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Research Article

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Efficacy of probiotics or synbiotics for critically ill adult patients: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Microbial dysbiosis in critically ill patients is a leading cause of mortality and septic complications. Probiotics and synbiotics have emerged as novel therapy on gut microbiota to prevent septic complications. However, current evidence on their effects is conflicting. This work aims to systematically review the impact of probiotics or synbiotics in critically ill adult patients.

Methods: A comprehensive search of the PubMed, CBM, Embase, CENTRAL, ISI, and CNKI databases was performed to identify randomized controlled trials that evaluate probiotics or synbiotics in critically ill patients. The quality assessment was based on the modified Jadad's score scale and the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1. The major outcome measure was mortality. Secondary outcomes included incidence of septic complications, sepsis incidence, length of intensive care unit (ICU) stay, incidence of non-septic complication, and ventilator day. Data synthesis was conduct by Review Manager 5.4.

Results: A total of 25 randomized controlled trials reporting on 5049 critically ill patients were included. In the intervention group, 2520 participants received probiotics or synbiotics, whereas 2529 participants received standard care or placebo. Pooling data from randomized controlled trials demonstrated a significant reduction in the incidence of ventilator-associated pneumonia (VAP) in the treatment group [(risk ratio (RR) 0.86; 95% confidence interval (CI): 0.78–0.95; $p < 0.003$, $I^2 = 85\%$)]. However, in the subgroup analysis, the reduction of incidence of VAP was only significant in patients receiving synbiotics (RR = 0.61, 95% CI: 0.47–0.80, $p = 0.0004$, $I^2 = 40\%$) and not significant in those receiving only probiotics (RR = 0.91, 95% CI: 0.82–1.01, $p = 0.07$, $I^2 = 65\%$). Moreover, sepsis incidence of critically ill patients was only significantly reduced by the addition of synbiotics (RR = 0.41; 95% CI: 0.22–0.72, $p = 0.005$, $I^2 = 0\%$). The incidence of ICU-acquired infections was significantly reduced by the synbiotics therapy (RR = 0.72; 95% CI: 0.58–0.89, $p = 0.0007$, $I^2 = 79\%$). There was no significant difference in mortality, diarrhea, or length of ICU stay between the treatment and control groups.

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Conclusions: Synbiotics is an effective and safe nutrition therapy in reducing septic complications in critically ill patients. However, in such patients, administration of probiotics alone compared with placebo resulted in no difference in the septic complications.

Key words: Critically ill patients, Probiotics, Synbiotics, Meta-analysis, Systematic review, Mortality, Ventilator-associated pneumonia

Highlights

- Synbiotics are an effective and safe therapy in reducing septic complications in critically ill patients.
- Among critically ill patients, the administration of probiotics alone, compared with placebo, resulted in no difference in septic complications.
- The effect of a mixture of probiotics is better than a single probiotic species.

Background

The gut is one of the most important organs in the human immune system. Moreover, it is also a leading target organ during stress, especially in burn, trauma and shock patients. The gut is known as the 'motor' of multiple organ dysfunction and bacterial translocation [1]. The latter is a major cause of mortality in critically ill patients [2,3]. Owing to the limitations of septic control strategies, the frequency of sepsis is increasing in intensive care units (ICUs). Protecting the commensal microbiota and gut function is becoming a novel strategy to reduce the risk of septic complications in critically ill patients in Europe [4].

Probiotics are live microorganisms that are beneficial to the host when administered in adequate quantities. Commensal microbiota are a vital barrier component of the intestine, helping prevent the spread of pathogens. Intestinal resistance could decrease because of deteriorating commensal microbiota in critically ill patients. Probiotics are commonly used as microbial nutritional supplements to maintain the balance of the intestinal microbiota [5,6]. On the other hand prebiotics are non-digestible foods that can benefit the host by stimulating the activity of selective dominant bacteria in the colon [7,8]. Synbiotics are a combination of probiotics and prebiotics in a single preparation. In 1990, supplementation with probiotics or synbiotics emerged as a potential therapy geared towards reducing the incidence of septic complications in critically ill patients.

The efficacy of probiotics and synbiotics has been demonstrated in elective surgery [9,10]. They are effective in treating diarrhea in patients with systemic inflammatory response syndrome (SIRS) [11,12]. Beneficial microbiota continue to decrease while pathogens increase in the intestines of patients with SIRS, which is the leading cause of decreased short-chain fatty acids (SCFAs). The pH of the gut mucosa can increase, which could further deteriorate the gut microbiota. This vicious cycle promotes the progression of SIRS and septic complications [11,13]. The hypothesized mechanism of probiotics or synbiotics breaks the vicious circle by increasing beneficial microbiota and altering the gut environment. Many randomized controlled trials (RCTs) have evaluated the effects of probiotics or synbiotics in reducing septic complications in critically ill patients, but their conclusions have been mixed. Some studies have shown that probiotics or synbiotics are more effective than placebo treatments in reducing mortality and the incidence of ventilator-associated pneumonia (VAP) [14,15]. However, other studies find probiotics useless or even engendering adverse effects [16–19]. Clinicians are puzzled by the conflicting nature of the evidence. A systematic review and meta-analysis to synthesize the current evidence is needed for practitioners faced with the decision of using probiotics or synbiotics. In this systematic review of RCTs, we examined the effects of probiotics or synbiotics on mortality and septic complications in critically ill patients.

Methods

Literature retrieval strategy

RCTs were identified from PubMed (US National Library of Medicine 1990–2021), Web of Science, The Cochrane Library (2021, Issue 11), China Knowledge Resource Integrated Database (CNKI), World Health Organization (WHO) Global Index Medicus and Chinese Biomedicine Database (CBM). Search terms were connected by AND/OR and included patients (adult critically ill patients and those with trauma), interventions (probiotic, prebiotic and synbiotic) and comparisons (placebo and standard treatment). References from RCTs were browsed and corresponding authors were consulted for any further information that may have been acquired by them but not been reported publicly. Ongoing RCTs were checked using clinical trial registers. The complete terms and strategies for identifying the articles (Table S1, see online supplementary material).

Inclusion and exclusion criteria

RCTs evaluating probiotics or synbiotics in adult critically ill patients (APACHE II scores >10) were included. Non-RCTs and RCTs that included pregnant women or patients younger than 18 years of age were excluded. Studies that did not address any primary or secondary outcomes, as previously mentioned, were excluded.

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Table 1. Methodological characteristics of studies included

Study	Population	PE (n)	PA(n)	Groups	Concealment	Blinding	Probiotic	Prebiotic	Synbiotic	Placebo/SC	Route	DoT	M.J.S.
Alberda *et al.*, 2007 [25]	Critically ill patients MV>2d	19	28	3	Identical packaging	Double blinded	*Lactobacillus casei, L. plantarum*, *Lactobacillus acidophilus* and *Lactobacillus delbrueckii* subsp. *Bulgaricus*, *Bifidobacterium longum, B. breve* and *B. Infantis, Streptococcus salivarius* subsp. *T*	–	–	Placebo	NG/NJ	7d	7/7
Arruda *et al.*, 2004 [26]	TBI, GCS5–12	20	20	2	NR	NR	*Lactobacillus johnsonii*	–	–	SC	NG/NJ	5d	4/7
Barraud *et al.*, 2010 [27]	Critically ill patients MV>2d	167	167	2	Envelopes	Double blinded	Mainly *Lactobacillus rhamnosus* GG, but also *L. casei*, *L. acidophilus* and *Bifidobacterium bifidum*	–	–	Placebo	NG/NJ	7d	7/7
Bleichner *et al.*, 1997 [28]	Critically ill patients	128	128	2	NR	Double blinded	*S. boulardii*	–	–	Placebo	NG/NJ	21d	5/7
Ferrie *et al.*, 2011 [29]	Critically ill patients	27	27	2	Identical packaging	Double blinded	*L. rhamnosus* GG	–	–	Placebo	NG	7d	7/7
Forestier *et al.*, 2008 [30]	Critically ill patients	208	208	2	Envelopes	Double blinded	*Lactobacillus*	–	–	Placebo	NG	7d	7/7
Frohmader *et al.*, 2010 [31]	Critically ill patients	45	45	2	Envelopes	Double blinded	*Lactic acid bacteria, lyophilized Bifidobacterium breve*, *B. longum, Bifidobacterium infantis, L acidophilus*, *Lactobacillus plantarum*, *L. casei, L bulgaricus, Streptococcus thermophilus*	–	–	Placebo	NG/NJ	7d	7/7
Giamarellors-Bourboulis *et al.*, 2009 [32]	Severe multiple injuries MV>2d	72	72	2	Envelopes	Double blinded	–	–	Synbiotic 2000Forte	Placebo	NG	15d	7/7
Jain *et al.*, 2004 [33]	Critically ill patients	90	90	2	Identical packaging	Double blinded	–	–	(*L. acidophilus La5*, *Bifidobacterium lactis Bb-12*, *S. thermophilus* and *L. bulgaricus*) and prebiotic oligofructose	Placebo	Oral or NG	10d	7/7

