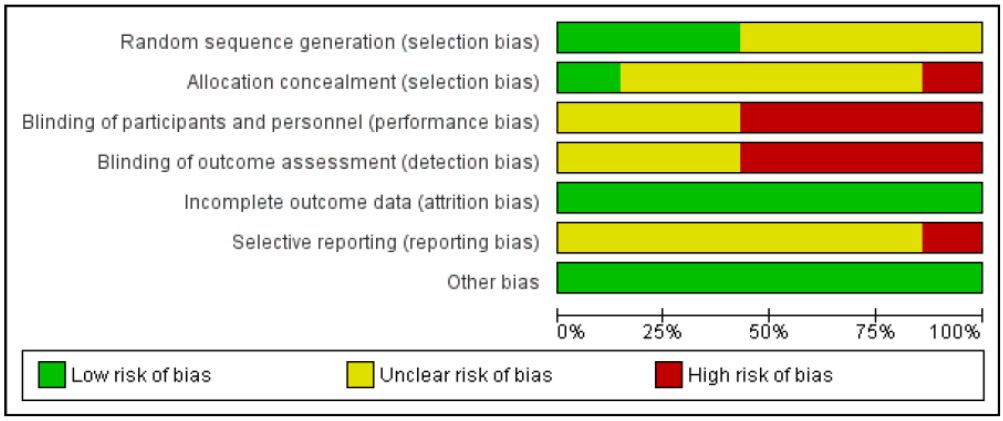
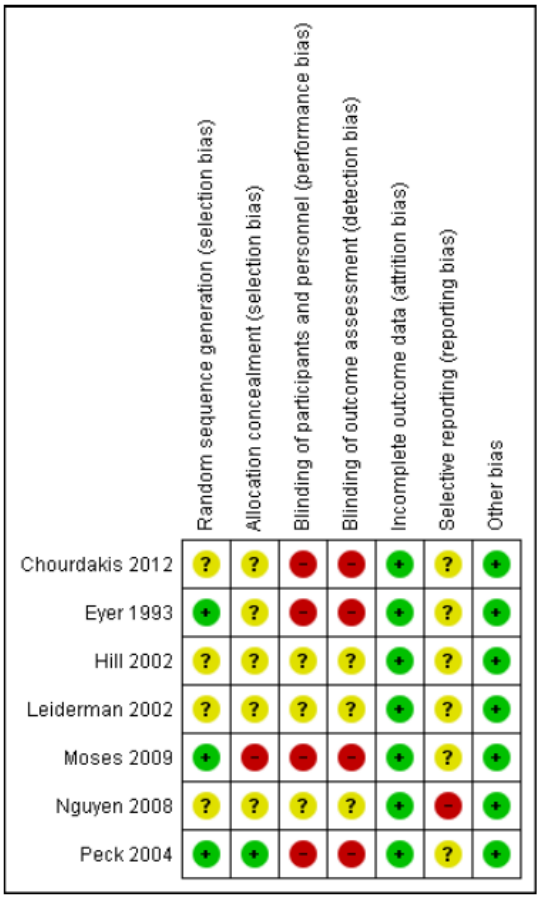
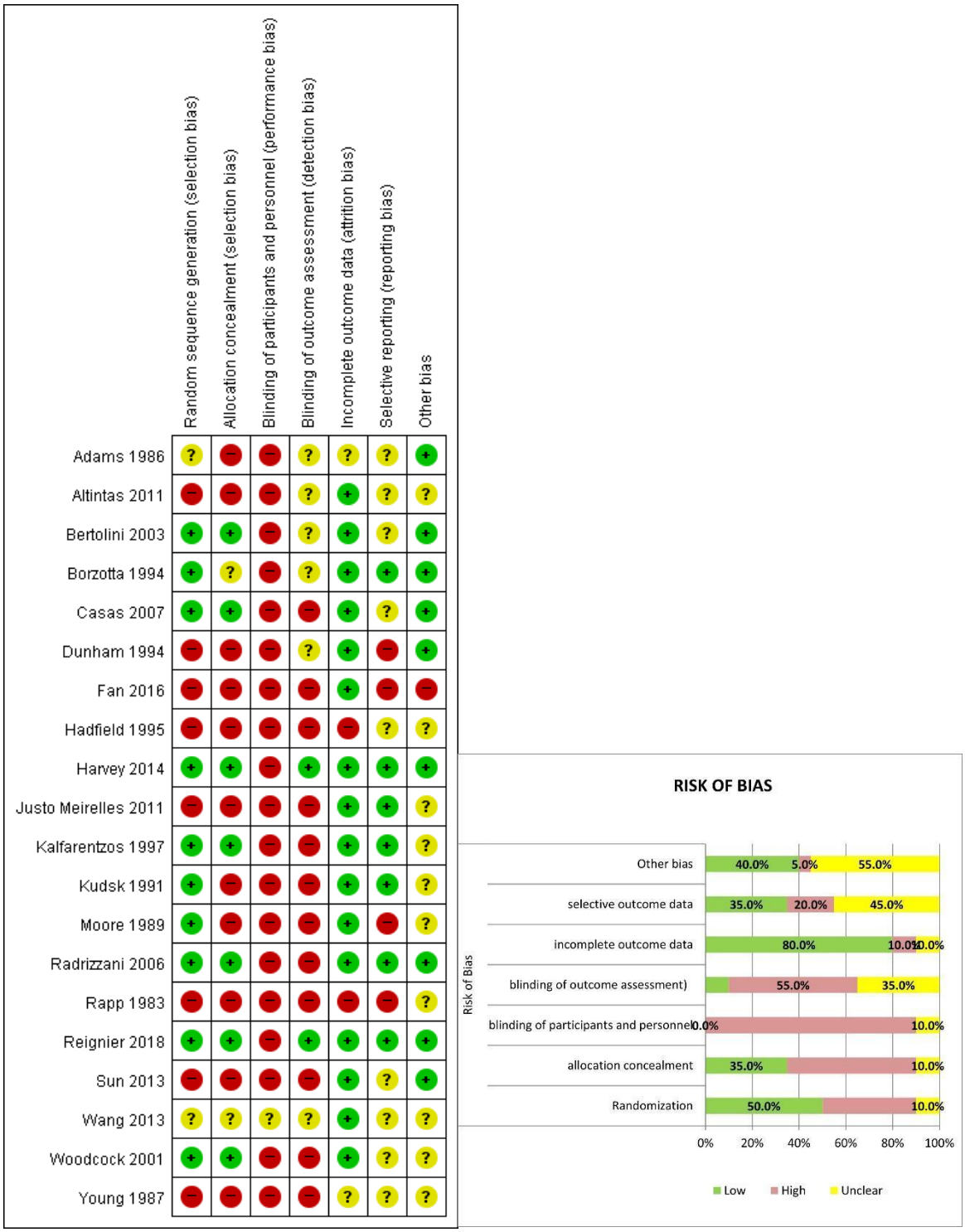
Supplement Fig. 1. Question 1 risk of bias.





Supplement Fig. 2. Question 2 risk of bias.



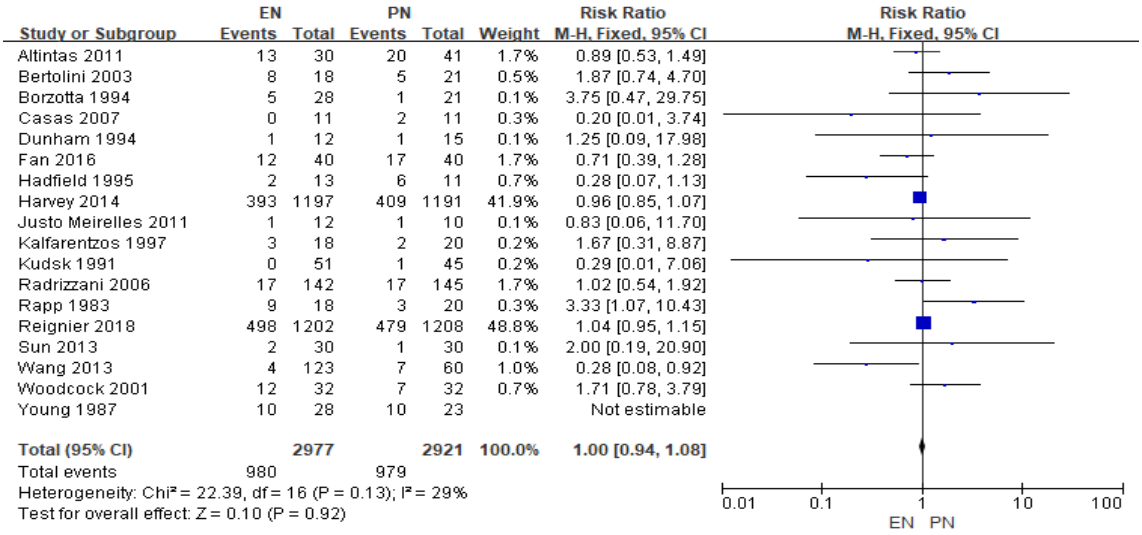
Supplement Fig. 3. Question 2 summary of evidence.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EN	PN	Relative (95% CI)	Absolute (95% CI)		
Mortality												
18	randomised trials	not serious	not serious	not serious	serious	none	980/2977 (32.9%)	979/2921 (33.5%)	**RR 1.00** (0.94 to 1.08)	**0 fewer per 1,000** (from 20 fewer to 27 more)	⨁⨁⨁◯ Moderate	CRITICAL
ICU LOS												
6	randomised trials	not serious	not serious	not serious	not serious	none	2510	2523	-	MD **0.88 lower** (1.32 lower to 0.45 lower)	⨁⨁⨁⨁ High	IMPORTANT
Infection rate												
12	randomised trials	not serious	not serious	not serious	not serious	none	473/2877 (16.4%)	552/2823 (19.6%)	**RR 0.61** (0.47 to 0.79)	**76 fewer per 1,000** (from 104 fewer to 41 fewer)	⨁⨁⨁⨁ High	IMPORTANT
MV day												
6	randomised trials	not serious	not serious	not serious	not serious	none	1364	1377	-	MD **1.36 lower** (2.08 lower to 0.64 lower)	⨁⨁⨁⨁ High	IMPORTANT
Blood stream infection												
9	randomised trials	not serious	not serious	not serious	not serious	none	115/2729 (4.2%)	153/2733 (5.6%)	**RR 0.77** (0.59 to 1.02)	**13 fewer per 1,000** (from 23 fewer to 1 more)	⨁⨁⨁⨁ High	CRITICAL
Pneumonia												
10	randomised trials	not serious	not serious	not serious	serious	none	308/2742 (11.2%)	331/2737 (12.1%)	**RR 0.90** (0.71 to 1.15)	**12 fewer per 1,000** (from 35 fewer to 18 more)	⨁⨁⨁◯ Moderate	CRITICAL
GI complications												
8	randomised trials	not serious	not serious	not serious	not serious	none	1137/2566 (44.3%)	789/2567 (30.7%)	**RR 1.56** (1.15 to 2.12)	**172 more per 1,000** (from 46 more to 344 more)	⨁⨁⨁⨁ High	IMPORTANT

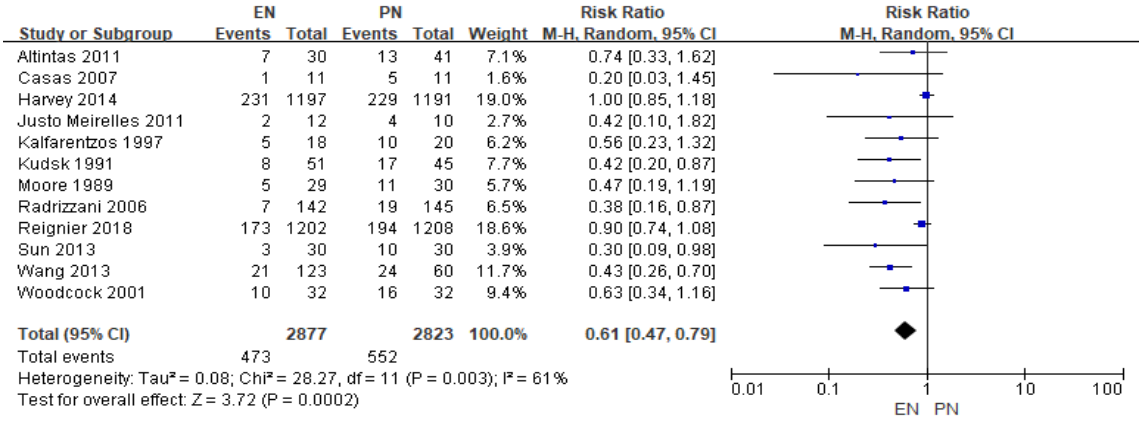
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Supplement Fig. 4. Question 2 forest plot for the clinical outcomes.

