Original paper

Evaluation of the effect of probiotics on septic complications in patients with severe acute pancreatitis. A systematic review and meta-analysis

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Abstract

Introduction: Severe acute pancreatitis (SAP) with major complications such as necrosis and multiple organ dysfunction syndrome (MODS) often leads to high mortality rates despite intensive treatment.

Aim: To evaluate the effect of symbiotics (probiotics) on septic complications in patients with SAP.

Material and methods: We searched the PubMed, Cochrane CENTRAL, SCOPUS, and Web of Science databases for relevant clinical trials and excluded observational studies. Quality appraisal was evaluated according to GRADE, and we assessed the risk of bias using Cochrane's risk of bias tool. We included the following outcomes: C-reactive protein (CRP), APACHE II score, hospital stay, multiorgan failure (MOF), systemic inflammatory response syndrome, infected pancreatic necrosis, septicaemia, need for operation, and death. We performed the analysis of homogeneous data under a fixed-effects model, while analysis of heterogeneous data were analysed under a random-effects model. We performed the analysis of dichotomous outcomes using the risk ratio (RR) and relative 95% confidence interval (CI).

Results: We included a total of 7 clinical trials. We found that there was no significant difference between both groups regarding MOF (RR = 0.60 (0.25, 1.44), $p = 0.26$), septicaemia (RR = 0.66 (0.29, 1.50), $p = 0.32$), death (RR = 0.66 (0.19, 2.26), $p = 0.51$), infected pancreatic necrosis (RR = 0.50 (0.18, 1.38), $p = 0.18$), SIRS (RR = 0.81 (0.29, 2.23), $p = 0.68$), CRP, APACHE II score, and hospital stay.

Conclusions: Contrary to some published trials, our meta-analysis concludes that the use of probiotics in patients with SAP is not effective in reducing the mortality rate, septic complications, and need for operation.

Introduction

Acute pancreatitis is the leading cause of hospitalization due to gastrointestinal diseases in the United States [1]. The incidence of acute pancreatitis is increasing by about 5% per year in Europe and the USA [2–4]. Acute pancreatitis is an inflammatory disorder in which the pancreas causes an increase in cytokine release as a first phase of the disease and subsequent systemic inflammatory response syndrome (SIRS) [5]. Gallstones and alcohol abuse are the main causes of acute pancreatitis in the UK. About 25% of acute pancreatitis cases are attributed to alcohol abuse [6]. Severe acute pancreatitis is associated with high morbidity and mortality rates, reaching about 30% in cases of severe acute pancreatitis, while the overall mortality rate in acute pancreatitis is 5% [6]. The mortality rate is mostly attributed to complications and infection of pancreatic necrotic tissue [3]. The most common complications of acute pancreatitis include peri-pancreatic fluid collection, pancreatic pseudocyst, acute pancreatic necrosis, multiple organ failure, and abscess [7–11]. The management of acute pancreatitis depends mainly on the severity of the disease and whether it is associated with complications or

not [12]. Early antibiotic treatment is associated with a significant improvement of necrotizing acute pancreatitis [13]. Previous studies reported that probiotics administration is associated with the reduction of complications and improvement of condition [14].

Probiotics are a mixture of living micro-organisms, which have beneficial effects on the host [15]. They improve the properties of the intestinal microflora [16]. This intestinal microflora aids the host in producing vitamins, degrading bile acids, and eliminating carcinogenic substances [17]. Prebiotics (symbiotics) are non-digestible fibres that help in gut integrity. Administration of prebiotics together with probiotics can improve their activity [18].

Bacterial translocation acts as a pathway by which the infection may reach the pancreatic necrosis [19]. Disturbed mucosal barrier and bacterial overgrowth are factors that help bacterial translocation [20]. Probiotics reduce the bacterial translocation in acute pancreatitis through beneficial effects on the immune system and the intestinal lumen. Probiotics also decrease the expression of pro-inflammatory cytokines such as IL6 and CRP. This action is mediated through toll-like receptors [21].

Aim

In our study, we aim to estimate the effect of probiotics in patients with acute pancreatitis.

Material and methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22] and the guidelines reported in the Cochrane Handbook for Systematic Reviews of Interventions [23].

Literature search

We searched 4 databases: SCOPUS, Web of Science, PubMed, and Cochrane CENTRAL, from inception until December 2020. We followed this search strategy with no restriction on time: (prebiotic OR probiotic OR symbiotic OR lactobacillus) AND (pancreatitis OR pancreatitides).

Eligibility criteria

We included all the studies that have the following criteria: (I) population: patients with acute pancreatitis, (ii) intervention: probiotic regardless of the dose and the mode of administration, (iii) comparator: placebo, or enteral feeding, (iv) outcomes: death, multiorgan failure (MOF), infected pancreatic necrosis, and SIRS as primary outcomes. The secondary outcomes were CRP (mg/l), APACHE II score, hospital stay (days), and ICU stay (days), (v) study design: we included only randomized clinical trials (RCTs). Our exclusion criteria were: (1) non-randomized controlled clinical trials, (2) studies that did not report data or measures for our selected outcomes, (3) single-armed trials, or (4) those with no available full text.

Screening of results

We exported the results of the search into Endnote X8.0.1 (Build 1044), with the removal of duplicates automatically by computer. After that, the studies were screened manually in 2 steps: first, title and abstract screening, then full-text screening for the preliminary included studies in the first step. Two independent authors performed the screening steps and obtained the full-text files for all included studies based on our eligibility criteria. A third author solved any deflection.

