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ORIGINAL ARTICLE

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Number of lung resections performed and long-term mortality rates of patients after lung cancer surgery: evidence from an Italian investigation

Federico Rea [a,b], Francesca Ieva [a,c,d], Ugo Pastorino [e], Giovanni Apolone[f], Sandro Barni[g], Luca Merlino[h], Matteo Franchi [a,b,*] and Giovanni Corrao [a,b]

[a] National Centre for Healthcare Research and Pharmacoepidemiology, Milan, Italy
[b] Laboratory of Healthcare Research & Pharmacoepidemiology, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy
[c] MOX, Department of Mathematics, Politecnico di Milano, Milan, Italy
[d] CADS—Center for Analysis Decisions and Society, Human Technopole, Milan, Italy
[e] Thoracic Surgery Unit, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy
[f] Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[g] Department of Oncology, ASST Bergamo Ovest, Bergamo, Italy
[h] Epidemiologic Observatory, Lombardy Regional Health Service, Milan, Italy

* Corresponding author. Dipartimento di Statistica e Metodi Quantitativi, Sezione di Biostatistica, Epidemiologia e Sanità Pubblica, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milan, Italy. Tel: +39-02-64485859; e-mail: matteo.franchi@unimib.it (M. Franchi).

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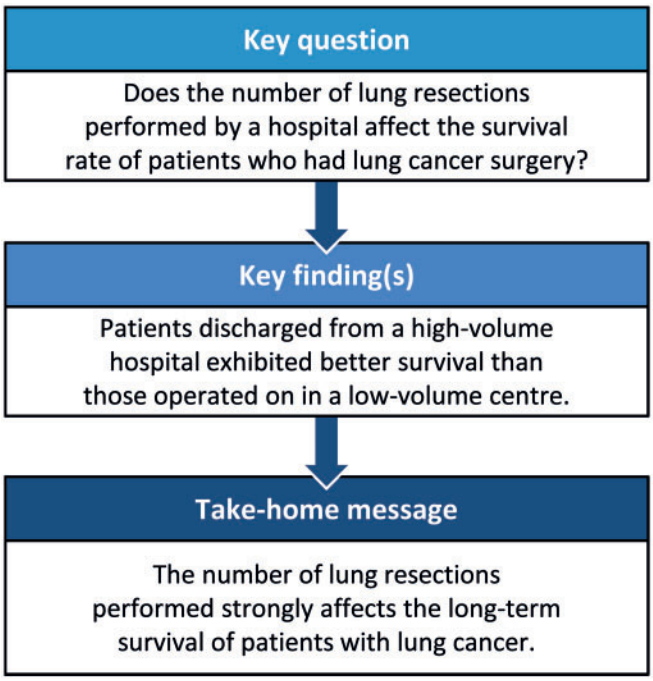

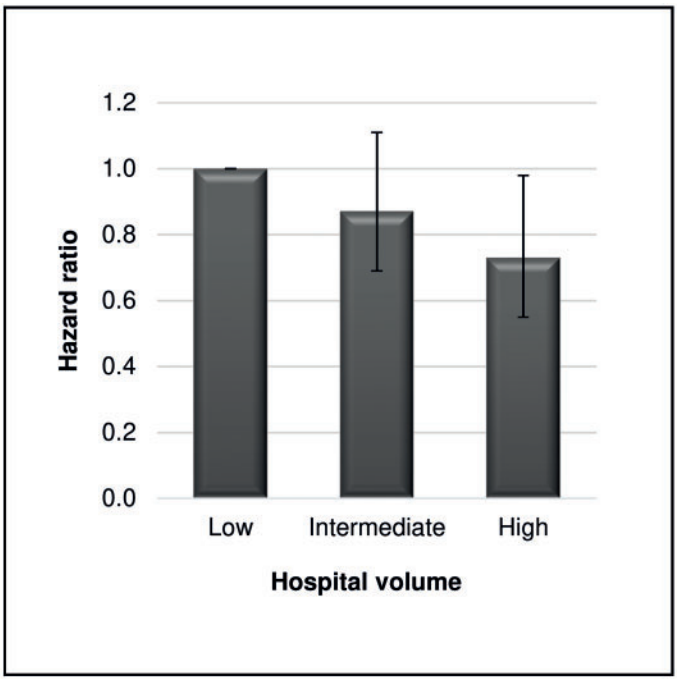

Abstract

OBJECTIVES: Although it has been postulated that patients might benefit from the centralization of high-volume specialized centres, conflicting results have been reported on the relationship between the number of lung resections performed and the long-term, all-cause mortality rates among patients who underwent surgery for lung cancer. A population-based observational study was performed to contribute to the ongoing debate.

