Oral immunotherapy prevents ventilator-associated pneumonia in premature infants: a meta-analysis and systematic review

Keywords
nursing, premature infants, care, ventilator-associated pneumonia, Oral immunotherapy

Abstract

Introduction
Ventilator-associated pneumonia (VAP) prevention and care is essential to the prognosis of premature infants. We aimed to evaluate the effects and safety of oral immune therapy (OIT) in premature infants, to provide evidence for the clinical treatment and nursing care of premature infants.

Material and methods
We systematically searched PubMed, Embase, Cochrane Library, Web of Science, Cumulative Index of Nursing and Allied Health Literature (CINAHL), China National Knowledge Infrastructure (CNKI), China Biomedical Documentation Service (CBM), Wanfang databases for randomized controlled trials (RCTs) on the effects and safety of OIT in preterm infants until July 16, 2022. Two researchers independently screened the literature and extracted data. Revman 5.3 software was used for data meta-analysis.

Results
10 RCTs involving 852 premature infants were included, 427 premature infants received OIT. Synthesized outcomes showed that OIT reduced the incidence of VAP [RR=0.34, 95%CI (0.22-0.53)], the detection rate of tracheal tube-causing microorganisms [RR=0.29, 95%CI (0.16-0.50)] and length of hospital stay [MD=-6.60, 95%CI (-11.66, -1.53)] in premature infants (all P<0.05). There were no statistically differences in the detection rate of oropharyngeal pathogenic microorganisms [RR=0.23, 95%CI (0.04-1.32)], duration of mechanical ventilation [MD=-0.67, 95%CI (-1.37, 0.03)], mortality [RR=0.60, 95%CI (0.31, 1.14)] between OIT and control group (all P>0.05).

Conclusions
OIT is a simple and effective nursing method, which provides a new approach for the prevention of VAP in premature infants. RCTs with high quality, larger sample size and multi-centers are still needed for further verification on the role of OIT in the future.

Title page

Title: Oral immunotherapy prevents ventilator-associated pneumonia in premature infants: a meta-analysis and systematic review

Running title: Oral immunotherapy & premature infants

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Conclusions: OIT is a simple and effective nursing method, which provides a new approach for

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Keywords: Oral immunotherapy; ventilator-associated pneumonia; premature infants; nursing; care.

Introduction

Ventilator-associated pneumonia (VAP) is the pneumonia that occurs in patients with endotracheal intubation or tracheotomy within 48 hours of receiving mechanical ventilation (MV) or within 48 hours of weaning and extubation[1]. Neonatal intensive care unit (NICU) is one of the common sites of nosocomial infections. According to statistics, the incidence of VAP in NICU can be as high as 45.11%, and the case fatality rate is as high as 19.04%[2-4]. VAP increase the NICU stay and length of hospital stay of MV premature infants, increase the cost of treatment and the economic burden of infants 's families[5, 6]. Therefore, the prevention and care of VAP is of great significance to the prognosis of premature infants.

Due to the low level of oral self-cleaning ability and the thin and tender oral mucosa, premature infants are vulnerable to injury and local infection[7]. Previous studies[8, 9] have reported that effective oral care can prevent bacterial colonization of the upper respiratory tract and reduce the occurrence of VAP. Oral immune therapy (OIT) is also known as colostrum oral instillation or smear, that is, a very small amount of colostrum (usually 0.2 ml) is applied to the oral mucosa with a sterile cotton swab or oral applicator[10]. Colostrum is rich in a variety of immune substances, such as sIgA, lactoferrin, lysozyme and complement, etc. Instilling or smearing colostrum on the oral and buccal mucosa of premature infants may improve the immunity of

premature infants. In MV infants, the establishment of artificial airway cannot realize the absorption of colostrum through the lymphoid tissue or oral mucosa of the oropharynx and exert an immune function, which loses the protective effect of colostrum to a certain extent[11, 12]. At present, many studies[13-15] have reported that the use of colostrum can enhance the immunity of newborns, prevent pathogenic bacteria from colonizing the respiratory tract and digestive tract mucosa, thereby protecting the mucosal immune barrier, but the sample size of the study is small and there are some different findings. Therefore, we conducted a meta-analysis to systematically evaluate the preventive effect of OIT on VAP in premature infants, aiming to provide evidence support for clinical VAP prevention and nursing care of premature infants.

Methods

This meta-analysis and systematic review was performed according to the statement of preferred reporting items for systematic reviews and meta-analyses (PRISMA)[16].

Literature search strategy

We systematically searched PubMed, Embase, Cochrane Library, Web of Science, Cumulative Index of Nursing and Allied Health Literature (CINAHL), China National Knowledge Infrastructure (CNKI), China Biomedical Documentation Service (CBM), Wanfang and VIP databases for randomized controlled trials (RCTs) on the effects and safety of OIT in premature infants. The database retrieval time was from the inception of database to July 16, 2022. The search formula used in the database search was ("infant" OR "newborn" OR "preterm" OR "premature" OR "low birth weight") AND ("milk" OR "breast milk" OR "mother's milk" OR "colostrum") AND ("oral care" OR "mouth care" OR "oral administration" OR "oropharyngeal administration" OR "oral immune therapy"). The database searches were conducted using the

combination of subject headings and keywords. In addition, we used a 'snowball' approach to trace relevant references of relevant RCTs and important reviews.

