Effect of Calories Delivered on Clinical Outcomes in Critically Ill Patients: Systemic Review and Meta-analysis

Legese Chelkeba, Mojtaba Mojtahedzadeh[1], Zeleke Mekonnen[2]

Departments of Clinical Pharmacy and [2]Medical Laboratory Sciences, College of Health Sciences, Jimma University, Jimma, Ethiopia, [1]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Introduction: International guidelines are promoting early enteral nutrition (EN) as a means of feeding critically ill adult patients to improve clinical outcomes. The question of how much calorie intake is enough to improve the outcomes still remained inconclusive. Therefore, we carried out a meta-analysis to evaluate the effect of low calorie (LC) versus high calorie (HC) delivery on critically ill patients' outcomes. **Methods:** We included randomized clinical trials (RCTs) that compared LC EN with or without supplemental parenteral nutrition with HC delivery in this meta-analysis irrespective of the site of nutritional delivery in the gastrointestinal tract. We searched PubMed, EMBASE, and Cochrane central register of controlled trials electronic databases to identify RCTs that compared the effects of initially different calorie intake in critical illness. The primary outcome was overall mortality. **Results:** This meta-analysis included 17 RCTs with a total of 3,593 participants. The result of analysis showed that there was no significant difference between the LC group and HC group in overall mortality (risk ratio [RR], 0.98; 95% confidence interval [CI], 0.87–1.10; $P = 0.74$; $I^2 = 6\%$; $P = 0.38$), or new-onset pneumonia (RR, 0.92; 95% CI, 0.73–1.16, $P = 0.46$; $I^2 = 38\%$, $P = 0.11$). **Conclusion:** The current meta-analysis showed that there was no significant difference in mortality of critically ill patients initially between the two groups.

Keywords: Critically ill patients, enteral nutrition, high calorie, low calorie, overall mortality, supplemental parenteral nutrition

Introduction

International guidelines recommended the initiation of early enteral nutrition (EN) to all Intensive Care Unit (ICU) patients who are not expected to receive a full oral diet within 2 or 3 days of ICU admission.[1-3] In support of these evidence-based guidelines, results from clinical trials and meta-analyses demonstrated that a statistically significant reduction in mortality,[4-6] ventilator-associated pneumonia,[4,7] duration of mechanical ventilations, and length of ICU[6,8,9] when initiated within the first 24 h of ICU admission. This reduction in clinical outcomes in turns associated with reduction in cost of care.[7] Interestingly enough, there is no any strong evidence so far suggesting the harmfulness of early initiation of EN in critically ill patients.[10]

Controversy exists in studies so far examining the effects of energy delivery and clinical outcomes in critically ill patients admitted to ICU. On the one hand, cumulative energy deficit has been associated with unwanted adverse outcomes such as prolonged ICU stay, and therefore, infectious complications.[11,12]

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Randomized clinical trials (RCTs) also demonstrated that enteral intake of full-calorie requirement was associated with a trend toward improvement of mortality.[13] Moreover, consensus regarding the early use supplemental parenteral nutrition (SPN) as a way to supply sufficient energy does not exist.[14] On the another hand, permissive underfeeding was associated with improved outcomes compared with full feeding[6,15-18] and even in some studies, the later was found to be associated with significantly higher mortality in critically ill patients with acute lung injury.[19]

Therefore, the question of how much calorie should be given to critically ill patients admitted to ICU remained to be a hot topic of debate. In response to this question, two recent meta-analyses were carried out to find the energy target for critically ill patients and reported that the initial calorie of

Address for correspondence: Dr. Legese Chelkeba, Department of Clinical Pharmacy, College of Health Sciences, Jimma University, Jimma, Ethiopia.
E-mail: legese.chelkeba@gmail.com

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33%–66% range was associated with a trend toward reduction in mortality.[20,21] However, the interpretation of published meta-analyses of trials comparing nutritional support through full feeding compared to permissive underfeeding in critically ill patients is complicated by small sample sizes due to their strict inclusion criteria, variable quality and bias. Recently, published RCTs are also challenging the benefits of delivering of a full calories compared to hypocaloric EN.[22-26] All together, these data revealed that the optimal and safe caloric intake in critically ill patients still remains inconclusive. Taking into account, the variation in the results of the currently available studies, we believed that a comprehensive updated meta-analysis of more recent RCTs is mandated. Therefore, this meta-analysis of 17 RCTs aimed to compare initial LC versus HC delivery in critically ill patients.

Methods

The meta-analysis reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[27]

Search strategy

Two investigators (LCH and ZM) independently searched electronic databases in PubMed, EMBASE, and the Cochrane database from inception to June 2016 using the terms "permissive underfeeding," or "hypocaloric feeding," or "trophic feeding," or "gradual enteral nutrition," or "low calorie nutrition," or "standard enteral nutrition," or "intensive enteral nutrition," or "eucaloric enteral nutrition," or "normocaloric enteral nutrition," or "concentrated enteral nutrition," or "hypercaloric enteral nutrition," or "full feeding," "overfeeding," or "gastrostomy tube," "delay feeding," or "early feeding," or "postpyloric feeding" or "nasogastric tube," or "J tube" or "G tube" combined with the terms "critically ill patients," or "critical illness," or "ICU," or "intensive care," in duplicate. A manual search for additional relevant studies using references from retrieved articles was also performed. Conference abstracts and unpublished studies were excluded from the study. We restricted the searches to human studies with language restriction to English placed on the searches.

Types of studies, participants, and interventions

The same authors (LCH and ZM) independently assessed the inclusion criteria and if there was disagreement, a third author consulted (MM). We included the studies if they met the following criteria: the study design was an RCT, the population comprised critically ill adult patients admitted to the ICU, had significantly different in calorie delivery by EN and/or supplemental parenteral nutrition between two or more arms ($P < 0.05$), nutritional intervention was >48 h and the mortality was reported as primary or secondary endpoint. Studies were excluded if either of the groups received no nutrition or identical calorie, nutritional intervention < 2 days and if mortality was not reported.

Outcome measures

The primary outcome was the overall mortality reported by each trial at the last follow-up duration. For instance, if a trial reported 28, 60, and 90 days of mortality, we considered 90-day mortality as overall mortality. When it was not reported, we excluded the trial(s) from the analysis. Other secondary outcomes considered in this meta-analysis were the incidence of new onset pneumonia and sepsis, the lengths of ICU and hospital stay, duration of mechanical ventilation, the incidence of hypoglycemia and average doses of insulin used per day, incidence of renal replacement therapy (RRT), and gastrointestinal intolerance. Subgroup analyses were conducted to find if mortality differed either by mode of delivery (EN with or without SPN), based on severity score (Acute Physiology and Chronic Health Evaluation II [APACHE II] >20 vs. APACHE II ≤20), the body mass index (BMI) (BMI ≥25 vs. <25), the amount of calorie intake by low calorie (LC) group of standard requirements (LC <33.3%, 33.33% < LC <66.6%, LC > 66%) based on the recent meta-analyses.[20,21]

Data abstraction and quality assessment

Two independent authors (LCH and ZM) extracted data from all eligible studies on to a standardized data abstraction sheet. We extracted information on study authors, year of publication, characteristics of the studies such as age (years), BMI in kg/m^2, severity scores, and total sample size (intervention plus control), and daily calorie delivered (kcal/day), average protein intake (g/day), and primary and secondary outcomes. The same authors independently assessed the included trials for bias according to the Handbook for Systematic Reviews of Interventions.[28] Disagreement also resolved by consulting the third author. The following parameters were assessed: sequence generation, allocation concealment, masking (blinding) of participants, personnel and outcome assessors, incomplete outcome data, and selective outcome reporting. Other sources of bias were a risk of bias related to the specific study design used or trial stopped early due to some data-dependent process or an extreme baseline imbalance in patients selected according to this handbook.

Statistical analysis

We followed the Cochrane handbook of data analysis and reported dichotomous outcome measures to assess the summary effects of treatment by calculated risk ratio (RR) with 95% confidence interval (CI). The overall weighted mean difference (WMD) with 95% CI was estimated for continuous variable. A random-effects model was used in this meta-analysis because of anticipated heterogeneity. Statistical heterogeneity among trials was expressed as the P value (Cochran's Q statistic), where a $P < 0.05$ and I^2 statistic >50% indicated significant heterogeneity. Sensitivity analysis was done by sequentially deleting a single study each time in an attempt to identify the potential influence of an individual study on mortality and stability of the result. The analyses were carried out using RevMan 5.3 software (The Nordic

Cochrane Center, Denmark) to create a forest plot and a summary finding tables.

Definitions

"High calorie" and "low calorie" simply to represent the intervention arms of individual trials received higher calorie relative to the comparator group (received LC) for the respective trials. They were not showing comparison of levels of calorie delivered between trials. Gastrointestinal intolerance was also defined high residual gastric volume, regurgitation, vomiting, noninfectious diarrhea, constipation, or abdominal distension. All definitions were defined according to the original studies although there were differences in definitions.

Results

Literature searches and selection

The details of our search strategy were depicted in Figure 1. Our initial research of electronic databases such as PubMed, EMBASE, and Cochrane yielded 6120 articles, from which 1206 records remained after removing 4914 duplications. A total of 1185 articles were not included; 520 were not adults, 371 articles were not RCTs, 85 articles were reviews or meta-analyses, 90 articles were about parenteral nutrition, no full text available for 6 articles, 32 articles were about timing, 7 articles were about immunonutrition, 40 articles were residual volume, and 34 articles were other procedures. Of the remaining 21 potentially relevant articles for qualitative analyses, 4 articles were excluded; 2 articles reported that group received no LC nutrition; and the remaining 2 articles reported that the two groups received similar calorie.

