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SYSTEMATIC REVIEW

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Effect of Inhaled Volatile and IV Anesthetics on Biological Markers of Inflammation in Adult ICU and Thoracic Surgical Patients: A Systematic Review and Meta-Analysis

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OBJECTIVES: Inhaled anesthetics may reduce alveolar and systemic inflammation in surgical and critically ill patients. This study aimed to perform a systematic review and meta-analysis comparing the effect of inhaled volatile and IV anesthetics on alveolar and plasma cytokines in patients with surgical or medical acute lung injury.

DATA SOURCES: Medline, Embase, and Cochrane CENTRAL databases from 2000 to July 2021.

STUDY SELECTION: Randomized control trials, prospective, and retrospective observational studies comparing inhaled volatile to IV anesthetics in ventilated adult patients with acute lung injury from lung resection or critical illness.

DATA EXTRACTION: A systematic review and meta-analysis was performed. Primary outcome was alveolar inflammatory cytokines levels that were meta-analyzed using a random effects model. Secondary outcomes were plasma inflammatory cytokine levels, mortality, pulmonary complications, and duration of hospital and ICU stay. The quality of studies was assessed using the Cochrane Risk of Bias tool for randomized control trials and the Cochrane Risk Of Bias In Non-randomized Studies of Interventions tool for retrospective cohort studies.

DATA SYNTHESIS: From 2522 screened studies, 28 (27 thoracic surgery and 1 ICU, $n = 4175$) were included. Meta-analysis of patients undergoing lung resection demonstrated lower levels of alveolar tumor necrosis factor-alpha (TNF-α) (standard mean difference 1.04; 95% CI, 0.32–1.77; $p < 0.01$; I^2 82%) and interleukin (IL)-6 (0.64; 95% CI, 0.52–0.75; I^2 0%; $p < 0.01$) at 1–2 hours in the inhaled anesthesia group, with no difference in other cytokines at various time points. The single ICU study demonstrated lower plasma TNF-α and IL-6 and alveolar TNF-α, IL-6, and IL-8 at 48 hours in patients sedated with sevoflurane compared with midazolam. Clinical outcomes were infrequently reported.

CONCLUSIONS: Limited evidence suggests that inhaled anesthesia may reduce proinflammatory cytokines TNF-α and IL-6 during lung resection and critical illness. Further studies are needed to clarify its effects on biological markers and clinical outcomes.

KEYWORDS: critical care; cytokine; inflammation; lung injury; lung resection; one-lung ventilation; thoracic surgery; volatile anesthetics

Inhaled volatile anesthetics are effective hypnotic agents that are capable of providing both surgical levels of anesthesia and sedation for critically ill patients (1, 2). They also possess excellent bronchodilator and anticonvulsant properties that are used to manage critically ill patients with medical

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KEY POINTS

Question: The goal of this study was to perform a systematic review and meta-analysis comparing the effect of inhaled volatile and IV anesthetics on alveolar and plasma cytokines in patients with surgical or medical acute lung injury.

Findings: Meta-analysis of patients undergoing lung resection (27 studies) demonstrated significantly lower levels of alveolar tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 at 1–2 hours in the inhaled anesthesia group compared with IV anesthetics. A single ICU study demonstrated lower plasma TNF-α and IL-6 and alveolar TNF-α, IL-6, and IL-8 at 48 hours in patients sedated with sevoflurane compared with midazolam.

Meaning: Limited evidence suggests that inhaled anesthesia may reduce proinflammatory cytokines TNF-α and IL-6 during lung resection and critical illness.

refractory status asthmatics and status epilepticus (3). Beyond their hypnotic properties, volatile anesthetics modulate immune function by suppressing proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6, and inhibiting toll-like receptor signaling (4). These effects are mediated through interactions with receptors expressed on neutrophils, macrophages, and lymphocytes, including gamma-aminobutyric acid type A, glycine, nicotinic acetylcholine, *N*-methyl-D-aspartate, and β2 integrins (5). Although largely derived from preclinical and perioperative studies, this mechanistic evidence supports their potential immunomodulatory role in critical illness (6, 7).

In patients with lung injury from either surgical lung resection with one-lung ventilation (OLV) or acute respiratory distress syndrome (ARDS) requiring ICU admission, inhalational anesthetic agents may offer patient and health system benefits such as improved oxygenation, lower morbidity and mortality, and shorter duration of mechanical ventilation and ICU stay (6, 8–10). Given the distinct clinical contexts and pathophysiology of OLV and ARDS, we analyze them separately in this review. A prior meta-analysis of cardiac surgery patients showed that inhalational anesthesia was associated with a lower risk of death, and pulmonary and non-pulmonary complications compared with IV anesthesia (9). These outcomes may in part be attributed to the immunomodulatory effects of inhalational anesthetics, including the reduction of proinflammatory cytokines such as TNF-α, IL-6, and IL-8. We selected these cytokines as primary markers of interest because they are central to the pathogenesis of acute lung injury—driving neutrophil recruitment, vascular permeability, and systemic inflammation—and are among the most consistently reported biomarkers in studies of inhaled anesthetics (4). Inhalational agents also exert broader effects on immune cells, including macrophages, lymphocytes, and neutrophils, through interaction with cellular receptors that modulate inflammatory signaling pathways (4).

