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Impact of surgical technique and analgesia on clinical outcomes after lung transplantation

A STROBE-compliant cohort study

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Abstract

There is paucity of data on the impact of surgical incision and analgesia on relevant outcomes.

A retrospective STROBE-compliant cohort study was performed between July 2007 and August 2017 of patients undergoing lung transplantation. Gender, age, indication for lung transplantation, and the 3 types of surgical access (Thoracotomy (T), Sternotomy (S), and Clamshell (C)) were used, as well as 2 analgesic techniques: epidural and intravenous opioids. Outcome variables were: pain scores; postoperative hemorrhage in the first 24 hours, duration of mechanical ventilation, and length of stay at intensive care unit (ICU).

Three hundred forty-one patients were identified. Thoracotomy was associated with higher pain scores than Sternotomy (OR 1.66, 95% CI: 1.01; 2.74, *P*: .045) and no differences were found between Clamshell and Sternotomy incision. The median blood loss was 800 mL [interquartile range (IQR): 500; 1238], thoracotomy patients had 500 mL [325; 818] ($P < .001$). Median durations of mechanical ventilation in Thoracotomy, Sternotomy, and Clamshell groups were 19 [11; 37] hours, 34 [IQR 16; 57.5] hours, and 27 [IQR 15; 50.5] hours respectively. Thoracotomy group were discharged earlier from ICU ($P < .001$).

Thoracotomy access produces less postoperative hemorrhage, duration of mechanical ventilation, and lower length of stay in ICU, but higher pain scores and need for epidural analgesia.

Abbreviations: C = Clamshell, COPD = chronic obstructive pulmonary disease, CPB = cardiopulmonary bypass, ECMO = extracorporeal membrane oxygenation, HR = hazard risk, ICU = intensive care unit, IQR = interquartile range, NHS = National Health Service, OR = odds ratio, S = sternotomy, SD = standard deviation, T = thoracotomy, UK = United Kingdom.

Keywords: acute pain, clinical outcomes, critical care, lung transplantation

1. Introduction

Lung transplantation is the definitive treatment option for carefully selected patients with end-stage lung disease.[1] At 1-year survival rate is 85% decreasing to 60% at 5 years.[2] The most common indications include chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary fibrosis and other interstitial lung disease, and pulmonary hypertension. Different surgical incisions, including bilateral thoracotomies (T), median sternotomy (S), and clamshell (C), can be used for access. Mechanical ventilation alone, cardiopulmonary bypass (CPB), or extracorporeal membrane oxygenation (ECMO) can be used intraoperatively.

Postoperative critical care for these patients mandates multidisciplinary team approach aiming at a fast convalescence

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and minimizing risk of graft dysfunction. The treatment includes optimal immunosuppression, protective lung ventilation, early spontaneous ventilation, hemodynamic optimization, and good pain control.[3] Use of lung protective ventilation and the shortest possible duration of mechanical ventilation are priorities in the postoperative period.[4] In these patients the graft is immediately used to completely take over the respiratory function.

Insufficient analgesia can hinder pulmonary mechanics, expectoration, and physiotherapy. Conversely, use of opioid analgesics can produce side effects such as respiratory depression, cough suppression, hypercapnia, drowsiness, and constipation, which could all impact on recovery of the patient.

Acute pain after lung transplantations has been studied in small case series with inconclusive findings, leading to different clinical practices in lung transplant centers.[5–7] Multimodal analgesia is the most common regime. In the past epidural analgesia has been the main analgesic modality. However, due to safety issues like spinal hematoma in the presence of possible anticoagulation and coagulopathy, it is not as popular in the last decades.

The aim of this study was to assess the impact of surgical and analgesic techniques on postoperative pain for different surgical approaches (T, S, or C) on lung transplantation outcomes in a larger single-center case series. Clinically relevant outcomes (blood loss, duration of mechanical ventilation, and duration of stay in the intensive care unit (ICU)) after lung transplantation were also studied.

2. Materials and methods

2.1. Study design

The study was a retrospective cohort, single-center, based on a prospectively compiled database (ICU clinical information system) of lung transplant recipients in a tertiary hospital, Royal Papworth NHS Foundation trust (Cambridge, UK).