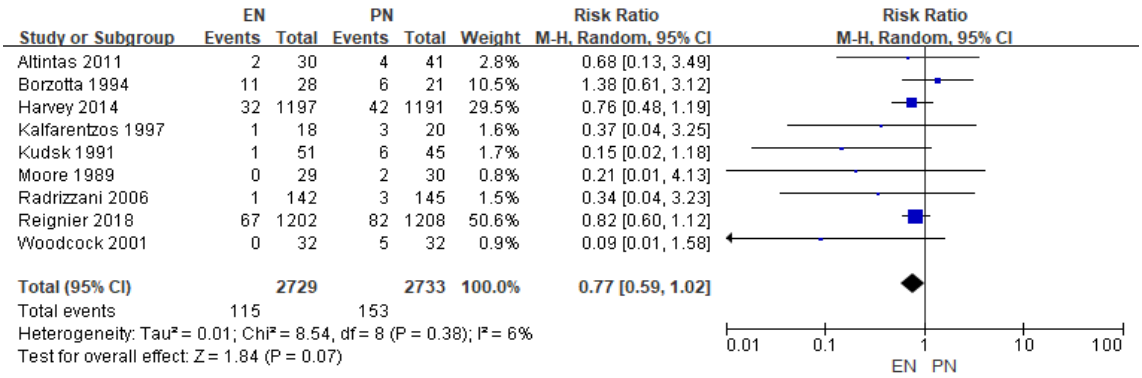
A. Mortality



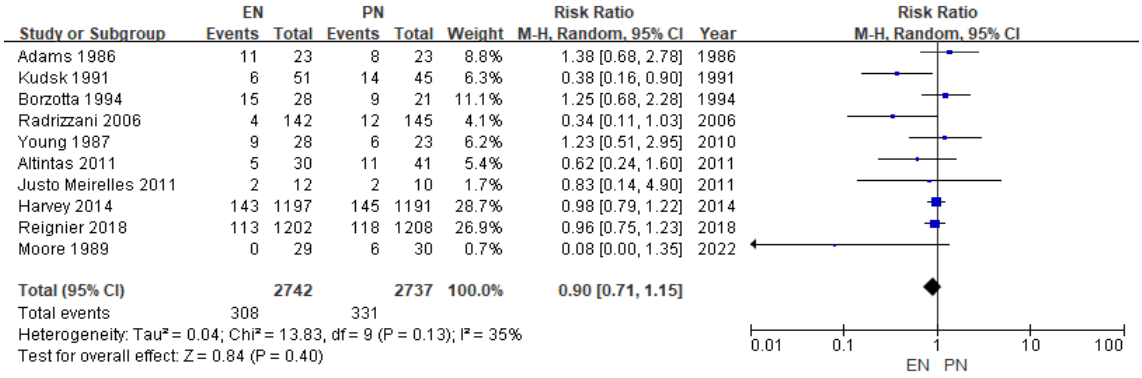
B. Infectious complications



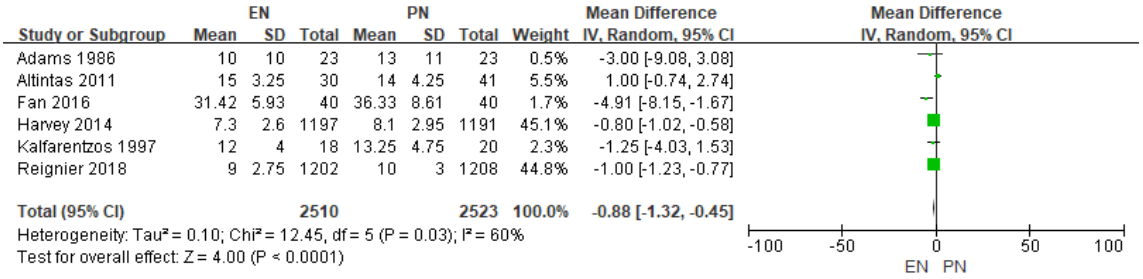
C. Blood stream infection



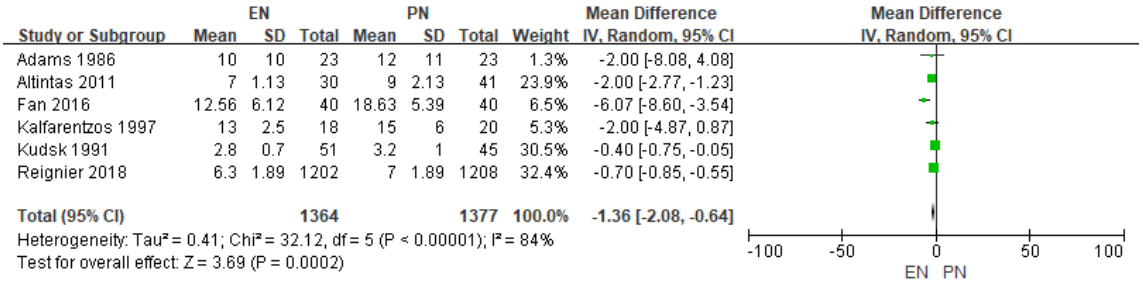
D. Pneumonia



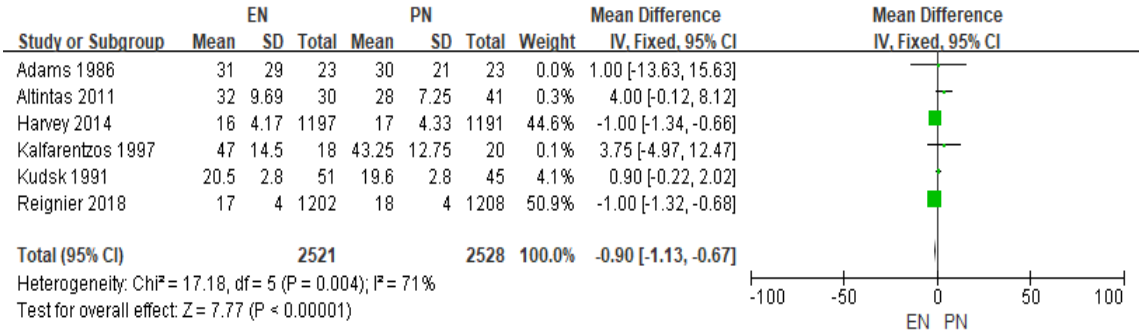
E. Length of stay in the ICU



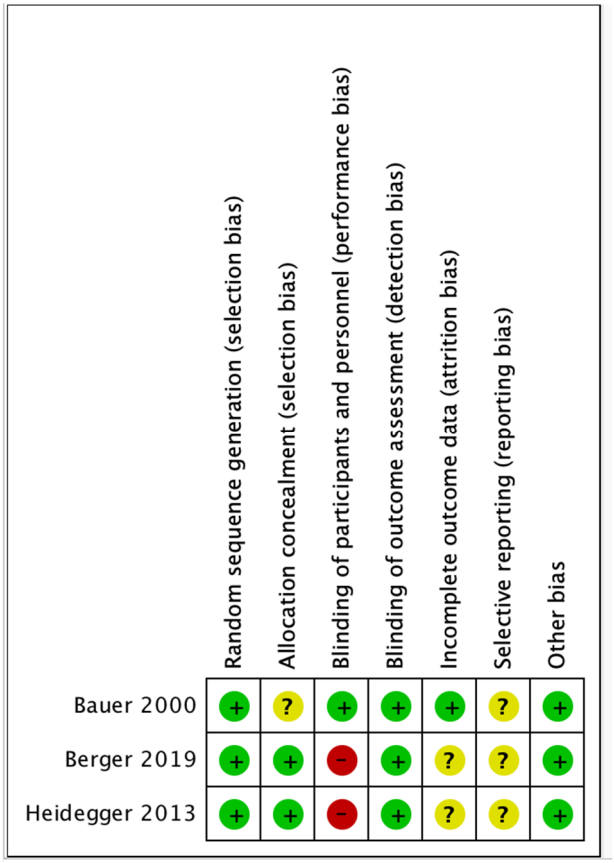
F. Days for the mechanical ventilation

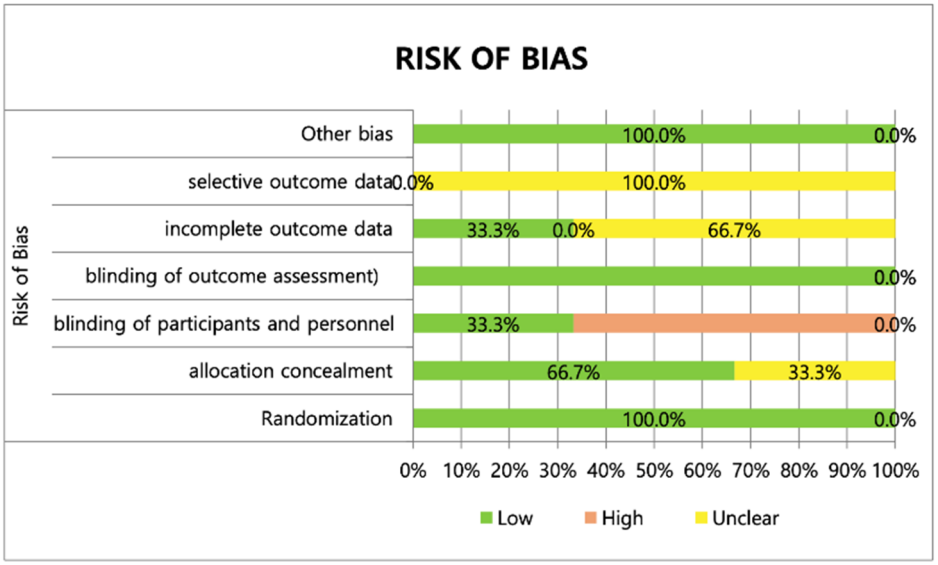


G. Length of stay at Hospital



Supplement Fig. 5. Question 3 risk of bias.





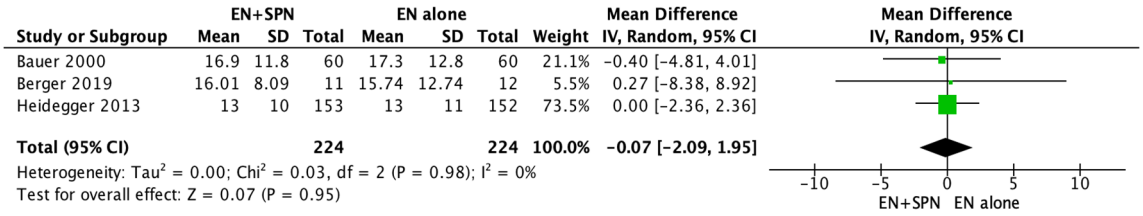
Supplement Fig. 6. Question 3 summary of evidence.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EN+SPN	EN alone	Relative (95% CI)	Absolute (95% CI)		
ICU mortality												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	8/153 (5.2%)	12/152 (7.9%)	**RR 0.66** (0.28 to 1.57)	**27 fewer per 1,000** (from 57 fewer to 45 more)	⨁⨁⨁◯ Moderate	CRITICAL
30-day mortality												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	20/153 (13.1%)	28/152 (18.4%)	**RR 0.71** (0.42 to 1.20)	**53 fewer per 1,000** (from 107 fewer to 37 more)	⨁⨁⨁◯ Moderate	CRITICAL
in-hospital mortlaity												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	0/11 (0.0%)	1/12 (8.3%)	**RR 0.36** (0.02 to 8.04)	**53 fewer per 1,000** (from 82 fewer to 587 more)	⨁⨁◯◯ Low	CRITICAL
90-day mortality												
1	randomised trials	not serious	not serious	not serious	serious[c]	none	17/60 (28.3%)	18/60 (30.0%)	**RR 0.94** (0.54 to 1.65)	**18 fewer per 1,000** (from 138 fewer to 195 more)	⨁⨁⨁◯ Moderate	CRITICAL
ICU LOS												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	224	224	-	MD **0.07 lower** (2.09 lower to 1.95 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Hospital LOS												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	224	224	-	MD **1.42 lower** (5.7 lower to 2.87 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
MV duration												
3	randomised trials	not serious	serious[d]	not serious	serious[a]	none	224	224	-	MD **0.1 lower** (1.03 lower to 0.84 higher)	⨁⨁◯◯ Low	IMPORTANT
UTI												
2	randomised trials	serious[e]	serious[f]	not serious	serious[g]	none	15/213 (7.0%)	18/212 (8.5%)	**RR 0.83** (0.45 to 1.55)	**14 fewer per 1,000** (from 47 fewer to 47 more)	⨁◯◯◯ Very low	IMPORTANT
Pneumonia or respiratory infection												
2	randomised trials	not serious	not serious	not serious	serious[h]	none	63/213 (29.6%)	51/212 (24.1%)	**RR 1.23** (0.90 to 1.68)	**55 more per 1,000** (from 24 fewer to 164 more)	⨁⨁⨁◯ Moderate	IMPORTANT

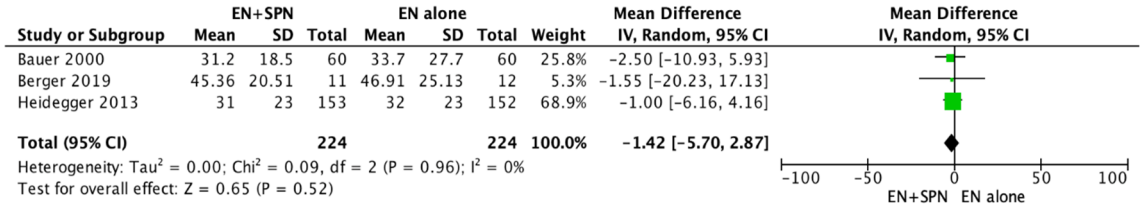
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Supplement Fig. 7. Question 3 forest plot for the clinical outcomes.

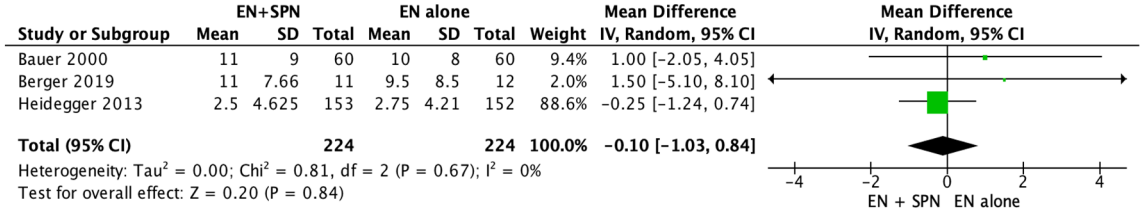
A. Length of stay in the ICU



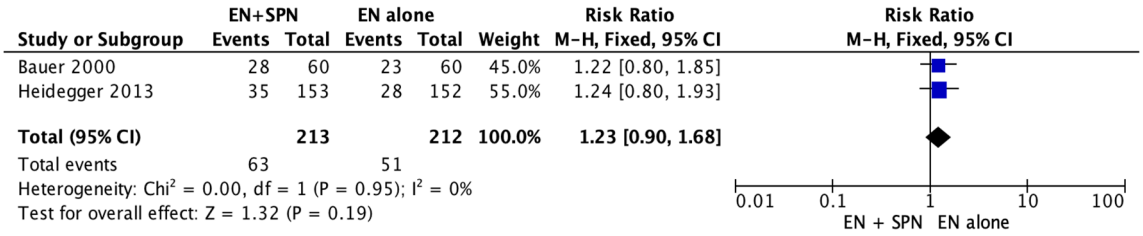
B. Length of stay at hospital



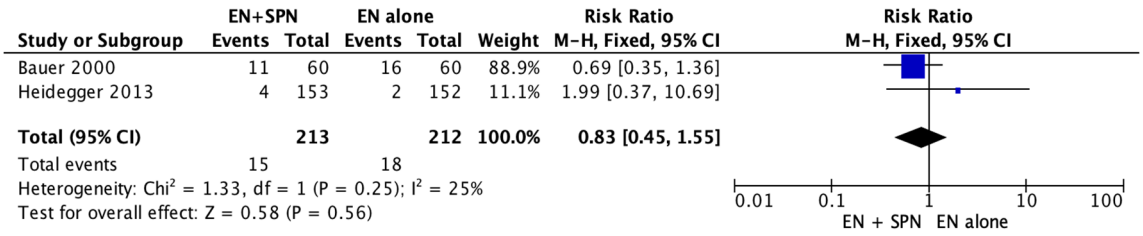
C. Days for mechanical ventilation



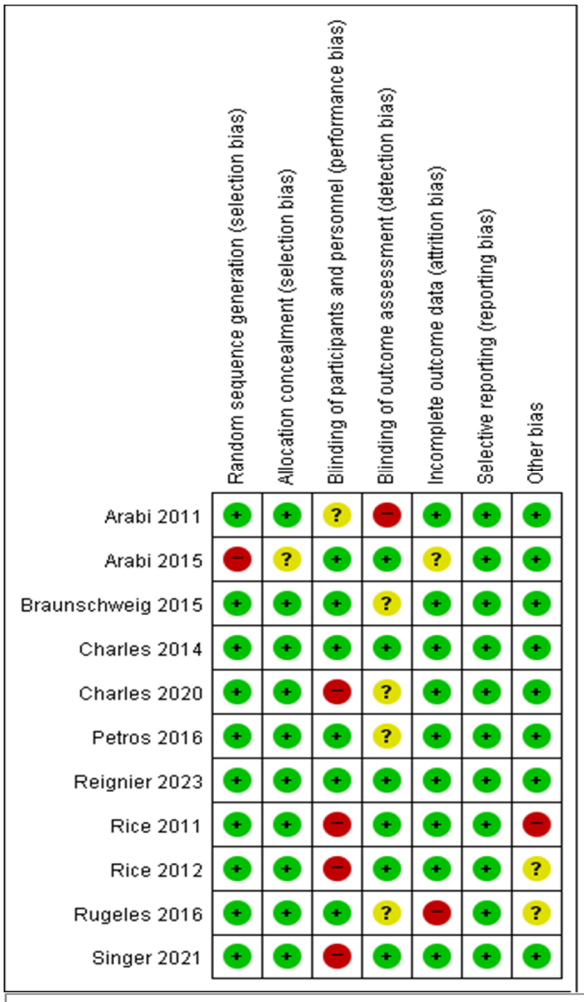
D. Pneumonia (respiratory infections)

