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ORIGINAL RESEARCH

Usefulness of combining clinical and biochemical parameters for prediction of postoperative pulmonary complications after lung resection surgery

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Abstract

Early detection of patients with a high risk of postoperative pulmonary complications (PPCs) could improve postoperative strategies. We investigated the role of monitoring systemic and lung inflammatory biomarkers during surgery and the early postoperative period to detect patients at high risk of PPCs after lung resection surgery (LRS). This is a substudy of a randomized control trial on the inflammatory effects of anaesthetic drugs during LRS. We classified patients into two groups, depending on whether or not they developed PPCs. We constructed three multivariate logistic regression models to analyse the power of the biomarkers to predict PPCs. Model 1 only included the usual clinical variables; Model 2 included lung and systemic inflammatory biomarkers; and Model 3 combined Models 1 and 2. Comparisons between mathematical models were based on the area under the receiver operating characteristic curve (AUROC) and tests of integrated discrimination improvement (IDI). Statistical significance was set at $p < 0.05$. PPCs were detected in 37 (21.3%) patients during admission. The AUROC for Models 1, 2, and 3 was 0.79 (95% CI 0.71–0.87), 0.80 (95% CI 0.72–0.88), and 0.93 (95% CI 0.88–0.97), respectively. Comparison of the AUROC between Models 1 and 2 did not reveal statistically significant values ($p = 0.79$). However, Model 3 was superior to Model 1 ($p < 0.001$). Model 3 had had an IDI of 0.29 ($p < 0.001$) and a net reclassification index of 0.28 ($p = 0.007$). A mathematical model combining inflammation biomarkers with clinical variables predicts PPCs after LRS better than a model that includes only clinical data. *Clinical registration number* Clinical Trial Registration NCT 02168751; EudraCT 2011-002294-29.

Keywords Perioperative period · Pulmonary inflammation · Postoperative complications · Cytokines bronchoalveolar lavage · Cytokines blood

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Abbreviations

AUROC	Area under receiver operating characteristic
BAL	Bronchoalveolar lavage fluid
CPAP	Continuous positive airway pressure
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
ICU	Intensive care unit
IL	Interleukin
LRS	Lung resection surgery
MMP	Matrix metalloproteinase
OLV	One-lung ventilation
PPC	Postoperative pulmonary complication

1 Introduction

Postoperative pulmonary complications (PPCs) continue to be one of the main causes of morbidity, mortality, and increased hospital stay in patients undergoing surgical procedures requiring anaesthesia [1]. The incidence of PPCs is particularly high in lung resection surgery (LRS) as a result of injury to structures associated with respiratory function (eg, resection of the lung parenchyma, respiratory muscle surgery, diaphragmatic dysfunction) and the frequent finding of smoking-related respiratory morbidity (chronic obstructive pulmonary disease, cancer) [2]. These inevitable predisposing causes of PPCs are compounded by the well-known harmful effects of one-lung ventilation (OLV) on postoperative lung function [3].

Early detection of patients at risk of PPCs can modify the clinical course of the disease in that stay in the intensive care unit (ICU) is prolonged and prophylaxis against the onset of PPCs is intensified (eg, lung re-expansion manoeuvres, close monitoring of gas exchange, antibiotic therapy) [2, 4, 5]. Similar studies that have analysed the effect of specific pre- and postoperative risk factors for PPCs after LRS are essentially based on spirometry testing and preoperative clinical conditions [2, 6, 7].

Chest surgery (LRS or oesophagectomy) is characterized by an exaggerated systemic and pulmonary inflammatory response resulting from surgical stress and from lung injury during OLV, both in the ventilated and non-ventilated lung [8].

An association has been proposed between this hyperinflammatory state and the onset of PPCs, although no in-depth research has been carried out on the usefulness of measuring inflammatory biomarkers during or immediately after surgery for detection of patients with a high risk of PPCs [9–11].

We hypothesized that our ability to identify patients at the greatest risk of PPCs could be improved by combining assessment of biomarkers of inflammation during surgery and during the first 6 h after surgery and assessment of the risk factors habitually assessed to predict PPCs in LRS. Our study aimed to investigate whether performing a joint assessment of clinical predictors of risk (pre- and intraoperative) and inflammatory markers (intraoperative and immediate postoperative) would increase our ability to detect patients who develop PPCs after LRS.

2 Methods

Patients were included in the study if they had participated in clinical trial NCT 02168751 or EudraCT 2011-002294-29 [12], both of which were approved by the Clinical Investigation Ethics Committee (No. 181/11) of Hospital Gregorio Marañón, Madrid, Spain (Chairperson Dr. Fernando Diaz) in August 2011. Informed consent was obtained from all patients included.

We analysed 174 patients, of whom only 160 were included. The remaining 14 cases were excluded because not all samples of plasma and bronchoalveolar lavage fluid (BAL) were available (11 pneumonectomies and 3 missing data).

The inclusion criteria were as follows: patients of either sex undergoing LRS; voluntary agreement to participate in the study; signed informed consent; age > 18 years and legally competent; scheduled surgery; forced expiratory volume in the first second (FEV_1) > 50% or forced vital capacity (FVC) > 50%. The exclusion criteria were as follows: pregnancy and breastfeeding; transfusion of blood products during the previous 10 days; impossibility of performing lung-protective ventilation; heart failure (New York Heart Association Functional Class 3 or 4) during the week before surgery; and previous long-term treatment with corticosteroids or immunosuppressive agents during the 3 months before surgery.

All of the study patients received the same perioperative care, with the exception of the hypnotic drug used during surgery. Induction was with propofol (2–3 mg kg^{-1}), fentanyl (3 µg kg^{-1}), and rocuronium (0.6–1 mg kg^{-1}). A double-lumen tube was then inserted and correct placement was verified using a fiberoptic bronchoscope.

Initially, the lungs were ventilated at a tidal volume of 8 ml kg^{-1} (ideal weight), a positive end expiratory pressure (PEEP) of 5 cmH_2O, FiO_2 of 0.4–0.5, and a breathing rate that enabled $EtCO_2$ to be maintained at 30–35 mmHg. During OLV, we applied a Vt of 6 ml kg^{-1} (ideal weight), PEEP of 5 cmH_2O, and FiO_2 of 0.6–1 to maintain SpO_2 > 90%. Recruitment manoeuvres were made and/or continuous positive airway pressure (CPAP) was applied to the nondependent lung if SpO_2 was < 90% despite using an FiO_2 of 1. Intra- and postoperative analgesia was maintained by paravertebral thoracic block. Administration of fluids was via a crystalloid solution at 2 $ml.kg^{-1}$ h^{-1} to maintain diuresis

above 0.5 ml h^{-1}. If urine output diminished, a bolus dose of 250 ml crystalloids was administered.

Clinical preoperative and intraoperative variables recorded are shown in "Appendix 1".

2.1 Laboratory data

2.1.1 Arterial blood gas values

Blood samples were taken from the arterial line to determine blood gas values (PaO_2, SaO_2, and $PaCO_2$) at 4 time points: in the operating room before starting OLV, 30 min after starting OLV, and on restarting two-lung ventilation, and 6 h after surgery was completed.

