JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Fiberoptic bronchoscopy for the prevention of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials

Haowei Tang[1], Zhi Yuan[1], Jingjie Li[1], Qun Wang[1], Weijie Fan[1]

[1] *Department of Respiratory Medicine, Fenghua District People's Hospital, Ningbo 315500, China*

Abstract

Introduction: Ventilator-associated pneumonia (VAP) causes increased time of mechanical ventilation (MV), prolonged intensive care unit (ICU) stay, and a higher mortality risk. The systematic review and meta-analysis aimed to compare the efficacies between fiberoptic bronchoscopy (FOB) and general sputum suction for the prevention of VAP in patients with invasive MV.

Methodology: Relevant randomized controlled trials (RCTs) were obtained via a search of PubMed, Embase, Cochrane Library, Wanfang, and CNKI databases. A random-effects model was used to pool the results if significant heterogeneity was observed. Otherwise, a fixed-effects model was used.

Results: Sixteen RCTs were included. Compared to general sputum suction, sputum suction with FOB was associated with a significantly reduced risk of VAP (risk ratio [RR]: 0.56, 95% CI: 0.47 to 0.67, $p < 0.001$; $I^2 = 0\%$). Subgroup analyses showed that the combination of FOB-assisted sputum suction with bronchoalveolar lavage (BAL) further reduced the risk of VAP as compared to FOB-assisted sputum suction alone (p for subgroup difference = 0.04). In addition, FOB-assisted treatment was also associated with a reduced MV time (mean difference [MD]: -2.19 days, 95% CI: -2.69 to -1.68, $p < 0.001$; $I^2 = 18\%$), a shorter ICU stay (MD: 2.9 days, 95% CI: -3.68 to -2.13, $p < 0.001$; $I^2 = 34\%$), and a reduced mortality risk (RR: 0.46, 95% CI: 0.24 to 0.90, $p = 0.02$; $I^2 = 0\%$) in patients with invasive MV.

Conclusions: FOB for sputum suction and BAL in patients with invasive MV is effective in reducing the incidence of VAP.

Key words: Ventilator-associated pneumonia; fiberoptic bronchoscopy; sputum suction; bronchoalveolar lavage; meta-analysis.

J Infect Dev Ctries 2024; 18(9):1413-1420. doi:10.3855/jidc.17866

(Received 29 December 2022 – Accepted 28 March 2023)

Introduction

Ventilator-associated pneumonia (VAP) is a hospital-acquired pneumonia that develops in patients receiving invasive mechanical ventilation (MV) for at least 48 hours [1,2]. According to previous studies, VAP is one of the most common nosocomial infections among patients who require MV, with a prevalence of 5 to 40% depending on the clinical settings and diagnostic criteria [2,3]. Clinically, the occurrence VAP poses a significant health risk for patients admitted to intensive care unit (ICU), causing increased mortality, longer hospital stays, and higher healthcare costs [1,3]. The risk factors of VAP include aging, multiple comorbidities, immunocompromised status, weakness of respiratory muscles, and male sex, etc. [3]. Pathophysiologically, endotracheal tubes interfere with the normal protective function of the upper airway, stimulate mucus production, and make the sputum clearance difficult, which become major mechanisms underlying the development of VAP [4,5]. Accordingly, intensive airway management is essential to prevent VAP in patients with MV [6]. Clinically, fiberoptic bronchoscopy (FOB) is a well-applied technique that could remove contamination and foreign materials from the airway and obtain pulmonary tissue samples for diagnosis [7]. Early use of FOB within 24 hours of intubation has been shown to improve the survival of patients with aspiration pneumonia [8]. In addition, the combination of FOB and bronchoalveolar lavage (BAL) can positively identify causative organisms in patients with aspiration-induced lung injury, and subsequently remove retained sputum from the airways of patients with obstinate pulmonary infection [9,10]. Interestingly, a recent clinical trial suggests that FOB may also be a useful treatment for VAP [11]. However, it remains unknown whether sputum suction assisted by FOB could reduce the risk of VAP as compared to general sputum suction in patients with invasive MV [12]. Accordingly, we performed a systematic review and meta-analysis of relevant randomized controlled trials (RCTs) to compare the efficacy of sputum suction assisted by FOB with general sputum suction for the prevention of VAP in these patients.

Methodology

This study adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [13,14] and Cochrane Handbook [15] guidelines during its design and implementation.

