Association Between Inflammatory Biomarkers and Acute Respiratory Distress Syndrome or Acute Lung Injury Risk: A Systematic Review and Meta-analysis

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Abstract

Background

The relationship between acute respiratory distress syndrome (ARDS)/acute lung injury (ALI) and levels of certain inflammatory factors remains controversial. The purpose of this meta-analysis was to summarize the available studies evaluated the association between levels of inflammatory factors and ARDS/ALI incidence.

Methods

We searched the PubMed, EmBase, and Cochrane databases for studies published in or before July 2017. For each inflammatory factor, a random effects model was employed to pool results from different studies.

Results

We identified 63 studies that included 6,243 patients in our meta-analysis. Overall, the results indicated that the levels of angiopoietin (ANG)-2 [standard mean difference (SMD): 1.34; $P < 0.001$], interleukin (IL)-1 β (SMD: 0.92; $P = 0.012$), IL-6 (SMD: 0.66; $P = 0.005$), and tumour necrosis factor (TNF)- α (SMD: 0.98; $P = 0.001$) were significantly higher in patients with ARDS/ALI than in unaffected individuals. No significant differences were observed between patients with ARDS/ALI and unaffected individuals in terms of the levels of IL-8 (SMD: 0.61; $P = 0.159$), IL-10 (SMD: 1.10; $P = 0.231$), and plasminogen activator inhibitor (PAI)-1 (SMD: 0.70; $P = 0.060$).

Conclusions

Our findings indicated that ARDS/ALI were associated with elevated levels of ANG-2, IL-1 β , IL-6, and TNF- α , but not with IL-8, IL-10, and PAI-1 levels.

Background

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are pulmonary diseases characterized by inflammatory pulmonary oedema, acute hypoxemia, and accumulation of bilateral pulmonary infiltrates.[1] In the United States, the annual number of ARDS cases is more than 140,000,[2] and the reported rates of ARDS and ALI are 59 and 79 cases for every 100,000 individuals, respectively, with reported mortality rates ranging from 22% to 41%.[3] ARDS and ALI are triggered by several factors that are associated with either direct or indirect injury. Direct injuries that trigger ARDS/ALI include serious pulmonary infection, aspiration of foreign bodies, pulmonary contusion, and oxygen poisoning. Indirect injuries associated with ARDS/ALI include severe systemic infection, severe non-pulmonary trauma, acute pancreatitis, major blood transfusion, and disseminated intravascular coagulation.[4, 5] Patients exposed to the abovementioned factors are at high risk for developing ARDS/ALI. Although the mechanisms underlying ARDS/ALI pathogenesis remain unclear, inflammation has been considered as one of its major inducing factors.

The pathology of ARDS is characterised by diffuse pulmonary interstitial and alveolar oedema due to capillary endothelial and alveolar epithelial cell injuries that lead to acute respiratory insufficiency or failure.[6] In the early stages of ARDS, oedema fluid is concentrated in the alveolar interstitial spaces, and neutrophils adhere to the surface of damaged vascular endothelial cells and migrate to pulmonary interstitial and alveolar cavities. Afterwards, pro-inflammatory factors, such as inflammatory cytokines and proteases, are released and promote neutrophil-mediated lung injury.[7] In the later stage of ARDS, the injured lung is characterized by severe fibrosis and alveolar destruction and reconstruction.[8] The majority of ARDS/ALI patients show rapid disease progression because of this acute inflammatory process.

Various inflammatory mediators that activate the inflammatory cascade and induce secondary diffuse lung parenchymal injury are the primary causes of ARDS/ALI.[9, 10] However, even low levels of inflammatory factors that do not contribute to the amplification of inflammation are associated with the onset of ARDS/ALI, suggesting their possible role as critical drivers of the disease. Therefore, inflammation-related factors can potentially serve as reliable predictors of ARDS/ALI risk.

A previous study systematically reviewed the relationship between plasma biomarkers and ARDS onset and found that levels of Krebs von den Lungen-6 (KL-6), lactate dehydrogenase (LDH), the soluble receptor for advanced glycation end products (RAGE), and von Willebrand factor (vWF) were significantly correlated with ARDS incidence.[11] However, the study did not investigate the inflammatory factors present in the pulmonary oedema fluid, and conclusions were based on a relatively small number of studies for each inflammatory factor. Therefore, further validation of these putative associations is required. This study provided update results by analysing recently published literature that investigated the relationships between specific inflammatory biomarkers and the onset of ARDS/ALI. Furthermore, these relationships were analysed according to different characteristics.

Methods

We conducted the meta-analysis in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12]

Search strategy

We systematically searched the PubMed, EmBase, and Cochrane Central Register of Controlled Trials databases for publications in or before July 2017 using the keywords “acute respiratory distress syndrome,” “acute lung injury,” “inflammation,” “C-reactive protein,” “interleukin,” “tumour necrosis factor,” “cytokines,” “interferon,” “transforming growth factor,” and “risk factor.” The search strategy used for the PubMed database is described in Supplement information (Searching strategy in PubMed). We restricted our search to reports published in English. We also included relevant articles cited as references of the studies.

Data selection and extraction

Literature search and selection were independently performed by two researchers, and any inconsistencies were resolved by group discussion. A study was eligible for inclusion if the following criteria were met: (1) The study included patients with ARDS/ALI; (2) Participants in the control group were not diagnosed with ARDS/ALI; (3). The primary outcomes of interest included ANG-2, IL-1 β , IL6, IL-8, IL10, PAI-1, and TNF- α , while the secondary outcomes included albumin, ANG-1, CC16, CRP, endotoxin, G-CSF, ICAM, IL-2, IL-4, IL-12, KL-6, LDH, MPQ, NF- κ B, PCT, protein C, RAGE, sE-selectin, SP-D, TGF- β 1, TF, TNFR-1, TNFR-2, VEGF, and VEGF. Reviews, editorials, non-human studies, letters, and conference papers were excluded because of insufficient data.

