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ORIGINAL ARTICLE

Could the probability of surgical indication be determined after first episode of primary spontaneous pneumothorax?

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Abstract

Objectives To develop a risk score model for primary spontaneous pneumothorax surgery (prolonged air leak or ipsilateral recurrence). The model was internally validated for risk estimation.

Methods We analyzed 453 patients with primary spontaneous pneumothorax between 2014 and 2018. Patients were randomly assigned a 2:1 ratio to the development dataset ($n=302$, study cohort) or the internal validation dataset ($n=151$, validation cohort). The final outcomes of patients with primary spontaneous pneumothorax, the presence or absence of surgical indications, were tracked. Multivariable logistic regression models were prepared to estimate the probability of surgical indication and a scoring model was created. It was internally validated using the validation cohort. Calibration was ascertained using the Hosmer–Lemeshow method and Brier score.

Results The surgery indication rate was 47.8% ($n=217$) (prolonged air leak, $n=130$; ipsilateral recurrence, $n=87$). There were no demographic or radiological differences between the validation and the study cohorts. Logistic regression analysis showed that the presence of bullae or blebs ($p<0.001$, odds ratio = 3.340, 95%CI = 1.753–6.363) and pneumothorax volume ($p<0.001$, odds ratio = 1.033, 95%CI = 1.019–1.048) were independent risk factors for surgical indication. The scoring model significantly predicted surgical indications (area under the curve, AUC = 0.768, 95%CI = 0.714–0.821, $p<0.001$). Our model showed acceptable discrimination with an AUC > 0.75 in the validation set (AUC = 0.777, 95%CI = 0.702–0.852, $p<0.001$) and had an adequate calibration (Hosmer–Lemeshow test $p=0.249$, Brier score = 0.25).

Conclusion The internally validated primary spontaneous pneumothorax scoring model was a good predictor of the need for surgery in patients with primary spontaneous pneumothorax. Prospective external validation studies with larger patient cohorts are required.

Keywords Primary spontaneous pneumothorax · Surgical indication · Probability · Modeling

Abbreviations

AUC	Area under the receiver operating characteristic curve
CI	Confidence interval
DSS	Dystrophic severity score
Log odds	Logarithm of the odds
NPV	Negative predictive value
PPV	Positive predictive value
PSP	Primary spontaneous pneumothorax
PAL	Prolonged air leak
ROC	Receiver operating curve

Introduction

Primary spontaneous pneumothorax (PSP) is a common condition. The universally accepted indications for surgical treatment of PSP are prolonged air leak (PAL) and ipsilateral recurrence of pneumothorax [1–3]. Many studies have been published regarding which patients are candidates for surgery after the first episode [4]. In these studies, many factors, such as low body mass index, presence of bulla/bleb, smoking, large PSP volume, female sex, height in males, and pleural thickening on chest radiography, were found to be risk factors for surgical indication [5–8]. However, there are

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still no established factors that predict surgical indications, and consequently, no method for risk-stratifying patients.

Several scoring systems exist for other diseases, such as the probability of cancer in pulmonary nodules, prediction of PAL in patients undergoing lung resection, probability of abnormal reflux, and prediction of percutaneous coronary intervention success [9–12]. However, to the best of our knowledge, no scoring system has been developed to determine surgical candidates for pneumothorax. It is still unknown whether a model, such as published risk models for different diseases, will be useful to identify patients with PSP who may require surgery. An accurate model would be able to predict the probability of surgery for PSP after the first episode, guide clinical decision-making, and may show which patients should be followed more closely.

We conducted a retrospective study to determine the factors that predict the probability of surgery for PSP after the first episode. We developed and validated models and calculators for predicting the probability of surgical candidates in patients with PSP using data from two separate cohorts.

Materials and methods

This study was approved by the Ethics Committee of the Bakırköy Sadi Konuk Hospital (No. 2022/073) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the patients.

Between January 2014 and December 2018, 508 consecutive patients with PSP were treated at our institution. Patients > 50 years ($n = 30$), those without follow-up ($n = 9$), those who had an emergency condition requiring surgical exploration (such as spontaneous hemopneumothorax) ($n = 8$), and those who had a serious concomitant illness or medical condition ($n = 8$) were excluded. Based on the exclusion criteria, 453 patients were included in the analysis.

