

Institutional review – Pulmonary

Applicability of logistic regression (LR) risk modelling to decision making in lung cancer resection

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Abstract

The objective of this study was to evaluate the performance of a locally derived risk-adjusted model to predict cardiorespiratory morbidity after major lung resection for bronchogenic carcinoma. A logistic regression risk model has been developed using a database of 515 patients undergoing major lung resection between 1994 and 2001. Independent studied variables were: age of the patient, body mass index, predicted postoperative forced expiratory volume in the first second (ppoFEV1%), cardiovascular co-morbidity, diabetes mellitus, induction chemotherapy, tumour staging, extent of resection, chest wall resection, and perioperative blood transfusion. The analyzed outcome was the occurrence of postoperative cardiorespiratory complications prospectively recorded and codified. Variables with an influence on the outcome on univariate analysis were entered in the risk model. The calculated probabilities of complication were compared to its actual occurrence in 53 consecutive cases operated on between January and June 2002 and a receiver operating characteristic (ROC) curve was constructed. On logistic regression analysis, age ($P < 0.001$) and ppoFEV1 ($P = 0.003$) independently correlated with the outcome. The accuracy for morbidity prediction (area under the ROC curve) was 0.55 (95% CI: 0.31–0.78). These data show that this locally derived lung resection risk-adjusted model fails to predict postoperative cardiorespiratory morbidity in individual patients.

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Keywords: Risk stratification; Lung resection; Bronchial carcinoma**1. Introduction**

In the last 5 years, several single-institution [1,2] or multi-institutional reports [3–5] have been carried on to identify clinical predictors of morbidity or mortality after major resection for lung carcinoma. Although these papers provide relevant clinical information, applicability of results to medical decision making has not been proved. The aim of this investigation is to evaluate the performance of a locally derived risk model to predict individual cardiorespiratory morbidity in a different subset of cases.

2. Methods**2.1. Patient population**

From January 1994 to December 2001, 515 patients (Series A) underwent lung resection (lobectomy or pneumonectomy) for bronchogenic carcinoma at our unit. Patients who underwent exploratory thoracotomy, staging procedures or segmentectomy have not been included in the

study. Data on this population served to calculate a logistic regression (LR) model of operative risk (see below).

Selection criteria for operation consisted in the absence of major co-morbidity refractory to medical therapy, pO_2 at rest over 50 mmHg, pCO_2 under 46 mmHg and predicted postoperative forced expiratory volume in the first second (ppoFEV1%) over 30% of the normal value. Calculation of the ppoFEV1% was based on the number of non-obstructed pulmonary segments to be resected [6].

From 1 January to 1 June 2002, 53 consecutive comparable cases have been operated on (Series B) and their data were used for the prospective evaluation of the performance of the risk prediction model. All cases received similar preoperative and postoperative care including chest physiotherapy and postoperative pain management by epidural anaesthesia.

2.2. Risk model calculation**2.2.1. Analyzed variables and outcome**

The independent variables included in the analysis were: age of the patient, body mass index, ppoFEV1 value (as a percentage of the normal), presence or absence of ischaemic heart disease (evidenced by EKG changes, stress test, or

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Table 1

Univariate analysis of binary variables (Fisher's exact test and risk calculation)

	Factor present (<i>n</i> (%))	<i>P</i>	Odds ratio (95% CI)
Pathological stage IIIA–IV	163 (31.7)	0.85	1.04 (0.68–1.58)
Arrhythmia	59 (11.5)	0.75	0.89 (0.45–1.6)
Cardiac ischaemia	40 (7.8)	0.36	1.37 (0.69–2.75)
Induction chemotherapy	51 (9.9)	0.18	0.57 (0.27–1.2)
Diabetes mellitus	56 (10.9)	0.63	0.82 (0.43–1.58)
Pneumonectomy	148 (28.8)	0.91	1.04 (0.68–1.6)
Chest wall resection	42 (8.2)	0.09	1.80 (0.93–3.48)
Blood transfusion	48 (9.3)	0.49	1.29 (0.68–2.47)

coronariography), preoperative cardiac arrhythmia, type I or II diabetes mellitus and preoperative chemotherapy, pathological tumour staging (pIA–pIIB vs. pIIIA–pIV), extent of resection (lobectomy or pneumonectomy), concomitant chest wall resection, and perioperative blood transfusion.

The studied outcome was the occurrence of cardiorespiratory morbidity after surgery. Any of the following postoperative events were considered: pulmonary atelectasis or pneumonia, respiratory or ventilatory insufficiency at discharge (pO_2 under 60 mmHg or pCO_2 over 45 mmHg), need for mechanical ventilation at any time after extubation in the operating room, pulmonary thromboembolism, arrhythmia, myocardial ischaemia or infarct and clinical cardiac insufficiency.

All variables and outcomes were prospectively recorded.

