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REVIEW

Nutritional Interventions on Physical Functioning for Critically Ill Patients: An Integrative Review

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Background: Poor physical functioning (PF) is a common issue among critically ill patients. It was suggested that reasonable nutrition accelerates PF recovery. However, the details and types of nutritional interventions on the PF of different intensive care unit (ICU) patients at present have not been well analyzed yet. This study aimed to systematically synthesize nutritional interventions on PF in different ICU populations.

Methods: Whittemore and Knafl's framework was employed. PubMed, EMBASE, Web of Science, CINAHL Plus with Full Text, and Cochrane Library were searched to obtain studies from January 2010 to September 2020, with a manual search of the included studies' references. Record screening, data extraction, and quality appraisal were conducted independently by each reviewer before reaching an agreement after discussion.

Results: Twelve studies were included reporting the effects of early parenteral nutrition, early enteral nutrition, early goal-directed nutrition, early adequate nutrition, higher protein delivery, higher energy delivery, low energy delivery, energy and protein delivery, intermittent enteral feeding on PF like muscle mass, muscle strength, and function. Function was the most common outcome but showed little improvements. Muscle strength outcomes improved the most. The mechanically ventilated were the most popular target ICU population. The commenced time of the interventions is usually within 24 to 48 hours after ICU admission.

Conclusion: Research on nutritional interventions on critically ill patients' PF is limited, but most are of a high level of evidence. Few intervention studies specified their evidence basis. Qualitative studies investigating timeframe of initiating feeding, perspectives of the patients' perspectives and caregivers are warranted to advance research and further discuss this topic.

Keywords: nutrition, physical functioning, intensive care units

Introduction

Physical functioning (PF) is the physical abilities allowing functional independence and those related to movement.[1] Poor PF, including decreased muscle mass, muscle strength, and function, is a frequent problem in critically ill patients,[2–4] since skeletal muscle proteolysis is enhanced due to the catabolism caused by the hypermetabolic state of acute illness,[5,6] which is associated with adverse clinical outcomes including infections, difficult weaning from mechanical ventilation (MV), a longer length of stay, increases mortality, higher financial costs, decreased quality of life of survivors.[4,7] Rapid muscle loss is independently correlated with increased intensive care unit (ICU) mortality and in-hospital mortality in ICU patients.[8] A study suggested that decreased PF was defined as the most critical outcome by ICU survivors,[9] who often experience permanent functional disability due to ICU-

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acquired weakness (ICU-AW).[10] These, along with skeletal muscle's immunologic and metabolic functions, highlight the importance of preserving muscle mass and promoting PF during acute illness.[11,12] Moreover, as Herridge pointed out, surviving critical illness is not the happy ending we imagined for our patients.[13]

Besides, ICU patients often have difficulty eating independently and are at high risk of malnutrition and lean body mass loss,[14] rendering them needing nutritional support most frequently among all patients.[15] It was found that optimal amounts and timely provision of nutritional intake relate to faster PF recovery and reduced infectious complications, time of MV, and mortality.[16–19] Reasonable nutrition is fundamental for ICU patients to maximize physical programs' benefits and support recovery.[14] While inadequate nutritional therapy results in loss of lean body mass, lack of adequate physical activity leads to muscle weakness and inability to mobilize.[20] Nevertheless, it is quite challenging to plan the right nutritional intervention for ICU patients.[15] The best way of performing nutritional therapy remains controversial.[21] Even though there are several nutritional guidelines specialized for the critically ill, such as the guidelines of the European Societies for Clinical Nutrition and Metabolism (ESPEN) (2018),[22] the European Society of Intensive Care Medicine (ESICM) (2017),[23] and the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) (2016),[24] adherence to these standards in clinical practice is limited. There is a significant discrepancy among nutritional interventions, hindering the interpretation of results, comparisons of trials, and the formation of strong evidence-based recommendations.[21,25] Furthermore, as a patient-centered outcome, PF outcomes are vital in clinical trials evaluating nutritional interventions.[26] These speak to the significance of understanding what types of nutritional interventions have been implemented on the PF (eg, muscle mass, muscle strength, function) of different categories of ICU patients at present, to provide a reference for clinical practice and future research design and promote the functional ability of the critically ill.

The effects of certain specific types of nutritional interventions in ICU patients, such as enteral nutrition, parenteral nutrition (PN), energy, and protein delivery, etc., were explored by several systematic reviews as well as meta-analyses,[7,27–29] with some targeting PF while others the overall clinical outcomes (with or without PF). However, to our knowledge, almost none described and summarized the various types of nutritional interventions of this topic across studies, hindering better understanding and future design of the nutritional interventions on the PF for ICU patients.

This integrative review aims to identify and analyze details of different nutritional interventions on PF for critically ill patients with different characteristic (eg, with organ failure, contradictions of enteral nutrition (EN), etc.) over the past decade. So as to benefit the critically ill more instead of simply helping them survive the critical illness.

Methods

Design

This review was guided by Whittemore and Knafl's framework[30] for integrative reviews, which is composed of five steps: (1) problem identification, (2) literature search, (3) data evaluation, (4) data analysis, and (5) presentation. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[31] were applied to present the flow diagram of the identification, screening, exclusion, and inclusion of the literature. Abstracts, conference proceedings, dissertations, commentaries, non-peer-reviewed journal articles, research protocols, case reports, reviews (not including systematic reviews and meta-analyses), and researches that did not study PF were excluded. According to ICF framework,[32] which was introduced by the World Health Organization (WHO) to provide a unified and standard language for the description of health and health-related well-being,[1] PF is composed of muscle mass, muscle strength, and function.[33] Muscle mass is a passive nonvolitional outcome enabling quantification of muscle morphology.[33] Muscle strength, as a dynamic measure, provides greater detail on the patient's level of impairment.[33] Function reflects activity limitation within the ICF framework.[33] If the intervention topic of the sub-analysis of one trial was the same as the original trial, it would be combined with the original trial and treated as one (eg, trial A + sub-analyses B, C of trial A= trial A). The details of the inclusion and exclusion criteria of this research are provided in Table 1.