The following parameters were extracted from the articles: first author, country, publication year, study design, sample size, and average age, gender, underlying disease of participants, patient disease status, method of ARDS/ALI diagnosis, specimen source, test time, and follow-up. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality of each study.[13] The NOS is based on the following three subscales: selection of the study group (four categories), comparability of the groups (one category), and outcome assessment (three categories). Data extraction and quality assessment were conducted independently by two authors, and results were examined and adjudicated by an additional author who referred to the original study.

Statistical analysis

In this meta-analysis, the standard mean difference (SMD) and 95% confidence interval (CI) were determined to evaluate the effect of sample size across studies.[14] We pooled the SMDs for each inflammatory factor using a random effects model.[15] The I^2 statistic was used to assess heterogeneity of the SMDs across multiple studies.[16] Means and variances were estimated from medians and ranges as previously described.[17] A sensitivity analysis was performed by sequentially removing each individual study from the meta-analysis.[16] Meta-regression was also conducted for ANG-2, IL-1 β , IL6, IL-8, IL10, PAI-1, and TNF- α based on sample size and mean age. Furthermore, stratified analyses were conducted based on sample size, mean age, patient status, and sample origin. Visual inspection of funnel plots from the Egger's[18] or Begg's test[19] was conducted to evaluate publication bias. All tests were two-tailed, and P-value < 0.05 was considered statistically significant. Data analyses were performed using STATA software (version 10.0; Stata Corporation, College Station, TX, USA).

Results

Literature search

In this study, a total of 302 articles were retrieved from PubMed, 704 from EmBase, and 28 from the Cochrane Library. After removing duplicates, 851 articles passed the inclusion criteria in the meta-analysis. A total of 757 articles were excluded because they were considered irrelevant after scanning the titles and abstracts. Furthermore, articles that were considered to be unrelated based on full-text assessment (n=5), a duplicate publication (n=1), mortality-related studies (n=18), studies with undesired outcomes (n=4), and studies with control groups without ARDS/ALI risk (n=3) were also excluded. Finally, 63 studies that studied a total of 6,243 patients were included in our systematic review (Figure 1).[20-82]

Study characteristics

A total of 59 studies implemented a prospective design, while the remaining four studies employed a retrospective design. Most studies included patient groups with an average age ranging from 40 to 60 years. All participants enrolled in the included studies were at risk of ARDS/ALI, and the majority of samples were collected less than one day after study recruitment. All included studies employed standardized American-European Consensus Conference (AECC) criteria, Berlin definition of ARDS, Lung Injury Score (LIS), and PaO₂/FiO₂ for ARDS/ALI diagnosis. In earlier studies, there were no general criteria for defining ARDS, so the criteria were defined by the authors of each study. The NOS quality analysis for all studies returned scores ranging from 6 to 8, indicating a good overall quality of the included studies (Table 1).

Inflammatory biomarkers and ARDS/ALI

The relationship between ARDS/ALI and angiopoietin (ANG)-2 levels is presented in Figure 2. The overall standard mean difference (SMD) from six studies showed that ARDS/ALI patients had higher ANG-2 levels than those of unaffected individuals [SMD: 1.34; 95% confidence interval (CI): 0.59 to 2.10; P<0.001]. However, significant heterogeneity was detected (I^2 =97.4%; P<0.001). Sensitivity analysis showed that the conclusion did not change after sequential removal of each study (Supplement information Table S1).

The relationship between ARDS/ALI and interleukin (IL)-1 β levels is presented in Figure 3. The pooled SMD from ten studies indicated that ARDS/ALI patients exhibited significantly higher IL-1 β levels than those of the individuals without ARDS/ALI (SMD: 0.92; 95% CI: 0.20 to 1.64; P=0.012). Although substantial heterogeneity was observed across all studies (I^2 =93.1%; P<0.001), the conclusion did not change after sequential exclusion of each study (Supplement information Table S2).

The relationship between ARDS/ALI and IL-6 levels is shown in Figure 4. Overall results showed that ARDS/ALI patients had higher IL-6 levels than those of individuals in the population without ARDS/ALI (SMD: 0.66; 95% CI: 0.20 to 1.13; P=0.005). Heterogeneity was observed at the same degree as the effect across the studies (I^2 =93.6%; P<0.001). Sensitivity analysis showed that the conclusion was not affected by the exclusion of any specific study from the pooled analysis (Supplement information Table S3).

The relationship between ARDS/ALI and IL-8 levels was analysed in 14 studies, and results are shown in Figure 5. No significant differences in IL-8 levels were observed between ARDS/ALI patients and individuals of the population without ARDS/ALI (SMD: 0.61; 95% CI: -0.24 to 1.46; P=0.159). Furthermore, substantial heterogeneity was detected (I^2 =97.8%; P<0.001). Based on sensitivity analysis, we excluded the study conducted by Calfee et al.,[57] which

specifically included a large sample size of trauma patients. We concluded that ARDS/ALI were associated with higher IL-8 levels (SMD: 0.76; 95% CI: 0.11 to 1.40; $P=0.021$) (Supplement information Table S4).