The study was carried out according to the Declaration of Helsinki and the study protocol was approved by the local institutional review board waiving ethical approval because it was considered a service evaluation project. All patients gave written informed consent for their medical information to be used for purposes of scientific research. The study covers a decade of our clinical practice, between July 2007 and August 2017. Due to the exploratory nature of our aim, no formal calculation of sample size was performed. The final sample size was defined simply as the number of all lung transplant recipients in our hospital for the 10 years 2007–2017. STROBE guidelines for conducting observational studies were followed.

2.2. Study population

The study included all adult (age ≥18 years) lung transplant recipients.

The following baseline data were gathered for all lung transplant recipients included in this study: gender, age at transplantation; indication for lung transplantation; date of surgery; surgical approach and clinical outcomes. Missing data was not included in the final analysis.

2.3. Anesthesia and surgical approach

Anesthesia. The hospital protocol for lung transplant anesthesia includes lung isolation if bypass is not used, and at the end of procedure exchanging double lumen tube to a single lumen endotracheal tube. If cardiopulmonary support with CPB or ECMO was needed systemic heparinization was used. Induction in anesthesia was with midazolam 0.05 to 0.1 mg/kg, propofol 1 to 1.5 mg/kg, fentanyl 10 to 20 mcg/kg, and pancuronium 0.08 to 0.1 mg/kg. Maintenance was provided with propofol infusion at 4 mg/kg/h. Methylprednisolone 500 mg was administered as part of immunosuppression regime during reperfusion of the graft. If prior to lung transplantation the patient was taking anticoagulants, this was reversed with prothrombin complex concentrate aiming for an INR < 1.5.

Surgical approach. The preferred surgical approach was determined at the time of listing. There was a preference for (T) whenever feasible. Patients with a mean pulmonary artery pressure greater than 40 mm of Hg, and patients in whom single lung ventilation was not possible were electively managed with intraoperative ECMO or CPB support. The final decision on the type of support was left with the implanting surgeon. Two chest drains were inserted in each operated lung in 3 surgical accesses.

2.4. Clinical outcomes after lung transplantation

All patients were admitted after surgery to ICU intubated and sedated with propofol infusion. Once hemodynamic and respiratory function were optimal and bleeding stopped, sedation was discontinued. Conventional extubation criteria included PO_2 10 kPa, $PaCO_2$ less than 6.5 kPa during spontaneous breathing trial on 40% oxygen and a PEEP of 5 cmH20.

2.4.1. Postoperative pain intensity scores. Regional analgesia was not used intraoperatively in any patient as there was possible need for anticoagulation to facilitate CPB or ECMO. After awakening, depending on pain score, the intensive care doctor in charge decided on best mode of postoperative analgesia. ICU pain management was based on paracetamol, codeine, and morphine plus optional epidural analgesia.

The epidurals catheters were inserted at thoracic level (T4–T6) using Portex kit with 16 G Tuohy needle, using loss of resistance technique with saline. The infusion was 0.1% bupivacaine and 5 mcg/mL fentanyl (infusion rate 5–10 mL/h) after a testing dose of Lidocaine 1%. In the opioid analgesia group, all patients were receiving morphine infusion of 1 to 2 mg/h, and the patients needing more analgesia received PCA delivered morphine with 1 mg bolus and 5 minutes lockout.

Pain intensity scores were recorded objectively by the bedside nurse at different times after surgery once verbal communication was re-established. Based on our clinical practice, in all patients a Likert scale was used: 0: no pain, 1: some pain, 2: considerable pain, and 3: very severe pain.[8] Institutional pain targets were ranging between 0 and 1 in the qualitative scale.

2.4.2. Blood loss. Blood loss in the chest tubes in first 24 hours was recorded (mL/24 h).

2.4.3. Mechanical ventilation. Duration (hours) of mechanical ventilation was defined as the time between ICU admission and extubation in ICU.

2.4.4. ICU stay. Duration (hours) of ICU was defined as the time between the admission and discharge from the ICU. Criteria for discharge were: Adequate oxygenation (Sats > 95%) in spontaneously ventilating patients, systolic blood pressure of at least 100 mm Hg, adequate ambulation and analgesia (no pain or some pain on the qualitative scale).

2.5. Statistical analysis

2.5.1. Sample size. The study included all lung transplant recipients in our hospital for the 10 years 2007 to 2017. Confounder variables were not included in the final analysis due to the nature of this pragmatic study.