2.1.2 Cytokines in BAL fluid

BAL samples were taken from both lungs during surgery and before and immediately after OLV had finished.

BAL fluid samples were taken by guiding a fiberoptic bronchoscope into the bronchus of the lower left lobe and lower right lobe until it met with resistance and could progress no further. At the end of surgery, in pneumonectomies, we only collect samples of dependent lung; In lobectomies we directed bronchoscope toward bronchus of lobe remanent of non-dependent lung. A first injection of saline solution 0.9% (25 ml) was then made, and the residual fluid was extracted and discarded. A new bolus of saline solution 0.9% (25 ml) was then injected, and the aspirate was used for analysis of the BAL samples. The biomarkers analysed were as follows: Interleukin (IL)-1, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, TNF-α, MCP-1, MMP2, MMP9. The relationship between pro-inflammatory and anti-inflammatory markers was measured using the ratios IL-8/IL-10 and IL-6/IL-10 [13, 14].

2.1.3 Cytokines in blood

Cytokine levels were determined in plasma by drawing blood from the arterial line when arterial blood gas values were being assessed. These samples were filtered using sterile gauze and centrifuged at 400X*g* for 15 min at 4 °C. The supernatant was stored at − 20 °C until analysis at a specialized laboratory. Concentrations of cytokines were analysed using ELISA. Blood biomarkers analysed were as follows: IL-1, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, TNF-α, MCP-1, MMP2, ratio IL8/IL10, and IL6/IL10.

2.2 Postoperative clinical data

All patients were extubated in the operating room, then remained at least 1 day in the ICU. Then they were transferred to the intensive care unit where they remained admitted for at least 24 h. Postoperative analgesia was provided by paravertebral block and we used intravenous analgesics on demand. At 6 h of stay in the ICU, patients were allowed to drink. A chest-X-ray was performed 24 h after surgery. Clinical data were collected as part of the study and during the postoperative hospital stay. PPCs were defined according to the criteria of ARISCAT "(Appendix 2)". The investigator who classified patients as PPC or non-PPC was blind to the type of anaesthesia used and to values for cytokines in plasma or in BAL fluid. The postoperative day on which the first PPC was diagnosed was also recorded. Another medical complications included cardiac complications (myocardial infarction, arrhythmias, miocardial arrest, and cardiac failure), deep venous trombosis or pulmonary embolism, renal failure defined by AKIN criteria [15], and hepatic failure. Surgical complications, included air leak, surgical wound infection, bleeding, reintervention chylothorax, empyema, and mediastinitis. In order to analyze the impact that surgical or medical complications could have on the postoperative course, we applied the Clavien-Dindo classification [16]. All the patients were followed up after surgery until discharge and during the first 30 days after surgery. We recorded the stay in the ICU and in the hospital and readmission to the ICU after discharge. All data were collected prospectively by study personnel.

2.3 Statistical analysis

Results are presented as median (interquartile range) for continuous, non-normally distributed variables and as mean (standard deviation) for continuous, normally distributed variables. Normality was analysed using the Kolmogorov–Smirnov test. Qualitative variables are expressed as frequency and percentage and were analysed using the Chi square test or Fisher exact test. Continuous variables were compared using a paired or unpaired *t* test and the Wilcoxon or Mann–Whitney test, as appropriate.

A univariate analysis was performed with all the variables collected before and during surgery and during the 6 h after surgery. Variables with $p < 0.1$ were used in the comparison of the PPC group with the non-PPC group. For the analysis, the 4 most relevant clinical variables were analysed. For the analysis of inflammatory biomarkers in blood, the 4 with the largest area under the receiver operating characteristic curve (AUROC) were recorded. Similarly, the 4 biomarkers obtained from the analysis of BAL fluid were also collected.

Multiple logistic regression was performed to predict PPCs that included the clinical variables (Model 1: type of anaesthesia, FEV_1, age and duration of surgery). We also ran another logistic regression model with cytokines only (Model 2) and a model with cytokines as well as clinical variables (Model 3). We applied the backward stepwise

Table 1 Demographic and intraoperative data

	PPC		p value
	No (n = 137)	Yes (n = 37)	
Age (years)	64 (56–70)	70 (63–76)	**0.005**
BMI	26 (22.9–28.7)	25.8 (23.8–28.9)	0.671
ASA	7/82/48/0	1/14/21/1	**0.018**
FVC pre (%)	103 (95–122)	99.8 (81–104)	**0.008**
FEV1pre (%)	98.6 (84–111)	78 (63–92)	**< 0.001**
Tifenneau Index	74.7 (68–82)	66 (59–75)	**< 0.001**
DLCOpre (%)	88.2 (77.8–102.4)	77 (62.6–88.6)	**0.02**
Length OLV	155 (107–210)	190 (128–268)	**0.017**
Cristalloids (ml/kg)	9.33 (7.3–12.6)	9.72 (7.2–13.1)	0.373
Side (R/L)	77/60	21/16	0.552
Surgery (N/L/S)	7/61/69	4/18/15	0.335

Data expressed as median (interquartile 25–75)

PPC postoperative pulmonary complications, *BMI* body mass index, *FVC pre* forced vital capacity predicted, *FEV1pre* forced expiratory volume in the first second predicted, *DLCOpre* diffusing capacity of lung for carbon monoxide predicted, *OLV* one-lung ventilation, *R* right, *L* left, *N* neumonectomy, *L* lobectomy, *S* Segmentectomy

method to select the most significant cytokines, leaving the clinical variables as fixed variables. The numerical variables were previously dichotomized using ROC curves and choosing the optimal cut-off provided by the Youden J index [17]. The criteria chosen for the selection of cytokines were $p < 0.05$ and > 0.1 to include and exclude terms, respectively.

We also used ROC curves to determine the ability of the models to predict PPCs. Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. ROC curves of models were compared following the method of Hanley and McNeil [18]. In addition, we calculated the integrated discrimination improvement and the net reclassification improvement as measures to evaluate discriminative ability between the 2 logistic regression predictive models (Model 1 vs Model 3) [19]. We´ve performed a 10-fold cross-validation to provide potential validity of the results.

All statistical tests were 2-tailed, and a p value of < 0.05 was considered statistically significant. The calculations were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, New York, USA) and the R package [20].