(Continued)

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Table 1. Continued

Study	Population	PE (n)	PA(n)	Groups	Concealment	Blinding	Probiotic	Prebiotic	Synbiotic	Placebo/SC	Route	DoT	M.J.S.
Johnstone *et al*., 2021 [18]	Critically ill patients MV>3d	1318	1332	2	Envelopes	Double blinded	*L. rhamnosus* GG	–	–	Placebo	Oral	60d	7/7
Klarin *et al*., 2005 [34]	Critically ill patients	15	15	2	Envelopes	Double blinded	*L. plantarum 299 (Lp299)*	–	–	Placebo	NG	7d	6/7
Klarin *et al*., 2008 [35]	Critically ill patients MV>1d	44	44	2	Envelopes	Double blinded	*L. plantarum 299 (Lp299)*	–	–	SC	NG	12d	6/7
Knight *et al*., 2009 [36]	Critically ill patients MV>2d	259	259	2	NR	Double blinded	–	–	Synbiotic 2000 Forte	Placebo	NG	10d	5/7
Kotzampassi *et al*., 2006 [37]	Trauma patients	65	65	2	NR	Double blinded	–	–	Synbiotic 2000 Forte	Placebo	NG	15d	5/7
Litton, 2021 [38]	Critically ill patients	110	108	2	Unblinded pharmacist	Double blinded	*L. plantarum 299 (Lp299)*	–	–	Placebo	Oral or NG	60d	7/7
Lopez de Toro *et al*., 2014 [39]	Multi-organ failure	89	89	2	Envelopes	Double blinded	–	–	Synbiotic drink	Placebo	NG	7d	7/7
Mahmoodpoor *et al*., 2019 [19]	Critically ill patients MV>2d	100	100	2	NR	Double blinded	*Lactobacillus* species (*casei, acidophilus, rhamnosus, bulgaricus*), *Bifidobacterium* species *(breve*, *longum)* and *S. thermophilus*	–	–	Placebo	NG/NJ	14d	7/7
Mcnaught *et al*., 2005 [40]	Critically ill patients	103	103	2	NR	Double blinded	*L. plantarum 299v*	–	–	SC	Oral or NG	9d	5/7
Morrow et al., 2010 [41]	Critically ill patients MV>3d	138	138	2	NR	Double blinded	*L. rhamnosus* GG	–	–	Placebo	NG	14d	5/7
Rongrungruang *et al*., 2015 [42]	Critically ill patients MV>3d	150	150	2	NR	NR	*L. casei* (*Shirota* strain)	–	–	Placebo	Oral or NG	12d	4/7
Sanaie *et al*., 2014 [43]	Critically ill patients	40	40	2	NR	Double blinded	Lactic acid bacteria, lyophilized *B. breve*, *B. longum*, *B. infantis*, *L acidophilus*, *L. plantarum*, *L. casei*, *L bulgaricus, S. thermophilus*	–	–	Placebo	NG	7d	5/7
Shimizu *et al*., 2018 [14]	Critically ill patients	72	72	2	NR	Single blinded	–	–	*B. breve* strain, *L. casei* strain and galactooli-gosaccha-rides	SC	NG	20d	5/7
Spindler-Vesel *et al*., 2007 [44]	Multiple injured patients	52	113	4	NR	NR	–	–	Synbiotic 2000 Forte	SC	NG	14d	4/7
Tan *et al*., 2011 [45]	TBI, GCS5–8	43	43	2	NR	Single blinded	*B. longum*, *Lactobacillus bulgaricus*, *S. thermophilus*.	–	–	Placebo	NG	21d	5/7
Zeng *et al*., 2016 [15]	Critically ill patients MV >2d	235	235	2	Envelopes	Double blinded	live *Bacillus subtilis* and *Enterococcus faecalis* (Medilac-S)	–	–	SC	NG	14d	7/7

PA participants analyzed, *PE* participants enrolled, *DoT* duration of treatment, *NG* nasogastric, *NJ* nasojejunal, *NR* not reported, *SC* standard care, *M.J.S.* modified Jadad score, *TBI* Traumatic brain injury, *GCS* Glasgow Coma Scale, *MV* mechanical ventilation

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The intervention groups received probiotics or synbiotics through any approach, preparation or duration. Participants with severe acute pancreatitis were excluded from the study. Control groups administered standard care or placebo did not receive any synbiotics or probiotics.

Outcome measures

The primary outcome was mortality in critically ill patients. Secondary outcomes included the incidence of VAP, incidence of septic complications, incidence of sepsis, length of ICU stay and non-septic complications.

Selection of studies

Two reviewers (KW and QZ) independently performed electronic literature searches and evaluated the eligibility of the studies based on the inclusion criteria. Relevant studies were initially screened using titles and abstracts. The potential articles were then assessed independently, and any disagreements were adjudicated by a third reviewer (HJ).

Data extraction and analysis

Data were extracted independently by two investigators (KW and QZ) from the full text of the studies and compiled into shared sheets. We collected the following information from the included studies: study identifier (first author and year of publication), duration of treatment, study design, inclusion and exclusion criteria, intervention and number of subjects, and primary and secondary outcomes. Data were validated by a third reviewer (HJ) using a standardized method. The methodological quality assessment shown in Table 1 was based on the Cochrane Reviewers' Handbook [20] and the modified Jadad scale [21,22]. The risk ratio (RR) was used to report discrete numerical variables along with 95% confidence intervals (CIs). The mean difference (MD) was reported to estimate the continuous outcomes. The I^2 statistic was used to quantify the heterogeneity, and forest plots were generated and double-checked by two reviewers (KXL and MWS). If $I^2 < 25\%$, the pooled outcomes were considered to have low statistical heterogeneity, and if $I^2 > 75\%$, the pooled outcomes were considered to have high statistical heterogeneity. Data synthesis was conducted by the Review Manager (RevMan) 5.4 and R (R package version 3.7–0.) software [23]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement to report the research protocol, outcome and relevant items in this systematic review [24].

