13.0 Combined High Protein and Early Physical Rehabilitation

Question:
Compared to usual care, does the combination of high protein and early physical rehabilitation improve clinical outcomes in critically ill adult patients?

Summary of Evidence: Four Level 2* randomized controlled trials were included.

Badjatia 2020 randomized 25 patients with aneurysmal subarachnoid hemorrhage to a combination of high protein (1.75 g/kg/day, with ≥3 g leucine/feeding) and neuromuscular electrical stimulation (NMES; two 30-minute session/day) versus lower protein (1.2-1.4 g/kg/day) and no NMES, for up to 14 days following admission or initial hemorrhage. The patients received a mean protein intake (g/kg/day) of 1.51±0.47 vs 0.88±0.36, p=0.001. Patients with renal failure (any established diagnosis of chronic renal insufficiency [any stage] or acute kidney injury) were *excluded*.
Azevedo 2021 randomized 211 patients (analyzed 181) to a combination of higher protein (2.0-2.2 g/kg/day) and cycle ergometry (two 15-min session/day) versus lower protein (1.4-1.5 g/kg/day) and usual care physical rehabilitation. The protein intervention started on day 5 of randomization and lasted for up to 14 days while in the ICU, whereas the cycle ergometry exercise lasted for up to 21 days while in the ICU. The patients received a mean protein intake (g/kg/day) of 1.23 (0.85-1.60) vs 0.82 (0.66-1.19), p<0.001 on day 3, and 1.90 (1.7-2.1) vs 1.34 (1.10-1.45), p<0.0001 on day 7. Patients with renal failure were **not** excluded.
Kagan 2022 randomized 62 patients to 3 groups: usual care (group 1), usual protein formula and cycle ergometry (group 2), and very-high-protein formula and cycle ergometry (group 3). The cycle ergometer was used passively for 20 min in sedated patients, or two sessions of 10 min or more for non-sedated patients who could actively cycle. The patients received a mean protein intake (g/day) of 63.6± 13.6 vs 67.2± 20.2 vs 83.7± 31.9, p=0.02. In our analysis, group 3 was compared with group 1. Patients with renal failure were **not** excluded.
Zhou 2022 randomized 150 patients to 3 groups: control group (nutrition or physiotherapy as ordered by the ICU physician), early mobilization group (within 24h of ICU admission, 20-30 min/session, 2 times/day until ICU discharge. The mobilization was individualized according to patients' daily functional status, measured by daily Barthel index, and early mobilization combined with early nutrition group (EN/PN based on nutrition risk within 48h of ICU admission+ early mobilization). Nutritional intake was not recorded (this is confirmed by the author). In our analysis, combined early mobilization and nutrition group was compared with the control group. Patients with renal failure were **not** excluded. As nutritional intake was not recorded, we assumed that the patients in the intervention group received higher protein, and we performed sensitivity analyses with and without Zhou 2022.

Physical function outcomes

No meta-analysis was performed as the measures of physical function varied between studies.

Badjatia 2020 reported no difference between groups for Modified Rankin Scale (lower score is better) and Short Physical Performance Battery (SPPB, higher score is better) at day 14. However, the median Modified Rankin Scale (1 [0-2] vs 2 [1-3]; p=0.04) and SPPB (12 [10-12] vs 9 [4-12]; p=0.01) score was significantly better in the intervention than the control group at day 90.

Zhou 2022 reported significantly higher Barthel Index score at ICU discharge in the intervention than the control group (65.4±20.3 vs 51.2±24.8; p=0.020)

ICU acquired weakness

Two studies reported ICU-acquired weakness (ICU-AW). Azevedo 2021 defined ICU-AW as handgrip strength <11kg for male and <7kg for female at ICU discharge or after 21 days of ICU stay. They found a trend towards significant less patients with ICU-AW in the intervention than the control group (29.1% vs 46.4%; p=0.05). Zhou 2022 defined ICU-AW as MRC-SS score <48 at ICU discharge. They found significant less patients with ICU-AW in the intervention than the control group (2% vs 16%; p=0.005). However, meta-analysis found no significant difference between group for the incidence of ICU-AW (RR 0.38, 95% CI 0.08, 1.88; p=0.24; 2 studies; **Fig 6**].