The relationship between ARDS/ALI and IL-10 levels was investigated in seven studies, and results are presented in Figure 6. We detected no significant differences in IL-10 levels between ARDS/ALI and non-ARDS/ALI patients (SMD: 1.10; 95% CI: -0.70 to 2.91; $P=0.231$). Substantial heterogeneity was observed ($I^2=98.3\%$; $P<0.001$). Sensitivity analysis indicated that ARDS/ALI patients had higher IL-10 levels than those of non-ARDS/ALI patients when the study conducted by Roubinian et al. was excluded (Supplement information Table S5).[82]

The relationship between ARDS/ALI and plasminogen activator inhibitor-1 (PAI-1) levels was investigated in seven studies, and results are presented in Figure 7. We detected no significant differences in PAI-1 levels between ARDS/ALI patients and non-ARDS/ALI individuals (SMD: 0.70; 95% CI: -0.03 to 1.43; $P=0.060$). Substantial heterogeneity was observed ($I^2=97.1\%$; $P<0.001$). Sensitivity analysis showed that this result changed after excluding the study conducted by Calfee et al. (Supplement information Table S6).[57]

The relationship between ARDS/ALI and tumour necrosis factor (TNF)- α levels was investigated in 16 studies, and results are shown in Figure 8. Pooled results showed that ARDS/ALI patients had significantly higher TNF- α levels than those of individuals without ARDS/ALI (SMD: 0.98; 95% CI: 0.41 to 1.56; $P=0.001$). Significant heterogeneity was detected across all included studies ($I^2=94.0\%$; $P<0.001$). These results did not change after sequential exclusion of any specific study (Supplement information Table S7).

The correlations between ARDS/ALI and other inflammatory factors based on sample origin are summarized in Table 2. Overall, ARDS/ALI patients showed higher levels of albumin (SMD: 2.15; $P=0.010$), ANG-1 (SMD: 4.60; $P<0.001$), KL-6 (SMD: 2.23; $P=0.044$), myeloperoxidase (MPO) (SMD: 1.75; $P<0.001$), transforming growth factor (TGF)- β 1 (SMD: 0.83; $P=0.013$), transfer factor (TF) (SMD: 5.57; $P<0.001$), and TNF receptor-1 (SMD: 5.40; $P<0.001$). Moreover, ARDS/ALI patients had lower levels of IL-12 (SMD: -1.47; $P<0.001$), surfactant protein D (SP-D) (SMD: -1.17; $P=0.012$), and vascular endothelial growth factor (VEGF) (SMD: -4.52; $P<0.001$) in the bronchial alveolar lavage fluid (BALF). In addition, ARDS/ALI patients had higher levels of KL-6 (SMD: 3.36; $P<0.001$), MPO (SMD: 2.58; $P<0.001$), procalcitonin (PCT) (SMD: 0.41; $P=0.038$), receptor for advanced glycation end products (RAGE) (SMD: 1.64; $P=0.031$), sE-selectin (SMD: 0.55; $P=0.011$), TF (SMD: 3.55; $P<0.001$), and TNF receptor-2 (SMD: 3.82; $P<0.001$) than unaffected individuals. ARDS/ALI was associated with lower IL-12 (SMD: -0.80; $P<0.001$) levels in the blood. No other significant differences were observed between ARDS/ALI and non-ARDS/ALI patients.

Meta-regression and subgroup analyses

A relatively large heterogeneity was observed among the studies included in our meta-analysis. We therefore performed a meta-regression analysis for ANG-2, IL-1 β , IL-6, IL-8, IL-10, PAI-1, and TNF- α ; results are presented in Supplement information Figures S1-S14. Overall, sample size was determined to influence the association between PAI-1 levels and ARDS/ALI ($P=0.025$); no other significant associations were observed. Subgroup analyses were also conducted based on sample size, mean age, patient status, and sample source (Table 3). First, ARDS/ALI did not show a significant influence on ANG-2 levels when the mean age was < 60.0 years, and patients with ALI. Second, ARDS/ALI was not associated with IL-1 β levels if the study sample size was ≥ 100 , patients with ALI, or samples were collected from the BALF. Third, no significant associations were detected between ARDS/ALI and IL-6 levels when the study sample size was ≥ 100 , the mean age was < 60.0 years, patients with ALI, and samples were collected from the blood. Fourth, ARDS/ALI were associated with higher IL-8 levels if the study sample size was < 100 , patients had ARDS, or samples were collected from BALF. Fifth, ARDS/ALI were significantly associated with higher IL-10 levels when the study sample size was < 100 , patients with ARDS, and samples were collected from the BALF. Sixth, ARDS/ALI patients showed significantly higher PAI-1 levels when the study sample size was < 100 , patients with ARDS or ARDS/ALI, and samples were collected from the BALF. Finally, ARDS/ALI were not associated with TNF- α levels if the study sample size was ≥ 100 , patients with ALI or ARDS/ALI.

