Clinical Nutrition 46 (2025) 119–130

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized Control Trials

Feasibility challenges in protein supplementation research: Insights from the convalescence of functional outcomes after intensive care unit stay in a Randomised Controlled Trial

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ARTICLE INFO

Article history:
Received 30 October 2024
Accepted 17 January 2025

Keywords:
Critical care
ICU survivors
Post-ICU
PICS
Nutrition
Protein

SUMMARY

Background & aims: Dietary protein supplementation may benefit physical outcomes in post-intensive care unit (ICU) patients suffering ICU-acquired weakness (ICU-AW). This study examines the impact of a six-week protein supplementation compared to an isocaloric carbohydrate on physical functioning outcomes in post-ICU patients with a follow-up of 12 weeks after ICU discharge. This paper presents descriptive data, feasibility outcomes, and the barriers faced while conducting this nutritional intervention study in post-ICU patients.

Methods: This two-arm, randomised, double-blind controlled intervention trial involved adult patients (≥18 y) who were admitted to the ICU for ≥72 h with moderate ICU-AW (Medical Research Council (MRC) score 24–48). Patients were randomly assigned to receive 22 g of collagen peptides supplementation or an isocaloric carbohydrate twice daily. The primary outcome was a composite score for physical functioning comprising handgrip strength, leg muscle strength, arm muscle strength, and exercise capacity, adjusted for age, sex, and body weight. Secondary endpoints included nutritional intake and biomarkers, scores in other post-intensive care syndrome (PICS) domains, and mortality rates. Descriptive data is presented, no between-intervention group analyses were conducted due to incomplete sample size.

Results: A total of 900 patients were screened for eligibility to participate in the study, of whom 59 met the requisite criteria between April 2022 and December 2023. The most common reasons for exclusion were treatment limitations, diabetes mellitus, or an MRC score <24 or above >48. Of the 59 patients deemed eligible, 15 patients were included to participate in the study. Due to the slow inclusion rate, the study was terminated early (at ~20 % of anticipated sample size). At baseline (ICU discharge), patients initially had lower physical scores than reference values but showed improved (higher) scores at three months post-ICU discharge. Differences between the groups regarding the primary outcome (composite score of physical functioning) could not be identified due to early termination. Factors affecting the feasibility of nutrition research in post-ICU patients were identified, including slow patient recruitment rates, low adherence to the intervention, and the inability to complete outcome assessments.

Conclusions: Patients exhibited initial physical functioning scores below the reference values yet demonstrated substantial physical recuperation by the 12-week mark following their ICU discharge in both groups. Patients exhibited lower scores in all domains of PICS compared to reference values, emphasising the necessity for further investigation into the potential role of nutrition interventions in preventing and alleviating PICS symptoms. Furthermore, this study describes the factors affecting the feasibility of post-ICU intervention studies and provides recommendations for future studies on effective design and conduction of studies to address PICS (This study was supported by Rousselot; Confucius ClinicalTrials.gov number, NCT05405764).

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https://doi.org/10.1016/j.clnu.2025.01.020

Nomenclature

Term:	Explanation
6MWD	6-Minute Walking Distance Health
ABW	Actual body weight
APACHE II	Acute Physiology and Chronic Evaluation II
BIA	Bioelectric Impedance Analysis
BMI	Body Mass Index
CK	Creatinine kinase
CPAx	Chelsea Critical Care Physical Assessment Tool
CRP	C-reactive protein
ECW	Extracellular water
ECW/TBW ratio	Extracellular water/total body water ratio
EQ-5D	EuroQol 5 Dimension
FFM	Fat-Free Mass
HADS	Hospital Anxiety and Depression Scale
ICU	Intensive Care Unit
ICU-AW	ICU-acquired weakness
LAPAQ	LASA Physical Activity Questionnaire
MMSE	Mini-Mental State Examination
MRC-sum Score	Medical Research Council sum score
NHP-1	Nottingham Health Profile Part 1
NRS-2002 score	Nutrition Risk Screening 2002
mNUTRIC Score	The modified Nutritional Risk in Critically Ill
PICS	Post-Intensive Care Syndrome
PTSD	Post-traumatic stress disorder
QoL	Quality of Life
RCT	Randomised Controlled Trial
SF-36	Short Form Health Survey 36
SOFA Score	Sequential Organ Failure Assessment Score
TCST	Time Chair-Stand-Test
TSQ	Trauma Screening Questionnaire
UPLC-MS/MS	Ultrahigh-pressure liquid chromatography coupled to tandem mass spectrometry
WUR	Wageningen University and Research