Table 2 Blood gas values and respiratory and hemodynamic data obtained during surgery

	PPC	Baseline		OLV		END	
		Median (IQ 25–75)	p	Median (IQ 25–75)	p	Median (IQ 25–75)	p
PaO_2/FiO_2	Yes	308 (233–373)	**0.016**	97 (83–125)	**0.493**	274 (211–362)	**0.136**
	No	350 (307–419)		102 (86–126)		319 (253–392)	
$PaCO_2$ (mmHg)	Yes	46 (42–52)	**0.044**	53 (48–59)	**< 0.001**	49.5 (45–56)	**0.092**
	No	44 (41–49)		47 (42–52)		47 (43–52)	
Grad CO2	Yes	13 (10.5–17)	**0.02**	16 (12–19.5)	**0.007**	13 (9–19.5)	**0.171**
	No	11 (8–13)		13 (10–16)		12 (8–16)	
Peak AP (cmH_2O)	Yes	20 (19–24)	**0.793**	26 (22–29)	**0.792**	21 (20–24)	**0.147**
	No	21 (19–23)		25 (22–29)		21 (18–24)	
Plateau AP (cmH_2O)	Yes	18 (16–20)	**0.833**	20 (17.5–22.5)	**0.202**	18 (15.5 – 22)	**0.385**
	No	18 (16–21)		21 (18–24)		18 (15–21)	
LC (cmH_2O)	Yes	39.5 (33–51)	**0.848**	28.4 (23–37)	**0.634**	37.3 (31–49)	**0.769**
	No	39.7 (34–46)		29 (24–35)		40 (31–49)	
DP (cmH_2O)	Yes	13.1 (11–15)	**0.794**	14.8 (12–17)	**0.266**	12.2 (10–16)	**0.697**
	No	12.9 (11–16)		15.6 (13–18)		13.1 (10–15)	
MAP (mmHg)	Yes	72 (64.5–80)	**0.027**	73 (64–80)	**0.436**	78 (67–85.5)	**0.055**
	No	79 (68–90)		75 (65–86)		82 (70–93)	
HR (bpm)	Yes	75 (64.5–84.5)	**0.012**	71 (62.5–83)	**0.688**	77 (69.5–90)	**0.135**
	No	69 (60.5–78.5)		71 (62–80.5)		73 (64–83)	
CI (ml min^{-1} m^{-2})	Yes	2.4 (1.9–3.1)	**0.35**	2.4 (2–2.8)	**0.514**	2.6 (2.4–2.9)	**0.341**
	No	2.5 (2.1–3.1)		2.5 (2.1–3)		2.7 (2.3–3.2)	
SVV (%)	Yes	14 (10–20)	**0.117**	9 (7–12)	**0.635**	10 (7–13)	**0.929**
	No	12 (9–17)		9 (7–12)		9 (7–14)	

Data are expressed as median (interquartile range)

PPC postoperative pulmonary complications, *OLV* one-lung ventilation, *END* end of OLV, *P* p value PPC versus non-PPC, *Grad CO2* gradient CO2 (PaCO2-EtCO2), *LC* lung compliance, *AP* airway pressure, *DP* driving pressure, *MAP* mean arterial pressure, *HR* heart rate, *CI* cardiac index, *SVV* stroke volume variation

3 Results

3.1 Respiratory complications

Of the 174 patients included in the study, 37 (21.3%) had PPCs during their postsurgical hospital stay. The demographic and surgical characteristics of both groups are shown in Table 1. The most common PPC was suspected respiratory infection (36/37 patients). A diagnosis of pneumonia was confirmed in 13 cases. The second most common PPC was respiratory insufficiency (32/37 patients) and four patients needed reintubation. Atelectasis was recorded in 7 of the 37 patients. There were no cases of bronchospasm, pneumothorax, or pleural effusion in the contralateral lung. All of the patients were extubated in the operating room at the end of surgery.

The time mean when the first PPC was detected based on clinical criteria was 3.32 (SD 1.76) days after surgery. No PPCs were detected on day 0 (day the patient underwent surgery).

Table 2 shows the main ventilatory and hemodynamic parameters assessed during surgery. At the beginning of surgery, patients who developed PPCs had a lower PaO_2/FiO_2 ratio and higher $PaCO_2$. During OLV, the only difference observed was greater $PaCO_2$ in patients who developed PPCs.

Table 3 Data obtained from bronchoalveolar lavage fluid during surgery

	PPC	Nondependent lung				Dependent lung			
		Baseline		End of OLV		Baseline		End of OLV	
		Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p
TNF ($pg{\cdot}ml^{-1}$)	Yes	15.2 (13.3–16.6)	**0.967**	23.4 (20.1–25.6)	0.062	15.1 (14–16)	0.949	22 (20.4–24.6)	0.506
	No	15.0 (13.8–15.9)		20.9 (20.1–23.8)		15 (14–16)		21 (19.9–25)	
IL-1 ($pg{\cdot}ml^{-1}$)	Yes	127 (114–133)	0.375	193 (173–218)	0.393	125 (113–143)	0.85	204 (173–236)	0.152
	No	128 (116–146)		188 (169–219)		127 (110–137)		187 (173–218)	
IL-2 ($pg{\cdot}ml^{-1}$)	Yes	2.14 (1.95–2.40)	0.896	3.54 (3.02–3.95)	0.124	2.19 (1.97–2.32)	0.17	3.57 (2.99–3.95)	0.011
	No	2.17 (1.97–2.36)		3.15 (2.91–3.77)		2.11 (1.97–2.25)		3.13 (2.92–3.56)	
IL-4 ($pg{\cdot}ml^{-1}$)	Yes	0.41 (0.39–0.44)	0.592	0.91 (0.72–0.97)	0.023	0.41 (0.39–0.46)	0.482	0.88 (0.74–0.97)	0.152
	No	0.41 (0.38–0.44)		0.82 (0.72–0.91)		0.41 (0.39–0.44)		0.81 (0.73–0.93)	
IL-6 ($pg{\cdot}ml^{-1}$)	Yes	6.46 (5.98–7.02)	0.106	7.73 (6.99–8.33)	0.013	6.41 (5.77–6.79)	0.726	7.6 (6.94–8.03)	0.153
	No	6.28 (5.82–6.82)		7.27 (6.88–7.85)		6.34 (5.87–6.87)		7.2 (6.88–7.78)	
IL-7 ($pg{\cdot}ml^{-1}$)	Yes	3.15 (2.94–3.45)	0.962	5.49 (4.99–5.97)	0.005	3.12 (2.94–3.49)	0.504	5.30 (5.05–5.88)	0.086
	No	3.17 (2.94–3.44)		5.10 (4.97–5.49)		3.23 (2.97–3.47)		5.11 (4.97–5.66)	
IL-8 ($pg{\cdot}ml^{-1}$)	Yes	2.63 (2.28–2.97)	0.745	53.3 (29.8–56.9)	0.039	2.70 (2.58–2.85)	0.369	47.7 (27.6–58.5)	0.102
	No	2.72 (2.50–2.95)		32.01 (26.3–53.5)		2.78 (2.54–3.05)		33.5 (24.9–57.2)	
IL-10 ($pg{\cdot}ml^{-1}$)	Yes	40.9 (39.5–42.2)	0.173	41.1 (39.6–43)	0.013	41.3 (40.2–41.9)	0.505	40.4 (38.6–45)	0.1
	No	41.4 (40.2–42.9)		42.7 (40.2–44.9)		41.5 (39.9–42.6)		42.6 (40–45.4)	
IL-12 ($pg{\cdot}ml^{-1}$)	Yes	0.066 (0.01–0.08)	0.072	0.144 (0.12–0.17)	0.004	0.068 (0.05–0.08)	0.756	0.131 (0.11–0.15)	0.501
	No	0.072 (0.06–0.08)		0.127 (0.11–0.14)		0.069 (0.06–0.08)		0.134 (0.11–0.15)	
MCP1 ($pg{\cdot}ml^{-1}$)	Yes	385 (363–404)	**0.37**	543 (533–568)	**0.684**	373 (349–393)	**0.652**	544 (517–573)	**0.911**
	No	378 (358–395)		545 (518–567)		376 (354–392)		543 (526–568)	
MMP2 ($pg{\cdot}ml^{-1}$)	Yes	4.56 (4.31–4.97)	**0.161**	9.58 (8.32–9.84)	**0.044**	4.36 (4.18–4.92)	**0.665**	8.82 (7.99–9.50)	**0.711**
	No	4.51 (4.23–4.81)		8.75 (7.82–9.76)		4.48 (4.20–4.86)		8.69 (7.77–9.78)	
MMP9 ($pg{\cdot}ml^{-1}$)	Yes	3.06 (2.74–3.59)	0.002	9.12 (7.14–9.99)	0.154	3.70 (3.3–4.08)	0.444	9.28 (7.87–9.91)	**0.11**
	No	3.63 (3.1–4)		8.10 (7.07–9.68)		3.65 (3.11–3.99)		8.26 (7.06–9.88)	
IL-6/IL-10	Yes	0.157 (0.15–0.17)	**0.032**	0.190 (0.17–0.207)	**0.001**	0.156 (0.14–0.17)	**0.945**	0.183 (0.17–0.21)	**0.085**
	No	0.15 (0.14–0.17)		0.168 (0.16–0.19)		0.153 (0.14–0.17)		0.172 (0.15–0.19)	
IL-8/IL-10	Yes	0.064 (0.06–0.07)	**0.931**	0.065 (0.06–0.07)	**0.021**	0.065 (0.06–0.071)	**0.484**	1.223 (0.64–1.48)	**0.073**
	No	0.065 (0.06–0.07)		0.068 (0.06–0.07)		0.068 (0.06–0.074)		0.752 (0.56–1.4)	