Publication bias

Funnel plots of inflammatory factors and ARDS/ALI incidence are presented in Supplement information Figures S15-S21. No significant publication biases were detected between ARDS/ALI and IL-1 β [P -value for Egger's test (P_{Egger}): 0.148; P -value for Begg's test (P_{Begg}): 0.283], IL-6 (P_{Egger} : 0.330; P_{Begg} : 0.161), IL-10 (P_{Egger} : 0.874; P_{Egger} : 1.000), PAI-1 (P_{Egger} : 0.184; P_{Begg} : 0.548), and TNF- α (P_{Egger} : 0.111; P_{Begg} : 0.224). Although results of the Begg's tests showed no evidence of publication bias for ANG-2 ($P=0.707$) and IL-8 ($P=0.827$), results of Egger's test showed potential publication bias (P -value for ANG-2: 0.048; P -value for IL-8: 0.013). Conclusions did not change after correction using the trim and fill method.[83]

Discussion

In our study, ARDS/ALI were found to be associated with higher levels of ANG-2, IL-1 β , IL-6, and TNF- α , whereas no significant associations were detected between ARDS/ALI and IL-8, IL-10, and PAI-1 levels. Furthermore, serum levels of KL-6, MPO, RAGE, sE-selectin, TF, and TNF receptor-2 were significantly higher in ARDS/ALI patients than in unaffected individuals. However, ARDS/ALI patients had lower IL-12 levels. BALF concentrations of albumin, ANG-1, KL-6, MPO, TGF- β 1, TF, and TNF receptor-1, were significantly higher in ARDS/ALI patients than in individuals without ARDS/ALI. In addition, ARDS/ALI were associated with lower levels of IL-12 and VEGF. However, heterogeneity among studies was substantial, and the amount of data available was insufficient. Therefore, more research is needed to verify the results of our meta-analysis.

Current treatment for ARDS/ALI consists of respiratory support and immunological therapy. Evidence suggests that the dynamic balance between pro-inflammatory and anti-inflammatory factors plays a key role in the pathogenesis and prognosis of ARDS/ALI.[84] However, cytokine interactions are highly complex and difficult to study. When pro-inflammatory and anti-inflammatory factors are unbalanced, excess inflammatory cytokines are released, which in turn damage the lung tissues or even whole body tissues. Therefore, studies that investigate on inflammatory factors present during the onset of ARDS/ALI

can help elucidate the mechanisms underlying ARDS/ALI pathogenesis and serve as the basis for the development of new treatment approaches against ARDS/ALI.

ANG-2 is a pro-inflammatory cytokine and a member of the vascular growth factor family. ANG-2 mainly promotes cell apoptosis and disrupts vascularization and can also act in conjunction with VEGF to promote neovascularization.[85, 86] The findings of the present study indicated that serum levels of ANG-2 were significantly higher in ARDS/ALI patients than in unaffected individuals. Similar to our current findings, serum levels of ANG-2 have been associated with other diseases, such as sepsis and pulmonary hypertension.[87] In particular, ANG-2 serum levels were associated with the onset of septic shock, and ANG-2 blood concentrations have been observed to increase during endothelial cell inflammation. Furthermore, elevated ANG-2 levels in the blood are known to promote vascular permeability and leakage. However, only a small number of studies have explored the relationship between ANG-2 and ARDS/ALI incidence, and the overall results might have been altered by more recent findings from subsequent studies.

Our current results demonstrated that ARDS/ALI patients had significantly higher serum levels of IL-1 β than individuals without ARDS/ALI. IL-1 β is synthesized and released by mononuclear macrophages. It is recognized as the primary pro-inflammatory cytokine that triggers inflammation and is known to exert multiple biological functions, such as promoting the activity of natural killer cells, increasing chemotaxis of macrophages and neutrophils, and regulating the immune response as an endogenous heat source.[88, 89] During infection or sepsis, IL-1 β can destroy the blood-brain barrier and increase the risk of patient mortality. IL-1 β has an inherent antagonist in the human body, IL-1ra, which can inhibit IL-1 β activity by competitively binding to its receptor. One study included in this analysis showed that IL-1ra is significantly upregulated in ARDS patients.[41] Anakinra is an IL-1 β antagonist approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis and other autoimmune diseases to reduce clinical symptoms and suppress joint destruction. [90] Determining whether this antagonistic effect can be also observed in ARDS patients is an interesting topic for future research.

IL-6 is an acute inflammatory mediator that is released by various cell types. IL-6 is not expressed under normal physiological conditions but is secreted upon stimulation by inflammatory factors.[91] Our study showed that IL-6 concentrations in the BALF were significantly higher in ARDS/ALI patients than in unaffected individuals. Consistent with these results, IL-6 is recognized as a reliable and objective indicator of local lung tissue damage.

IL-8 is a member of the CXC subfamily of chemokines and is produced by various cell types.[92] IL-8 plays a significant role in neutrophil chemotaxis and also inhibits neutrophil apoptosis. In response to local lung tissue injury, IL-8 specifically binds to its receptor, which in turn induces neutrophil aggregation and triggers the release of proteolytic enzymes that mediate inflammation and severe tissue damage. Our findings suggested that IL-8 concentrations are associated with ARDS/ALI incidence.

IL-10 is an anti-inflammatory cytokine that inhibits the secretion of TNF- α , IL-1, and IL-6.[93] IL-10 can also suppress NF- κ B activity and regulate the JAK-STAT pathway. Our analysis suggested that IL-10 levels are correlated with ARDS/ALI incidence. However, the elevated IL-10 levels could have been caused by inflammation in the lungs.

PAI-1 is mainly secreted by vascular endothelial cells, and its production is a risk factor for thrombosis and atherosclerosis.[94] During ARDS pathogenesis, the coagulation-fibrinolysis system is impaired, leading to disseminated intravascular coagulation. Increased PAI-1 levels may lead to local fibrin deposition in lungs. Our results support the idea that PAI-1 plays an important role in the development of ARDS. In addition, PAI-1 has been demonstrated to promote local formation of diseased connective tissue and has been used as an indicator of prognosis of ARDS patients.