Five electronic databases were included in this integrative review: PubMed, EMBASE, Web of Science,

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Human patients ≥18 years of age	• Conference proceedings, dissertations, commentaries, non-peer reviewed journal articles, research protocols, pilot studies, case reports, reviews (except systematic reviews and meta-analyses)
• Patients receiving treatment in the ICU	• Combined with other types of interventions (eg, exercise, electrical stimulation)
• Featured a nutritional intervention, which is defined in this study as 1) route of administration: enteral nutrition, parenteral nutrition; 2) the administration of non-pharmacological/non-immune-modulating agents: calories, protein, micronutrients, micronutrients etc.; 3) timing for initiation of feeding; 4) continuous or intermittent feeding; and 5) feeding speed and amount[15,26,73,74]	• Exploring the effects of any of 1) pharmacological agents: insulin, growth hormone, ghrelin agonists, anabolic steroids etc.; 2) immune-modulating agents: glutamine, selenium, fish oil, zinc, vitamin D etc.; 3) antioxidants: vitamin C, vitamin E etc.; and 4) monitoring/management of nutritional effects: GRV, gastrointestinal syndrome (diarrhea, abdominal distension, abdominal pain, nausea or vomiting, etc.), blood electrolytes (potassium, magnesium etc.) etc.
• Reported a physical functioning outcome, including muscle mass, muscle strength (eg, muscle wasting, muscle weakness, fatigue, hand grip etc.), function (eg, walk, daily living tasks, etc.)[21,33]	
• Reported in English language	

Abbreviations: ICU, intensive care unit; GRV, gastric residual volume.

CINAHL Plus with Full Text, and Cochrane Library, with time-limited from January 2010 to September 2020. Reference lists of the included studies were manually searched. Subject headings, key terms, and the complete search strategy can be accessed in Supplementary File 1.

Data Extraction and Quality Appraisal

The level of evidence (LOE) for each study was evaluated independently by two researchers (WZ and SR) using the Rating System for the Hierarchy of Evidence for Intervention and Treatment Questions by Melnyk and Fineout-Overholt.[34] The LOE of the literature is designated as follows: systematic reviews or meta-analyses of randomized controlled trials (RCT), and clinical guidelines based on systematic reviews or meta-analyses (Level 1); well-designed RCTs (Level 2); controlled trials with no randomization (Level 3); case-control or cohort study (Level 4); systematic reviews of descriptive and qualitative studies (Level 5); single descriptive or qualitative study (Level 6); expert opinions (Level 7) (not included in this review).[34]

Data Analysis

The articles were classified into a literature matrix that included author, year, country, duration, design, commenced time, total sample size, target population, description of the intervention, PF measure, finding, and level of evidence.

Results

Article Characteristics

An initial search of the literature generated 3109 articles. A total of 12 articles were included in this integrative review after final screening and quality appraisal. The PRISMA checklist[31] was utilized to outline the retrieval process (see Figure 1).

Almost 84% (n = 10) of included studies were published from 2015 to 2020. Four (30.77%) studies were conducted in Australia, one (7.69%) was conducted in New Zealand, Belgium, Japan, United States, Denmark, United Kingdom, and China each, and two (15.38%) not applicable. The numbers of studies conducted in single-center and multi-center settings were both five (41.67%).

Article types consisted of six (50%) randomized controlled trials, three (25%) descriptive studies, two (16.67%) systematic reviews, and one (8.33%) non-randomized control trial. One hundred to two hundred (n = 4, 33.33%) was the common sample size of study followed by 0 to 100 (n = 3, 25%), above 1000 (n = 2, 16.67%), and 200 to 1000 (n = 1, 8.33%). The LOE of the articles was two (16.67%) for Level 1, six (50%) for Level 2, one (8.33%) for Level 3, and three (25%) for Level 6 (see Table 2).

