A meta-analysis of the effects of probiotics on various parameters in critically ill ventilated individuals

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Abstract

Background. According to reports, ventilator-associated pneumonia affects critically ill patients more frequently than any other nosocomial infection. Probiotic usage as a prophylactic intervention has shown promising results in numerous studies.

Objectives. We performed a meta-analysis to evaluate the effect of probiotics on different parameters in critically ill ventilated subjects.

Materials and methods. A systematic literature search up to June 2022 was performed and 5893 critically ill ventilated subjects at the baseline of the studies were identified; 2912 of them were using the probiotics, and there were 2981 controls. Odds ratio (OR) and mean difference (MD) with 95% confidence interval (95% CI) were calculated to assess the effect of probiotics on different parameters in critically ill ventilated subjects using the dichotomous and contentious methods with a random or fixed effects model.

Results. The probiotics caused a significantly lower incidence of ventilator-associated pneumonia (OR = 0.52; 95% CI: 0.40–0.68, $p < 0.001$), shorter duration of mechanical ventilation (MD = –2.22; 95% CI: –3.33––1.11, $p < 0.001$), shorter intensive care unit (ICU) stay (MD = –2.09; 95% CI: –3.41––0.77, $p = 0.002$), shorter hospital stay (MD = –2.36; 95% CI: –4.54––0.19, $p = 0.03$), and lower oropharyngeal colonization (OR = 0.59; 95% CI: 0.36–0.96, $p = 0.03$) in critically ill ventilated subjects compared with controls. However, probiotic use had no significant difference in terms of diarrhea incidence (OR = 0.74; 95% CI: 0.52–1.07, $p = 0.11$) and in-hospital mortality (OR = 0.90; 95% CI: 0.79–1.03, $p = 0.14$) in critically ill ventilated subjects compared with controls.

Conclusions. Probiotics caused a significantly lower ventilator-associated pneumonia incidence, shorter duration of mechanical ventilation, shorter ICU and hospital stay, and lower oropharyngeal colonization. However, there was no significant difference in terms of diarrhea incidence and in-hospital mortality in subjects who used probiotics compared with controls. The low sample size of 9 out of 27 researches and the small number of studies in several comparisons requires attention when analyzing the results.

Key words: probiotic, ventilator-associated pneumonia, length of hospital stay, critically ill ventilated adult, oropharyngeal colonization

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Introduction

According to reports, ventilator-related pneumonia affects critically ill subjects more frequently than any other nosocomial infection,[1] with a frequency of 2–16 sessions per 1000 ventilator days.[2] Ventilator-related pneumonia is said to be the most common cause of mortality among nosocomial infections.[3] Although the pathophysiology of ventilator-related pneumonia is extremely complex, pathogenic bacterial colonization of the aerodigestive tract and bacterial translocation are the main contributing factors of the disease.[4] Several trials and investigations have been conducted to determine the most effective pharmacological preventative techniques, including the use of probiotics or antibiotics for specific gastrointestinal or oral disinfection. Numerous studies have revealed that using probiotics as a preventative measure offers promising outcomes[5]; however, antibiotic resistance and price have been connected to the use of antibiotics for specific gastrointestinal or oral disinfection, respectively.[6] Probiotics are living, nonpathogenic microorganisms that have been demonstrated to decrease bacterial translocation by promoting mucosal immunity and regulating the release of pro-inflammatory cytokines.[4] They prevent the growth of pathogenic bacteria through a number of ways, such as the production of different chemicals, e.g., organic acid, hydrogen peroxide and bacteriocins, competition for nutrients, prevention of pathogen attachment, and inhibition of the effect of microbial toxins. Probiotics similarly contribute to maintaining the mucosal protective barrier by stimulating the formation of the normal epithelium.[7] Prebiotics are indigestible sugars that promote the development of particular bacterial colonies through synbiotics that are a concoction of probiotics and prebiotics.[8] In recent years, numerous randomized controlled trials (RCTs) have been carried out to assess the efficacy of probiotics in the inhibition of ventilator-related pneumonia, due to their promising nature in critically ill subjects. Latest meta-analyses demonstrated the effectiveness of probiotics in reducing the incidence of ventilator-related pneumonia.[1,4] However, it is worth noting that some of the trials included in the study were of poor quality.

Objectives

The goal of the study was to assess the impact of probiotic use on the incidence of ventilator-related pneumonia, length of hospital stay, length of stay in an intensive care unit (ICU), duration of mechanical ventilation, incidence of diarrhea, frequency of oropharyngeal colonization, and in-hospital mortality in critically ill ventilated subjects.

Materials and methods

Eligibility criteria

Studies included in the analysis evaluated the impact of probiotics on different parameters in critically ill ventilated subjects. The analyses regarding the influence of the probiotics compared with controls were summarized.[9]

All studies involved humans as participants. Inclusion was unaffected by language or study size. Review articles, comments and research that failed to provide a measure of an association were all eliminated from the list of analyzed publications. Figure 1 depicts the entire course of the study. The inclusion criteria were as follows:

1. The research was either prospective, observational, retrospective, or a controlled trial.
2. The intended subjects were critically ill ventilated individuals.
3. The intervention regimen relied on probiotics.
4. The study compared probiotic use with controls.

