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Predicting survival following surgical resection of lung cancer using clinical and pathological variables: The development and validation of the *LNC-PATH* score

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ABSTRACT

Introduction: The aim of this study was to develop and validate a simple prognostic scoring system using readily available clinical and pathological variables that could stratify patients according to the risk of death following lung cancer resection. We hypothesized that by using additional pathological variables not accounted for by pathological stage alone coupled with markers of overall fitness a new prognostic tool could be developed.
Methods: Multivariable logistic regression analysis of pathological and other clinical variables from patients undergoing surgical resection of non-small cell lung cancer (NSCLC) were used to determine factors independently associated with 2-year overall survival and so derive the scoring system. The model was then validated in an external multi-centre dataset.
Results: Using multivariable logistic regression on a large dataset (n = 1,421) the ***'LNC-PATH'*** (**L**ymphovascular invasion, **N**-stage, adjuvant **C**hemotherapy, **P**erformance status, **A**ge, **T**-stage, **H**istology) prognostic score was devised and then validated using an external dataset (n = 402). This can be used to risk stratify patients into low, moderate and high-risk groups with a statistically significant difference between the three groups in their survival distributions. 83.8% of patients in the low-risk group survived two years after surgery compared to 55.6% in the moderate-risk group and 26.2% in the high-risk group. The score was shown to perform moderately well with an Area Under the Receiver Operating Characteristic curve (AUROC) value of 0.76 (95% CI: 0.73–0.79) and 0.70 (95% CI: 0.64–0.76) in the derivation and validation cohorts respectively.
Discussion: The *LNC-PATH* score predicts 2-year overall survival after surgery for NSCLC. This may allow the development of risk stratified follow-up protocols in survivorship clinics which could be the subject of future prospective studies.

1. Introduction

The optimal approach to follow patients up after surgical resection of non-small cell lung cancer (NSCLC) is keenly debated; including what imaging modality to use and the intensity of clinical assessments. A systematic review in 2012 concluded that "the paucity of evidence precludes firm evidence based guidelines" [1]. This uncertainty leads to a variability of practice nationally and internationally, which ranges

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from routine physical examination plus chest X-ray (CXR) [2] to more intensive protocols including routine computed tomography (CT) of the thorax, bronchoscopy, abdominal ultrasound, CT brain and bone scans for all patients [3]. Numerous international guidelines recommend that all patients receive regular clinical assessments usually at three to six month intervals [4–6]. The potential benefits of intensive follow-up and cross-sectional imaging include the early detection of recurrent disease confined to the thorax, detection of distant recurrence prior to a decline in performance status, early intervention in symptom control and the detection of asymptomatic second primary lung cancers suitable for further radical treatment. All of these outcomes have the potential to improve survival by facilitating more radical therapy and improving access to systemic therapies. Gourcerol et al investigated an intensive protocol of cross-sectional imaging in 162 patients following NSCLC surgery and identified 11 patients with asymptomatic intra-thoracic recurrence that were treated radically and alive three years following the recurrence (33 life years gained) [3]. In a further French study of 192 patients, seven patients identified with asymptomatic isolated thoracic recurrence were treated radically and alive three years later (21 life years gained) [7]. However the costs of intensive follow-up protocols [3], the potential harm from investigating false positive imaging findings [8] and the impact on overall survival need consideration. The lung cancer community is eagerly awaiting the full published results of a large randomized controlled trial of CT versus CXR follow-up [9] which may provide answers to the question of imaging modalities in follow-up regimes. The aim of this study was to develop a prognostic scoring system using simple and readily accessible clinical and pathological variables that categorises the risk of death from any cause within the first two years following surgical resection. Our hypothesis was that by incorporating pathological factors known to be associated with a poorer prognosis, e.g. lymphovascular invasion [10], and clinical factors known to influence survival, e.g. performance status, a more comprehensive and precise prediction model could be developed which may perform better than pathological stage alone. Such a tool might, in the future, be used to inform the intensity of follow-up regimes potentially allowing clinicians to intensify the follow-up in high risk patients and de-intensify those low risk patients.

