Review Article

Identifying biomarkers of ventilator induced lung injury during one-lung ventilation surgery: a scoping review

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Background: Ventilator-induced lung injury (VILI) can occur as a result of mechanical ventilation to two lungs. Thoracic surgery often requires one-lung ventilation (OLV). The potential for VILI is likely higher in OLV. The impact of OLV on development of post-operative pulmonary complications is not well understood. We aimed to perform a scoping review to determine reliable biomarkers of VILI after OLV.

Methods: A scoping review was performed using Cochrane Collaboration methodology. We searched Medline, EMBASE and SCOPUS. Gray literature was searched. Studies of adult human or animal models without pre-existing lung damage exposed to OLV, with biomarker responses analyzed were included.

Results: After screening 5,613 eligible papers, 89 papers were chosen for full text review, with 29 meeting inclusion. Approximately half (52%, n=15) of studies were conducted in humans in an intra-operative setting. Bronchoalveolar lavage (BAL) & serum analyses with enzyme-linked immunosorbent assay (ELISA)-based assays were most commonly used. The majority of analytes were investigated by a single study. Of the analytes that were investigated by two or more studies (n=31), only 16 were concordant in their findings. Across all sample types and studies 84% (n=66) of the 79 inflammatory markers and 75% (n=6) of the 8 anti-inflammatory markers tested were found to increase. Half (48%) of all studies showed an increase in TNF-α or IL-6.

Conclusions: A scoping review of the state of the evidence demonstrated that candidate biomarkers with the most evidence and greatest reliability are general markers of inflammation, such as IL-6 and TNF-α assessed using ELISA assays. Studies were limited in the number of biomarkers measured concurrently, sample size, and studies using human participants. In conclusion these identified markers can potentially serve as outcome measures for studies on OLV.

Keywords: One-lung ventilation (OLV); ventilator-induced lung injury (VILI); thoracic surgery; biomarker; inflammation

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Introduction

Thoracic surgery is part of curative therapy for lung cancer, which is the leading cause of cancer-related mortality worldwide (1). Thoracic surgery is also used to treat many other malignant and benign conditions, such as the respiratory failure induced by SARS-Cov-2 (2). The majority of thoracic surgery requires that the operated lung be isolated from the contralateral lung, and not

ventilated during the operation. Thus, the non-operated lung experiences one-lung ventilation (OLV). It is known that undergoing mechanical ventilation puts patients at risk for ventilator induced lung injury (VILI) (3-5). This has been shown in patients undergoing prolonged two-lung ventilation (TLV) (i.e., many days), predominantly in the intensive care setting. Some evidence also exists for the role of VILI in patients undergoing surgery requiring shorter periods of exposure to TLV (4). Although the exact mechanisms that underlie VILI have yet to be elucidated, studies to date have suggested that the main risk factors for OLV-induced VILI are iatrogenic (6). These risk factors include high tidal volume (Vt), high airway pressures and high fraction of inspired oxygen (FiO_2) all of which can contribute to lung parenchyma stress and mechanical injury that induces inflammation (7). Common pro-inflammatory cytokines, such as TNFα and IL-6, are increased in patients that have undergone OLV, while anti-inflammatory cytokines like IL-10 are decreased in abundance (8-10). Based on current knowledge and understanding, we hypothesize that patients undergoing OLV are at greater risk for VILI compared to patients undergoing TLV for two major reasons: (I) OLV is primarily used in a population that already has pre-existing lung damage; and (II) in OLV, all the potentially injurious factors are exerted on one lung rather than being distributed between two lungs.

One of the major causes of mortality after thoracic surgery is acute lung injury (ALI) or ARDS. ALI can occur in up to 4% of patients after OLV, with a mortality rate as high as 70% (4,5,11-13). Thus, OLV has potential to be a major risk factor for ALI after thoracic surgery, but the pathophysiology and determinants of OLV-induced VILI are poorly understood (4,12).

Studying and identifying these biomarkers is important as it will facilitate identification of high-risk patients for pre-operative, intra-operative and post-operative interventions to reduce the risk of VILI and respiratory complications. It is also important as a method of monitoring/tracking the response to such interventions. Moreover, studying and identifying these biomarkers is also important for studies that aim to understand the mechanisms behind such interventions. The aim of this scoping review is to identify biomarkers that have been linked to post-OLV lung injury. By providing an analysis of the current state of the literature, we hope to identify knowledge gaps, and provide guidance for further identification of reliable biomarkers for post-OLV VILI. We present the following article in accordance with the PRISMA-ScR reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-20-2301/rc).

Methods

Study inclusion was based on PIO criteria. Population: All human and animal studies that used OLV as an exposure and investigated any analyte response as an outcome were considered. Studies using neonate models were excluded. Only English language studies or studies with an English translation were included. Intervention: Studies must utilize OLV. Studies that induced lung injury unrelated to VILI (i.e., lipopolysaccharide-induced injury) were excluded. Outcome: Studies must measure the effect of one lung ventilation on a biomarker.

In collaboration with a librarian (TG), a highly sensitive search strategy was used (Tables S1,S2). Electronic databases EMBASE, SCOPUS, and Medline were searched (inception to January 7, 2021). A gray literature search was conducted by an expert in this research area (BK). Bibliographies of included studies were hand-searched for relevant studies.

After abstract eligibility screening the data extracted from each study was; Title, year, authors, citation count, sample size, population type (type of animal or human), VILI induction method, blood product tested, intraoperative or post-operative measurement, histological findings, biomarker quantification method, biomarkers quantified and biomarker response including direction, magnitude, and statistical significance.

A calibration exercise was conducted initially for screening. During this calibration, screening of 50 studies was performed independently by 2 authors (BK and AB). Once calibration was achieved, all further screening was performed by a single author (AB) who assessed titles and abstracts for inclusion eligibility. Full text analysis, assessment for final inclusion and data extraction of the included studies was conducted independently by 2 authors (AB and RM). Chance-corrected agreement was calculated. All disagreements were resolved through discussion and consensus without the need for a third reviewer (BK).

Results

The search yielded 5,609 results after duplicates were removed with 4 manual additions. Twenty-nine studies were included for data synthesis as summarized in *Table 1*; the most common reason for exclusion was lack of OLV as an exposure, followed by lack of biomarker measurement (*Figure 1*).