Search strategy

To search Medline (PubMed), Embase (Ovid), CENTER (Cochrane Library), Wanfang, and CNKI (China National Knowledge Infrastructure) databases, the following strategies were used: (1) "bronchoscope" OR "bronchoscopic"; and (2) "ventilator-associated pneumonia" OR "VAP". Only studies including human subjects were considered. As a part of the final database search, references from related reviews and original articles were also screened. The final database search was carried out on September 28, 2022.

Study selection

The PICOS principle was followed in designating the inclusion criteria of the meta-analysis. P (patients): Patients with critical illnesses who were treated with invasive MV; I (intervention): A treatment group of FOB-assisted sputum suction with or without the combination of bronchoalveolar lavage (BAL); C (control): A control group of general sputum suction without the assistance of FOB; O (outcomes): The primary outcome was the incidence of VAP compared between patients of the FOB and the control groups. The secondary outcomes were the difference in MV time, ICU stay, and the risk of mortality between groups; S (study design): Parallel-group RCTs published as full-length articles in English or Chinese.

Non-randomized studies, studies including patients with noninvasive MV, studies evaluating the role of FOB as a treatment of VAP, studies without using FOB, or studies that did not report the outcomes of interest were excluded. For studies with overlapped patient populations, the one with the largest sample size was selected for the meta-analysis.

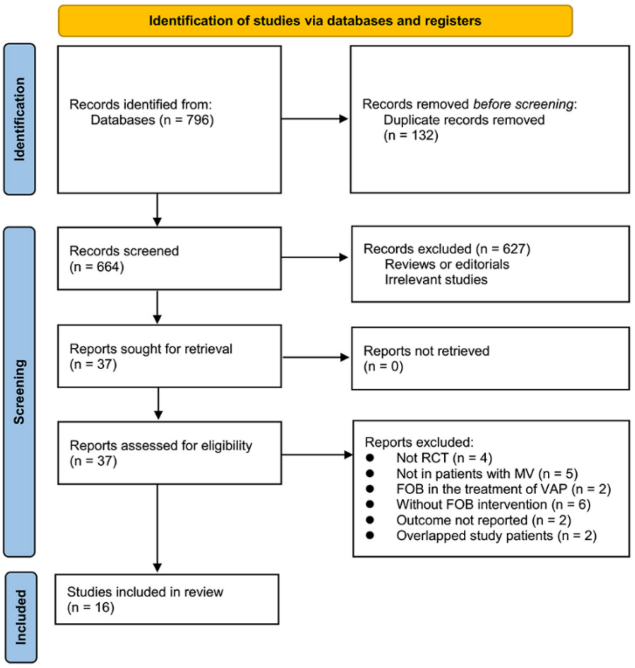
Data collection and quality evaluation

Database searches, data collection, and quality assessment were carried out by two authors independently. Discussions with the corresponding author were conducted if disagreements occurred. We collected data on study information (first author, publication year, and study country), study design (blind or open-label), patient information (diagnosis, number of patients, mean age, and sex), details of FOB-assisted treatment, details of controls, follow-up duration, diagnostic methods for VAP, and the outcomes. The Cochrane Risk of Bias Tool was used to determine the quality of the included RCTs [15] according to the following aspects: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data addressed, selective reporting, and other sources of bias.

Statistical analysis

Outcomes of discontinuous variables were summarized as risk ratio (RR) and corresponding 95% confidence interval (CI), while outcomes of continuous variables were presented as mean difference (MD) and 95% CI. Heterogeneity was assessed using the Cochrane Q test [15]. The I^2 statistic was also calculated, with $I^2 > 50\%$ indicating significant heterogeneity [16]. A random-effects model was used if significant between-study heterogeneity was observed; otherwise, a fixed-effects model was used [15]. Influencing analyses by excluding one study at a time from the meta-analysis were performed to evaluate the effect of each study on the pooled results [15]. Analysis of predefined subgroups was conducted to evaluate whether the result was consistent in studies with or without the combination of BAL, and in studies with clinically or microbiologically diagnosed VAP. An evaluation of publication bias was conducted via visual inspection of funnel plots and performing Egger's regression asymmetry test [17]. A $p < 0.05$ was considered as statistically significant. Statistical

Figure 1. Flowchart of literature search.



analyses were conducted using the RevMan (Version 5.1; Cochrane, Oxford, UK) software.