The results of our study suggested a strong correlation between TNF- α concentrations in the BALF and ARDS incidence. TNF- α is considered as one of the most important pro-inflammatory factors in ARDS/ALI.[95] TNF- α is a multifunctional pro-inflammatory factor that stimulates the secretion of endothelin and nitric oxide by endothelial cells, promotes the expression of adhesion molecules by endothelial cells and leukocytes, and contributes to the progression of severe microcirculatory disorder. Therefore, TNF- α inhibition can potentially serve as an important approach for ARDS prevention and treatment.

The general objective of this study was to identify inflammatory factors that can serve as drug targets to reduce the incidence of ARDS/ALI. Multiple lines of evidence have suggested that pro-inflammatory cytokines participate in or trigger the inflammatory response in the lungs. However, currently available clinical data are insufficient to verify the correlations between the levels of pro-inflammatory factors and ARDS/ALI incidence.

Our current meta-analysis has several limitations. First, results were based on other studies, but not at the individual level. Second, the included studies showed significant heterogeneity, making it difficult to eliminate alternative explanations for the results, such as differences in the definition of ARDS/ALI, underlying diseases, and sample collection times. Third, grey literature and articles written in other languages were not searched, which could have skewed the obtained results.

Conclusions

In conclusion, our study indicated that ARDS/ALI are associated with elevated levels of ANG-2, IL-1 β , IL-6, and TNF- α , but does not significantly affect IL-8, IL-10, and PAI-1 levels. Furthermore, ARDS/ALI incidence was also determined to be significantly associated with several other inflammatory factors. However, further studies using large sample sizes are required to verify our conclusions. Future studies should also measure the levels of inflammatory factors over time. Log transformation of the measures of inflammatory factors is recommended to obtain a normally distributed data, especially in studies with small sample sizes.

List Of Abbreviations

ARDS: acute respiratory distress syndrome; ALI: acute lung injury; ANG: angiopoietin; SMD: standard mean difference; IL: interleukin; TNF: tumour necrosis factor; PAI: plasminogen activator inhibitor; KL: Krebs von den Lungen; LDH: lactate dehydrogenase; RAGE: receptor for advanced glycation end products; vWF:

Declarations

Ethics approval and consent to participate

No ethical approval was required.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Daishun Liu conceived and designed the experiments. Zhenfeng Liu, Guoqi Zhou, Yugang Zou, Haixia Wang, Xiao Li and DeliangZheng performed the experiments. Zhenfeng Liu analyzed the data and wrote the paper. Daishun Liu contributed reagents/materials/analysis tools. All authors have read and approved the final version of this manuscript.

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Tables

Table 1. Characteristics of subjects in eligible studies

Authors	Country	Year	Study design	Sample size	Mean or median age	Gender (m/f)	Underlying disease	Patients' status	Judgments method of ARDS/ALI	Specimen source
Hoeboer [12]	Netherlands	2015	Prospective	101	64.0	69/32	Fever	ARDS	Berlin definition/LIS Defined	Blood
Roubinian [13]	U.S	2015	Prospective	317	58.0	153/164	Pulmonary transfusion reactions hypoxemia	ALI		Blood
Jones [14]	U.S	2013	Prospective	43	45.6	40/9	Inhalation and Burns	ALI	PaO ₂ /FiO ₂	BAL
Agrawal [15]	U.S	2013	Prospective	230	65.0	79/88	Critically ill	ALI	Berlin definition LIS	Blood
Schultz [16]	Netherlands	2012	Retrospective	20	59.0	13/7	Mechanical ventilation	ALI	AECC	BAL
Quesnel [17]	France	2012	Retrospective	122	49.0	79/43	Critically ill	ALI/ARDS	AECC	BAL
Osaka [18]	Japan	2011	Prospective	27	50.0	12/15	Pneumonia	ALI	PaO ₂ /FiO ₂	Blood
Guervilly [19]	France	2011	Prospective	74	58.0	53/21	Critically ill	ALI	AECC	Blood/B
Jabaudon [20]	France	2011	Prospective	64	59.0	41/23	Severe Sepsis	ALI	AECC	Blood
Aman [21]	Netherlands	2010	Prospective	83	60.0	65/18	Mechanical ventilation	ALI/ARDS	AECC	Blood
Kohno [22]	Japan	2011	Prospective	20	71.0	15/5	Thoracic aortic aneurysm repair	ARDS	PaO ₂ /FiO ₂	Blood
Determann [23]	Netherlands	2010	Prospective	36	58.0	22/14	Mechanical ventilation	ALI/ARDS	LIS	Blood
Determann [24]	Netherlands	2010	Prospective	150	61.0	99/51	Mechanical ventilation	ALI	LIS	Blood/B
Fremont [25]	U.S	2010	Retrospective	192	39.0	131/61	Traumatic injuries	ALI	PaO ₂ /FiO ₂	Blood
Determann [26]	Netherlands	2009	Retrospective	22	65.0	17/5	Ventilator-associated pneumonia	ALI/ARDS	AECC	BAL
Chi [27]	China	2009	Prospective	27	NA	NA	Orthotopic liver transplantation	ALI	PaO ₂ /FiO ₂	Blood
Kropski [28]	U.S	2009	Prospective	32	43.0	15/17	Mechanical ventilation	ARDS	AECC	Blood/B
Calfee [29]	U.S	2009	Prospective	67	51.0	40/27	Hydrostatic pulmonary edema	ALI	AECC	Blood/B
van der Heijden [30]	Netherlands	2008	Prospective	112	56.0	NA	Critically ill	ALI/ARDS	AECC/LIS	Blood
Kurzius-Spencer [31]	U.S	2008	Prospective	21	NA	20/1	Smoke inhalation injury	ARDS	AECC/PaO ₂ /FiO ₂	BAL
Nathani [32]	U.K	2008	Prospective	42	62.0	24/18	ARDS risk population	ARDS/ALI	AECC	Blood/B
Ganter [33]	U.S	2008	Prospective	208	41.0	155/53	Traumatic injuries	ALI	AECC	Blood
Gallagher [34]	U.S	2008	Prospective	63	67.0	35/28	Critically ill	ALI/ARDS	AECC	Blood
Calfee [35]	U.S	2007	Prospective	1451	52.0	609/839	Trauma	ALI	Defined	Blood
Ware [36]	U.S	2007	Prospective	878	52.0	514/364	Acute cardiogenic pulmonary edema	ALI/ARDS	Defined	Blood
Perkins [37]	UK	2007	Prospective	54	NA	NA	ARDS risk population	ALI/ARDS	AECC	BAL
El Solh [38]	U.S	2006	Prospective	51	36.6	22/29	Aspiration pneumonitis	ALI	AECC	Blood/B
Parsons [39]	U.S	2005	Prospective	49	NA	NA	Critically ill	ALI	AECC	Blood
Bouros [40]	Greece	2004	Prospective	59	51.7	43/16	Critically ill	ALI	AECC	Blood/B
Nakae [41]	Japan	2003	Prospective	21	62.0	15/6	Sepsis	ARDS	Defined	Blood
Sato [42]	UK	2004	Prospective	37	39.5	32/5	Mechanical ventilation	ARDS	AECC	Blood
Nys [43]	Belgium	2003	Prospective	67	54.0	43/24	Pneumonia	ARDS	PaO ₂ /FiO ₂	BAL
Gessner [44]	Germany	2003	Prospective	35	60.0	16/19	Acute respiratory failure	ARDS	AECC	BAL
Ishizaka [45]	Japan	2004	Prospective	35	68.0	27/8	Cardiogenic pulmonary edema	ALI	AECC	BAL
Prabhakaran [46]	U.S	2003	Prospective	51	50.0	29/22	Hydrostatic Edema	ARDS	AECC	Blood/B
Grissom [47]	U.S	2003	Prospective	39	51.0	16/17	ARDS risk population	ARDS	AECC	Blood/B
Agouridakis	Greece	2002	Prospective	65	44.0	40/25	Mechanical	ARDS	AECC	Blood/B