Study characteristics

Finally, 17 RCTs published between 1992 and 2016 fulfilling the inclusion criteria were included in the final quantitative analyses.[6,13,15,18,19,22-26,29-35] The sample size of the included trials ranged from 19[35] to 1000[22] with a total number of 3593 patients, of which 1800 were assigned to the LC and 1793 to high calorie (HC) group. The mean age of the patients included in the study was >50 years with the exception of one which reported as <28 in the LC and <35 in the HC.[30] The mean BMI of patients was ≥25 kg/m^2 in 11 studies,[6,13,18,19,22-26,29,34] 25< kg/m^2 in two studies[31,32] and not available for four studies[15,30,33,35] The APACHE II scores in ten studies were >20[6,13,15,18,19,23,25,31,34,35] and ≤20 in five studies.[24,26,30,32,33] One study reported simplified acute physiology score (SAPS)[29] and one study used APACHE III scores[22] as shown in Table 1. The average daily calories delivered were different among all studies ($P < 0.05$). This ranges from 126 to 1480 kcal/day in LC group and 474–2086 kcal/day in HC delivery group. The mean daily percentage of calories in LC group in three studies was <33%,[15,22,23] 33%–66% in nine studies,[6,18,19,24-26,30,33,35] and >66% in five studies.[13,29,31,32,34] The mean calorie target in HC group was <70% in four studies,[15,30,33,35] >70% in seven studies,[6,18,19,22-25] and >90% in six studies.[13,26,29,31,32,34] Ten of the 17 RCTs reported amount gram of protein delivered per day and ranges from (mean ± standard

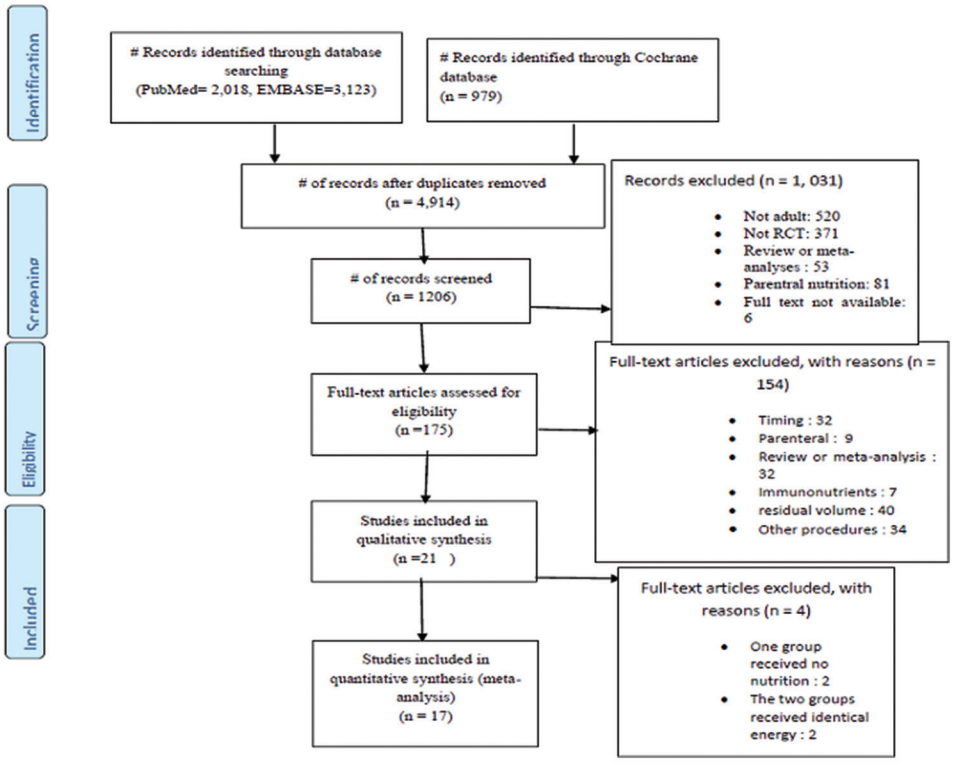

Figure 1: Study flow diagram according to Preferred Reporting Items for Systematic Reviews and Meta-analysis

deviation) 5.5 ± 5.3–86 ± 6 g/day in the LC group and 18.7 ± 15.4–83 ± 6 g/day for the HC delivery gro up[6,13,15,18,19,23,24,31,33,34] as indicated in Table 2.

Risk of bias in included studies

We used the Cochrane collaboration tool to assess the risk of bias of individual study. Only one study used a double-blind design because of the need for adjustment of the nutritional support according to feeding tolerance and gastric residual volume and at lower risk of bias across all domains.[13] Other five trials had also low risk of bias except for blinding of patients and personnel.[18,19,23,24,31] The rest trials had either high or unclear risk of bias in one or more domains in addition to bias in blinding domain as shown in Figures 2 and 3. Funnel plot was used to assess possible reporting or publication bias on mortality. Figure 4 shows the approximate symmetry of the funnel plot for mortality. We performed a sensitivity analysis by removing a

Table 1: The baseline characteristics of included patients in meta-analysis

Author, year	Age in year (mean±SD)		BMI in kg/m² (mean±SD)		Severity score (mean±SD)		Number of patients included	
	LC	HC	LC	HC	LC	HC	LC	HC
Arabi, 2011[6]	50.3±21.3	51.9±22.1	28.5±7.4	28.5±8.4	25.2±7.5	25.3±8.2	120	120
Arabi, 2015[18]	50.2±19.5	50.9±19.4	29.0±8.2	29.7±8.8	21.0±7.9	21.0±8.2	448	446
Braunschweig, 2014[19]	58.6±16.2	52.5±17.1	30.1±8.9	29.8±9.3	27.7±7.9	23.4±9.3	38	40
Charles, 2014[24]	50.4±2.8	53.4±2.7	32.9±2.0	28.1±0.9	16.6±0.9	17.3±0.8	41	42
Desachy, 2008[29]	64±13	58±19	27±5	25±3	40±11#	42±17	50	50
Peake, 2014[13]	56.5±16	56.4±16.8	26.2±6.4	27.8±7.9	22±8.90	23±9.1	55	57
Rice, 2011[23]	53±19	54±17	29.2±10	28.2±9.4	26.9±8.1	26.9±6.6	98	102
Rice, 2012[22]	52±17	52±16	29.99±7.8	30.4±8.2	92±28**	90±27	508	492
Taylor, 1999[30]	28*	34*	NA	NA	14*	14*	41	41
Rugeles, 2016[26]	53.8±19	51.8±20.3	25±1.9	25±1.9	13.5±6.4	13.7±6.8	60	60
Petros, 2014[25]	67.6±11.5	64.3±11.5	28.6±6.5	27.1±6.8	30.5±8.5	27.7±8.4	46	54
Montecalvo, 1992[35]	44.8±15.9	50.5±21.5	NA	NA	21.7±8.2	24±6.7	19	19
Kearns, 2000[33]	49±4	54±3	NA	NA	20±1	22±2	23	21
Ibrahim, 2002[15]	61±19	57±16	NA	NA	26±8	25±8	75	75
Hsu, 2009[31]	68±15.3	70±13.1	23.1±4.1	23.5±5.8	20.3±6.9	20.5±6.4	62	59
Singer, 2011[34]	62±17	59±18	27.4±7.3	27.8±6.3	22.4±6.8	22.1±7.4	65	65
Huang, 2012[32]	68.3±6.2	70.9±13.2	23.4±4.1	24±6.1	19.6±6.2	21±6.8	51	50

*SD not reported, **Reported APACHE III score, #Reported SAPS. SD: Standard deviation; BMI: Body mass index; LC: Low calorie; HC: High calorie; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; NA: Not available

Table 2: Amount of calorie delivered and overall mortality

First Author, year	Calorie delivered daily in kcal/days (SD)		Daily caloric goal (%)		Protein (g/day)		Average protein (g/day)	SPN	Overall mortality (*n*/*N*)	
	LC	HC	LC	HC	LC	HC			LC	HC
Arabi, 2011[6]	915.9 (346.6)	1102.8 (451)	59	71.4	47.5 (21.5)	43.6 (18.6)	46	No	38/120	52/120
Arabi, 2015[18]	835 (297)	1299 (467)	46	71	57 (24)	59 (25)	58	Yes	131/448	140/446
Braunschweig, 2015[19]	1221 (423)	1798 (509)	55.4	84.7	60.6 (24)	82 (23)	71	Yes	6/38	16/40
Charles, 2014[24]	982 (61)	1338 (92)	40.5	73	86 (6)	83 (6)	85	Yes	3/41	4/42
Desachy, 2008[29]	1297 (33)	1715 (331)	76	95	NA	NA	NA	No	11/50	14/50
Peake, 2014[13]	1259 (428)	1832 (381)	72	100	69 (24)	68 (21)	69	No	14/55	10/57
Rice, 2011[23]	300 (149)	1418 (686)	15	74.8	10.9 (6.8)	54.4 (33.2)	32	No	22/98	20/102
Rice, 2012[22]	425.9 (140.8)	1385 (45.9)	25	80	NA	NA	NA	No	118/508	109/492
Taylor, 1999[30]	NA	NA	36.8	59.2	NA	NA	NA	No	6/41	5/41
Rugeles, 2016[26]	NA	NA	50	100	NA	NA	NA	No	18/60	16/60
Petros, 2014[25]	523.9 (38.2)	323.2 (20.2)	42.6	75.5	NA	NA	NA	Yes	18/46	18/54
Montecalvo, 1992[35]	1182 (603)	1209 (344)	46.9	61	NA	NA	NA	No	5/19	5/19
Kearns, 2000[33]	812 (122)	1157 (86)	47	69	31 (5)	44 (4)	38	No	6/23	5/21
Ibrahim, 2002[15]	126 (115)	474 (400)	7	27.9	5.3 (5.3)	18.7 (15.4)	12	No	20/75	15/75
Hsu, 2009[31]	1426 (110)	1658 (118)	83	95	58.8 (4.9)	67.9 (4.9)	63	No	24/62	26/59
Singer, 2011[34]	1480 (356)	2086 (460)	80.5	106	53 (16)	76 (16)	66	Yes	27/65	16/65
Huang, 2012[32]	NA	NA	76.2	90	NA	NA	NA	No	17/51	20/50

SD: Standard deviation; LC: Low calorie; HC: High calorie; NA: Not available; SPN: Supplemental parenteral nutrition

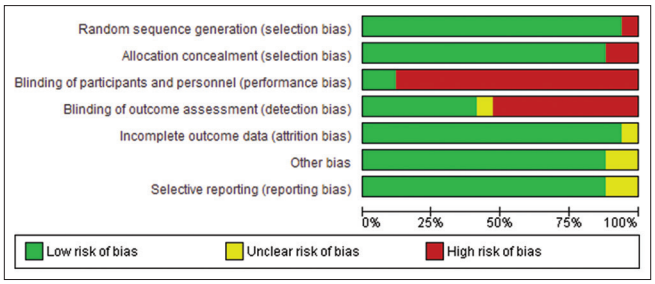

Figure 2: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

single study at a time to evaluate the stability and robustness of the pooled mortality outcome. We obtained statistically similar results after omitting each of the studies as described in Table 3. This indicates that the good degree of stability in the findings of this meta-analysis about the primary outcome.

