High protein provision of more than 1.2 g/kg improves muscle mass preservation and mortality in ICU patients: A systematic review and meta-analyses

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Meta-analyses

High protein provision of more than 1.2 g/kg improves muscle mass preservation and mortality in ICU patients: A systematic review and meta-analyses

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SUMMARY

Background: ICU patients lose muscle mass rapidly and maintenance of muscle mass may contribute to improved survival rates and quality of life. Protein provision may be beneficial for preservation of muscle mass and other clinical outcomes, including survival. Current protein recommendations are expert-based and range from 1.2 to 2.0 g/kg. Thus, we performed a systematic review and meta-analysis on protein provision and all clinically relevant outcomes recorded in the available literature.

Methods: We conducted a systematic review and meta-analyses, including studies of all designs except case control and case studies, with patients aged ≥18 years with an ICU stay of ≥2 days and a mean protein provision group of ≥1.2 g/kg as compared to <1.2 g/kg with a difference of ≥0.2 g/kg between protein provision groups. All clinically relevant outcomes were studied. Meta-analyses were performed for all clinically relevant outcomes that were recorded in ≥3 included studies.

Results: A total of 29 studies published between 2012 and 2022 were included. Outcomes reported in the included studies were ICU, hospital, 28-day, 30-day, 42-day, 60-day, 90-day and 6-month mortality, ICU and hospital length of stay, duration of mechanical ventilation, vomiting, diarrhea, gastric residual volume, pneumonia, overall infections, nitrogen balance, changes in muscle mass, destination at hospital discharge, physical performance and psychological status. Meta-analyses showed differences between groups in favour of high protein provision for 60-day mortality, nitrogen balance and changes in muscle mass.

Conclusion: High protein provision of more than 1.2 g/kg in critically ill patients seemed to improve nitrogen balance and changes in muscle mass on the short-term and likely 60-day mortality. Data on long-term effects on quality of life are urgently needed.

1. Background

Mechanically ventilated patients in the intensive care unit (ICU) depend on enteral or parenteral feedings as nutritional support. A wide range of studies on nutrition in ICU patients have been performed on e.g. type, timing and nutrients, among which protein are represented. A high protein provision is suggested to limit loss of muscle mass, which occurs rapidly in ICU patients because of limited protein synthesis and activated muscle proteolysis [1,2]. By minimizing muscle loss, survival rates and quality of life may be improved [3]. A high protein provision may however also limit autophagy, possibly leading to an inverse effect [4]. Current protein

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recommendations are expert based and range from 1.2 to 2.0 g/kg [5,6]. It is even more difficult to provide evidence-based recommendations for subgroups of patients [7–9].

Four systematic reviews on the topic of protein provision in the critically ill were previously conducted [10–13]. Hoffer and colleagues first aimed to set a safe upper limit for protein provision in 2012 (n = 13), including multiple study designs, and found 2.0–2.5 g/kg to be safe for most ICU patients [10]. Davies et al. (2017) (n = 14) found no effect of protein provision on mortality by studying varying amounts of delivered protein [11]. In 2020, Fetterplace et al. (n = 6) studied protein provision ≥1.2 and <1.2 g/kg in relation to pre-established outcomes (i.e. muscle mass at ICU or hospital discharge and mortality), and found no effect [12]. The most recent systematic review was performed by Lee et al. (2021) (n = 19), who compared protein doses ranging from 0.24 g/kg to 1.69 g/kg in randomized controlled trials (RCT's), including studies which aimed to be isocaloric, in relation to clinical and patient-centered outcomes, and no effect was found [13]. The three latest systematic reviews included RCT's only, excluding a large part of performed studies [11–13]. Fetterplace et al. (2020) was the only one studying the difference between a pre-established protein intake in both groups: ≥1.2 g/kg vs. <1.2 g/kg [12].

Our aim was to perform a systematic review and meta-analyses on protein provision (≥1.2 g/kg vs <1.2 g/kg with a difference of ≥0.2 g/kg) and all clinically relevant outcomes recorded in the available literature, including a wide range of study designs.

2. Material & methods

This review was carried out according to the Nordic Nutrition Recommendations (NNR) 2022 structure and rationale of qualified systematic reviews [14]. The protocol has been filed on 31 October 2021 in the International Prospective Register of Systematic Reviews under #CRD42021266852.

2.1. Eligibility criteria

Studies including patients ≥18 years with an ICU stay of ≥2 days and a administered mean amount of protein ≥1.2 g/kg as compared to <1.2 g/kg with a difference of ≥0.2 g/kg between protein provision groups were eligible to be included in this review. Studies with enteral and/or parenteral and oral nutrition regimes were included whereas studies on exclusively intravenous amino acid infusions or exclusively oral nutrition were excluded. Case control and case study designs were excluded, as well as conference abstracts, seminar reviews and expert opinions. In case of studies reported in any other language than English or the unavailability of a full-text to the reviewers, studies were excluded as well.

2.2. Information sources and search strategy

Searches were conducted in PubMed, Embase (via Ovid) and Cochrane Central Register of Controlled Trials (CENTRAL) from 2002 to 19 October 2022. Reference lists were screened for backward citations. Forward citation searches were carried out for all included studies using Web of Science. More information on the search strategy is described in Supplementary File 1-A.

2.3. Selection process

Study inclusion and risk of bias assessment were carried out by two independent reviewers (JA and IR). Data extraction of the included studies was split between reviewers after which the reviewers checked each other's records. A pilot of the search strategy was carried out in 10% of studies originating from the first search, after which modification of the search strategy was not indicated. In case of missing or unclear data that was crucial for inclusion of the study, corresponding authors were contacted. Any discrepancies between the reviewers were discussed, and presented to a third reviewer (PW) if consensus was not met.

