Development of a Predictive Model of Difficult Hemostasis following Endobronchial Biopsy in Lung Cancer Patients

Saibin Wang

Department of Respiratory Medicine, Jinhua Municipal Central Hospital, No. 365, East Renmin Road, Jinhua 321000, Zhejiang Province, China

Correspondence should be addressed to Saibin Wang; saibinwang@hotmail.com

Received 13 January 2019; Accepted 5 February 2019; Published 26 February 2019

Academic Editor: Wolfgang Miesbach

Copyright © 2019 Saibin Wang. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Endobronchial biopsy (EBB)-induced bleeding is fairly common; however, it can be potentially life-threatening due to difficult hemostasis following EBB. The aim of this study was to develop a predictive model of difficult hemostasis post-EBB. A total of 620 consecutive patients with primary lung cancer who had undergone EBB between 2014 and 2018 in a large tertiary hospital were enrolled in this retrospective single-center cohort study. Patients were classified into the difficult hemostasis group and the nondifficult hemostasis group according to hemostatic measures used following EBB. The LASSO regression method was used to select predictors and multivariate logistic regression was applied to develop the predictive model. The area under the curve (AUC) of the model was calculated. Bootstrapping method was applied for internal validation. Calibration curve analysis and decision curve analysis (DCA) were also performed. A nomogram was constructed to display the model. The incidence of difficult hemostasis post-EBB was 11.9% (74/620). Eight variables were selected by the LASSO regression analysis and seven (histological type of cancer, lesion location, neutrophil percentage, activated partial thromboplastin time, low density lipoprotein cholesterol, apolipoprotein-E, and pulmonary infection) of them were finally included in the predictive model. The AUC of the model was 0.822 (95% CI, 0.777-0.868), and it was 0.808 (95% CI, 0.761-0.856) in the internal validation. The predictive model was well calibrated and DCA indicated its potential clinical usefulness, which suggests that the model has great potential to predict lung cancer patients with a more difficult post-EBB hemostasis.

1. Introduction

Bleeding is a very common complication during endobronchial biopsy (EBB), and biopsy-induced difficult hemostasis not only affects further bronchoscopic procedures but also can be life-threatening [1–3]. Currently, the common biopsy modalities of EBB used include forceps biopsies, cryobiopsies, bronchial brushing, and needle aspiration biopsies [4], among which forceps biopsy is the most widely used biopsy methods in clinical practice [5]. Although several risk factors for bleeding during bronchoscopy have been proposed [6, 7], difficult hemostasis is often unexpected following biopsy.

Malignant tissue is more likely to bleed compared to benign tissue during bronchoscopy [8]. Patients with lung cancer frequently undergo bronchoscopy and the incidence of EBB-induced hemorrhage exceeds 30% in lung cancer patients [2]. Generally, most EBB-induced bleeding is self-stopping or hemostasis may be induced just by local intrabronchial instillation of hemostatic drugs, such as 4°C physiological saline or diluted adrenalin (1:10000-1:100000) [9]. However, difficult hemostasis following EBB may also occur, requiring the administration of argon plasma coagulation (APC), electrocoagulation, or endobronchial balloon tamponade to control bleeding [10].

Since uncontrolled endobronchial bleeding is still the main cause of death during bronchoscopy [1, 3, 11], a preoperative prediction for the occurrence of difficult hemostasis would help adjust biopsy modality, reduce the number of biopsies, and prepare hemostasis measures in advance, thereby improving the safety of EBB. However, to our knowledge, no relative predictive model is available to date. In the current study, clinical characteristics, tumor features, and laboratory tests of patients with lung cancer who had undergone EBB were retrospectively investigated to develop a predictive model of difficult hemostasis following EBB.
2. Materials and Methods

2.1. Study Population and Ethics Statement. This study was based on a single-center retrospective cohort study. A total of 620 lung cancer patients who had consecutively undergone EBB between January 2014 and February 2018 were enrolled at a 2600-bed tertiary hospital in this study. The study was approved by the institutional ethics committee of the hospital (No. 2018001007). Because all patient information used in this study was anonymous, patient informed consent was waived.