Data extraction and analysis

After the screening step, we extracted the data from the selected studies and categorized the data into 2 main groups: 1) baseline and demographic data of patients in each study including age, sample size, sex, alcoholism, APACHE II score, CRP level, Imrie score, and mean duration of symptoms before admission. 2) Data for analysis including outcome values of death, multiorgan failure (MOF), infected pancreatic necrosis, SIRS, CRP (mg/l), APACHE II score, hospital stay (days), and ICU stay (days). In addition to the previous 3 categories, we extracted data about the 7 domains assessing the risk of bias according to Cochrane's risk of bias [24].

Data analysis

We used Review Manager Software (RevMan 5.4.1) to perform our analysis implementing the inverse variance method. We expressed dichotomous outcomes using the percentage and total, while continuous outcomes were expressed using mean difference (MD) and standard deviations (SD), relative to the 95% confidence interval (CI). Two main tests were used to indicate inconsistency among studies [25]: the I-square test I^2 and the p-value of the χ^2 test. The outcomes with $I^2 > 50\%$, $p < 0.1$ were considered heterogeneous, while outcomes with $I^2 < 50\%$, $p > 0.1$ were considered homogeneous, according to the Cochrane Handbook. Homogenous data were analysed using a fixed-effects model, while heterogeneous outcomes were analysed using a random-effects model.

Quality assessment

We evaluated the quality of this systematic review and meta-analysis using the Grading of Recommen-

dations Assessment, Development, and Evaluation (GRADE) guidelines. We included only the controlled trials and excluded the observational evidence. According to the Cochrane risk of bias (ROB) tool for clinical trials, we performed the risk of bias (ROB) for the included studies. The tool depends on the following domains for assessment of the risk of bias: 1) proper randomization, 2) blinding allocation of the included patients into each group, 3) blinding of patients only (single-blinding), blinding of both personnel and participants (double-blinding), or not blinding at all, 4) attrition bias, 5) selection bias (outcomes reported matches with that of the protocol or not), 6) awareness of the outcome assessor (whether blinded or not), and 7) other bias. The total risk of bias for the studies was also assessed.

Results

Summary of included studies

We illustrated the results of the literature search in Figure 1. The analysis of 711 patients from 7 studies was performed [14, 26–31]. The patients received either probiotics or no treatment for the management of acute pancreatitis. A total of 359 patients were included in the probiotics group, while 352 patients were included in the control group. The mean age of patients in the probiotic group was 48.4 ±15 years, while that of the control group was 49 ±15.38 years. Table I shows

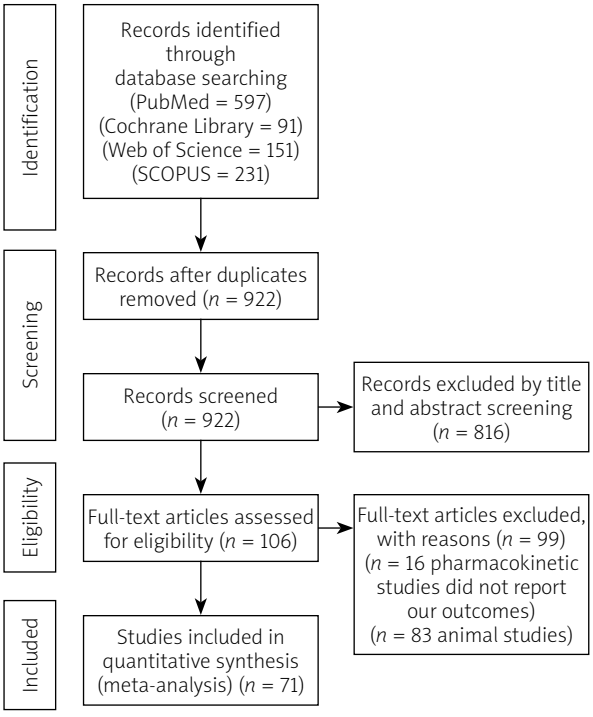


Figure 1. A PRISMA flow diagram of our literature search

Table I. Data are reported as mean ± SD or *n* (%) unless otherwise specified

Study	Sample size		Age [years] (mean ± SD)		Sex (male/female)		Alcoholics, *n* (%)		CRP level (mean ± SD)		Imrie score (mean ± SD)		Mean duration of symptoms before admission [h] (mean ± SD)	
	Probiotics	Control	Probiotics	Control	Probiotics	Control	Probiotics	Control	Probiotics	Control	Probiotics	Control	Probiotics	Control
Besselink 2008	152	144	60·4 ±16·5	59.0 ±15.5	91/61	83/61	27 (18)	28 (19)	268 ±127	270 ±122	3.3 ±1.7	3.4 ±1.6	18 ±18	18 ±18
Olah 2002	22	23	44.1 ±11.1	46.5 ±13.6	16/6	17/6	13 (59)	16 (69.5%)	NR	NR	NR	NR	26.1 ±13.3	21.4 ±14.1
Olah 2007	33	29	48 ±14.75	48.25 ±15.25	NR	NR	20 (60.6)	16 (55.17)	216.7 ±98.6	191.2 ±115.0	2.9 ±1.2	3.1 ±1.5	NR	NR
Plaudis 2012	30	32	NR	NR	11/19	12/20	NR	NR	152.57 ±80.86	108.59 ±86		NR	NR	NR
Qin 2007	36	38	54.3 ±13.1	58.4 ±19.1	11/25	12/26	1 (2.6)	2 (5.55)	125 ±17	136 ±21	NR	NR	26.4 ±24.3	24.1 ±20
Sharma 2011	24	26	41 ±20.72	40.19 ±17.43	12/12	11/15	NR	NR	NR	NR	NR	NR	68.62 ±41.58	49.84 ±27.92
Wang 2013	62	60	42.6 ± 13.8	41.7 ±11.4	32/30	34/26	12 (19.35)	13 (21.66)	NR	NR	NR	NR	NR	NR

NR – not reported, CRP – C-reactive protein.

a detailed summary of the baseline characteristics of the included studies and participants, the number of patients drinking alcohols, the mean duration of symptoms before admission (hours) (mean ± SD), and the APACHE II score (mean ± SD).

