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Association between anaesthetic technique and unplanned admission to intensive care after thoracic lung resection surgery: the second Association of Cardiothoracic Anaesthesia and Critical Care (ACTACC) National Audit*

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Summary

Unplanned intensive care admission is a devastating complication of lung resection and is associated with significantly increased mortality. We carried out a two-year retrospective national multicentre cohort study to investigate the influence of anaesthetic and analgesic techniques on the need for unplanned postoperative intensive care admission. All patients undergoing lung resection surgery in 16 thoracic surgical centres in the UK in the calendar years 2013 and 2014 were included. Critical care admission was defined as the unplanned need for either tracheal intubation and mechanical ventilation or renal replacement therapy. Association was sought between mode of anaesthesia (total intravenous anaesthesia vs. volatile) and analgesic technique (epidural vs. paravertebral) and need for intensive care admission. A total of 253 out of 11,208 patients undergoing lung resection in the study period were admitted unplanned to intensive care in the postoperative period, giving an incidence of ICU admission of 2.3% (95% CI 2.0-2.6%). In patients admitted unplanned to ICU, mortality was higher (29.00% vs. 0.03%, $p<0.001$) and hospital stay was increased (26 vs. 6 days, $p<0.001$). Across univariate, complete-case and multiple imputation (multivariate) models there was a strong and significant effect of both anaesthetic and analgesic technique on the need for critical care admission. Patients receiving total intravenous anaesthesia (OR 0.50 (95% CI 0.34-0.70)), and patients receiving epidural analgesia (OR 0.56 (95% CI 0.41-0.78)) were less likely to be admitted unplanned to intensive care after thoracic surgery. This large retrospective study suggests a significant effect of both anaesthetic and analgesic technique on outcome in patients undergoing lung resection. We must emphasise that the observed association does not directly imply causation and suggest that well-conducted, large-scale randomised controlled trials are required to address these fundamental questions.

Introduction

~~Lung cancer is the second most common cancer in the UK and the leading cause of cancer death. In suitable cases, the best chance of 'cure' is surgery.~~ Patients undergoing lung resection are often elderly and have underlying cardiorespiratory comorbidities leading to a high risk of peri-operative complications, many of which necessitate intensive care unit (ICU) admission after surgery. Whilst there has been a great deal of research focusing on specific postoperative complications following lung resection e.g. atrial fibrillation or lung injury, the population requiring unplanned ICU admission have received relatively little attention.

Unplanned ICU admission (as distinguished from elective admission in extremely high-risk patients or after extensive surgery) is generally accepted to be associated with a marked increase in mortality, especially if due to respiratory compromise requiring tracheal re-intubation and mechanical ventilation of the lungs [1]. Whilst acute kidney injury therapy following thoracic surgery is also associated with increased rates of reintubation and prolonged hospital stay [2], in one historical cohort the combination of needing mechanical ventilation and renal replacement therapy was described as *"universally fatal"* underscoring the high risk of poor outcome in this patient group [1].

Following a successful single centre pilot study [3], we decided to undertake a multicentre retrospective study, co-ordinated by the Association of Cardiothoracic Anaesthesia and Critical Care (ACTACC) to examine unplanned ICU admission following lung resection over a period of two years. The study had three main aims. Firstly, we sought to characterise this population, by providing an up-to-date estimate of the incidence of unplanned ICU admission, describing the demographics of the patients requiring critical care and recording the indication for escalating support. Secondly, we sought to assess the burden of disease by recording ICU and hospital stay, resource use, mortality and post-ICU outcomes. Finally, and the principle focus of this manuscript, we sought to identify the effect of a number of peri-operative exposures of interest on the need for postoperative ICU admission. The optimal method of providing both general anaesthesia and postoperative analgesia to patients undergoing lung resection has long been the subject of much study and debate. Therefore, we investigated the potential influences of anaesthetic and analgesic technique on the incidence of postoperative ICU admission in patients undergoing lung resection surgery.

Methods

The study was a conducted as a multicentre retrospective cohort study of all patients undergoing lung resection surgery in participating UK hospitals during the calendar years 2013 and 2014. As this was an audit of routinely collected data for the National Health Service (NHS) in the UK, waiver of the need for research ethics committee approval was confirmed on behalf of the National Research Ethics Committee. Individual participating centres obtained local hospital approval as required. Consent for analysis of data was obtained from London School of Hygiene and Tropical Medicine Research Ethical Committee.

