Preventive Effect of Probiotics on Ventilator-Associated Pneumonia; A Meta-analysis of 2428 Patients

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Introduction

- Ventilator-associated pneumonia (VAP) is a pulmonary infection that develops in patients on mechanical ventilation (MV) for more than 48 hours and is caused by pathogens predominantly present in hospital settings.

- occur in 10% to 40% of mechanically ventilated patients

- Mortality ranging from 15% to 70%.

Introduction

- Probiotics are live microbes that, when administered in adequate amounts, confer health benefits on their hosts.

- Studies have shown that the use of probiotics offer a potential strategy for preventing ICU-associated diarrhea, *Clostridioides difficile* infections, multiple organ dysfunction syndrome (MODS), and VAP.

Objectives

To explore the efficacy and safety of probiotics on:

- -incidence of VAP
- -length of ICU stay
- -length of hospital stay
- -Mortality
- -Days of mechanical ventilation
- -Days of using antibiotics
- -Days to VAP after intubation
- Bacterial colonization
- Bacterial infection
- Diarrhea
- Constipation
- Bacteremia
- Gastric residual

Methods

- PROSPERO (CRD42020201695)
- medical databases, including PubMed, Web of Science, EMBASE, MEDLINE, Cochrane Library, Ovid, and EBSCO.
- GRADEprofiler 3.6.1 was used to reevaluate the quality of the study.
- studies were grouped by study design (double blind, single blind, open label), method of administration (nasogastric tube/orally, oral care, slurry to the oropharynx/nasogastric tube), and type of probiotics (single type of probiotic, compound preparation of multiple probiotics).
- Statistical analysis was performed using Stata/MP 16.0.

Results

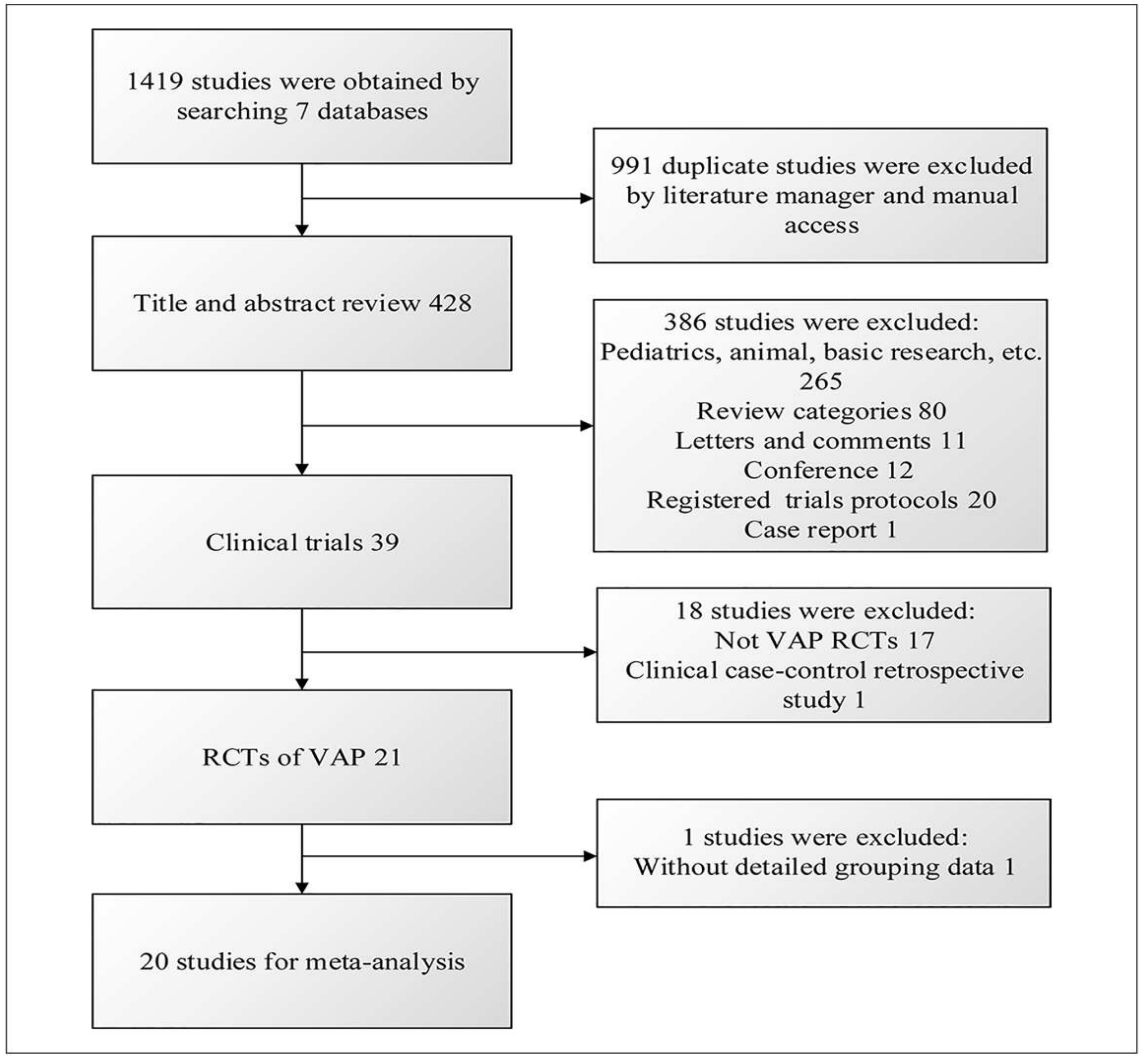


Figure 1. Flowchart of selection for the meta-analysis.
Abbreviations: RCT, randomized controlled trial; VAP, ventilator-associated pneumonia.

Table 1. Characteristics of the Included Studies.[a]

First author	Year	Nation	Study design	Total number of patients	Duration	Method of administration	Treatment intervention	Control intervention	Definition of VAP	Number of outcomes
Kotzampassi et al[19]	2006	Greece	MC, DB, RCT, pilot	65	15 Days	Endoscopic gastrostomy/ nasogastric tube	2000FORTE, 12 g, qd	Powdered glucose polymer	A new or progressive pulmonary radiological infiltrate; purulent tracheal secretions; T > 38.5 °C, WBC >12 × 10^9/L or <4 × 10^9/L; microbiologically confirmed by the isolation of a potentially pathogenic microorganisms in BAL in concentrations of 10^5 CFU mL or more	8
Forestier et al[20]	2008	France	SC, DB, RCT, pilot	208	From the third day after admission to the ICU until discharge or death	Nasogastric tube/ orally	*Lactobacillus casei rhamnosus*,10^9 CFU, bid	Placebo	Respiratory pathogen diagnosis by *Pseudomonas aeruginosa*	7
Klarin et al[21]	2008	Sweden/ Denmark	SC, OP, RCT, pilot	44	NA	Oral care	Lp299, 10^{10} CFU, bid	CHX	A new, persistent or progressive infiltrate on chest radiograph; at least 3 of: a purulent tracheal aspirate; positive culture of tracheal aspirates occurring after 48 hours of mechanical ventilation; T >38.0 °C or <35.5 °C; WBC >12 × 10^9/L or <3 × 10^9/L.	8
Giamarellos-bourboulis et al[22]	2009	Greece/UK	MC, DB, RCT, pilot	72	15 days	Nasogastric tube/ gastrostomy	2000FORTE, 12 g, qd	Placebo	A new or persistent consolidation in lung X-ray; purulent tracheobronchial secretions; CPIS >6	6
Knight et al[23]	2009	New Zealand/ UK	SC, DB, RCT, prospective	259	Within 24 hours of admission to ICU, to day 28 after admission, death or discharge from a critical care area	Nasogastric/ orogastric tube	2000FORTE, 10^{10} CFU, bid	Placebo	A new progressive, or persistent infiltration on chest radiograph; at least 2 of: T >38.0 °C; WBC >12 × 10^9/L or <4 × 10^9/L; purulent TBSs; clinical, radiological, and sequential microbiological data 48 hours after intubation	10
Morrow et al[24]	2010	United States	SC, DB, RCT, prospective	138	Until extubation, tracheostomy placement, or death	Slurry to the oropharynx/ nasogastric tube	*Lactobacillus rhamnosus* GG, 10^9 CFU, bid	Inert plant starch inulin	ACCP clinical criteria	13
Barraud et al[25]	2010	France	SC, DB, RCT, prospective	167	After weaning from the ventilator, treatment was given for 2 additional days and then stopped in the case of successful extubation or continued in the case of extubation failure	Enteral feeding tube	5 Ergyphilus, qd	Placebo capsules contained the excipient	A new and persistent infiltrate on chest radiograph; at least 1 of: purulent tracheal secretions, T >38.3 °C, WBC >10 × 10^9/L. Positive quantitative cultures of distal pulmonary secretions obtained from BAL (>10^4 CFU/mL)	9
Oudhuis et al[26]	2011	Netherlands	MC, OP, CROSS, prospective	254	Until ICU discharge, death, or final removal of the tube	Nasogastric tube	Lp 299/299v, 5 × 10^9 CFU, with 6 g of rose-hip, bid	0.5 g Of an oral paste, applied to the buccal cavity, containing 2% polymyxin E, 2% tobramycin, and 2% amphotericin B; 100 mg polymyxin E, 80 mg tobramycin, and 500 mg amphotericin B administered through gastric tubes, qid	A new, persistent, or progressive infiltrate on chest radiography; more than 10 leukocytes per high-power field in Gram stain of tracheal aspirate; positive culture of tracheal aspirate; T >38 °C or <35 °C; WBC > 10 000/mm^3 or <3000/mm^3 and/ or left shift	3
Tan et al[27]	2011	China	SC, SB, RCT, prospective	52	21 Days	Nasogastric tube/ orally	Golden Bifid, 7 sachets, tid	Placebo	48 Hours after intubation; both a new or progressive radiographic infiltrate, at least 2 of: T >38.0 °C, WBC >12 × 10^9/L or <4 × 10^9/L, purulent TBSs, and positive semiquantitative cultures of TBSs	8
Rongrungruang et al[28]	2015	Thailand	SC, OP, RCT, prospective	150	NA	Oral care and enteral feeding tube	Lactobacillus, 80 mL, oral care, QD, 80 mL, enteral feeding, QD	Placebo	NA	3
Zarinfar et al[29]	2016	Iran	SC, DB, RCT, prospective	60	NA	NA	*Lactobacillus rhamnosus* GG, tid	Placebo	NA	5