Muscle Strength

Zhou 2022 found no significant difference between groups for medica research council sum score (MRC-SS) score (58.9±3.3 vs 56.0±6.3)

Muscle and Nutritional outcomes

Badjatia 2020 reported significant less muscle atrophy as measured at day 14 by computed tomography of the mid-thigh cross-sectional area in the intervention than the control group (-6.5±4.1% vs -12.5±6.4%; p=0.01).

Zhou 2022 reported significant less patients were malnourished (SGA class C) at ICU discharge in the intervention than the control group (4% vs 22%; p=0.031).

Mortality

Four studies reported ICU and three studies reported hospital mortality. The combined intervention had no effect on ICU (RR 0.80, 95% CI 0.36, 1.77; p=0.58; I^2=24%; 4 studies; **Fig 1a**) and hospital mortality (RR 0.77, 95% CI 0.33, 1.79; p=0.54; I^2=54%; 3 studies; **Fig 2**). No significant difference between groups in ICU mortality was found in sensitivity analysis without Zhou 2022 (**Fig 1b**).

Infectious complications

No significant difference in hospital-acquired infection (2/12 [25%] vs 6/13 [46%]; p=0.41) was found between group in one study (Badjatia 2020)

Duration of mechanical ventilation and ICU/Hospital length of stay

No significant difference was found between groups for days on mechanical ventilation (Mean Difference (MD) -0.06 days, 95% CI -1.02, 0.90; p=0.91; I^2=0%; 3 studies; **Fig 3a**) and hospital length of stay (MD 2.54 days, 95% CI -7.52, 12.59; p=0.62; I^2=0%; 2 studies; **Fig 5**).

There was a trend towards shorter ICU length of stay in the combination group (MD -0.81 days, 95% CI -1.70, 0.08; p=0.07; I^2=0%; 3 studies; **Fig 4a**) compared with the control group. In sensitivity analysis without Zhou 2022, no significant differences between groups were found for days on mechanical ventilations and ICU LOS (**Fig 3b and 4b**).

Renal function

Badjatia 2020 found that urea level was significantly higher in the combination group than the control group on day 7 and 14 of randomization. However, creatinine level was not significantly different between groups. There was no incidence of renal replacement therapy in any of the patients during the study period.

Azevedo 2021 reported a trend towards lower incidence of acute kidney injury (36.8% vs 47.9%; p=0.167) and significantly lower incidence renal replacement therapy (18.4% vs 31.9%; p=0.037) in the combination of protein/rehab vs. control group.

Kagan 2022 and Zhou 2022 did not report renal function outcomes.

Quality of life

Badjatia 2020 measured the short-form NeuroQOL at day 90. No significant differences between groups were found for Fatigue and Cognition. A trend towards significant better lower extremity mobility was found in the intervention than the control group (90±8 vs 73±27; p=0.05)

Azevedo 2021 found significant higher SF-36 physical component score (PCS) at 3 (24.4 [0-49.12] vs 0 [0-37.0]; p=0.01) and 6 (33.6 [0-71.61] vs 0 [0-55.1]; p=0.01) months in the intervention than the control gorup.

Adverse events

All studies found no incidence of adverse events associated with the combined intervention. Badjatia 2020 reported two patients had transient muscle soreness that did not impair their ability to continue NMES. Kagan 2022 reported one patent died several hours after a cycle ergometry session but the event was not attributed to the cycling session.

Conclusions

1) Combined high protein and early physical rehabilitation may be associated with better activities of daily living at ICU discharge and physical performance at day 90. However, these outcomes were respectively reported in just one study, more studies are needed to confirm these findings.
2) Combined high protein and early physical rehabilitation has no effect on ICU-acquired weakness at ICU discharge.
3) Combined high protein and early physical rehabilitation has no effect on muscle strength at ICU discharge. However, this is only reported in one study.
4) Combined high protein and early physical rehabilitation may be associated with less muscle atrophy in the ICU and better nutritional status at ICU discharge. However, these outcomes were respectively reported in just one study, more studies are needed to confirm these findings.
5) Combined high protein and early physical rehabilitation has no effect on ICU and hospital mortality
6) Combined high protein and early physical rehabilitation has no effect on infectious complications
7) Combined high protein and early physical rehabilitation has no effect on days on mechanical ventilation and hospital length of stay but may be associated with a shorter ICU length of stay.
8) Combined high protein and early physical rehabilitation may be associated with lower incidence of renal replacement therapy. However, this was attributed to one study, more studies are needed to confirm this finding.
9) No adverse events due to the combined high protein and early physical rehabilitation intervention were reported.