2.2. Variables Collection. In this cohort study, difficult hemostasis was defined as the requirement of APC or electrocoagulation for hemostasis following EBB; the remaining patients with either no bleeding, bleeding stopped on its own, or bleeding stopped with intrabronchial instillation of hemostatic drugs (4°C physiological saline or diluted adrenaline) were placed in the nondifficult hemostasis group. The following variables were collected from this study: patient's gender, age, brachial artery systolic pressure and diastolic pressure, weight, smoking history (yes or no), coexisting diabetes, COPD (chronic obstructive pulmonary disease) or CHD (coronary heart disease), pulmonary infection (yes or no); tumor features: lesions location, cancer histological type and stage (based on the TNM staging, the stage I-II was classified as early and stage III-IV, as advanced); laboratory tests on admission: white blood cell count, neutrophil percentage, neutrophil counts, hemoglobin, platelets, prothrombin time, activated partial thromboplastin time (APTT), aspartate aminotransferase, alanine aminotransferase, total cholesterol level, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, apolipoprotein-E, apolipoprotein-B and C-reactive protein (CRP).

2.3. Biopsy Procedures. The procedure (fiberoptic bronchoscopy, BF-IT60) was performed through a laryngeal mask airway under general anesthesia with the patients in the supine position. At the same location of the lesion 3-5 biopsies were usually performed using rigid endoscopic biopsy forceps. Generally, for obvious bleeding following EBB, intrabronchial instillation of 4°C physiological saline and/or diluted adrenaline (1:10000) was the first choice for hemostasis with repeats several times as needed. Electrocoagulation or APC was required when the bleeding failed to reach hemostasis by the means of the aforementioned drugs. All biopsies were performed by two experienced bronchoscopists.

2.4. Statistical Analysis. In this study, multiple imputation method was employed to account for missing data, and the baseline characteristics of the participants were summarized. Categorical variables are expressed as the number (percentage) and continuous variables as median (interquartile). Between two groups comparison, unpaired t-test or Kruskal-Wallis rank sum test, Pearson chi-squared test or the Fisher's exact test was performed as appropriate. The least absolute shrinkage and selection operator (LASSO) regression method was used for predictor selection and regularization. Multivariable logistic regression analysis using backward stepwise procedure and the likelihood ratio test on the basis of Akaike's information criterion (AIC) [12] were used to develop the predictive model. A nomogram was constructed to predict difficult hemostasis following EBB in lung cancer patients. The area under the curve (AUC) was calculated to determine the discriminatory capacity of the model, and internal validation was performed using bootstrapping (resampling = 1000) [13]. Calibration was tested using calibration plots and the Hosmer-Lemeshow test. Decision curve analysis (DCA) was conducted to assess the potential clinical usefulness of the model [14]. Statistical analysis was done using R software (version 3.5.1), and P value < 0.05 was considered statistically significant.

3. Results

Among the 620 patients, 74 (11.9%, 95% confidence interval [CI], 9.4%-14.5%) experienced post-EBB difficult hemostasis, and no patient died of severe bleeding after electrocoagulation and APC hemostasis. Smoking, pulmonary infection, histological types of cancer, lesion location, neutrophil percentage, CRP, APTT, HDL-C, alanine aminotransferase, and apolipoprotein-E were statistically different as assessed by univariate analysis. Patient's baseline characteristics, tumor features, and laboratory tests are shown in Table 1.

