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SCIENTIFIC ARTICLE

Predictive value of plasma cytokines for acute kidney injury following lung resection surgery: prospective observational study



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surgery;
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Abstract

Background and objectives: Patients undergoing lung resection surgery are at risk of developing postoperative acute kidney injury. Determination of cytokine levels allows the detection of an early inflammatory response. We investigated any temporal relationship among perioperative inflammatory status and development of acute kidney injury after lung resection surgery. Furthermore, we evaluated the impact of acute kidney injury on outcome and analyzed the feasibility of cytokines to predict acute kidney injury.

Methods: We prospectively analyzed 174 patients scheduled for elective lung resection surgery with intra-operative periods of one-lung ventilation periods. Fiberoptic broncho-alveolar lavage was performed in each lung before and after one-lung ventilation periods for cytokine analysis. As well, cytokine levels were measured from arterial blood samples at five time points. Acute kidney injury was diagnosed within 48 h of surgery based on acute kidney injury criteria. We analyzed the association between acute kidney injury and cardiopulmonary complications, length of intensive care unit and hospital stays, intensive care unit re-admission, and short-term and long-term mortality.

Results: The incidence of acute kidney injury in our study was 6.9% (12/174). Acute kidney injury patients showed higher plasma cytokine levels after surgery but differences in alveolar cytokines were not detected. Although no patient required renal replacement therapy, acute kidney injury patients had higher incidence of cardiopulmonary complications and increased overall mortality. Plasma interleukin-6 at 6 h was the most predictive cytokine of acute kidney injury (cut-off point at 4.89 pg.mL⁻¹).

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Conclusions: Increased postoperative plasma cytokine levels are associated with acute kidney injury after lung resection surgery in our study, which worsens the prognosis. Plasma interleukin-6 may be used as an early indicator for patients at risk of developing acute kidney injury after lung resection surgery.

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PALAVRAS-CHAVE

Lesão renal aguda;
Cirurgia de ressecção pulmonar;
Ventilação monopulmonar;
Inflamação;
Citocinas;
Interleucina-6

Valor preditivo das citocinas plasmáticas para lesão renal aguda após cirurgia de ressecção pulmonar: estudo observacional prospectivo

Resumo

Justificativa e objetivos: os pacientes submetidos à cirurgia de ressecção pulmonar apresentam risco de desenvolver lesão renal aguda pós-operatória. A determinação dos níveis de citocinas permite detectar uma resposta inflamatória precoce. Investigamos a relação temporal entre o estado inflamatório perioperatório e o desenvolvimento de lesão renal aguda após cirurgia de ressecção pulmonar. Além disso, avaliamos o impacto da lesão renal aguda no desfecho e analisamos a viabilidade das citocinas para prever este tipo de lesão.

Métodos: No total, foram analisados prospectivamente 174 pacientes agendados para cirurgia eletiva de ressecção pulmonar com períodos intraoperatórios de ventilação monopulmonar. Lavado bronco-alveolar com fibra óptica foi realizado em cada pulmão antes e após os períodos de ventilação monopulmonar para análise das citocinas. Os níveis de citocina foram medidos a partir de amostras de sangue arterial em cinco momentos. A lesão renal aguda foi diagnosticada dentro de 48 horas após a cirurgia, com base nos critérios para sua verificação. Analisamos a associação entre lesão renal aguda e complicações cardiopulmonares, tempo de internação em unidade de terapia intensiva e de internação hospitalar, reinternação em unidade de terapia intensiva e mortalidade a curto e longo prazos.

Resultados: A incidência de lesão renal aguda no estudo foi de 6,9% (12/174). Os pacientes com lesão renal aguda apresentaram níveis mais altos de citocinas plasmáticas após a cirurgia, mas não foram detectadas diferenças nas citocinas alveolares. Embora nenhum paciente tenha precisado de terapia renal substitutiva, os com lesão renal aguda apresentaram maior incidência de complicações cardiopulmonares e aumento da mortalidade geral. A interleucina-6 plasmática em 6 horas foi a citocina mais preditiva de lesão renal aguda (ponto de corte em $4,89 \text{ pg.mL}^{-1}$).

Conclusões: O aumento dos níveis plasmáticos de citocinas no pós-operatório está associado à lesão renal aguda após cirurgia de ressecção pulmonar no estudo, o que piora o prognóstico. A interleucina-6 plasmática pode ser usada como um indicador precoce para pacientes com risco de desenvolver lesão renal aguda após cirurgia de ressecção pulmonar.

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Introduction

Postoperative acute kidney injury (AKI) is a severe complication after major surgical procedures with a high impact on morbidity and mortality. It may occur after non-cardiac thoracic surgery with incidence rates of 5%–7%^{1–3} after Lung Resection Surgery (LRS).

In the field of thoracic surgery, several conditions have been proposed as predisposing factors for the appearance of AKI such as hypertension, preoperative use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, an impaired preoperative renal function and open procedures.^{2,3} In the same way, the inflammatory response following a thoracic surgery could be considered as another trigger for the development of postoperative AKI.⁴

Traditionally, AKI has been recognized as renal function deterioration owing to a structural damage and is typically diagnosed through serum creatinine changes and reduced urinary output. However, considering that AKI is also an inflammatory process, determination of the proteins involved in its pathogenesis may provide unique tools for its assessment and prediction before considerable renal damage has been established. Interleukins (ILs) are inflammatory cytokines believed to exercise a fundamental role in the pathophysiology of AKI. Concretely, IL-6 has been suggested to simultaneously promote an injurious inflammatory response and protect kidneys from further injury,⁵ although elevated plasma IL-6 levels after major surgery are related to postoperative mortality.⁶

We carried out a prospective observational study of adult patients undergoing non-cardiac thoracic surgery to deter-

minate any temporal relationship among perioperative local and systemic inflammatory response with postoperative AKI. We hypothesized that patients with higher inflammatory status would have higher incidence of postoperative AKI. The main objective of our work was to evaluate the feasibility of alveolar and plasma ILs as predictive inflammatory biomarkers in the early diagnosis of AKI following LRS with the application of One-Lung Ventilation (OLV).