9 *(continued)*

First author	Year	Nation	Study design	Total number of patients	Duration	Method of administration	Treatment intervention	Control intervention	Definition of VAP	Number of outcomes
Zeng et al[8]	2016	China	MC, OP, RCT, prospective	235	14 Days	Nasogastric tube	Medilac-S capsule, 0.5 g, tid	WHAS strategies, same as probiotics group	A new, persistent, or progressive infiltrate on chest radiograph that persisted for at least 48 hours; at least 2 of: T >38.0 °C or T <35.5 °C; WBC >12 × 10^9/L or <3 × 10^9/L or left shift; purulent tracheal aspirates	13
Kooshki et al[30]	2018	Iran	MC, DB, RCT, prospective	60	Until events, such as extubation, tracheotomy placement, discharge, and/or death occurred	Nasogastric tube	Fenugreek seed, 3 g, bid	None	ACCP clinical criteria	8
Shimizu et al[31]	2018	Japan	SC, SB, RCT, prospective	72	Within 3 days after admission when enteral nutrition was started via nasal tube and continued until oral intake was initiated	Nasogastric tube/ orally	Synbiotics: Seichoyaku, 3 g and galacto-oligosaccharides 10 g, qd	None	Pneumonia occurring more than 48 to 72 hours after intubation	7
Klarin et al[32]	2018	Sweden	MC, OP, RCT, prospective	137	NA	Oral care	Lp299, 10^{10} CFU, bid	Toothpaste, CHX	A new, persistent or progressive infiltrate on chest radiograph, at least 3 of: a purulent tracheal aspirate; positive culture of tracheal aspirates occurring after 48 hours of mechanical ventilation; T >38.0 °C or <35.5 °C; WBC >12 × 10^9/L or <3 × 10^9/L or a rapid increase in WBC without suspicion of infection in another organ	8
Jin et al[33]	2019	China	SC, SB, RCT, prospective	56	14 Days	Nasogastric tube	Golden Bifid, 4 tablets, tid	None	Pneumonia occurring more than 48 hours after intubation or 48 hours within extubation	2
Mahmoodpoor et al[34]	2019	Iran	MC, DB, RCT, prospective	102	14 days	Feeding tube	Mixed-probiotic, 2 capsules, bid	Sterile maize starch powder	A new or persistent infiltration on chest X-ray; at least 2 of: T >38 °C or <36 °C, leukocytosis or leucopenia, or purulent sputum underwent BAL. BAL >10^4 CFU/mL when mechanically ventilated for >48 hours	12
Anandarajet al[35]	2019	India	SC, DB, RCT, prospective	146	7 Days or until extubation	Nasogastric tube	Lactobacillus, 10^9 CFU, bid	Placebo contained base powder	New and persistent infiltrates on the chest X-ray; at least 2 of: fever/hypothermia, leukocytosis or leucopenia, and purulent sputum; tracheobronchial aspiration culture >10^5 CFU; CPIS after 72 hours	6
Tsaousi et al[36]	2019	Greece	SC, RCT, prospective	58	15 Days	Nasogastric tube and oropharynx	One 4-probiotic capsule, nasal feeding, qd; one 4-probiotic capsule, oropharynx, qd	Placebo	Not detailed	4
Wu et al[37]	2019	China	SC, OP, RCT, prospective	93	NA	Feeding tube	Bifidobacterium, *Lactobacillus* and *Enterococcus* capsule, 2 × 10^7 CFU, tid	None	NA	1

Abbreviations: ACCP, American College of Chest Physicians; BAL, bronchoalveolar lavage; CFU, colony forming unit; CHX, chlorhexidine; CPIS, Clinical Pulmonary Infection Score; CROSS, crossover trial; DB, double blind; ICU, intensive care unit; LP299, *Lactobacillus plantarum* 299; MC, multicenter; NA, not available; OP, open label; RCT, randomized controlled trial; SB, single blind; SC, single center; T, rectal or bladder temperature; TBS, tracheobronchial secretion; VAP, ventilator-associated pneumonia; WBC, white blood cell.

[a]ACCP clinical criteria: new and persistent infiltrates on chest radiographs, 2 or 3 supporting factors: T >38.5 °C or <35.0 °C), leukocytosis (WBC >10 000 mm^3 or <3000 mm^3), and purulent sputum. 2000FORTE: a symbiotic, combination of 10^{11} CFU of each of 4 probiotics—*Pediococcus pentoseceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* ssp 19, and *Lactobacillus plantarum* 2362—as well as 2.5 g each of inulin, oat bran, pectin, and resistant starch. Ergyphilus: 2 × 10^{10} of revivable bacteria (mainly *Lactobacillus rhamnosus* GG, but also *L casei, Lactobacillus acidophilus*, and *Bifidobacterium bifidum*). Golden Bifid (sachet): Each sachet contained 0.5 × 10^8 *Bifidobacterium longum*, 0.5 × 10^7 *Lactobacillus bulgaricus*, and 0.5 × 10^7 *Streptococcus thermophiles*. Medilac-S: each probiotic capsule contained active *Bacillus subtilis* 4.5 × 10^9/0.25 g and *Enterococcus faecalis* 0.5 × 10^9/0.25 g. WHAS: The standard preventive strategies of VAP included daily screening for weaning potential and weaning from mechanical ventilation as soon as possible, hand hygiene, aspiration precautions, and prevention of contamination. Seichoyaku: 1 × 10^8 living bacteria of the Bifidobacterium *breve* strain Yakult/g and 1 × 10^8 living bacteria of the *L casei* strain Shirota/g. Fenugreek seeds: contain 45% to 60% carbohydrates, mainly mucilaginous fiber (galactomannans) that act as prebiotics. Golden Bifid (tablet): each tablet contained 0.5 × 10^7 *Bifidobacterium longum*, 0.5 × 10^6 *Lactobacillus bulgaricus*, and 0.5 × 10^6 *Streptococcus thermophiles*. Mixed probiotic (capsule): each capsule contained 10^{10} CFU consisting of *Lactobacillus* species (*casei, acidophilus, rhamnosus, bulgaricus*), *Bifidobacterium* species (*breve, longum*), and *Streptococcus thermophile*.

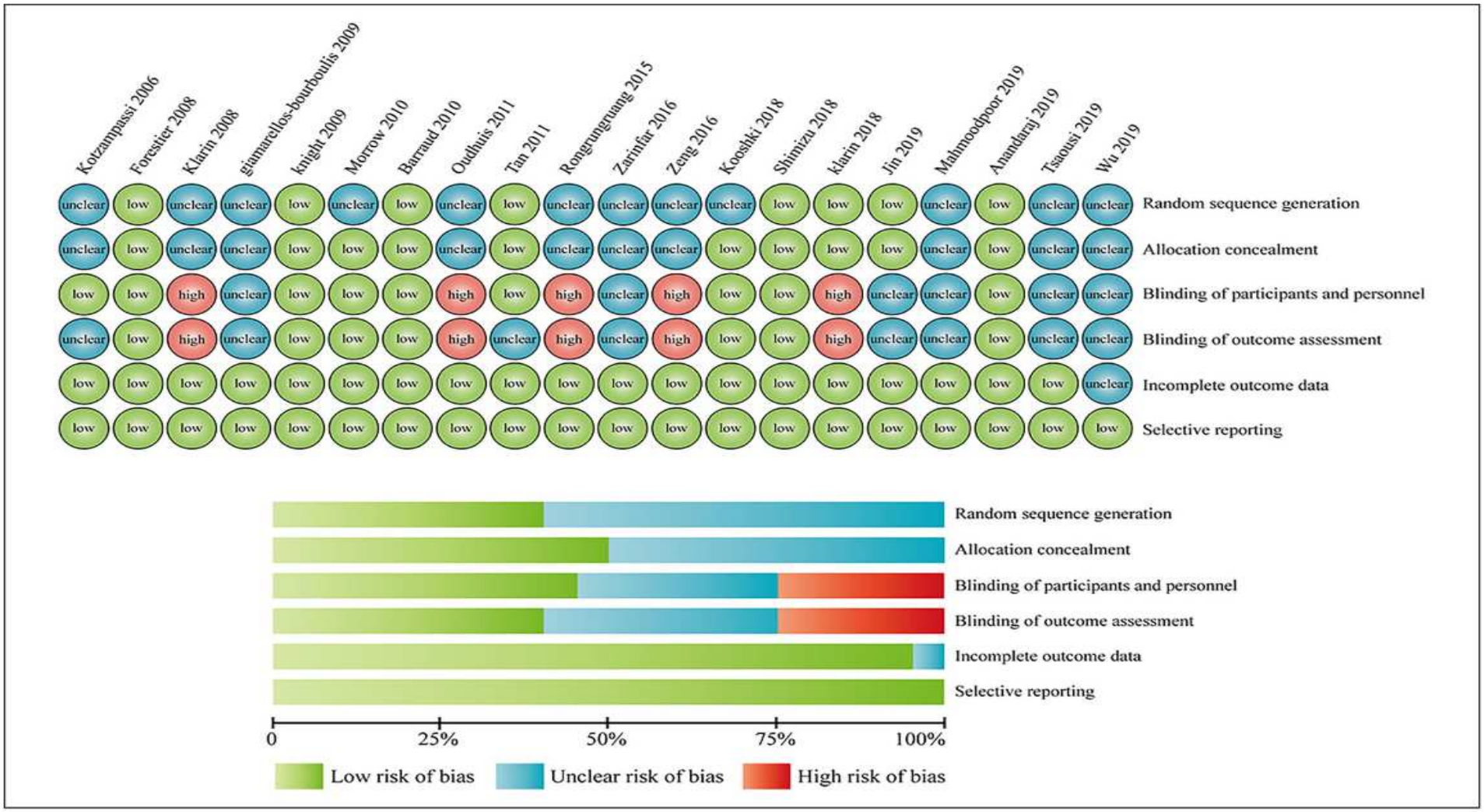


Figure 2. Risk of bias summary and graph: judgments about each risk of bias and percentages across all included studies.

