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Individualised, perioperative open-lung ventilation strategy during one-lung ventilation (iPROVE-OLV): a multicentre, randomised, controlled clinical trial

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Summary

Background It is uncertain whether individualisation of the perioperative open-lung approach (OLA) to ventilation reduces postoperative pulmonary complications in patients undergoing lung resection. We compared a perioperative individualised OLA (iOLA) ventilation strategy with standard lung-protective ventilation in patients undergoing thoracic surgery with one-lung ventilation.

Methods: This multicentre, randomised controlled trial enrolled patients scheduled for open or video-assisted thoracic surgery using one-lung ventilation in 25 participating hospitals in Spain, Italy, Turkey, Egypt, and Ecuador. Eligible adult patients (age ≥18 years) were randomly assigned to receive iOLA or standard lung-protective ventilation. Eligible patients (stratified by centre) were randomly assigned online by local principal investigators, with an allocation ratio of 1:1. Treatment with iOLA included an alveolar recruitment manoeuvre to 40 cm H_2O of end-inspiratory pressure followed by individualised positive end-expiratory pressure (PEEP) titrated to best respiratory system compliance, and individualised postoperative respiratory support with high-flow oxygen therapy. Participants allocated to standard lung-protective ventilation received combined intraoperative 4 cm H_2O of PEEP and postoperative conventional oxygen therapy. The primary outcome was a composite of severe postoperative pulmonary complications within the first 7 postoperative days, including atelectasis requiring bronchoscopy, severe respiratory failure, contralateral pneumothorax, early extubation failure (rescue with continuous positive airway pressure, non-invasive ventilation, invasive mechanical ventilation, or reintubation), acute respiratory distress syndrome, pulmonary infection, bronchopleural fistula, and pleural empyema. Due to trial setting, data obtained in the operating and postoperative rooms for routine monitoring were not blinded. At 24 h, data were acquired by an investigator blinded to group allocation. All analyses were performed on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, NCT03182062, and is complete.

Findings Between Sept 11, 2018, and June 14, 2022, we enrolled 1380 patients, of whom 1308 eligible patients (670 [434 male, 233 female, and three with missing data] assigned to iOLA and 638 [395 male, 237 female, and six with missing data] to standard lung-protective ventilation) were included in the final analysis. The proportion of patients with the composite outcome of severe postoperative pulmonary complications within the first 7 postoperative days was lower in the iOLA group compared with the standard lung-protective ventilation group (40 [6%] *vs* 97 [15%], relative risk 0·39 [95% CI 0·28 to 0·56]), with an absolute risk difference of –9·23 (95% CI –12·55 to –5·92). Recruitment manoeuvre-related adverse events were reported in five patients.

Interpretation Among patients subjected to lung resection under one-lung ventilation, iOLA was associated with a reduced risk of severe postoperative pulmonary complications when compared with conventional lung-protective ventilation.

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Introduction

Postoperative pulmonary complications have an important impact on postoperative morbidity, mortality, and health-care costs.[1,2] Mechanical ventilation is the most relevant factor associated with the development of postoperative pulmonary complications, since it can

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Research in context

Evidence before this study

We searched PubMed, Scopus, and MEDLINE for papers published from database inception up to May 15, 2023. The terms used were: "one lung ventilation", "thoracic surgery", "lung resection", "protective ventilation", "recruitment maneuver", "recruitment manoeuvre", "positive end-expiratory pressure", "high flow oxygen therapy", "high flow nasal cannula", and "postoperative pulmonary complications". Patients undergoing lung resection are especially prone to lung damage. One-lung ventilation, which by itself is associated with increased risk for ventilator-induced lung injury, usually coexists with other injurious mechanisms such as direct surgical injury, ischaemia-reperfusion, and loss of surfactant. In such a high-risk population, the use of perioperative (intra-operative and postoperative) lung-protective ventilation might have the greatest benefit. Although intraoperatively, the benefits of individualised positive end-expiratory pressure (PEEP) in reducing postoperative pulmonary complications during one-lung ventilation was confirmed in a meta-analysis, the most recent multicentre trial did not report a reduction in postoperative pulmonary complications when comparing a reduced driving pressure-guided PEEP strategy with conventional lung-protective ventilation. Additionally, the latest meta-analysis and guidelines recommend the use of high-flow nasal cannula (HFNC) to prevent postoperative pulmonary complications in high-risk surgical patients. However, thus far, no trials showing its benefits in patients undergoing lung resection have been reported.

Added value of this study

To our knowledge, this is the first study in which the ventilatory strategy is personalised to the patient´s lung condition during the intraoperative and postoperative period in patients subjected to lung resection. We compared a perioperative individualised open-lung approach (iOLA) with the most standard ventilatory management, using in both groups an identical protective tidal volume following current guidelines. We found that the perioperative iOLA, including intraoperative alveolar recruitment manoeuvres plus individualised PEEP and postoperative individualisation of oxygen therapy (HFNC or conventional oxygen therapy) based on oxygenation while breathing room air, significantly reduces postoperative pulmonary complications compared with conventional lung-protective ventilation. These findings might be of clinical relevance as the inclusion and exclusion criteria ensured the evaluation of a representative population of patients subjected to lung resection in terms of surgical risk, type of surgery, surgical techniques, or intraoperative anaesthetic management, contributing to high generalisability of our findings.

Implications of all the available evidence

Current evidence supports the use of recruitment manoeuvre plus individualised PEEP in patients submitted to one-lung ventilation. Individualised PEEP, when reducing driving pressure, confers benefits in terms of a reduction in postoperative pulmonary complications. Postoperatively, our results add to the current evidence for the use of HFNC to prevent postoperative pulmonary complications in high-risk surgical patients, a specific population of thoracic surgery patients.

result in lung damage caused by excessive lung tissue stretching when the lungs are globally or regionally overinflated.[3] The risk of overinflation is higher during one-lung ventilation or when tidal volume is unevenly distributed, especially in the presence of lung collapse.[4] The end result is an inflammatory response favouring the development of ventilator-induced lung injury,[3] which in turn triggers postoperative pulmonary and extrapulmonary complications.[5]