Literature Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis were: (1) Study design: RCTs on the OIT in premature infants. (2) Research population: Premature infants who met the diagnostic criteria for premature infants and were admitted to the NICU 24 hours after birth, with no oral mucosal damage and infection. (3) Intervention measures: the control group received routine oral care or 0.9% sodium chloride solution or sterile water for oral care, and the intervention group received OIT. (4) The article reported the relevant outcome indicators, including the incidence of VAP, the duration of MV, the detection rate of oropharyngeal pathogenic microorganisms, the detection rate of pathogenic microorganisms in endotracheal tube, the length of hospital stay and mortality. The exclusion criteria for this meta-analysis were: (1) duplicate published literature; (2) literature for which full text or related data could not be obtained by various methods.

Literature screening and data extraction

Two researchers independently screened the literature and extracted data strictly according to the inclusion and exclusion criteria, and they cross-checked the obtained results. In case of disagreement, consensus was reached after discussion or a third party was consulted. The content extracted in this meta-analysis included the first author of the study, publication year, country, sample size, intervention measures, and outcome indicators.

Literature quality evaluation

Two researchers independently evaluated the quality of the included RCTs according to the evaluation criteria recommended by the Cochrane library, and consulted a third party if they

disagreed. This quality assessment method includes randomization methods, allocation concealment, blinding of interventionists and participants, blinding of outcome assessors, completeness of outcome data, selective reporting, and other biases. Every item can be rated as "low", "unclear", or "high" risk of biases.

Statistical methods

We used Revman 5.3 software to perform meta-analysis on the data. For continuous variables we used mean difference (MD) as the effect index, and for dichotomous variables we used relative risk (RR) as the effect index. All analyses used 95% confidence intervals (CIs) as effect sizes. The statistical heterogeneity of the studies was tested by the chi-square test. If $P > 0.1$ and $I^2 < 50\%$, a fixed-effect model was selected for meta-analysis; otherwise, a random-effect model was applied. Publication bias was assessed with funnel plots, and the asymmetry was evaluated by conducting Egger regression test. Besides, we performed sensitivity analyses to evaluate the impact of single study on the synthesized results. In this meta-analysis, $P < 0.05$ was considered as a statistically significant difference between the groups

Results

Literature search results

227 related literatures were initially detected. After removing duplicate literatures, 216 articles remained. After reading the title, abstract, 170 articles that did not meet the inclusion criteria were excluded. The full text was searched and the remaining 46 articles were read through, and 36 articles were further excluded. Finally, 10 RCTs[17-26] were included for meta-analysis. The literature screening process is shown in Figure 1.

Figure 1 The PRISMA flow diagram of RCT selection

Characteristics of included studies

Of the 10 RCTs[17-26] included, a total of 852 premature infants were involved, of which 427 premature infants received OIT and 425 were in the control group. The included studies were from China, Egypt, South Korea, the United States and India. The basic characteristics of the included studies are shown in Table 1.

Table 1 The characteristics of included RCTs

Quality evaluation of included RCTs

The risk of bias for included RCTs are showed in Figures 2 and 3. All included RCTs mentioned randomization in their reports, but two RCTs did not report the detailed methods used to generate random sequence. Four RCTs reported the methods to perform allocation concealment. The performance bias and blinding design in the outcome assessment remained unclear. No other biases were found amongst the included RCTs.

Figure 2 Risk of bias graph

Figure 3 Risk of bias summary

Meta-analysis

- *The incidence of VAP* A total of 9 RCTs reported the effect of OIT on the incidence of VAP in premature infants. There was no significant statistical heterogeneity among the studies

(I^2=0%, P=0.48), so the fixed effect model was used for statistical analysis. The results showed that the incidence of VAP in the OIT group was less than that in the control group, and the difference was statistically significant [RR=0.34, 95%CI (0.22-0.53), P<0.001, Figure 4A].

- *The detection rate of pathogenic microorganisms in the tracheal tube* A total of 4 RCTs reported the effect of OIT on the detection rate of pathogenic microorganisms in the tracheal tube in premature infants. There was no significant statistical heterogeneity among the studies (I^2=0%, P=0.42), so the fixed effect model was used for statistical analysis. The results showed that the detection rate of pathogenic microorganisms in the tracheal tube in the OIT group was less than that in the control group, and the difference was statistically significant [RR=0.29, 95%CI (0.16-0.50), P<0.001, Figure 4B].
- *The detection rate of oropharyngeal pathogenic microorganisms* A total of 4 RCTs reported the effect of OIT on the detection rate of oropharyngeal pathogenic microorganisms in premature infants. There was significant statistical heterogeneity among the studies (I^2=68%, P=0.04), so the random effect model was used for statistical analysis. The results showed that there was no statistically difference in the detection rate of oropharyngeal pathogenic microorganisms between OIT and control group [RR=0.23, 95%CI (0.04-1.32), P=0.10, Figure 4C].

Figure 4 The forest plots for synthesized outcomes

- *The duration of MV* A total of 6 RCTs reported the effect of OIT on the duration of MV in premature infants. There was significant statistical heterogeneity among the studies (I^2=92%,

P<0.001), so the random effect model was used for statistical analysis. The results showed that there was no statistically difference in the duration of MV between OIT and control group [MD=-0.67, 95%CI (-1.37, 0.03), P=0.06, Figure 5A].

