

1.0 Nutritional Prescription: Use of Indirect Calorimetry vs. Predictive Equations

Question: Does the use of indirect calorimetry vs. a predictive equation for determining energy needs and targeting the nutrition delivery to those needs result in better outcomes critically ill adult patients?

Summary of evidence: There was one level 1 study and eight level two studies reviewed that compared the effectiveness of Indirect Calorimetry (IC) guided nutrition to predictive equations. In six of the studies, enteral nutrition (EN) was supplemented with parenteral nutrition (PN) to make up for the energy deficit in both groups (Singer 2011, Yang 2016, Allingstrup 2017, Gonzalez-Granda 2018, Zhao 2019 and Singer 2020).

Mortality: When the data from all the studies were aggregated, IC guided nutrition had a trend towards lower overall mortality compared to predictive equation guided nutrition (RR 0.84, 95% CI 0.68, 1.04, $p=0.11$, test for heterogeneity $I^2=3\%$, see Figure 1). No differences in mortality were found between groups for hospital mortality (RR 0.86, 95% CI 0.59, 1.27, $p=0.46$, test for heterogeneity $I^2=24\%$, see Figure 2) and ICU mortality (RR 0.87, 95% CI 0.69, 1.11, test for heterogeneity $I^2=0\%$, Figure 3).

Infections: Based on three studies (Singer 2011, Singer 2020, Allingstrup 2017), indirect calorimetry compared to weight-based predictive equation had no effect on total infections (RR 1.29, 95% CI 0.71, 2.36, $p=0.40$, test for heterogeneity $I^2=78\%$, Figure 4) or ventilator associated pneumonia (RR 1.33, 95% CI 0.65, 2.75, $p=0.44$, test for heterogeneity $I^2=62\%$, Figure 5).

LOS: Indirect calorimetry guided nutrition had no effect on hospital length of stay (WMD 0.49, 95% CI -1.76, 2.74, $p=0.67$, for heterogeneity $I^2=0\%$, Figure 6) or ICU length of stay (WMD -0.23, 95% CI -3.84, 3.37, $p=0.90$, test for heterogeneity $I^2=83\%$, Figure 7).

Ventilator days: Compared to predictive equations, indirect calorimetry guided nutrition had no effect on duration of mechanical ventilation (WMD -0.31, 95% CI -1.43, 2.06, $p=0.72$, test for heterogeneity $I^2=58\%$, Figure 8).

Nutritional Outcomes: In the Saffle study, diarrhea, hyperglycemia, electrolyte imbalance did not differ between the two groups. Singer et al 2020 reported higher rates of hyperglycemia and use of insulin in the group that received nutrition guided by IC. No differences in number of events of hyperglycemia were seen in Yang 2016 while Allingstrup 2017 reported no significant differences in the highest blood glucose levels in ICU between the two groups. Actual protein intake (grams/day) was significantly higher in the groups receiving EN via IC in all the studies that reported on this

outcome (Saffle 1990, Singer 2011, Allingstrup 2017, Gonzalez-Granda 2018, Azevedo 2019 and Singer 2020). A similar increase in energy intakes or % energy goals met was also seen with IC when compared to predictive equations in some studies (Singer 2011, Allingstrup 2017, Gonzalez-Granda 2018 and Singer 2020) while was not observed in others (Saffle 1990, Landes 2016) and or was not reported (Yang 2016, Zhao 2019).

Conclusions:

- 1) The use of IC compared to predictive equations to meet nutrition needs may reduce overall mortality.
- 2) The use of IC compared to predictive equations as a guide to nutritional delivery has no effect on infections or ventilator associated pneumonia.
- 3) The use of IC compared to predictive equations as a guide to nutritional delivery has no effect on hospital, ICU length of stay, or duration of ventilation.
- 4) The use of IC compared to predictive equations may be associated with improved nutritional intake.