An adequate lung-protective ventilation strategy, aiming to mitigate ventilator-induced lung injury, should include the judicious use of low tidal volume plus positive end-expiratory pressure (PEEP).[6] Although the role of low tidal volume in decreasing postoperative pulmonary complications has been established, there is a debate regarding the level of PEEP that best protects the lungs.[6,7] Two meta-analyses suggest that a ventilation strategy combining alveolar recruitment manoeuvres (which consist of a controlled increase in alveolar pressure to reopen alveolar collapse) with post-recruitment individualisation of PEEP using respiratory system mechanics such as driving pressure or compliance, the so-called open-lung approach (OLA), enhances the potential for lung protection compared with more constant PEEP setting approaches.[8,9] However, these meta-analyses did not include the findings of the largest clinical trial in which the OLA did not reduce postoperative pulmonary complications.[10] During the immediate postoperative period, there is an increased risk of postoperative atelectasis and pulmonary dysfunction due to several factors, including patient characteristics, type of surgery, and general anaesthesia, that might further promote additional postoperative pulmonary complications. Postoperative respiratory support could prevent postoperative pulmonary complications in high-risk surgical patients.[11]

Patients undergoing lung resection are especially prone to lung damage. One-lung ventilation, which by itself is associated with increased risk for ventilator-induced lung injury, usually coexists with other injurious mechanisms such as direct surgical injury, ischaemia-reperfusion, and loss of surfactant.[12,13] In such a high-risk population, the use of perioperative (intraoperative and postoperative) lung-protective ventilation might have the greatest benefit. To date, the benefits of the individualisation of open-lung ventilatory management during and after the

surgical procedure—the perioperative individualised OLA (iOLA)—and its potential to reduce postoperative pulmonary complications have not been evaluated in the population of patients undergoing lung resection.

We hypothesised that a perioperative iOLA would reduce the rate of postoperative pulmonary complications compared with a conventional approach in patients undergoing thoracic surgery requiring one-lung ventilation. We examined whether an iOLA strategy (as defined by the use of low tidal volume, alveolar recruitment manoeuvres, individualised PEEP, and individualisation of postoperative respiratory support) reduces the rate of severe postoperative pulmonary complications.

Methods

Study design

The individualised PeRioperative Open-lung Ventilatory stratEgy in patients submitted to One-Lung Ventilation (iPROVE-OLV) trial was an international, multicentre, randomised, controlled clinical trial (RCT) performed in 25 hospitals in five countries (Spain, Italy, Turkey, Egypt, and Ecuador). This trial was designed in compliance with the fundamental principles established in the Declaration of Helsinki and the Convention of the European Council related to human rights and biomedicine. The trial was registered with ClinicalTrials.gov (NCT03182062) and the complete protocol was published before patient enrolment.[14] The final protocol was approved by local Ethics Committee in all participating centres. Written informed consent was obtained from all patients. A Steering Committee monitored the study, and an independent data and safety monitoring board was established to review the interim analysis of the trial. We followed the Consolidated Standards of Reporting Trials.[15]

Participants

We screened adult patients (≥18 years of age) who were scheduled for open or video-assisted thoracic surgery under one-lung ventilation with an expected operating time of 2 h or longer. Patients without any of the following exclusion criteria were enrolled: (1) pregnancy or breast-feeding, (2) acute respiratory distress syndrome, (3) heart failure, (4) intracranial hypertension, (5) mechanical ventilation in the previous 15 days, (6) pneumothorax or giant bullae, (7) chronic obstructive pulmonary disease (COPD) requiring oxygen or continuous positive airway pressure, (8) participation in another interventional study with similar primary outcomes, and (9) previous lung resection; full details of exclusion criteria are available in the online appendix (p 3). After informed consent was obtained, the patients were randomly assigned to iOLA or the standard perioperative approach.

Randomisation and masking

Eligible patients (stratified by centre) were randomly assigned online by local principal investigators, via the iPROVE website using the Mersenne–Twister algorithm with an allocation ratio of 1:1. For blinding, a minimum of two investigators were required in each participating centre. Due to study characteristics, data obtained in the operating and postoperative rooms for routine monitoring were not blinded; then, at 24 h, data were acquired by a second investigator who was blinded to group allocation (appendix p 3).

Procedures

Patients were monitored and managed following general high standard-of-care practices. Intraoperative and immediate postoperative anaesthetic management (unrelated to ventilatory management) was decided by the attending physician, following established protocols at each centre.

Intraoperative monitoring included electrocardiogram (ECG), pulse oximetry (SpO_2), capnography, temperature, anaesthetic depth, neuromuscular blockade (with train-of-four), and non-invasive or invasive blood pressure. Ventilatory parameters monitored by the anaesthesia machine included: tidal volume, respiratory rate, PEEP, inspiratory oxygen fraction (FiO_2), peak airway pressure, plateau pressure, and dynamic compliance of the respiratory system calculated as tidal volume divided by (peak pressure−PEEP). Postoperative monitoring included at least ECG, SpO_2, and arterial pressure.

With regard to general intraoperative ventilator management, all patients were protectively ventilated in volume control, with tidal volume of 8 mL/kg predicted bodyweight during two-lung ventilation and 5–6 mL/kg predicted bodyweight during one-lung ventilation.[16,17] When plateau pressure reached 25 cm H_2O or more, tidal volume was decreased by 1 mL/kg steps until plateau pressure decreased to less than 25 cm H_2O. Respiratory rate was set to maintain an end-tidal CO_2 of 35–45 mm Hg, an inspiratory to expiratory ratio of 1:2, and inspiratory pause time of 5–10% of inspiratory time. FiO_2 of 0·8 was set throughout the procedure.[18] PEEP was set to 4 cm H_2O (standard lung-protective ventilation group) or individualised (iOLA group). Intraoperative hypoxaemic episodes (SpO_2 ≤92% with FiO_2 0·8) were managed with protocolised rescue manoeuvres, specific for each trial group (appendix p 6), after excluding common causes (endobronchial tube displacement, bronchospasm, pneumothorax, or haemodynamic instability). At the end of one-lung ventilation, a recruitment manoeuvre was performed in all patients without a PEEP titration. The level of PEEP was the same as that applied before the recruitment manoeuvre. During extubation, neither a PEEP level higher than the value assigned per protocol nor endotracheal suctioning were allowed. If needed, suctioning was performed at least 10 min before extubation, and the patient immediately returned to the protocol ventilation mode. Patients in the iOLA group received a recruitment manoeuvre. Once extubated, FiO_2 was decreased to

