Cigarette smoking as a risk factor for acute respiratory distress syndrome: a systematic review and meta-analysis

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Abstract

Background and objectives: Numerous experimental studies have linked cigarette smoking to lung injury. However, it is still debated on whether cigarette smoking is a risk factor for the development of acute lung injury/acute respiratory distress syndrome (ALI/ARDS). The study aimed to solve the controversy by performing systematic review and meta-analysis.

Methods: Electronic databases including Pubmed, Google scholar, Embase and Scopus were searched from inception to April 2014. Studies investigated the association of cigarette smoking and ALI/ARDS were included. Non-randomized studies were assessment for their methodological quality by using Newcastle-Ottawa scale. Meta-analysis was performed by using random effects model and subgroup analyses were performed to address the clinical heterogeneity. Publication bias was assessed by using Egger’s test.

Main result: Of the 17 studies included in our analysis, 15 provided data on effect size and were meta-analyzable. Component studies involved heterogeneous populations including major surgery, trauma, septic shock, general population, influenza A infection and transfusion. The combined results showed that cigarette smoking was not a risk factor for the development of ALI/ARDS (OR: 1.00, 95% CI: 0.99-1.01). In subgroup analysis, the same result was obtained in general population (OR: 2.03, 95% CI: 0.06-4.01), patients with major surgery or trauma (OR: 1.20, 95% CI: 0.48-1.93) and patients with other risks of ALI/ARDS (OR: 1.00, 95% CI: 0.99-1.01).

Conclusion: Our study demonstrates that cigarette smoking is not associated with increased risk of ALI/ARDS in critically ill patients. However, the relationship in general population is still controversial and requires further confirmation.
Introduction

Acute respiratory distress syndrome (ARDS) is a major cause of mortality and morbidity in intensive care unit (ARDS). The incidence of ARDS is reported to be ranged between 4 to 20 cases / 100,000 population / year according to differences in the methodology used to define ARDS or ALI.[1-3] In a large cohort study involving 78 European ICUs, Brun-Buisson C and coworkers reported that acute lung injury (ALI) occurred in 7.1% of ICU admissions and in 16.1% of mechanically ventilated patients.[4] ALI/ARDS is associated with a mortality rate ranging from 30% to 75%, depending on different patient mix. Although some report showed a declining mortality of ARDS, most cohort studies reported similar mortality rate to that of previous decades.[5] Management of ALI/ARDS is multidisciplinary and requires combined interventions that includes but not limited to optimization of volume status, protective ventilation strategy and treatment of underlying diseases.[6 7] However, some interventions appear to be beneficial only in severe form of ARDS, those include extracorporeal membrane oxygenation (ECMO) and prone position ventilation.[8] This raises the importance of risk stratification of ALI/ARDS. Although the commonly used method nowadays in risk stratification is based on oxygenation index, it is limited in timeliness that at the time of occurrence of severe hypoxia patients may immediately die.

Therefore, it could be clinically helpful to identify patients with risk of ALI/ARDS as early as possible and this motivates investigators to look for risk factors of ALI/ARDS. Cigarette smoking has long been established to be an important risk factor for varieties of lung diseases including lung cancer and chronic obstructive pulmonary disease.[9] However, it is still unknown whether cigarette smoking increases risk of ALI/ARDS in acute setting. Although several studies have reported an association between smoking and ALI/ARDS, this cannot be replicated in other studies.[10-13] Therefore, we conducted a systematic review and meta-analysis to explore whether smoking was a true risk factor for ALI/ARDS.

Methods

Searching strategy and study selection

The study was approved by the ethics committee of Jinhua municipal central hospital. Electronic databases including Pubmed, Google scholar, Embase and Scopus were searched from inception to April 2014. The core search terms consisted of cigarette smoking and ALI/ARDS. Detailed searching strategy and results performed in Pubmed were shown in appendix file. The searching strategy was adapted to other databases and results were not shown here.

Studies were included if they investigated the association of cigarette smoking and ALI/ARDS. Both cohort and case-control studies were included irrespective of they were retrospective or prospective in design. Methodology used to investigate the association between smoking and ALI/ARDS included multivariable analysis and matching technique. Exclusion criteria were 1) non-human experimental studies; 2) studies investigate the prognostic value of cigarette smoking in ARDS patients (patients were already confirmed to have ARDS at enrollment); and 3) studies used duplicated cohort with other studies.