Methods

The present study was designed as a prospective, observational, single-center sub-study of a phase IV clinical trial – Study of pulmonary and systemic inflammatory response secondary to pulmonary resection surgery using intravenous anesthesia versus inhalational anesthesia with halogenated agents⁷ (EudraCT 2011-002294-29 at www.clinicaltrialsregister.eu and NCT 02168751 at www.clinicaltrials.gov), which was approved by the Clinical Investigation Ethics Committee (Chairman Dr. Díaz Otero, dated August 1st, 2011, code FIBHGM-ECNC003-2011, Madrid, Spain) and was carried out in accordance with the Declaration of Helsinki principles. Eligible participants signed an informed consent.

Patient population

The study population included patients of either gender and older than 18 years who were scheduled for elective LRS. We excluded from the study any patient with at least one of the following criteria: forced expiratory volume in the first second $\leq 50\%$ or forced vital capacity $\leq 50\%$ of the predicted values, treatment with corticosteroids or immunosuppressive agents during the previous 3 months, blood transfusion during the previous 10 days, heart failure (New York Heart Association functional status III–IV) during the previous week, inability to perform a lung protective ventilation strategy, pregnancy and breastfeeding.

Participants were consecutively recruited and randomly allocated into two groups depending on the drug used during the intraoperative period (propofol vs. sevoflurane). There were no differences between groups in perioperative management.

Intervention

Anesthesia was induced with fentanyl $3 \mu\text{g}\cdot\text{kg}^{-1}$, propofol $2\text{--}3 \text{ mg}\cdot\text{kg}^{-1}$ and rocuronium $0.6\text{--}1 \text{ mg}\cdot\text{kg}^{-1}$. Orotracheal intubation was performed with a double-lumen tube (35–37 Fr for women and 39–41 Fr for men) and tube placement was verified by fiber-bronchoscopy. Endobronchial blockers were never used. Anesthesia was maintained with propofol or sevoflurane to have a bispectral index value at 40–60. Analgesia was administered through a paravertebral catheter placed in the corresponding surgical hemithorax at a Dorsal (D) D5–D6 level, through which 0.5% bupivacaine was given at an initial bolus dose of $0.15 \text{ mL}\cdot\text{kg}^{-1}$ followed by a continuous infusion rate of $6\text{--}10 \text{ mL}\cdot\text{h}^{-1}$.

Patients were managed with volume-controlled ventilation by means of a Primus ventilator (Drägerwerk, AG&Co. KGaA, Lübeck, Germany). The respiratory parameters used during Two-Lung Ventilation (TLV) were as follows: Tidal Vol-

ume (TV) $8 \text{ mL}\cdot\text{kg}^{-1}$ of Ideal Body Weight (IBW), Positive End-Expiratory Pressure (PEEP) $5 \text{ cm H}_2\text{O}$, Fractional inspired oxygen (FiO_2) 0.4–0.5 and Respiratory Rate (RR) to get an end-tidal carbon dioxide (etCO_2) pressure at 30–35 mmHg. During OLV, the next adjustments took place: TV $6 \text{ mL}\cdot\text{kg}^{-1}$ of IBW, PEEP $5 \text{ cm H}_2\text{O}$, FiO_2 0.6–1 to get peripheral oxygen saturation (SpO_2) $>90\%$ and RR to allow permissive hypercapnia. To deal with hypoxemia during OLV despite FiO_2 1, alveolar recruitment maneuvers and Continuous Positive Airway Pressure (CPAP) were applied to the non-dependent lung.

A radial artery catheter (FloTrac sensor, Edwards Lifesciences Corporation, Irvine, California, USA) was inserted to monitor hemodynamic data including Cardiac Output (CO), Cardiac Index (CI), Stroke Volume (SV), Stroke Volume Variation (SVV), Stroke Volume Index (SVI) and Invasive Arterial Pressure (IAP). A restrictive intravenous fluid therapy was established according to which fluid infusion rate was set at $2 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ with the objective to maintain urine output $\geq 0.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. If urine output diminished, a bolus dose of crystalloids 250 mL was administered.

The recorded intraoperative parameters included TV, RR, minute volume, FiO_2 , SpO_2 , etCO_2 , airway pressures (peak, plateau, mean, end-expiratory and driving pressures), lung dynamic compliance and hemodynamic parameters (CO, CI, SV, SVV, SVI and IAP), all of which were measured with the patient in the lateral decubitus' position at three time points: immediately before OLV establishment (baseline), 30 min after OLV initiation and immediately after TLV restoration.

Sample and measurement methods

Arterial blood samples were removed at five time points: immediately before OLV establishment (baseline), 30 min after OLV initiation, immediately after TLV restoration, 6 h after surgery and 18 h after surgery. Likewise, inflammatory biomarker levels were determined 5 min before OLV initiation and at TLV restoration from Bronchoalveolar Lavage (BAL) samples, which were taken from each lung using a 4.5 mm fiber-bronchoscope advanced into the left lower bronchus and to the right lower or middle bronchus until resistance was encountered. A first injection with 0.9% saline solution 25 mL was made and the supernatant was discarded, followed by a second injection with 0.9% saline solution 25 mL from which the suctioned fluid was analyzed.

The blood and the BAL samples were filtered with sterile gauze and centrifuged at 400 g for 15 min at 4°C . The supernatant was stored at -20°C until it was analyzed at a specialized laboratory. Apart from carbon monoxide (CO) which was analyzed by Omura and Sato method, the remaining biomarkers (IL-1, IL-2, IL-4, IL-6, IL-10), Tumor Necrosis Factor- α (TNF- α), Nitric Oxide (NO), Matrix Metalloproteinase-2 (MMP-2) and Monocyte Chemoattractant Protein-1 (MCP-1); were analyzed using Western Blot.