Of the 31 variables, 8 variables were filtered based on nonzero coefficients calculated by the LASSO regression analysis using the minimum criteria (Figure 1). These variables were lesions location, cancer histological type, pulmonary infection, neutrophil percentage, APTT, HDL-C, LDL-C, and apolipoprotein-E.
| Variables                        | Difficult hemostasis | P value |
|---------------------------------|----------------------|---------|
|                                 | No (n = 546)         | Yes (n = 74) |
| **Gender, n (%)**               |                      |          |
| Female                          | 124 (22.71)          | 9 (12.16) | 0.038   |
| Man                             | 422 (77.29)          | 65 (87.84) |         |
| **Age (years)**                 | 65 (59-70)           | 65 (59-70) | 0.757   |
| **Smoking, n (%)**              |                      |          |
| No                              | 214 (39.19)          | 16 (21.62) | 0.003   |
| Yes                             | 332 (60.81)          | 58 (78.38) |         |
| **SBP (mmHg)**                  | 131 (119-145)        | 128 (111-143) | 0.184   |
| **DBP (mmHg)**                  | 78 (70-86)           | 70 (70-88)  | 0.326   |
| **Weight (kg)**                 | 60 (53-66)           | 60 (53-70)  | 0.353   |
| **COPD, n (%)**                 |                      |          |
| No                              | 511 (93.59)          | 70 (94.59)  | 0.738   |
| Yes                             | 35 (6.41)            | 4 (5.41)   |         |
| **Diabetes, n (%)**             |                      |          |
| No                              | 516 (94.51)          | 72 (97.30)  | 0.410   |
| Yes                             | 30 (5.49)            | 2 (2.70)   |         |
| **CHD, n (%)**                  |                      |          |
| No                              | 529 (96.89)          | 71 (95.95)  | 0.722   |
| Yes                             | 17 (3.11)            | 3 (4.05)   |         |
| **Pulmonary infection, n (%)**  |                      | <0.001   |
| No                              | 340 (62.27)          | 28 (37.84)  |         |
| Yes                             | 206 (37.73)          | 46 (62.16)  |         |
| **Cancer stage, n (%)**         |                      | 0.824    |
| Early                           | 295 (54.03)          | 41 (55.41)  |         |
| Advanced                        | 251 (45.97)          | 33 (44.59)  |         |
| **Histological types, n (%)**   |                      | <0.001   |
| Adenocarcinoma                  | 161 (29.49)          | 5 (6.76)   |         |
| Squamous cell carcinoma         | 254 (46.52)          | 59 (79.73)  |         |
| SCLC                            | 101 (18.50)          | 8 (10.81)   |         |
| Others                          | 30 (5.49)            | 2 (2.70)   |         |
| **Lesion location, n (%)**      |                      | <0.001   |
| Left main bronchus              | 29 (5.31)            | 8 (10.81)   |         |
| Left upper lobar bronchi        | 129 (23.63)          | 13 (17.57)  |         |
| Left lower lobar bronchi        | 98 (17.95)           | 10 (13.51)  |         |
| Right main bronchus             | 16 (2.93)            | 8 (10.81)   |         |
| Right upper lobar bronchi       | 137 (25.09)          | 14 (18.92)  |         |
| Right middle bronchus           | 21 (3.85)            | 8 (10.81)   |         |
| Right middle lobar bronchi      | 27 (4.95)            | 2 (2.70)   |         |
| Right lower lobar bronchi       | 84 (15.38)           | 7 (9.46)   |         |
| The trachea                     | 5 (0.92)             | 4 (5.41)   |         |
| **Hospitalization, (days)**     | 11 (7-15)            | 10 (7-14)  | 0.360   |
| WBC (x10^9/L)                   | 6.80 (5.45-8.50)     | 6.89 (5.43-8.88) | 0.914   |
| Neutrophil (%)                  | 69.2 (61.8-75.6)     | 72.6 (65.8-80.9) | 0.004   |
| Neutrophils (x10^9/L)           | 4.54 (3.50-6.35)     | 5.10 (3.82-6.70) | 0.787   |
| Hemoglobin (g/dl)               | 128 (116-140)        | 126 (112-137) | 0.256   |
| Platelets (x10^9/L)             | 222 (173-280)        | 245 (171-317) | 0.086   |
| CRP (mg/L)                      | 5.9 (1.1-31.8)       | 18.66 (3.8-44.5) | <0.001 |
| PT (s)                          | 13.0 (12.1-13.6)     | 13.3 (12.2-13.9) | 0.663   |
| APTT (s)                        | 34.8 (31.5-38.2)     | 36.2 (33.0-41.2) | 0.034   |
| ALT (IU/L)                      | 17.0 (12.0-26.0)     | 15.1 (12.0-21.4) | 0.184   |
| AST (IU/L)                      | 23.0 (19.0-29.0)     | 23.0 (18.0-27.1) | 0.233   |
| Homocysteine (µmol/L)           | 13.3 (10.7-16.6)     | 12.7 (10.1-15.7) | 0.627   |
Table 1: Continued.