Data on following aspects were extracted from included studies: first author’s name, year of
publication, study population and settings, study design (prospective vs retrospective), sample size, incidence of ALI/ARDS, definitions of cigarette smoking, the number of covariates used for risk adjustment, and outcome of interest (ARDS or ALI or both), odds ratio (OR) or risk ratio (RR) of smoking for ALI/ARDS development. For studies reported OR or RR for more than one multivariable models, we extracted the one adjusted by the largest number of covariates.

Quality assessment with Newcastle-Ottawa scale
Non-randomized studies were assessment for their methodological quality by using Newcastle-Ottawa scale.[14] The scale comprised three major parts: selection, comparability and outcome. Selection was assessed from four aspects including representativeness of exposed cohort, selection of non-exposed cohort, ascertainment of exposure and demonstration that outcome of interest was not present at start of study. One star can be assigned to each item if the condition was satisfied. Comparability was assessed on the basis of the design or analysis. A maximum of 2 stars can be allotted in this category. Outcome comprised three components: assessment of outcome, was follow-up long enough for outcomes to occur and adequacy of follow-up cohort. One star can be assigned to each item if the condition is considered to be adequate.

Statistical analysis
Due to expected heterogeneity in study population, we used random effects model for analysis. The parameter $\tau^2$ (tau-squared) is the between study variance and can be estimated by using DerSimonian and Laird method:

$$\tau^2 = \frac{Q - df}{C},$$

where

$$Q = \sum_{i=1}^{k} W_i Y_i - \left( \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \right)^2$$

$$df = k - 1$$

where $k$ is the number of included studies, and

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$$

Then, the total variance was composed of the between-study variance and within study variance, and the mean OR was estimated by using inverse-variance method.[15] Heterogeneity was quantified as the proportion of between-study variance in the total variance, and can be written as

$$I^2 = \left( \frac{Q - df}{Q} \right) \times 100\%$$

Values on the order of 25%, 50% and 75% can be considered as low, moderate and high heterogeneity.

When studies reported RR to estimate relative risk of smoking on ALI/ARDS development, we
transformed RR to OR by the equation:

\[
\text{OR} = \frac{RR \times (1 - P_0)}{1 - P_0 \times RR}
\]

Where RR is relative risk, OR is odds ratio and P0 indicates absolute risk in the non-smoker group, given as a fraction (e.g. fill in 10% risk as 0.1).[16] When P0<0.1, we approximate OR with RR:

\[ OR \approx RR. \]

Publication bias was assessed by using Egger’s test. Standard normal deviate (SND), defined as the odds ratio divided by its standard error, was regressed against the precision of OR. Precision of OR was defined as the inverse of the standard error.

\[ \text{SND} = a + b \times \frac{1}{\text{standard error}} \]

Where a is the intercept and b is the slope indicating the size and direction of the effect.

Intercept a provides a measure of asymmetry: the larger its deviation from zero the more pronounced the asymmetry.[17]

All statistical analysis was performed by using Stata 13.1 (StataCorp, College Station, Texas 77845 USA). Two-tailed \( p<0.05 \) was considered to be statistically significant.

Results

Our initial search identified 314 citations and 153 of them were excluded by inspection of the title and abstract (figure 1). The remaining 161 citations were retrieved for further review and 144 were excluded because they were irrelevant studies (n=72), review articles (n=30), experimental studies (n=16), studies on smoking inhalation injury (n=12), case reports (n=8), prognosis of ARDS (n=4; patients with ARDS on enrollment), and letters (n=2). As a result, a total of 17 studies were included in our analysis.[10-13 18-30]

Characteristics of included studies are shown in table 1. Six studies(10,12,18,20,25) involved patients underwent major surgery; three studies(11,13,26) were population based studies; and others involved patients with other risks of ALI/ARDS such as septic shock(19), influenza A infection(22-24), trauma(23,27), transfusion(30). Five studies were prospective in design and 11 were retrospective. The sample sizes varied substantially across studies ranging from 16 to 121012. Population-based studies had much larger sample size than others and the incidence of ALI/ARDS was expectedly much lower. In general population, the incidence of ARDS was 0.046%.[11] whereas the incidence of ARDS can be as high as 40% in patients with septic shock[19] or severe blunt trauma[27]. Smoking can be classified into current, former, and never. However, the definitions of cigarette smoking varied substantially across studies. Some studies defined in both the number of cigarette (pack-years) and the time (the last time of smoking), while others defined in terms of the number of cigarette. The number of covariates ranged from 4 to 26. Three studies reported unadjusted OR,[23 29 30] and one study used matching technique.[26] Most studies used ARDS as the outcome of interest. Three studies[27 28 30] used ALI as the outcome of interest and one[26] used recurrent ALI as the outcome.

