Predicting death from surgery for lung cancer: A comparison of two scoring systems in two European countries

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Abstract

Objectives

Current British guidelines advocate the use of risk prediction scores such as Thoracoscore to estimate mortality prior to radical surgery for non-small cell lung cancer (NSCLC). A recent publication used the National Lung Cancer Audit (NLCA) to produce a score to predict 90 day mortality (NLCA score). The aim of this study is to validate the NLCA score, and compare its performance with Thoracoscore.

Materials and Methods

We performed an internal validation using 2858 surgical patients from NLCA and an external validation using 3191 surgical patients from the Danish Lung Cancer Registry (DLCR). We calculated the proportion that died within 90 days of surgery. The discriminatory power of both scores was assessed by a receiver operating characteristic (ROC) and an area under the curve (AUC) calculation.

Results

Ninety day mortality was 5% in both groups. AUC values for internal and external validation of NLCA score and validation of Thoracoscore were 0.68 (95% CI 0.63-0.72), 0.60 (95% CI 0.56-0.65) and 0.60 (95% CI 0.54-0.66) respectively. Post-hoc analysis was performed using NLCA records on 15554 surgical patients to derive summary tables for 30 and 90 day mortality, stratified by procedure type, age and performance status.

Conclusions

Neither score performs well enough to be advocated for individual risk stratification prior to lung cancer surgery. It may be that additional physiological parameters are required; however this is a further project. In the interim we propose the use of our summary tables that provide the real-life range of mortality for lobectomy and pneumonectomy.

Keywords:

Lung cancer

Thoracic surgery

Mortality

Validation study

1 Introduction

Current British Thoracic Society (BTS) guidelines advocate the use of a risk prediction score such as Thoracoscore to estimate, prior to surgery, the risk of death following radical surgical management in those with non-small cell lung cancer (NSCLC).(1) However, Thoracoscore was developed to predict in-hospital mortality only and was not derived from a population with solely malignant disease but included patients undergoing thoracic surgery for a range of indications from the relatively minor spontaneous pneumothorax to complicated pneumonectomy for lung cancer. Recent work has suggested that using in-hospital or 30 day mortality may underestimate the risk of early death following surgery for lung cancer.(2, 3) In addition, two studies have tried to validate Thoracoscore, but found it to be of limited discriminative ability to predict mortality in lung cancer patients.(4, 5) Despite this some surgical centres in the United Kingdom (UK) use this score routinely pre-surgery to provide an estimation of risk. Powell et al(6) used the National Lung Cancer Audit (NLCA) linked to Hospital Episode Statistics (HES) to produce a new score to predict 90 day mortality after surgery in those with lung cancer. The aim of the present study is to validate this score, henceforth called the NLCA score, and compare its performance with Thoracoscore in patients with lung cancer using an updated NLCA dataset and the Danish Lung Cancer Registry (DLCR).

2 Methods

2.1 Internal validation

2.1.1 Patient population and data source

The NLCA is a prospective database which has collated information provided by 157 English NHS hospitals on demographic, tumour and treatment for patients with primary lung cancer since 2004. It is linked to data from Hospital Episode Statistics (HES), used to derive co-morbidity information from coded inpatient episodes alongside information regarding interventions and procedures performed, and Office of National Statistics (ONS) which provides information on date of death.

We identified patients from NLCA data who underwent curative surgery for NSCLC (using Office of Population Censuses and Surveys Classification of Interventions (OPCS-4) coding) between 1st January 2004 and 31st March 2012. Those with stage 3b or stage 4 lung cancer were excluded, as were those with International Classification of Diseases- revision 10(ICD-10) codes for metastases recorded prior to the procedure date. The original predictive score was derived from NLCA patient data for operations performed between 1st January 2004 and 31st March 2010 so we limited our internal validation cohort to those who underwent surgery between 1st April 2010 and 31st March 2012 to ensure that this was an independent population.

