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Meta-analyses

Optimal delivery of enteral protein in the critically ill: A systematic review and meta-analysis of randomised controlled trials

Matthew J. Summers [a,b,*], Julia L.M. Bels [c,d], Amalia Karahalios [e,f], Rukshala K. Gunaratne [e,f], Jeffrey J. Presneill [g,h,i], Mark P. Plummer [a,b,j], Zheng-Yii Lee [k,l,m], Daren K. Heyland [n], Dieter Mesotten [o,p], Christian Stoppe [l,m,q], Marcel C.G. van de Poll [c,d,r], Sandra Peake [a,g,s], Adam M. Deane [h,i], Lee-anne S. Chapple [a,b,g,j]

[a] Discipline of Acute Care Medicine, The University of Adelaide, Adelaide, South Australia, Australia
[b] Intensive Care Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia
[c] Department of Intensive Care Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
[d] School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands
[e] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Victoria, Australia
[f] Methods and Implementation Support for Clinical and Health (MISCH) Research Hub, Faculty of Medicine, Dentistry, and Health Sciences, University of Melbourne, Melbourne, Victoria, Australia
[g] Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Victoria, Australia
[h] Department of Critical Care, The University of Melbourne, Melbourne, Australia
[i] Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia
[j] National Health and Medical Research Council of Australia, Centre for Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Adelaide, South Australia, Australia
[k] Department of Anaesthesiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[l] Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Würzburg, Würzburg, Germany
[m] Department of Cardiac Anaesthesiology and Intensive Care Medicine, Charité, Berlin, Germany
[n] Department of Critical Care Medicine, Queen's University, Kingston, ON, Canada
[o] Department of Intensive Care Medicine, Ziekenhuis Oost-Limburg Genk, Belgium
[p] UHasselt, Faculty of Medicine and Life Sciences, Diepenbeek, Belgium
[q] UTHealth, Center for Outcomes Research and Department of Anaesthesiology, Houston, TX, USA
[r] Department of Surgery, Maastricht University Medical Centre, Maastricht, the Netherlands
[s] Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Woodville South, South Australia, Australia

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SUMMARY

Background and aim: Critically ill patients experience acute muscle wasting, associated with impaired clinical outcomes. It has been suggested that greater dietary protein delivery may attenuate muscle wasting and improve outcomes, but the optimal dose is unknown. The aim of this systematic review and meta-analysis was to evaluate the effect of enteral protein delivered to achieve doses recommended within international guidelines (1.2–2.0 g/kg bodyweight/day) compared to enteral protein delivered below international guidelines (<1.2 g/kg/day) on mortality and clinical, patient-centred, and muscle outcomes.

Methods: A systematic review of databases MEDLINE, EMBASE, CINAHL, and CENTRAL was performed from database inception through to 2 July 2025. Randomised controlled trials (RCTs) of adult critically ill patients comparing 'greater protein' delivery (1.2–2.0 g/kg/day) versus 'lesser protein' delivery (<1.2 g/kg/day) predominantly via enteral nutrition (EN), with similar energy delivery, were identified. Risk ratios were pooled for binary outcomes and mean differences or standardised mean differences for continuous outcomes using random-effects models. Subgroup analyses investigated the effect of exclusive EN; acute kidney injury (AKI) as defined within individual trials; and higher severity of illness (Sequential Organ Failure Assessment score ≥9) for the primary outcome (mortality).

Results: From a total of 10,414 citations, 14 RCTs were included, comprising n = 6553 patients (n = 3248 greater protein; n = 3305 lesser protein) from 13 individual patient RCTs and one cluster randomised

* Corresponding author. University of Adelaide North Terrace, Adelaide, South Australia, 5000, Australia.
E-mail address: Matthew.summers@adelaide.edu.au (M.J. Summers).

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cross-over trial. Greater protein delivery did not affect mortality (pooled RR 1.01, 95% CI 0.92, 1.12, p = 0.795; I^2= 0%; τ^2= 0.00; 12 RCTs: greater protein n = 3197; lesser protein n = 3243). Other clinical outcomes were not different; however, the point estimate suggested decreased quality of life for greater protein compared to lesser protein (pooled standardised mean difference −0.11, 95% CI -0.24, 0.01, p = 0.081; I^2= 0%; τ^2= 0.00; 2 RCTs, n = 921: greater protein n = 456; lesser protein n = 465). In patients with an AKI (as defined within individual trials), greater protein delivery was associated with increased mortality (pooled effect estimate 1.29, 95% CI 1.05, 1.58, p = 0.015; I^2= 0%; τ^2= 0.00; 3 RCTs, n = 755: greater protein n = 390; lesser protein n = 365), with ICEMAN evaluation suggesting that the evidence for effect modification was of moderate credibility.

Conclusions: Greater protein delivery does not reduce mortality or improve any clinical outcomes compared with lesser protein, and may be associated with increased mortality in patients with AKI, though subgroup definitions varied across trials.

Systematic review registration: CRD42025547923.

1. Introduction

Muscle wasting occurs early and rapidly during an intensive care unit (ICU) admission [1,2]. This muscle wasting is associated with increased ICU and hospital length of stay [3] and poor functional recovery that persists for months following discharge from the acute care setting [4].

It is thought that greater dietary protein delivery during critical illness could attenuate muscle atrophy [5] and thereby improve functional recovery [6]. As such, current international clinical practice guidelines recommend delivering higher protein doses than recommended in healthy individuals (0.8 g protein/kg body weight/day) [7], predominantly based on low level of evidence. The American Society of Parenteral and Enteral Nutrition (ASPEN) recommend 1.2–2.0 g/kg/day [8], and the European Society of Clinical Nutrition and Metabolism (ESPEN) recommend 1.3 g/kg/day, delivered progressively [9], with enteral protein being the preferred route of delivery for critically ill patients when oral intake is not possible [8,9].

Eight systematic reviews have previously examined protein delivery in the critically ill [5,10–16], seven of which included a meta-analysis [5,11–16]. While these reviews largely concluded that higher protein doses delivered during critical illness had no statistically significant effect on mortality, or length of ICU or hospital stay, the most recent systematic review using a Bayesian framework found a considerable probability of an increased mortality risk with greater protein delivery (22 RCTs, n = 4164 patients: median risk ratio for mortality 1.01 (95% CrI 0.84, 1.16)) [16]. Of the eight reviews published since 2012, only three have compared protein delivery within international recommendations (≥1.2 g/kg/day) to protein delivery below recommendations (<1.2 g/kg/day; representative of usual care) [12,14,15], and only one has compared protein delivery predominately via the enteral route [12]. Since this time, three large multi-centre randomised controlled trials (RCTs) have been conducted evaluating higher enteral protein doses delivered in critical illness [17–19], providing additional data to support increased certainty of evidence.

The aim of this systematic review and meta-analysis was to evaluate data from RCTs in critically ill patients that assessed the effect of protein delivered predominantly via the enteral route and achieved doses delivered within international guidelines (1.2–2.0 g/kg/day) compared to enteral protein delivered below international guidelines (<1.2 g/kg/day) on mortality, and/or clinical, patient-centred, and/or muscle outcomes.

2. Methods

2.1. Study design

This systematic review and meta-analysis was conducted in line with methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions [20] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Material – page 30–32) [21]. The protocol was registered on 20 January 2025 with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42025547923), and the protocol was pre-published [22].

2.2. Eligibility criteria

Trials were included if they:

- Were an RCT.
- Were designed to include only adults as defined by the primary publication.
- Included critically ill patients – defined as patients treated in an ICU e.g. with mechanical ventilation or, if this was unable to be ascertained, then a mortality of >5% in the control group [5].
- Compared protein doses predominately delivered via enteral nutrition (EN) – 'predominant EN' was defined as studies that provided nutrition therapy via the enteral route in preference to parenteral nutrition (PN) [12]. Trials were included if supplemental PN was administered.
- Had one arm that received a mean/median of 1.2–2.0 g protein/kg/day ('greater protein'), and another arm that received a mean/median of <1.2 g protein/kg/day ('lesser protein'). The bodyweight used was not specified (e.g. ideal versus actual versus adjusted bodyweight) but was as defined in the primary trial.
- Reported similar overall mean/median energy delivery between groups.
- Reported mortality at any timepoint and/or a clinical, patient-centred, and/or muscle outcome, suitable for contribution to one or more of the primary or secondary aims of the meta-analysis.

Trials were excluded if: 1) different protein doses delivered were secondary to the delivery of specific amino acid/s or their

metabolites e.g. glutamine, arginine, or hydroxymethylbutyrate (HMB) supplementation; 2) predominately (>50%) elective surgery patients were included; or 3) only biochemical, metabolic, or nutritional outcomes were reported.

2.3. Information sources and search strategies

A systematic search of the literature was conducted using four databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via Ovid, Excerpta Medica Database (EMBASE) via Ovid, Cumulative Index of Nursing and Allied Health Literature (CINAHL) via EBSCOhost, and Cochrane Central Register of Controlled Trials (CENTRAL). All databases were searched from their inception to the last specified search date. The search term logic grid was developed with four major concepts: 1) critical illness; 2) EN support; 3) dietary protein; and 4) RCT. Search strategies for each database were developed in consultation with a senior librarian experienced in medical systematic reviews. Strategies to enhance the search synonyms were added, and major database subject headings and controlled vocabularies used, as previously described [22]. In addition, reference lists of key review articles and clinical guidelines were reviewed to capture any trials not identified through database searches. The search strategies are shown in Supplementary Material (page 2–5).

