SUPPLEMENTARY MATERIALS

Table of contents

The search strategy in this meta-analysis

A total of 1475 records searched from PUBMED:

1. ((((((((((((((((((Enteral Nutrition[MeSH Terms]) OR Enteral Feeding) OR Force Feeding) OR Force Feedings) OR Tube Feeding) OR Gastric Feeding Tube*) OR Feeding Tube*) OR Gastric Feeding) OR enteric feeding) OR enteral nutrition) OR enteric nutrition) OR intestinal feeding*) OR intraintestinal feeding*) OR enteral) OR feeding*) OR diet*) OR dietary) OR Trophic feed*) OR Permissive underfeeding) OR artificial feeding* (1514390 records)
2. ((((((((((((((((((Energy Intake[MeSH Terms]) OR Nutritional Status[MeSH Terms]) OR Nutritional Support[MeSH Terms]) OR Hypocaloric nutrition) OR Energy intake) OR Nutritional Support) OR caloric intake) OR Energy Intake) OR Nutritional Status) OR Nutrition Status) OR dietary energy) OR nutrition* state) OR nutritional therap*) OR nutrition*) OR underfed) OR underfeeding) OR underfeed) OR overfed) OR overfeeding) OR overfeed (1944488 records)
3. (((((Critical Care[MeSH Terms]) OR intensive care[MeSH Terms]) OR Critical Illness[MeSH Terms]) OR Intensive Care Units[MeSH Terms])) OR ((((((((Critical Care) OR intensive care) OR Critical* illness) OR Intensive Care Unit*) OR ICU) OR ICUs) OR intensive illness) OR critically ill) (440737 records)
4. #1 and #2 and #3 (13909 records)
5. ((((((((Randomized Controlled Trial[MeSH Terms]) OR Random allocation[MeSH Terms]) OR randomized controlled trials as topic[MeSH Terms]) OR Randomized controlled trial*) OR Random allocation) OR randomized stud*) OR randomized trial*) OR Controlled Clinical Trial*) OR randomized (997611 records)
6. #4 and #5 (2571 records)
7. #4 and #5 Sort by: Best Match Filters: Clinical Trial; Humans (1475 records)

A total of 2594 records searched from EMBASE:

1. 'enteral nutrition'/exp OR 'enteral nutrition' OR (enteral AND ('nutrition'/exp OR nutrition)) OR 'enteral feeding'/exp OR 'enteral feeding' OR (enteral AND ('feeding'/exp OR feeding)) OR 'force feeding' OR (('force'/exp OR force) AND ('feeding'/exp OR feeding)) OR 'force feedings' OR (('force'/exp OR force) AND feedings) OR 'tube feeding'/exp OR 'tube feeding' OR (('tube'/exp OR tube) AND ('feeding'/exp OR feeding)) OR (gastric AND ('feeding'/exp OR feeding) AND tube*) OR (('feeding'/exp OR feeding) AND tube*) OR 'gastric feeding'/exp OR 'gastric feeding' OR (gastric AND ('feeding'/exp OR feeding)) OR 'enteric feeding'/exp OR 'enteric feeding' OR (enteric AND ('feeding'/exp OR feeding)) OR 'enteric nutrition'/exp OR 'enteric nutrition' OR (enteric AND ('nutrition'/exp OR nutrition)) OR (intestinal AND feeding*) OR (intraintestinal AND feeding*) OR enteral、feeding* OR diet* OR dietary OR (trophic AND feed*) OR 'permissive underfeeding' OR (permissive AND ('underfeeding'/exp OR underfeeding)) OR (artificial AND feeding*) (1141771 records)
2. 'energy intake'/exp OR 'energy intake' OR (('energy'/exp OR energy) AND intake) OR 'nutritional status'/exp OR 'nutritional status' OR (nutritional AND status) OR 'nutritional support'/exp OR 'nutritional support' OR (nutritional AND ('support'/exp OR support)) OR 'hypocaloric nutrition' OR (hypocaloric AND ('nutrition'/exp OR nutrition)) OR 'caloric intake'/exp OR 'caloric intake' OR (caloric AND intake) OR 'nutrition status'/exp OR 'nutrition status' OR (('nutrition'/exp OR nutrition) AND status) OR 'dietary energy'/exp OR 'dietary energy' OR (dietary AND ('energy'/exp OR energy)) OR (nutrition* AND ('state'/exp OR state)) OR (nutritional AND therap*) OR underfed OR 'underfeeding'/exp OR underfeeding OR underfeed OR overfed OR 'overfeeding'/exp OR overfeeding OR overfeed (967826 records)
3. 'critical care'/exp OR 'critical care' OR (critical AND ('care'/exp OR care)) OR (intensive AND ('care'/exp OR care)) OR (critical* AND ('illness'/exp OR illness)) OR 'intensive care'/exp OR 'intensive care' OR (intensive AND ('care'/exp OR care) AND unit*) OR icu OR icus OR 'intensive illness' OR (intensive AND ('illness'/exp OR illness)) OR 'critically ill'/exp OR 'critically ill' OR (critically AND ill) (1721445 records)

4. #1 and #2 and #3 (38254 records)
5. #4 AND 'randomized controlled trial'/de (2594 records)

A total of 1070 records searched from Web of Science:

1. TS= (Enteral Nutrition) OR TS= (Enteral Feeding) OR TS= (Force Feeding*) OR TS= (Tube Feeding) OR TS= (Gastric Feeding Tube*) OR TS= (Feeding Tube*) OR TS= (Gastric Feeding) OR TS= (enteric feeding*) OR TS= (enteric nutrition) OR TS= (intestinal feeding*) (302550 records)
2. TS= (intraintestinal feeding*) OR TS= (enteral、feeding*) OR TS= (diet*) OR TS= (dietary) OR TS= (Trophic feed*) OR TS= (Permissive underfeeding) OR TS= (artificial feeding*) (1415921 records)
3. #1 or #2 (1660650 records)
4. TS= (Energy Intake) OR TS= (Nutritional Status) OR TS= (Nutritional Support) OR TS= (Hypocaloric nutrition) OR TS= (caloric intake) OR TS= (Nutrition Status) OR TS= (dietary energy) OR TS= (nutrition* state) OR TS= (nutritional therap*) OR TS= (nutrition*) (2052294 records)
5. TS= (underfed) OR TS= (underfeeding) OR TS= (underfeed) OR TS= (overfed) OR TS= (overfeeding) OR TS= (overfeed) (6391 records)
6. #4 or #5 (2054509 records)
7. TS= (Critical Care) OR TS= (intensive care) OR TS= (Critical* Illness) OR TS= (Intensive Care Units) OR TS= (Intensive Care Unit*) OR TS= (overfeed) OR TS= (ICU) OR TS= (ICUs) OR TS= (intensive illness) OR TS= (critically ill) (423441 records)
8. #3 and #6 and #7 (13014 records)
9. TS= (Randomized Controlled Trial*) OR TS= (Random allocation) OR TS= (randomized stud*) OR TS= (randomized trial*) OR TS= (Controlled Clinical Trial*) OR TS= (randomized) (1327190 records)
10. #8 and #9 (3303 records)
11. #10 Refined by: DOCUMENT TYPES: (CLINICAL TRIAL) (1070 records)

A total of 779 records searched from Cochrane Library:

1. MeSH descriptor: [Enteral Nutrition] explode all trees (1703 records)
2. (enteral nutrition):ti,ab,kw OR (Enteral Feeding):ti,ab,kw OR (Force Feeding*):ti,ab,kw OR (Tube Feeding*):ti,ab,kw OR (Gastric Feeding Tube*):ti,ab,kw (5337 records)
3. (Feeding Tube*):ti,ab,kw OR (Gastric Feeding*):ti,ab,kw OR (enteric feeding*):ti,ab,kw OR (enteral nutrition):ti,ab,kw OR (enteric nutrition):ti,ab,kw (6085 records)
4. (intestinal feeding*):ti,ab,kw OR (intraintestinal feeding*):ti,ab,kw OR (enteral feeding*):ti,ab,kw OR (diet*):ti,ab,kw OR (dietary):ti,ab,kw (70095 records)
5. (Trophic feed*):ti,ab,kw OR (Permissive underfeeding*):ti,ab,kw OR (artificial feeding*):ti,ab,kw (820 records)
6. #1 or #2 or #3 or #4 or #5 (72803 records)
7. MeSH descriptor: [Energy Intake] explode all trees (4987 records)
8. (Hypocaloric nutrition):ti,ab,kw OR (Energy intake):ti,ab,kw OR (Nutritional Support):ti,ab,kw OR (caloric intake):ti,ab,kw OR (Nutritional Status):ti,ab,kw (20757 records)
9. (Nutrition Status):ti,ab,kw OR (dietary energy):ti,ab,kw OR (nutrition* state):ti,ab,kw OR (nutritional therap*):ti,ab,kw OR (nutrition*):ti,ab,kw (33406 records)
10. (underfed):ti,ab,kw OR (underfeed*):ti,ab,kw OR (overfed):ti,ab,kw OR (overfeed*):ti,ab,kw (186 records)
11. #7 or #8 or #9 or #10 (37823 records)
12. (Critical Care):ti,ab,kw OR (intensive care):ti,ab,kw OR (Critical* illness):ti,ab,kw OR (Intensive Care Unit*):ti,ab,kw AND (ICU):ti,ab,kw (32873 records)
13. (ICUs):ti,ab,kw OR (intensive illness):ti,ab,kw OR (critically ill):ti,ab,kw (9945 records)
14. #11 or #12 (34326 records)
15. ("randomized controlled trial"):pt (465593 records)
16. #6 and #11 and #14 and #15 (779 records)

Table S1. The reasons for exclusion of 45 ineligible studies

Reasons	Studies
Irrelevant studies with ineligible comparisons (13 trials)	Harvey/2014[s1]; Bauer/2000[s2]; Huschak/2005[s3]; Reynolds/1997[s4]; Ibrahim/2005[s5]; Chen/2006[s6]; Nguyen/2007[s7]; Montejo/2010[s8]; Acosta-Escribano/2010[s9]; Reignier/2013[s10]; van Zanten/2014[s11]; Montejo/2002[s12]; Berg/2013[s13]
More than 70% of daily caloric requirements in both groups (15 trials)	Desachy/2008[s14]; Huang/2012[s15]; Kagan/2015[s16]; Peake/2014[s17]; Schneider/2011[s18]; Heidegger/2013[s19]; Hsu/2009[s20]; White/2009[s21]; Singer/2011[s22]; Jakob/2017[s23]; Gonzalez-Granda/2018[s24]; Moreno/2014[s25]; Lu/2018[s26]; Caparrós/2011[s27]; Grau-Carmona/2011[s28]
Less than 70% of daily caloric requirements in both groups (8 trials)	Montecalvo1992[s29]; MacLeod/2007[s30]; Qiu/2017[s31]; Charles/2014[s32]; Rugeles/2013[s33]; Taylor/1999[s34]; Montecalvo/1992[s35]; Kearns/2000[s36]
No data on proportion of daily caloric intake to goal caloric requirements (2 trials)	Efremov/2017[s37]; Doig/2015[s38]
Retrospective studies (3 trials)	Hartl/2018[s39]; Song/2016[s40]; Arabi/2010[s41]
Abstract without full-text (2 trial)	Theodorakopoulou/2016[s42]; Norouzy/2013[s43]
Ineligible patients (2 trials)	Wischmeyer/2017[s44]: This study enrolled critically ill adult patients in the ICU who received EN <60% estimated needs within 48 hours of ICU admission, then the eligible patients were randomized to receive either EN or PN + EN Ridley/2018[s45]: This study enrolled ICU patients who received <80% of estimated nutrition requirements from EN in the 24 hours prior to randomization, then the eligible patients were randomized to receive either EN or PN + EN, moreover, patients in the PN + EN group had received PN as the main source of nutrition

Supplementary reference

s1. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med, 2014;371(18):1673-84.

s2. Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N. Parenteral with enteral nutrition in the critically ill. Intensive Care Med, 2000;26(7):893e900..

s3. Huschak G, Zur Nieden K, Hoell T, Riemann D, Mast H, Stuttmann R. Olive oil based nutrition in multiple trauma patients: a pilot study. Intensive Care Med, 2005;31(9):1202e8..

s4. Reynolds JV, Kanwar S, Welsh FKS, Windsor ACJ, Murchan P, Barclay GR, et al. Does the

route of feeding modify gut barrier function and clinical outcome in patients after major upper gastrointestinal surgery? J Parenter Enteral Nutr, 1997;21(4):196e201..

s5. Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, Fraser V, et al. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. J Parenter Enteral Nutr, 2002; 26:174-181.

s6. Chen YC, Chou SS, Lin LH, Wu LF. The effect of intermittent nasogastric feeding on preventing aspiration pneumonia in ventilated critically ill patients. J Nurs Res, 2006;14(3):167–80.

s7. Nguyen NQ, Chapman M, Fraser RJ, Bryant LK, Burgstad C, Holloway RH. Prokinetic therapy for feed intolerance in critical illness: one drug or two? Crit Care Med, 2007;35(11):2561–7.

s8. Montejo JC, Minambres E, Bordeje L, Mesejo A, Acosta J, Heras A, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. Intensive Care Med, 2010;36(8):1386–93.

s9. Acosta-Escribano J, Fernandez-Vivas M, Grau Carmona T, Caturla-Such J, Garcia-Martinez M, Menendez-Mainer A, et al. Gastric versus transpyloric feeding in severe traumatic brain injury: a prospective, randomized trial. Intensive Care Med, 2010;36(9):1532–9.

s10. Reignier J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec F, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA, 2013;309(3):249–56.

s11. van Zanten AR, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. JAMA, 2014, 6;312(5):514-24.

s12. Montejo JC, Grau T, Acosta J, Ruiz-Santana S, Planas M, García-De-Lorenzo A, et al. Multicenter, prospective, randomized, single-blind study comparing the efficacy and gastrointestinal complications of early jejunal feeding with early gastric feeding in critically ill patients. Crit Care Med, 2002;30(4):796-800.

s13. Berg A, Rooyackers O, Bellander BM, Wernerman J. Whole body protein kinetics during hypocaloric and normocaloric feeding in critically ill patients. Crit Care, 2013,24;17(4):R158.

s14. Desachy A, Clavel M, Vuagnat A, Normand S, Gissot V, François B. Initial efficacy and tolerability of early enteral nutrition with immediate or gradual introduction in intubated patients. Intensive Care Med, 2008;34(6):1054e9.

s15. Huang H-H, Chang S-J, Hsu C-W, Chang T-M, Kang S-P, Liu M-Y. Severity of illness influences the efficacy of enteral feeding route on clinical outcomes in patients with critical illness. J Acad Nutr Dietetics, 2012;112(8):1138e46.

s16. Kagan I, Cohen J, Stein M, Bendavid I, Pinsker D, Silva V, et al. Preemptive enteral nutrition enriched with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in severe multiple trauma: a prospective, randomized, double-blind study. Intensive care Med, 2015;41(3):460e9.

s17. Peake SL, Davies AR, Deane AM, Lange K, Moran JL, O'Connor SN, et al. Use of a concentrated enteral nutrition solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical trial. Am J Clin Nutr, 2014;100(2):616e25.

s18. Schneider A, Markowski A, Momma M, Seipt C, Luettig B, Hadem J, et al. Tolerability and efficacy of a low-volume enteral supplement containing key nutrients in the critically ill. Clin Nutr, 2011;30(5):599e603.

s19. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet, 2013;381:385-93.

s20. Hsu CW, Sun SF, Lin SL, Kang SP, Chu KA, Lin CH, et al. Duodenal versus gastric feeding in medical intensive care unit patients: a prospective, randomized, clinical study. Crit Care Med, 2009;37(6):1866–72.

s21. White H, Sosnowski K, Tran K, Reeves A, Jones M. A randomised controlled comparison of early post-pyloric versus early gastric feeding to meet nutritional targets in ventilated

intensive care patients. Crit Care, 2009;13(6):R187.
s22. Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med, 2011;37(4):601–9.
s23. Jakob SM, Bütikofer L, Berger D, Coslovsky M, Takala J. A randomized controlled pilot study to evaluate the effect of an enteral formulation designed to improve gastrointestinal tolerance in the critically ill patient-the SPIRIT trial. Crit Care, 2017;21(1):140.
s24. Gonzalez-Granda A, Schollenberger A, Haap M, Riessen R, Bischoff SC. Optimization of Nutrition Therapy with the Use of Calorimetry to Determine and Control Energy Needs in Mechanically Ventilated Critically Ill Patients: The ONCA Study, a Randomized, Prospective Pilot Study. JPEN J Parenter Enteral Nutr, 2018. doi: 10.1002/jpen.1450. [Epub ahead of print]
s25. Moreno C, Trépo E, Louvet A, Degré D, Bastens B, Hittelet A, et al. Impact of intensive enteral nutrition in association with corticosteroids in the treatment of severe alcoholic hepatitis: A multicenter randomized controlled trial. Hepatology, 2014; 60: 269A-270A.
s26. Lu K, Zeng F, Li Y, Chen C, Huang M. A more physiological feeding process in ICU: Intermittent infusion with semi-solid nutrients (CONSORT-compliant). Medicine (Baltimore), 2018;97(36):e12173.
s27. Caparrós T, Lopez J, Grau T. Early enteral nutrition in critically ill patients with a high-protein diet enriched with arginine, fiber, and antioxidants compared with a standard high-protein diet. The effect on nosocomial infections and outcome. JPEN J Parenter Enteral Nutr, 2001;25(6):299-308; discussion 308-9.
s28. Grau-Carmona T, Morán-García V, García-de-Lorenzo A, Heras-de-la-Calle G, Quesada-Bellver B, López-Martínez J, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. Clin Nutr, 2011;30(5):578-84.
s29. Montecalvo MA, Steger KA, Farber HW, Smith BF, Dennis RC, Fitzpatrick GF, et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. The Critical Care Research Team. Crit Care Med, 1992;20(10):1377-87.
s30. MacLeod JB, Lefton J, Houghton D, Roland C, Doherty J, Cohn SM, et al. Prospective randomized control trial of intermittent versus continuous gastric feeds for critically ill trauma patients. J Trauma, 2007;63(1):57-61.
s31. Qiu C, Chen C, Zhang W, Kou Q, Wu S, Zhou L, et al. Fat-Modified Enteral Formula Improves Feeding Tolerance in Critically Ill Patients: a Multicenter, Single-Blind, Randomized Controlled Trial. JPEN J Parenter Enteral Nutr, 2017;41(5):785-795.
s32. Charles EJ, Petroze RT, Metzger R, Hranjec T, Rosenberger LH, Riccio LM, et al. Hypocaloric compared with eucaloric nutritionaql support and its effect on infection rates in a surgical intensive care unit: a randomized controlled trial. Am J Clin Nutr, 2014;100:1337–1343.
s33. Rugeles SJ, Rueda JD, D´ ıaz CE, Rosselli D. Hyperproteic hypocaloric enteral nutrition in the critically ill patient: a randomized controlled clinical trial. Indian J Crit Care Med, 2013;17(6):343-349.