Level 1 study: *if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*

Level 2 study: *If any one of the above characteristics are unfulfilled.*

Table 1. Randomized studies evaluating indirect calorimetry vs. predictive equation in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)	
				Indirect Calorimetry	Predictive Equation	Indirect Calorimetry	Predictive Equation
1) Saffle 1990*	Burns 47 % TSBA N=49	C.Random: not sure ITT: yes Blinding: no (7)	EN via Indirect calorimetry with measurements X 3/week vs. Curreri formula. Within each arm, patents were further divided to receive 1 Kcal/mL lower protein formula (Osmolite HN) vs. 1 Kcal/mL higher protein formula (Isotene HN) Isocaloric, non isonitrogenous	3/26 (12)	2/23 (9)	NR	NR
2) Singer 2011	Mechanically ventilated critically ill patients (Mixed medical, surgical, trauma) N=130	C.Random: Yes ITT: No Blinding: No (8)	EN via indirect calorimetry with measurements Q48H supplemented with PN and energy delivery adjusted accordingly vs. EN (using 25kcal/kg/day and not readjusted for 14 days). PN attempted to make up shortfall Non isocaloric, non-isonitrogenous	ICU 16/56 (29) Hospital 16/56(29) 60-day 24/56 (58)	ICU 17/56 (30) Hospital 27/56 (48) 60-day 29/56 (48)	Total 37/56 (66) VAP 18/56 (32)	Total 20/56 (36) VAP 9/56 (16)
3) Landes 2016	Mechanical ventilated patients N=27	C.Random: Yes ITT: Yes Blinding: Yes (9)	EN via indirect calorimetry with measurements at study start and every week X 3 weeks vs. EN (Harris Benedict equation or 25 Kcal/kg/day) Isocaloric. Isonitrogenous: ?	NR	NR	NR	NR
4) Yang 2016	Mechanical ventilated hemodynamically	C.Random: no ITT: yes Blinding: no	EN via indirect calorimetry with measurements at day 0, 3, 7 and 14 vs. EN	28 day 1/30 (3.3)	28 day 7/30 (23.3); p=0.02	NR	NR

	stable patients with sepsis N=60	(7)	(Harris Benedict equation). PN used if needed. Isocaloric, isonitrogenous:?				
5) Allingstrup 2017	Mixed ICU patients. Single centre. N=203	C.Random: yes ITT: no Blinding: single (8)	EN via indirect calorimetry with protein dosed at 1.5 g/kg/d, 100% of nutrition prescription given on first full study day vs. feeds dosed at 25 kcal/kg, EN started within 24h and gradually increased. PN as needed. Non-isocaloric, non-isonitrogenous	Day 28 20/100 (20) Day 90 30/100 (30) 6 Months 37/100 (37)	Day 28 21/99 (21); p=0.83 Day 90 32/99 (32); p=0.72 6 Months 34/99 (34); p=0.70	Any nosocomial infection 19/100 (19)	Any nosocomial infection 12/99 (12); p=0.18
6) Gonzalez-Granda 2018	Mechanical ventilated patients N=76	C.Random: Not sure ITT: no Blinding:no (6)	EN via indirect calorimetry with measurements within 24-72 hrs after intubation and weekly for 3 weeks vs. EN (25 Kcal/kg/day). PN used to supplement calories. Non-isocaloric, non-isonitrogenous.	ICU 3/20 (15) Hospital 5/20 (25)	ICU 3/20 (15) Hospital 3/20(15)	NR	NR
7) Azevedo 2019	Mechanical ventilated patients expected to stay in ICU ≥2 days N=138	C.Random: no ITT: no Blinding:no (5)	EN via indirect calorimetry with measurements daily for first 3 days, then every 2 days until day 10) and protein 2.0-2.2g/kg vs. EN based on 25 kcal/kg/day & protein 1.4-1.5 g/kg/day Isocaloric, non-isonitrogenous.	ICU 22/57 (38.5) Hospital 26/57 (45.6)	ICU 28/63 (44.4); p=0.69 Hospital 29/63 (46); p=0.88	NR	NR
8) Zhao 2019	Mechanical ventilated patients expected to receive EN/PN for >7days N=76	C.Random: No ITT: no Blinding:no (6)	EN via indirect calorimetry with measurements from day 1-7 vs. EN via Harris Benedict equation Day 1-7. PN used if needed. Isocaloric, isonitrogenous:?	28 day 5/29 (17.2)	28 day 7/29 (24.1); p=0.52	NR	NR

9) Singer 2020**	Ventilated critically ill patients N=417 Multicenter N=7	C.Random: Yes ITT: Yes Blinding: No (9)	EN (80-100% energy needs) via indirect calorimetry with measurements vs. EN (using 20-25kcal/kg/day). PN was used to make up shortfall in EN energy from day 3 onwards. Non isocaloric, non-isonitrogenous	ICU 45/209 (21.5) 3 month 67/209 (32.1) 180 day 79/209 (37.8)	ICU 53/208 (25.5) 3 month 75/208 (36.1) 180 day 78/208 (37.5)	31/209 (14.8) VAP 22/209 (10.5)	40/208 (19.2) VAP 23/208 (11.1)
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Table 1. Randomized studies evaluating indirect calorimetry vs. predictive equation in critically ill patients (continued)

