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Special Article

Rationale and Study Design for an Individualized Perioperative Open Lung Ventilatory Strategy in Patients on One-Lung Ventilation (iPROVE-OLV)

Albert Carramiñana, MD[*], Carlos Ferrando, MD, PhD[*,†,1], M. Carmen Unzueta, MD, PhD[‡], Ricard Navarro, MD, PhD[*], Fernando Suárez-Sipmann, MD, PhD[†,§,¶], Gerardo Tusman, MD, PhD[‖], Ignacio Garutti, MD, PhD[#], Marina Soro, MD, PhD[**], Natividad Pozo, BSc, PhD[††], Julián Librero, MD, PhD[‡‡], Lucía Gallego, MD, PhD[§§], Fernando Ramasco, MD, PhD[¶¶], José M. Rabanal, MD, PhD[‖‖], Aurelio Rodriguez, MD, PhD[##], José Sastre, MD, PhD[***], Jesús Martinez, MD, PhD[†††], Silvia Coves, MD[‡‡‡], Pablo García, MD, PhD[§§§], Pilar Aguirre-Puig, MD, PhD[¶¶¶], José Yepes, MD, PhD[‖‖‖], Aitana Lluch, MD, PhD[###], Daniel López-Herrera, MD, PhD[****], Sonsoles Leal, MD, PhD[††††], Marc Vives, MD, PhD[‡‡‡‡], Soledad Bellas, MD[§§§§], Tania Socorro, MD[¶¶¶¶], Ramón Trespalacios, MD, PhD[‖‖‖‖], Claudia J. Salazar, MD[####], Ana Mugarra, MD[**], Gilda Cinnella, MD, PhD[*****], Savino Spadaro, MD[†††††], Emmanuel Futier, MD, PhD[‡‡‡‡‡], Leopoldo Ferrer, MD, PhD[§§§§§], María Cabrera, MD, PhD[¶¶¶¶¶], Helder Ribeiro, MD[‖‖‖‖‖], Catarina Celestino, MD[#####], Evrim Kucur, MD, PhD[******], Oriol Cervantes, MD[††††††], Diego Morocho, MD, PhD[‡‡‡‡‡‡], Dalia Delphy, MD[§§§§§§], Carolina Ramos, MD[¶¶¶¶¶¶], Jesús Villar, MD, PhD[†,‖‖‖‖‖‖‖‖], Javier Belda, MD, PhD[**], and the iPROVE-OLV Network[######]

[*]*Department of Anesthesia and Critical Care, Hospital Clínic i Provincial, Barcelona, Spain*
[†]*CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain*
[‡]*Department of Anesthesia and Critical Care, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[§]*Intensive Care Unit, Hospital de La Princesa, Madrid, Spain*
[¶]*Hedenstierna Laboratory, Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden*
[‖]*Department of Anesthesia, Hospital Privado de Mar de Plata, Mar de Plata, Argentina*
[#]*Department of Anesthesia and Critical Care, Hospital Universitario Gregorio Marañon, Madrid, Spain*

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[1]*Address reprint requests to* Carlos Ferrando, MD, PhD, Department of Anesthesia and Critical Care, Hospital Clínic i Provincial, Villarroel 170, 08036 Barcelona, Spain.

E-mail address: cafeornaestesia@gmail.com (C. Ferrando).

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[**]Department of Anesthesia and Critical Care, Hospital Clínico of Valencia, Valencia, Spain
[††]Institute INCLIVA, Hospital Clinico Universitario de Valencia, Valencia, Spain
[‡‡]Navarrabiomed-Fundación Miguel Servet, Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Pamplona, Spain
[§§]Department of Anesthesia and Critical Care, Hospital Miguel Servet, Zaragoza, Spain
[¶¶]Department of Anesthesia and Critical Care, Hospital La Princesa, Madrid, Spain
[||||]Department of Anesthesia and Critical Care, Hospital Marqués de Valdecilla, Santander, Spain
[##]Department of Anesthesia, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain
[***]Department of Anesthesia and Critical Care t, Hospital de Salamanca, Salamanca, Spain
[†††]Department of Anesthesia and Critical Care, Hospital Universitari Mutua of Terrassa, Terrassa, Spain
[‡‡‡]Department of Anesthesia and Critical Care, Hospital Univeristari de Vinalopó, Elche, Spain
[§§§]Department of Anesthesia and Critical Care, Hospital 12 de Octubre, Madrid, Spain
[¶¶¶]Department of Anesthesia and Critical Care, Hospital Álvaro Cunqueiro, Vigo, Spain
[|||||]Department of Anesthesia and Critical Care, Clínica Universitaria Pamplona, Spain
[###]Department of Anesthesia and Critical Care, Hospital Universitario La Fe, Valencia, Spain
[****]Department of Anesthesia and Critical Care, Hospital Virgen del Rocio, Sevilla, Spain
[††††]Department of Anesthesia and Critical Care, Hospital Povisa, Vigo, Spain
[‡‡‡‡]Department of Anesthesia and Critical Care, Hospital Dr. Josep Trueta, Girona, Spain
[§§§§]Department of Anesthesia and Critical Care, Fundación Jiménez Díaz, Madrid, Spain
[¶¶¶¶]Department of Anesthesia, Complejo Universitario Materno-Insular, Las Palmas, Spain
[||||||]Department of Anesthesia and Critical Care, Hospital Universitario Central de Asturias, Oviedo, Spain
[####]Department of Anesthesia and Critical Care, Hospital Universitario de Canarias, Tenerife, Spain
[*****]Department of Anesthesia and Critical Care, Università di Foggia, Foggia, Italy
[†††††]Department of Anesthesia and Critical Care, Università di Ferrara, Ferrara, Italy
[‡‡‡‡‡]Anesthesia and Critical Care, Centre Hospitalier Universitaire, Clermont-Ferrand, France
[§§§§§]Department of Anesthesia, Universidad El Bosque, Bogotá, Colombia
[¶¶¶¶¶]Department of Anesthesia, Hospital Clínico de la Fuerza Aérea de Chile, Las Condes, Chile
[|||||||]Department of Anesthesia and Critical Care, Centro Hospitalar Sao Joao, Porto, Portugal
[#####]Department of Anesthesia and Critical Care, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal
[******]Anesthesia and Critical Care, Medical Park Bahçelievler Hospital, Istanbul, Turkey
[††††††]Department of Anesthesia and Critical Care, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[‡‡‡‡‡‡]Critical Care Department, Hospital de especialidades Eugenio Espejo, Quito, Ecuador
[§§§§§§]Department of Anesthesia, Alexandria University Hospital and Kafrelsheikh University Hospital, Alexandria, Egypt
[¶¶¶¶¶¶]Department of Anesthesia and Critical Care, Hospital Universitario Ntra Sra de Candelaria, Santa Cruz de Tenerife, Spain
[||||||||]Research Unit, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain

Objective: The aim of this clinical trial is to examine whether it is possible to reduce postoperative complications using an individualized perioperative ventilatory strategy versus using a standard lung-protective ventilation strategy in patients scheduled for thoracic surgery requiring one-lung ventilation.