2.4. Trial selection process

Search results were compiled, and duplicates removed using Covidence (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Title and abstract screening were performed independently and in duplicate (MJS or JLMB or LSC), and full texts retrieved for potentially relevant articles. Full texts were screened independently and in duplicate against eligibility criteria by two authors (MJS and JLMB), with discrepancies resolved by a third author (LSC).

2.5. Data extraction

Data were independently extracted from included trials in duplicate by two authors (MJS and JLMB) using a pre-specified data extraction form in Microsoft Excel. Authors reviewed and reconciled discrepancies through discussion or resolved in conjunction with additional authors (LSC or AK). Extracted data included publication information, patient demographics and clinical characteristics, intervention details, and outcomes as further detailed in the published protocol [22]. If protein delivery was reported in the primary paper as g/day, the corresponding author was contacted via email to obtain protein delivered in g/kg/day.

2.6. Outcomes

The primary outcome was 90-day mortality. If a trial did not report 90-day mortality, mortality at the nearest timepoint was used in the following order: 60-day, 28-day, 180-day, hospital, and ICU [22].

Secondary outcomes were:

- Clinical outcomes – defined as infectious complications (as per primary trial definition), duration of invasive mechanical ventilation, and length of ICU and hospital stay.
- Patient-centred outcomes – defined as physical function, discharge to a rehabilitation facility, and quality of life scores.
- Muscle outcomes – defined as muscle mass or strength or change in muscle mass or strength [22].

2.7. Data analysis

Prespecified random-effects meta-analyses for all outcomes were chosen because the intervention and its implementation were expected to vary across trials. For estimates arising from cluster cross-over trials, the effect estimates (95% CI) from an analysis that accounted for the cluster design and time trends (i.e., for cross-over trials) (e.g. from a multilevel model) were extracted or obtained from the trial authors [19]. Binary outcomes (mortality, infectious complications such as ventilator-associated pneumonia or pneumonia, and discharge to a rehabilitation facility) were synthesised as risk ratios with 95% confidence intervals using the DerSimonian and Laird inverse-variance random-effects model. For each trial, we pooled the log-transformed risk ratios and the corresponding standard errors. Continuous outcomes reported on the same scale (duration of ICU admission in days, duration of hospital admission in days, and length of invasive mechanical ventilation in days) were pooled as mean differences under a random-effects model with between-study variance (τ^2) estimated by restricted maximum likelihood (REML). Continuous outcomes reported on different scales (health-related quality of life measured with EQ-5D-5L) were pooled as standardised mean differences using a random-effects model with τ^2 estimated by REML. When trials reported medians and interquartile ranges or ranges, these were converted to means and standard deviations using the method of Wan et al. [23] before pooling, and cross-sectional endpoints were chosen for trials using longitudinal follow-up. Statistical heterogeneity and inconsistency were measured using τ^2 and I^2 statistics. Forest plots were presented to visualise the distribution of effects across included trials separately for each outcome. If more than 10 trials met the eligibility criteria for a given outcome, small study effects were assessed visually using funnel plots [24]. Because measures of physical function, muscle mass, and muscle strength were reported using non-comparable instruments/scales, these outcomes were not pooled and were instead summarised narratively. Data analyses were undertaken in R version 4.4.0 using the *metafor* package [25].

2.8. Analysis of subgroups

Subgroup analyses were conducted for the primary outcome [1]: patients receiving exclusive EN versus EN including supplemental PN [2]; patients with acute kidney injury (AKI) versus patients with no AKI/not known to have AKI (as defined in the primary trial); and [3] patients with higher severity of illness (defined as Sequential Organ Failure Assessment (SOFA) score $\geq$9) versus patients with lower severity of illness (defined as SOFA score <9) [22]. For each trial, we pooled the subgroup specific log-transformed effect estimate and the corresponding standard errors. Note that trials did not report consistent effect estimates for this subgroup analysis but were pooled assuming that mortality is a rare outcome. Only one trial reported SOFA score $\geq$9 versus SOFA score <9 as a subgroup [17], so the subgroup analysis was not possible. The likely direction of any subgroup effect was prespecified. The Credibility of Effect Modification Analyses (ICEMAN) tool was used to assess the credibility of any subgroup effect identified [26].

2.9. Sensitivity analyses

For the primary outcome (90-day mortality), sensitivity analyses were conducted to assess the robustness of the findings. First, the effect was re-estimated using only trials that explicitly reported 90-day mortality. Second, the analysis was restricted to trials judged to be low risk of bias. In addition, for the primary

outcome (90-day mortality) we had pre-specified that when this was not available, we would use the nearest timepoint reported. However, the trial by Van Zanten et al. [27] did not report 90-day mortality but reported 28- and 42-day mortality. Given that 42-day mortality was closer to our primary outcome, the meta-analysis for our primary outcome was repeated to include the estimate for 42-day mortality as a sensitivity analysis. We conducted a *post-hoc* sensitivity analysis of the subgroup with AKI removing the TARGET Protein trial [19] when assessing subgroup analysis for patients with AKI versus patients with no AKI/not known to have AKI (as defined in the primary trial). This was performed because the TARGET Protein trial [19] used a different definition to that used in the EFFORT Protein [17] and PRECISe trials [18].

2.10. Trial quality and risk of bias assessment

For each analysed outcome, each included trial was independently evaluated for risk of bias by two reviewers (MJS and LSC) using the Cochrane Risk of Bias tool for randomised trials version 2 (RoB 2) or cluster randomised trials as applicable [28], with discrepancies resolved by a third author (JLMB). Risk of bias assessments were categorised as low risk, some concerns, or high risk.

2.11. Certainty of the evidence

The certainty of evidence for primary and secondary outcomes were rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [29]. Evidence certainty was determined by assessing whether greater protein dose leads to beneficial or harmful effects. Evidence from RCTs was initially rated as high certainty but could have been downgraded due to methodological limitations or concerns such as bias, inconsistency, indirectness, imprecision, and publication bias [30].

3. Results

3.1. Trial selection process

The literature search from inception through 2 July 2025 identified 10414 articles. After title and abstract screening and removing duplicates and irrelevant papers, 61 articles underwent full text review with 47 excluded (eTable 1) and 14 trials eligible for inclusion (Fig. 1) [17–19,27,31–40]. A total of 6553 patients were enrolled across these 14 trials: 3248 patients received greater protein, and 3305 patients received lesser protein. Thirteen trials were individual patient RCTs (n = 3243: greater protein n = 1516; lesser protein n = 1527) [17,18,27,31,33–41] and one trial was a cluster randomised cross-over trial, with 8 clusters (n = 3397: greater protein n = 1681; lesser protein n = 1716) [19].

3.2. Trial characteristics

Trial characteristics are summarised in Table 1. The number of patients randomised in respective trials ranged from 25 to 3411. The study population included mixed medical and surgical populations (11 trials) [17–19,27,31,34–39], patients with stroke or head injury (two trials) [32,33], only surgical (emergency and elective) patients (one trial) [40]. Trials were published from 2013 to 2025, with eight trials being single-centre [31–33,35–39] and six multi-centre [17–19,27,34,40] (Table 1). Four trials were conducted in Europe [18,27,33,36], three in Australia/New Zealand [19,34,37], three in North America [17,32,40], three in South America [31,35,39], and one in Asia [38]. The mean/median duration of intervention delivery ranged from 5 to 11 days (Table 2).

3.3. Protein and energy delivery

All included trials reported weight-based protein delivery, with mean/median protein doses ranging from 1.20 to 1.69 g/kg/day in the greater protein group compared with 0.75–1.19 g/kg/day in the lesser protein group (Table 2). A variety of documented weights were used to calculate weight-based protein delivery: seven used ideal body weight, using different calculation methods [17–19,27,33,34,36]; and seven did not state the weight used [31,32,35,37–40]. Energy delivery was similar between the greater protein and lesser protein groups with mean/median energy delivery ranging from 12.0 to 27.0 kcal/kg/day in the greater protein group versus 13.2–24.6 kcal/kg/day in the lesser protein group.

3.4. Mortality - primary outcome

Twelve trials reported a mortality outcome [17–19,27,31,33,35–38,40] (n = 6440: greater protein n = 3197; lesser protein n = 3243). For mortality, three trials reported 90-day mortality [18,19,34], three trials reported 60-day mortality [17,33,37], two trials reported hospital mortality [31,40], two trials reported 28-day mortality [27,38], one trial reported 180-day mortality [35], and one trial reported ICU mortality [36] (Fig. 2). No difference was observed between the greater protein and lesser protein groups for mortality (pooled RR 1.01, 95% CI 0.92, 1.12, p = 0.795; I^2= 0%; τ^2= 0.00). Visual inspection of the funnel plot shows an asymmetry, with smaller studies clustered to the left. This pattern suggests a potential small-study effect or publication bias (eFig. 1a).

3.5. Sensitivity analysis for primary outcome

Three trials reported 90-day mortality [18,19,34] (n = 4355: greater protein n = 2159; lesser protein n = 2196). There was no difference in 90-day mortality between the greater protein and the lesser protein groups (pooled RR 1.06, 95% CI 0.95, 1.19; p = 0.287; I^2= 0%; τ^2= 0.00; eFig. 2a). Four trials had a low risk of bias for the primary outcome [17,18,34,37] (n = 2308: greater protein n = 1150; lesser protein n = 1158), and there was no statistically significant difference in mortality between the greater protein and the lesser protein groups, although the 95% CI was largely compatible with increased mortality (pooled RR 1.07, 95% CI 0.97, 1.19, p = 0.173; I^2= 0%; τ^2= 0.00; eFig. 2b). The sensitivity analysis repeated to include the estimate for 42-day mortality showed there was no difference between the greater protein and the lesser protein groups (RR 1.01, 95% CI 0.92, 1.12; p = 0.774; I^2= 0%; τ^2= 0.00; eFig. 2c).