METHODS: The 2613 patients, all residents of the Lombardy region (Italy), who underwent lung resection for lung cancer from 2012 to 2014 were entered into the cohort and were followed until 2018. The hospitals were classified according to the annual number of

pulmonary resections performed. Three categories of lung resection cases were identified: low (≤30), intermediate (31–95) and high (>95). The outcome of interest was all-cause death. A frailty model was used to estimate the death risk associated with the categories of numbers of lung resections performed, taking into account the multilevel structure of the data. A set of sensitivity analyses was performed to account for sources of systematic uncertainty.

RESULTS: The 1-year and 5-year survival rates of cohort members were 90% and 63%. Patients operated on in high-volume centres were on average younger and more often women. Compared to patients operated on in a low-volume centre, the mortality risk exhibited a significant, progressive reduction as the numbers of lung resections performed increased to intermediate (-13%; 95% confidence interval +10% to -31%) and high (-26%; 0% to -45%). Sensitivity analyses revealed that the association was consistent.

CONCLUSIONS: Further evidence that the volume of lung resection cases performed strongly affects the long-term survival of lung cancer patients has been supplied.

Keywords: Lung cancer • Lung resection • Survival • Hospital volume • Health care utilization database • Multilevel modelling

ABBREVIATIONS

CI	Confidence interval
HR	Hazard ratio
MCS	Multisource comorbidity score
MHR	Median hazard ratio
NHS	National Health System

INTRODUCTION

Lung cancer is one of the major health challenges of the third millennium, with 1.2 million annual deaths, and a 5-year survival rate below 20% [1]. Lung resection is the standard of care for early-stage lung cancer: 70% of patients classified as stage I/II undergo pulmonary resection [2].

Improving the quality of cancer care at sustainable costs is a hot topic of ongoing debate. The outcome of high-risk, low-volume procedures, such as oesophageal and pancreatic resections, is especially thought to improve when they are centralized in high-volume specialized centres [3]. Although the number of lung resection procedures is greater than those for pancreatic and oesophageal cancer, lung resection is also considered a low-volume, high-risk operation [4]. However, limited evidence exists to support volume standards in lung cancer surgery. In fact, whereas decreasing numbers of postoperative and short-term deaths with increasing numbers of hospital lung resections was observed by a meta-analysis [4] and other subsequent investigations [5–7], no evidence that the number of lung resection procedures performed affected either the short-term mortality rate [8] or the long-term survival rate[4], was reported by others.

A population-based observational study was performed to contribute to the ongoing debate. The relationship between the surgical volume of pulmonary resection cases and the long-term, all-cause mortality rate was investigated in a large cohort of beneficiaries of the National Health System (NHS) from the Italian region of Lombardy who had lung cancer surgery from 2012 to 2014.

MATERIALS AND METHODS

Ethical statement

The ethical committee of the University of Milano-Bicocca evaluated the protocol and established that the study (i) was exempt from informed consent (according to General Authorization for the Processing of Personal Data for Scientific Research Purposes Issued by the Italian Privacy Authority on 15 December 2016; http://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/5805552); (ii) provided sufficient guarantees of anonymizing individual records; and (iii) was designed according to quality standards of good practice of observational research based on secondary data.

Setting

The data used for the present study were retrieved from the health care utilization databases of Lombardy, a region of Italy that accounts for about 16% (almost 10 million) of its population. In Italy, the NHS covers the entire population. In Lombardy, it has been associated since 1997 with an automated system of databases designed to collect health information such as (i) demographic and administrative data on NHS beneficiaries, including information on the date of entry (birth or immigration) and exit (death or emigration); (ii) inpatient diagnoses and procedures (coded according to the ICD-9-CM classification system); (iii) outpatient drug prescriptions (coded according to the Anatomical Therapeutic Chemical classification system); and (iv) outpatient services (including visits to specialist walk-in clinics and diagnostic laboratories). For each patient, we linked the foregoing databases via a single identification code. To preserve privacy, each identification code was automatically converted into an anonymous code. The inverse process was prevented by deletion of the conversion table. Details of Italian health care utilization databases and of their use for cancer observational investigations have been reported elsewhere [9, 10].