Study	LOS days		Ventilator days		Other	
	Indirect Calorimetry	Predictive Equation	Indirect Calorimetry	Predictive Equation	Indirect Calorimetry	Predictive Equation
1) Saffle 1990*	Hospital 48.8 ± 4.5 (26)	Hospital 48.5 ± 5.2 (23)	NR	NR	Diarrhea 34.6 %	34.8 %
					Hyperglycemia 38.5 %	43.5 %
					Nausea 26.9 %	34.8 %
					Electrolyte imbalance 30.8 %	39.1 %
					Actual calories intake (kcal/day) 3530 ± 134	3490 ± 132
					Actual protein intake (g/day) 153 ± 7.1	116 ± 6.7; p<0.01
2) Singer 2011	ICU 17.2 ± 14.6 (56) Hospital 33.8 ± 22.9 (56)	ICU 11.7 ± 8.4 (56) Hospital 31.8 ± 27.3 (56)	16.1 ± 14.7 (56)	10.5 ± 8.3 (56)	Energy (kcal/day) 2086 ± 460	1480 ± 356
					Protein (g/day) 76 ± 16	53 ± 16

3) Landes 2016	NR	NR	48.6±21.7 (15)	46.0±31.2 (12)	Energy intake (Kcal/day) 1976.2±481.1 2067.33±340.8 % Energy received 86.5±12.4% 77±17.6%
4) Yang 2016	ICU 8.06 (7.18-12.07)	ICU 10.31 (8.11-16.38); p=0.039	6.67 (4.68-9.48)	6.56 (3.88-9.72); p=0.774	Prescribed energy intake Kcal, day 0 1892 (1697-2206) vs. 1540 (1436-1731), Prescribed energy intake Kcal, day 3 1938 (1753-2259) vs. 1487 (1349-1724), Prescribed energy intake Kcal, day 7 1927 (1740-2287) vs. 1487 (1290-1647), Prescribed energy intake Kcal, day 14 1879 (1636-2397) vs. 1461 (1215-1575) # events of bilirubin ≥2 times normal 36/95 (37.9) vs. 27/93 (31.1); p=0.20 # events of hyperglycemia 11/95 (11.6) vs. 8/93 (8.6); p=0.78 # events of hypoglycemia 3/95 (3.2) vs. 3/93 (3.2); p=0.78
5) Allingstrup 2017	ICU, 6 month survivors 7 (5-22) Hospital, 6 month survivors 30 (12-53)	ICU, 6 month survivors 7 (4-11); p=0.21 Hospital, 6 month survivors 34 (14-53); p=1.0	NR	NR	% of energy goals met 97 (91-100) vs. 64 (40-84), p<0.001 % of protein goals met 97 (75-115) vs. 45 (27-62); p<0.001 Protein intake g/kg/d 1.47 (1.13-1.69) vs. 0.5 (0.29-0.69) Highest blood glucose in ICU, mmol/L 11.0 (9.3-12.4) vs. 9.4 (8.5-10.9)
6) Gonzalez-Granda 2018	ICU 13 ± 8 (20) Hospital 31 ± 24 (20)	ICU 24 ± 20 (20) Hospital 40 ± 23 (20)	9 ± 8 (20)	10 ± 5 (20)	Energy Intake (Kcal/kg/day) 20.4 ± 5.7 20.0 ± 7.5 % energy intake 98%± 8% 79% ±29% p<0.05 Protein intake (g/kg/d) 78±18 59±2 p<0.01 % protein intake 91±24 73±33 p=0.12