Postoperative data

AKI was diagnosed within 48 h of surgery based on the AKIN criteria⁸ as an increase of at least $0.3 \text{ mg}\cdot\text{dL}^{-1}$ creatinine and/or a decrease of urine output below $0.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ during more than 6 h.

We also reported the development of postoperative pulmonary complications such as atelectasias (collapse of pulmonary parenchyma on radiographs and/or need for CPAP or fiber-bronchoscopy), pneumonia (new consolidation in one or more lobes, hyperleukocytosis, temperature $>38^{\circ}\text{C}$, positive culture) and respiratory failure ($\text{PaO}_2 < 60$ mmHg in room air, $\text{PaO}_2/\text{FiO}_2 < 300$ or $\text{SpO}_2 < 90\%$ and requiring oxygen therapy), as well as the development of postoperative cardiac complications including myocardial infarct (CPK typical curve, $\text{CK-MB}/\text{CPK} \geq 6\%$ or troponin-I ≥ 1.5 ng.mL $^{-1}$ with at least one of the following criteria: chest pain, ST-segment elevation or depression, pathologic Q waves, coronary artery procedure), unstable arrhythmias (supraventricular and ventricular tachyarrhythmias with unstable hemodynamic tolerance that requires antiarrhythmic therapy and/or electrical cardioversion) and congestive heart failure (clinical, hemodynamic and radiologic evidence of pulmonary water overloading requiring diuretics, vasodilators or sympathomimetic support).

In addition, we recorded the length of Intensive Care Unit (ICU) and hospital stays, ICU re-admission, short-term mortality (at 30 days and at 6 months) and long-term mortality (at 1 year and at 3 years).

Subjects were followed up until hospital discharge and during the first three years after surgery.

Statistical analysis

Results are presented as absolute frequencies for categorical parameters. Continuous normally distributed data are expressed as mean and Standard Deviation (SD) while continuous non-normally distributed data are expressed as median and Interquartile Range (IR). Kolmogorov-Smirnov test was used to investigate the normality of data distribution.

Qualitative variables were analyzed with Chi-square test or Fisher's exact probability test if at least one cell had an expected count < 5 . Continuous data comparison was realized employing unpaired Student's *t*-test or Mann-Whitney *U*-test, as appropriate. We employed Pearson's *r*-correlation coefficient to study the lineal association degree between cytokine levels in blood and alveolar samples at TLV restoration.

Binary logistic regression models (Wald method), obtaining estimate-adjusted Odds Ratio (OR) and their 95% Confidence Intervals (95% CI), were used to establish the most significant determinants of postoperative AKI after LRS. In a first model, all demographic and surgical variables with significant differences between the AKI and non-AKI groups were considered as candidate variables for backward selection. A second logistic regression analysis was carried out to determine the most predictive cytokines of postoperative AKI among the measured biomarkers with significant differences between the AKI and non-AKI groups. Only variables showing a *p*-value < 0.05 were retained in the final regression models.

Receiver-operating characteristic (ROC) curves were created to estimate the cytokines' cut-off points for the diagnosis of AKI between those that were retained in the regression model. Sensitivity and specificity were calculated, and an optimal cut-off point was established based on Youden's index statistic.

Statistical analysis was performed with SPSS base 22.0 for Windows (SPSS, Chicago, IL USA). A *p*-value < 0.05 was considered as statistically significant.

Results

180 consecutive patients programmed for elective LRS were included in the study. Six subjects were excluded due to protocol deviation. The remaining participants successfully finished the study (Fig. 1).

Patient demographics and surgical data

The AKI group had higher age and body mass index than the non-AKI group. As well, preoperative hypertension was significantly different between groups and surgical duration was longer in the AKI group (Table 1). Intraoperative respiratory and hemodynamic information was similar for both groups (Tables 2 and 3). Twelve patients (6.9%) developed postoperative AKI.

Lung and systemic inflammatory response (Tables 4 and 5)

At baseline, the only significant difference between the AKI and non-AKI groups were higher plasma NO values in the former 33.87 (30.09–36.98) mmol.mL $^{-1}$ vs. 30.85 (28.44–32.60) mmol.mL $^{-1}$, respectively. During the intraoperative time point, no significant differences were detected between groups, neither in plasma nor in alveolar cytokine levels, neither in the dependent nor in the non-dependent lung.

AKI patients exhibited significant higher levels of diverse plasma cytokines following intervention as compare with non-AKI patients – 6 h TNF- α : 11.22 (9.18–12.93) pg.mL $^{-1}$ vs. 9.02 (7.58–11.48) pg.mL $^{-1}$, 6 h IL-1: 43.64 (41.76–47.93) pg.mL $^{-1}$ vs. 31.55 (24.52–45.17) pg.mL $^{-1}$, 6 h IL-2: 1.44 (1.29–1.47) pg.mL $^{-1}$ vs. 1.01 (0.92–1.41) pg.mL $^{-1}$, 6 h IL-6: 5.33 (4.44–6.19) pg.mL $^{-1}$ vs. 3.66 (2.99–4.91) pg.mL $^{-1}$, 18 h IL-4: 0.44 (0.41–0.48)–pg.mL $^{-1}$ vs. 0.39 (0.36–0.44)–pg.mL $^{-1}$, respectively (Fig. 2).

Postoperative course (Table 6)

None of the twelve AKI patients required renal replacement therapy. There were no significant differences regarding length of ICU and hospital stays; however, AKI patients showed a significant increase in postoperative complications ($p < 0.05$) and in the overall mortality at any time point ($p < 0.001$).

Correlation analysis

Most plasma cytokines were highly significantly and positively correlated with alveolar cytokines at TLV restoration, including TNF- α ($r = 0.378$, $p < 0.0001$), IL-1 ($r = 0.199$, $p = 0.011$), IL-2 ($r = 0.532$, $p < 0.0001$), IL-6 ($r = 0.296$, $p < 0.0001$), IL-10 ($r = 0.365$, $p < 0.0001$), NO ($r = 0.329$, $p < 0.0001$) and MMP-2 ($r = 0.697$, $p < 0.0001$).