Clinical outcomes

Overall mortality

Mortality data were available in all 17 trials included in the meta-analysis; two trials reported 180-day mortality at the last follow-up,[6,18] one trail reported 90-day mortality,[13] one trail 60-day mortality,[22] one trial 28-day mortality,[26] one trail ICU mortality,[34] five trials hospital mortality,[15,23,25,29,32] and six trials reported unidentified mortality.[19,24,30,31,33,35] The aggregate result of this study showed that the overall mortality rate in LC delivery group was 484 (26.9%) of 1800 participants and 491 (27.4%) of 1793 in HC group which was not statistically significantly different (RR, 0.98; 95% CI, 0.87–1.10; P = 0.74; I^2 = 6%; P = 0.38) as depicted in Figure 5. Close observation of these results shows that the absolute reduction of mortality by LC delivery is 1.6%. No significant difference effect was observed on mortality based on the subgroup analysis according to:

1. Mode of calorie delivery: EN with SPN (RR, 106; 95% CI, 0.73–1.53; P = 0.76; I^2 = 63%, P = 0.03) versus without SPN (RR, 0.98; 95% CI, 0.84–1.10, P = 0.57; I^2 = 0%, P = 0.86) [Figure 6]
2. Severity score: APACHE II >20 (RR, 1.00; 95% CI, 0.82–1.22, P = 1.00; I^2 = 41%, P = 0.08) versus APACHE II ≤20 (RR, 0.98; 95% CI, 0.70–1.1.36, P = 0.89; I^2 = 0%, P = 0.93) [Figure 7]
3. The BMI: BMI ≥25 kg/m^2 (RR, 0.99; 95% CI, 084–1.16, P = 0.90; I^2 = 34%, P = 0.13) versus <25 kg/m^2 (RR, 0.86; 95% CI, 0.62–1.19, P = 0.37; I^2 = 0%, P = 0.88) [Figure 8]
4. Amount of calorie delivered by LC of standard requirement: <30% LC (RR, 1.09; 95% CI, 0.89–1.33, P = 0.39; I^2 = 0%, P = 0.74) versus 33%–66% LC (RR, 0.90; 95% CI, 0.77–1.04, P = 0.15; I^2 = 0%, P = 0.48) versus >66% (RR, 1.06; 95% CI, 0.78–1.44, P = 0.73; I^2 = 36%, P = 0.18) [Figure 9].

Pneumonia

Ten of the 17 studies reported new-onset pneumonia which included 2950 patients.[6,15,18,22-24,31,33-35] The incidence of pneumonia was not significantly different between the groups (RR, 0.92; 95% CI, 0.73–1.116; P = 0.46; I^2 = 38%; P = 0.11) as shown in Figure 10.

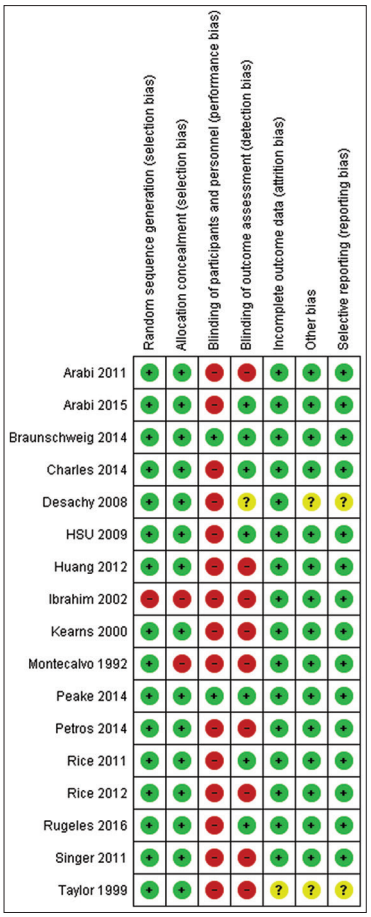

Figure 3: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study

Table 3: Sensitivity analysis for overall mortality by omitting each study in random-effects model

Study omitted	RR (95% CI)	*P*	I^2 (%)
Arabi, 2011	1.01 (0.90-1.13)	0.85	0
Arabi, 2015	1.00 (0.87-1.15)	0.99	10
Braunschweig, 2014	0.99 (0.89-1.11)	0.90	0
Charles, 2014	0.98 (0.87-1.11)	0.81	11
Desachy, 2008	0.99 (0.88-1.12)	0.86	10
Peake, 2014	0.97 (0.87-1.09)	0.62	5
Rice, 2011	0.98 (0.86-1.10)	0.69	10
Rice, 2012	0.97 (0.85-1.11)	0.65	10
Taylor, 1999	0.98 (0.87-1.11)	0.75	2
Ruseles, 2016	0.98 (0.86-1.11)	0.71	11
Petros, 2014	0.97 (0.86-1.10)	0.67	9
Hsu, 2009	0.99 (0.87-1.13)	0.90	11
Huang, 2012	0.99 (0.88-1.12)	0.89	10
Kearns, 2000	0.98 (0.87-1.11)	0.77	12
Ibrahim, 2002	0.97 (0.86-1.09)	0.60	6
Montecalvo, 1992	0.98 (0.87-1.11)	0.79	12
Singer, 2011	0.95 (0.86-1.06)	0.40	0

CI: Confidence interval; RR: Risk ratio

Blood stream infection or bacteremia or sepsis

Seven out of the 17 trials reported either sepsis or bacteremia or bloodstream infection:[6,18,22-24,31,34,35] these studies included 2506 patients. Sepsis or bacteremia or bloodstream infection was not significantly different between the groups (RR, 1.02; 95% CI, 0.86–1.21; $P = 0.84$; $I^2 = 0\%$; $P = 0.70$) [Figure 11].

Lengths of Intensive Care Unit and hospital stay

Information on the length of ICU stay was available for 13 of the 17 studies.[6,13,15,18,19,24,26,29,31-35] These 13 studies included 2211 patients and there was no significant difference between the two groups (WMD, −0.34; 95%, CI, −0–1.26 to 0.57, $P = 0.46$; $I^2 = 48\%$, $P = 0.03$) as shown in Figure 12. Information on the length of hospital stay available for nine studies[6,13,18,19,24,29,31,33,34] [Figure 13]. Patients initially receiving LC delivery had significantly lower length of hospital stays compared with those initially receiving HC delivery (WMD, −2.72; 95% CI, −4.04–1.39, $P < 0.0001$; $I^2 = 0\%$, $P = 0.46$).

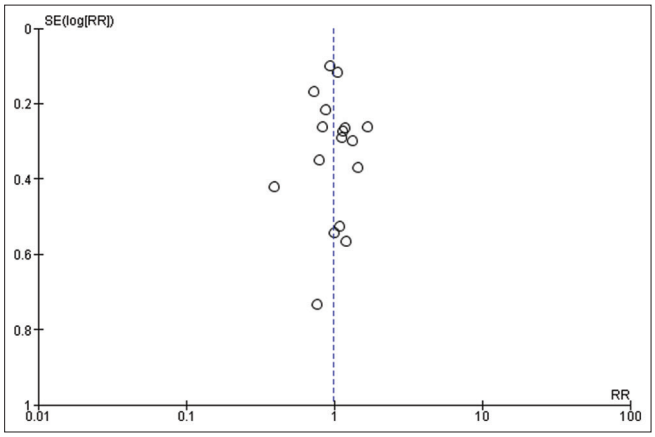

Figure 4: The impact of initial LC on mortality. LC: Low calorie; RR: Risk ratio; SE: Standard error

Duration of mechanical ventilation

Data on duration of mechanical ventilation were available for eight studies:[6,15,18,23,24,26,31,35] these data included 1846 participants. The analysis of the data of these eight studies showed that patients assigned initially to LC delivery had significantly lower duration of ventilator dependency compared with those assigned to HC delivery (WMD, −0.80; 95% CI, −1.39 to − 0.21, $P = 0.0001$; $I^2 = 11\%$, $P = 0.35$) [Figure 14]. This indicates a 19.2 h reduction of ventilator dependency for patients received LC compared to those received HC artificial nutrition.

Hypoglycemic

Four out of 17 trials reported data on incidence of hypoglycemia[6,18,19,25] as shown in Figure 15. The result of analysis of these data on 1312 participants showed that there was no significant difference between the two groups with regard to the occurrence of hypoglycemia (RR, 1.17; 95% CI, 0.83–1.66, $P = 0.37$; $I^2 = 0\%$, $P = 0.65$).

Average dose insulin used per day

Five out of 17 trials reported the doses of insulin used per day[6,13,18,19,24] [Figure 16]. The five studies included 1407 participants. The result of analysis showed there was significant difference between patients assigned to LC compared with those assigned to HC with the former group received less daily dose of insulin than the latter group (WMD, −7.81; 95% CI, −14.32 to −1.30, $P = 0.02$; $I^2 = 37\%$, $P = 0.17$).