<p>7) Azevedo 2019</p>	<p>ICU 21 (13-33) 18</p>	<p>ICU 18 (10-35); p=0.56</p>	<p>9 (5-14)</p>	<p>9 (5-14); p=0.64</p>	<p>Energy requirement, kcal/day 1554 (1383-1862) vs. 1450 (1300-1625); p=0.02 Protein requirement, g/kg/day 2.1 (2.1-2.1) vs. 1.45 (1.45-1.45) ; p<0.0001 Energy received, kcal/day 1139 (890-1278) vs. 1140 (889-1331); p=0.70 Protein received, g/kg/day 1.69 (1.33-1.80) vs. 1.13 (0.97-1.34); p<0.0001 Handgrip strength at ICU discharge Males 18 (15-25) (n=15) vs. 23.5 (13.7-32.0) (n=14); p=0.35 Females 8 (2-17) (n=9) vs. 14 (7-22.5) (n=13); p=0.18</p>
<p>8) Zhao 2019</p>	<p>ICU 8.45 ± 2.44 (29)</p>	<p>ICU 10.41 ± 3.11 (29); p=0.009</p>	<p>3.89 ± 1.14 (29)</p>	<p>4.71 ± 1.08 (29); p=0.007</p>	<p>Prescribed energy intake Kcal/day Day 1-7, mean SD 1567.34±143.39 vs. 1615.49± 159.69</p>
<p>9) Singer 2020</p>	<p>ICU 13.1± 12.5 (199) Hospital 26.8 ± 28.9 (199)</p>	<p>ICU 12.2 ± 8.9 (207) Hospital 25.2 ± 16 (207)</p>	<p>10.2 ± 9.3 (199)</p>	<p>9.8 ± 8.0 (207)</p>	<p>Mean Energy delivered (kcal/day) 1746±755 1301±535 p=0.04 Mean daily energy balance (kcal) -282±896 - 885±535 p<0.001 Mean Protein delivered (g/day) 77.3±53.0 62.4±33.9 p =0.03 Daily highest blood glucose (mg/dL) 187±59 148±68, p=0.16 Administered insulin (iu) 72±43 48±49, p=0.06</p>

* Saffle 1990: for this section, the data shown is the combined high protein and low protein IC vs. high protein and low protein Curreri groups

** Singer 2020: mortality, infection and VAP data may differ from publication but confirmed by author

C.Random: concealed randomization
 † presumed hospital mortality unless otherwise specified
 ITT: intent to treat
 NR: not reported
 (): mean ± standard deviation (number)
 VAP: ventilator associated pneumonia
 ICU: intensive care unit
 LOS: length of stay