***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: Population, methodological scoring, interventions, and nutritional intake

Study	Population	Methods (score)	Combined Intervention i) Protein & ii) Early physical rehabilitation	Nutritional intake
1) Badjatia 2020 (USA)	Single-center (n=25) Adult (age >18) with aneurysmal subarachnoid hemorrhage and expected neuro ICU stay >72h **Exclude**: unlikely to remain in the ICU for >7d, BMI <15 or >40, neuromuscular disorder known **renal failure (**any established diagnosis of chronic renal insufficiency [any stage] or acute kidney injury**)^**	C.Random: not sure ITT: yes Blinding: single (9) Level 2	i) **Protein**: 1.75 g/kg/d (with ≥3g leucine/feeding) vs 1.2-1.4 g/kg/d ii) **NMES: two 30-min session/day,** amplitude titrated to achieve visible muscle contraction without causing pain. Device: L300 Plus® system (Bioness,Inc,Valencia, CA) vs No NMES *Interventions up until post-bleed day 14. Median: 12 (range 9-14) days	**Energy**: 20.0±7.1 vs 19.8±9.9 kcal/g, p=0.97 **Protein**: 1.51±0.47 vs 0.88±0.36 g/kg/d, p=0.001
2) Azevedo 2021 (Brazil)	Single-center (n=181; enrolled 211) Adult (age>18) MV, expected ICU stay ≥4d, included 3/87 (4%) and 2/94 (3%) patients with renal diagnosis at ICU admission **Exclude**: MV>96h before enrolment, unable to walk without assistance prior illness that lead to ICU admission, neuromuscular disorder, severe liver disease. ***Patients with renal impairments were not excluded.** **At baseline:**	C.Random: not sure ITT: No Blinding: No (6) Level 2	i) D3 of randomization: 50% of measured energy expenditure and 0.8-1.0 g/kg protein (both groups) **D5 of randomization**: **2.0-2.2 vs 1.4-1.5 g/kg/d** *recorded nutritional intake up to 14 days, discharge or death ii) **Cycle ergometry**: **Two 15-min sessions/day.** Device: Motomed Letto II cycle ergometer (REckTechnik, Germany) vs usual care *Interventions up to 21 days, discharge, or death	**Energy** **D3**: 13.7 (11.3-17.0) vs 15 (12-18), p=0.18; **D7:** 19.5 (16-22), 19.0 (14.3-21.4), p=0.32 **Protein** **D3:** 1.23 (0.85-1.60) vs 0.82 (0.66-1.19), p<0.001; **D7:** 1.90 (1.7-2.1) vs 1.34 (1.10-1.45), p<0.0001 **Overall**: **% of measured energy expenditure**: 81 (74.4-86.2) vs 81.7 (74.0-90.2), p=0.26 **Protein**: 1.48 (1.25-1.64) vs 1.19 (0.96-1.26) g/kg/d, p<0.0001
3) Kagan 2022 (Israel)	Single-center (n=41 per protocol; 62 intention to treat) Adult (age 18-90), MV≥48h, expected ICU stay≥7d **Exclude**: lower limb impairment, neuromuscular disorder ***Patients with renal impairments were not excluded.**	C.Random: Yes ITT: Yes Blinding: No (11) Level 2	**Group 1 (control) vs 2 vs 3** i) Conventional EN ***vs*** conventional EN ***vs*** very-high-protein formula ii) Conventional physiotherapy ***vs*** cycle ergometer ***vs*** cycle ergometer passively for 20 min in sedated patients, and two bouts of 10 min or more for actively cycle patients (Motomed Viva 2, UK) *Interventions up to 28 days, discharge or death <u>Note:</u> Group 1 - usual care Group 2 - low protein + cycle Group 3 - high protein + cycle Control = group 1; intervention = group 3	**Energy:** 1557.6± 309.6 vs 1648.2± 375.8 vs 1372.7 ± 530.8; NS **Protein:** 63.6± 13.6 vs 67.2± 20.2 vs 83.7± 31.9; p=0.02 **^Author replied and can't provide data for g/kg/day.**
4) Zhou 2022 (China)	Two-centers (n=150)	C.Random: Yes ITT: Yes	**Usual care vs combined early nutrition and mobilization**	**^Author replied: no data on nutritional intake was recorded.**