The quality of component studies was assessed by using the Newcastle-Ottawa scale (figure 2).
Because ALI/ARDS is an acute process, follow up of cohorts were deemed adequate for all studies. Ascertainment of smoking history was adequate in 12 studies (52.9%). Comparability of cohorts were not adequate in 8 studies (47.1%, no star), one star was assigned in 3 studies (17.6%), and two stars were assigned for 6 studies (35.3%). Outcome of interest was not present in all cohorts. Representativeness of the exposed and control cohort was not adequate in 5 studies (29.4%).

Five studies did not report effect size (OR or RR) of cigarette smoking for ALI/ARDS development. Two studies[10-18] stated cigarette smoking is an independent risk factor for ARDS, but the effect size was not reported. One study[19] employed smoking as a covariate to adjust for other variable of interest. One study[20] reported that all patients in the cohort had history of smoking. The last study[24] did not linked smoking with respiratory failure quantitatively. Four studies demonstrated cigarette smoking as a risk factor for the development of ALI/ARDS,[11 12 22 27] whereas the remaining studies did not show any increased risk of ALI/ARDS in patients with history of smoking (figure 3). Although there was no statistical heterogeneity (I-squared=0%), we still combined the result with random-effects model because of the heterogeneous study populations. The combined results showed that cigarette smoking was not a risk factor for the development of ALI/ARDS (OR: 1.00, 95% CI: 0.99-1.01). In subgroup analysis, the same result was obtained in general population (OR: 2.03, 95% CI: 0.06-4.01), patients with major surgery or trauma (OR: 1.20, 95% CI: 0.48-1.93) and patients with other risks of ALI/ARDS (OR: 1.00, 95% CI: 0.99-1.01). Publication bias was present with Egger’s test (figure 4). The result showed that small studies reported larger OR (smoking as a risk factor for ALI/ARDS) were more likely to be published (95% confidence interval did not include the reference line).

Discussion
The study demonstrates that cigarette smoking is not significantly associated with ALI/ARDS. However, only one study[11] investigated the association of cigarette smoking and ARDS in general population and found that smoking was associated with significantly increased risk of ARDS (OR: 4.59, 95% CI: 2.13-9.88). The other population-based study[26] used recurrent ALI as the outcome of interest and showed no significant association between smoking and recurrent ALI. Because the event rate in population-based study was very low, the positive finding can happen by chance and require further confirmation. In the author’s view, placing ALI/ARDS in general population is of limited interest to clinicians because of extremely low incidence in general healthy population. In contrast, investigating ALI/ARDS in high risk patients is more relevant, that is, we are more interested in patients who are at risk of ALI/ARDS and for whom particular interventions can be initiated to prevent or postpone its occurrence.

Our study refutes previous findings that cigarette smoking can be an underlying cause of ALI/ARDS. In experimental studies, active smoking is associated with morphological alterations in lung epithelium and endothelium similar to that seen in ARDS.[31-33] Furthermore, studies involving human subjects have shown that smokers (as compared with non-smokers) have greater pulmonary epithelial permeability which is considered to be a hallmark of ARDS. Active smoking also reduces the expression of ion channels that are responsible for resolving
pulmonary edema.[34-36] However, these experimental studies were conducted in strictly controlled experimental conditions that may not be replicable in real world setting. There are numerous confounding factors in the real world that may act to mask the biological effect of cigarette smoking. Alternatively, the effect of cigarette smoking may be too small as compared to other precipitating factors to be detected in studies with limited sample size.