All thoracic surgical centres in the UK and Ireland were invited to apply through the ACTACC 'Linkman programme', through word of mouth and by direct advertising at ACTACC scientific congresses. A total of 16 centres out of 34 agreed to take part and provided data. With a methodology similar to the successful Royal College of Anaesthetists National Audit Projects [4], we asked centres to provide data on a numerator (patients admitted to ICU following lung resection) and denominator (all patients undergoing lung resection not admitted to ICU) basis. For the purposes of the study, intensive care admission (the numerator) was defined as "*unplanned ICU admission and need for invasive mechanical ventilation and/or renal replacement therapy",* intentionally excluding patients admitted to ICU on a precautionary basis but ultimately not requiring ICU interventions, or those simply nursed in ICU for logistical reasons. Patients whose tracheas were not extubated immediately following surgery and transferred to the ICU for mechanical ventilation and postoperative care were included as 'unplanned ICU admissions' if postoperative mechanical ventilation was unplanned and the duration exceeded 12 hours.

A detailed dataset was recorded in each 'case' (patient satisfying the inclusion criteria as having an unplanned intensive care admission), containing baseline characteristics (including age, sex, resection type, operative side, pulmonary function test results, comorbidities and Thoracoscore [5]), anaesthetic and surgical technique, reason for admission and ICU outcomes. To allow calculation of an overall incidence of ICU admission, a denominator was sought which reflected the number of patients undergoing lung resection in a given centre during the study period. Given the retrospective nature of the study, and to avoid excessively burdening collaborators, data collection on this cohort was restricted to demographic data that was readily available. To allow exploration of the risk modifying effect of exposures of interest, investigators were also asked to provide a detailed dataset on a contemporaneous control group which included the five patients who underwent lung resection in each centre before each ICU admission. Data collection for this 'detailed denominator' dataset included age, sex, resection and side, pulmonary function test results, comorbidities, Thoracoscore and anaesthetic and surgical techniques.

The incidence of ICU admission was calculated for each centre and the sample as a whole. Individual centre estimates were compared with the overall incidence in the sample using a funnel plot with limits of agreement at two and three standard deviations from the overall incidence estimate [6].

Two separate models were initially fitted on complete records to investigate the association between the anaesthetic and analgesic techniques and odds of ICU admission. The crude effect of these techniques was first estimated with a univariate logistic regression model with only the variable of interest as the predictor variable. Secondly, remaining variables which could be associated with both the exposure of interest and the outcome, and with less than 20% missing records, were considered for inclusion as potential confounders in multivariate models. Each variable was first screened for univariate association between exposure of interest and ICU admission. Each model was then subsequently built using a forward approach, adjusting for one covariate at a time and looking at change in effect estimate. The covariate resulting in the greatest relative change of the log odds ratio for ICU admission was then added to the model. The process was repeated for each covariate showing univariate association, in order of decreasing strength of association. A 10% change in log odds was used as a cut-off point to determine which variables to keep in the model at each stage. Age and sex are known to play a role in a range of health outcomes therefore we chose to correct for them regardless of the univariate results.

Finally, where candidate predictor variables of interest had over 20% missing values, we devised a multiple imputation by chained equations model. Ten imputations were deemed appropriate for minimal loss of power and efficiency. Functional form of the covariates in each model was tested by including age as a squared term; results from the likelihood ratio test comparing this to the model with linear age suggested that the square term does not provide additional benefit in terms of model fit ($p>0.1$ for all three models).

The outcome modifying effect of anaesthetic and analgesic techniques is therefore presented as univariate, 'adjusted complete case' and 'adjusted multiple imputation' models. All data analysis was performed using STATA 15.0 Software (StataCorp LLC, Texas).