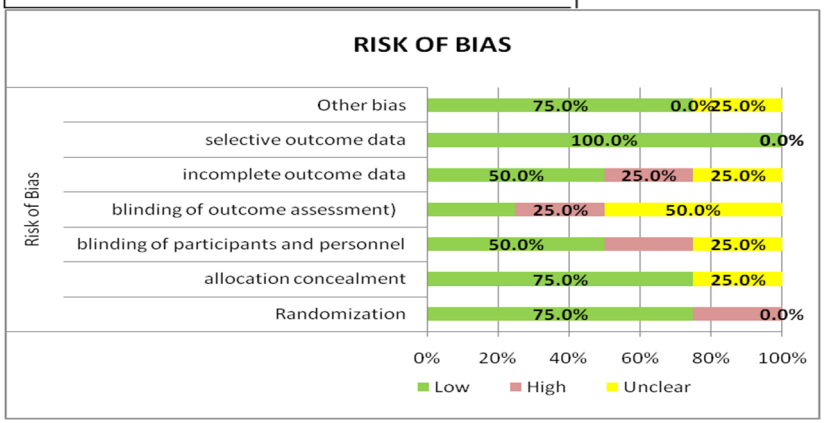


E. Urinary tract infections



Supplement Fig. 8. Question 4 risk of bias.





Supplement Fig. 9. Question 4 summary of evidence.

Author(s):
Question: Hypocaloric compared to Normocaloric for ICU
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypocaloric	Normocaloric	Relative (95% CI)	Absolute (95% CI)		
Motality												
11	randomised trials	serious[a]	not serious	not serious	not serious	none	811/3069 (26.4%)	856/3067 (27.9%) 0.0%	**RR 0.95** (0.87 to 1.03)	**14 fewer per 1,000** (from 36 fewer to 8 more) **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Mechanical ventilation day												
6	randomised trials	not serious	not serious	not serious	not serious	none	912	915	-	MD **0.76 higher** (1.47 lower to 0.05 lower)	⨁⨁⨁⨁ High	IMPORTANT
Diarrhea event												
4	randomised trials	not serious	not serious	not serious	not serious	none	623/2523 (24.7%)	717/2507 (28.6%) 0.0%	**RR 0.86** (0.79 to 0.95)	**40 fewer per 1,000** (from 60 fewer to 14 fewer) **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ High	IMPORTANT
ICU Length of stay												
6	randomised trials	serious[a]	not serious	not serious	not serious	none	836	844	-	MD **1.99 higher** (2.51 lower to 1.48 lower)	⨁⨁⨁◯ Moderate	IMPORTANT
Hospital Length of stay												
6	randomised trials	not serious	not serious	not serious	not serious	none	836	844	-	MD **1.4 higher** (0.33 higher to 2.46 higher)	⨁⨁⨁⨁ High	IMPORTANT
Infection (total)												
9	randomised trials	not serious	not serious	not serious	not serious	none	586/2988 (19.6%)	701/2968 (23.6%)	**OR 0.77** (0.51 to 1.16)	**44 fewer per 1,000** (from 100 fewer to 28 more)	⨁⨁⨁⨁ High	NOT IMPORTANT
Hypoglycemia												
5	randomised trials	not serious	not serious	serious	not serious	none	145/2173 (6.7%)	122/2177 (5.6%) 0.0%	**RR 1.20** (0.96 to 1.51)	**11 more per 1,000** (from 2 fewer to 29 more) **0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	NOT IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

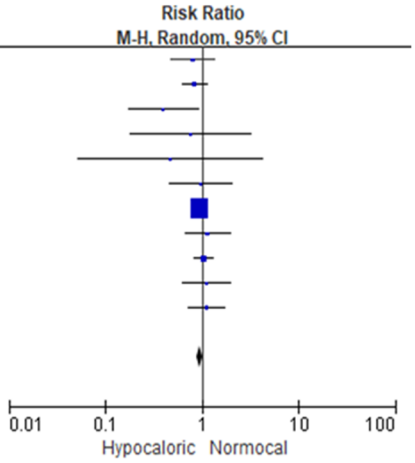
a. Motality : Arabi2011, detection bias// Arabi 2015 selection bias

Supplement Fig. 10. Question 4 forest plots for clinical outcomes.

A. Mortality

Study or Subgroup	Hypocaloric Events	Total	Normocaloric Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arabi 2011	21	120	26	120	2.4%	0.81 [0.48, 1.35]
Arabi 2015	72	448	85	446	8.0%	0.84 [0.63, 1.12]
Braunschweig 2015	6	38	16	40	1.0%	0.39 [0.17, 0.90]
Charles 2014	3	41	4	42	0.3%	0.77 [0.18, 3.22]
Charles 2020	1	22	3	31	0.1%	0.47 [0.05, 4.22]
Petros 2016	10	46	12	54	1.2%	0.98 [0.47, 2.05]
Reignier 2023	504	1521	533	1515	66.7%	0.94 [0.85, 1.04]
Rice 2011	22	98	20	102	2.2%	1.14 [0.67, 1.96]
Rice 2012	118	508	109	492	12.4%	1.05 [0.83, 1.32]
Rugeles 2016	18	60	16	60	2.0%	1.13 [0.64, 1.99]
Singer 2021	36	167	32	165	3.6%	1.11 [0.73, 1.70]
Total (95% CI)		**3069**		**3067**	**100.0%**	**0.95 [0.87, 1.03]**
Total events	811		856			

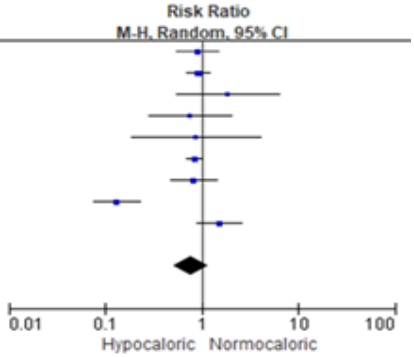
Heterogeneity: Tau² = 0.00; Chi² = 7.93, df = 10 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)



B. Infections

Study or Subgroup	Hypocaloric Events	Total	Normocaloric Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arabi 2011	53	120	56	120	12.8%	0.90 [0.54, 1.50]
Arabi 2015	161	448	169	446	14.9%	0.92 [0.70, 1.21]
Braunschweig 2015	8	38	5	40	6.6%	1.87 [0.55, 6.32]
Charles 2020	29	41	32	42	8.3%	0.76 [0.28, 2.01]
Petros 2016	3	46	4	54	4.8%	0.87 [0.18, 4.11]
Reignier 2023	233	1521	265	1515	15.5%	0.85 [0.70, 1.03]
Rice 2011	44	98	51	102	12.3%	0.81 [0.47, 1.42]
Rice 2012	15	508	92	492	12.3%	0.13 [0.08, 0.23]
Singer 2021	40	168	27	157	12.4%	1.50 [0.87, 2.60]
Total (95% CI)		**2988**		**2968**	**100.0%**	**0.77 [0.51, 1.16]**
Total events	586		701			

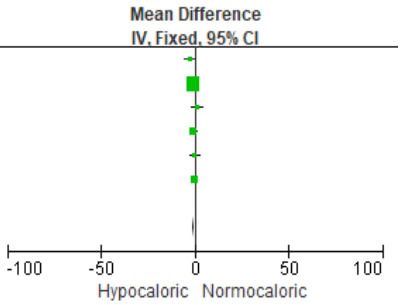
Heterogeneity: Tau² = 0.27; Chi² = 48.65, df = 8 (P < 0.00001); I² = 84%
Test for overall effect: Z = 1.26 (P = 0.21)



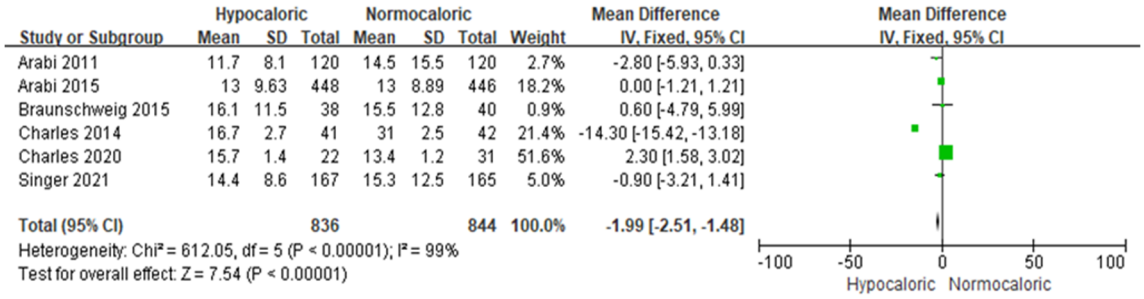
C. Days for mechanical ventilation

Study or Subgroup	Hypocaloric Mean	SD	Total	Normocaloric Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Arabi 2011	10.6	7.6	120	13.2	15.2	120	5.5%	-2.60 [-5.64, 0.44]
Arabi 2015	9	7.41	448	10	8.15	446	48.4%	-1.00 [-2.02, 0.02]
Braunschweig 2015	7	8.15	38	6	4.44	40	5.9%	1.00 [-1.93, 3.93]
Charles 2014	27.3	4	41	28.3	4.3	42	15.8%	-1.00 [-2.79, 0.79]
Rice 2011	17.9	10.4	98	17.8	10.5	102	6.0%	0.10 [-2.80, 3.00]
Singer 2021	11.7	7.7	167	11.9	7.7	165	18.4%	-0.20 [-1.86, 1.46]
Total (95% CI)			**912**			**915**	**100.0%**	**-0.76 [-1.47, -0.05]**

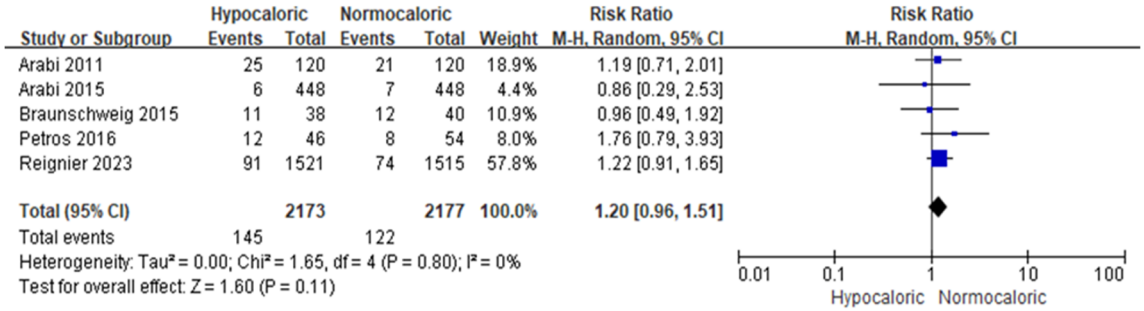
Heterogeneity: Chi² = 3.85, df = 5 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)



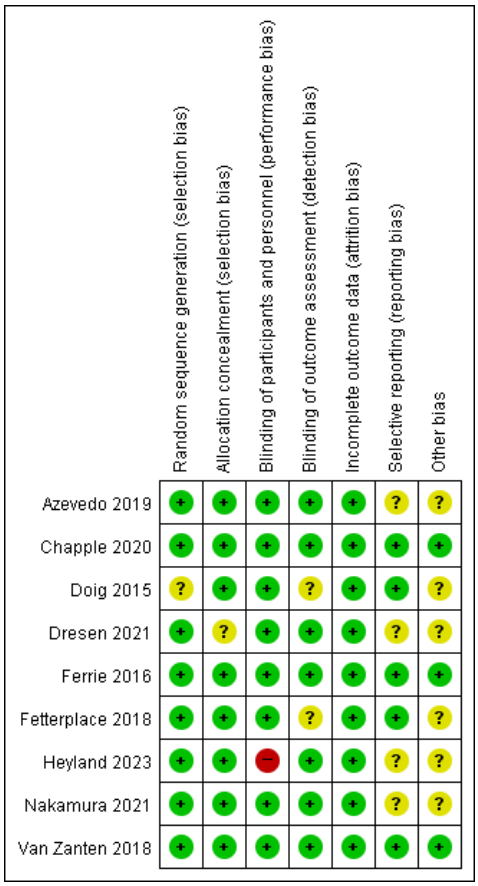
D. Length of stay in the ICU

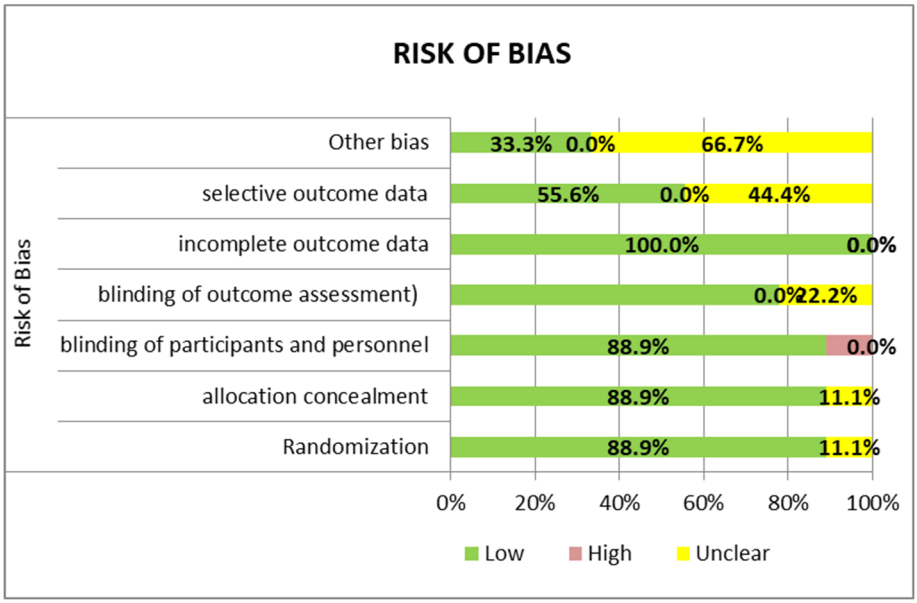


E. Hypoglycemia event



Supplement Fig. 11. Question 5 risk of bias.