The exclusion criteria were: 1) studies that did not examine the influence of probiotics compared to controls in critically ill ventilated subjects, 2) research on subjects treated without probiotics or controls, and 3) studies without the emphasis on the significance of comparison outcomes.

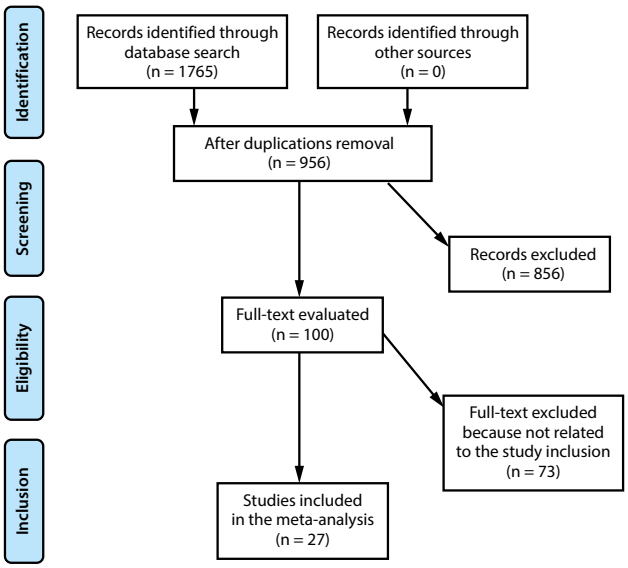

Fig. 1. Flowchart of the study process

Search strategy

According to the PICOS concept,[10] a protocol of search strategy was created and defined as follows: P (population) – critically ill ventilated subjects; I (intervention/exposure) – probiotics; C (comparison) – probiotic use compared with controls; O (outcome) – ventilator-related pneumonia incidence, mechanical-ventilation period, length of ICU stay, length of hospital stay, oropharyngeal colonization, diarrhea incidence, and in-hospital mortality; S (study design) – no restrictions.[11]

Table 1. Search strategy for each database

Database	Search strategy
PubMed	#1 "critically ill ventilated adult" [MeSH terms] OR "probiotic" [all fields] OR "length of hospital stay" [all fields] OR "diarrhea" [all fields] #2 "oro-pharyngeal colonization" [MeSH terms] OR "critically ill ventilated adult" [all fields] OR "length of hospital stay" [all fields] OR "ventilator-related pneumonia" [all fields] OR "in-hospital mortality" [all fields] #3 #1 AND #2
Embase	#1 "critically ill ventilated adult"/exp OR "probiotic"/exp OR "length of hospital stay"/exp OR "diarrhea" #2 "oro-pharyngeal colonization"/exp OR "length of hospital stay"/exp OR "ventilator-related pneumonia"/exp OR "in-hospital mortality" #3 #1 AND #2
Cochrane Library	#1 "critically ill ventilated adult": ti,ab,kw OR "probiotic": ti,ab,kw OR "length of hospital stay": ti,ab,kw (word variations have been searched) #2 "diarrhea": ti,ab,kw OR "oro-pharyngeal colonization": ti,ab,kw OR "length of hospital stay": ti,ab,kw OR "ventilator-related pneumonia": ti,ab,kw OR "in-hospital mortality": ti,ab,kw (word variations have been searched) #3 #1 AND #2

MeSH – medical subject headings; ti,ab,kw – terms in either title or abstract or keyword fields; exp – exploded indexing term.

First, using the arrangement of key words and correlated terms presented in Table 1, we conducted a thorough search of the OVID, Embase, Cochrane Library, PubMed, and Google Scholar databases for studies published until June 2022. All found papers were listed in an EndNote file (EndNote; Clarivate Analytics, London, UK), duplicates were removed, and the titles and abstracts were examined in order to exclude studies that did not show a relationship between probiotics and controls in critically ill ventilated people.

Data collection process

The data were gathered using the following criteria: last name of the first author, study period, publication year, country or region where the study was performed, population type, clinical and management characteristics, qualitative and quantitative technique of assessment, information source, results assessment, and statistical analysis.[12]

Data items

When there were various results from a single study, data were collected independently, based on the evaluation of the impact of complications of probiotics compared to controls in critically ill ventilated subjects.

Study risk of bias assessment

Two authors independently assessed the methods used in chosen publications in order to determine the likelihood of bias in each study. The methodological quality was evaluated using the "risk of bias instrument" from the Cochrane Handbook for Systematic Reviews of Interventions v. 5.1.0.[13]

In terms of the assessment criteria, each study was rated and assigned to one of the 3 risk of bias levels: low – if all quality criteria were met; moderate – if one or more of the quality criteria were partially met or unclear; or high – if one or more of the criteria were not met or not included. Any inconsistencies were addressed after a re-evaluation of the original article.

Effect measures

Sensitivity studies were only performed on research that reported and examined the influence of the probiotics compared with controls. Other comparisons between probiotics and controls were used for sensitivity and subclass analysis.

Statistical analyses

Odds ratio (OR) and mean difference (MD) with a 95% confidence interval (95% CI) were calculated using a random or fixed effects model with dichotomous and contentious methods. The heterogeneity (I^2) index was calculated, with a range of 0–100%. No, low, moderate, and high heterogeneity were indicated by values around 0%, 25%, 50%, and 75%, respectively.[14] When I^2 was higher than 50%, the random effects model was selected, and when it was lower than 50%, the fixed effects model was selected. The subclass analysis was completed by stratifying the first evaluation based on the previously specified outcome categories. The value of $p < 0.05$ was used in the analysis to indicate statistical significance for differences across subcategories.