Design: International, multicenter, prospective, randomized controlled clinical trial.

Setting: A network of university hospitals.

Participants: The study comprises 1,380 patients scheduled for thoracic surgery.

[######]iPROVE-OLV Network investigators: Pablo Monedero, Samira Martínez, Oscar Comino, Alberto Coy, Laura Armengol, Patricia Piñeiro, Patricia Cruz, Patricia Duque, Francisco Andrés de la Gala, Guillermo Sánchez, Luis Olmedilla, Elena de la Fuente, Iñaqui Erquicia, Almudena Reyes, Elena López, Maria Palencia, Beatriz Bunger, Rafael Ramos, Estrella Terradillos, Carolina Almaraz, Laura Mínguez Luján, Amparo López, Francisco Femenia, Santiago Botella, Bonifacio Cimadevilla, Rebeca Pascual, Sara Pardo, Miren Gonzalez, Carlos López, Sonia Trabanco, Estibaliz Zaldibar, Maria J. Barolomé, Denis Pereira, Teresa Otero, Luisa Blanco, Jose Ramón Repáraz, Reyes Ceresuela, Pedro Castellano, Pedro Martínez, Olga Martínez, Juan Franco, Jessica Hernandez, Oriana Pastor, Sara Pérez, Jorge Solera, Elisabet Guerra, Zoraya Hussein Dib, Roberto Fariña, Sergio Cabrera, Maria Pilar Arribas, Jose Alfonso Sastre, Isabel de Celis, Maria Jesus Pascual, Belén García-Barberena, Enrique Arango, Oswaldo Amaya, Guillermo Madrid, Carlos Triana, Stefanie Pabón, Diana Paola Díaz, Fernando Ortells, Bernardino Perez, Ruth Aracil, Raquel Sanchez, Jesús Acosta, Manuel de la Matta, Domingo González, Lucia Mirabella, Michela Rauseo, Angela Lamanna, Carlo Alberto Volta, Riccardo Ragazzi, Marta Cachapuz, Inês Correia, Ana Parera, Marta Argilaga, Gonzalo Azparren, Marc Bausili, Rosa Almajano, Cristián Aragón, Ana Colás, Ignacio Cotera, Raúl Embún, Pilar Forcada, Cristina Garcés, Fernando Gil, Alejandro Gracia, Miriam Herrero, Blanca Izquierdo, Primitivo Martínez, Irene Molinos, Nadia Muñoz, María Puértolas, Natividad Quesada, José Luis Recuero, Íñigo Royo, Blanca Romero, Borja Rubio, Francisco Sandín, T. Alberto Sanjuán-Villarreal, Jorge Vallés-Torres, Sara Visiedo, José Córdoba, Jesús Pintor, Antonio Planas, Jesús M. Nieves, Esther Garcia, Carmen Vallejo, Sheila Santidrian, Paloma Rofso, Blanca Arocas, Andrea Gutierrez, Pedro Charco, Maria José Parra, Jose Antonio Carbonell, Ana Jurado, Ferran Serralta, Laura Sancho, Elizabeth Barcena, Laura Lascorz, Luis Belmonte, Javier Cuervo, Raluca Florea, Sara Martínez, Berta Monleón, Sara Pérez, Laura García, Luis Hurtado, Pablo Pardo, Nasara Segura, Esther Utrera, Beatriz Martin, Patricia Mellado, José Juan Arcas, Nuria Martínez, Marina Maric, Luis Enrique Muñoz, Raquel Callejas González, Jordi Busquets, Marta Homs, Anabel Jimenez, Teresa Pintanel, Esther Martinez, Enric Moret, Gokhan Sercakacılar, María Díaz, João Tiago Souteiro, Alba Benito, Alba Cebrián, Gerard Mestres, Mohamed Ibrahim Mohamed, Shahira Ahmed Yousef, Yasser Mohamed Osman, Andres Moreno, Andres Tutillo, Henry Pilco, Andrea Peña, Miguel Llano, Elizabeth Carrillo, Claudia Salazar, David Domínguez, Elena Espinosa

Interventions: The individualized group will receive intraoperative recruitment maneuvers followed by individualized positive end-expiratory pressure (open lung approach) during the intraoperative period plus postoperative ventilatory support with high-flow nasal cannula, whereas the control group will be managed with conventional lung-protective ventilation.
Measurements and Main Results: Individual and total number of postoperative complications, including atelectasis, pneumothorax, pleural effusion, pneumonia, acute lung injury; unplanned readmission and reintubation; length of stay and death in the critical care unit and in the hospital will be analyzed for both groups. The authors hypothesize that the intraoperative application of an open lung approach followed by an individual indication of high-flow nasal cannula in the postoperative period will reduce pulmonary complications and length of hospital stay in high-risk surgical patients.