2.4. Data collection process, items and study risk of bias assessment

Data that was collected from the studies include publication details (title, author, year and country, journal), study design (aims of study, method of data collection, response rate, recruitment methods, eligibility criteria, duration of study), details of study patients (number, diagnostic group, sex, BMI, age, Acute Physiology and Chronic Health Evaluation (APACHE) II/IV or Sequential Organ Failure Assessment (SOFA) score), intervention measures (type of feeding, duration of intervention, protein delivery (g/kg), energy delivery (kcal/kg)) and data for all clinically relevant outcomes. Risk of bias assessment was undertaken using the Revised Cochrane's Risk of Bias tool for RCT's, ROBINS-I tool for non-randomized trials and Risk of Bias for Nutrition Observational studies tool for observational studies [15–17].

2.5. Outcome measures

The main outcome was mortality at any point of time. Additional outcomes were all clinically relevant outcomes mentioned in eligible articles. Outcomes that were reported in <3 studies were not described in this review.

2.6. Statistical analysis

Meta-analysis was performed for all outcomes reported in ≥3 studies. R Studio version 4.2.1 and tidyverse, meta, metaphor, dmetar and devtools packages were used. For dichotomous outcomes, the pooled estimates risk ratio (RR) and 95% confidence intervals (95% CI) for ≥1.2 g/kg versus <1.2 g/kg was calculated, regardless the design of the study, resulting in a more conservative effect estimate for retrospective studies. For continuous outcomes, heterogeneity was studied by I^2 statistic. The random effects model (REM) by the DerSimonian and Laird method was studied as a result of the heterogeneity regarding the difference in intervention (g/kg) and study population of included studies [18]. Publication bias was assessed by a funnel plot for visual inspection and Egger's test [19]. Outcomes that were reported as medians and interquartile range in the original studies were recalculated as means and standard deviation using Wan's estimation [20]. In the event that studies reported separate outcomes for multiple groups within one protein provision group (subgroups of <1.2 g/kg or ≥1.2 g/kg), combined mean and standard deviation was recalculated [21]. Statistical significance was set at p=<0.05.

3. Results

3.1. Search results

The search strategy identified 3306 records. Through additional reference and citation searches, another 1541 records were found. After the removal of duplicates, 3015 records were excluded based on title and abstract screening. In total, 269 full-text articles were assessed for eligibility of which 240 records were excluded for various reasons. A flow diagram showing the in- and exclusion process is enclosed in Supplementary File 1-B.

3.2. Study selection

A total of 29 studies [7,8,22–48] were included of which 14 were RCT's [23,25,26,28–32,36,38,42,44,46,47], 5 were prospective observational studies [7,22,39,40,43] and 8 were retrospective studies [8,24,27,33–35,41,48]. Two studies compared a prospective observational cohort with a retrospective cohort [37,45].

3.3. Study characteristics

The included studies were published between 2012 and 2022. Diagnostic groups varied from mixed [7,8,22–25,29,30,32,33,35–39,41–43,45,47,48], medical [40], surgical [31,46], traumatic brain injury [44], brain injury [28], septic [7], non-septic [7] and COVID-19 [27]. Time frames of measured protein provision varied from 2 to 4 days to total ICU stay. The vast majority provided enteral nutrition or a combination of enteral- and parenteral nutrition [7,8,22–25,27–34,38–48]. Four studies also included oral nutrition [26,35–37]. Two studies, Badjatia et al. (2020) and Nakano et al. [37], co-treated patients in the high protein group with neuro-electrical muscle stimulation [26,37]. In the study by De Azevedo et al. (2021), patients in the high protein group received cycle ergometry daily [30]. Study characteristics are presented in Table 1. In total, 7190 patients were included of whom 1972 received ≥1.2 g/kg, and 5218 received <1.2 g/kg. Patient characteristics are presented in Table 2.

Outcomes reported in the included studies were ICU-, hospital-, 28-day-, 30-day, 42-day, 60-day, 90-day and 6-month mortality, ICU- and hospital length of stay (LOS), duration of mechanical ventilation, vomiting, diarrhea, gastric residual volume, pneumonia, overall infections, nitrogen balance, changes in muscle mass, destination at hospital discharge, physical performance and psychological status. All outcomes are presented in Supplementary File 2.

3.4. Risk of bias assessment

For the included RCT's, the quality of the majority of studies was considered to have some concerns, mostly due to non-blinding of the intervention and the lack of pre-published statistical analysis plans [23,25,26,28–31,36,38,42,44,46,47]. One RCT was considered to have low concerns [32]. The quality for the observational studies mostly had serious concerns due to low scores on the confounding domain. Two observational studies had a moderate risk of bias [35,39]. Three studies had a critical risk of bias due to deviations from the intended intervention or evident differences in baseline statistics [27,34,48]. An overview of risk of bias assessments are presented in Supplementary File 3.

3.5. Mortality

Mortality was reported in 25 studies [7,8,22,23,25–34,36,37,39–43,45–48] of which 12 studies reported ICU mortality [7,22,25,29–31,33,39,40,42,43,47], 12 studies reported hospital mortality [7,25,27,30,33,34,37,40,42,43,45,46], 10 studies reported 28-day mortality [23,28,29,31,32,36,41–43,48], 1 study reported 30-day mortality [45], 1 study reported 42-day mortality [42], 4 studies reported 60-day mortality [8,28,32,40], 4 studies reported 90-day mortality [23,26,29,41] and 3 studies reported 6-month mortality [8,23,30].

A difference in favour of high protein was only found for 60-day mortality (RR 0.72, 95% CI 0.52 to 0.99; I^2 = 14%, p = 0.32 for

Table 1
Included studies: study designs.