Categorical variables were presented as the number of cases and percentages, while continuous variables were presented as the mean and standard deviation (SD) or median and interquartile range (IQR).

Logistic regression models were used to evaluate the effect of surgical incision and other demographic data on pain. Two groups were created for the analysis: low pain group (patients with no pain and some pain, score 0 or 1) and high pain group (patients with considerable pain and very severe pain, score 2 and 3). Odds ratios and their corresponding 95% confidence intervals were derived from these models.

Mann–Whitney *U* test was used to compare postoperative bleeding ("blood loss") between surgical incision groups. Duration of mechanical ventilation and length of stay at the intensive care unit were assessed using the Kaplan–Meier analysis.

The log-rank test was used to compare duration of intubation and ICU length of stay between the study groups. The Cox proportional hazards model was used to perform multivariate analyses, and these were reported as the hazard ratio (HR) and 95% confidence intervals (CIs). Data analysis was carried out using the R statistical programming environment (version 3.5 for windows, R Core Team, 2015).

3. Results

3.1. Patient characteristics

A total of 341 patients undergoing, either single or double, lung transplantation during the study period (between July 2007 and August 2017): 146 (43%) female and 195 (57%) male, with a mean (SD) age of 49.4 (14) years. Sequential T was the preferred surgical access performed in 148 (43%), patients followed by S in 98 (29%) and C in 95 (28%) patients (Table 1).

3.2. Clinical outcomes related to surgical access after lung transplantation

3.2.1. Postoperative pain. As first option in ICU pain management, systemic opioid (morphine) was the most popular analgesic regime in 249 (73%) patients, and epidural analgesia without morphine was used in 92 (27%) patients.

In 76 (31%) out of 249 patients in whom systemic opioids were not sufficient, they were converted to epidural analgesia. Therefore, in 173 (51%) out of 341 patients systemic opioids was the sole analgesic regimen.

Analyzing the impact of surgical technique on pain intensity, we found that T was associated with higher pain scores than S (OR: 1.66, 95% CI: 1.01; 2.74, *P* value: .045) and there seemed to be no differences between C and S incision. Thoracotomy was associated with more acute pain than rest of 2 other incisions. Two independent protective factors for high pain scores (considerable pain and very severe pain) were found: increased age (OR 0.98, 95% CI: 0.97; 1,00, *P* value: .025), and single lung transplantation (OR 0.49, 95% CI: 0.28; 0.85 *P* value: .010).

In the epidural analgesia group (n = 92), T was also the most frequent access: 54 patients (59%); followed by C in 34 (37%) and S in 4 (4%). Indications for lung transplantation revealed no differences in frequency of epidural analgesia: 29 COPD patients (21%), 23 cystic fibrosis (31.5%), 18 pulmonary fibrosis (28.1%), 17 interstitial lung disease (37.7%), and 5 in pulmonary hypertension (23.8%). Median [IQR] of number of pain score measurements per patient was 50.5 [31; 92].

3.2.2. Blood loss. Postoperative blood loss data in the first 24 hours was available for 327 patients missing in 14. Amongst all groups the median of blood loss was 800 [IQR: 500; 1238] mL/24 hours. T group had statistically significant lower blood loss during the first 24 hours than the other 2 surgical incisions (*P* value: < .001) (Table 2). Single lung transplantation patients had a median blood loss of 480 [IQR: 291; 928] mL while double lung patients had a bleeding of 875 [IQR: 600; 1350] mL/24 h, *P* value < .001.

3.2.3. Mechanical ventilation. Duration of mechanical ventilation was available for 327 patients (Table 2), missing in 14. The duration of mechanical ventilation for the Thoracotomy group was significantly lower (median [IQR] of 19 [11; 37] hours) than the C group 34 [IQR 16; 57.5] hours (*P* value: .012)) and in the S group 27 [IQR 15; 50.5] hours (*P* value: .012). Figure 1 shows the impact of the type of surgical incision on the duration of mechanical ventilation.

Table 1

Demographic data of patient according to surgical incision.