Reporting the assessment of bias

Using the Egger's regression test and funnel plots showing the logarithm of ORs compared to their standard errors, the publication bias was evaluated both intuitively and quantitatively (the publication bias was considered present when $p \geq 0.05$).[10]

Certainty assessment

All p-values were calculated using two-tailed tests. The statistical analysis was conducted and the graphs were obtained using Review Manager v. 5.3 (The Cochrane Collaboration, Copenhagen, Denmark).

Results

A total of 27 articles published between 2006 and 2022 that matched the inclusion criteria were chosen from a total of 1765 evaluated studies.[6,15–40] Table 2 displays

Table 2. Characteristics of the selected studies for the meta-analysis

Study, year	Country	Total	Probiotic	Controls
Kotzampassi et al., 2006[15]	Greece	65	35	30
Spindler-Vesel et al., 2007[16]	Slovenia	113	26	87
Forestier et al., 2008[17]	France	202	99	103
Knight et al., 2009[18]	UK	259	130	129
Giamarellos-Bourboulis et al., 2009[19]	Greece	72	36	36
Morrow et al., 2010[6]	USA	138	68	70
Barraud et al., 2010[20]	France	149	78	71
Oudhuis et al., 2011[21]	Netherlands	248	129	119
Tan et al., 2011[22]	China	35	16	19
Li et al., 2012[23]	China	165	82	83
Banupriya et al., 2015[24]	India	142	70	72
Rongrungruang et al., 2015[25]	Thailand	150	75	75
Malik et al., 2016[26]	Malaysia	49	24	25
Zeng et al., 2016[27]	China	235	118	117
Amiri, 2016[28]	Iran	60	30	30
Shimizu et al., 2018[29]	Japan	72	35	37
Angurana et al., 2018[30]	India	100	50	50
Kooshki et al., 2018[31]	Iran	80	40	40
Klarin et al., 2018[32]	Sweden	137	69	68
Anandaraj et al., 2019[33]	India	146	72	74
Mahmoodpoor et al., 2019[34]	Iran	102	48	54
Habib et al., 2020[35]	Egypt	65	32	33
Nazari et al., 2020[36]	Iran	147	73	74
Johnstone et al., 2021[37]	Canada	2650	1318	1332
Boraey et al., 2021[38]	Egypt	80	40	40
Tsilika et al., 2022[39]	Greece	112	59	53
Prasoon et al., 2022[40]	India	120	60	60
Total		5893	2912	2981

the data from these publications. The chosen studies comprised 5893 critically ill ventilated participants in the trials' baseline; 2912 of them were using probiotics and there were 2981 controls. At the commencement of the trials, there were between 35 and 2650 individuals under study in total. Twenty-five studies presented data grouped according to the incidence of ventilator-related pneumonia, 16 studies presented data grouped according to the mechanical ventilation period, 17 according to the length of ICU stay, 8 according to the length of hospital stay, 5 according to oropharyngeal colonization rate, 6 according to diarrhea incidence, and 15 according to in-hospital mortality.

The probiotic use resulted in a significantly lower ventilator-related pneumonia incidence (OR = 0.52; 95% CI: 0.40–0.68, $p < 0.00001$) with moderate heterogeneity ($I^2 = 65\%$), shorter mechanical ventilation period (MD = –2.22; 95% CI: –3.33––1.11, $p < 0.00001$) with high heterogeneity ($I^2 = 92\%$), shorter ICU stay (MD = –2.09; 95% CI: –3.41––0.77, $p = 0.002$) with high heterogeneity ($I^2 = 89\%$), shorter hospital stay (MD = –2.36; 95% CI: –4.54––0.19, $p = 0.03$) with high heterogeneity ($I^2 = 83\%$), and lower rate of oropharyngeal colonization (OR = 0.59; 95% CI: 0.36–0.96, $p = 0.03$) with moderate heterogeneity ($I^2 = 63\%$) in critically ill ventilated subjects compared with controls (Fig. 2–6).

However, probiotics caused no significant difference in terms of diarrhea incidence (OR = 0.74; 95% CI: 0.52–1.07, $p = 0.11$) with low heterogeneity ($I^2 = 45\%$), and in-hospital mortality (OR = 0.90; 95% CI: 0.79–1.03, $p = 0.14$) with no heterogeneity ($I^2 = 0\%$) in critically ill ventilated subjects compared with controls (Fig. 7,8).

Due to the lack of available data on certain factors, such as gender, age and ethnicity, stratified models could not be used to investigate their impact on comparison outcomes. The visual assessment of the funnel plot and quantitative measurements using the Egger's regression test revealed no evidence of publication bias, as shown in Supplementary Fig. 1–7. However, it was shown that the majority of the included RCTs had poor methodological quality, no bias in selective reporting and only minimal outcome data, as shown in Fig. 9.