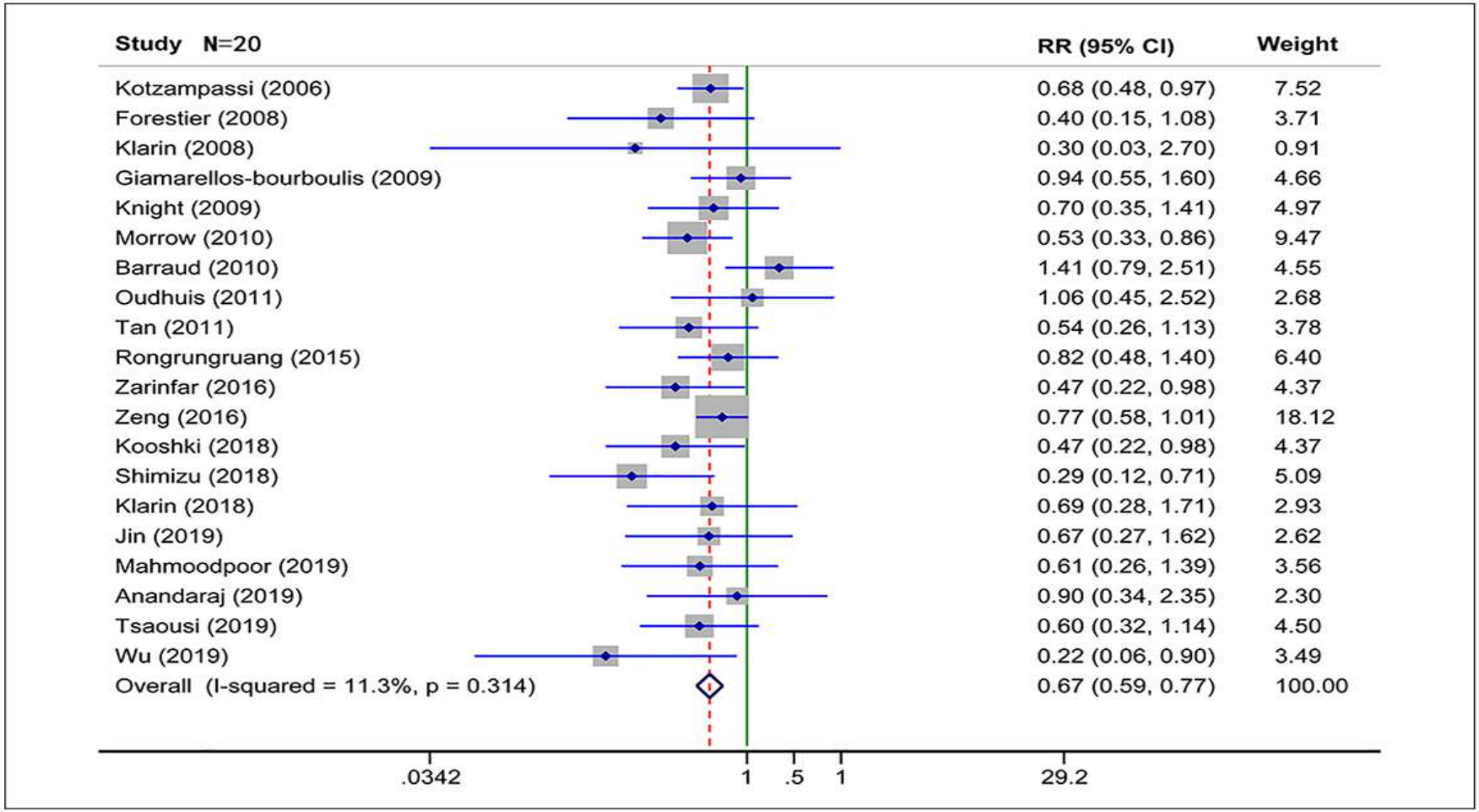
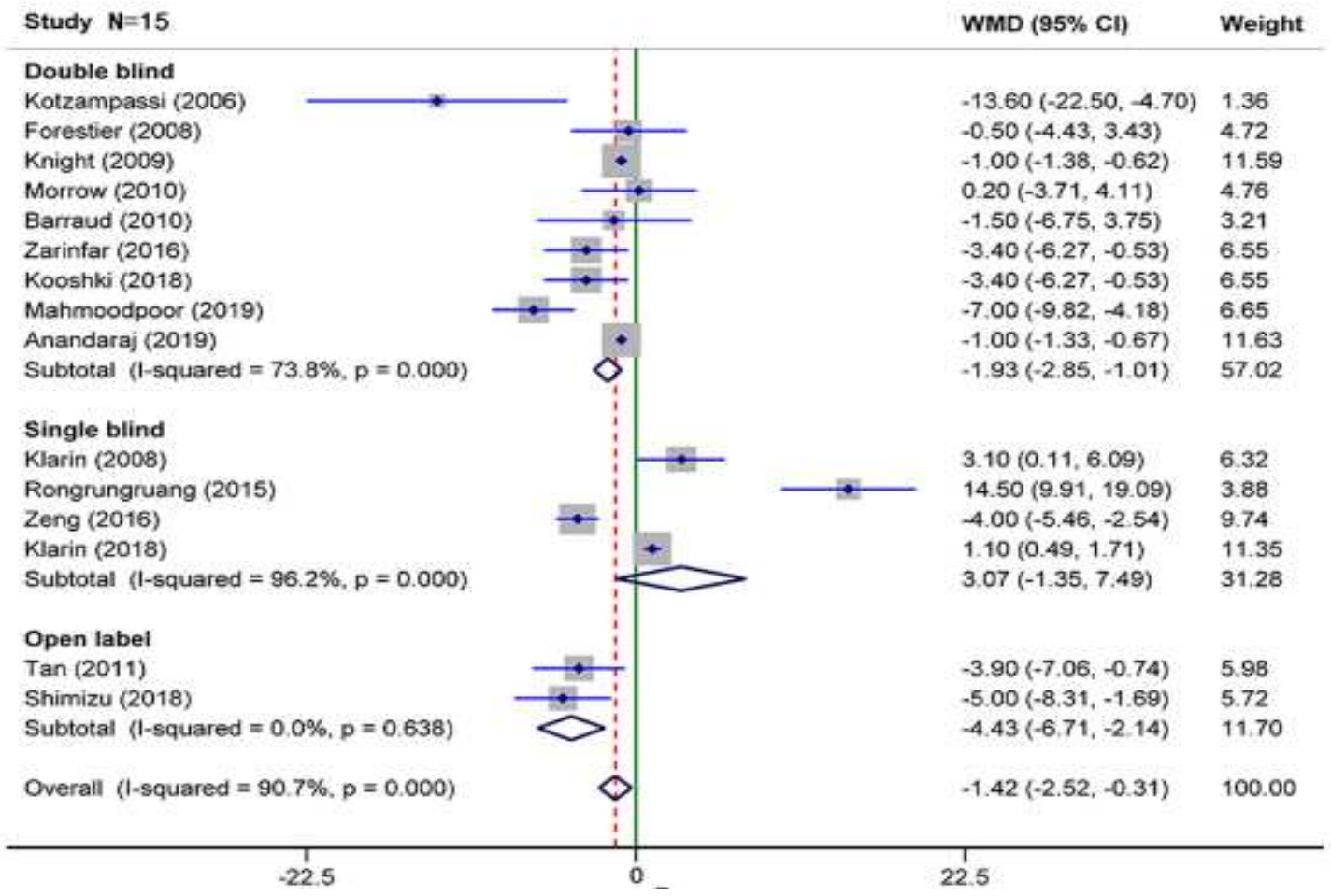
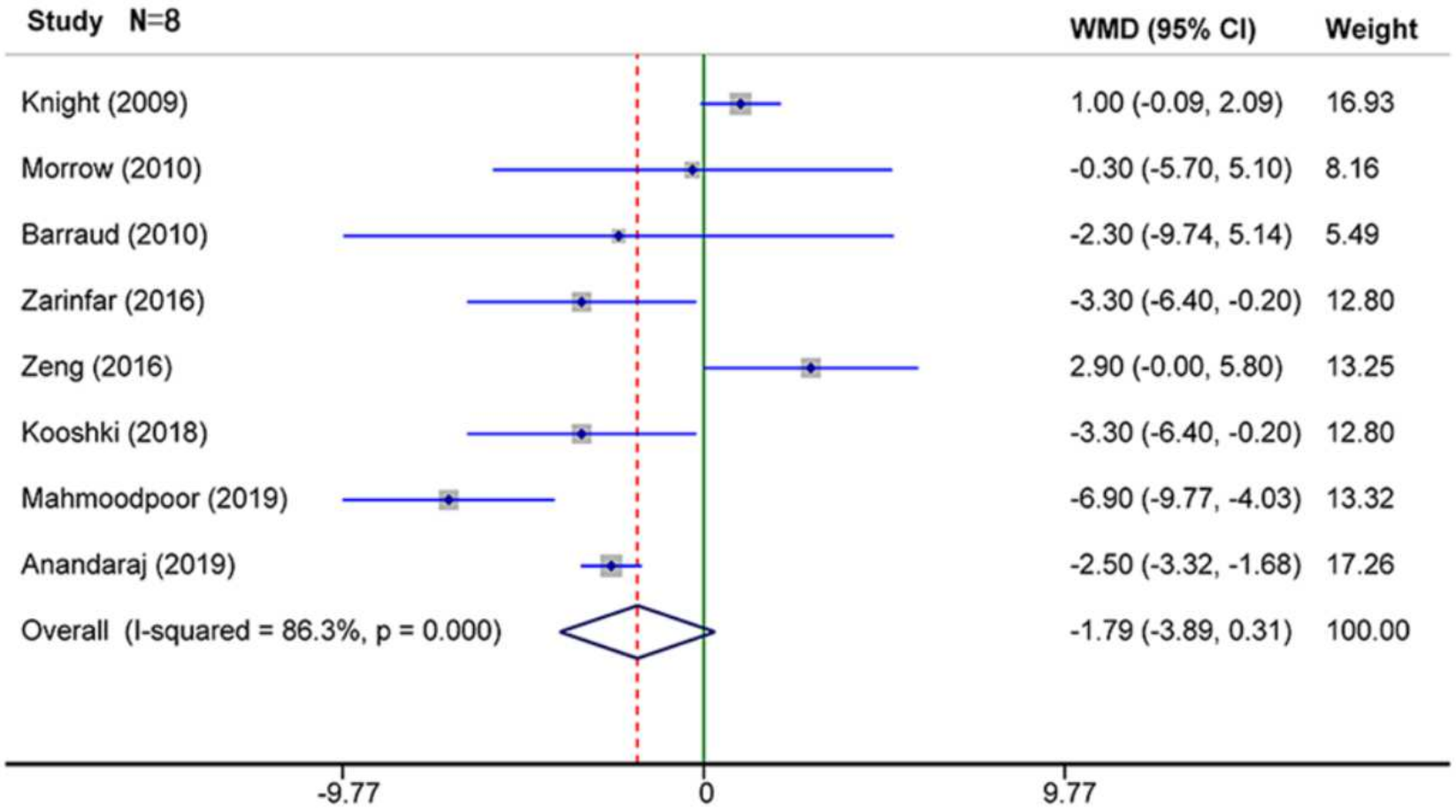


Figure 3. Effect of probiotic therapy on VAP. Pooling model: fixed, Mantel-Haenszel.
Abbreviations: RR, risk ratio; VAP, ventilator-associated pneumonia.