3.6. Other clinical outcomes

Five trials reported infectious complications [18,32,33,36,38], all of which were pneumonia (n = 1313: greater protein n = 662; lesser protein n = 651), with no difference between groups (RR 0.98, 95% CI 0.83, 1.16; p = 0.826; I^2= 20%; τ^2= 0.01; Fig. 3a). Thirteen trials reported ICU length of stay [17,19,27,31–40] (n = 5705: greater protein n = 2829; lesser protein n = 2876), with no difference between groups (mean difference −0.25 days, 95% CI -0.95, 0.44; p = 0.476; I^2= 0%; τ^2= 0.00; Fig. 3b). Visual inspection of the funnel plot showed most trials clustered toward the top and publication of only one small trial (i.e., with small sample size) (eFig. 1b). Eight trials reported hospital length of stay [17,19,27,34,35,37,38,40] (n = 5237: greater protein n = 2598; lesser protein n = 2639), with no difference between groups (mean difference 1.05 days, 95% CI -0.21, 2.31; p = 0.102; I^2= 0%;

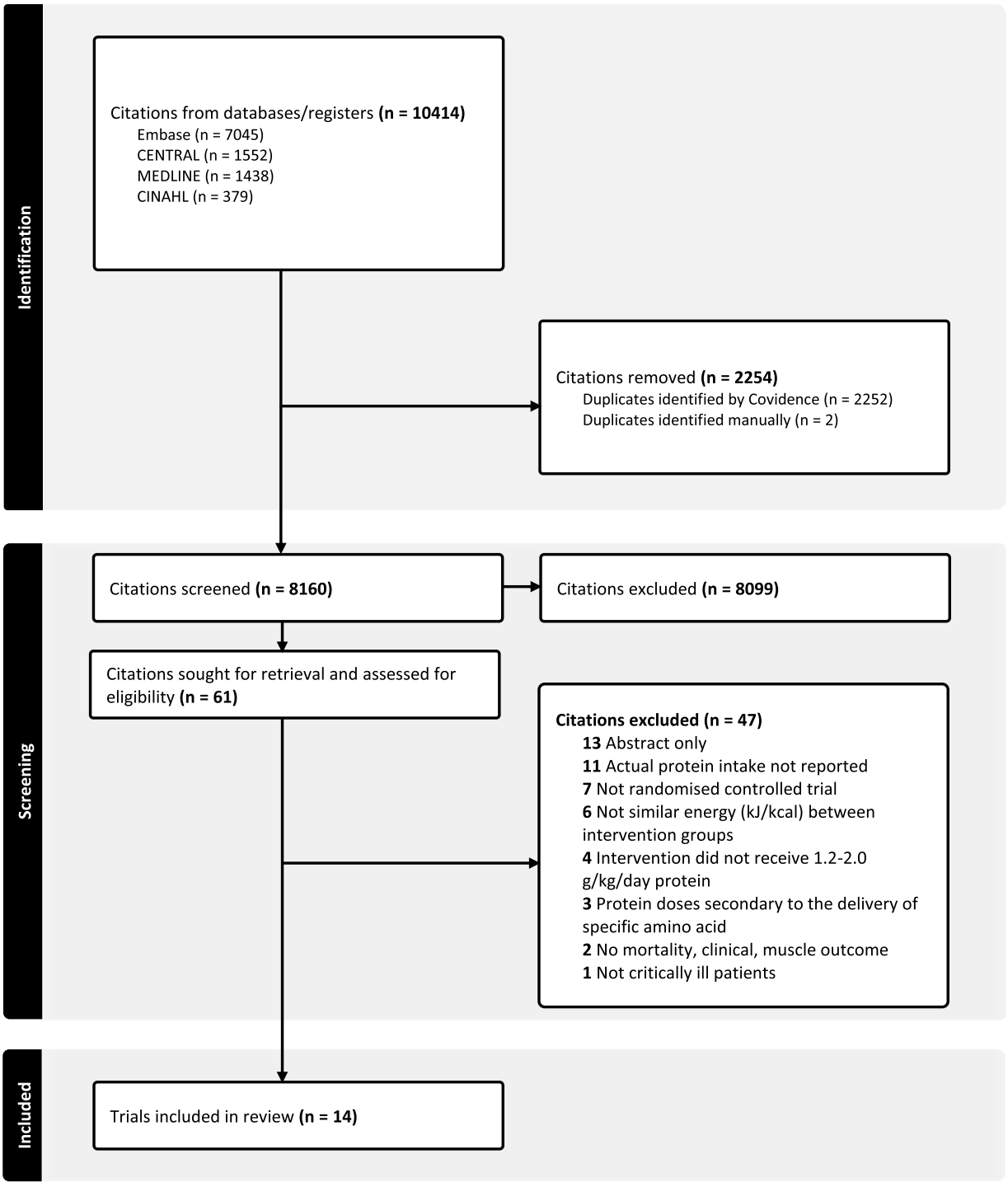


Fig. 1. PRISMA flow diagram illustrating the identification, screening, eligibility, and inclusion of trials in this systematic review and meta-analysis.

τ^2= 0.00; Fig. 3c). Ten trials reported duration of invasive mechanical ventilation [17,19,27,31,33,35–39] (n = 5537: greater protein n = 2743; lesser protein n = 2794), with no difference between groups (mean difference −0.04 days, 95% CI -0.61, 0.54; p = 0.899; I^2= 24%; τ^2= 0.17; Fig. 3d).

3.7. Patient-centred outcomes

Two trials reported EQ-5D-5L quality of life assessments at day 90 [18,34] (n = 921: greater protein n = 456; lesser protein n = 465). There were differences in how data were reported with one trial using a survivor-only approach [19] and the other imputing deaths as zero [18]. Quality of life was lower for those in the greater protein group compared to lesser protein group (standardised mean difference −0.11, 95% CI -0.24, 0.01; p = 0.081; I^2= 0%; τ^2= 0.00; Fig. 4a). Five trials reported hospital discharge location to a rehabilitation facility [18,19,32,34,37] (n = 4118: greater protein n = 2028; lesser protein n = 2090) with no difference between groups (RR 1.05, 95% CI 0.84, 1.31; p = 0.675; I^2= 0%; τ^2= 0.00; Fig. 4b).

Table 1
Summary of methods and baseline characteristics for included trials.

Author, Year, Country	Design	Trial Population	Number of patients randomised	Treatment groups		Primary Outcome	Age, years[a]		Sex, males n (%)		BMI at baseline, kg/m^2[a]	
				Greater Protein	Lesser Protein		Intervention	Control	Intervention	Control	Intervention	Control
Azevedo, 2019, Brazil [31]	Individual randomised, Single-blinded, Single-centre	Mixed medical and surgical	Total: 120 Greater protein: 57 Lesser protein: 63	Protein target of 2.0–2.2 g/kg/day and caloric target determined by indirect calorimetry.	Protein target of 1.4–1.5 g/kg/day and caloric target of 25 kcal/kg/day	Physical Component summary score obtained from Medical Outcomes Study 36 - Item Short - Form Health Survey (SF-36) tool at 3 and 6 months	65.0 ± 18.8	67.4 ± 18.9	34 (59.7)	32 (50.8)	NS	NS
Azevedo, 2021, Brazil [35]	Individual randomised, Single-blinded, Single-centre	Mixed medical and surgical	Total: 211 Greater protein: 99 Lesser protein: 112	Indirect calorimetry to determine energy prescription and protein target 2.0–2.2 g/kg/day from day 5.	Indirect calorimetry to determine energy prescription and protein target 1.4–1.5 g/kg/day from day 5.	Physical component summary score at 3 and 6 months	67.6 ± 17.8	65.3 ± 19.7	53 (61)	46 (49)	NS	NS
Badjatia, 2021, USA [32]	Individual randomised, Open-label, Single-centre	Stroke or head injury	Total: 25 Greater protein: 12 Lesser protein: 13	Enteral boluses of whey protein powder with protein target of 1.75 g/kg/day	Protein target 1.2–1.4 g/kg/day	Percentage difference in the cross-sectional area from baseline to post bleed day 14 on computed tomography scan.	60 ± 8	58 ± 14	5 (42)	5 (38)	27 ± 3	27 ± 6
Bels, 2024, Netherlands [18]	Individual randomised, Double-blinded, Multi-centre	Mixed medical and surgical	Total: 935 Greater protein: 470 Lesser protein: 465	Protein target 2.0 g/kg/day	Protein target 1.3 g/kg/day	EQ-5D-5L healthy utility score at 30 days, 90 days and 180 days after randomisation	62 ± 14	63 ± 14	291 (62)	309 (67)	28 ± 6	27 ± 5
Carteron, 2021, France [33]	Individual randomised, Open-label, Single-centre	Stroke or head injury	Total: 206 Greater protein: 103 Lesser protein: 93	Hypercaloric (1.5 kcal/ml) polymeric formula	Hypercaloric (1.5 kcal/ml) semi-elemental formula	Percentage of patients who received both 60% of the daily energy goal at 3 days and 100% of the daily energy goal at 5 days after inclusion	57 (44, 65)	55 (40, 65)	67 (67)	53 (56)	26 (23, 29)	26 (23, 29)
Chapple, 2021, Australia [34]	Individual randomised, Double-blinded, Multi-centre	Mixed medical and surgical	Total: 120 Greater protein: 60 Lesser protein: 60	Very high protein EN formula 100 g protein/1000 ml	High protein EN formula 63 g protein/1000 ml	Mean daily protein delivery (g/kg/day)	60 (50, 72)	61 (46, 68)	39 (67)	44 (76)	29 (26, 33)	30 (25, 34)
Dresen, 2021, Germany [36]	Individual randomised, Single-blinded, Single-centre	Mixed medical and surgical	Total: 48 Greater protein: 25 Lesser protein: 23	Indirect calorimetry to determine energy prescription and protein target 1.8 g/kg/day	indirect calorimetry to determine energy prescription and protein target 1.2 g/kg/day	Quadricep muscle layer thickness via ultrasound	66 ± 16	64 ± 15	15 (71)	15 (71)	NS	NS

