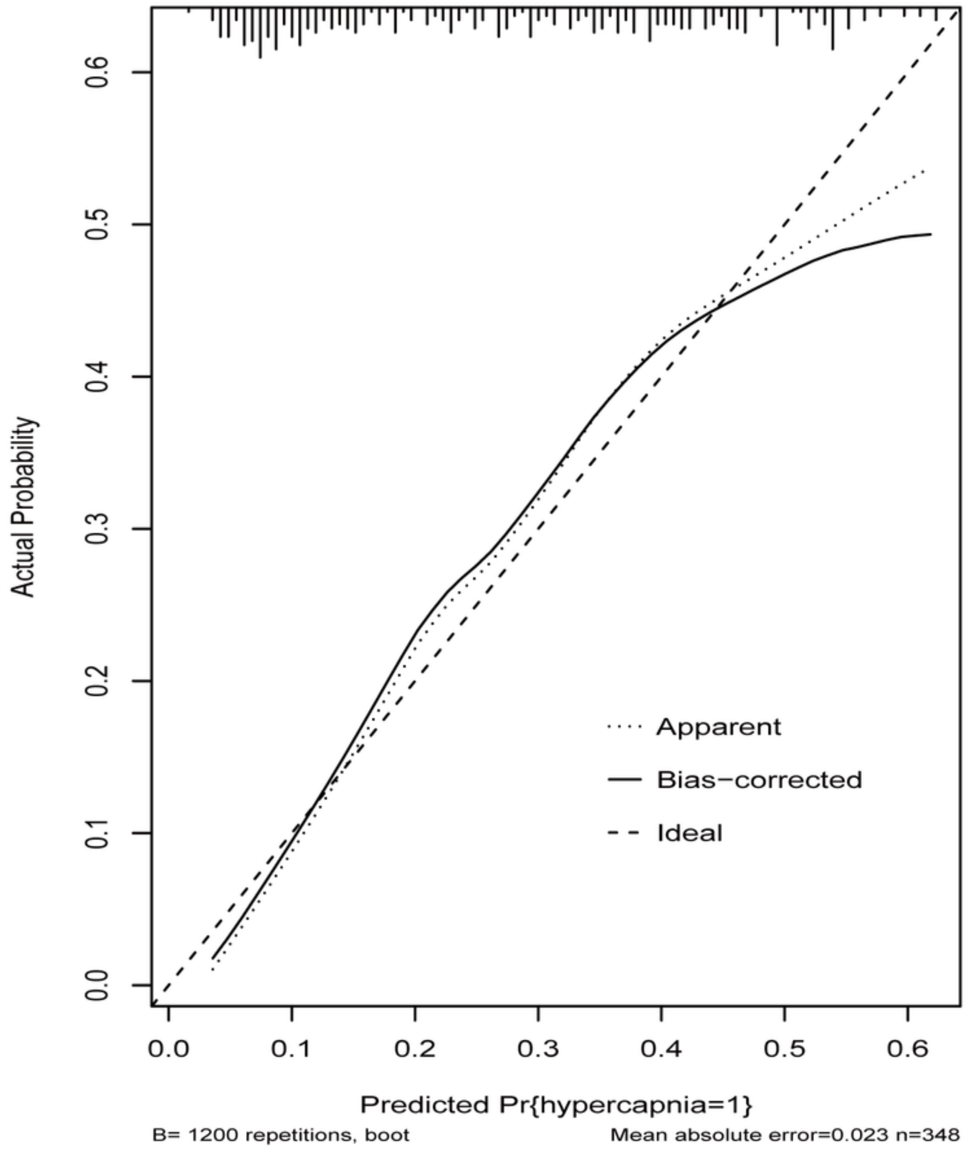

Figure 6 Calibration plot of the nomogram.
"ideal" represents the representation of an ideal nomogram.
"Apparent" represents the apparent accuracy of the nomogram without correction for overfitting.
"Bias-corrected" represents the bootstrap corrected nomogram.

Figure 6

See image above for figure legend.