Establishment of cohorts and added variables for risk factors

As the present study was not a clinical drug study, we decided to apply unequal randomization. Patients were randomly assigned, applying a 2:1 ratio to the development dataset (study cohort) or the internal validation dataset (validation cohort). A randomization scheme was generated using the Randomization.com website (http://www.randomization.com).

In both cohorts, we recorded variables that have been determined to affect recurrence or PAL in previous studies, such as age, sex, pneumothorax side, smoking habits, pneumothorax volume, dystrophic severity score (DSS), and presence of bullae/blebs [4–8, 13]. A recent study showed that Kircher's method was the best predictor for surgical indication of PSP and we adopted this method to calculate pneumothorax volume [8, 14]. In Kircher's method, the atelectatic area of the hemithorax (C × D) is subtracted from the total hemithorax area (A × B) and the result is divided by the total hemithorax area (A × B) (Fig. 1). The DSS, as described by Casali et al. [15], was calculated via chest computed tomography (CT) and was based on the type, distribution, and number of dystrophic lesions. The formula of the DSS based on the air-containing pulmonary lesion(s) is the sum of scores for type (one point for blebs or two points for bullae), number (one point for single or two points for multiple), and distribution (one point for unilateral or two points for bilateral). If the air-containing pulmonary lesions (blebs or bullae) are seen on CT, the DSS ranged from 3 to 6 points. If there are no blebs or bullae in CT, the DSS is recorded as 0 point.

There is still no evidence of the ideal timing for surgical intervention in cases of PAL. In the past, a cut-off point of 7 days was widely accepted arbitrarily; however, more recently, surgery is recommended if the air leak persists for more than approximately 5 days [1, 3]. In our clinical practice, if an air leak persists for more than 5 days, surgery is recommended.

Initially, patients are referred to our thoracic surgery clinic department, which is a 24-h emergency thoracic surgery center in Istanbul, and will be consulted before deciding on the course of treatment. For this reason, we can be reasonably sure that the patients will refer back to our center in cases of recurrence. Since some patients might have

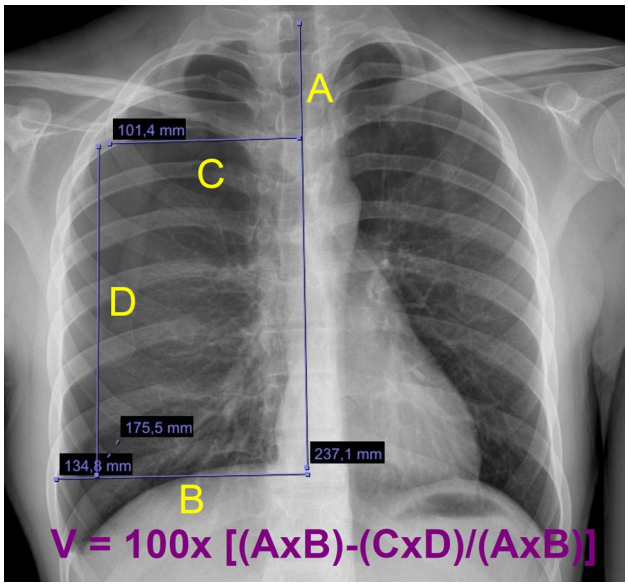


Fig. 1 Calculation of the pneumothorax volume using Kircher's method. V volume. In Kircher's method, the atelectatic area of the hemithorax (C × D) is subtracted from the total hemithorax area (A × B), and the result is divided by the total hemithorax area (A × B)

possibly gone to other centers, the information (recurrence or no recurrence) of all patients was confirmed using both the electronic national health application (https://enabiz.gov.tr/) and by telephone.

Statistical analysis and development of the model

The collected data were analyzed using the Statistical Package for the Social Sciences (version 23.0; IBM Corp., Armonk, NY, USA). Variables were characterized using the mean, maximum, and minimum values, and percentages were used as qualitative variables. The normality of the distributions was determined using the Kolmogorov–Smirnov analysis. Data with normal distributions are reported as mean ± standard deviation (SD) and were analyzed using the Student's *t* test. Pearson's Chi-square test was used to analyze qualitative variables. Data with non-normal distributions are reported as median values and interquartile ranges (IQR). Nonparametric continuous variables were compared using the Mann–Whitney *U* test. Statistical significance was set at $P < 0.05$.