s34. Taylor S, Fettes S, Jewkes C, Nelson R. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Criti Care Med, 1999;27:2525.
s35. Montecalvo MA, Steger KA, Farber HW, Smith BF, Dennis RC, Fitzpatrick GF, et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. The Critical Care Research Team. Crit Care Med, 1992;20(10):1377–87.
s36. Kearns PJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM. The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. Crit Care Med, 2000;28(6):1742–6.
s37. Efremov S, Lomivorotov V, Stoppe C, Shilova A, Shmyrev V, Deryagin M, et al. Standard vs. Calorie-Dense Immune Nutrition in Haemodynamically Compromised Cardiac Patients:

A Prospective Randomized Controlled Pilot Study. Nutrients, 2017;9(11). pii: E1264.
s38. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, singleblind controlled trial. Lancet Respir Med, 2015;3(12):943–52.
s39. Hartl WH, Bender A, Scheipl F, Kuppinger D, Day AG, Küchenhoff H. Calorie intake and short-term survival of critically ill patients. Clin Nutr, 2019;38(2):660-667.
s40. Song S, Hong SK. Iinitial calorie delivery and clinical outcomes in critically ill surgical patients. Clinical Nutrition, 2016, 35: S142-S143.
s41. Arabi YM, Haddad SH, Tamim HM, Rishu AH, Sakkijha MH, et al. Near-target caloric intake in critically ill medical-surgical patients is associated with adverse outcomes. JPEN J Parenter Enteral Nutr, 2010;34(3):280-8.
s42. Theodorakopoulou M, Diamantakis A, Kontogiorgi M, Chrysanthopoulou E, Christodoulopoulou T, Frantzeskaki F, et al. Permissive underfeeding of mechanically ventilated septic ICU Patients. Intensive Care Medicine Experimental, 2016, 4(Suppl 1):27.
s43. Norouzy A, Kazemi M, Samini F, Nematy M. Early permissive enteral underfeeding in critically ill head trauma patients: A double blind randomized controlled trial. Clinical Nutrition, 2013, 32: S27.
s44. Wischmeyer PE, Hasselmann M, Kummerlen C, Kozar R, Kutsogiannis DJ, Karvellas CJ, et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. Crit Care, 2017;21(1):142.
s45. Ridley EJ, Davies AR, Parke R, Bailey M, McArthur C, Gillanders L, et al. Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study. Crit Care, 2018;22(1):12.

Table S2. The detailed characteristics of all included trials

First author /Publication year	Design (location)	Sample size	Population	Setting	Body-mass index (kg/m²)		APACHE II/III/SAPS II score (points)		Duration of intervention	Actual calories received	Protein delivery (% target)		Daily caloric intake (% target)	
					hypocaloric	standard	hypocaloric	standard			hypocaloric	standard	hypocaloric	standard
Allingstrup/2017	Single-centre (Denmark)	199	Mechanically ventilated ICU patients anticipated to stay in ICU for > 3 days	Mixed ICU	22 (20–25)	22 (20–26)	48 (39–59)	47 (37–54)	until tracheal extubation or ICU discharge	EN, and PN if need, and propofol	0.50 (0.29–0.69) g/kg/day (33.3%) 1.47 (1.13–1.69) g/kg/day (98.0%)		1061(745–1470) kcal/day (56.2%) 1877(1567–2254) kcal/day (90.7%)	
Arabi/2011	Single-center (Saudi Arabia)	240	ICU patients expected to stay for >48 hours	Mixed ICU	28.5±7.4	28.5±8.4	25.2±7.5	25.3±8.2	until discharge from the ICU	EN, and dextrose and propofol	47.5±21.2 g/day (65.2%) 43.6±18.9 g/day (63.7%)		1066.6±306.1 kcal/day (59.0%) 1251.7±432.5 kcal/day (71.4%)	
Arabi/2015	Multi-centre (Saudi Arabia and Canada)	894	ICU patients fed enterally within 48 hours after ICU admission	Medical or surgical ICU	29.0±8.2	29.7±8.8	21.0±7.9	21.0±8.2	14 days or until ICU discharge, initiation of oral feeding, death, or withholding of nutrition	EN, and propofol, dextrose, and PN if need	57±24 g/day (68%) 59±25 g/day (69%)		835±297 kcal/day (46%) 1299±467 kcal/day (71%)	
Braunschweig/2015	Single-centre (USA)	78	ICU patients with acute lung injury	Medical or surgical ICU	30.1±8.9	29.8±9.3	27.7±7.9	23.4±9.3	until hospital discharge	EN, propofol, dextrose, and PN; oral dietary was initiated after extubation, if allowed	60.4±24 g/day (54.4%) 82±23 g/day (76.1%)		1221±423 kcal/day (55.4%) 1798±509 kcal/day (84.7%)	
Chapman/2018	Multi-centre (Australia and New Zealand)	3957	ICU patients receiving invasive mechanical ventilation and were about to commence EN, or had commenced EN within the previous 12 hours	Medical or surgical ICU	29.3±7.9	29.2±7.7	22.1±8.5	22.0±8.3	28 days or until discontinued EN, died, or discharged from ICU	EN, and PN if need, and other source	69.4±17.2 g/day (77%) 69.6±17.8 g/day (78%)		1262±313 kcal/day (69%) 1863±478 kcal/day (103%)	
Liu/2014	Single-centre (China)	116	Septic patients in ICU who were expected to stay in ICU >72 hours	Surgical ICU	22.65±3.72	20.34±3.80	21.98±7.60	20.43±5.74	unclear	EN, and PN if need, and propofol and glucose	unclear		4671.6±1205.6 kJ/day (66%) 5655.3±1373.0 kJ/day (100%)	
Ma/2018	Single-centre (China)	82	patients requiring mechanical ventilation admitted to ICU	Mixed ICU	unclear		20.6±8.2	22.8±7.4	7 days	EN, and PN if need	unclear		50% of daily caloric requirements 100% of daily caloric requirements	
Petros/2016	Single-centre (Germany)	100	ICU patients needed for artificial nutrition	Medical ICU	28.6±6.5	27.1±6.8	30.5±8.5	27.7±8.4	7 days	EN, and PN if need	The daily protein dose in hypocaloric group was		11.3±3.1 kcal/kg/day (42.6%)	

			support for ≥3 days									significantly lower than standard group (P<0.001)	19.7±5.7 kcal/kg/day (75.5%)
Rice/2011	Single-center (USA)	200	ICU patients expected to require mechanical ventilation for ≥ 72 hours	Medical ICU	29.2±10.2	28.2±9.4	26.9±8.1	26.9±6.6	6 days	EN	10.9±6.8 g/day (unknow) 54.4±33.2 g/day (unknow)	300±149 kcal/day (15.8%) 1418±686 kcal/day (74.8%)
Rice/2012	Multi-centre (USA)	1000	Patients within 48 hours of ALI onset who had received mechanical ventilation for <72 hours	Medical or surgical ICU	29.9±7.8	30.4±8.2	92±28	90±27	until death, extubation, or day 6	EN	unclear	approximately 400 kcal/day (25%) approximately 1300 kcal/day (80%)
Rugeles/2016	Single-centre (Colombia)	120	ICU patients expected to require EN through nasoenteric tube for ≥96 hours	Mixed ICU	25±2.5	25±2.5	13.5±6.4	13.7±6.8	7 days	EN	1.3±0.3 g/kg/d (86.7%) 1.3±0.3 g/kg/d (86.7%)	12.1±2.6 kcal/kg/day (48.4%) 19.2±4.3 kcal/kg/day (76.8%)

The data were presented as mean± standard deviation or median (interquartile rang);
APACHE acute physiology and chronic health evaluation; SAPS Simplified Acute Physiology Score; ICU intensive care unit; EN enteral nutrition; PN parenteral nutrition.

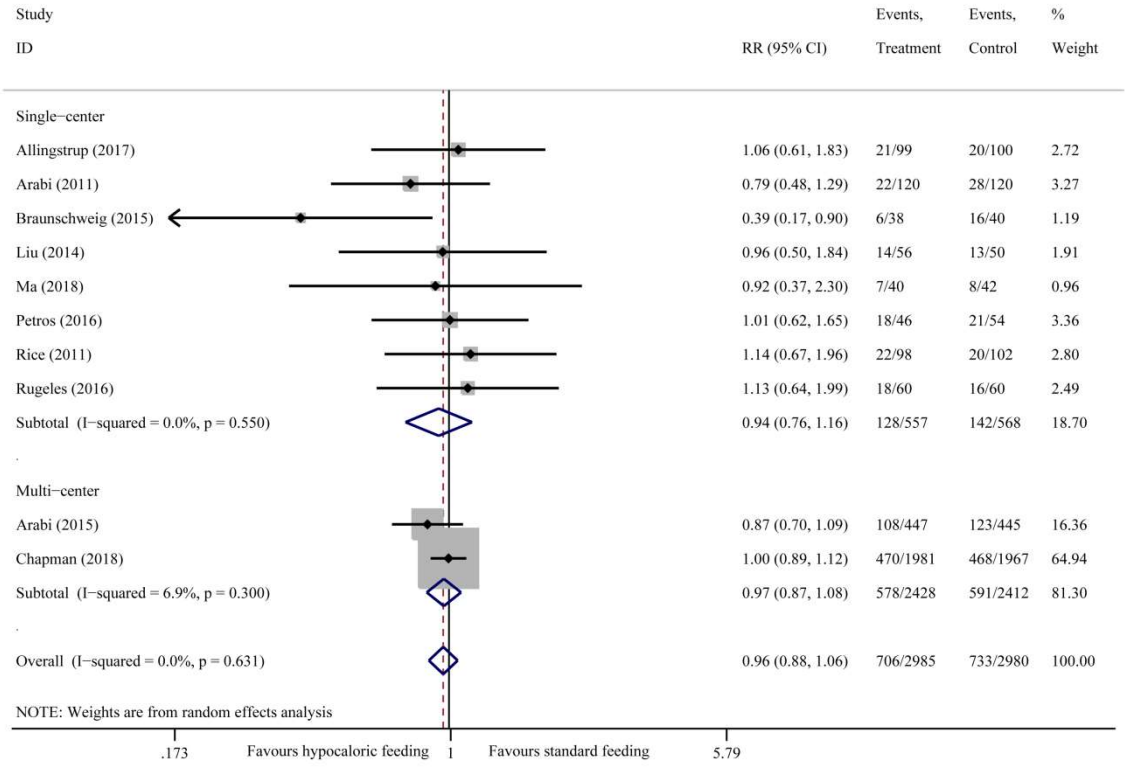
Table S3. The detailed data on clinical outcomes in all included trials

First author /Publication year	Short-term mortality (death/total)		Long-term mortality (death/total)		Duration of ICU stay (days) [mean±SD/median(IQR)]		Duration of in-hospital stay (days) [mean±SD/median(IQR)]		Duration of MV (days) [mean±SD/median(IQR)]		Incident of hypoglycemia (events/total)		Incident of GI intolerance (events/total)	
	hypocaloric	standard	hypocaloric	standard	hypocaloric	standard	hypocaloric	standard	hypocaloric	standard	hypocaloric	standard	hypocaloric	standard
Allingstrup/2017	28-day mortality		90-day mortality											
	21/99	20/100	34/99	37/100	7(4-11)	7(5-22)	34(14-53)	30(12-53)	—	—	1/99	2/100	—	—
Arabi/2011	28-day mortality		180-day mortality											
	22/120	28/120	38/116	52/117	11.7±8.1	14.5±15.5	70.2±106.9	67.2±93.6	10.6±7.6	13.2±15.2	25/120	21/120	—	—
Arabi/2015	In-hospital mortality		180-day mortality											
	108/447	123/445	131/438	140/436	13(8-21)	13(8-20)	28(15-54)	30(14-63)	9(5-15)	10(5-16)	6/448	7/446	97/448	117/446
Braunschweig/2015	30-day mortality													
	6/38	16/40	—	—	16.1±11.5	15.5±12.8	25.1(12.7-28)	25.1(12.3-28)	7(3-14)	6(4-10)	11/38	12/40	—	—
Chapman/2018	In-hospital mortality		90-day mortality											
	470/1981	468/1967	505/1966	523/1948	10.6(4.9-28)	11(5-28)	25.1(12.7-28)	25.1(12.3-28)	8(3-28)	8(3-28)	28/1986	29/1971	309/1966	370/1959
Liu/2014	28-day mortality		60-day mortality											
	14/56	13/50	21/56	14/50	14.9±9.6	11.0±6.4	32.0±22.5	26.8±7.0	11.0±8.2	8.4±6.3	—	—	—	—
Ma/2018	28-day mortality								Hours					
	7/40	8/42	—	—	7.52±1.62	6.34±1.87	—	—	162.4±20.4	153.5±18.7	—	—	—	—
Petros/2016	28-day mortality								Hours					
	18/46	21/54	—	—	—	—	—	—	254.5(155.5-686.3) 178.5(69.5-403.3)		12/46	8/54	9/46	23/54
Rice/2011	In-hospital mortality													
	22/98	20/102	—	—	7(4-21.5)	7(4-18.7)	16(7-28)	11.5(7-28)	5.5±5.4	5.7±6.4	—	—	26/98	40/102
Rice/2012	—	—	60-day mortality											
			118/508	109/492	13.6(12.7-14.5) 13.3(12.4-14.2)		—	—	13.1(12.2-14.1) 13.0(12.1-13.9)		—	—	109/387	151/388
Rugeles/2016	28-day mortality													
	18/60	16/60	—	—	12(7.3)	10.5(8.0)	—	—	9(8.3)	9(8.3)	—	—	—	—

First author /Publication year	Incident of nosocomial infection (events/total)		Incident of pneumonia (events/total)		Incident of bloodstream infection (events/total)	
	hypocaloric	standard	hypocaloric	standard	hypocaloric	standard
Allingstrup/2017	12/99	19/100	4/99	4/100	4/99	5/100
Arabi/2011	53/120	56/120	14/120	10/120	6/120	10/120
Arabi/2015	161/448	169/446	81/448	90/446	11/447	19/445
Braunschweig/2015	8/38	5/40	—	—	—	—
Chapman/2018	1658/1985	1662/1971	—	—	221/1984	228/1971
Liu/2014	51/56	42/50	—	—	—	—
Ma/2018	18/40	20/42	—	—	—	—
Petros/2016	12/46	6/54	—	—	—	—
Rice/2011	14/98	18/102	14/98	18/102	—	—
Rice/2012	112/508	92/492	37/508	33/492	59/508	46/492
Rugeles/2016	—	—	—	—	—	—