| Variables                | Difficult hemostasis | P value |
|--------------------------|-----------------------|---------|
|                          | No (n = 546)          |         |
|                          | Yes (n = 74)          |         |
| Triglyceride (mmol/L)    | 1.08 (0.79-1.46)      | 0.006   |
| TC (mmol/L)              | 4.10 (3.46-4.77)      | 0.720   |
| HDL-C (mmol/L)           | 1.14 (0.94-1.37)      | 0.072   |
| LDL-C (mmol/L)           | 2.75 (2.26-3.30)      | 0.074   |
| Apolipoprotein-B (g/L)   | 0.96 (0.77-1.18)      | 0.425   |
| Apolipoprotein-E (mg/dL) | 3.60 (2.90-4.80)      | 0.006   |

SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; SCLC, small-cell lung carcinoma; WBC, white blood cell; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Figure 2: The AUC represents the discriminatory ability of the model. (a) shows AUC of the predictive model and (b) shows AUC of the internal validation with the bootstrap method (resampling times = 1000). The dotted vertical lines represent 95% confidence interval. AUC, area under the curve.

The aforementioned 8 predictors were included in multivariable logistic regression analysis. Backward stepwise selection was applied to develop a predictive model and 7 predictors (excluding HDL-C) were eventually incorporated into the model according to the likelihood ratio test with AIC. The AUC for the predictive model reached was 0.822 (95% CI, 0.777-0.868), and it was 0.808 (95% CI, 0.761-0.856) in the internal validation using bootstrapping (resampling times = 1000) (Figure 2). A nomogram was constructed to display the predictive model (Figure 3), providing a quantitative tool to predict the probability of difficult hemostasis following EBB.

As is shown in Figure 4, the model was well calibrated. A nonsignificant statistical value (P = 0.985) was yielded in the Hosmer-Lemeshow test with an Emax value of 0.027 and Eavg value of 0.006, indicating that there was no departure from a perfect fit between predicted and observed values.

The decision curve (Figure 5) demonstrated that application of this model to predict post-EBB difficult hemostasis would add more benefit compared with either the treat-all or the treat-none strategies. Specifically, when the threshold probability of difficult hemostasis following EBB is < 90% based on the predictive model, the clinical use of this predictive model can benefit lung cancer patients undergoing EBB.

4. Discussion

In the present study, a predictive model of difficult hemostasis following EBB was developed. This model incorporated 7 predictors, including histological type of cancer, lesion location, pulmonary infection, neutrophil percentage, APTT, LDL-C, and apolipoprotein-E. The model showed good discriminatory ability in the derivation cohort and in the internal
Figure 3: Nomogram for difficult hemostasis following endobronchial biopsy in lung cancer patients. Firstly, find point for each predictor of an individual on the uppermost rule. Secondly, add all points together and find the “total points” on rule. At last, the corresponding predicted probability of difficult hemostasis following endobronchial biopsy could be found on the lowest rule. Codes annotation: histological type of lung cancer: 0, adenocarcinoma; 1, squamous cell carcinoma; 2, small-cell lung carcinoma; 3, other types. Lesion location: 1, left main bronchi; 2, left upper lobar bronchi; 3, left lower lobar bronchi; 4, right main bronchus; 5, right upper lobar bronchi; 6, right middle bronchus; 7, right middle lobar bronchi; 8, right lower lobar bronchi; 9, the trachea. Pulmonary infection: 0, no; 1, yes. APTT, activated partial thromboplastin time; LDL-C, low density lipoprotein cholesterol; ApoE, apolipoprotein-E.

validation. The model was well-calibrated and showed potential clinical usefulness.

EBB-induced bleeding has always been a common concern for bronchoscopists [1, 3, 11]. Unexpected difficult hemostasis could occur during EBB leading to severe bleeding that may prove being life-threatening [3, 15]. It has been reported that the incidence of bleeding during bronchoscopy ranges from <1% to 20% [16]. However, bleeding risk significantly increases when transbronchial biopsies are performed [17]. Additionally, the incidence of biopsy-induced bleeding is related to the biopsy tissue. When compared with benign mucosal lesions, malignant tissue is more susceptible to bleeding following EBB [2, 8]. It should also be noted that lung cancer patients have become the main population receiving EBB.

In previous studies, several risk factors for bleeding during bronchoscopy had been proposed, such as immunosuppression, thrombocytopenia, anticoagulant drug use, or coagulation dysfunction [6, 7]. However, it is still difficult to predict the occurrence of difficult hemostasis after a biopsy in patients who do not have a significant risk of bleeding. To our knowledge, no predictive model for post-EBB difficult hemostasis is available to date.