Results of risk of bias assessment

The result of the risk of bias assessment yielded an overall moderate risk of bias, according to Cochrane's tool [24]. Regarding randomization, the majority of included studies reported randomization, so they were considered to be at low risk of bias [14, 26–28, 30, 31] except for the report from Plaudis *et al.* [29], which did not report sufficient data about randomization, Therefore, it was considered as unclear risk of bias. Concerning selection bias, Besselink *et al.* [26] reported adequate allocation concealment, while all the other included studies did not show adequate concealment [14, 27–31], so they were categorized as "unclear risk". Participants and personnel were blinded in most of the included studies; therefore, they were considered as low risk of bias [14, 26–28, 30, 31] except for the study by Plaudis *et al.* [29], which did not report sufficient detail about blinding of participants and personnel, so it was categorized as "unclear risk". Three studies reported adequate blinding of outcome assessment [26–28] and were thus categorised as low risk of bias, while the other 4 studies [14, 29–31] included insufficient data about the blinding of outcome assessment, so they were categorized as "unclear risk". The remaining domains are illustrated in detail in Figure 2.

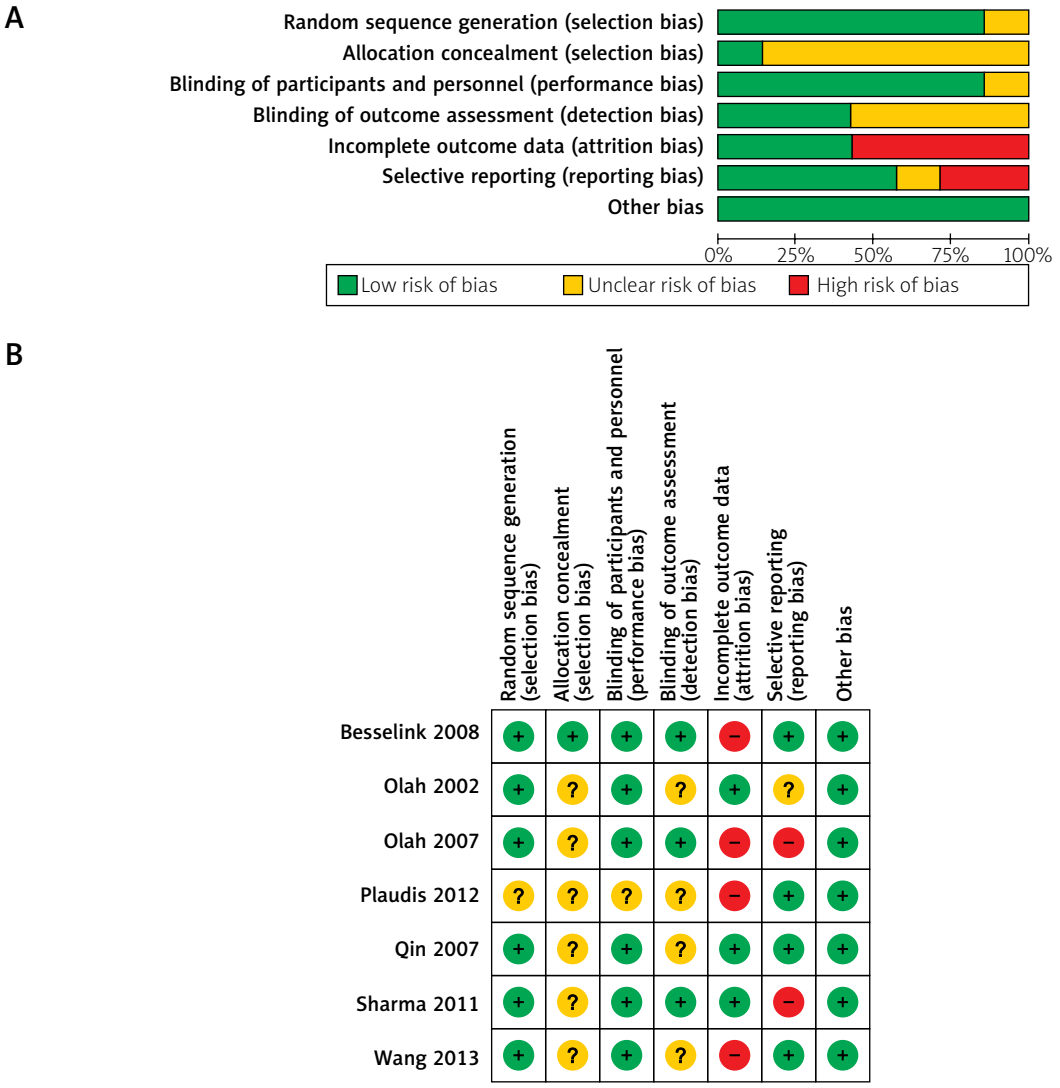
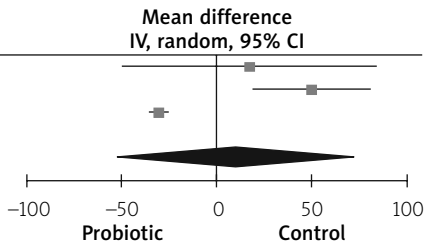