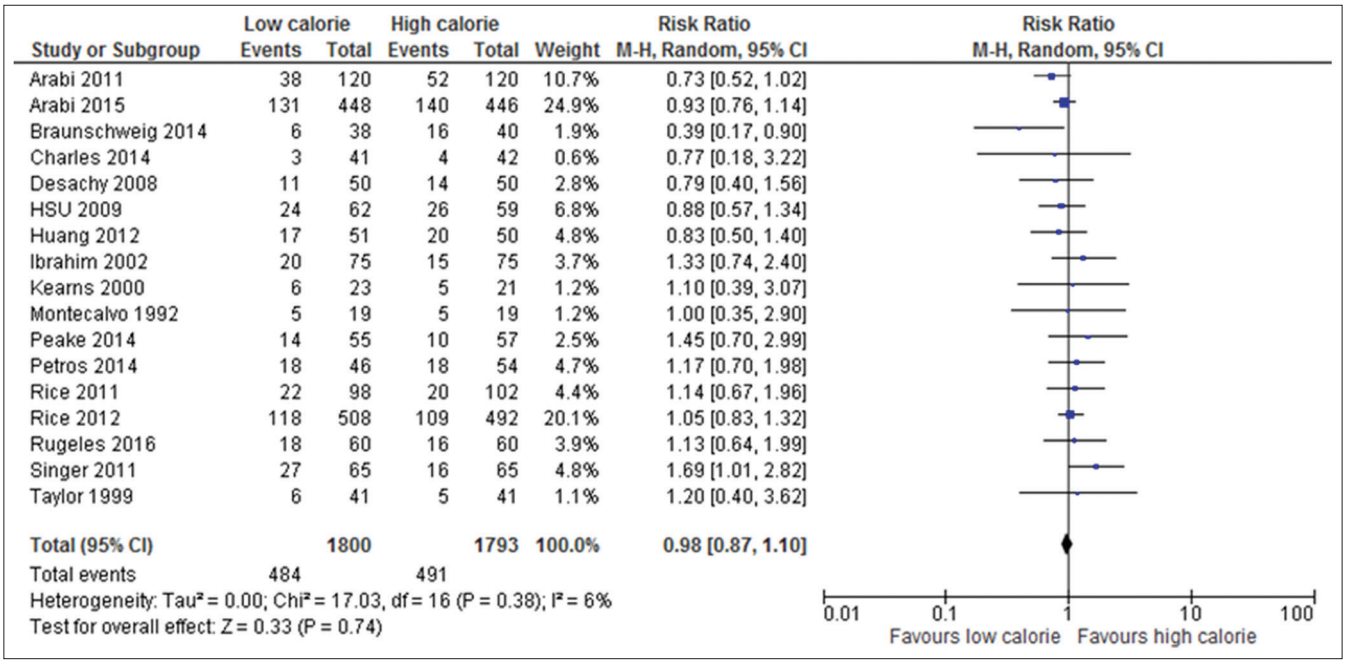

Figure 5: Forest plot showing the impact of daily calories goals on overall mortality in critically ill adult patients. M-H: Mantel-Haenszel; CI: Confidence interval

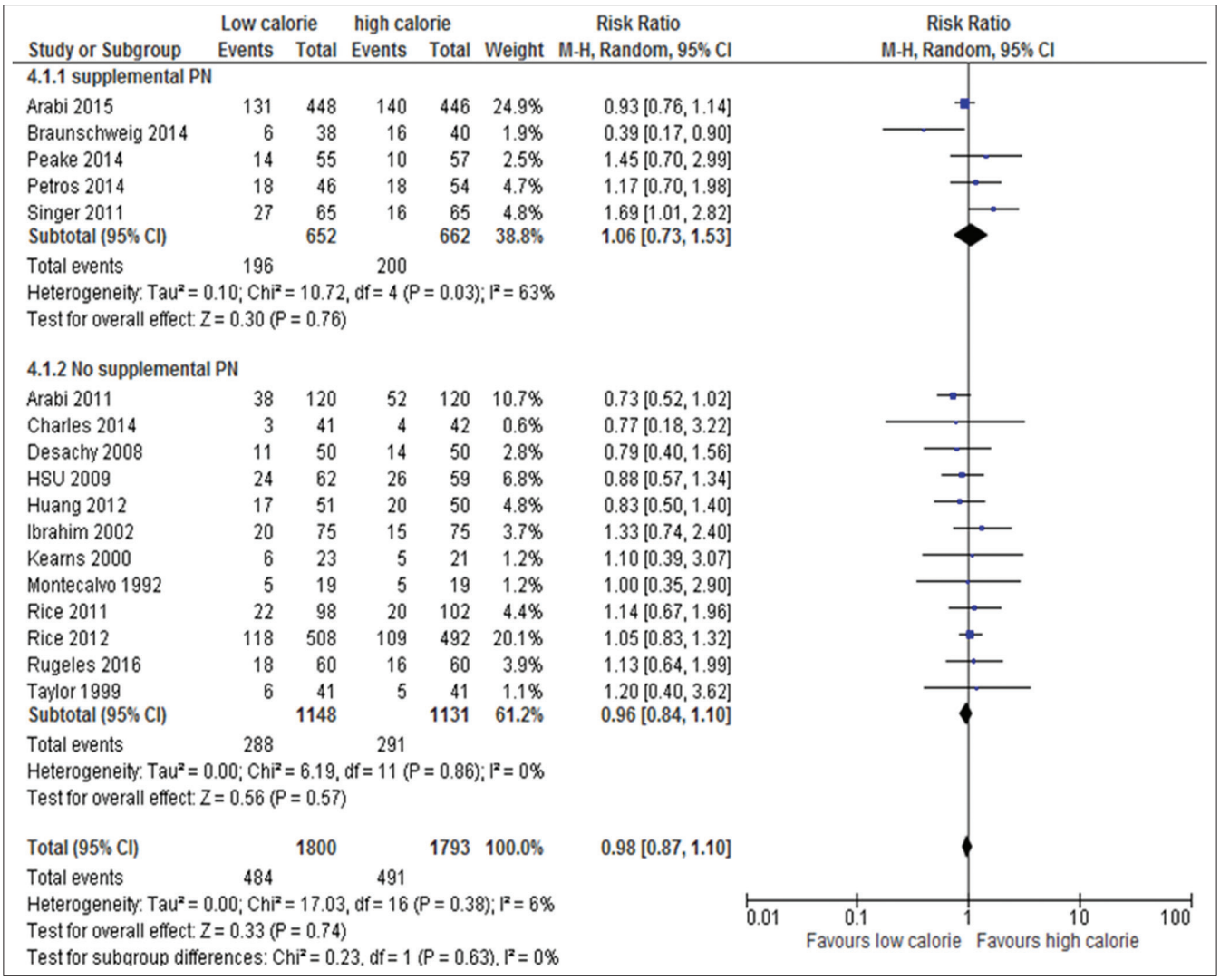

Figure 6: Forest plot showing the impact of daily calories goals by EN with or without SPN on mortality in critically ill patients. M-H: Mantel-Haenszel; CI: Confidence interval; LC: Low calorie; EN: Enteral nutrition; PN: Parenteral nutrition

Incidence of renal replacement therapy

Four out of 17 trials include 1322 participants reported about incidence of RRT[6,15,18,34] [Figure 17]. Initially, delivery of LC was associated with less incidence of RRT compared with those assigned to initial HC nutrition (RR, 0.73; 95% CI, 0.55–0.98, $P = 0.01$; $I^2 = 0\%$, $P = 0.92$).

Gastrointestinal intolerance

Eight of the 17 studies reported gastrointestinal intolerance; these studies included 1347 participants[6,13,18,22,23,25,26,29] [Figure 18]. Patients received initial LC had significantly decreased risk of gastrointestinal intolerance compared with those initially received HC feeding (RR, 0.79; 95% CI, 0.70–0.91; $P = 0.0007$; $I^2 = 0\%$; $P = 0.38$).

Discussion

In this meta-analysis of 17 RCTs enrolled around 3600 critically ill adult patients, compared to initial LC delivery of EN with or without SPN, HC delivery was not shown statistically significant reduction in mortality. The mortality rates in those initially underfeeding and full-feeding patients were 26.9% and 27.4%, respectively. Moreover, neither the subgroup analysis performed based on the presence or absence of SPN, baseline severity score, BMI nor stratified amount of calorie delivered by LC of standard requirement of nutritional interventions declared any evidence of survival benefits of initial HC delivery compared with under-feeding.

Two recently published meta-analyses have also reported the effect of calorie delivery on clinical outcomes of critically ill adult patients.[20,21] The subgroup analysis done by these authors based on tertiles of standard calorie requirement showed that mortality was significantly reduced in those fed on 33% to 66% calorie provision compared to those fed on HC. The current meta-analysis was unable to find the survival benefit of the middle tertile energy provision in the two meta-analyses mentioned above. The discrepancy could be more probably due to the difference in the sample size. Therefore, interpretation of