OLV one-lung ventilation, *PPC* postoperative pulmonary complications, *IL* interleukin, *TNF* tumor necrosis factor, *MCP* monocyte chemoattractant protein

Table 4 Cytokines obtained from blood samples during and after surgery

	PPC	BASELINE		OLV-30		OLV-END		PO 6 h	
		Median (IQR)	P value	Median (IQR)	P value	Median (IQR)	P value	Median (IQR)	P value
TNF-α ($pg{\cdot}ml^{-1}$)	Yes	6.86 (6.3–7.3)	0.352	8.78 (8.2–9.4)	0.147	10 (8.4–11.4)	0.039	10.41 (8–11.5)	0.196
	No	6.96 (6.4–7.5)		8.5 (7.6–9.1)		9.04 (7.9–10.7)		8.7 (7.5–11.5)	
IL-1 ($pg{\cdot}ml^{-1}$)	Yes	26.5 (24.2–31.4)	0.398	33.6 (28.7–35.4)	0.39	32.4 (28.1–36.8)	0.349	41.5 (26.5–46.8)	0.059
	No	27.8 (24.9–31.7)		30.6 (28.5–34.2)		31.2 (28–35.8)		30 (24.4–44.8)	
IL-2 ($pg{\cdot}ml^{-1}$)	Yes	0.853 (0.82–0.89)	0.622	1.34 (1.17–1.54)	0.421	1.37 (0.87–1.54)	0.249	1.34 (0.98–1.46)	0.007
	No	0.857 (0.8–0.9)		1.2 (1.16–1.54)		0.996 (0.88–1.52)		0.979 (0.91–1.37)	
IL-4 ($pg{\cdot}ml^{-1}$)	Yes	0.35 (0.31–0.38)	0.075	0.345 (0.32–0.37)	0.554	0.346 (0.32–0.38)	0.774	0.367 (0.35–0.4)	0.661
	No	0.333 (0.3–0.36)		0.341 (0.31–0.37)		0.347 (0.31–0.38)		0.37 (0.34–0.4)	
IL-6 ($pg{\cdot}ml^{-1}$)	Yes	3.09 (2.87–3.21)	0.067	3.75 (3.02–4.01)	0.922	4.09 (3.55–5.06)	0.651	4.88 (3.19–5.14)	0.006
	No	2.96 (2.83–3.11)		3.65 (3.27–4)		3.92 (3.55–5.07)		3.47 (2.96–4.9)	
IL-7 ($pg{\cdot}ml^{-1}$)	Yes	2.93 (2.59–3.3)	0.057	3.12 (2.84–3.56)	0.087	6.13 (4.81–7.19)	0.038	7.05 (4.28–8)	0.007
	No	2.73 (2.41–3.06)		3.01 (2.71–3.25)		5.04 (4.13–6.85)		4.22 (3.92–7.2)	
IL-8 ($pg{\cdot}ml^{-1}$)	Yes	0.96 (0.78–1.26)	0.452	2.73 (1.93–3.54)	0.069	42.7 (26.5–56.5)	0.009	22.4 (9.2–29.6)	< 0.001
	No	0.93 (0.68–1.13)		2.95 (2.51–3.35)		29.3 (22.9–43.4)		9.56 (6.87–21.5)	
IL-10 ($pg{\cdot}ml^{-1}$)	Yes	0.084 (0.08–0.09)	0.294	0.092 (0.08–0.11)	0.156	0.092 (0.09–0.1)	0.365	0.092 (0.09–0.1)	0.705
	No	0.087 (0.08–0.09)		0.098 (0.09–0.12)		0.097 (0.09–0.11)		0.091 (0.08–0.1)	
MMP2 ($pg{\cdot}ml^{-1}$)	Yes	223 (192–241)	0.827	356 (341–387)	0.012	510 (423–531)	0.007	576 (418–634)	0.032
	No	219 (193–251)		342 (310–365)		416 (375–524)		415 (374–619)	
IL-8/IL-10	Yes	11.5 (8.7–14.6)	0.279	27.8 (22.7–34.4)	0.435	476 (271–634)	0.01	241 (120–321)	< 0.001
	No	10.4 (8.2–14)		29.8 (22.7–36.4)		322 (209–473)		110 (75–233)	
IL-6/IL-10	Yes	35.7 (31.5–41.2)	0.249	40.2 (29.6–47.8)	0.461	46.5 (33.7–56.4)	0.504	49.5 (41.7–59.6)	0.005
	No	34.1 (30.3–39.1)		35.1 (29.2–46.5)		41.7 (33.5–55.5)		42.8 (31.7–53.8)	
MCP1 ($pg{\cdot}ml^{-1}$)	Yes	220 (184–274)	0.039	248 (221–284)	0.192	359 (318–384)	0.878	355 (327–386)	0.672
	No	244 (218–271)		260 (232–293)		350 (321–378)		361 (338–386)	

Data are expressed as median (interquartile 25–75)

OLV one-lung ventilation, *OLV 30* OLV 30 min after starting OLV, *End OLV* OLV when surgery complete but prior to tracheal extubation, *PO* postoperative, *IL* interleukin, *TNF* tumor necrosis factor; *MCP* monocyte chemoattractant protein

3.2 Lung inflammatory markers (Table 3)

In samples taken at the beginning of surgery, before OLV was started, expression of cytokines in BAL fluid from both lungs was similar in patients who experienced PPCs and those who did not. However, the same comparisons yielded different data when they were made at the end of surgery, since patients who developed PPCs had higher levels of pro-inflammatory cytokines in the operated lung than those of the non-PPC group, whereas in the dependent lung, the difference was only significantly greater for IL-2 levels.