Cohort selection

The target population comprised all beneficiaries of the NHS living in Lombardy aged 18 years or older. Of these, those who underwent lung resection for lung cancer during 2012 to 2014 were identified. The first hospital admission for pulmonary resection during this period was labelled as the index admission. Those patients who (i) died during the index hospitalization, (ii) received a lung cancer diagnosis more than a year before the index admission, (iii) had been hospitalized for malignancy (and/or used drugs for cancer) during the period between the date of the index admission and the previous 5 years and (iv) started their status as an NHS beneficiary less than 5 years ago were excluded.

The remaining patients were included in the final cohort, whose members accumulated person-years of follow-up from the index hospital discharge until death (outcome) or censoring (i.e. emigration or 30 June 2018), whichever came first.

Numbers of lung resections

The number of lung resections performed was defined as the annual number of lung cancer resections performed by each hospital averaged over the period 2012 through 2014. High-volume centres were defined as those that sustained the 90th percentile of the lung resection volume distribution, whereas low-volume centres were defined as those with 30 resections per year or less. Thus, 3 categories of lung resection volumes were identified, accounting for ≤30, from 31 to 95 and >95 resections per year, respectively.

Covariates

Baseline characteristics included gender, age, resection type (segmentectomy, lobectomy and pneumonectomy), length of hospital stay and use of neoadjuvant chemotherapy within 6 months before the date of the index hospitalization. In addition, the multisource comorbidity score (MCS), a simple score recently developed and validated in Italy [11], was used to assess the general clinical profile of each cohort member. In this study, the weights of the conditions that contributed to the score were recalculated by considering the cohort of cancer patients rather than the general population, as was done in the original version of the MCS (Supplementary Material, Appendix).

Data analyses

The χ^2 test for the trend was used to test between-patient differences in demographic and clinical characteristics among the categories of numbers of lung resections performed. Cox proportional hazard models were used to identify independent predictors of all-cause mortality and calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Because our population presented a clear multilevel structure with patients (level 1) nested within the hospital (level 2), random effects were included in the Cox models, which were thus denoted frailty models [12]. This random effect can be thought of as a 'frailty' increasing the hospital's susceptibility to short survival times when it is large and decreasing this susceptibility when it is small [13]. The magnitude of random effects was estimated by measuring their heterogeneity through the median hazard ratio (MHR) [14]. The MHR is the median relative change in the hazard of the outcome occurrence when comparing identical subjects from 2 randomly selected different hospitals that are ordered by risk.

In this application, the hospital was always included in the model as a random variable, assuming that the distribution of the frailty term followed a gamma distribution. Three Cox frailty models were fitted, including (i) the hospital frailty random effect alone (first null model), (ii) together with the hospital volume of lung resections (second lung resection volume-adjusted model) and (iii) with the hospital volume of lung resections and the aforementioned baseline covariates (third entirely adjusted model). The portion of the hazard of death variation still explained by the hospital random effect after adjustment for fixed-effect individual characteristics was derived by comparing the MHR values. Within each model, the variance of the distribution of the random effects was used for testing the null hypothesis of no hospital random effect.

Sensitivity analyses

To verify the robustness of our findings, we performed 4 further analyses. First, because the adopted categorization of the lung resection volume was arbitrary, we used alternative lung resection volume thresholds, i.e. by progressively lowering the threshold for defining low-volume centres. Second, the main analysis was repeated including patients who died during the index hospitalization. Third, because cohort members admitted to the low- and high-volume hospitals might have different clinical profiles and other relevant characteristics, the high-dimensional propensity score was calculated to account for both measured and residual confounders [15]. The probability of being admitted to a high-volume centre (i.e. the propensity score) was estimated using a logistic regression model that included as covariates the previously mentioned baseline data, plus all the possible reasons for hospital discharge, surgical procedures and examinations experienced by and all the drugs prescribed to cohort members in the 2-year period prior to the index lung resection. The 50 most predictive covariates were selected. The frailty model was again fitted by adopting a 1:1 high-dimensional propensity score matching design using the nearest neighbour matching algorithm without replacement [16]. Fourth, the rule-out approach was applied to investigate the potential bias associated with unmeasured confounders (e.g. socioeconomic status) by detecting the extension of the confounding required to fully account for the exposure–outcome association [17]. We set the possible generic unmeasured confounder (i) to have a 30% prevalence in the study population; (ii) to increase the mortality risk by up to 10-fold in patients exposed to the confounder compared to those not exposed to the confounder and (iii) to be up to 10-fold less common in patients discharged from a hospital that performed a high volume of lung resections than among those discharged from a low-volume hospital.