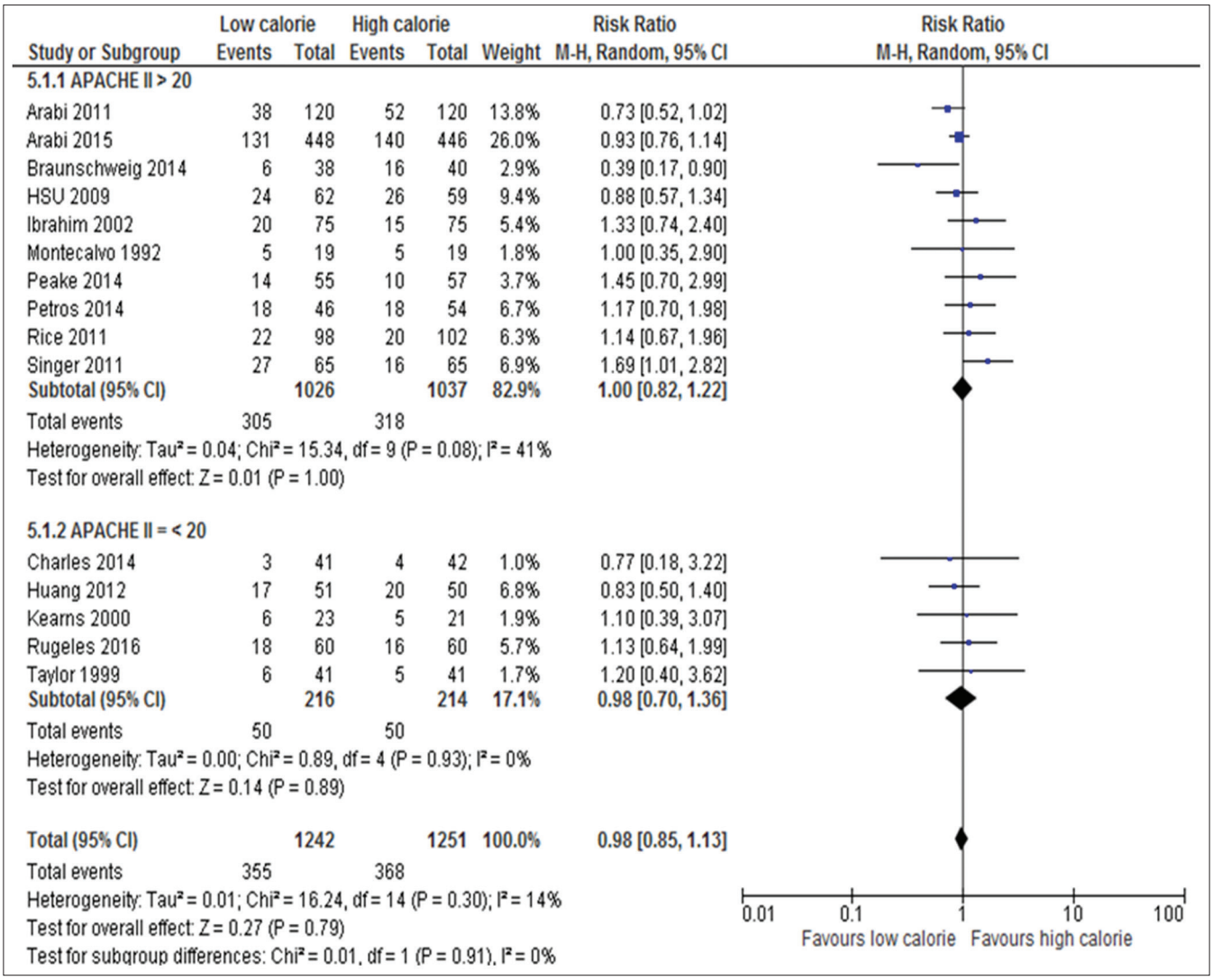

Figure 7: Forest plot showing the impact of daily calories goals based on disease severity score on mortality in critically ill adult patients. M-H: Mantel-Haenszel; CI: Confidence interval; APACHE II: Acute Physiology and Chronic Health Evaluation II

the two meta-analyses should be with considerable causation since the result based on small sample size, low quality, and biased studies.

Why the aggregate result of 17 RCTs can't predict the treatment effect of different doses of artificial nutrition on mortality? Or why there is no statistically significant difference between high calories compared to low calorie delivery with regard to mortality in critically ill adult patients?

The answer is more likely due to the fact that artificial nutrition in critically ill patients is a medicine provided to malnourished patients, is unphysiologic, and may evoke complications and unwanted side effects that should be weighed against any expected effect as stated by Schetz *et al*.[36] Therefore, it seems that the so called "one-size-fits-all" seems inapplicable and individualization of nutritional therapy should be considered in daily clinical practice. Close observation of the trials included in this meta-analysis showed that almost all the patients included in each trial had normal nutritional status or slightly overweight (BMI >25 kg/m^2) indicating that they might not derive benefits from overfeeding. This could partly explain lack of survival benefits of HC delivery compared to LC delivery in this meta-analysis. Similarly, a large multinational prospective observational study reported an inverse relationship between calorie input and mortality and risk of mortality was significantly for patients with BMI <25 or >35 kg/m^2 compared with BMI of 25–35 kg/m^2.[37]

Moreover, all of the participants in these studies received early EN that was approved to be beneficial in those patients who need nutrition (malnourished patients before ICU admission). What being tested in these studies was the amount of nutrition that the patients received and it is not expected that nutrition to be beneficial to all patients the same. A body of literatures reported that those patients at high risk nutritionally speaking are more likely derive an effect of increased delivery of protein and calorie on infection, resolution of organ failure or mortality.[36,38,39] Indeed, studies included in this meta-analysis

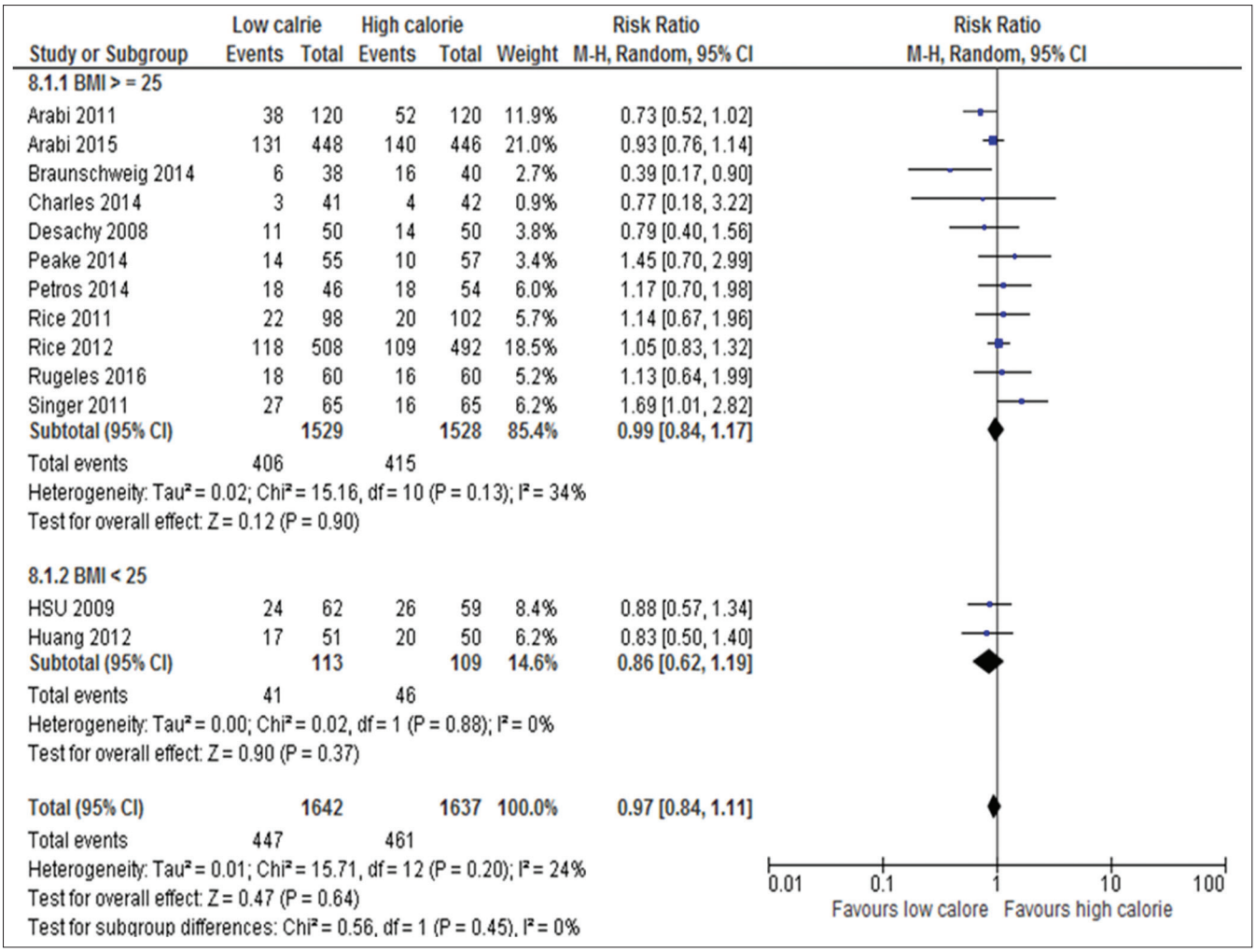

Figure 8: Forest plot showing the impact of daily calories goals based on BMI on mortality in critically ill patients. M-H: Mantel-Haenszel; CI: Confidence interval; BMI: Body mass index

also composed of patients at low risk of malnutrition before ICU admission. Therefore, it is perceivable that no matter how powerful the study is, if low risk patients are randomized to different doses of nutritional therapy, it is impossible to detect the treatment effect. We recommend better quality research concentrating on specific group of malnourished patients is therefore urgently needed.

We also found no significant between-group difference with respect to ICU-acquired infections (both new-onset pneumonia and sepsis), a finding that is consistent with the results of other studies.[6,22-24] The explanation for the absence of difference might be due to improvement in the current vascular access, and prevention of ventilatory associated pneumonia.

The length of hospital stays and duration of mechanical ventilation significantly shortened in LC delivery group, a result similar to a retrospective study which reported the reduced energy intake during 1st week in ICU was associated with a reduced length of hospital stays and mechanical ventilation.[40] However, the two recent meta-analyses failed to find the difference possibly due sample size.[20,21] Tian *et al*.[20] included in the analysis 4 out of 6 trials reported about length of hospital stay and 2 out of 6 studies reported on the duration of mechanical ventilations. Their explanation for the exclusion of those trails reported the endpoints of interest were the studies reported median instead of mean and they believed the comparison should not be done. However, we tried to overcome the problem by converting the median to mean by the formula reported in literature[41] to boost our sample size to detect the differences.