Table 1 Study model and exposure

Year, author (reference)	Model [n]	Intervention groups
2011 Bastin (8)	Human [30]	OLV group: Vt 6.60±1.50 mL/kg; duration 147 min (121–196 min); plateau pressure 23.00±4.50 cmH_2O
2011 Breunig (14)	Human [15]	OLV group: Vt <7 mL/kg; PEEP 3–5 cmH_2O; PIP <30 cmH_2O; FiO_2 set to 1.0 initially, gradually reduced based on arterial oxygen tension
2020 Dai (15)	Pig [15]	Control: Vt 10 mL/kg; PEEP 5 cmH_2O; FiO_2 0.5; left pneumonectomy
		Volume-control: Vt 20 mL/kg; PEEP 5 cmH_2O; RR to maintain $ETCO_2$ 35–45 mmHg; FiO_2 0.5; left pneumonectomy
		Adaptive-control: ASV% of 60% minute ventilation of two lungs to maintain $ETCO_2$; left pneumonectomy
2015 Feng (16)	Human [30]	Propofol group: Vt 6–8 mL/kg; RR 14–16/min; I:E 1:2; $ETCO_2$ 35–45 mmHg; FiO_2 1.0; anaesthetic: propofol
		Sevoflurane group: Vt 6–8 mL/kg; RR 14–16 breath/min; I:E 1:2; $ETCO_2$ 35–45 mmHg; FiO_2 1.0; anaesthetic: sevoflurane
2018 Fiorelli (17)	Human [28]	OLV group: Vt 8–10 mL/kg; PEEP 5 cmH_2O; PIP 35 cmH_2O; FiO_2 0.5
2017 de la Gala (18)	Human [174]	Propofol group: Vt 6 mL/kg; PEEP 5 cmH_2O; FiO_2 0.6–1; SaO_2 >90%; permissive hypercapnia; anaesthetic: propofol
		Sevoflurane group: Vt 6 mL/kg; PEEP 5 cmH_2O; FiO_2 0.6–1; SaO_2 >90%; permissive hypercapnia; anaesthetic: sevoflurane
2003 Gama de Abreu (19)	Female European rabbit [18] (Isolated perfused lung model)	OLV group: Vt 8 mL/kg; RR 30/min; PEEP 1 cmH_2O; I:E 1:1; recruitment maneuver every 30 min
		Protective OLV group: Vt 8 mL/kg; RR 30/min; PEEP 1 cmH_2O; I:E 1:1; recruitment maneuver every 10 min
		TLV group: Vt 8 mL/kg; RR 30/min; PEEP 1 cmH_2O; I:E 1:1; recruitment maneuver every 10 min
2015 García-de-la-Asunción (20)	Human [28]	OLV group: Vt 6 mL/kg; RR 12–14/min; PEEP 5–7 cmH_2O; I:E 1:2; $ETCO_2$ <40 mmHg; FiO_2 0.5; SaO_2 >92%
2017 Liu (21)	Japanese white rabbit [36]	Sham: ventilatory parameters not specified
		OLV: ventilatory parameters not specified
		OLV + sevoflurane (four groups): 1%, 2%, 3%, 4% sevoflurane concentrations tested
2018 Liu (22)	Dog [18]	OLV 100% collapsed: Vt 10–15 mL/kg; duration 2 h; RR 12–16/min; FiO_2 1; $ETCO_2$ 35–45 mmHg; right lung collapsed fully
		OLV 90% collapsed: Vt 10–15 mL/kg; duration 2 h; RR 12–16/min; FiO_2 1; $ETCO_2$ 35–45 mmHg; right lung 90% collapsed
		OLV 50% collapsed: Vt 10–15 mL/kg; duration 2 h; RR 12–16/min; FiO_2 1; $ETCO_2$ 35–45 mmHg; right lung 50% collapsed
2013 Liu (23)	New Zealand Rabbit [36]	OLV group: Vt 10 mL/kg; duration 0, 2, or 4 h; RR 50/min; PEEP 0 cmH_2O; I:E 1:1; FiO_2 0.4
		TLV group: Vt 10 mL/kg; duration 0, 2, or 4 h; RR 50/min; PEEP 0 cmH_2O; I:E 1:1; FiO_2 0.4
2018 Liu (9)	Human [60]	OLV group: Vt 10 mL/kg; RR 12/min; PEEP 0 cmH_2O; I:E 1:1.5; $ETCO_2$ 35–40 mmHg; FiO_2 1.0; no inspiratory time pause
		OLV protective ventilation group: Vt 6 mL/kg; RR 12/min; PEEP 6 cmH_2O; I:E 1:1.5; $ETCO_2$ 35–40 mmHg; FiO_2 1.0; no inspiratory time pause

Table 1 (*continued*)

Table 1 (*continued*)

Year, author (reference)	Model [n]	Intervention groups
2011 Mahmoud (24)	Human [50]	Propofol group: Vt 10 mL/kg; duration 80 min; RR set to maintain $ETCO_2$ 45 mmHg; PEEP 5 cmH_2O; PIP 30 cmH_2O; FiO_2 0.8–1.0; PaO_2 80 mmHg; anaesthetic: propofol
		Isoflurane group: Vt 10 mL/kg; duration 78 min; RR set to maintain $ETCO_2$ 35–45 mmHg; PEEP 5 cmH_2O; PIP 30 cmH_2O; FiO_2 0.8–1.0; PaO_2 80 mmHg; anaesthetic: isoflurane
2020 Pan (25)	Sprague-Dawley rat [30]	Sham: no ventilation
		OLV-2 h: Vt 10 mL/kg; duration 2 h; RR 60/min; I:E 1:1.5; FiO_2 1.0
		OLV-3 h: Vt 10 mL/kg; duration 3 h; RR 60/min; I:E 1:1.5; FiO_2 1.0
		LIG-2 h: Vt 10 mL/kg; duration 2 h; RR 60/min; I:E 1:1.5; FiO_2 1.0; Ligustrazine HCl injection 100 mg/kg 30 min prior OLV
		LIG-3 h: Vt 10 mL/kg; duration 3 h; RR 60/min; I:E 1:1.5; FiO_2 1.0; Ligustrazine HCl injection 100 mg/kg 30 min prior OLV
2005 Schilling (26)	Human [32]	OLV tradition ventilation group: Vt 10 mL/kg; duration 71 min; RR set for $PaCO_2$ 35–45 mmHg; PEEP 0 cmH_2O
		OLV protective ventilation group: Vt 5 mL/kg; duration 68 min; RR set for $PaCO_2$ 35–45 mmHg; PEEP 0 cmH_2O
2007 Schilling (10)	Human [50]	Propofol group: Vt 10 mL/kg; duration 65 min; RR set for $PaCO_2$ 4.8–5.8 kPa; PEEP 5 cmH_2O; PIP 35 cmH_2O; FiO_2 between 0.8 to 1.0; anaesthetic: propofol
		Desflurane group: Vt 10 mL/kg; duration 61 min; RR set for $PaCO_2$ 4.8–5.8 kPa; PEEP 5 cmH_2O; PIP 35 cmH_2O; FiO_2 between 0.8 to 1.0; anaesthetic: desflurane
2011 Schilling (27)	Human [63]	Propofol group: RR set for $PaCO_2$ 36–44 mmHg; PEEP 5 cmH_2O; PIP 30 cmH_2O; FiO_2 0.4–0.5; pressure-controlled ventilation; anaesthetic: propofol 1.5–2 mg/kg
		Desflurane group: RR set for $PaCO_2$ 36–44 mmHg; PEEP 5 cmH_2O; PIP 30 cmH_2O; FiO_2 0.4–0.5; pressure-controlled ventilation; anaesthetic: desflurane 1 min alveolar concentration per air
		Sevoflurane group: RR set for $PaCO_2$ 36–44 mmHg; PEEP 5 cmH_2O; PIP 30 cmH_2O; FiO_2 0.4–0.5; pressure-controlled ventilation; anaesthetic: sevoflurane 1 min alveolar concentration per air
2006 Schreiber (28)	Male Wistar Rat [26]	High Vt group: Vt 20 mL/kg; OLV duration 2 h; RR 40 breath/min; PEEP 4.5 cmH_2O; FiO_2 0.5
		Low Vt group: Vt 8 mL/kg; OLV duration 2 h; RR 40 breath/min; PEEP 4.5 cmH_2O; FiO_2 0.5
2012 Siegl (29)	Female BALB/c and C57BL/6 mice [24] (isolated perfused lung model)	Balb/c groups
		High pressure group: Vt 200 µL; duration 240 min; RR 90/min; EIP –25 cmH_2O; EEP –3 cmH_2O; deep breath (30 cmH_2O) every 5 min; lungs perfused with 0.5 mM p38; MAPK inhibitor SB203580
		Low pressure group: Vt 200 µL; duration 240 min; RR 90/min; EIP –8 cmH_2O; EEP –3 cmH_2O; deep breath (30 cmH_2O) every 5 min; lungs perfused with 0.5 mM p38; MAPK inhibitor SB203580
		C57BL/6 groups
		High pressure group: Vt 200 µL; duration 240 min; RR 90/min; EIP –25 cmH_2O; EEP –3 cmH_2O; deep breath (30 cmH_2O) every 5 min
		Low pressure group: Vt 200 µL; duration 240 min; RR 90/min; EIP –8 cmH_2O; EEP –3 cmH_2O; deep breath (30 cmH_2O) every 5 min
2018 Tan (30)	Human [60]	Pressure controlled ventilation group: Pressure set for Vt of 6 mL/kg; $PETCO_2$ 30–45 mmHg; PEEP 0 cmH_2O; FiO_2 1.0; oxygen flow rate 1 L/min
		Volume controlled ventilation group: Vt 6 mL/kg; $PETCO_2$ 30–45 mmHg; PEEP 0 cmH_2O; FiO_2 1.0; oxygen flow rate 1 L/min