Results

A total of 11,208 patients underwent lung resection in the 16 collaborating centres during the study period, and 253 patients required unplanned ICU admission, resulting in an overall incidence of 2.3% (95%CI 2.0-2.6%). Visual analysis of the funnel plot displaying incidence of ICU admission against number of resections by centre (Figure 1) revealed no significant underperforming outliers amongst the 16 UK centres. Due to differences in the extent of audit data captured prospectively during the study period in each centre, some centres were able to provide detailed datasets on many more, if not all control patients, whilst others were only able to provide a detailed dataset in five contemporaneous controls following detailed retrospective case note reviews. Of the 11,208 patients included in the study, substantial data was available for a total of 7,431 patients; 7,178 controls and all 253 cases. Case-control data for these 7,431 patients was used for all other analyses. Demographic and surgical data for these patients are shown in Table 1. Patients admitted to ICU following lung resection were older, more likely to be female, were likely to have undergone more extensive lung resection and were less likely to have undergone video-assisted thoracoscopic surgery (VATS) compared with patients not admitted to ICU. Hospital stay and mortality were significantly increased in patients admitted to ICU (Table 1).

The vast majority of patients admitted to ICU were admitted for mechanical ventilation (234, 94.7%) predominantly as a result of respiratory failure (171, 68.1%). The most common causes of respiratory failure were pulmonary infection (69, 27.3%) and sputum retention (39, 15.4%, (Table 2)). Thirteen patients (5.3%) were admitted to ICU solely for renal replacement therapy. The median IQR [range]) duration of ICU stay was 12.5 (5-27 [0-88]) days; hospital stay was considerably prolonged in patients admitted to ICU who survived to hospital discharge. Hospital mortality in patients admitted to ICU was 29.0% (95% CI 23.2-35.3%), versus 0.03% (95% CI 0.01-0.10%), in patients not admitted to ICU ($p<0.001$).

Data on the anaesthetic technique (volatile or total intravenous anaesthesia (TIVA)) were available for 4,070 control patients and 248 ICU cases. Following multivariate analysis, the odds of unplanned ICU admission postoperatively was less for patients receiving TIVA compared with those receiving a volatile anaesthetic (OR 0.50, 95%CI 0.34-0.70, Table 3). Sufficient data was available to allow multivariate adjustment for the potential confounding variables of age, sex, resection type, resection side and surgical approach (thoracotomy versus VATS). Resection side was not independently associated with the outcome or any of the exposures of interest and was excluded from the final models. All other factors were independently associated with odds of ICU admission and were included in the adjusted compete-case analysis. Results of both the complete case analysis and the multiple imputation models supported the finding of a significant reduction in the odds of ICU admission with TIVA compared with volatile anaesthesia (Table 3).

Data on the provision of regional anaesthesia was available for 3436 control patients and 247 ICU cases. Of these, 1540 patients received thoracic epidural blockade and 990 received paravertebral blockade. Of the remainder, 826 patients received no regional analgesic technique whilst 317 patients received an ‘other’ technique. Analyses were performed to compare the influence of epidural and paravertebral blocks on the odds of unplanned ICU admission. Following multivariate analysis, the odds of unplanned ICU admission were less for patients receiving epidural compared with paravertebral block (OR 0.56, 95%CI 0.41-0.78, Table 3), a finding which was again consistent across both complete case analysis and the multiple imputation models.

Sensitivity analyses were performed comparing the incidence of ICU admission in patients undergoing lobectomy surgery only, via either a thoracotomy or VATS approach; the results of these are presented in Supplementary Tables S1 and S2. Following thoracotomy and lobectomy only, the results of these sensitivity analyses are supportive of the primary analysis demonstrating a consistent and significant reduction in the odds of unplanned ICU admission in patients receiving TIVA or epidural blockade. For patients undergoing VATS lobectomy only, the odds ratios appear consistent with those seen in the primary analysis, but the confidence intervals are broad and statistical significance is lost. This analysis however is confounded by the low number of patients requiring ICU admission following VATS surgery (28 of 1,146 VATS lobectomies within the study (2.4%)) and the low use of epidural use following VATS surgery (83 of 709 patients included in the univariate analysis of analgesic technique (11.7%)).