Results

Studies included

A total of 186 potential studies were identified in the initial literature retrieval. The initial screening resulted in 45 candidate studies. The PRISMA diagram shows the details of the selection process and exclusion criteria (Figure 1). Finally, 25

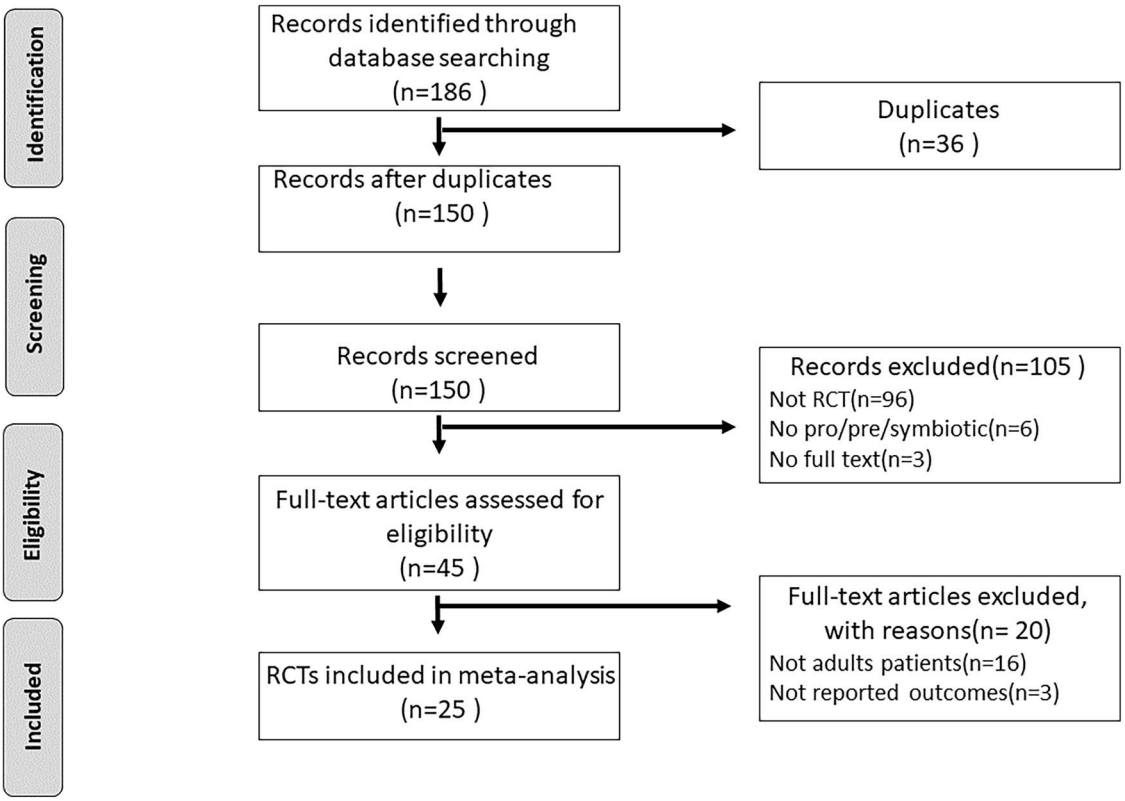

Figure 1. PRISMA diagram detailing the literature search and the study selection/exclusion process. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-analyses, *RCT* randomized controlled trials

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Table 2. Summary of side effects and complications associated with probiotics or synbiotics in the randomized controlled trials (RCTs) included. Serious adverse events were *Lactobacillus* isolates resulting in persistent or significant disability or incapacity or life-threatening situations or resulting in death

Study	Probiotics	Synbiotics	Placebo or standard care	*P*
Alberda *et al*., 2007 [25]	Diarrhea:1/10	–	Diarrhea:2/9	–
Arruda *et al*., 2004 [26]	Not stated	–	Not stated	–
Barraud *et al*., 2010 [27]	Diarrhea:48/87	–	Diarrhea:42/80	–
Bleichner et *al*., 1997 [28]	Diarrhea:18/36	–	Diarrhea:24/36	0.26
Ferrie *et al*., 2011 [29]	Diarrhea:2/13	–	Diarrhea:2/14	0.08
Forestier *et al*., 2008 [30]	Not stated		Not stated	–
Frohmader *et al*., 2010 [31]	Diarrhea:5/20		Diarrhea:3/25	0.03
Giamarellors-Bourboulis *et al*., 2009 [32]	–	Not stated	Not stated	–
Jain *et al*., 2004 [33]	–	Not stated	Not stated	–
Johnstone *et al*., 2021 [18]	Diarrhea:836/1318	–	Diarrhea:855/1332	–
	Adverse events: 13/1318	–	Adverse events: 1/1332	0.001
	Serious adverse events: 2/1318		Serious adverse events: 0/1318	0.001
Klarin *et al*., 2005 [34]	Not stated	–	Not stated	–
Klarin *et al*., 2008 [35]	Not stated	–	Not stated	–
Knight *et al*., 2009 [36]	–	Not stated	Not stated	–
Kotzampassi *et al*., 2006 [37]	–	Diarrhea:5/35	Diarrhea:10/30	0.34
	–	severe constipation: 4/35	Severe constipation: 6/35	0.04
	–	Gastric residuals: 7/35	Gastric residuals: 15/35	0.01
Litton, 2021 [38]	Not stated	–	Not stated	–
Lopez de Toro *et al*., 2014 [39]	–	Not stated	Not stated	–
Mahmoodpoor *et al*., 2019 [19]	Diarrhea:7/48	–	Diarrhea:15/54	0.08
	Gastric residuals: 14/48	–	Gastric residuals: 31/54	0.26
	Gastric bacterial colonization: 14/48	–	Gastric bacterial colonization: 20/54	
	Oropharyngeal bacterial colonization: 23/48		Oropharyngeal bacterial colonization: 34/54	0.11
Mcnaught *et al*., 2005 [40]	Not stated	–	Not stated	–
Morrow *et al*., 2010 [41]	*Clostridium difficile* diarrhea:4/68	–	*Clostridium difficile* diarrhea:13/70	–
Rongrungruang *et al*., 2015 [42]	Diarrhea:19/75	–	Diarrhea:14/75	–
Sanaie *et al*., 2014 [43]	Not stated	–	Not stated	–
Shimizu *et al*., 2018 [14]	–	Enteritis:2/35	Enteritis:10/37	–
Spindler-Vesel *et al*., 2007 [44]	–	Not stated	Not stated	–
Tan *et al*., 2011 [45]	Not stated	–	Not stated	–
Zeng *et al*., 2016 [15]	Not stated	–	Not stated	–

RCTs [14,15,18,19,25–45] were deemed appropriate for full analysis. The characteristics of the included studies and their designs are listed in Table 1. Of the 25 studies included in the final meta-analysis, 7 used synbiotics as the intervention and the other 18 used probiotic therapy. In total, 5049 patients were included in this meta-analysis, of whom 2520 were randomly treated with probiotic or synbiotic therapy, whereas the remaining 2529 received placebo or standard care.

Patients and interventions

The mean (standard deviation) age of patients who received probiotics or synbiotic treatment was 58.2 (16.8) years and the mean age for those in the control group was 58.8 (17.5) years. A variety of diagnostic categories were included: respiratory, cardiac, neurological, sepsis, trauma, thoracic, acute illnesses and surgery. Of the 18 studies receiving probiotics alone, only 5 used a mixture of probiotics, while the remainder received a single probiotic species (*Lactobacillus* or *Saacharomyces boulardii)*. Seven studies administered synbiotics using a mixture of probiotics. Eleven studies reported side effects or complications associated with the intervention [14,18,19,25,27–29,31,37,41,42]. There were two serious adverse events reported in a randomized clinical trial [18]. Compared to the placebo or standard treatment group, rates of diarrhea, vomiting, abdominal bloating and abdominal pain were not significantly increased in participants in the treatment group (Table 2).