Author	Year	Country	Study design	Route of feeding	Feeding Duration	Study Population
Allingstrup [22]	2012	Denmark	P	EN/PN	ICU stay	Mixed
Allingstrup [23]	2017	Denmark	RCT	EN/PN	≤90 days	Mixed
ApSimon [24]	2020	Canada	R	EN	First 5 days	Mixed
Badjatia [26]	2020	USA	RCT	EN/ON	9–14 days	Neurological
Buckley [27]	2021	USA	R	EN	Mean of 7 days	COVID-19
Carteron [28]	2021	France	RCT	EN	10 days	Brain injury
Chapple [29]	2021	Australia, New-Zealand	RCT Multicenter	EN	≤28 days	Mixed
De Azevedo [25]	2019	Brazil	RCT	EN/PN	≤14 days	Mixed
De Azevedo [30]	2021	Brazil	RCT	EN/PN	≤14 days	Mixed
Dresen [31]	2021	Germany	RCT	EN/PN	28 days	Surgical
Fetterplace [32]	2018	Australia	RCT	EN/PN	≤15 days	Mixed
Franzosi [33]	2012	Brazil	R	EN/PN	7 days	Mixed
Kim [34]	2020	South Korea	R	EN/PN	ICU stay	Neurological
Lin [48]	2022	China	R Multicenter	EN/PN	≤7 days	Mixed
Looijaard [8]	2019	The Netherlands	R	EN/PN	2–4 days	Mixed
Matsushima [35]	2021	Japan	R	EN/PN/ON	7 days	Mixed
Nakamura [36]	2020	Japan	RCT	EN/PN/ON	10 days	Mixed
Nakano [37]	2021	Japan	P/R	EN/PN/ON	10 days	Mixed
Rugeles [38]	2013	Colombia	RCT	EN	7 days	Mixed
Salciute-Simene [39]	2021	Lithuania	P	EN	ICU stay	Mixed
Song [40]	2017	South Korea	P	EN/PN	7 days	Medical
Suzuki [41]	2020	Japan	R	EN/PN	≤7 days	Mixed
Van Zanten [42]	2018	Belgium, France, The Netherlands	RCT Multicenter	EN/PN	7 days	Mixed
Weijs [43]	2012	The Netherlands	P	EN/PN	≥5 days	Mixed
Weijs [7]	2014	The Netherlands	P	EN/PN	≥4 days	Mixed
Xiong [44]	2021	China	RCT	EN/PN	7 days	Traumatic brain injury
Yeh [45]	2017	USA	P/R	EN	≤14 days	Mixed
Yeh [46]	2020	USA	RCT	EN	ICU stay	Surgical
Zhang [47]	2022	China	RCT	EN	ICU stay	Mixed

EN = enteral nutrition, ON = oral nutrition, P = prospective study, PN = parenteral nutrition, P/R = prospective retrospective study, R = retrospective study, RCT = randomized controlled trial.

Table 2
Included studies: patient characteristics and nutrition information.