RESULTS

Patients

A flow chart of exclusion criteria is shown in Fig. 1. Of the 4850 patients who underwent lung resection for lung cancer from 2012 to 2014, a total of 2613 met the inclusion criteria and formed the study cohort. The cohort members accumulated 10 192 person-years (on average 25 months per patient) and generated 988 deaths (mortality rate being 97 every 1000 person-years). The 1-year and 5-year survival rates were 90% and 63%, respectively.

Overall, 56 hospital centres performed at least 1 lung cancer resection during the study period, 38, 13 and 5 of which had low, intermediate and high volume, respectively. Table 1 shows that, in comparison to patients who had resections in low-volume centres, those operated on in high-volume centres were on average younger, more often women and with a shorter length of stay. Conversely, there was no evidence that surgery type and neoadjuvant therapy differed among the different categories of patients with cancer. Notably, although the MCS, when applied to cancer patients, performed better when used to

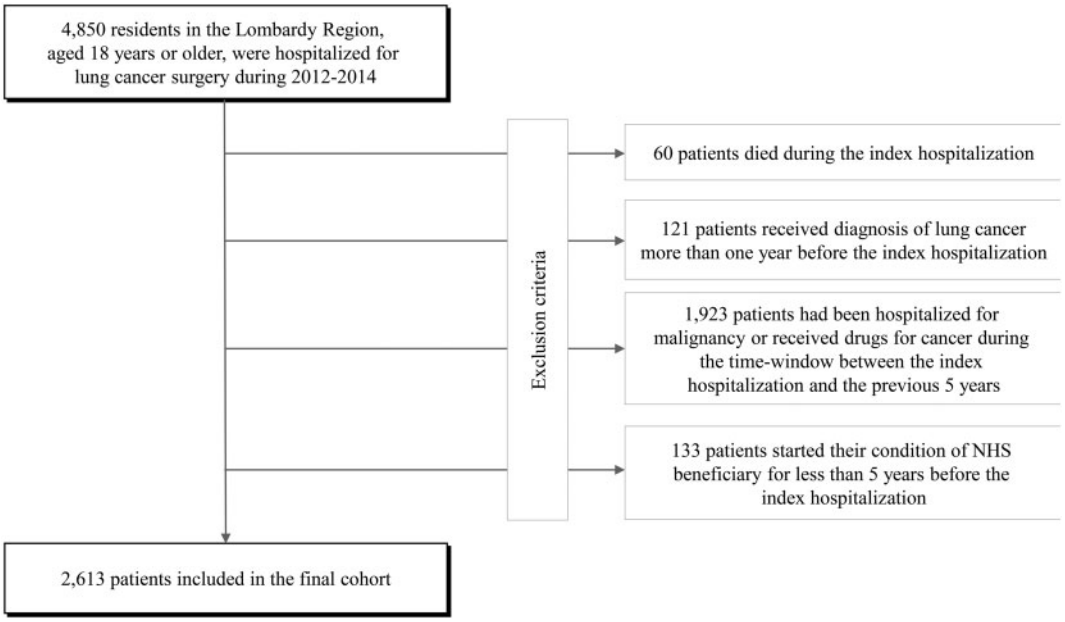

Figure 1: Flow chart of inclusion and exclusion criteria. NHS: National Health System.

Table 1: Characteristics of patients with lung cancer who had pulmonary resection according to the volume of lung resections performed (Lombardy Region, Italy, 2012–2014)