Fetterplace, 2018, Australia [37]	Individual randomised, Single-blinded, Single-centre	Mixed medical and surgical	Total: 60 Greater protein: 30 Lesser protein: 30	High-protein EN with volume-based nutrition protocol - plus supplemental protein powder	Standard nutrition formula	Co-primary outcomes: 1. mean daily protein delivery over the 15-day study period 2. mean daily energy delivery over the 15-day study period	55 ± 13	57 ± 16	23 (77)	21 (70)	30 ± 7.1	29 ± 5.3
Heyland, 2023, Canada [17]	Individual randomised, Single-blinded, Multi-centre	Mixed medical and surgical	Total: 1329 Greater protein: 659 Lesser protein: 670	Protein target of at least 2.2 g/kg/day	Protein target of 1.2 g/kg/day or less	Time-to-discharge-alive from hospital to 60 days from randomisation	57 ± 17	57 ± 17	395 (61)	388 (59)	28 ± 10	29 ± 9
Nakamura, 2021, Japan [38]	Individual randomised, Single-blinded, Single-centre	Mixed medical and surgical	Total: 134 Greater protein: 68 Lesser protein: 66	Protein target 1.8 g/kg/day	Protein target 0.9 g/kg/day	Femoral muscle volume change (%) from day 1 to day 10	68.3 ± 14.3	67.9 ± 14.9	35 (58.3)	38 (66.7)	21.3 ± 3.9	21.5 ± 4.5
Rugeles, 2013, Colombia [39]	Individual randomised, Single-blinded, Single-centre	Mixed medical and surgical	Total: 115 Greater protein: 53 Lesser protein: 62	15 kcal/kg/day, with protein target of 1.5 g/kg/day	Standard nutritional regimen with a goal of 25 kcal/kg/day.	Change in SOFA score at 48 h	53.3 ± 19.5	55.7 ± 19.5	22 (55)	24 (60)	23.7 ± 3.3	24.3 ± 4.4
Summers, 2025, Australia [19]	Cluster randomised, crossover, Open-label, Multi-centre	Mixed medical and surgical	8 clusters Total: 3411 Greater protein: 1693 Lesser protein: 1718	Very high protein EN formula −100 g protein/1000 ml	High protein EN formula - 63 g protein/1000 ml	The number of days free of the index hospital and alive at day 90	61.0 (48.0, 70.0)	61.0 (48.0, 71.0)	1070 (63.7)	1087 (63.3)	27.6 (24.1, 32.6)	27.5 (23.8, 32.3)
Van Zanten, 2018, Netherlands [27]	Individual randomised, Double-blinded, Multi-centre	Mixed medical and surgical	Total: 44 Greater protein: 22 Lesser protein: 22	Very high protein EN formula - 8g/100 kcal	Standard protein formula - 5g/100 kcal	Protein intake from study product at day 5	63.9 ± 13.3	60.8 ± 15.2	9 (40.9)	13 (59.1)	30.3 ± 4.1	30.7 ± 8.4
Yeh, 2020, USA [40]	Individual randomised, Open-label, Multi-centre	Mixed emergency and elective surgical	Total: 36 Greater protein: 19 Lesser protein: 17	Semi-elemental formula and protein supplementation	Standard polymeric formula	Nutrition adequacy over the first 12 ICU days after randomisation	49.1 ± 24.7	50.6 ± 15.6	18 (95)	12 (71)	28.5 ± 6.7	30.2 ± 6.1

Abbreviations: EN = enteral nutrition; g = grams; ICU = intensive care unit; kg = kilograms; ml = millilitres; NS = not stated; SOFA = sequential organ failure assessment.
[a] Presented as median (interquartile range) or mean ± standard deviation.

Table 2
Macronutrient delivery of included trials.

Author, Year, Country	Duration of nutrition intervention (days)		Weight used to calculate protein/ energy delivery	Protein delivered (g/kg/day)		Energy delivered (kcal/kg/day)		Fat in intervention relative to control (more, similar, less)[a]	Carbohydrate in intervention relative to control (more, similar, less)[a]
	Greater Protein	Lesser Protein		Greater Protein	Lesser Protein	Intervention	Control		
Azevedo 2019	NS	NS	NS	1.69 (1.33, 1.80)	1.13 (0.97, 1.34)	NS[b]	NS[b]	NS	NS
Azevedo 2021	NS	NS	NS	1.48 (1.25, 1.64)	1.19 (0.96, 1.26)	19.5 (16, 22)	19.0 (14.3, 21.4)	NS	NS
Badjatia 2022	NS	NS	NS	1.51 ± 0.47	0.88 ± 0.36	20.0 ± 7.1	19.8 ± 9.9	NS	NS
Bels 2024	10 (5, 21)	9 (4, 19)	Ideal body weight	1.48 ± 0.70	0.95 ± 0.44	19 ± 9	19 ± 9	Similar	Less
Carteron 2021	NS	NS	Ideal body weight	1.3 ± 0.4	1.1 ± 0.3	20.2 ± 6.3	21.0 ± 6.5	Similar	Less
Chapple 2021	8.7 ± 7.3	8.1 ± 6.3	Ideal body weight	1.52 ± 0.52	0.99 ± 0.27	19.2 ± 6.5	19.6 (5.4)	Similar	Less
Dresen 2021	NS	NS	Ideal body weight	1.5 ± 0.5	1.0 ± 0.4	27.0 ± 8.9	24.6 ± 9.8	Similar	Less
Fetterplace 2018	8.0 ± 4.4	7.0 ± 4.5	NS	1.2 ± 0.30	0.75 ± 0.11	23 ± 5.7	21 ± 3.3	NS	NS
Heyland 2023	11.0 (6.0, 11.0)[c]	10.0 (6.0, 11.0)[c]	Ideal body weight	1.6 ± 0.5	0.9 ± 0.3	14.7 ± 6.9	13.2 ± 6.4	NS	NS
Nakamura 2021	8 (5, 9)	8 (5, 9)	NS	Median: 1.5[d]	Median: 0.8[d]	NS[e]	NS[e]	More	Similar
Rugeles 2013	NS	NS	NS	Mean: 1.4[d]	Mean: 0.76[d]	12[d]	14[d]	Similar	Similar
Summers 2025	87.0 (36.4, 187.0)[f]	84.0 (34.0, 182.4)[f]	Ideal body weight	1.33 (0.88, 1.78)	0.84 (0.49, 1.11)	17 (11, 22)	17 (10, 22)	Similar	Less
Van Zanten 2018	NS	NS	Ideal body weight	1.3 (0.7, 1.9)	0.7 (0.5, 0.9)	16.6 (8.9, 23.3)	14.4 (10.9, 18.8)	Similar	Less
Yeh 2020	NS	NS	NS	1.2 ± 0.4	0.9 ± 0.4	15.9 ± 5.5	14.8 ± 5.7	NS	NS

Abbreviations: g = grams; Kcal = kilocalories; kg = kilograms, NS = not stated.
Median (interquartile range) or mean ± standard deviation.
[a] Fat and carbohydrate in the intervention relative to control as stated in the primary publication.
[b] Reported as kcal/day with no significant difference.
[c] Reported as number of nutrition evaluable days post randomisation with a maximum of 12 days, which are the number of days the patients received nutritional support (i.e. enteral or parenteral nutrition), before progressing to permanent oral intake.
[d] Mean/median reported without standard deviation/interquartile range.
[e] Reported a non-significant difference without reporting actual energy delivered.
[f] Reported in hours.