Major outcome: mortality

Among all the included studies, 22 reported on the primary outcome (mortality) [14,15,18,19,25,27,29,31–45]. There was no heterogeneity among the 22 studies and a fixed model was used for meta-analysis. The mortality of patients

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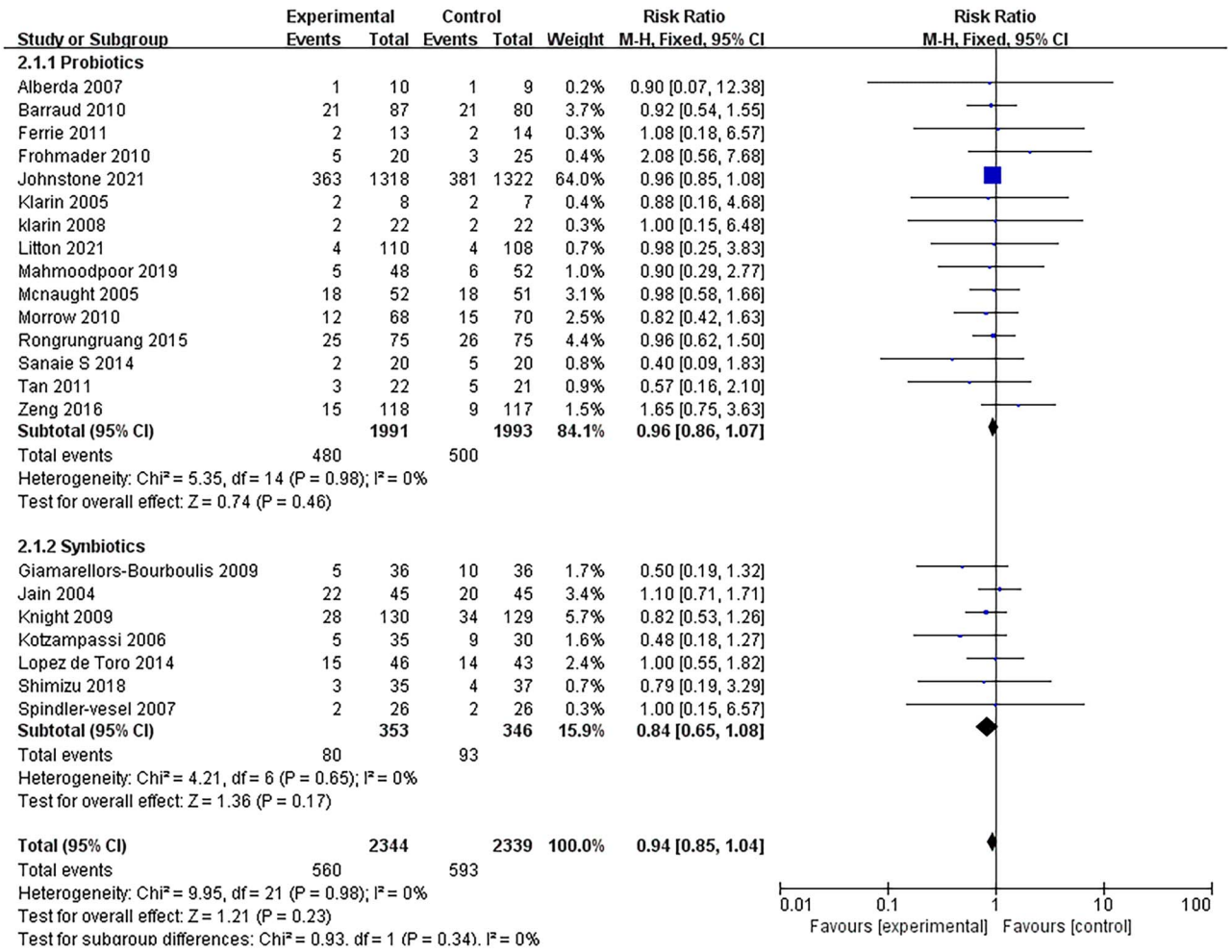

Figure 2. Forest plot of pooled weighted mean difference from RCTs evaluating the effect on risk ratio for mortality with probiotics and synbiotics therapy. *RCTs* randomized controlled trials, *CI* confidence intervals

receiving probiotics or synbiotics was not significantly reduced compared to those who received placebo treatment or standard care (RR = 0.94, 95% CI: 0.85–1.04, $p = 0.23$, $I^2 = 0\%$) (Figure 2). In the subgroup analysis, there were no significant differences in mortality between patients receiving probiotics and those who received synbiotics.

Septic complications

The incidence of VAP Fourteen studies [14,15,18,19,26,27,30,32,36,37,41,42,44,45] reported data on the incidence of VAP. Quantitative pooling of data revealed a significant reduction in the incidence of VAP in patients receiving probiotics or synbiotics (Figure 3). The risk of developing VAP was reduced in the intervention group (RR = 0.86, 95% CI: 0.78–0.95; $p = 0.003$; $I^2 = 85\%$). However, in the subgroup analysis, the reduction in the incidence of VAP was only significant in patients receiving synbiotics (RR = 0.61, 95% CI: 0.47–0.80, $p = 0.0004$, $I^2 = 40\%$) and not significant in those receiving only probiotics (RR = 0.91, 95% CI: 0.82–1.01, $p = 0.07$, $I^2 = 65\%$).

All ICU-acquired infections and sepsis incidence Twelve RCTs [14,18,26,27,33,37–40,43–45] reported data on the incidence of ICU-acquired infections. Pooling data from RCTs demonstrated that there was no significant difference in the incidence of ICU-acquired infections between the treatment and control groups (RR = 0.92; 95% CI: 0.84–1.01, $p = 0.09$, $I^2 = 63\%$) (Figure 4). The I^2 test revealed a significantly high heterogeneity. We then conducted a subgroup analysis that found that studies using synbiotics might be the source of heterogeneity. Furthermore, in the subgroup analyses of the 5 RCTs [14,33,37,39,44] that administered synbiotics, there was a significant reduction in the incidence of ICU-acquired infections (RR = 0.72; 95% CI: 0.58–0.89, $p = 0.0007$, $I^2 = 79\%$). However, in 7 trials [18,26,27,38,40,43,45] that administered probiotics alone, there was no effect on infections (RR = 0.96; 95% CI: 0.87–1.07, $p = 0.48$; $I^2 = 37\%$). These results also confirmed the incidence of sepsis. In 2 studies [32,37] that administered synbiotics, there was a significant reduction in the incidence of sepsis (RR = 0.41; 95% CI: 0.22–0.72, $p = 0.005$, $I^2 = 0\%$) (Figure 5).

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Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Probiotics						
Arruda 2004	5	10	10	10	1.8%	0.52 [0.29, 0.96]
Barraud 2010	23	87	15	80	2.6%	1.41 [0.79, 2.51]
Forestier 2008	24	102	24	106	4.0%	1.04 [0.63, 1.71]
Johnstone 2021	289	1318	284	1322	47.7%	1.02 [0.88, 1.18]
Mahmoodpoor 2019	31	48	51	54	8.1%	0.68 [0.55, 0.85]
Morrow 2010	17	68	33	70	5.5%	0.53 [0.33, 0.86]
Rongrungruang 2015	18	75	22	75	3.7%	0.82 [0.48, 1.40]
Tan 2011	7	16	13	19	2.0%	0.64 [0.34, 1.21]
Zeng 2016	43	118	59	117	10.0%	0.72 [0.54, 0.97]
Subtotal (95% CI)		**1842**		**1853**	**85.3%**	**0.91 [0.82, 1.01]**
Total events	457		511			
Heterogeneity: Chi² = 22.98, df = 8 (P = 0.003); I² = 65%						
Test for overall effect: Z = 1.81 (P = 0.07)						
2.3.2 Synbiotics						
Giamarellos-Bourboulis 2009	15	36	16	36	2.7%	0.94 [0.55, 1.60]
Knight 2009	12	130	17	129	2.9%	0.70 [0.35, 1.41]
Kotzampassi 2006	19	35	24	30	4.3%	0.68 [0.48, 0.97]
Shimizu 2018	5	35	18	37	2.9%	0.29 [0.12, 0.71]
Spindler-vesel 2007	4	26	11	26	1.9%	0.36 [0.13, 1.00]
Subtotal (95% CI)		**262**		**258**	**14.7%**	**0.61 [0.47, 0.80]**
Total events	55		86			
Heterogeneity: Chi² = 6.65, df = 4 (P = 0.16); I² = 40%						
Test for overall effect: Z = 3.57 (P = 0.0004)						
Total (95% CI)		**2104**		**2111**	**100.0%**	**0.86 [0.78, 0.95]**
Total events	512		597			
Heterogeneity: Chi² = 32.55, df = 13 (P = 0.002); I² = 60%						
Test for overall effect: Z = 2.93 (P = 0.003)						
Test for subgroup differences: Chi² = 7.08, df = 1 (P = 0.008), I² = 85.9%						