	Adult ≥18, either MV or not MV (30% MV), expected ICU stay ≥72h, conscious within the next 24h to respond to 3/5 simple orders, had a Barthel Index (BI) ≥70 at 2 weeks before ICU admission **Exclude**: paralysis, limb impairments, preexisting primary systemic neuromuscular disease, intracranial/spinal processes affecting motor function, GI surgery within 1 month, no expectation of nutritional intake in the next 48h, moribund ***Patients with renal impairments were not excluded** (18% vs 26% in the control and intervention group had renal failure at baseline, respectively)	Blinding: No (10) Level 2	i) Timing and route of nutrition are determined by the ICU physician ***vs*** Early nutrition within 48h of ICU admission, and the route of nutrition was determined by NRS-2002 and SGA. ii) Routine physiotherapy as ordered by ICU physician - involved mostly passive mobilization, 15 min/session, once daily ***vs*** early mobilization within 24h of ICU admission, 20-30min/session, 2X/day until ICU discharge. (The mobilization was individualized according to patients' daily functional status, measured by daily Barthel index) *Interventions up to ICU discharge Note: this study randomized patients into 3 groups, the early mobilization group was not analyzed Note: at baseline	

AE: adverse event, BUN: blood urea nitrogen, CSA: cross-sectional area, CT: computed tomography, MV: mechanically ventilated, NMES: neuromuscular electrical stimulation, NR: not reported, NS: not significant, QOL: quality of life, SAE: serious adverse event, SPPB: short physical performance battery
^Data from authors

Table 2: Outcomes and adverse events (Intervention vs Control)