Regarding hypoglycemia and average insulin dose, LC was associated with lower blood glucose levels and reduced insulin requirements, findings that are consistent with those of other studies.[6,18,22] The current meta-analysis also showed that the incident of RRT in LC underfeeding group was significantly lower compared with the HC full-feeding group, a similar finding with another large RCT.[18] This notion supports the fact that higher calorie intake may be associated with kidney injury. It has been shown in animal model of acute renal injury that calorie restriction was renoprotective through several mechanisms including increasing insulin sensitivity.[42-44]

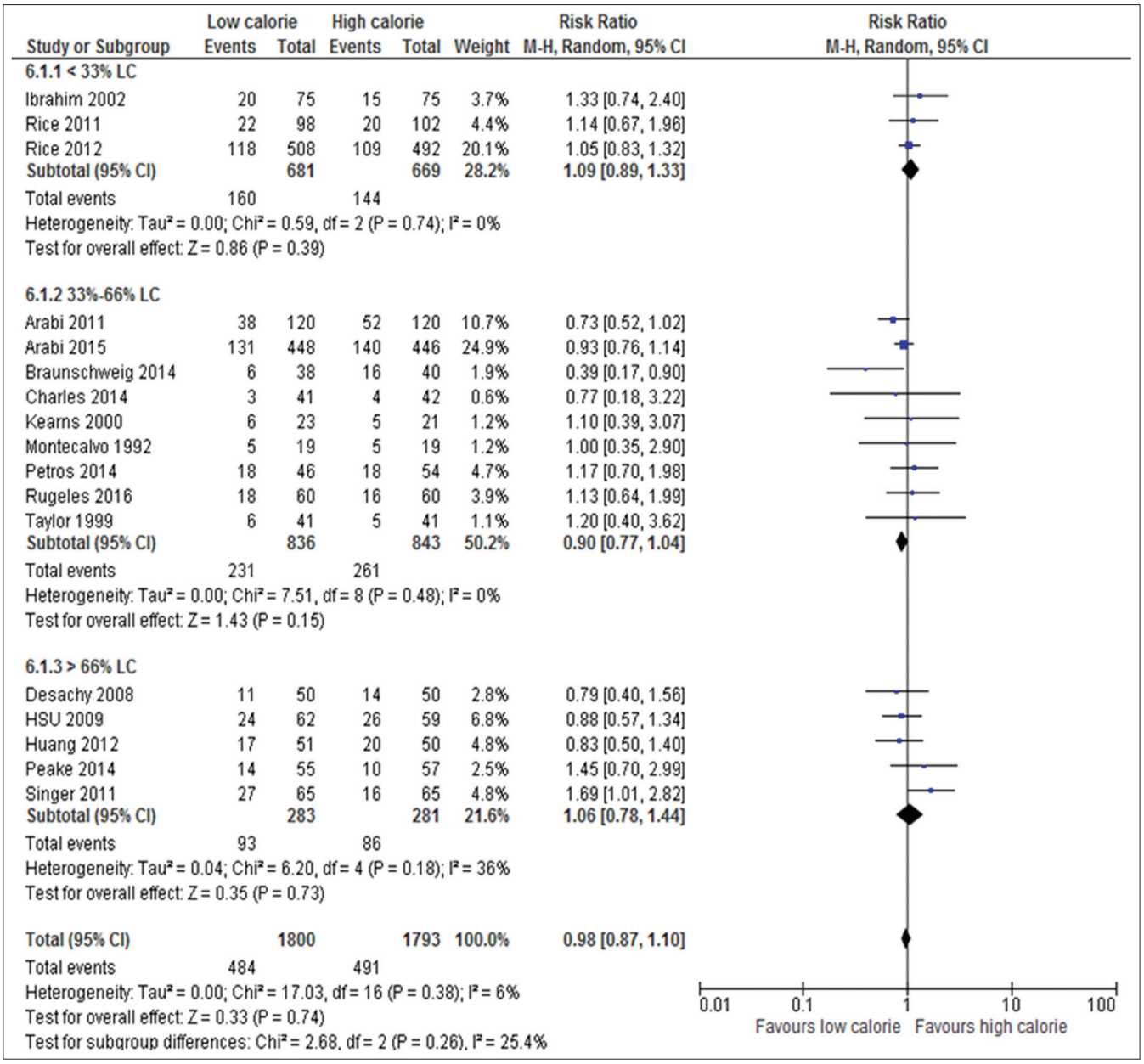

Figure 9: Forest plot showing the impact of percentage of daily calories goals on mortality in critically ill patients. M-H: Mantel-Haenszel; CI: Confidence interval

Another study by secondary analysis of 1456 patients from RENA trial (after correction for multiple confounding variables and the application of different statistical modeling techniques) found that a lower mean delivery of caloric intake was not robustly independently associated with increased risk of death at 90 days, or with other major clinical outcomes.[45] We found also that there was significant gastrointestinal intolerance (regurgitation, vomiting, diarrhea, constipation, or abdominal distension) in HC feeding group compared with LC feeding group in contrast to the two recently done meta-analyses.[20,21] The difference seems due to the underpowered nature of those studies compared with the present study.

Strengths and limitations

Our meta-analysis has some strength that the previously done meta-analyses failed to find out due to the limited number of studies they included (small sample size). Including more studies using wide searching strategies and loss restrictive of inclusion criteria, we were able to reveal that there were significant differences between the permissive underfeeding and full-feeding with regards to length of hospital stays (measure of health care consumption), duration of mechanical ventilation and gastrointestinal intolerance. Moreover, some more endpoints which have good clinical implication for critically ill patients (incident of hypoglycemia, average daily dose of insulin used per day and RRT) were also

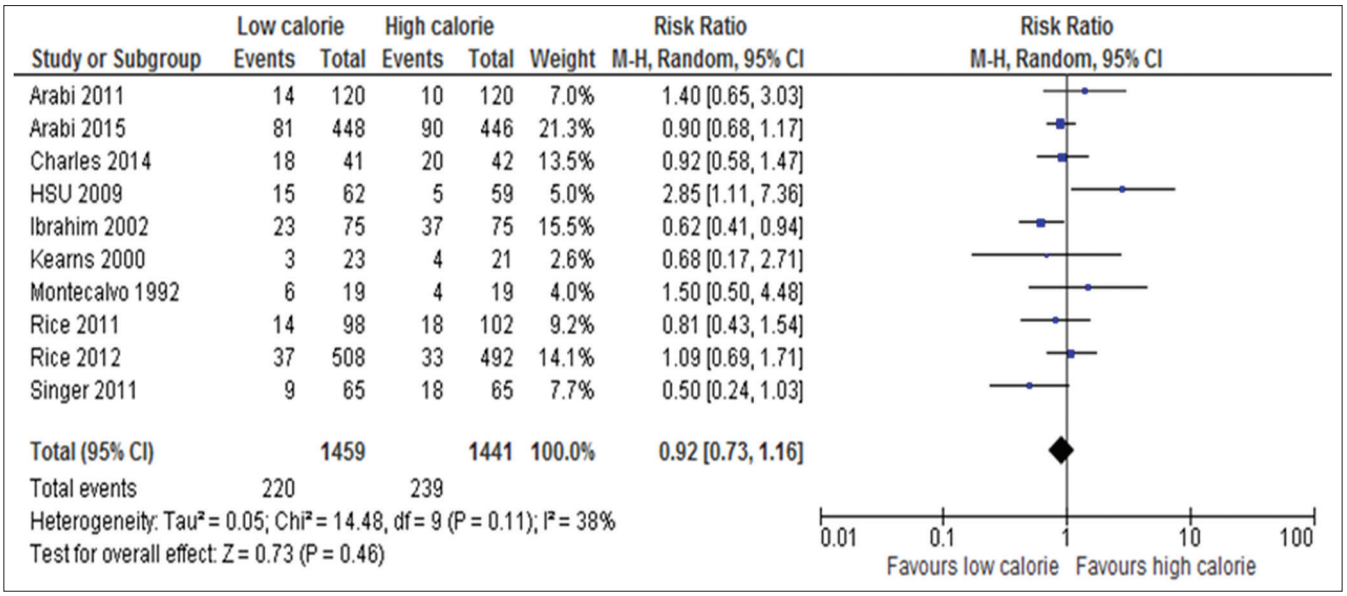

Figure 10: Forest plot showing the impact of daily calorie goals on new onset pneumonia in critically ill adult patients. M-H: Mantel-Haenszel; CI: Confidence interval

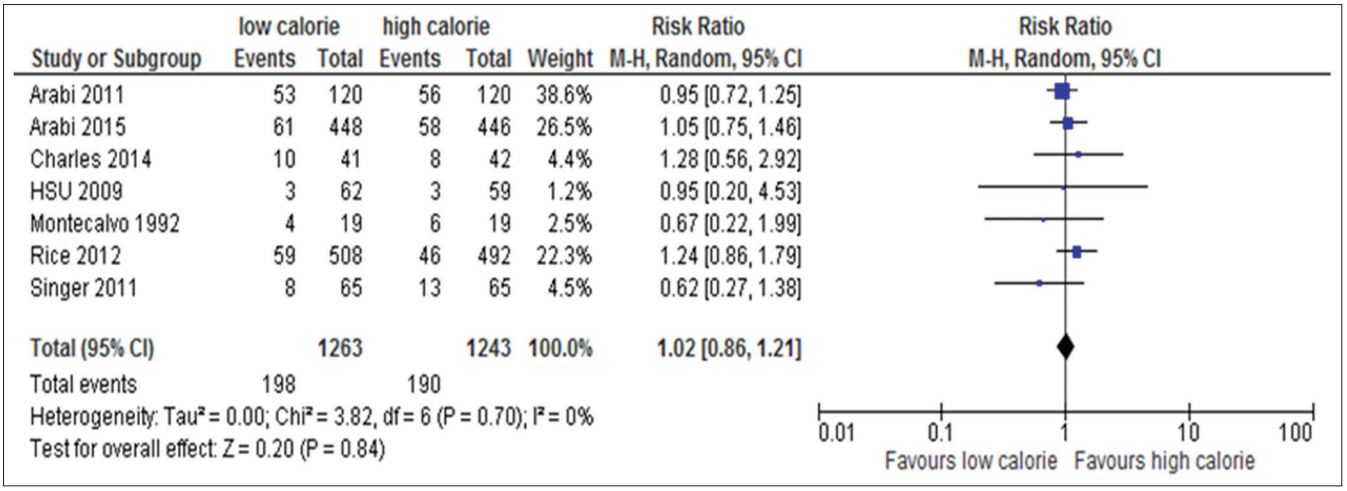

Figure 11: Forest plot showing the impact of daily calorie goals on sepsis in critically ill adult patients. M-H: Mantel-Haenszel; CI: Confidence interval

included. Despite these differences, the collective results of our study and the two previous meta-analyses add to a growing body of literature that suggests over-feeding goals in critically ill patients do not improve clinical outcomes.