Table 1 (*continued*)

Table 1 (*continued*)

Year, author (reference)	Model [n]	Intervention groups
2015 Tojo (31)	Specific pathogen free male Sprague-Dawley rat [32]	Bilateral *vs.* unilateral ventilation experiment
		Bilateral ventilation: Vt 8 mL/kg; RR 80/min; PEEP 4 cmH_2O; FiO_2 1.0 reduced to 0.6
		Unilateral ventilation: Vt 8 mL/kg; RR 80/min; PEEP 4 cmH_2O; FiO_2 1.0 reduced to 0.6. Right lung collapsed
		60% O_2 *vs.* 100% N_2 high Vt experiment
		Unilateral ventilation group: Vt 8 mL/kg; RR 80/min; PEEP 4 cmH_2O; FiO_2 1.0 reduced to 0.6. Right lung collapsed
		Bilateral 60% oxygen group: Left lung—Vt 8 mL/kg; RR 80/min; PEEP 4 cmH_2O; FiO_2 0.6. Right lung—Vt 4 mL/kg; RR 80/min; PEEP 4 cmH_2O; FiO_2 0.6
		Bilateral 0% oxygen group: Left lung—Vt 8 mL/kg; RR 80/min; PEEP 4 cmH_2O; FiO_2 0. Right lung—Vt 4 mL/kg; RR 80/min; PEEP 4 cmH_2O; FiO_2 0
2017 Xu (32)	New Zealand Rabbit [30]	Sham TLV group: Vt 10 mL/kg; 3 h duration; RR 40/min; PEEP 0 cmH_2O; I:E 1:2; FiO_2 0.6
		1.0 FiO_2 OLV group: Vt 10 mL/kg; 3 h duration; RR 40/min; PEEP 0 cmH_2O; I:E 1:2; FiO_2 1.0
		0.6 FiO_2 OLV group: Vt 10 mL/kg; 3 h duration; RR 40/min; PEEP 0 cmH_2O; I:E 1:2; FiO_2 0.6
2018 Yang (33)	Japanese white rabbit [36]	Sham-operated group: TLV; Vt 20 mL/kg; duration 2 h; RR 30/min; I:E 1:2; FiO_2 1
		OLV group: Right lung OLV; Vt 20 mL/kg; duration 2 h; RR 30/min; I:E 1:2; FiO_2 1
		OLV + sevoflurane inhalation group: Vt 20 mL/kg; duration 2 h; RR 30/min; I:E 1:2; FiO_2 1; sevoflurane 2.5% used
		Club cells exfoliated + sham-operated group: TLV; Vt 20 mL/kg; duration 2 h; RR 30/min; I:E 1:2; FiO_2 1; exposure to naphthalene vapour 100 mg/L for 12 h
		Club cells exfoliated + OLV group: right lung OLV; Vt 20 mL/kg; duration 2 h; RR 30/min; I:E 1:2; FiO_2 1
		Club cells exfoliated + OLV + sevoflurane inhalation group: Right lung OLV; Vt 20 mL/kg; duration 2 h; RR 30/min; I:E 1:2; FiO_2 1; exposure to naphthalene vapour 100 mg/L for 12 h; sevoflurane 2.5% used
2020 Yao (34)	Human [60]	Volume controlled ventilation group: VCV mode gradually increases flow rate and pressure; Vt 6 mL/kg; RR 14–18/min; PEEP; lung cancer patients undergoing thoracoscopic lobectomy
		Pressure controlled ventilation-volume guaranteed group: PCV-VG mode delivers Vt at lowest preset pressure; Vt 6 mL/kg; RR 14–18/min; PEEP; lung cancer patients undergoing thoracoscopic lobectomy
2019 Yin (35)	New Zealand white rabbit [24]	TLV-S group: Vt 6 mL/kg; RR 40/min; PEEP 3 cmH_2O; PIP <20 cmH_2O; FiO_2 1.0; I:E 1:1.5. Treatment order: TLV 2.5 h. Intraperitoneal saline: 1.5 mL/kg; TLV 1 h
		OLV-S group: Vt 6 mL/kg; RR 40/min; PEEP 3 cmH_2O; PIP <20 cmH_2O; FiO_2 1.0; I:E 1:1.5. Treatment order: OLV 2.5 h. Intraperitoneal saline: 1.5 mL/kg; OLV 0.5 h; TLV 0.5 h
		U-OLV group: Vt 6 mL/kg; RR 40/min; PEEP 3 cmH_2O; PIP <20 cmH_2O; FiO_2 1.0; I:E 1:1.5. Treatment order: Intraperitoneal URB937 1.5 mL/kg; OLV 3 h; TLV 0.5 h
		OLV-U group: Vt 6 mL/kg; RR 40/min; PEEP 3 cmH_2O; PIP <20 cmH_2O; FiO_2 1.0; I:E 1:1.5. Treatment order: OLV 2.5 h; intraperitoneal URB937 1.5 mL/kg; OLV 0.5 h; TLV 0.5 h
2012 You (36)	Japanese rabbit [30]	Sham OLV group: Vt 10 mL/kg; RR 40 /min; I:E 1:2; FiO_2 1.0; Sham tracheostomy
		OLV group: Vt 10 mL/kg; RR 40 /min; I:E 1:2; FiO_2 1.0
		TLV group: Vt 10 mL/kg; RR 40 /min; I:E 1:2; FiO_2 1.0
		OLV PDTC group: Vt 10 mL/kg; RR 40 /min; I:E 1:2; FiO_2 1.0; pretreatment with 50 mg/kg NF-κB inhibitor pyrrolidine dithiocarbamate
		TLV PDTC group: Vt 10 mL/kg; RR 40 /min; I:E 1:2; FiO_2 1.0; pretreatment with 50 mg/kg NF-κB inhibitor pyrrolidine dithiocarbamate

Table 1 (*continued*)

Table 1 (*continued*)