Figure 2. A, B – the risk of bias assessment graph

A

Study or subgroup	Probiotic Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Olah 2002	206.5	119.5	22	188.7	108.3	23	26.6	17.80 [–48.93, 84.53]
Plaudis 2012	291.28	64	30	241.02	60	32	35.1	50.26 [19.33, 81.19]
Qin 2007	84	9	36	114	12	38	38.3	–30.00 [–34.82, –25.18]
Total (95% CI)			**88**			**93**	**100.0**	**10.88 [–51.43. 73.18]**

Heterogeneity: $\tau^2 = 2633.18$; $\chi^2 = 27.06$, $df = 2$ ($p < 0.00001$); $I^2 = 93\%$
Test for overall effect: $Z = 0.34$ ($p = 0.73$)



B

Study or subgroup	Probiotic Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Olah 2002	206.5	119.5	22	188.7	108.3	23	17.7	17.80 [–48.93, 84.53]
Plaudis 2012	291.28	64	30	241.02	60	32	82.3	50.26 [19.33, 81.19]
Qin 2007	84	9	36	114	12	38	0.0	–30.00 [–34.82, –25.18]
Total (95% CI)			**52**			**55**	**100.0**	**44.52 [16.46, 72.58]**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.75$, $df = 1$ ($p = 0.39$); $I^2 = 0\%$
Test for overall effect: $Z = 3.11$ ($p = 0.002$)

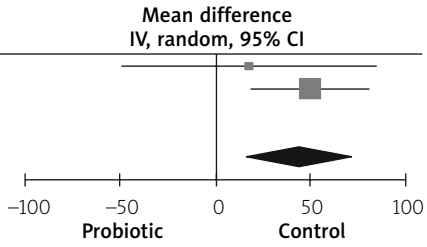


Figure 3. A, **B** – a forest plot for the analysis of C-reactive protein outcome

Analysis of outcomes

CRP (mg/l)

Three studies reported CRP [14, 27, 29]. The overall mean difference showed no significant difference between both groups (MD = 10.88 (–51.43, 73.18), $p = 0.73$). The data were heterogeneous ($p < 0.01$, $I^2 = 93\%$), as shown in Figure 3 A. To solve heterogeneity we excluded the study by Qin *et al.* 2007 [30] ($p = 0.39$, $I^2 = 0\%$). The pooled analysis after solving heterogeneity showed that CRP was significantly decreased in the control group (MD = 44.52 (16.46, 72.58), $p = 0.002$), as shown in Figure 3 B.

APACHE II score

Three studies reported APACHE II score outcomes [27, 30, 31]. The overall mean difference did not show any significant difference between both groups (MD = –2.44 (–7.67, 2.78), $p = 0.36$). Pooled analysis were heterogeneous ($p < 0.01$, $I^2 = 99\%$), as shown in Figure 4. We could not solve heterogeneity by excluding one study or by subgroup analysis.

Hospital stay (days)

Duration of hospital stay was reported by 3 studies [26–28]. The combined mean difference showed no variation between both groups (MD = 2.81 (–2.31,

Study or subgroup	Probiotic Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI
Olah 2007	11.7	1.9	33	10.4	1.5	29	33.2	1.30 [0.45, 2.15]
Qin 2007	3.2	1.7	36	4.5	1.3	38	33.3	–1.30 [–1.99, –0.61]
Wang 2013	6.1	0.7	62	13.4	2	60	33.4	–7.30 [–7.84, –6.76]
Total (95% CI)			**131**			**127**	**100.0**	**–2.44 [–7.67, 2.78]**

Heterogeneity: $\tau^2 = 21.19$; $\chi^2 = 353.48$, $df = 2$ ($p < 0.00001$]; $I^2 = 99\%$
Test for overall effect: $Z = 0.92$ ($p = 0.36$)

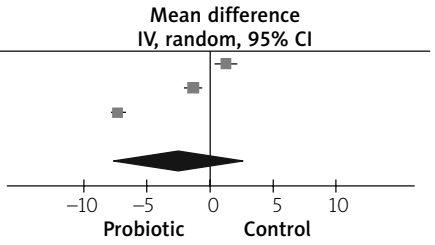


Figure 4. A forest plot for the analysis of APACHE II score outcome

Study or subgroup	Probiotic Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, fixed, 95% CI
Besselink 2008	28.9	41.5	152	23.5	25.9	144	42.6	5.40 [–2.44, 13.24]
Olah 2007	14.9	30	33	19.7	17	29	18.3	–4.80 [–16.76, 7.16]
Sharma 2011	13.3	18.19	24	9.69	9.69	26	39.1	3.54 [–4.64, 11.72]
Total (95% CI)			**209**			**199**	**100.0**	**2.81 [–2.31, 7.92]**

Heterogeneity: $\chi^2 = 2.01$, $df = 2$ ($p = 0.37$); $I^2 = 0\%$
Test overall effect: $Z = 1.08$ ($p = 0.28$)

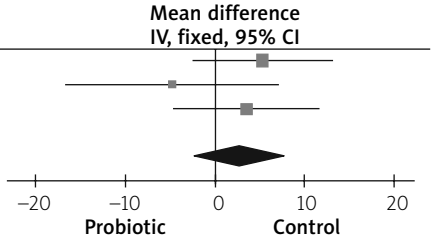


Figure 5. A forest plot for the analysis of Hospital stay (days) outcome

7.92), $p = 0.28$). The analysis was homogeneous ($p = 0.37$, $I^2 = 0\%$), as shown in Figure 5.

