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## CLINICAL RESEARCH

### Implementation of an ERAS program in patients undergoing thoracic surgery at a third-level university hospital: an ambispective cohort study

Soledad Bellas-Cotán <sup>a,\*</sup>, Rubén Casans-Francés<sup>b</sup>, Cristina Ibáñez<sup>a</sup>, Ignacio Muguruza<sup>c</sup>, Luis E. Muñoz-Alameda<sup>a</sup>

<sup>a</sup> Hospital Universitario Fundación Jiménez Díaz, Department of Anaesthesiology, Madrid, Spain

<sup>b</sup> Hospital Universitario Infanta Elena, Department of Anaesthesiology, Valdemoro, Madrid, Spain

<sup>c</sup> Hospital Universitario Fundación Jiménez Díaz, Department of Thoracic Surgery, Madrid, Spain

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#### KEYWORDS

Fast-track  
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#### Abstract

**Objective:** To analyze the effects of an ERAS program on complication rates, readmission, and length of stay in patients undergoing pulmonary resection in a tertiary university hospital.

**Methods:** Ambispective cohort study with a prospective arm of 50 patients undergoing thoracic surgery within an ERAS program (ERAS group) versus a retrospective arm of 50 patients undergoing surgery before the protocol was implemented (Standard group). The primary outcome was the number of patients with 30-day surgical complications. Secondary outcomes included ERAS adherence, non-surgical complications, mortality, readmission, reintervention rate, pain, and hospital length of stay. We performed a multivariate logistic analysis to study the correlation between outcomes and ERAS adherence.

**Results:** In the univariate analysis, we found no difference between the two groups in terms of surgical complications (Standard 18 [36%] vs. ERAS 12 [24%],  $p=0.19$ ). In the ERAS group, only the readmission rate was significantly lower (Standard 15 [30%] vs. ERAS 6 [12%],  $p=0.03$ ). In the multivariate analysis, ERAS adherence was the only factor associated with a reduction in surgical complications (OR [95% CI]=0.02 [0.00, 0.59],  $p=0.03$ ) and length of stay (HR [95% CI]=18.5 [4.39, 78.4],  $p<0.001$ ).

**Conclusions:** The ERAS program significantly reduced the readmission rate at our hospital. Adherence to the ERAS protocol reduced surgical complications and length of stay.

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\* Corresponding author.

E-mail: [soledad.bellas@quironsalud.es](mailto:soledad.bellas@quironsalud.es) (S. Bellas-Cotán).

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## Introduction

Lung cancer is the leading cause of cancer death worldwide, representing 20.55% and 14% of cancer deaths in Spain<sup>1</sup> and the United States,<sup>2</sup> respectively. Pulmonary resection is currently the treatment of choice for lung cancer.<sup>3</sup> However, this procedure is associated with significant complications in almost 50% of cases and can delay patient recovery and increase hospitalization costs.<sup>4</sup>

Professor Henrik Kehlet first described ERAS programs at the end of the last century.<sup>5</sup> He believed that applying specific, evidence-based measures during the perioperative period could decrease the stress produced by surgical aggression.<sup>6</sup> Thus, in recent years, ERAS programs have proven effective in reducing surgical complications, length of stay, and hospital costs.<sup>7–9</sup>

Specific ERAS approaches have recently been described for thoracic surgery.<sup>10–12</sup> Nevertheless, there is still insufficient evidence to support ERAS programs for pulmonary resection surgery, particularly in terms of the clinical outcomes associated with minimally invasive procedures.

We hypothesized that the ERAS program in patients undergoing pulmonary resection in a tertiary university hospital would reduce complications, readmissions, and length of stay.