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See Online for appendix

For the **iPROVE website** see https://iprove-network.es

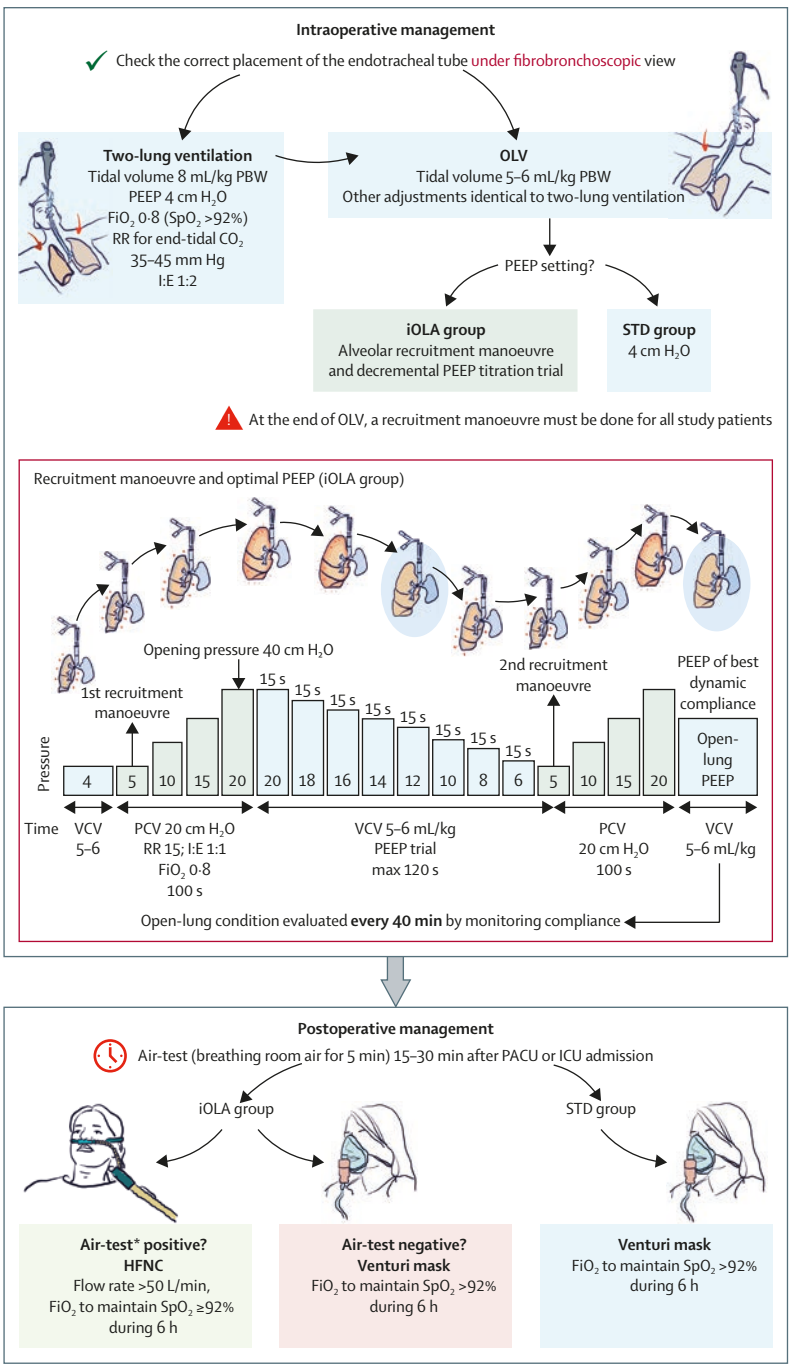

Figure 1: **Perioperative ventilatory management**
The colours do not represent any group. Green bars represent the recruitment manoeuvre and blue bars represents the PEEP titration trial (individualised PEEP). FiO_2=inspiratory oxygen fraction. HFNC=high-flow nasal cannula. ICU=Intensive care unit. I:E=inspiration to expiration ratio. iOLA=perioperative individualised open-lung approach. OLV=one-lung ventilation. PACU=post-anaesthesia care unit. PBW=predicted bodyweight. PCV=pressure-controlled ventilation. PEEP=positive end-expiratory pressure. RR=respiratory rate (breaths per min). STD=standard lung-protective ventilation. SpO_2=peripheral oxyhaemoglobin saturation. VCV=volume-controlled ventilation. *SpO_2 ≤96% after performing a vital capacity manoeuvre at the end of the air-test.

0·5 through a Venturi mask within the first 30 min (figure 1; appendix pp 4–5).

In the iOLA group, there was an additional protocol for specific intraoperative ventilatory management. A recruitment manoeuvre was performed immediately after selective ventilation was initiated followed by a PEEP titration trial (appendix pp 5–6). Before the recruitment manoeuvre, the clinician ensured that there was haemodynamic stability (mean arterial pressure >70 mm Hg or a cardiac index >2·5 mL/min per m²) for at least 5 min, stroke volume variation of less than 10%, and adequate neuromuscular blockade (0 of 4 by train-of-four).

Details of the alveolar recruitment manoeuvre have been previously described,[19] and are also presented in the appendix (pp 5–6). In brief, the ventilator was changed from volume-controlled ventilation to pressure-controlled ventilation with a 20 cm H_2O driving pressure and respiratory rate of 15 breaths per min, inspiration to expiration ratio of 1:1, FiO_2 0·8, and PEEP 5 cm H_2O. For the recruitment phase, PEEP level was increased in 5 cm H_2O steps every five respiratory cycles, up to 20 cm H_2O of PEEP to reach a final airway opening pressure of 40 cm H_2O and maintained for ten respiratory cycles (total manoeuvre time of 100 s).

If haemodynamic instability occurred during the recruitment phase (defined as >50% decrease in cardiac index or mean arterial pressure), the recruitment manoeuvre was interrupted and 5–15 mg ephedrine or 0·05–0·15 mg phenylephrine was administered. Once haemodynamic stabilisation was re-established, a new recruitment manoeuvre was performed.

Titration of the optimal individual PEEP was done by means of a decremental PEEP trial (figure 1). At the end of the last recruitment step when PEEP was 20 cm H_2O, the mode was switched back to volume-controlled ventilation with a tidal volume of 5–6 mL/kg, respiratory rate of 15 breaths per min, inspiration to expiration ratio of 1:2, and FiO_2 0·8. Then, PEEP was decreased in 2 cm H_2O steps every 15 s until the highest dynamic compliance of the respiratory system was observed on the ventilator screen (ie, until dynamic compliance of the respiratory system started decreasing or did not increase further).