2. Materials and methods

The Manchester Thoracic Oncology Centre (MTOC) at the Manchester University NHS Foundation Trust is a large regional lung cancer centre in the United Kingdom (UK). The Thoracic Surgery Department currently performs over 400 NSCLC resections per year. Each surgical resection specimen is analysed and reported by a specialist thoracic histopathologist using the Royal College of Pathology Dataset for Lung Cancer. For this retrospective study all pathological reports for NSCLC resections from 01/01/2011 to 31/12/2014 were reviewed. Only patients with adenocarcinoma, large cell NSCLC, other NSCLC, and squamous cell carcinoma were included. Small cell lung cancers and carcinoid tumours were excluded given their differing prognosis to NSCLC. If there were two records from the same patient on the same date (synchronous lung cancers resected simultaneously), one record was excluded (the lower stage). If there were two records from the same patient on different dates (metachronous lung cancers resected), the earliest record was included and censored at the time of the second date. If mean survival could not be calculated due to missing data, the case was excluded. The following variables were recorded for all patients: age, gender, type of surgery (sub-lobar resection, bi/lobectomy, pneumonectomy), T-stage (T1a, T1b, T2a, T2b, T3, and T4 (TNM7)), N-stage (N0, N1, and N2 (TNM7)), single station versus multistation disease in cases of N2, adequacy of intra-operative lymph node sampling measured against the International Association for the Study of Lung Cancer (IASLC) recommendations (at least three mediastinal lymph nodes, station 7 in all cases, station 5/6 in left upper lobe tumours and station 9 in lower lobe tumours), presence or absence of extracapsular nodal disease, presence or absence of lymphovascular invasion, grade of pleural invasion (PL0, PL1, PL2 and PL3), grade of tumour differentiation (well, moderate, poor and undifferentiated), and the presence or absence of microscopic residual disease (R0, R1). T-stage, N-stage, pleural invasion and residual disease were all reported in line with the IASLC 7th Edition Staging Manual [11]. Pre-operative performance status and post-operative adjuvant chemotherapy data was acquired through case note reviews. Survival data for all patients was obtained through a national death registry. Patients that died within the first 30 days of surgery were removed from the analysis as this is likely to reflect surgical complications. The analysis was undertaken from January 2017 to ensure a minimum of 2-years follow-up for all patients. An independent dataset of the same variables was acquired from three other UK surgical centres (Bristol, Glasgow and Leeds) for all patients with NSCLC that underwent surgical resection in the calendar year 2014 and used for validation. The study was discussed with the regional ethics committee in writing and confirmation was received that no formal ethical approval was required.

3. Statistical methods

Demographic and clinically important variables were summarised using means, standard deviations (SD) and ranges for continuous variables and frequencies and percentages were used for binary and categorical variables. Single variable logistic regressions were used to assess the relationship between 2-year mortality and the variables of interest. 2-year mortality was chosen as a timeframe as this is the highest risk period for disease recurrence and represents the time period likely to require the most intensive follow-up interventions [12]. All variables in the single variable analysis were considered in the multivariable logistic regression model. Both backward and forward stepwise selection procedures were used to select the final multivariable model. The backward stepwise selection procedure began with a model including all variables, the least significant variable was removed and then the model was run again. This process was repeated until only variables that were significant at the 5% significance level remained. The forward stepwise selection procedure began with a logistic regression including the most significant variable and then attempted to include further significant variables in order of significance. The procedure stopped when no additional variable could be included that was significant at the 5% significance level in the multivariable model. N-stage was considered a clinically important variable and as such was kept in the model regardless of statistical significance. A risk score was produced based on the regression coefficients of the final 2-year mortality model. Three risk groups were selected from the scores and assessed against survival using a Kaplan-Meier graph and log-rank tests. The risk model was validated using an independent dataset. Model calibration was carried out using the Hosmer-Lemeshow goodness of fit test. All analyses were performed using SPSS 22 and Stata 14. Statistical significance was at the 5% level unless otherwise stated.

4. Results

The database contained 1,421 patient records covering this period. Of these, 123 cases were excluded due to non-NSCLC histology (n = 76), duplicate entries (n = 31) or missing data (n = 16). A total of 1,298 patients were included in the analysis. There were 26 deaths within the first 30 days after surgery and were excluded from the analysis. Of the remaining 1,272 patients there were 306 deaths (24.1%) within two years and 238 patients (18.7%) who were censored before the second year and could not have their 2-year mortality determined. Therefore there were 1,034 patients included in each analysis unless otherwise stated. Mean age was 67.6 ± 8.7 and 48.4% (500/1034) were female. The predominant histological sub-types were adenocarcinoma (54.1%, 559/1034) and squamous cell carcinoma (39.3%, 406/1034). Of the Adenocarcinomas the predominant pattern was

Table 1
Descriptive statistics of the dataset analysed.