Author	Protein Group	N	Male (%)	Age	BMI	APACHE II/IV* or SOFA** score	Protein (g/kg), (Mdn)* or range**	Energy (kcal/kg)
Allingstrup (2012) [22]	≥1.2 g/kg	38	NI	56.7 ± 18.5	25.9 ± 5.0	22.1 ± 6.8	1.46 ± 0.29	27.2 ± 6.7
	<1.2 g/kg	38	NI	62.1 ± 15.4	26.7 ± 4.7	21.9 ± 5.9	1.06 ± 0.23	24.7 ± 5.7
	<1.2 g/kg	37	NI	59.7 ± 17.4	24.0 ± 3.9	23.2 ± 7.4	0.79 ± 0.29	21.7 ± 6.7
Allingstrup (2017) [23]	≥1.2 g/kg	100	65	63 [51–72]	22 [20–26]	8 [6–11]**	1.47 [1.13–1.69]*	NI
	<1.2 g/kg	99	60	68 [52–75]	22 [20–25]	8 [5–10]**	0.50 [0.29–0.69]*	NI
ApSimon [24]	≥1.2 g/kg	20	80.0	56.8 ± 12.4	43.0 ± 13.9	18.8 ± 7.1	1.46 ± 0.35	17.1 ± 4.3
	<1.2 g/kg	20	75.0	53.3 ± 16.6	31.4 ± 6.5	21.4 ± 4.3	1.10 ± 0.24	19.0 ± 4.3
Badjatia [26]	≥1.2 g/kg	12	42.0	60 ± 8	27 ± 3	20 ± 5	1.51 ± 0.47	20.0 ± 7.1
	<1.2 g/kg	13	38.0	58 ± 14	27 ± 6	18 ± 10	0.88 ± 0.36	19.8 ± 9.9
Buckley [27]	≥1.2 g/kg	5	NI	67 ± 22	30 ± 3	23 ± 6	1.2 ± 0.4	17 ± 3
	<1.2 g/kg	17	NI	65 ± 13	30 ± 7	23 ± 7	0.8 ± 0.8	11 ± 9
Carteron [28]	≥1.2 g/kg	100	67	57 [44–65]	26 [23–29]	NI	1.3 ± 0.4	20.2 ± 6.3
	<1.2 g/kg	95	56	55 [40–65]	26 [23–29]	NI	1.1 ± 0.3	21.0 ± 6.5
Chapple [29]	≥1.2 g/kg	58	67	60 [50–72]	29 [26–33]	22 [16–26]	1.52 ± 0.52	19.2 ± 6.5
	<1.2 g/kg	58	76	61 [46–68]	30 [25–34]	22 [16–27]	0.99 ± 0.27	19.6 ± 5.4
De Azevedo (2019) [25]	≥1.2 g/kg	57	59.7	65.0 ± 18.8	NI	81.1 ± 32.4*	1.69 [1.33–1.80]	NI
	<1.2 g/kg	63	50.8	67.4 ± 18.9	NI	77.2 ± 30.7*	1.13 [0.97–1.34]	NI
De Azevedo (2021) [30]	≥1.2 g/kg	87	61	67.6 (17.8)	NI	5 (3–9)**	1.48 [1.25–1.64]	NI
	<1.2 g/kg	94	49	65.3 (19.7)	NI	6 (3.7–8)**	1.19 [0.96–1.26]	NI
Dresen [31]	≥1.2 g/kg	21	71.4	66.0 ± 16.0	NI	NI	1.5 ± 0.5	27.0 ± 8.9
	<1.2 g/kg	21	71.4	64.0 ± 15.0	NI	NI	1.0 ± 0.4	24.6 ± 9.8
Fetterplace [32]	≥1.2 g/kg	30	77.0	55.0 ± 13.0	30.0 ± 7.1	22.0 ± 6.2	1.20 ± 0.3	21 ± 5.2
	<1.2 g/kg	30	70.0	57.0 ± 16.0	29.0 ± 5.3	20.0 ± 5.9	0.75 ± 0.11	18 ± 2.7
Franzosi [33]	≥1.2 g/kg	92	53.4	59.0 ± 19.0	26.0 ± 6.2	21.0 ± 7.0	1.4 [0.9–2.1]	23.9 [9.5–39.5]
	<1.2 g/kg	34	58.5	61.0 ± 12.0	25.8 ± 8.3	23.0 ± 9.0	0.4 [0–1.0]	9.5 [0.7–24.1]
Kim [34]	≥1.2 g/kg	35	37.1	56.4 ± 15.7	22.5 ± 3.8	21 [15–24]	1.58 ± 0.4	25.6 ± 7.3
	<1.2 g/kg	140	53.6	60.3 ± 18.1	23.0 ± 4.0	24 [19–28]	0.58 ± 0.48	11.7 ± 9.5
Lin [48]	≥1.2 g/kg	126	60.3	62 [52–78]	21.5 [18.4–23.5]	20 [15–25]	1.56 [1.37–1.86]	30.5 [23.8–34.9]
	<1.2 g/kg	1146	65.4	64 [51–76]	22.5 [20.8–24.2]	18 [14–23]	0.78 [0.66–0.92]	18.9 [15.9–22.4]
	<1.2 g/kg	919	70.1	61 [46–72]	23.4 [21.6–25.4]	19 [14–24]	0.40 [0.29–0.49]	10.4 [7.2–12.8]
Looijaard [8]	≥1.2 g/kg	73	62.0	62 [55–72]	23.5 [21.5–24.9]	23.0 ± 8.0	1.39 ± 0.17	30.3 ± 6.5
	<1.2 g/kg	372	70.0	67 [54–75]	24.5 [22.8–26.8]	25.0 ± 8.0	0.62 ± 0.33	16.6 ± 6.9
	≥1.2 g/kg	34	47.0	50 [30–63]	24.5 [23.0–25.8]	23.0 ± 8.0	1.38 ± 0.14	28.9 ± 4.0
	<1.2 g/kg	260	63.0	52 [37–65]	25.7 [23.5–27.8]	21.0 ± 7.0	0.61 ± 0.31	16.0 ± 6.8
Matsushima [35]	≥1.2 g/kg	20	55.0	72.5 [26–91]	20.1 [11.8–42.4]	25.4 ± 6.4	1.3 ± 0.2	25.2 ± 5.2
	<1.2 g/kg	20	60.0	71.0 [40–85]	21.5 [15.3–38.1]	25.4 ± 5.7	0.7 ± 0.2	15.2 ± 5.3
Nakamura [36]	≥1.2 g/kg	60	58.3	68.3 ± 14.3	21.3 ± 3.9	18.6 ± 8.1	1.5*	NI
	<1.2 g/kg	57	66.7	67.9 ± 14.9	21.5 ± 4.5	18.2 ± 6.0	0.8*	NI
Nakano [37]	≥1.2 g/kg	56	69.6	70.9 ± 14.5	NI	17.7 ± 6.5	1.4 ± 0.4	20.1 ± 5.7
	<1.2 g/kg	45	75.6	70.9 ± 14.2	NI	16.0 ± 5.7	0.8 ± 0.3	16.6 ± 5.6
Rugeles [38]	≥1.2 g/kg	40	55.0	53.3 ± 19.5	23.7 ± 3.3	13.9 ± 4.8	1.4	12
	<1.2 g/kg	40	60.0	55.7 ± 19.5	24.3 ± 4.4	15.1 ± 6.2	0.76	14
Salciute-Simene [39]	≥1.2 g/kg	50	70.0	63.5 ± 22.5	27.9 ± 8	20 ± 8	1.2 ± 0.4	NI
	<1.2 g/kg	23	78.3	65.7 ± 10.4	28.6 ± 7	19 ± 7	1.0 ± 0.3	NI
Song [40]	≥1.2 g/kg	34	47.0	65.0 ± 16.0	18.5 ± 3.3	23.2 ± 6.6	1.3 ± 0.1	27.7 ± 4.2
	<1.2 g/kg	25	56.0	72.0 ± 12	22.2 ± 2.6	24.8 ± 7.2	0.9 ± 0.1	23.6 ± 2.0
	<1.2 g/kg	152	70.0	64.0 ± 13	22.9 ± 3.9	24.4 ± 7.2	0.6 ± 0.2	15.2 ± 5.0
Suzuki [41]	≥1.2 g/kg	66	66.7	68.2 ± 13.2	22.4 ± 4.1	21.7 ± 8.1	1.6 ± 0.3	25.1 ± 7.7
	<1.2 g/kg	66	62.1	66.8 ± 16.1	22.6 ± 3.6	22.6 ± 7.4	0.9 ± 0.2	22.0 ± 6.9
Van Zanten [42]	≥1.2 g/kg	22	40.9	63.9 ± 13.3	30.3 ± 4.1	25 [21–28]	1.3 [0.7–1.9]	16.6 [8.9–23.3]
	<1.2 g/kg	22	59.1	60.8 ± 15.2	30.7 ± 8.4	24 [18–27]	0.7 [0.5–0.9]	14.4 [10.9–18.8]
Weijs (2012) [43]	≥1.2 g/kg	245	53.1	62.7 ± 15.7	24 ± 6	23 ± 8	1.31 ± 0.18	NI
	<1.2 g/kg	205	55.1	63.8 ± 16.6	25 ± 5	23 ± 8	1.06 ± 0.14	NI
	<1.2 g/kg	412	72.1	62.6 ± 16.0	27 ± 6	23 ± 8	0.83 ± 0.23	NI
Weijs (2014) [7]	≥1.2 g/kg	307	60.3	61.3 ± 17.1	25.0 ± 5.8	22.5 ± 7.5	1.33 ± 0.28	NI
	<1.2 g/kg	419	64.9	63.2 ± 16.4	26.3 ± 5.2	17.9 ± 8.1	0.69 ± 0.43	NI
	<1.2 g/kg	117	64.1	64.2 ± 14.2	25.4 ± 5.8	25.4 ± 8.3	1.00 ± 0.53	NI
Xiong [44]	≥1.2 g/kg	26	65.4	48.3 ± 10.4	22.0 ± 1.4	21.3 ± 2.2	1.2–1.7**	NI
	<1.2 g/kg	27	74.1	49.4 ± 14.9	21.6 ± 1.3	21.4 ± 2.1	0.5–0.7**	NI
Yeh (2017) [45]	≥1.2 g/kg	119	71.0	60.2 ± 18.6	27.5 ± 6.6	17.1 ± 8.1	1.2 ± 0.4	18.6 ± 5.0
	<1.2 g/kg	94	71.0	62.6 ± 17.1	27.2 ± 6.3	14.0 ± 6.3	0.8 ± 0.3	16.5 ± 5.9
Yeh (2020) [46]	≥1.2 g/kg	19	95.0	49.1 ± 24.7	28.5 ± 6.7	19.6 ± 7.3	1.2 ± 0.4	15.9 ± 5.5
	<1.2 g/kg	17	71.0	50.6 ± 15.6	30.2 ± 6.1	17.5 ± 10.1	0.9 ± 0.4	14.8 ± 5.7
Zhang [47]	≥1.2 g/kg	20	60.0	64.5 ± 16.2	22.2 ± 3.9	21.8 ± 7.2	1.70 ± 0.21	33.46 ± 2.78
	<1.2 g/kg	21	85.7	69.2 ± 18.2	22.8 ± 4.4	20.5 ± 7.0	1.06 ± 0.21	25.75 ± 4.81