Death

Mortality outcomes were reported by 5 studies [14, 26–28, 31]. No significant difference was observed between both groups (RR = 0.66 (0.19, 2.26), $p = 0.51$). Data were heterogeneous ($p = 0.02$, $I^2 = 67\%$), as shown in Figure 6 A. We solved heterogeneity by excluding the study by Besselink *et al.* 2008 [26] ($p = 0.50$, $I^2 = 0\%$). The pooled analysis after solving the heterogeneity favoured the probiotic group (RR = 0.38 (0.15, 0.98), $p = 0.04$), as shown in Figure 6 B.

Multiorgan failure (MOF)

MOF was reported by 6 studies [14, 26, 27, 29–31]. The overall risk ratio did not show any difference between both groups (RR = 0.60 (0.25, 1.44), $p = 0.26$). Analysis was heterogeneous ($p = 0.07$, $I^2 = 76\%$), as shown in Figure 7 A. We solved heterogeneity by excluding the study by Besselink *et al.* 2008 [26] ($p = 0.51$, $I^2 = 0\%$). The overall analysis after solving heterogeneity favoured the probiotics group (RR = 0.41 (0.25, 0.67), $p = 0.04$), as shown in Figure 7 B.

SIRS

Three studies reported SIRS outcomes [14, 27, 30]. The overall risk ratio showed no significant variation between both groups (RR = 0.81 (0.29, 2.23), $p = 0.68$). Pooled analysis was heterogeneous ($p = 0.04$, $I^2 = 70\%$), as shown in Figure 8 A. Heterogeneity was solved by excluding the study by Olah *et al.* 2002 ($p = 0.85$, $I^2 = 0\%$). The pooled analysis after solving heterogeneity showed that use of probiotics decreases SIRS significantly (RR = 0.47 (0.23, 0.96), $p = 0.04$), as shown in Figure 8 B.

Infected pancreatic necrosis

Four studies reported infection pancreatic necrosis outcomes [14, 26, 27, 31]. The combined risk ratio showed no statistically significant difference between both groups (RR = 0.50 (0.18, 1.38), $p = 0.18$). Data were heterogeneous ($p = 0.01$, $I^2 = 73\%$), as shown in Figure 9 A. Heterogeneity was solved by exclusion of one study [26] ($p = 0.98$, $I^2 = 0\%$). The pooled analysis after exclusion favoured the probiotics group over the control group (RR = 0.31 (0.17, 0.58), $p = 0.02$), as shown in Figure 9 B.

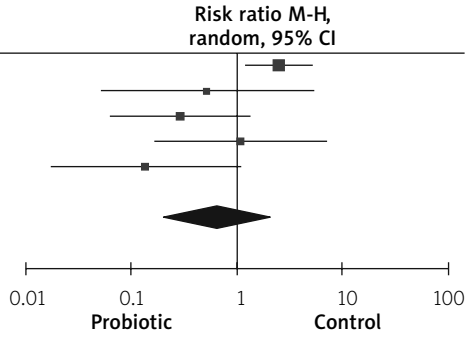
Septicaemia

Five studies reported septicaemia outcomes [14, 26, 28–30]. The analysis did not show any significant variation between both groups (RR = 0.66 (0.29, 1.50), $p = 0.32$). Data were heterogeneous ($p = 0.08$, $I^2 = 51\%$), as shown in Figure 10 A. To solve heterogeneity, we excluded one study [26] ($p = 0.72$, $I^2 = 0\%$). Pooled analysis after solving heterogeneity favoured the probiotics

A

Study or subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight (%)	Risk ratio M-H, random, 95% CI
Besselink 2008	24	152	9	144	28.7	2.53 [1.22, 5.25]
Olah 2002	1	22	2	23	14.9	0.52 [0.05, 5.36]
Olah 2007	2	33	6	29	21.4	0.29 [0.06, 1.34]
Sharma 2011	2	24	2	26	18.3	1.08 [0.17, 7.10]
Wang 2013	1	62	7	60	16.8	0.14 [0.02, 1.09]
Total (95% CI)		**293**		**282**	**100.0**	**0.66 [0.19, 2.26]**
Total events	30		26			

Heterogeneity: $\tau^2 = 1.23$; $\chi^2 = 12.14$, $df = 4$ ($p = 0.02$); $I^2 = 67\%$
Test for overall effect: $Z = 0.66$ ($p = 0.51$)



B

Study or subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight (%)	Risk ratio M-H, random, 95% CI
Besselink 2008	24	152	9	144	0.0	2.53 [1.22, 5.25]
Olah 2002	1	22	2	23	16.3	0.52 [0.05, 5.36]
Olah 2007	2	33	6	29	38.1	0.29 [0.06, 1.34]
Sharma 2011	2	24	2	26	24.9	1.08 [0.17, 7.10]
Wang 2013	1	62	7	60	20.7	0.14 [0.02, 1.09]
Total (95% CI)		**141**		**138**	**100.0**	**0.38 [0.15, 0.98]**
Total events	6		17			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.35$, $df = 3$ ($p = 0.50$); $I^2 = 0\%$
Test for overall effect: $Z = 2.01$ ($p = 0.04$)

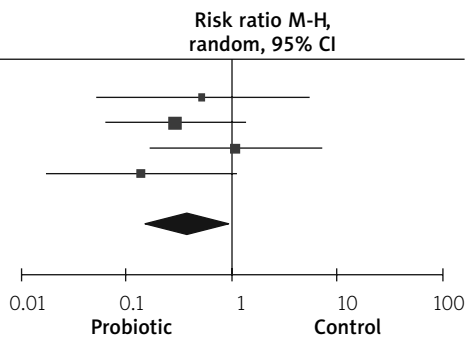
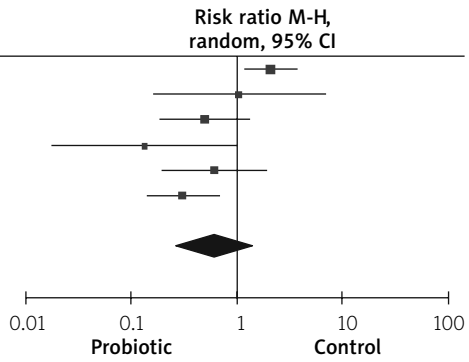