Although several studies have examined the effect of inhalational compared with IV anesthesia and sedation on inflammatory cytokines, these data have not been systematically summarized across studies. This systematic review and meta-analysis evaluate the effect of inhaled (intervention) vs. IV (comparison) anesthetics on levels of TNF-α, IL-6, and IL-8 (outcomes), in adult patients with acute lung injury (population) resulting from either surgical OLV or ARDS.

METHODOLOGY

This protocol was developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (11) and registered with PROSPERO (CRD42023444105).

Study Eligibility Criteria

Inclusion Criteria. (1) Studies in mechanically ventilated adult patients 18 years old or older admitted to critical care settings with acute lung injury/ARDS, and surgical patients undergoing OLV, (2) randomized controlled trials, (3) prospective and retrospective observational studies, (4) studies that compare inhaled volatile and IV sedative agents (studies with only one group were not included), (5) inhalational agents include sevoflurane, isoflurane, desflurane, enflurane, and (6) published in English only from 2000 to July 2021. We limited our search to this date range to ensure applicability to contemporary clinical practice, as anesthetic agents and perioperative management strategies have evolved significantly over the past 2

decades, with a shift from older agents such as halothane to modern volatile anesthetics like isoflurane, sevoflurane, and desflurane.

Exclusion Criteria. (1) Quasi-randomized studies, crossover studies, case reports, and case series, (2) preclinical studies and animal studies, (3) studies involving noninvasive ventilation, (4) studies involving pediatric or pregnant patients, (5) abstracts only, and (6) editorial articles without original data.

Outcomes

The primary outcomes were cytokine levels measured in either bronchoalveolar lavage (BAL) fluid or plasma. Although BAL may provide a more direct assessment of local pulmonary inflammation, plasma cytokine levels are more routinely measured and clinically relevant; therefore, we report BAL and plasma data separately. Specific cytokines studied included proinflammatory cytokines TNF-α, IL-6 and IL-8, and anti-inflammatory cytokine IL-10. We selected TNF-α, IL-6, IL-8, and IL-10 as cytokines of interest based on their central role in the inflammatory response associated with acute lung injury, with TNF-α, IL-6, and IL-8 representing key proinflammatory mediators and IL-10 serving as a principal anti-inflammatory regulator. These cytokines are also the most consistently reported across relevant studies, facilitating data comparison and synthesis. In addition to these outcomes, reviewers extracted study details (year, location, number of patients, funding), patient demographics (age, sex), population (thoracic surgery or acute lung injury/ARDS), ventilation details, anesthetic agent use/dose, duration of anesthesia, all cytokines measured and time points for measurements (when available). Secondary outcomes included plasma levels of cytokines TNF-α, IL-6, IL-8, and IL-10, as well as clinical outcomes such as duration of ventilation, ventilator-free days, pulmonary complications (e.g., bronchospasm, atelectasis, pneumonia, pulmonary edema, ARDS), length of ICU and hospital stay, and death reported at any time points. We aimed to quantify clinical outcomes from these studies but this was not feasible given the paucity and heterogeneity of clinical outcome information after data extraction. Primary authors were not contacted for missing information. Quality assessment of all included studies was performed. The Cochrane Risk of Bias (RoB) tool was used for randomized control trials. Retrospective cohort studies were assessed using the Cochrane Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) tool.

Electronic Search

Systematic literature searches were conducted in MEDLINE, Cochrane Central Register of Controlled Trials, and Embase (all via Ovid platform) electronic databases from 2000 to July 2021 and were restricted to adults (older than 18 years). The search was conducted by a medical information specialist with formal training in search strategies for systematic reviews in consultation with the review authors. Only English studies were reviewed. Studies from animal experiments were excluded. Review articles were cross-referenced for additional studies. Authors were not contacted for unpublished data. A sensitive search strategy was developed by combining synonymous searches comprised of controlled vocabularies, such as Medical Subject Headings in Medline or EMTree descriptors in Embase, and free-text terms into the search blocks of two distinct permutations: 1) Volatile/Inhalation anesthetics + (Critical/Intensive care or Thoracic Surgery requiring intubation and ventilation or One-Lung Ventilation) + IV Anesthesia + Inflammation, and 2) Volatile anesthetics + ventilation + IV agents. The search strategies were modified for each database using various types of thesaurus terms and fields within the database. To identify additional relevant studies that met inclusion criteria, the reference lists of the relevant studies were examined, and "clinicaltrials.gov" (National Institutes of Health) and the World Health Organization International Clinical Trials Registry Platform were searched to identify unpublished trials.