- *The length of hospital stay* A total of 7 RCTs reported the effect of OIT on the length of hospital stay in premature infants. There was significant statistical heterogeneity among the studies (I^2=98%, P<0.001), so the random effect model was used for statistical analysis. The results showed that the length of hospital stay in the tracheal tube in the OIT group was less than that in the control group, and the difference was statistically significant [MD=-6.60, 95%CI (-11.66, -1.53), P=0.01, Figure 5B].
- *Mortality* A total of 6 RCTs reported the effect of OIT on the mortality in premature infants. There was no significant statistical heterogeneity among the studies (I^2=0%, P=0.84), so the fixed effect model was used for statistical analysis. The results showed that there was no statistically difference in the mortality between OIT and control group [RR=0.60, 95%CI (0.31, 1.14), P=0.12, Figure 5C].

Figure 5 The forest plots for synthesized outcomes

Publication bias and sensitivity analysis

The funnel plots on the risk of publication bias are presented in Figure 6, and the results of Egger test showed that there was no publication bias amongst the synthesized outcomes (all P >0.05). We excluded every RCT on each result one by one to check that if the overall results were changed, and we found that the overall results were not altered by removing any one of included RCTs.

Figure 6 The funnel plots for synthesized outcomes

Discussions

VAP is one of the main complications of invasive MV and a common type of nosocomial infection, which seriously affects the prognosis of neonates[27, 28]. Relevant studies[29, 30] have found that oral colonization flora is an important source of pathogenic bacteria that cause VAP. The oral mucosa of premature infants is thin and tender with abundant blood vessels, the salivary glands are not fully developed and secreted less than adults, the oral mucosa is dry and vulnerable to injury and local infection[31]. The establishment of artificial airways makes it impossible for infants to breastfeed orally. It destroys the natural barrier function of the oral and nasal cavity of children to bacteria, so effective oral intervention for MV infants is of great significance to prevent the occurrence of VAP[32, 33]. The results of this present meta-analysis have found that compared with routine oral care in premature infants, OIT is beneficial to reduce the incidence of VAP, the detection rate of tracheal tube-causing microorganisms and length of hospital stay in premature infants, which is worthy of clinical application.

Colostrum is rich in cytokines and immune agents, which can provide antibacterial, bactericidal, antiviral, anti-inflammatory, immune regulation and anti-infection protection[34]. Colostrum oral smear can be used as a nutritional feeding supplement and potential immunotherapy. Rodriguez et al.[35] described oral smearing of colostrum in premature infants from a theoretical perspective, showing that colostrum can provide the greatest range of protection for very low birth weight (VLBW) infants. In previous studies[36-38], the safety and feasibility of applying colostrum to the oral cavity are preliminarily explored. The vital signs of the children before and after OIT operation are stable, and no adverse reactions occur. Moreover, the time for children in the OIT

group to reach complete enteral feeding is significantly earlier, indicating that the use of colostrum smearing in the oral cavity is simple and easy, and it can be well tolerated by ultra-low birth weight infants in critical condition. OIT is economical and good safety, and it may bring positive clinical significance.

In a previous study[39], VLBW infants were randomly divided into a colostrum group and a normal saline solution control group. The intervention started within 48 hours after birth, and the oral smear was performed every 2 hours for 48 hours, quantitative detection was performed 6 hours after the intervention. The content of sIgA, lactoferrin and other immune substances in urine and saliva increased after oral application of colostrum, indicating that the abundant immune factors in colostrum and the stimulation of oropharyngeal lymphoid tissue through the oropharyngeal pathway strengthens the immune system of immature neonates and it can provide early immune protection for premature infants. In addition, a study [40] retrospectively analyzed inftants with a body weight of ≤1500g in a hospital's NICU who were using MV. After oral smearing of colostrum for these infants, the number of days on the machine and the number of days in hospital were not statistically significant between the two groups. But the positive rate indicators of tracheal secretion culture and blood culture decreased after the intervention. At the same time, some studies[41, 42] have shown that the intervention of oral smearing of colostrum in VLBW infants can last for 48 hours to affect the colonization of oral microorganisms, which provides a basis for OIT to prevent VAP in premature infants.

The dosage of colostrum smear in OIT is relatively uniform in various literatures, all of which are 0.2 mL/time, 0.1 mL on each side, and the dosage is small for precise control. During the OIT, it is recommended to accurately apply colostrum to both sides of the oral mucosa of the infants, pay

attention to gentle movements, maintain the integrity of the oral mucosa, and prevent the cotton swab or cotton ball from falling off and causing choking or suffocation in the infant's mouth[43]. The starting time is generally 48 to 96 hours after birth, and the frequency is smeared every 2 to 3 hours or 3 to 4 hours for 48 hours or until the child can be fed orally[44]. It must be noted that most NICUs in China are mother-infant separation wards, and visitors are not allowed during hospitalization[45]. Fresh colostrum or refrigerated colostrum is required for each oral application, and family members are required to actively cooperate with daily delivery of fresh breast milk to the hospital. Therefore, the importance of oral smearing of colostrum should be informed to the family members of the children through various forms of education, and the collection, storage and transportation of colostrum should be explained in detail, and the family members should be involved in the work of caring for the infants[46, 47]. Active help and nursing care from health care providers can increase family members' confidence in treatment and relieve the mother's guilt and anxiety that she cannot directly care for the child. For the storage of colostrum, freezing will destroy the protein molecular structure in colostrum and inactivate the active substances in colostrum[48, 49]. Therefore, fresh colostrum or refrigerated colostrum should be used for OIT to ensure the safety and effect of OIT[50, 51].