If highest dynamic compliance of the respiratory system was maintained unchanged during several PEEP steps, the PEEP resulting in lowest driving pressure (plateau pressure–PEEP) was selected. Once the best dynamic compliance of the respiratory system was identified, a new recruitment manoeuvre was performed and PEEP was adjusted according to best compliance of the respiratory system. In case of accidental airway depressurisation, a new recruitment manoeuvre was performed while an identical PEEP was set (figure 2). The need for new recruitment manoeuvres and a PEEP trial were evaluated every 40 min by measuring dynamic compliance of the respiratory system. If there was a drop

of more than 20% of dynamic compliance of the respiratory system, a new recruitment manoeuvre and a PEEP trial were performed.

Management of the first 30 min of care in the postoperative unit, other than postoperative respiratory support, was left to the discretion of attending physicians following established protocols in each centre. Initially, all patients received supplemental oxygen via a Venturi face mask at FiO_2 0·5. After 15–30 min, once patients were awake, collaborative, and under pain control (appendix pp 6–7), lung collapse was assessed by performing an air-test (ie, reducing the FiO_2 from 0·5 to 0·21 for at least 5 min). The air-test was not performed in patients with SpO_2 of less than 96%. In patients who were still intubated, the above management was applied after extubation. Postoperative rescue manoeuvres during this period were protocolised for each group (appendix pp 7–8).

Specific postoperative ventilatory management for the standard lung-protective ventilation group included oxygenation via a Venturi mask with a minimum FiO_2 for SpO_2 of at least 92%; whereas in the iOLA group, patients with a negative air-test (SpO_2 ≥97%) were managed with the minimum FiO_2 for SpO_2 of at least 92% and patients with a positive air-test (SpO_2 ≤96%) were treated with high-flow oxygen therapy at 50 L/min and a minimum FiO_2 for SpO_2 of at least 92% during the subsequent 6 postoperative hours (figure 2; appendix p 7).

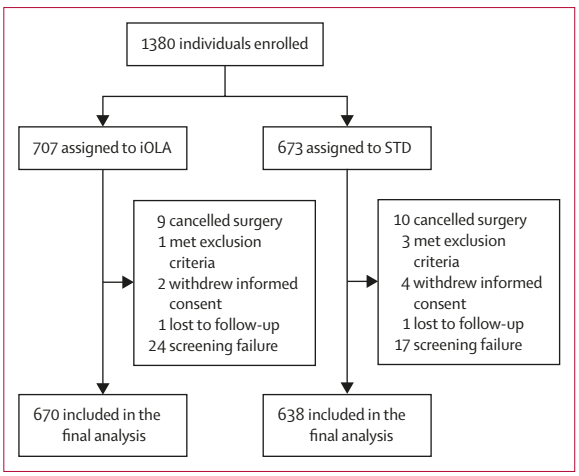

Figure 2: **Trial profile**
iOLA=individualised, perioperative open-lung approach. STD=standard lung-protective ventilation.

Outcomes

The primary outcome was a composite of severe postoperative pulmonary complications occurring within the first 7 postoperative days: atelectasis requiring bronchoscopy, severe respiratory failure, contralateral pneumothorax, early extubation failure (rescue with continuous positive airway pressure, non-invasive ventilation, invasive mechanical ventilation, or reintubation), acute respiratory distress syndrome, pulmonary infection, bronchopleural fistula, and pleural empyema. Postoperative complications included as perioperative outcome measures were defined according to the joint taskforce of the European Society of Anaesthesiology and the European Society of Intensive Care Medicine (appendix pp 8–9).[20] Secondary outcomes were: (1) a composite of severe postoperative pulmonary complications within the first 30 postoperative days and a composite of all severe and non-severe postoperative pulmonary complications within the first 7 and 30 postoperative days; (2) non-severe postoperative pulmonary complications: atelectasis not requiring bronchoscopy, mild acute respiratory failure, pleural effusion, bronchospasm, aspiration pneumonitis, pulmonary thromboembolism, and COPD decompensation; (3) a composite of infectious complications: surgical site and other infections (catheter, urinary tract, etc), and sepsis and septic shock within the first 7 and 30 postoperative days; (4) a composite of cardiac complications: myocardial ischaemia and cardiac arrhythmias within the first 30 postoperative days; and (5) any complication within the first 30 postoperative days (appendix p 9). Primary and secondary outcomes were recorded at 1, 2, 5, 7, and 30 postoperative days. Preoperative baseline and intraoperative and postoperative variables were also recorded. Adverse events related to iOLA such as arrythmia and pneumothorax were also reported.

Statistical analysis

Assuming a confidence level of 95% and an 18% risk of pulmonary complications at 7 days post-intervention,[7] a total of 655 patients per group were required to detect an absolute reduction of 5% in pulmonary complications with a power of 80%. Assuming possible losses of 5%, the final sample size was 1380 patients (690 per group). Randomisation was stratified by centre.

Categorical variables are reported as number and percentage. Normally distributed variables are reported as mean and SD, non-normally distributed as median and IQR. Normal distribution of data was assessed with the Kolmogorov–Smirnov test or the Shapiro–Wilk test. To compare continuous variables between iOLA and standard lung-protective ventilation groups, Student's t-test or Mann–Whitney U-test were used, as appropriate. To test categorical variables, including the composite primary outcome, χ^2 test, relative risks (RRs), in addition to the absolute risk reduction and number needed to treat with 95% CI were calculated. Other statistical models were introduced to re-analyse the effects of the interventions on the primary and secondary outcomes, considering a possible hospital effect; we used generalised linear (logistic) mixed models with a random intercept of hospital to assess the protocol outcome of any complications, expressing the effect as odds ratio with 95% CI. Baseline characteristics were compared