Study Selection and Extraction

Seven reviewers (S.R., S.G., C.H., H.R., A.G., A.J., M.S.) independently screened abstracts for study eligibility criteria. All studies were reviewed by two independent individuals and conflicts were resolved by a third reviewer. Full-text editions were obtained for all selected studies. Data extraction was performed using a standardized extraction tool in Excel and confirmed by a second independent reviewer. A plot digitizing tool (WebPlotDigitizer, San Francisco, CA) was used to extract quantitative data from graphical displays when numerical data were unavailable (12). Complete data will be made available upon reasonable request to the authors.

Statistical Analysis

Given the distinct clinical contexts and pathophysiology of OLV and ARDS, we analyzed these two patient cohorts separately. Descriptive statistics were used to describe studies using mean (SD) and frequency (percentage) for continuous and categorical variables respectively. Cytokines measured for patients undergoing thoracic surgery or admitted to ICU with acute lung injury/ARDS were separately described. Given limited data for ICU patients, a meta-analysis was performed only for patients undergoing thoracic surgery. The inflammatory cytokines TNF-α, IL-6, IL-8, and IL-10 were analyzed separately with levels measured at baseline (before incision), and then at 1–2 hours and 3–4 hours; these time points were chosen after reviewing common timing of cytokine level measurements, and time points of 1–2 hours and 3–4 hours coincided with performing OLV and two-lung ventilation during routine lung/esophageal resection. All levels of cytokines were compared between the IV and inhaled groups using mean difference (95% CI) in a meta-analysis. The meta-analysis used a random effects model with restricted maximum likelihood to estimate between study variance, and CIs calculated using Knapp-Hartung adjustment. Heterogeneity was assessed using I^2 (moderate heterogeneity I^2 25–50%, severe heterogeneity $I^2 > 75\%$) and Cochran's Q test, and invariance methods to assess study weighting. If the full-text article had data presented as median, interquartile range, and range, the mean and SD were calculated using the methods outlined by Wan et al and Cochrane Handbook (13, 14). Meta-analyses were conducted using R studio, Version 2023 12.1 (R Foundation for Statistical Computing, Vienna, Austria). The number of available studies reporting cytokine levels at the above time points differed between the cytokines with a maximum of eight studies. Assessment of publication bias via funnel plots and Egger's statistic required a minimum of ten studies using our statistical software, and was thus not performed; however, we acknowledge the potential for such bias as a limitation of our findings.

RESULTS

Study Cohort

The search identified 2522 studies and full-text assessment was performed on 433 studies. Of these, 28 studies met eligibility with 27 thoracic surgery (n = 4,125) and one ICU ARDS (n = 50) study (**Fig. 1**) (6, 8, 15–40). All studies were single center with patient numbers ranging from 20 to 555 and compared sevoflurane to propofol in 86% surgical studies, and sevoflurane to midazolam in the single ICU acute lung injury study (**Supplemental Table 1**, https://links.lww.com/CCX/B524). Study patient characteristics included 56% males with a mean (SD) age of 54.1 (11.8) in the thoracic surgery group, and 72% males with a mean age of 64.5 (12) in the ICU patients. Mean duration of drug use was 4.7 (1.6) hours for thoracic surgical patients and 48 hours for the ICU patients (Supplemental Table 1, https://links.lww.com/CCX/B524).

Thoracic Surgery Patients

Serial change in cytokines TNF-α, IL-6, IL-8, and IL-10 between IV and inhaled anesthetic groups are shown in **Figure 2**.

The number of studies measuring TNF-α included in our meta-analysis were 6 (n = 390) (6, 16, 19, 25, 29, 30) and 6 (n = 514) (6, 15, 19, 21, 25, 30) in BAL and plasma samples respectively. At baseline, there was no significant difference in BAL and plasma TNF-α levels. At 1–2 hours, TNF-α levels were higher in the IV group in Five of six BAL studies (n = 390) with the meta-analysis showing a significant mean difference of 1.04 (95% CI, 0.32–1.77; $p < 0.01$; I^2 82%) (6, 16, 19, 25, 29, 30). Plasma TNF-α levels were higher in the IV group in Three of six studies (n = 514) (6, 15, 19, 21, 25, 30) with no significant difference overall (**Table 1**). At the 3–4 hours timepoint, one study from BAL samples (total 2 studies, 80 patients) (25, 29) and two studies among plasma samples (total 3 studies, 258 patients) (15, 21, 25) demonstrated higher TNF-α levels in the IV group compared with the inhaled group but the pooled meta-analysis revealed no significant difference overall (Table 1).