Results

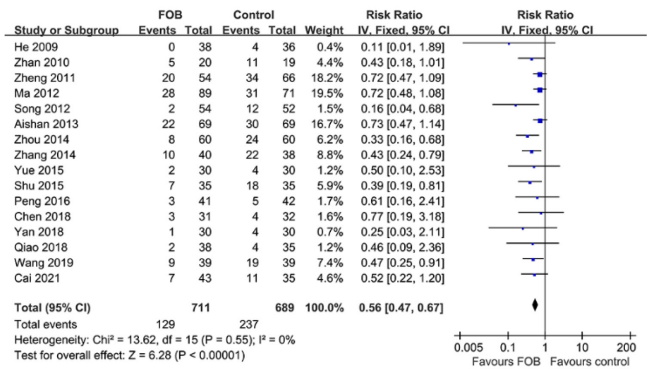
Literature search

The process of database searching and study identification is illustrated in Figure 1. Briefly, a database search yielded 796 articles, and 664 were retrieved after the duplicate records were excluded. Six hundred twenty-seven articles were subsequently excluded based on titles and abstracts, primarily because they were unrelated to the objective of the meta-analysis. Then, 21 out of the 37 articles that received full-text reviews were further excluded for the reasons illustrated in Figure 1. Finally, 16 RCTs [18-33] were considered to be eligible for the meta-analysis.

Study characteristics and data quality

An overview of the included studies can be found in Table 1. Overall, 16 RCTs involving 1,400 critically ill patients (mostly with respiratory failure) who were treated with invasive MV in the ICU were included in the meta-analysis [18-33]. All these studies were published between 2009 and 2021 and were performed in China. The mean ages of the patients varied between 39 and 75 years. The patients allocated to the intervention group received FOB-assisted sputum suction every 24 to 72 hours in all of the included studies, with [18,19,22,24,27,28,30-33] or without [20,21,23,25, 26,29] BAL. For patients allocated to the control group, general sputum suction without BAL was performed. The observational durations were within ICU stay or hospitalization. All of the included studies reported the outcome of VAP incidence, which were clinically [21,23,24,26,27,29-32] microbiologically [18-20,22,25,28,33] diagnosed. Using the Cochrane Risk of Bias Tool, Table 2 provides a detailed analysis of the included RCTs. All of the included studies were open-label. Details of random sequence generation were reported in seven studies [18,26,28-32], while none of them reported the details of allocation concealment. No evidence of selective reporting or other source of bias was detected.

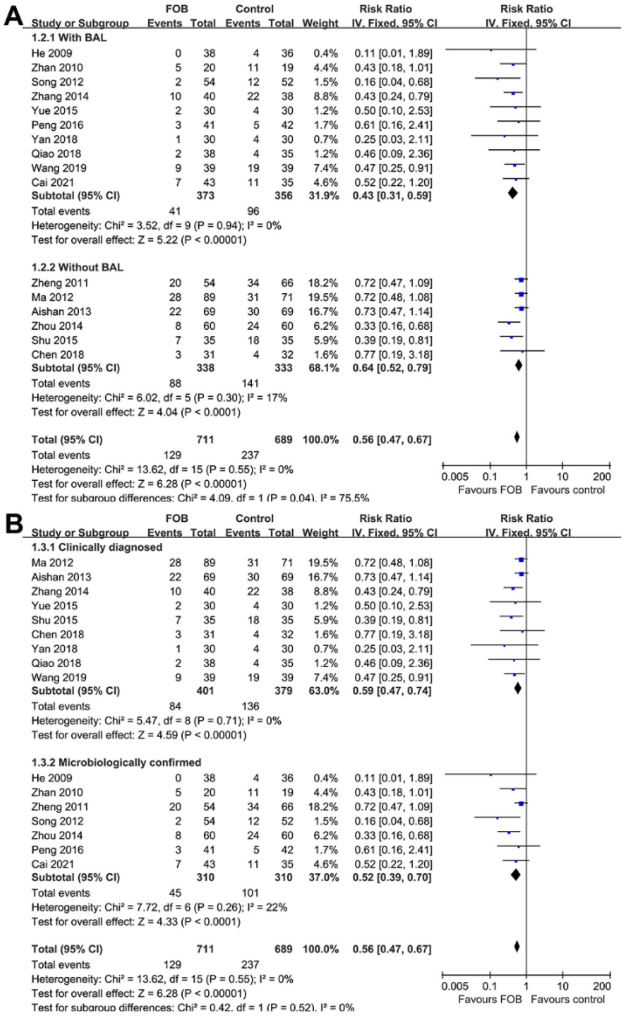
Figure 2. Forest plots for the meta-analysis comparing FOB-assisted sputum suction with general sputum suction on the incidence of VAP.