3.3 Systemic inflammatory markers (Table 4)

Levels of all proinflammatory cytokines increased from the beginning of surgery until the last determination. Expression of cytokines after induction of anaesthesia and at 30 min after initiation of OLV was greater in the PPC group than in the other group. Proinflammatory cytokines analysed were significantly greater in some of the readings taken after surgery in the PPC group than in the non-PPC group. In contrast, expression of IL-10 did not differ significantly at any of the time points analysed.

3.4 Factors predicting respiratory complications

The multivariate logistic regression model included only clinical variables as independent variables (Model 1), namely anaesthesia group, age, FEV_1, and duration of surgery. The AUROC of the model for prediction of PPCs was 0.79 (95% CI 0.71–0.87).

We then ran a second multivariate logistic regression model, which included only values for cytokines analysed in blood and BAL during surgery and immediately after surgery (6 h) (Model 2). A stepwise approach revealed the variables to be IL-12 and IL-6 in BAL fluid from the non-dependent lung and MMP-9 from the same lung measured at initiation of OLV and the IL-8/IL-10 ratio measured in plasma at 6 h after surgery. The AU-ROC curve of this

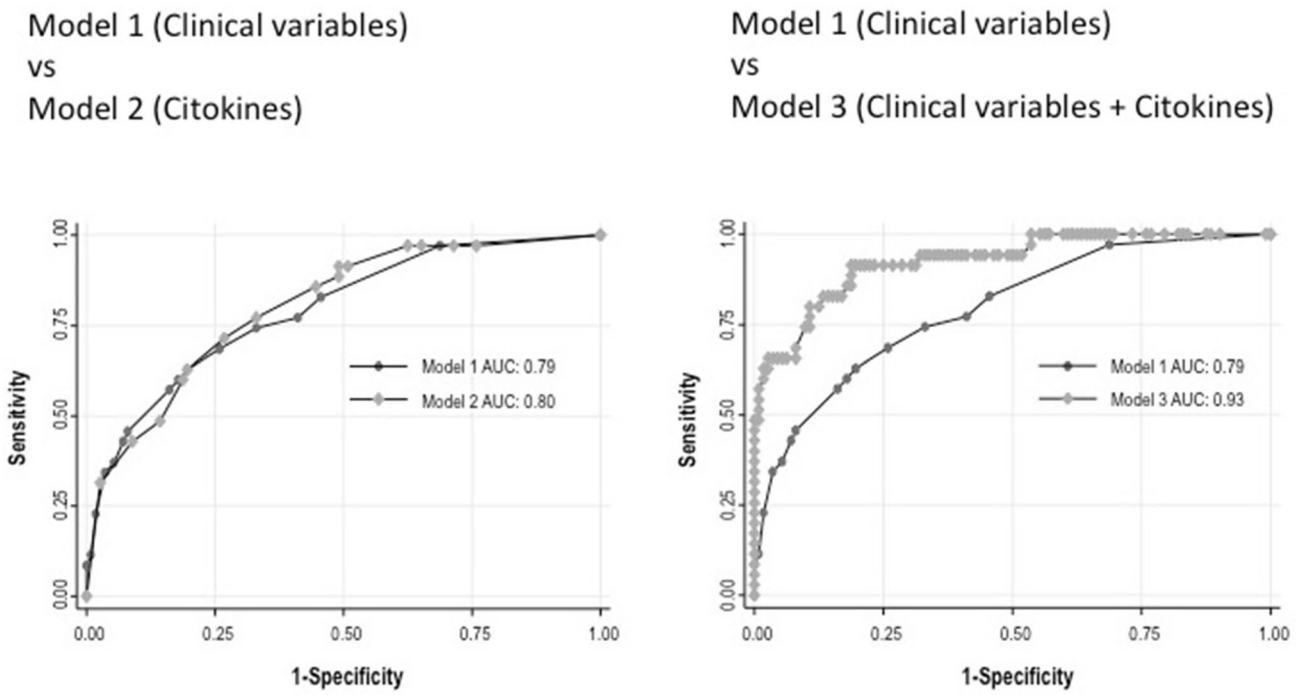

Fig. 1 Comparison of logistic regression models 1 versus 2 and 1 versus 3. *Model 1* only usual clinical variables, *Model 2* only inflammatory biomarkers, *Model 3* clinical and inflammatory biomarkers, *AUC* Area under ROC curve

Table 5 Area under the receiver operating characteristic curve

	AUROC (CI 95%)	p
Age	0.65 (0.545–0.754)	0.005
Length OLV	0.631 (0.529–0.733)	0.015
FEV_1 pre	0.732 (0.636–0.827)	< 0.001
Sevoflurane	0.608 (0.507–0.709)	0.044
IL-2 BS PO	0.648 (0.549–0.746)	0.007
IL-6 BS PO	0.650 (0.550–0.749)	0.006
IL-8 BS PO	0.704 (0.612–0.797)	< 0.001
IL-8/IL-10 BS PO	0.705 (0.613–0.797)	< 0.001
MMP3 BAL NDL BAS	0.668 (0.568–0.769)	0.002
IL-6/IL-10 BAL NDL END	0.676 (0.582–0.770)	0.001
IL-12 BAL NDL END	0.657 (0.549–0.764)	0.004
IL-7 BAL NDL END	0.652 (0.543–0.761)	0.005
IL-2 BAL DL END	0.637 (0.527–0.746)	0.011
IL-10 BAL NDL END	0.364 (0.271–0.458)	0.013
IL-6 BAL NDL END	0.635 (0.527–0.742)	0.013

AUROC area under the receiver operating characteristic curve, *OLV* one-lung ventilation, *FEV1 pre* forced expired volume in the first second predicted, *BS* blood samples, *BAL* bronchoalveolar lavage, *PO* postoperative, *DL* dependent lung, *NDL* nondependent lung, *BAS* baseline, *END* at the end of OLV

Table 6 Postoperative data

	PPC No	PPC Yes	p
Length of stay (days)	6 (5–8)	9 (6–18)	< 0.001
ICU stay (hours)	19 (16–21)	21 (18.5–30.5)	0.001
AKIN (%)	6 (4.3%)	6 (16.2%)	0.012
PCC (%)	8 (6.2%)	7 (18.9%)	0.012
Readmission to ICU (%)	6 (4.4%)	10 (27%)	< 0.001
Reintubation	0 (0)	4 (10.8%)	0.001
Mortality first month (%)	0 (0)	3 (8.1%)	0.001
Mortality first year (%)	6 (4.3%)	7 (18.9%)	0.003
$PaO2/FiO_2$ 6 h PO	344 (290–425)	285 (260–367)	0.007
$PaO2/FiO_2$ 18 h PO	391 (333–465)	302 (260–368)	< 0.001
Prolonged air leak (%)	14 (10.2%)	10 (27%)	0.009
Clavien-Dindo classification (0/1/2/3/4)	92/4/36/3/2	0/0/20/8/9	< 0.001

Data expressed as median (interquartile range) or number of patients and percentage

PPC postoperative pulmonary complications; *ICU* intensive care unit, *AKIN* acute kidney injury network, *PCC* postoperative cardiac complications

model was 0.80 (95% CI 0.72–0.88). The result of the comparison of the ROC curves between Models 1 and 2 was not statistically significant (p = 0.79).