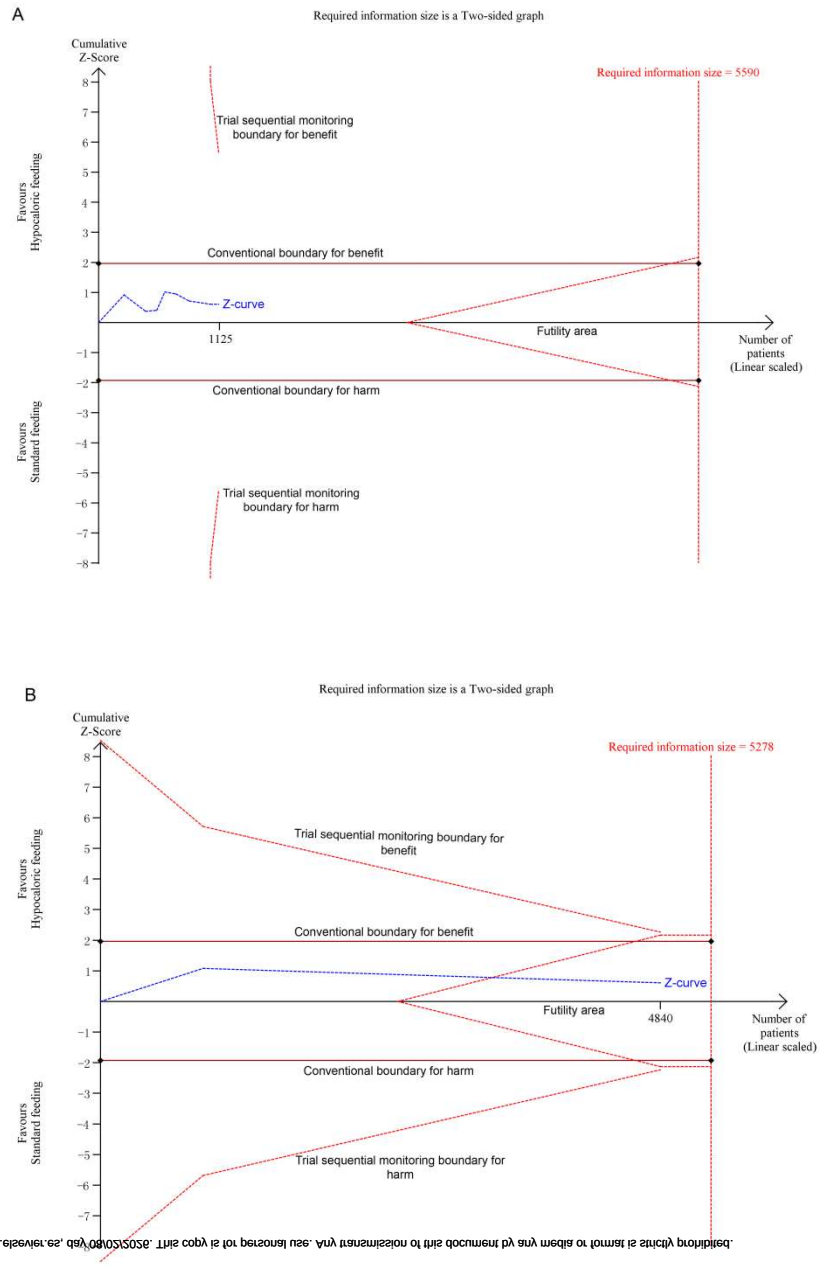
GI gastrointestinal; ICU intensive care unit; MV mechanical ventilation; SD standard deviation; IQR interquartile rang

Figure S1. Forest plot of sub-analysis of trials stratified based on the design type for the short-term mortality



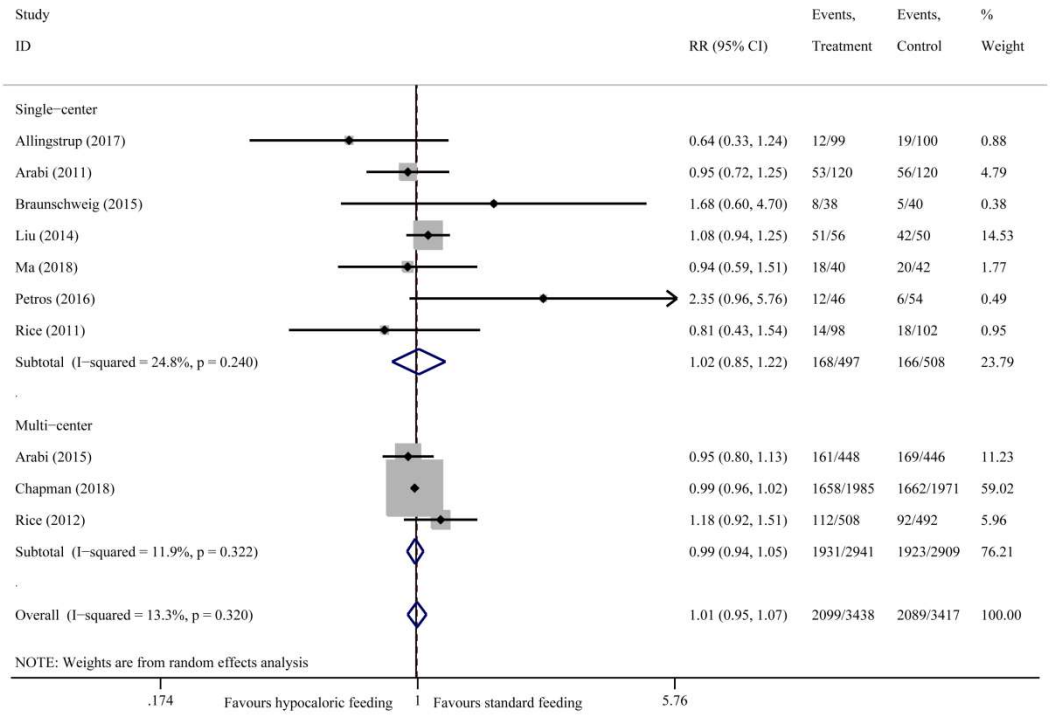
RR relative risk.

Figure S2. Trial sequential analysis for the short-term mortality



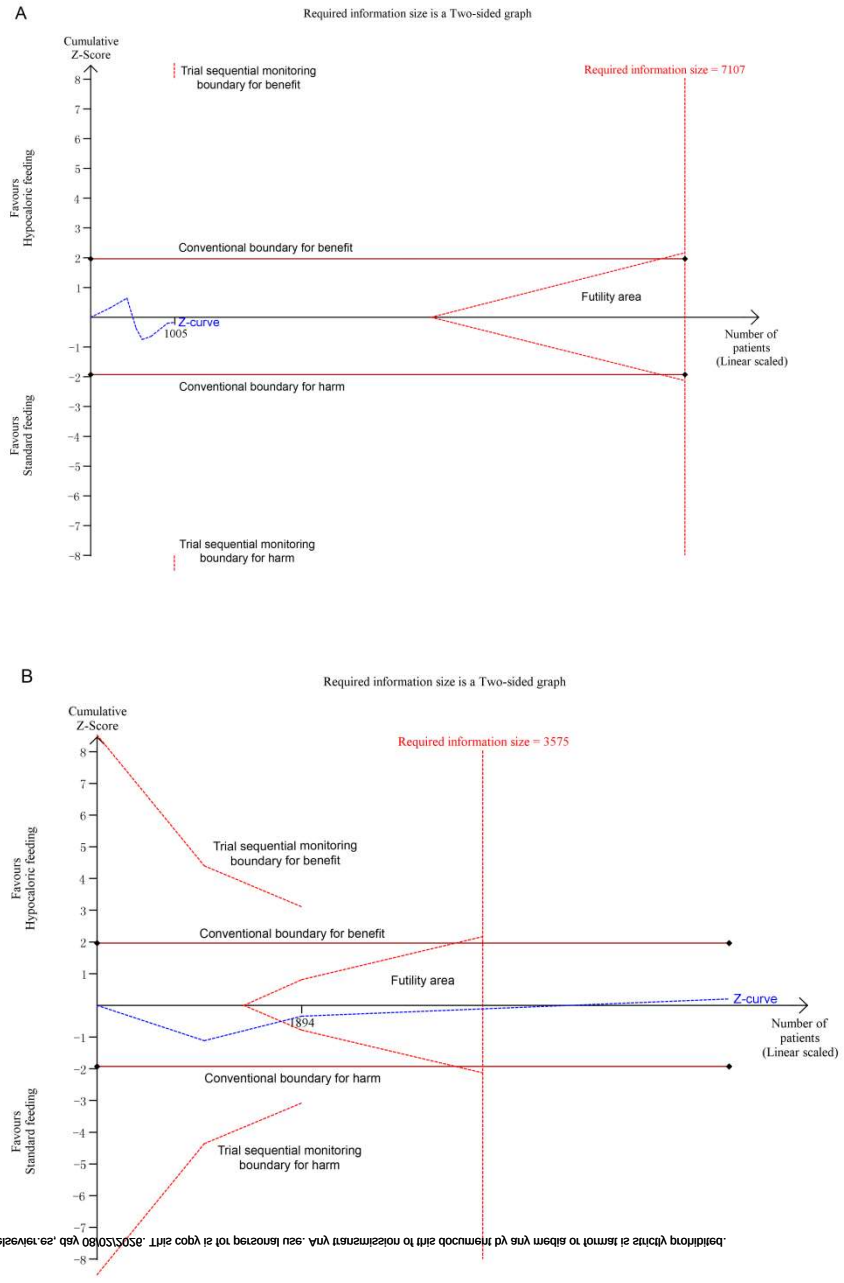
Trial sequential analysis using random-effects model with an adjusted family-wise error rate of 3.3%, power of 80%, for a relative risk reduction of 15% in control event proportion. (panel A) In single-center trials, control event proportion of 25.0%, D^2 of 20% (the actual measured D2 was 0%). The cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 0.94 is 0.52 to 1.70. (panel B) In multi-center trials, control event proportion of 24.5%, D^2 of 13%, the cumulative Z-curve cross the futility area, but do not reach the required information size of 5278 participants. The TSA-adjusted 95% CI for an RR of 0.97 is 0.86 to 1.10. RR relative risk; TSA trial sequential analysis.

Figure S3. Forest plot of sub-analysis of trials stratified based on the design type for the incident of nosocomial infection



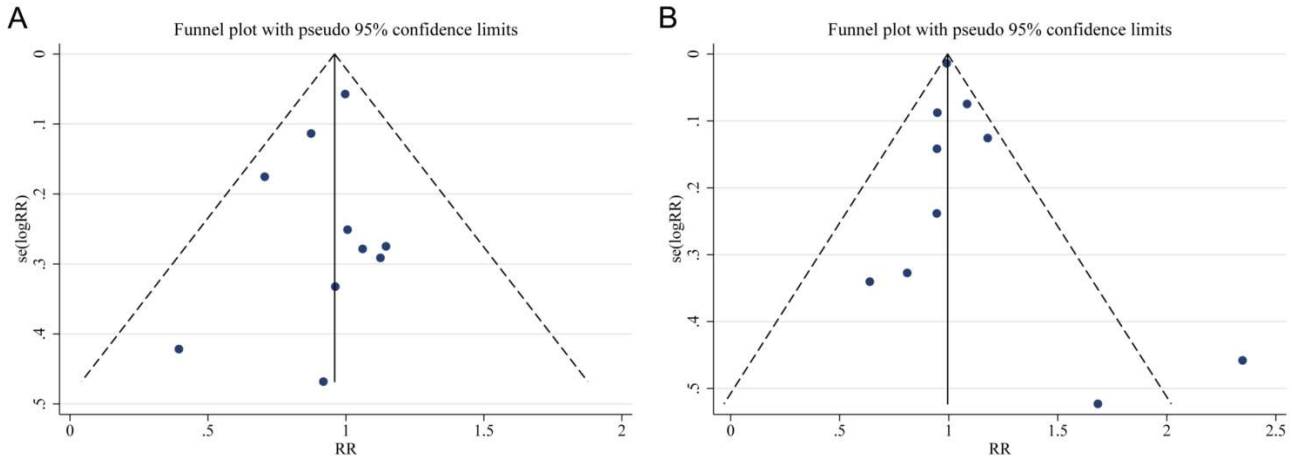
RR relative risk

Figure S4. Trial sequential analysis for the incident of nosocomial infection



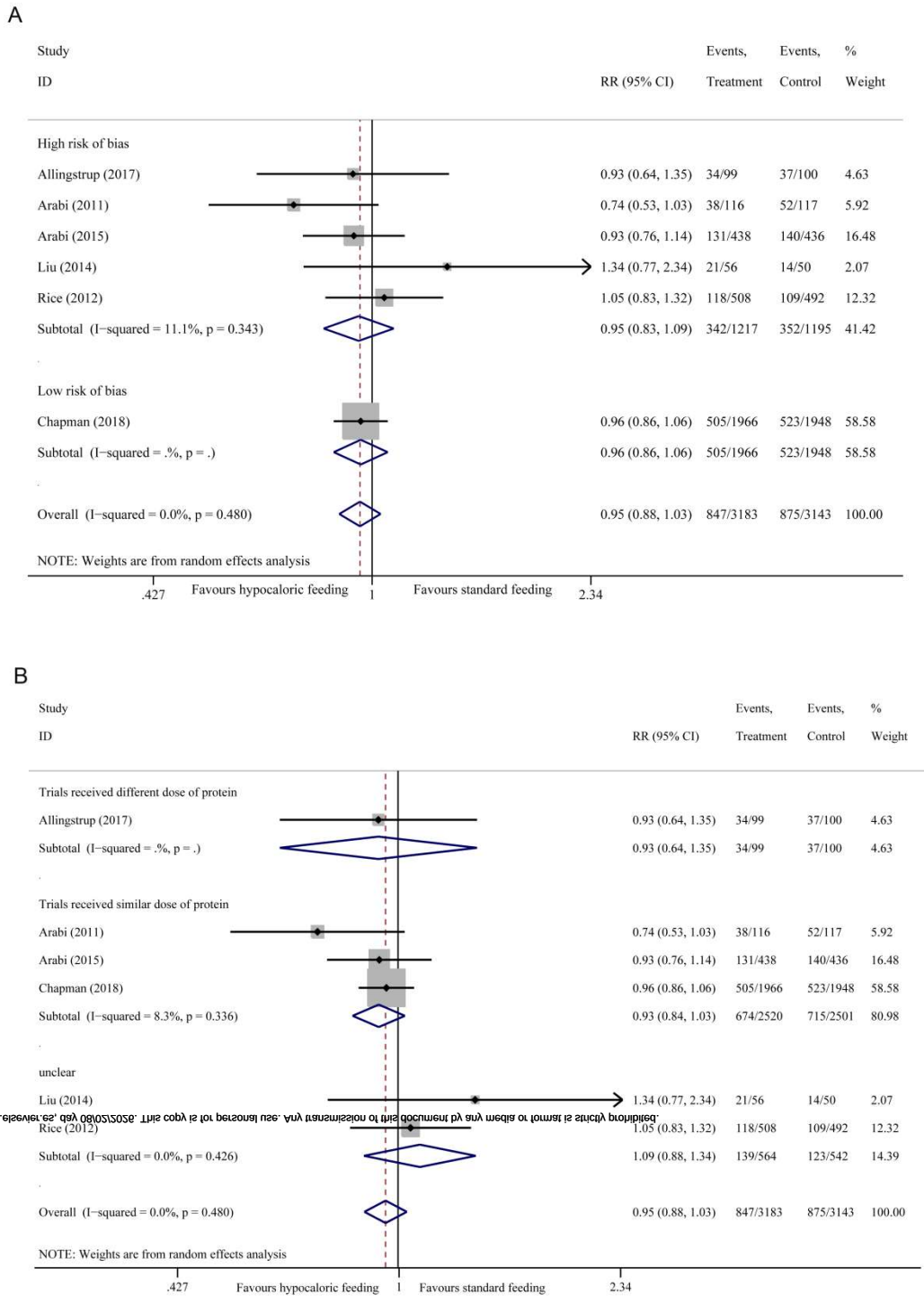
Trial sequential analysis using random-effects model with an adjusted family-wise error rate of 3.3%, power of 80%, for a relative risk reduction of 15% in control event proportion. (panel A) In single-center trials, control event proportion of 32.7%, D^2 of 56%. The cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 1.02 is 0.49 to 2.12. (panel B) In multi-center trials, control event proportion of 66.1%, D^2 of 76%, the cumulative Z-curve cross the futility area and reach the required information size of 3575 participants. The TSA-adjusted 95% CI for an RR of 0.99 is 0.91 to 1.08. RR relative risk; TSA trial sequential analysis.

Figure S5. Funnel plots for evaluating publication bias of included trials

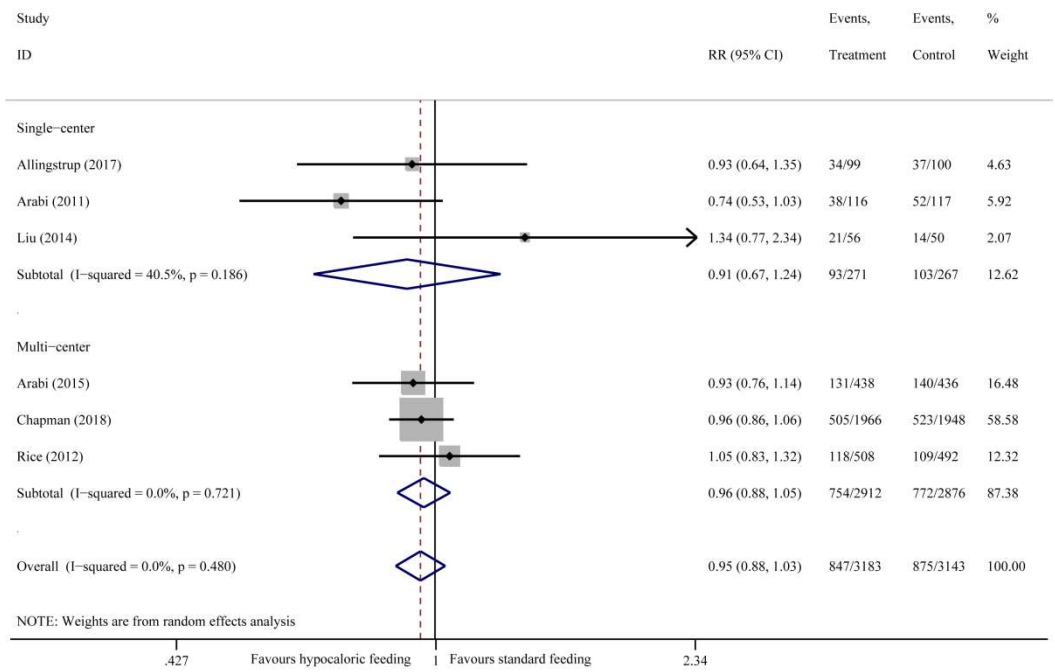


(Panel A) For the short-term mortality; (Panel B) For the incident of nosocomial infection. Both funnel plots are visually symmetric, and the Begg's and Egger's tests reveals no significant publication bias.
RR relative risk.