Figure 1. Overall Mortality

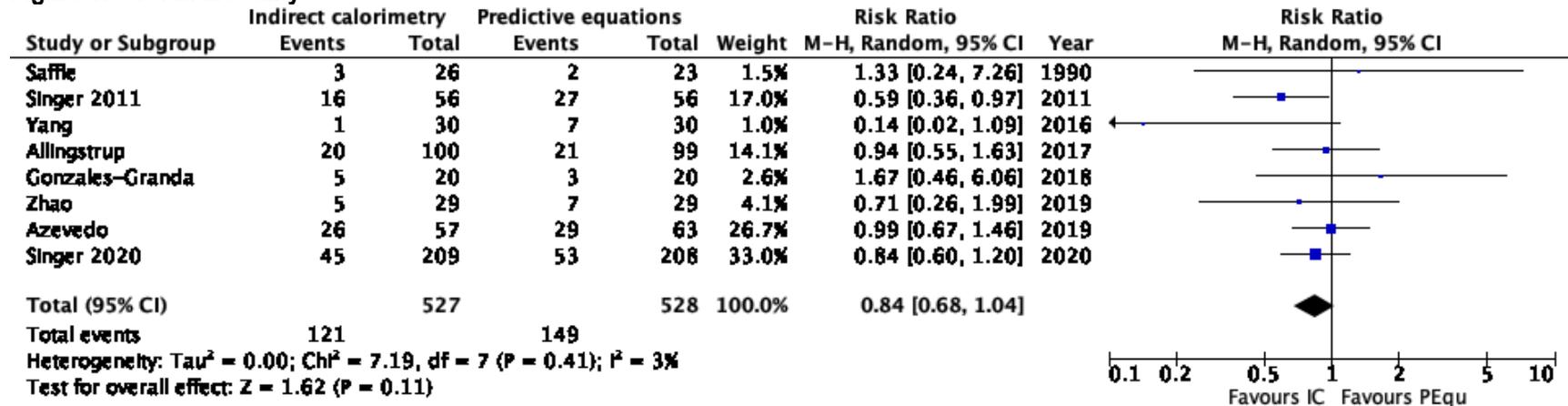


Figure 2. Hospital Mortality

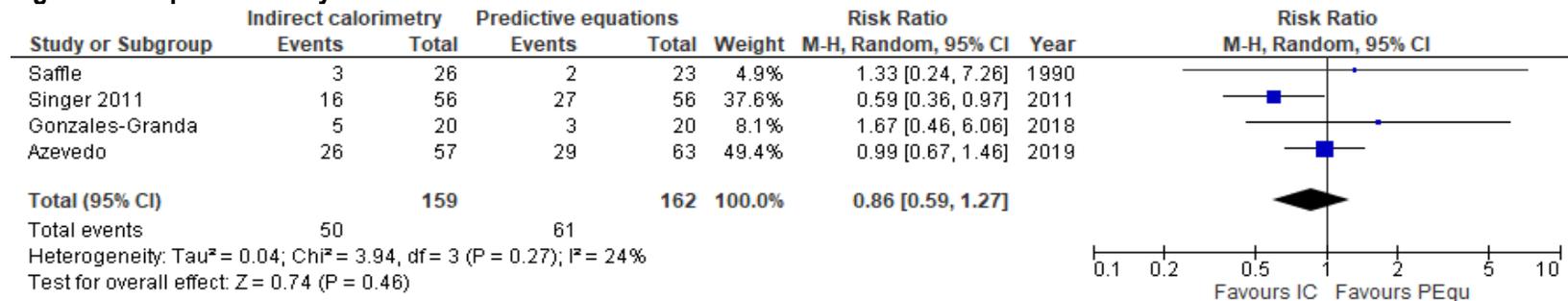


Figure 3. ICU Mortality



Figure 4. Total Infections

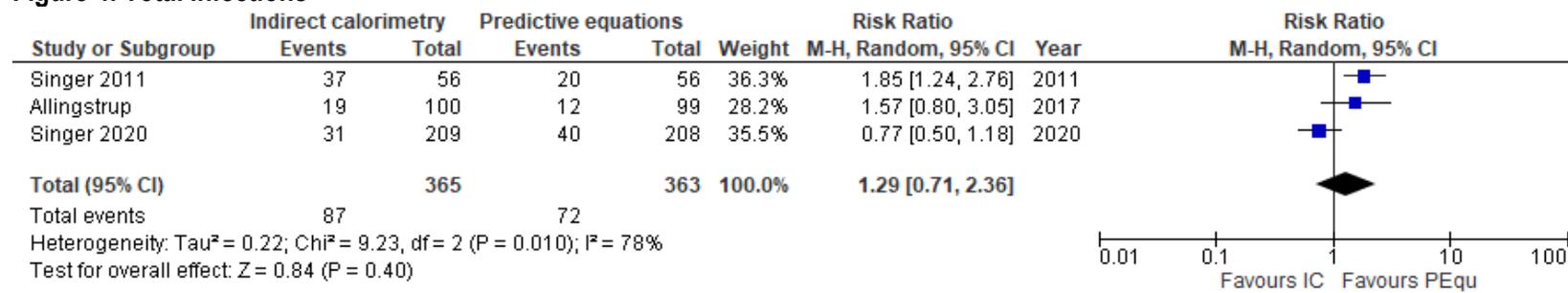