Year, author (reference)	Model [n]	Intervention groups
2019 Zeng (37)	Sheep [6]	OLV group: Vt 10 mL/kg; duration 8 h; PEEP 0–2 cmH_2O; left thoracotomy performed for lung collapse; collapsed and aerated lungs compared
2016 Zhang (38)	Human [60]	Inverse ratio group: Vt 7 mL/kg; RR 12 breath/min; PEEP 5 cmH_2O; FiO_2 1.0; I:E 2:1
		Control group: Vt 7 mL/kg; RR 12 breath/min; PEEP 5 cmH_2O; FiO_2 1.0; I:E 1:2
2020 Zhao (39)	Human [121]	Sham group: Vt 8–10 mL/kg; RR 10–15/min; FiO_2 1.0; I:E 1.15; OLV with operated lung collapse; patients received the electrodes without electrical stimulation.
		TEAS group: Vt 8–10 mL/kg; RR 10–15/min; FiO_2 1.0; I:E 1.15; OLV with operated lung collapse; prior to anaesthesia patients received transcutaneous electrical acupoint stimulation. Patients received acupuncture at 6 locations, with electrical stimulation of 100 Hz for 10 s with 3 s intervals, with 20–25 mA

OLV, one-lung ventilation; Vt, tidal volume; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure; FiO_2, fraction of inspired oxygen; RR, respiratory rate; $ETCO_2$, end-tidal CO_2 partial pressure; ASV, adaptive support ventilation; I:E, inspiration:expiration ratio; TLV, Two-lung ventilation; SaO_2, Oxygen saturation; HCl, hydrochloride; MAPK, mitogen-activated protein kinase; EIP, end-inspiratory pressure; EEP, end-expiratory pressure; $PETCO_2$, patient end-tidal carbon dioxide; VCV, volume control ventilation; PCV-VG, pressure-controlled ventilation-volume guaranteed; OLV-S, one-lung ventilation + saline; U-OLV, intraperitoneal URB937 + one-lung ventilation; OLV-U, one-lung ventilation + intraperitoneal URB937; PDTC, pyrrolidine dithiocarbamate; TEAS, transcutaneous electrical acupoint stimulation.

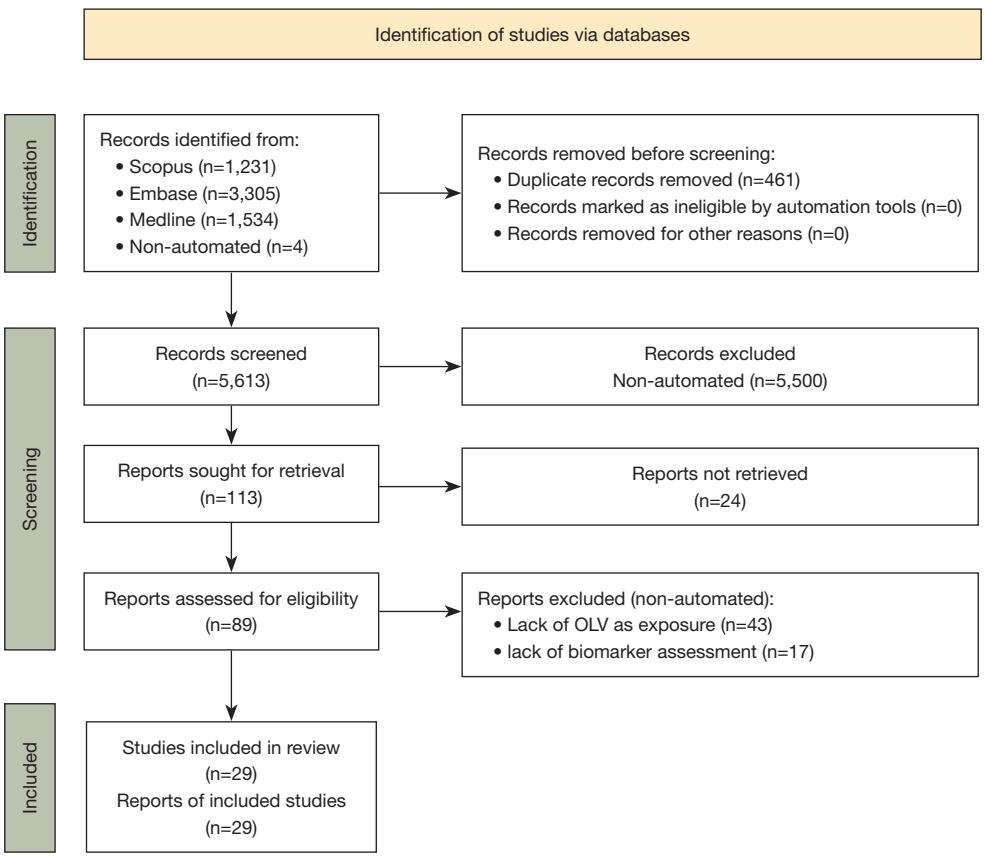

Figure 1 Flow diagram for flow of scoping review. OLV, one-lung ventilation.

Table 1 describes the study subjects, and the ventilatory parameters, ventilation mode (e.g., the methodological designs were limited to human observational studies, human interventional studies testing anaesthetic effects, and animal studies. The most common model was human patients (52% of studies). Of the animal studies 50% utilized rabbit and 22% used rat. Mouse, pig, sheep, and dog were each used by a single study (15,22,29,37). Of the human studies, the average sample size was 57, with an average Vt of 7.8 mL/kg in the VILI group. Of the animal studies, the average sample size was 25. A quarter of the human studies were interventional in nature, testing the effect of different anaesthetic methods on cytokine levels, or investigating the difference between two ventilation strategies.

Table 2 describes the analytical methodology used to detect markers and the major findings of each study. The most commonly used analytic method to detect biomarkers was enzyme-linked immunoassay, which was used in 69% (n=20) of studies. The most used sample type was blood (45%, n=13), followed by bronchoalveolar lavage fluid (BALF) (41%, n=12) and tissue (41%, n=12). Exhaled breath condensate was used in three studies (8,15,20) and plural fluid and perfusate were both used singularly by Gama de Abreu *et al.* (19).

Figures 2,3 describe the change in abundance of each analyte in blood and BAL, respectively. A total of 27 analytes were investigated in blood across included studies. The studies investigating these analytes primarily used human subjects (69%, n=9). Only 6 analytes were investigated by ≥2 studies: IL-1β, IL-6, IL-8, IL-10, IL-12, and TNF-α. The bulk of markers investigated in blood were pro-inflammatory (81%, n=22 markers). Across studies investigating these markers 68% (n=30) of the assays found an increase. There were only three anti-inflammatory markers investigated in the blood (SOD, IL-10, and HO-1). Across studies 70% (n=7) of assays showed an increase in these markers.

Twenty-nine analytes were investigated in BALF samples. There were 17 markers that were investigated by more than one study, and of those 10 had disagreement between studies. Much of this discordance is attributed to the 2018 study by Fiorelli *et al.* who found that all 12 of the cytokine analyzed in BALF had no change in abundance or were undetected after OLV (17). Eight out of 12 of the findings by Fiorelli *et al.* were in discordance with other studies, and they speculate that this is a result of positive end expiratory pressure (PEEP) playing a protective role against inflammation. Studies using BALF samples selected pro-inflammatory markers almost exclusively (90%, n=26). Across all studies, 66% (n=45) of findings showed an increase in inflammatory markers in lavage, with 24% of findings showing no significant change. Two anti-inflammatory markers were investigated (IL-10, SOD). Two studies found that IL-10 will either increase or decrease in BALF during OLV depending on the type of anaesthetic used (9,18), and three studies finding a decrease or no significant change (17,26,28).