Discussion

This multicentre study is the largest to date examining ICU admission following lung resection (Table 4). The reported incidence of unplanned ICU admission of 2.3% (95%CI 2.0-2.6%) compares favourably with previous reports where the incidence of ICU admission ranged from 2.6% to 25%. This may in part reflect the hard definition of 'unplanned ICU admission' used in the current study, which is likely to restrict 'ICU cases' to a more unwell cohort of patients than in previous reports, where patients admitted to the ICU on a precautionary basis are likely to have been included (Table 4).

Whilst only occurring in a small minority of patients, unplanned ICU admission was often prolonged, and was associated with markedly increased hospital stay and mortality. In the majority of cases, ICU admission necessitated mechanical ventilation due to respiratory complications. A number of strategies to prevent postoperative respiratory complications have been trialled in patients undergoing lung resection with limited success. Thoracic anaesthetists were early adopters of lung protective mechanical ventilation [7], though robust prospective data demonstrating an associated reduction in respiratory complications is still lacking. Oropharyngeal and nasopharyngeal decontamination with chlorhexidine gluconate had no effect on the incidence of respiratory infections in a recent multicentre French trial [8]. Whilst routine use of prophylactic non-invasive ventilation did not reduce the incidence of 'acute respiratory events' in high risk patients undergoing 'major lung resection' [9], a reduction in hospital stay has been demonstrated following the prophylactic use of high flow nasal oxygenation as part of an enhanced recovery programme after lung resection surgery, although this study did not report the incidence of respiratory complications [10].

The intriguing supposition of the current study is that routine anaesthetic and analgesic techniques may significantly influence the risk of ICU admission. Whilst historically, thoracic epidural blockade has been considered the gold standard method of providing postoperative analgesia for patients undergoing lung resection, anecdotal and published reports have documented a reduction in the use of epidurals and an increase in the use of paravertebrals [11]. Though a Cochrane review reported no difference between paravertebral and epidural in terms of death or major complications in patients undergoing thoracotomy [12], this trend towards paravertebral use has been fuelled by the parallel uptake of minimally-invasive VATS techniques and by observational reports [13], randomised controlled trials [14] and meta-analyses [15] suggesting an increased incidence of complications in patients receiving epidurals compared with paravertebrals. The current findings challenge these observations however, but as a retrospective analysis and can only indicate a possible association and not causation. An imminent, large randomised controlled trial comparing epidural and paravertebral for the prevention of chronic pain in over 1000 patients undergoing lung resection by thoracotomy in the UK is in progress and should provide better data (TOPIC-2, ClinicalTrials.gov NCT03677856).

Total intravenous anaesthesia use is 'over-represented' within thoracic surgery; in the Royal College of Anaesthetists' Fifth National Audit Project Anaesthetic Activity Survey, 26% of thoracic anaesthetics used a TIVA technique compared with just 8% of the overall dataset (Personal communication, Dr M. Sury, lead author of the NAP5 Anaesthetic Activity Survey [16]). This may reflect the theoretical benefits of TIVA to the thoracic anaesthetist in terms of preservation of hypoxic pulmonary vasoconstriction and the convenience of separating the provision of anaesthesia from airway maintenance and lung isolation [17]. Though a 2013 Cochrane review concluded "*that no evidence indicated that the drug used to maintain anaesthesia during one-lung ventilation affected participant outcomes*" [18] there is a significant body of randomised controlled trial data suggesting a reduced incidence of pulmonary inflammation and/or pulmonary complications in thoracic patients receiving volatile anaesthesia [19-21]. This is perceived to stem from an immunomodulatory effect of volatile anaesthesia [22]. Conversely, propofol is well recognised to have anti-oxidant properties both in vitro and in vivo, and there is a substantial animal literature supporting a protective effect of propofol in preventing lung injury via inhibition of oxidative stress mediated cellular damage [23,24].

The apparently greater incidence in postoperative ICU admission in patients undergoing thoracotomy versus video assisted thoracoscopic (VATS) lung resection should be interpreted with caution; in a retrospective study of this sort it was impossible to identify which resections had begun via a VATS approach but had then undergone on the table conversion to thoracotomy, an instance which often occurs in the event of complications. Furthermore, patients identified as being suitable for VATS lung resection are often selected on the basis of favourable surgical anatomy and are likely therefore to be 'systematically different' to patients undergoing thoracotomy, potentially influencing their baseline risk of ICU admission.