Figure S6. Forest plot of meta-analysis for the long-term mortality

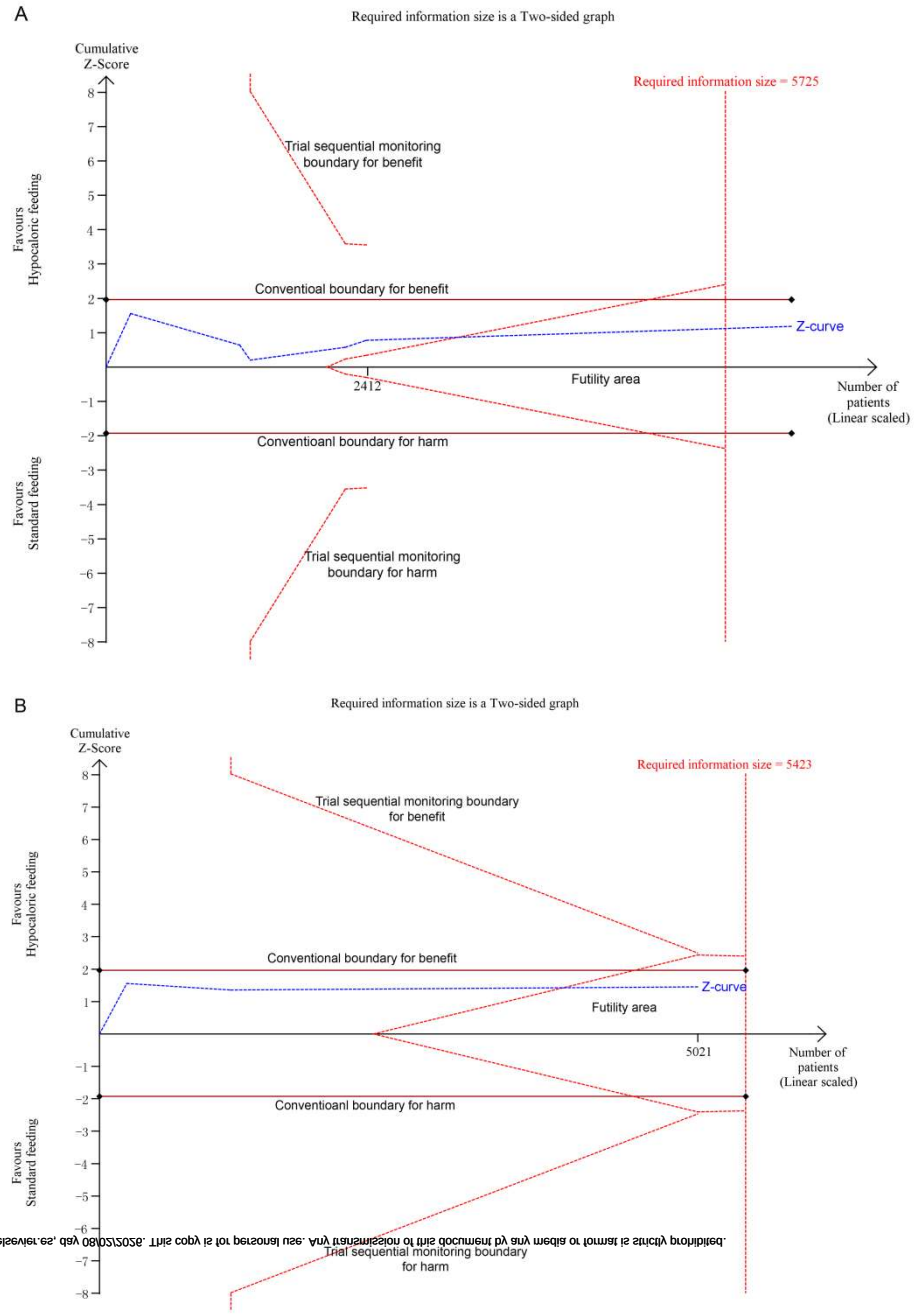


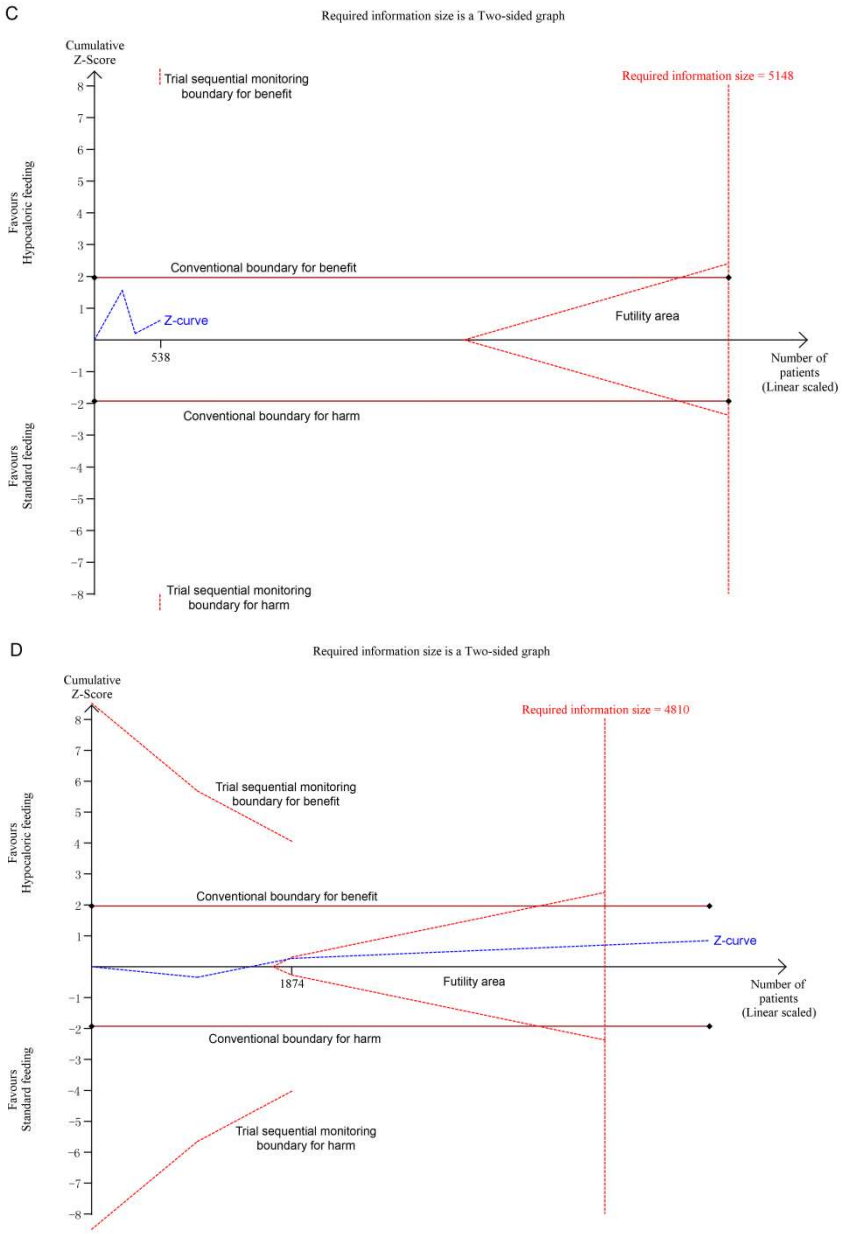
C



(panel A) Sub-analysis of trials with low or high risk of bias; (panel B) Sub-analysis of trials received similar or different dose of protein; (panel C) Sub-analysis of single-center or multi-center trials.
RR relative risk.

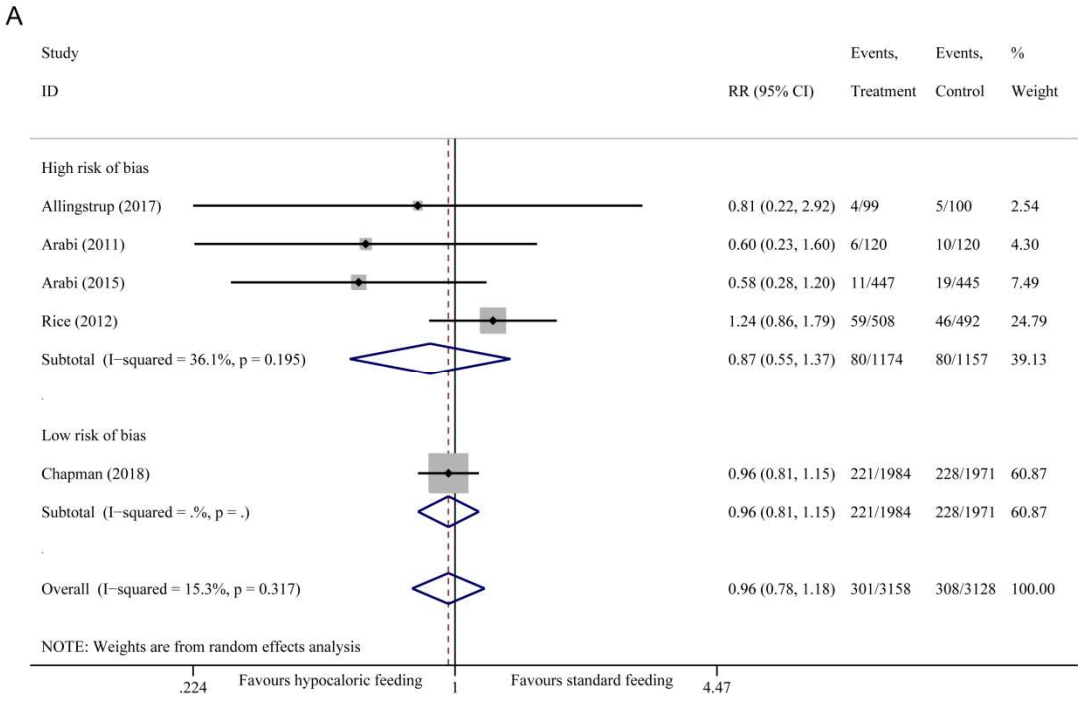
Figure S7. Trial sequential analysis for the long-term mortality

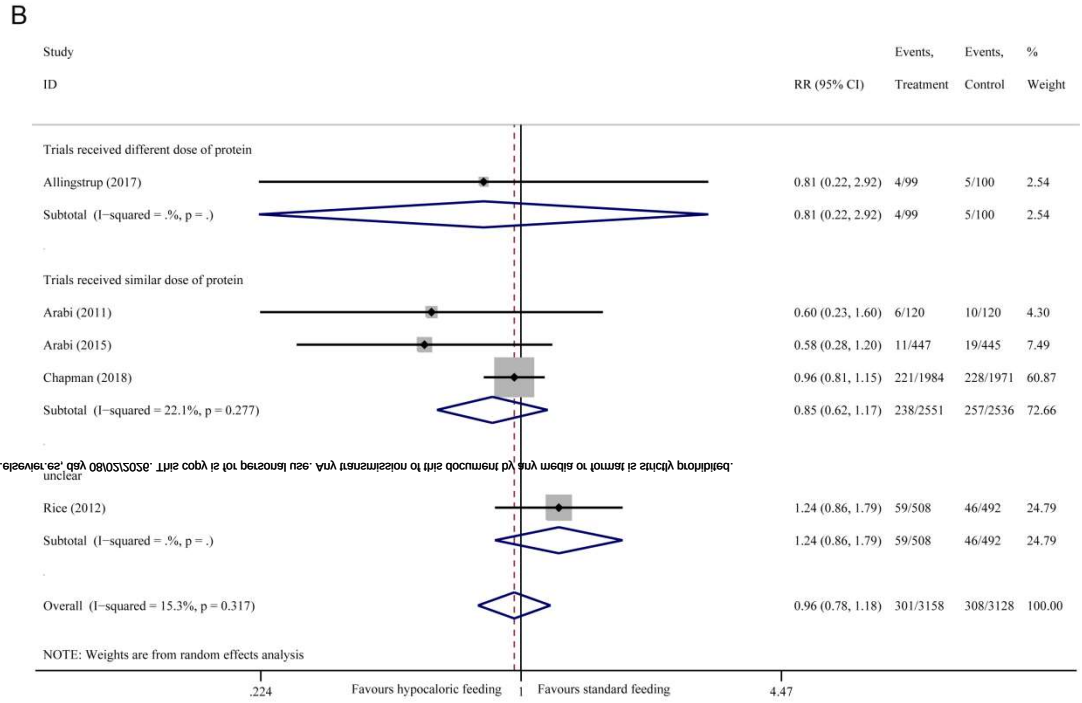




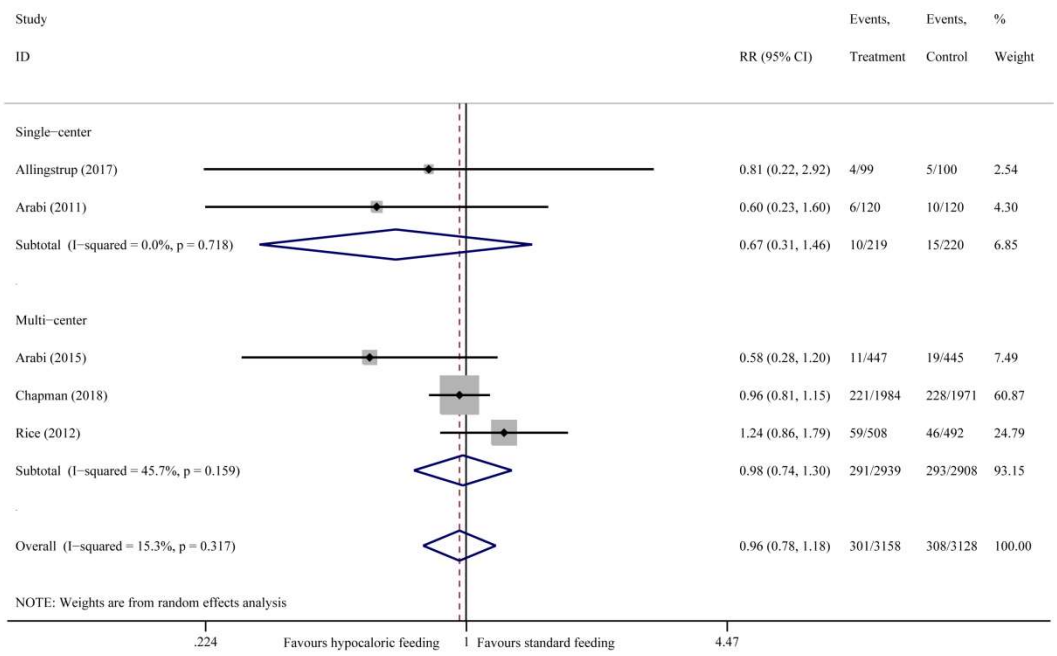
Trial sequential analysis using random-effects model with an adjusted family-wise error rate of 1.7%, power of 80%, for a relative risk reduction of 15% in control event proportion. (panel A) In all included trials, control event proportion of 27.8%, D^2 of 20% (the actual measured D2 was 0%). The cumulative Z-curve cross the futility area and reach the required information size of 5725 participants. The TSA-adjusted 95% CI for an RR of 0.95 is 0.83 to 1.11. (panel B) In trials received similar dose of protein, control event proportion of 28.6%, D^2 of 19%, the cumulative Z-curve cross the futility area, but do not reach the required information size of 5423 participants. The TSA-adjusted 95% CI for an RR of 0.93 is 0.82 to 1.05. (panel C) In single-center trials, control event proportion of 38.6%, D^2 of 45%. The cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 0.91 is 0.26 to 3.16. (panel D) In multi-center trials, control event proportion of 26.8%, D^2 of 20%(the actual measured D2 was 0%), the cumulative Z-curve cross the futility area and reach the required information size of 4810 participants. The TSA-adjusted 95% CI for an RR of 0.96 is 0.81 to 1.15. RR relative risk; TSA trial sequential analysis.