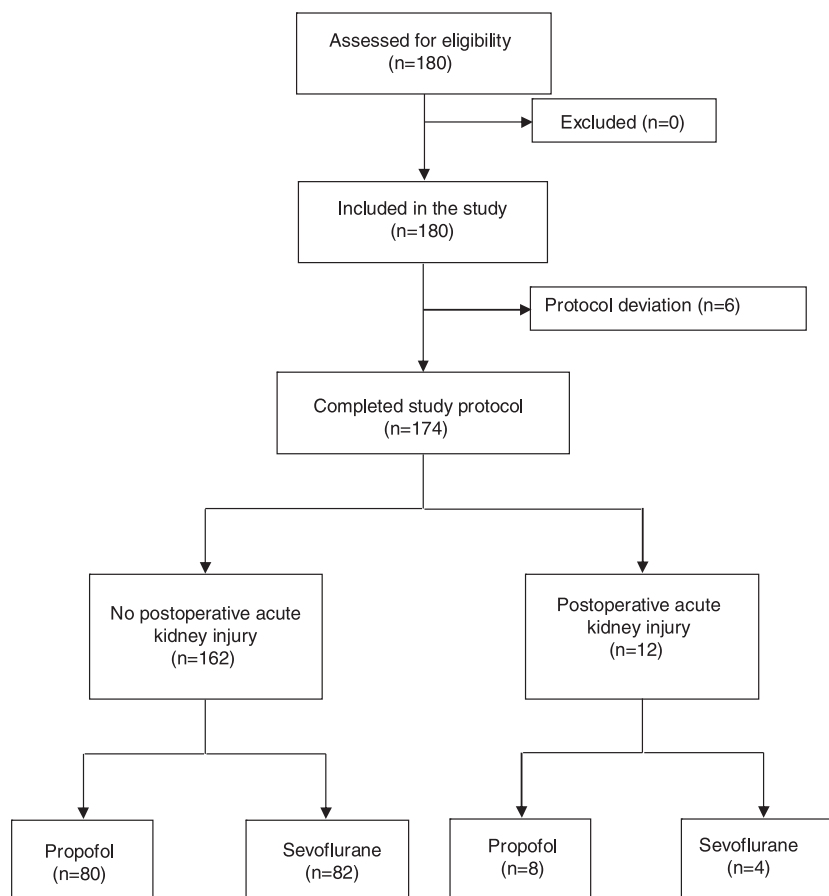


Figure 1 Flow-diagram of patient progress through the phases of the trial.

Table 1 Patient demographics and surgical data.

	Non-AKI	AKI	<i>p</i> value
Sex (male/female)	101/61	11/1	0.041
Age (years)	65 (56–70)	73 (64–77)	0.037
Weight (kg)	70 (62–80)	85 (65–107)	0.043
Height (cm)	166 (160–171)	170 (162–177)	0.197
BMI (kg.m ⁻²)	26 (23–28)	29 (25–33)	0.036
FEV ₁ (% predicted value)	94 (79–111)	88 (63–97)	0.058
FVC (% predicted value)	102 (93–119)	100 (90–103)	0.115
FEV ₁ /FVC ratio (% predicted value)	73 (66–81)	71 (64–80)	0.699
Hypertension (presence/absence)	67/95	12/0	<0.0001
ASA (I/II/III/IV)	8/94/59/1	0/2/10/0	0.016
Side (right/left)	91/71	7/5	0.021
Surgical duration (min)	293 (227–350)	413 (300–486)	0.002
Surgical type (Pneumonectomy/Lobectomy/Atypical)	9/72/81	2/7/3	0.129
Anesthesia maintenance (Propofol/Sevoflurane)	80/82	8/4	0.248

AKI, Acute Kidney Injury; BMI, Body Mass Index; FEV₁, Forced Expiratory Volume in the first second; FVC, Forced Vital Capacity; ASA, American Society of Anesthesiologists' physical status.

Data are expressed as absolute frequencies or median (P25–P75).

p-value, The Chi-square test or Fisher's exact probability test for non-continuous variables and the unpaired Student's *t*-test or Mann-Whitney *U*-test for continuous variables, as appropriate.

Table 2 Intra-operative respiratory parameters.

		Non-AKI	AKI	<i>p</i> -value
PaO ₂ /FiO ₂ (mmHg)	Baseline	347 (286–391)	319 (217–427)	0.560
	OLV	101 (86–124)	111 (81–176)	0.431
	TLV	313 (234–392)	318 (246–356)	0.593
PaCO ₂ (mmHg)	Baseline	44 (41–49)	49 (44–51)	0.208
	OLV	48 (43–53)	50 (45–53)	0.582
	TLV	48 (43–53)	49 (44–52)	0.904
Peak airway pressure (cm.H ₂ O ⁻¹)	Baseline	21 (19–23)	22 (19–22)	0.929
	OLV	25 (22–29)	26 (24–29)	0.296
	TLV	21 (18–24)	22 (21–26)	0.116
Plateau airway pressure (cm.H ₂ O ⁻¹)	Baseline	18 (16–21)	18 (16–19)	0.356
	OLV	21 (18–23)	21 (19–23)	0.929
	TLV	18 (15–21)	21 (16–22)	0.114
Compliance (mL.cm.H ₂ O ⁻¹)	Baseline	40 (34–46)	46 (36–57)	0.176
	OLV	29 (24–35)	30 (27–39)	0.438
	TLV	39 (31–49)	41 (28–52)	0.760
Driving pressure (cm.H ₂ O ⁻¹)	Baseline	13 (11–16)	12 (11–15)	0.557
	OLV	15 (12–18)	16 (13–17)	0.771
	TLV	13 (10–15)	12 (11–17)	0.934

AKI, Acute Kidney Injury; PaO₂, Arterial Oxygen Partial Pressure; FiO₂, Fractional Inspired Oxygen; PaCO₂, Arterial Carbon Dioxide Partial Pressure; OLV, One-Lung Ventilation; TLV, Two-Lung Ventilation; Baseline, immediately before initiating OLV; OLV, 30 min after OLV initiation; TLV, immediately after TLV restoration.