We also ran a third multivariate logistic regression model by adding the cytokines analysed to the clinical variables (Model 3). The cytokine-related factors with the best predictive ability in this model were the IL-8/IL-10 ratio in blood at 6 h after surgery and IL-12 measured in the non-dependent lung at the end of OLV. The AUROC for Model 3 was 0.93 (95% CI 0.88–0.97), and the result of the comparison with Model 1 was significantly higher (p < 0.001). This model had an integrated discrimination improvement of 0.29 (p < 0.001) and a net reclassification index of 0.28 (p = 0.007). In other words, the net improvement in the classification of PPC events from Model 3 with respect to Model 1 was 28% (Fig. 1).

Table 5 shows the AUROC values for the 4 variables selected from the clinical parameters analysed, the 4 inflammatory biomarkers obtained from blood, and the 4 mediators obtained from the BAL fluid samples for which the highest AUROC values were detected. After the cross-validation process, the areas under the ROC curve were smaller, but the model 3 was still superior to previous models. The AUROC for Models 1, 2, and 3 was 0.75 (95% CI 0.66–0.85), 0.73 (95% CI 0.64–0.82), and 0.87 (95% CI 0.81–0.93), respectively.

3.5 Postoperative complications

Patients in the PPC group had lower PaO_2/FiO_2 values than the non-PPC patients, both at 6 h and at 18 h after the intervention. Furthermore, these patients showed a significant increase with respect to patients from the non-PPC group in the incidence of other postsurgical complications, hospital stay, duration of stay in the ICU, and mortality at 1 month and 1 year after surgery (Table 6).

4 Discussion

The most important finding in our study was that the determination of cytokines combined with classic clinical variables considerably facilitates prediction of PPCs after LRS. Furthermore, a predictive model based only on inflammatory mediators has a predictive power similar to that of the clinical variables analysed separately. These findings confirm the strong association between inflammation and the pathogenesis of PPCs after LRS.

The development of probability models that are able to predict PPCs early after LRS and with a high predictive capacity is of major importance, given that they facilitate application of preventive strategies immediately after surgery and before clinical signs of complications appear. Consequently, we can slow down or attenuate the development of disease and eventually reduce the impact of PPCs on clinical course. Such models will also enable us to improve upon those used to date to decrease the frequency of PPCs (prolongation of ICU stay, prophylaxis with CPAP, intensification of chest physiotherapy, and even antibiotic therapy). In contrast, hospital resources could be saved in patients who do not present clinical or laboratory risk factors (1).

Therefore, many studies have run logistic regression models in an attempt to identify factors that could prove more able to predict postsurgical findings. As in most other similar studies, we found that specific perioperative characteristics—age, FEV_1, duration of surgery—were relevant for prediction of PPCs [2, 6, 10, 21]. However, a series of issues must be addressed. First, to our knowledge, none of the previous studies have introduced type of anesthesia (inhalatory versus intravenous) as a variable. Our logistic regression model showed that the type of anaesthesia used was more closely associated with the development of complications than other variables in the model that only included peri- and preoperative data [OR, 2.94 (95% CI 1.23–7.04)]. According to a recent meta-analysis by Sun et al. [22], the close association between the anaesthetic drug used and onset of PPCs could be explained by the attenuation of the intraoperative pulmonary inflammatory response associated with the use of inhaled anaesthetic in LRS. Another relevant finding of our study was that patients who developed PPC had lower $PaCO_2$ and CO_2 Gradient, despite use the same tidal volume/kg/ ideal weight in both groups. We think that greater dead space related with previous pulmonary illness could be the cause of these differences.

4.1 Cytokines

Surgery leads to marked suppression of cellular immunity, which is in turn associated with increased susceptibility to PPCs, especially infection [23]. The lung is considered one of the main organs in the exaggerated inflammatory response. The proinflammatory cytokines IL-1, IL-6, IL-8, and TNF are early mediators in the host response, and, in situations of a heightened inflammatory response, neutrophils are sequestered in the alveoli [10, 24]. The end consequences of increased cytokine levels after trauma/surgery are associated with more frequent lung infections [25], lung injury [26], and postoperative morbidity and mortality [27]. The relevance of some cytokines in the development of PPCs after LRS has been reinforced by the fact that the expression of specific genes that code for cytokine production, especially that of IL-6 and TNF-alfa, leave the patient more susceptible to PPCs [28, 29].

Determination of cytokine levels in BAL is a key method for detection of changes in the alveoli of patients

undergoing mechanical ventilation and for better understanding of the pathogenic mechanisms most frequently associated with the postoperative lung injury that is often observed after LRS. Previous studies—albeit with small sample sizes—in patients undergoing thoracic surgery (oesophagectomy or LRS) found that a more pronounced pulmonary inflammatory response (based on BAL cytokine levels) was associated with PPCs [30–32]. We found that expression of proinflammatory mediators in BAL was more pronounced immediately after OLV-related lung injury, especially in the nondependent lung of patients who developed PPCs. We also observed that measurement of this initial inflammatory response was highly predictive of PPCs. In addition, we verified that predictive ability was greater in BAL samples from the collapsed lung than in the dependent lung. We believe that this was mainly due to the ischemia/reperfusion (I/R) injury that ensues after the collapse and subsequent re-expansion of the lung and that interleukins play a major role in this process. Alveolar macrophages and the release of a potent chemoattractant, such as IL-8, have been linked to lung damage, especially due to I/R phenomena. Initially it was found that the increase in IL-8 after collapse and lung reexpansion was related to the appearance of severe pulmonary edema [33]. Subsequently, two classic studies that analyzed early graft function after lung transplantation showed the role of this cytokine measured in BAL on postoperative lung damage [34, 35]. More recently, Jones et al. showed that an increase in the release of pro and anti-inflammatory cytokines from monocytes was associated with the appearance of postoperative pneumonia [32]. Furthermore, prevention of complete lung collapse using CPAP in the operated lung has been shown to attenuate the expression of proinflammatory mediators, reinforcing the relevance of I/R during OLV [36]. By the other hand, we cannot rule out the impact on inflammatory response in non-dependent lung injury produced by surgical manipulation of the parenchyma [37]. I/R injury is characterized biochemically by the generation of reactive oxygen species resulting from intense oxidative stress. This injury manifests as massive infiltration by neutrophils, in which alveolar cytokines play a major role [34]. Overproduction of reactive oxygen species is observed in patients with ventilation-related pneumonia and generates more pronounced oxidative stress than patients who do not become infected [38]. Our group previously reported preliminary results of the first 40 patients anaesthetized with sevoflurane, and although we verified the association between cytokine expression and development of PPC [39], we found no differences when we compared the inflammatory response in each lung of patients who had developed PPCs. The results of the present study indicate that one of the main reasons for the lower rate of PPCs was the clearly superior protective effect of sevoflurane on pulmonary I/R mechanisms compared with that of propofol [40].