There are some limitations of this meta-analysis that deserve careful consideration. Firstly, the RCTs included in this meta-analysis generally have problems of allocation concealment and insufficient blinding, resulting in the possibility of bias to varying degrees. Secondly, there are relatively few studies on the prevention of VAP in premature infants by OIT, and the sample size of the studies is relatively small, the long-term impact of OIT on premature infants remains to be explored. Thirdly, most of the included research reports were from a few countries such as China,

and there may be some population and regional differences in the research results. The effect and safety of OIT still need to be further explored in follow-up studies with large samples and multiple regions.

Conclusions

In conclusion, the results of this meta-analysis show that OIT can prevent VAP in premature infants, reduce the detection rate of pathogenic microorganisms in the tracheal tube, and shorten the length of hospital stay. It is recommended that follow-up studies adopt a more rigorous design, and clarify the gestational age, birth weight, frequency of intervention, frequency of intervention, etc. More large-sample, multi-center, high-quality RCT should be carried out to further evaluate the effect of OIT on the duration of MV, the detection rate of pathogenic microorganisms in the oropharynx, and the mortality of premature infants. Besides, the direct immune effect of OIT should be quantified to assess the effect of oral smearing of colostrum on the oral flora of premature infants, to provide more insights to the clinical treatment and care of premature infants.

Declarations

Ethics approval and consent to participate

In this study, all methods were performed in accordance with the relevant guidelines and regulations. Ethics approval and consent to participate are not necessary since our study is a meta-analysis.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Author contributions

Y Y, C T, F Y designed research; Y Y, C T, L H, Y J, H R, F Y conducted research; Y Y, C T, L H analyzed data; Y Y, F Y wrote the first draft of manuscript; Y Y had primary responsibility for final content. All authors read and approved the final manuscript.

Acknowledgments

None.

List of abbreviations

VAP: ventilator-associated pneumonia

NICU: neonatal intensive care unit

OIT: oral immune therapy

CINAHL: Cumulative Index of Nursing and Allied Health Literature

CNKI: China National Knowledge Infrastructure

CBM: China Biomedical Documentation Service

RCTs: randomized controlled trials

PRISMA: preferred reporting items for systematic reviews and meta-analyses

MD: mean difference

RR: relative risk

CI: confidence interval

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Figure legends

Figure 1 The PRISMA flow diagram of RCT selection

Figure 2 Risk of bias graph

Figure 3 Risk of bias summary

Figure 4 The forest plots for synthesized outcomes

Figure 5 The forest plots for synthesized outcomes

Figure 6 The funnel plots for synthesized outcomes

Table 1 The characteristics of included RCTs

RCT	Country	Sample size		Gestational age (weeks)		Birth weight (g)		Interventions		OIT frequency	OIT duration
		OIT group	Control group	OIT group	Control group	OIT group	Control group	OIT group	Control group		
Abd 2019	Egypt	100	100	8.90±2.05	28.80±2.26	1050±246	1022±249	Colostrum oropharyngeal instillation 0.2 ml/time	Routine care	q 2～4 h	NA
Du 2018	China	45	45	30.50±1.30	30.70±1.20	1281±205	1221±191	Colostrum oropharyngeal 0.2 ml/time	0.9% sodium chloride solution 0.2 ml/time	q 3h	7d
He 2020	China	28	29	30.73±1.84	30.77±2.00	1551.07±438.61	1611.03±552.12	Colostrum oropharyngeal 0.2 ml/time	0.9% sodium chloride solution 0.2 ml/time	q 4h	NA
Hu 2022	China	43	43	33.92 ± 1.66	33.86 ± 1.81	1670 ±350	1650±380	Colostrum oropharyngeal 0.2 ml/time	0.9% sodium chloride solution	q 4h	5~7d
Lee	Korea	22	21	26（24,	26（24,	815(610, 1003)	830(701, 993)	Colostrum	sterile	q 3h	7d

2015				27）	27）			oropharyngeal 0.2 ml/time	water 0.2 ml/time		
Li 2020	China	51	53	27.01±0.98	26.59±1.21	775.01±223.18	809.01±180.18	Colostrum oropharyngeal 0.2 ml/time	0.9% sodium chloride solution	q 4h	5d
Sharma 2020	India	59	58	29.10±1.80	29.20±1.90	1146±58	1158±61	Colostrum oropharyngeal instillation	Routine care	q 2h	72 h
Sohn 2016	USA	6	6	27(25, 30)	27(25, 28)	1092(490, 1350)	1015(735, 1300)	Colostrum oropharyngeal instillation 0.2 ml/time	Routine care	q 2h	46 h
Song 2020	China	40	40	34.61±1.44	34.22±1.56	2068±470	2069±450	Colostrum oropharyngeal 0.2 ml/time	0.9% sodium chloride solution	q 3h	72 h
Zan 2021	China	33	30	NA	NA	2940±870	2670±750	Colostrum oropharyngeal 0.2 ml/time	2% Sodium Bicarbonate oral care	q 3~4h	NA