## Methods

### Study design and participants

This study analyzes the implementation of an ERAS in the thoracic surgery service of a third level hospital (Hospital Fundación Jiménez Díaz, Madrid, Spain). To this end, we designed an ambispective cohort study, with a prospective arm of patients undergoing lobectomy within an ERAS program (ERAS group) versus a retrospective arm of patients undergoing surgery before the protocol was implemented (Standard group). The study was approved by the hospital's research ethics committee before the start of patient recruitment in January 2018 (Reference: E0071-18.FJD; ClinicalTrials.gov Identifier: NCT04579601). The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.<sup>13</sup>

After obtaining informed consent, we included patients consecutively after implementation of the ERAS program, except for those who refused to take part or were under 18 years of age. We also asked for informed consent from patients included in the retrospective cohort. We calculated the sample size on the assumption that the ERAS program would result in a 25% reduction in the absolute risk of presenting surgical complications in our center. As our surgical complication rate in 2016 was 40%, a type-I error of 5%, and a power of 80% would require 47 patients per arm.

## Procedures

We recruited 50 patients during 2018 and 2019 and compared them with data from the last 50 patients in 2016, the year for which data on the surgical complication rate were avail-

able. We followed up patients for 30 days after surgery using hospital and primary care medical records. We collected demographic and comorbidity data from all patients, which were used to calculate the Charlson's comorbidity index.<sup>14</sup>

Our center's ERAS program includes different strategies for the preoperative, intraoperative, and postoperative periods. During the preoperative period, the patients and their families received comprehensive multidisciplinary information about the protocol, the steps to be taken during each day of hospitalization, and the expected discharge date. Patients were taught a series of pulmonary expansion exercises to be performed until surgery by a team specialized in treating lung diseases. Smoking cessation interventions and nutritional screening were also performed at this stage.

Patients underwent Video-Assisted Thoracoscopic Surgery (VATS) whenever possible, placing a chest tube for drainage at the end of the surgery. All subjects received antibiotics and antithrombotic prophylaxis. None of the patients in either group fasted for more than 2 hours before surgery. We performed general anesthesia combined with regional techniques for pain control, avoiding benzodiazepines and opioids. The anesthesiologist was free to choose between thoracic epidural analgesia, intercostal block, and erector spinae block. If a thoracic epidural catheter was placed, it was left in for postoperative patient-controlled analgesia. We also used a hot air system to warm patients during surgery to maintain normothermia. In both groups, no more than 2 mL.kg<sup>-1</sup>.h<sup>-1</sup> fluids were administered. Extubation was performed as soon as possible after the end of the surgery, and we encouraged early removal of the urinary catheter.

After extubation, patients started oral intake, respiratory physiotherapy exercises, and early ambulation. Patients were discharged when they were free of complications, without severe pain, and the urinary catheter or chest tube had been removed.

## Outcomes

The primary outcome was the number of patients with 30-day surgical complications. We defined air leakage, bleeding, infection, and reintervention as surgical complications, classifying all other complications as "non-surgical complications" or "other complications". Secondary outcomes included ERAS adherence, non-surgical complications, mortality, readmission, reintervention rate, pain (defined as any level of pain level that prevented early ambulation), and hospital length of stay. ERAS adherence was evaluated on the basis of seven items: VATS approach, regional analgesia, oral intake within 6 hours, urinary catheter removal within 24 hours, ambulation within 24 hours, respiratory physiotherapy within 24 hours, and chest tube removal within 48 hours.

## Statistical analysis

We analyzed outcomes depending on whether the patient belonged to the ERAS program or the retrospective standard cohort. We describe discrete and continuous variables as number and percentage and median (Interquartile Range

**Table 1** Patient demographics and comorbidity. Pearson or Wilcoxon tests were applied depending on whether the variable was discrete or continuous. Significance is set at  $p < 0.05$ .