1. Introduction

More than half of the individuals who survived the Intensive Care Unit (ICU) encounter Post-Intensive Care Syndrome (PICS), a collection of symptoms that may persist for years following discharge from the ICU [1,2]. These symptoms include severe muscle weakness, physical impairments, neurocognitive deficits, and psychological issues [3–5]. One of the most debilitating and commonly reported aspects of PICS among ICU survivors is poor physical recovery [6]. This poor physical recovery can also reduce the patient's autonomy, potentially affecting their ability to live independently, perform daily activities, return to work, and overall health-related quality of life [7–9]. Nutritional support can improve recovery and functional outcomes in medical patients at nutritional risk [10]. Ensuring adequate nutritional intake, with dietary protein in particular, for ICU survivors is important, given that their protein requirements are higher than average due to increased metabolic activity from inflammation, prolonged muscle disuse, and physical inactivity [11,12]. Failure to meet these protein requirements result in a negative protein balance due to impaired muscle protein synthesis and increased muscle protein catabolism, resulting in the loss of skeletal muscle proteins [11,13,14].

Despite the significance of optimal nutritional intake during recovery from critical illness, nutritional intake often declines significantly after ICU discharge [15–17]. Patients who rely on an oral diet alone consume between 55 and 75 % of the prescribed energy and 27 and 74 % of the prescribed protein during the early recovery phase post-ICU [18]. Although nutritional goals in the post-ICU ward are often not met through oral intake alone, a tendency remains to not initiate enteral, parenteral, or oral nutrition supplementation [19]. Even after hospital discharge, ICU survivors report having a lower nutritional intake than healthy individuals [20,21]. Dietary protein effectively stimulates muscle protein synthesis [13,22], with absolute protein consumption levels and even protein distribution being key factors for muscle protein synthesis and the regulation of muscle mass [22,23]. Meta-analyses indicate that higher protein delivery (above >1.0 or >1.2 g/kg/day) during critical illness can result in the attenuation of muscle loss and improvements in daily activities [24,25]. However, the optimal protein requirements following ICU discharge remain unclear.

Given that the recommended protein intake is frequently unmet in post-ICU patients and that higher protein delivery might effectively attenuate muscle loss, protein supplementation after ICU discharge may prove beneficial in facilitating recovery. A randomised controlled trial examined the combined effects of a 6-week program of rehabilitation and amino acid supplementation (essential amino acids + glutamine mixture) in patients recovering from critical illness and observed that the group receiving the combined intervention exhibited higher exercise capacity and a reduction in anxiety and depression [26]. Moreover, in a study of elderly patients, the combination of 12 weeks of collagen peptide and resistance training resulted in improved body composition, characterised by increases in fat-free mass and muscle strength [27]. Collagen-derived protein sources may have the capacity to stimulate and/or support connective tissue protein synthesis rates and promote connective tissue remodelling, which is essential for recovery and functional performance [28]. However, the potential benefits of collagen peptides supplementation in the post-ICU phase remain to be fully elucidated.

This randomised, controlled, study aims to investigate the effect of a six-week intervention with collagen peptides supplementation compared to an isocaloric carbohydrate (maltodextrin) on physical function outcomes and quality of life during the post-ICU period, up to 12 weeks after ICU discharge. Since post-ICU patients frequently fail to meet their protein requirements [15–17], we hypothesise that daily protein supplementation will improve functional outcomes. Additionally, we hypothesise regarding secondary outcomes that patients receiving collagen peptides supplementation will have increased protein intake levels and possibly improved scores in other PICS domains. Due to challenges in completing the entire study sample, the present paper presents descriptive data of the primary and secondary outcomes in a part of the anticipated study sample, along with feasibility outcomes. The main focus of this paper, however, is on exploring the barriers encountered in conducting nutritional intervention studies in post-ICU patients, intending to improve long-term functional outcomes and quality of life in ICU survivors.