The number of studies measuring IL-6 included in our meta-analysis were 5 (n = 350) (6, 16, 19, 30, 32) and 9 (n = 630) (6, 15, 19, 21, 23, 27, 30, 33, 36) in BAL and plasma samples, respectively. At baseline, there was no significant difference in BAL or plasma IL-6 between groups. At 1–2 hours, BAL IL-6 levels were higher among IV groups in three of five studies (n = 350) (6, 16, 19, 30, 32) with a significantly higher

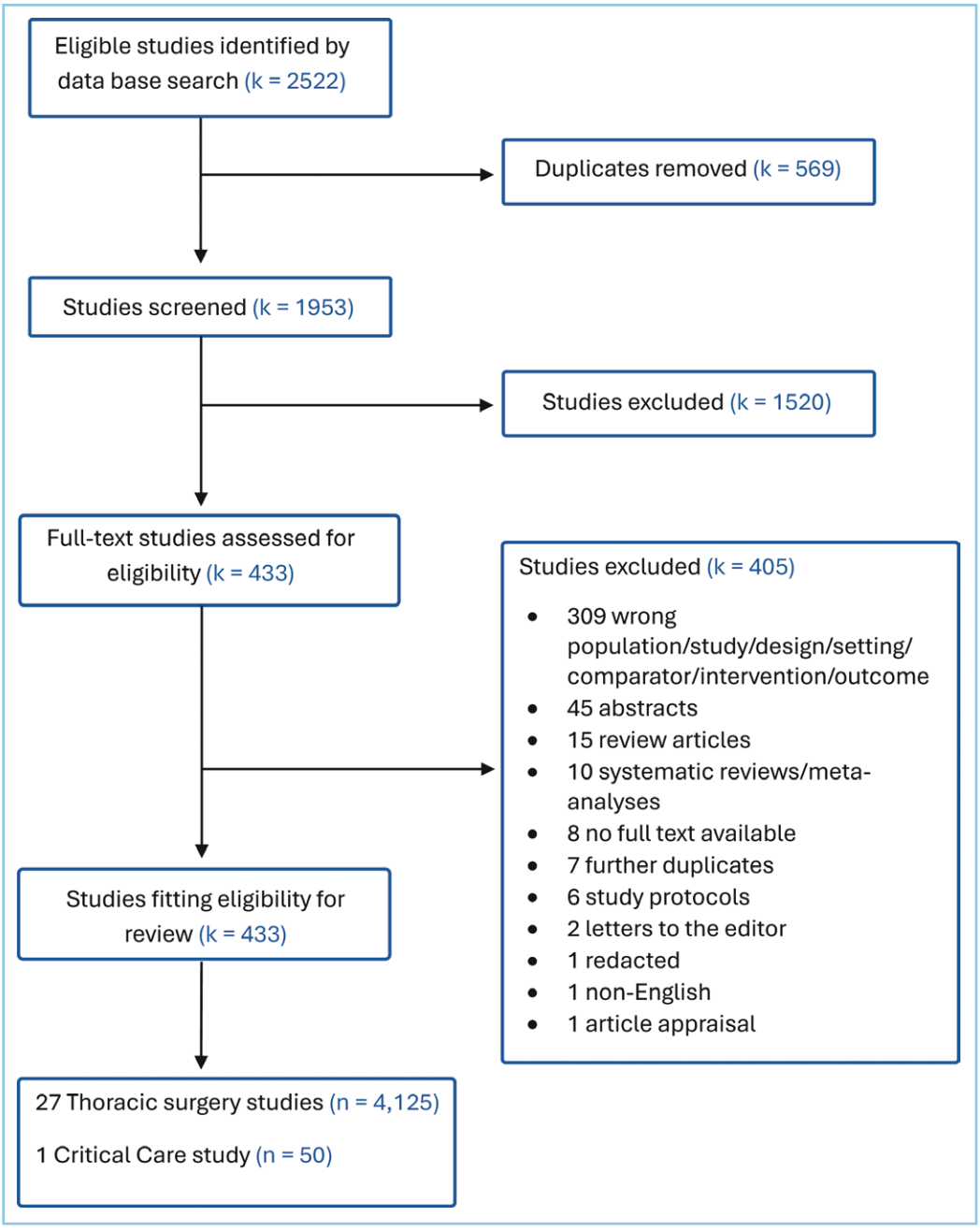

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis study flowchart.

pooled mean difference (0.64; 95% CI, 0.52–0.75; I^2 0%; $p < 0.01$). Plasma IL-6 levels were higher in the IV group in two of seven studies ($n = 562$) (6, 15, 19, 21, 27, 30, 33), whereas four studies showed no difference, and one study showed higher levels among the inhaled anesthetic arm. Overall the meta-analysis revealed no significant difference between the groups. At 3–4 hours, IL-6 was measured in BAL in only one study (36), and in plasma in five studies (15, 21, 23, 27, 36), with pooled meta-analysis data demonstrating no overall difference.

The number of studies measuring IL-8 included in the meta-analysis were 6 ($n = 390$) (6, 16, 25, 29, 30, 32) and 4 ($n = 286$) (6, 19, 30, 36) in BAL and plasma samples, respectively. At baseline, there was no significant difference in BAL or plasma IL-8 between groups. At 1–2 hours, IL-8 levels were higher among the IV anesthetic group in three of six BAL studies ($n = 278$) (6, 16, 25, 29, 30, 32); however overall, there was a nonsignificant standard mean difference of 1.50 (95% CI, –0.27–3.26; $p = 0.08$; I^2 96.6%). Similarly, two of three studies (6, 25, 30) with plasma samples showed higher values of IL-8 among the IV anesthetic group compared with the inhaled anesthetic group with no significant pooled mean difference overall. IL-8 was measured at 3–4 hours in three studies with BAL samples (25, 29, 36) and three studies with plasma samples (25, 27, 36), and the pooled meta-analysis revealed no significant difference overall.