Supplement Fig. 12. Question 5 summary of evidence.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High protein	Low protein	Relative (95% CI)	Absolute (95% CI)		
ICU Mortality												
6	randomised trials	not serious	not serious	not serious	serious[a]	none	79/456 (17.3%)	93/459 (20.3%)	RR 0.87 (0.67 to 1.13)	26 fewer per 1,000 (from 67 fewer to 26 more)	⊕⊕⊕◯ Moderate	CRITICAL
Hospital Mortality												
4	randomised trials	not serious	not serious	not serious	serious[a]	none	77/377 (20.4%)	84/380 (22.1%)	RR 0.94 (0.72 to 1.23)	13 fewer per 1,000 (from 62 fewer to 51 more)	⊕⊕⊕◯ Moderate	CRITICAL
ICU Length of stay												
9	randomised trials	not serious	not serious	not serious	not serious	none	1209	1217	-	MD 0.8 higher (0.59 higher to 1.01 higher)	⊕⊕⊕⊕ High	IMPORTANT
Hospital Length of stay												
7	randomised trials	not serious	not serious	not serious	not serious	none	1110	1109	-	MD 1.15 higher (0.67 higher to 1.63 higher)	⊕⊕⊕⊕ High	IMPORTANT
Mechanical ventilation day												
8	randomised trials	not serious	not serious	not serious	not serious	none	1133	1144	-	MD 0 (0.09 lower to 0.08 higher)	⊕⊕⊕⊕ High	IMPORTANT

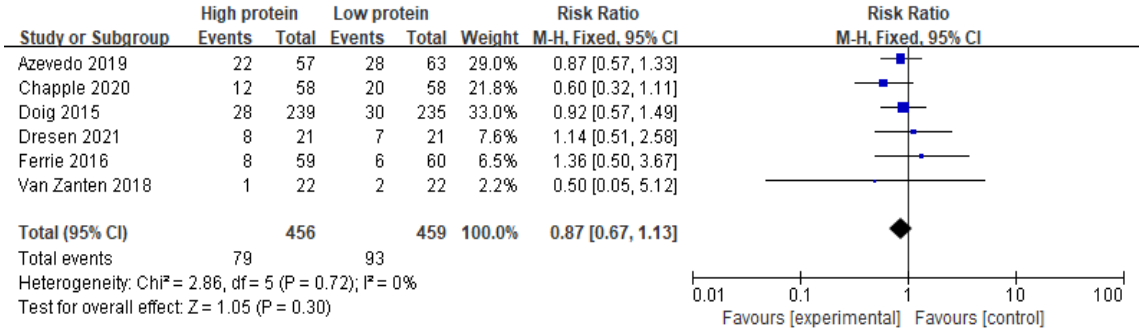
CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

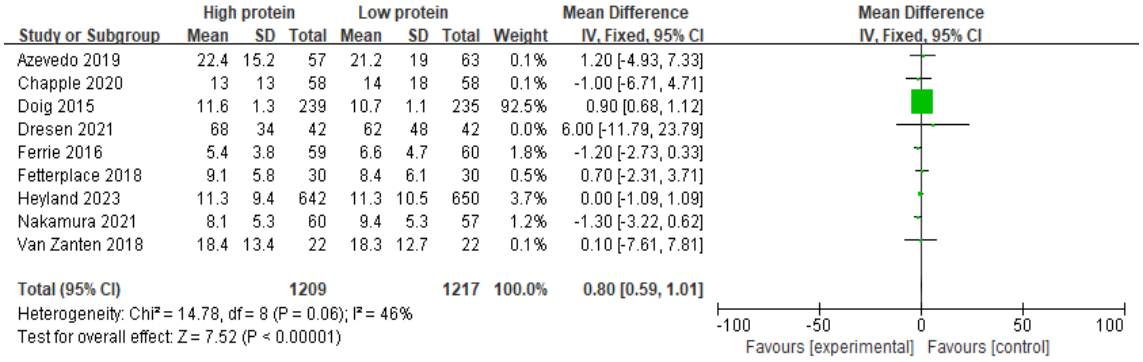
a. Total sample size is less than what is typically necessary to power mortality findings

Supplement Fig. 13. Question 5 forest plots for clinical outcomes.

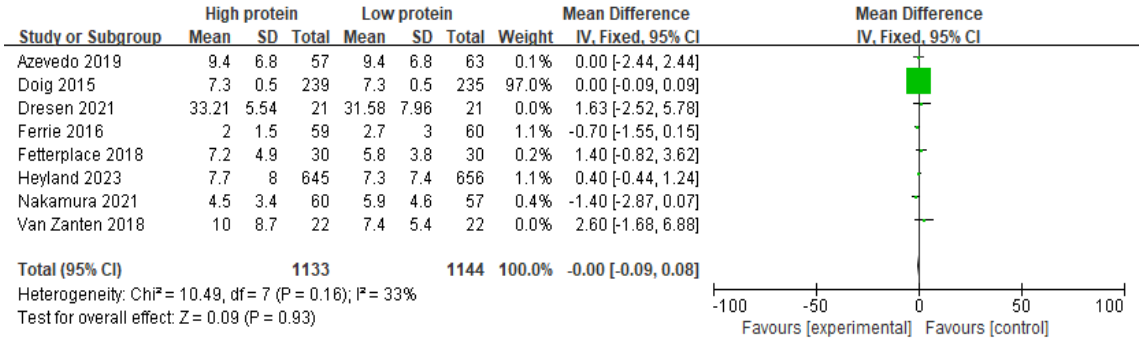
A. ICU Mortality



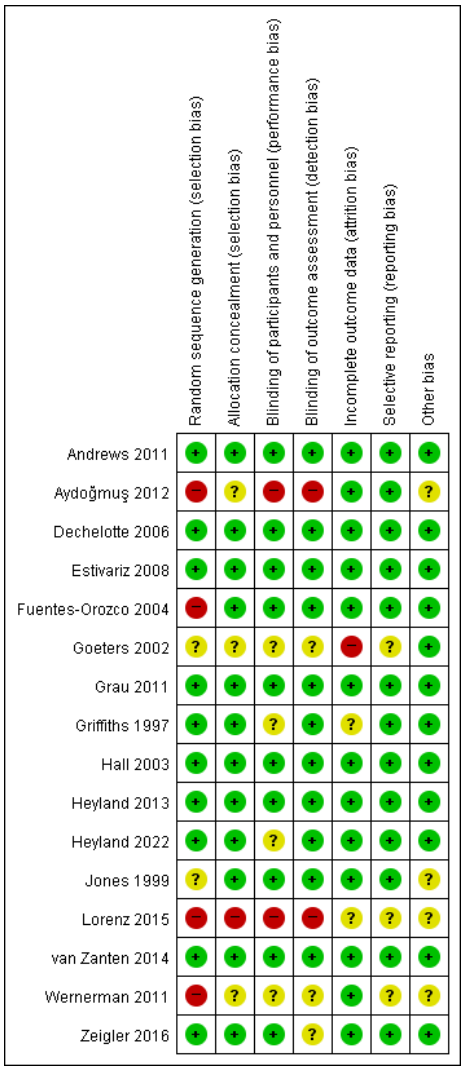
B. Length of stay in the ICU

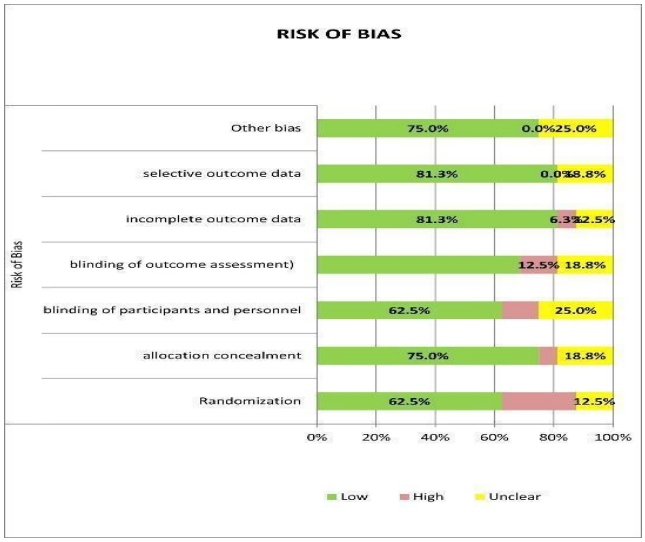


C. Days for mechanical ventilation



Supplement Fig. 14. Question 6 risk of bias.





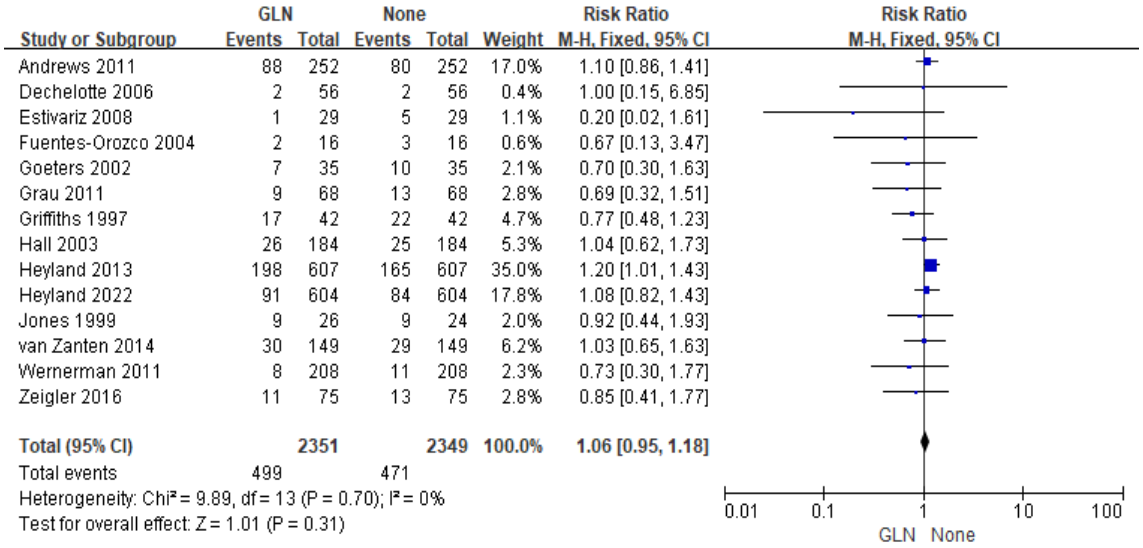
Supplement Fig. 15. Question 6 summary of evidence.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GLN	None	Relative (95% CI)	Absolute (95% CI)		
Overall Mortality												
14	randomised trials	not serious	not serious	not serious	not serious	none	499/2351 (21.2%)	471/2349 (20.1%)	**RR 1.06** (0.95 to 1.18)	**12 more per 1,000** (from 10 fewer to 36 more)	⨁⨁⨁⨁ High	CRITICAL
28/30D Mortality												
6	randomised trials	not serious	not serious	not serious	not serious	none	287/1258 (22.8%)	258/1258 (20.5%)	**RR 1.11** (0.96 to 1.29)	**23 more per 1,000** (from 8 fewer to 59 more)	⨁⨁⨁⨁ High	CRITICAL
Infection rate												
11	randomised trials	not serious	not serious	not serious	not serious	none	423/1292 (32.7%)	441/1306 (33.8%)	**RR 0.94** (0.79 to 1.11)	**20 fewer per 1,000** (from 71 fewer to 37 more)	⨁⨁⨁⨁ High	CRITICAL
Pneumonia												
7	randomised trials	not serious	not serious	not serious	not serious	none	105/434 (24.2%)	136/428 (31.8%)	**RR 0.74** (0.58 to 0.95)	**83 fewer per 1,000** (from 133 fewer to 16 fewer)	⨁⨁⨁⨁ High	CRITICAL
ICU LOS												
9	randomised trials	not serious	not serious	not serious	not serious	none	1275	1284	-	MD **0.56 lower** (0.73 lower to 0.39 lower)	⨁⨁⨁⨁ High	IMPORTANT
H LOS												
7	randomised trials	not serious	not serious	not serious	not serious	none	1553	1570	-	MD **0.68 lower** (1.04 lower to 0.33 lower)	⨁⨁⨁⨁ High	IMPORTANT
MV day												
2	randomised trials	not serious	not serious	not serious	not serious	none	76	84	-	MD **0.97 lower** (1.62 lower to 0.32 lower)	⨁⨁⨁⨁ High	IMPORTANT

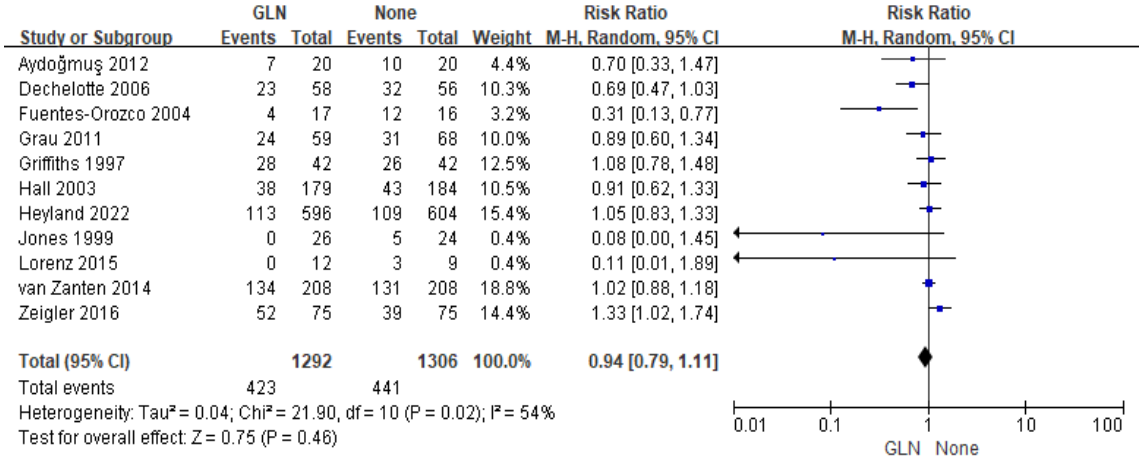
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Supplement Fig. 16. Question 6 forest plots for clinical outcomes.