Key Words: mechanical ventilation; postoperative pulmonary complications; one-lung ventilation; positive end-expiratory pressure; recruitment maneuvers

LUNG RESECTION SURGERY is associated with a high risk of postoperative pulmonary complications (PPCs),[1-3] including the development of atelectasis, pneumonia, and acute respiratory distress syndrome. Ventilator-induced lung injury and acute respiratory distress syndrome are the main causes of morbidity and mortality after surgical lung resection.[4] These complications have a significant effect on healthcare costs in surgical patients.[5] PPCs increase the need for and duration of mechanical ventilation (MV) in the postoperative period, increase the unscheduled readmissions in the intensive care unit (ICU), and lengthen the stay in the ICU and hospital.[6-10]

In patients with healthy lungs, MV can promote PPCs.[11-13] The main mechanisms of lung injury during MV are volutrauma (tissue damage caused by the excessive stretching of tissues that occurs when the lung is overinflated) and atelectrauma (injury caused by the repetitive reopening of closed lung units),[11,14] causing an inflammatory response that favors the development of ventilator-induced lung injury[12,15] and extrapulmonary organ dysfunction.[16] Lung-protective ventilation with low tidal volume (VT) and moderate-to-high levels of positive end-expiratory pressure (PEEP) has been shown to reduce PPCs.[17,18] Driving pressure, calculated as the plateau pressure (Pplat) minus PEEP, recently has been considered an independent risk factor for the development of PPCs.[19] Although it is well-accepted that low VT MV decreases PPCs,[19,20] there is some controversy about the benefits of PEEP in reducing PPCs.[21] During one lung-ventilation (OLV), PEEP improves oxygenation, mitigates atelectrauma, and attenuates lung injury.[22-26] However, the level of adequate PEEP during OLV is questionable.[27,28]

There are no reports describing the optimal PEEP levels during OLV for preventing PPCs. Recent evidence suggests that an adequate lung-protective strategy is a judicious combination of low VT and PEEP.[19] The authors of the present study recently reported their experience with an individualized ventilatory approach,[29-32] achieving the lowest value of driving pressure. During the immediate postoperative period, there is an increased risk of respiratory dysfunction due to different factors related to the patient, type of surgery, and general anesthesia. Because oxygenation through a high-flow nasal cannula (HFNC) decreases the respiratory work, maintains functional residual capacity, and washes carbon dioxide,[33,34] the use of HFNC during the initial postoperative phase could be beneficial.

Study Rationale

The authors assume that a pragmatic and standardized adjustment of PEEP, which currently is the common clinical practice, is erroneous because a PEEP lower or equal to the alveolar closing pressure will favor the reappearance of alveolar collapse after a recruitment maneuver (RM). On the contrary, if PEEP is greater than needed, it will increase the risk of overdistention. Both factors are recognized as determinants of deterioration of lung function during the intraoperative period and increase the risk of postoperative lung injury.

Although it has been reported that driving pressure is the most important independent risk factor for PPCs, there are no prospective, randomized controlled studies supporting that statement. Results of different studies performed by the authors' group suggest that an individualized open lung approach (OLA) strategy decreases driving pressure for a given VT, potentially increasing the protective effect of this strategy. Finally, the authors propose that HFNC could reduce PPCs during the immediate postoperative period. In postoperative patients, this strategy has never been applied individually or in combination with an intraoperative OLA.

Hypothesis and Objectives

The primary hypothesis of the study is that an individualized perioperative OLA ventilatory strategy (including low VT, alveolar RM, individualized adjustment of PEEP, and individualization of ventilatory support in the immediate postoperative period) will reduce PPCs in patients undergoing thoracic surgery requiring OLV. It has been formulated as a null hypothesis of no differences in PPCs between individualized and standardized ventilatory management in moderate- to high-risk patients.

The primary objective of the study is to examine the efficacy of the experimental ventilatory strategy in reducing PPCs during the first 7 days after surgery compared with conventional ventilatory management. The secondary objectives are to examine the efficacy of the experimental ventilatory strategy in reducing PPCs and systemic complications,

unscheduled ICU and hospital admissions, and ICU and hospital length of stay during the first 30 days after surgery compared with conventional ventilatory management.

Methods

Study Design

This trial has been designed in accordance with the fundamental principles established in the Declaration of Helsinki, the Convention of the European Council relating to human rights and biomedicine, and the Universal Declaration of United Nations Educational, Scientific, and Cultural Organization on the human genome and human rights; with the requirements established by Spanish legislation in the field of biomedical research; the protection of personal data; and bioethics, which was classified by the Spanish Agency of Drugs and Medical Devices as a clinical randomized study without drugs on September 7, 2017. The study was registered on ClinicalTrials.gov (NCT03182062) in 2017. Approval of the final protocol by the local ethics committee at each participating center was required before patient enrollment.

The Individualized Perioperative Open-lung Ventilatory Strategy in patients submitted to one lung ventilation (IPROVE-OLV) trial is an international, multicenter, controlled, unmasked, clinical trial with random assignment of patients to 2 parallel groups of ventilatory management (Fig 1). In the STD-O2 group, after initiating selective pulmonary ventilation, all patients will receive lung-protective ventilation with a VT of 5 to 6 mL/kg of ideal body weight, PEEP of 4 cmH_2O, and fraction of inspired oxygen (F_iO_2) of 0.8. During the first 6 postoperative hours, patients will be oxygenated with the minimum F_iO_2 to maintain peripheral capillary oxygen saturation (SpO_2) $\geq$92%. In the iOLA-iHFNC group, after initiating selective pulmonary ventilation, an alveolar RM followed by a PEEP titration trial will be performed on all patients. Patients included in this group will be ventilated intraoperatively with a VT of 5 to 6 mL/kg of ideal body weight, open-lung PEEP, and F_iO_2 of 0.8. After extubation, approximately 15 minutes after entering the postanesthesia care unit (PACU), an air test, which consists in breathing at F_iO_2 0.21 for 5 minutes, will be performed.[35] During the first 6 postoperative hours (in case of a negative air test [SpO_2 $\geq$97%]), patients will be oxygenated with the minimum F_iO_2 to maintain an SpO_2 $\geq$92%. In case of a positive air test (SpO_2 $\leq$96%), oxygen therapy with HFNC at 50 L/min flow will be indicated with the minimum F_iO_2 to maintain SpO_2 $\geq$92%.

In both groups, a new RM will be performed at the end of OLV. After the RM in the STD-O2 group, a protocolized PEEP of 4 cmH_2O will be set. In the iOLA-iHFNC group, the last OLA-PEEP will be adjusted. Also, once extubation has been performed in the operating room, all patients will be oxygenated with 0.5 F_iO_2 through a Venturi mask during the first 30 minutes until the air test is performed.

Study Population

The study population will comprise adult males and females $\geq$18 years old scheduled for an open or video-assisted thoracic surgery with selective pulmonary ventilation and an expected operating time of $\geq$2 hours. Patients who meet all the inclusion criteria and none of the exclusion criteria will be consecutively included.