Studies	Mortality # (%)		Infections # (%)		Length of stay (days)		Muscle mass, physical function and QOL		AE/SAE
1) Badjatia 2020 (USA)	**0/12^**	**0/13^**	**Hosp-acquired infection** 3/12 (25)	**Hosp-acquired infection** 6/13 (46); p=0.41	**ICU** 18±7 (12)	**ICU** 20±8 (13)	**CT mid-thigh CSA (D0-2 to D14), %** -6.5±4.1 (12) **Modified Rankin Scale** D14: 4 (2-4) D90: 1 (0-2) **SPPB** D14: 2 (0-7.8) D90: 12 (10-12) **D90 Short-form NeuroQOL** i) Fatigue: 29±15 ii) Lower extremity mobility: 90±8 (12) iii) Cognition: 35±5	**CT mid-thigh CSA (D0-2 to D14), %** -12.5±6.4 (13) **Modified Rankin Scale** D14: 4 (3-5); p=0.5 D90: 2 (1-3); p=0.04 **SPPB** D14: 1 (0-5); p=0.44 D90: 9 (4-12); p=0.01 **D90 Short-form NeuroQOL** i) Fatigue: 41±28; p=0.2 ii) Lower extremity mobility: 73±27 (13); p=0.05 iii) Cognition: 31±12; p=0.27	**No AE or SAE** Two subjects had transient muscle soreness that did not impair their ability to continue NMES **BUN (mg/dL)** **D7:** 22±6 vs 16±6 (p=0.04); **D14**: 23±7 vs 14±5 (p=0.003) **Creatinine (mg/dL)** **D7:** 0.7±0.2 vs 0.7±0.2 (p=0.66); **D14**: 0.6±0.2 vs0.6 0.2 (p=0.69) **Incidence of renal replacement therapy**: 0/12 vs 0/13^
2) Azevedo 2021 (Brazil)	**ICU** 23/87 (26.4) **Hosp** 25/87 (31.2) **6-mo** 29/87 (33.3)	**ICU** 41/94 (43.6); p=0.01 **Hosp** 47/94 (53.4); p=0.002 **6-mo** 51/94 (54.2); p=0.005	**NR**	**NR**	**N=87** **MV days** 10 (5-19) 16.9±30.9^ **ICU** 18 (12-36) 29.2±34.2^ **Hosp** 38 (18-70) 53.1±48.5^	**N=94** **MV days** 12 (7-21); p=0.09 17.0±14.8; p=0.96^ **ICU** 23 (16-36); p-0.11 33.4±27.6; p=0.64^ **Hosp** 40 (21-60); p=0.96 50.2±44.6; p-0.74^	**PCS score** **3 months** (n=87)**:** 24.4 (0-49.12) **6 months** (n=87)**:** 33.6 (0-71.61**)** **ICU-acquired weakness (handgrip strength <11kg for male and <7kg for female) at ICU discharge or after 21 days of ICU stay** 16/87 (29.1)	**PCS score** **3 months** (n=94)**:** 0 (0-37.0); p=0.01 **6 months** (n=94)**:** 0 (0-55.1); p=0.01 **ICU-acquired weakness (handgrip strength <11kg for male and <7kg for female) at ICU discharge or after 21 days of ICU stay** 26/94 (46.4); p=0.05	**No adverse events were observed^** **Incidence of acute kidney injury^:** 32/87 (36.8) vs 45/94 (47.9); p=0.167 **Incidence of renal replacement therapy^**: 16/87 (18.4) vs 30/94 (31.9); p=0.037
3) Kagan 2022 (Israel)	**ICU** 3/19 (15.8) **Hosp** 5/19 (26.3)	**ICU** 1/22 (4.5); NS **Hosp** 4/22 (18.2); NS	**NR**	**NR**	**Gp 3 (n=19)** **MV days** 11.7±9.7 **ICU LOS** 18.8±10.5 **Hosp LOS** 35.2±25.7	**Gp1 (n=22)** **MV days** 10.2±9.5; NS **ICU LOS** 17.2±9.6; NS **Hosp LOS** 33.1±22.6; NS	**NR**	**NR**	**No adverse events were observed^** No data available about renal function like urea, creatinine, urine output or incidence of renal replacement therapy^
4) Zhou 2022 (China)	**ICU** 2/50 (4)	**ICU** 2/50 (4)	**NR**	**NR**	**N=50** **MV days** 1.47±2.23^ **ICU LOS**	**N=50** **MV days** 1.57±2.75^ **ICU LOS**	**At ICU discharge** **ICU-acquired weakness (MRC-SS <48)** 1/50 (2%)	**At ICU discharge** **ICU-acquired weakness (MRC-SS <48)** 8/50 (16%) (p=0.005	**No adverse events were observed^**

					4.26±2.21^	5.06±2.45^	**MRC-SS** 60.0 (60.0-60.0) 58.9±3.3^ **Barthel Index** 70.0 (55.0-80.0) 65.4±20.3^ **SGA class B** 22/50 (44) **SGA class C** 2/50 (4)	**MRC-SS** 60.0 (56.5-60.0); p=NS 56.0±8.3^ **Barthel Index** 57.5 (38.8-70.0); p=0.020 51.2±24.8^ **SGA class B** 23/50 (46); p=NS **SGA class C** 11/50 (22) (p=0.031)	

AE: adverse event, BUN: blood urea nitrogen, CSA: cross-sectional area, CT: computed tomography, MV: mechanically ventilated, NMES: neuromuscular electrical stimulation, NR: not reported, NS: not significant, QOL: quality of life, SAE: serious adverse event, SPPB: short physical performance battery