	Volume of lung resections			*P*-value
	Low	Intermediate	High	
Number of hospitals	38	13	5	
Number of patients	407	1211	995	
Age, *n* (%)				
≤65 years	104 (25.6)	314 (25.9)	314 (31.6)	0.005
>65 years	303 (74.4)	897 (74.1)	681 (68.4)	
Gender, *n* (%)				
Women	120 (29.5)	370 (30.5)	354 (35.6)	0.008
Men	287 (70.5)	841 (69.5)	641 (64.4)	
MCS, *n* (%)				
0–2	183 (45.0)	573 (47.3)	498 (50.1)	0.065
3–5	157 (38.6)	472 (39.0)	362 (36.4)	
6–8	47 (11.5)	119 (9.8)	87 (8.7)	
9–11	15 (3.7)	34 (2.8)	31 (3.1)	
≥12	5 (1.2)	13 (1.1)	17 (1.7)	
Lung resection type, *n* (%)				
Segmentectomy	113 (27.8)	231 (19.1)	251 (25.2)	0.084
Lobectomy	284 (69.8)	901 (74.4)	687 (69.1)	
Pneumonectomy	10 (2.4)	79 (6.5)	57 (5.7)	
Length of stay (days), mean (SD)	13.1 (8.8)	13.3 (8.8)	12.6 (8.3)	0.043
Neoadjuvant chemotherapy, *n* (%)				
No	396 (97.3)	1189 (98.2)	970 (97.5)	0.857
Yes	11 (2.7)	22 (1.8)	25 (2.5)	

Categories of hospital volumes: low (≤30 resections per year), intermediate (31–95) and high (>95).
P-values are based on χ^2 test for the trend.
MCS: multisource comorbidity score; SD: standard deviation.

predict long-term mortality rates than did other more commonly used scores (Supplementary Material, Appendix), the null hypothesis of clinical complexity homogeneity among categories of lung resection volumes should not be rejected. In addition, there was no evidence that intrahospital mortality rates differed between groups: 0.7%, 1.0% and 1.1% from low- to high-volume centres, respectively ($P = 0.916$).

Hospital effect

The MHR values of the models, including the random-effect only model, together with the number of lung resections and the individual characteristics were, respectively, 1.30, 1.27 and 1.23. The estimated variance of the hospital-specific random effect was still significant for the entirely adjusted model (0.0448; $P < 0.001$).

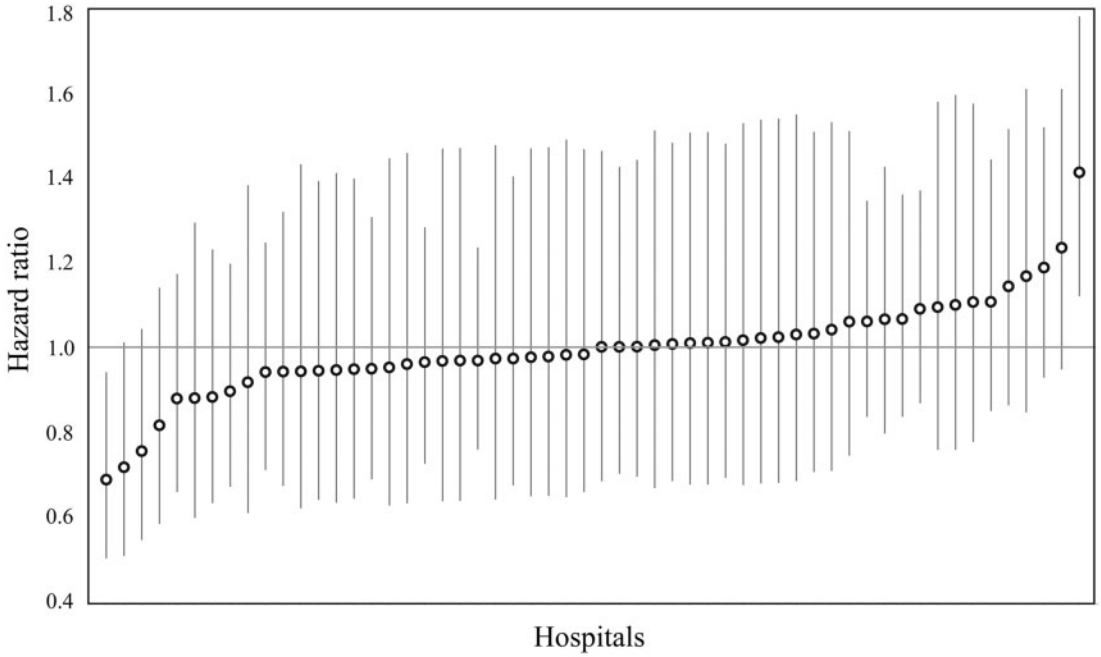

Figure 2: Frailty model estimates of hazard ratio of all-cause mortality rates associated with hospitals where the patients were operated on, showing the point estimate (circle) and the respective 95% confidence interval band.