2.2.2. Statistics

The univariate influence of binary variables on the outcome was assessed by contingency tables, Fisher's two-tailed exact test and risk calculation (odds ratio and its 95% confidence interval). Unpaired *t*-tests were performed to evaluate the difference of the means between the groups of patients with and without postoperative morbidity.

Variables with an influence on the outcome on univariate analysis ($P < 0.05$) were entered in a step-wise LR analysis and the logistic function was constructed with the calculated values of the β coefficient for the LR model and for each independent variable.

2.3. Evaluation of the homogeneity of both populations

Overall mortality and cardiorespiratory morbidity (Fisher's exact tests) and mean age and ppoFEV1% (unpaired *t*-

tests) were compared to evaluate the homogeneity of both subsets of cases.

2.4. Accuracy of the risk model

The performance of the LR prediction model was tested preoperatively on Series B cases. A probability of postoperative cardiorespiratory complication was calculated by one of us (G.V.) using the logistic function. Calculated risk was blinded to the rest of the team, so surgical indication was decided on the same basis as in Series A. A receiver operating characteristic (ROC) curve was constructed to evaluate the accuracy of risk prediction.

All calculations were performed by SPSS 10.0 software.

3. Results

Series A overall mortality and cardiorespiratory morbidity were, respectively, 6% (31 cases) and 26.5% (136 cases). In Series B, one patient died in the first 30 days after hospital discharge (1.9%) and cardiorespiratory morbidity was 18.2% (eight cases). Morbidity and mortality rates were similar in both groups ($P = 0.28$ and 0.5 , respectively). The mean age of the patients was 63.6 years (Series A) and 61.7 (Series B; $P = 0.21$). The mean ppoFEV1% was 63.4 (Series A) and 68.2 (Series B; $P = 0.09$).

On univariate analysis of Series A, none of the binary variables had an influence on the outcome (Table 1), but the age of the patient and low ppoFEV1% correlated with postoperative cardiorespiratory morbidity (Table 2). Both variables (Table 3) had an independent influence on the outcome on multivariate analysis ($P < 0.001$ and $P = 0.003$, respectively).

The probability of postoperative cardiorespiratory morbidity for Series B was calculated according to the

Table 2

Comparison of continuous variables in Series A; complicated vs. non-complicated cases

	Age (mean (SD))	ppoFEV1% (mean (SD))	BMI (mean (SD)) ^a
Complicated (<i>n</i> = 136)	65.8 (8.7)	58.9 (16.1)	25.7 (3.9)
Non-complicated (<i>n</i> = 379)	62.9 (10.1)	65.2 (17.9)	25.5 (4.1)
<i>P</i> value	0.003	< 0.001	0.58

^a BMI, body mass index.

Table 3
Multivariate LR model of cardiorespiratory morbidity^a

Variable	β coefficient	P	Odds ratio (95% CI)
Age	0.037	0.001	1.04 (1.01–1.06)
ppoFEV1%	– 0.022	0.003	0.98 (0.97–0.99)
Constant	– 2.047	0.02	

^a Hosmer–Lemeshow statistic, $P = 0.45$.

formula:

$$P = 1/[1 + \exp(2.047 - \text{Age} \times 0.037 + \text{ppoFEV1}\% \times 0.022)]$$

Using this calculated probability as a new prognostic continuous variable in Series B to construct a ROC curve (Fig. 1), we have obtained a C-index of 0.55 (95% CI: 0.31–0.78).

4. Discussion

In the last years, a number of articles have been published in which independent variables correlating to mortality or morbidity after major pulmonary resection are depicted [1–3]. Although knowledge of these variables can help to prevent postoperative morbidity, the applicability of these data to individual decisions has not been demonstrated.

In this report we have studied the utility of several variables to predict the risk of postoperative morbidity. We have considered an intermediate outcome instead of operative mortality because of the low probability of death, which would have required a considerably higher number of cases. Then, we used data of a series of patients operated

on in a single institution to calculate a LR model to estimate the risk of cardiorespiratory postoperative morbidity and prospectively tested the model on a different, but comparable, subset of cases. Finally, we have constructed a ROC curve with the calculated probability of complication for each case.

ROC curve analysis is a useful method to classify patients on the basis of the expected probability of operative death or complication [7]. The method has been used by Harpole et al. [3] in an excellent report on a multi-institutional database of 3516 operated cases. These authors have constructed a well-fit LR model with a C-index of around 0.63, when tested in the same population. Although the authors conclude that their data could be useful for prospective evaluation in individual cases, we have not found further information on the clinical applicability of the model. The only published prospective report we have found is that of Brunelli et al. [8]. In their investigation, they apply a previously designed scoring system (POSSUM) to predict operative risk in a series of 250 cases, finding a C-index of 0.67. Although the data presented are indeed interesting, the POSSUM score includes clinical data, such as respiratory status and Glasgow coma score, which are not applicable to scheduled lung cancer cases.