2. Methods

2.1. Trial design

We designed a single-centre, parallel, two-arm, randomised, double-blind, investigator-initiated trial, to assess the effect of

collagen peptides supplementation versus an isocaloric carbohydrate control (maltodextrin) on CONvalescence of FUnCtional outcomes after IcU Stay (CONFUCIUS trial) [29]. The study was conducted at the Gelderse Vallei Hospital in Ede, the Netherlands, from April 2022 to December 2023. The protocol was approved by the Medical Ethical Committee (METC Oost-Nederland), first submitted to a trial registry (clinicalTrials.gov, NCT05405764) on April 13th, 2022, and fully registered on June 6th, 2022, after the trial commenced. The procedures followed were in accordance with the ethical standards outlined in the Helsinki Declaration of 1975, as revised in October 2013, for the use of human subjects and tissue.

2.2. Study participants

All patients admitted to the ICU were screened according to the inclusion and exclusion criteria. The inclusion criteria were being over 18 years of age, having a minimum ICU stay of 72 h, and living at home before hospital admission. The full list of exclusion criteria can be found in Supplementary Table 1. All eligible patients were informed by the research team or physician, both verbally and in writing, about the study's purpose, the experimental procedures, and possible risks before giving written informed consent to participate.

2.3. Trial randomisation

Randomisation was performed by an independent member of the research group using a 1:1 ratio through a web-based random number generator (Research Randomizer) in nine random blocks of 8 (4:4) [30]. The numerical data was associated with a circular or quadrilateral shape, enclosed in a sealed, opaque envelope. All patients, physicians, dieticians, and outcome assessors were blinded for the assigned intervention. Sachets with collagen peptides supplementation or an isocaloric carbohydrate had been sealed before delivery to the hospital. Each participant received 84 supplement sachets for the entire study duration which were instructed to be taken twice daily for six weeks. The supplementation was to be administered via a feeding tube (if present) or consumed orally dissolved in food products, such as yoghurt, in the morning and afternoon (provided with the meals) to stimulate maximal protein synthesis during the entire day [31]. The intervention group was given twice daily a 22-g collagen peptides supplement (Rousselot), containing 20 g of protein (equivalent to 80 kcal) and 2 g of moisture and minerals/salts (full nutritional specifications are provided in Supplementary Table 2). The control group received a 21-g maltodextrin supplement (Rousselot) twice daily, containing 0 g of protein and providing 82 kcal per serving.

2.4. Study procedures

At ICU discharge, patients' baseline characteristics were collected, including demographics (age, sex), anthropometric measurements (height, body weight), disease severity scores on admission to the ICU (The modified Nutritional Risk in Critically Ill (mNUTRIC) score, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and the Sequential Organ Failure Assessment (SOFA) score), length of stay in the ICU, duration of mechanical ventilation, and cumulative protein and energy deficiencies during the ICU stay. The investigators calculated nutritional requirements (for energy and protein) during ICU stay using a step-up protocol and adjusted targets for refeeding syndrome, with targets set at 1.3 g/kg actual body weight (ABW)/day of protein and 25 kcal/kg ABW/day of energy, in accordance with the ESPEN guidelines [32]. Follow-up visits were scheduled at hospital discharge, six weeks after ICU discharge (end of study intervention), and three months after ICU discharge for final follow-up (Fig. 1). Patients were visited in rehabilitation centres or nursing homes if a personal follow-up visit was impossible.