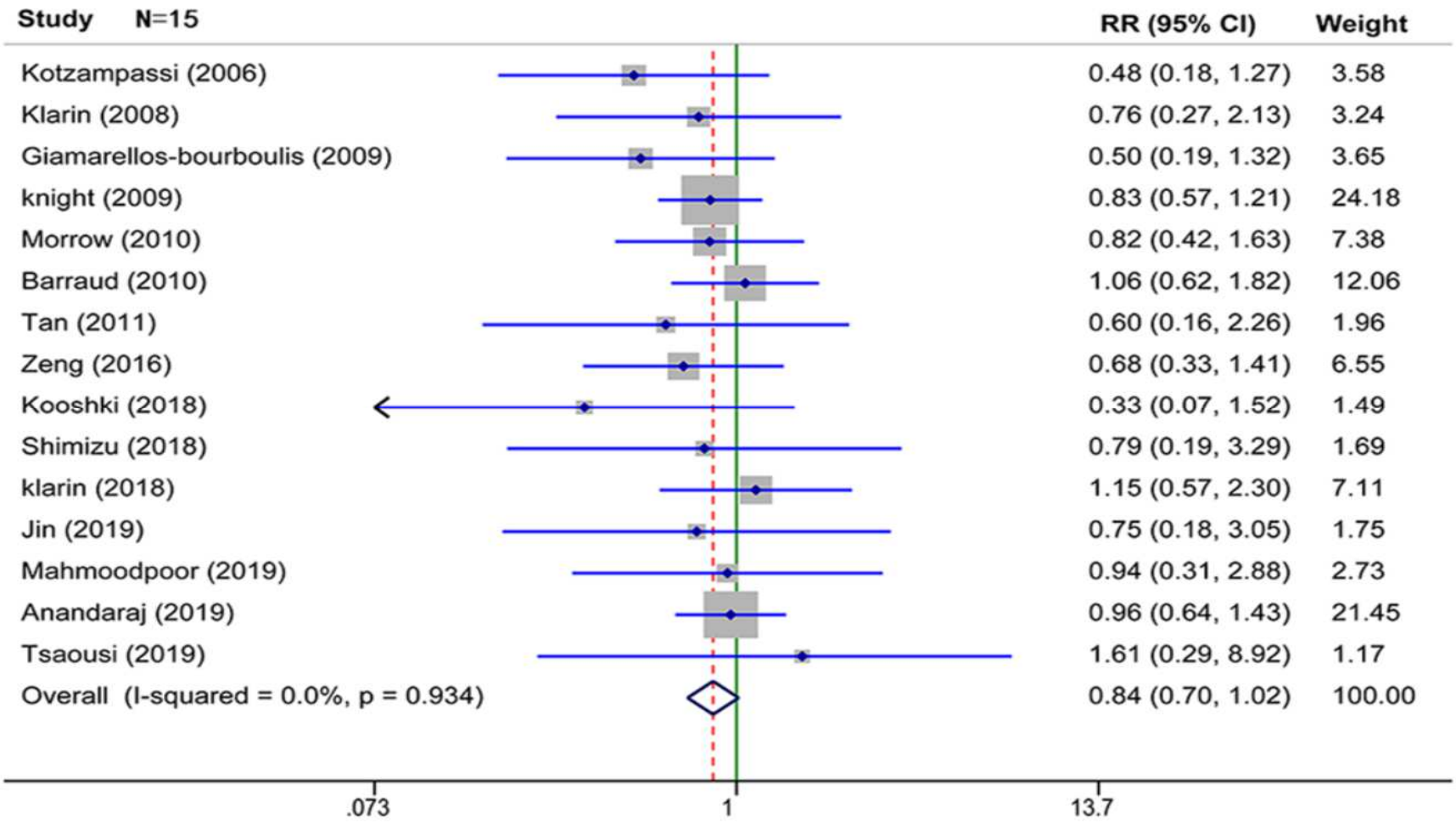
(RR = 0.672; 95% CI = 0.585 to 0.772; P < 0.001; N = 2428, 20 studies)



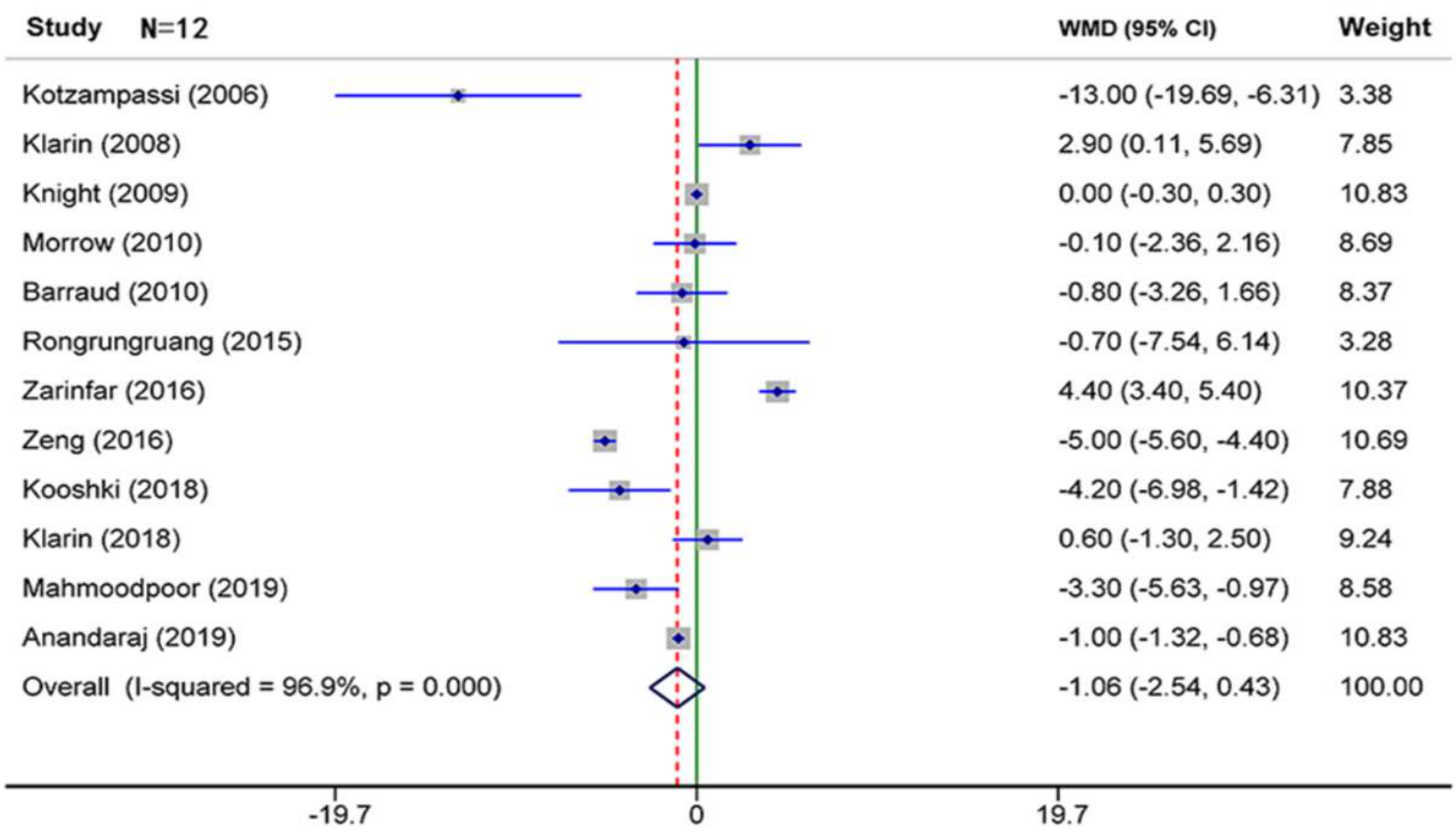
Length of ICU stay (days) (WMD = −1.417, 95% CI = −2.520 to −0.313, P = 0.012, n = 1895, 15 studies)



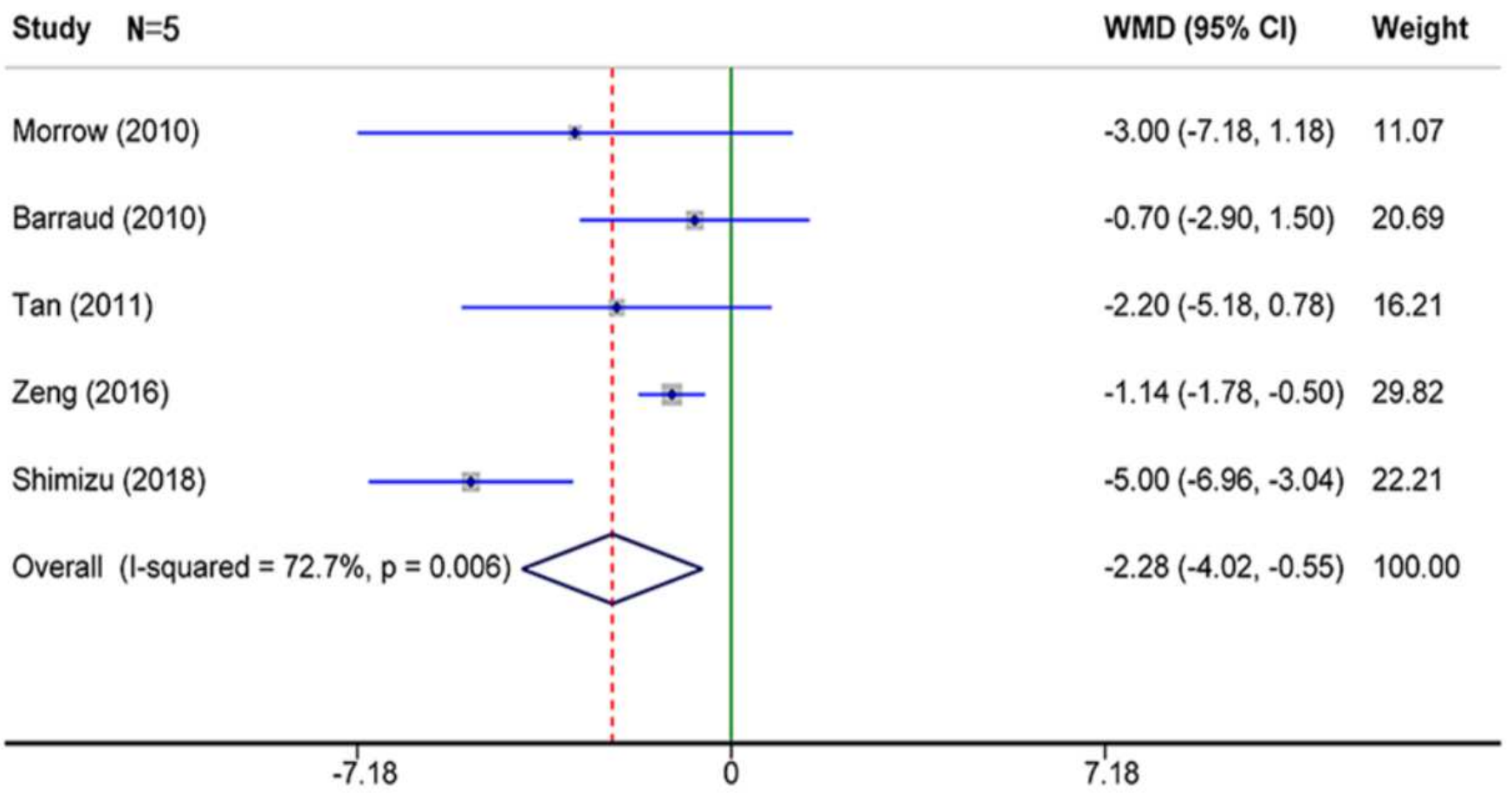
length of hospital stay (WMD = −1.793, 95% CI = −3.893 to−0.307, P = 0.094, n = 1161, 8 studies)