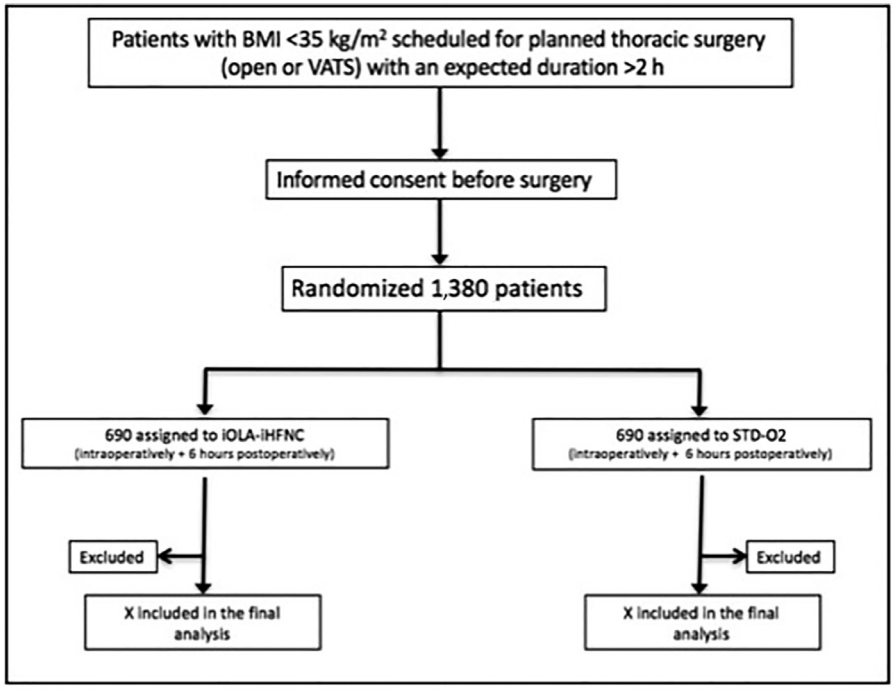

Fig 1. Flow diagram of iPROVE-OLV. BMI, body mass index; HFNC, high-flow nasal cannula; iOLA, individualized open lung approach; VATS, video-assisted thoracic surgery.

Exclusion criteria include pregnancy or breastfeeding; moderate or severe acute respiratory distress syndrome, defined as partial pressure of oxygen (PaO_2)/FiO_2 <200 mmHg; diagnosis of heart failure, defined as IC <2.5 mL/min/m^2 and/or inotropic support before surgery and/or suspicion of heart failure according to clinical signs (hypotension, oliguria, pulmonary edema) together with Brain Natriuretic Peptide (NT-proBNP) >13 pg/mL; diagnosis or suspicion of intracranial hypertension (>15 mmHg); MV in the last 15 days (including continuous positive airway pressure [CPAP]); presence of pneumothorax or giant bullae on a chest radiograph or computed tomography; patients with chronic obstructive pulmonary disease requiring oxygen or CPAP; patients participating in another interventional study with similar primary outcomes; and previous lung resection.

Method of Randomization and Bias Minimization

Informed consent will be obtained from each participant before enrollment into the study. Patients who meet all the inclusion criteria and none of the exclusion criteria will be consecutively included and randomly assigned into 1 of the 2 study arms (see Fig 1). Patients will be randomly assigned by the first investigator online via http://iprove.incliva.es using the Mersenne Twister algorithm with an allocation rate of 1:1.

Blinding

At least 2 investigators will be required in each participating center because the study characteristics do not allow for the blinding of investigators in the operating and postoperative room so data acquired in these sites will not be blinded. After 24 hours, all data will be acquired by the second investigator who will be blinded to the randomization arm.

Study Variables and Definitions

The primary outcome of the iPROVE trial is a composite of the primary pulmonary complications on the basis of standard definitions[31] experienced by the study population in the first 7 days after surgery:

1. Atelectasis requiring bronchoscopy: Atelectasis is defined as chest x-ray images suggesting lung opacities with a shift in the mediastinum, hilum, or hemi-diaphragm toward the affected area and compensatory overinflation in the adjacent non-atelectatic lung.
2. Severe respiratory failure: Hypoxemia (defined as SpO_2 ≤92% with 0.21 F_iO_2 or SpO_2 ≤95% with 0.5 F_iO_2) requiring ventilatory support.
3. Contralateral pneumothorax: Air in the pleural space and the mediastinum is shifted to the opposite side (a chest x-ray will be performed for suspected cases of auscultation hoarseness).
4. Early extubation failure or requirements of reintubation: If the patient has mild (PaO_2 <60 mmHg, PaO_2/F_iO_2 <300 mmHg, SpO_2 <90% and requiring oxygen therapy) or severe acute respiratory failure (PaO_2 <60 mmHg, PaO_2/F_iO_2 <300 mmHg, SpO_2 <90% and requiring noninvasive ventilation, including CPAP, or invasive ventilation).
5. Acute respiratory distress syndrome (using the Berlin definition, which includes all of the following):
   - Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms
   - Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
   - Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
   - Oxygenation: Mild—PaO_2/F_iO2 between 26.7 and 40.0 kPa (200-300 mmHg) with PEEP or CPAP ≥5 cmH_2O; moderate—PaO_2/F_iO_2 between 13.3 and 26.6 kPa (100-200 mmHg) with PEEP ≥5 cmH_2O; severe—PaO_2/F_iO_2 13.3 kPa (100 mmHg) with PEEP ≥5 cmH_2O
6. Suspicion of pulmonary infection or pneumonia: Treatment with antibiotics and/or the presence of a new pulmonary infiltrate and/or progression of previous pulmonary infiltrates on a chest x-ray plus at least 2 of the following criteria—(1) leukocytosis with >12,000 white blood cell/mm^3 or leukopenia with <4,000 white blood cell/mm^3, (2) fever >38.5°C or hypothermia <36°C, and (3) increased secretions with purulent sputum and a positive bronchial aspirate.
7. Bronchopleural fistula: Presence of a continuous air leak through the bronchial stump diagnosed with fiberbronchoscopy.
8. Pleural empyema with or without surgical reintervention: Collection of pus in the pleural cavity, confirmed by thoracentesis and positive bacterial culture.