	iOLA (n=670)	STD (n=638)
Age, years	65·0 (10·2)	64·2 (10·9)
Gender*		
Male	434 (65%)	395 (62%)
Female	233 (35%)	237 (37%)
Height, cm	161·0 (33·4)	160·6 (32·2)
Weight, kg	73·8 (14·0)	72·3 (14·0)
BMI, kg/m²	26·4 (6·6)	25·8 (4·3)
ASA physical status†		
I	15 (2%)	10 (2%)
II	307 (47%)	281 (44%)
III	329 (50%)	337 (53%)
IV	4 (1%)	5 (1%)
ARISCAT score		
Moderate (26–44 points)	354 (54·5)	357 (57·6)
Preoperative SpO_2, %	97·0 (1·8)	96·9 (1·8)
Preoperative haemoglobin, mg dL	13·7 (1·6)	13·6 (1·6)
Preoperative respiratory infection	30 (4·5)	34 (5·3)
Charlson Index	3·6 (2·5)	3·8 (2·6)
Medical history		
Hypertension	328 (49%)	299 (47%)
Coronary artery disease	66 (10%)	55 (9%)
Diabetes type I	11 (2%)	11 (2%)
Diabetes type II	119 (18%)	111 (17%)
Chronic pulmonary obstructive disease	160 (24%)	163 (26%)
Renal failure	45 (7%)	52 (8%)
Liver failure	9 (1%)	15 (2%)
Alcohol abuse	66 (10%)	73 (11%)
Obesity (BMI >30 kg/m²)	2 (<1%)	8 (1%)
Smoking status‡		
Current smoker	181 (27%)	173 (27%)
Ex-smoker	281 (43%)	275 (44%)
Never smoked	193 (29%)	183 (29%)
Chronic medication		
Antihypertensives	315 (47%)	286 (45%)
Aspirin	143 (22%)	125 (20%)
Statins	243 (36%)	229 (36%)
Oral antidiabetics	107 (16%)	96 (1%)
Insulin	38 (6%)	24 (4%)
Corticosteroids	65 (10%)	66 (10%)
Inhalers	101 (15%)	97 (15%)
Antibiotics (last 3 months)	75 (11%)	64 (10%)
Preoperative chemotherapy	85 (13%)	69 (11%)
Preoperative radiotherapy	32 (5%)	35 (6%)
Type of Surgery		
Oncological	601 (90%)	577 (90%)
Toracotomy	203 (30%)	219 (34%)
(Table 1 continues in next column)		
(Continued from previous column)		
Surgical procedure‡		
Pneumonectomy	15 (2%)	23 (4%)
Bilobectomy	26 (4%)	20 (3%)
Lobectomy	417 (63%)	391 (62%)
Segmentectomy	116 (18%)	114 (18%)
Others	87 (13%)	83 (13%)
Surgical position		
Supine	11 (2%)	11 (2%)
Right lateral decubitus§	301 (50%)	301 (51%)

Data are mean (SD) or n (%). ARISCAT=Assess Respiratory Risk in Surgical Patients in Cataloni. ASA=American Society of Anaesthesiology clinical status. iOLA=perioperative individualised open-lung approach. SpO_2=peripheral oxyhaemoglobin saturation. STD=standard lung-protective ventilation. *Data were not provided nor could they be recovered by the hospitals for three of the patients in the iOLA group and six of those in the STD group. †Data were available for 655 patients in the iOLA group and 631 in the STD group. ‡Data were available for 661 patients in the iOLA group and 631 in the STD group. §Data were available for 602 patients in the iOLA group and 590 in the STD group.

Table 1: **Patients' characteristics at baseline**

and no adjustment was required. Secondary outcomes were assessed as total occurrence within the observation window, or as yes or no occurrence. To calculate the time-to-event curves, we used the Kaplan-Meier method and Cox regression with cluster effect by centre. We assessed differences in length of hospital stay using negative binomial expressed as incidence rate ratios. All analyses were performed on an intention-to-treat basis. Numbers of participants with valid values of analysed variables are described in the appendix (pp 12–14). For all comparisons, a two-sided $p<0·05$ was considered statistically significant.

Since less than 5% of data for postoperative primary complications were missing or unavailable, without differences between groups, handling of missing data was not applied.[14] We did two interim analyses following the monitoring plan based on the modified Haybittle-Peto boundaries for stopping trials. The data and safety monitoring board did not recommend stopping the trial (appendix p 10). We did all analyses with R (version 4.2.3).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Sept 11, 2018 to June 14, 2022, we enrolled 1380 patients (appendix p 11); of whom 707 were randomly assigned to iOLA and 673 to standard lung-protective ventilation. 72 patients were excluded (figure 2), resulting in 1308 patients for the final analysis: 670 patients in the iOLA group and 638 patients in the standard lung-protective ventilation group. Baseline characteristics were similar between groups (table 1, appendix p 14).

Intraoperatively, mean individualised PEEP was higher in the iOLA group than in the standard lung-protective ventilation group (8·1 [SD 2·1] cm H_2O *vs* 4·7 [1·5] cm H_2O,

	iOLA (n=670)	STD (n=638)
Positive end-expiratory pressure, cm H_2O		
Baseline	4·5 (2·2)	4·2 (0·6)
One-lung ventilation	8·1 (2·1)	4·7 (1·5)
End of surgery	7·8 (2·3)	4·7 (1·4)
Tidal volume, mL		
Baseline	502·7 (75·8)	498·5 (81·9)
One-lung ventilation	380·1 (61·1)	378·1 (63·5)
End of surgery	492·8 (81·1)	488 (82·7)
Plateau pressure, cm H_2O		
Baseline	16·2 (4·1)	16·1 (3·9)
One-lung ventilation	19·3 (4·2)	18·6 (4·1)
End of surgery	19·0 (4·1)	17·6 (4·2)
Driving pressure, cm H_2O*		
Baseline	11·5 (4·6)	11·7 (3·9)
One-lung ventilation	11·2 (4·4)	13·8 (3·9)
End of surgery	11·5 (9·4)	13·5 (10·8)
Respiratory system compliance, mL/cm H_2O		
Baseline	48·5 (15·7)	46·9 (14·6)
One-lung ventilation	42·9 (15·4)	33·5 (10·8)
End of surgery	46·9 (15·5)	42·4 (14·0)
SpO_2, %		
Baseline	98·9 (1·12)	99·0 (1·2)
One-lung ventilation	98·4 (1·9)	97·7 (2·2)
End of surgery	99·1 (4·0)	99·1 (1·1)
PaO_2/FiO_2, mm Hg		
Baseline	276·9 (115·2)	281·0 (113·7)
One-lung ventilation	191·8 (96·4)	160·8 (90·2)
End of surgery	319·9 (96·9)	280·4 (105·7)
$PaCO_2$, mm Hg		
Baseline	43·5 (6·4)	43·2 (6·6)
One-lung ventilation	47·1 (8·1)	47·2 (7·9)
End of surgery	44·1 (7·7)	44·2 (6·9)
Mean arterial pressure, mm Hg		
Baseline	83·9 (49·0)	81·4 (50·9)
One-lung ventilation	79·3 (12·2)	79·7 (32·5)
End of surgery	79·6 (12·5)	79·8 (12·5)
Cardiac index, mL/min per m^2		
Baseline	2·89 (0·69)	2·89 (0·71)
One-lung ventilation	2·96 (0·71)	2·92 (0·72)
End of surgery	3·06 (0·79)	3·02 (0·74)
Volume of fluids administered, L		
Crystalloids	996·5 (514·0)	989·8 (446·9)
Coloids	58·9 (168·3)	65·9 (193·2)
Red blood cell transfusion	18 (3%)	14 (2%)
Blood loss, mL	217·5 (296·5)	213·4 (226·7)
Vasoactive drugs†	291 (43%)	279 (44%)
Regional analgesia	464 (69%)	437 (69%)
Neuromuscular blocker monitoring	369 (55%)	375 (59%)
Neuromuscular blocker reversal	604 (90%)	585 (92%)
Prophylaxis of PONV	612 (91%)	593 (93%)
Antibiotic prophylaxis	631 (98%)	612 (98%)
Duration of one-lung ventilation, min	165·8 (81·4)	159·8 (73·5)
Duration of surgery, min	182·1 (89·0)	180·4 (82·3)
Duration of ventilation, min‡	213·7 (95·3)	216·0 (112·8)
Intraoperative hypoxaemia	54/600 (9%)	94/494 (19%)
Intraoperative rescue manoeuvres	49/612 (8%)	82/482 (17%)
First 6 postoperative hours		
pH	7·38 (0·05)	7·38 (0·04)
PaO_2/FiO_2, mm Hg	345·0 (93·2)	347·8 (92·6)
$PaCO_2$, mm Hg	40·0 (6·1)	40·2 (5·3)
Positive air-test§	295/639 (46%)	314/579 (54%)
Postoperative high-flow oxygen therapy	269 (40%)	19 (3%)
Postoperative rescue manoeuvres	7 (1%)	27 (4%)