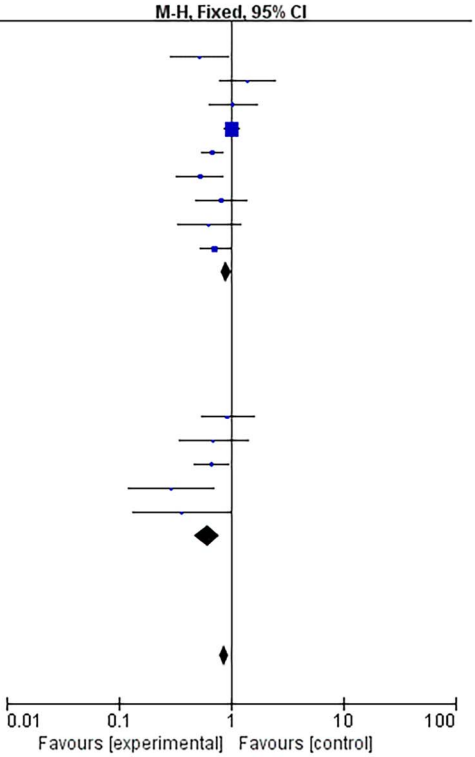

Figure 3. Forest plot of randomized controlled trials evaluating the efficacy for reducing the incidence of VAP. *VAP* ventilator-associated pneumonia, *CI* confidence intervals

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Probiotics						
Arruda 2004	5	10	10	10	1.7%	0.52 [0.29, 0.96]
Barraud 2010	30	87	30	80	5.1%	0.92 [0.61, 1.38]
Johnstone 2021	414	1318	418	1322	68.6%	0.99 [0.89, 1.11]
Litton 2021	8	110	5	108	0.8%	1.57 [0.53, 4.65]
Mcnaught 2005	21	52	22	51	3.7%	0.94 [0.59, 1.48]
Sanaie S 2014	2	20	5	20	0.8%	0.40 [0.09, 1.83]
Tan 2011	9	22	15	21	2.5%	0.57 [0.32, 1.01]
Subtotal (95% CI)		**1619**		**1612**	**83.3%**	**0.96 [0.87, 1.07]**
Total events	489		505			
Heterogeneity: Chi² = 9.52, df = 6 (P = 0.15); I² = 37%						
Test for overall effect: Z = 0.71 (P = 0.48)						
2.2.2 Synbiotics						
Jain 2004	33	45	26	45	4.3%	1.27 [0.93, 1.72]
Kotzampassi 2006	17	35	23	30	4.1%	0.63 [0.43, 0.94]
Lopez de Toro 2014	9	46	13	43	2.2%	0.65 [0.31, 1.36]
Shimizu 2018	10	35	25	37	4.0%	0.42 [0.24, 0.75]
Spindler-vesel 2007	5	26	13	26	2.1%	0.38 [0.16, 0.92]
Subtotal (95% CI)		**187**		**181**	**16.7%**	**0.72 [0.58, 0.89]**
Total events	74		100			
Heterogeneity: Chi² = 19.14, df = 4 (P = 0.0007); I² = 79%						
Test for overall effect: Z = 3.07 (P = 0.002)						
Total (95% CI)		**1806**		**1793**	**100.0%**	**0.92 [0.84, 1.01]**
Total events	563		605			
Heterogeneity: Chi² = 29.40, df = 11 (P = 0.002); I² = 63%						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 6.08, df = 1 (P = 0.01), I² = 83.6%						

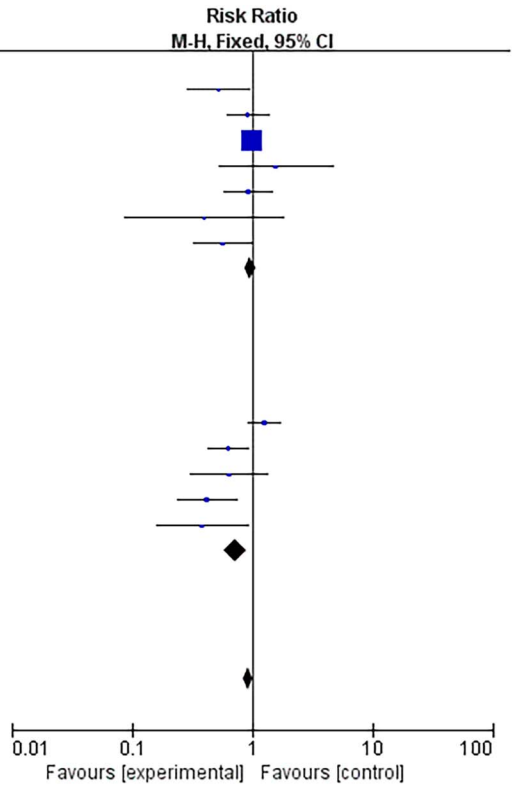

Figure 4. Forest plot of pooled data form RCTs demonstrating the reduction in risk of ICU-acquired infections. *RCTs* randomized controlled trials, *CI* confidence intervals, *ICUs* intensive care units

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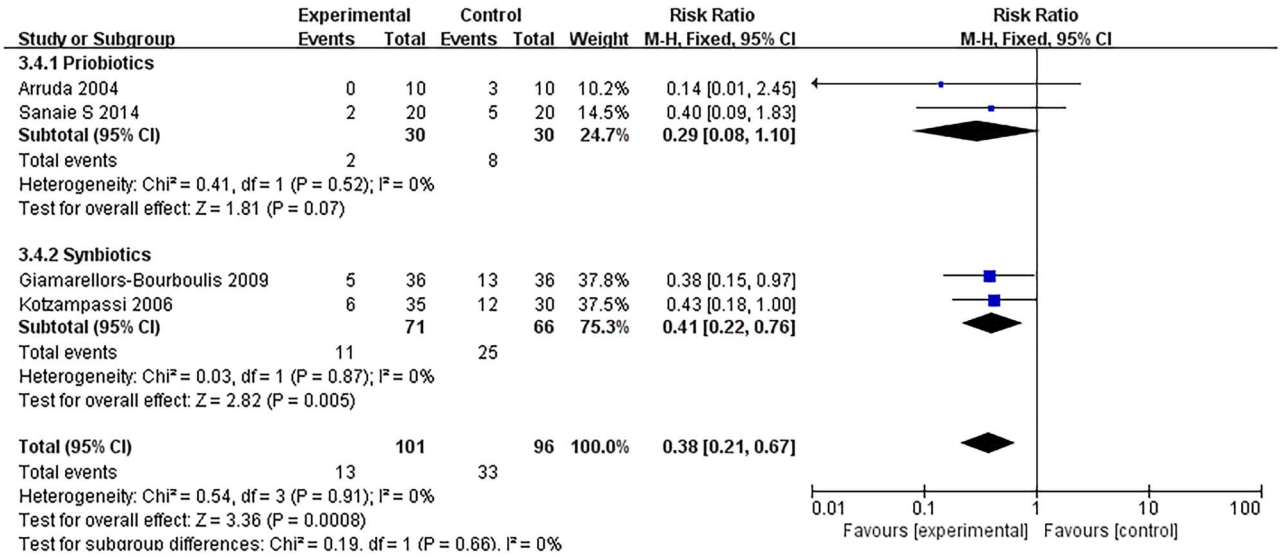