These findings suggest that the hospital significantly affects the mortality rate, independent of other measured predictors. Despite the statistical significance, however, frailty estimates of hospital-specific adjusted HRs, depicted with their respective 95% confidence bands in Fig. 2, indicated a small residual variability in the corresponding adjusted HRs of 0.69–1.41. Notably, only 1 hospital had a frailty estimate significantly greater than 1 and 1 hospital had a frailty estimate significantly lower than 1.

Effect of the number of lung resections performed and other covariates

The comparison between MHR for the fully adjusted frailty model (=1.23; reciprocal, 0.81) and HRs for the patient-level characteristics, shown in Table 2 (whose minimum values range from 0.74 to 2.34), indicates that the median effect of the hospital was always less than the effect of the patient characteristics under consideration. The latter included significant predictors of death: age (patients aged ≥ 65 years had 40% greater risk of death than younger patients); gender (the mortality rate of men was 65% greater than that of women); clinical complexity (patients with MCS ≥ 12 had 100% greater risk than those with MCS < 3); type of surgery (patients who had a pneumonectomy had 134% excess of death than those who had segmentectomy); and use of neoadjuvant chemotherapy (excess of mortality rate of 45%). Compared to patients operated on in a low-volume centre, the risk decreased progressively as lung resection numbers increased to intermediate (-13%; 95% CI +10% to -31%) and high levels (-26%; 95% CI 0% to -45%); the trend in the HR was significant (*P*-value: 0.049).

Table 2: Effect of patient characteristics and lung resection volume on all-cause mortality according to the Cox frailty model

	HR (95% CI)
Age	
≤65 years	1.00 (Ref.)
>65 years	1.40 (1.20–1.64)
Gender	
Women	1.00 (Ref.)
Men	1.65 (1.42–1.92)
MCS	
0–2	1.00 (Ref.)
3–5	1.12 (0.90–1.39)
6–8	1.31 (1.14–1.51)
9–11	1.43 (1.04–1.98)
≥12	2.00 (1.27–3.15)
Lung resection type	
Segmentectomy	1.00 (Ref.)
Lobectomy	0.91 (0.78–1.06)
Pneumonectomy	2.34 (1.84–2.98)
Length of stay (days)	1.02 (1.02–1.03)
Neoadjuvant chemotherapy	
No	1.00 (Ref.)
Yes	1.45 (0.99–2.12)
Lung resection volume	
Low	1.00 (Ref.)
Intermediate	0.87 (0.69–1.10)
High	0.74 (0.55–1.00)
P-trend	0.049

Categories of lung resection volume are the following: low (≤30 procedures per year), intermediate (31–95) and high (>95).
CI: confidence interval; HR: hazard ratio; MCS: multisource comorbidity score; Ref.: reference value.

Sensitivity analyses

The results of the sensitivity analyses are shown in Table 3. The protective effect in patients who had lung resections in high-volume centres increased by progressively lowering the threshold under which a centre was considered low volume. Moreover, the progressive reduction in the risk of death in centres with a high

Table 3: Trends in hazard ratio (and 95% confidence intervals) of all-cause mortality associated with categories of volumes of lung resections estimated according to the sensitivity analyses, i.e. by changing the categorization of the volume of lung resections performed, including patients who died during the index hospitalization and from a 1:1 high-dimensional propensity score matching design

	HR (95% CI)
Changing hospital volume categorization	
Low (≤20)	1.00 (Ref.)
Intermediate (21–95)	0.79 (0.62–1.00)
High (>95)	0.69 (0.52–0.92)
Low (≤10)	1.00 (Ref.)
Intermediate (11–95)	0.71 (0.53–0.95)
High (>95)	0.63 (0.45–0.88)
Including intrahospital deaths	
Low (≤30)	1.00 (Ref.)
Intermediate (31–95)	0.88 (0.69–1.12)
High (≥95)	0.72 (0.54–0.96)
According to the hdPS approach	
Low (≤30)	1.00 (Ref.)
High (≥95)	0.71 (0.51–0.99)

CI: confidence interval; HR: hazard ratio; hdPS: high-dimensional propensity score.

volume of lung resections was also observed by including deaths that occurred during the index hospitalization and using a propensity score matching design.

The results of the residual confounding analysis obtained by the rule-out approach are shown in Fig. 3. Assuming that patients operated on in a high-volume centre had four-fold lower odds of exposure to the confounder than those operated on in a low-volume centre, the confounder should increase the outcome risk by 5.5-fold to nullify the observed favourable effect of high volume on survival. Weaker confounder–outcome associations are required to move to the null the effect of the number of lung resections for confounders more intensely unbalanced between low- and high-volume centres (e.g. relative $risk_{confounder-outcome}$ = 3 and odds $ratio_{confounder-exposure}$ = 9).