(Table 2 continues in next column)

(Continued from previous column)

Data are n (%) or mean (SD). iOLA=perioperative individualised open-lung approach. $PaCO_2$=partial pressure of arterial carbon dioxide. PaO_2/FiO_2=ratio of partial pressure of arterial oxygen to inspiratory oxygen fraction. PONV=postoperative nausea and vomiting. SpO_2=peripheral oxyhaemoglobin saturation. STD=standard lung-protective ventilation. *Driving pressure was calculated as plateau pressure minus positive end-expiratory pressure. Plateau pressure was determined at the end of the inspiratory pause (time of 5–10% of inspiratory time). †Vasoactive drugs: patients who received vasopressors or inotropes not related to the recruitment manoeuvres. ‡Defined as the time between skin incision and closure of the incision. §Defined as SpO_2 <97% while breathing room air.

Table 2: **Perioperative characteristics**

p<0·001; table 2, appendix p 15). Driving pressure was lower in the iOLA group (11·2 [4·4] cm H_2O *vs* 13·8 [3·9] cm H_2O, p<0·0001; table 2, appendix p 16). 311 (46%) of 670 patients required more than one recruitment manoeuvre in the iOLA group to maintain the open-lung condition (appendix p 17). A total of 652 (97%) patients from the iOLA group completed the alveolar recruitment manoeuvre and PEEP titration trial (appendix p 17). The iOLA group had fewer intraoperative hypoxaemic episodes than the standard lung-protective ventilation group (54 *vs* 94, p<0·0001) and required fewer intraoperative rescue manoeuvres (49 *vs* 82, p<0·0001; table 2, appendix p 17). Recruitment manoeuvre-related adverse events were reported in five patients in the iOLA group (appendix p 17).

Postoperatively, individualised high-flow oxygen therapy was used in 249 (40%) patients in the iOLA group. Postoperative rescue manoeuvres were needed in five (1%) patients in the iOLA group and 22 (3%) in the standard lung-protective ventilation group (p<0·0001; table 2, appendix p 17). There were no differences in haemodynamics, use of vasopressors, regional anaesthesia, red blood cell transfusions, antibiotic prophylaxis, neuromuscular blocker reversal, duration of one-lung ventilation, or surgery between groups (table 2).

Risk of the primary outcome of severe postoperative pulmonary complications within the first 7 postoperative days was lower in patients receiving iOLA when compared with those receiving standard lung-protective ventilation (40 [6%] *vs* 97 [15%], RR 0·39

	iOLA (n=670)	STD (n=638)	Relative risk (95% CI); p value	Odds ratio (95% CI);* p value
Primary outcome				
Patients with severe postoperative pulmonary complications within the first 7 postoperative days	40 (6%)	97 (15%)	0·39 (0·28–0·56); <0·0001	0·33 (0·12–0·49); <0·0001
Secondary outcomes				
Patients with any postoperative pulmonary complications during the first 7 postoperative days	104 (16%)	175 (27%)	0·57 (0·46–0·70); <0·0001	0·44 (0·33–0·58); <0·0001
Patients with severe postoperative pulmonary complications during the first 30 postoperative days	48 (7%)	103 (16%)	0·44 (0·32–0·61); <0·0001	0·37 (0·26–0·54); <0·0001
Patients with any postoperative pulmonary complications during the first 30 postoperative days	111 (17%)	184 (29%)	0·57 (0·47–0·71); <0·0001	0·44 (0·33–0·58); <0·0001
Patients with any complication during the first 30 postoperative days	161 (24%)	227 (36%)	0·57 (0·45–0·73); <0·0001	0·53 (0·41–0·68); <0·0001
Infectious complication during the first 30 postoperative days†	19 (3%)	27 (4%)	0·66 (0·38–1·19); 0·18	0·68 (0·37–1·25); 0·22
Cardiac complication during the first 30 postoperative days	14 (2%)	15 (2%)	0·89 (0·43–1·85); 0·85	0·88 (0·42–1·85); 0·75
Acute kidney failure during the first 30 postoperative days	12 (2%)	19 (3%)	0·60 (0·29–1·23); 0·203	0·56 (0·27–1·18); 0·13
Median (IQR) hospital length of stay, days	5 (3–7)	5 (3–8)	0·74	..
Death within 30 days‡	9 (1%)	3 (<1%)	2·86 (0·78–10·50); 0·15	..