Variable	Standard (n = 50)	ERAS (n = 50)	p
Age (y), median (IQR)	64.5 (53.5–70)	64 (57–70.8)	0.82
Weight (kg), median (IQR)	70 (63–80)	73 (61–82.8)	0.77
Height (cm), median (IQR)	160 (160–163)	165 (158–171.5)	0.04*
BMI, median (IQR)	27.5 (24.7–29.9)	25.3 (22.7–29.4)	0.16
Men, n (%)	31 (62.0)	25 (50.0)	0.23
ASA class, n (%)			0.25
I	2 (4.0)	2 (4.0)	
II	21 (42.0)	30 (60.0)	
III	23 (46.0)	17 (34.0)	
IV	4 (8.0)	1 (2.0)	
ASA class > 2	26 (52.0)	15 (30.0)	0.03*
Hypertension, n (%)	29 (58.0)	17 (34.0)	0.02*
Cardiac Arrest, n (%)	5 (10.0)	7 (14.0)	0.54
Chronic Heart Failure, n (%)	2 (4.0)	0 (0.0)	0.49
Vascular Disease, n (%)	0 (0.0)	0 (0.0)	1
Stroke, n (%)	1 (2.0)	1 (2.0)	1
Diabetes, n (%)	7 (14.0)		1
Dementia, n (%)	0 (0.0)	0 (0.0)	1
Chronic Kidney Disease, n (%)	3 (6.0)	0 (0.0)	0.24
COPD, n (%)	12 (24.0)	4 (8.0)	0.03*
AIDS, n (%)	0 (0.0)	1 (2.0)	1
Metastasis, n (%)	0 (0.0)	1 (2.0)	1
Charlson Comorbidity Index, median (IQR)	2 (1–3)	2 (1–3)	0.9

\* $p < 0.05$ .

[IQR]), and differences were analyzed using the Pearson test or the Wilcoxon rank-sum tests. We performed a multivariate logistic analysis of adherence to ERAS items in both cohorts in order to determine the correlation between complication rates, readmission, or pain and ERAS adherence, clinical and demographic data, showing the results in forest plots as odds ratio with 95% Confidence Interval. Similarly, we used Cox regression for the multivariate analysis of length of stay, showing the results as hazard ratio with 95% Confidence Interval. To avoid errors due to multiple comparisons, we calculated the respective  $q$ -value for each  $p$ -value to keep the false discovery rate below 5%.<sup>15</sup> We considered comparisons in which  $p$ -value and  $q$ -value were below 0.05 as being statistically significant.

## Results

No patients refused to take part in the study. Patient demographics and comorbidities are shown in Table 1. The cohorts were not totally homogeneous: a higher number of patients in the Standard cohort versus the ERAS cohort presented hypertension (26 [52%] vs. 15 [30%],  $p = 0.03$ ) and chronic obstructive pulmonary disease (12 [24%] vs. 4 [8%],  $p = 0.02$ ), respectively. Although the number of patients with ASA class > 2 was higher in the standard group versus the ERAS group (26 [52%] vs. 15 [30%]), we found no difference between the cohorts in terms of the Charlson's comorbidity index. We included these three items, along with age and sex, in the subsequent multivariate analyses.

Data on ERAS adherence and compliance for each of the protocol items are shown in Table 2. Adherence to items in the ERAS protocol was significantly higher in the ERAS vs. the Standard cohort (median: Standard 0.29 [0.14–0.43] vs. ERAS 0.71 [0.57–0.82],  $p < 0.001$ ). The VATS approach was more common in the ERAS group (29 [58%] vs. 11 [22%],  $p < 0.001$ ), and more patients in the ERAS group ambulated on the first postoperative day [40 (80%) vs. 0 (0%),  $p < 0.001$ ], but no difference was found in the use of regional analgesia. Time to oral intake and removal of the urethral catheter were also lower in the ERAS group; median (h): Standard 24 (24–24) vs. ERAS 6 (6–7.5), and Standard 48 (24–48) vs. ERAS 19 (6–24), respectively.

The primary and secondary outcomes are shown in Table 3. We found no difference between the two groups in terms of surgical complications (Standard 18 [36%] vs. ERAS 12 [24%],  $p = 0.19$ ), non-surgical complications (Standard 21 [42%] vs. ERAS 12 [24%],  $p = 0.06$ ) or length of stay (median [days]: Standard 4 [3–6] vs. ERAS 4 [3–5],  $p = 0.19$ ); only the readmission rate was significantly lower in the ERAS group (Standard 15 [30%] vs. ERAS 6 [12%],  $p = 0.03$ ). No deaths were recorded in the ERAS group compared to two deaths in the retrospective cohort.