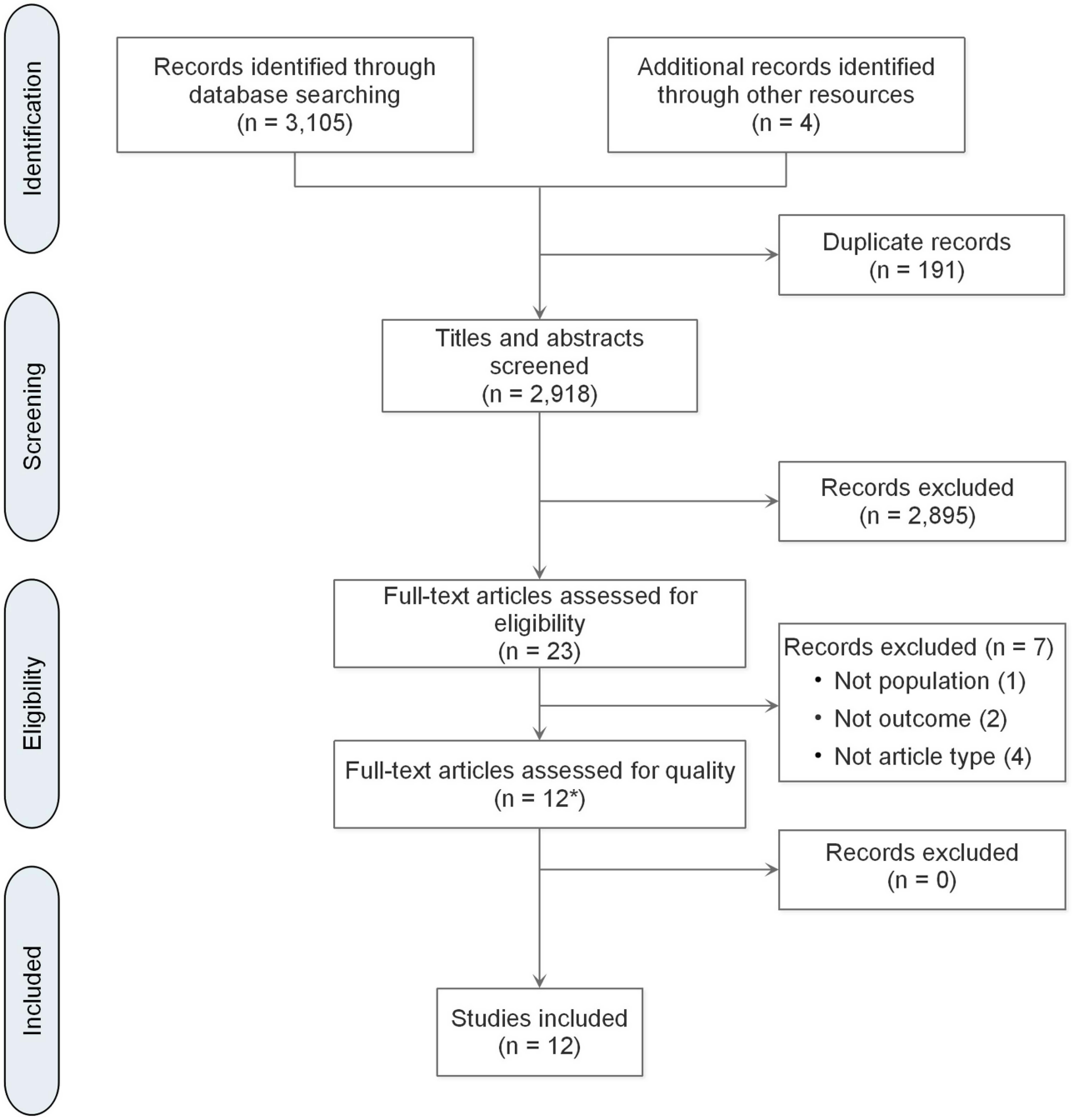

Figure 1 PRISMA flow chart. *Original Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study and four sub-analyses of it were treated as one EPaNIC study. **Notes:** PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). Creative Commons.[31]

Participant Characteristics

The target population in the included studies were ICU patients with mechanically ventilated (n = 6, 50.00%), chronic critical illness (n = 1, 8.33%), relative contraindications to early EN (n = 1, 8.33%), and a requirement of PN (n = 1, 8.33%) (see Table 2). Three (25.00%) articles included all types of ICU patients.

Synthesis of Interventions, Outcomes, and Results

Description of Nutritional Interventions

Altogether, nine nutritional interventions were evaluated in 12 studies. Table 2 shows that the majority of nutritional intervention type is early PN (n = 2, 16.67%) and low energy delivery (n = 2, 16.67%). Other interventions like

Table 2 The Characteristics of Included Studies

Characteristic	Number	Percentage (%)
Publication year		
2015–2020	10	83.33
2010–2014	2	16.76
Country of origin		
Australia	4	30.77
New Zealand	1	7.69
Belgium	1	7.69
Japan	1	7.69
United States	1	7.69
Denmark	1	7.69
United Kingdom	1	7.69
China	1	7.69
N/A	2	15.38
Location of study		
Single-center	5	41.67
Multi-center	5	41.67
N/A	2	16.66
Study design		
RCT	6	50.00
Descriptive study*	3	25.00
Systematic review	2	16.67
Non-randomized control trial	1	8.33
Sample size		
0–100(39)	3	25.00
>100–200	4	33.33
>200–1000	1	8.33
>1000	2	16.67
N/A	2	16.67
Commenced time		
Within 24 hours after ICU admission	3	23.08
Within 48 hours after ICU admission	3	23.08
Within 72 hours after ICU admission	2	15.38
Unspecified	3	23.08
Others	2	15.38
Target ICU population		
Mechanically ventilated**	6	50.00
Chronic critical illness	1	8.33
Relative contraindications to early enteral nutrition (EN)	1	8.33
A requirement of parenteral nutrition (PN)	1	8.33
ALL***	3	25.00
Nutritional intervention type		
Early PN	2	16.67
Early EN	1	8.33
Early goal-directed nutrition (EGDN)	1	8.33
Early adequate nutrition	1	8.33
Higher protein delivery	1	8.33
Higher energy delivery	1	8.33
Low energy delivery	2	16.67
Energy and protein delivery	1	8.33
Intermittent enteral feeding	1	8.33
N/A	1	8.33
Physical functioning measure(s)		
Function	12/1[#]	54.55/8.33[##]
Muscle strength	6/3[$]	27.27/50.00[$]
Muscle mass	4/1[&]	18.18/25.00[&&]
LOE		
I	2	16.67
II	6	50.00
III	1	8.33
VI	3	25.00

Notes: *Descriptive study consists of prospective and retrospective studies. **Mechanically ventilated consists of mechanically ventilated and expected to receive enteral nutrition for at least 2 days/acutely admitted/with sepsis/ with multiorgan failure/for at least 48 hours/ for at least 24 hours. ***ALL means that all ICU patient was qualified to enroll in a study. [#]Total function outcome measure (n)/total function outcome measure improved (n). [##]Total function outcome measure (%)/total function outcome measure improved (%). [$]Total muscle strength outcome measure (n)/total muscle strength outcome measure improved (n). [$]Total muscle strength outcome measure (%)/total muscle strength outcome measure improved (%). [&]Total muscle mass outcome measure (n)/total muscle mass outcome measure improved (n). [&&]Total muscle mass outcome measure (%)/total muscle mass outcome measure improved (%).

Abbreviations: N/A, not applicable (systematic reviews/meta-analyses); RCT, randomized control trial; ICU, intensive care unit; LOE, level of evidence.

early EN, early goal-directed nutrition (EGDN), early adequate nutrition, higher protein delivery, higher energy delivery, energy and protein delivery, and intermittent enteral feeding were one (8.33%) each. Almost half of the interventions are characterized as early nutrition delivery (41.67%). Nearly half concerned with energy and protein delivery (41.67%). Details of the interventions are presented in Table 3.