Secondary outcomes are the composite of PPCs over the first 30 postsurgical days and include the following[36,37] (Appendix 1):

1. Atelectasis without bronchoscopy: Positive air test (SpO_2 ≤96% when removing the oxygen mask and having the patient breathe room air for at least 5 min).
2. Hypoxemia without requirements of supplementary oxygen or ventilator support[38]: Peripheral capillary oxygen saturation <90%.
3. Contralateral pleural effusion: Chest x-ray with the presence of costophrenic angle blunting, displacement of adjacent anatomic structures, and blunting of the hemidiaphragmatic silhouette in the supine position.
4. Bronchospasm: Presence of expiratory wheezing treated with bronchodilators.
5. Aspiration pneumonitis: Respiratory failure after the inhalation of regurgitated contents.
6. Pulmonary thromboembolism: A new blood clot or thrombus within the pulmonary arterial system.
7. Chronic obstructive pulmonary disease exacerbation: Sustained worsening of the patient's condition from the stable

state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment.
8. Hemothorax with or without surgical reintervention or transfusion: Presence of blood in the pleural space, specifically when the hematocrit of the pleural fluid is ≥50% of that of the peripheral blood.
9. Clavien-Dindo classification.
10. ICU and hospital length of stay.
11. ICU and hospital readmission in the first 30 days after surgery.
12. Mortality within the first 30 days.

The following are secondary outcomes that are systemic complications on the basis of standard definitions[36] (see Appendix 1):

1. Cardiac ischemia
2. New atrial fibrillation
3. Sepsis or septic shock
4. Acute kidney failure
5. Surgical site infection
6. Other infections (eg, catheter, urinary tract)

The primary and secondary outcome variables will be recorded at 1, 2, 5, 7, and 30 days after surgery. Plasma samples will be taken preoperatively and 2 days after surgery. If the patient is not extubated in the operating room, the first 4 data time points will be taken from the time of extubation.

Other Follow-Up Variables

Baseline variables will be recorded preoperatively, including age, sex, height, weight, body mass index, American Society of Anesthesiologists physical status,[39] Charlson comorbidity index,[40] preoperative pulmonary function test, Sequential Organ Failure Assessment score,[41] ARISCAT risk score,[42] type of intervention, and medical history.

The following intraoperative parameters will be recorded at 3 different time points (post-induction, 60 min after induction, and pre-extubation): arterial blood gases; SpO_2; F_iO_2; respiratory variables (VT, PEEP, peak airway pressure, Pplat, respiratory system compliance, respiratory system resistance; hemodynamics (cardiac index, mean arterial pressure, stroke volume variation and/or pulse pressure variation); diuresis and body temperature. Other relevant data, including the types of anesthetic drugs used, type and volume of fluids, blood loss and transfusion requirements, need for vasoactive drugs, diuresis, nasogastric tube insertion, duration of surgery, MV time, number of RMs performed, and the need for rescue therapy, also will be recorded.

General Procedures

All participating patients, regardless of the study arm into which they are randomly assigned, will be monitored and managed on the basis of general standard-of-care practices aimed at maintaining optimal conditions. Both intraoperative and immediate postoperative (6 h) anesthetic management (unrelated to ventilatory management) will be decided on by the attending physician as he or she sees fit, following the established protocols at each center. However, in order to ensure a high standard of anesthetic management, a number of common strategies have been established, including the following: halogenated agents will be given to maintain anesthesia, intraoperative and postoperative pain will be controlled with neuraxial anesthetics, and fluids will be administered after goal-directed therapy principles. Appropriate antibiotic prophylaxis will be administered and pharmacologic prevention of postoperative nausea and vomiting will be adopted. Finally, when nasogastric tube insertion is required, it should be withdrawn before extubation, when possible. All these data will be collected and analyzed.

Monitoring

Intraoperative monitoring will include an electrocardiogram (ECG), pulse oximetry, capnography, bladder or esophageal temperature, anesthetic depth analysis (bispectral analysis) and a neuromuscular blockade (with train of four), invasive blood pressure measurements, and advanced hemodynamic monitoring with minimally invasive monitoring (optional depending on the standard clinical practice and availability of equipment at each hospital). The following ventilatory parameters will monitored using the anesthesia machine: VT, PEEP, F_iO_2, peak airway pressure, Pplat, driving pressure, and dynamic compliance of the respiratory system (Cdyn). Postoperative monitoring will include at least an ECG, pulse oximetry, and invasive arterial pressure measurements.

General Intraoperative Ventilator Management

Pre-oxygenation will be performed for 5 minutes at an F_iO_2 of 1.0 with a tightly sealed facemask before induction. Patients will be ventilated in volume control mode (VCV) with squared flow, VT of 8 mL/kg of the predicted body weight during two-lung ventilation and 5 to 6 mL/kg of the predicted body weight during OLV, PEEP of 4 cmH_2O, and a Pplat of ≤25 cmH_2O. If the Pplat reaches or exceeds 25 cmH_2O, VT will be decreased in 1 mL/kg steps until the Pplat drops to ≤25 cmH_2O. The respiratory rate (RR) will be set to maintain an end-tidal carbon dioxide partial pressure between 35 and 45 mmHg, with an inspiratory to expiratory ratio (I:E) of 1:2 (it could be modified under the criteria of the attending physician) and an inspiratory pause time of 5% to 10% of the inspiratory time. F_iO_2 will be set at 0.8 throughout the entire procedure. During the awakening period from general anesthesia (patients with spontaneous ventilation), an F_iO_2 of 1.0 will be applied at the same end-expiratory pressure used with either PEEP or CPAP.

In all the study patients, adequate selective ventilation must be corroborated with the fiberoptic bronchoscope. Extubation will not be allowed by applying a positive pressure above the previously set PEEP or CPAP or while suctioning through the tracheal device. If necessary, aspiration can be performed at least 10 minutes before extubation. After suctioning, the patient will