We have to recognize some limitations and bias in our study, the first being the number of cases in Series B. Single institution series have the advantage of homogeneous patient selection and perioperative management criteria; unfortunately, numerical results of such reports, due to the small number of cases, have to be cautiously considered because of the differences between the upper and lower limits of the confidence intervals. Multi-institutional series offer the opportunity to evaluate a large number of cases but recently, Pinna Pintor et al. [9], studying the performance of four different multi-institutional risk-adjusted models for coronary surgery, concluded that all tested models were inaccurate in predicting mortality in individual patients. To date, there is not a large multicentre lung cancer resection database available in Europe to be tested.

The second investigation bias is that all the cases were selected on the basis of several preoperative clinical criteria. The independent variables used in our investigation are usually cited in other reports [1–5,8,9]. We have not included the measure of the diffusion capacity of CO (DLCO) as a standard test before surgery. DLCO as been shown to correlate with operative mortality [10] in a non-selected series of cases. Unfortunately, we have included its measure only in selected cases with low ppoFEV1, so we have decided not to analyze the results in this investigation.

The age of the patient is discussed as a risk factor by Pagni et al. [11]. On the other hand, Damhuis and Schutte [12] have reported that lung cancer resection rates in elderly patients are lower than in the younger population, while overall operative mortality in this subset of cases is higher.

In opposition to data presented by other investigators [1], we have previously reported that preoperative chemother-

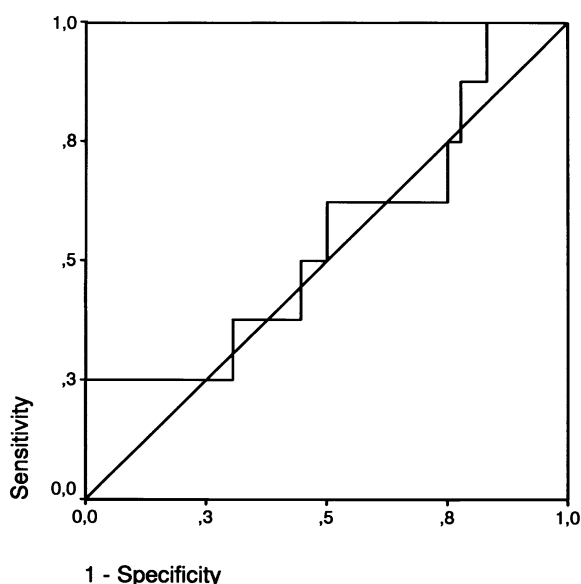


Fig. 1. ROC curve for the calculated risk in Series B. C-index: 0.54 (95% CI: 0.31–0.78).

apy is not a risk factor for postoperative morbidity [13]. In the report by Bernard et al. [1], induction chemotherapy should have been considered as a protective factor against postoperative complications because the odds ratio on multivariate analysis is reported to be 0.48 (95% CI: 0.25–0.93).

Besides the studied risk factors in our investigation, several clinical and biological predictive variables have been included in other reports, such as: peripheral vascular disease alone [4,5] or as a component of a co-morbidity index [1]; preoperative blood gas analysis [1,4,5] or pulmonary function tests [1,3–5]; tobacco [2–4] or alcohol abuse [3]; clinical functional status [1,3,4]; tumour pathology [4]; peripheral cell count [5]; serum albumin [3]; renal dysfunction [5]; and extent of resection (pneumonectomy vs. lesser resection) [1,3–5]. Among all these prognostic variables, only peripheral vascular disease [4] and pneumonectomy [1,3,5] have been found to have an influence on postoperative morbidity.

In the article from Duque et al. [4], the concept of vascular disease is not defined. If it includes all kinds and degrees of peripheral venous and arterial diseases, it could not be clinically useful as a risk marker.

We have not studied pneumonectomy as a risk factor. Instead, we have preferred to evaluate ppoFEV1. Three cited reports in which pneumonectomy has been depicted as a postoperative morbidity related variable, include in the study wedge and segmental resections [1,4,5], exploratory thoracotomies [5] or non-malignant diseases [1]. Furthermore, in none of these reports has ppoFEV1 been considered as a risk factor; so, postoperative morbidity related to pneumonectomy could be rather related to poor pulmonary function.

In our investigation we have included variables that are not preoperatively known such as blood transfusion. Harpole et al. [3] are the only investigators we know to differentiate between risk factors known pre- or intraoperatively. This is a very important point to keep in mind since most decisions concerning operability are taken on the basis of preoperatively known variables.

As we have stated before, clinical selection criteria constitute a limitation for the investigation since patients suspected to belong to a high risk group could receive different (more intensive) perioperative care. Even if this is the case, both Series A and B were affected by the same non-controllable bias.

To conclude, our data suggest that, although locally derived lung resection risk-adjusted models can be useful to depict clinical variables related to the outcome, they lack sensitivity and specificity. Due to previously discussed bias this conclusion has to be cautiously regarded and tested in a larger patient database.

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