Variable	Mean (SD), range
Age (years)	67.6 (8.7), 20-87
	Frequency (%)
Gender – female	500 (48.4%)
Year	
2011	160 (15.5%)
2012	307 (29.7%)
2013	403 (39.0%)
2014	164 (15.9%)
Histology	
Squamous Cell Carcinoma	406 (39.3%)
Large cell NSCLC	49 (4.7%)
Other NSCLC	20 (1.9%)
Adenocarcinoma:	559 (54.1%)
-Acinar	280 (50.0%)
-Lepidic	111 (19.9%)
-Papillary/Micropapillary	35 (6.3%)
-Solid	113 (20.2%)
-Unknown	20 (3.6%)
Type of surgery	
Sub-lobar	109 (10.5%)
Lobectomy	838 (81.0%)
Pneumonectomy	87 (8.4%)
T stage	n = 1031
pT1a	206 (20.0 %)
pT1b	154 (15.0%)
pT2a	361 (35.0%)
pT2b	107 (10.4%)
pT3	175 (17.0%)
pT4	28 (2.7%)
N stage with multi-station information	n = 1033
pN0	654 (63.3%)
pN1	171 (16.6%)
pN2 – single station	108 (10.5%)
pN2 – multi-station	53 (5.1%)
pNX	47 (4.5%)
Extracapsular spread – yes	142/1032 (13.8%)
Lymphovascular invasion – yes	257/1033 (24.9%)
Pleural invasion	n = 1028
PL0	654 (63.6%)
PL1	230 (22.4%)
PL2	68 (6.6%)
PL3	76 (7.4%)
Grade of differentiation	n = 902
Poor	274 (30.4%)
Moderate	365 (40.5%)
Well	199 (22.1%)
Unknown	64 (7.1%)
R0/R1 resection – R1	168/1033 (16.3%)
Adequacy of nodal sampling – Adequate	342/1031 (33.2%)
	Frequency (%)
PS	n = 946
0	275 (29.1%)
1	587 (62.1%)
2	79 (8.4%)
3	5 (0.5%)
Adjuvant Chemotherapy – yes	360/1006 (35.8%)

Acinar (50.1%, 280/559). The descriptive statistics of the dataset variables are summarised in Table 1.

Single variable analysis showed 11 of 14 pre-defined variables to have a statistical significance at 5% (Table 2). Multivariable analysis using backward and forward selection identified seven variables that maintained independent associations with survival (Histological subtype, pathological T-Stage, pathological N-stage, lymphovascular invasion, age, performance status and adjuvant chemotherapy) (Table 2). Based on the 2-year mortality model using the above seven variables a scoring model, the *LNC-PATH* score (**L**ymphovascular invasion, **N**-stage, adjuvant **C**hemotherapy, **P**erformance status, **A**ge, **T**-stage, **H**istology), was produced from the regression coefficients of the paramenters, with an Area Under the Receiver Operating Characteristic curve (AUROC) of 0.76 (95% CI: 0.73-0.79). Table 3 outlines the scoring system. An individual score can range from 0 to 8.5. A number of cut-offs were considered for risk catagorisation by analsysing the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of various score ranges. Patients can be catagorised into low-risk (Score ≤ 3), moderate-risk (score 3.5–4.5) and high-risk (score ≥ 5) groups. 83.8% (469/560) of patients in the low-risk group survived two years after surgery compared to 55.6% (154/277) in the moderate-risk group and only 26.2% (22/84) in the high-risk group. The Kaplan-Meier survival curves for the three sub-groups are shown in Fig. 1. There is a statistically significant difference between the three groups in their survival distributions: the high-risk group having shorter survival times than the moderate-risk group and the low-risk group (overall log-rank test $p < 0.001$, all pairwise comparisons – low vs moderate, low vs high, moderate vs high – $p < 0.001$). The hazard ratio from a Cox proportional hazards model for moderate vs low-risk was 2.95 (95% CI: 2.33–3.72) and for high vs low-risk was 7.04 (95% CI: 5.24–9.46).