Figure S8. Forest plot of meta-analysis for the incident of bloodstream infection



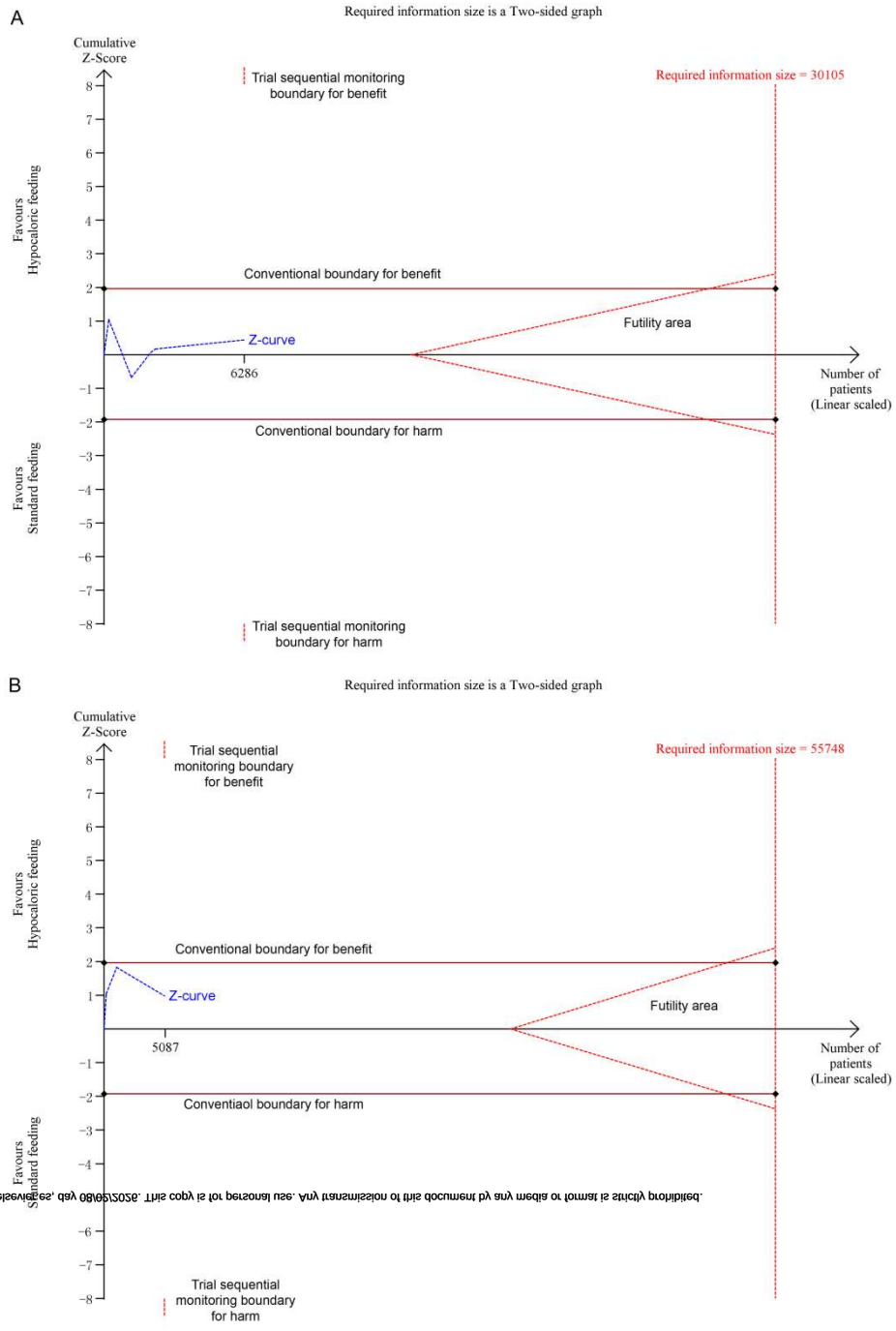


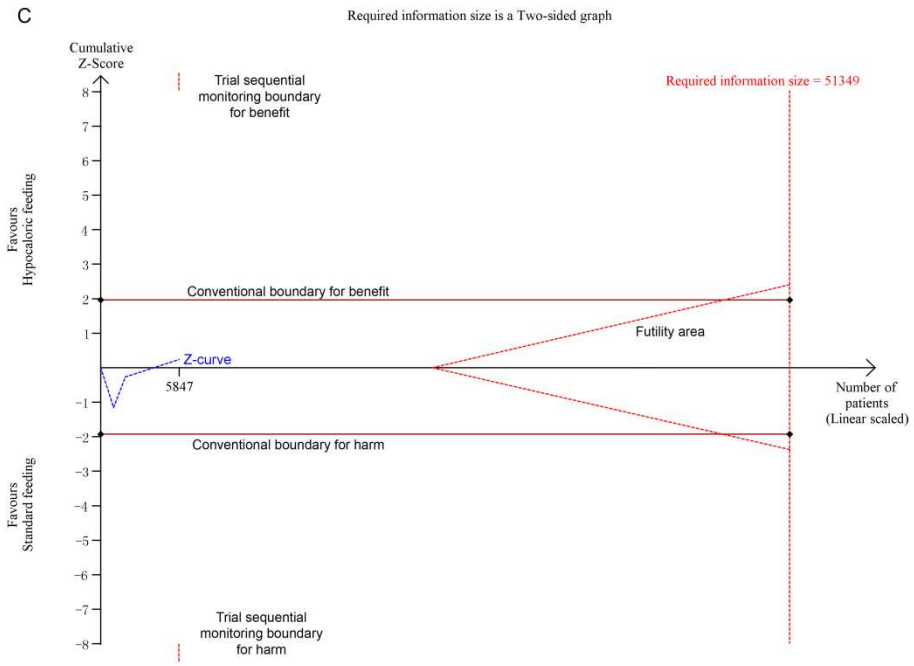
C



(panel A) Sub-analysis of trials with low or high risk of bias; (panel B) Sub-analysis of trials received similar or different dose of protein; (panel C) Sub-analysis of single-center or multi-center trials.
RR relative risk.

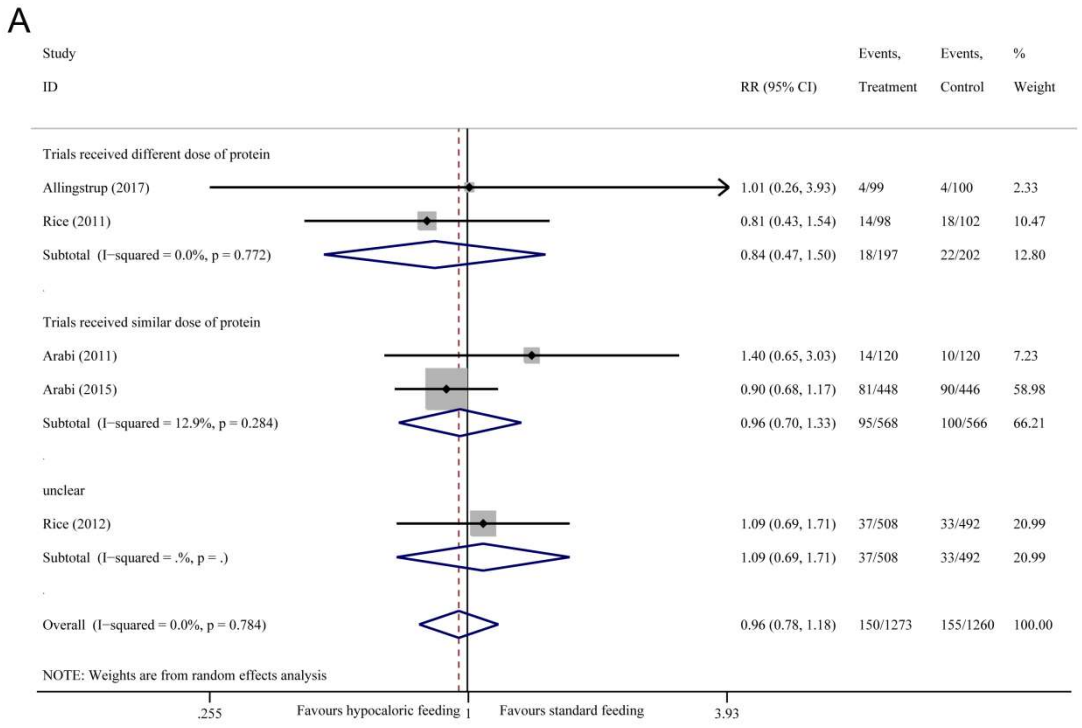
Figure S9. Trial sequential analysis for the incident of bloodstream infection

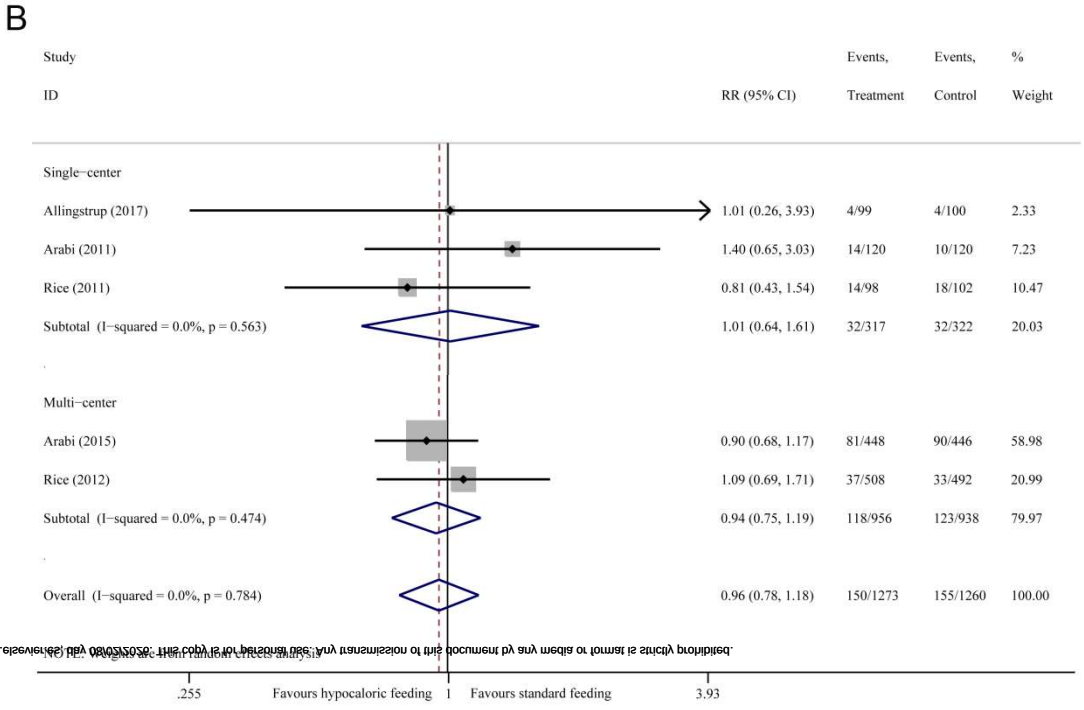




Trial sequential analysis using random-effects model with an adjusted family-wise error rate of 1.7%, power of 80%, for a relative risk reduction of 15% in control event proportion. (panel A) In all included trials, control event proportion of 9.8%, D^2 of 47%. The cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 0.96 is 0.41 to 2.25. (panel B) In trials received similar dose of protein, control event proportion of 10.1%, D^2 of 72%, the cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 0.85 is 0.23 to 3.10. (panel C) In multi-center trials, control event proportion of 10.1%, D^2 of 70%. The cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 0.98 is 0.31 to 3.08. RR relative risk; TSA trial sequential analysis.

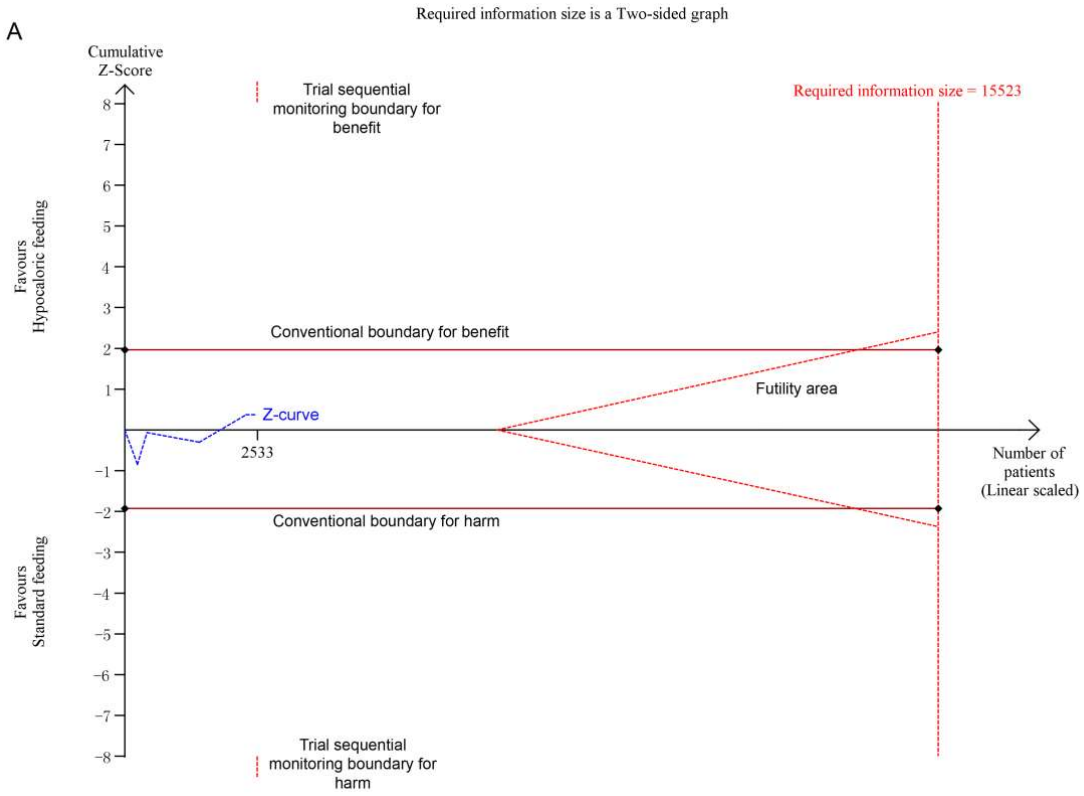
Figure S10. Forest plot of meta-analysis for the incident of pneumonia

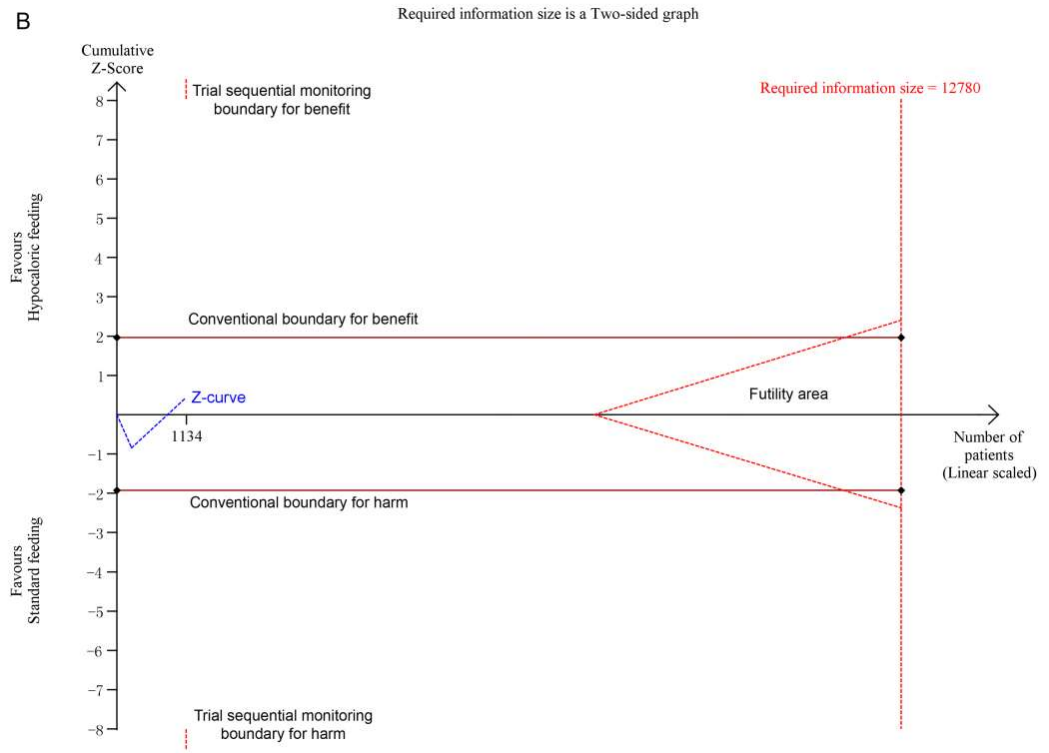


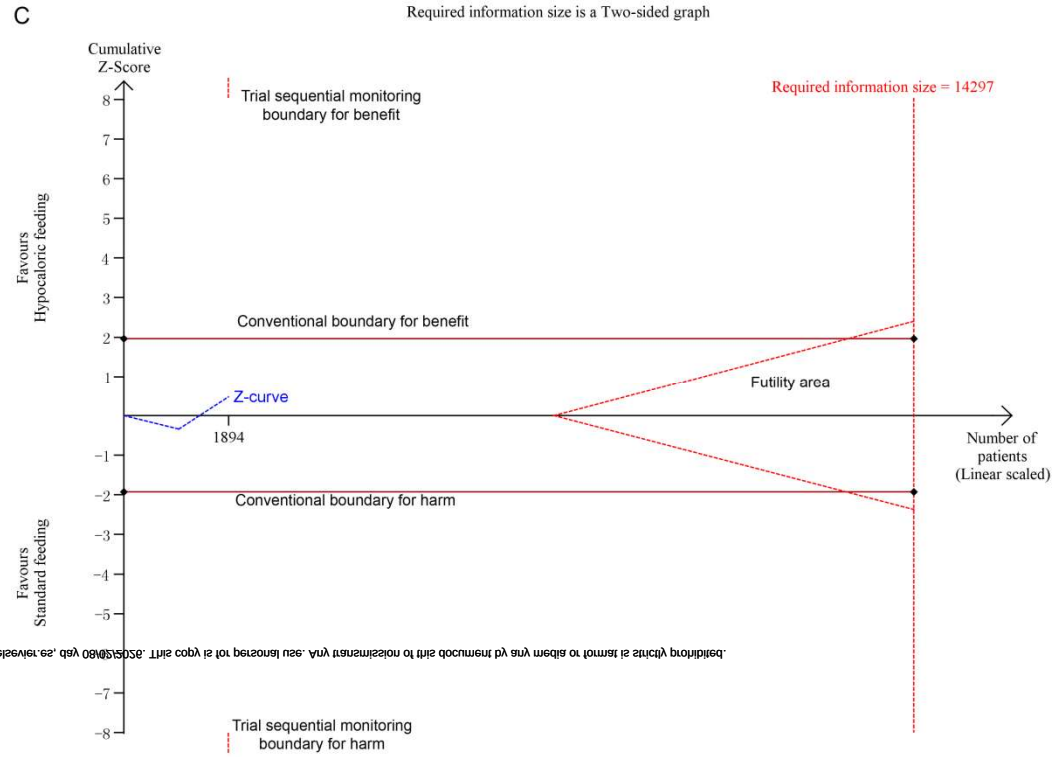


(panel A) Sub-analysis of trials received similar or different dose of protein; (panel B) Sub-analysis of single-center or multi-center trials.
RR relative risk.