However, the study failed to show significant association of cigarette smoking and ALI/ARDS in varieties of conditions such as major surgery, severe trauma, transfusion, septic shock and influenza A infection. The incidence of ALI/ARDS in these conditions was much higher than that in general population. The difference between general population and these medical conditions lies in the fact that patients are more critically ill and requires ICU admission. Such severe conditions may obliterate the impact of cigarette smoking because this impact is so small that it is negligible as compared with other precipitating factors. A small effect size is subject to false negative findings if statistical power is compromised by limited sample size. As a matter of fact, the sample sizes in studies involving critically ill patients were relatively small, which may partly explain the negative findings in these sub-populations. Furthermore, the publication bias was identified by using Egger’s test, that is, studies with negative findings in terms of the association of cigarette smoking and ALI/ARDS were less likely to report the effect size (OR or RR). For instance, the study by Moss M and coworkers used cigarette smoking as a covariate to adjust for other variables of interest but finally did not reported the coefficient for cigarette smoking.[19] The publication bias further support our finding that cigarette smoking is less likely to increase the risk of ALI/ARDS in critically ill patients. Small study effect is a phenomenon in meta-epidemiological field that meta-analyses including small study are more likely to report larger effect size.[37] Such effect may also take place in the current meta-analysis in which component studies involving critically ill patients were generally small. However, due to the neutral finding in the study, the small study effect acts as a confirmation on the neutral effect of cigarette smoking.

In aggregate, our study demonstrates that cigarette smoking is not associated with increased risk of ALI/ARDS in critically ill patients. However, the relationship in general population is still controversial and requires further confirmation.


16. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of


Figure legends

Figure 1. Flow chart of study selection.

Figure 2. Quality assessment of non-randomized studies using Newcastle-Ottawa scale. The abscissa axis shows the proportion of studies which were assigned with one, two or zero star; and the vertical axis displays the scaling items.

Figure 3. Forest plot showing odds ratio and relevant 95% confidence interval for each study and for pooled results for group and subgroups. The combined results showed that cigarette smoking was not a risk factor for the development of ALI/ARDS (OR: 1.00, 95% CI: 0.99-1.01). In subgroup analysis, the same result was obtained in general population (OR: 2.03, 95% CI: 0.06-4.01), patients with major surgery or trauma (OR: 1.20, 95% CI: 0.48-1.93) and patients with other risks of ALI/ARDS (OR: 1.00, 95% CI: 0.99-1.01).

Figure 4. Publication bias assessed using Egger's test. Standard normal deviate was regressed against the precision of log (OR). Note the significant deviation of the intercept from zero (95% confidence interval did not include zero), which is the sign of publication bias.
## Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Setting</th>
<th>Design</th>
<th>Sample size</th>
<th>Incidence (%)</th>
<th>Definition of smoker</th>
<th>No. of covariates</th>
<th>Outcome of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaul TK 1998[10]</td>
<td>CPB</td>
<td>R.</td>
<td>4318</td>
<td>2.5</td>
<td>&lt;3 months</td>
<td>-</td>
<td>ARDS</td>
</tr>
<tr>
<td>Iribarren C 2000[11]</td>
<td>Population-based</td>
<td>R.</td>
<td>121012</td>
<td>0.046</td>
<td>&lt;1 year, &gt;5 cigarettes per week</td>
<td>4</td>
<td>ARDS</td>
</tr>
<tr>
<td>Tandan S 2001[12]</td>
<td>Oesophagectomy</td>
<td>R.</td>
<td>168</td>
<td>23.8 for ALI; 14.5 for ARDS</td>
<td>NR</td>
<td>5</td>
<td>ARDS</td>
</tr>
<tr>
<td>Chen XF 2003[18]</td>
<td>Thoracotomy</td>
<td>R.</td>
<td>4186</td>
<td>0.74</td>
<td>&gt;100 cigarettes per year</td>
<td>-</td>
<td>ARDS</td>
</tr>
<tr>
<td>Moss M 2003[19]</td>
<td>Septic shock</td>
<td>P.</td>
<td>220</td>
<td>42.3</td>
<td>NR</td>
<td>-</td>
<td>ARDS</td>
</tr>
<tr>
<td>Lokendra T 2009[21]</td>
<td>ICU</td>
<td>R.</td>
<td>1357</td>
<td>5.67</td>
<td>&gt;20 pack-years</td>
<td>8</td>
<td>ARDS</td>
</tr>
<tr>
<td>Dai B 2010[22]</td>
<td>Severe influenza A</td>
<td>R.</td>
<td>92</td>
<td>40.2</td>
<td>Smoking index&gt;1†</td>
<td>-</td>
<td>ARDS</td>
</tr>
<tr>
<td>Ferro TN 2010[23]</td>
<td>Trauma</td>
<td>R.</td>
<td>327</td>
<td>10.1</td>
<td>NR</td>
<td>Unadjusted</td>
<td>ARDS</td>
</tr>
<tr>
<td>Bice T 2011[26]</td>
<td>Population-based</td>
<td>R.</td>
<td>15425</td>
<td>0.12</td>
<td>&gt;20 packs per year</td>
<td>Matched study</td>
<td>Recurrent ALI</td>
</tr>
<tr>
<td>Calfee CS 2011[27]</td>
<td>Severe blunt trauma</td>
<td>P.</td>
<td>144</td>
<td>43.1</td>
<td>NR</td>
<td>5</td>
<td>ALI</td>
</tr>
<tr>
<td>Gajic O 2011[28]</td>
<td>Patients with ALI risk factors</td>
<td>P.</td>
<td>5584</td>
<td>6.8</td>
<td>NR</td>
<td>26</td>
<td>ALI</td>
</tr>
</tbody>
</table>
† Smoking index was defined as number of cigarette per day multiplied by number of smoking years.