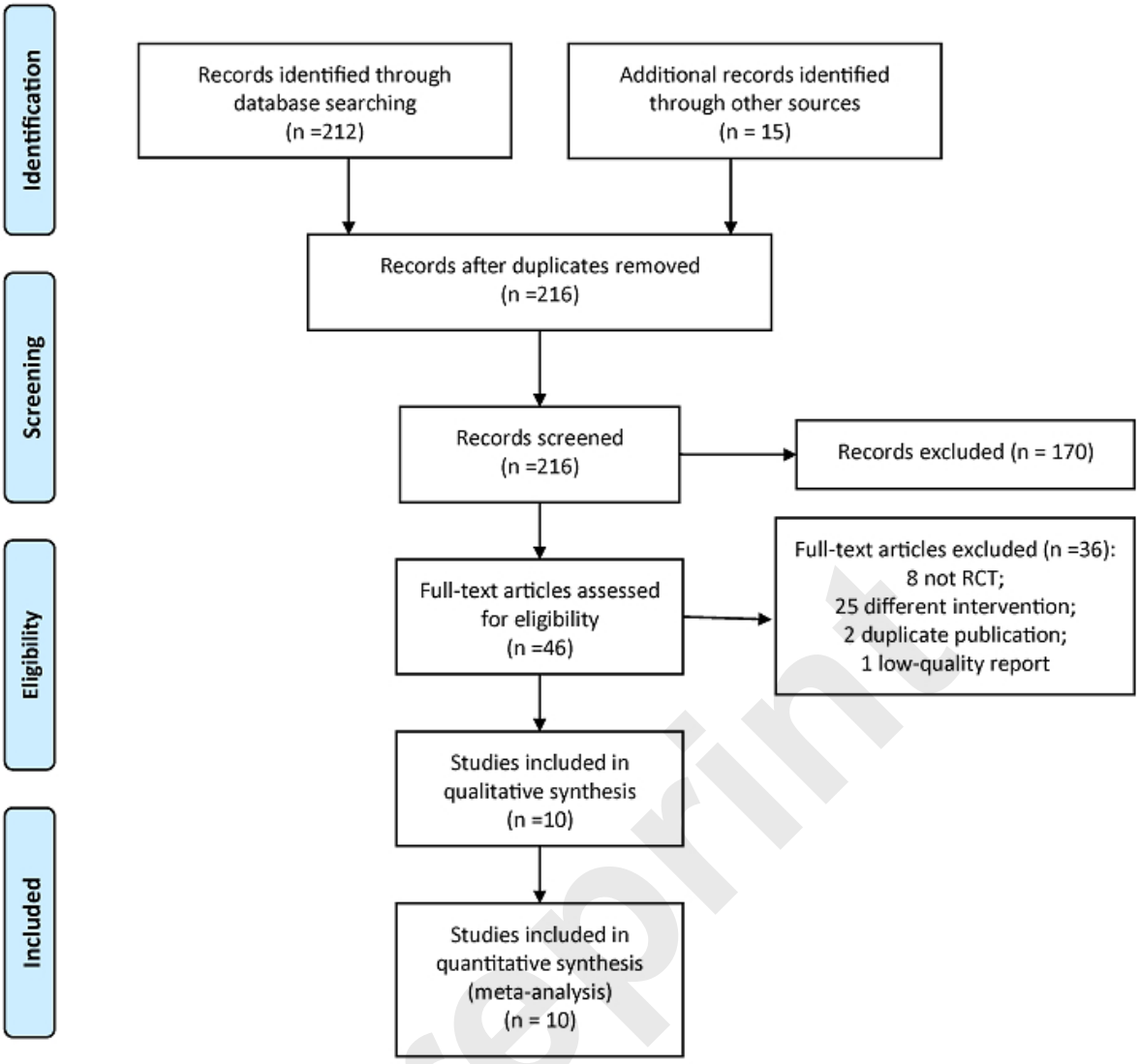


Figure 1 The PRISMA flow diagram of RCT selection

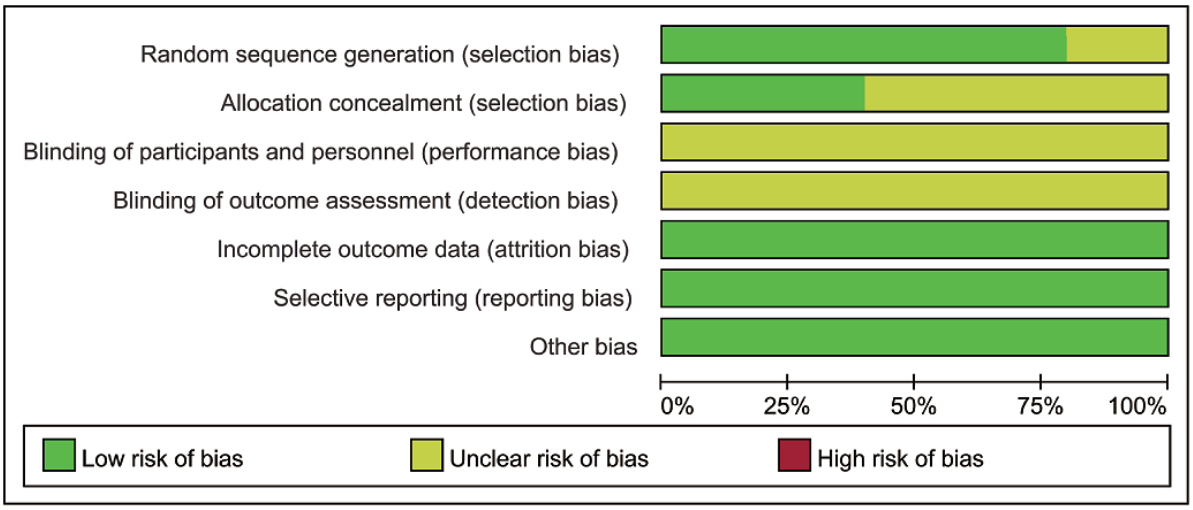