Figure S11. Trial sequential analysis for the incident of pneumonia



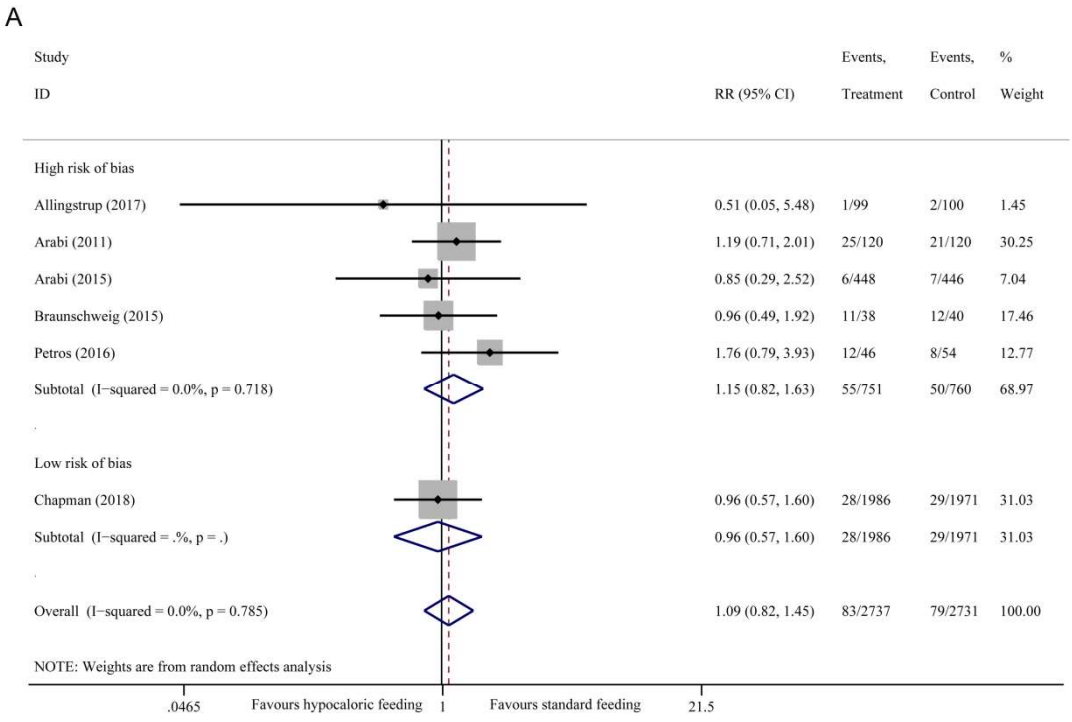


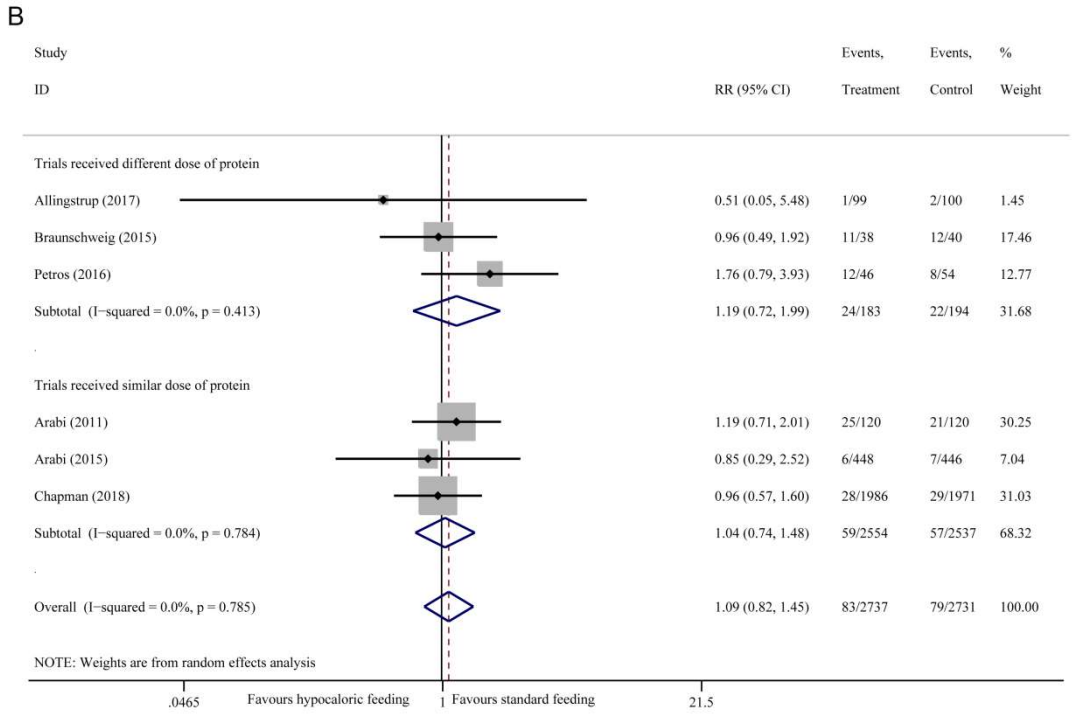


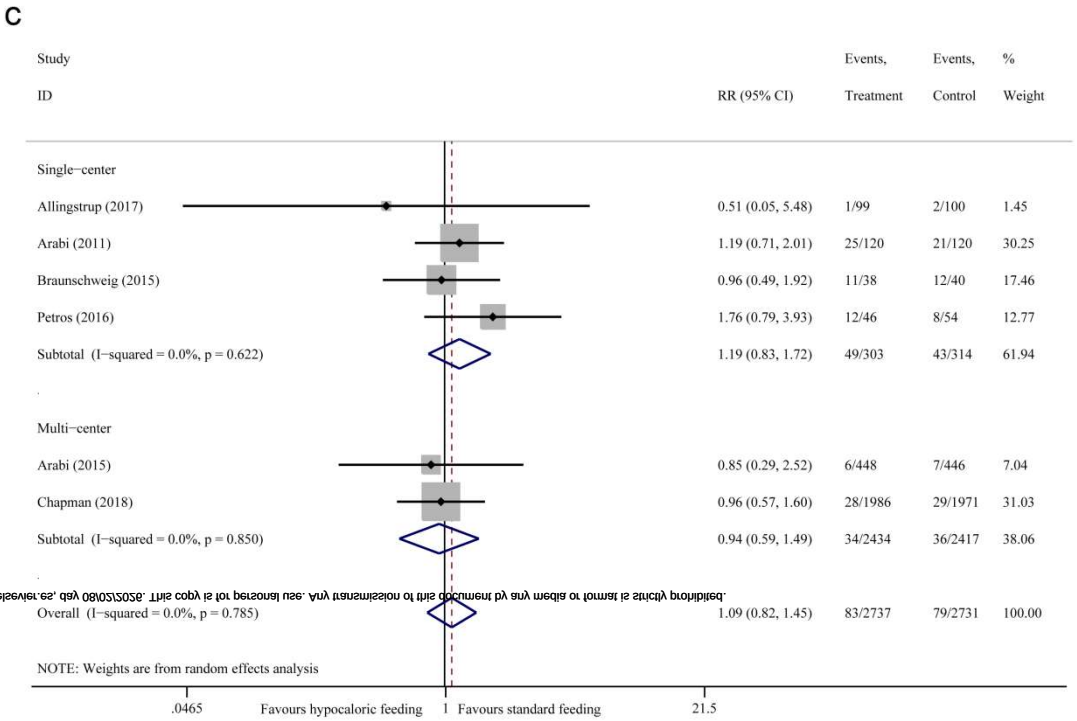
Trial sequential analysis using random-effects model with an adjusted family-wise error rate of 1.7%, power of 80%, for a relative risk reduction of 15% in control event proportion. (panel A) In all included trials, control event proportion of 12.3%, D2 of 20% (the actual measured D2 was 0%). The cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 0.96 is 0.41 to 2.23. (panel B) In trials received similar dose of protein, control event proportion of 17.7%, D^2 of 37%, the cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 0.96 is 0.26 to 3.56. (panel C) In multi-center trials, control event proportion of 13.1%, D2 of 20% (the actual measured D2 was 0%). The cumulative

Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 0.94 is 0.37 to 2.43. RR relative risk; TSA trial sequential analysis.

Figure S12. Forest plot of meta-analysis for the incident of hypoglycemia

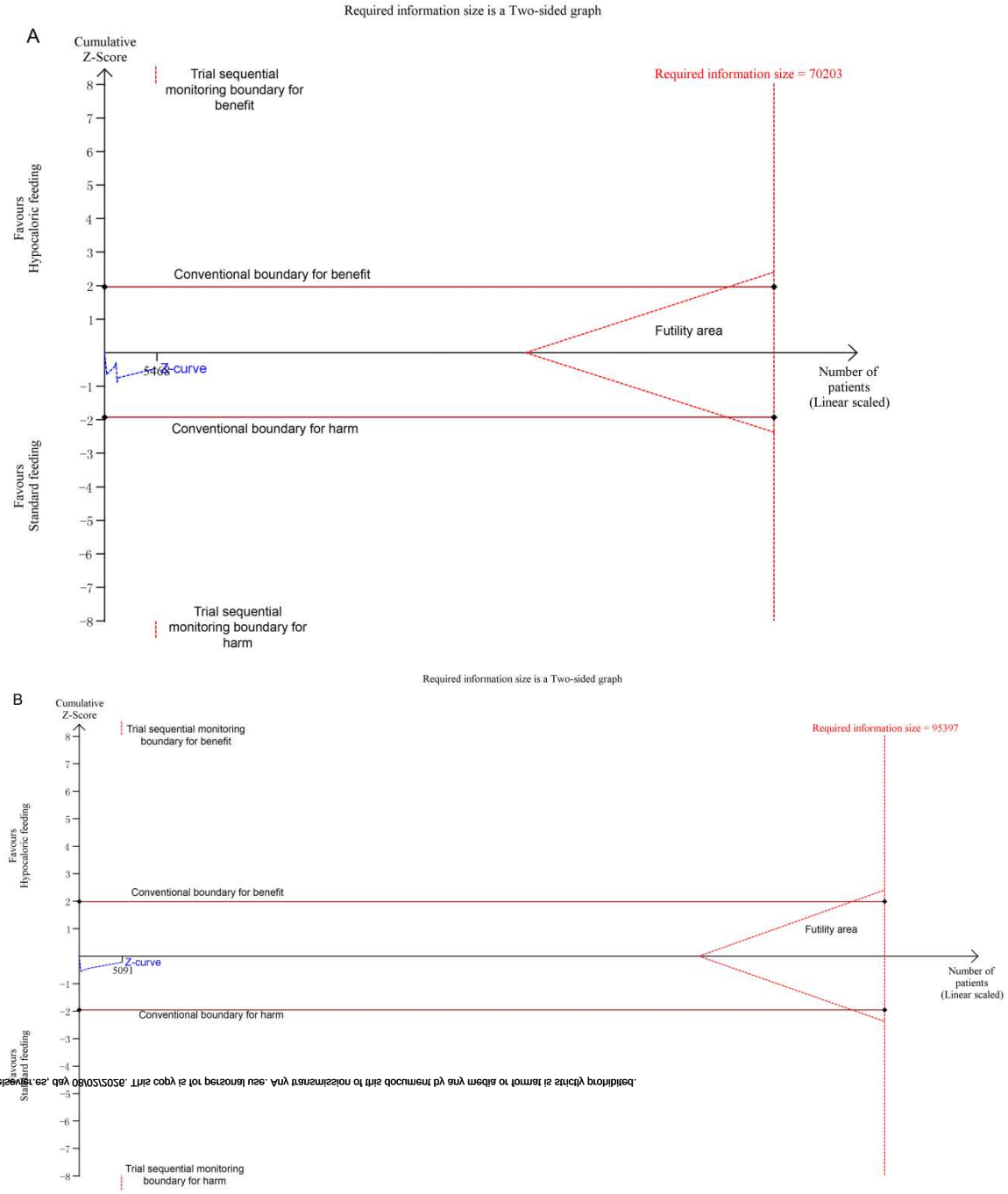






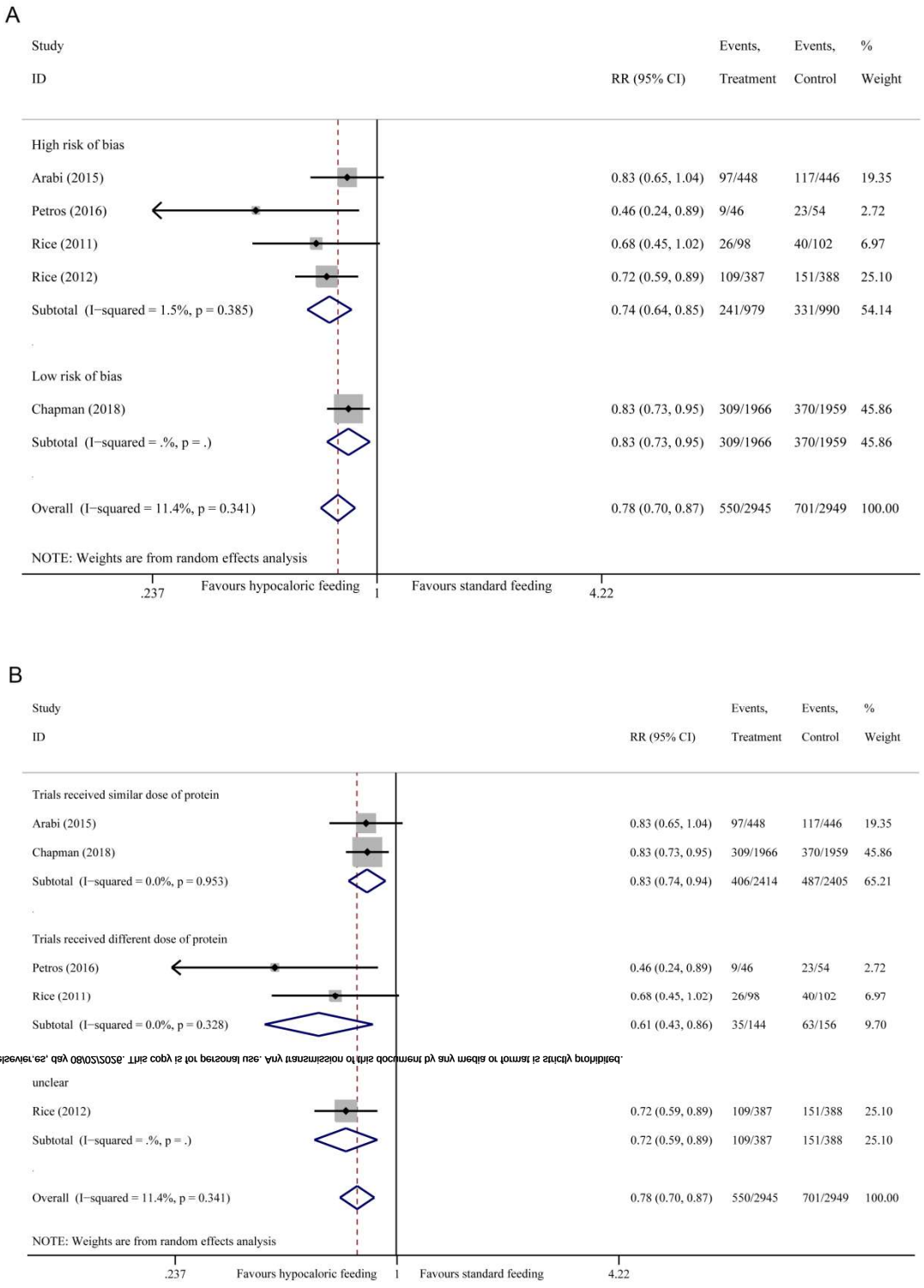
(panel A) Sub-analysis of trials with low or high risk of bias; (panel B) Sub-analysis of trials received similar or different dose of protein; (panel C) Sub-analysis of single-center or multi-center trials. RR relative risk.