Values represented as M±SD. Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, BMI = Body Mass Index, NI = no information, SOFA = Sequential Organ Failure Assessment.

heterogeneity; Supplementary file 4-E, Fig. 1). Analysis showed no difference between groups for ICU mortality (RR 0.89, 95 CI% 0.73 to 1.10; $I^2 = 38\%$, p = 0.09 for heterogeneity; Supplementary file 4-A), hospital mortality (RR 0.89, 95% CI 0.73 to 1.08; $I^2 = 51\%$, p = 0.02 for heterogeneity, Supplementary file 4-B), 28-day mortality (RR 0.90, 95% CI 0.65 to 1.25; $I^2 = 54\%$, p = 0.02 for heterogeneity; Supplementary file 4-C), combined 28-, 30-, 42- and 60-day mortality (RR 0.88, 95% CI 0.65 to 1.19; I = 62%, p=<0.01 for

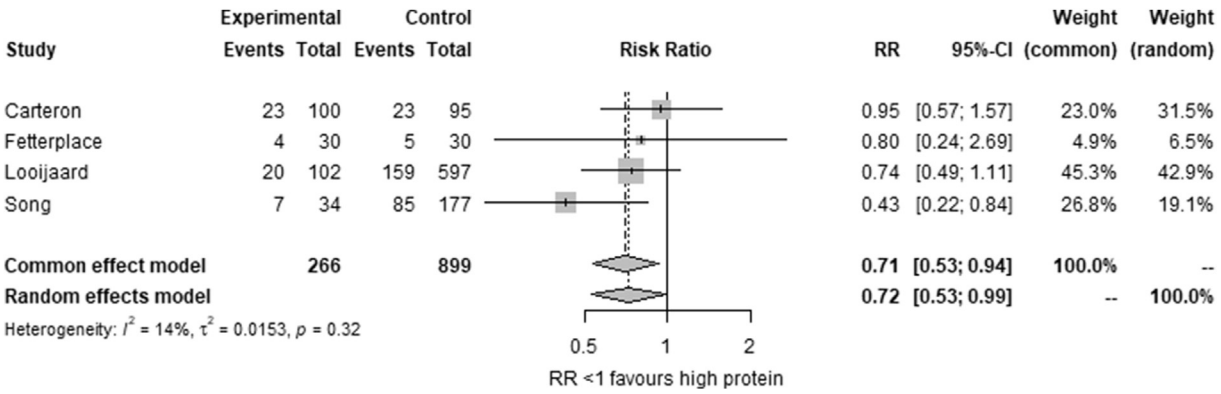

Fig. 1. Forest plot for 60-day mortality.

heterogeneity; Supplementary file 4-D), 90-day mortality (RR 0.43, 95% CI 0.07 to 2.74; I^2 = 82%, p = 0.02 for heterogeneity; Supplementary file 4-F) and 6-month mortality (RR 0.85, 95% CI 0.62 to 1.17; I^2 = 61%, p = 0.08 for heterogeneity; Supplementary file 4-G). After removal of an outlier [48] in the combined 28-, 30-, 42- and 60-day mortality analysis, the association improved (RR 0.80, 95% CI 0.62 to 1.02; I^2 = 32%, p = 0.14 for heterogeneity).