Among the seven intervention trials identified, the energy targets of six were individualized, namely using equations (the Harris-Benedict equation,[35] the Quark RMR Indirect Calorimeter,[36] and the modified Penn State Equation[37] in three trial respectively), indirect calorimetry (around 25 kcal/kg/d (24 kcal/kg/d for the higher protein group, 26 kcal/kg/d for the lower protein group),[38] 25–30 kcal/kg/d (25 kcal/kg/d initially)[39] and 1.5 kcal/kg/h[40]) in three trials respectively, etc. to

Table 3 Summary of Included Studies

Study, Duration	Design, Sample (n), Commenced Time, Provider(s)	Target ICU Population	Description of Intervention	Physical Functioning Measure(s)	Finding(s)	LOE
1) Casaer,[41,75] Hermans,[76,77] Vanhorebeek[78] et al*. 2011–2013 Belgium	Multi-center RCT N = 4640 Within 48 hours after ICU admission (early-initiation group), after day 8 (late-initiation group) Trained experts (organ-failure and sepsis scores), research nurses, assistants, attending physicians, residents, and nurses (securing informed consent, ensuring protocol compliance and patient care)	All	- Experimental group: early parenteral nutrition (PN): PN initiated within 48 hours after ICU admission. The target for total energy intake was 400 kcal per day on ICU day 1 and 800 kcal per day on day 2. On day 3, parenteral nutrition was initiated, with the dose targeted to 100% of the caloric goal through combined enteral and parenteral nutrition. Caloric needs calculations are based on corrected ideal body weight, age and gender. The maximum caloric goal for all patients was 2880 kcal per day. A protocol for the early initiation of enteral nutrition was applied to both groups, and insulin was infused to achieve normoglycemia. - Control group: late PN: PN initiated on day 8. Tolerate macronutrient deficit. 5% glucose solution in a volume equal to the hydration of the early PN group. If enteral nutrition was insufficient after 7 days in the ICU, parenteral nutrition was initiated on day 8 to reach the caloric goal.	Function (walk, daily living tasks), muscle mass (muscle loss, myofiber integrity, muscle atrophy), muscle strength (muscle weakness)	1) Distance on 6-min walk test - ≠ (n = 4640) 2) Activities of daily living - ≠ (n = 4640) 3) Wasting of skeletal muscle - ∨ (n = 31) 4) Amount of adipose tissue within the muscle compartments - ∨ (n = 31) 5) Incidence of ICU-AW at first evaluation - ∨ (n = 558) 6) Recovery from ICU-AW - ∨ (n = 558) 7) ICU-AW at worst and last MRC evaluation - ∨ (n = 558) 8) Myofiber density - ∨ (n = 142) 9) Autophagosome formation marker microtubule-associated protein light chain 3 (LC3)-II/LC3-I - ∨ (n = 142) 10) Myofiber cross-sectional area - ≠ (n = 142) 11) Expression of mRNA encoding contractile myofibrillary proteins - ≠ (n = 142) 12) E3-ligase expression - ≠ (n = 142)	II

2) Doig et al[35] 2013 Australia, New Zealand 2 months	Multi-center RCT N = 1372 Within 24 hours of ICU admission Attending clinician, site investigators, and safety and data monitoring committee	Relative contraindications to early enteral nutrition (EN)	- Experimental group: early PN: provide parenteral nutrition within 24 hours of ICU admission from a ready-to-mix 3-chamber bag, with starting rates and rate increases defined by study protocol and trace elements, minerals, and vitamins added as clinically appropriate. Targets were to be achieved by study day 3. The protocol reminded clinicians to consider additional vitamins and minerals on each study day and to consider enteral or oral nutrition on study day 3. The protocol also defined timing and rates for parenteral nutrition discontinuation. Energy targets were calculated using the Harris-Benedict equation, allowing for stress factors. Targets were capped at 35 kcal/kg/d, and obese patients were fed to their ideal body weight (BMI=21). - Control group: standard care: the attending clinician selected the route, starting rate, metabolic targets, and composition of nutrition to be provided to patients receiving standard care based on current practice in their ICU.	Muscle strength (muscle wasting), function	1) Subjective Global Assessment (SGA) of muscle wasting - ∧ 2) RAND-36 physical function - ≠	II

(*Continued*)

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Table 3 (Continued).

Study, Duration	Design, Sample (n), Commenced Time, Provider(s)	Target ICU Population	Description of Intervention	Physical Functioning Measure(s)	Finding(s)	LOE
3) Ferrie et al[38] 2016 Australia 10 days or until ICU discharge	Single-center RCT N = 119 Commenced time undefined ICU dietitian, study investigators, nursing staff, and a single operator (ultrasound measurements)	Requirement of PN and expected to receive PN for at least 3 days	- Experimental group: higher protein/amino acid provision: receive blinded PN solutions containing amino acids at 1.2 g/kg. Target infusion rate was set at 0.92 mL/h per kg body weight, aiming to supply daily energy at 24 kcal/kg. - Control group: standard amino acid intake: receive PN solutions containing amino acids at 0.8 g/kg. Target infusion rate was set at 0.92 mL/h per kg body weight, aiming to supply daily energy at 26 kcal/kg.	Muscle strength (hand grip, fatigue), muscle mass (muscle thickness)	1) Grip strength at ICU discharge - ≠ 2) Grip strength at ICU discharge at study day 7 - ∧ 3) Chalder scale (fatigue score) - ∧ 4) Sum of 3 muscle sites (forearm, biceps and thigh) - ∧ 5) Forearm muscle thickness on ultrasound - ∧ 6) Biceps muscle thickness on ultrasound - ≠ 7) Thigh muscle thickness on ultrasound - ∧	II
4) Reid et al[40] 2016 Australia 12 months	Multi-center RCT N = 39 Commenced time unspecified Investigators (unspecified)	Mechanically ventilated and expected to receive enteral nutrition for at least 2 days	- Experimental group: augmented early nutritional energy delivery: receive a 1.5-kcal/kg/h enteral nutrition solution for 10 days. Protein and fiber contents in the 2 groups were similar (protein: around 0.056 g/mL, fiber: around 0.015 g/mL). The study enteral nutrition was delivered at a goal rate of 1 mL • kg ideal body weight (IBW) 21^{-1} • $h21^{-1}$ in both groups. - Control group: standard energy intake: receive a 1.0-kcal/mL enteral nutrition solution at the same rate with the experimental group.	Function (mobility, daily living tasks)	1) SF-36v2 physical function summary score - ≠ 2) EQ-5D-5L Physical Component Summary - ≠ 3) EQ-5D-5L usual activities - ≠ 4) EQ-5D-5L mobility - ≠	II