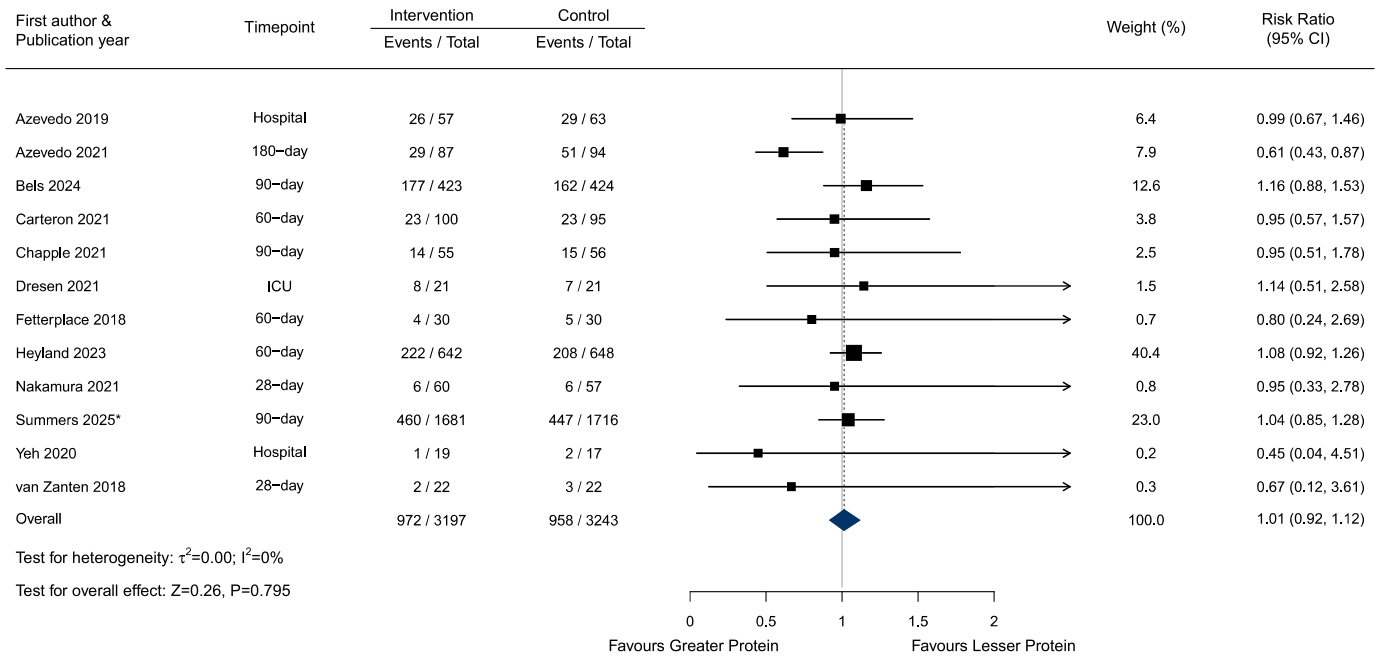


Fig. 2. Forest plot of primary outcome - Mortality.

Physical function was reported in six trials [18,31,32,35,37,38] (n = 870: greater protein n = 414; lesser protein n = 456; eTable 2). Three trials used the physical component summary score of the Short Form-36 [18,31,35], one trial used the functional status score for the ICU (FSS-ICU) [38], one trial used the physical function in ICU test [37], one trial used the Barthel Index [38], one trial used the 6-min walk test [18], and one trial used the short physical performance battery [32]. Three trials found improvement in physical function in survivors of the greater protein group [18,32,35]; however, one trial reported physical function in only a small proportion of survivors [18] and two trials had a high risk of bias or some concerns [32,35].

3.8. Muscle outcomes

Four trials reported muscle mass measurements [32,36–38] (n = 231: greater protein n = 117; lesser protein n = 114; eTable 3). Two trials reported ultrasound-derived quadriceps muscle layer thickness [36,37], one trial reported change in femoral muscle volume via computed tomography (CT) scan [38], and one trial reported percentage of CT-derived muscle atrophy in the quadriceps muscle via CT scan [32]. Three out of the four trials showed attenuated muscle mass in the greater protein group compared to the lesser protein group [32,37,38].

Three trials reported muscle strength measurements [18,31,37] (n = 495: greater protein n = 231; lesser protein n = 264; eTable 4). Three trials used hand grip strength [18,31,37], and two trials used Medical Research Council sum score [18,37]. No trials showed a significant difference between the greater protein and lesser protein groups.

3.9. Trial quality assessments

The RoB2 assessments are presented in eFig. 3. Of the 12 trials that reported mortality as an outcome, four (33.3%) were low risk of bias [17,18,34,37], seven (58.3%) had some concerns [19,27,31,33,36,38,40]; and one (8.3%) was deemed high risk of bias [35] (eFig. 3a).

3.10. GRADE certainty assessments

The summary of findings and the certainty of evidence of the effect of greater protein on outcomes using the GRADE system are presented in eTable 5. Greater protein delivery did not affect pooled mortality (moderate certainty of evidence). The certainty of evidence of the effect of greater protein on other outcomes was low to moderate.

3.11. Subgroup analyses

Four trials prohibited the use of supplemental PN [32,33,39,40], while ten trials allowed supplemental PN at the treating clinicians' discretion [17–19,27,31,34–38]. Of the twelve trials which reported a mortality outcome, two trials received exclusive EN [33,40] and ten trials received supplemental PN [17–19,27,31,34–38]. The results of the subgroup analysis for patients receiving exclusive EN showed no difference between the greater protein group compared to the lesser protein group (pooled RR 0.92, 95% CI 0.56, 1.50; p = 0.734; I^2= 0%; τ^2= 0.00; n = 231: greater protein n = 119; lesser protein n = 112) and no difference between the greater protein group compared to the lesser protein group for patients receiving EN plus supplemental PN (pooled RR 1.01, 95% CI 0.90, 1.13; p = 0.912; I^2= 0%; τ^2= 0.00; n = 6209: greater protein n = 3078; lesser protein n = 3131; p for interaction = 0.7027; Fig. 5a).

Three trials reported AKI as a subgroup with differing definitions [17–19]. Two trials defined AKI using Kidney Disease Improving Global Outcomes (KDIGO) criteria, with stage 1–3 defined as the presence of AKI prior to randomisation [17,18], and one trial defined AKI as new renal replacement therapy between hospital admission and commencement of trial nutrition [19]. For patients with AKI, there was increased risk of mortality with

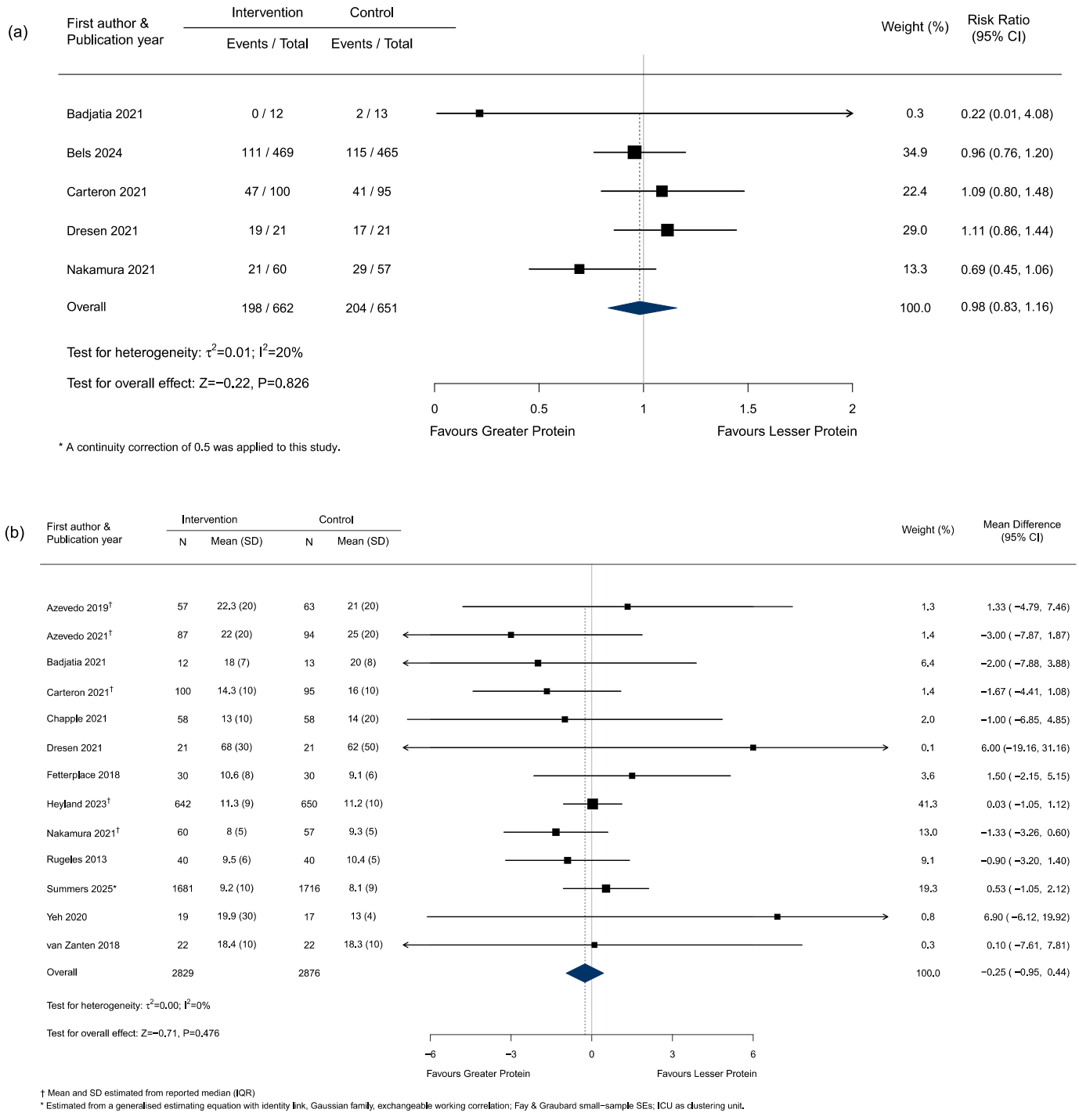
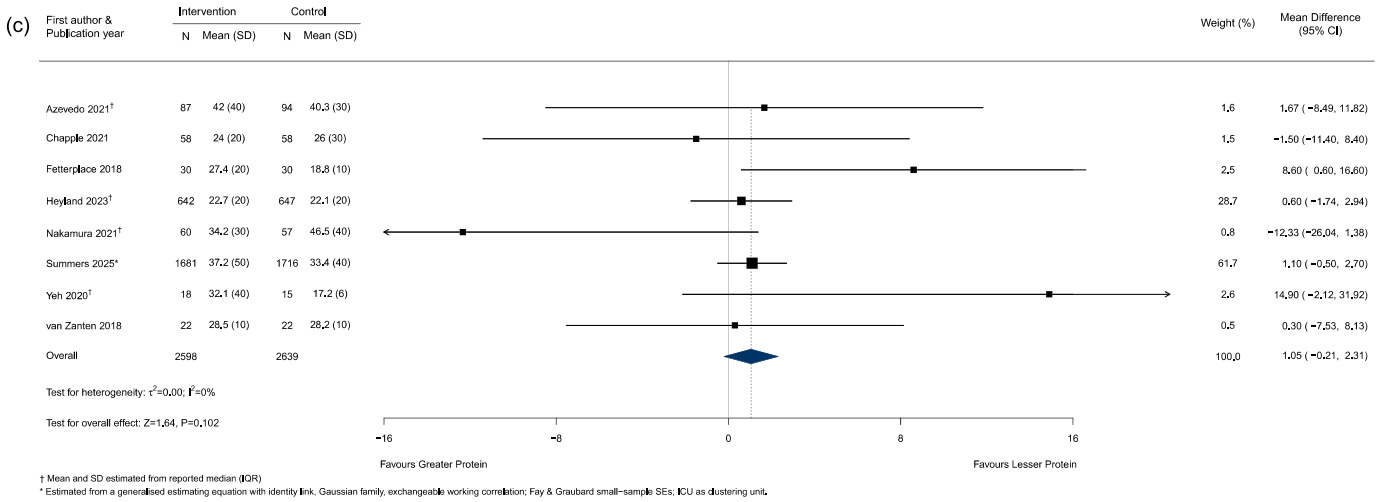