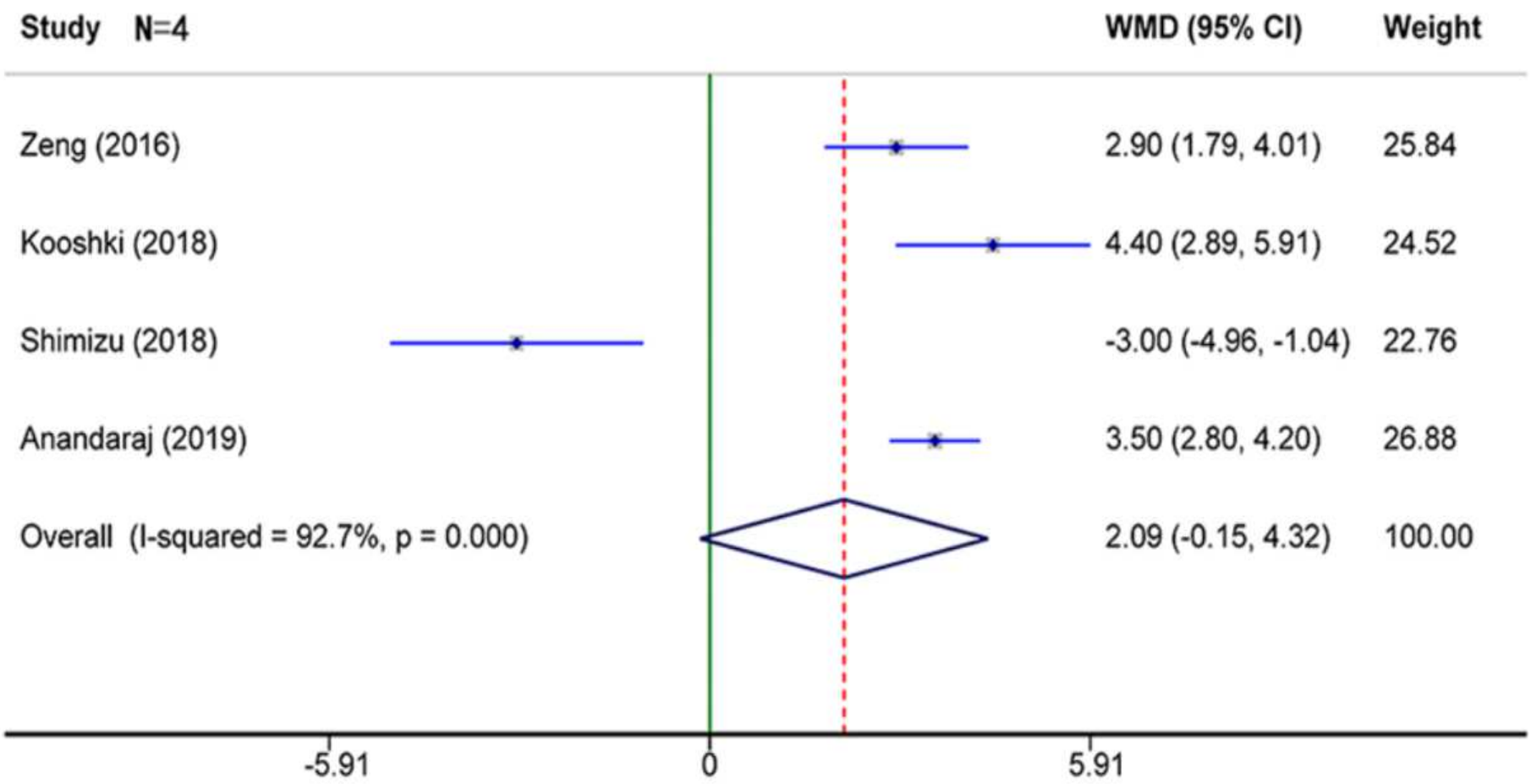
mortality rates (RR = 0.830, 95% CI = 0.702 to 1.016, P = 0.074, n = 1959, 15 studies)



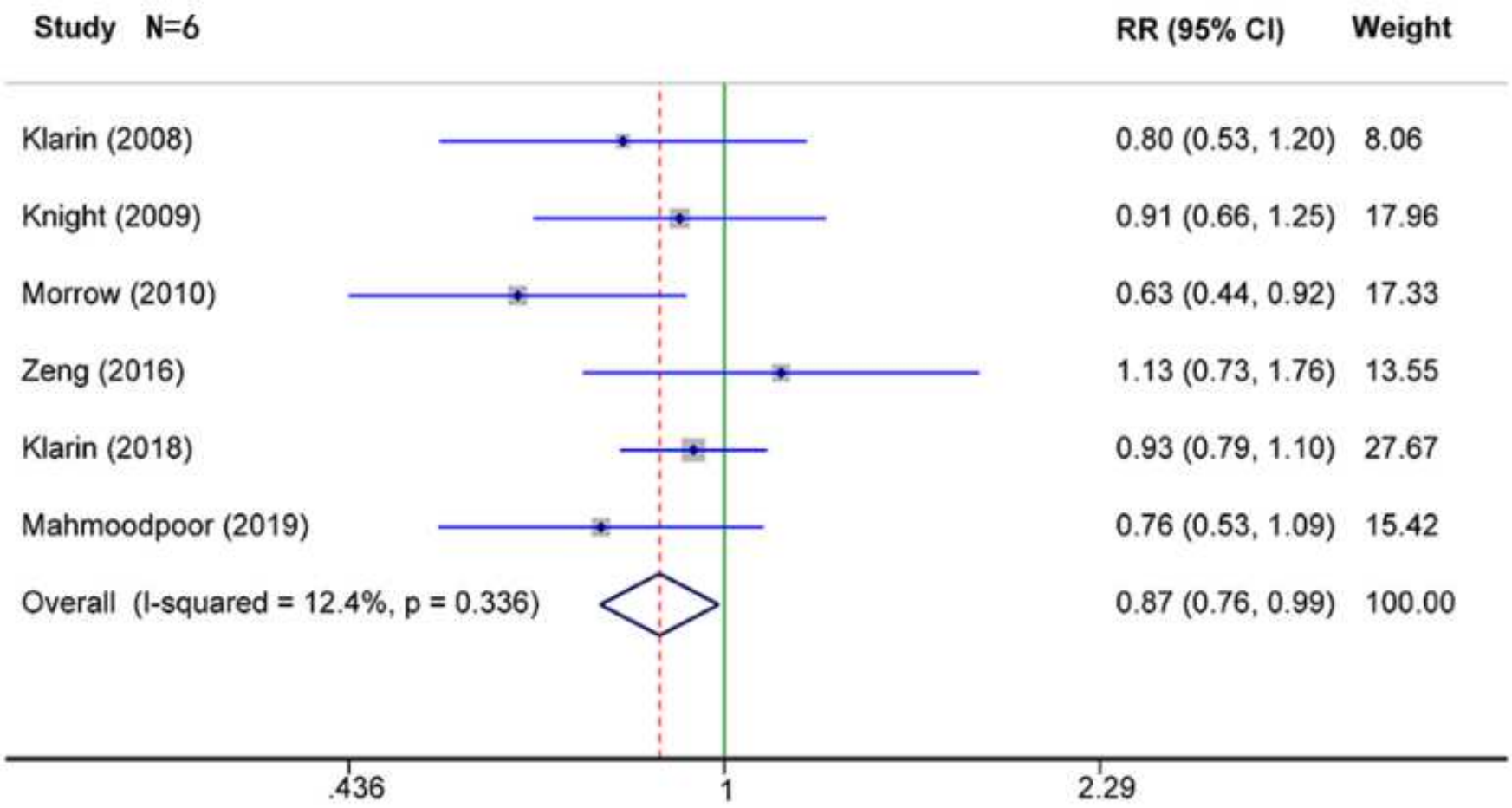
Days of mechanical ventilation (WMD = −1.056, 95% CI = −2.539 to 0.427, P = 0.163; n = 1563, 12 studies)



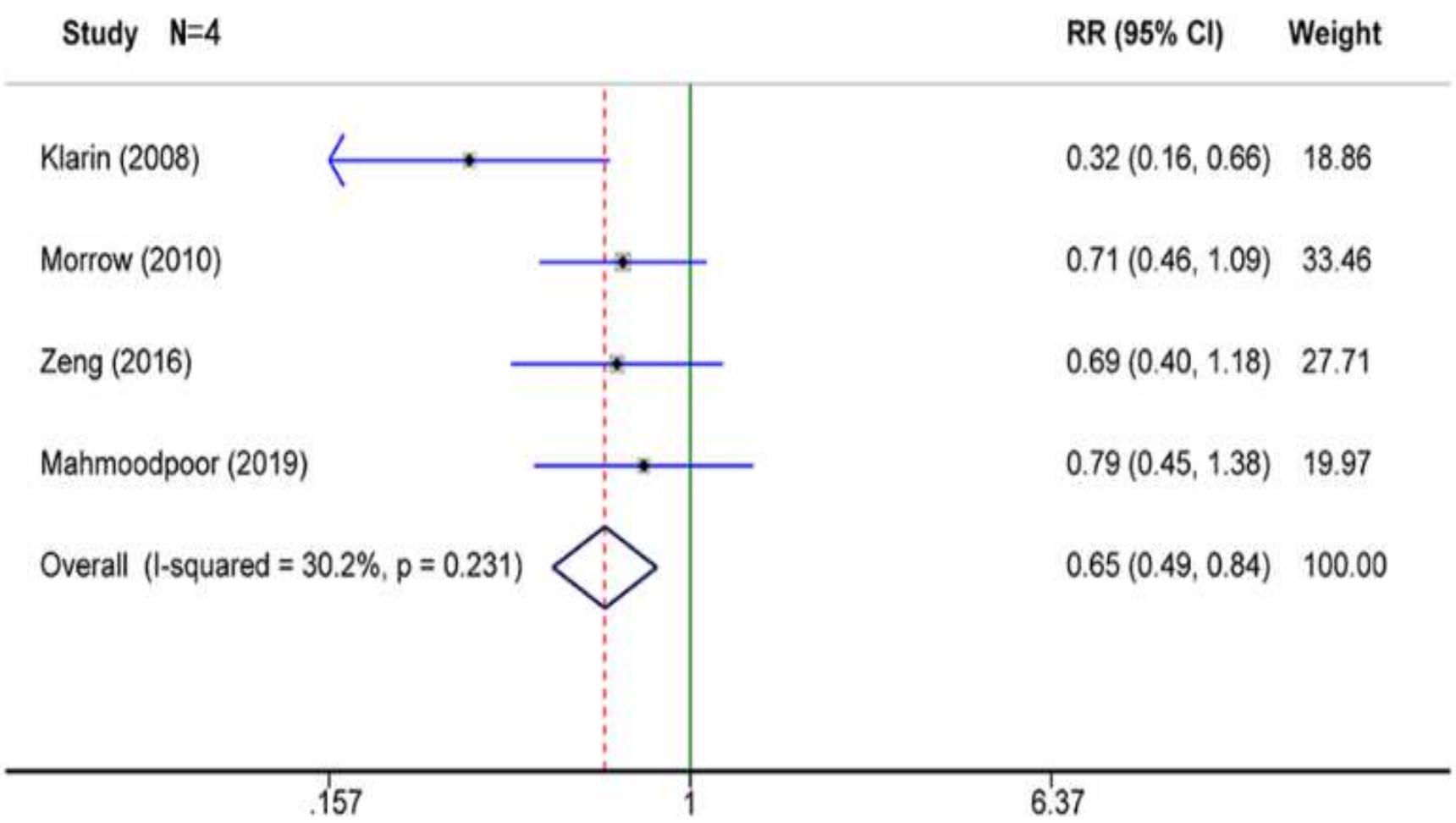
Days of using antibiotics ((WMD = −2.284; 95% CI = −4.018 to −0.550; P = 0.010; n = 664; 5 studies)