2.2 External validation

2.2.1 Data source and patient population

The Danish Lung Cancer Registry (DLCR) contains data on over 90% of patients diagnosed with lung cancer in Denmark from 2005 onwards. Registry data are linked with data from national databases: demographic information is retrieved from the Central Population

Register, pathology information from the National Pathology Registry and comorbidity data from the National Hospital Register.

All patients who underwent curative surgery for NSCLC between 2005 and 2011 were identified from the DLCR to form our external validation cohort.

2.3 Covariates

For the purposes of validation procedure type was classified as pneumonectomy, bi-lobectomy/lobectomy/wedge/segmentectomy, or other. Where there were multiple procedure codes for an individual the most extensive procedure type was included; the most recent procedure date was included if there was more than one for any individual. Comorbidity was classified according to Charlson index using our established methods.(7-9) Patients were then categorised into two groups based on their Charlson index (0-1 and ≥ 2). Percentage predicted forced expiratory volume in 1 second (FEV_1) was categorised into four groups (>80%, 61-80%, 40-60% and <40%) and WHO performance status into three groups (PS: 0, 1-2, ≥3). Pre-treatment records in NLCA and DLCR records linked to National Pathology Registry were used for stage (grouped as IA, IB, IIA/IIB and IIIA) according to the 7th edition of UICC TNM, with post-treatment stage used if pre-treatment records were missing. Age was categorised into four groups (<55, 55-65, 66-85 and >75). Those with missing data from any of the covariates listed were excluded from the validation.

2.4 Statistical analysis

All statistical analyses were conducted using Stata MP V.12 (StataCorp, Texas, USA). All patients in the NLCA and DLCR datasets were assigned a risk score using the coefficients and constants from the multivariable model in the NLCA score (6) using the equation: risk score

= constant + sum of β coefficients at different values of each covariate. We then identified those who died within 90 days of surgery.

The NLCA dataset only was then used to assign each patient a risk score based on Thoracoscore in the same way using the β coefficients and constant derived for Thoracoscore.(10) Since the NLCA dataset does not contain fields for American Society of Anesthesiologists (ASA) score or Medical Research Council (MRC) dyspnoea score which are required to generate Thoracoscore, we used data that were available to estimate these scores for the purposes of validation as follows; patients are given a coefficient in Thoracoscore if their ASA grade is ≥ 3; which refers to severe systemic disturbance from any cause. It is not possible to state an absolute measure of severity, as this is a matter of clinical judgement. We therefore used a combination of Charlson co-morbidity score and performance status (as a measure of functional capacity) to derive the ASA grade. Those with a Charlson score of ≥ 2 and performance status ≥ 2 were given an ASA grade of 3 for the purposes of this analysis. Patients with MRC dyspnoea score of ≥ 3 are allocated a coefficient in Thoracoscore. This refers to those with some limitation of activity due to breathlessness during daily life. Those who had FEV1 < 60% predicted were assigned MRC dyspnoea score of ≥ 3. A sensitivity analysis was performed using various thresholds of Charlson score, performance status and FEV1 to assign MRC dyspnoea score and ASA grade to the population, all of which produced very similar results in the validation. Once we had assigned all patients a coefficient for all covariates we identified all those who died in hospital (date of death prior to or the same as discharge date for their surgical procedure).

The discriminatory power of each score to predict mortality was assessed by means of a receiver operating characteristic (ROC) curve and an area under the curve (AUC) calculation.

We also repeated the validation in the NLCA dataset using multiple imputation to create substituted values for the missing data fields for FEV1, performance status and stage.

3 Results

3.1 NLCA patients

We identified 17687 patients in the NLCA who received curative surgery for NSCLC between 1st January 2004 and 31st March 2012. Of these we excluded 670 patients who had an ICD-10 code for metastases prior to their operation date, 612 patients who had missing or incongruous diagnosis dates and 851 in whom the procedure date was >3 months before or >6 months after the NLCA diagnosis date. This left 15554 patients of which 6080 had a procedure date between 1st April 2010 and 31st March 2012. We excluded a further 3222 with incomplete data on FEV1, missing performance status or missing stage, leaving a final validation cohort of 2858 patients.