‡ Risk factors included sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery.

Abbreviations: NR: not reported; P.: prospective; R.: retrospective; ALI: acute lung injury; ARDS: acute respiratory distress syndrome.
A total of 314 citations identified

- 153 involved non-human study

161 citations were screened further

- 144 were excluded because
  - Irrelevant studies (n=72)
  - Review articles (n=30)
  - Experimental (n=16)
  - Smoke-inhalation (n=12)
  - Case report (n=8)
  - Prognosis of ARDS (N=4)
  - Letter (n=2)

17 studies included for final analysis
### Groups and subgroups

<table>
<thead>
<tr>
<th>Population-based</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iribarren C 2000</td>
<td>4.59 (2.93, 9.88)</td>
<td>0.00</td>
</tr>
<tr>
<td>TenHoorn T 2001</td>
<td>1.20 (0.50, 3.00)</td>
<td>0.01</td>
</tr>
<tr>
<td>Bice T 2011</td>
<td>2.41 (0.84, 11.20)</td>
<td>0.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 27.7%, p = 0.264)</td>
<td>2.03 (0.68, 4.01)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major surgery or trauma</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tandan S 2001</td>
<td>9.95 (1.97, 92.70)</td>
<td>0.00</td>
</tr>
<tr>
<td>Ferro TN 2010</td>
<td>1.04 (0.47, 2.27)</td>
<td>0.01</td>
</tr>
<tr>
<td>Zingg U 2010</td>
<td>1.06 (0.35, 3.19)</td>
<td>0.00</td>
</tr>
<tr>
<td>Calfee CS 2011</td>
<td>2.83 (1.25, 6.39)</td>
<td>0.00</td>
</tr>
<tr>
<td>Paul DJ 2001</td>
<td>2.06 (0.80, 12.10)</td>
<td>0.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.749)</td>
<td>1.20 (0.48, 1.93)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At risk of ARDS or ALI</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lokendra T 2009</td>
<td>1.00 (0.99, 1.01)</td>
<td>99.90</td>
</tr>
<tr>
<td>Dai B 2010</td>
<td>8.66 (1.28, 50.80)</td>
<td>0.00</td>
</tr>
<tr>
<td>Gajic O 2011</td>
<td>1.06 (0.75, 1.49)</td>
<td>0.07</td>
</tr>
<tr>
<td>Toy P 2011</td>
<td>1.06 (0.95, 4.20)</td>
<td>0.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.607)</td>
<td>1.00 (0.99, 1.01)</td>
<td>99.97</td>
</tr>
</tbody>
</table>

| Overall (I-squared = 0.0%, p = 0.737)    | 1.00 (0.99, 1.01)    | 100.00   |

**NOTE:** Weights are from random effects analysis.

**Diagram:**

- Smoking is protective
- Smoking is a risk factor

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