Primary outcome

Overall, 16 studies [18-33] reported the influences of FOB-assisted sputum suction on the incidence of VAP. Results of the Cochrane Q test ($p = 0.55$) and I^2 statistic (0%) suggested a low between-group heterogeneity. Accordingly, results of the meta-analysis with a fixed-effects model showed that sputum suction with FOB was associated with a significantly low risk of VAP (RR: 0.56, 95% CI: 0.47 to 0.67, $p < 0.001$; Figure 2). Influencing analyses by excluding one study at a time showed consistent results ($p < 0.05$). Subgroup

Figure 3. Subgroup analyses comparing FOB-assisted sputum suction with general sputum suction on the incidence of VAP. A, subgroup analysis according to whether BAL was used; and B, subgroup analysis according to the diagnostic methods for VAP.



analyses showed that the combination of FOB-assisted sputum suction with BAL was associated with a further reduced risk of VAP (RR: 0.43, 95% CI: 0.31 to 0.59, $p < 0.001$) as compared to FOB-assisted sputum suction alone (RR: 0.64, 95% CI: 0.52 to 0.79, $p < 0.001$; p for subgroup difference = 0.04; Figure 3A). In addition, consistent results were observed in studies with clinically diagnosed VAP (RR: 0.59, 95% CI: 0.47 to 0.74, $p < 0.001$) and microbiologically confirmed VAP (RR: 0.52, 95% CI: 0.39 to 0.70, $p < 0.001$; p for subgroup difference = 0.52; Figure 3B). No severe adverse events were reported that were deemed to be relevant to the FOB-assisted treatment.

Secondary outcomes

Pooled results with 11 studies [18,20-23,25-30] using a fixed-effects model showed that sputum suction with FOB was also associated with a reduced time of MV (MD: -2.19 days, 95% CI: -2.69 to -1.68, $p < 0.001$; $I^2 = 18\%$; Figure 4A). Besides, meta-analyses of six studies [18, 20-23, 28] indicated that FOB-assisted sputum suction was also associated with a shorter ICU stay (MD: 2.90 days, 95% CI: 3.68 to 2.13, $p < 0.001$; $I^2 = 34\%$; Figure 4B). Finally, pooled results from four studies [18,25,29,30] suggested that FOB-assisted sputum suction was also associated with a reduced mortality risk during ICU stay or hospitalization (RR:

Table 1. Study characteristics.