In the study cohort, a multivariable logistic regression model was prepared to estimate the risk of PSP surgery associated with potential predictors, including sociodemographic and radiological variables. The full logistic regression prediction model was used instead of the parsimonious prediction model because previous studies [5–8] have demonstrated that the variables used in the present study are predictors for surgery.

We used a previously described method, which investigated solitary pulmonary nodule malignancy risk in adults, to calculate surgical probability [10]. Regardless of the *P* value for the variables, the beta regression coefficients calculated for each variable in the logistic regression analysis were entered individually for each patient. Using the sum of the regression coefficients and constant (intercept), the logarithm of the odds (log odds) value was calculated for each patient. The probability of surgery was calculated using the following formula: $\text{Probability} = (100 \times (e^{(\text{Log\_odds})} / (1 + e^{(\text{Log\_odds})}))$.

In the study cohort, the predictive performance of the model was evaluated by assessing its discrimination, which was measured using the area under the receiver operating characteristic curve (AUC). The reported AUC values were presented with 95% confidence intervals (CI). The optimal cut-off point for indicating surgery in patients with PSP was determined using the best sensitivity and specificity scores, which were calculated using receiver operating curve (ROC) analysis. The negative predictive value (NPV), positive predictive value (PPV), and accuracy rate for this cut-off point were also calculated. The prediction model developed in the study cohort was validated internally by assessing discrimination in the validation cohort data. The performance of the model was assessed by calculating AUC in the validation cohort.

The calibration of the model's predictive performance (whether probabilities predicted by the model match the observed probabilities) was evaluated using the Brier score, which indicated how accurate our prediction was. The Brier score is the mean-squared difference between the predicted and actual outcomes. Therefore, a Brier's score of 0 shows accurate predictive ability, and a score of 1 shows poor predictive ability.

Calibration was also assessed using the Hosmer–Lemeshow goodness-of-fit test of predicted versus observed event rates. The patients were grouped into 10 risk classes based on expected PSP surgery, which was calculated using the results of the logistic regression model. Thus, we examined whether PSP surgeries performed in these groups overlapped with the predictions (absolute error = observed ratio-expected ratio).

In addition, the rates of surgical need in patients within each 10% probability were evaluated (probability ratio versus actual event ratio).

Results

The demographic and radiological data of the patients are presented in Table 1. The median follow-up duration for all patients was 875 days (min = 370, max = 2227 days, IQR = 693). Surgery was indicated for 217 patients (47.94%) because of PAL or ipsilateral recurrence. Video-assisted thoracoscopic surgery was performed in 130 patients (28.7%) with PAL after the first PSP episode. The remaining 323 patients were discharged after conservative treatment due to re-expansion of the lung and absence of air leakage. Ipsilateral recurrence was detected in 87 patients (26.9%) during follow-up.

Patients were randomly divided into two subgroups: study cohort ($n = 302$) and validation cohort ($n = 151$). There were no statistically significant differences between the two cohorts in terms of the variables (Table 1).

Development of the model with the study cohort results

Logistic regression analysis showed that the presence of bullae/blebs (odds ratio = 3.340, 95%CI = 1.753–6.363, $p < 0.001$) and pneumothorax volume (odds ratio = 1.033, 95%CI = 1.019–1.048, $p < 0.001$) were independent risk factors for surgical indication. The total log odds value for each patient was calculated using the formula for beta coefficients, according to the results in Table 2.

The formula was created according to the results of the analysis, as follows: log odds = (− 0.007*

Table 1 Patient characteristics and comparison between the cohorts

	Total ($n=453$)	Study cohort ($n=302$)	Validation cohort ($n=151$)	p value
Age, median years (IQR)	23 (10)	24 (10)	23 (9)	0.878
Sex, *n* (%)				
Male	412 (90.9)	271 (89.7)	141 (93.4)	
Female	41 (9.1)	31 (10.3)	10 (6.6)	0.203
Smoking, *n* (%)	304 (67.1)	208 (68.9)	96 (63.6)	0.258
Smoking, median pack/years	6 (6)	6 (6)	6 (6)	0.693
Side, *n* (%)				
Left	213 (47.0)	142 (47.0)	71 (47.0)	
Right	240 (53.0)	160 (53.0)	80 (53.0)	1.000
Kircher PSP median volume, %	35.6 (29.9)	35.4 (28.4)	35.6 (31.3)	0.747
Presence of bullae/blebs, *n* (%)	191 (42.2)	131 (43.4)	60 (39.7)	0.459
DSS, median score (IQR)	0 (2)	0 (2)	0 (3)	0.852
Prolonged air leak, *n* (%)	130 (28.7)	89 (29.5)	41 (27.2)	0.607
Ipsilateral recurrence, *n* (%)*	87 (26.9)	60 (28.2)	27 (24.5)	0.487