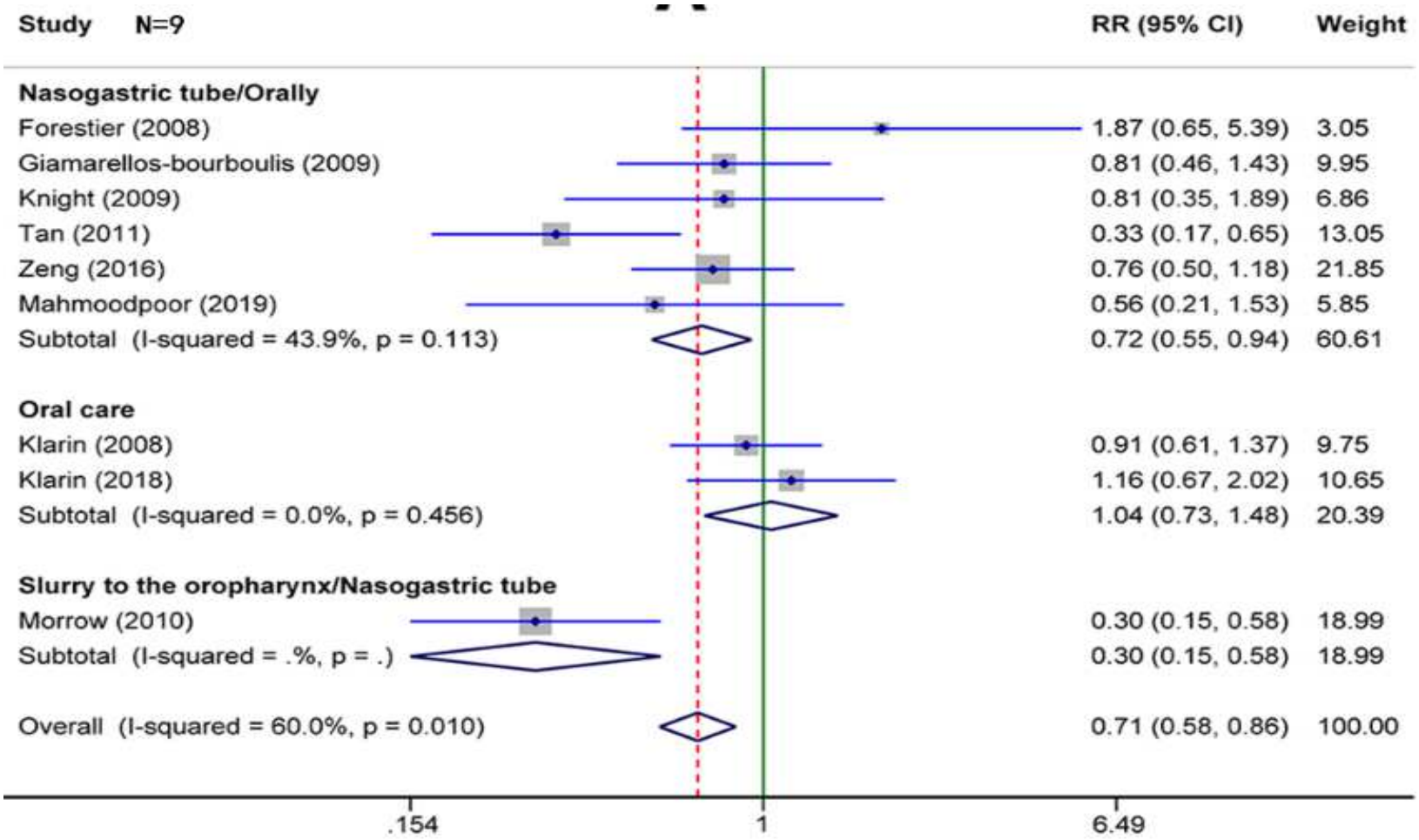
Days to VAP after intubation; probiotics likely did not delay the onset of VAP following intubation (WMD = 2.086; 95% CI = −0.149 to 4.321; P = 0.067; n = 265; 4 studies)



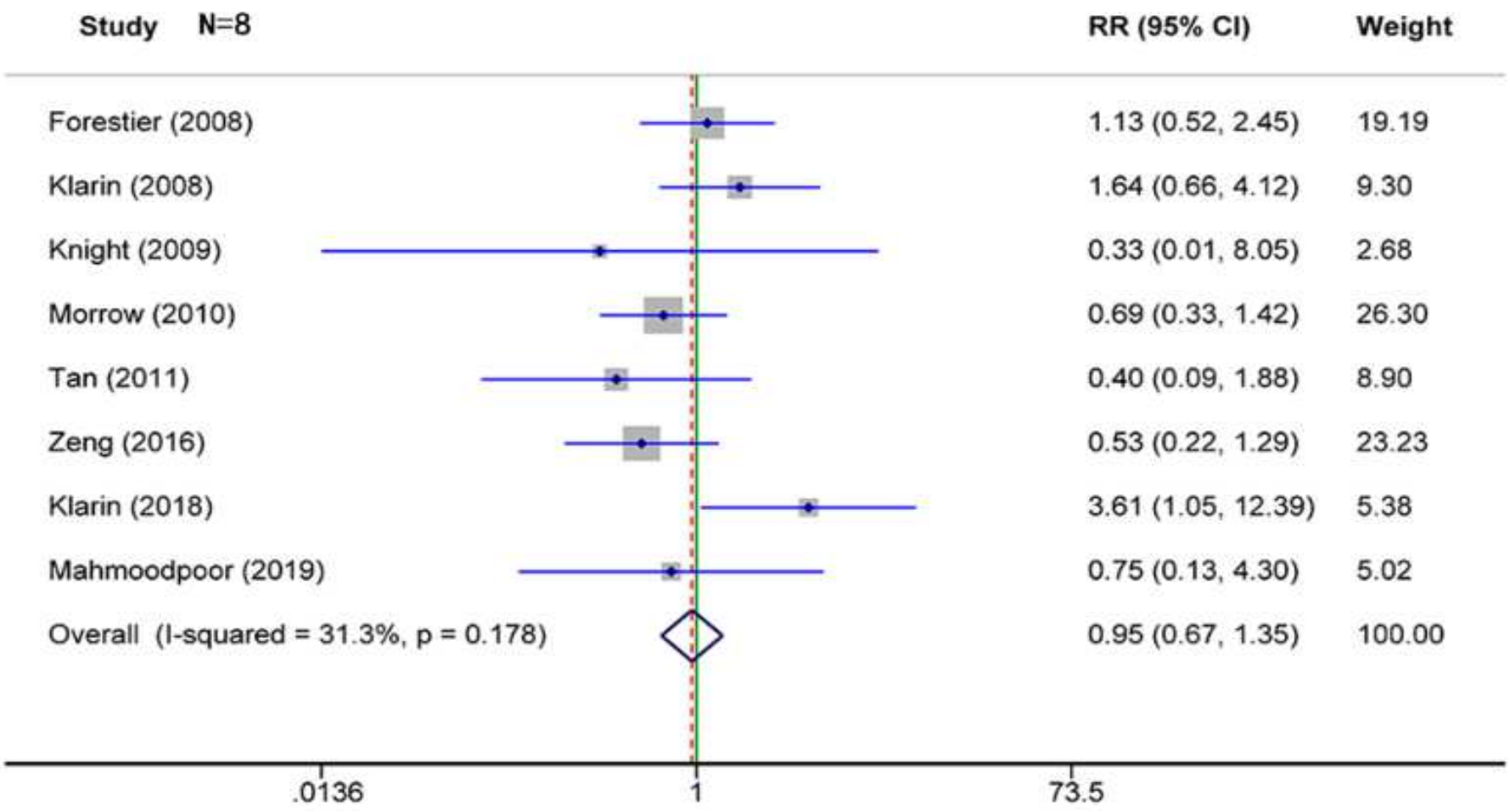
Oropharyngeal colonization (RR = 0.866, 95% CI = 0.760 to 0.987, P = 0.031, n = 915, 6 studies)



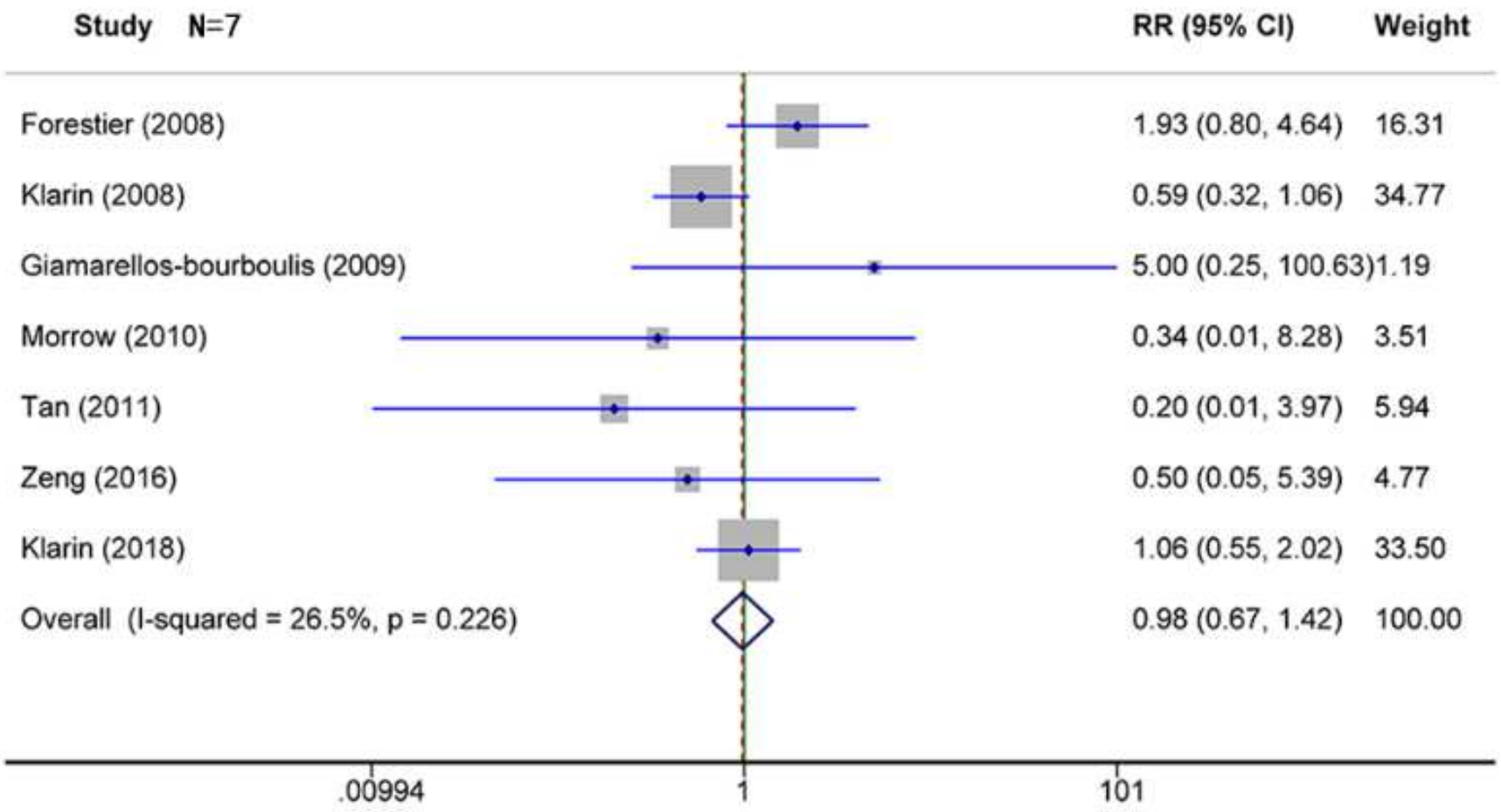
Gastric colonization (RR = 0.645, 95% CI = 0.494 to 0.842, P < 0.001, n = 519, 4 studies)