For bronchoscopists, to predict intraoperative EBB-induced bleeding risk can help guide their preoperative clinical decision making and select appropriate hemostasis measures during EBB. Currently, commonly used hemostasis measures during EBB include intrabronchial instillation of 4°C physiological saline and/or diluted adrenaline, which is suitable for hemostasis with microbleeding or mild-bleeding [18]. For moderate-bleeding or difficult-to-stop bleeding after repeated use of the aforementioned drugs, electrocoagulation, APC and intravenous infusion of pituitrin are usually required. In case of massive bleeding, endobronchial balloon tamponade for persistent hemoptysis and surgery may be needed [10, 19]. Because of its frequent occurrence and
potential hazard, difficulty in hemostasis following EBB was the main focus of this study.

The predictive model for post-EBB difficult hemostasis in the present study was developed based on 7 predictors, including histological type of cancer, lesion location, pulmonary infection, neutrophil percentage, APTT, LDL-C, and apolipoprotein-E. These predictors were filtered by LASSO regression analysis, which was considered to surpass the technique of choosing predictors based on their univariable association strength with outcome [20, 21]. Additionally, all 7 predictors are readily accessible clinically. The prediction model showed both good discrimination ability and calibration. DCA is a recommended novel method for evaluating the clinical value of a predictive model [22, 23]. The decision curve based on this model revealed that when the threshold probability of a subject was < 90%, applying this model to predict post-EBB difficult hemostasis would benefit when compared to either treat-all or treat-none strategies. In addition, a nomogram was also constructed to facilitate the application of the model.

Some limitations of this predictive model are worth noting. Firstly, this model was constructed based on a single-center retrospective study, which inevitably suffered from confounding bias; for example, indication of the specific tools (APC, electrocoagulation, or endobronchial balloon tamponade) used for the stop bleeding is related to the decision of the physician, which is difficult to be reconciled among bronchoscopists. 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. Thirdly, the mechanism underlying some predictors in bleeding is still unclear, such as LDL-C. In addition, during hemostasis, the time and frequency of use of electrocoagulation and/or APC may further distinguish the degree of difficulty in hemostasis; however, these variables were not available in the original data. Despite these limitations, the present study is the first to develop a predictive model for difficult hemostasis following EBB.

5. Conclusion

A difficult hemostasis risk prediction model for EBB-induced bleeding in lung cancer patients was developed, which incorporated 7 readily available clinical variables. This model showed good discriminatory ability and potential clinical usefulness, and thus it may be of great value to facilitate the prediction and management of EBB-induced difficult hemostasis.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The author declares that he has no conflicts of interest.
Authors’ Contributions
Saibin Wang was responsible for conception, design, data collection, data analysis, and manuscript preparation.

Acknowledgments
I appreciate the help and support of all the participants involved in the study. This study was supported by the Medical and Health Science and Technology Plan Project of Zhejiang Province (2018RCC079), the Youth Research Fund of Jinhua Hospital of Zhejiang University (YJ2017205), the Science and Technology Key Project of Jinhua City (20163011), and the Chinese Medicine Science and Technology project of Jinhua City (2017jzk05).

References
[1] C. T. Bolliger, T. G. Sutedja, J. Strausz, and L. Freitag, “Therapeutic bronchoscopy with immediate effect: laser, electrocautery, argon plasma coagulation and stents,” European Respiratory Journal, vol. 27, no. 6, pp. 1258–1271, 2006.

[2] S. Wang, Q. Ye, J. Tu, and Y. Song, “The location, histologic type, and stage of lung cancer are associated with bleeding during endobronchial biopsy,” Cancer Management and Research, vol. 10, pp. 1251–1257, 2018.

[3] K. Chinsky, “Bleeding risk and bronchoscopy: in search of the evidence in evidence-based medicine,” CHEST, vol. 127, no. 6, pp. 1875–1877, 2005.

[4] E. Gunay, N. T. Hoca, A. Yilmaz et al., “Endobronchial cryobiopsy or forceps biopsy for lung cancer diagnosis,” Annals of Thoracic Medicine, vol. 5, no. 4, pp. 242–246, 2010.

[5] J. Fallon and A. R. L. Medford, “Endobronchial and transbronchial biopsy experience: A United Kingdom survey,” Thoracic Cancer, vol. 8, no. 4, pp. 291–295, 2017.