Thirty-two markers were used in the analysis of lung tissue after OLV, but only nine of those markers were investigated by more than one study (arachidonic acid, C-PLA2, CCSP, IL-1β, IL-6, IL-8, MPO, NF-kB binding activity, and TNF-α). In those nine markers there was a 67% (n=6) consensus between studies regarding the effect of OLV on markers concentrations. The markers chosen by researchers to quantify in tissue were primarily inflammatory mediators (75%, n=24). Ninety-one percent (n=31) of the lung tissue inflammatory marker measurements across all studies found a statistically significant increase after OLV.

Twelve publications also used less common bio-samples (*Table 3*). Diverse biomarkers were assayed, including intracellular signaling pathways that control oxidative stress (HO-1, HIF-1α), gene transcription (NF-κB, HIF-1α), trophic and secretory cell responses (ERK, JNK, p38, AKT phosphorylation), as well as secreted cytokines, chemokines and growth factors (*Table 3*).

If one considers the same analyte (i.e., IL-6) in a different sample medium (i.e., blood versus BALF) as a unique biomarker, there were a total of 98 markers tested. If not, there were 73 truly unique biomarker candidates: 29 were analyzed in the BALF, 27 in blood, 32 in lung tissue, and six in both the exhaled breath condensate and cell culture, 3 in pleural fluid, 2 in perfusate. Thirty-three analytes were investigated in more than one study, leaving 65 analytes examined by a single study. The most studied analytes were TNF-α (n=14), followed by IL-6 (n=13), IL-8 (n=9), and IL-10 (n=7). The majority of human studies utilized blood samples, while only a single animal study tested for analytes in blood. Animal studies utilized tissue samples more often (43% *vs.* 8%).

Discussion

We sought to determine the state of the evidence regarding potential biomarkers of VILI secondary to OLV. Although we identified 93 unique biomarker candidates, only 33 of

Table 2 Analytical methods and major findings

Study	Marker test	Major finding
2011 Bastin (8)	Plasma analytes: ELISA; vWF: immunoturbidimetric method (latex agglutination)	Exhaled breath condensate pH ↑. Plasma KL-6 and SP-D ↓. Plasma RAGE, vWF, and IL-6 ↑
2011 Breunig (14)	ELISA: BALF, pleural fluid, blood	BALF, blood, pleural fluid IL-6 ↑ post-operative BALF, pleural fluid IL-1RA ↑. Blood no change. GROα ↑ in pleural fluid, BALF no change, blood undetected
2020 Dai (15)	ELISA: BALF, EBC, venous serum; RT-PCR: lung tissue miRNA	BALF IL-1β, IL-6, IL-8, and total protein ↑ all groups. BALF TNF-α no change all groups. Serum IL-1β, IL-6 ↑. EBC IL-1β and IL-6 ↑ after 3 h OLV. Tissue miR-144-5p, miR-449-3p and miR-451 ↑ in more damaging ventilatory mode
2015 Feng (16)	Blood MDA: TBA method; total protein: Bradford assay; lung tissue HO-1 protein expression: Western blot; lung tissue HO-1 mRNA: RT-PCR	Venous blood MDA ↑ with sevoflurane, ↑↑ with propofol. Venous blood HO-1 ↑ with propofol, ↑↑ with sevoflurane. Lung tissue HO-1 mRNA ↑ with propofol, ↑↑ with sevoflurane
2018 Fiorelli (17)	Markers analyzed with cytokine & growth factor arrays from Evidence Investigator Biochip Array technology®	BALF IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, VEGF, EGF, and MCP-1 no change. BALF IL-8 and IFN-ɣ out of detection range
2017 de la Gala (18)	Western blot: BALF, blood samples	BALF and arterial blood VEGF, IL-2, IL-4, IL-7, and IL-8 ↑ in all groups. Arterial MCP-1 ↑ in all groups. BALF MCP-1, IL-12 no change in all groups. BALF and arterial blood TNF-α, IL-1, and IL-6 ↑ with sevoflurane and ↑↑ with propofol. BALF and arterial blood IL-10 ↑ with sevoflurane, ↓ with propofol
2003 Gama de Abreu (19)	Perfusate TXB2: ELISA	Lung perfusate TXB2 ↑, pH no change
2015 García-de-la-Asunción (20)	EBC and plasma 8-iso-PGF2α : competitive enzyme immunoassay after alkaline hydrolysis	EBC H_2O_2 ↑ during 20 min after resuming TLV. EBC 8-iso-PGF2α ↑ 20 min before TLV resumption. Plasma 8-iso-PGF2α ↑ 5 min before TLV. EBC NO_2 + NO_3 ↑ 20 min before TLV. No change in plasma. EBC pH no change
2013 Liu (23)	Western blot: lung tissue protein expression; RT-PCR: lung tissue mRNA	Tissue CCSP protein and mRNA ↓ in all groups compared to sham, but ↑ in sevoflurane groups compared to OLV. Tissue C-PLA2 protein and mRNA ↑ in all groups
2017 Liu (21)	BALF TNF-α: ELISA; tissue TNF-α: immunohistochemistry techniques; total RNA: spectrophotometry and agarose gel electrophoresis; RNA expression: RT-PCR	BALF TNF-α ↑ and TNF-α mRNA ↑
2018 Liu (22)	Arterial cytokines: ELISA	Plasma TNF-α, IL-6, IL-10, and CRP ↑
2018 Liu (22)	ELISA: arterial serum cytokines	Arterial serum TNF-α, ICAM-1, IL-6 ↑
2011 Mahmoud (24)	BALF and blood cytokines: ELISA; SOD activity: pyrogallol auto-oxidation; albumin concentration: nephelometry; alveolar cell numbers: Coulter Counter	BALF and plasma TNF-α and IL-8 ↑ in all groups. BALF albumin and alveolar cell count ↑ in all groups. BALF and plasma SOD ↑ w/ propofol, no change w/isoflurane. BALF and plasma MDA ↑ with isoflurane, ↓ with propofol
2020 Pan (25)	IκBα: western blot; IκBα phosphorylation: RT-PCR; ELISA: tissue cytokines	Lung tissue IκBα and NFκB-65 phosphorylation ↓. Lung tissue TNF-α, IL-1β, IL-6, IL-8 ↑
2005 Schilling (26)	BALF IL-8, IL-10, and sICAM-1: ELISA; TNF-α and PMN cell elastase: immunoassay	BALF total protein concentration, albumin concentration, TNF-α, PMN elastase, intra-alveolar cell count, and IL-8 ↑; BALF IL-10 ↓

Table 2 (*continued*)

Table 2 (*continued*)