Fig. 3. Forest plot of clinical outcomes (a) Infectious complications. (b) Intensive care unit length of stay (days). (c) Hospital length of stay (days). (d) Duration of mechanical ventilation (days).

greater protein compared to lesser protein (pooled effect estimate 1.29, 95% CI 1.05, 1.58, p = 0.015; I^2= 0%; τ^2= 0.00; n = 755: greater protein n = 390; lesser protein n = 365). Note that this did not materially change when we excluded the TARGET Protein trial [19] from the subgroup analysis (pooled effect estimate 1.26, 95% CI 0.96, 1.65, p = 0.099, I^2= 36%, τ^2= 0.02; eFig. 4). For patients with no AKI/not known to have AKI, there was no difference in mortality (pooled effect estimate 1.00, 95% CI 0.83, 1.19; p = 0.974; I^2= 32%; τ^2= 0.01; n = 4878: greater protein n = 2406; lesser protein n = 2472; p for interaction = 0.0643; Fig. 5b). The ICEMAN evaluation suggests that the evidence for effect modification was of moderate credibility (Supplementary Material, page 27–29).



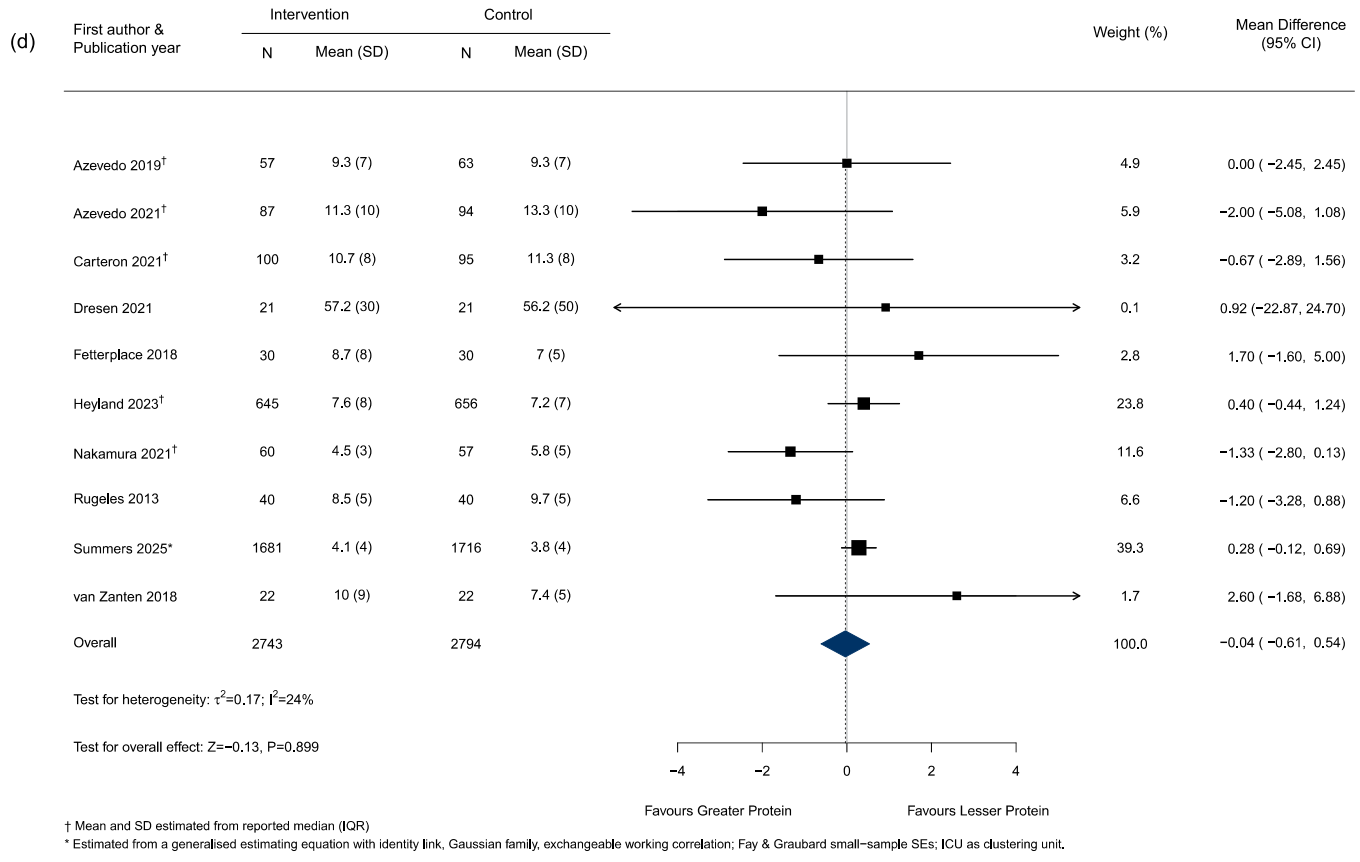


Fig. 3. (*continued*).

4. Discussion

In this systematic review and meta-analysis of RCTs in critically ill patients comparing delivered enteral protein doses recommended within international guidelines ('greater protein' 1.2–2.0 g/kg/day) to those below the international guidelines ('lesser protein' <1.2 g/kg/day), there was no signal of benefit with greater protein. Greater protein delivery was associated with increased mortality in the subgroup of patients with AKI; however, the definition used differed between trials.

This is the first systematic review and meta-analysis conducted that incorporates all three large RCTs conducted in the critically ill to evaluate the impact of higher protein dose, delivered predominately via the enteral route, on patient outcomes. As EN is the preferred route recommended in critical care guidelines [8,9], this systematic review provides a clinically relevant synthesis of the literature. The previous systematic review by Fetterplace et al. in 2020, used a similar approach, including only trials that delivered protein predominately via the enteral route in critically ill patients to achieve internationally recommended protein doses compared to usual care [12]. Fetterplace et al. included six RCTs comprising a total of 511 patients and concluded there was insufficient data to support improved patient outcomes with current international recommendations on protein provision [12]. Our current review