Figure 5. Forest plot of pooled data form RCTs demonstrating the reduction in risk of sepsis. *RCTs* randomized controlled trials, *CI* confidence intervals

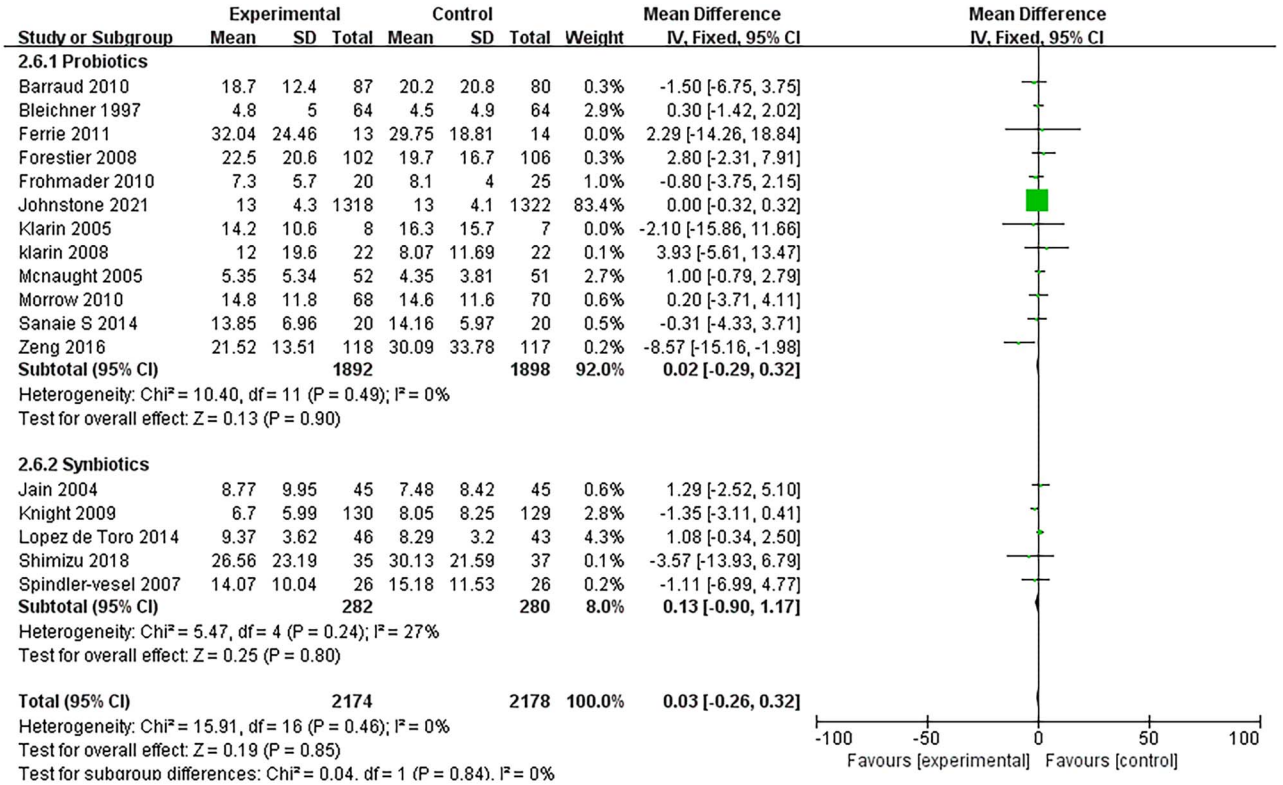

Figure 6. Forest plot of pooled weighted mean difference from RCTs evaluating the risk ratio for length of ICU stay. *RCTs* randomized controlled trials, *CI* confidence intervals, *ICUs* intensive care units

Length of ICU stay Data on the length of ICU stay was reported in only 17 studies [14,15,18,27–31,33–36,39–41,43,44]. There was no significant difference in the length of ICU stay between the intervention and control groups (MD: 0.03; 95% CI: −0.26 to 0.32, $p = 0.85$, I^2 = 0%) (Figure 6). The same result was obtained in subgroup analysis.

Non-septic complications Some RCTs reported data on non-septic complications. Eleven studies [14,18,19,25,27–29,31,37,41,42] provided a count of the number of patients with diarrhea. Pooling data from RCTs showed no significant difference between the intervention and control groups (RR = 0.99; 95% CI: 0.93–1.07, $p = 0.87$, I^2 = 51%) (Figure 7). However, in the subgroup analysis, the reduction

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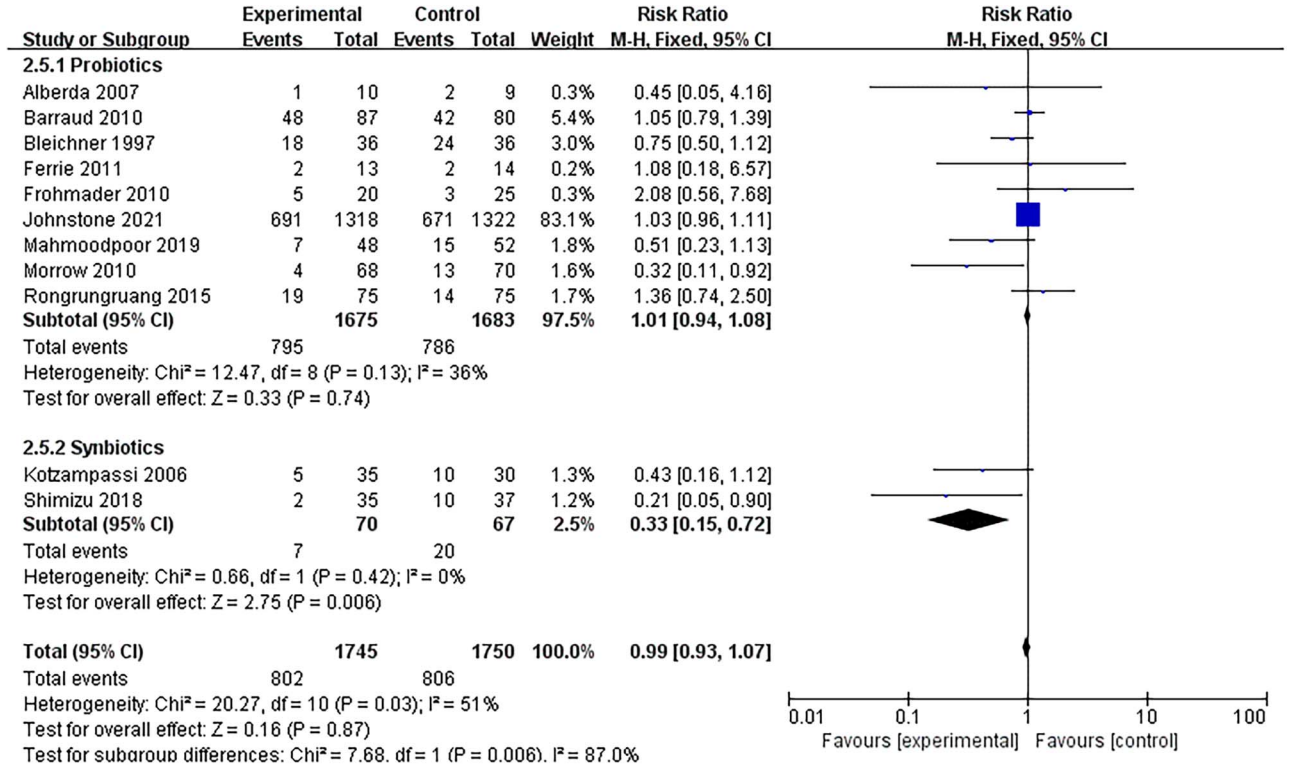