An external independent dataset of 402 patients was used to validate the scoring system. This consisted of patient data from three separate cardiothoracic units across the UK: Bristol (n = 214), Glasgow (n = 96) and Leeds (n = 92). All patients underwent surgical resection of NSCLC at these surgical centres in the calendar year 2014. The AUROC from the *LNC-PATH* score for the validation dataset was 0.70 (95% CI: 0.64–0.76). Survival analysis of this second dataset revealed that the *LNC-PATH* risk groups had similar hazard ratio trends for mortality as the initial derivation dataset (Fig. 1). In the validation group the hazard ratio from a Cox proportional hazards model for moderate vs low-risk was 1.86 (95% CI: 1.29–2.68) and for high vs low-risk was 3.23 (95% CI:1.96–5.31).

The AUROC for the LNC-PATH score (0.76, 95% CI: 0.73–0.79) was statistically significantly higher when compared to overall stage alone in the derivation dataset (0.67, 95% CI: 0.63-0.70; $p < 0.001$) but not in the validation dataset (0.70 vs 0.66, $p = 0.19$). A comparison of the single variable Cox proportional hazards models in the derivation cohort for overall stage and the *LNC-PATH* risk groups showed the model fit was better for the *LNC-PATH* risk groups (921 patients: Akaike's information criterion (AIC) for overall stage: 4473; AIC for *LN-PATH* risk groups: 4400). A model calibration was carried out using the Hosmer-Lemeshow goodness of fit test, which was non-significant ($p = 0.57$). This shows the model is a good fit to the observed data.

5. Discussion

The *LNC-PATH* scoring system is a simple tool calculated with readily accessible variables from within medical records and standardised pathological reports following lung cancer resection. It has been validated within a multi-centre dataset in a diverse population from the UK separate to the population from which the tool was derived. It provides a potential clinical tool for assessing the risk of mortality within the first two years following surgical resection of lung cancer. However, it is important to note that the *LNC-PATH* model demonstates only a moderate ability to predictic survival with an AUROC value of 0.76 and 0.70 in the derivation and validation datasets respectively. Analysis of the external validation dataset suggests the *LNC-PATH* model did not offer significantly improved mortality predcition over pathological stage alone, which in turn also demonstrated only a moderate ability to predict mortality. This once again emphasises the challenges in predicting survival after surgical treatment of NSCLC with currently available tools and the need for development of better predictive measures and progostics scores in the future.

Tools that predict survival following radical treatment have a number of potential clinical applications including selection for adjuvant treatment, assuming the mortality is driven by cancer

Table 2
Single and multivariable analysis.