5) Allingstrup et al[36] 2017 Denmark 6 months	Single-center RCT N = 199 Within 72 hours of ICU admission Investigators, clinicians, research nurses, and ICU specialists	Mechanically ventilated (acutely admitted)	- Experimental group: early goal-directed nutrition (EGDN): measure nutritional requirements by indirect calorimetry (Quark RMR Indirect Calorimeter, COSMED, Rome, Italy) and 24-h urinary urea aiming at covering 100% of requirements from the first full trial day using enteral and parenteral nutrition. Protein was provided at least 1.5 g/kg/day during admission, regardless of urea excretion. Calories from any propofol administration were included in the calculation of total calories. Enteral nutrition was initiated within 24 hours of randomization and supplemented parenterally if necessary, to reach goal requirements. In the case of sustained hyperglycemia, authors reduced the provision of glucose, and at plasma urea above 20 mmol/l, they reduced the provision of protein by 0.2 g/kg/day. - Control group: standard care: provide 25 kcal/kg/day by enteral nutrition. If this was not met by day 7, patients were supplemented with parenteral nutrition.	Function	1) Physical component summary (PCS) score of the Medical Outcomes Study 36-item short form health survey at 6 months - ≠	II

(*Continued*)

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Table 3 (Continued).

Study, Duration	Design, Sample (n), Commenced Time, Provider(s)	Target ICU Population	Description of Intervention	Physical Functioning Measure(s)	Finding(s)	LOE
6) Lambell et al[7] 2018 Country N/A Duration N/A	N/A (systematic review) Systematic review N = N/A Within 2 weeks of ICU admission Provider N/A	All	This systematic literature review was conducted to examine the association of energy and/or protein provision on changes in skeletal muscle mass in critically ill patients. Key databases were searched up until March 2016 to identify studies that measured skeletal muscle mass and/or total body protein (TBP) at 2 or more time points during acute critical illness (up to 2 weeks after an ICU stay).	Muscle mass	1) The association between energy and protein delivery and changes in skeletal muscle mass - ≠	I
7) Liu et al[39] 2018 China 28 days	Single-center Non-randomized control trial N = 63 Within 48 hours of ICU admission Provider unspecified	Mechanically ventilated with sepsis	- Experimental group: early enteral nutrition (EN): receive enteral nutrition treatment within 48 hours of being admitted to ICU. The target calories and protein contents in this study were 25 kcal/kg/d (Ideal body weight) and 1.2 g/kg/d, respectively. The EN tolerance was assessed every day to gradually increase the dose to gain the goal of calorie 25–30 kcal/kg/d and protein content 1.2–2.0 g/kg/d. the Warming infusion of the nutrient solution was performed at uniform speed using the reverse Trendelenburg position. - Control group: delayed enteral nutrition: received enteral nutrition treatment after 48 hours of admission.	Muscle strength (muscle weakness)	1) Incidence of ICU-AW - ∧	III

8) Fetterplace et al[48] 2019 Australia 24 months	Single-center Descriptive (prospective observational) N = 47 Within 48 hours of ICU admission Provider N/A	Mechanically ventilated (for at least 48 hours)	In this prospective study, the cumulative energy deficit was determined from artificial nutrition delivery compared to targets. Measurements included: (1) At recruitment and ICU discharge, weight, fat-free mass, and malnutrition. (2) At awakening and ICU discharge, physical function (Physical Function in Intensive Care Test-scored), and muscle strength (Medical Research Council sum-score (MRC-SS).	Muscle strength (muscle weakness), function	1) The association between cumulative energy deficit (per 1000 kcal) and greater odds of ICU-AW - ∧ 2) The association between cumulative energy deficit and decrease in physical function scores- ∧	VI
9) Taverny et al[21] 2019 Country N/A Duration N/A	N/A (systematic review) Systematic review N = N/A Commenced time undefined Provider N/A	All	This systematic literature review was conducted to describe the outcomes used in recent randomized controlled trials (RCTs) assessing nutritional interventions in critically ill patients. The objective was to set the foundation for the development of a core set of outcome measures for use in future RCTs.	Function (daily living tasks, upper limb function (dexterity), lower limb function (walking or mobility), spinal function, walking distance), muscle strength	1) Physical function - ∨ 2) Muscle strength - ∨	I
10) Yatabe et al[47] 2019 Japan 11 months	Multi-center Descriptive (observational) N = 398 Commenced time undefined Provider N/A	Mechanically ventilated (for at least 24 hours)	This observational study aimed to assess the nutritional management in Japanese ICUs and investigate the impact of nutritional management and rehabilitation on the physical outcome (the author defined good physical status as more than end sitting and poor physical status as bed rest and sitting). Participants were divided the into 2 groups, the good physical status group (good group) and poor physical status group (poor group) for analysis of the secondary outcome.	Function (more than sitting)	1) The association between low caloric intake (less than 10 kcal/kg/day) until day 3 and good physical status - ∧	VI

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Table 3 (Continued).