Data are expressed as median (P25–P75).

p-value, The unpaired Student's *t*-test or Mann-Whitney *U*-test, as appropriate.

Table 3 Intra-operative hemodynamic data.

		Non-AKI	AKI	<i>p</i> -value
Mean arterial pressure (mmHg)	Baseline	76 (67–90)	73 (62–80)	0.109
	OLV	75 (65–86)	64 (62–72)	0.024
	TLV	81 (70–92)	78 (70–87)	0.702
Heart rate (bpm)	Baseline	71 (61–79)	70 (64–89)	0.605
	OLV	71 (62–80)	68 (60–84)	0.630
	TLV	74 (64–85)	76 (71–81)	0.647
Cardiac index (mL.min ⁻¹ .m ⁻²)	Baseline	2.5 (2.1–3.1)	2.4 (2.1–3)	0.819
	OLV	2.45 (2–3)	2.15 (2–2.5)	0.058
	TLV	2.7 (2.3–3.2)	2.65 (2.4–3.2)	0.974
Stroke volume variation (%)	Baseline	12 (9–17)	13.5 (8.5–16)	0.950
	OLV	9 (7–12)	8.5 (7–11)	0.816
	TLV	9.5 (7–13)	9.5 (7–12)	0.898
Stroke volume index (mL.min ⁻¹)	Baseline	35 (29–42)	35 (32–39)	0.995
	OLV	35 (30–44)	33 (29–36)	0.117
	TLV	37 (31–43)	36 (30–45)	0.659
Hemoglobin (g.dL ⁻¹)	Baseline	13 (12–14)	13 (12–14)	0.919
	OLV	13 (12–14)	12 (12–15)	0.929
	TLV	13 (12–14)	12 (11–15)	0.661

AKI, Acute Kidney Injury; OLV, One-Lung Ventilation; TLV, Two-Lung Ventilation; Baseline, immediately before initiating OLV; OLV, 30 min after OLV initiation; TLV, immediately after TLV restoration.

Data are expressed as median (P25–P75).

p-value, The unpaired Student's *t*-test or Mann-Whitney *U*-test, as appropriate.

Backward Wald binary logistic regression analysis

After adjustment for demographics and surgical information, the main predictors of AKI after LRS were preoperative hypertension (OR = 0.088, 95% CI 0.002–0.174, *p* = 0.04),

ASA physical status (I–II vs. III–IV; OR = 0.082, 95% CI 0.001–0.165, *p* = 0.05), length of surgery (OR = 0.001, 95% CI 0.000–0.001, *p* < 0.01) and plasma IL-6 level at 6 h following surgery (OR = 1.171, 95% CI 1.211–8.596, *p* = 0.01). After adjustment for anti-hypertensive medication, the

Table 4 Postoperative acute kidney injury and plasma biomarkers.

	AKI	Baseline	OLV	TLV	6 h PO	18 h PO
TNF- α (pg.mL ⁻¹)	Yes	6.84 (6.09–7.23)	8.61 (7.56–9.81)	8.35 (7.14–11.31)	11.22 (9.18–12.93) ^a	9.12 (7.59–9.90)
	No	6.99 (6.48–7.43)	8.58 (7.85–9.13)	9.12 (7.98–11.08)	9.02 (7.58–11.48)	8.44 (7.46–9.46)
IL-1 (pg.mL ⁻¹)	Yes	25.72 (20.00–29.36)	34.12 (29.07–38.26)	31.93 (29.84–37.16)	43.64 (41.76–47.93) ^a	35.05 (26.03–44.61)
	No	27.88 (24.91–31.74)	30.92 (28.52–34.42)	31.51 (27.98–35.94)	31.55 (24.52–45.17)	32.53 (26.01–42.69)
IL-2 (pg.mL ⁻¹)	Yes	0.87 (0.86–0.95)	1.54 (1.18–1.79)	1.30 (0.88–1.51)	1.44 (1.29–1.47) ^a	1.27 (0.95–1.49)
	No	0.85 (0.81–0.90)	1.24 (1.16–1.53)	1.02 (0.87–1.52)	1.01 (0.92–1.41)	1.00 (0.93–1.39)
IL-4 (pg.mL ⁻¹)	Yes	0.33 (0.31–0.34)	0.34 (0.31–0.35)	0.35 (0.30–0.36)	0.38 (0.36–0.40)	0.44 (0.41–0.48) ^a
	No	0.34 (0.31–0.37)	0.34 (0.31–0.37)	0.35 (0.31–0.38)	0.37 (0.34–0.40)	0.39 (0.36–0.44)
IL-6 (pg.mL ⁻¹)	Yes	2.93 (2.38–3.12)	3.47 (2.60–3.91)	4.57 (3.63–4.87)	5.33 (4.44–6.19) ^b	4.18 (3.07–4.32)
	No	3.00 (2.84–3.12)	3.75 (3.26–4.00)	4.01 (3.55–5.08)	3.66 (2.99–4.91)	3.67 (3.01–4.40)
IL-10 (pg.mL ⁻¹)	Yes	0.09 (0.08–0.10)	0.09 (0.07–0.13)	0.10 (0.09–0.10)	0.10 (0.09–0.10)	0.09 (0.08–0.10)
	No	0.09 (0.08–0.10)	0.10 (0.08–0.12)	0.10 (0.09–0.11)	0.09 (0.08–0.10)	0.09 (0.09–0.10)
CO (pmoL.mL ⁻¹)	Yes	2.68 (2.48–2.86)	2.82 (2.50–2.91)	2.82 (2.65–2.86)	3.01 (2.76–3.21)	3.03 (2.87–3.22)
	No	2.61 (2.45–2.84)	2.83 (2.64–2.99)	2.80 (2.65–3.00)	2.79 (2.68–2.93)	2.91 (2.78–3.01)
NO (mmoL.mL ⁻¹)	Yes	33.87 (30.09–36.98) ^a	33.93 (30.28–38.17)	32.12 (27.83–41.38)	27.29 (25.81–29.32)	30.36 (28.69–34.44)
	No	30.85 (28.44–32.60)	31.88 (25.16–39.06)	33.38 (29.74–40.99)	27.53 (25.37–30.92)	29.13 (26.07–31.08)
MMP-2 (pg.mL ⁻¹)	Yes	222.70 (217.64–246.50)	350.43 (321.11–365.55)	489.55 (409.21–533.00)	619.97 (576.02–637.01)	625.74 (471.53–640.17)
	No	219.76 (192.62–249.88)	348.59 (311.76–368.20)	445.30 (382.89–527.47)	433.69 (378.99–618.81)	509.42 (439.72–620.49)
MCP-1 (pg.mL ⁻¹)	Yes	232.59 (188.49–247.25)	244.36 (211.87–300.84)	340.27 (323.75–370.28)	366.14 (349.90–394.43)	381.22 (352.23–389.99)
	No	243.54 (211.45–278.30)	258.78 (228.85–290.40)	351.11 (319.41–379.73)	360.28 (334.67–386.01)	367.04 (343.74–391.07)