Data are n (%), unless otherwise indicated. The composite of severe postoperative pulmonary complications included: atelectasis requiring bronchoscopy, severe respiratory failure, contralateral pneumothorax, early extubation failure (rescue with continuous positive airway pressure, non-invasive ventilation, invasive mechanical ventilation, or reintubation), acute respiratory distress syndrome, pulmonary infection, bronchopleural fistula, and pleural empyema. The composite of any postoperative pulmonary complications included severe postoperative pulmonary complications plus: atelectasis without bronchoscopy, mild hypoxaemia (mild acute respiratory failure), contralateral pleural effusion, aspiration pneumonitis, pulmonary thromboembolism, chronic obstructive pulmonary disease exacerbation, haemothorax. The composite of infectious complications included: surgical site infection, other infections (catheter, urinary tract, etc), and sepsis and septic shock. The composite of cardiac complications included myocardial ischaemia and cardiac arrhythmias. iOLA=perioperative individualised open-lung approach. ICU=intensive care unit. STD=standard lung-protective ventilation. *Measures adjusted for centre. †Multiple events could occur in individual patients. ‡Complementary data are described in the appendix (p 20).

Table 3: **Primary and secondary outcomes**

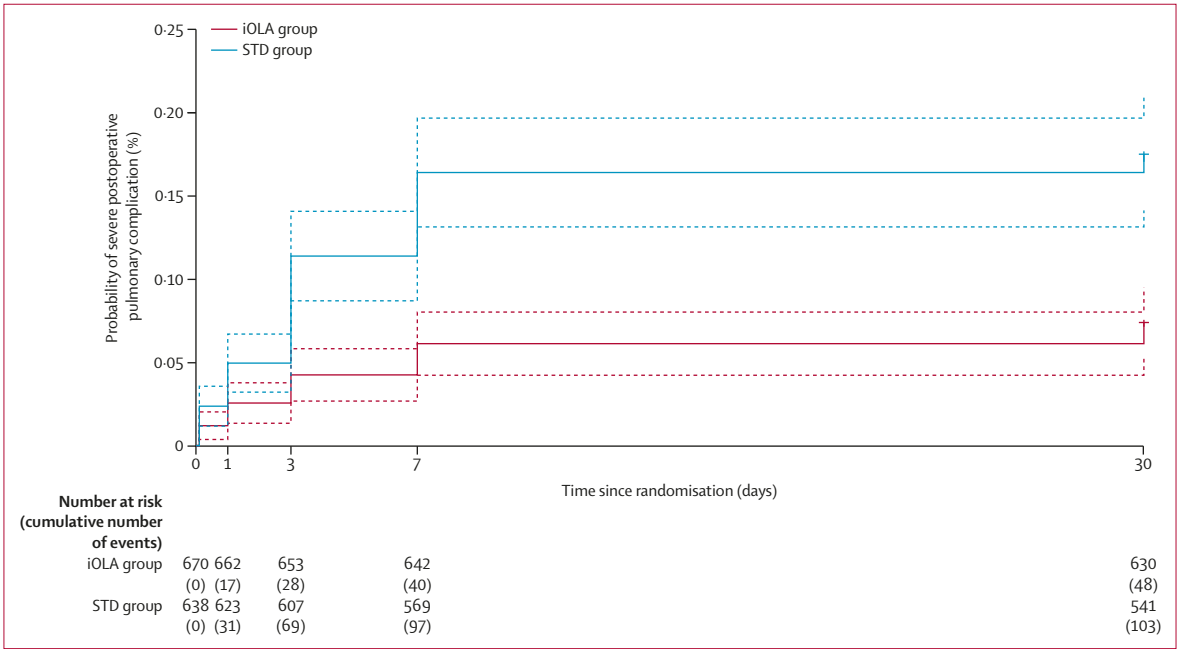

Figure 3: **Patients at risk of severe postoperative pulmonary complications from day 1 to day 30**
iOLA was associated with a reduction in the risk of postoperative pulmonary complications, with a relative risk of 0·39 (95% CI 0·28–0·56) at postoperative day 7 and a relative risk of 0·44 (0·32–0·61) at day 30. iOLA=perioperative individualised open-lung approach ventilatory strategy. STD=standard lung-protective ventilation.

[95% CI 0·28 to 0·56]; p<0·0001) in the intention-to-treat analysis (table 3, figure 3, appendix p 21), with an absolute risk difference of –9·23 (95% CI –12·55 to –5·92) and a number need to treat of 11 (95% CI 8 to 17). Fewer patients in the iOLA group had severe postoperative pulmonary complications within the first 30 postoperative

days (48 [7%] *vs* 103 (16%), RR 0·44 [95% CI 0·32 to 0·61]; p<0·0001) and postoperative pulmonary complications of any kind within the first 7 postoperative days (104 [16%] *vs* 175 [27%], 0·57 [0·46 to 0·70]; p<0·0001) and 30 postoperative days (111 [17%] *vs* 184 [29%], 0·57 [0·47 to 0·71]; p<0·0001; table 3). During the first 7 postoperative days, differences were also found in the risk of atelectasis requiring bronchoscopy (ten [1%] *vs* 26 [4%], 0·37 [0·18 to 0·75]; p=0·006), severe respiratory failure (ten [1%] *vs* 36 [6%], 0·26 [0·13 to 0·53]; p<0·0001), and pulmonary infection (20 [3%] *vs* 37 [6%], 0·51 [0·30 to 0·88]; p=0·014) between iOLA and standard lung-protective ventilation, respectively; these differences were still evident at 30 days (appendix pp 18–19). No statistical differences between the two groups were found in infectious, cardiac, or renal complications within the first 30 postoperative days (table 3, appendix p 20).

There were no differences in hospital length of stay and number of deaths (nine [1%] *vs* three [<1%], RR 2·87 [95% CI 0·78–10·50]; p=0·15) within the first 30 postoperative days between groups (table 3, appendix p 9). However, patients with severe postoperative pulmonary complications had a longer length of stay than those who did not develop a severe postoperative pulmonary complication (prespecified analysis; appendix p 22). Details for the 12 postoperative deaths are described in the appendix (p 23).

Discussion

In this large, multicentre RCT, use of the iOLA during and after the surgical procedure, which included intraoperative recruitment manoeuvres with individualised PEEP and individualised postoperative respiratory support, reduced the risk of severe postoperative pulmonary complications when compared with standard lung-protective ventilation management. This perioperative iOLA reduced the risk of a composite combining all types of postoperative pulmonary complication and use of intraoperative and postoperative rescue interventions, with no differences in extrapulmonary complications between groups.