Study, Duration	Design, Sample (n), Commenced Time, Provider(s)	Target ICU Population	Description of Intervention	Physical Functioning Measure(s)	Finding(s)	LOE
11) McNelly et al[37] 2020 United Kingdom 10 days	Multi-center RCT N=121 Within 24 hours of ICU admission Dietitian, investigator, ICU nurse, and physiotherapist	Mechanically ventilated with multiorgan failure	- Experimental group: intermittent enteral feeding: receive intermittent enteral feeding from six 4-hourly feeds per 24 hours, administered via nasogastric tube using a syringe over 3 to 5 min. Depending on each Trust's approved supplier, either Ensure Compact (energy content, 2.4 kcal/mL; protein content, 0.104 g/mL; Abbott Nutrition) or Fortisip Compact Protein (energy content, 2.4 kcal/mL; protein content, 0.144 g/mL; Nutricia) was used, with a range of starter bolus sizes of 60 to 80 mL according to the participants' initial individual nutritional targets (energy targets measured by the modified Penn State Equation; protein target at least 1.2 g/kg/day). - Control group: standard continuous enteral feeding: total volume of feed administered over 24 hours, as per local feeding protocols.	Muscle mass (muscle loss), function (sit-to-stand, bed-to-chair transfer)	1) 10-day loss of rectus femoris muscle cross-sectional area determined by ultrasound - ≠ 2) Physical function milestones (sit-to-stand test post-ICU, bed-to-chair transfer post-ICU) - ≠	II
12) Rosenthal et al[49] 2020 United States 12 months	Single-center Descriptive (retrospective) N = 168 Within 24 hours of ICU admission Provider N/A	Chronic critical illness	This retrospective study aimed to document how chronic critical illness (CCI) patients (who received early, adequate nutrition per an established surgical ICU protocol) responds to adequate evidence-based ICU nutrition.	Function (physical activity)	1) Functional status (Zubrod score) - ∨ 2) Short Physical Battery Testing - ∨	VI

Notes: ∧Outcome improved after the intervention. ∨Outcome worsened after the intervention. ≠Outcome unchanged after the intervention. *Original Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study[41] and four sub-analyses of it.[75–78]

Abbreviations: LOE, level of evidence; N/A, not applicable (systematic reviews/meta-analyses); RCT, randomized control trial; ICU, intensive care unit; ICU-AW, intensive care unit-acquired weakness.

dynamically measure individuals' energy targets. Only one trial[41] of the seven ones had its energy targets fixed in specific amounts (400 kcal on day 1, 800 kcal on day 2, and 2880 kcal/d after day 2).

Four out of the seven intervention trials had individualized protein targets (0.8 g/kg or 1.2 g/kg,[38] 1.2–2.0 g/kg/d (1.2 g/kg/d initially),[39] at least 1.2 g/kg,[37] and at least 1.5 g/kg[36]), which were set based on the patients' weight only. One of the rests of the seven trials had a fixed protein target (0.056 g/mL).[40] The others did not specify their protein delivery targets.

Most of the seven trials (five) were carried out by multidisciplinary teams, of which clinicians and nursing staff were the most common members. Two teams[37,38] included dietitians, and one[37] of them had a physiotherapist to assess the PF. The above five studies all clarified each team member's corresponding tasks, of which one study by McNelly et al[37] demonstrated most clearly by showing a chart of this information. Two[39,40] of the seven trials specified neither the professions of the research members nor their responsibilities.

Among the seven intervention studies, three[36,38,41] were designed based on well-accepted evidence. The one by Casaer et al[41] was based on the guidelines for early initiation of parenteral nutrition, but without mentioning which specific guidelines were utilized. The protein delivery of the trial conducted by Ferrie et al[38] was based on the 2006 ESPEN guidelines,[42] the 2009 ESPEN guidelines,[43] and the 2009 ASPEN guidelines.[44] The energy expenditure measurement of the one by Allingstrup et al[36] was based on the 2009 ESPEN guidelines,[45] the 2016 SCCM, and the ASPEN guidelines.[46]

The most common commenced time for included articles was within 24 hours and within 48 hours after ICU admission (n = 3, 23.08%, both). Within 72 hours after ICU admission was the least (n = 2, 15.38%), and many were unspecified (n = 3, 23.08%).

Description of Physical Functioning Related Outcome Measures

Function (n = 12, 54.55%), including walk, sitting and daily living tasks, was the primary PF measure, followed by muscle strength (n = 6, 27.27%, consisting of muscle weakness, handgrip, fatigue, etc.) and muscle mass (n = 4, 18.18%, consisting of muscle thickness and muscle loss, etc.).

Description of Physical Functioning Related Results

Function

Among the nine studies that studied the influence of nutritional interventions on function, only one multi-centered observational study by Yatabe et al[47] found that low caloric intake (less than 10 kcal/kg/day) until day three was associated with good physical status in mechanically ventilated (for at least 24 hours) patients, which was defined as more than end sitting.

Five studies[35–37,40,41] found no significant effect on function from nutritional interventions. One prospective observational study[48] found that cumulative energy deficit was associated with decreased function scores in the mechanically ventilated (for at least 48 hours).

One systematic review[21] found that nutritional interventions deteriorated ICU patients' function. Similarly, one retrospective study[49] found that adequate evidence-based ICU nutrition worsened chronic critical illness (CCI) patients' function.

Muscle Strength

Three studies showed that muscle strength benefited from nutritional interventions, including early PN in patients with relative contraindications to early EN,[35] higher protein/amino acid provision in those requiring PN,[38] early EN in mechanically ventilated patients with sepsis.[39] One prospective observational study[48] found that cumulative energy deficit was associated with greater ICU-AW odds in mechanically ventilated patients (for at least 48 hours).