Figure 2 Risk of bias graph

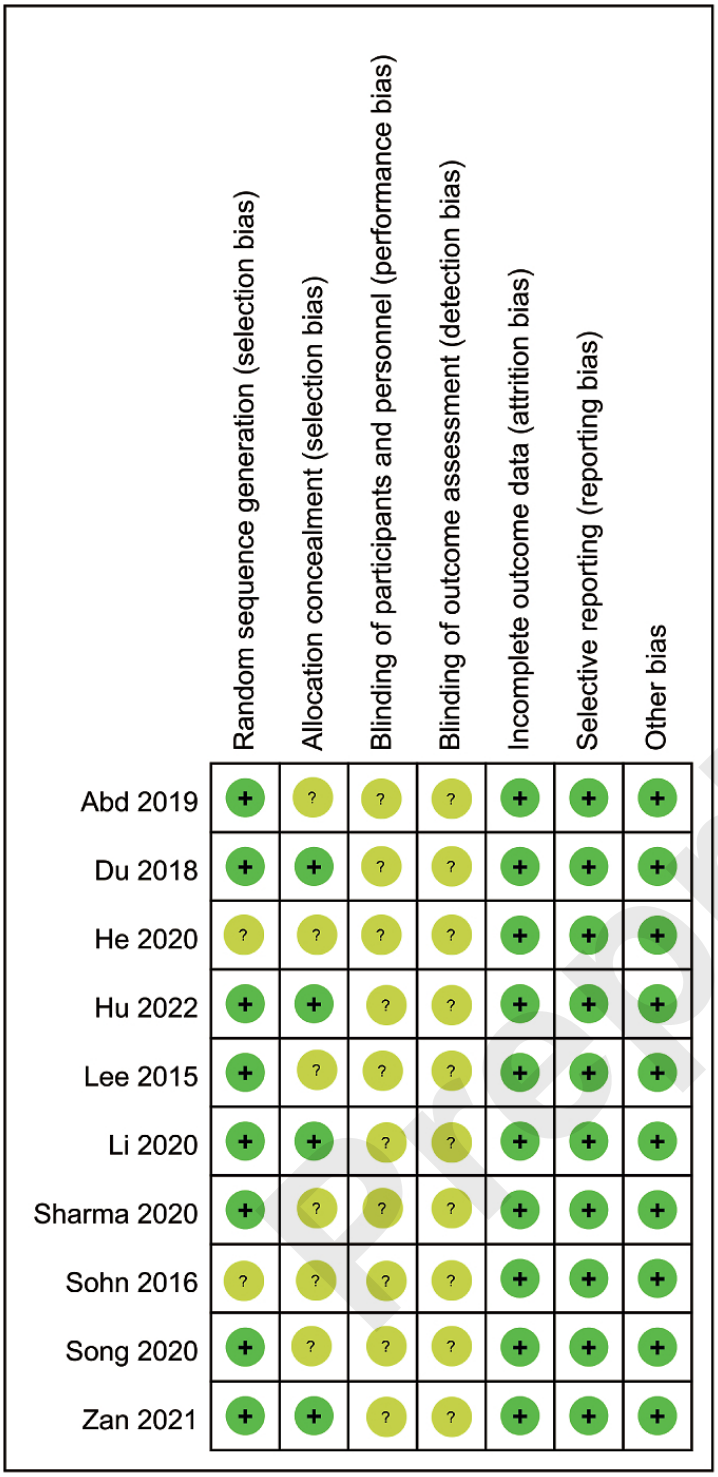
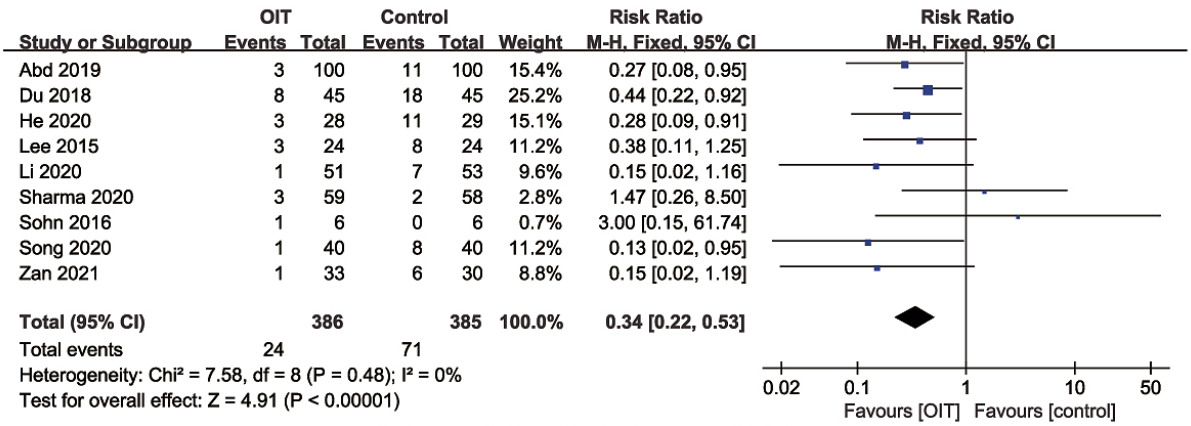
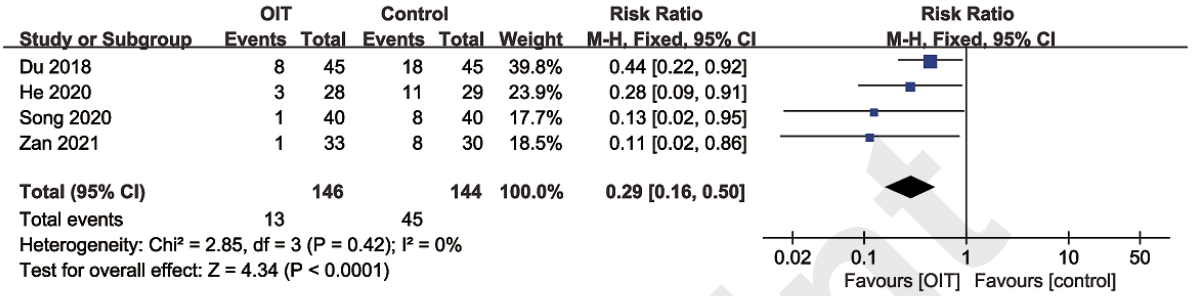