DSS dystrophy severity score; *IQR* interquartile range; *PSP* primary spontaneous pneumothorax; *n* number

*This calculation was performed by excluding patients who had prolonged air leakage and who underwent surgery ($n=130$) during the first pneumothorax attack

Table 2 Prediction model for the probability of surgery in patients with PSP in the study cohort after the first attack

Variables	Odds ratio	95%CI	p value	Beta coefficient$^{\alpha}$
Age (per year)*	0.993	0.948–1.041	0.774	−0.007
Sex (Male vs. Female)	1.234	0.503–3.031	0.646	0.210
Smoking (No vs. Yes)	1.077	0.546–2.126	0.830	0.075
Smoking (per pack/years)*	1.019	0.965–1.075	0.503	−0.018
Side (Left vs Right)	1.098	0.647–1.863	0.729	0.093
Kircher pneumothorax volume (per volume)*	1.033	1.019–1.048	**< 0.001**	0.033
Presence of bullae/blebs	3.340	1.753–6.363	**< 0.001**	1.206
Dystrophy severity score (per score)*	1.079	0.961–1.210	0.110	0.076
Model constant	−2.158			
Nagelkerke R Square	0.284			

PSP primary spontaneous pneumothorax, *CI* confidence interval

$^{\alpha}$Regardless of the p value for the variables, the beta regression coefficients calculated for each variable in the logistic regression analysis were entered individually for each patient. With the sum of the regression coefficients and constant (intercept), the logarithm of the odds (log odds) value was calculated for each patient

*Age is centered on the mean of 24 years, cigarette pack/years is 6 packs/years, Kircher pneumothorax volume is centered at 41%, and dystrophy severity score is centered on 2 (i.e., 24 is subtracted from the actual age, 6 is subtracted from the actual number of packs/years, 41 is subtracted from the actual Kircher pneumothorax volume, and 2 is subtracted from the actual dystrophy severity score)

(age-24)) + sex + history of smoking + (−0.018* (pack/years-6)) + pneumothorax side + (0.033* (Kircher pneumothorax volume-41)) + presence of bulla/bleb + (0.076*(DSS-2)). The probability of PSP surgery was calculated individually for each patient.

The median probability of PSP surgery in the study cohort was 18.6% (min = 3.0%, max = 80.9%, IQR = 28.8, mean ± SD = 25.5% ± 20.0%). The probability of patients with an indication for surgery was significantly higher than those without (median 30.4% vs. 10.6%, $p < 0.001$).

The model developed using the results of the study cohort predicted the patients who had surgical indications (AUC = 0.768, 95%CI = 0.714–0.821) (Fig. 2). The optimal cut-off point for PSP surgery was 21.1% for patients with PSP in the study cohort (sensitivity, 68.4%; specificity, 74.5%; PPV, 72.3%; NPV, 70.8%; accuracy, 71.5%).