Despite our effort to reduce bias, the results of the study should be treated with caution because of some limitations. First, the disease severity reported by the studies differed; some reported APACHE II score, two studies reported APACHE III and one study SAPS. Second, the calculated calorie intake had significant variation which can potentially affect the aggregated results of our study. Third, in almost all of the selected studies there had been high exclusion criteria for high disease severity, important comorbidities and inclusion of patients with BMI of 20–35 kg/m^2 thus limiting the generalizability of this finding. Forth, we are so conservative to give suggestion about the optimal dose of daily protein intake for a couple of reasons. It is difficult to consider the analysis of effect of protein intake on clinical outcomes due to the diverse protein dose among studies and the low dose of protein intake in all studies below the daily recommended dose by guidelines (1.2–1.5 g/kg) with the exception of one (Rugeles;[26] reported 1.7 g/kg/day). Lastly, there was apparent absence of a beneficial outcomes with more protein intake in secondary analyses of a randomized controlled trial (EPaNIC; n = 4640) performed in seven ICUs from three departments in two Belgian Hospitals.[46] Therefore, we feel that there is a need for good quality study about the optimal and safe range of daily protein intake in diverse groups of critically ill adult patients before any recommendation.

Finally, by any means, we are not announcing absolute clinical change by this work. However, we believe that this paper

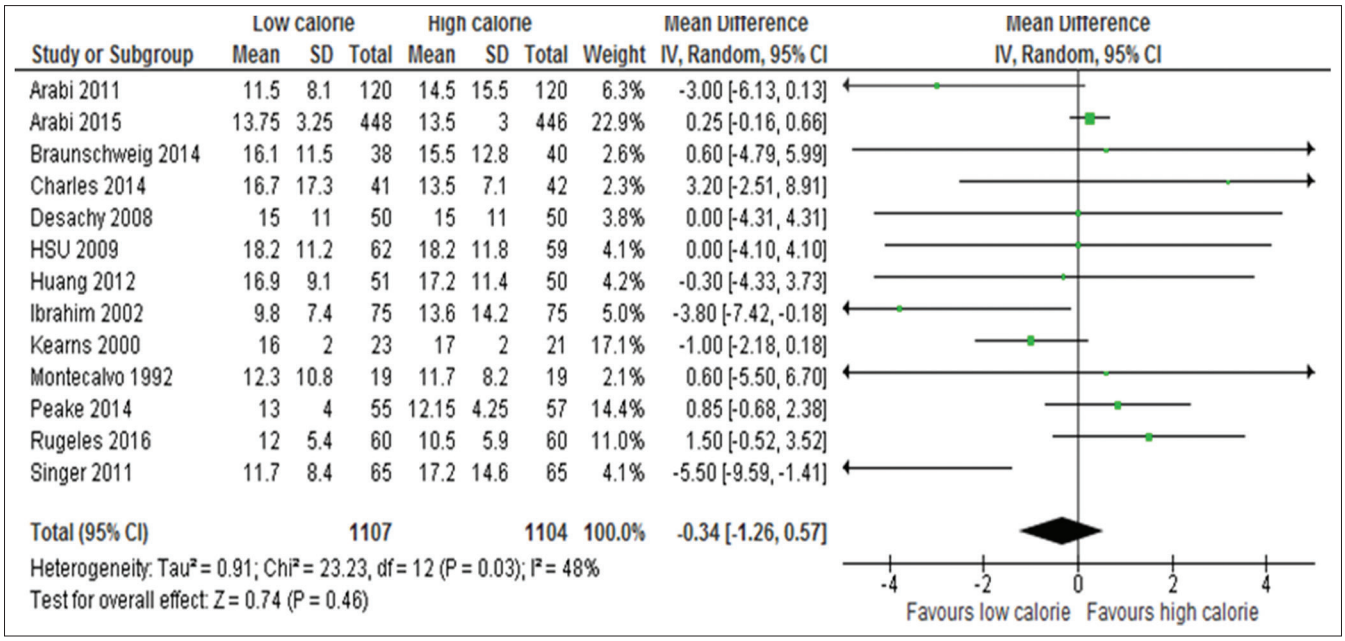

Figure 12: Forest plot showing the impact of daily calorie goals on lengths of ICU stay in critically ill adult patients. IV: Inverse variance; CI: Confidence interval; ICU: Intensive Care Unit; SD: Standard deviation

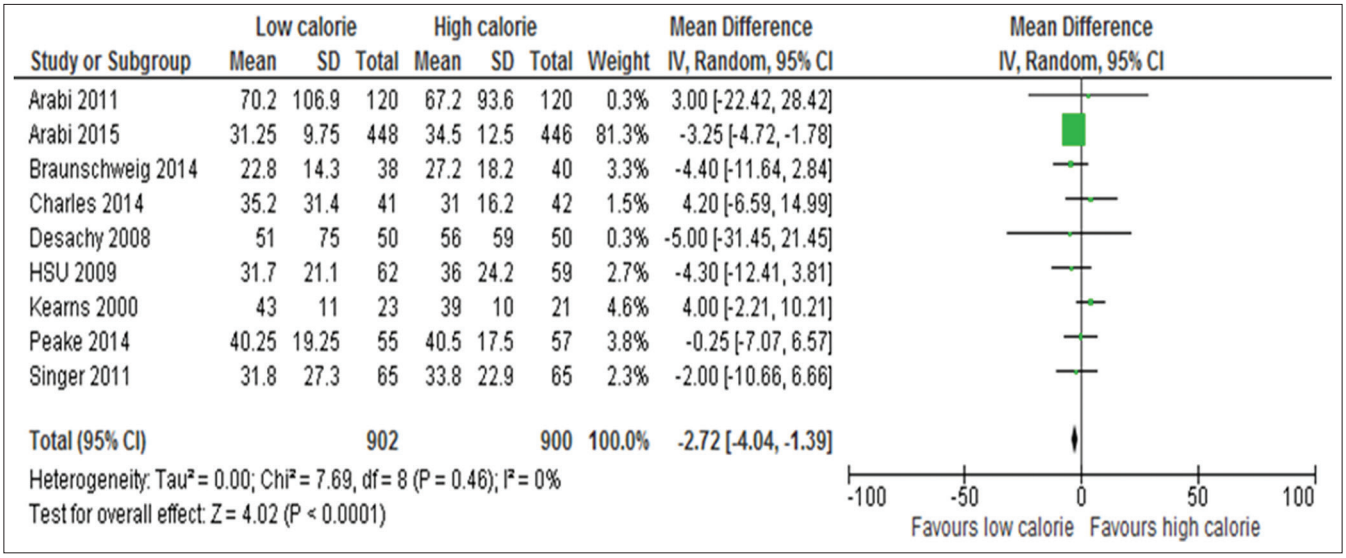

Figure 13: Forest plot showing the impact of daily calorie goals on length of hospital stay in critically ill patients. IV: Inverse variance; CI: Confidence interval; SD: Standard deviation

is a pivotal paper that may lead to considerable debate and discussion among practitioners and clinical scientists in the field and serve as an impetus for further research.

What do we learn from this meta-analysis?

This meta-analysis confirmed that HC intake is not associated with better outcome compared with LC intake in any endpoints analyzed so far in patients with low risk of malnutrition prior to ICU admission.

What is the role of nutrition in this group of patients then?

To achieve non-nutrition benefits early EN is of paramount importance than any other aspect of feeding in the critical care setting.[47-49] McClave *et al*. 2014[48] explained that early enteral nutrients stimulate the gastrointestinal response (maintaining blood flow and gut integrity, reducing gut-lung axis of inflammation, maintaining gut associated lymphoid tissue [GALT]), the endocrine response (improves insulin sensitivity, enhance fuel utilization) and the immune response (maintain GALT, decrease bacterial translocation, maintaining bacterial commensal). This nonnutritional benefits may be achieved by permissive underfeeding and is probably needed in every patients admitted to ICU, which has been suggested by this meta-analysis (i.e. no

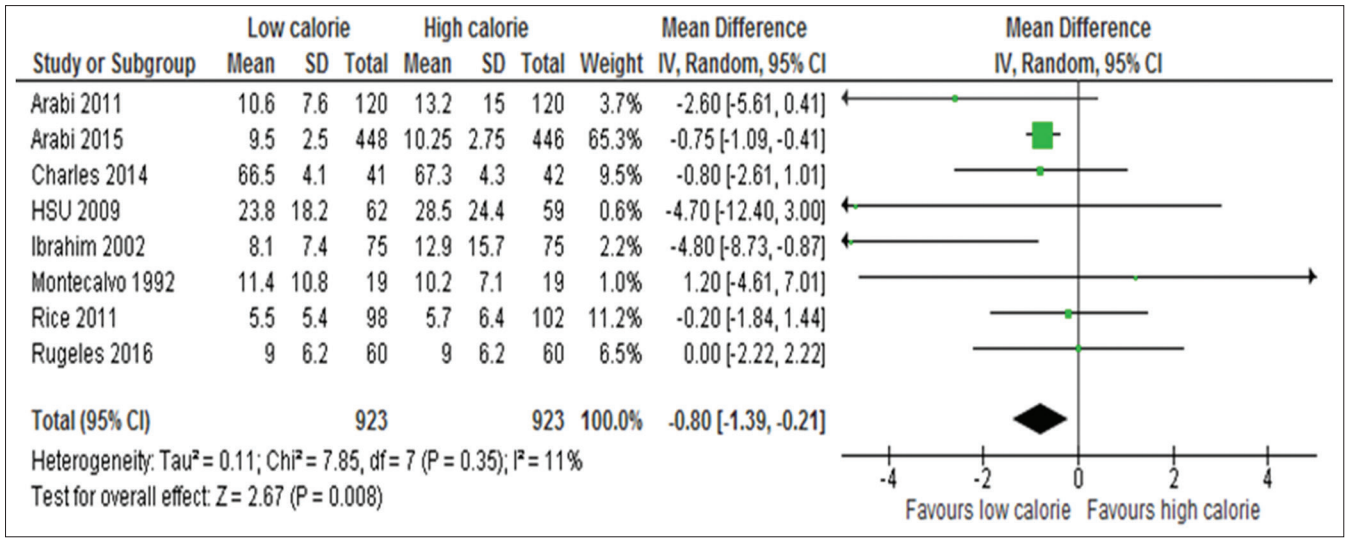

Figure 14: Forest plot showing the impact of daily calorie goals on duration of mechanical ventilation in critically ill patients. IV: Inverse variance; CI: Confidence interval; SD: Standard deviation