Figure S13. Trial sequential analysis for the incident of hypoglycemia

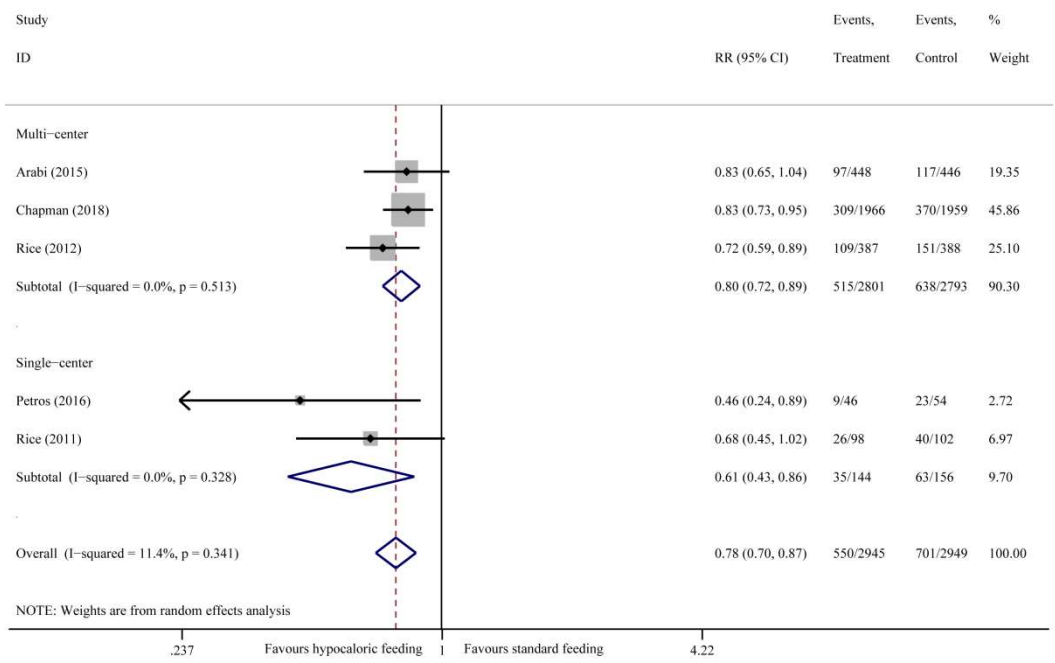


Trial sequential analysis using random-effects model with an adjusted family-wise error rate of 1.7%, power of 80%, for a relative risk reduction of 15% in control event proportion. (panel A) In all included trials, control event proportion of 2.9%, D^2 of 20% (the actual measured D^2 was 0%). The cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 1.09 is 0.34 to 3.51. (panel B) In trials received similar dose of protein, control event proportion of 2.2%, D^2 of 20% (the actual measured D^2 was 0%), the cumulative Z-curve cross no boundaries. The TSA-adjusted 95% CI for an RR of 1.04 is 0.25 to 4.30. RR relative risk; TSA trial sequential analysis.

Figure S14. Forest plot of meta-analysis for the incident of gastrointestinal intolerance

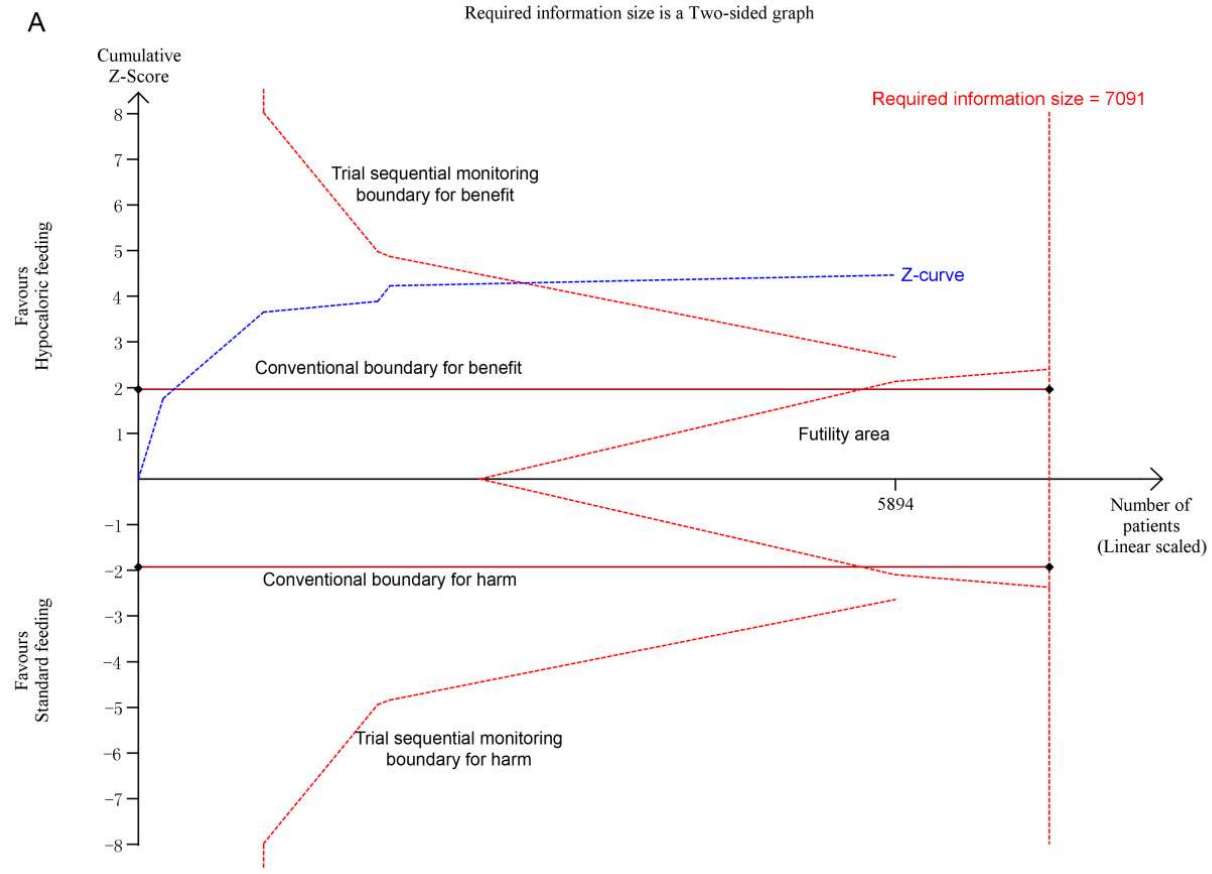


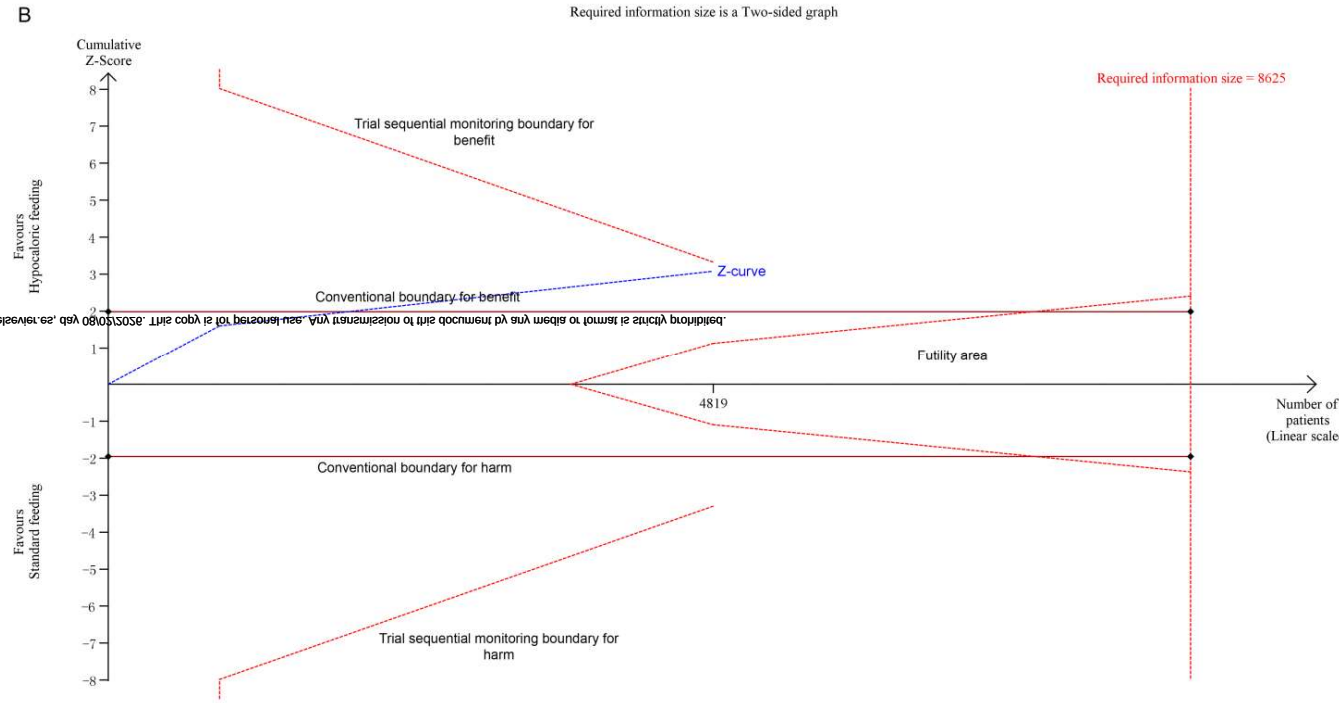
C

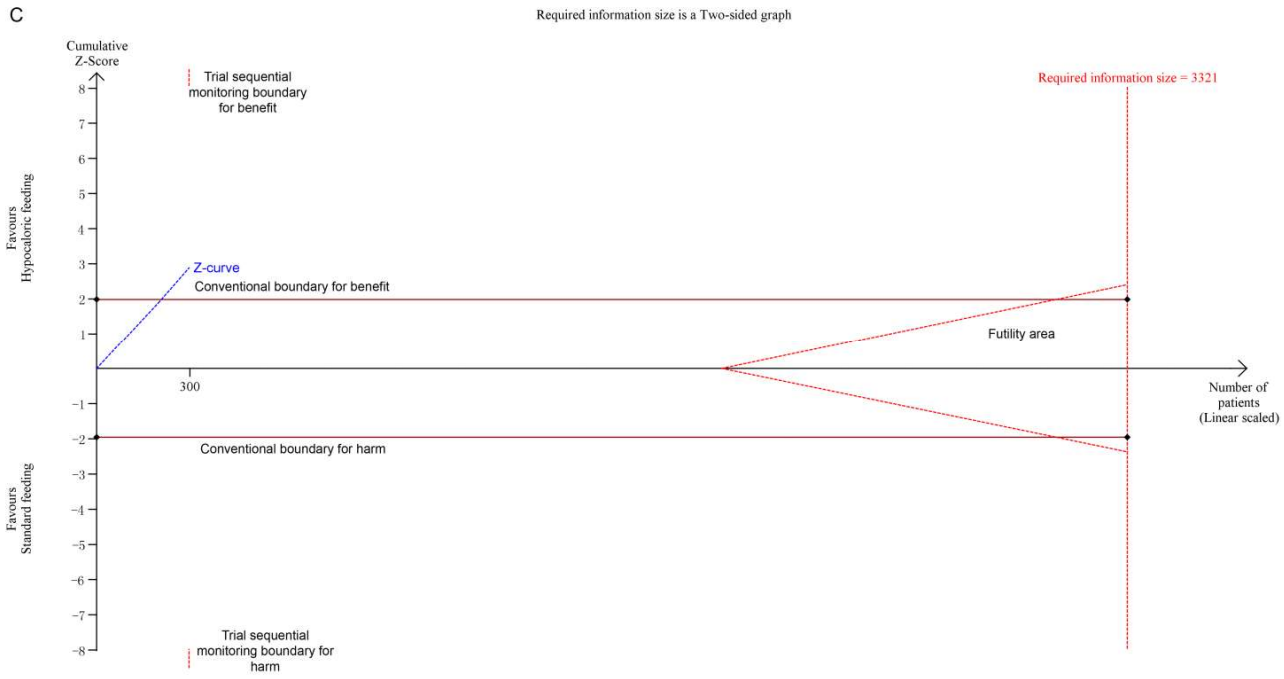


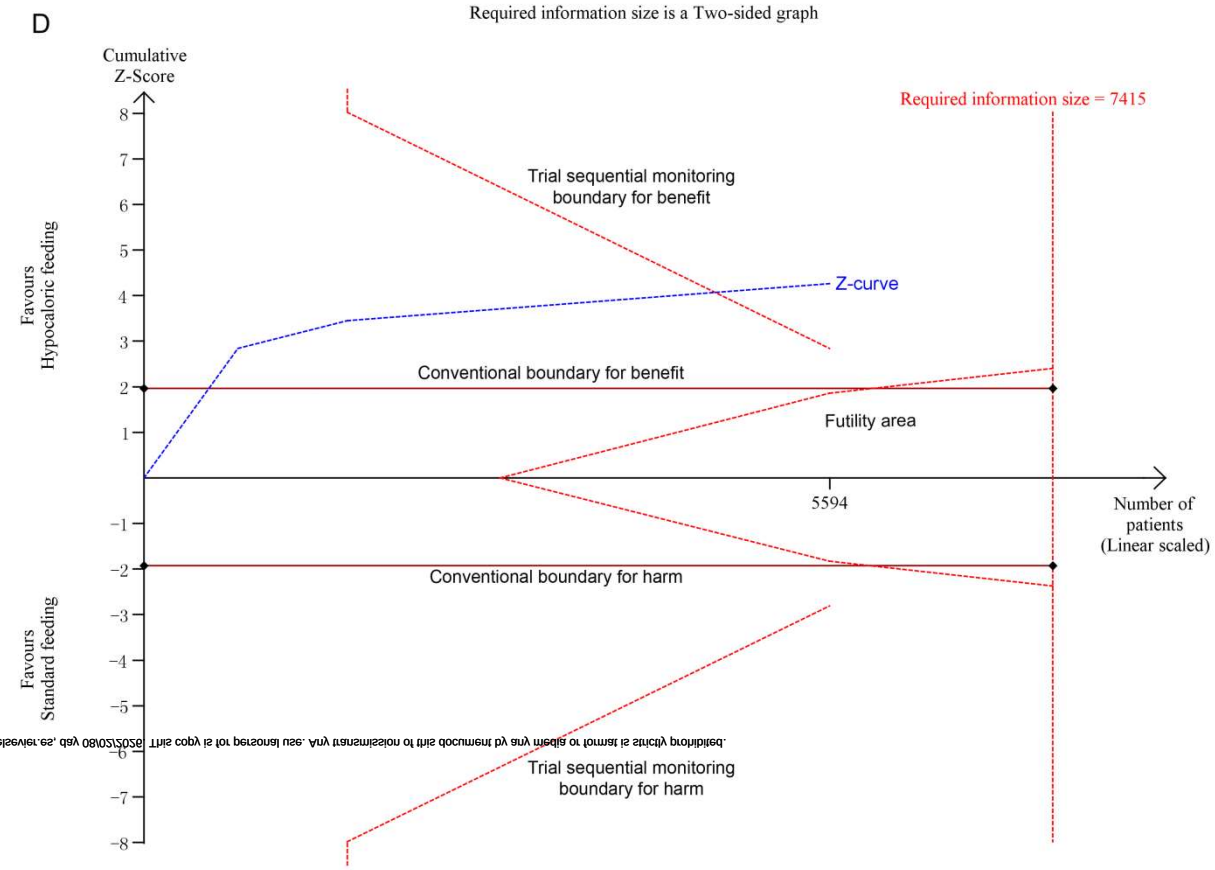
(panel A) Sub-analysis of trials with low or high risk of bias; (panel B) Sub-analysis of trials received similar or different dose of protein; (panel C) Sub-analysis of single-center or multi-center trials. RR relative risk.