3.2 Multiple imputation

Due to the amount of missing data in the NLCA we performed multiple imputation to create substituted values for the missing variables. We performed the analysis with the entire 6080 patients using the imputed values for FEV1, performance status and stage, where these were missing. There was minimal change in the area under the ROC curve, so the results of the original validation, restricted to those with complete data are reported.

3.3 DLCR patients

Our DLCR cohort comprised 4234 patients who underwent curative surgery from 2005 onwards. We excluded 1043 patients with missing data on FEV1, performance status or stage, giving a validation cohort of 3191 patients.

3.4 Demographic features

Those in the NLCA validation cohort were older than those in DLCR, with a median age of 69 years (interquartile range (IQR) 63-75 years) versus 66 years (interquartile range (IQR) 60-73

years) in the DLCR. There were proportionally more women in the DLCR group (49% versus 46%) and their cohort also had a greater proportion of patients who were classified as WHO performance status 0 (54% compared with 43%). Pneumonectomy was infrequent in both groups with 9% of those in DLCR and 8% in NLCA undergoing that procedure. Despite these differences, both groups had a similar 90 day mortality of 5% (288 patients died within 90 days of surgery in NLCA and 204 patients in DLCR overall). Features of the NLCA and DLCR groups are summarised in table 1.

3.5 Validation of NLCA score

The ROC curve generated from the application of the NLCA score to the NLCA validation cohort is shown in figure 1 (internal validation) and application to the DLCR cohort in figure 2 (external validation). Area under the ROC curve was 0.68 (95% confidence interval (CI) 0.63-0.72) and 0.60 (95% CI 0.56-0.65) respectively.

3.6 Validation of Thoracoscore

When the coefficients derived from Thoracoscore were used to compute risk probability scores in the NLCA validation cohort the area under the curve was 0.60 (95% CI 0.54-0.66). The ROC curve is presented in figure 3.

3.7 Post-hoc analysis: Summary tables

Neither Thoracoscore nor the NLCA score performed well enough to be advocated for routine use to predict surgical mortality in lung cancer patients. In the work by Powell et al(6) age, procedure type and performance status were identified as the major drivers of post-operative mortality. We therefore performed a post hoc analysis using data from the NLCA on all 15554 patients who underwent curative surgery for NSCLC between 1st January 2004 and 31st March 2012 to derive summary tables for 30 and 90 day mortality, stratified

by procedure type, age and performance status. We excluded those sub groups which contained fewer than 50 patients as we were unable to provide accurate estimations of mortality due to the small numbers. Results for 30 day mortality are summarised in table 2 and for 90 day in table 3. In general, these show increasing risks of mortality with increasing age and worsening performance status regardless of procedure type, however those undergoing pneumonectomy have higher predicted post-operative mortality than the lobectomy group for each age and performance status sub group.

Discussion

We used two independent datasets to compare the performance of the recently derived NLCA score (6) with the currently recommended scoring system (Thoracoscore) for predicting early mortality after lung cancer surgery. There are several scales which are used for AUC value interpretation but, in general, ROC curves with an AUC < 0.75 are not considered to be clinically useful. Our results suggest therefore, that neither of these scoring systems has sufficient predictive or discriminative ability to be advocated for use in predicting risk of mortality for individual patients prior to surgery for NSCLC.

3.8 Strengths and limitations

The strength of this study is that we were able to perform both an internal and external validation using large UK and non-UK lung cancer populations to fully explore the performance of these risk scoring systems. The NLCA has previously been shown to be representative of the UK lung cancer population (11) and likewise the DLCR contains high quality data (12). However both datasets are made up of a predominantly white population so extrapolation of these results to different ethnic groups is difficult.

Although data completeness is improving in the NLCA, missing data are still a challenge. A substantial proportion of patients do not have data on FEV1 (49% in our validation cohort). This is likely to represent data that were unavailable to the administrators at the time of data entry as all patients will have had some measure of their lung function performed prior to undergoing surgical resection. Likewise the DLCR has some fields which have a lot of missing data, namely performance status (17% missing) and stage (19%) although their recording of FEV1 is complete in 98% of records. Even after we had excluded those with missing data fields sample sizes remained large and our multiple imputation analysis did not

change any of the results substantially suggesting that the missing data did not affect the validity of our findings.