Study	Country	Design	Diagnosis	Setting	Patient number	Mean age	Male	Intervention	Control	Follow-up duration	Diagnosis of VAP	Outcomes reported
He 2009	China	RCT, OL	AECOPD and RF	RICU	74	67.1	85.1	BSS and BAL every 24-72 hours	RSS	Within RICU stay	Microbiologically confirmed	VAP, mortality, MV time and ICU stay
Zhan 2010	China	RCT, OL	RF patients with respiratory muscle weakness	ICU	39	46.1	61.5	BSS and BAL every 24-72 hours	RSS	Within ICU stay	Microbiologically confirmed	VAP
Zheng 2011	China	RCT, OL	RF	ICU	120	NR	80	BSS every 24 hours	RSS	Within hospitalization	Microbiologically confirmed	VAP, MV time and ICU stay
Ma 2012	China	RCT, OL	Older people with RF	ICU	160	74.5	58.1	BSS every 48 hours	RSS	Within ICU stay	Clinically diagnosed	VAP, MV time and ICU stay
Song 2012	China	RCT, OL	AECOPD and RF	RICU	106	67.9	76.4	BSS and BAL every 24-48 hours	RSS	Within RICU stay	Microbiologically confirmed	VAP, MV time and ICU stay
Aishan 2013	China	RCT, OL	Older people with RF	ICU	138	NR	NR	BSS every 48 hours	RSS	Within hospitalization	Clinically diagnosed	VAP, MV time and ICU stay
Zhou 2014	China	RCT, OL	Critically ill patients	ICU	120	47	85	BSS every 24 hours	RSS	Within hospitalization	Microbiologically confirmed	VAP, mortality, and MV time
Zhang 2014	China	RCT, OL	RF patients with respiratory muscle weakness	ICU	78	51	61.5	BSS and BAL every 24-72 hours	RSS	Within ICU stay	Clinically diagnosed	VAP
Yue 2015	China	RCT, OL	AECOPD and RF	ICU	60	67.2	53.3	BSS and BAL every 24-72 hours	RSS	Within hospitalization	Clinically diagnosed	VAP, and MV time
Shu 2015	China	RCT, OL	Patients with RF	ICU	70	60.3	55.7	BSS every 72 hours	RSS	Within hospitalization	Clinically diagnosed	VAP, and MV time
Peng 2016	China	RCT, OL	Patients with RF	ICU	83	65.3	72.3	BSS and BAL every 48-72 hours	RSS	Within hospitalization	Microbiologically confirmed	VAP, MV time and ICU stay
Chen 2018	China	RCT, OL	Patients with ARDS	ICU	63	54.9	54	BSS every 24 hours	RSS	Within hospitalization	Clinically diagnosed	VAP, mortality, and MV time
Yan 2018	China	RCT, OL	RF patients with respiratory muscle weakness	ICU	60	58.4	68.3	BSS and BAL every 24-72 hours	RSS	Within hospitalization	Clinically diagnosed	VAP
Qiao 2018	China	RCT, OL	AECOPD and RF	ICU	73	64.8	58.5	BSS and BAL every 24-72 hours	RSS	Within hospitalization	Clinically diagnosed	VAP, mortality, and MV time
Wang 2019	China	RCT, OL	RF patients with respiratory muscle weakness	ICU	78	53.8	55.1	BSS and BAL every 24-72 hours	RSS	Within hospitalization	Clinically diagnosed	VAP
Cai 2021	China	RCT, OL	Coma patients on MV	EICU	78	39.4	70.5	BSS and BAL every 24-72 hours	RSS	Within hospitalization	Microbiologically confirmed	VAP

VAP, ventilator-associated pneumonia; ICU, intensive care unit; RICU, respiratory ICU; EICU, emergency ICU; RCT, randomized controlled trial; OL, open-label; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; RF, respiratory failure; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; BAL, bronchoalveolar lavage. BSS, Bronchoscopic sputum suction; RSS, Routine sputum suction when necessary.

Table 2. Quality evaluation by the Cochrane Risk of Bias Tool.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other sources of bias
He 2009	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Zhan 2010	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Zheng 2011	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Ma 2012	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Song 2012	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Aishan 2013	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Zhou 2014	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Zhang 2014	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Yue 2015	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Shu 2015	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Peng 2016	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Chen 2018	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Yan 2018	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Qiao 2018	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Wang 2019	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Cai 2021	Unclear	Unclear	High risk	High risk	Low risk	Low risk	Low risk

0.46, 95% CI: 0.24 to 0.90, $p = 0.02$; $I^2 = 0\%$; Figure 4C).

Publication bias

The funnel plots for the meta-analyses comparing FOB-assisted treatment with controls on the risk of VAP and the duration of ICU stay are shown in Figures 5A and 5B. The plots were symmetrical on vision inspection, suggesting low risks of publication biases. Egger's regression tests also suggested low risks of publication biases ($p = 0.15$ and 0.29, respectively).

Discussion

In this meta-analysis, we pooled the results of 16 RCTs, and the results showed that compared to general sputum suction, FOB-assisted sputum suction could significantly reduce the incidence of VAP in patients who were treated with invasive MV. Moreover, subgroup analyses showed that FOB-assisted sputum suction combined with BAL could further reduce the risk of VAP as compared to FOB-assisted sputum suction alone. In addition, the preventative efficacy of FOB-assisted sputum suction on VAP was consistent in studies with clinically diagnosed VAP and

Figure 4. Forest plots for the meta-analysis comparing FOB-assisted sputum suction with general sputum suction on the time of MV, ICU stay, and mortality. A, forest plots for the outcome of MV duration; B, forest plots for the outcome of ICU stay, and C, forest plots for the outcome of mortality.