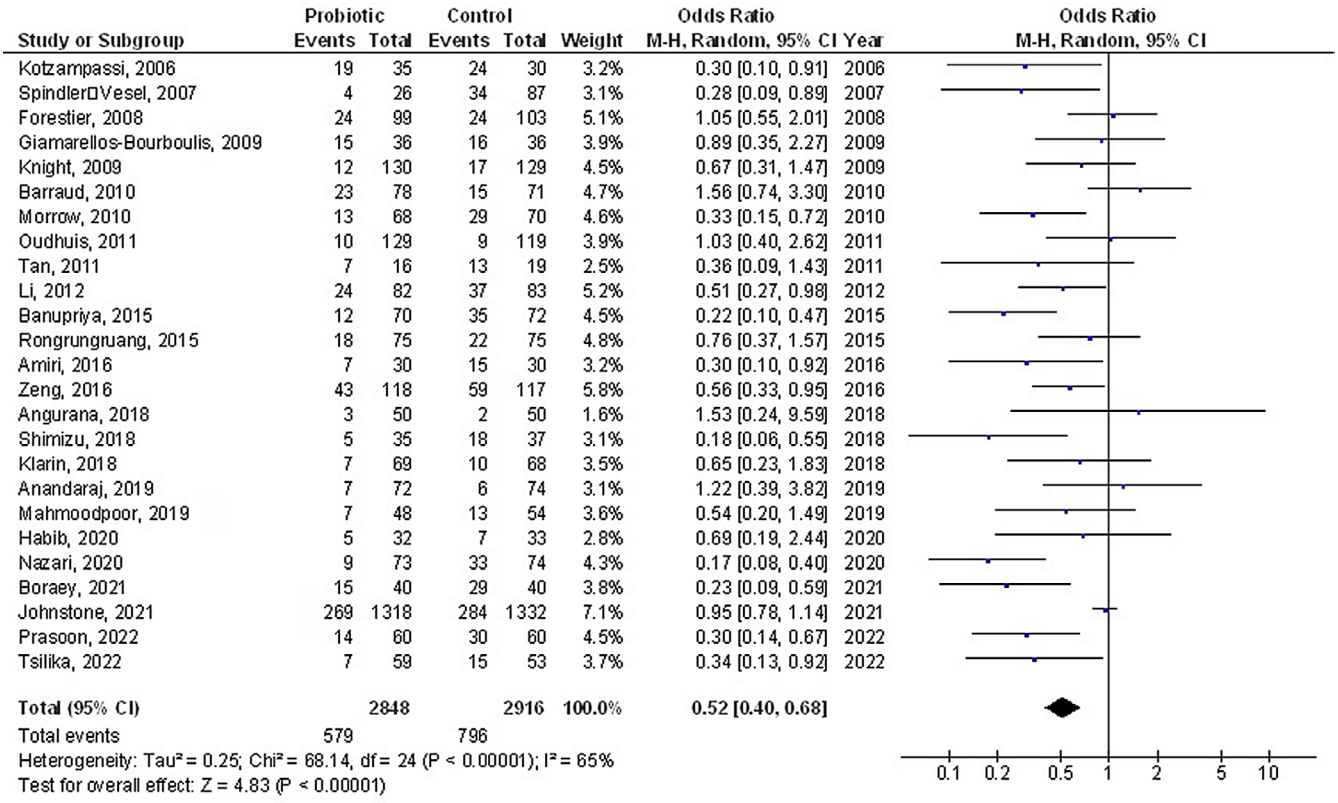

Fig. 2. Forest plot of the influence of probiotic use compared to controls on the frequency of the ventilator-related pneumonia incidence outcomes in critically ill ventilated subjects

95% CI – 95% confidence interval; df – degrees of freedom.

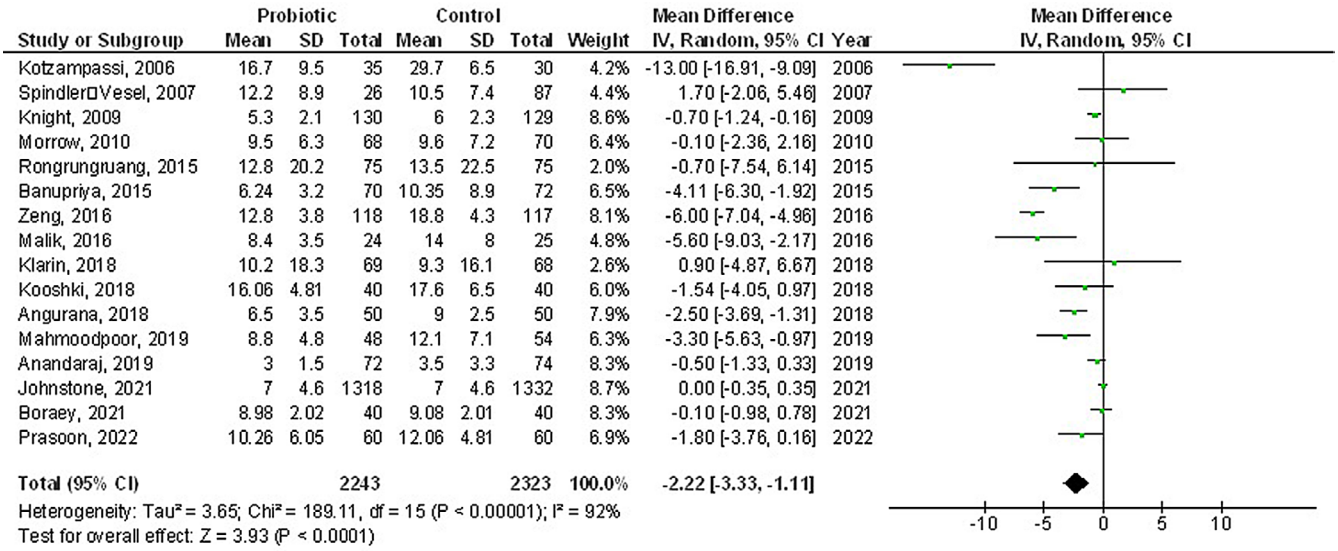

Fig. 3. Forest plot of the influence of probiotic use compared to controls on the mechanical ventilation period outcomes in critically ill ventilated subjects