[48]							ventilation			
Agouridakis [49]	Greece	2002	Prospective	34	49.0	23/11	Mechanical ventilation	ARDS	AECC	Blood/B
Thickett [50]	UK	2002	Prospective	68	65.0	45/23	ARDS risk population	ARDS	AECC	BAL
Hamacher [51]	France	2002	Prospective	36	43.0	28/8	ARDS risk population	ARDS	AECC	BAL
Takala [52]	Finland	2002	Prospective	52	54.0	29/19	Critically ill	ARDS	AECC	Blood
Park [53]	Switzerland	2001	Prospective	69	43.8	41/28	ARDS risk population	ARDS	AECC	BAL
Hirani [54]	UK	2001	Prospective	56	48.0	NA	Major trauma	ARDS	AECC	BAL
Geerts [55]	Belgium	2001	Prospective	26	52.0	19/7	ARDS risk population	ARDS	AECC	BAL
Siemiatkowski [56]	Poland	2000	Prospective	36	44.3	27/9	Major trauma	ARDS	LIS	Blood
Armstrong [57]	UK	2000	Prospective	67	62.0	44/23	Critically ill	ARDS/ALI	AECC	BAL
Bauer [58]	Spain	2000	Prospective	66	57.2	NA	Pneumonia	ARDS	AECC	Blood
Gando [59]	Japan	1999	Prospective	58	58.0	37/21	Critically ill	ARDS	Defined	Blood
Donnelly [60]	Scotland	1999	Prospective	61	NA	NA	Trauma	ARDS	Defined	BAL
Parsons [61]	U.S	1997	Prospective	77	37.5	53/24	ARDS risk population	ARDS	Defined	Blood
Schutte [62]	Germany	1996	Prospective	56	54.5	45/11	Pneumonia	ARDS	AECC	Blood/B
Chollet-Martin [63]	France	1996	Prospective	14	61.0	NA	Pneumonia	ARDS	LIS	Blood/B
Ricou [64]	U.S	1996	Prospective	33	48.0	24/9	Critically ill	ARDS	LIS	Blood/B
Schwartz [65]	U.S	1996	Prospective	12	45.0	7/5	Mechanical ventilation	ARDS	LIS	BAL
Jorens [66]	UK	1995	Prospective	35	56.6	31/4	Cardiopulmonary bypass	ARDS	Defined	BAL
Fuchs-buder [67]	Switzerland	1996	Prospective	21	NA	NA	Critically ill	ARDS	LIS	BAL
Leff [68]	U.S	1993	Prospective	26	NA	NA	Sepsis	ARDS	Defined	Blood
Sakamaki [69]	Japan	1995	Prospective	48	49.0	29/19	Sepsis	ARDS	Defined	Blood
Donnelly [70]	U.S	1994	Prospective	82	49.5	NA	ARDS risk population	ARDS	LIS	Blood
Moalli [71]	U.S	1989	Prospective	47	66.0	NA	ARDS risk population	ARDS	Defined	Blood
Rubin [72]	U.S	1990	Prospective	45	NA	NA	Sepsis	ARDS	LIS	Blood
Roten [73]	Switzerland	1990	Prospective	50	49.0	31/19	Critically ill	ARDS	Defined	Blood
Parsons [74]	U.S	1992	Prospective	103	46.0	77/26	ARDS risk population	ARDS	Defined	Blood