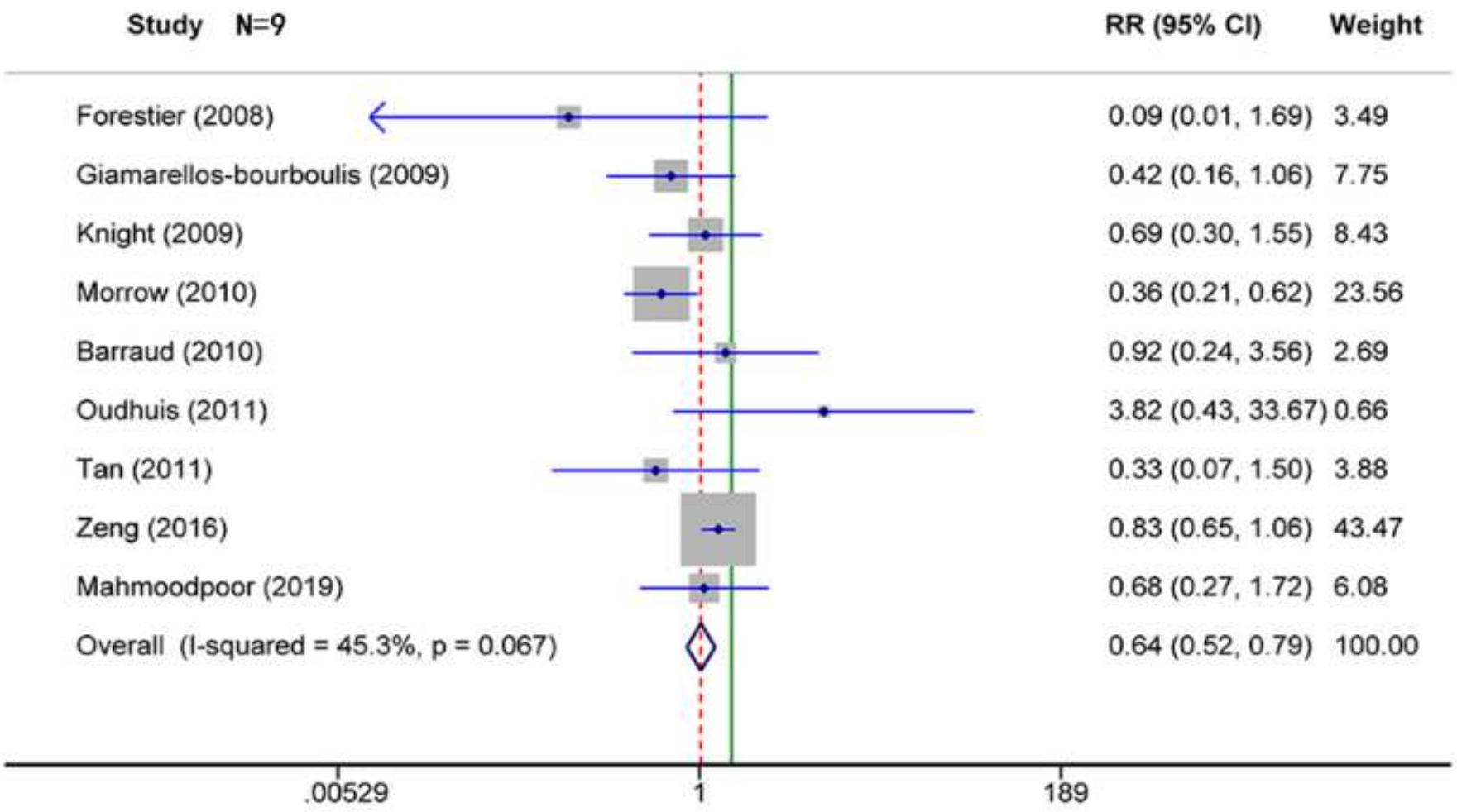
Gram-negative bacteria culture positive in tracheobronchial secretion/sputum (RR = 0.576, 95% CI = 0.577 to 0.864, P = 0.010, n = 1247, 9 studies)



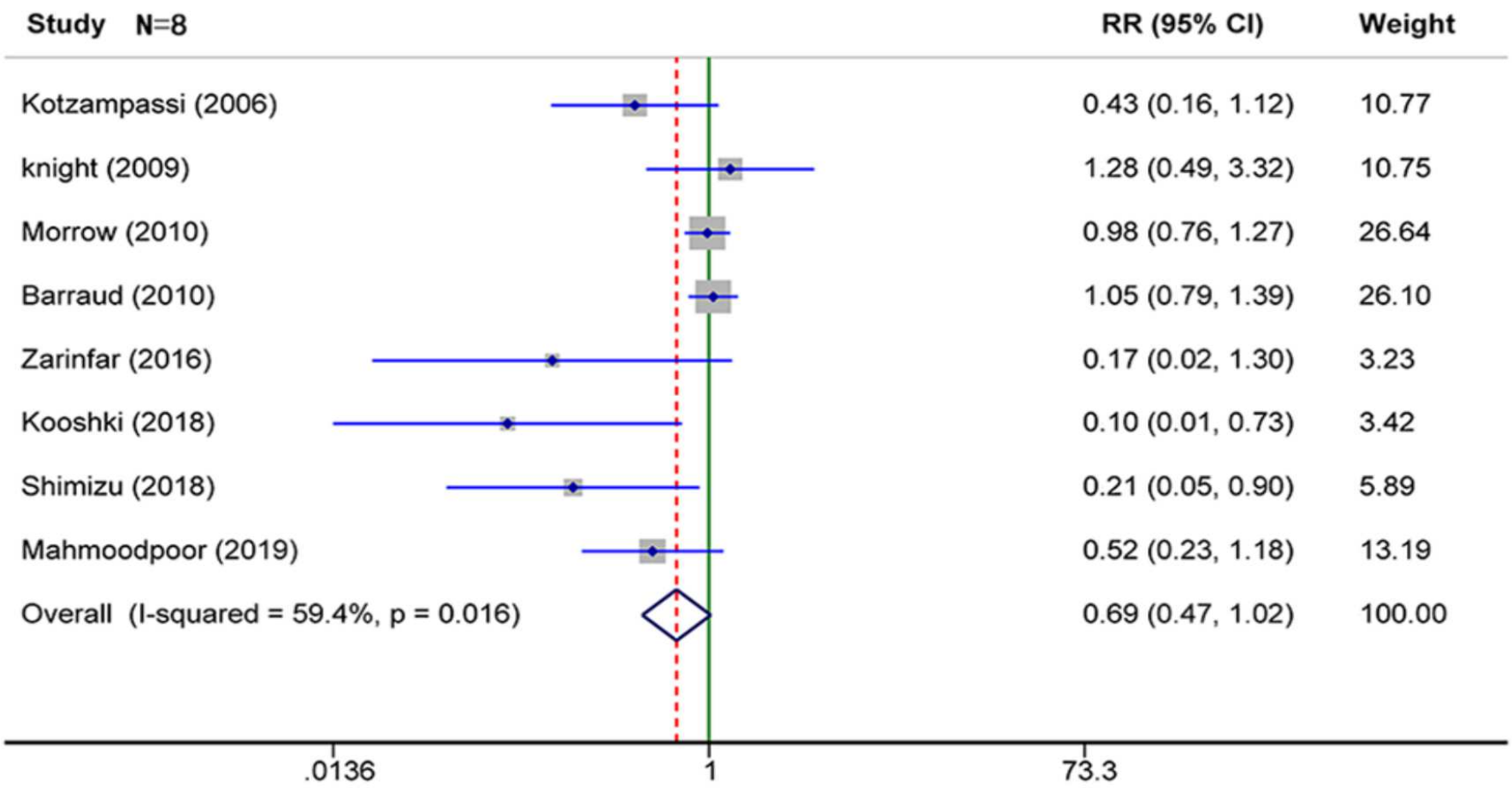
Gram-positive bacteria culture positive in tracheobronchial secretion/sputum (RR = 0.951, 95% CI = 0.671 to 1.349, P = 0.780, n = 1175, 8 studies)



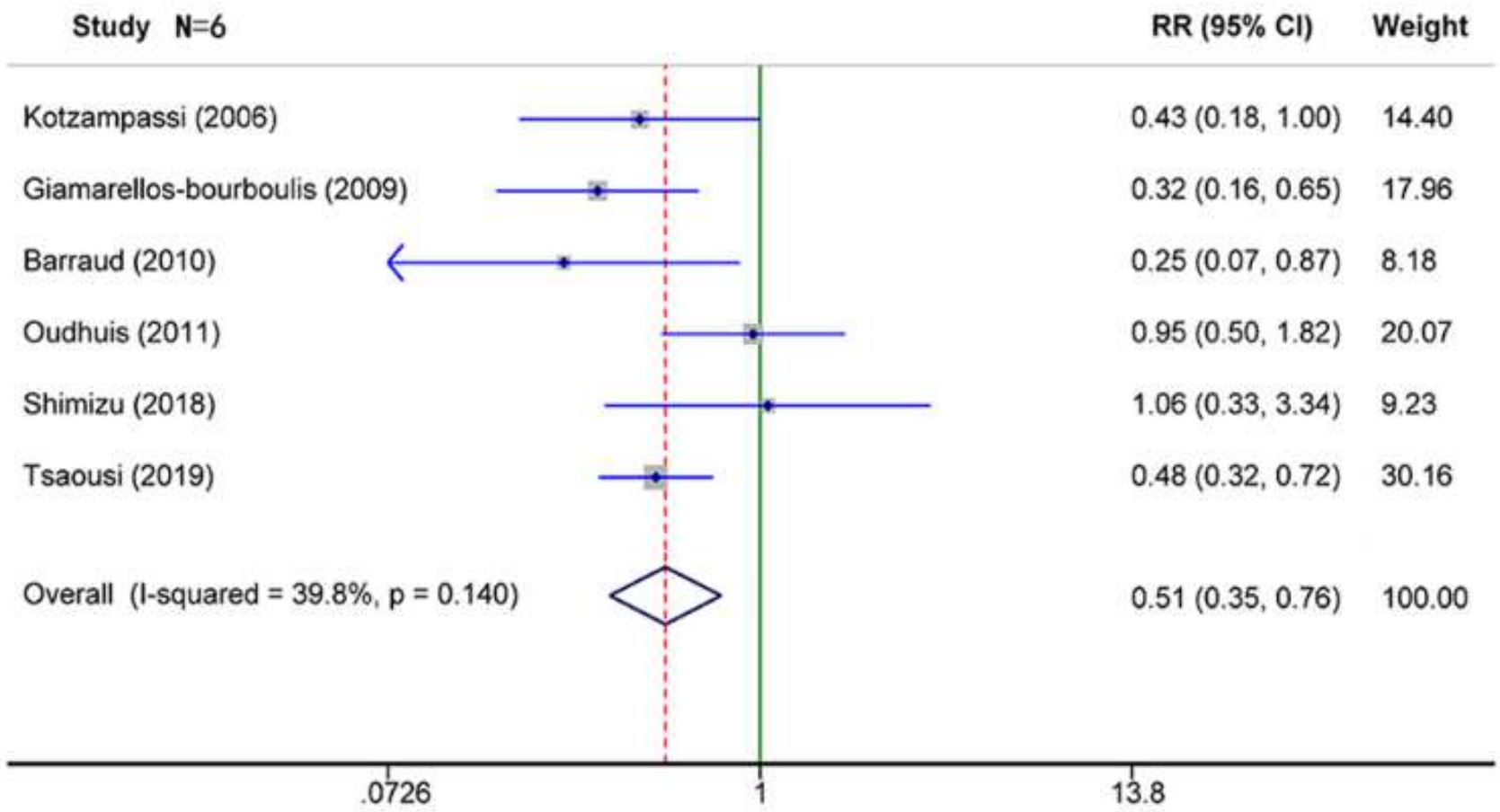
Fungi culture positive in tracheobronchial secretion/sputum (RR = 0.980, 95% CI = 0.674 to 1.425, P = 0.914, n = 886, 7 studies)