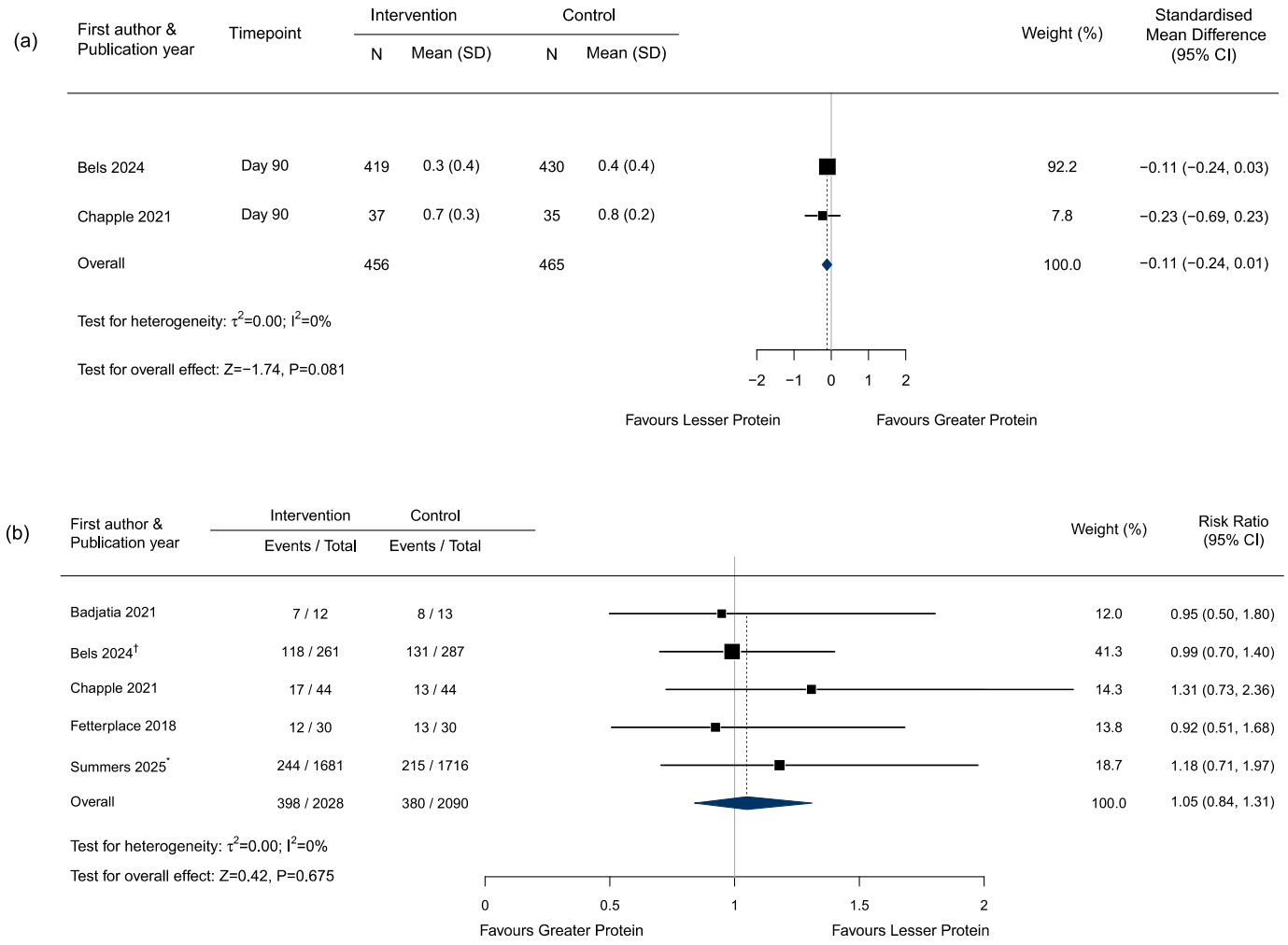


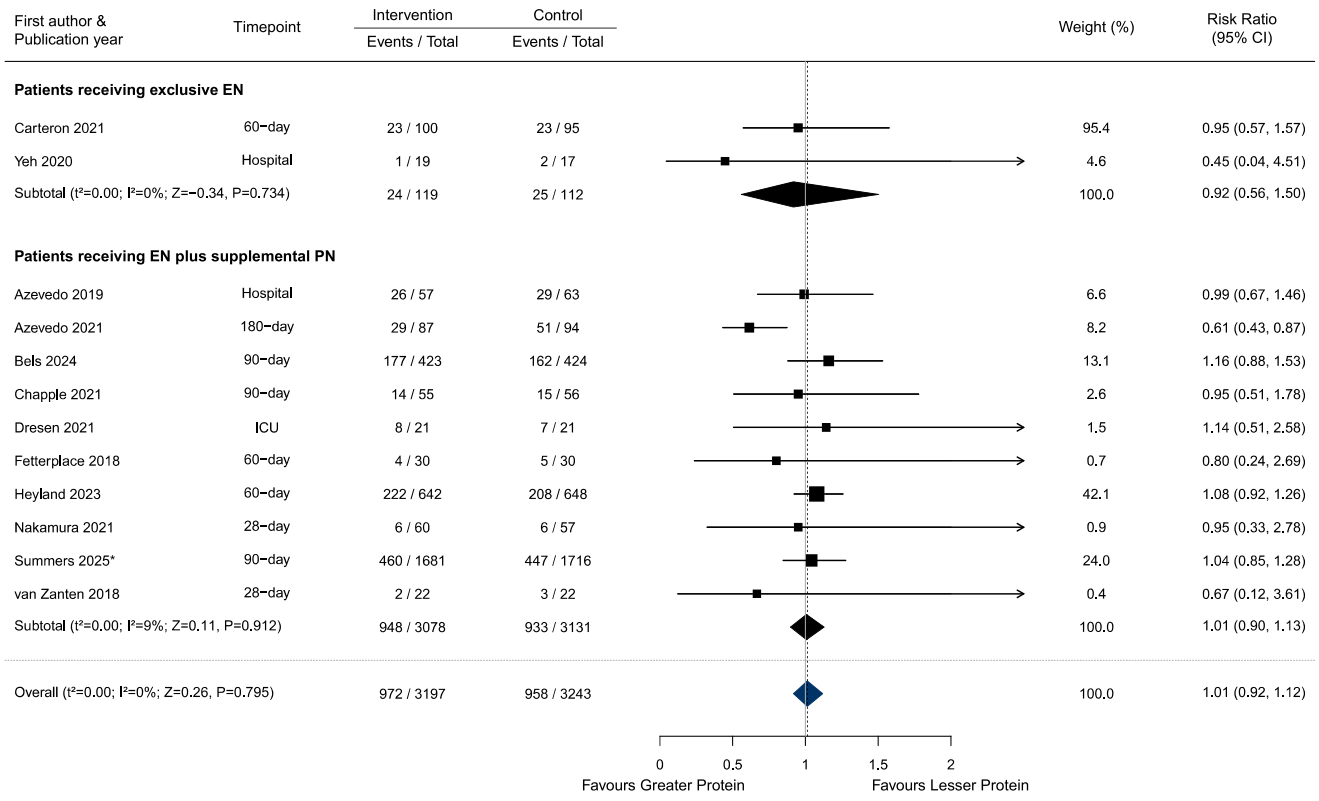
Fig. 4. Forest plot of patient-centred outcomes
(a) Quality of life measurements.
(b) Discharged to rehabilitation.

adds a substantial number of patients to this evidence base, with 6553 patients included across thirteen parallel RCTs and one cluster randomised cross-over trial. This provides evidence that delivering enteral protein doses within international guidelines (1.2–2.0 g/kg/day) has no benefit on clinical or patient-centred outcomes, with potential harm, and that previous associations between higher protein delivery and decreased mortality risk demonstrated in retrospective/observational studies [42] are no longer supported by the current evidence. Therefore, there is increased confidence that the observed potential harm reflects protein dosing, independent of route of nutrition delivery.

Our review suggests that greater enteral protein doses may increase mortality in the subgroup of patients with an AKI, with moderate credibility, using pooled data from three trials. A major limitation that impacts interpretation of these findings is the different definitions used for AKI across each trial: including AKI pre-randomisation; and new renal replacement therapy prior to trial commencement, with inconsistent results amongst individual trials and analyses. The lack of a uniform definition of baseline AKI across the included studies may have introduced heterogeneity and potential misclassification, which may have influenced the pooled effect estimate. The 2024 systematic review and meta-analysis by Lee et al. also reported greater protein doses may increase mortality in patients with AKI, and also used differing definitions of AKI [5]. Similarly, a post-hoc analysis of the EFFORT Protein trial reported that greater protein dose was associated with slower time-to-discharge alive from hospital and greater 60-day mortality, when compared to lower protein dose, in patients with an AKI within seven days of ICU admission prior to randomisation, yet this relationship was not consistent in patients receiving kidney replacement therapy [43]. The delivery of higher protein doses in critically ill patients with an AKI, regardless of the definition used, has not been shown to provide benefit, and as such, current ICU nutrition guidelines advocating for higher protein doses in AKI warrant revision.