Figure 6. A forest plot for the analysis of death outcome: **A** – before leave-one-out, **B** – after leave-one-out

A

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Besselink 2008	33	152	15	144	22.0	2.08 [1.18, 3.67]
Olah 2002	2	22	2	23	11.5	1.05 [0.16, 6.79]
Olah 2007	5	33	9	29	18.6	0.49 [0.18, 1.29]
Plaudis 2012	1	30	8	32	10.5	0.13 [0.02, 1.00]
Qin 2007	4	36	7	38	17.1	0.60 [0.19, 1.89]
Wang 2013	7	62	22	60	20.3	0.31 [0.14, 0.67]
Total (95% CI)		**335**		**326**	**100.0**	**0.60 [0.25, 1.44]**
Total events	52		63			

Heterogeneity: $\tau^2 = 0.82$; $\chi^2 = 21.19$, $df = 5$ ($p = 0.0007$); $I^2 = 76\%$
Test for overall effect: $Z = 1.14$ ($p = 0.26$)



B

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Besselink 2008	33	152	15	144	0.0	2.08 [1.18, 3.67]
Olah 2002	2	22	2	23	7.1	1.05 [0.16, 6.79]
Olah 2007	5	33	9	29	26.2	0.49 [0.18, 1.29]
Plaudis 2012	1	30	8	32	6.1	0.13 [0.02, 1.00]
Qin 2007	4	36	7	38	19.1	0.60 [0.19, 1.89]
Wang 2013	7	62	22	60	41.5	0.31 [0.14, 0.67]
Total (95% CI)		**183**		**182**	**100.0**	**0.41 [0.25, 0.67]**
Total events	19		48			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.29$, $df = 4$ ($p = 0.51$); $I^2 = 0\%$
Test for overall effect: $Z = 3.51$ ($p = 0.0004$)

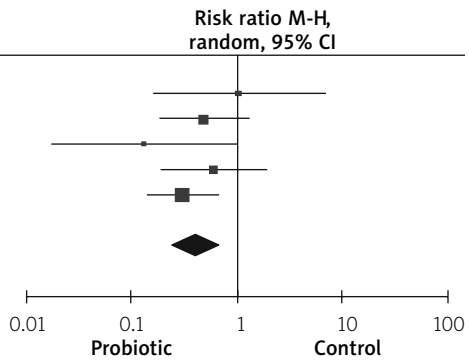
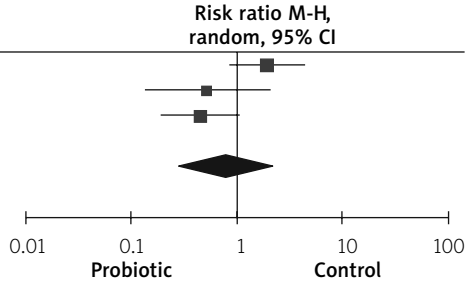


Figure 7. A forest plot for the analysis of multi-organ failure outcome: **A** – before leave-one-out, **B** – after leave-one-out

A

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Olah 2002	11	22	6	23	37.2	1.92 [0.86, 4.29]
Olah 2007	3	33	5	29	26.3	0.53 [0.14, 2.02]
Qin 2007	6	36	14	38	36.5	0.45 [0.20, 1.05]
Total (95% CI)		**91**		**90**	**100.0**	**0.81 [0.29, 2.23]**
Total events	20		25			

Heterogeneity: $\tau^2 = 0.55$; $\chi^2 = 6.63$, $df = 2$ ($p = 0.04$); $I^2 = 70\%$
Test for overall effect: $Z = 0.42$ ($p = 0.68$)



B

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Olah 2002	11	22	6	23	0.0	1.92 [0.86, 4.29]
Olah 2007	3	33	5	29	28.2	0.53 [0.14, 2.02]
Qin 2007	6	36	14	38	71.8	0.45 [0.20, 1.05]
Total (95% CI)		**69**		**67**	**100.0**	**0.47 [0.23, 0.96]**
Total events	9		19			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.04$, $df = 1$ ($p = 0.85$); $I^2 = 0\%$
Test for overall effect: $Z = 2.06$ ($p = 0.04$)

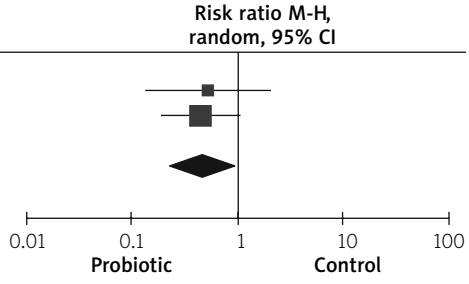
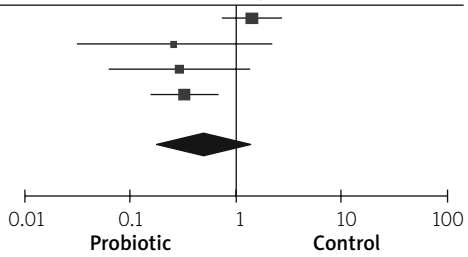


Figure 8. A forest plot for the analysis of severe inflammatory response syndrome outcome: **A** – before leave-one-out, **B** – after leave-one-out