At each measurement time point, functional performance measurements were performed by a specialised physical therapist for handgrip strength (Jamar dynamometer (Fabrication Enterprises Inc., Irvington, NY, USA)), leg and arm muscle strength of the quadriceps femoris and biceps brachii (microFET hand-held dynamometer (Biometrics, Almere, The Netherlands)), and exercise capacity with a 6-min walk distance. Measurements were taken three times for both handgrip and muscle strength tests, and the best measurement was used. If a patient was physically unable to perform the 6-min walk test, a score of 0 was assigned. Each instrument gave a score that represented the percentage of performance compared to a reference population, adjusted for sex, age, and weight [33–35]. In addition, the physiotherapist determined the Medical Research Council (MRC) sum score as a total of six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and ankle dorsiflexion) [36], determined the Chelsea Critical Care Physical Assessment Tool (CPAx) [37] and measured the five-times sit-to-stand test (TCST) [38]. If the five sit-stand tests were not completed within the 2-min allotted time, a score of 120 s was assigned. The body composition assessment was conducted using bioelectrical impedance analysis (BIA), performed by trained researchers using the InBody S10® device (InBody Co., Ltd., Seoul, Korea). To account for fluid overload, known to overestimate fat free mass, a recalculated value for extracellular water (ECW) was subtracted from the fat-free mass. The recalculation employed a standard extracellular water/total body water (ECW/TBW) ratio of 0.380, as delineated in the following formula: dry lean mass = measured lean mass - (measured ECW - ((intracellular water × 0.380)/0.620)) [39].

Various questionnaires were used to assess the domains of PICS, including the physical domain with the Barthel Score, the Rockwood Clinical Frailty Score and the LASA Physical Activity Questionnaire (LAPAQ); the cognitive domain with the Mini-Mental State Examination (MMSE); and the mental domain with the Hospital Anxiety and Depression Scale (HADS) and the Trauma Screening Questionnaire (TSQ); the mental domain with the Hospital Anxiety and Depression Scale (HADS) and the Trauma Screening Questionnaire (TSQ); and the quality of life/general domains with the 5-item EuroQol 5D (EQ-5D-5L), the Nottingham Health Profile (NHP) and the Short Form Health Survey (SF-36). Many of the recommended instruments for Post-Intensive Care Syndrome (PICS) were used to assess patients across all PICS domains [40]. Furthermore, blood samples were collected to determine haemoglobin, creatinine, urea, creatine kinase (CK), C-reactive protein (CRP), and plasma amino acid levels. At the time of ICU discharge, these were obtained via an indwelling arterial catheter, while follow-up samples were collected through venipuncture. The plasma amino acid samples were subsequently stored in a freezer at −80° °C and analysed at the laboratory of the Division of Human Nutrition and Health of Wageningen University and Research (WUR) using ultrahigh-pressure liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) based method that was adapted from a previously published protocol [41]. Dietary intake was assessed by 24-h telephone recalls at weeks 4, 6, 8, and 10 after ICU discharge and documented using the Compl-eat web-based platform (WUR). This survey entailed a complete review of the patient's food diaries, calculating energy and macronutrient intake from two days per week. Daily intake was calculated using the weight at the 6-week follow-up after ICU discharge or, if unavailable, the nearest available value. Adverse events were documented by the patients on a designated form and subsequently reviewed after the study period. Additionally, the