Missing data is a major challenge of retrospective research of this kind. In designing the study, a pragmatic line had to be drawn between the volume of data sought, and the practicalities of participating centres being able to provide this data. Many centres store large volumes of audit data prospectively and so were able to provide detailed control datasets on most patients, whilst others performed laborious case note reviews and so could only provide smaller and at times incomplete control datasets. We believe however that our statistical approach, in performing univariate, adjusted complete case and adjusted multiple imputation models robustly accounts for missing data. Indeed, the strong and consistent effect observed across all models in both the main and sensitivity analyses offers confidence in the result obtained. It remains possible that the 'detailed denominator' control group may not be representative of the UK thoracic surgical population as a whole, but by including in excess of 7,000 patients across 15 centres undergoing surgery contemporaneously to patients admitted to ICU we have we have sought to provide as large and generalisable control population as possible.

Whilst, as discussed, the results presented have biological plausibility, the potential remains that unmeasured confounders could be responsible for the associations observed. Whilst patient age, sex, resection type and surgical approach were adjusted for, the potential effects of baseline (patient) risk, surgical factors, anaesthetist experience and case frequency, the use of lung protective ventilation, positive end-expiratory pressure and the conduct of one lung ventilation could not be accounted for. It is interesting to speculate on the potential influence of the thoracic anaesthetist, as choice of analgesic technique and mode of anaesthetic maintenance will on many occasions be an 'individual choice'. A recently published analysis, performed by ACTACC, examined the effect of individual patient risk, surgical centre, surgeon and anaesthetist on outcomes after cardiac surgery. This study reported that the principal component of variation in outcome was patient risk, that the impact of the surgeon and centre was moderate whereas the impact of the anaesthetist was negligible[25]. Whilst no such data is available for thoracic surgery, the widely perceived importance of fluid balance and the conduct of one-lung ventilation in dictating patient outcome could make anaesthetic factors more important determinants of outcome. As an alternative to the hypotheses that TIVA and TEB improve outcome due to biologically plausible clinical effects, one might speculate that at the time of this studies conduct, the 'specialist' thoracic anaesthetist may be more likely to choose TIVA, more confident in the practice of TEB in view of familiarity and has the potential to positively influence outcome.

In conclusion, whilst the need for unplanned ICU admission following lung resection was rare, the consequences were considerable with markedly prolonged hospital stay and increased mortality, and significant implications for health care utilisation and cost. The current study reports in a large and nationally representative retrospective dataset, an apparently consistent protective effect of TIVA and epidural blockade in patients undergoing lung resection. Whilst this data challenges current trends in the practice of thoracic anaesthesia, the results have clear biological plausibility and mandate that we at least reconsider the less than definitive evidence base on which we base our current thoracic anaesthetic practices. The thoracic anaesthetic community must consider whether these age-old questions require further attention in the form of either large scale prospective audit or randomised controlled trials.

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Appendix 1 – CALoR 2 Investigators

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Table 1. Demographic and surgical details and outcomes of 7431 undergoing lung resection during the study period. Dichotomised by need for unplanned ICU admission**.** Values are mean (SD), number (proportion) or median (IQR [range]).

	No ICU admission; n= 7178				ICU admission; n=253			p value
	Missing	n			Missing	n		
Age; years	0	7178	64.1 (13.2)		0	253	69.2 (9.4)	<0.001
Sex	1200				0			
Female		3092	51.7%			149	58.9%	0.025
Male		2886	48.3%			104	41.1%	
Type of resection	551				0			
Pneumonectomy		257	3.9%			25	9.88%	<0.001
LVRS		25	0.4%			5	1.98%	
Lobectomy / bilobectomy		3840	57.9%			192	75.5%	
Sub-lobar		2505	37.8%			31	12.65%	
Side of surgery	940				0			
Left		2549	40.9%			93	36.8%	0.356
Right		3681	59.0%			160	63.2%	
Bilateral		8	0.1%			0	0.0%	
Surgical technique	873				4			
Open		3716	58.9%			204	81.9	<0.001
VATS		2589	41.0%			45	18.1	
Hospital stay	2057				27			
Duration (days)		6 (4-8 [2-142])				26 (13-45 [0-129])		<0.001
Mortality	25				22			<0.001
Survivors		7151	99.5%			164	71%	
Deceased		2	0.03%			67	29%	

LVRS, lung volume reduction surgery; VATS, video-assisted thoracoscopic surgery.