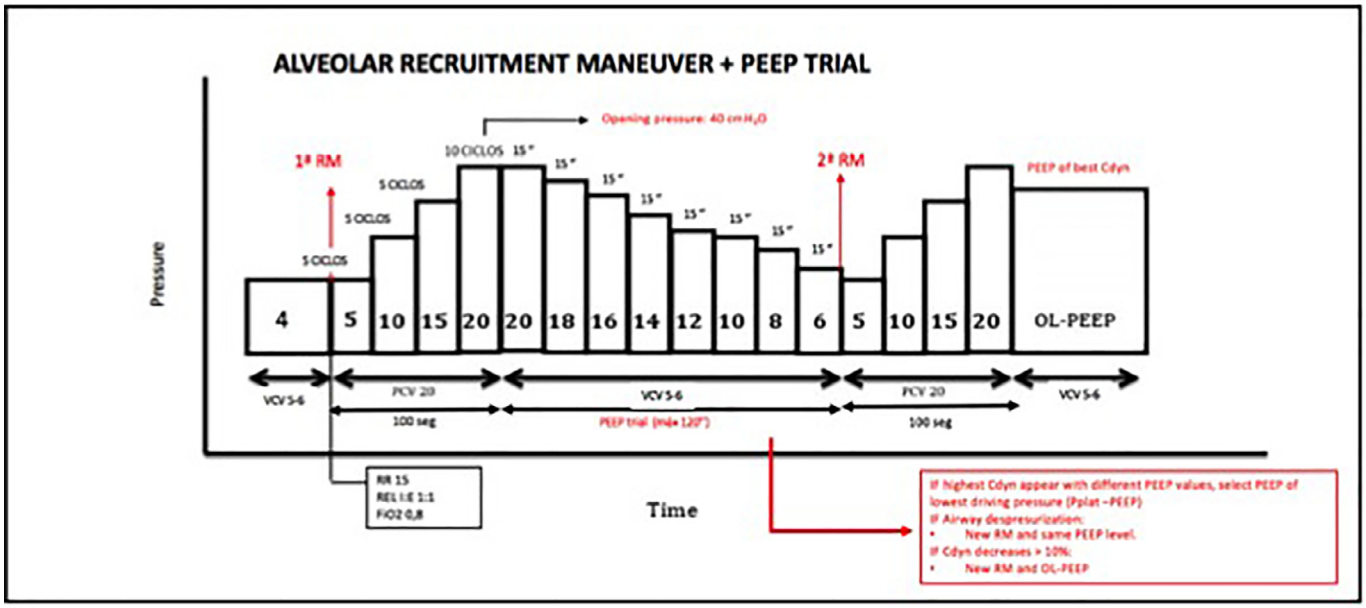

Fig 2. Recruitment maneuver plus positive end-expiratory pressure trial. F_iO_2, fraction of inspired oxygen; PCV, pressure control ventilation; PEEP, positive end-expiratory pressure; RM, recruitment maneuver; RR, respiratory rate; VCV, volume control ventilation.

be returned to MV. If the patient is randomly assigned to the iOLA-iHFNC group, a new alveolar RM will be performed. Once extubation has been performed, all study patients will be oxygenated with 0.5 F_iO_2 through a Venturi mask during the first 30 minutes.

Specific Intraoperative Ventilatory Management

In the STD-O2 group, patients will be ventilated as previously described in the general intraoperative ventilator management section. For patients in the iOLA-iHFNC group, an RM will be performed immediately after selective ventilation is initiated followed by a PEEP titration trial. Before the RM is performed, the clinician must ensure that there is hemodynamic stability (mean arterial pressure >70 mmHg and/or a cardiac index >2.5 mL/min/m^2) for at least 5 minutes, a stroke volume variation <10%, and an adequate neuromuscular blockade (0 of 4 by train of four). Alveolar RMs are performed as described in the following section.

Alveolar RMs

Recruitment will be performed as previously described.[43] The ventilator will be changed from VCV to pressure-controlled ventilation with a 20 cmH_2O driving pressure and RR of 15 breaths per minute (rpm), I:E of 1:1, F_iO_2 of 0.8, and PEEP of 5 cmH_2O. For the recruitment phase, the PEEP level will be increased in 5 cmH_2O steps every 5 respiratory cycles, up to 20 cmH_2O of PEEP, to produce an airway opening pressure of 40 cmH_2O and will be maintained for 10 respiratory cycles in the opening pressure (total maneuver time 100 s). If hemodynamic instability appears during the recruitment phase (>50% decrease in the cardiac index or mean arterial pressure), the RM will be interrupted and 5 to 15 mg ephedrine or 0.05 to 0.15 mg phenylephrine will be given; after hemodynamic stabilization, a new RM will be performed. After lung recruitment is accomplished, optimal PEEP will be titrated through a decremental PEEP trial, as described in the next section (Fig 2).

Titration of Optimal Individual PEEP: Decremental PEEP Trial

At the end of the last step of the pressure control ventilation recruitment phase when the PEEP is 20 cmH_2O, the mode will be switched to VCV with a VT of 5 to 6 mL/kg, RR of 15 rpm, I:E of 1:2, and F_iO_2 of 0.8. After this, PEEP will be decreased in 2 cmH_2O steps every 15 seconds until the highest Cdyn is observed on the ventilator's monitor (until Cdyn starts decreasing or does not increase). In case the highest Cdyn appears with several PEEP values, the PEEP with the lowest driving pressure (Pplat − PEEP) will be selected. Once the best Cdyn is known, a new RM will be performed and the PEEP for the best Crs will be adjusted. In the case of accidental airway depressurization, a new alveolar RM will be performed while an identical PEEP is set (see Fig 2).

The need for new RMs and a PEEP trial will be evaluated every 40 minutes by measuring the Cdyn. If there is a decrease >20% of the Cdyn, a new recruitment and PEEP trial will be performed.

Intraoperative RMs

In the case of arterial hypoxemia (SpO_2 ≤92% with F_iO_2 0.8), after excluding endobronchial tube displacement, bronchospasm, pneumothorax, or a hemodynamic cause, a protocol for rescue therapy has been devised for each group.

For the STD-O2 group, the 0.1 F_iO_2 will be increased until SpO_2 >95%. If arterial hypoxemia persists with 1.0 F_iO_2, the PEEP will be increased in steps of 2 cmH_2O (until a maximum of 10 cmH_2O). If hypoxemia persists, CPAP in the nondependent lung will be allowed.

In the iOLA-iHFNC group, a new RM and PEEP trial will be performed. If SpO_2 is <92% (0.8 F_iO_2), F_iO_2 will be increased in 0.1 steps. If hypoxemia persists, CPAP in the nondependent lung will be allowed.

Lung RM in the Nondependent Lung

If it is necessary to perform a lung RM for a leak test or as a rescue maneuver for hypoxemia, this will be done by connecting a CPAP system with adequate oxygen flow and increasing the level of CPAP in 5 cmH_2O steps from 5 to 10 cmH_2O every 5 seconds.

For leak tests, the lung will be thereafter depressurized again. If the RM is performed as a rescue maneuver, the minimum level of CPAP that maintains an SpO_2 ≥92% will be adjusted.

General Postoperative Management in the Postoperative Care Unit

General postoperative management in the PACU or ICU that is not related to ventilator management will be decided by the attending physician on the basis of the established protocols at each center. Patients will be oxygenated with F_iO_2 0.5 through a Venturi mask for the first 15 to 30 minutes (see Fig. 3).