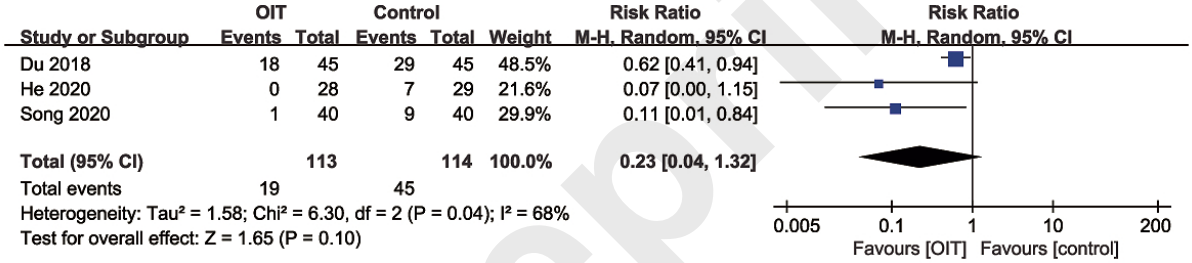
Figure 3 Risk of bias summary



A Forest plot for the incidence of VAP

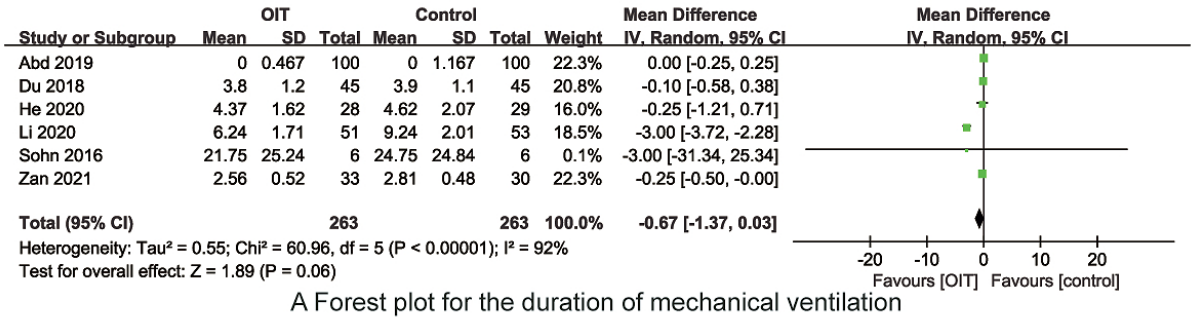


B Forest plot for the detection rate of pathogenic microorganisms in the tracheal tube