Figure 5. Ventilator Associated Pneumonia

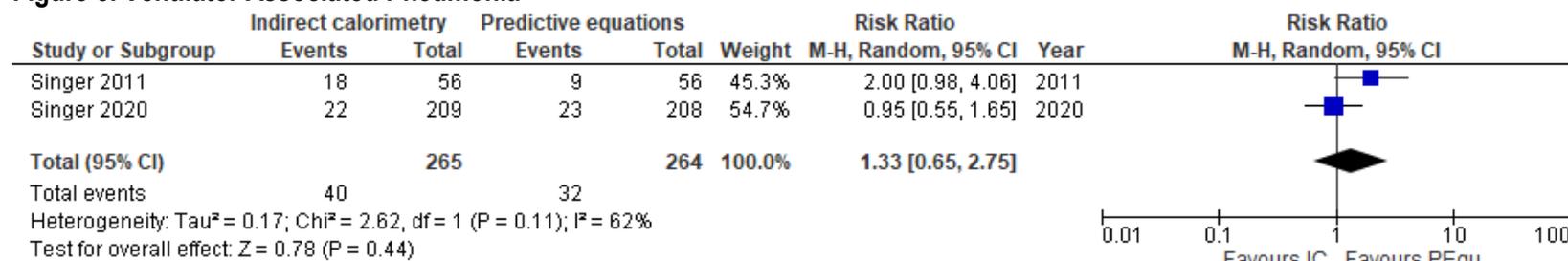


Figure 6. Hospital Length of stay

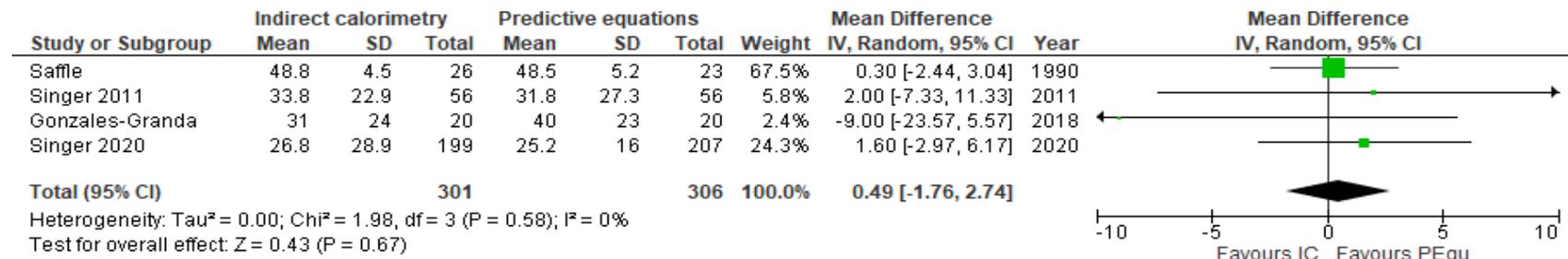


Figure 7. ICU Length of Stay

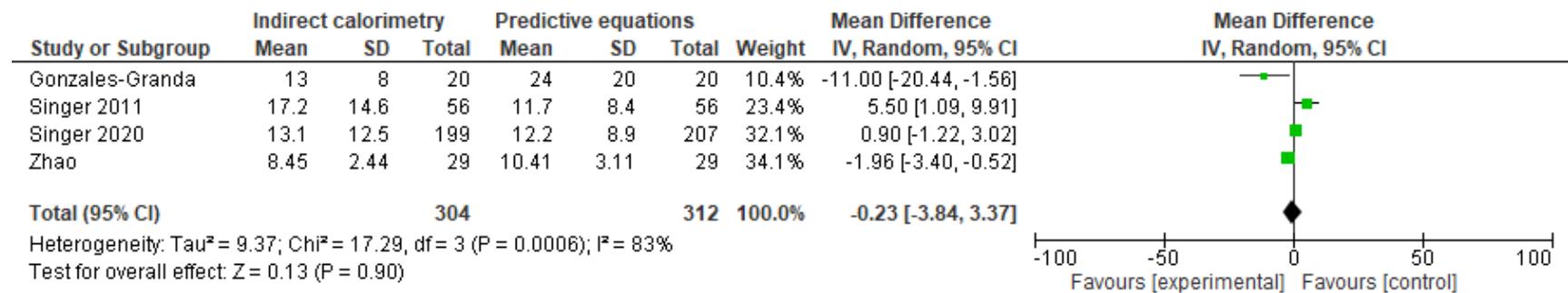
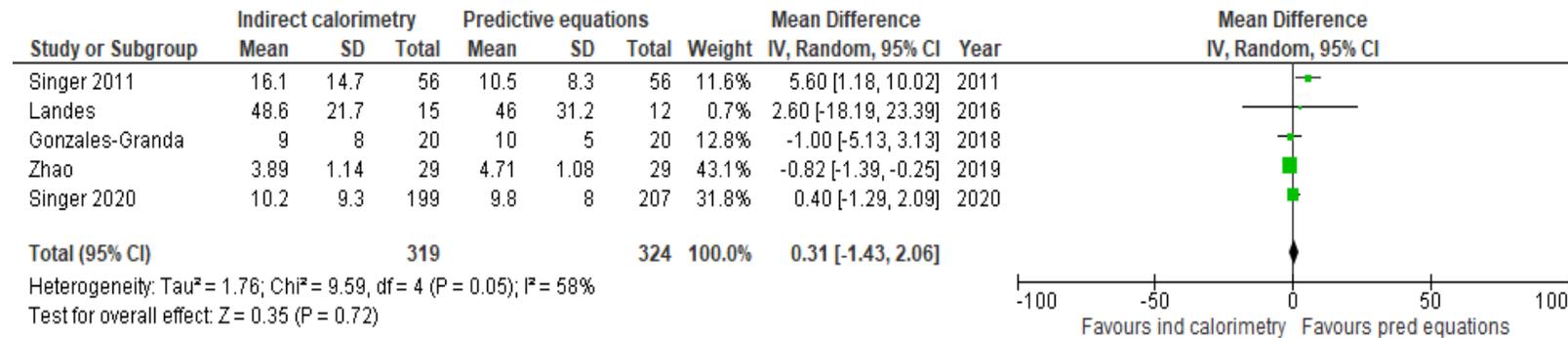