Our results are in agreement with a previous RCT enrolling 322 patients, in which individualised driving pressure-guided PEEP reduced a composite of postoperative pulmonary complications within the first 3 postoperative days when compared with conventional lung-protective ventilation.[21] Of note, ventilation in their control group was similar to that in our trial (tidal volume 6 mL/kg predicted bodyweight, PEEP 5 cm H_2O). In contrast to our study, lung-protective ventilation was applied only during one-lung ventilation, recruitment manoeuvres were not protocolised, and no postoperative respiratory support was included. The benefits of individualised PEEP in reducing postoperative pulmonary complications during one-lung ventilation were confirmed in a meta-analysis of 849 patients included in eight RCTs.[9] In a recent multicentre RCT including 1170 patients, Park and colleagues[10] did not report a reduction in postoperative pulmonary complications when comparing a reduced driving pressure-guided PEEP strategy with conventional lung-protective ventilation. Several features of their protocol could help to explain the observed absence of differences. First, recruitment manoeuvres were used in both groups, resulting in low levels of driving and plateau pressures. Second, it is plausible that the recruitment manoeuvre strategy (reaching 30 cm H_2O of inspiratory pressure) was insufficient to reach an open-lung condition in many patients.[22] As a result, atelectasis, a recognised ventilator-induced lung injury stress-raiser, was similarly present in both groups. Third, the progressive increase in driving pressure is suggestive of some degree of derecruitment, which is further supported by low levels of PEEP in both groups. In our study, almost half of patients (46%) in the iOLA group did not maintain an open-lung condition throughout the protocol and required more than one recruitment manoeuvre.

As opposed to Park and colleagues' study,[10] we included a protocol for postoperative respiratory support. Protocolised adjustments (high-flow oxygen therapy) were made in 40% of patients receiving iOLA due to the development of atelectasis, as assessed by the air-test.[23,24] The importance of including a postoperative respiratory support strategy is highlighted by our previous findings, in which postoperative pulmonary complications occurred in 11% (as compared with 6% in our current study) when an OLA approach was limited to the intraoperative period without including a postoperative respiratory support strategy.[25] The use of composite outcomes of general postoperative pulmonary complications with different prognostic weights by Park and colleagues,[10] instead of our composite of severe postoperative pulmonary complications, might also explain the observed differences. Park and colleagues[10] reported a high rate of hypoxaemia, which was not considered a postoperative pulmonary complication when occurring in the immediate postoperative period in our study. Our choice to use a composite of severe postoperative pulmonary complications based on established accepted definitions strengthens our findings, which matched the prevalence of severe postoperative pulmonary complications from previous studies.[7,26,27] The safety of intraoperative OLA has been questioned because it could cause transient haemodynamic instability. In our study, it was successfully completed in 652 (97%) of 670 patients allocated to iOLA, with only marginal short-lasting adverse events. Fluid or vasoactive requirements did not differ between groups. This tolerance is similar to that observed in previous studies in thoracic and abdominal surgery patients.[10,27] By contrast, the standard lung-protective ventilatory strategy was associated with more rescue manoeuvres due to the higher rate of intraoperative hypoxaemic events. Taken together, these findings

confirm that the OLA is a safe and feasible intraoperative strategy.

Postoperatively, HFNC can reduce postoperative pulmonary complications in high-risk surgical patients by several well described physiological mechanisms when compared with conventional oxygen therapy, and the reduction in postoperative pulmonary complications has been confirmed in a meta-analysis.[28] However, when tested in lung resection patients, results have been controversial.[29] Our results support the use of HFNC when individually indicated and with a synergistic strategy of intraoperative OLA, in line with previous findings in abdominal surgery patients, in which HFNC reduced postoperative pulmonary complications when compared with conventional oxygen therapy in those patients who benefited from an intraoperative open-lung strategy.[30]

Several aspects of our study strengthen its clinical relevance. To the best of our knowledge, iPROVE-OLV is the first trial in patients scheduled for thoracic surgery with one-lung ventilation in whom ventilatory management is continuously individualised and adapted to the lung condition during the entire perioperative period. Inclusion and exclusion criteria ensured the evaluation of a representative population of patients subjected to lung resection in terms of surgical risk, type of surgery, surgical techniques, and intraoperative anaesthetic management, contributing to high generalisability of our findings. In addition, the proposed individualised strategy performed better than the standard practice of 4 cm H_2O of PEEP when combined with the recommended protective tidal volume.[17,31] Based on these findings, an individualised perioperative OLA strategy should become the standard-of-care for patients undergoing lung resection.

We acknowledge some limitations of our study. First, the design of the trial did not allow us to establish whether the intraoperative period, the postoperative period, or both ventilation strategies were responsible for the findings reported in this study. However, as suggested by previous reports,[7] it is likely that the combination of both strategies adapted and individualised to the different phases of the perioperative period reduced the risk of postoperative pulmonary complications. Second, although high standard-of-care practices were recommended, many interventions such as fluid therapy, regional analgesia, or neuromuscular blockade management, known to have an effect on postoperative pulmonary complications, were not controlled in an attempt to increase the generalisability of our findings. Although they could have influenced the results, we did not see any differences in those interventions between groups. Third, we did not differentiate patients by the presence or absence of lung collapse for enrolment. Finally, the use of a composite outcome can limit the interpretation of the results. However, as suggested by the European Society of Anaesthesiology–European Society of Intensive Care Medicine joint taskforce on perioperative outcome measures,[20] we selected variables of similar clinical relevance for the primary composite outcome. The longer length of stay of patients with severe postoperative pulmonary complications supports the proper selection of composite variables.

In conclusion, among patients undergoing lung resection supported by mechanical one-lung ventilation, a perioperative OLA reduces severe postoperative pulmonary complications when compared with standard lung-protective ventilation.

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Contributors

CF, AC, JL, CU, JVi, FJB, GT, and FS-S designed the study. CF, AC, JL, CU, JVi, FJB, GT, and FSS analysed the data. CF, AC, SS, GS, OC, AP, MA, GH, MV, KR, MC-R, MSL, FR, JN-A, EGa, AR-P, RF, EGu, SC, LG-L, AH-I, JV-T, PP, IG, SR, DL-H, MDLM, SG, EK, AM, MS, LG, JAS, PA, CJS, MCR, DRM, RT, FE-F, LM, AL, LPC, DL, SB, CL, RN-R, SM, JVa, AJ, MJY-T, CU, JL, JVi, FJB, GT, and FS-S drafted the manuscript and interpreted the data. iPROVE-OLV Network Investigators acquired the data and critically reviewed the manuscript. CF and JL have accessed and verified all the data in the study and take responsibility for the integrity of the data and accuracy of data analysis. All authors had access to the data presented in the manuscript and appendix. Individual authors had access to the data from their respective hospitals. All authors accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing statement

The data supporting the findings of this study are available from the corresponding author (CF), upon reasonable request and always indicating the plan for use of the data.

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