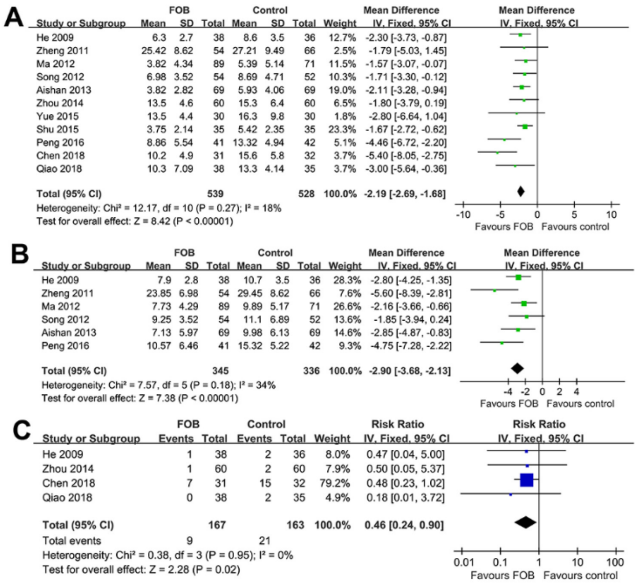
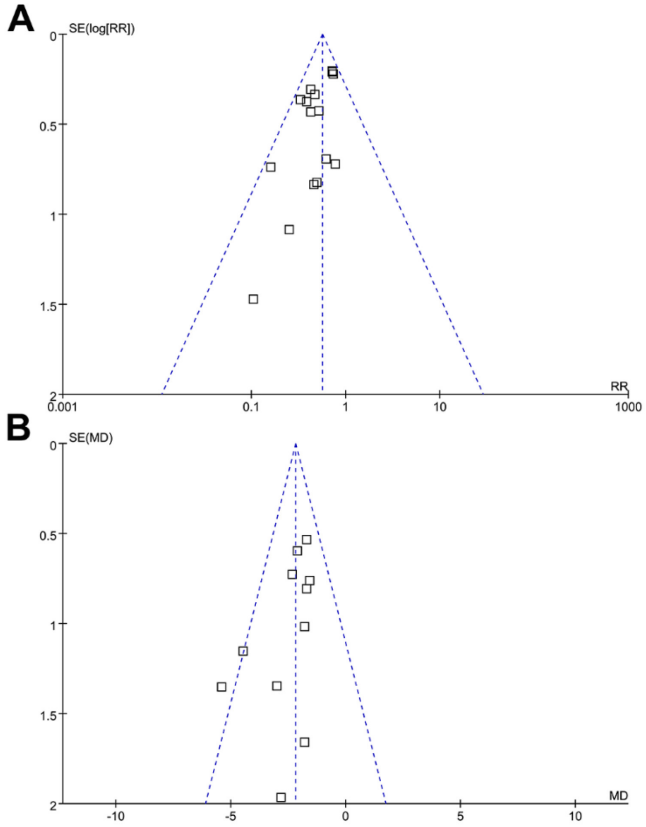


Figure 5. Funnel plots for the meta-analysis evaluating the publication biases of the meta-analyses. A, funnel plots for the outcome of VAP risk; and B, funnel plots for the outcome of mortality.



microbiologically confirmed VAP. Finally, subsequent meta-analyses showed that FOB-assisted sputum suction was also associated with a reduced MV time, a shortened ICU stay, and a decreased mortality in patients who were treated with invasive MV. Collectively, these findings indicate that the use of FOB assisted sputum suction and BAL could reduce the incidence of VAP in patients with invasive MV.

To the best of our knowledge, this may be the first meta-analysis that systematically evaluated the role of FOB-assisted sputum suction in patients who were treated with invasive MV. The methodological strengths of the meta-analysis include the following. First, an extensive literature search was performed in five electronic databases, which retrieved the most up-to-date RCTs according to the aim of the meta-analysis. Second, for the primary outcome of VAP, we performed multiple sensitivity and subgroup analyses, and the consistent results of these analyses further confirmed the robustness of the findings. Finally, besides investigating the influence of FOB-assisted sputum suction on VAP, we also explored the effects of FOB on other clinical outcomes that have been confirmed to be related to VAP. The benefits of FOB on these secondary outcomes such as MV time, ICU stay, and mortality may be directly related to the preventative efficacy of FOB-assisted sputum suction on VAP incidence.