3.6. ICU- and hospital LOS

A total of 25 studies reported ICU LOS [7,8,22,23,25–32,34–43,45–47] and 18 studies reported hospital LOS [7,8,23,27,29,30,32–37,39,40,42,43,45,46]. Analysis showed no difference between groups for both ICU LOS (MD -0.0, 95% CI -1.7 to 1.7; I^2 = 80%, p=<0.01 for heterogeneity; Supplementary file 4-H) and hospital LOS (MD 1.0, 95% CI -3.7-5.7; I^2 = 80%, p=<0.01 for heterogeneity, Supplementary file 4-I). After removal of outliers [34,43,45], the association for ICU LOS (MD 0.3, 95% CI -0.7 to 1.3; I^2 = 23%, p = 0.17 for heterogeneity) and hospital LOS (MD 2.2, 95% CI -2.5 to 6.9; I^2 = 78%, p=<0.001 for heterogeneity) remained robust.

3.7. Duration of mechanical ventilation

Duration of mechanical ventilation was reported in 17 studies [7,8,25,27,28,30–32,35–40,42,43,47]. Analysis showed no difference between groups (MD 0.8, 95%CI -0.7 to 2.4; I^2 = 75%, p=<0.01 for heterogeneity; Supplementary file 4-J). After removal of an outlier [43], results remained robust (MD 0.8, 95% CI -0.7 to 2.4; I^2 = 77%, p=<0.001 for heterogeneity).

3.8. Feeding intolerance: vomiting, diarrhea, gastric residual volume

Data on vomiting was reported by 5 studies [28,29,36,42,46]. Analysis showed no difference between groups (RR 1.04, 95% CI 0.61 to 1.76, I^2 = 0%, p = 0.45 for heterogeneity; Supplementary file 4-K). Data on diarrhea was reported by 5 studies [28,29,32,36,42]. Analysis neither showed a difference between groups (RR 1.01, 95% CI 0.76 to 1.33; I^2 = 24%, p = 0.26 for heterogeneity; Supplementary file 4-L). Data on gastric residual volume, both amounts and number of times above a pre-defined volume, were reported by 6 studies [24,28,29,32,36,42]. Analysis, on the number of times gastric residual volume was above a pre-defined volume, showed no difference between groups (RR 0.92, 95% CI 0.45 to 1.92, I^2 = 51%, p = 0.11; Supplementary file 4-M). Egger's test indicated the presence of funnel plot asymmetry (p = 0.020).

3.9. Pneumonia and infections

Data on pneumonia were reported in 5 studies [23,26,28,31,36]. Analysis showed no difference between groups (RR 0.98, RR 0.77 to 1.25; I^2 = 29%, p = 0.23 for heterogeneity; Supplementary file 4-N). Data on overall infections were reported in 6 studies [23,26,31,44,45,48]. Analysis on studies that reported overall infections showed no difference between groups (RR 0.74, 95%CI 0.74 to 1.86; I^2 = 70%, p = 0.04 for heterogeneity; Supplementary file 4-O).

3.10. Nitrogen balance

Nitrogen balance was measured in 5 studies [22,26,27,34,37]. Timing of reported nitrogen balance measurements varied from day 2–4 of admission to cumulative- and average of total admission. The model showed a difference in favour of high protein (SMD 1.2, 0.3 to 2.1; I^2 = 92%, p=<0.01 for heterogeneity; Supplementary file 4-P). The forest plot for nitrogen balance is presented in Fig. 2.

3.11. Changes in muscle mass

Data on changes in muscle mass was reported by 6 studies [26,31,32,36,37,47], measured as quadriceps muscle cross-sectional area with computed tomography (CT) scan [26], quadriceps muscle layer tissue with sonography [31], mid upper arm circumference [32], femoral muscle cross sectional area with CT scan [36,37] and diaphragm volume with CT scan [47]. Changes in muscle mass were measured between baseline (day 0–2 of admission) and 5 weeks after admission. Analysis showed a difference between groups in favour of high protein (SMD 0.8, 95% CI 0.4 to 1.3; I^2 = 71%, p=<0.01 for heterogeneity; Supplementary file 4-Q). The forest plot for changes in muscle mass is presented in Fig. 3.

3.12. Destination at hospital discharge

Destinations at hospital discharge were reported in 6 studies [8,26,29,32,35,45]. Analysis on discharge to home showed no difference between groups (RR 1.18, 95% CI 0.94 to 1.48; I^2 = 8%, p = 0.36 for heterogeneity; Supplementary file 4-R).

3.13. Physical performance

Data on physical performance were presented by 9 studies [23,25,26,30,32,34–37]. Outcomes were handgrip strength (HGS) [25,32,35,37], physical component summary (PCS) after 3 months [25,30] and 6 months [23,25,30], modified Rankin Scale (mRS) after

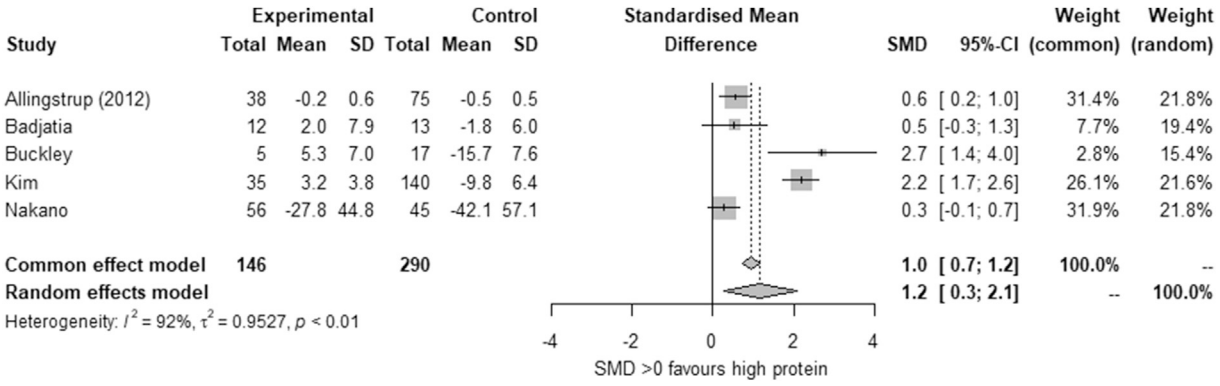

Fig. 2. Forest plot for nitrogen balance.