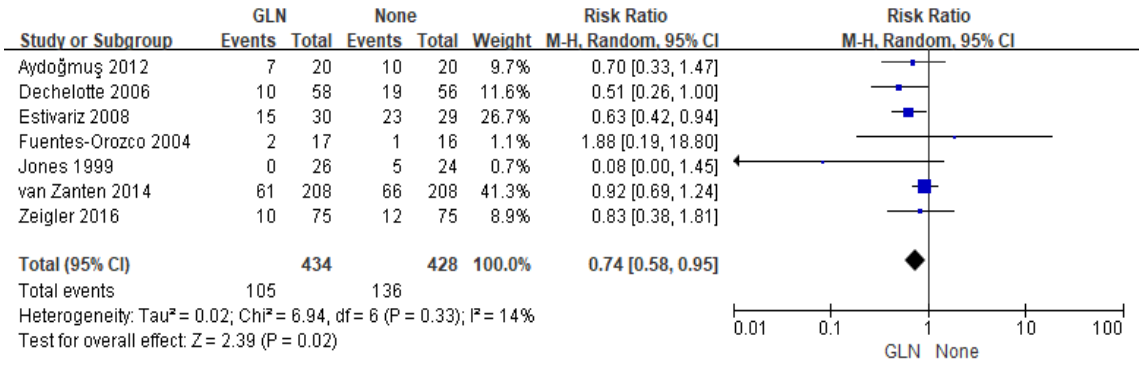
A. Mortality (overall)



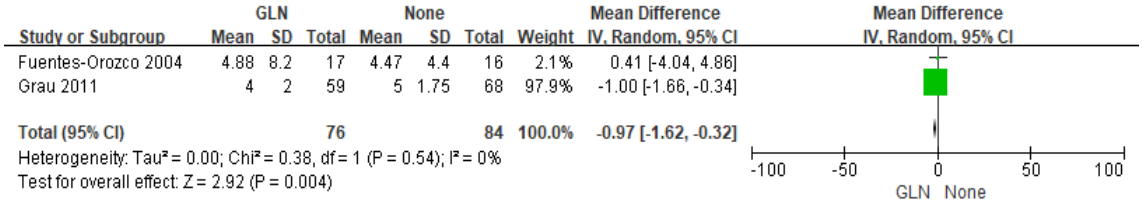
B. Nosocomial infection



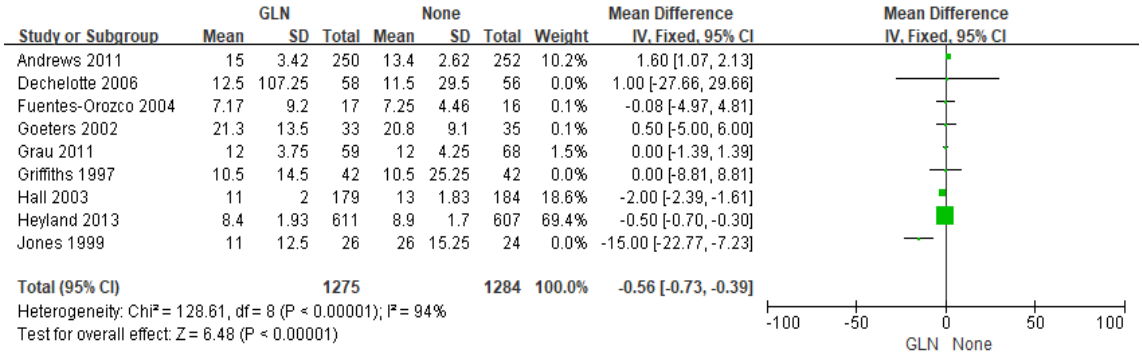
C. Pneumonia



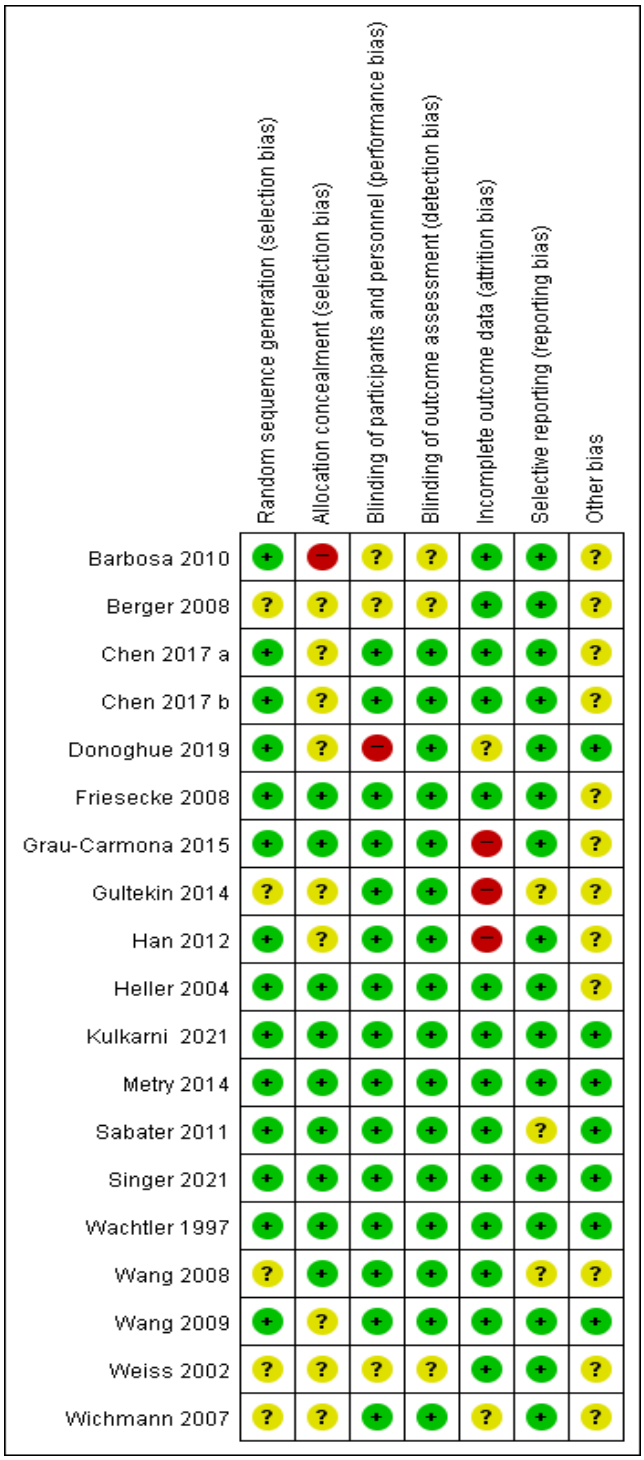
D. Days for mechanical ventilation

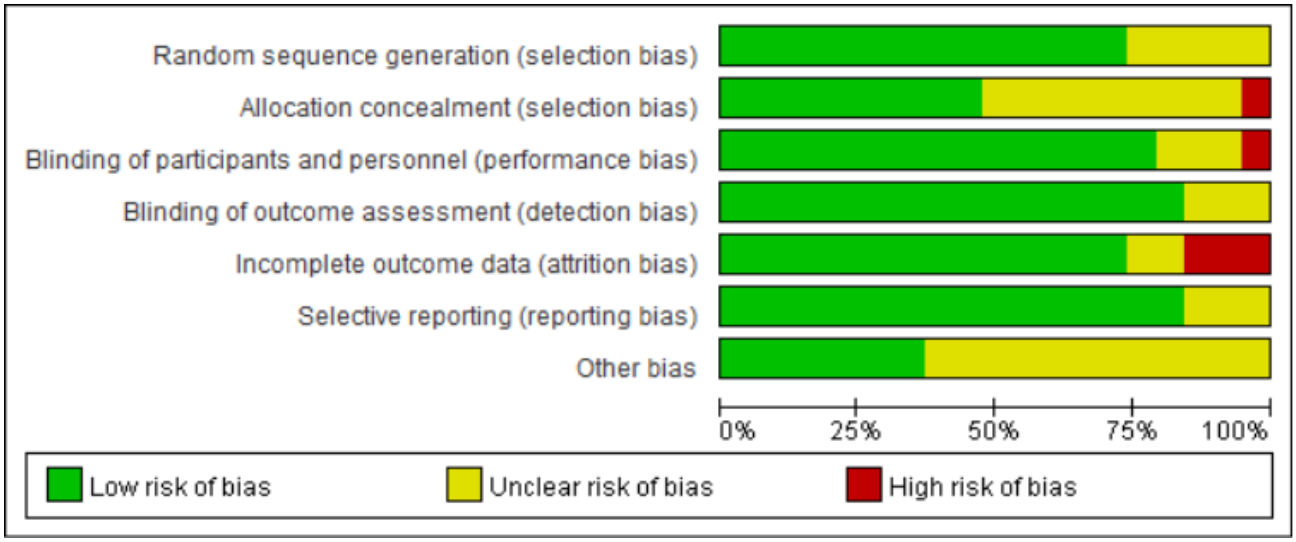


E. Length of stay in the ICU



Supplement Fig. 17. Question 7 risk of bias.




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

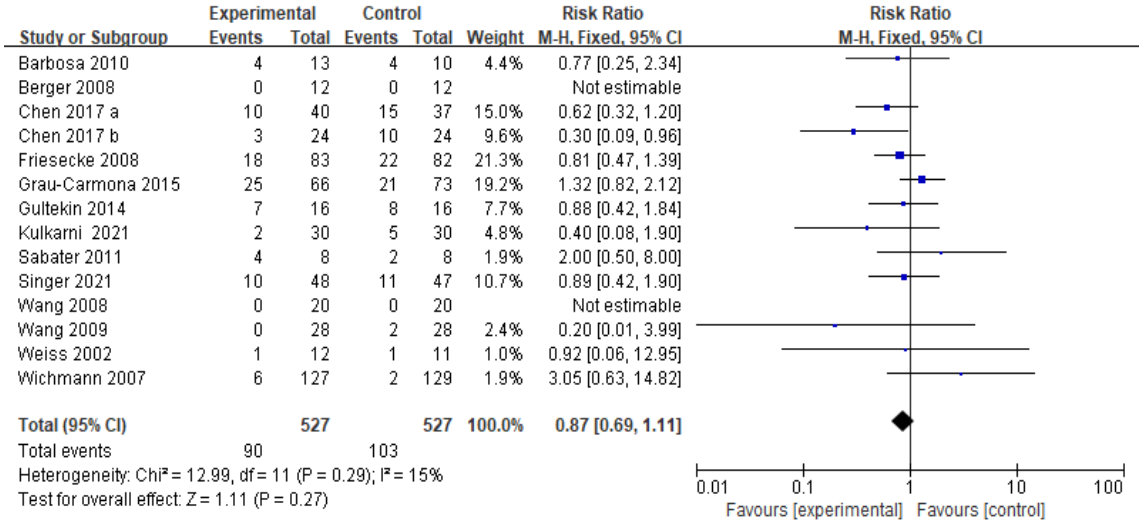
Supplement Fig. 18. Question 7 summary of evidence.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omega-3 fatty acid containing lipid supplements	control	Relative (95% CI)	Absolute (95% CI)		
infection rates												
9	randomised trials	not serious	not serious	not serious	serious[a]	none	57/428 (13.3%)	84/421 (20.0%)	**RR 0.65** (0.48 to 0.88)	**70 fewer per 1,000** (from 104 fewer to 24 fewer)	⨁⨁⨁◯ Moderate	
sepsis rate												
4	randomised trials	not serious	not serious	not serious	serious[a]	none	12/196 (6.1%)	27/200 (13.5%)	**OR 0.38** (0.18 to 0.79)	**79 fewer per 1,000** (from 108 fewer to 25 fewer)	⨁⨁⨁◯ Moderate	
mortality (28-30days)												
14	randomised trials	not serious	serious[b]	not serious	serious[c]	none	90/527 (17.1%)	103/527 (19.5%)	**OR 0.83** (0.60 to 1.15)	**28 fewer per 1,000** (from 68 fewer to 23 more)	⨁⨁◯◯ Low	
length of hospital stay												
12	randomised trials	not serious	serious[d]	not serious	serious[c]	none	469	477	-	MD **2.78 lower** (4.8 lower to 0.77 lower)	⨁⨁◯◯ Low	
length of ICU stay												
12	randomised trials	not serious	serious[d]	not serious	not serious	none	487	486	-	MD **1.83 lower** (3.17 lower to 0.49 lower)	⨁⨁⨁◯ Moderate	
MV LOS												
5	randomised trials	serious[a]	not serious	not serious	serious[f]	none	253	245	-	MD **0.18 higher** (0.37 lower to 0.74 higher)	⨁⨁◯◯ Low	

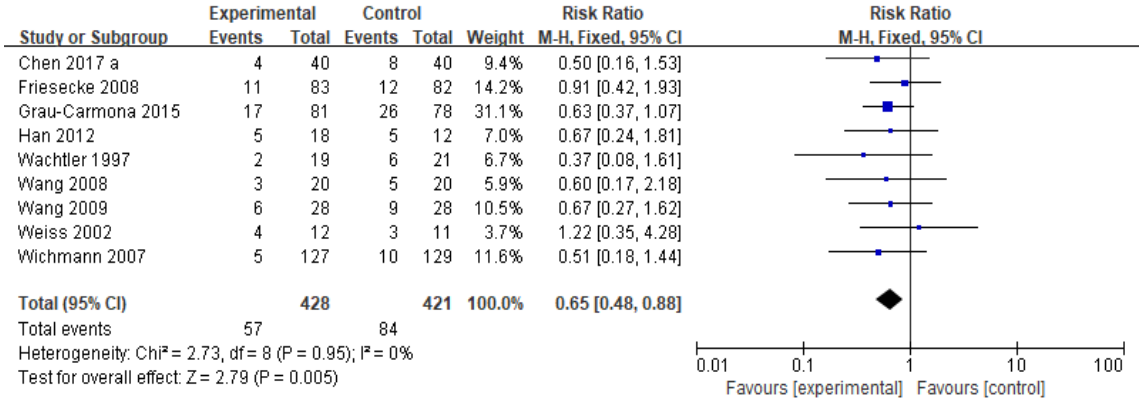
CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio

Supplement Fig. 19. Question 7 forest plots for clinical outcomes.