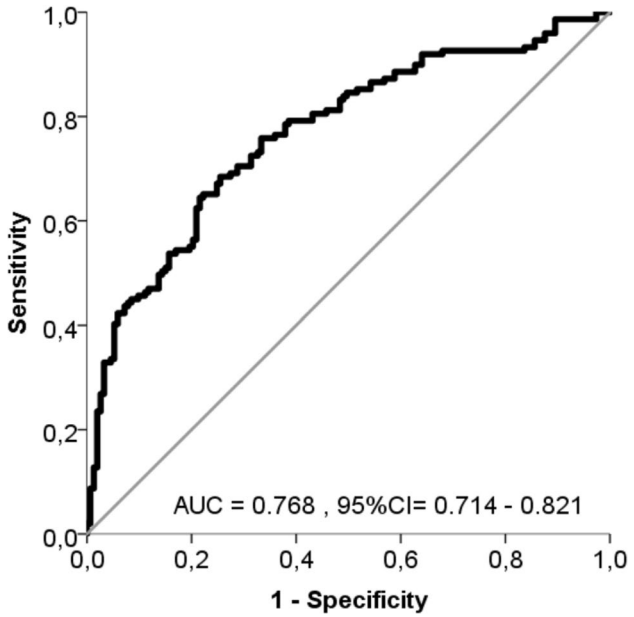


Fig. 2 The ROC analysis in the study cohort to investigate the ability of the developed model to predict surgery indication in patients with PSP. *AUC* area under curve, *CI* confidence interval, *ROC* receiver operating curve, *PSP* primary spontaneous pneumothorax

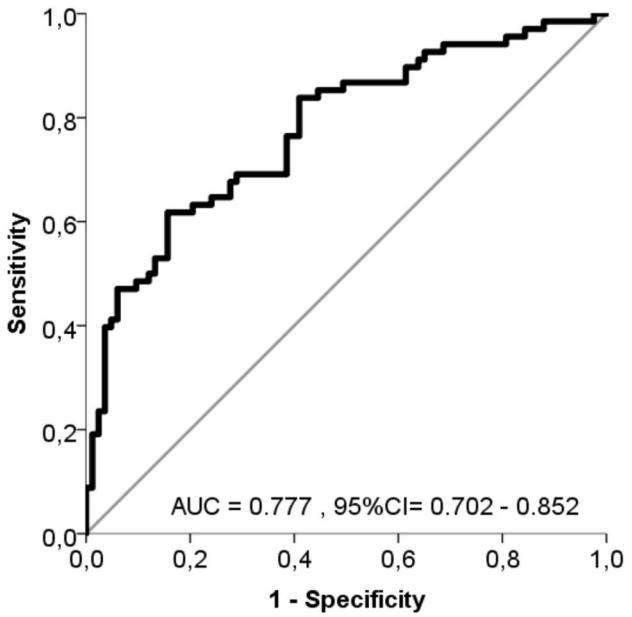


Fig. 3 The ROC analysis in the validation cohort to validate the developed model. *AUC* area under curve, *CI* confidence interval, *ROC* receiver operating curve

According to the calculated cut-off percentage value, patients in the study cohort were divided into two subgroups: low PSP score (≤ 21.1%, $n = 161$) and high PSP score (> 21.1%, $n = 141$). The surgical indication rate was significantly higher in patients with a high PSP score ($n = 102$, 72.3%) than those with a low PSP score ($n = 47$, 29.2%) (odds ratio = 6.344, 95%CI = 3.842–10.476, $p < 0.001$).

Validation of the model

The median probability of PSP surgery in the validation cohort was 16.6% (min = 4.0%, max = 86.2%, IQR = 24.1, mean ± SD = 25.1% ± 20.3%). The probability percentages of patients with an indication for surgery were statistically higher than those without it (median 29.6% vs. 10.7%, $p < 0.001$).

The results for the validation set data were consistent with those of the development set data, indicating that the model was robust. Our model, which was developed using the study cohort results, showed acceptable discrimination in the validation cohort (AUC = 0.777, 95%CI = 0.702–0.852, $p < 0.001$) (Fig. 3). Patients in the validation cohort were divided into two subgroups: low PSP score ($n = 82$) and high PSP score ($n = 69$), according to the calculated cut-off percentage value (21.1%) in the study cohort. The surgical indication rate was significantly higher in patients with a high PSP score ($n = 46$, 66.7%) than those with a low PSP score ($n = 22$, 26.8%) (odds ratio = 5.455, 95%CI = 2.710–10.978, $p < 0.001$). The accuracy of the model was 70.1% in the validation cohort.