^Data from authors

Figure 1a: ICU Mortality

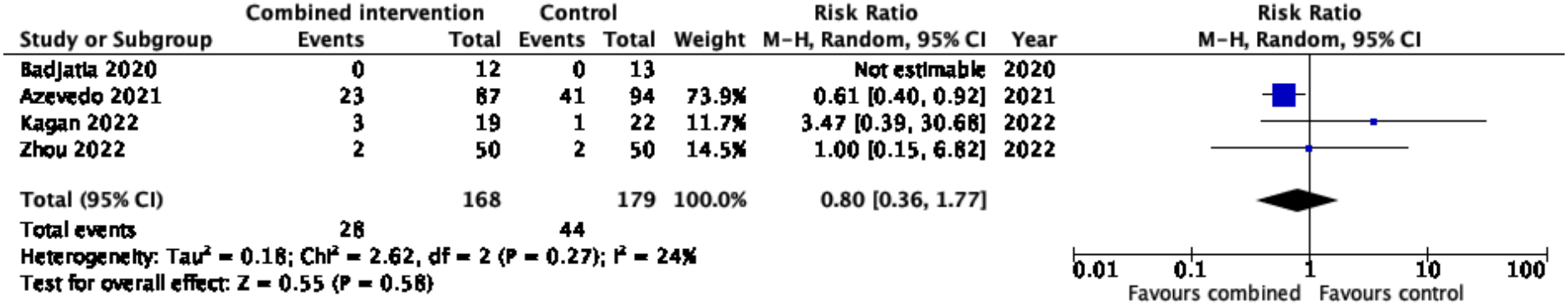


Figure 1b: ICU Mortality (sensitivity analysis without Zhou 2022)