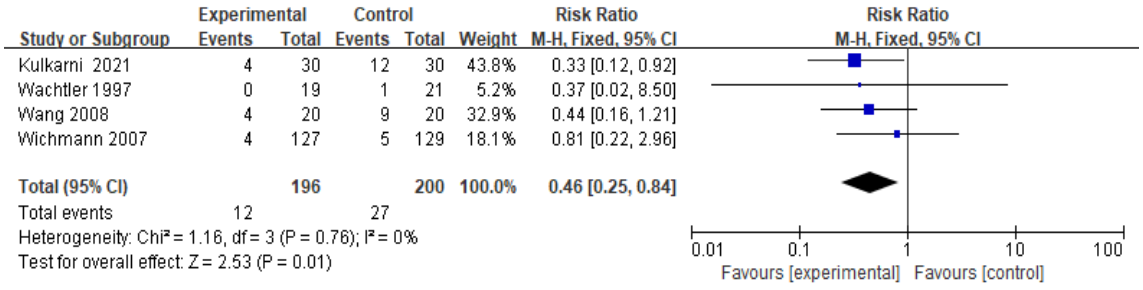
A. Mortality



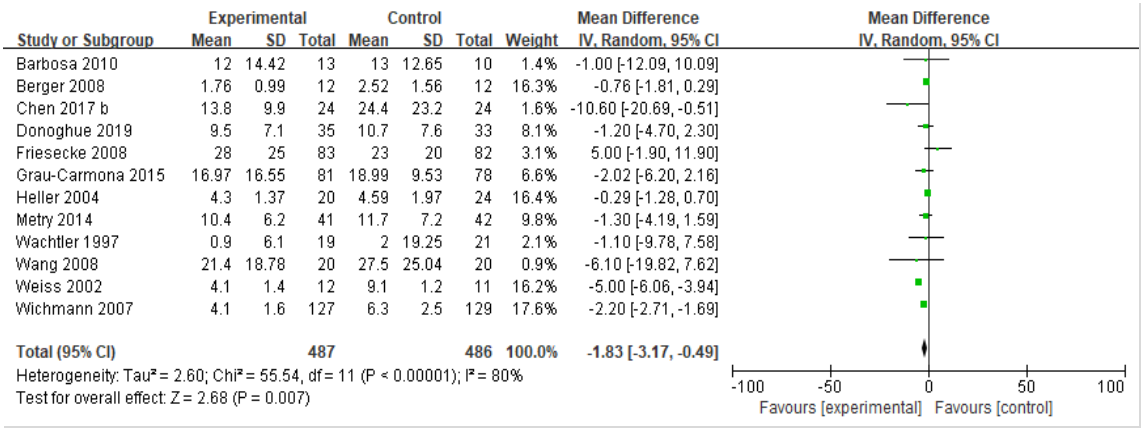
B. Infection



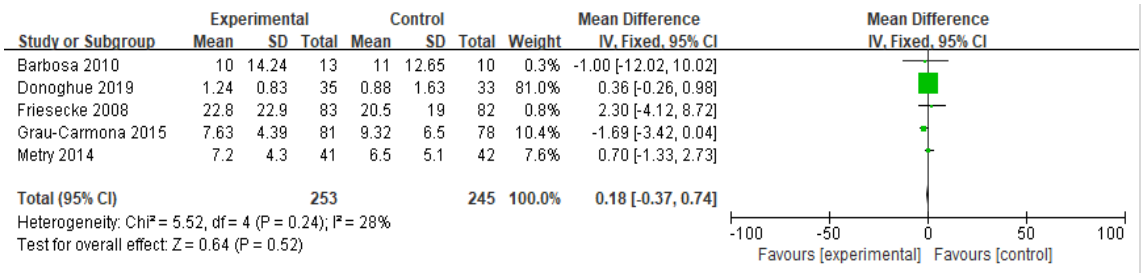
C. Sepsis



D. Length of stay in the ICU



E. Days for mechanical ventilation



Supplement Table 1. Question 1 summary of included studies for literature review

Author	Year	Design	Number of participants	Methods	Inclusion criteria	Primary outcomes	Secondary outcomes
Fuentes Padilla	2019	Meta-analysis	N=345	Searching of CENTRAL (2019, Issue 4), MEDLINE Ovid (1946 to April 2019), Embase Ovid SP (1974 to April 2019), CINAHL EBSCO (1982 to April 2019), ISI Web of Science (1945 to April 2019), Turning Research Into Practice (TRIP), trial registers (ClinicalTrials.gov, ISRCTN registry), and scientific conference reports, including the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism. All RCTs that compared early versus delayed enteral nutrition, with or without supplemental parenteral nutrition, in adults who were in the ICU for longer than 72 hours.	Six trials (318 participants) assessed early versus delayed enteral nutrition in general, medical, and trauma ICUs in the USA, Australia, Greece, India, and Russia.	Five studies (259 participants) measured mortality. It is uncertain whether early enteral nutrition aects the risk of mortality within 30 days (RR 1.00, 95% CI 0.16 to 6.38; 1 study, 38 participants; very low-quality evidence). Four studies (221 participants) reported mortality without describing the timeframe; we did not pool these results. None of the studies reported a clear dierence in mortality between groups. Three studies (156 participants) reported infectious complications. We were unable to pool the results due to unreported data and substantial clinical heterogeneity. The results were inconsistent across studies. One trial measured feed intolerance or gastrointestinal complications; it is uncertain whether early enteral nutrition aects this outcome (RR 0.84, 95% CI 0.35 to 2.01; 59 participants; very low-quality evidence).	One trial assessed hospital length of stay and reported a longer stay in the early enteral group (median 15 days (IQR 9.5 to 20) versus 12 days (IQR 7.5 to15); P=0.05; 59 participants; very low-quality evidence). Three studies (125 participants) reported the duration of mechanical ventilation. We did not pool the results due to clinical and statistical heterogeneity. The results were inconsistent across studies. It is uncertain whether early enteral nutrition aects the risk of pneumonia (RR 0.77, 95% CI 0.55 to 1.06; 4 studies, 192 participants; very low-quality evidence).

Taylor	2016	Meta-analysis	N=936	A committee of multidisciplinary experts in clinical nutrition composed of physicians, nurses, pharmacists, and dietitians was jointly convened by the two societies. Literature searches were then performed using key words (critically ill, critical care, intensive care, nutrition, enteral, parenteral, tube feeding, and those related to assigned topics such as pancreatitis, sepsis, etc.) to evaluate the quality of evidence supporting a response to those questions, which were then used to derive a subsequent treatment recommendation. The literature search included MEDLINE, PubMed, Cochrane Database of Systemic Reviews, the National Guidelines Clearing House and an Internet search using the Google search engine for scholarly articles through an end date of December 31, 2013 (including ePub ublications). While preference was given to RCTs, other forms of resource material were used to support the response, including non-randomized cohort trials, prospective observational studies, and retrospective case series.	Of an updated meta-analysis of 21 RCTs that met our inclusion criteria comparing the provision of early EN versus delayed EN, all reported on mortality, with 13 reporting on infection	Provision of early EN was associated with a significant reduction in mortality (RR=0.70; 95% CI, 0.49–1.00; P=0.05), compared to withholding early EN (delayed EN or standard therapy).	Provision of early EN was associated with a significant reduction in infectious morbidity (RR=0.74; 95% CI, 0.58–0.93, P=0.01), compared to withholding early EN (delayed EN or standard therapy).

Reintam Blaser	2017	Meta-analysis	N=662	We performed a systematic review of "early" EN (EEN) vs. early parenteral nutrition (PN) and EEN vs. delayed EN in adult critically ill patients. After critical appraisal of identified studies and in accordance with current guidelines, we defined EEN as EN started within 48 h of admission independent of the type or amount. Thereafter, we predefined conditions in which EN is frequently delayed and performed a systematic review for each of these questions. If RCTs were available, we gave an evidence-based recommendation; if not, our recommendations were based on expert opinion (very low quality evidence), as all observational studies evaluating EEN are intrinsically biased	Fourteen studies fulfilled the criteria and were included in the meta-analysis	For mortality, we included 12 RCTs (662 patients). EEN did not reduce mortality compared to delayed nutritional intake (RR 0.76; 95% CI 0.52–1.11; P=0.149; I^2=0%).	For infection, we included 11 RCTs (597 patients). EEN reduced risk of infection compared to delayed EN (RR 0.64; 95% CI 0.46–0.90; P=0.010; I^2=25%).
Singer	2023	Expert opinions	(-)	The PubMed and Cochrane Library databases were searched for studies and systematic reviews published between 2000 and June 2017 using a broad filter with the key words. Only articles published in English or with an English abstract, and studies in human adults were considered. RCTs, meta-analyses, and systematic reviews were hand-searched for studies that were missing in the initial database	To provide levels of evidence for literature selection, the SIGN evidence levels have been elaborated. SIGN evidence ranks the evidence from 1++ for high quality studies (meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias) to low level of	In comparing early EN with delayed EN (six studies in ICU patients and four studies including non-ICU patients), and similar to an earlier meta-analysis [13], a reduction of infectious complications with early EN (RR 0.76, CI 0.59, 0.97, P<0.03) was observed	When comparing early EN with early PN (six studies in ICU patients and seven studies with non-ICU patients included) a reduction of infectious complications with EN (RR 0.50, 95% CI 0.37–0.67, P=0.005), as well as shorter ICU (RR -0.73, 95% CI –1.30 to –0.16, P=0.01) and hospital stay (RR –1.23, 95% CI –2.02 to –0.45, P=0.002) was

				search. The search for literature was updated several times during the working process for the last time in August 2017.	evidence graded as 4 in the case of expert opinion. For literature not included into meta-analyses, evidence tables were created which are available online as Supplemental Materials. A clear and straightforward consensus procedure was adopted using voting by the experts involved in writing the manuscript during a consensus conference preceded by a web-based Delphi procedure open to ESPEN members.		observed, while mortality was not different. However, recent RCTs do not demonstrate a clear advantage of EN over PN, and the observed benefit of EN in earlier studies may be due to the higher energy and amino acid/protein content provided by PN compared to EN.
Pu	2018	Meta-analysis	N=527	Medline (www.PubMed.org), Embase (www.EMBASE.com), and the China National Knowledge Infrastructure (www.cnki.com.cn) were searched using appropriate statements and terms. Experts were contacted, and reference lists of published reviews and guidelines were hand searched. The close out date was May 1, 2018. All RCTs comparing early EN to any other intervention published in any language were retrieved in full text and screened for inclusion. Early EN was	RCTs reporting mortality conducted in adult populations with major burn injuries were eligible for inclusion and were reviewed in detail. A major burn was defined as thermal, chemical, or electrical injury to greater than 20% of TBSA	The primary outcome of interest was mortality (odds ratio, 0.36; 95% CI, 0.18–0.72; P=0.003; I^2=0%).	Gastrointestinal hemorrhage (odds ratio, 0.21; 95% CI, 0.09–0.51; P=0.0005; I^2=0%), sepsis (odds ratio, 0.23; 95% CI, 0.11–0.48; P<0.0001; I^2=0%), pneumonia (odds ratio, 0.41; 95% CI, 0.21–0.81; P=0.01; I^2=63%), renal failure (odds ratio, 0.27; 95% CI, 0.09–0.82; P=0.02; I^2=32%), and duration of hospital stay (–15.31 d; 95% CI, –20.43 to –10.20; P<0.00001; I^2=0%) were evaluated as

				defined as a “standard” EN formula provided via any feeding tube route within 24 hours of injury or admission to an ICU or burns unit.			secondary outcomes.

CI = confidence interval; EN = enteral nutrition; EEN = early enteral nutrition; ESPEN = European Society for Clinical Nutrition and Metabolism; ICU = intensive care unit; IQR = interquartile range; RCT = randomized controlled trial; RR = relative risk; SIGN = Scottish Intercollegiate Guidelines Network.

Supplement Table 2. Question 2 summary of the included studies

Authors	Year	Population	Numbers of patient			Intervention
			Total	EN	PN	
Rapp	1983	Head injured patients admitted to the NCU	38	18	20	TPN within 48 h vs. EN via NG tube as soon as such feedings could be tolerated
Adams	1986	Trauma patients undergoing an emergent laparotomy, 18–60 years of age, 80%–130% of desirable weight, without a history of hepatic or renal failure	46	23	23	TPN via subclavian line or EN via an 8F Witzel jejunostomy
Young	1987	Severe head injury	51	28	23	TPN within 48 h postoperatively vs. EN as soon as the feeding tube was inserted
Moore	1989	Adults patients undergoing emergency celiotomy with an abdominal trauma index 16–39	59	29	30	immediate TEN via NCJ vs. TPN via central venous catheter, start NS within 12 hours of surgery
Kudsk	1992	Patients 18 years of age or older, with an intra-abdominal injury requiring laparotomy, who sustained an ATI of at least 15,	96	51	45	EN via jejnostomy tube vs.PN
Dunham	1994	Adult patients with blunt trauma, GCS≥5, ISS≥15	27	12	15	TEN vs. TPN vs. EN+PN
Borzotta	1994	Adult (18–60 years) patients with head injuries with GCS of 8 or less and coma persisting over 24 hours	49	28	21	TPN vs. EN via surgical jejunal tube
Hadfield	1995	Patients admitted to the adult ICU for more than 3 d requiring nutritional support	24	13	11	EN vs. PN

Kalfarentzos	1997	Patients requiring intensive monitoring for more than 72 h with severe acute pancreatitis	38	18	20	EN via nasoenteric tube vs. PN via subclavian catheter
Woodcock	2001	All patients aged 18 years or over who required adjuvant nutritional support	64	32	32	TPN via peripheral or CVC vs. EN vial NG tube or gastrostomy or jejunostmy
Bertolini	2003	ICU patients with severe sepsis those aged over 18 years, in a high level of care, who were judged to need artificial ventilation and nutrition for at least 4 days	39	18	21	TPN vs EN
Radrizzani	2006	Patients admitted with nonserverly septic	287	142	145	PN vs. EN
Casas	2007	18 years or older with a Severe Acute Pancreatitis (ward+ICU)	22	11	11	TPN via central venous catheter vs. TEN via NJ tube
Altintas	2011	All patients who needed invasive mechanical ventilation in the ICU	71	30	41	PN via central or peripheral routs vs. EN via gastric or postpyloric placement
Justo Meirelles	2011	Adult patients (18–60 years old) admitted to the ICU with moderate traumatic brain injury (GCS 9–12)	22	12	10	EN via oro- or naso-enteral tube or NPT via central venous catheter as soon as they were hemodinamically stable
Wang	2013	Patients diagnosed with SAP who were admitted to the intensive care unit	183	123	60	PN via CVC vs. EN via NJ tube
Sun	2013	All adult SAP patients (aged 18–70 years) admitted within 3 d of symptom onset to the Surgical Intensive Care Unit (SICU),	60	30	30	EEN via NJ tube within 48 h after admission vs DEN via NJ tube on the 8th D after admission (TPN in DEN group for 1 week)
Harvey	2014	Adults ICU patients who expected to require nutritional support for at least 2 days, as determined by a clinician within 36 hours after an unplanned ICU admission that was	2,388	1,197	1,191	Nutritional support was initiated as soon as possible after randomization (within 36 hours after admission) and used exclusively for 5 days (120 hours) or until transition to exclusive oral feeding, discharge from the

		expected to last at least 3 days				ICU, or death
Fan	2016	Adult patients who admitted to the Nuero ICU with servere traumatic brain injury (GCS 6–8)	80	40	40	TPN via central venous catheter within 48 hours vs. EN via NG tube withing 48 hours
Reignier	2018	adults (18 years or older) ICU patients receiving invasive mechanical ventilation (more than 48 h) and vasopressor support for shock	2,410	1,202	1,208	PN via CVC for at least 72 h vs. EN within 24 h after intubation

Supplement Table 3. Question 2 summary of clinical outcomes of the randomized controlled studies

Study	Group	Total No.	Mortality (n)		Infection (n)	BSI/vascular (n)	Pneumonia (n)	ICU – LOS Mean (SD)	MV (d) Mean (SD)	H – LOS Mean (SD)	GI complications (n)	Organ dysfunction (n)
Rapp	EN	18	Overall	9								
	PN	20	Overall	0								
Adams	EN	23		NA			11	10 (10)	10 (10)	31 (29)	11	
	PN	23		NA			8	13 (11)	12 (11)	30 (21)	6	
Young	EN	28	18 day	5			9				23	
	PN	23	18 day	7			6				13	
Moore	EN	29		NA	5	0	0					
	PN	30		NA	11	2	6					
Kudsk	EN	51		NA	8	1	6		2.8 (0.7)	20.5 (2.8)		
	PN	45		NA	17	6	14		3.2 (1.0)	19.6 (2.8)		
Dunham	EN	12	Overall	1								
	PN	15	Overall	1								
Borzotta	EN	28	Overall	5		11	15				8	
	PN	21	Overall	1		6	9				13	
Hadfield	EN	13	Overall	2								
	PN	11	Overall	6								
Kalfarentzos	EN	18	Overall	3	5	1		12 (4)	13 (2.5)	47 (14.5)	6	