Study	Marker test	Major finding
2007 Schilling (10)	BALF cytokines: ELISA and immunoassay; protein concentration: colorimetric detection assay; cell counts: flow cytometry	BALF TNF-α, IL-8, PMN elastase ↑ in all groups. BALF lymphocyte count ↓ in all groups. BALF post-operative intra-alveolar cell count and granulocyte count ↑ with propofol, no change with desflurane. BALF total protein, albumin, alveolar macrophage count no change in all groups. BALF sICAM-1 ↓ with desflurane, no change with propofol. BALF IL-10 ↓ with propofol, no change with desflurane
2011 Schilling (27)	Multiplex bead immunoassay: arterial serum analytes, BALF	Serum IL-6 ↑. Serum TNF-α, IL-1β, IL-8, IL-10, IL-12 no change. Serum IL-1β no change. Serum IL-8 no change. Dependent lung BALF TNF-α, and IL-1β no change in volatile anaesthetic group, ↑ in propofol group. Dependent lung BALF IL-6 and IL-8 ↑
2006 Schreiber (28)	BALF IL6, TNF-α: PharMingen commercial rat assay; BALF protein concentration: turbidimetry; Neutrophils count: hemocytometer and cell smear using Greunwald stain	BALF protein concentration, neutrophil count, TNF-α, IL-6 ↑
2012 Siegl (29)	BALF analytes: ELISA; Kinase activity: Western blot; protein concentrations: BCA kit; RNA: RT-PCR	Lung tissue ERK, JNK, p38, and AKT phosphorylation ↑. Lung tissue *IL-1β, Tnf, Cxcl1, Cxcl2, Areg* mRNA ↑. BALF IL-1β, IL-6, CXCL-1, CXCL-2, and amphiregulin ↑. BALF TNF ↑ with C57BL/6 strain
2018 Tan (30)	Serum analytes: ELISA	Arterial blood TNF-α, IL-6 and IL-10 ↑
2015 Tojo (31)	Lung tissue analytes: ELISA; RNA: RT-PCR and qPCR	Lung tissue TNF-α, CXCL-1, CCL-2, MPO ↑; HIF-1α ↑ in nonventilated lung; Cell culture NF-κB binding activity (atelectatic lung), HIF-1α, HIF-1 downstream gene *VEGFA* mRNA, *GLUT1* mRNA ↑
2017 Xu (32)	Lung tissue analytes: ELISA; RNA: RT-PCR	Lung tissue MPO ↑. Lung tissue TNF-α, IL-6, ratio of NF-κB to β-actin expression↑ positive correlation with FiO_2. Arterial pH no change
2018 Yang (33)	ELISA: lung tissue arachidonic acid; RT-PCR: lung tissue mRNA	Lung tissue arachidonic acid ↑. Lung tissue C-PLA2 mRNA ↑. Lung tissue CCSP mRNA ↓
2020 Yao (34)	ELISA: venous blood analytes	Venous blood neutrophil elastase, TNF-a, and IL-8 ↓. Venous blood IL-6 ↑
2019 Yin (35)	ELISA, liquid chromatography mass spectrometer	Lung tissue anandamide no change. Lung tissue arachidonic acid, PGI2, TXA2, and LTB4 ↑. Lung tissue PGI2/TXA2 ↓
2012 You (36)	Protein concentration: Bradford assay; NF-κB DNA binding activity: electrophoretic mobility; NF-κB p65: Western blot; BALF TNF-α and IL-8: ELISA	Lung tissue NF-κB, NF-κB DNA binding activity, cytosolic p65 ↑. BALF TNF-α and IL-8 ↑
2019 Zeng (37)	Tissue sample RNA from each lung before and after ventilation: NextGen RNA sequencing	Collapsed lung tissue endothelial barrier gene set expression ↑. Collapsed lung tissue inflammation/immune response gene set expression ↓. Aerated lung tissue inflammation/immune response gene set expression ↑
2016 Zhang (38)	BALF analytes: ELISA	BALF IL-1β, IL-6 and IL-8 ↑
2020 Zhao (39)	Venous serum analytes: ELISA	Venous serum TNF-α, IL-6, IL-10 ↑

Analytical methodology used to detect markers and the major findings of each study. ↑ indicates that the analyte abundance or activity increased with OLV, and ↓ indicates that it decreased with OLV. ELISA, enzyme-linked immunosorbent assay; vWF, von Willebrand factor; BALF, bronchoalveolar lavage fluid; EBC, exhaled breath condensate; RT-PCR, reverse transcription polymerase chain reaction; miRNA, microRNA; MDA, malondialdehyde; TBA, thiobarbituric acid; mRNA, messenger RNA; TNF, tumor necrosis factor; RAGE, receptor for advanced glycation end products; SOD, superoxide dismutase; IL, interleukin; PMN, polymorphonuclear; BCA, bicinchoninic acid; qPCR, quantitative polymerase chain reaction; NF-κB, nuclear factor κB; KL-6, Krebs von den Lungen 6; SP-D, surfactant protein D; IL-1RA, interleukin 1 receptor antagonist; GROα, growth-regulated oncogene α; OLV, one-lung ventilation; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; MCP-1, monocyte chemoattractant protein-1; IFN-ɣ, interferon-ɣ; TXB2, thromboxane B2 ; TLV, two-lung ventilation; CCSP, clara cell secretory protein; CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; MPO, myeloperoxidase; PGI2, prostaglandin I2; TXA2, thromboxane A2 ; LTB4, leukotriene B4.

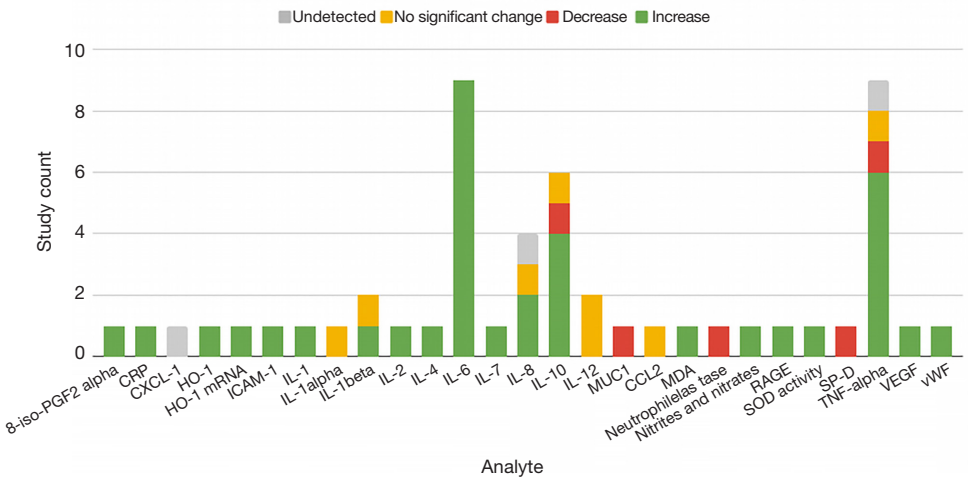

Figure 2 Summary of change in analyte abundance measured in human blood. The height of the bar corresponds with the number of studies that analyzed each biomarker in the blood. Green, red, grey, and orange segments of the bars indicates a study that found that the analyte increased, decreased, did not change, was undetected, or was dependent on the anaesthetic used, respectively. A multicolored bar is indicative of a lack of consensus between studies. CRP, C-reactive protein; CXCL-1, chemokine (C-X-C motif) ligand 1; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; MDA, malondialdehyde; RAGE, receptor for advanced glycation end products; SOD, superoxide dismutase; SP-D, surfactant protein D; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