The number of studies measuring anti-inflammatory cytokine IL-10 that were included in the meta-analysis were 3 ($n = 236$) (6, 30, 36) and 5 ($n = 350$) (6, 17, 21, 30, 33) in BAL and plasma samples, respectively. At 1–2 hours, one of two studies ($n = 216$) (6, 30) measuring BAL levels showed higher levels of IL-10 in the inhaled group but the pooled mean difference was not significantly different between groups.

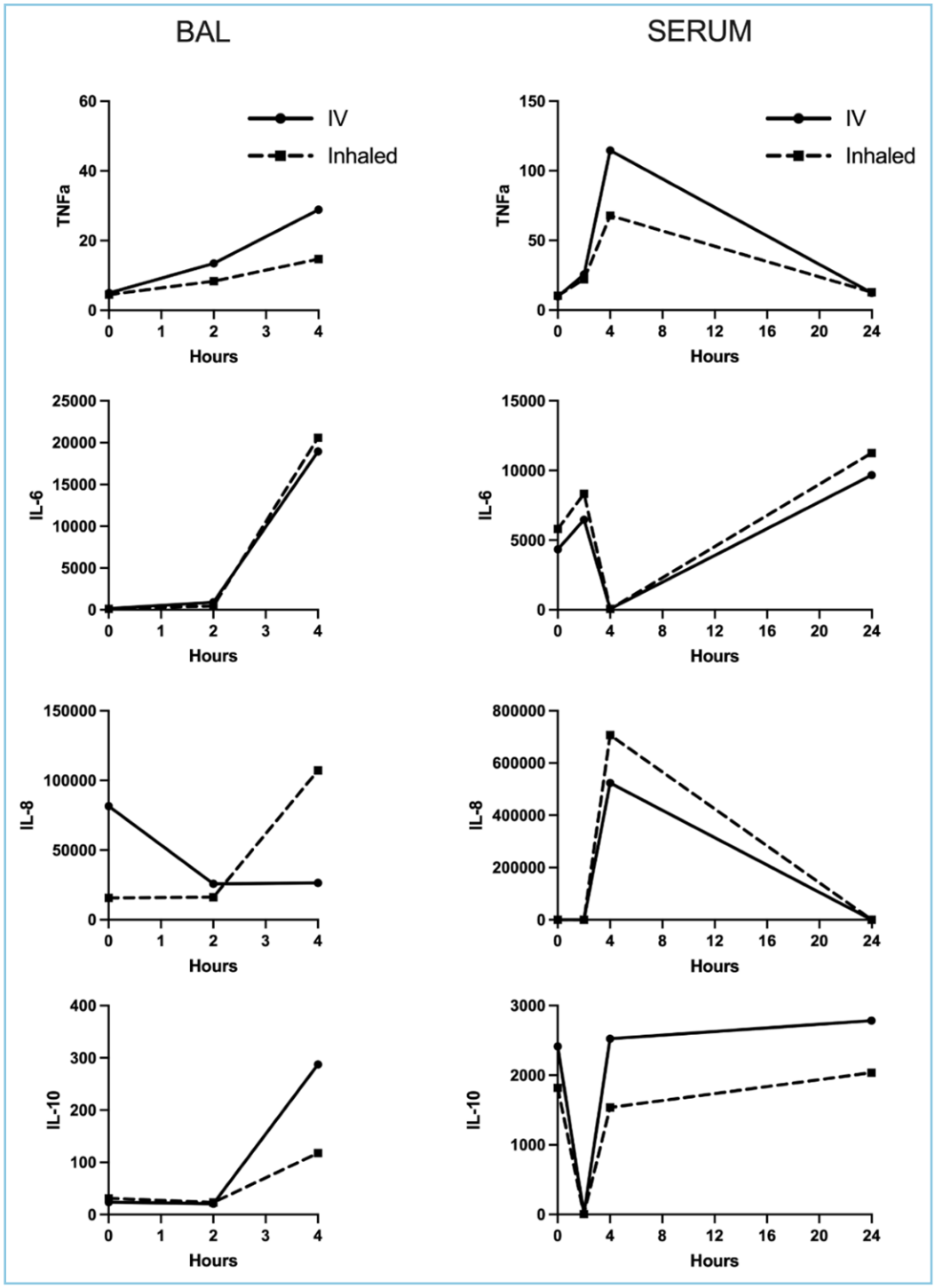

Figure 2. Temporal changes in mean bronchoalveolar lavage (BAL) and plasma cytokine levels across studies. Units are in pg/mL. IL = interleukin, TNF-α = tumor necrosis factor-alpha.