AKI, Acute Kidney Injury; OLV, One-Lung Ventilation; TLV, Two-Lung Ventilation; PO, Postoperative; TNF- α , Tumor Necrosis Factor- α ; IL, Interleukin; CO, Carbon Monoxide; NO, Nitric Oxide; MMP-2, Matrix Metalloproteinase 2; MCP-1, Monocyte Chemoattractant Protein 1. Baseline, immediately prior to initiating OLV; OLV, 30 min after OLV initiation; TLV, immediately after TLV restoration; 6 h PO, 6 h after surgery; 18 h PO, 18 h after surgery.

Data are expressed as median (P25-P75).

p-value, The unpaired Student's *t*-test or Mann-Whitney *U*-test, when appropriate.

^a *p* < 0.05.

^b *p* < 0.01.

Table 5 Postoperative acute kidney injury and alveolar biomarkers.

	AKI	Non-dependent lung		Dependent lung	
		Baseline	End	Baseline	End
TNF- α (pg.mL ⁻¹)	Yes	14.72 (13.70–16.95)	21.83 (20.84–23.86)	15.09 (14.12–16.02)	22.79 (20.45–25.81)
	No	14.96 (13.71–15.89)	21.12 (20.11–24.35)	15.03 (14.02–15.95)	21.18 (19.94–24.79)
IL-1 (pg.mL ⁻¹)	Yes	134 (106–169)	199 (173–209)	126 (112–130)	192 (177–257)
	No	128 (117–143)	189 (169–219)	127 (110.5–138)	190.5 (172–220)
IL-2 (pg.mL ⁻¹)	Yes	2.15 (2.00–2.41)	3.12 (3.00–4.06)	2.20 (1.95–2.48)	3.45 (3.07–4.04)
	No	2.16 (1.97–2.36)	3.22 (2.93–3.82)	2.14 (1.98–2.26)	3.18 (2.92–3.61)
IL-4 (pg.mL ⁻¹)	Yes	0.41 (0.39–0.45)	0.84 (0.68–0.93)	0.42 (0.37–0.50)	0.83 (0.72–0.90)
	No	0.41 (0.38–0.43)	0.84 (0.72–0.92)	0.41 (0.39–0.44)	0.83 (0.73–0.94)
IL-6 (pg.mL ⁻¹)	Yes	6.33 (5.94–6.73)	7.47 (7.06–8.25)	6.55 (5.70–7.18)	7.38 (6.94–7.93)
	No	6.31 (5.86–6.85)	7.34 (6.90–8.00)	6.34 (5.89–6.84)	7.25 (6.89–7.85)
IL-10 (pg.mL ⁻¹)	Yes	42.40 (40.00–44.00)	42.55 (40.00–43.70)	41.70 (40.60–42.60)	40.85 (39.05–44.75)
	No	41.20 (40.00–42.20)	42.30 (40.05–44.75)	41.40 (39.90–42.60)	42.35 (40.00–45.20)
CO (pmoL.mL ⁻¹)	Yes	6.58 (5.68–7.22)	8.51 (7.42–9.31)	5.87 (5.21–7.04)	8.01 (7.02–8.56)
	No	6.46 (5.74–7.24)	8.13 (7.52–8.74)	6.48 (5.88–7.20)	8.01 (7.38–8.69)
NO (mmoL.mL ⁻¹)	Yes	0.30 (0.19–0.42)	0.31 (0.28–0.53)	0.27 (0.20–0.31)	0.39 (0.28–0.82)
	No	0.28 (0.21–0.37)	0.35 (0.25–0.64)	0.28 (0.21–0.35)	0.39 (0.29–0.76)
MMP-2 (pg.mL ⁻¹)	Yes	4.39 (4.15–5.01)	8.34 (7.67–9.63)	4.32 (3.99–5.02)	8.93 (7.26–9.44)
	No	4.52 (4.24–4.84)	9.17 (7.96–9.78)	4.48 (4.21–4.87)	8.63 (7.89–9.74)
MCP-1 (pg.mL ⁻¹)	Yes	382.99 (356.29–391.11)	531.52 (512.44–549.75)	369.45 (361.82–376.14)	549.49 (532.63–565.95)
	No	380.99 (358.50–396.55)	545.12 (523.77–566.02)	375.71 (352.58–391.99)	543.13 (525.42–568.23)

AKI, Acute Kidney Injury; TNF- α , Tumor Necrosis Factor- α ; IL, Interleukin; CO, Carbon Monoxide; NO, Nitric Oxide; MMP-2, Matrix Metalloproteinase 2; MCP-1, Monocyte Chemoattractant Protein 1; Baseline, immediately prior to initiating one-lung ventilation; End, immediately after two-lung ventilation restoration.