However, the RCT by Casaer et al[41] demonstrated that an early PN intervention was detrimental to muscle strength. One systematic review[21] found that nutritional interventions worsened muscle strength.

Muscle Mass

Only the one by Ferrie et al[38] found nutritional interventions beneficial to muscle mass (sum of 3 muscle sites (forearm, biceps, and thigh), forearm muscle thickness, thigh muscle thickness), but with no significant effect on biceps muscle thickness.

The one by Casaer et al[41] found that early EN either worsened muscle mass or have no significant effect on it. One systematic review[7] found no significant association

between energy and protein delivery and changes in skeletal muscle mass. One RCT[37] found that intermittent enteral feeding did not significantly affect muscle mass in mechanically ventilated patients with multiorgan failure.

Discussion

To our knowledge, this is the first integrative review to focus exclusively on studies concerned with nutritional interventions on PF for ICU patients. It shows that the related studies over the past decade have been mostly quantitative, of which are primarily multicentered RCTs and have ample sample sizes, allowing them to show the actual effect and generalizability of their interventions and demonstrating a relatively high level of evidence of the studies of this topic. One included systematic review was conducted in 2016 but was published two years later, with the inclusion of only six studies, of which merely two were RCTs, while others were observational ones, which might render the evidence found in this included systematic review inconclusive. We found that most included studies were published in recent five years, suggesting that this realm is a relatively new research hotspot. It is an inevitable trend to explore more about the nutritional interventions on PF in the future to contribute to the form of evidence to deliver nutrition in a way that prevents the deterioration of the PF of critically ill patients. It thus adds to the possibility of a better quality of life after a critical illness.[50]

Given the rapid onset of muscle wasting within hours of MV,[50] it is imperative to pay close attention to the PF-related changes of mechanically ventilated ICU patients, which is corresponding with what we found in our review that the majority of the target ICU population is the mechanically ventilated. Nevertheless, as pointed out by Chapple et al,[51] the number of patients who are either never mechanically ventilated or only ventilated for a short time during their ICU stay is growing, while current nutrition guidelines provide limited recommendations specific for this population. Therefore, the nutritional needs of this population are to be ascertained in future trail designs. As recommended by the ESPEN guideline (2018),[22] which is one of the most updated nutritional guidelines for the critically ill to date, the nutrition delivery should be commenced within 48h of ICU admission, and almost half of the included studies in this review set their commenced time accordingly and have focal considerations of early administration of nutrition. However, one limitation of the guidelines to date is that they concern little to the effects of nutrition on ICU patients' PF. So there is great possibility that the most suitable time to start feeding benefiting PF lies elsewhere (like 17 h for instance). Therefore, though with studies of high quality in the field in terms of the feeding commenced time (eg, early/late PN/EN), the best commenced time of nutritional intervention on PF still requires further exploration. More large-scale observational studies concerning the starting timeframe are warranted, before the design of experimental studies, to find the possible suitable commenced time in different populations, either the distinct types of ICU population (eg, disease type, mechanically ventilated or not) or the various races of population (eg, country, northern or the southern part of one country). In order to get a knowing of what timeframe is possibly better to start what kind of nutrition for the sake of the patient's PF through observation in the first place, as well as which category of patients might benefit more from certain interventions. Then plan and carry out experimental studies to further pin down the suitable time, nutrition therapy, and the population afterwards.

More than half of the reviewed studies' assessed PF are function, which showed little improvement. This finding, both on the proportion and the result of function, is similar to what has been found in a systematic review by Taverny et al.[21] One possible reason why almost all function outcomes failed to improve is that this PF outcome is relatively hard to measure in ICU patients than in general wards. For one thing, the needed treatments to the patient's critical illness (eg, sedation, continuous renal replacement therapy (CRRT)) along with the caregivers' fear of causing adverse events (eg, fall, tube peeling) impedes the patient to perform the movements (eg, walking, transfer from bed to chair, using the toilet) needed for measuring his or her function.[50,52] For another, the critical illness itself, which commonly needs a relatively long time to recover and usually will not be fully healed even when the patient is going to be discharged from ICU, render the muscle strength and activity tolerance of the patient too limited to do the required movements even when it is the time that he or she is ready to get out of ICU.[53] Besides, even after the critical illness is cured, the function impaired during the disease still requires some time to recover from fulfilling higher movement goals,[54] of which the degree of difficulty is much greater than their last achieved ones, take, for example, the Barthel Index which is common in function assessment of ICU patients,[55,56] from lying in bed

incapable of walking to propelling a wheelchair independently at least 50 yards.[55]

Among the six muscle strength outcomes measured, half were improved by nutritional interventions, and most muscle strength outcomes were muscle weakness primarily assessed by the Medical Research Council sum score (MRC-SS), which is commonly used for the detection of ICU-AW.[57] This satisfying improvement is probably due to the relative easiness for the critically ill patient to perform the movements (eg, wrist extension, elbow flexion, knee extension) required for assessing muscle strength in contrast to the assessment of function since the patient do not have to get out of bed to do these movements.[58] Furthermore, achieving a higher goal in terms of muscle strength (eg, from resisting partial force to resisting full force when extending the wrist) is less demanding than that of function.

In terms of the measurement of energy target/energy expenditure (EE), around half of the included interventional trials applied predictive equations, and about half adopted indirect calorimetry. Indirect calorimetry is preferred over predictive equations in most updated critical nutrition guidelines (A.S.P.E.N. (2016)[24] and ESPEN (2018)[22]), due to the significant inaccuracy (up to 60%) of predictive equations as a result of the difficulty of assessing body weight accurately.[22,59] In the absence of indirect calorimetry, oxygen consumption (VO_2) from pulmonary arterial catheter or carbon dioxide production (VCO_2) from the ventilator can be more accurate on the evaluation of EE than predictive equations, though less than indirect calorimetry.[22] If indirect calorimetry, VO 2 or VCO 2 measurements are all unavailable, simple weight-based equations (eg, 20–25 kcal/kg/d) may be preferred.[22]

Two out of seven intervention studies did not specify their protein delivery when their intervention is mainly on energy delivery. Two out of seven intervention studies did not specify what discipline the persons made up of their research team and what responsibility each member took. Despite the relatively small proportion these studies account for, it is worth noting that researchers should provide a detailed report of the provision of energy and protein, as well as the details of the constituent disciplines of the team members and their respective responsibilities in their research since transparency on these details, will promote the uptake of research evidence into practice.[60–62] Otherwise, questions such as "How much protein/energy should we deliver to our patients?" and "Which discipline of personnel should we include in our research team and what kind of task he or she should shoulder?" will be challenging to answer and therefore hamper both the design and the replication of the intervention.