Figure 7. Effect on the incidence of diarrhea with probiotics or synbiotics therapy. *CI* confidence intervals

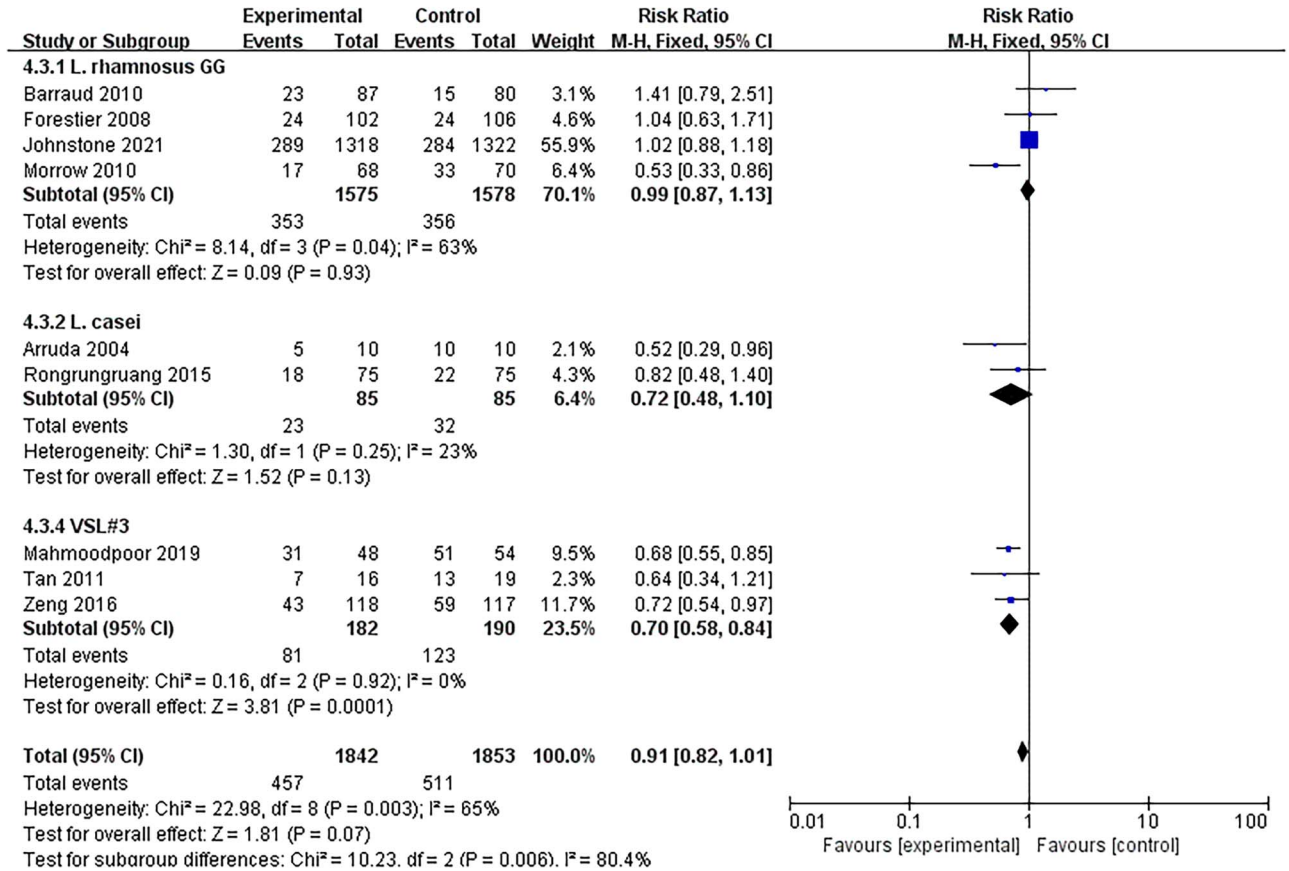

Figure 8. Subgroup analysis: effects of different bacterial species on incidence of VAP. VSL#3 is a specific mixture of different bacterial species, consisting of four strains of Lactobacillus, three strains of Bifidobacterium and *Streptococcus salivarius* subsp. *CI* confidence intervals, *VAP* ventilator-associated pneumonia

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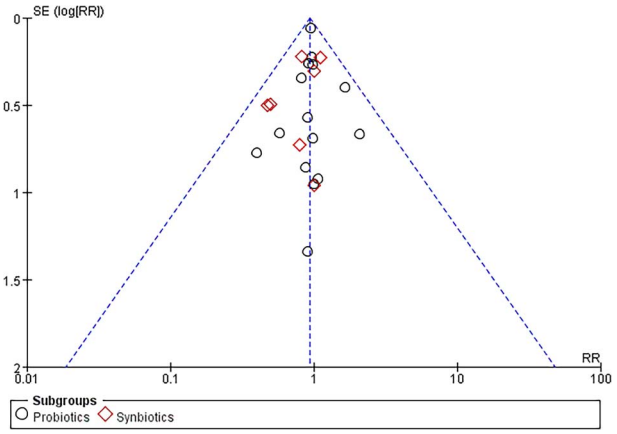

Figure 9. Funnel plot of included randomized controlled trials. *RR* risk ratio, *SE* standard error

in the incidence of diarrhea was significant in the synbiotic group (RR = 0.33; 95% CI: 0.15–0.72, $p = 0.006$, $I^2 = 0\%$).

Subgroup analysis depending on probiotics Considering that different bacterial species may have different effects on critically ill patients, we performed a subgroup analysis depending on probiotics such as *Lactobacillus rhamnosus* GG, *Lactobacillus casei*, *Lactobacillus plantarum* 299 and VSL#3 (a specific mixture of different bacterial species). It may be a better strategy to distinguish between beneficial and unbeneficial probiotics. Subgroup analyses showed that the risk of developing VAP was reduced only by VSL#3 (RR = 0.70, 95% CI: 0.58–0.84, $p = 0.0001$, $I^2 = 0\%$) (Figure 8). *L. rhamnosus* GG and *L. casei* did not reduce the incidence of VAP. None of the other outcomes, including mortality, diarrhea, sepsis, other ICU-acquired infections or length of ICU stay, showed a significant difference among these four types of probiotics.

Publication bias and sensitivity analysis It is well known that studies with positive outcomes are easier to publish. Consequently, all valid studies cannot be truly represented merely by those studies that end up being published. A funnel plot was used to assess publication bias. The evaluation of publication bias based on mortality demonstrated no asymmetry in favor of positive studies (Figure 9). Moreover, the risk of the included RCTs is shown in Figure 10. To evaluate the stability of the results, a sensitivity analysis was conducted by excluding one study at a time. The combined RR of risks was confirmed to be consistent and without apparent fluctuations.