Variable	Single variable analysis (n = 1034)		Multivariable analysis (n = 921)	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Histology sub-type		< 0.001		< 0.001
Squamous Cell Carcinoma	1 (-)		1 (-)	
Large cell NSCLC	3.30 (1.80-6.05)	< 0.001	3.95 (1.98-7.88)	< 0.001
Other NSCLC	1.86 (0.75-4.60)	0.18	1.54 (0.54-4.42)	0.42
Acinar	0.72 (0.51-1.01)	0.058	0.79 (0.52-1.19)	0.25
Lepidic	0.41 (0.24-0.72)	0.002	0.38 (0.19-0.77)	0.007
Papillary/Micropapillary	0.91 (0.42-1.95)	0.81	0.80 (0.33-1.91)	0.61
Solid	1.45 (0.94–2.24)	0.093	1.70 (1.02–2.81)	0.040
Unknown	0.97 (0.37–2.60)	0.96	0.75 (0.21–2.67)	0.66
Type of surgery		0.001		
Sub-lobar	1 (-)		–	–
Lobectomy	1.27 (0.80–2.03)	0.31		
Pneumonectomy	2.85 (1.55–5.23)	0.001		
T stage	n = 1031	< 0.001		< 0.001
pT1a	1 (-)		1 (-)	
pT1b	1.27 (0.74–2.19)	0.39	1.37 (0.73–2.56)	0.33
pT2a	2.04 (1.31–3.15)	0.001	1.94 (1.16–3.26)	0.012
pT2b	2.89 (1.68–4.97)	< 0.001	3.33 (1.74–6.38)	< 0.001
pT3	5.55 (3.45–8.93)	< 0.001	6.84 (3.82–12.27)	< 0.001
pT4	5.24 (2.29–12.01)	< 0.001	5.12 (1.83–14.27)	0.002
N stage with multi-station information	n = 1033	< 0.001		0.008
pN0	1 (-)		1 (-)	
pN1	2.28 (1.59–3.25)	< 0.001	2.32 (1.31–4.12)	0.004
pN2 – single station	2.97 (1.95–4.53)	< 0.001	3.09 (1.60–5.94)	0.001
pN2 – multi-station	3.86 (2.19–6.83)	< 0.001	3.12 (1.39–6.98)	0.006
pNX	1.18 (0.60–2.34)	0.63	1.29 (0.55–3.03)	0.55
Extracapsular spread	n = 1032	< 0.001		
No	1 (-)		–	–
Yes	2.53 (1.76–3.63)			
Lymphovascular invasion	n = 1033	< 0.001		0.030
No	1 (-)		1 (-)	
Yes	2.86 (2.13–3.85)		1.78 (1.06–2.98)	
Pleural invasion	n = 1028	< 0.001		
PL0	1 (-)			
PL1	2.06 (1.49–2.85)	< 0.001	–	–
PL2	1.88 (1.11–3.20)	0.019		
PL3	5.29 (3.22–8.68)	< 0.001		
Grade of differentiation	n = 902	0.012		
Poor	1 (-)			
Moderate	0.89 (0.64–1.25)	0.51	–	–
Well	0.56 (0.37–0.86)	0.008		
Unknown	1.40 (0.80–2.45)	0.24		
R0/R1 resection	n = 1033	< 0.001		
R0	1 (-)		–	–
R1	2.29 (1.63–3.22)			
Adequacy of nodal sampling	n = 1031	0.48	–	–
Inadequate	1 (-)		–	–
Adequate	1.11 (0.83–1.47)			
Gender		0.17		
Female	1 (-)		–	–
Male	1.20 (0.92–1.57)			
Age		< 0.001		0.001
< 75	1 (-)		1 (-)	
≥75	1.96 (1.44–2.66)		1.89 (1.28–2.79)	
Performance Status	n = 964	0.003		0.030
0	1 (-)		1 (-)	
1	1.37 (0.99–1.90)	0.057	1.05 (0.72–1.54)	0.78
2/3	2.44 (1.47–4.07)	0.001	2.10 (1.17–3.79)	0.014
Adjuvant Chemotherapy	n = 1006	0.70		< 0.001
No	1 (-)		1 (-)	
Yes	1.06 (0.80–1.40)		0.38 (0.25–0.58)	

(- = Not significant in the multivariable analysis).

Table 3
The LNC-PATH prognostic score calculation.

Variable	Score
Lymphovascular invasion (**L**NC-PATH)	
No	0
Yes	0.5
N-stage (L**N**C-PATH)	
pN0	0
pN1	1
pN2	1
pNX	0
Adjuvant Chemotherapy (LNC-PATH)	
No	1
Yes	0
Performance Status (LNC-**P**ATH)	
0	0
1	0
2/3	1
Age (years) (LNC-P**A**TH)	
< 75	0
≥75	0.5
T-stage (LNC-PA**T**H)	
pT1	0
pT2	1
pT3	2
pT4	2
Histology sub-type (LNC-PAT**H**)	
Squamous Cell Carcinoma	1
Large cell NSCLC	2.5
Other NSCLC	1.5
Acinar	0.5
Lepidic	0
Papillary/Micropapillary	0.5
Solid	1.5
Unknown	0.5

recurrence, and personalising follow-up protocols and survivorship programmes through risk stratification. Using the *LNC-PATH* model as an example, 'low-risk' patients (approximately 60% of patients in our study) might warrant a less intense follow-up programme to minimise risks such as unnecessary radiation from intensive imaging surveillance, false positive imaging results with subsequent investigation as well as limiting surveillance costs and optimising clinic slot utilisation. In 'high-risk' patients (approximately 10% of patients in our study) a more intensive follow-up programme may be justified to try to address the high mortality rate within this group.