	All N = 341	Sternotomy N = 98	Clamshell N = 95	Thoracotomy N = 148
Gender	F 146, M 195	F 50, M 48	F 41, M 54	F 55, M 93
Age, mean (SD)	49, 4 (14)	49, 6 (13.3)	47, 2 (13.5)	50, 8 (14.6)
Analgesia technique				
Epidural	92 (27%)	4 (4.08%)	34 (35.8%)	54 (36.5%)
Morphine	249 (73%)	94 (95.9%)	61 (64.2%)	94 (63.5%)
Organ				
Single lung	77 (22.6%)	38 (38.8%)	2 (2.11%)	37 (25%)
Double lung	264 (77.4%)	60 (61.2%)	93 (97.9%)	111 (75%)
Indication				
Cystic fibrosis	73 (21.4%)	17 (17.3%)	15 (15.8%)	41 (27.7%)
COPD	138 (40.5%)	50 (51%)	42 (44.2%)	46 (31.1%)
Pulmonary fibrosis	64 (18.8%)	15 (15.3%)	20 (21.1%)	29 (19.6%)
Pulmonary hypertension	21 (6.16%)	5 (5.1%)	7 (7.3%)	9 (6.08%)
Interstitial lung disease	45 (13.2%)	11 (11.2%)	11 (11.6%)	23 (15.5%)

COPD = chronic obstructive pulmonary disease, SD = standard deviation.

Table 2

Outcomes variables in relation with surgical access.

	All N=341	Sternotomy N=98	Clamshell N=95	Thoracotomy N=148	N
CPB					341
Yes	199 (58.4%)	98 (100%)	36 (37.9%)	65 (43.9%)	
No	142 (41.6%)	0 (0%)	59 (62.1%)	83 (56.1%)	
Bleeding first 24 h					327
Median mL [Q1; Q3].	800 [500; 1238]	1000 [660; 1568]	1140 [839; 1475]	500 [325; 818]	
Mechanical ventilation, h, median [Q1; Q3].	22 [13;46.5]	27 [15.0;50.0]	24 [16.0;57.5]	19.0 [11.0;37.0]	327
ICU length of stay					320
h, Median [Q1; Q3]	72 [48;144]	96 [72; 204]	72 [48; 180]	72 [48; 120]	

CPB = cardiopulmonary bypass, ICU = intensive care unit.

In the linear regression analysis, the analgesic technique (only systemic opioid or systemic opioid and epidural analgesia) was not associated with differences on duration of mechanical ventilation. In order to further analyze this relationship a Cox model was performed. In the univariate analysis T (HR: 1.41, 95% CI: 1.08; 1.83), single lung transplantation (HR 1.43, 95% CI: 1.09; 1.86) and absence of cardiopulmonary by-pass (HR 1.32, 95% CI: 1.06; 1.65) were associated with earlier extubation. In the multivariate model similar relations were gathered with T showing an HR: 1.40 (95% CI: 1.08; 1.8) for extubation, Single lung transplantation HR: 1.58 (95% CI: 1.18; 2.1) for extubation and absence of cardiopulmonary by-pass HR: 1.29 (95% CI: 0.99; 1.7) for extubation.

3.2.4. Length of ICU stay. Intensive care unit length of stay was not documented in 21 patients. The duration for different groups was as follows: T group spent a median [IQR] of 72 [48; 120] hours, C group 72 [48; 180] hours, and 96 [72; 204] in S group. Survival curves showed that T group were discharged earlier from ICU (*P* value: < .001) than S group and C group (Fig. 2). Analgesic technique did not influence the length of stay in ICU in univariate Cox model (HR 1.16 [0.91;1.48], *P* value: .223). In the multivariate analysis single lung transplantation was associated with a shorter admission in ICU (HR 1.337 [1.014;1.8], *P* value: .039).

3.2.5. Safety. During the study period no epidural hematoma or abscess was diagnosed. There were 2 recorded complications of epidural analgesia: One dural tap, which did not require further treatment as there was very mild headache. One epidural was placed too low not providing optimal analgesia and it had to be repositioned within the first 24 hours.