The results of the multivariate analyses are shown in Figures 1, 2 and 3. ERAS adherence was the only factor associated with a reduction in surgical complications (OR [95% CI] = 0.02 (0.00, 0.59),  $p = 0.03$ ) (Fig. 1A), and post-operative pain (OR [95% CI] = 0.01 [0.00, 0.28],  $p = 0.01$ ) (Fig. 2A). It was also associated with a lower readmission rate (OR (95% CI) = 0.01 [0.00, 0.24],  $p = 0.007$ ) (Fig. 2B) and

**Table 2** ERAS adherence. Pearson or Wilcoxon tests were applied depending on whether the variable was discrete or continuous. Significance was set at  $p < 0.05$ .

Variable	Standard (n = 50)	ERAS (n = 50)	p
ERAS Adherence, median (IQR)	0.29 (0.14–0.43)	0.71 (0.57–0.82)	< 0.001*
Antithrombotic prophylaxis, n (%)	50 (100.0)	50 (100.0)	1
Nutritional screening, n (%)	50 (100.0)	50 (100.0)	1
Avoid fasting, n (%)	50 (100.0)	50 (100.0)	1
Surgical approach, n (%)			< 0.001*
Thoracotomy	37 (74.0)	16 (32.0)	
VATS	11 (22.0)	29 (58.0)	
Reconverted	2 (4.0)	4 (8.0)	
Robotic	0 (0.0)	1 (2.0)	
Regional analgesia, n (%)	42 (84.0)	42 (84.0)	1
Analgesia type, n (%)			0.01*
Intravenous	7 (14.0)	8 (16.0)	
Thoracic epidural	34 (68.0)	26 (52.0)	
Intercostal block	9 (18.0)	7 (14.0)	
Erector spinae block	0 (0.0)	9 (18.0)	
Regional analgesia administration, n (%)			0.69
No regional analgesia	7 (14.0)	8 (16.0)	
Bolus	9 (18.0)	12 (24.0)	
Catheter	34 (68.0)	30 (60.0)	
Mobilization on POD-0, n (%)	0 (0.0)	40 (80.0)	< 0.001*
Time to oral Intake (h), median (IQR)	24 (24–24)	6 (6–7.5)	< 0.001*
Time to respiratory physiotherapy (h), median (IQR)	25 (24–24)	26 (24–24)	0.33
Time to chest drain removal (h), median (IQR)	72 (48–96)	48 (48–72)	0.18
Time to urethral catheter removal (h), median (IQR)	48 (24–48)	19 (6–24)	< 0.001*

\* $p < 0.05$ .

**Table 3** Results of main and secondary outcomes. Pearson or Wilcoxon tests were applied depending on whether the variable was discrete or continuous. Significance was set at  $p < 0.05$ .

Variable	Standard (n = 50)	ERAS (n = 50)	p
Surgical complications, n (%)	18 (36.0)	12 (24.0)	0.19
Other complications, n (%)	21 (42.0)	12 (24.0)	0.06
Mortality, n (%)	2 (4.0)	0 (0.0)	0.49
Reintervention, n (%)	2 (4.0)	0 (0.0)	0.49
Readmission, n (%)	15 (30.0)	6 (12.0)	0.03*
ICU readmission, n (%)	0 (0.0)	0 (0.0)	1
Pain, n (%)	16 (32.0)	10 (20.0)	0.17
Death, n (%)	2 (4.0)	0 (0.0)	0.49
Length of stay (d), median (IQR)	4 (3–6)	4 (3–5)	0.39

\* $p < 0.05$ .