Data are expressed as median (P25–P75).

p-value, the unpaired Student's *t*-test or Mann-Whitney *U*-test, when appropriate.

presence of preoperative hypertension was indeed associated with the development of AKI after LRS (OR = 0.133, 95% CI 0.009–0.256, *p* = 0.03).

ROC curves

ROC curves were created to assess the accuracy of plasma IL-6 at 6 h following LRS for the diagnosis of postoperative AKI. The Area Under the Curve (AUC) was 0.80 (95% CI 0.65–0.96). The optimal IL-6 at 6 h cut-off point to predict AKI with maximum sensitivity and specificity (75% and 73%, respectively) was 4.89 pg.mL⁻¹.

Discussion

This is one of the first large-scale validations of inflammatory biomarkers in human studies in the setting of AKI following LRS. The main finding of our work was a greater postoperative inflammatory response for patients who developed AKI after LRS. We noticed important differences in plasma levels of TNF- α , IL-1, IL-2 and IL-6 at 6 h and in plasma levels of IL-4 at 18 h after surgery between subjects who did and those who did not suffer from AKI. In addition, prognosis worsened in the AKI group.

Non-cardiac thoracic surgery represents a well characterized trigger of the inflammatory cascade depending on the nature of the disease (benign vs. malign), the surgical approach (open vs. thoracoscopic) and the application of OLV during surgery, especially for patients with previ-

ous lung injuries due to tobacco, bronchial reactivity or malignancies. Previous reports evaluated the inflammatory response related to non-cardiac thoracic surgeries^{9–11} and demonstrated that the inflammatory status following them is higher than after other types of procedures like abdominal surgeries,¹² which could be linked to a higher incidence of AKI in the former. Our investigation now expands previous findings by highlighting systemic inflammatory status as a factor related to the development of AKI after LRS.

Systemic inflammation is associated with increased plasma cytokine levels, which cause organ damage, including kidney dysfunction. The release of inflammatory cytokines to the bloodstream affects kidneys' vascular, tubular and glomerular functions.¹³ Firstly, general vasodilatation decreases mean arterial pressure below a specific range, limiting the renal ability to auto-regulate its own blood flow. Secondly, an impaired tubular reabsorption of sodium and the activation of the renal sympathetic nervous system increase the afferent arteriolar tone. Thirdly, the efferent arteriolar tone decreases with negative consequences for maintenance of the glomerular filtration pressure. All these processes contribute to decrease the Glomerular Filtration Rate (GFR), which may end up in oligoanuria under inflammatory circumstances.¹³ Thus, the development of AKI partly depends on the magnitude of the inflammatory response following surgery. Moreover, AKI itself also contributes to systemic inflammation by increasing the production and reducing the clearance of inflammatory cytokines.¹⁴

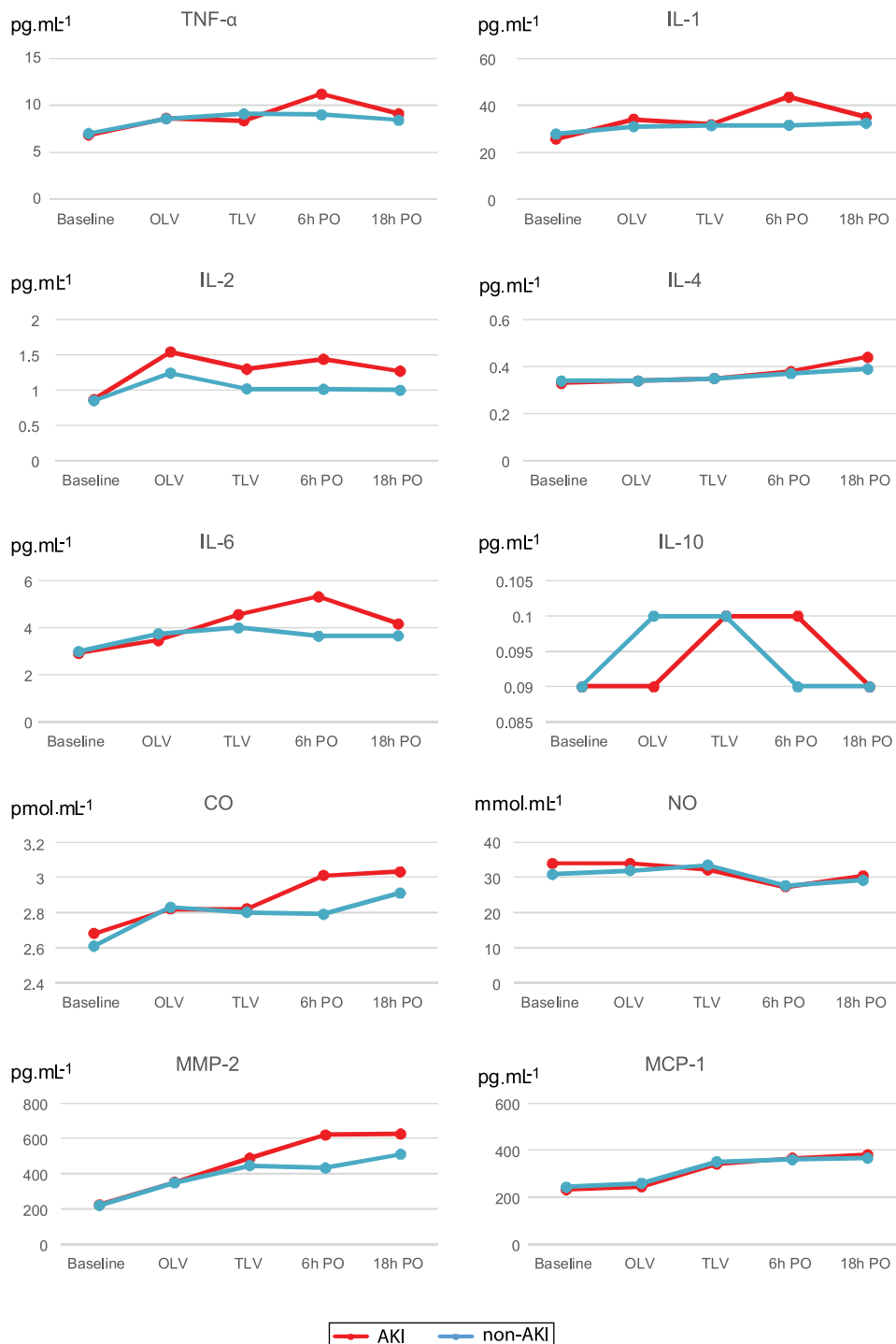


Figure 2 Plasma cytokine levels in the AKI and non-AKI groups at different time points.