95% CI – 95% confidence interval; df – degrees of freedom; SD – standard deviation.

Discussion

This meta-analysis had 5893 critically ill ventilated participants in the trials' baseline; 2912 of them were using probiotics and there were 2981 controls.[6,15–40] The probiotic use resulted in a significantly lower ventilator-related pneumonia incidence, shorter mechanical ventilation period, shorter ICU and hospital stay, and lower oropharyngeal colonization rate in critically ill ventilated subjects compared with controls. However, probiotics had caused no significant difference in diarrhea incidence and in-hospital mortality in critically ill ventilated subjects compared with controls.

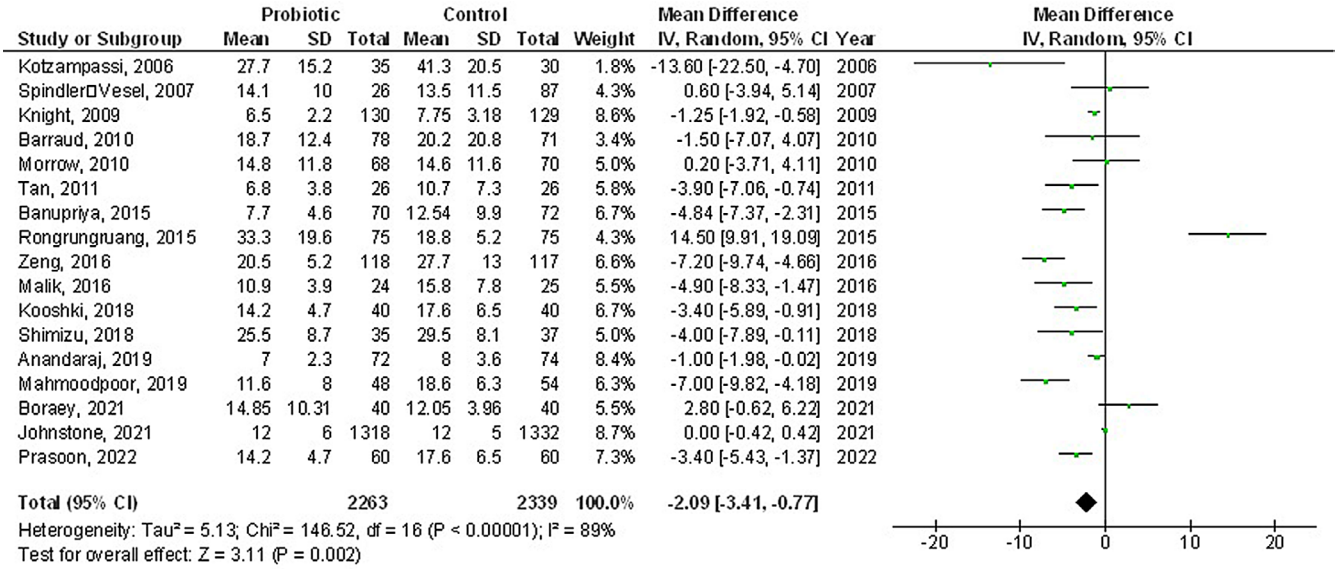

Fig. 4. Forest plot of the influence of probiotic use compared to controls on the length of intensive care unit stay outcomes in critically ill ventilated subjects

95% CI – 95% confidence interval; df – degrees of freedom; SD – standard deviation.

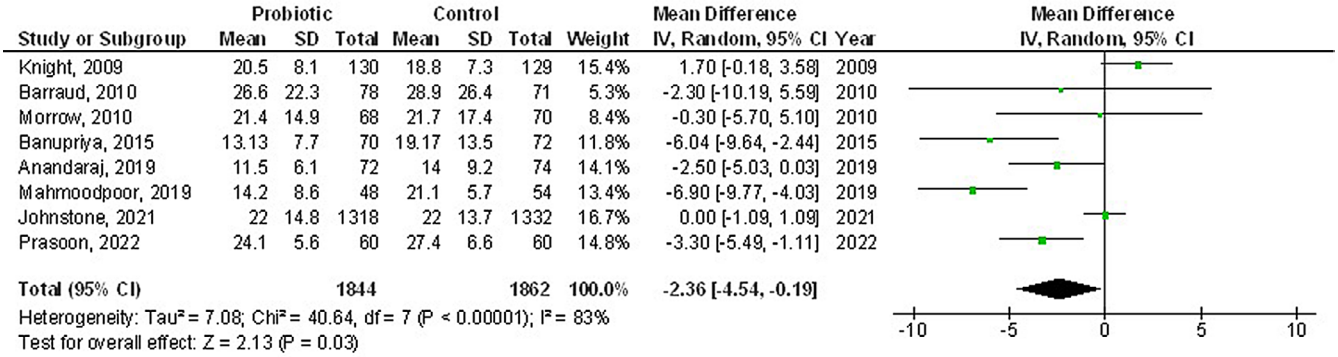

Fig. 5. Forest plot of the influence of probiotic use compared to controls on the length of hospital stay outcomes in critically ill ventilated subjects

95% CI – 95% confidence interval; df – degrees of freedom; SD – standard deviation.