	PN	20	Overall	2	10	3		13.25 (4.75)	15 (6)	43.25 (12.75)	3	
Woodcock	EN	32	Overall	12	10	0						
	PN	32	Overall	7	16	5						
Bertolini	EN	18	28 day	8								
	PN	21	28 day	5								
Radrizzani	EN	142	28 day	17	7	1	4					45
	PN	145	28 day	17	19	3	12					56
Casas	EN	11	Overall	0	1							0
	PN	11	Overall	2	5							2
Altintas	EN	30	Hospital	13	7	2	5	15 (3.25)	7 (1.13)	32 (9.69)	3	
	PN	41	Hospital	20	13	4	11	14 (4.25)	9 (2.13)	28 (7.25)	1	
Justo Meirelles	EN	12	Overall	1	2		2					
	PN	10	Overall	1	4		2					
Wang	EN	123	Overall	4	21							22
	PN	60	Overall	7	24							22
Sun	EN	30	Overall	2	3			9 (2.25)				5
	PN	30	Overall	1	10			12 (3.25)				13
Harvey	EN	1197	30 day	409	231	32	143	7.3 (2.6)		16 (4.17)	194	
	PN	1191	30 day	393	229	42	135	8.1 (2.95)		17 (4.33)	100	
Fan	EN	40	Overall	12			20	31.42 (5.93)	12.56 (6.12)		24	

	PN	40	Overall	17			8	36.33 (8.61)	18.63 (5.39)		6	
Reignier	EN	1202	28 day	443	173	67	113	9 (2.75)	6.3 (1.89)	17 (4)	868	
	PN	1208	28 day	422	194	82	118	10 (3)	7 (1.89)	18 (4)	647	
EN = enteral nutrition; PN = parenteral nutrition; BSI = blood stream infection; ICU = intensive care unit; LOS = length of stay; H = hospital; GI = gastrointestinal.												

Supplement Table 4. Question 3 summary of included studies

Author	Year	Design	Number of participants	Settings	Primary diagnosis	Duration	Inclusion criteria	Exclusion criteria	Intervention
Heidegger	2013	RCT	N=305 EN alone group (n=152) Age, mean (SD): 60(±16) yrs Gender, M/F: 105/47 APACHE II, mean (SD) :23(±7) SAPS II, mean (SD): 47(±15) EN+SPN group(n=153) Age, mean (SD): 61(±16) yrs Gender, M/F: 110/43 APACHE II, mean (SD): 22(±7) SAPS II, mean (SD): 49(±17)	Two-center (medial and surgical ICU of two tertiary care hospitals)	Shock, neurological, cardiac surgery, polytrauma, pneumonia, cardiac arrest, respiratory failure, myocardial infarction, acute pancreatitis, and liver failure	5 days	Adults with functional gastrointestinal tract and expected ICU stay exceeding 5 days, expected survival rate exceeding 1 week and had received less than 60% of their energy requirement from EN on the third day of ICU admission	People who were receiving PN, Had persistent gastrointestinal dysfunction and ileus, Were pregnant, Refused to consent, Had been readmitted to the ICU after previous randomization	Patients were randomly assigned to receive EN or SPN+EN. Energy targets were calculated using indirect calorimetry or by multiplying 25–30 kcal per kg of ideal body weight

Berger	2019	RCT	N=23 EN alone group(n=12) Age, mean (SD): 68.34(±10.65) yrs Gender, M/F: 10/2 APACHE II, mean (SD): 23.36(±7.21) SAPS II, mean (SD): 47.81(±19..04) EN+SPN group (n=11) Age, mean (SD): 63.73(±15.26) yrs Gender, M/F: 9/2 APACHE II, mean (SD): 22.42(±7.63) SAPS II, mean (SD): 48.89(±19.51)	Single center (multidisciplinary ICU)	Medical and surgical patients	5 days	Adults in ICU, mechanically ventilated patients with a functional gut, who received <60% of their energy requirements by day 3	People who were receiving PN, Had persistent gastrointestinal dysfunction and ileus, Were pregnant, Refused to consent, Had been readmitted to the ICU after previous randomization, Severe brain injury, cardiac arrest because of likely metabolic difference, absence of endotracheal intubation to ensure a precise indirect calorimetry determination of energy goals	Patients were randomly assigned to EN or SPN+EN with the target energy requirements validated by indirect calorimetry
Bauer	2000	RCT	N=120 EN alone group(n=60) Age, mean (SD): 55(±18) yrs Gender, M/F: 42/18 SAPS II, mean (SD): 41(±13) EN+SPN group(n=60) Age, mean (SD): 53(±18) yrs Gender, M/F: 40/20	Single-center	Multiple trauma, respiratory failure, stroke, sepsis, coronary artery disease, poisoning, renal failure, gastrointestinal bleeding	7 days	>18 years of age, admitted to the ICU for >2 days, expected to stay alive >2 days. Expected to eat <20 kcal/kg/d	Post-elective surgery patients People with contraindication to enteral or parenteral feeding History of allergy to vitamins	Patients were randomly assigned to receive either parenteral plus enteral nutrition or enteral nutrition plus placebo for 4–7 days after starting

			SAPS II, mean (SD): 43(±14)				for >2 days, and EN to be progressively administered for >2 days		nutritional support. The energy target was 25 kcal/kg
RCT = randomized controlled trial; EN = enteral nutrition; SPN = supplemental parenteral nutrition; ICU = intensive care unit; SD = standard deviation.									

Supplement Table 5. Question 3 summary of clinical outcomes of included studies

Study	Group	Total No.	ICU Mortality (n)	In-hospital mortality (n)	28-day mortality (n)	90-day mortality (n)	ICU LOS, day Mean (SD)	MV duration, day Mean (SD)	Hospital LOS, day Mean (SD)	GI events (n)	Infectious events (n)				
										Diarrhea	BSI	Abdominal infection	Pneumonia or respiratory infection	UTI	Other infection
Heidegger	EN alone	152	12		28		13 (11)	2.75 (4.21)	32 (23)		6	4	28	2	3
	EN+SPN	153	8		20		13 (10)	2.5 (4.625)	31 (23)		10	1	35	4	2
Berger	EN alone	12		1			15.74 (12.74)	9.5 (8.5)	46.91 (25.13)						
	EN+SPN	11		0			16.01 (8.09)	11 (7.66)	45.36 (20.51)						
Bauer	EN alone	60				18	17.3 (12.8)	10 (8)	33.7 (27.7)	27			23	16	
	EN+SPN	60				17	16.9 (11.8)	11 (9)	31.2 (18.5)	48			28	11	

EN = enteral nutrition; SPN = supplemental parenteral nutrition; BSI = blood stream infection; ICU = intensive care unit; LOS = length of stay; GI = gastrointestinal; UTI = urinary tract infection; SD = standard deviation.

Supplement Table 6. Question 4 summary of included studies

Authors (Year)	Population	Protocol				Number of patients			Duration for interventions
		Calorie		Protein					
		Hypo-caloric	Normo-caloric	Hypo-caloric	Normo-caloric	Total	Hypo-caloric	Norm-caloric	
Rice (2011)	Adult patients with respiratory failure in med ICU (mean BMI: 28.2 vs. 29.2)	300±149 kcal/d	1,418±686 kcal/d	10.9±6.8 g/d	54.4±33.2 g/d	200	98	102	5 days
Rice (2012)	Adult with ALI in 44 ICUs (mean BMI: 30.4 vs. 29.9)	About 400 kcal/d	About 1,300 kcal/d	-	-	1,000	508	492	5days
Charles (2014)	Adult patients in surg ICU (mean BMI: 28.1 vs. 32.9)	12.5–15 kcal/kg/d (adjusted body weight)	25–30 kcal/kg/d (adjusted body weight)	1.5 g/kg/d	1.5 g/kg/d	83	41	42	Mean 10–13 days
Petros (2016)	Adult patients in med ICU (mean BMI: 27.1 vs. 28.6)	11.3±3.1 kcal/kg/d (actual body weight)	19.7±5.7 kcal/kg/d (actual body weight)	Varying levels of protein supply (not assessed quantitatively)		100	46	54	7 days
Reignier (2023)	Adults (≥18 years) receiving invasive MV care and vasopressor support for shock were randomly assigned to early nutrition	6 kcal/kg/d	25 kcal/kg/d	0.4 g/kg/d	1.0–1.3 g/kg/d	3,044	1,521	1,515	7 days
Singer (2021)	adult ventilated ICU patients that were planned to stay more than 48 h in the ICU departments	20–25 kcal/kg/d (IBW)	80%–100% of calculated energy requirement by indirect	62.4±33.9 g/d	77.3±53.0 g/d	332	167	165	-

	(mean BMI 28.6 vs. 28.1)		calorimetry						
Arabi (2011)	Adult patients in med ICU (age≥18 y) (mean BMI: 28.5 vs. 28.5)	60%–70% of the standard caloric requirement	90%–100% of the standard caloric requirement	47.5±21.2 g/d	43.6±21.2 g/d	240	120	120	7 days
Arabi (2015)	Critically ill adults with a medical, surgical, or trauma admission category (mean BMI: 29.0 vs. 29.7)	40% to 60% of calculated caloric requirements	70% to 100% of calculated caloric requirements	1.2–1.5 g/kg/d	1.2–1.5 g/kg/d	894	448	446	Maximum 14 days
Charles (2020)	Adult, obese critically ill surgical patients	12.5±0.9 kcal/d	17.4±1.2 kcal/d	1.1 g/kg/d	1.1 g/kg/d	53	22	31	10–11 days
Rugeles (2016)	Critically ill patients (median BMI 25 vs. 25)	12.1±2.6 kcal/kg/d	19.2±4.3 kcal/kg/d	1.7 g/kg/d	1.7 g/kg/d	120	60	60	-
Braunschweig (2015)	Adult (≥18 years) patients in medical or surgical ICU with a diagnosis of ALI (mean BMI: 30.1 vs. 29.8)	16.6 kcal/kg/d (obese : adjusted body weight, non-obese : ideal body weight)	25.4 kcal/kg/d (obese : adjusted body weight, non-obese : ideal body weight)	1.5 g/kg/d	1.5 g/kg/d	78	38	40	7–10 days

Supplement Table 7. Question 4 summary of clinical outcomes of included studies

Study	Group	Total No.	Mortality (over-all) (n)	MV-care Mean (SD)	Diarrhea (n)	LOS–ICU Mean (SD)	LOS–H Mean (SD)	Infection (n)	Hypoglycemia (n)
Rice (2011)	Hypo-caloric	98	22	17.9 (10.4)				44	
	Normo-caloric	102	20	17.8 (10.5)				51	
Rice (2012)	Hypo-caloric	508	118		84			15	
	Normo-caloric	492	109		92			92	
Charles (2014)	Hypo-caloric	41	3	27.3 (4.0)		16.7 (2.7)	35.2 (4.9)		
	Normo-caloric	42	4	28.3 (4.3)		31.0 (2.5)	31.0 (2.5)		
Petros (2016)	Hypo-caloric	46	10		3			3	
	Normo-caloric	54	12		4			4	
Reignier (2023)	Hypo-caloric	1521	504		439			233	91
	Normo-caloric	1515	533		504			265	74
Singer (2021)	Hypo-caloric	167	36	11.7 (7.7)		14.4 (8.6)	26.9 (16.2)	40	
	Normo-caloric	165	32	11.9 (7.7)		15.3 (12.5)	31.0 (1.0)	27	
Arabi (2011)	Hypo-caloric	120	21	10.6 (7.6)		11.7 (8.1)	70.2 (106.9)	53	25
	Normo-caloric	120	26	13.2 (15.2)		14.5 (15.5)	67.2 (93.6)	56	21
Arabi (2015)	Hypo-caloric	448	72	9 (7.41)	97	13 (9.63)	28 (28.89)	161	6
	Normo-caloric	446	85	10 (8.15)	117	13 (8.89)	30 (36.3)	169	7
Charles (2020)	Hypo-caloric	22	1			15.7 (1.4)	32.6 (3.8)	29	
	Normo-caloric	31	3			13.4 (1.2)	22.0 (30.5)	32	
Rugeles (2016)	Hypo-caloric	60	18						
	Normo-caloric	60	16						
Braunschweig (2015)	Hypo-caloric	38	6	7 (8.15)		16.1 (11.5)	22.8 (14.3)	8	11
	Normo-caloric	40	16	6 (4.44)		15.5 (12.8)	27.2 (18.2)	5	12

ICU = intensive care unit; LOS = length of stay; H = hospital.

Supplement Table 8. Question 5 summary of the prospective randomized controlled studies

Authors	Year	Population	Protocol				Number of patients		
			Calorie (kcal/kg/d), median (IQR) or mean±SD		Protein (g/kg/d) median (IQR) or mean±SD				
			High	Low	High	Low	Total	High	Low
Doig	2015	Mean BMI: 28.9 vs. 29.5 Patients in 16 med/surg ICUs	NR	NR	max.2	NR	474	239	235
Ferrie	2016	BMI: NR Patients requiring PN in med/surg ICU	23.1±3.9	24.9±4.2	1.1±0.2	0.9±0.2	119	59	60
Fetterplace	2018	Mean BMI: 30 vs. 29 Patients in med ICU	21±5.2	18±2.7	1.2±0.3	0.8±0.1	60	30	30
van Zanten	2018	Mean BMI: 30.3 vs. 30.7 Overweight ICU patients (BMI≥25) with med, surg, or trauma diagnosis	16.6 (8.9–23.3)	14.4 (10.9–18.8)	1.3 (0.7–1.9)	0.7 (0.5–0.9)	44	22	22
Azevedo	2019	BMI: NR Patients in both a surgical intensive care unit (13 beds) and a medical intensive care unit (32 beds) of a tertiary hospital	1,139 kcal/d (890-1,278)	1,140 kcal/d (889-1,331)	1.69 (1.33-1.80)	1.13 (0.97-1.34)	120	57	63
Chapple	2021	Median BMI: 29 vs. 30 admitted to the ICU; undergoing invasive mechanical ventilation	19.2±6.5	19.6±5.4	1.52±0.52	0.99±0.27	116	58	58
Dresen	2021	BMI: NR (i) age range >18–90 years, (ii) necessity of MV, (iii) overcoming the early period of	27.0±8.9	24.6±9.8	1.5±0.5	1.0±0.4	42	21	21

		hemodynamic instability (iv) pre-diction of a long-term ICU stay							
Nakamura	2021	Mean BMI: 21.3 vs. 21.5 medical and surgical ICU	target 20	target 20	target 1.5	target 0.8	117	60	57
Heyland	2023	Mean BMI: 28 vs. 29 Patients in med ICU	14.7±6.9	13.2±6.4	1.6±0.5	0.9±0.3	1301	645	656

Supplement Table 9. Question 5 summary of clinical outcomes of the randomized controlled studies

Authors	Total number (n)		ICU LOS, Mean (SD)		Hospital LOS, Mean (SD)		MV, Mean (SD)		ICU Mortality, (n)		Hospital Mortality, (n)	
	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low
Doig	239	235	11.6 (1.3)	10.7 (1.1)	26 (2.8)	24.8 (2.7)	7.3 (0.5)	7.3 (0.5)	28	30	37	43
Ferrie	59	60	5.4 (3.8)	6.6 (4.7)	27.9 (18.6)	34.4 (28.1)	2 (1.5)	2.7 (3)	8	6	12	9
Fetterplace	30	30	9.1 (5.8)	8.4 (6.1)	25.2 (25.8)	16.7 (11.8)	7.2 (4.9)	5.8 (3.8)				
van Zanten	22	22	18.4 (13.4)	18.3 (12.7)	28.5 (13.3)	28.2 (13.2)	10 (8.7)	7.4 (5.4)	1	2	2	3
Azevedo	57	63	22.4 (15.2)	21.2 (19)			9.4 (6.8)	9.4 (6.8)	22	28	26	29
Chapple	58	58	13 (13)	14 (18)	24 (21)	26 (32)			12	20		
Dresen	21	21	68 (34)	62 (48)			33.2 (5.5)	31.6 (8)	8	7		
Nakamura	60	57	8.1 (5.3)	9.4 (5.3)	34.6 (30.4)	34.6 (30.4)	4.5 (3.4)	5.9 (4.6)				
Heyland	645	656	11.3 (9.4)	11.3 (10.5)	22.8 (21.8)	22.2 (21.2)	7.7 (8)	7.3 (7.4)				

ICU = intensive care unit; LOS = length of stay.