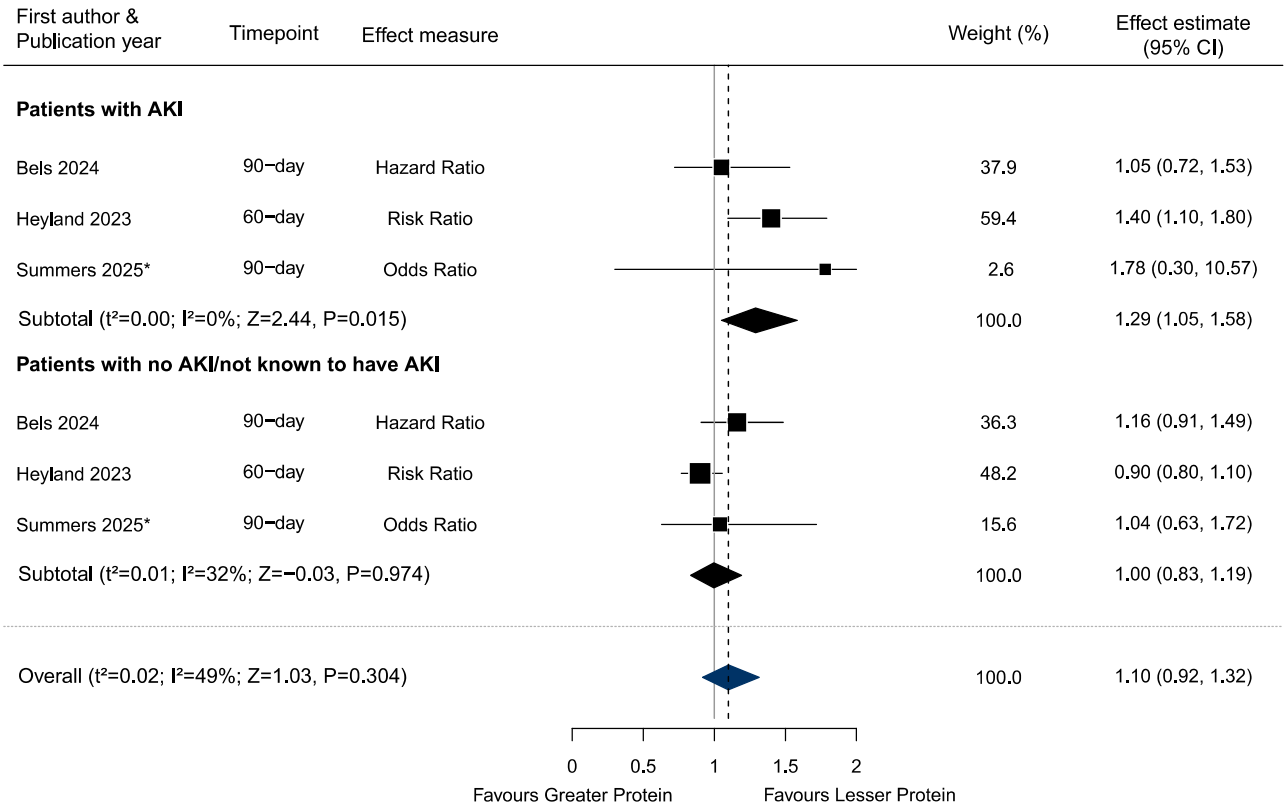
In our meta-analysis, quality of life (using EQ-5D-5L at day 90) point estimates favoured lesser protein with confidence intervals including possible small clinically important harm with greater protein, with defined minimally important differences for EQ-5D-5L which ranges from 0.04 to 0.07 [44]. This suggests that for the two trials contributing data to this analysis, there was a potential for clinically meaningful effect for worse quality of life with

(a)



* Summers et al conducted a cluster cross over trial. The risk ratio is estimated from a generalised estimating equation (GEE),which accounts for the trial design. The GEE used a log link, binomial distribution, exchangeable correlation structure, and Fay and Graubard's correction.

(b)



* Summers et al conducted a cluster cross−over trial. The odds ratio is estimated from a generalised estimating equation (GEE), which accounts for the trial design. The GEE used a log link, binomial distribution, exchangeable correlation structure, and Fay & Graubard's correction.

greater protein dose [18,34]. Two studies were included to the meta-analysis of health-related quality of life. The primary outcome of the PRECISe trial [18] was health-related quality of life measured at 30, 90 and 180 days after ICU admission, and so needed to account for the competing risk of death as a high mortality rate was expected. This was analysed with a restricted maximum likelihood linear mixed-effects regression model adjusted for baseline EQ-5D-5L health utility score. Meanwhile, the TARGET Protein feasibility trial [34] included health-related quality of life at 90 days as a secondary outcome and as such reported a survivor-only analysis. A survivor-only analysis versus assigning deaths as zero may overestimate quality of life and importantly disregards death as a potential competing risk [45]. The PRECISe trial retained deceased patients in the intention-to-treat analysis by applying the specific ability of the EQ-5D-5L instrument to handle death as a potential outcome by assigning it with a score of zero within a range from negative values (health state worse than death) to 1.0 (perfect health state). To enable pooling of these trials in the current meta-analysis, 90 day health-related quality of life, a post-hoc endpoint of the PRECISe trial, was chosen. However, this does reduce power and assessment of functional recovery over time in comparison with the original trial. Given these limitations, the level of evidence and credibility of the conclusions of the original PRECISe trial should be valued higher than those of the combined data. In addition, to enable data pooling we used a post-hoc cross-sectional EQ-5D-5L health utility score at day 90 from the PRECISe trial [18]. This inevitably resulted in an underestimation of the statistically and clinically significant detrimental effect of high protein doses that was found during the longitudinal follow-up period to 180 days in the PRECISe trial. The direction of harm is in line with a recent systematic review and meta-analysis conducted in a Bayesian framework that indicated a negative impact of greater protein delivery on quality of life (mean difference −0.12 (95% CrI −0.47, 0.13) with a clinical benefit from higher protein delivery appearing improbable [16]. Heuts et al. included one trial that used a PN intervention and pooled two different quality of life tools [16], while our review included two trials of EN interventions using the same quality of life tool [18,34]. Based on the combined evidence for worse quality of life with greater protein doses, enteral protein dosing in critically ill patients should be approached with caution.

The mechanism for harm with greater protein for specific outcomes or in certain patient cohorts are not yet understood. Data from our group using stable amino acid isotope methodology demonstrates an impaired efficiency to use dietary protein for muscle protein synthesis in critical illness, relative to health [46], and that greater protein dosage is unable to overcome this anabolic resistance to dietary protein [47]. It is therefore plausible, in the critically ill, that excess protein not used for muscle protein synthesis results in increased urea production [17,19]. Alternatively, greater oxidation and gluconeogenesis [48,49] may increase burden on metabolic processes. Mechanisms behind harm require further exploration.

4.1. Strengths and limitations

A major strength of our systematic review and meta-analysis is the comprehensive literature search and analysis, in addition to the published protocol and prespecified analysis plan [22]. We included RCTs that delivered predominately EN at distinct dosages, a greater protein dose (protein delivery within international guidelines) compared to a lesser protein dose (protein delivery below international guidelines), thereby eliminating potential confounding effects of specific amino acids or their metabolites. In addition, by only including trials with similar energy delivery, we reduced potential confounding effects related to differences in energy provision.

The present meta-analysis does have limitations. The three recent large RCTs included (one of which was a cluster randomised trial) make up ~85% of the patients included in this review. In contrast, the other 11 RCTs contribute less than 100 patients to each group. There was also substantial variation in protein dose delivered, with mean/median protein delivery ranging from 1.20 to 1.69 g/kg/day in the greater protein group versus 0.75–1.19 g/kg/day in the lesser protein group, with only two trials achieving protein doses at the upper end (>1.6 g/kg/day) of the international guideline recommendations. Additionally, a limitation of the results of this review are that diagnostic subgroups were not evaluated - such as patients with major burns - limiting the generalizability to specific patient cohorts. Finally, the variability in how protein prescriptions and delivery were normalised to body weight across trials is a limitation, with some trials using actual body weight, others using ideal body weight, and several trials not specifying the method used. There is no universally accepted approach to adjusting weight for patients who are overweight/obese, with discrepancies reported in the literature as to the method used in clinical practice [50].This inconsistency may have introduced heterogeneity in the reported protein doses and affected the comparability of results across trials.

4.2. Future directions

The included trials assessed protein dose delivered throughout the ICU stay, achieving a median duration of nutrition intervention of up to 10 days. It is important to emphasize that the impact of protein dose in the post-critical illness phase, such as following ICU and hospital discharge, is still uncertain. The results of this SRMA may be strengthened by the conduct of an individual patient data meta-analysis, which will allow for more precise evaluation of effect estimates and explore subgroup effects more accurately.

Finally, future trials exploring enteral protein dose include the currently recruiting REPLENISH trial, which compares very high protein EN (supplemental protein added to standard EN to achieve protein doses of 2.0–2.4 g/kg/day) versus moderate protein EN (standard EN with no supplemental protein to achieve protein doses of 0.8–1.2 g/kg/day) commenced from day 5 of ICU admission, on 90-day all-cause mortality [51,52]. Conversely, future high quality RCTs should explore the impact of lower protein doses at or even below that recommended in healthy individuals (0.8 g/kg/day) during the entire ICU stay, in comparison with the current guideline recommendations of 1.2 g/kg/day during critical illness [8,9].

5. Conclusion

This systematic review and meta-analysis of RCTs in critically ill patients compared enteral delivery of protein doses delivered recommended within international guidelines (1.2–2.0 g/kg/day) to delivery below international guidelines (<1.2 g/kg/day), providing increased certainty of evidence. These results suggest

Fig. 5. Forest plot of subgroup analyses
(a) Patients receiving EN plus supplemental PN versus patients receiving exclusive EN.
(b) Patients with AKI versus patients with no AKI/not known to have AKI.

that greater protein delivery does not improve clinical outcomes compared with lesser protein delivery, and greater protein delivery may be associated with higher mortality in patients who develop AKI.

Author contributions

Matthew Summers: conceptualisation, design, acquisition, interpretation of the data, writing – original draft and review and editing, final approval and agreement of accountability.

Julia Bels: acquisition, interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Amalia Karahalios: design, acquisition, analysis, interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Rukshala Gunaratne: analysis, interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Jeffrey Presneill: interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Mark Plummer: interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Zheng-Yii Lee: interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Daren Heyland: interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Dieter Mesotten: interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Christian Stoppe: interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Marcel van de Poll: interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Sandra Peake: interpretation of the data, writing – review and editing, final approval and agreement of accountability.

Adam Deane: conceptualisation, design, interpretation of the data, writing – original draft and review and editing, final approval and agreement of accountability.

Lee-anne Chapple: conceptualisation, design, acquisition, interpretation of the data, writing – original draft and review and editing, final approval and agreement of accountability.

No one eligible for authorship has been excluded from the list of authors.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2026.106665.

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