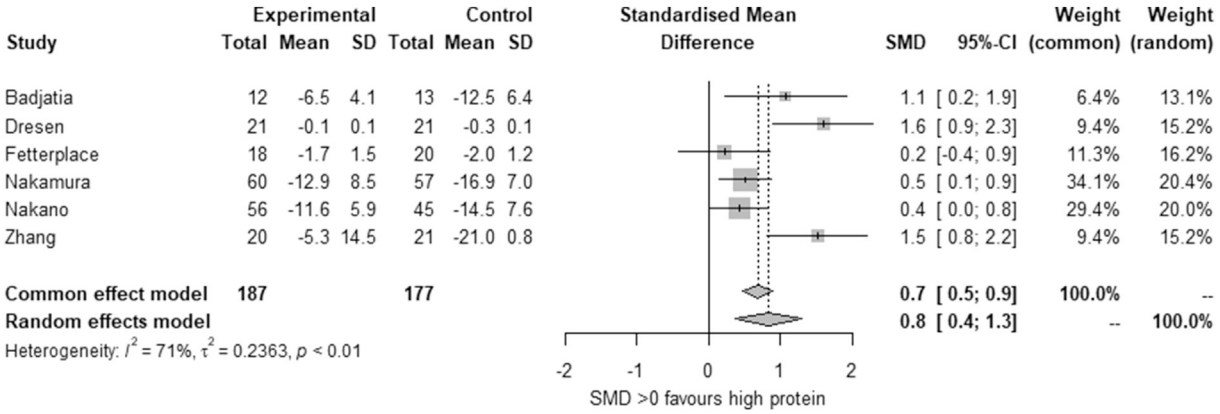

Fig. 3. Forest plot for changes in muscle mass.

14 days [26] and 90 days [26,34], short physical performance battery (SPPB) and Quality of Life [26], Physical Function in ICU test (PFIT-s) [32], Medical Research Council score (MRC sum score) [32,35,37], Functional Status Score for the ICU (FSS-ICU) [36,37], Barthel Index [36,37], persistent inflammation, immunosuppression and catabolism syndrome (PIICS) [36] and ICU mobility score (IMS) [37].

Analysis (Supplementary file 4-S) on handgrip strength showed no difference in between groups (MD 0.6, 95%CI -4.5 to 5.8, $I^2 = 60\%$, p = 0.06). Egger's test indicated the presence of funnel plot asymmetry (p = 0.007).

Meta-analysis for other physical performance outcomes than handgrip strength was not performed as various measurement methods were used. Badjatia et al. (2020) combined high protein provision and neuromuscular electrical stimulation and found increased mRS and SPPB in the high protein group at 90 days (mRS; 1 [0–2] vs. 2 [1–3], p = 0.04 and SPPB; 12 [10–12] vs. 9 [4–12], p = 0.01), but not at 14 days (mRS; 4 [2–4] vs. 4 [3–5], p = 0.5 and SPPB; 2 [0–7.8] vs. 1 [0–5], p = 0.44). Additionally, they found increased muscle atrophy to be associated with lower mRS (p = −0.4, p = 0.04) and SPPB (p = −0.31, p = 0.1) at 90 days. In the high protein provision group, they also found higher scores in the lower extremity mobility component of a Quality of Life assessment (90 ± 8 vs. 73 ± 27, p = 0.05) [26]. Kim et al. (2020) did find higher mRS scores (0–3) in the high protein group at 3 months (65.7% vs. 33.6% p = 0.001) [34]. Fetterplace et al. (2018) found no difference in PFIT-s outcomes and MRC sum scores after awakening at 15 days [32]. Matsushima et al. (2021) found higher MRC sum score (52 [48–54.5] vs. 48 [33–49.5] kg, p = 0.004) at ICU discharge in favour of the high protein group [35]. Nakano et al. (2021) performed neuromuscular electrical stimulation in the high protein group. They found no differences in MRC sum score and FSS-ICU score at ICU discharge or Barthel Index at hospital discharge. Days to reach IMS 1 also did not differ, but days to reach IMS 3 and 4 were lower in the high protein provision group (IMS 3; 3.0 [2.0–6.0] vs. 5.0 [3.0–5.8], p = 0.01 and IMS 4; 3.0 [2.0–6.0] vs. 5.0 [4.0–7.0], p = 0.02) [37]. Nakamura et al. (2021) found no difference in FFS-ICU at ICU discharge and Barthel Index at hospital discharge. The number of patients adhering to PIICS criteria at day 10 was higher in the low protein group (11.7 vs. 26.3%, p = 0.041). After stratification for treatment with and without neuromuscular electrical stimulation, results remained robust [36].

3.14. Psychological health

Psychological health measures were reported by 4 studies using diverse methods (36-Item Short Form survey, Montreal Cognitive Assessment, Quality of Life, EQ5DL). None of these studies found a difference between groups [23,26,29,36].

4. Discussion

From this review, it appears that high protein provision of ≥1.2 g/kg indeed improved nutritional outcomes like nitrogen balance and short-term muscle atrophy. It also appeared that there is a trend for a relation between the recommended protein provision of ≥1.2 g/kg and overall survival of ICU patients at various time points, particularly after ICU discharge. The latter however only substantiated with studies on 60-day mortality. As from a patient journey's point of view, it may be hypothesized that the favourable

effect of higher protein provision starts off with higher nitrogen balance leading to reduced loss of muscle mass, which then may contribute to improved 60-day survival.