In order to validate Thoracoscore we had to derive two covariates (MRC dyspnoea score and ASA grade) as these fields were not available in the NLCA. A sensitivity analysis performed using different cut offs to assign ASA grade and MRC dyspnoea score did not change the results of the validation so we do not feel that this is an important limitation. ASA grade is allocated based on clinician judgement and studies have shown that there is only moderate agreement between anaesthetists regarding allocation of a score to an individual(13-15), suggesting that even in datasets where this is included, patients with similar co-morbidities and functional capacity may be assigned different ASA grades.

3.9 Comparison with other studies

A UK study assessed the ability of Thoracoscore to predict mortality following elective lung resection in 703 patients (of whom 91% had underlying malignancy). (4) They showed that Thoracoscore has limited discriminative and poor predictive ability to determine mortality, with area under the ROC value of 0.68 (95% CI 0.56–0.80). They also assessed the performance of the revised Thoracoscore (EPITHOR)(16) and the updated European Society for Thoracic Surgery mortality score (5) and found poor discriminative ability for both (area under ROC 0.61 (95% CI 0.46-0.76) and 0.68 (95% CI 0.54-0.82) respectively. A second publication addressed the ability of Thoracoscore to predict mortality in a population undergoing pneumonectomy (largely but not exclusively for underlying malignancy).(17) Again the discriminatory power of Thoracoscore in this population was poor with an area under the ROC value of 0.44. Both studies suggest that Thoracoscore tends to under-estimate mortality in those at low-risk and over-estimate risk in high-risk cases.

In the previous study by Powell et al(6) three hypothetical patients were used to compare the predicted post-operative mortality using Thoracoscore and the NLCA score. This comparison showed that the predicted mortality for low risk patients was very similar but mortality in the medium and high-risk patients were much higher using the NLCA score (likely reflecting the difference between in-hospital and 90 day mortality).

It is possible that intraoperative factors affect morbidity and mortality. One score comprising intraoperative features (the POSSUM score) has been validated in the thoracic surgical population. The POSSUM score was originally devised as a tool to facilitate general surgical audit. (18) It consists of 12 physiological features (physiologic score (PS)) and an operative severity score (OSS), which comprises 6 variables associated with the surgical procedure. Brunelli et al(19) used an Italian cohort of 250 lung cancer patients to validate POSSUM as a tool for thoracic surgery. A composite end point of morbidity, which included mortality, was used and both models showed only moderate discriminative ability (area under ROC curve of 0.66 and 0.67). In order to calculate POSSUM both the PS (scored at the time of surgery) and OSS (scored post-operatively) are required to be complete which means that this score cannot be used to provide an estimation of pre-operative risk.

3.10 Clinical relevance

The question is raised regarding what clinicians should use to inform pre-operative conversations about surgical risk with patients; by using scoring systems which do not predict individual mortality accurately we may be misleading them. In support of this the European Respiratory Society/ European Society of Thoracic Surgeons (ERS/ ESTS) (20) reviewed the risk scores available to predict post-operative mortality and concluded that current scoring systems do not provide an adequate assessment for individual patients. However, they suggest that risk scores could be utilised for benchmarking and risk stratification among groups of surgical candidates.

Therefore, communicating a range of risk, such as that described in our summary tables (tables 2 and 3), taking into account performance status, age and procedure type, may be the simplest and most appropriate method of exploring the concept of procedural risk with patients. In some ways these are more accessible to patients and surgeons. The population-level summary tables we have derived show that, particularly in those patients who are older or who have poorer performance status, the range of post-operative mortality is much broader than in the lowest risk group, which may explain in part why individual scores have not shown good discriminative ability. Individual risk assessment may be possible in the future if improved risk prediction models are developed incorporating physiological measurements. Ensuring that risk assessment and scoring systems are validated and robust is equally important with the proposal that thoracic surgeons should publish surgeon specific outcome data.