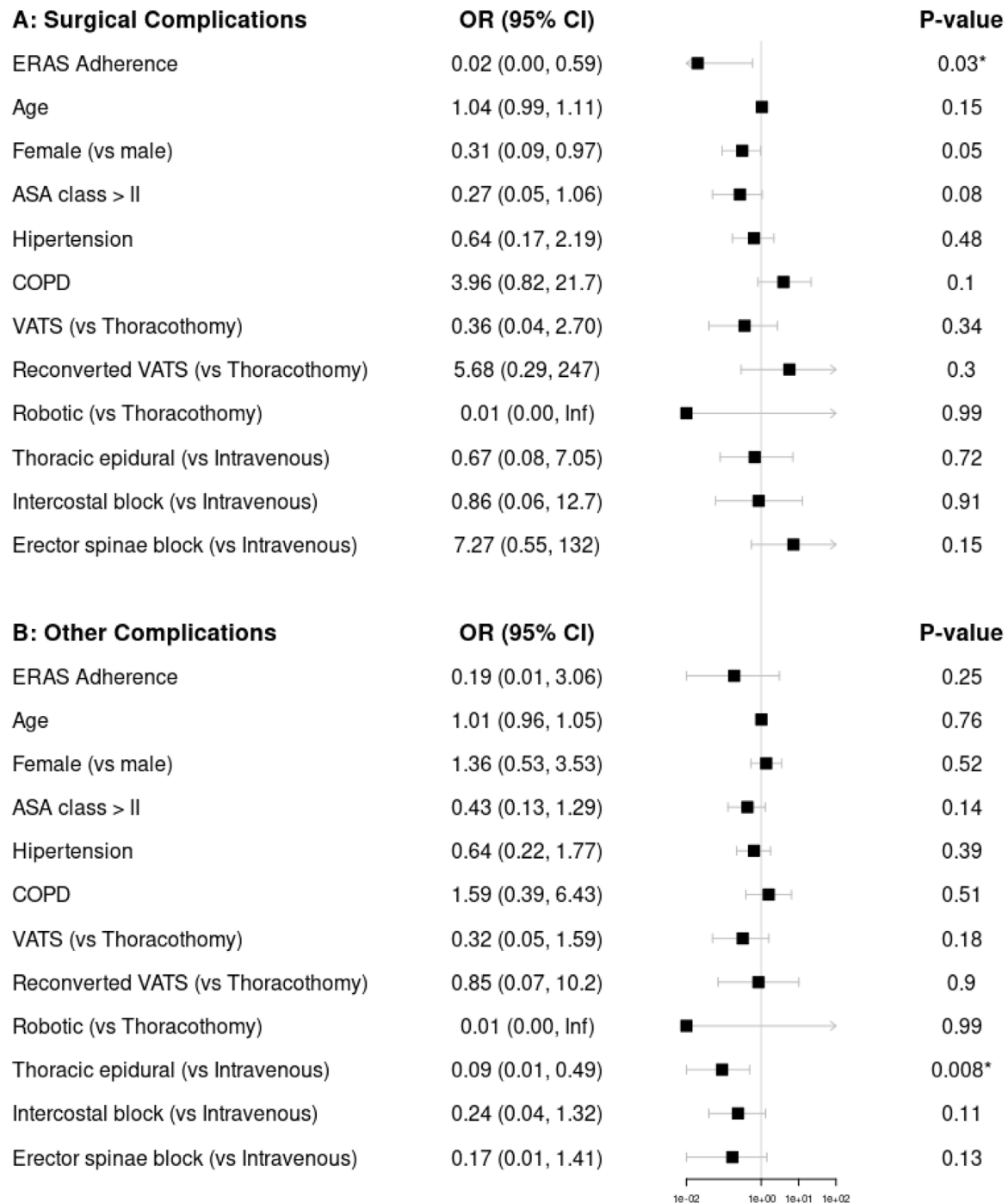
an increased likelihood of early discharge from the hospital (HR [95% CI] = 18.5 [4.39, 78.4],  $p < 0.001$ ) (Fig. 3). Thoracic epidural analgesia was the only factor that showed an association with lower rates of non-surgical complications (OR [95% CI] = 0.09 [0.01, 0.49],  $p = 0.008$ ) (Fig. 1B). It was also associated with lower rates of postoperative pain (OR [95% CI] = 0.16 [0.03, 0.86],  $p = 0.03$ ) (Fig. 2A) and increased likelihood of discharge from the hospital (HR [95% CI] = 3.14 [1.39, 7.07],  $p = 0.006$ ) (Fig. 3). Intercostal blockade also increased this likelihood (HR [95% CI] = 7.55 [2.94, 19.3],  $p < 0.001$ ) (Fig. 3).

No significant  $p$ -value was rejected after calculating the  $q$ -value within the multiple comparability study.