The clinical importance of higher protein provision does not rely on mechanically realistic intermediate endpoints like nitrogen balance and muscle atrophy, but should preferably be demonstrated with objective hard functional and clinical outcome measures. We mainly found data on mortality (on various time-points), and mortality may not be an ideal outcome parameter. Considering ICU mortality, at least at short-term, it might be suggested that effects of higher protein provision are not expected to be present. While it is interesting to see a long-term effect of ICU nutrition on survival, it may be questionable how only a few days of improved nutrition during ICU stay may save a patients' life in the long run, as there are many other factors involved in overall survival. Also, if patients stay in the ICU for a relatively short time, nutrition has no realistic time frame to improve (or at least not worsen) nutritional status. In long-stay ICU patients, and considering a somewhat longer path of high protein provision to act on nutrition-related parameters, and beyond the acute phase of critical illness, it is more realistic to expect effect on outcomes. Whether this explains why we only find a conclusive effect on 60-day mortality remains to be confirmed.

Considering the above, it is of interest that nitrogen balance and muscle atrophy both seemed to be improved convincingly in the group that received protein provision $\geq$1.2 g/kg. This was not just observed based on a statistically significant effect size, but importantly also in the consistency among studies which all reported a mean improvement. There is a direct, realistic and theoretically framed relationship between higher protein provision and improvement of nitrogen balance as well as muscle atrophy. This may be the base for short-term as well as longer-term effects on outcomes that have never been adequately studied. One of the logic outcome measures is physical performance, but these outcomes remain inconclusive. Although a bit more challenging to measure, it might be stated that the immunological response depends on adequate provision of protein, but outcomes for pneumonia and infection also remain inconclusive. So far, no prove of harm could be detected either. This appears to be true for other nutrition related parameters like diarrhea, vomiting and gastric residual volume as well; no harm related to higher protein provision was detected. Moreover, outcomes related to duration of mechanical ventilation and length of stay in ICU or hospital stay indicated no harm as well.

Considering the relation between high protein provision and mortality in this review, it appears that this relationship is very limited when considering mixed ICU patient groups across countries and other differences. At the same time, we might conclude that no harm could be detected based on mortality; if anything, the relation between protein provision and mortality is a positive one.

As reported earlier, nutrition provision cannot be expected to be a one size fits all policy. We have suggested, based on cohort data, that septic patients may not benefit from high protein provision of $\geq$1.2 g/kg [7,9]. A pre-existing or acute kidney-dysfunction may also be reason for a profound negative effect of high protein provision [49–51], while in continuous renal replacement therapy we did find an association in favour of high protein provision [9]. In the recently published EFFORT-trial, they found a favourable effect of usual protein dose compared to high protein dose in patients with high organ failure scores on time to discharge alive and 60-day mortality [51]. It appears to be logical that an intensive nutrition therapy with high protein provision is most adequate for malnourished patients based on adequate nutritional assessment [8,52]. It is in subgroups categorized to muscle mass that we report an advantage of high protein provision of $\geq$1.2 g/kg (or not), including adequate adjustment for energy overfeeding [8]. This in turn may be a relevant tipping point for survival to be improved or not. However, analysis in subgroups in our review was not possible. Lee et al. (2021) included studies with similar energy intake between groups that compared high vs. low protein provision in their review. They found no improvements in clinical or patient-centered outcomes. As they did not adhere to specific protein provision cut-off points but selected studies on higher versus lower protein provision, they included different studies and analyzed patients as being in the high protein provision group, that in the current review would be considered as being in the <1.2 g/kg protein provision group (and vice versa). Nevertheless, studies with mean or median protein provision of $\geq$1.2 g/kg that were included in the current review, will also comprise of patients with both protein provision $\geq$1.2 g/kg and <1.2 g/kg.

4.1. Strengths and limitations

We included a variety of research methods, leading to a higher number of included studies, compared to previously performed reviews, and thereby increased power of our analysis [10–13]. Besides, it has previously been described that effect estimates of observational studies may not be different from those obtained in RCT's [53]. In case of uncertainties on reported data, we contacted the author of the concerning study.

One may criticize the application of meta-analyses in studies with high heterogeneity. Nevertheless, we upfront decided to use a random effects model as studies had substantially different methods. Furthermore, the vast majority of included observational studies had at least a serious risk of bias due to confounding. Our meta-analyses were not adjusted for disease severity and energy provision even though we know these factors substantially influence patient outcomes. Not surprisingly, in most studies, the high protein group also received higher energy provision which may lead to underestimation of the favourable effect of high protein provision [7]. We did not specify a timeframe in which the amount of protein had to be administered. This resulted in the inclusion of studies with timeframes varying from 2 to 4 days to total ICU stay. However, previous studies have shown a time-dependent effect of protein provision in critically ill patients [54]. Nonetheless, information regarding timing of protein nutrition is lacking in the majority of studies, making specification of a timeframe for protein not feasible in the current review. We call future studies to provide information regarding the timing of protein provision initiation to make exploration of time-dependent effects of protein provision in critically ill patients possible. Besides, this review includes studies that were not designed to study different protein provision groups. Additionally, we did not account for whether studies adjusted protein provision for patients with BMI $\geq$27.5. Even though there were no sufficient subgroups specified in studies to perform subgroup analysis in e.g., this should be taken into account as we previously showed that one size does not fit all, and optimal protein provision may be different between patient groups [7–9].

5. Conclusion

In this systematic review, we included 29 studies with different research methods and a variety of patient groups, with a total of 7190 patients. We found an association in favour of high protein provision in critically ill patients on nitrogen balance, changes in muscle mass and 60-day mortality when comparing $\geq$1.2 vs. <1.2 g/kg protein provision. We did not find an association for ICU mortality, hospital mortality, 6-month mortality, ICU LOS, hospital LOS, duration of mechanical ventilation, vomiting, diarrhea, gastric residual volume, pneumonia, overall infections, discharge

destination, physical performance and psychological status. As our analyses were not adjusted for disease severity and energy provision, the favourable effect of high protein may be underestimated.

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Conflict of Interest

The authors declare that they have no competing interest.

Author contributions

IR, JA, PW, AB, and FEJ designed the study. IR and JA obtained the data, performed statistical analysis, and drafted the paper. PW and AB coordinated the study. PW, AB and SS helped to draft the paper. All authors read and approved the final paper.

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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.2023.09.026.

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