3.11 Conclusions

These results suggest that although the recently derived NLCA score performs slightly better than Thoracoscore in our UK population, neither performs well enough to be advocated for routine use prior to lung cancer surgery. It may be that either the addition of physiological parameters to demographic and procedural data or risk stratification using physiological measurements alone is needed to better predict individual mortality; and this should form the basis of further research. In the interim we propose that our summary tables provide clinicians and patients with easy-access to the actual range of post-operative mortality in the UK for lobectomy and pneumonectomy according to performance status and age.

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Table 1: Demographics of NLCA and DLCR validation cohorts

		NLCA cohort N=6080		DLCR cohort N=4234	
		n	%	n	%
Age	**<55**	415	6.83	490	11.6
	55-65	1660	27.3	1331	31.4
	66-75	2589	42.58	1643	38.8
	>75	1416	23.29	770	18.2
Sex	**Male**	3291	54.13	2155	50.9
	Female	2789	45.87	2079	49.1
Performance status	**0**	2618	43.06	2279	53.8
	1-2	2624	43.16	1224	28.9
	≥3	48	0.79	31	0.7
	Missing	790	12.99	700	16.5
% predicted FEV1	**>80%**	1453	23.9	2413	57
	61-80%	1064	17.5	1056	24.9
	40-60%	504	8.29	588	13.9
	<40%	88	1.45	83	2
	Missing	2971	48.87	94	2.2
Procedure type	**(Bi-)lobectomy, wedge or segmentectomy**	5333	87.71	3837	90.6
	Pneumonectomy	475	7.81	397	9.4
	Other	475	7.81	-	-
Charlson score	**0-1**	4020	66.12	3107	73.4
	≥2	2060	33.88	1127	26.6
Stage	**IA**	1747	28.73	1248	29.5
	IB	1478	24.31	1135	26.8
	IIA or IIB	1499	24.65	712	16.8
	IIIA	871	14.33	331	7.8
	Missing	485	7.98	808	19.1

Table 2: Summary table for 30 day mortality for those undergoing lobectomy (Table 2a) and pneumonectomy (Table 2b). The 95% confidence intervals are presented in brackets below the risk %, with the total number in this group underneath

Table 2a: 30 day mortality following lobectomy

	Performance status		
Age (years)	**0**	**1**	**2**
< 70	**1%** (0-1%) 2534	**2%** (1-2%) 1467	**3%** (1-5%) 222
70-80	**2%** (1-3%) 1361	**3%** (2-4%) 1420	**5%** (2-8%) 219
>80	**3%** (1-5%) 263	**4%** (2-6%) 377	**8%** (2-15%) 72

Table 2b: 30 day mortality following pneumonectomy

	Performance status		
Age (years)	**0**	**1**	**2**
< 70	**5%** (3-7%) 436	**6%** (3-8%) 289	-
70-80	**11%** (6-16%) 143	**6%** (3-10%) 154	-

Table 3: Summary table for 90 day mortality for those undergoing lobectomy (Table 3a) and pneumonectomy (Table 3b). The 95% confidence intervals are presented in brackets below the risk %, with the total number in each group underneath

Table 3a: 90 day mortality following lobectomy

	Performance status		
Age (years)	**0**	**1**	**2**
< 70	**2%** (1-2%) 2534	**3%** (2-4%) 1467	**7%** (3-10%) 222
70-80	**4%** (3-6%) 1361	**6%** (5-7%) 1420	**8%** (5-12%) 219
>80	**6%** (3-9%) 263	**7%** (5-10%) 377	**17%** (8-25%) 72

Table 3b: 90 day mortality following pneumonectomy

	Performance status		
Age (years)	**0**	**1**	**2**
< 70	**7%** (5-10%) 436	**12%** (8-16%) 289	-
70-80	**18%** (12-25%) 143	**12%** (7-18%) 154	-