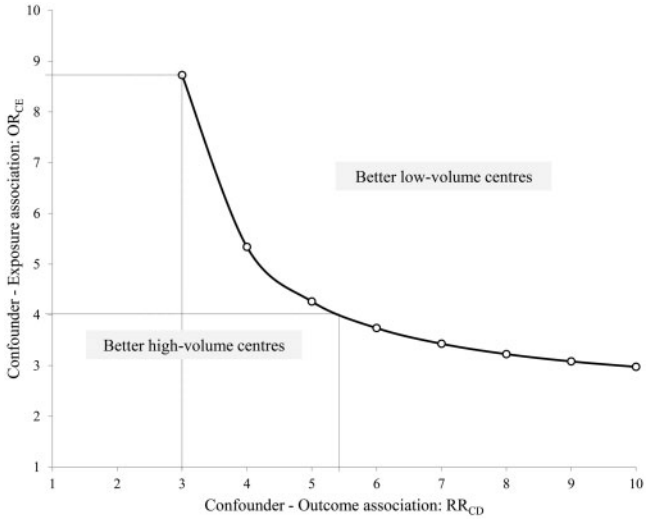

Figure 3: Influence of a confounder on the relationship between lung resection volume (exposure) and all-cause mortality (outcome). The graph indicates the RR_{CD}–OR_{CE} combinations (i.e. the confounder–outcome and the confounder–exposure associations, respectively) that would be required to move the observed protective effect of high-volume centres towards the null. OR_{CE}: odds $ratio_{confounder-exposure}$; RR_{CD}: relative $risk_{confounder-outcome}$.[a] [a]For better understanding, we might consider the lung cancer stage at baseline as the confounder. Stage, in fact, is expected to be associated with both the outcome (mortality rate is expected to be higher among patients with lung cancer who are at the worst stage than among those at the best stage) and the exposure (here we assume that patients operated on in low-volume centres were on average at the worst stage compared with those at high-volume centres). The graph shows that, even if patients exposed to the confounder (i.e. those at the worst stage) should have a risk of death more than five-fold that of those not exposed (best stage), they should be at least 4 times more frequently among the exposed (i.e. high-volume centres should have admitted patients with lung cancer at the worst stage with a frequency four-fold higher than that of the low-volume centres) to nullify the observed association.

DISCUSSION

Our observational investigation shows significant differences in long-term mortality rates due to hospital classification. After adjustment for several well-known prognostic factors, the risk of death was reduced by 26% in high-volume centres (i.e. those accumulating 96 resections every year) compared with low-volume centres (≤30 procedures). Several reasons may explain this finding. First, accurate staging is believed to result in the more appropriate use of cancer therapy and therefore better outcomes [18]. Careful assessment of eligibility for resection (e.g. by measuring expiratory volume and performance status [19, 20]) unavoidably leads to the selection of patients with better chances of survival [21]. Because it is unknown whether centres with a high volume of lung resections more accurately perform staging and histological typing, determination of resection eligibility and completeness of resection, we are unable to exclude the idea that the better survival rates observed for patients operated on in high-volume centres is actually due to more accurate staging and typing to carefulness in assessing eligibility for resection.

Second, our inability to measure patients' characteristics known to predict prognosis (e.g. forced expiratory volume, performance status and the severity of comorbidities) might have resulted in confounding bias. In other words, although there was no evidence of differences in type of surgery, neoadjuvant therapy and clinical profile, we are unable to exclude that the better survival rates observed for patients who had resections in high-volume centres were actually due to their better prognosis at baseline.

Third, lead-time bias may also explain our findings. Lead-time bias occurs when the onset of observation varies among patients classified according to the exposure of interest. In our application, if high-volume centres work in systems of care that more expeditiously work up, refer and treat patients, then it is possible that our results suffer from lead-time bias because we measured survival time based on the date of resection [22]. Nevertheless, if this were the reason for survival differences, then our results would still be consistent with the notion that high-volume centres provide more expeditious and higher quality care than other centres [18].