Similarly, two of four studies (21, 30) showed higher plasma levels of IL-10 in the IV group at 1–2 hours, with no significant pooled mean difference between groups overall. Two studies measured BAL IL-10 levels (n = 50) (29, 36) and four studies measured plasma IL-10 levels (n = 170) (17, 21, 27, 33) at 3–4 hours. Pooled data showed no significant difference in BAL or plasma IL-10 levels between groups.

Several other biomarkers were presented infrequently among thoracic surgery studies, including inflammatory factor matrix metalloproteinase-9 (MMP-9) and metrics of oxidative stress such as malondialdehyde (MDA). MMP-9 was only reported in plasma samples in two studies (37, 39) demonstrating increased plasma concentration in the sevoflurane group at chest closure. MDA was measured in plasma samples in two studies (18) with only Yang et al (39) demonstrating significantly higher levels in the sevoflurane arm compared with propofol after chest closure. A comprehensive list of reported biomarkers for each study is presented in Supplemental Table 1 (https://links.lww.com/CCX/B524).

Clinical outcomes were infrequently reported among the thoracic surgery studies. Of the 27 studies, ICU and hospital length of stay were recorded in 6 (n = 406) (6, 16, 23, 25, 35, 38) and 7 (n = 2,177) (6, 23, 25, 26, 34, 38, 40) studies, respectively. ICU length of stay was significantly longer in the propofol arm of three studies (16, 25, 38), with the remainder showing no significant difference between groups. Among studies reporting hospital length

TABLE 1.

Summary of Heterogeneity and Standard Mean Difference of Bronchoalveolar Lavage and Plasma Cytokine Levels in Patients Undergoing IV vs. Inhaled Anesthesia

Biomarker	Timepoint (hr)	Studies/ Participants	IV vs. Inhaled Standard Mean Difference (95% CI)	*p*	I^2 (%, Cochran Q, *p*)
Bronchoalveolar lavage data					
TNF-α					
	Baseline	5/336	0.23 (−0.43 to 0.88)	0.39	59.5, 9.87, 0.04
	1–2	6/390	1.04 (0.32 to 1.77)	0.01[a]	82. 27.80, < 0.01
	3–4	2/80	0.79 (−7.16 to 8.74)	0.43	85, 6.66, 0.01
IL-6					
	Baseline	5/316	0.15 (−0.24 to 0.54)	0.33	36.2, 6.27, 0.18
	1–2	5/350	0.64 (0.52 to 0.75)	< 0.01[a]	0, 0.58, 0.96
	3–4	1/20	−0.11 (−0.99 to 0.76)	0.8	Not available
IL-8					
	Baseline	6/356	0.22 (−0.07 to 0.52)	0.11	12.9, 5.74, 0.33
	1–2	6/390	1.50 (−0.27 to 3.26)	0.08	96.6, 146.21, < 0.01
	3–4	3/100	1.02 (−7.09 to 9.12)	0.64	97.1, 68.50, < 0.01
IL-10					
	Baseline	3/236	−0.27 (−0.88 to 0.34)	0.2	14.1, 2.33, 0.31
	1–2	2/216	−0.79 (−10.85 to 9.27)	0.5	95, 20.02 < 0.01
	3–4	2/50	0.48 (−3.40 to 4.35)	0.36	8.9, 1.10, 0.29
Plasma data					
TNF-α					
	Baseline	6/514	−0.11 (−0.45 to 0.23)	0.44	42.9, 8.76, 0.12
	1–2	6/514	0.67 (−0.42 to 1.76)	0.18	93.4, 76.16, < 0.01
	3–4	3/258	0.94 (−4.13 to 6.02)	0.51	96.7, 60.56, < 0.01
IL-6					
	Baseline	9/630	−0.16 (−0.55 to 0.22)	0.36	72.3, 28.85, < 0.01
	1–2	7/562	0.24 (−0.69 to 1.18)	0.55	94.9, 117.31, < 0.01
	3–4	5/312	0.44 (−1.08 to 1.97)	0.46	91.1, 45.19, < 0.01
IL-8					
	Baseline	4/286	−0.05 (−0.39 to 0.29)	0.66	0, 2.45, 0.48
	1–2	3/266	1.70 (−2.49 to 5.88)	0.22	95.1, 40.52, < 0.01
	3–4	3/106	0.77 (−2.03 to 3.58)	0.36	90.2, 20.32, < 0.01
IL-10					
	Baseline	5/350	0.31 (−1.75 to 2.38)	0.69	94.8, 76.97, < 0.01
	1–2	4/292	0.01 (−0.33 to 0.34)	0.95	0, 2.38, 0.50
	3–4	4/170	1.25 (−2.29 to 4.80)	0.34	96.0, 74.51; < 0.01

IL = interleukin, TNF-α = tumor necrosis factor-alpha.

[a]Statistical significance ($p < 0.05$).