Table 2. Indications for unplanned intensive care admission

	ICU cases (N=253)		
	Missing	n	%
Reason for ICU admission	6		
Mechanical ventilation		181	73.3%
Renal replacement therapy		13	5.3%
Both		53	21.5%
Primary admission diagnosis	2		
Airway complication		15	6.0%
Acute Kidney Injury		13	5.2%
Anaphylaxis		0	0.0%
Bleeding		16	6.4%
Cardiac arrest		12	4.8%
Respiratory failure		171	68.1%
Sepsis		7	2.8%
Other		17	6.8%
Perceived cause of respiratory failure	25		
No respiratory failure		40	15.8%
ALI/ARDS		16	6.3%
Aspiration		5	2.0%
Broncho-pleural fistula		2	0.8%
Cardiac failure		6	2.4%
Infection		69	27.3%
Persistent air leak / surgical emphysema		17	6.7%
Pulmonary embolism		4	1.6%
Sputum retention		39	15.4%
Other		25	9.9%
Multiple causes		5	2.0%

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Table 3. Influence of anaesthetic and analgesic technique on the odds of unplanned intensive care admission following lung resection.

	Model								
Exposure	**Univariate**			**Adjusted complete-case***			**Adjusted multiple imputation***		
	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI
Anaesthetic technique	4,318			3,683			7,325		
- Volatile		1			1			1	
- TIVA		0.59	(0.41-0.83)		0.46	(0.32-0.65)		0.50	(0.34-0.70)
Analgesic technique	3,683			3,668			7,431		
- PVB		1			1			1	
- Epidural		0.77	(0.57-1.05)		0.57	(0.41-0.78)		0.56	(0.41-0.78)

*Adjusted for age, sex, resection type, surgical approach

Table 4: Studies reporting the incidence of 'unplanned ICU admission following lung resection'.

Author	Year(s) of data collection	Country	No of ICU patients	Incidence of ICU admission	ICU / hospital mortality in ICU patients	Inclusion criteria for 'ICU cases'
Pilling et al. [1]	1998-2001	UK	28	7.1%	46%	Salvage mechanical ventilation
Brunelli et a. l[26]	2000-6	UK and Italy	118	7.2%	36%*	Major cardiopulmonary complications and receiving active life-supporting treatment
Song et al. [27]	2001-5	Korea	94	8.6%	33%	Signs of inadequate tissue perfusion, significant hemodynamic instability, requirement of invasive monitoring, use of inotropes, frequent nasotracheal suction, noninvasive ventilation, or mechanical ventilation
Axelsson et al. [28]†	2001-10	Iceland	21	8%	N/A	Not defined
Melley et al. [29]	2002-3	UK	52	30%	9.6%	Not defined
Okiror et al[. 30]	2003-8	UK	30	7%	17%	Requiring ICU monitoring and/or treatment
Petrella et al. [31]#	2004-11	Italy	29	11.6%	31%	Urgent admission
Pinheiro et al. [32]	2009-12	Brazil	30	25% (30/120)‡	N/A	Mechanical ventilation or re-intubation, acute renal failure, shock or other complication
Jung et al. [33]	2011-3	South Korea	63	3.3%	25.4%	Re-admission after initial recovery
McCall et al. [3]¶	2013-4	UK	30	2.6%	26.7%	Unplanned ICU admission and need for invasive mechanical ventilation and/or renal replacement therapy
Shelley et al. (ACTACC)	2018	UK	253	2.3%	35.6%	Unplanned ICU admission and need for invasive mechanical ventilation and/or renal replacement therapy

*Derived from a subset of 82 ICU patients in a 'derivation dataset'.

†Paper in Icelandic – data extracted from abstract only.

#Pneumonectomy population only.

‡Study tested a model for predicting need for ICU admission. In event, 25% clinically required ITU admission postoperatively.

N/A – not reported, and not calculable from the data provided in the manuscript.

¶This single-centre study was the pilot study for the current report – patients in this study are included in the current manuscript.