Finally, our results are compatible with the hypothesis that patients with lung cancer might benefit from the introduction of a minimal volume standard because of the specialization of high-volume centres. Although other authors have suggested that the centralization results in an increasing travel burden for patients

and thus causes a barrier to some subsets of the population to access quality care [23], a recent prospective multicentre study showed that distance from a surgery department is not associated with having an operation or with death [24]. Moreover, future studies should address if the health care system could benefit from the centralization of specialized health care services because it remains unclear whether centralization results in economies of scale and is cost-effective [25].

Our study provides the following additional results. One, the 5-year survival rate of our cohort (63%) is in line with those of other investigations [26, 27]. Two, patients referred to high-volume centres were on average younger and more likely to be women than those operated on in low-volume centres, but, as mentioned above, there was no evidence of differences in surgery type, neoadjuvant therapy and clinical profile. Three, our study also confirms that the patients who had pneumonectomy as well as those who had neoadjuvant chemotherapy had worse survival rates than those who had lobectomy or segmentectomy and who did not experience neoadjuvant chemotherapy [27, 28]. Finally, our study stimulated us to revise the new, recently developed MCS [11] to make it suitable to measure clinical complexity in patients with cancer. The score better predicts the mortality rate than conventional scores such as the Charlson and Elixhauser scores, at least in the general population of Italy.

Limitations

The strengths of the present study are the following: (i) the investigation was based on a large unselected population, which was possible because in Italy a cost-free health care system extends to virtually all citizens; (ii) multilevel modelling techniques were adopted to take into account the clustering of subjects within hospitals and to adjust for potentially overdispersed variance estimates; and (iii) the data provided by the main analysis were confirmed by sensitivity analyses. In particular, the main finding was also confirmed by the high-dimensional propensity score approach in which measured and residual confounders were taken into account by matching cohort members admitted to low- and high-volume hospitals according to all their contacts with the NHS (i.e. hospital admissions, surgical procedures, examinations and drugs) before the index lung resection (HR = 0.71).

Potential limitations must also be considered. First, the choice of thresholds for classifying a hospital according to the number of lung resections performed was completely arbitrary, certainly not with the aim of identifying the volume that maximizes the survival benefit. Moreover, thresholds used in this study cannot be applied in other settings in Italy, nor can they be applied outside Italy, because the number of procedures performed annually is markedly influenced by the study population and by the nature and quality of the health care system.

The main limitation, however, is the previously mentioned lack of histological and clinical information common to all administrative databases such as ours. Despite the well-known influence of cancer stage on the prognosis of patients with lung cancer, one should consider that (i) it is unlikely that patients at an advanced stage were surgically treated in very low-volume centres and (ii) our analyses were adjusted for several factors, including type of resection and use of neoadjuvant chemotherapy. Other unmeasured factors, however, might affect our conclusions. For example, by assuming that low socioeconomic status (i) likely reduced accessibility to highly specialized centres [29] and (ii) negatively affected the prognosis of patients with lung cancer [30], it should be emphasized that our findings might be partially or entirely explained by differences in socioeconomic status of patients operated on in both low- and high-volume centres. For this reason, we also performed a sensitivity analysis showing that the observed association between the number of lung resections performed and the long-term survival rate was not nullified after correction for the action of a generic unmeasured confounder, if one does not assume a confounder action so strong that it can reasonably be excluded. However, because some clinical data are not available in our databases, as mentioned previously, residual confounding cannot be completely excluded.

CONCLUSION

In conclusion, our observational investigation offers further evidence that the number of lung resections performed by a hospital strongly affects the long-term survival of patients with lung cancer. Understanding the reasons underlying these differences will likely help develop interventions aimed at mitigating heterogeneity in care and outcomes. Patients, surgeons, physicians and other stakeholders should recognize the potential risks and benefits associated with centralization of care and other policy-level interventions aimed at improving the quality of thoracic surgical care.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Author contributions

Federico Rea: Formal analysis; Methodology; Software; Writing—original draft; Writing—review & editing. **Francesca Ieva:** Formal analysis; Methodology; Writing—review & editing. **Ugo Pastorino:** Conceptualization; Supervision; Writing—review & editing. **Giovanni Apolone:** Conceptualization; Supervision; Writing—review & editing. **Sandro Barni:** Conceptualization; Supervision; Writing—review & editing. **Luca Merlino:** Data curation; Writing—review & editing. **Matteo Franchi:** Formal analysis; Methodology; Software; Writing—review & editing. **Giovanni Corrao:**

Conceptualization; Methodology; Supervision; Writing—original draft; Writing—review & editing.

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