In all study patients, arterial oxygenation will be evaluated 15 to 30 minutes later when patients are awake and collaborative (Glasgow Coma Score >13) without any residual anesthetic effect (Richmond scale −1 to +1) and under pain control (visual analog scale <4) by decreasing the F_iO_2 to 0.21 for at least 5 minutes (air test). The air test will not be performed if the patient's SpO_2 already is <96% with F_iO_2 0.5. When the patient arrives in the PACU or ICU with invasive MV, the aforementioned management will be applied after extubation.

Specific Postoperative Ventilatory Management

In the STD-O2 group, patients will be oxygenated through a Venturi mask with the minimum F_iO_2 that maintains an SpO_2 ≥92%. In the iOLA-iHFNC group, supplemental oxygen at F_iO_2 0.5 will be delivered through a Venturi mask. During the first 6 postoperative hours (in case of negative air test [SpO_2 ≥97%]), the patient will be oxygenated with the minimum F_iO_2 to maintain an SpO_2 ≥92%. In case of a positive air test (SpO_2 ≤96%), high-flow oxygen therapy (HFNC) will be indicated with 50 L/min flow and the minimum F_iO_2 to maintain an SpO_2 ≥92%.

Postoperative RM

In patients with persistent hypoxemia and/or hypercapnia ($PaCO_2$ >50 mmHg with a pH <7.30) or tachypnea (RR >25 rpm) or in those with increased activity of accessory respiratory muscles, inspiratory support with noninvasive ventilation (NIV) will be started.

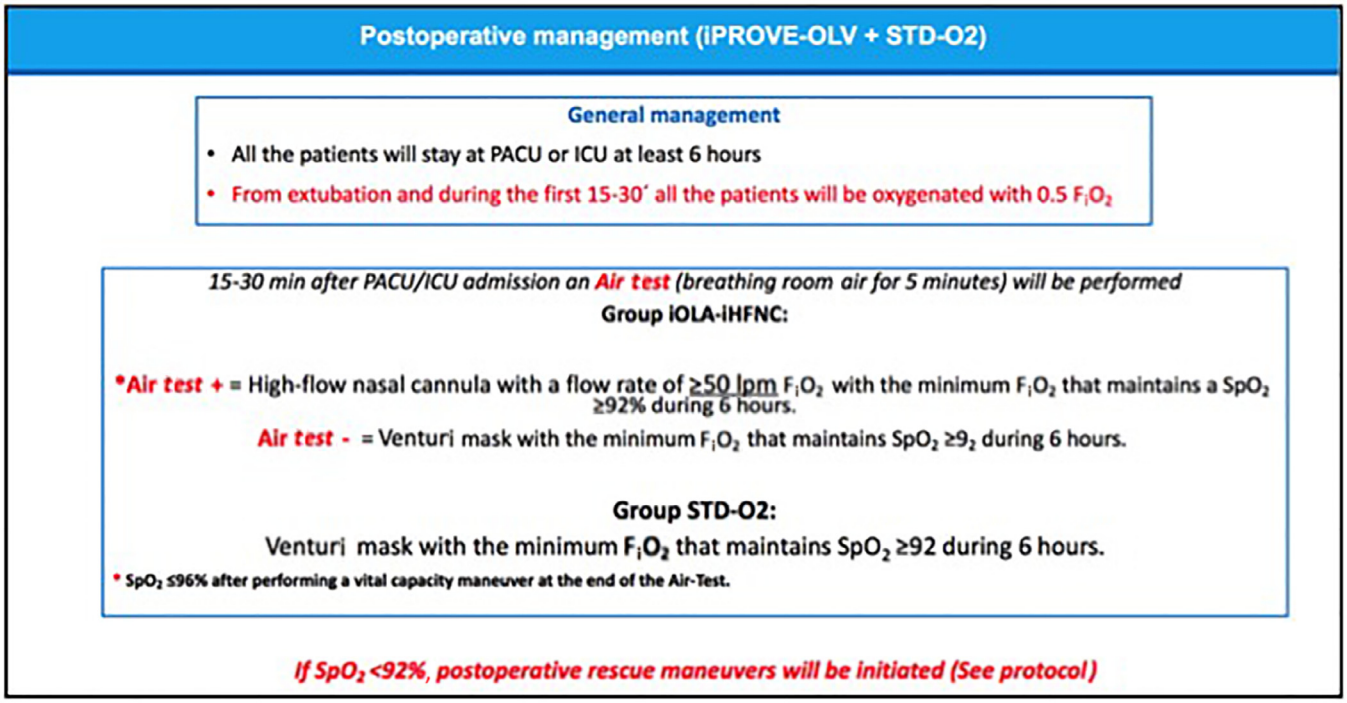

Fig 3. General and specific postoperative ventilatory management. F_iO_2, fraction of inspired oxygen; ICU, intensive care unit; PACU, postanesthesia care unit; SpO_2, peripheral capillary oxygen saturation.

NIV

The ventilator (specific for NIV or with software for NIV) and interface for NIV will be chosen by the attending physician and based on hospital availability. Positive pressure will start with an inspiratory positive airway pressure of 5 cmH_2O greater than the expiratory positive airway pressure and will be increased in steps of 5 cmH_2O up to 15 cmH_2O. The expiratory positive airway pressure will be increased to a maximum of 10 cmH_2O (15 cmH_2O if the body mass index exceeds 30).

Invasive Ventilation

Direct tracheal intubation (without NIV trial) will be indicated if the patient also meets at least 1 of the following criteria:

1. Hemodynamic instability (a systolic blood pressure <80 mmHg or <40% of the basal or vasoactive drug requirements for more than 2 h is required to maintain the systolic blood pressure >80 mmHg).
2. Ventricular arrhythmias with hemodynamic instability or ECG signs of myocardial ischemia.
3. Glasgow Coma Score <9.
4. Sedation requirement due to agitation.

Tracheal intubation after 1 hour of NIV will be indicated in patients meeting at least 1 of the following criteria:

1. Severe hypoxemia (SpO_2 <92%).
2. Respiratory acidosis (pH <7.30 with a $PaCO_2$ >50 mmHg).
3. Signs of distress with increased use of accessory respiratory muscles or paradoxical thoracic-abdominal respiratory movements.