[6] F. J. F. Herth, H. D. Becker, and A. Ernst, “Aspirin does not increase bleeding complications after transbronchial biopsy,” CHEST, vol. 122, no. 4, Article ID 37821, pp. 1461–1464, 2002.

[7] G. B. Diette, C. M. Wiener, and P. J. White, “The higher risk of bleeding in lung transplant recipients from bronchoscopy is independent of traditional bleeding risks: results of a prospective cohort study,” CHEST, vol. 115, no. 2, pp. 397–402, 1999.

[8] M. A. Özgül, A. Turna, P. Yıldız, E. Ertan, S. Kahraman, and V. Yılmaz, “Risk factors and recurrence patterns in 203 patients with hemoptysis,” Tüberkuloz ve Toraks, vol. 54, no. 3, pp. 243–248, 2006.

[9] S. Wang, Q. Ye, and X. Lu, “Plasma apolipoprotein e level is associated with the risk of endobronchial biopsy-induced bleeding in patients with lung cancer,” Lipids in Health and Disease, vol. 17, no. 1, p. 166, 2018.

[10] S. Correia, J. Dionisio, and J. J. Duro, “Modified technique of endobronchial balloon tamponade for persistent hemoptysis,” Journal of Bronchology & Interventional Pulmonology, vol. 21, no. 4, pp. 361–365, 2014.

[11] M. M. Wahidi, A. T. Rocha, J. W. Hollingsworth, J. A. Govert, D. Feller-Kopman, and A. Ernst, “Contraindications and safety of transbronchial lung biopsy via flexible bronchoscopy: a survey of pulmonologists and review of the literature,” Respiration, vol. 72, no. 3, pp. 285–295, 2005.

[12] A. J. Vickers, A. M. Cronin, E. B. Elkin, and M. Gonen, “Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers,” BMC Medical Informatics and Decision Making, vol. 8, no. 53, 2008.

[13] G. S. Collins, J. B. Reitsma, D. G. Altman, and K. G. M. Moons, “Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement,” Annals of Internal Medicine, vol. 162, no. 1, pp. 55–63, 2015.

[14] L. Grandjean, A. Crossa, R. H. Gilman et al., “Tuberculosis in household contacts of multidrug-resistant tuberculosis patients,” The International Journal of Tuberculosis and Lung Disease, vol. 15, no. 9, pp. 1164–1169, 2011.

[15] F. J. Herth, “Bronchoscopy and bleeding risk,” European Respiratory Review, vol. 26, no. 145, p. 170052, 2017.

[16] E. M. Cordasco Jr., A. C. Mehta, and M. Ahmad, “Bronchoscopically induced bleeding: a summary of nine years’ cleveland clinic experience and review of the literature,” CHEST, vol. 100, no. 4, pp. 1141–1147, 1991.

[17] D. C. Zavala, “Pulmonary hemorrhage in fiberoptic transbronchial biopsy,” CHEST, vol. 70, no. 5, pp. 584–588, 1976.

[18] R. I. A. Du, J. Blaikley, R. Booton et al., “British thoracic society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE,” Thorax, vol. 68, 1, pp. ii–i44, 2013.

[19] M. Metin, A. Sayar, A. Turna et al., “Emergency surgery for massive haemoptysis,” Acta Chirurgica Belgica, vol. 105, no. 6, pp. 639–643, 2005.

[20] R. Tibshirani, “The lasso method for variable selection in the cox model,” Statistics in Medicine, vol. 16, no. 4, pp. 385–395, 1997.

[21] Y.-Q. Huang, C.-H. Liang, L. He et al., “Development and validation of a radiomics nomogram for preoperative prediction of lymph node metastasis in colorectal cancer,” Journal of Clinical Oncology, vol. 34, no. 18, pp. 2157–2164, 2016.

[22] A. J. Vickers and E. B. Elkin, “Decision curve analysis: a novel method for evaluating prediction models,” Medical Decision Making, vol. 26, no. 6, pp. 565–574, 2006.

[23] V. P. Balachandran, M. Gonen, J. J. Smith, and R. P. DeMatteo, “Nomograms in oncology: More than meets the eye,” The Lancet Oncology, vol. 16, no. 4, pp. e173–e180, 2015.