Data are presented as standard mean difference (95% CI).

of stay, there was no significant difference observed between groups. Ventilator-free days were not recorded in any of the included studies. Postoperative pulmonary complications were reported in 11 studies (n = 2,200) (6, 16, 23–27, 35, 36, 38, 40), with varying definitions and reporting standards. Among these, three studies (6, 16, 25) showed an increased rate of postoperative complications in the propofol group, with the remainder showing no difference between groups. Eight studies (n = 2,620) reported on death after surgery during hospitalization, at 30 days or at 1 year (6, 16, 23–25, 27, 38, 40). Only one study (6) reported significantly increased mortality in the IV group, with the remaining seven studies showing no significant difference in mortality between groups. Duration of ventilation was infrequently reported, and was estimated based on other reported metrics such as duration of anesthesia, or total surgical time, with no difference noted between groups (**Supplemental Table 2**, https://links.lww.com/CCX/B524).

ARDS Patients in the ICU

A single ARDS study (n = 50) (8) measured several biomarkers including s-RAGE (soluble receptor for advanced glycation end-products), TNF-α, IL-6, and IL-8. s-RAGE is released from type I alveolar cells in ARDS (41) and was shown to be significantly lower after 48 hours of sevoflurane therapy compared with IV midazolam (p = 0.02 and 0.04 in plasma and BAL, respectively). This study also showed significantly lower alveolar levels of TNF-α, IL-6 and IL-8, and plasma levels of TNF-α and IL-6 in the sevoflurane group compared with the midazolam group at 48 hours. Clinical outcomes measured in this study included pulmonary oxygenation, which was significantly higher at 48 hours among the sevoflurane group compared with midazolam (Pao_2/Fio_2 ratio 205 [56] vs. 166 [59], p = 0.04 for post hoc comparisons). Other clinical outcomes, such as ICU length of stay, ventilator-free days and death, were not significantly different between treatment arms.

Risk of Bias

The risk of bias assessment performed for each study is summarized in **Supplemental Table 3** (https://links.lww.com/CCX/B524). Of the 27 included studies, 25 randomized control trials (RCTs) were assessed by the RoB tool, and two retrospective cohort studies were assessed by the ROBINS-I tool. Among the 25 RCTs, nine studies were identified as low risk of bias, and seven were of uncertain risk. The remainder showed intermediate to high risk, in the domains of deviation from intended interventions (lack of blinding in most RCTs), and bias in missing outcomes/measurement of outcomes. The two non-randomized studies were deemed low risk of bias overall.

DISCUSSION

This systematic review and meta-analysis evaluates and compares the levels of inflammatory cytokines in BAL and plasma between patients receiving inhaled vs. IV anesthetics in patients with acute lung injury resulting from either surgical OLV or ARDS. Our meta-analysis demonstrated higher levels of inflammatory cytokines TNF-α and IL-6 in BAL samples among surgical patients receiving IV compared with inhaled anesthesia—particularly at the 1–2 hours mark during the point of maximal inflammatory insult of OLV and lung resection. No significant differences was seen in pooled data for plasma concentrations of inflammatory cytokines. In a single study of ventilated ARDS patients, sevoflurane, when compared with midazolam reduced alveolar levels of inflammatory cytokines s-RAGE, TNF-α, IL-6 and IL-8, and plasma levels of TNF-α and IL-6.

Both proinflammatory (e.g., TNF-α, IL-6, IL-8) and anti-inflammatory cytokines (e.g., IL-10) are implicated in the pathogenesis of acute lung injury and ARDS (42–46). Local elevations in inflammatory cytokines are seen almost immediately after an initial insult; in the setting of lung injury from OLV or ARDS, this signal would first be expected in alveolar fluid (47–49). TNF-α is released early in the proinflammatory cascade and is known to amplify downstream cytokines, including IL-6, IL-8, and several others (44, 50). In certain lung pathologies (e.g., COVID-19), over-production of TNF-α is persistent and related to poorer prognosis (51). This study may support the hypothesis that inhaled anesthetics such as sevoflurane and isoflurane help attenuate acute alveolar inflammatory responses by modulating the expression of proinflammatory cytokines TNF-α and IL-6. Potential mechanisms implicated in this include activation of mitochondrial K-adenosine triphosphate channels, which preserves mitochondrial function and reduces

cellular injury during inflammatory stress. Inhaled anesthetics also inhibit toll-like receptor signaling, suppress NF-κB activation, and modulate protein kinase pathways, providing a plausible biological basis for their ability to reduce cytokine release and mitigate inflammatory lung injury (4, 5, 52, 53).

There was no significant difference in alveolar or plasma levels of proinflammatory cytokine IL-8 and anti-inflammatory cytokine IL-10 in our meta-analysis.