## Discussion

Our study has shown that adherence to the ERAS protocol is one of the essential factors in reducing complications in patients undergoing pulmonary resection. An increase in the adherence rate was associated with a reduction in the number of complications and the length of stay. In other words, although the small marginal gains caused by each of the items in isolation have little effect on the results, it is the combination of all the measures applied that is responsible for the improvement. These findings are consistent with those of Madani et al.,<sup>10</sup> who observed that compliance with

### Complications (multivariate logistic regression)



**Figure 1** Forest plot of multivariate logistic analysis of the influence of patient comorbidity and ERAS on complications. A, Surgical complications. B, Non-surgical complications. Results are shown as odds ratio with a 95% Confidence Interval. A value of less than 1, left of the y-axis, implies risk reduction. We accept  $p < 0.05$  as significant.

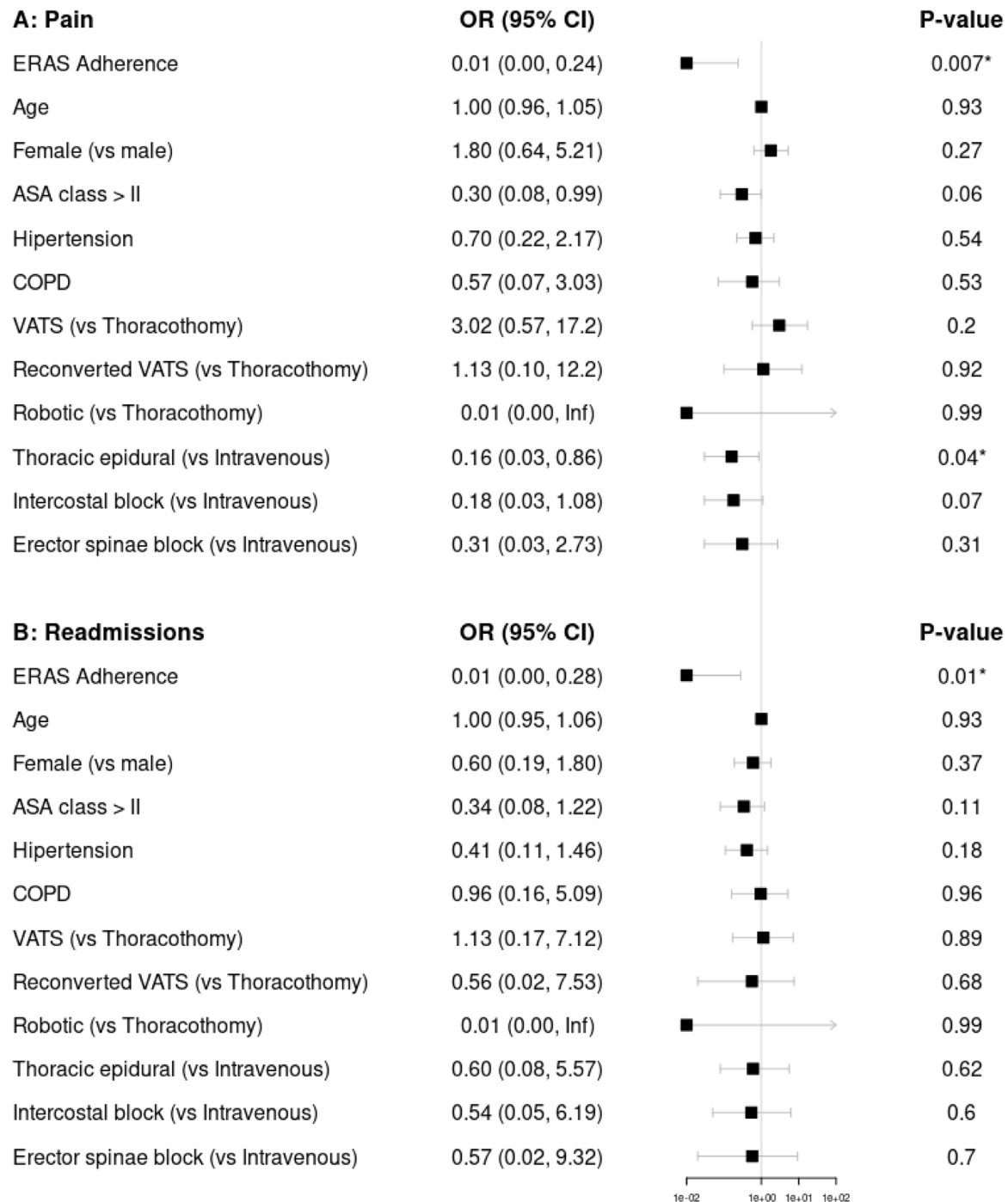
the full ERAS program is probably the most critical factor, more than individually applied elements.