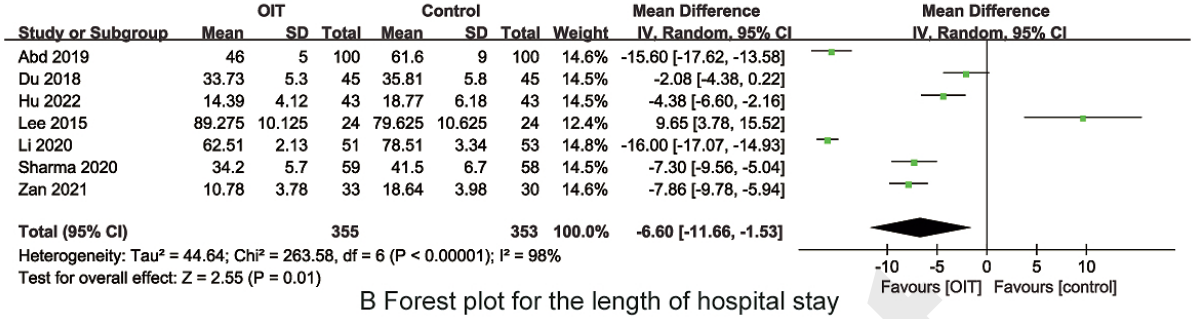


C Forest plot for the detection rate of oropharyngeal pathogenic microorganisms

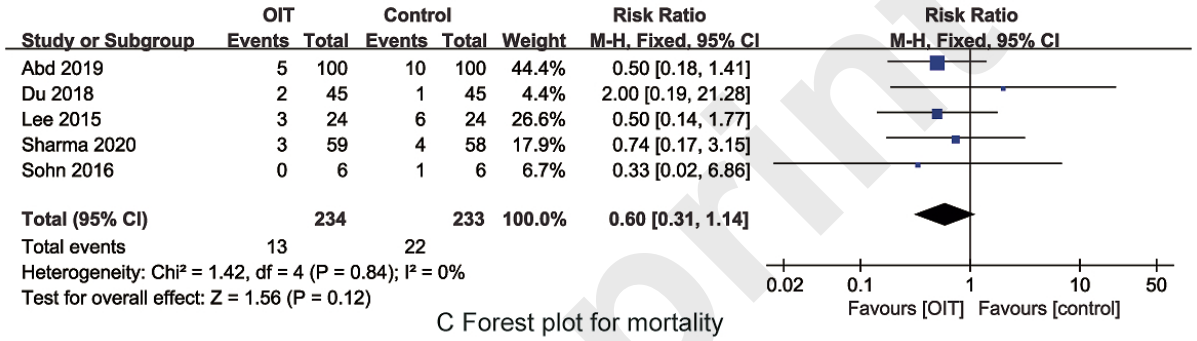
Figure 4 The forest plots for synthesized outcomes



A Forest plot for the duration of mechanical ventilation



B Forest plot for the length of hospital stay



C Forest plot for mortality

Figure 5 The forest plots for synthesized outcomes

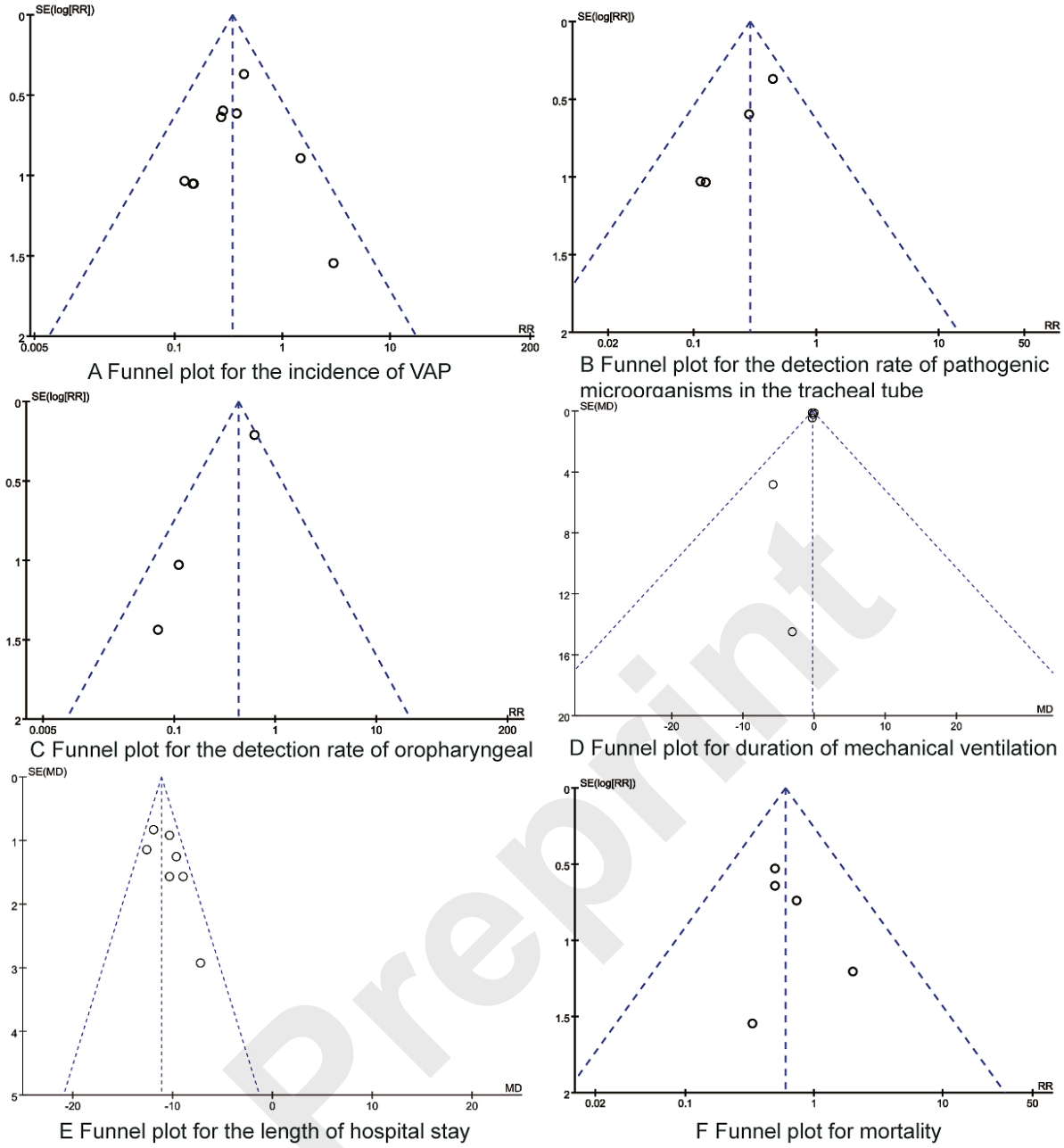


Figure 6 The funnel plots for synthesized outcomes