Sample Size

Assuming a confidence level of 95% and a percentage of pulmonary complications of 18% at 7 days post-intervention,[19] a total of 655 patients per group (intervention and control groups) are required to detect an absolute reduction of 5% in the prevalence of pulmonary complications with a power of 80%. Assuming 5% of possible losses, the final sample size is 1,380 patients (690 per group).

Statistical Analysis

Patient characteristics will be described using frequencies and percentages for categorical variables and mean and standard deviation or median and interquartile range for continuous variables, depending on normality. The categorical variables will be compared using the chi-square or Fisher exact test, and the magnitude of the association with relative risks or odds ratios will be established. Continuous variables will be compared using the Student *t* test or the Mann-Whitney *U* test, depending on normality. The baseline characteristics of the control group and the intervention group will be compared, and if any difference in potentially confounding variables is found, they will be included as adjustment variables in the corresponding multivariate models. The main outcome variable will be expressed as a proportion of complications with a 95% confidence interval. A difference of proportions test will be performed, or multivariate logistic regression, including potential confounders, will be applied to compare the intervention and control groups. Time-to-event variables such as time to primary or secondary outcome will be analyzed using Kaplan-Meier curves and univariate or multivariate, as appropriate, Cox proportional hazards models. Variables with different measures over time will be analyzed using mixed linear models. All analyses will be performed by intention to treat, and the missing data will be imputed using multiple imputation methods when more than 5% appear in the primary or secondary outcome variables. A level of significance of $\alpha = 0.05$ will be considered.

Data Safety Monitoring Board Stopping Rules

The stopping rule is based on the modification of the limits of Haybittle-Peto. The analysis of the main outcome variable will be presented to the Data and Safety Management Board blindly to the study groups. The intermediate analysis will be performed once the efficacy variables of the first 655 patients are obtained. If the analysis is significant ($p < 0.001$) both positively and negatively for the intervention group, the safety committee will be able to paralyze the inclusion of new patients. Given this blinded monitory strategy, the authors will not assume any alpha spending function approach and, subsequent analysis will follow the level of predetermined level of significance ($\alpha = 0.05$)

Discussion

MV in healthy lungs can promote the development of PPCs. Contemporary reports have shown that ventilation with high VT and low PEEP favors the appearance of PPCs. The use of lung-protective ventilation with low VT and adequate PEEP could reduce PPCs, the need for postoperative ventilator support, unplanned ICU and hospital readmissions, and ICU and hospital length of stay.[17,21] Likewise, during the immediate postoperative period there is an increased risk of developing pulmonary dysfunction due to different causes, both anesthetic and surgical. Some studies have shown that the ventilatory support during this phase could reduce postoperative complications.[44,45]

Although lung-protective MV has decreased the prevalence of PPCs, its prevalence in patients undergoing thoracic surgery is around 20% to 30%.[1,2,19] The appearance of complications worsens the patient's prognosis and increases the consumption of health resources.

Different ventilatory strategies such as the use of a physiologically low VT, RMs, individualized PEEP, and HFNC in the postoperative period, which are not widely used in routine clinical practice,[46,47] have been shown to reduce the incidence of PPCs. However, there are no prospective, controlled, and

randomized clinical studies demonstrating that the use of a perioperative OLA strategy consisting of performing RMs plus individualized PEEP adjustment during the intraoperative period along with the postoperative individualized indication of HFNC decreases PPCs with respect to a standardized ventilation strategy in patients undergoing lung resection.

In this study, the effectiveness of the application of a perioperative open lung strategy will be evaluated. If it were shown that it reduces PPCs, it would represent a notable advance in the clinical management of these patients. In addition, a reduction in these complications would reduce the use of healthcare resources.

Trial Status

The iPROVE-OLV screening for patients began in September 2018.

Conflict of Interest

The authors declare no conflicts of interest.

Appendix 1

Systemic complications following standard definitions:

1. Cardiac ischemia: Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least 1 value >99th percentile upper reference limit and at least 1 of the following criteria: 10 symptoms of ischemia; new or presumed new significant ST segment or T wave electrocardiogram (ECG) changes or new left bundle branch block; development of pathological Q waves on ECG; radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus on angiography or at autopsy.
2. New atrial fibrillation: ECG evidence of cardiac rhythm disturbance (atrial fibrillation).
3. Sepsis or septic shock: Sepsis is defined as an infectious focus identified plus organ dysfunction (defined as an increase in Sequential Organ Failure Assessment ≥2). Septic shock is defined as severe sepsis with hypotension and hypoperfusion that is unresponsive to fluids.
4. Acute kidney failure on the basis of the Acute Kidney Injury Network scale as follows:
   - Stage I: Diuresis <0.5 mg/kg (6 h) or increase in serum creatinine >0.3 mg/dL
   - Stage II: Diuresis <0.5 mg/kg (12 h) or basal creatinine × 2 mg/dL
   - Stage III: Diuresis <0.3 mg/kg (24 h) or anuria (12 h) or basal creatinine × 3 mg/dL, or creatinine >4 mg/dL or renal replacement therapy
5. Surgical site infection: Defined by the US Centers for Disease Control and Prevention as meeting the following criteria: (1) infection occurs within 30 days after surgery, (2) involves only skin and subcutaneous tissue of the incision, and (3) the patient has at least 1 of the following—(a) purulent drainage from the superficial incision; (b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; (c) at least one of the following symptoms or signs of infection: pain or tenderness, localized swelling, redness or heat, superficial incision deliberately opened by surgeon and is culture-positive or not cultured (a culture-negative finding does not meet this criterion); and (d) diagnosis of an incisional surgical site infection by a surgeon or attending physician.
6. Other infections (eg, catheter, urinary tract).

Other secondary outcomes include the following:

1. Clavien-Dindo classification
   - Grade I: Any deviation from the expected postoperative course that does not require specific treatment
   - Grade II: Complications requiring drug therapy, blood transfusions, or nutritional support
   - Grade III: Postoperative changes that require invasive treatment (puncture, drainage, and redo surgeries)
     - Grade IIIa: Without general anesthesia
     - Grade IIIb: With general anesthesia
   - Grade IV: Complications with imminent risk of death and need for intensive care
     - Grade IVa: 1 organ dysfunction
     - Grade IVb: 2 or more organs dysfunction
   - Grade V: Postoperative death
2. ICU and hospital length of stay
3. ICU and hospital readmission in the first 30 days after surgery
4. Mortality within the first 30 days

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