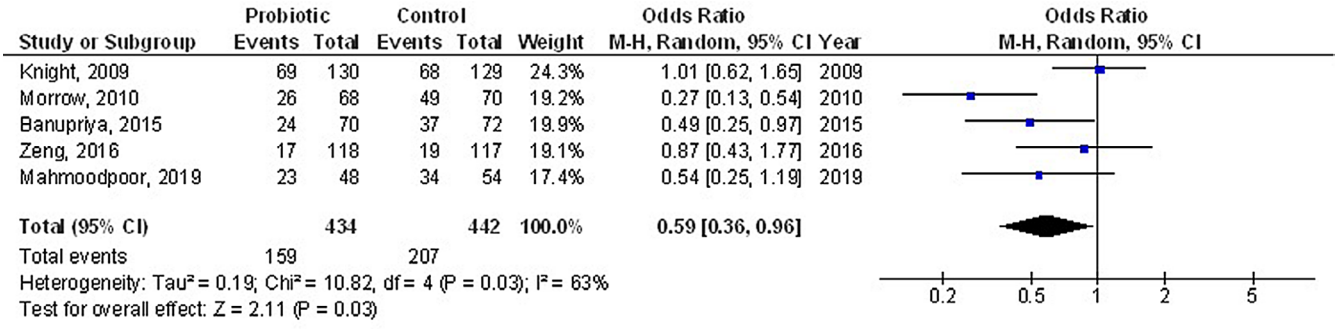

Fig. 6. Forest plot of the influence of probiotic use compared to controls on the oropharyngeal colonization outcomes in critically ill ventilated subjects

95% CI – 95% confidence interval; df – degrees of freedom.

The meta-analysis performed by Bo et al. also demonstrated that probiotics had a favorable impact on the incidence of ventilator-related pneumonia, even after studies with a high risk of bias were eliminated.[41] Probiotic use was related to a statistically significant decline in the incidence of ventilator-related pneumonia and a decrease in the duration of antibiotic treatment, according to the latest meta-analysis by Song et al.[42] Our meta-analysis has shown that administering probiotics significantly lowers the risk of ventilator-related pneumonia occurrence, shortens the duration of mechanical ventilation and the time spent in the ICU, and reduces in-hospital mortality when compared to using a placebo.

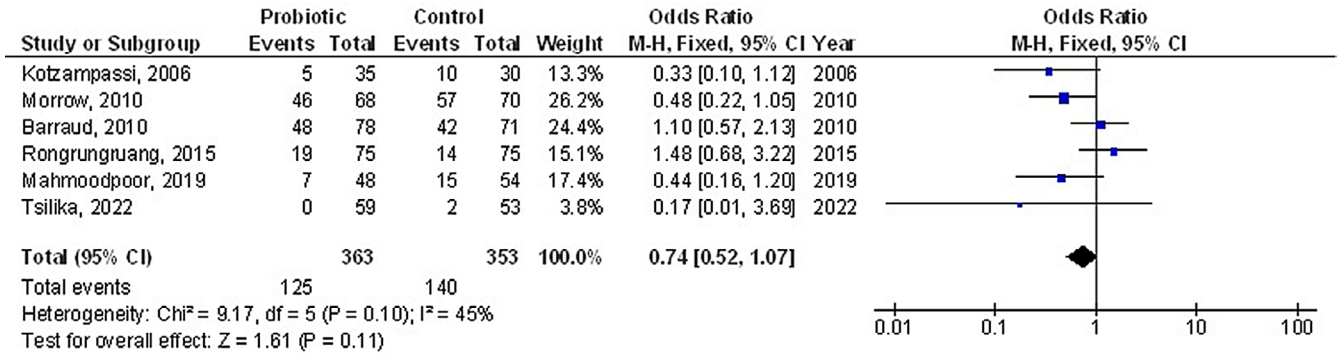

Fig. 7. Forest plot of the influence of probiotic use compared to controls on the diarrhea incidence outcomes in critically ill ventilated subjects

95% CI – 95% confidence interval; df – degrees of freedom.