The reduction in BAL concentrations of inflammatory cytokines with inhaled vs. IV anesthesia did not translate in to corresponding changes in plasma cytokine levels within our meta-analysis. A number of hypotheses are postulated. First, the inflammatory insult of OLV may be insufficient for inducing a systemic inflammatory response. Second, the relatively narrow observation time (up to 4 hr) may be insufficient to detect changes in systemic inflammatory response. Cytokine measurements at later time points such as 24 hours after surgery showed no difference between anesthetic groups but were reported by very few studies that precluded meaningful pooling of data (6, 21, 23, 33, 36). Only a single study gathered data beyond the 24 hours time point (26). Third, the paucity of studies measuring plasma cytokine concentrations in surgical patients undergoing OLV also limits the power to detect any such differences. Fourth, the effect of inhaled anesthetic concentration and duration of exposure may impact the systemic inflammatory response, but this was not studied. This is best illustrated in the single ARDS study, where longer exposure to inhaled anesthetic and longer observation period enabled detection of inflammatory response in both BAL and plasma samples, as well as detection of of attenuating effect in inhaled anesthetics arm at 48 hours (8). These explanations remain hypotheses, and the current data are insufficient to directly evaluate them. Further studies with standardized sampling timepoints, larger sample sizes, and longer follow-up are needed to better understand compartment-specific cytokine dynamics and the systemic effects of inhaled anesthetics.

An important finding of this review is methodologic heterogeneity with respect to the type of markers being measured, assays that are used, and variable measurement time points. It also demonstrates a marked gap in reporting clinical correlation of biomarker findings with patient and health system outcomes such as mortality, morbidity and duration of ventilation and ICU stay. Although the clinical implications remain uncertain, reduced BAL cytokine levels may reflect attenuated pulmonary inflammation, which could contribute to improved gas exchange, less lung injury, and potentially shorter durations of ventilation and ICU stay. Future studies should aim to correlate these biomarker changes with clinical outcomes.

Overall, there was paucity of studies reporting standardized and comprehensive datasets. Given the growing interest that inhaled anesthetics possess immunomodulatory properties, our study highlights the urgent need to mandate imbedding measurement of cytokines and other inflammatory biomarkers into future clinical trials and developing standards for collecting, measuring and reporting these biomarkers as well as related patient and health system outcomes. Future studies should also consider assessing more comprehensive biomarker panels such as proteomics or RNA sequencing.

Additional limitations of this study include the low number of available studies, small sample size, and lack of data on clinical and surgical complexity. We attempted to mitigate this by selecting the most commonly represented cytokines, and in summarizing the data in the most parsimonious way possible, particularly with respect to amalgamating common time points among studies. Due to the paucity of data, a meta-analysis of ICU ARDS patients was not possible. Given extensive heterogeneity in reporting of patient and health system outcomes, a meta-analysis of these variables was also not performed.

Despite these limitations, our study suggests the postulated anti-inflammatory properties of inhaled anesthetics as a possible plausible biologic mechanism for improved outcomes in patients with lung injury from thoracic surgery. Building on knowledge regarding TNF-α dynamics and its role in disease progression (44, 50), this study accordingly highlights a rationale for earlier administration of inhaled anesthetics to improve clinical and biochemical outcomes. Furthermore, it highlights the importance of imbedding measurement of biomarkers into clinical trials to provide mechanistic information in how clinical interventions such as type of anesthetic agents can impact biologic processes and alter the pathophysiology of underlying disease states. Importantly, this may inform the development of future targeted therapeutic interventions. Our study identifies a need for standardization of the methodologic aspects

of biomarker research in this space including choice of biomarker assays, timing of sample collections, and routine reporting of core patient and health system outcomes along with the biomarker data. Finally, it highlights the importance of continuing work in characterizing the immunomodulatory effects of inhaled anesthetics, as novel inflammatory biomarkers are discovered and integrated in clinical research.

This works supports several active large clinical trials (NCT05327296, NCT05312385, NCT04341350, NCT04415060) that will improve our knowledge on the effect of inhaled anesthetics on patient outcomes and help establish protocols for the delivery of inhaled anesthetics in the ICU, guide best practices for administration, ventilator optimization, and troubleshooting. To facilitate broader adoption of inhalational anesthetics, it is essential to collaborate with anesthesia critical care specialists and anesthesiologists to ensure safe and effective implementation (3). In addition, surveying ICU providers to identify barriers, logistical challenges, and educational needs will be crucial in developing tailored strategies that support the integration of inhaled anesthetics into routine critical care practice.

CONCLUSIONS

In patients undergoing OLV for thoracic surgery, inhaled anesthesia was associated with attenuation of proinflammatory cytokines TNF-α and IL-6 compared with IV anesthesia. In ICU patients with ARDS, one RCT reported a similar effect, although this finding remains preliminary and should be interpreted with caution given the limited evidence base. Given the paucity of data and significant heterogeneity among studies, it is not clear if the same effect extends to other reported cytokines, and if these effects translate into meaningful improvement inpatient or health system outcomes. Future research should strive toward standardizing collection and analysis of inflammatory biomarkers, linking biomarker data to standard patient (mortality, morbidity) and health system (duration of ventilation and ICU stay) outcomes, and use of novel inflammatory biomarker assays as they become available for clinical research.

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