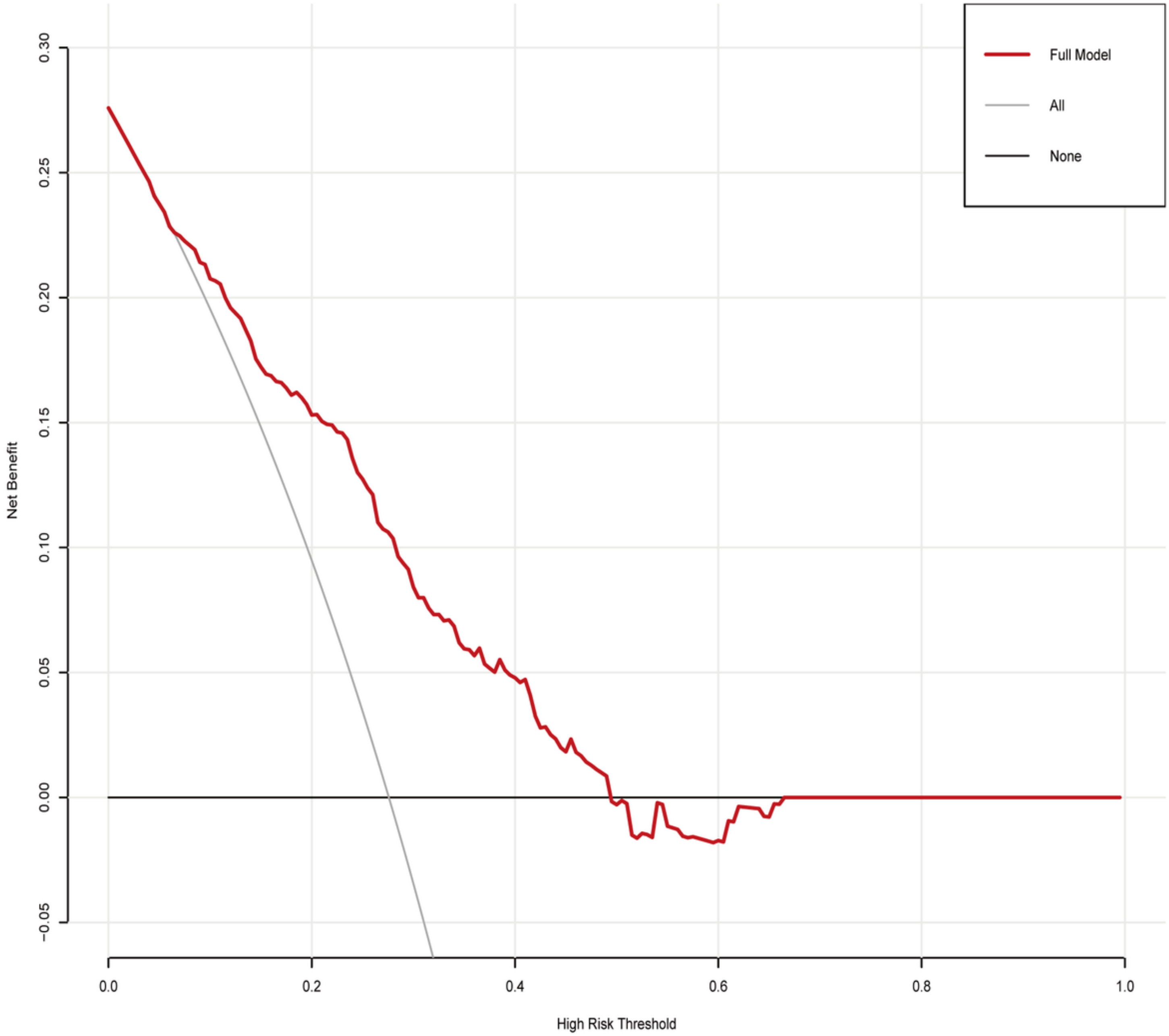

Figure 7 Clinical decision curve (DCA) between one-lung ventilation and hypercapnia during pulmonary surgery. The vertical axis represents the value of the net benefit, and the horizontal axis represents the threshold level (possible probability entry point). The decision curve is obtained by plotting the net benefit as a function of the threshold level. The solid red line represents the performance of the prediction model on DCA.

Figure 7

See image above for figure legend.