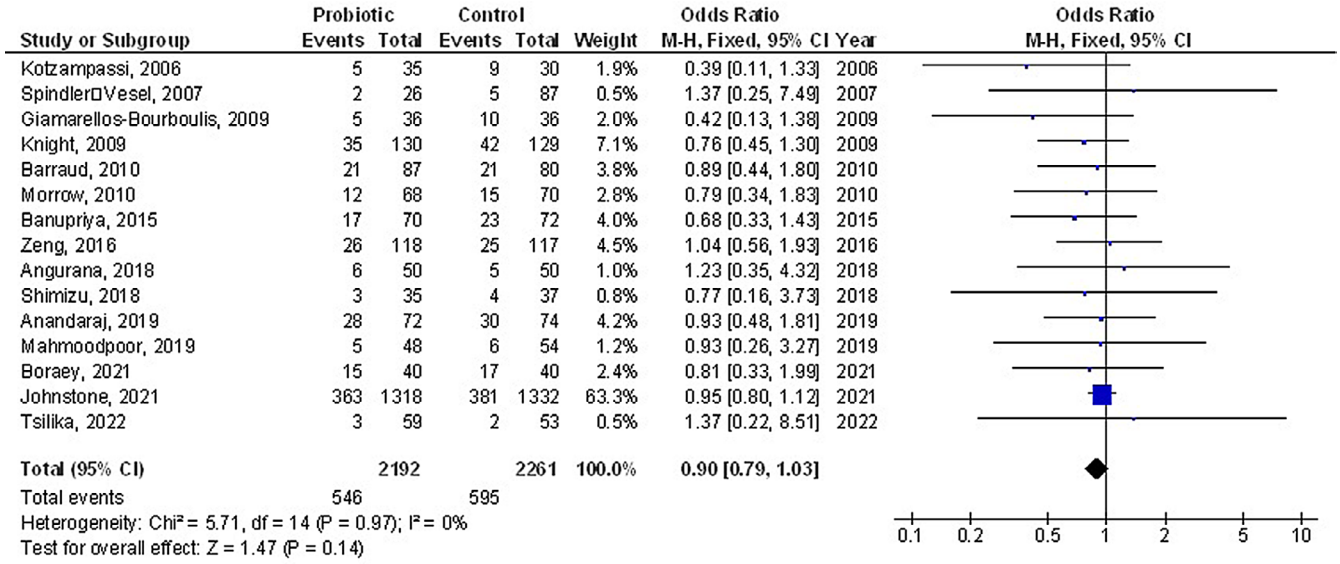

Fig. 8. Forest plot of the influence of probiotic use compared to controls on the in-hospital mortality outcomes in critically ill ventilated subjects

95% CI – 95% confidence interval; df – degrees of freedom.

According to previous meta-analyses,[42–48] the incidence of ventilator-related pneumonia decreased after the probiotic treatment. The incidence of ventilator-related pneumonia did not, however, statistically significantly decline after probiotic delivery, according to 2 meta-analyses by Gu et al.[49] and Wang et al.[50] In our meta-analysis, there was no statistically significant reduction in diarrhea incidence or in-hospital mortality. However, our investigation found a statistically significant decrease in the incidence of ventilator-related pneumonia, length of the ICU stay and mechanical-ventilation period that was not described in prior meta-analyses.[42–48] According to the meta-analysis by Siempos et al. published in 2010, the *Pseudomonas aeruginosa* colonization of the respiratory tract and the length of the ICU stay decreased following the probiotic administration.[51] Probiotic administration was shown to shorten the ICU stay, as described by Gu et al.[52] However, the study by Siempos et al.[51] is outdated, and several new RCTs have since been published. The meta-analysis by Gu et al. included 2 papers only, which is a statistically insignificant quantity to describe the length of ICU stay.[52]

The RCTs included in the present met-analysis employed varying definitions of ventilator-related pneumonia. Two ventilator-related pneumonia rates (one for microbiological and one for clinical cases) were provided in 2 of the RCTs.[6,27] For our meta-analysis, we chose the microbiological definition of ventilator-related pneumonia because it has been adopted by the majority of authors in different RCTs and meta-analyses. Since we relied on the stated definitions and since there is no standard definition provided in the RCTs, the ventilator-related pneumonia definition is a significant drawback to our meta-analysis. To precisely assess the impact of probiotics on ventilator-related pneumonia incidence, a sizable multicenter RCT with a standardized objective definition of a ventilator-related incident is required. According to Centers for Disease Control and Prevention (CDC), a ventilator-related incident happens when the subject's oxygenation declines after a period of stability or improvement. The colonization rate on day 7 of the ICU stay was chosen to calculate the frequency of oropharyngeal colonization. The majority of studies defined diarrhea as 3 or more liquid stools per day.[6,20,34]