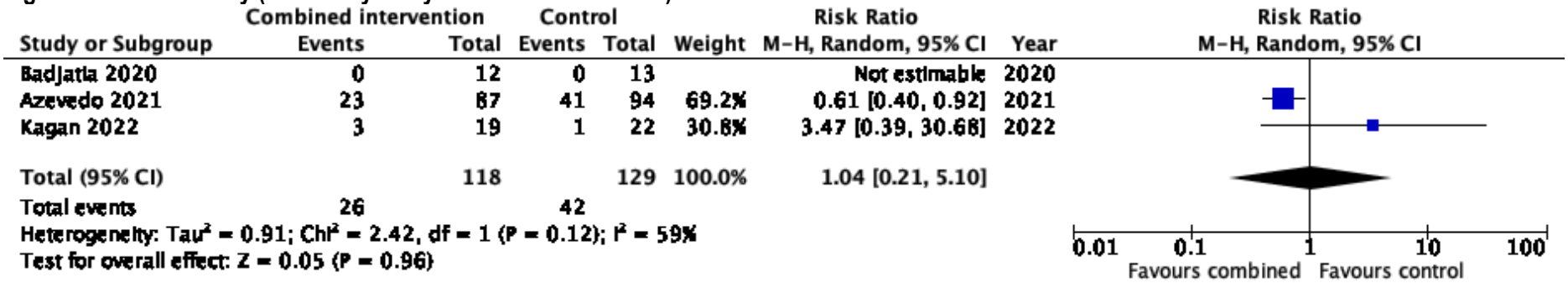


Figure 2: Hospital Mortality

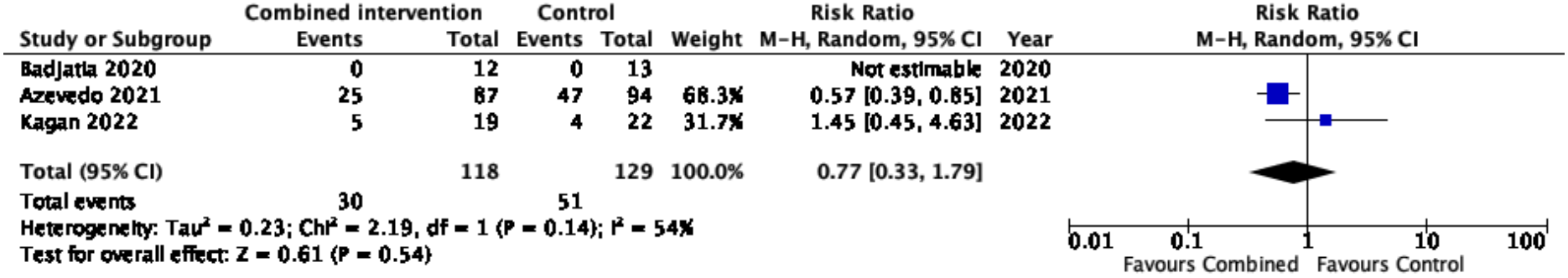


Figure 3a: Days on Mechanical Ventilation

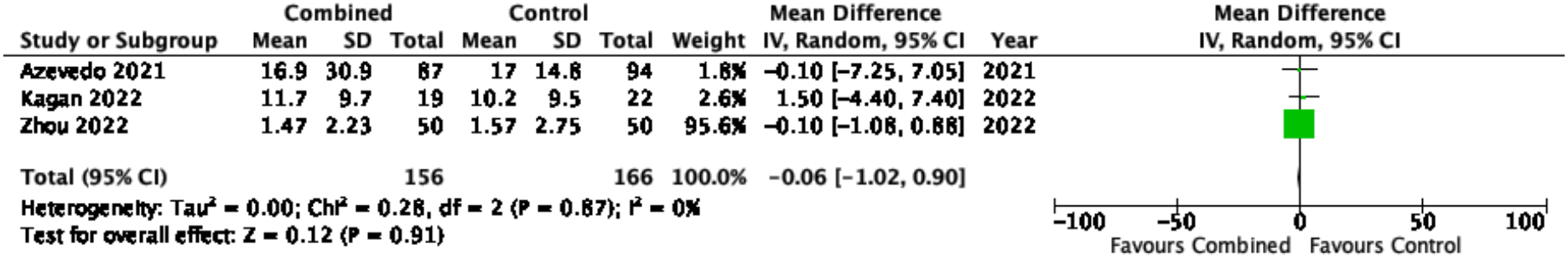


Figure 3b: Days on Mechanical Ventilation (sensitivity analysis without Zhou 2022)

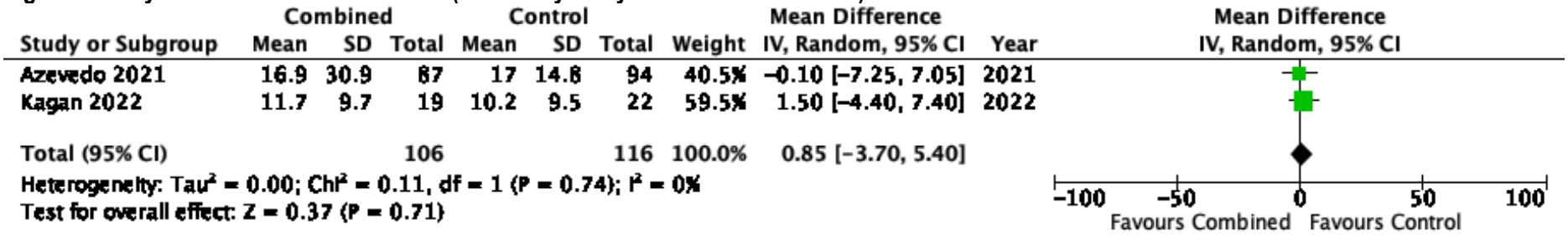


Figure 4a: ICU LOS

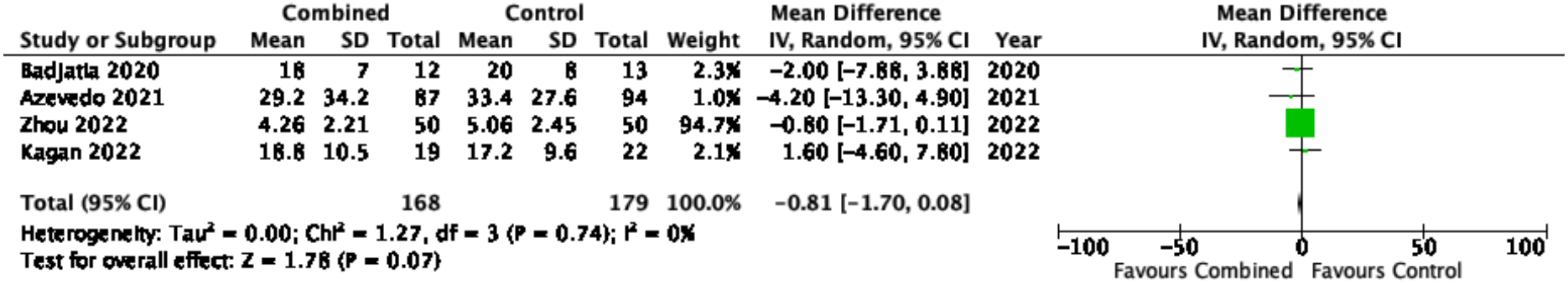


Figure 4b: ICU LOS (sensitivity analysis without Zhou 2022)