Table 2. The summary results of the association of other inflammatory factors with ARDS/ALI based on specimen source

Factors	No. of studies	Groups	SMD	95% CI	P value	Heterogeneity (%)	P for heterogeneity
Albumin	1	Blood	-0.82	-1.79 to 0.14	0.095	-	-
	2	BALF	2.15	0.51 to 3.79	0.010	82.2	0.018
ANG-1	1	Blood	0.80	0.28 to 2.30	0.676	-	-
	1	BALF	4.60	3.09 to 6.12	<0.001	-	-
CC16	3	Blood	-0.31	-2.7 to 2.08	0.799	96.8	<0.001
	4	BALF	-0.44	-3.06 to 2.18	0.742	96.1	<0.001
CRP	3	Blood	1.64	-0.31 to 3.59	0.100	92.2	<0.001
Endotoxin	2	BALF	0.30	-0.15 to 0.75	0.191	0.0	0.887
G-CSF	2	Blood	-0.49	-1.47 to 0.49	0.326	93.9	<0.001
ICAM	4	Blood	-0.14	-2.47 to 2.20	0.909	99.4	<0.001
	2	BALF	0.79	-1.61 to 3.18	0.520	96.3	<0.001
IL-2	2	Blood	0.01	-0.26 to 0.28	0.934	0.0	0.817
	1	BALF	-0.36	-1.16 to 0.44	0.380	-	-
IL-4	2	Blood	0.69	-0.16 to 1.54	0.111	81.1	0.022
	1	BALF	0.30	-0.38 to 0.99	0.387	-	-
IL-12	1	Blood	-0.8	-1.09 to -0.50	<0.001	-	-
	1	BALF	-1.47	-2.18 to -0.75	<0.001	-	-
KL-6	3	Blood	3.36	2.50 to 4.21	<0.001	49.5	0.138
	3	BALF	2.23	0.06 to 4.41	0.044	93.0	<0.001
LDH	2	Blood	1.82	-0.23 to 3.87	0.082	85.9	<0.001
MPO	1	Blood	2.58	2.20 to 2.97	<0.001	-	-
	1	BALF	1.75	0.90 to 2.60	<0.001	-	-
NF- κ β	2	BALF	0.86	-0.45 to 2.17	0.198	67.1	0.081
PCT	2	Blood	0.41	0.02 to 0.80	0.038	23.7	0.252
Protein C	2	Blood	-2.00	-7.15 to 3.16	0.447	99.9	<0.001
RAGE	4	Blood	1.64	0.15 to 3.14	0.031	96.3	<0.001
	1	BALF	0.16	-0.68 to 1.00	0.704	-	-
sE-selectin	3	Blood	0.55	0.13 to 0.97	0.011	15.2	0.307
SP-D	4	Blood	-0.05	-1.65 to 1.55	0.950	98.5	<0.001
	1	BALF	-1.17	-2.08 to -0.25	0.012	-	-
TGF- β 1	4	BALF	0.83	0.17 to 1.49	0.013	81.2	<0.001
TF	1	Blood	3.55	2.71 to 4.39	<0.001	-	-
	1	BALF	5.57	3.55 to 7.60	<0.001	-	-
TNFR-1	2	Blood	1.61	-4.42 to 7.64	0.601	98.9	<0.001
	1	BALF	5.40	4.22 to 6.58	<0.001	-	-
TNFR-2	1	Blood	3.82	2.80 to 4.83	<0.001	-	-
	2	BALF	3.22	-2.62 to 9.05	0.280	98.4	<0.001
VEGF	1	Blood	0.49	-0.23 to 1.04	0.063	-	-
	1	BALF	-4.52	-5.43 to -3.61	<0.001	-	-
vWF	6	Blood	0.81	-0.94 to 2.54	0.365	99.2	<0.001

Table 3. Subgroup analysis of inflammatory related factors and incidence of ARDS/ALI