Mediators other than cytokines can play a role in lung injury. Matrix metalloproteinases (MMPs) can degrade components of the extracellular matrix, including the basement membrane of the alveolar epithelium and endothelial cells, and have been associated with the pathogenesis of acute lung injury and acute respiratory distress syndrome [41]. Increased MMP-2 levels in BAL fluid have been reported to be a marker of lung injury, and there is thought to be an association between production of reactive oxygen species and increased MMP-2 [41]. Furthermore, given that MMPs participate in cell repair processes during lung injury, in many cases, it is unknown whether the presence of MMPs is beneficial or destructive [42]. As in other studies, we verified the protective role of MMP-9 against lung injury, since expression of this MMP in the nondependent lung was poorer in patients with PPCs before OLV. This could have facilitated the cell repair process and thus protected patients in the present study against PPCs [42].

However, analysis of the balance between the proinflammatory state and the anti-inflammatory state could be even more important than monitoring proinflammatory cytokine levels in plasma or in BAL fluid [43]. A balance between both states has been thought to improve postoperative prognosis [44, 45]. We observed that an increase in the inflammatory response with respect to the anti-inflammatory response (IL8/IL10 or IL6/IL10 ratio) is highly predictive of the onset of PPCs.

Measurement of inflammatory cytokines enables us to better predict the onset of PPC. Furthermore, given the window period between the tests and the clinical manifestation of PPCs, we could implement measures aimed at attenuating them or at reducing their incidence, for example, early antibiotic therapy, chest physiotherapy, or even longer stays in specialized postsurgical care units where patients can be more closely monitored or care can be intensified after surgery.

The risk/benefit ratio of taking bronchoalveolar lavage samples has not bees studied during LRS, since most of the information that exists about this technique comes from patients admitted to ICUs (with suspected pulmonary infection) or patients for diagnostic procedures performed under sedation and without intubation. It has been describe several complications (hemodynamic or respiratory) related with BAL. In our study we didn´t observed any inmmediate complication during the technique. However, we can not rule out that some of the infectious pulmonary complications that appeared in the postoperative period could have been facilitated by bronchoalveolar lavage. Previously, some rare cases of respiratory infection have been

described after performing a bronchoscopy with biopsy or brush pulmonary [46]. A 25% incidence of fever after bronchoscopy has been described, but it has been mainly related to an inflammatory etiology [47], and the use of prophylactic antibiotics is not currently accepted for the performance of bronchoscopy. By the other side, PPCs are recognized as a large healthcare burden, and it is considered that strategies that allow early recognition of high-risk patients can provide important savings in healthcare resources [1]. With the taking of BAL samples, the greatest cost comes from the measurement of inflammatory markers since the use of bronchoscopy today is widespread during LRS.

4.2 Limitations

Although our study is part of a randomized controlled trial, the predictive models were retrospective. The use of cytokine-based predictive models should take into account the curves of expression over time for each cytokine, and biomarkers that respond more quickly to surgical insult should be used.

A key limitation of the study is the fact that cytokine levels in BAL fluid were only measured during surgery: we would probably have obtained more information if we had continued to collect samples after surgery, although such an approach is not recommended in this clinical scenario.

Also, we do not know if the results would have been the same if we had used a ventilatory strategy with lower Vt and inidividualizing PEEP levels during OLV or if we had included patients with severe COPD.

In conclusion, combining systemic and pulmonary biomarkers with clinical variables increases the ability of models based only on clinical data to identify PPC early and could prove useful when deciding which hospital resources will be used after LRS. The optimal biomarkers are those associated with the balance between inflammatory and anti-inflammatory mediators, thus confirming the importance of these pathways in the pathogenesis of PPC.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix 1: Clinical preoperative and intraoperative variables recorded

Preoperative

Age; height, weight, body mass index, ASA classification, arterial blood gases, haemoglobin, forced vital capacity predicted; Forced expiratory volume in the first second predicted; Diffusing capacity of lung for carbon monoxide; comorbidity, and preoperative pharmacological treatment.

Intraoperative

Kind of surgery: (Pneumonectomy; Lobectomy; Segmentectomy). Side of surgery.

Length surgery, length one-lung ventilation.

Anaesthetic used to maintain hypnosis: propofol or sevoflurane.

Amount of crystalloids and colloids administered.

Three moments (Previous to one-lung ventilation, 30 min after start one-lung ventilation, and during re-establishment of two lung ventilation).

- Respiratory rate, peak airway pressure, plateau airway pressure, mean airway pressure, positive end expiratory pressure, lung dynamic compliance, and the driving pressure. Fraction inspired oxygen, Saturation peripheral arterial oxygen, end tidal CO2
- Amount of crystalloids and colloids infused
- Blood samples: Arterial blood gases (PaO2, PaCO2, pH). Inflammatory biomarkers IL-1, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, MPP-2, TNF-α, and monocyte chemoattractant protein. Ratios IL-8/IL-10 and IL-6/IL-10

Two moments (Previous to one-lung ventilation, and during re-establishment of two lung ventilation).

- Bilateral bronchoalveolar samples: IL-1, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL12, TNF-α, monocyte chemoattractant protein, MMP-2, and MMP-9. Ratios IL-8/IL-10 and IL-6/IL-10

Appendix 2

See Table 7.

Table 7 Definition of postoperative pulmonary complications

Pulmonary complication	Definition
Respiratory infection	When a patient received antibiotics for a suspected respiratory infection and met at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever, leukocyte count > 12,000/μ
Respiratory failure	When postoperative PaO_2 < 60 mmHg on room air, a ratio PaO_2 to inspired oxygen fraction < 300 or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy
Pleural effusion	Chest X-ray demonstrating blunting of the costophrenic angle, lost of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity on one hemithorax with preserve vascular shadows
Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent nonatelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleural
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents

References

1. Sabaté S, Mazo V, Canet J. Predicting postoperative pulmonary complications: implications for outcomes and costs. Curr Opin Anaesthesiol. 2014;27:201–9.
2. Agostini P, Cieslik H, Rathinam S, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? Thorax. 2010;65:815–8.
3. Baudouin S. Lung injury after thoracotomy. Br J Anaesth. 2003;91:132–42.
4. Taylor A, DeBoard Z, Gauvin JM. Prevention of postoperative pulmonary complications. Surg Clin North Am. 2015;95:237–54.
5. Smetana GW. Strategies to reduce postoperative pulmonary complications in adults. King TE, Aronson MD, Hines R, ed. UpToDate. Waltham, MA, 2018.
6. Yepes-Temiño MJ, Monedero P, Pérez-Valdivieso JR. Grupo Español de Anestesia Toracica. Risk prediction model for respiratory complications after lung resection: an observational multicentre study. Eur J Anaesthesiol. 2016;33:326–33.
7. Li Y, Ma YL, Gao YY, Wang DD, Chen Q. Analysis of the risk factors of postoperative cardiopulmonary complications and ability to predicate the risk in patients after lung cancer surgery. J Thorac Dis. 2017;9:1565–73.
8. Lohser J, Slinger P. Lung injury after one-lung ventilation: a review of the pathophysiologic mechanisms affecting the ventilated and the collapsed lung. Anesth Analg. 2015;121:302–18.
9. D'Journo XB, Michelet P, Marin V, et al. An early inflammatory response to oesophagectomy predicts the occurrence of pulmonary complications. Eur J Cardiothorac Surg. 2010;37:1144–51.
10. Miskovic A, Lumb AB. Postoperative pulmonary complications. Br J Anaesth. 2017;118:317–34.
11. Misthos P, Katsaragakis S, Theodorou D, Milingos N, Skottis I. The degree of oxidative stress is associated with major adverse effects after lung resection: a prospective study. Eur J Cardiothorac Surg. 2006;29:591–5.
12. de la Gala F, Piñeiro; P, Reyes A, Vara E, Olmedilla L, Cruz P. I. Garutti. Postoperative pulmonary complications, pulmonary and systemic inflammatory responses after lung resection surgery with prolonged one-lung ventilation. Randomized controlled trial comparing intravenous and inhalational anaesthesia. Br J Anaesth. 2017;119:655–63.
13. Sander M, Irwin M, Sinha P, Naumann E, Kox WJ, Spies CD. Suppression of interleukin-6 to interleukin-10 ratio in chronic alcoholics: association with postoperative infections. Intensive Care Med. 2002;28:285–92.
14. Sun J, Su J, Xie Y, Yin MT, Huang Y, Xu L, Zhou Q, Zhu B. Plasma IL-6/IL-10 Ratio and IL-8, LDH, and HBDH level predict the severity and the risk of death in AIDS patients with pneumocystis pneumonia. J Immunol Res. 2016. https://doi.org/10.1155/2016/1583951.
15. Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13.
17. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3:32–5.
18. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology. 1983;148:839–43.
19. Pencina MJ, D' Agostino RB, Sr D' Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27:157–72.
20. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna 2016. https://www.R-project.org/.
21. Stéphan F, Boucheseiche S, Hollande J, Flahault A, Cheffi A, Bazelly B, Bonnet F. Pulmonary complications following lung resection* a comprehensive analysis of incidence and possible risk factors. Chest. 2000;118:1263–70.
22. Sun B, Wang J, Bo L, et al. Effects of volatile vs. propofol-based intravenous anesthetics on the alveolar inflammatory responses to one-lung ventilation: a meta-analysis of randomized controlled trials. J Anesth. 2015;29:570–9.
23. Angele MK, Faist E. Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. Crit Care. 2002;6:298–305.
24. Lee WL, Downey GP. Neutrophil activation and acute lung injury. Curr Opin Crit Care. 2001;7:1–7.
25. Von Dossow V, Rotard K, Redlich U, Hein OV, Spies CD. Circulating immune parameters predicting the progression from hospital-acquired pneumonia to septic shock in surgical patients. Crit Care. 2005;9:R662-9.
26. Donnelly TJ, Meade P, Jagels M, et al. Cytokine, complement, and endotoxin profiles associated with the development of the adult respiratory distress syndrome after severe injury. Crit Care Med. 1994;22:768–76.

27. Parsons PE, Eisner MD, Thompson BT, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med. 2005;33:1–6.
28. Shaw AD, Vaporciyan AA, Wu X, et al. Inflammatory gene polymorphisms influence risk of postoperative morbidity after lung resection. Ann Thorac Surg. 2005;79:1704–10.
29. Hildebrandt MA, Roth JA, Vaporciyan AA, Pu X, Ye Y, Correa AM, Kim JY, Swisher SG, Wu X. Genetic variation in the TNF/TRAF2/ASK1/p38 kinase signaling pathway as markers for postoperative pulmonary complications in lung cancer patients. Sci Rep. 2015;13:5:12068.
30. Kooguchi K, Kobayashi A, Kitamura Y, et al. Elevated expression of inducible nitric oxide synthase and inflammatory cytokines in the alveolar macrophages after esophagectomy. Crit Care Med. 2002;30:71–6.
31. Tsukada K, Hasegawa T, Miyazaki T, et al. Predictive value of interleukin-8 and granulocyte elastase in pulmonary complication after esophagectomy. Am J Surg. 2001;181:167–71.
32. Jones RO, Brittan M, Anderson NH, et al. Serial characterisation of monocyte and neutrophil function after lung resection. BMJ Open Respir Res. 2014;16:1:e000045.
33. Nakamura H, Ishizaka A, Sawafuji M, et al. Elevated levels of interleukin-8 and leukotrien B4 in pulmonary edema fluid of a patient with reexpansion pulmonary edema. Am J Respir Crit Care Med. 1994;149:1037–40.
34. De Perrot M, Sekine Y, Fischer S, et al. Interleukin-8 release during ischemia-reperfusion correlates with early graft function in human lung transplantation. J Heart Lung Transplant. 2001;20:175–6.
35. Fisher AJ, Donnelly SC, Hirani N, et al. Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation. Am J Respir Crit Care Med. 2001;163:259–65.
36. Verhage RJ, Boone J, Rijkers GT, et al. Reduced local immune response with continuous positive airway pressure during one-lung ventilation for oesophagectomy. Br J Anaesth. 2014;112:920–8.
37. Sánchez-Pedrosa G, Vara Ameigeiras E, Casanova Barea J, Rancan L, Simón Adiego CM. Garutti Martínez I. Role of surgical manipulation in lung inflammatory response in a model of lung resection surgery. Interact Cardiovasc Thorac Surg. 2018. https://doi.org/10.1093/icvts/ivy198.
38. Duflo F, Debon R, Goudable J, Chassard D, Allaouchiche B. Alveolar and serum oxidative stress in ventilator-associated pneumonia. Br J Anaesth. 2002;89:231–6.
39. de la Gala F, Piñeiro P, Garutti I, et al. Systemic and alveolar inflammatory response in the dependent and nondependent lung in patients undergoing lung resection surgery: a prospective observational study. Eur J Anaesthesiol. 2015;32:872–80.
40. Casanova J, Garutti I, Simon C, et al. The effects of anesthetic preconditioning with sevoflurane in an experimental lung autotransplant model in pigs. Anesth Analg. 2011;113:742–8.
41. Fligiel SE, Standiford T, Fligiel HM, et al. Matrix metalloproteinases and matrix metalloproteinase inhibitors in acute lung injury. Hum Pathol. 2006;37:422–30.
42. Greenlee KJ, Werb Z, Kheradmand F. Matrix metalloproteinases in lung: multiple, multifarious, and multifaceted. Physiol Rev. 2007;87:69–98.
43. Martin TR. Cytokines and the acute respiratory distress syndrome (ARDS): a question of balance. Nat Med. 1997;3:272–3.
44. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis. 2013;13:260–8.
45. Dimopoulou I, Armaganidis A, Douka E, et al. Tumour necrosis factor-alpha (TNFα) and interleukin-10 are crucial mediators in post-operative systemic inflammatory response and determine the occurrence of complications after major abdominal surgery. Cytokine. 2007;37:55–61.
46. Aelony Y, Finegold S. Serious infectious complications after flexible fibreoptic bronchoscopy. West J Med. 1979;131:327–33.
47. Rubinstein-Aguñín. P Infectious complications following bronchoscopy: does sedation play a role? J Lung Pulm Respir Res. 2018;5(4):112–8.

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