However, what is uncertain is if the researchers reflect that their interventions are founded on principles of specific guidelines. Only 28.57% of the intervention studies stated their theoretical base clearly, which limits understanding of nutritional interventions on PF in ICU patients within a broader context, including the significant transition of interventions into practice.[63,64]

Implications for Future Research

Future nutritional interventions on PF in ICU patients are especially encouraged to incorporate the following details. Firstly, the intervention should be based on well-accepted evidence, which should be specified in the report to guarantee the research's rationality and provide further guidance in the implementation process. Moreover, every delivered nutrition ingredient's details are to be explicated even if only one component is the primary intervention to promote the intervention's generalization. Also, the disciplines of the research members and their respective tasks should be stated clearly. The addition of muscle strength-related measures (ICU-AW especially) can also be considered since this PF is more possible to be performed within the ICU setting.

As mentioned above, more large-scale observational studies concerning the starting timeframe are required to find the possible suitable commenced time of feedings in different populations, facilitating the further design of experimental studies.

Besides, it is pointed out by a research that the optimal nutritional management among ICU patients with lower body mass index (BMI) remains unclear,[47] calling for more researches in terms of this population since it will benefit most Asian population and lean Western and Oceanian population. Additionally, the nutritional management of ICU patients who are not mechanically ventilated or only ventilated for a short period requires further exploration.[51]

Most included studies adopted quantitative approaches in investigating nutritional interventions on PF in ICU patients, but almost all failed to take the feeling and experience of the patients and/or their caregivers into account, so were the qualitive ones, not in line with the wholistic health concept advocated by the World Health Organization (WHO).[65] As suggested in a study, patients might be

burdened by the nutritional treatment both during hospitalization and after discharge.[66] Considering that qualitative research could contribute to practical intervention delivery insights, this review highlights the need for more qualitative studies investigating the perspectives of the patients and/or their caregivers, in an effort to treat the person as a whole. Current qualitative studies have investigated the association between nutrition and the PF of ICU patients in either a nation (ie, Japan)[47] or certain types of ICU patients (ie, chronic critical illness patients).[49] However, depth interviews are needed to provide more insight into the patients' own experience of having certain types of nutrition delivery and especially on their PF in or out of ICU, as well as their caregivers' (medical staffs, family members) perspectives and experience when taking care of them, which is practically ignored in the current studies. Nutritional interventions on PF in the critically ill could then be optimized and improve the patients' outcomes, and meanwhile, taking into account the patients' and the caregivers' feeling and experience rather than focus merely on the symptoms. Moreover, it is suggested that the incorporation of co-design including both clinicians/researchers and patients should be adopted in the trial design of nutritional interventions on the critically ill,[51,67] which is likely to benefit from the investigation of patients'/caregivers' insights. Theories about wholistic health could be applied in various types of research studies concerning this topic.

Apart from nutritional interventions solely, it is recommended that bundled or synergistic therapies should be taken into consideration,[51] such as combined nutritional and physical interventions, as this enhanced synergistic treatment may increase muscle mass, and improve activities of daily living within a short period after discharge for ICU patients.[66]

Furthermore, our results can be used as a guideline for design of the research and practice related to nutritional interventions on the critically ill's PF, such as the energy/protein target, patient populations, PF, etc.

Limitations

First of all, it is essential to highlight that only a minimal number of sources were identified for inclusion, a challenging factor for conducting a systematic review or meta-analysis and drawing clear conclusions from the evidence. However, the aim of this review is to summarize the details of the researches concerning the nutritional intervention on functioning of critically ill patients, promoting a more comprehensive understanding of this topic, in order to provide references for future studies, instead of paying more attention to the level of evidence of the current researches and pinning down the effects of this type of intervention like in the case of systematic reviews.[68,69] Moreover, compared to scoping reviews, which aim to identify and mapping certain characteristics or concepts of studies as well as analyze the knowledge gaps,[70,71] the integrative review design, focusing on using diverse data sources to develop holistic understanding of the topic of interest,[72] suits our aim best. In addition, even though muscle mass, muscle strength, and function, constituting the PF analyzed in this review, share a common background, mechanisms leading to their impairments are not similar. So we analyzed these outcomes separately to make up for this shortcoming. Besides, protocols and pilot studies were excluded in this review, considering the former's lack of results and the latter's flimsy evidence. However, this review included both primary and secondary studies with a range of objectives, as well as various research types (quantitative studies, qualitative studies and systematic reviews/meta-analyses), and thus it offers broad coverage of literature in this area.

Conclusions

This review demonstrates that research on nutritional interventions on critically ill patients' PF is limited in number, but most of these are large-scale RCTs of a high level of evidence. However, though of high quality, there are still gaps to be filled in this field. Firstly, few intervention studies specified their evidence basis. Qualitative studies are warranted to further investigate the timeframe of feeding commencement in the best interest of PF. Additionally, the management of ICU patients with lower BMI lacks evidence of this topic. Moreover, the existing research highlights a need for more studies to the wholistic health of the related patients, especially qualitative studies, looking into the perspectives of the patients themselves and their medical caregivers as well as their families during or after the provision of certain types of nutrition to the patients, to advance research and to trigger a further discussion on this topic.

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