Inflammatory factors	Groups	No. of studies	SMD	95%CI	P value	Heterogeneity (%)	P for heterogeneity
ANG-2	Sample size						
	≥ 100	5	1.30	0.47 to 2.13	0.002	97.8	<0.001
	< 100	1	1.59	0.97 to 2.20	<0.001	-	-
	Mean age (years)						
	≥ 60.0	3	1.74	1.30 to 2.18	<0.001	51.1	0.129
	< 60.0	3	0.98	-0.02 to 1.98	0.055	98.4	<0.001
	Patients' status						
	ARDS	1	2.15	1.65 to 2.64	<0.001	-	-
	ALI	3	1.38	-0.19 to 2.93	0.085	98.3	<0.001
	ARDS/ALI	2	0.91	-0.34 to 2.16	0.152	93.7	<0.001
	Specimen source						
	Blood	6	1.34	0.59 to 2.10	<0.001	97.4	<0.001
	BALF	0	-	-	-	-	-
	IL-1β						
IL-6	Sample size						
	≥ 100	2	-0.33	-1.05 to 0.40	0.379	79.7	0.026
	< 100	8	1.26	0.48 to 2.04	0.002	89.9	<0.001
	Mean age (years)						
	≥ 60.0	1	-0.75	-1.34 to -0.15	0.014	-	-
	< 60.0	7	1.33	0.43 to 2.23	0.004	94.4	<0.001
	Patients' status						
	ARDS	6	1.39	0.41 to 2.37	0.005	91.8	<0.001
	ALI	4	0.22	-0.59 to 1.04	0.590	88.0	<0.001
	Specimen source						
	Blood	5	1.39	0.15 to 2.62	0.028	95.3	<0.001
	BALF	6	0.73	-0.19 to 1.66	0.121	90.2	<0.001
	IL-8						
	Sample size						
IL-8	≥ 100	5	0.45	-0.26 to 1.16	0.215	96.1	<0.001
	< 100	8	0.83	0.11 to 1.55	0.024	91.6	<0.001
	Mean age (years)						
	≥ 60.0	3	1.49	0.37 to 2.61	0.009	92.1	<0.001
	< 60.0	10	0.43	-0.06 to 0.92	0.088	93.1	<0.001
	Patients' status						
	ARDS	7	0.80	0.03 to 1.57	0.043	92.6	<0.001
	ALI	6	0.54	-0.12 to 1.20	0.108	95.3	<0.001
	Specimen source						
	Blood	11	0.37	-0.04 to 0.77	0.074	88.8	<0.001
	BALF	7	1.33	0.24 to 2.42	0.016	93.2	<0.001
	IL-10						
	Sample size						
	≥ 100	4	0.06	-1.84 to 1.95	0.953	99.2	<0.001
IL-10	< 100	10	0.74	0.15 to 1.33	0.014	87.7	<0.001
	Mean age (years)						
	≥ 60.0	2	2.87	-1.95 to 7.70	0.243	96.6	<0.001
	< 60.0	9	0.52	-0.61 to 1.65	0.364	98.5	<0.001
	Patients' status						
	ARDS	6	1.28	0.34 to 2.21	0.007	90.4	<0.001
	ALI	7	0.13	-1.13 to 1.40	0.834	98.6	<0.001
	ARDS/ALI	1	-0.37	-0.93 to 0.20	0.201	-	-
	Specimen source						
	Blood	9	0.67	-0.50 to 1.85	0.262	98.3	<0.001
	BALF	8	0.78	0.08 to 1.48	0.029	86.1	<0.001
	PAI-1						
	Sample size						
	≥ 100	2	-0.90	-7.01 to 5.21	0.772	99.6	<0.001
PAI-1	< 100	5	1.89	0.59 to 3.19	0.004	93.4	<0.001
	Mean age (years)						
	≥ 60.0	0	-	-	-	-	-
	< 60.0	6	1.29	-0.75 to 3.32	0.216	98.6	<0.001
	Patients' status						
	ARDS	3	1.62	0.05 to 3.19	0.043	91.7	<0.001
	ALI	4	0.73	-2.15 to 3.61	0.618	99.0	<0.001
	Specimen source						
	Blood	4	0.18	-2.64 to 3.00	0.899	99.0	<0.001
	BALF	4	1.90	0.12 to 3.68	0.037	94.3	<0.001
	Sample size						
	≥ 100	3	0.42	-0.78 to 1.61	0.497	98.8	<0.001
	< 100	4	0.89	0.52 to 1.27	<0.001	42.1	0.159
	Mean age (years)						
	≥ 60.0	1	0.31	-0.35 to 0.96	0.363	-	-
PAI-1	< 60.0	6	0.77	-0.04 to 1.57	0.063	97.6	<0.001
	Patients' status						
	ARDS	2	0.68	0.06 to 1.29	0.030	61.1	0.109
	ALI	4	0.77	-0.54 to 2.08	0.250	98.1	<0.001
	ARDS/ALI	1	0.66	0.45 to 0.87	<0.001	-	-
	Specimen source						
	Blood	6	0.44	-0.34 to 1.22	0.267	97.2	<0.001
	BALF	3	1.57	0.77 to 2.36	<0.001	69.6	0.037
	TNF-α						
	Sample size						
	≥ 100	4	1.66	-0.10 to 3.43	0.065	98.3	<0.001
	< 100	12	0.76	0.27 to 1.24	0.002	85.5	<0.001
	Mean age (years)						

≥ 60.0	3	0.51	0.17 to 0.84	0.003	0.0	0.482
< 60.0	10	1.36	0.52 to 2.20	0.002	96.0	<0.001
Patients' status						
ARDS	9	1.05	0.11 to 1.99	0.028	94.7	<0.001
ALI	5	0.90	-0.14 to 1.95	0.090	95.1	<0.001
ARDS/ALI	2	0.92	-0.14 to 1.97	0.089	86.5	0.007
Specimen source						
Blood	9	1.00	0.12 to 1.89	0.026	95.7	<0.001
BALF	10	0.91	0.26 to 1.57	0.006	87.6	<0.001

Figures

Figure 1

PRISMA flowchart illustrating the process of study selection in our analysis.

Figure 2

Forest plot comparing ANG-2 levels between ARDS/ALI patients and unaffected individuals.

Figure 3

Forest plot comparing IL-1 β levels between ARDS/ALI patients and unaffected individuals.

Figure 4

Forest plot comparing IL-6 levels between ARDS/ALI patients and unaffected individuals.

Figure 5

Forest plot comparing IL-8 levels between ARDS/ALI patients and unaffected individuals.

Figure 6

Forest plot comparing IL-10 levels between ARDS/ALI patients and unaffected individuals.

Figure 7

Forest plot comparing PAI-1 levels between ARDS/ALI patients and unaffected individuals.

Figure 8

Forest plot comparing TNF- α levels between ARDS/ALI patients and unaffected individuals.

Supplementary Files

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