However, it is also important to note that it is one thing to include a patient in an ERAS program, and another to have the patient comply with all the program items. Resistance to change, especially in the initial stages of the program,

can make it hard for patients to complete the program.<sup>16</sup> Added to this is the lack of multidisciplinary often found among clinicians and the difficulties involved in overcoming patient passivity. In these cases, ERAS programs can appear to be ineffective. In Spain, this was clearly shown by the POWER study,<sup>17</sup> a prospective multi-center study of



Other outcomes (multivariate logistic regression)

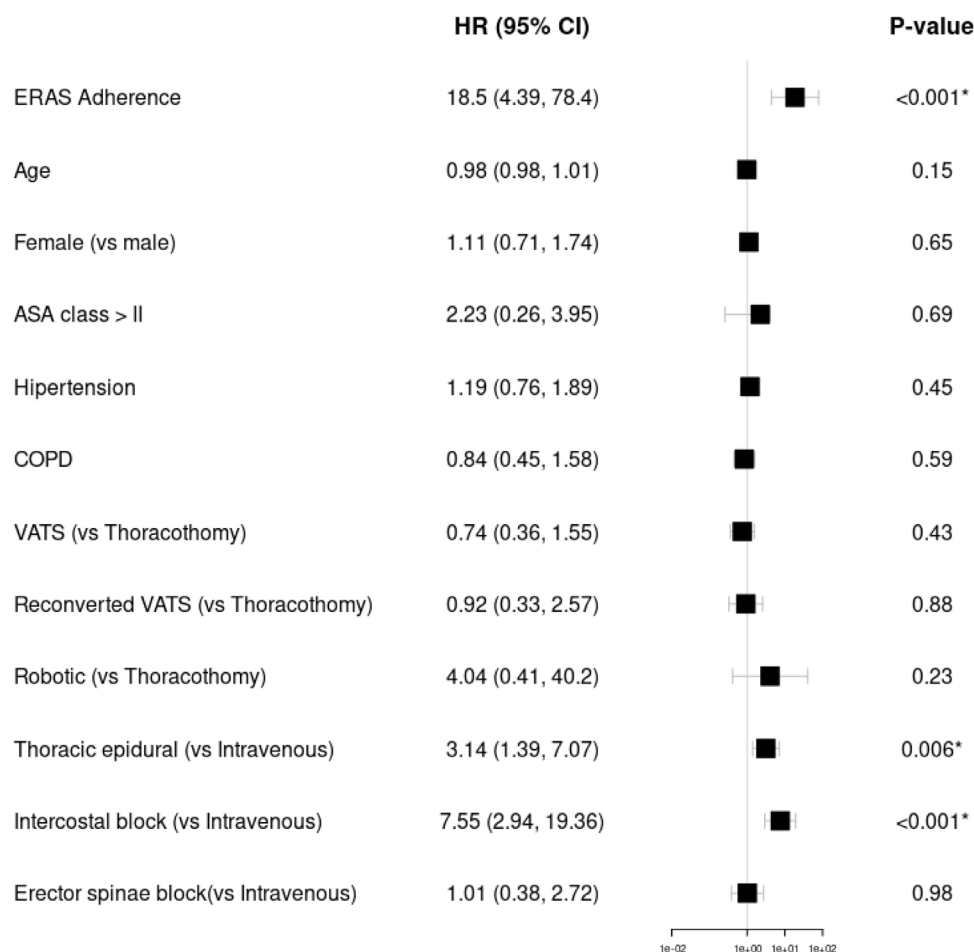


**Figure 2** Forest plot of multivariate logistic analysis of the influence of patient comorbidity and ERAS on other outcomes. A, Pain. B, Readmission. Results are shown as odds ratio with a 95% Confidence Interval. A value of less than 1, left of the y-axis, implies risk reduction. We accept  $p < 0.05$  as significant.