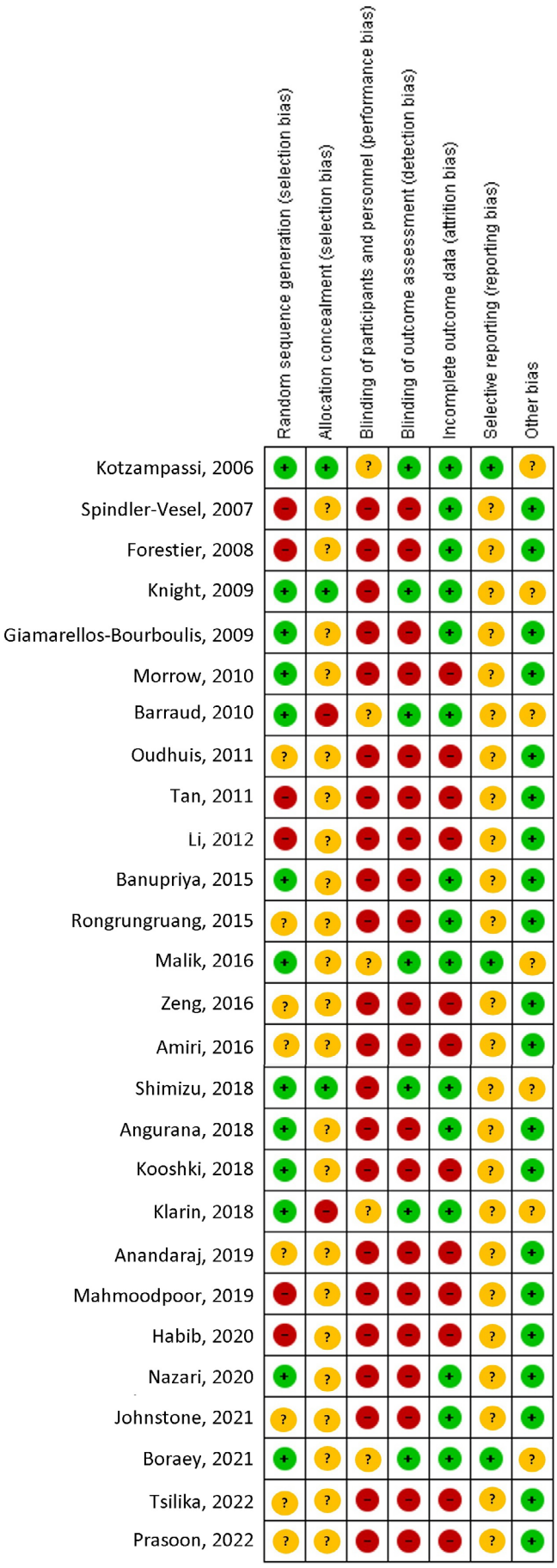

Fig. 9. Risk of bias assessment

This meta-analysis had few restrictions. First, there were differences in the probiotics' type, dosage and manner of delivery throughout RCTs. In a few studies, the length of the treatment was too brief to provide any conclusive data. Second, various definitions of ventilator-related pneumonia were used in the RCTs, including a subjective component. Although the most recent definition of a ventilator-related event from the CDC is more objective, none of the published RCTs on probiotics have applied it. The effects of probiotics on 2 additional clinically significant endpoints – the duration of antibiotic treatment and antibiotic use – is due to variable and sparse reporting of the aforementioned endpoints across trials. Next, immunocompromised subjects were not included in the RCTs that were part of the meta-analysis. Therefore, it is impossible to determine how probiotics are used by this particular subject population. Furthermore, no study found any negative consequences of probiotic use. The use of probiotics (best type, dose and method of administration) for ventilator-related pneumonia in an immunocompromised subject population is therefore in need of a large, multicenter RCT that would additionally assess the potential negative effects of probiotics.

This meta-analysis demonstrated how probiotics affect critically ill ventilated subjects.[53–60] Further research is still required to clarify these potential connections as well as to assess the impact of probiotics on the outcomes under investigation. Larger, more homogeneous samples are required for such research. This was also mentioned in a previous study that employed a similar meta-analysis technique and found comparable favorable outcomes for probiotic benefits.[42–48] Because our meta-analysis was unable to determine whether the differences in gender, age and ethnicity are related to the outcomes, meticuolously conducted RCTs are required to evaluate these factors as well as the combination of different gender, age, ethnicities, and other variants.

Limitations

There may have been a selection bias since several papers identified through the database search were excluded. However, the omitted publications did not adhere to the inclusion criteria. Nine out of 27 papers that were selected had sample size <100. Furthermore, we were unable to ascertain whether age and ethnicity had an impact on the results. The purpose of this study was to compare the effects of probiotics compared to the controls in critically ill ventilated patients. Data from prior studies were used, which may have introduced bias due to missing or incorrect information. The subjects' nutritional states as well as the characteristics of age, sex and gender were all potential sources of bias. There may be some unpublished articles and missing data that could skew the results.

Conclusions

Critically ill ventilated participants treated with probiotics had significantly reduced incidence of ventilator-related pneumonia, shorter duration of mechanical ventilation, shorter ICU and stay, and decreased oropharyngeal colonization rate. Patients who were administed probiotics did not significantly differ from controls in terms of diarrhea incidence or in-hospital mortality in critically ill ventilated individuals. Analyzing the results requires caution due to the small sample size of 9 out of 27 studies included in the meta-analysis and the lack of studies in numerous comparisons.

Availability of data

The corresponding author agrees to make the meta-analysis database available upon reasonable request.

Supplementary materials

Supplementary figures are available at https://doi.org/10.5281/zenodo.7340993. The package consists of the following files:

Supplementary Fig. 1. Ventilator-associated pneumonia incidence funnel plot (Egger's test, p = 0.86).

Supplementary Fig. 2. Mechanical ventilation duration funnel plot (Egger's test, p = 0.84).

Supplementary Fig. 3. Length of ICU stay funnel plot (Egger's test, p = 0.86).

Supplementary Fig. 4. Length of hospital stay funnel plot (Egger's test, p = 0.85).

Supplementary Fig. 5. Oropharyngeal colonization funnel plot (Egger's test, p = 0.91).

Supplementary Fig. 6. Diarrhea incidence funnel plot (Egger's test, p = 0.87).

Supplementary Fig. 7. In-hospital mortality funnel plot (Egger's test, p = 0.92).

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