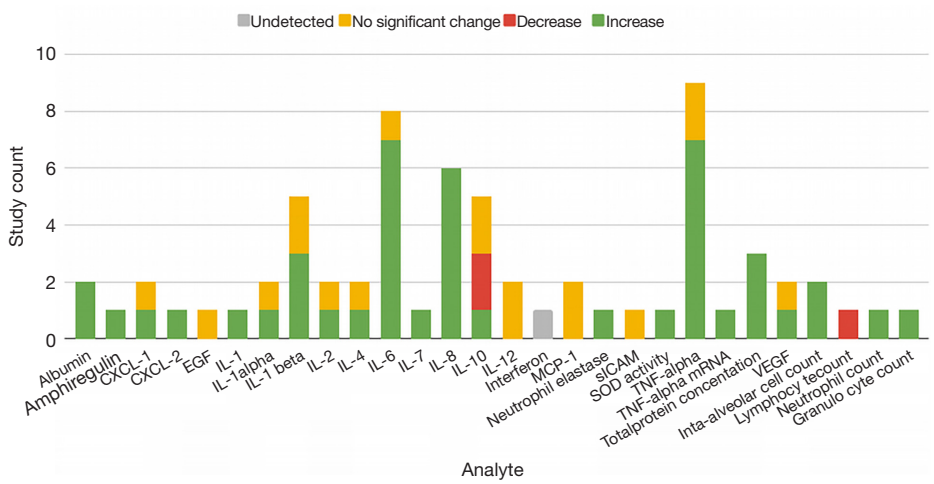

Figure 3 Summary of changes in analyte abundance measured in human and animal BAL samples. The height of the bar corresponds with the number of studies that analyzed each biomarker in the blood. Green, red, grey, and orange segments of the bars indicates a study that found that the analyte increased, decreased, did not change, was undetected, or was dependent on the anaesthetic used, respectively. A multicolored bar is indicative of a lack of consensus between studies. CXCL-1, chemokine (C-X-C motif) ligand 1; EGF, epidermal growth factor; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; sICAM, soluble intercellular adhesion molecule; SOD, superoxide dismutase; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; BAL, bronchoalveolar lavage.

these were measured in more than one study. Thus, 65% of the analytes were identified in only a single study. Of the markers identified in more than one study, fewer than half (n=16) showed concordance with respect to their change in abundance after an OLV intervention. For example, our synthesis of data from multiple studies showed that IL-10 levels may be either elevated, decreased or unchanged after OLV. It is unclear whether this discordance is driven by

Table 3 Analytes in lung tissue, EBC, cell culture, and pleural fluid

Sample type	Analyte	Finding
Human model		
Lung tissue	HO-1 mRNA	↑ Feng 2015 (16)
Exhaled breath condensate	pH	↑ Bastin 2011 (8), no change García-de-la-Asunción 2015 (20)
	H_2O_2	↑ García-de-la-Asunción 2015 (20)
	8-iso-PGF2α	↑ García-de-la-Asunción 2015 (20)
	$NO_2 + NO_3$	↑ García-de-la-Asunción 2015 (20)
Pleural fluid	GROα	↑ Breunig 2011 (14)
	IL-6	↑ Breunig 2011 (14)
	IL-1RA	↑ Breunig 2011 (14)
Animal model		
Sample type	Analyte	Finding
Lung tissue	Anandamide	No change; Yin 2019 (35)
	Arachidonic acid	↑ Yang 2018 (33), Yin 2019 (35)
	ERK, JNK, p38, AKT phosphorylation	↑ Siegl 2012 (29)
	IL-1β, *Tnf, Cxcl1, Cxcl2, Areg* gene expression	↑ Siegl 2012 (29)
	TNF-α	↑ Tojo 2015 (31), Xu 2016 (32), Pan 2020 (25)
	CXCL-1	↑ Tojo 2015 (31)
	MCP-1	↑ Tojo 2015 (31)
	MPO	↑ Tojo 2015 (31), Xu 2016 (32)
	IL-1β	↑ Pan 2020 (25)
	IL-6	↑ Xu 2016 (32), Pan 2020 (25)
	IL-8	↑ Pan 2020 (25)
	HIF-1α	↑ in nonventilated lung; Tojo 2015 (31)
	NF-κB, NF-κB DNA binding activity	↑ You 2012 (36), ↓ Pan 2020 (25)
	NF-κB:β-actin expression	↑ Xu 2016 (32)
	IF-κB phosphorylation	↓ Pan 2020 (25)
	Cytosolic p65	↑ You 2012 (36)
	miR449b-3p, miR451-5p, miR144-5p microRNA	↑ Dai 2020 (15)
	CCSP and CCSP mRNA	↓ Liu 2013 (23), Yang 2018 (33)
	C-PLA2 and C-PLA2 mRNA	↑ Liu 2013 (23), Yang 2018 (33)
	TXA2	↑ Yin 2019 (35)
	PGI2	↑ Yin 2019 (35)
	LTB4	↑ Yin 2019 (35)
	Immune response gene set expression	↑ Yang 2018 (33)
Lung perfusate	TXB2	↑ Gama de Abreu 2003 (19)
	pH	No change; Gama de Abreu 2003 (19)
Exhaled breath condensate	IL-1β	↑ Dai 2020 (15)
	IL-6	↑ Dai 2020 (15)

Analytes measured in parenchymal lung tissue, pleural fluid, lung perfusate, or exhaled breath condensate. ↑ indicates that the analyte abundance or activity increased with OLV, and ↓ indicates that it decreased with OLV. EBC, exhaled breath condensate; GROα, growth-regulated oncogene α; IL, interleukin; IL-1RA, interleukin 1 receptor antagonist; TNF, tumor necrosis factor; CXCL-1, chemokine (C-X-C motif) ligand 1; MCP-1, monocyte chemoattractant protein-1; MPO, myeloperoxidase; NF-κB, nuclear factor κB; CCSP, Clara cell secretory protein; TXA2, thromboxane A2 ; PGI2, prostaglandin I2; LTB4, leukotriene B4; OLV, one-lung ventilation.

differences in analytic techniques, differences in exposures during OLV between studies, or both factors. If analytes in different sample mediums are considered distinct (e.g., IL-6 in blood *vs.* IL-6 in BALF), there was little overlap between analytes investigated by animal and human studies. This is primarily a consequence of the tendency of animal studies to use predominantly tissue samples and of human studies to use predominantly blood samples. There were four examples when animal and human studies did investigate the same analyte in the same sample medium (IL-6, IL-8, TNF-α, and total protein concentration in BALF). In these, there was consensus between human and animal results. There is gap in the literature regarding assessment of both BALF and blood in the same experiment. This is an important gap to address for future research. There may be important changes in both the systemic and local stress response; focusing only on just local (i.e., BALF) or systemic (i.e., blood) responses may result in an incomplete understanding of the processes involved in VILI after OLV.

The analytes most frequently assayed and identified as reliable biomarkers of OLV-induced lung injury in the BALF included the pro-inflammatory cytokines TNF-α (increased in 8 out of 10 studies), IL-8 (increased in 7 out of 7 studies), and IL-6 (increased in 7 out of 8 studies). In the lavage fluid inflammatory markers were found to increase in 67% of investigations. Biomarker results assessing the systemic response to OLV appear to be more consistent; in blood analyses, IL-6 (increased in 9 of 9 studies), and TNF-α (increased in 6 of 8 studies) appeared to be the most consistent biomarker candidates. TNF-α is a part of the primary immune response and can induce synthesis and release of other proinflammatory cytokines in the lung during injury (40). IL-6 has been shown to have a dual nature in animal models of lung injury, as it's effect can be inflammatory, or anti-inflammatory, depending on the model employed (40). Systemic IL-10 levels increased in 4 out of 6 studies that investigated it, while local findings were much less concordant. IL-10 was found to decrease or not significantly change in three studies, and in two studies it was found that the direction of change from baseline was dependent on the anaesthetic used during ventilation. IL-10 is an anti-inflammatory cytokine that can inhibit the expression of inflammatory mediators while having no effect on anti-inflammatory mediators (41,42). Studies of lung injury using animal models have shown that IL-10 can reduce lung injury and plays a protective role in systemic inflammation (43). The most commonly used analytical method was enzyme-linked immunosorbent assay (ELISA) (72% of studies), which lends itself well to protein biomarker detection, as it is highly sensitive and can be calibrated to determine absolute concentrations (44). The most common sample types analyzed were bronchoalveolar lavage (BAL) (55% of studies) and blood (43%), samples routinely taken during thoracic surgery, and that represent local and systemic responses to OLV-induced VILI, respectively.