80 hospitals and more than 2000 patients. Hospitals were asked to state whether they used ERAS programs on their patients, and then independently collected ERAS compliance data. The results showed that although moderate or severe complications did not differ between non-ERAS and ERAS groups, differences were observed when the patients

were divided into adherence quartiles. In our study, we observed a similar trend in respect of length of stay, insofar as we did not find differences between groups, but a very high adjusted hazard ratio was observed when compliance with the protocol increased.

**Length of Stay (Hazard Ratio, Cox's regression)**



**Figure 3** Forest plot of Cox regression of the influence of patient comorbidity and ERAS on length of stay. Results are shown as hazard ratio with a 95% Confidence Interval. A value of more than 1, right of the y-axis, implies an increased probability of early hospital discharge. We accept  $p < 0.05$  as significant.

One of the critical points of the ERAS program is that it facilitates standardization in perioperative patient care. This standardization, as several studies have shown, tends to translate into improved outcomes. Cerfolio et al.<sup>18</sup> implemented an ERAS program for pulmonary resections with an approach focused on patient education, epidural analgesia, standardized and early withdrawal of urethral catheters and chest drains, and early ambulation. These interventions enabled early discharge without negatively affecting morbidity or mortality. Another example is the randomized controlled clinical trial conducted by Muehling et al.,<sup>19</sup> who observed how a protocol based on avoidance of extended fasting, administration of regional analgesia, early oral intake, and early ambulation resulted in a significant reduction in pulmonary complications.

The sum of the marginal effects of each individual factor is responsible for the benefit of ERAS programs. However, this does not mean that all items are equally important – some have a greater effect than others. It is as yet unclear whether adherence to the program or the weight of specific items is responsible for the improvement in thoracic

surgery. However, experience in colorectal surgery indicates that both approaches may be correct.<sup>20</sup>

We found that only regional analgesia improved outcomes, and this effect was only found in multivariate analyses. This factor has a substantial impact on other protocol items influenced by pain, such as immobility. Immobility after thoracic surgery is not uncommon due to factors such as pain, nausea, or the presence of a chest tube.<sup>21</sup> Early mobilization is a critical factor in reducing complications in ERAS programs,<sup>22</sup> but we did not observe this to have an effect on our study outcomes. Another influential factor is the early removal of chest tubes. Although our analysis did not show this to have any impact, the literature indicates that the earlier the withdrawal, the better the results.<sup>23,24</sup>

We also found that VATS did not affect our results. Minimally invasive surgery seems to be an independent predictor of favorable outcomes after colorectal cancer surgery in ERAS programs.<sup>25</sup> The use of VATS for pulmonary resection surgery has gradually increased following the publication of new data showing that it is effective, and can potentially improve outcomes.<sup>26,27</sup>

Many clinicians fear that implementing an ERAS program for pulmonary resection surgery will increase the number of readmissions, a factor that is associated with reduced survival in both the short and long term.<sup>28</sup> An increase in readmissions has not been observed after implementing ERAS programs for pulmonary resection.<sup>10</sup> In our study, the readmission rate was 12%, and it was the only outcome that improved due to inclusion in the ERAS program, a finding consistent with other published studies.<sup>28</sup> We found no relationship between improved functionality and certain items of the ERAS protocol. We believe that this was due to the main limitation of our study, i.e., our over-optimism about the theoretical effect of the ERAS protocol on the complication rate. The estimated 25% absolute risk reduction resulted in a reduction in the theoretical sample size and decreased power. A more conservative value would have increased the power of the study.

In conclusion, the ERAS program significantly reduced the readmission rate at our hospital. Likewise, adherence to the ERAS protocol helped reduce the number of surgical complications and length of stay.

## Level of authorship

Studio design: SBC, IM, LEMA. Studio execution: SBC, CI. Statistical analysis: RCF. First draft: SBC, RCF, Final Draft: SBC, RCF, LEMA.

## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.bjane.2021.04.014>.

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