The major strengths of this study are the size and quality of the collated data, the robust statistical methods applied and the vaildation process. The variables identified in the scoring model are readily available easy to use and clinically applicable after surgical resection. This risk stratification model uses both clinical variables that reflect co-morbidty and fitness as well as pathological varaibles that reflect the risk of cancer recurrence. This could therefore facilitate a holistic process of survivorship whereby those patients with the greatest need and greatest risk of poor outcomes can be targeted for the most intensive surveillance regime and most effective use of resources. However there are a number of limitations of this study to consider. Firstly the performance of the model for mortality predcition is modest and is unlikely to offer signifcantly better predcition than pathological stage alone. Furthermore survival does not necessarily equate to symptom burden. The suggestion that those at highest risk of death warrant more intensive follow-up may miss a cohort of patients with significant symptom burden worthy of medical intervention but who are at low risk of death from cancer recurrence. For example the model is unlikely to pick out those patients with significant treatment related side effects such as post-thoracotomy pain who may require a more intensive period of intervention for symptom control which may not have impacted on overall survival. Although the model does include performance status, overall symptom burden is influenced by the number and type of co-morbidities which this scoring system does not take into account. It therefore has the potential to overlook patients with a significant need for survivorship interventions unrelated to cancer recurrence and overall survival. Variables such as lung function (e.g. forced expiratory volume in one second) and co-morbidity are more challenging to reliably access in this retrospective study and both may change significantly in the peri-operative period. Finally, the analysis does not take into account certain variables that may have impacted on survival outcomes such as the use of second line treatments for lung cancer recurrence (e.g. thoracic radiotherapy for nodal recurrence).

In conclusion we have developed and validated the *LNC-PATH* scoring system which attempts to identify those patients at highest risk of death within the first two years following lung cancer resection. This may have applications in personalised and risk stratified follow-up although there remains a urgent need for more robust tools to identify those at greatest risk of death following lung cancer surgery, from both

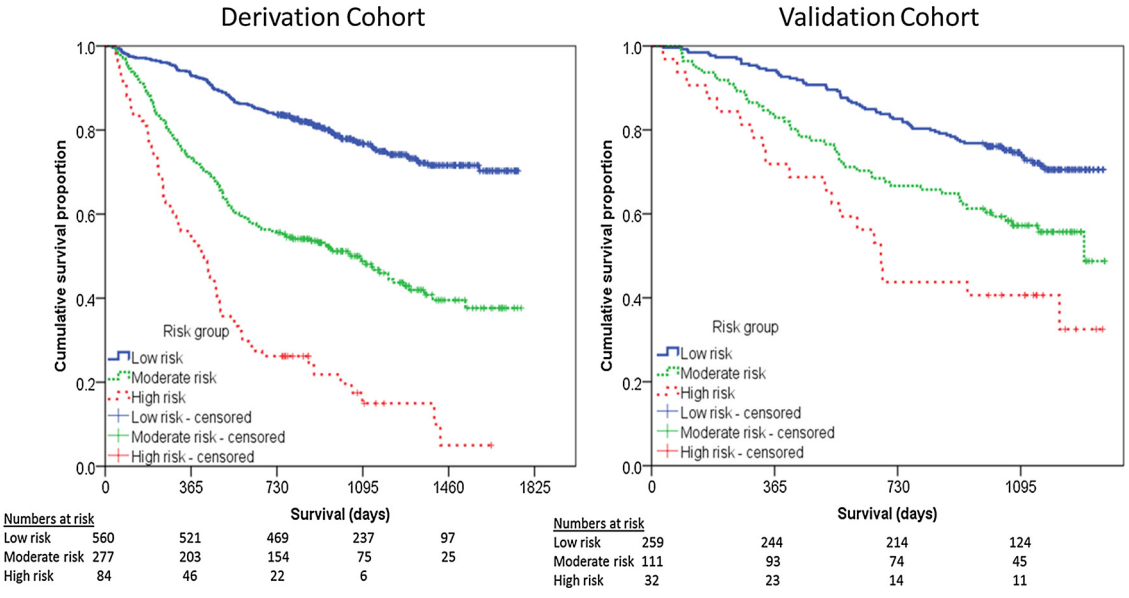

Fig. 1. Kaplan-Meier survival curves for the three risk groups (low risk ≤3, moderate risk 3.5–4.5, high risk ≥5) in Derivation cohort and Validation cohort.

cancer recurrence or other co-morbidity. Perhaps such tools will emerge from the rapidly evolving genomic landscape in lung cancer which may have the potential to truly personalise cancer care.

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