The calibration of the model

The mean Brier score for all the patients was 0.24; 0.25 in the study cohort and 0.23 in the validation cohort ($p = 0.467$). The calibration of the model was tested using the Hosmer–Lemeshow method with all patients. Table 3 presents the predicted and observed PSP surgeries assigned to the 10 risk groups. This corroborated a valid concordance

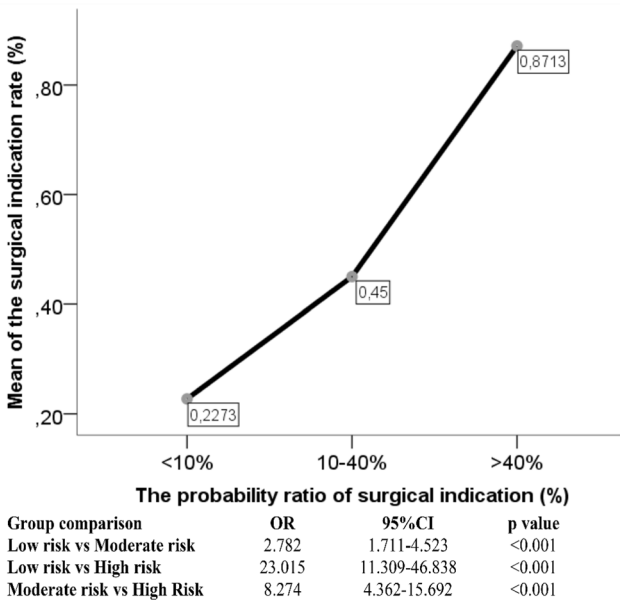
Table 3 Contingency table for Hosmer–Lemeshow test

	Surgical indication = no		Surgical indication = yes		Total
	Observed	Expected	Observed	Expected	
Step 1					
1	38	37,717	7	7,283	45
2	35	35,209	10	9,791	45
3	35	33,241	10	11,759	45
4	26	30,978	19	14,022	45
5	25	27,323	20	17,677	45
6	28	22,608	17	22,392	45
7	21	18,532	24	26,468	45
8	18	14,789	27	30,211	45
9	6	10,105	39	34,895	45
10	4	5,498	44	42,502	48

between predicted and observed PSP surgery in the 10 different risk groups ($p = 0.249$).

The surgical necessity rates corresponding to every 10% probability are shown in Fig. 4. Although the probability and actual event ratios were not equal, the actual event ratio increased, while the probability ratio increased.

The actual event ratio was very high when the probability ratio exceeded 40%. Therefore, risk groups were created for convenience in clinical practice: low risk (< 10%), moderate risk (10–40%), and high risk (> 40%). The rate of surgical indication in the low-risk group was 22.7%, 45% in the moderate-risk group, and 87.1% in the high-risk group ($p < 0.001$) (Fig. 5).



Group comparison	OR	95%CI	p value
Low risk vs Moderate risk	2.782	1.711-4.523	<0.001
Low risk vs High risk	23.015	11.309-46.838	<0.001
Moderate risk vs High Risk	8.274	4.362-15.692	<0.001

Fig. 5 PSP surgery indication rate in low-, moderate-, and high-risk groups. *OR* odds ratio, *CI* confidence interval, *PSP* primary spontaneous pneumothorax

Discussion

The recurrence rate of pneumothorax has been reported to be approximately 20–54%, and the prevalence of PAL varies between 15 and 25% after the first episode of PSP [4–8, 15–17]. Despite these high rates, it is still not clear which patients will require surgery after the first pneumothorax [1–3]. Therefore, the optimal treatment for PSP remains unclear. The main considerations are whether high-risk relapse patients can be identified beforehand, whether they can be offered conservative surgery during the first episode of PSP, and whether there are any predictors for the indication for surgery [4–6]. There is no conclusive evidence on the benefit of surgery following the first episode, and there are very few studies on this subject with a large number of patients. Although video-assisted thoracoscopic surgery (VATS), which has recently become very popular, is reserved for recurrent pneumothorax and PAL, many thoracic surgeons now offer preventive VATS to patients with the first presentation of PSP, despite existing guidelines [18].

However, overtreatment should be avoided and the rhetoric of primum non nocere (first, do no harm), which has been around since the time of Hippocrates, must be adhered to. Thus, the following question arises: Can a probability model, such as lung cancer risk models [19] or solitary pulmonary nodule risk models [20, 21], be used in patients with PSP? This will enable physicians to better determined how often patients should be followed or which patients should be closely observed. Informed consent for VATS can then provisionally be provided during the first episode in high-risk PSP patients. A reliable model to predict PSP surgery may be extremely helpful regarding informed consent and

Fig. 4 Comparison of the probability ratio with the actual event ratio

guidance to thoracic surgeons. Without considering different risk profiles, surgeons following patients may appear to provide low quality treatment.