A

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Besselink 2008	21	152	14	144	33.2	1.42 [0.75, 2.69]
Olah 2002	1	22	4	23	14.3	0.26 [0.03, 2.16]
Olah 2007	2	33	6	29	20.5	0.29 [0.06, 1.34]
Wang 2013	8	62	24	60	32.0	0.32 [0.16, 0.66]
Total (95% CI)		**269**		**256**	**100.0**	**0.50 [0.18, 1.38]**
Total events	32		48			

Heterogeneity: $\tau^2 = 0.70$; $\chi^2 = 11.25$, $df = 3$ ($p = 0.01$); $I^2 = 73\%$
Test for overall effect: $Z = 1.34$ ($p = 0.18$)



B

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Besselink 2008	21	152	14	144	0.0	1.42 [0.75, 2.69]
Olah 2002	1	22	4	23	8.6	0.26 [0.03, 2.16]
Olah 2007	2	33	6	29	16.6	0.29 [0.06, 1.34]
Wang 2013	8	62	24	60	74.8	0.32 [0.16, 0.66]
Total (95% CI)		**117**		**112**	**100.0**	**0.31 [0.17, 0.58]**
Total events	11		34			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.04$, $df = 2$ ($p = 0.98$); $I^2 = 0\%$
Test for overall effect: $Z = 3.68$ ($p = 0.0002$)

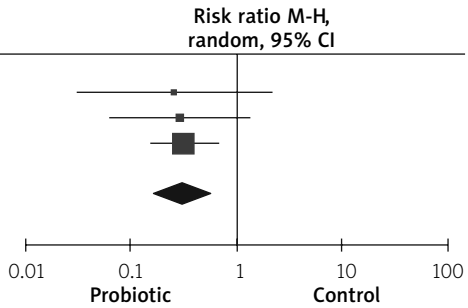
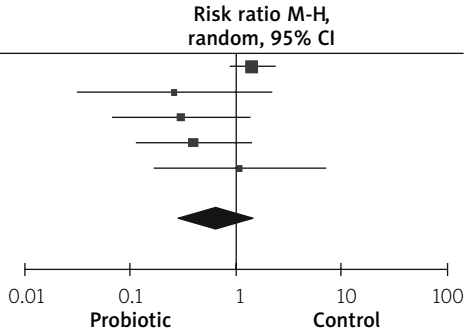


Figure 9. A forest plot for the analysis of infected pancreatic necrosis outcome: **A** – before leave-one-out, **B** – after leave-one-out

A

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Besselink 2008	33	152	22	144	36.6	1.42 [0.87, 2.32]
Olah 2002	1	22	4	23	11.1	0.26 [0.03, 2.16]
Plaudis 2012	2	30	7	32	17.7	0.30 [0.07, 1.35]
Qin 2007	3	36	8	38	21.4	0.40 [0.11, 1.38]
Sharma 2011	2	24	2	26	13.2	1.08 [0.17, 7.10]
Total (95% CI)		**264**		**263**	**100.0**	**0.66 [0.29, 1.50]**
Total events	41		43			

Heterogeneity: $\tau^2 = 0.42$; $\chi^2 = 8.23$, $df = 4$ ($p = 0.08$); $I^2 = 51\%$
Test for overall effect: $Z = 1.00$ ($p = 0.32$)



B

Study or subgroup	Probiotic Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random, 95% CI
Besselink 2008	33	152	22	144	0.0	1.42 [0.87, 2.32]
Olah 2002	1	22	4	23	14.0	0.26 [0.03, 2.16]
Plaudis 2012	2	30	7	32	28.1	0.30 [0.07, 1.35]
Qin 2007	3	36	8	38	40.2	0.40 [0.11, 1.38]
Sharma 2011	2	24	2	26	17.7	1.08 [0.17, 7.10]
Total (95% CI)		**112**		**119**	**100.0**	**0.41 [0.19, 0.91]**
Total events	8		21			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.36$, $df = 3$ ($p = 0.72$); $I^2 = 0\%$
Test for overall effect: $Z = 2.18$ ($p = 0.03$)

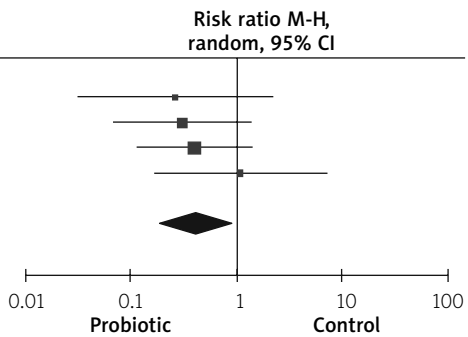


Figure 10. A forest plot for the analysis of septicaemia outcome: **A** – before leave-one-out, **B** – after leave-one-out