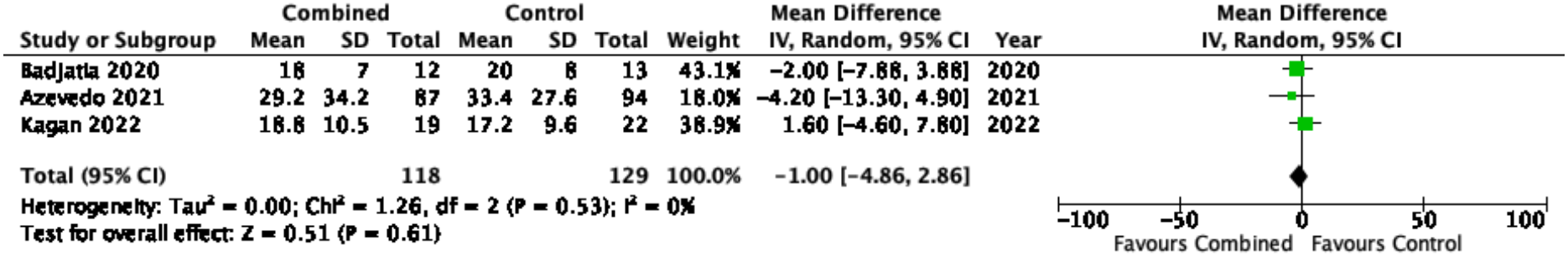


Figure 5: Hospital LOS

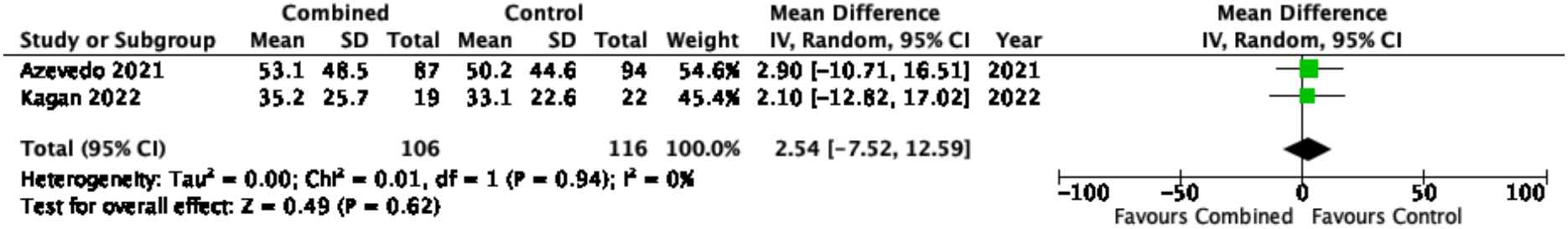
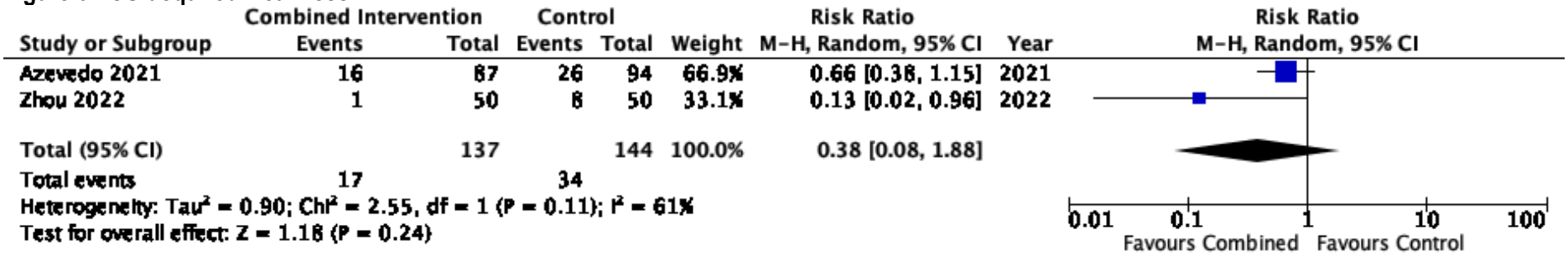


Figure 6: ICU-acquired weakness



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