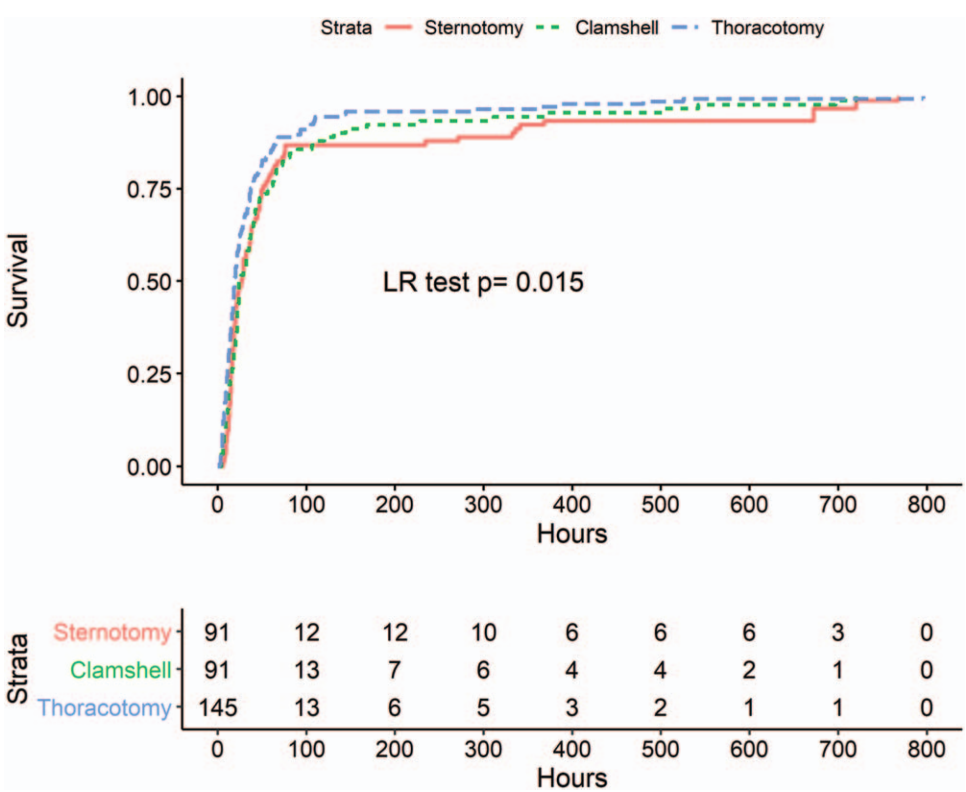

Figure 1. Survival curve of duration of mechanical ventilation and multivariate analysis.

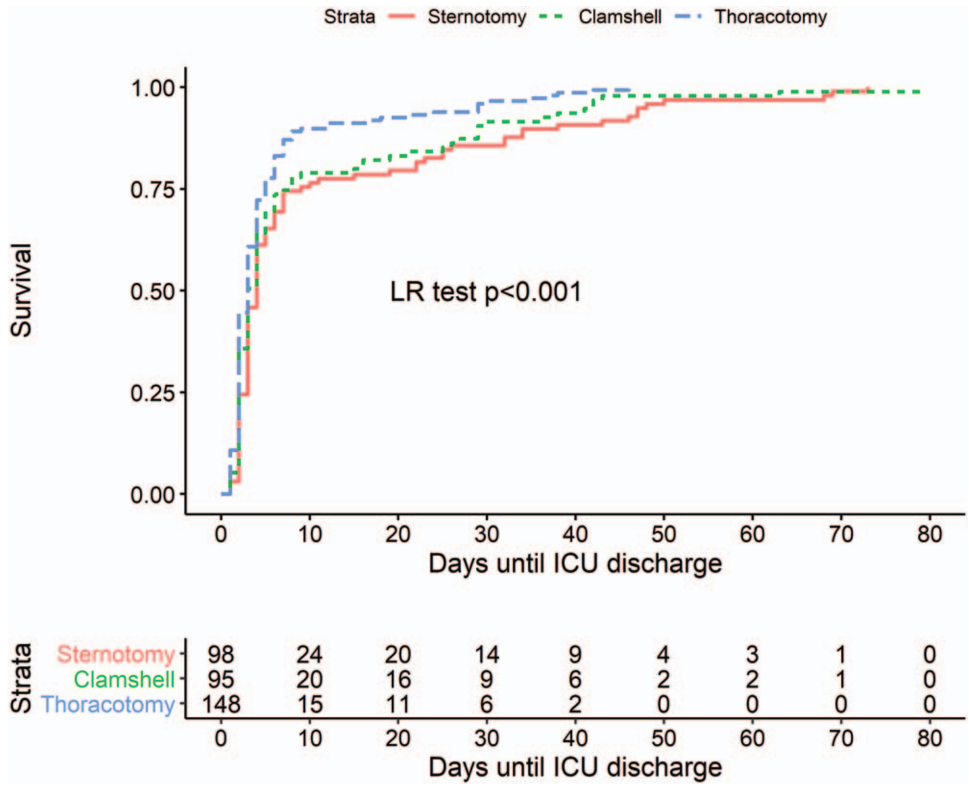

Figure 2. ICU length of stay. ICU = intensive care unit.