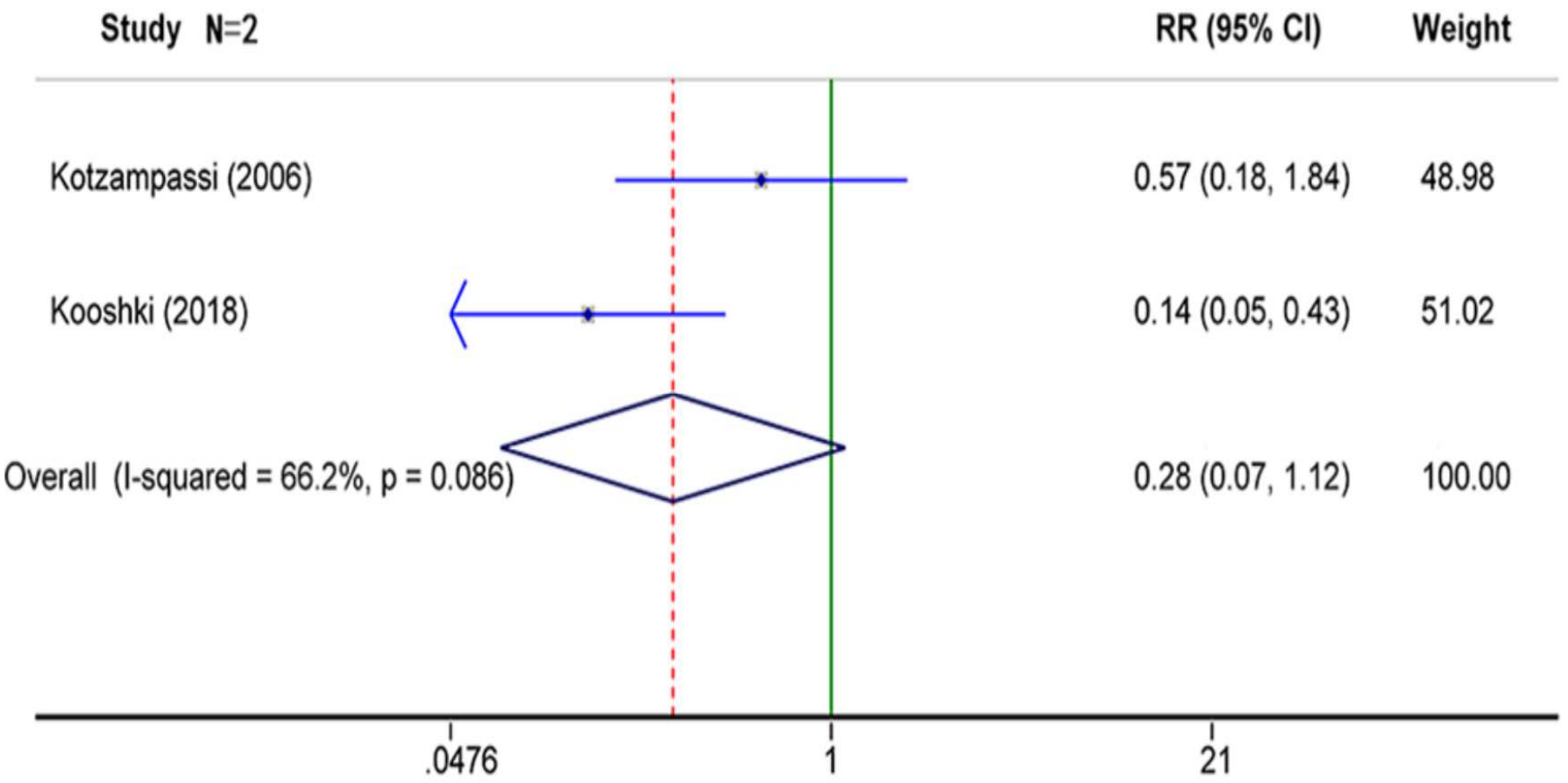
Multiple resistant bacteria culture positive in tracheobronchial secretion/sputum (RR = 0.643, 95% CI = 0.524 to 0.789, P < 0.001, n = 1487, 9 studies)



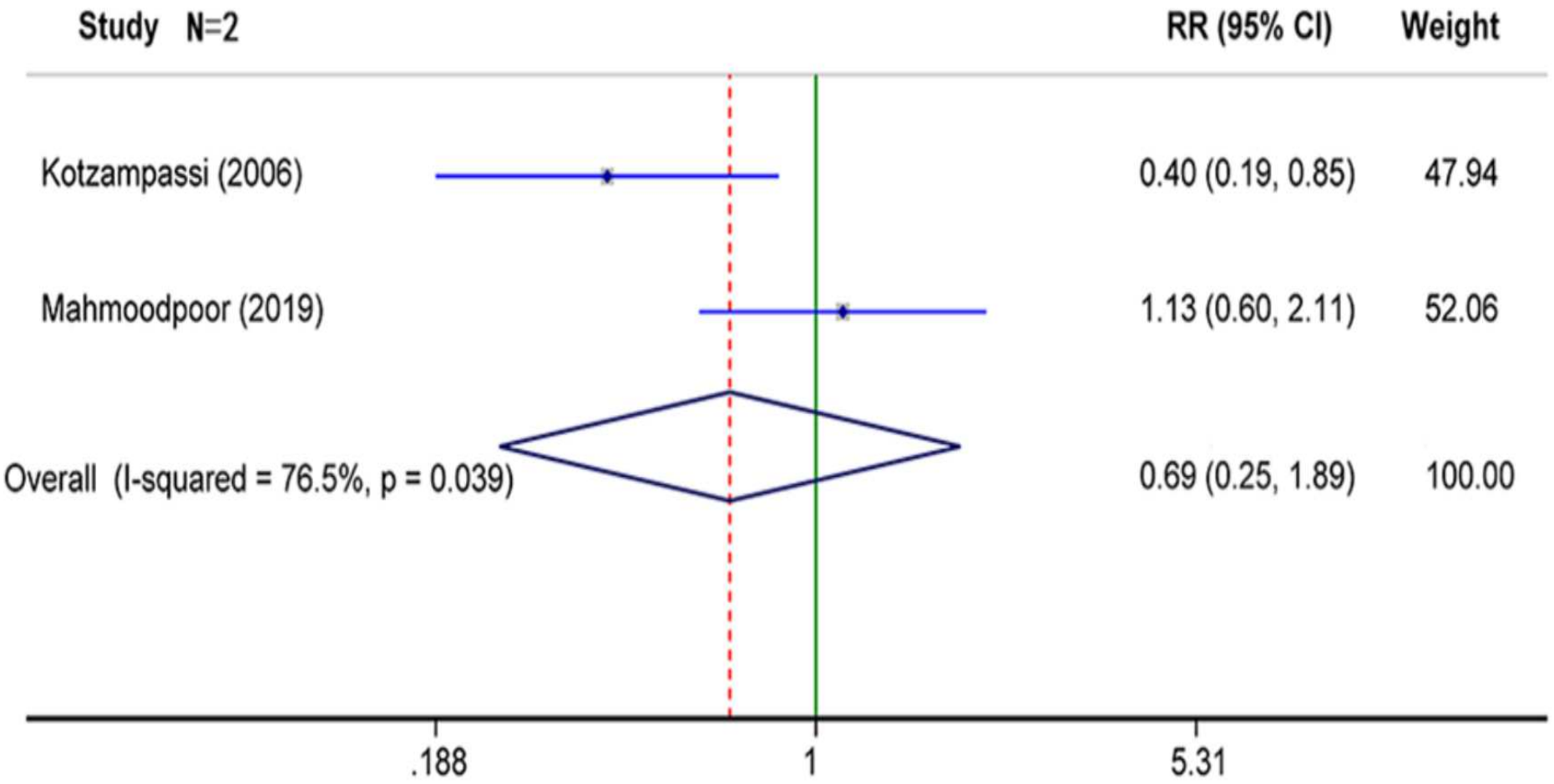
Diarrhea (RR = 0.691, 95% CI = 0.467 to 1.022, P = 0.064, n = 1219, 8 studies)



Bacteremia (RR = 0.514, 95% CI = 0.347 to 0.761, P = 0.001, n = 688, 6 studies)



Constipation (RR = 0.282, 95% CI = 0.071 to 1.117, P = 0.071, n = 125, 2 studies)



Gastric residual (RR = 0.685, 95% CI = 0.249 to 1.886, P = 0.464, n = 167, 2 studies)

Discussion

- Gut flora are not only related to gut metabolism, but also to the immune system. Previous studies have shown that patients with systemic inflammatory response syndrome had 100 to 10 000 times fewer total anaerobic bacteria (including Bifidobacterium and Lactobacillus) in the gut compared with healthy volunteers.

Discussion

- Some basic studies have demonstrated that probiotics could reduce the risk of sepsis by inhibiting pathogen adhesion, improving intestinal mucosal barrier function, reducing bacterial translocation, modulating immunity, and promoting gastrointestinal immune defense.

- Previous research has shown that probiotics could reduce the incidence of Clostridium difficile–associated diarrhea by 66%.

Limitations

- Lower number of studies for assessing diarrhea and constipation in ICU.
- Lack of scoring of disease severity (like SOFA, APACHE II)

Conclusion

- probiotics may reduce the risk of VAP.
- The results also suggest that probiotics do not cause adverse effects.

- Repeated strains:

1. Lactobacillus rhamnosus 2*10 billion CFU ,

2. 2000FORTE (consists of 20*10 billion CFU of each of Pediococcus pentoseceus 5–33:3, Leuconostoc mesenteroides 32–77:1, L. paracasei ssp paracasei 19 and L. plantarum 2362, as well as 2.5 g inulin, oat bran, pectin and resistant starch),

3. Lactobacillus plantarum 299v® (LP299v®) 20*10 billion CFU

Thank you for your attention