Risk scoring systems are used for several purposes, such as predicting aspects of a patient's care (cost, risk of re-hospitalization, etc.), health management (total length of hospital stay, days away from the workforce, etc.), and stratifying a population for targeted screening. In thoracic surgery, individual-based decision-making for a patient with PSP requires information on both the natural history of the pneumothorax disease and the assumed risk of follow-up. The scoring system included a mix of all risk factors for PSP surgery (both PAL and recurrence) and was developed using indicators from the patients. Our aim was to determine whether a risk model could be developed for patients with PSP. The aim of this model was not to change the clinical judgment or rush the process leading to surgery. However, to make surgical outcomes comparable, a valid risk adjustment model is mandatory in contemporary biotechnology medicine.

In the present study, the area under the ROC curve for the developed model was calculated to exceed 0.75, thereby demonstrating an acceptable to good quality of discrimination for the scoring system model. The sensitivity and specificity of the model appear robust enough to aid in the clinical judgment of patients with PSP. Moreover, the model developed to assess the surgical indications of patients with PSP provided good discrimination in the validation dataset. In addition, the Hosmer–Lemeshow method and scaled Brier score exhibited sufficient concordance in the predicted and observed mortalities. Thus, the calibration of the model is acceptable.

We found that the existing risk stratification model underestimated PSP surgery observed in our patient population. In such models, the results of underestimation, rather than overestimation, may help avoid overtreatment. However, the absolute error decreased as the percentage of surgery risk increased. Although the underestimation rate was higher in the first percentile groups, it declined to an error level of less than 10% in the 50% and above risk groups. When the risk groups such as low, moderate, and high were created, it was found that PSP surgery indications increased 23 times more in patients who had a high risk than in those who had a low risk.

Limitations

The present study has some limitations. First, it was a retrospective study. Therefore, a selection bias may have occurred. Second, the scientists who created the study consisted of individuals who followed the patients and performed the surgeries. Therefore, this may have caused a bias toward surgery. Third, a CT scan for each patient to detect bullae/blebs is not cost-effective. Fourth, there is an ongoing need for regular updating of predictive algorithms and their validation at the local level [22]. Fifth, some confounding factors such as smoking and cigarette pack/years, and the presence of bullae/blebs and the DSS were simultaneously used in the logistic regression analysis. Although smoking and cigarette pack/years and the presence of bulla/blep and the distribution of bulla/bleps are different entities, their combined use may have had a reinforcing effect on the results. In addition, re-evaluation of risk prediction models are especially important to keep up with the emergence of new therapies and to avoid misinterpretation of former and ongoing clinical trials.

This study had several strengths. Although this was a single-center study, it is important to standardize patient management. An adequate follow-up period was achieved in patients with PSP. Lastly, to the best of our knowledge, the present study is the first to investigate risk score modeling in patients with PSP.

Conclusion

It is clear that a scoring system is needed since the recurrence rates and PAL after the first episode of pneumothorax are very high. Whether it can be applied clinically, has also been investigated. The scoring system allows for the comparison of predicted and observed surgical indications for PSP surgery in low-, moderate-, and high-risk groups. Thus, it primarily enables a risk-adjusted benchmark of outcomes and fosters efforts to continuously improve the quality of follow-up of patients with PSP. Our scoring system may guide interventions to improve the follow-up of patients with PSP. It can be re-evaluated and recalibrated based on prospective multicenter results and the data sent to the mandatory national benchmarking project. We believe that this scoring system is a reliable tool for discussing and developing treatment guidelines. Our scoring system can be applied to other populations, thus testing its predictive accuracy. Further validation of our prediction model in patients with PSP in different medical centers and developing efficient acute and chronic care protocols to modify treatable medical conditions are our goals for future research. Therefore, we encourage other thoracic surgeons to apply this score in their patients.

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Author contribution NÇ: formal analysis; investigation; software; writing—original draft; conceptualization; methodology; resources; validation; visualization; writing—review and editing; supervision; and project administration. SÖ: data curation; investigation; writing—original draft; resources; visualization; writing—review, and editing. SK: investigation, software, validation, and supervision.

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Data availability The authors have full control of all primary data and that we agree to allow the journal to review their data if requested. The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. However, the data will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest The authors declare no conflict of interest.

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