Fifty-two percent of the studies were conducted in humans. Human biomarker studies may be more relevant for clinical applications but present their own challenges. For ethical reasons, the acceptable experimental exposure human patients may be subjected to is significantly less damaging than animal models, which may explain why only a third (5 of 15) of human studies compared a protective ventilation protocol to a more historical and damaging one (Vt 10–15 mL/kg) (3). Ethically, it is not possible to justify purposefully exerting anesthetic exposures that are thought to be injurious. Thus, the literature is limited to observational studies that have retrospectively assessed the effect of potentially injurious historical ventilation practices.

The effects of OLV exposure on the anti-inflammatory cytokine IL-10 in BALF was the most discordant finding of the studies we reviewed. This may be due to the varying immunomodulatory effects of the anaesthetics employed during mechanical ventilation. For example, de la Gala *et al.* found that IL-10 increased with inhaled sevoflurane, and decreased with propofol (18). The authors suggest that sevoflurane protects against mechanical forces on the lung tissue by reducing alveolar capillary permeability, in agreement with the findings of Voigtsberger *et al.* (45). De la Gala *et al.* note that propofol may induce less of an inflammatory response than volatile anaesthetic in non-thoracic surgery.

There are limitations to our findings. Some of these are limitations of the scoping review but many are inextricably linked to the limitations in the data synthesized for this review. Discordant findings between studies, a relatively small number of studies on this topic, small sample sizes of the existing studies, and the short period of observation of the studies all contribute to limiting the strength of conclusions, and in uncovering the critical gaps in knowledge. Discordant findings between studies may be due to differences in OLV procedure and/or analytical method. Variations in experimental design between studies, such as the difference between studies that only employed protective ventilation practices and studies that used traditional practices, may have led the researchers to different conclusions with or without the availability of a

well-defined control. Furthermore, even in those studies that managed to have control groups, ethical limitations in purposefully exerting "harmful" ventilation practices may have resulted in "experimental" and "control" groups experiencing exposures that were too similar; this has the potential of dampening or suppressing a true effect of clinically relevant OLV. Another limitation is that included studies did not account for potential interaction between pre-ventilation lung function and each analyte.

Another important caveat is that our review reports the response of analytes to OLV-induced lung injury. The FDA's Biomarker Qualification Program requires preclinical biomarkers to not only show correlation with changes induced in the biological process, but it must be demonstrated that the response of the biomarker is exclusive to the change placed on the process (46). Our study cannot fully conclude that these biomarker profiles are entirely driven by exposure to OLV, as some component of inflammatory changes may be driven by the surgical insult. This is an issue which needs to be addressed in the design of future studies.

Conclusions

We sought to identify the evidence regarding candidate biomarkers of VILI caused by OLV. The candidate biomarkers with the most evidence and greatest reliability are general markers of inflammation, such as IL-6 and TNF-α. There is a gap in the literature regarding assessment of both local and systemic response in the same experiment. There remains a substantial body of biomarkers that remain unknown, including the response of individual lungs to OLV. Future studies should assess both in order to obtain more complete understanding of the processes involved in VILI after OLV. A reliable constellation of biomarkers for OLV-induced VILI could allow for rapid preclinical diagnosis to better allocate resources after surgery. Such biomarkers may allow identification of patients at highest risk for developing VILI after thoracic surgery and therefore allocate nursing, monitoring and preventive resources to these patients. Biomarkers for OLV-induced VILI may be used to measure effect of and response to novel preventative or therapeutic interventions. Finally, reliable biomarkers may also one day provide targets for novel interventions, such as immune-modulating drugs that could be used to prevent or reduce the risk of ARDS/ALI after thoracic surgery.

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Footnote

Reporting Checklist: The authors have completed the PRISMA-ScR reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-20-2301/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-20-2301/coif). AJGB, RM, THG, SKS, and LT report that this work was supported by the Optimization of Perioperative Care in Thoracic Surgery Grant (University Medical Group, University of Manitoba) Optimization of Perioperative Care in Thoracic Surgery Grant (University Medical Group, University of Manitoba). AJH participated in a Canadian Thoracic Society advisory panel for a topic unrelated to this publication, sponsored by Boehringer Ingelheim Canada Inc., and received honorarium for lecture facilitation in local research rounds featuring an external speaker from AstraZeneca Canada (topic of presentation not relevant to work in manuscript), and reports grants from Canada Research Chairs Program and Children's Hospital Research Institute of Manitoba (CHRIM). BK and GB received honoraria from AstraZeneca as part of a consultancy board concerning lung cancer treatment and report Optimization of Perioperative Care in Thoracic Surgery Grant (University Medical Group, University of Manitoba). The other authors have no conflict of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Medline search strategy

	Search completed on June 14, 2018	Results
1	Ventilator-Induced Lung Injury/	802
2	vili.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	614
3	vali.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	150
4	(ventilator adj3 (associated or induced)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7854
5	(lung adj3 injur*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	31156
6	4 and 5	2068
7	exp Respiratory Distress Syndrome, Adult/	17465
8	ards.mp.	10344
9	(respiratory adj3 distress*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	49621
10	7 or 8 or 9	50892
11	(ventilator adj3 (associated or induced)).mp.	7854
12	10 and 11	1197
13	1 or 2 or 3 or 6 or 12	2563
14	exp Biomarkers/ or biomark*.mp.	763416
15	(assay* or test*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4449201
16	cytokine*.mp.	360472
17	biochem*.mp.	411054
18	measure*.mp.	3061547
19	histopatholog*.mp.	199176
20	ELISA.mp. or exp Enzyme-Linked Immunosorbent Assay/	226171
21	(enzyme* adj5 assay*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	210191
22	(gel adj3 zymography).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	414
23	exp Histological Techniques/ or histolog*.mp.	1495655
24	(RNA or mRNA).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1100453
25	exp Reverse Transcriptase Polymerase Chain Reaction/ or Rt-PCr.mp.	233434
26	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	9238855
27	13 and 26	1346
28	(neonat* or infant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1280581
29	27 not 28	1222

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Table S2 EMBASE search strategy

	Search Completed on June 14, 2016	Results
	Searches	
1	exp ventilator induced lung injury/	1797
2	vili.mp.	1138
3	vali.mp.	353
4	manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	14681
5	manufacturer, device trade name, keyword, floating subheading word, candidate term word]	55407
6	4 and 5	3605
7	exp respiratory distress syndrome/	66076
8	ards.mp.	17593
9	manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	89748
10	7 or 8 or 9	103805
11	manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	14681
12	10 and 11	2806
13	1 or 2 or 3 or 6 or 12	4889
14	biomarkers.mp. or exp biological marker/	341021
15	exp cytokine/ or cytokine*.mp.	1413210
16	biochemistry/ or biochem*.mp. or exp metabolism/	5329892
17	measure*.mp.	3837486
18	exp histopathology/ or histopatholog*. mp.	606984
19	elisa.mp. or exp enzyme linked immunosorbent assay/	357632
20	manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	409792
21	histology.mp. or exp histology/	409792
22	manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1380721
23	exp RNA directed DNA polymerase/	15350
24	rt-pcr.mp. or exp reverse transcription polymerase chain reaction/	325022
25	manufacturer, device trade name, keyword, floating subheading word, candidate term word]	5618937
26	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	13963706
27	13 and 26	2829
28	manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1078191
29	27 not 28	2633

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