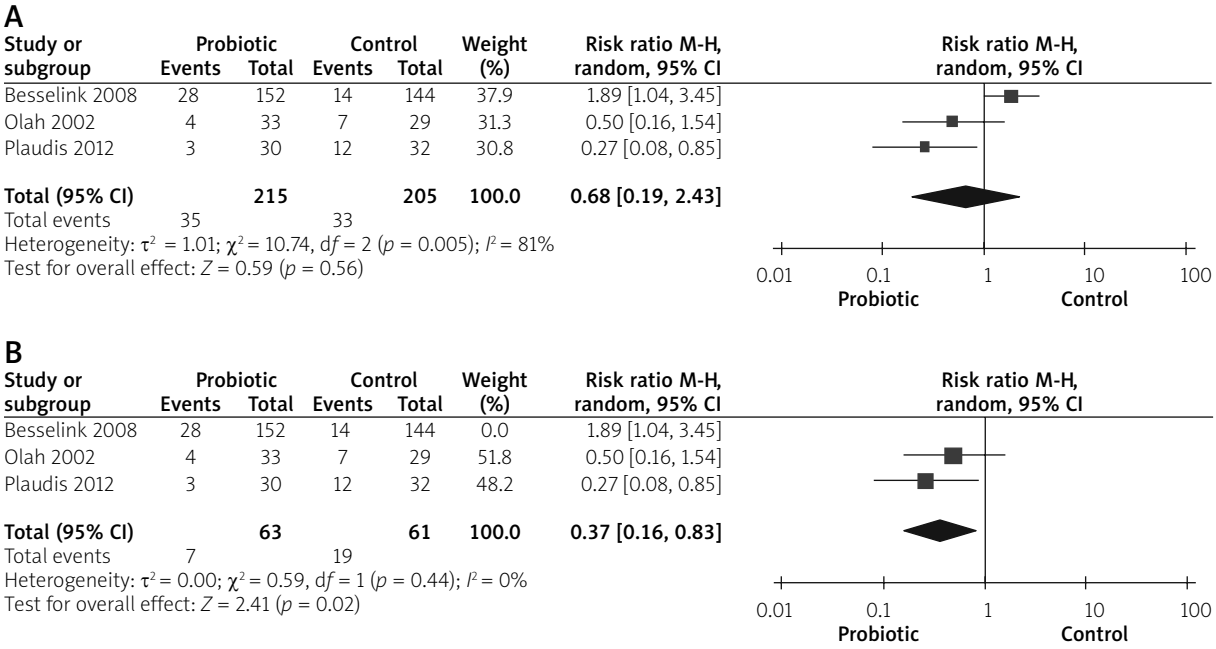


Figure 11. A forest plot for the analysis of need of operations protein outcome: **A** – before leave-one-out, **B** – after leave-one-out

group significantly (RR = 0.41 (0.19, 0.91), $p = 0.03$), as shown in Figure 10 B.

Need for operations

Three studies reported the need for operation outcomes [14, 26, 29]. The overall risk ratio did not show any significant difference between both groups (RR = 0.68 (0.19, 2.43), $p = 0.56$). Pooled analysis was heterogeneous ($p = 0.005$, $I^2 = 81\%$), as shown in Figure 11 A. After solving heterogeneity by excluding study Besselink *et al.* 2008 [26] ($p = 0.44$, $I^2 = 0\%$), the analysis favoured the probiotics group significantly (RR = 0.37 (0.16, 0.83), $p = 0.02$), as shown in Figure 11 B.

Discussion

In our meta-analysis, we found that there are no beneficial or harmful effects of probiotics over placebo concerning all important outcomes.

The large randomized "PROPATRIA" [26] trial was abandoned because of the harmful effects of probiotics in SAP. Sharma *et al.* [28] also reported that probiotics do not help in maintaining gut integrity or decreasing infectious complications because no change was observed in gut permeability and endotoxaemia. A meta-analysis by Gou *et al.* [32] showed the same results with significant heterogeneity. Conversely, Plaudis *et al.* [29], Qin *et al.* [30], Wang *et al.* [31], Oláh *et al.* [14], and Oláh *et al.* [27] showed that probiotics play a role in maintaining gut integrity and decreasing infectious complications.

As regards mortality, the analysis showed no difference between the probiotics and placebo in reducing the mortality rates with significant heterogeneity. The heterogeneity is attributed to the PROPATRIA trial. The types of probiotics may lead to different clinical outcomes, because different bacteria have variable adherence sites and different immunogenic effects. The probiotics used in the PROPATRIA trial, *L. acidophilus* and *L. casei*, (Ecologic 641; Winclove Bio Industries, Amsterdam, the Netherlands) were different from those used in the other included trials (Synbiotic 2000 Forte).

C-reactive protein reflects the inflammatory response in both groups. Plaudis *et al.* [29], and Oláh *et al.* [14] showed that the plasma CRP levels in the probiotic group demonstrate similar patterns to those in the control group, and probiotics may worsen the condition. However, Qin *et al.* [30] reported a significant reduction in CRP levels in the probiotic group.

Some strains of probiotics have anti-inflammatory effects because they reduce mucosal inflammation and modulate the cytokine levels [33]. They increase the glutathione (GSH) levels, which in turn scavenges superoxide and hydroxyl radicals, and decreases the interleukin-6 (IL-6) in adipocytes [34].

The APACHE II score is a multi-factorial scoring system that reflects the severity of different diseases. It is applied within 24 h of patient admission to the ICU [35]. Three trials: Qin *et al.* [30], Wang *et al.* [31], and Oláh *et al.* [27] demonstrated significant advantages of

probiotics treatment in severe acute pancreatitis with a large reduction in infectious complications.

Regarding the hospital stay, Besselink *et al*. [26] and Sharma *et al*. [28] showed that there was no difference in the duration of hospital stay in the placebo and probiotic groups. However, Oláh *et al*. [27] reported a significant reduction in hospital stay.

Our meta-analysis estimates the effects of probiotics in patients with SAP. We only included randomized clinical trials, which ensures the highest evidence according to GRADE. All the included studies were at low risk of bias in general, which is another strength, and we conducted the analysis on a large sample size (711 patients). We solved the heterogeneity among studies using appropriate methodologies reported by Cochrane's handbook [24].

The main limitation of our meta-analysis is the heterogeneity in some outcomes. However, we managed to elicit the attributing factors and overcome this inconsistency among the studies.

Conclusions

Probiotics have no beneficial effects in the management of AP because they do not affect mortality and hospital stay. Also, there is no decrease in infectious complications with the use of probiotics.

Conflict of interest

The authors declare no conflict of interest.

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