Other working groups¹⁵⁻¹⁷ previously indicated that inflammation exerted a fundamental role on the pathogenesis of AKI, which is confirmed by our results. Conversely, Zakrzewski and colleagues failed to demonstrate that the excessive postoperative inflammatory response contributed to the development of AKI, although they observed an association between postoperative AKI and preoperative inflammatory status.¹⁸ This fact could be explained by the included population in their study (patients with

diabetes Type 2 or impaired glucose tolerance). Hyperglycemia itself activates inflammatory cytokines which, as explained before, results in renal hypoperfusion and decreased GFR. Thus, including a population with elevated cytokine levels preoperatively could have diminished the relative importance of the postoperative inflammatory response to the development of AKI.

It is important to highlight the lack of relationship among the drugs used for anesthesia maintenance with the

Table 6 Postoperative evolution in patients with acute kidney injury and patients without such complication.

	Non-AKI	AKI	p-value
PO pulmonary complications (presence/absence)	31/131	6/6	0.012
PO cardiac complications (presence/absence)	12/150	3/9	0.036
Infection (presence/absence)	33/129	6/6	0.018
Length of ICU stay (h)	21 (15.5–66)	20 (17–21)	0.138
Length of hospital stay (days)	6 (5–8.25)	8.5 (5.75–11.5)	0.383
ICU re-admission (presence/absence)	13/149	3/9	0.050
Mortality at 1 month (presence/absence)	1/161	2/10	<0.001
Mortality at 6 months (presence/absence)	4/158	3/9	<0.001
Mortality at 1 year (presence/absence)	9/153	4/8	<0.001
Mortality at 3 years (presence/absence)	35/127	9/3	<0.001

AKI, Acute Kidney Injury; ICU, Intensive Care Unit; PO, Postoperative. Data are expressed as absolute frequencies or median (P25–P75). p-value, the Chi-square test or Fisher's exact probability test for non-continuous variables and the unpaired Student's *t*-test or Mann–Whitney *U*-test for continuous variables, as appropriate.

occurrence of AKI in our study. On one hand, propofol exerts anti-inflammatory properties through modifying nitric oxide production, weakening prostaglandin synthesis or blocking adhesion molecules' expression, among others. On the other hand, sevoflurane is metabolized into nephrotoxic products for animals,¹⁹ although most human studies have failed to demonstrate a real association between sevoflurane administration and nephrotoxic consequences for humans. In our study, we demonstrated neither a renoprotective action for propofol nor a renotoxic effect for sevoflurane.

Our data also disclose no differences in alveolar biomarker levels between both lungs, which has already been communicated by others.^{10,11} So that, our results do not support the hypothesis of surgical lung parenchyma origin for the release of inflammatory cytokines in patients who will develop AKI.

We found that AKI was associated with a higher incidence of postoperative cardiopulmonary complications and increased mortality, as previously reported in selected population of thoracic surgical patients.¹ Besides, we assessed the main determinants for AKI in patients undergoing LRS and confirmed some of the risk factors that have been communicated before, such as hypertension,^{2,20–23} ASA physical status (I–II vs. III–IV)^{1,24} and surgical duration.¹ However, due to the small number of patients that experienced AKI, only significant variables were included in the multivariate model, so we were not able to check other possible underlying conditions previously suggested, like surgical approach.² But, in contrast to other study groups, we measured inflammatory biomarkers and our regression analysis showed that plasma IL-6 levels at 6 h following LRS was the only cytokine that predicts AKI after adjustment for patient characteristics and surgical data.

Plasma IL-6 levels increase quickly after surgery and their monitoring after non-cardiac thoracic surgery could be beneficial to identify patients at increased risk of postoperative inflammatory complications far before their clinical onset, but no specific IL-6 cut-off point has been reported for AKI after LRS. Only one report evaluated the accuracy of IL-6 in predicting inflammation after major thoracic surgery and set the cut-off point at 2.56 pg.mL⁻¹ on the operative day.²⁵ In our investigation, the diagnostic value of IL-6 at 6 h after LRS was highest with a cut-off point of 4.89 pg.mL⁻¹, suggesting

that the optimal cut-off point for prediction of inflammatory complications following thoracic surgery is somewhere between 3.00 and 4.50 pg.mL⁻¹.

Limitations of this study include the observational nature of our research and the relatively low proportion of participants who exhibited AKI according to the defining criteria we employed, although our incidence was similar to previous reports.^{1–3} The AKI group presented clinical differences with the non-AKI group due to the strict inclusion and exclusion criteria that did not guarantee a similar sample between groups. Although these differences were controlled for in our regression models, we cannot exclude the possibility that demographic and cardiometabolic risk factors might have influenced the results. We also acknowledge that there are inherent limitations to biochemical determinations as well as to the long duration of OLV, possibly leading to an increased incidence of cardiopulmonary complications. Finally, our data are only applicable to patients with similar surgical profile as ours. Further studies in wider samples and with an independent validation cohort are required to verify our findings.

Conclusion

Postoperative systemic inflammatory response was greater for patients who developed AKI following LRS, which was related to increased cardiopulmonary complications and mortality. Plasma cytokine levels' measurement may be a useful strategy to identify people at risk of postoperative AKI at an early stage. Plasma IL-6 is a sensitive and accurate biomarker of AKI after LRS.

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Conflicts of interest

The authors declare no conflicts of interest.

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