Supplement Table 10. Question 6 summary of the prospective randomized controlled studies

Authors	Year	Population	Protocol				Number of patients		
			Control	Glutamine supplement	Route	Supplement period	Total	Control	Glutamine supplement
Andrews	2011	≥50% of nutritional requirements by PN	12.5 g nitrogen, 2,000 kcal	Add 20.3 g glutamine	PN	Maximum of 7days	502	252	250
Aydoğmuş	2012	Mechanical support for at least 7 days	25–30 kcal/kg/d	Add 40 g glutamine	PN	Daily	40	20	20
Déchelotte	2006	Multiple trauma, complicated surgery, pancreatitis	1.5 g amino acid/kg/d and 37.5 kcal	Isocaloric isonitrogenous, 0.5 g/kg/d	PN		114	56	58
Estívariz	2008	SICU patients underwent surgery Require PN for at least 7 subsequent days	1.5 g/kg/d amino acid	Isonitrogenous, 0.5 g/kg/d	PN	Maximum of 21 days	59	29	30
Fuentes-Orozco	2004	Secondary peritonitis	Standard TPN	Add 0.4 g/kg/d	PN	10 Consecutive days	33	16	17
Goeters	2002	Expected stay on ICU for >5 days	1.5 g/kg/d amino acid	Isonitrogenous, 0.3 g/kg/d	PN		68	35	33
Grau	2011	APACHE II score >12, requiring PN for 5-9days	0.25 g nitrogen/kg/d, 25 kcal/kg/d	Isonitrogenous, 0.5 g/kg/d	PN	Maximum of 9 days	127	68	59
Griffiths	1997	APACHE II score ≥11	Standard TPN	Isonitrogenous, 18 g	PN	Until death or as long as clinically required	84	42	42

Hall	2003	ICU patients without liver failure	Add 20 g/L glycine	Add 20 g/L	EN		363	184	179
Heyland	2013	Mechanical ventilation and 2 or more organ failure	PN: add placebo EN: add placebo	PN: add 0.5 g/kg/d EN: add 30 g/d	EN+PN	Maximum of 28 days	1218	607	611
Heyland	2022	Major burn	Add placebo	Isocaloric, Add 0.5 g/kg/d	EN	Until 7 days after the last skin graft or discharged from ICU, 3 months after admission	1200	604	596
Jones	1999	APACHE II score ≥11	Standard EN formula	Isonitrogenous, 5 g	EN	Until death or normal oral diet was established	50	24	26
Lorenz	2015	ENT tumor surgery or multiple-trauma	Standard EN formula	Isonitrogenous supplement	EN		21	9	12
van Zanten	2014	Ventilated for more than 72 hours EN within 48 hours, more than 72 hours	High-protein EN formula	Immune-modulating EN, 25 kcal/kg, maximum 2,500 kcal/d	EN	Maximum of 28 days	301	149	152
Wernerman	2011	APACHE II score ≥10	Placebo (saline)	Add 0.283 g/kg/d	PN	Entire ICU stay	413	208	208
Ziegler	2016	SICU after gastrointestinal, vascular, cardiac surgery	1.5 g/kg/d amino acid, x1.3 estimated basal energy expenditure	Isocaloric isonitrogenous, 0.5 g/kg/d	PN	Maximum of 28 days	150	75	75

Supplement Table 11. Question 6 summary of clinical outcomes of included studies

Study	Group	Total No.	Mortality, n				Infection, n					Length of treatment, mean (SD)		
			Overall	28/30D	ICU	In-hospital	Nosocomial	Wound	UTI	BSI	Pneumonia	Mechanical ventilation	ICU stay	Hospital stay
Andrews	Control	252	80	-	80	-	-	-	-	-	-	-	13.4 (2.62)	-
	GLN	250	88	-	88	-	-	-	-	-	-	-	15 (3.42)	-
Aydoğmuş	Control	20	-	-	-	-	10	-	-	-	10	-	-	-
	GLN	20	-	-	-	-	7	-	-	-	7	-	-	-
Déchelotte	Control	56	2	-	-	2	32	7	4	2	19	-	11.5 (29.5)	26 (100.75)
	GLN	58	2	-	-	2	23	3	0	1	10	-	12.5 (107.25)	30 (139.75)
Estívariz	Control	29	5	-	-	-	-	2	11	12	23	-	-	-
	GLN	30	1	-	-	-	-	2	8	4	15	-	-	-
Fuentes-Orozco	Control	16	3	-	-	-	12	-	-	-	1	4.47(4.4)	7.25 (4.46)	16.69 (7.04)
	GLN	17	2	-	-	-	4	-	-	-	2	4.88(8.2)	7.17 (9.2)	16.52 (8.9)
Goeters	Control	35	10	11	10	-	-	-	-	-	-	-	20.8 (9.1)	39.4 (31.1)
	GLN	33	7	7	7	-	-	-	-	-	-	-	21.3 (13.5)	46 (19.4)
Grau	Control	68	13	-	13	-	31	17	-	-	-	5(1.75)	12 (4.25)	31 (9.5)
	GLN	59	9	-	9	-	24	13	-	-	-	4(2)	12 (3.75)	35 (8.25)
Griffiths	Control	42	22	-	22	42	26	-	-	-	-	-	10.5	-

													(25.25)	
	GLN	42	17	-	17	18	28	-	-	-	-	-	10.5 (14.5)	-
Hall	Control	184	25	25	-	-	43	30	37	-	-	-	13 (1.83)	30 (4.33)
	GLN	179	26	26	-	-	38	30	31	-	-	-	11 (2)	25 (4.33)
Heyland	Control	607	168	-	-	188	-	-	-	-	-	-	8.9 (1.7)	17.1 (4.61)
	GLN	611	198	-	-	277	-	-	-	-	-	-	8.4 (1.93)	16 (4.33)
Heyland	Control	604	84	-	-	84	109	-	-	109	-	-	-	30 (5.83)
	GLN	596	91	-	-	91	113	-	-	113	-	-	-	32 (5.5)
Jones	Control	24	9	-	9	9	5	-	-	-	5	-	26 (15.25)	-
	GLN	26	9	-	9	10	0	-	-	-	0	-	11 (12.5)	-
Lorenz	Control	9	-	-	-	-	9	-	-	-	-	-	-	-
	GLN	12	-	-	-	-	0	-	-	-	-	-	-	-
van Zanten	Control	149	29	25	29	33	131	6	17	12	66	-	-	-
	GLN	152	30	31	30	38	134	3	16	15	61	-	-	-
Wernerman	Control	208	11	20	-	-	-	-	-	-	-	-	-	-
	GLN	208	8	14	-	-	-	-	-	-	-	-	-	-
Ziegler	Control	75	13	12	-	13	39	9	3	13	12	-	-	-
	GLN	75	11	11	-	11	52	9	7	18	10	-	-	-

ICU = intensive care unit; UTI = urinary tract I infection; BSI = blood stream infection.

Supplement Table 12. Question 7 summary of the included studies

Authors	Year	Population	Numbers of patient			Lipid emulsion		% FO on total lipid dosage
			Total	FO	Non-FO	FO	Non-FO	
Wachtler	1997	Cancer, major intestinal surgery	40	19	21	SO/MCT/FO	SO/MCT	NA
Weiss	2002	Gastrointestinal surgery	23	12	11	SO/FO	SO	NA
Heller	2004	Cancer, major abdominal surgery	44	20	24	SO/FO	SO	20
Wichmann	2007	Major abdominal surgery	256	127	129	SO/MCT/FO	SO	10
Berger	2008	Abdominal aortic aneurism surgery	24	12	12	SO/MCT/FO	SO/MCT	10
Friesecke	2008	Critically ill medical	165	83	82	SO/MCT/FO	SO/MCT	16.7
Wang(a)	2008	Severe acute pancreatitis	40	20	20	SO/FO	SO	NA
Wang(b)	2009	Severe acute pancreatitis	56	28	28	SO/FO	SO	NA
Barbosa	2010	SIRS or sepsis	23	13	10	SO/MCT/FO	SO/MCT	10
Sabater	2011	ARDS	16	8	8	SO/MCT/FO	SO	NA
Han	2012	Major surgery	38	18	12	SO/MCT/FO	SO/MCT	20
Gultekin	2014	ICU patients with sepsis	32	16	16	SO/OO/FO	SO/OO	10
Metry	2014	Postoperative patients in surgical ICU	83	41	42	SO/MCT/OO/FO	SO	NA
Grau-Carmona	2015	Medical and surgical ICU patients	175	81	78	SO/MCT/FO	SO/MCT	10
Chen(a)	2017	Severe sepsis with Grade III acute gastrointestinal injury	78	41	37	SO/FO	SO	20
Chen(b)	2017	Patients with septicaemia and intestinal dysfunction	48	24	24	Standard TPN/FO	Standard TPN	NA

Donoghue	2019	ARDS or SIRS in surgical ICU	68	35	33	SO/MCT/OO/FO	SO	15
Kulkarni	2021	Acute-on chronic liver failure (ACLF)	60	30	30	FO	SO	10
Singer	2021	ICU patients requiring mechanical ventilation	100	48	47	SO/MCT/FO	SO/MCT	2

Supplement Table 13. Question 7 summary of clinical outcomes of the randomized controlled studies

Study	Group	Total No.	Mortality (n)		Sepsis in ICU patients (n)	Infection (n)	H – LOS Mean (SD)	ICU – LOS Mean (SD)	MV (d) Mean (SD)
Wachtler	FO	19		NA	0	2	20.1 (29.64)	0.9 (6.1)	NA
	Non-FO	21		NA	1	6	22.4 (49.49)	2 (19.25)	NA
Weiss	FO	12	30 day	1	NA	4	17.8 (3)	4.1 (1.4)	NA
	Non-FO	11	30 day	1	NA	3	23.5 (3)	9.1 (1.2)	NA
Heller	FO	20		NA	NA	NA	19.1 (47.03)	4.3 (1.37)	NA
	Non-FO	24		NA	NA	NA	18.8 (37.57)	4.59 (1.97)	NA
Wichmann	FO	127	30 day	6	4	5	17.2 (6.7)	4.1 (1.6)	NA
	Non-FO	129	30 day	2	5	10	21.9 (8.7)	6.3 (2.5)	NA
Berger	FO	12	30 day	0	NA	NA	9.54 (1.84)	1.76 (0.99)	NA
	Non-FO	12	30 day	0	NA	NA	11.08 (2.46)	2.52 (1.56)	NA
Friesecke	FO	83	30 day	18	NA	11	28 (25)	23 (20)	22.8 (22.9)
	Non-FO	82	30 day	22	NA	12	28 (25)	23 (20)	20.5 (19)
Wang(a)	FO	20	30 day	0	4	3	62.2 (32.65)	21.4 (18.78)	NA
	Non-FO	20	30 day	0	9	5	70.5 (40.7)	27.5 (25.04)	NA
Wang(b)	FO	28	30 day	0	NA	6	NA	NA	NA
	Non-FO	28	30 day	2	NA	9	NA	NA	NA
Barbosa	FO	13	30 day	4	NA	NA	22 (25.24)	12 (14.42)	10 (14.24)
	Non-FO	10	30 day	4	NA	NA	55 (50.6)	13 (12.65)	11 (12.65)
Sabater	FO	8	30 day	4	NA	NA	NA	NA	NA

	Non-FO	8	30 day	2	NA	NA	NA	NA	NA
Han	FO	18		NA	NA	5	NA	NA	NA
	Non-FO	12		NA	NA	5	NA	NA	NA
Gultekin	FO	16	30 day	7	NA	NA	31.6 (17.2)	NA	NA
	Non-FO	16	30 day	8	NA	NA	30.6 (17.2)	NA	NA
Metry	FO	41	30 day	3	NA	NA	15.7 (11.4)	10.4 (6.2)	7.2 (4.3)
	Non-FO	42	30 day	3	NA	NA	19.4 (12.6)	11.7 (7.2)	6.5 (5.1)
Grau-Carmona	FO	81	30 day	25	NA	17	32.97 (29.09)	16.97 (16.55)	7.63 (4.39)
	Non-FO	78	30 day	21	NA	26	40.7 (25.23)	18.99 (9.53)	9.32 (6.5)
Chen(a)	FO	41	30 day	10	NA	4	20.3 (2.29)	NA	NA
	Non-FO	37	30 day	15	NA	8	21 (2.68)	NA	NA
Chen(b)	FO	24	30 day	3	NA	NA	NA	13.8 (9.9)	NA
	Non-FO	24	30 day	10	NA	NA	NA	24.4 (23.2)	NA
Donoghue	FO	35		NA	NA	NA	NA	9.5 (7.1)	1.24 (0.83)
	Non-FO	33		NA	NA	NA	NA	10.7 (7.6)	0.88 (1.63)
Kulkarni	FO	30	30 day	2	4	NA	NA	NA	NA
	Non-FO	30	30 day	5	12	NA	NA	NA	NA
Singer	FO	48	28 day 90 day	10 15	NA	NA	33	23	NA
	Non-FO	47	28 day 90 day	11 11	NA	NA	39	24	NA
FO = fish oil; SO = soybean oil; MCT = medium-chain triglycerides; OO = olive oil; ICU = intensive care unit; LOS = length of stay; H = hospital; MV = mechanical ventilator.									