Figure 8. Duration of Mechanical Ventilation



References

Included Studies

1. Saffle JR, Larson CM, Sullivan J. A randomized trial of indirect calorimetry-based feedings in thermal injury. *J Trauma*. 1990 Jul;30(7):776-82.
2. Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, Grozovski E, Theilla M, Frishman S, Madar Z. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med*. 2011 Apr;37(4):601-9. Epub 2011 Feb 22. PubMed PMID: 21340655.
3. Landes, S., McClave, S. A., Frazier, T. H., Lowen, C. C., & Hurt, R. T. (2016). Indirect Calorimetry: Is it Required to Maximize Patient Outcome from Nutrition Therapy? *Current nutrition reports*, 5(3), 233-239. <https://doi.org/10.1007/s13668-016-0171-9>
4. Yang X, Ma G, Wang LJ, Ma XD. Comparison of respiratory indirect calorimetry and Harris–Benedict coefficient in guiding energy target inpatients with sepsis. *Chin J Clin Nutr*. 2016;24(004):193–8.
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7. Azevedo JRA, Lima HCM, Montenegro WS, et al. Optimized calorie and high protein intake versus recommended caloric-protein intake in critically ill patients: a prospective, randomized, controlled phase II clinical trial. Comparação entre ingestão ideal de calorias mais alto teor de proteínas e ingestão calórico-proteica recomendada em pacientes críticos: um ensaio clínico fase II, prospectivo, randomizado e controlado. *Rev Bras Ter Intensiva*. 2019;31(2):171-179. Published 2019 May 23. doi:10.5935/0103-507X.20190025
8. Zhao S, Duan L, Yu G, Zou Q, Wu Q, Wang H, He X. Changing laws of rest energy expenditure in critically ill patients and the intervention effect for nutritional support: a prospective study. *Zhonghua wei zhong bing ji jiu yi xue*. 2019;31(12):1512–6.
9. Singer P, De Waele E, Sanchez C, Ruiz Santana S, Montejo JC, Laterre PF, Soroksky A, Moscovici E, Kagan I. TICACOS international: A multi-center, randomized, prospective controlled study comparing tight calorie control versus Liberal calorie administration study. *Clin Nutr*. 2020 May 30:S0261-5614(20)30259-4. doi:10.1016/j.clnu.2020.05.024. Epub ahead of print. PMID: 32534949

Excluded Studies	Reasons
Brandi LS, Bertolini R, Calafa M. Indirect calorimetry in critically ill patients: Clinical applications and practical advice. <i>Nutrition</i> 1997;13(4):349-358	Not RCT
Nataloni S, Gentili N, Marini B, Guidi A et al. Nutritional assessment in head injured patients through the study of rapid turnover visceral proteins. <i>Clin Nutr</i> 1999;18(4):247-51	No clinical outcomes
Mentec H, Dupont H, Bocchetti M et al. Upper digestive intolerance during enteral nutrition in critically ill patients: Frequency, risk factors, and complications. <i>Crit Care Med</i> 2001;29(10):1955-1961	Not RCT
Cheng CH, Chen CH, Wong Y et al. Measured versus estimated energy expenditure in mechanically ventilated critically ill patients. <i>Clin Nutr</i> 2002;21(2):165-72	Not RCT
Lo HC, Lin CH, Tsai LJ. Effects of hypercaloric feeding on nutrition status and carbon dioxide production in patients with long-term mechanical ventilation. <i>JPEN J Parenter Enteral Nutr</i> 2005;29(5):380-397	Patients in chronic respiratory care unit; no clinical outcomes
Shi J, Xi L, Chi T, Song J, Wang Z. Application value of resting energy monitoring in nutritional support therapy for mechanical ventilation patients. <i>Zhonghua wei zhong bing ji jiu yi xue</i> . 2019;31(1):98-101	No clinical outcomes