Figure S15. Trial sequential analysis for the incident of gastrointestinal intolerance





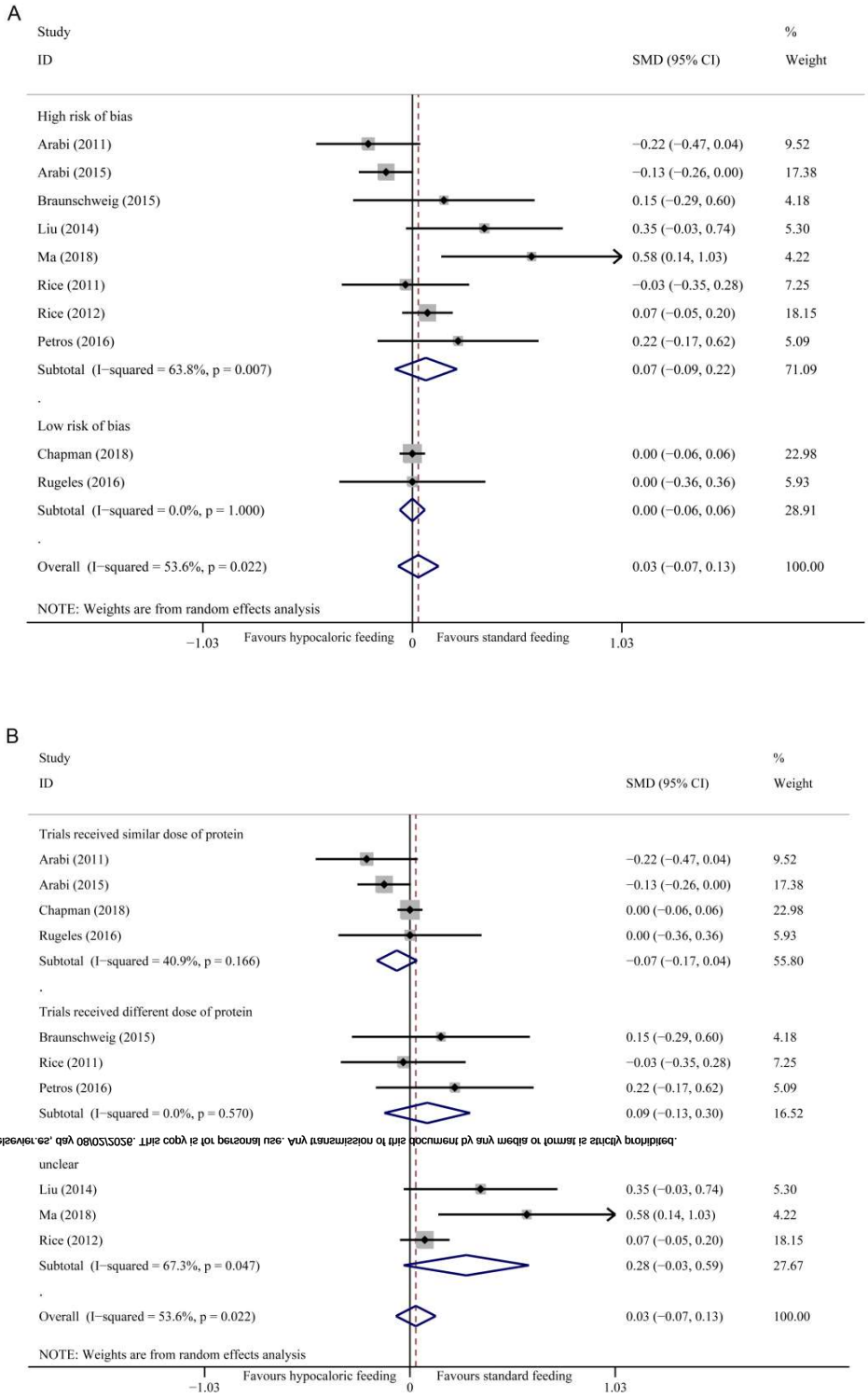




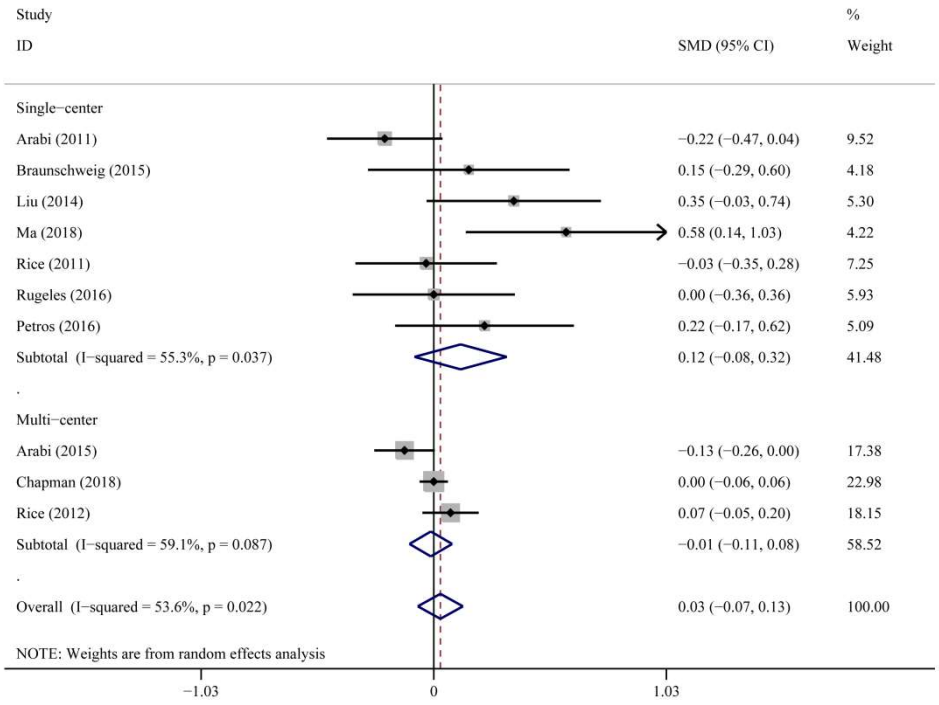
Trial sequential analysis using random-effects model with an adjusted family-wise error rate of 1.7%, power of 80%, for a relative risk reduction of 15% in control event proportion. (panel A) In all included trials, control event proportion of 23.8%, D^2 of 21%. The cumulative Z-curve cross the trial sequential monitoring boundary for benefit. The TSA-adjusted 95% CI for an RR of 0.78 is 0.67 to 0.90. (panel B) In trials received similar dose of protein, control event proportion of 20.2%, D^2 of 20% (the actual measured D^2 was 0%), the cumulative Z-curve cross the conventional boundary for benefit, but not the trial sequential monitoring

boundary for benefit. The TSA-adjusted 95% CI for an RR of 0.83 is 0.68 to 1.02. (panel C) In trials received different dose of protein (all were single-center trials), control event proportion of 40.4%, D^2 of 20% (the actual measured D^2 was 0%), the cumulative Z-curve cross the conventional boundary for benefit, but not the trial sequential monitoring boundary for benefit. The TSA-adjusted 95% CI for an RR of 0.61 is 0.15 to 2.51. (panel D) In multi-center trials, control event proportion of 22.8%, D^2 of 20% (the actual measured D^2 was 0%). The cumulative Z-curve cross the trial sequential monitoring boundary for benefit. The TSA-adjusted 95% CI for an RR of 0.80 is 0.69 to 0.93. RR relative risk; TSA trial sequential analysis.

Figure S16. Forest plot of meta-analysis for the duration of mechanical ventilation

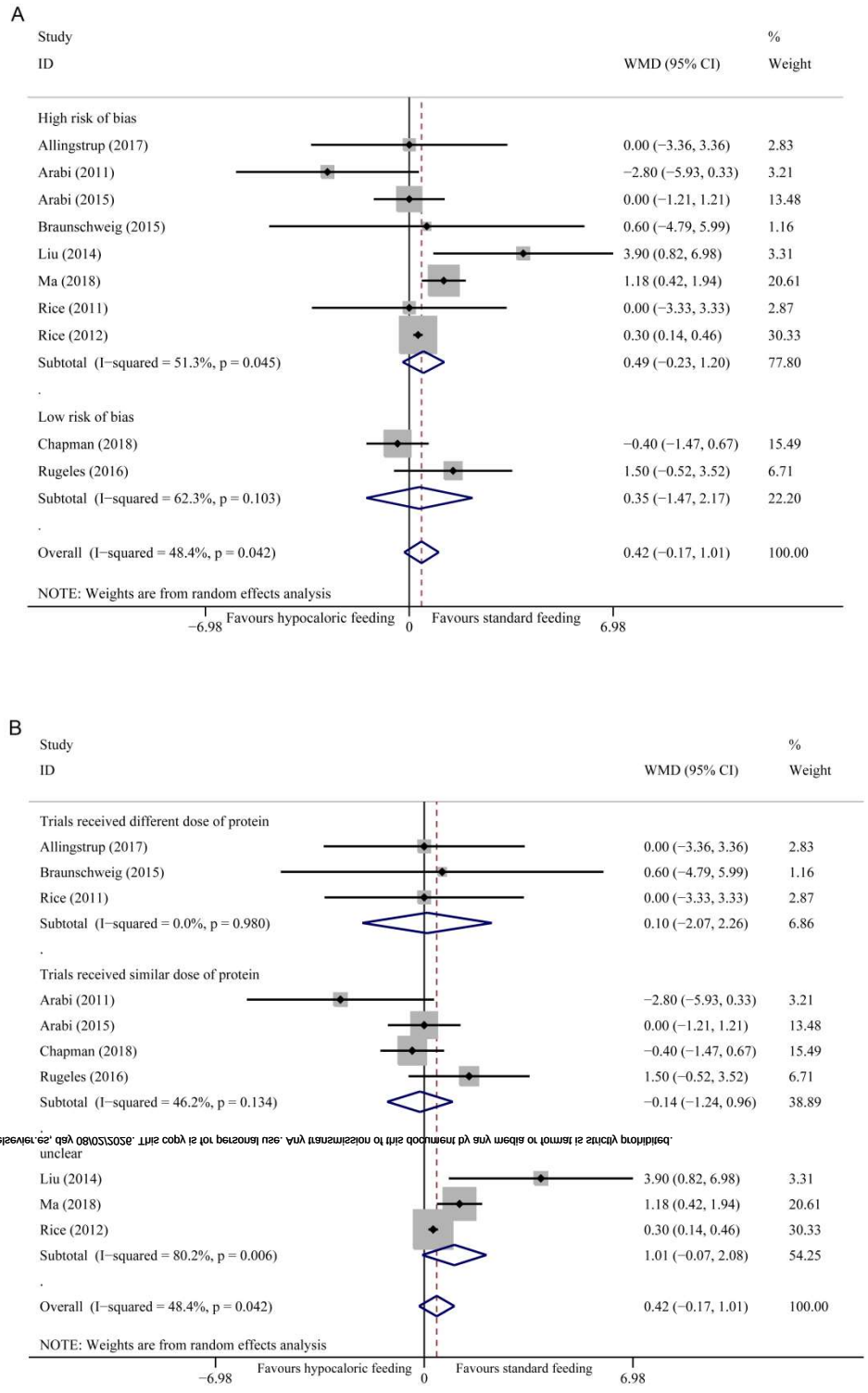


C

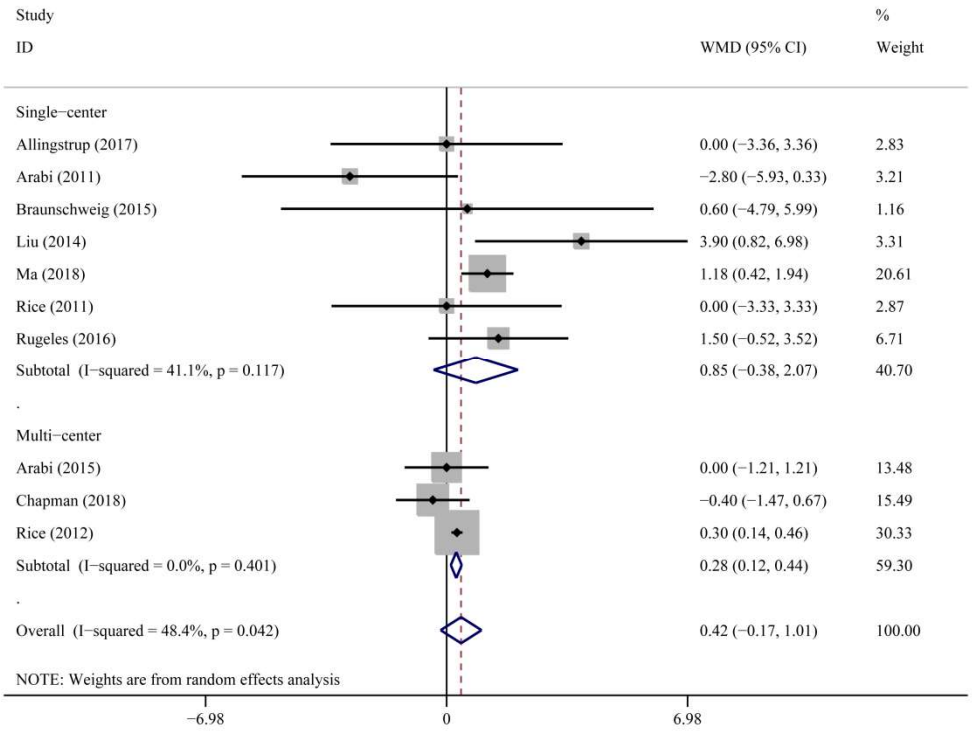


(panel A) Sub-analysis of trials with low or high risk of bias; (panel B) Sub-analysis of trials received similar or different dose of protein; (panel C) Sub-analysis of single-center or multi-center trials. RR relative risk.

Figure S17. Forest plot of meta-analysis for the duration of ICU stay

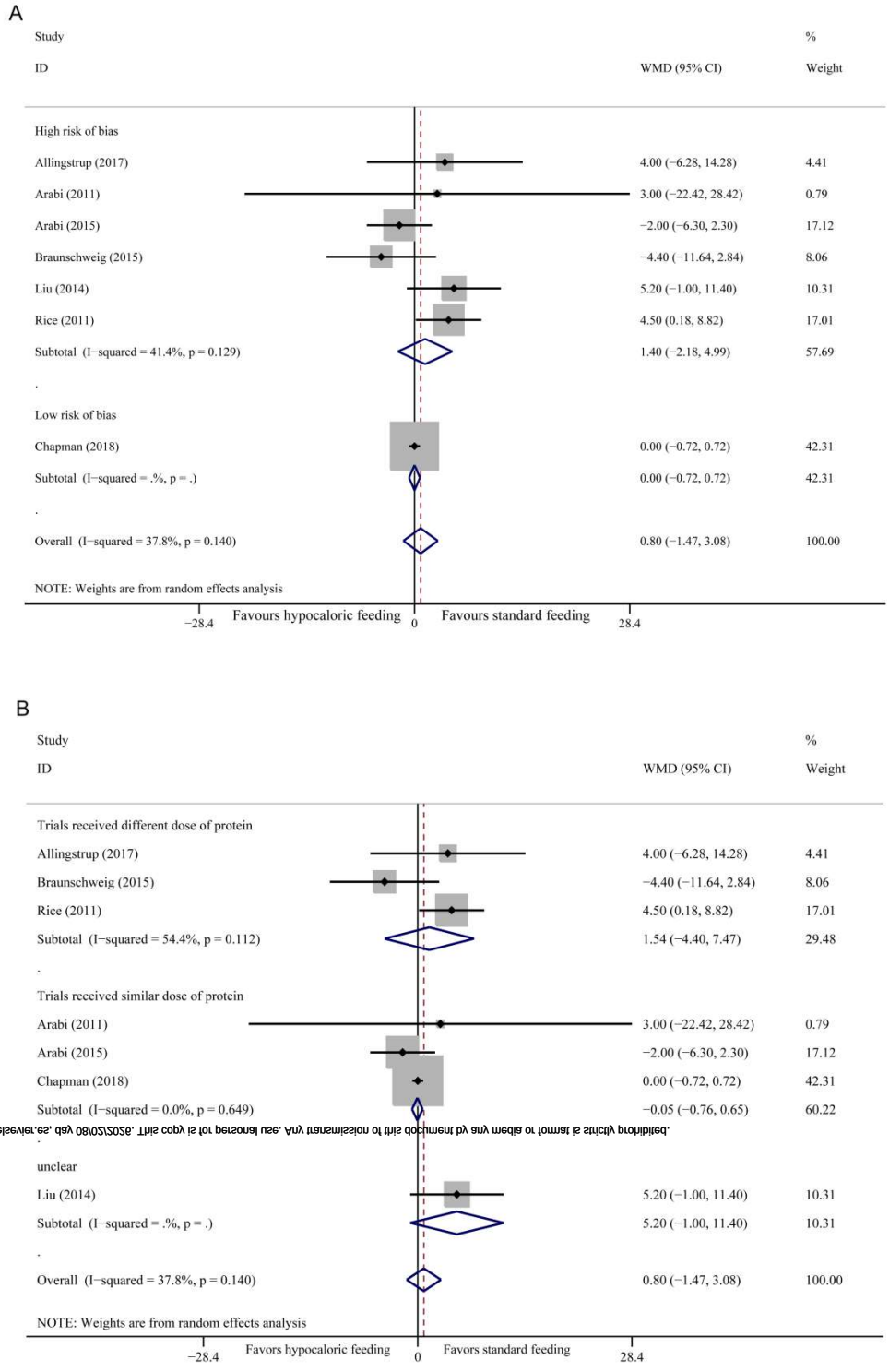


C

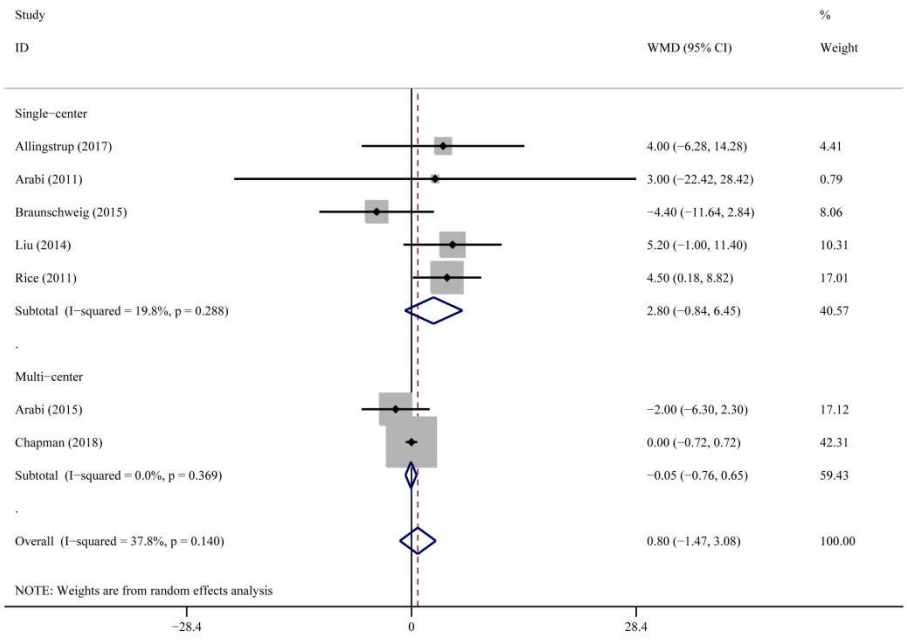


(panel A) Sub-analysis of trials with low or high risk of bias; (panel B) Sub-analysis of trials received similar or different dose of protein; (panel C) Sub-analysis of single-center or multi-center trials. RR relative risk; ICU intensive care unit.

Figure S18. Forest plot of meta-analysis for the duration of in-hospital stay



C



(panel A) Sub-analysis of trials with low or high risk of bias; (panel B) Sub-analysis of trials received similar or different dose of protein; (panel C) Sub-analysis of single-center or multi-center trials. RR relative risk; ICU intensive care unit.