Discussion

This meta-analysis of pooled data from 25 RCTs revealed that synbiotic therapy significantly reduced the risk of septic complications. Furthermore, the incidence of sepsis in critically ill patients is significantly reduced by the administration of synbiotics. In contrast, probiotic or synbiotic administration had no effect on mortality, length of ICU stay or non-septic complications. The probiotic or synbiotic therapy duration of the included studies was not uniform. The mean (standard

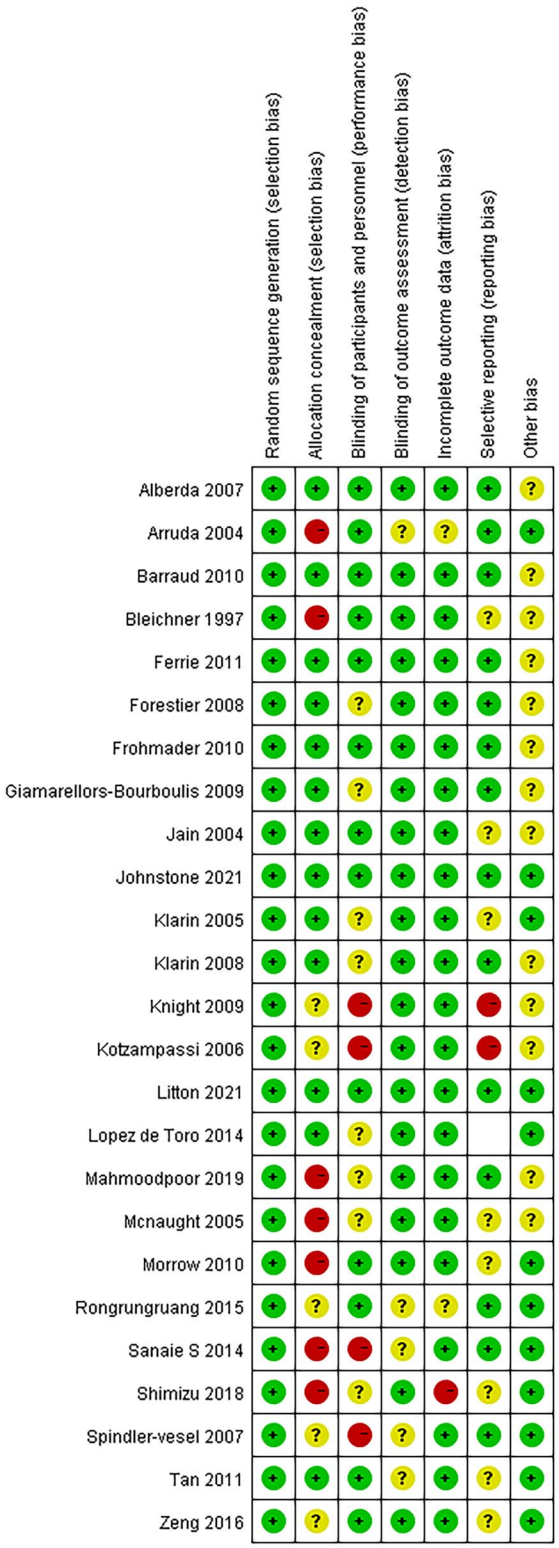

Figure 10. Risk of bias assessment for the randomized controlled trials (RCTs) included

deviation) duration was 11.59 (4.75) days. However, the reduction risk of septic complications remained whether the duration was more than 11.59 days or less. Thus, it was difficult to infer the optimal duration of therapy from this

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meta-analysis. The reduction in septic complications revealed in this study is consistent with the results of other meta-analyses [10,46]. In addition, Chowdhury *et al.* [9] demonstrated that synbiotics are more effective than probiotics in reducing infection risks and length of hospital stay.

On the whole, probiotics and synbiotics are safe and well tolerated [9,14,47]. Whelan and Myers systematically evaluated the safety issue and adverse effects of probiotics in patients receiving nutritional support [47]. They indicated that in some specific patient groups (e.g. severe acute pancreatitis or liver transplantation), the adverse events may increase after probiotic intervention. Besselink *et al*. reported that bowel ischemia may occur after probiotic administration in patients with severe acute pancreatitis, although the occurrence was found to be relatively low (6%) [48]. *Lactobacillus*- and *S. boulardii*-related sepsis have also been reported in some studies, especially in ICU patients who have inserted central venous catheters (CVCs). However, the researchers indicated that these kinds of infections may also be associated with environmental contamination with the probiotic (for example, *S. boulardii* products may be introduced into CVC lines by unintentional hand contamination) [47]. Thus, the relationship between probiotic products and sepsis in the ICU is weak and requires more evidence. This meta-analysis revealed that synbiotics were better tolerated than probiotics. This is consistent with a recent study by Johnstone *et al*. that reported that serious adverse events occurred in patients receiving *L. rhamnosus* GG [18].

Due to the variable species of probiotics used in the studies included, it is difficult to evaluate which one was most effective. We performed a subgroup analysis based on probiotics such as *L. rhamnosus* GG, *L. casei*, *L. plantarum* 299 and VSL#3. The analysis showed that the risk of developing VAP was reduced only with VSL#3. Administration of *L. rhamnosus* GG, *L. casei* or *L. plantarum* 299 alone could not reduce the incidence of VAP, mortality, diarrhea, sepsis or other ICU-acquired infections. VSL#3 is a mixture of different bacterial species. The use of a complex mixture of different bacterial species promotes the balance of the microbial composition of the intestines and stomach through the synergistic actions of the different strains. The same may improve microbial dysbiosis in order to lower septic complications in critically ill patients, create a better balance by adding good (probiotic) bacteria to help control the bad bacteria, help to protect and strengthen the intestinal barrier, and prevent bad bacteria from sticking to and irritating the gastrointestinal tract. Therefore, it ultimately reduces the immune response and inflammation caused by the bacteria. However, the same probiotic therapy may have different effects in different patient groups [49].

The results of this meta-analysis are consistent with the proposed theory that the gut is the 'motor' of multiple organ dysfunction and the origin of sepsis. Gut motility is often decreased by ischemia, fluid overload and opioids in critically ill patients. Consequently, the mucosal permeability for bacteria and SIRS incidence could increase due to motor stasis and gut intolerance [50]. Montejo [51] found that the complication of intolerance to enteral feeding was significantly increased in critically ill patients. Probiotics and synbiotics alter the gut microbiota and environment to lower septic complications in patients with severe SIRS [12]. Although evidence for the mechanism of probiotic and synbiotic therapy was not provided by this meta-analysis, one of the hypotheses is that the increasing levels of *Lactobacillus* and *Bifidobacterium* lead to increased production of SCFAs in the gut. The gut microbiota and environment maintained by SCFAs that increase the pH in the gut may decrease mucosal permeability and septic complications.

Limitations of the study

There are some limitations to this study that need further attention. First, the duration and preparation of probiotics or synbiotic therapy was different among studies included [25,26,28,30,31,41,42]. There were no uniform standards. Second, some studies did not use a placebo to reduce unintentional physical cues and prejudice [14,15,26,35,40,44]. Although there are many published studies regarding the use of probiotics or synbiotics in critically ill adult patients, few of them meet the high-quality standards of evidence-based medicine. Large high-quality multicenter RCTs are needed to reduce heterogeneity and influence.

Conclusions

Synbiotics are an effective and safe nutrition therapy that can be used to reduce septic complications in critically ill patients. However, in critically ill patients, administration of probiotics alone compared with placebo resulted in no difference in septic complications. The effect of a mixture of probiotics was better than that of a single probiotic species.

Abbreviations

APACHEII scores:Acute Physiology and Chronic Health Evaluation II scores; CI: Confidence interval; CVC: Central venous catheter; GCS:Glasgow Coma Scale; ICU: Intensive care unit; MD: Mean difference; MV:Mechanical ventilation; RCT: Randomized controlled trial; RR: Risk ratio; SCFA: Short-chain fatty acid; SIRS: Systemic inflammatory response syndrome; TBI:Traumatic brain injury; VAP: Ventilator-associated pneumonia.

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Authors' contributions

KW, QZ and HJ performed the study design and conceptualization. KXL, YW, LW, KW and QZ completed the literature retrieval and data extraction. Mathematical modeling and meta-analysis were conducted with the help of KW and MWS. KW and QZ drafted the

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manuscript. JZ and HJ contributed to the visualization and edited the final version of the manuscript. All authors approved the manuscript.

Conflicts of Interest

None declared.

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