4. Discussion

To our knowledge, this study provides largest cohort data on clinical outcomes related to analgesia and surgical approach for lung transplantation.

Patients undergoing lung transplantation via T had significantly lower postoperative blood loss in first 24 hours, were extubated earlier, and had a shorter admission at ICU. They did however have higher pain scores and more likely to need epidural analgesia. Single lung transplantation was associated with shorter stay at ICU and duration of mechanical ventilation. Use of CPB was also associated with later extubation. Single lung transplantation was associated with less postoperative blood loss in first 24 hours when compared with double lung transplantation. The use of clam shell incision or sternotomy and need for CPB with anticoagulation for more difficult surgical dissections could be plausible explanations of these outcomes.

Postoperative acute pain and its management after cardiothoracic procedures is a well-identified cause of complications.[9,10] A wide range of surgical and anesthetic interventions may be implicated. Location and extension of surgical incision, number of chest drainage tubes, institution of hypothermia, administration of glucocorticoids, and anesthetic drug administration can all impact magnitude of acute pain.[11,12] Following lung transplantation the management of acute pain is important in order to facilitate respiratory weaning. When analyzing qualitative pain scale, T access was associated with worse pain scores (considerable pain and very severe pain), whilst there were no significant differences on pain scores between C incision and median S. Single lung transplantation and age were protective factors for considerable and very severe pain. Epidural analgesia was reserved for the patients with worse pain scores as compared with opioid analgesia. T patients needed this analgesic technique more frequently. Nevertheless, this study was not powered to compare effectiveness of the 2 analgesic techniques. Efficacy of epidural has been validated in previously published smaller series.[6,7,13,14] Further studies addressing newer analgesic techniques like paravertebral blocks, serratus anterior block, and erector spinal plane block would be needed to scientifically address optimal pain control in patients undergoing lung transplantation via T.

Overall, the duration of mechanical ventilation in our cohort was in line with published data where a 65% of respondents were aiming for extubation at 36 hours postoperative,[15] bearing in mind that avoidance of long periods of mechanical ventilation may protect against deleterious effects of recently implanted graft.[16] In a recently published study severe postoperative hemorrhage was associated with use of pre or postoperative ECMO and it was linked to worse 60- day survival after lung transplantation.[17]

Current intraoperative use of extracorporeal support with Veno-Arterial ECMO may affect duration of postoperative mechanical ventilation and hemorrhage. Also the interaction of analgesic drugs with oxygenator and tubings of ECMO circuit could impact analgesia efficacy.[18,19] An anticipatory multimodal pain strategy could be used according to different risk of postoperative pain identified in this cohort. However, dedicated acute pain team with daily assessments for lung transplant recipients may improve the expertise in decision making and treatment, and potentially offer better outcomes.

Our study has several limitations. The cohort has a relatively small sample size and subjects were not randomly assigned to the surgical approach groups. The population analyzed in a single-center study makes it difficult to extrapolate our results beyond the population and conditions studied. Additionally, the retrospective nature of study and the 10 years period of patient recruitment may induce historical bias. Qualitative pain scale and heterogeneity on number of pain score amongst all patients could add some noise in the interpretation. However, this same scale has been used by same group and others[20,21] and in our clinical setting it is very pragmatic. Despite all these limitations, this study was able to provide data on outcomes related to analgesia and surgical approach after lung transplantation in real clinical practice.

In summary, our results provide evidence that thoracotomy is associated with higher pain scores and need for epidural analgesia but with better outcomes in terms of postoperative hemorrhage, duration of mechanical ventilation, and stay in ICU. While hoping for further multicenter studies to address the effects of epidural analgesia on lung transplant outcomes, our results show that epidural analgesia is safe. Surgical access would have to be a part of such studies as it has impact on postoperative hemorrhage, duration of mechanical ventilation, and length of stay in the ICU.

Author contributions

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