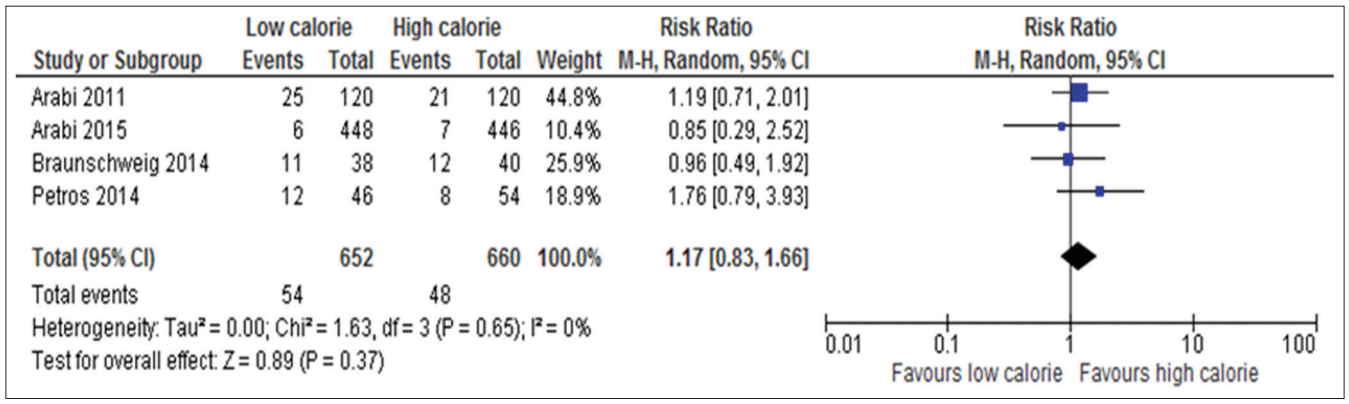

Figure 15: Forest plot showing the impact of daily calorie goals on incident hypoglycemia in critically ill adult patients. M-H: Mantel-Haenszel; CI: Confidence interval

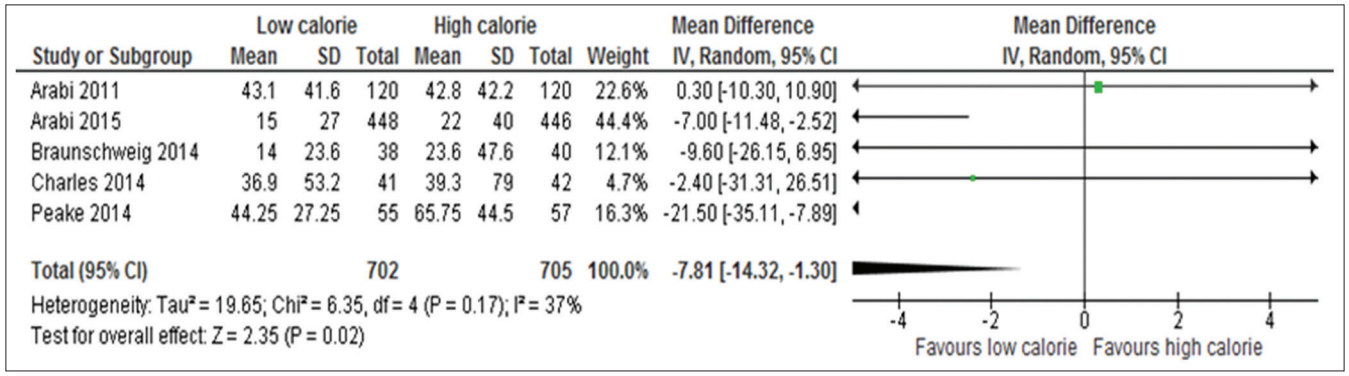

Figure 16: Forest plot showing the impact of daily calorie goals on average of insulin used per day in critically ill adult patients. IV: Inverse variance; CI: Confidence interval; SD: Standard deviation

beneficial endpoint observed by overfeeding compared to underfeeding).

The bottom line is that patients at low risk of malnutrition before ICU admission should receive trophic feeding to achieve nonnutrition benefits of nutrients therapy. However, patients with reduced nutritional status (high-risk patients) before ICU admission should receive high dose closer to goal feeding to maintain lean body mass, correcting micronutrients deficits, antioxidants deficit, and maximizing protein synthesis as stated by McClave *et al*.[48]

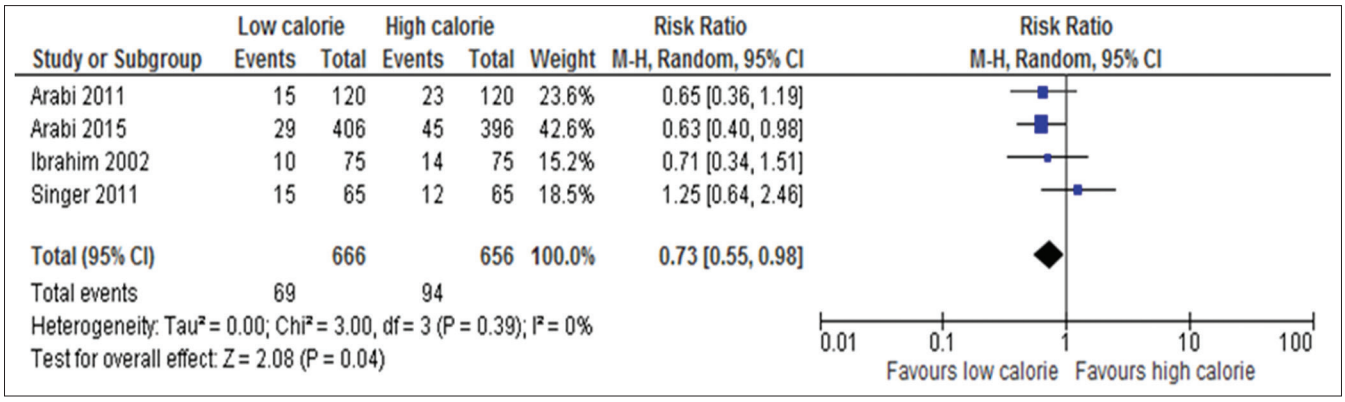

Figure 17: Forest plot showing the impact of daily calorie goals on incident of RRT in critically ill adult patients. M-H: Mantel-Haenszel; CI: Confidence interval; RRT: Renal replacement therapy

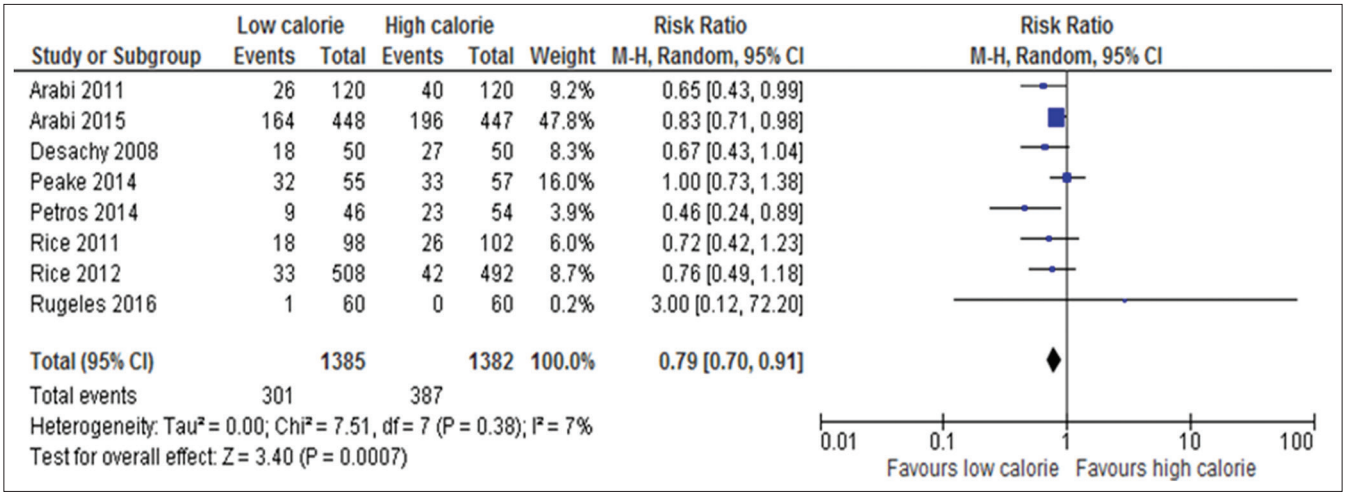

Figure 18: Forest plot showing the impact of daily calorie goals on gastrointestinal intolerance in critically ill adult patients. M-H: Mantel-Haenszel; CI: Confidence interval

Conclusion

The current meta-analysis showed that there was no significant difference between the LC and HC delivery groups in terms of the mortality in critically ill patients. However, initial LC delivery for critically ill patients resulted in shortening of length of hospital stay and duration of mechanical ventilation, low average daily dose of insulin use, low incidence of RRT, and gastrointestinal intolerance without significant effects on other secondary outcomes considered in the analysis.

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Conflicts of interest

There are no conflicts of interest.

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