An early retrospective study showed that although diagnostic FOB was associated with shorter hospital stays and duration of antibiotics in patients with VAP, a therapeutic FOB failed to show a benefit on clinical outcomes in these patients [34]. However, as acknowledged by the authors of the study, no definition conclusion could be made regarding the role of therapeutic FOB for VAP because of the limitations of a retrospective design. A recent RCT showed that using FOB-assisted sputum suction every other day could more effectively control the fever symptoms, reduce the leukocyte count, and lower APACHE II scores in patients with VAP as compared to the group of general sputum suction [11], suggesting a potential benefit of therapeutic FOB in patients with VAP. Since optimized airway management is a key process to prevent VAP in patients with invasive MV, some small-scale RCTs have been performed to evaluate the potential role of FOB in the prevention of VAP. Given the limited sample sizes of these studies, a meta-analysis was performed in this study for a comprehensive evaluation. Results of the current meta-analysis support that FOB-assisted sputum suction is effective in reducing the risk of VAP as compared to general sputum suction. These results were consistent with the previously observed benefits of therapeutic FOB in patients with aspiration pneumonia [8] and refractory pneumonia [35]. These findings indicate that therapeutic FOB is especially beneficial for patients with aspiration pneumonia [36]. Interestingly, our subgroup analysis showed that FOB-assisted sputum suction combined with BAL could further reduce the risk of VAP compared to FOB-assisted sputum suction alone. As shown in previous studies, a diagnostic BAL is more effective to provide the microbiological diagnosis of pneumonia and thereby guide the adjustment of the antibiotics [37]. In addition, therapeutic BAL may also be helpful in removing retained sputum from the airways of patients with obstinate pulmonary infection, such as patients who were treated with MV in the ICU [9]. Collectively, these findings suggest that FOB sputum suction combined with BAL should be applied to prevent VAP in high-risk patients who were treated with MV.

Our meta-analysis has several limitations. First, all the included studies were from China. Studies should be performed in other countries for validation. Moreover, all the included studies were open-label. However, blinded studies are difficult to conduct in this clinical scenario by using FOB. In addition, a pulmonary infection control (PIC) window is an important parameter that is used to reflect control of the infection at which time patients undergo extubation and transition to non-invasive ventilation. By influencing the timing of extubation, PIC may confound the duration of MV and the incidence of VAP. However, only one of the included studies [30] confirmed that patients from both groups were treated with sequential invasive–noninvasive mechanical ventilation at the PIC window. The imbalance of PIC between groups may affect the findings of the studies. Furthermore, the experience of physicians who performed the FOB-assisted sputum suction and BAL may affect the results of the meta-analysis, which should be evaluated in future studies. Besides, an optimal protocol and frequency of therapeutic FOB in high-risk patients for VAP remains to be determined. Additionally, only studies published as full-length articles in peer-reviewed journals were included, and we did not include grey literature such as conference abstracts or unpublished data because these literatures are not likely to be peer-reviewed. Grey literature may have less reliable results, and including these data in the meta-analysis may compromise the validity of the findings. We acknowledged that excluding this literature may lead to publication bias. However, funnel plots and Egger's regression tests in this meta-analysis did not suggest a significant risk of publication bias. Finally,

limited studies were included in the meta-analysis regarding the influence of FOB on the mortality of patients receiving invasive MV. These findings should be validated in large-scale RCTs.

Conclusions

In conclusion, the results of the meta-analysis indicate that the use of FOB for sputum suction could reduce the risk of VAP in patients with invasive MV, and the preventative efficacy of FOB for VAP could be reinforced if BAL is combined with FOB. These findings suggest that BAL-assist sputum suction is effective in preventing VAP and improving the clinical outcomes in high-risk patients who are treated with invasive MV.

Authors' contributions

Haowei Tang and Zhi Yuan conceived the study. Haowei Tang and Jingjie Li performed literature review and data collection. Haowei Tang, Qun Wang, and Weijie Fan performed data statistics and interpreted the results. Haowei Tang drafted the manuscript. All authors approved the submission of the manuscript.

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Corresponding author

Dr. Zhi Yuan,
Department of Respiratory Medicine,
Fenghua District People's Hospital,
36 Gongyuan Road, Ningbo 315500, China
Telephone: 86-574-88587000
Fax: 86-574-88587000
Email: zhiyuan_9328@21cn.com

Conflict of interests: No conflict of interests is declared.