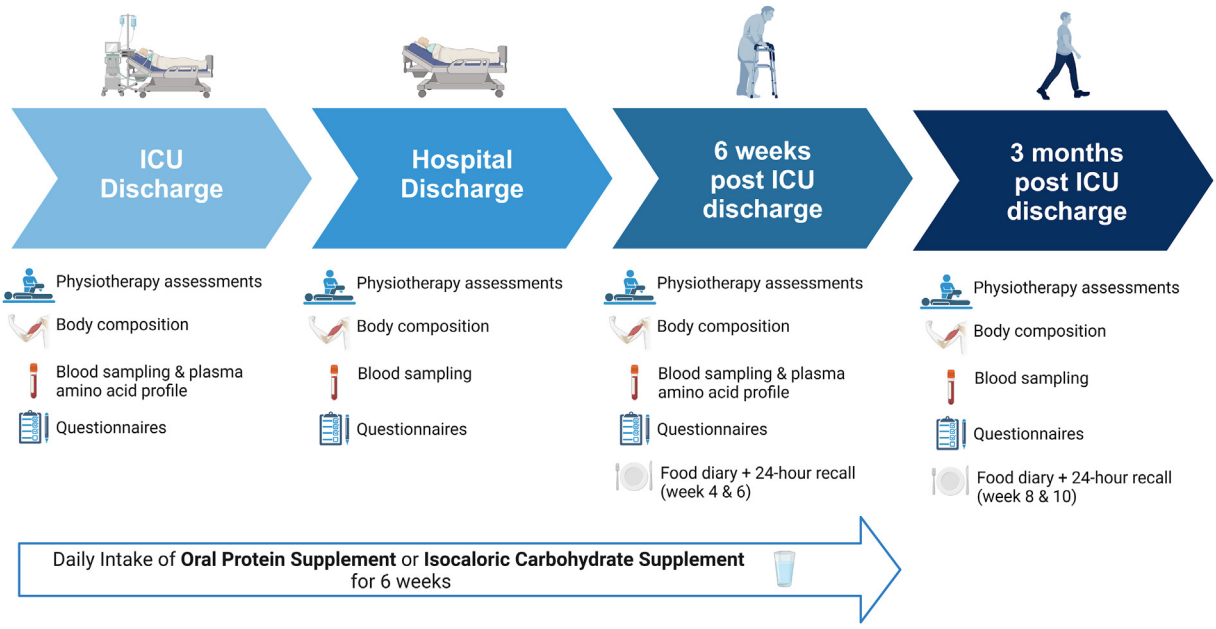

Fig. 1. Overview diagram of measuring points.
An overview of the study measurements during a six-week protein compared to isocaloric carbohydrate supplementation RCT, with a follow-up of 12 weeks after ICU discharge, in post-ICU patients. Created with Biorender.com.

frequency of readmission to the ICU within the same hospitalisation and to the hospital within six months was quantified.

2.5. Trial outcomes

The primary outcome is the difference in physical function (composite score of four independent tests) through three time points after ICU discharge (at hospital discharge, six weeks after ICU discharge, and 12 weeks after ICU discharge) compared to ICU admission. This composite score was composed of the outcomes of maximal handgrip strength, arm and leg muscle strength, and exercise capacity. The composite score was the sum of these four measurements and presented as % to reference values. A composite score was calculated if all four individual physical scores were completed, otherwise it was recorded as missing. Secondary outcomes included the PICS domains (through questionnaires), plasma amino acid concentrations, nutritional intake, and overall survival; for a complete overview, see the study protocol [29].

2.6. Statistical analysis and study size adjustment

The initial sample size calculation ($n = 72$) aimed to detect a difference of 14 % in the mean composite endpoint with a power of 80 % and an alpha of 0.05. The standard deviation was set at 39, with an anticipated dropout rate of 15 % at the 90-day follow-up [29]. After over 1.5 years, only 20 % of the target sample size had been achieved. Despite efforts to establish a multicentre setup for the study, these attempts were unsuccessful. Consequently, at a Steering Group meeting on December 19th, 2023, it was determined that patient enrolment in the study would be halted due to slow enrolment rates, resulting in an unacceptably long study duration. The Medical Ethical Committee was informed about this decision. The study did not attain the requisite sample size for statistical power, because the population was insufficient to draw definitive conclusions. Consequently, the study is considered as exploratory due to the limitations imposed by the included sample size. In a Steering Group meeting, it was agreed that the main focus of the research project would shift to the feasibility aspects of conducting post-ICU nutritional research, to provide insights that would be valuable for future research endeavours.

All data are presented on an intention-to-treat basis. Data were extracted from electronic medical patient records and electronic case report forms (Castor) and exported into Microsoft Excel 2016 for basic descriptive analysis. Categorical data are presented as numbers and percentages, and continuous variables are presented as medians with ranges (lowest and highest number). Further statistical analysis (within and between group analysis) was not conducted due to the limited sample size of the study groups.

3. Results

Of the 900 patients screened for eligibility between April 19th, 2022, and December 19th, 2023, 59 were eligible (Fig. 2). The follow-up was completed on March 14th, 2023, three months after the last patient was included. Ultimately, 15 of the 59 eligible patients (25.4 %) provided informed consent, comprising seven in the protein supplementation group and eight in the isocaloric carbohydrate group.

The total included patients ($n = 15$) had a median age of 59 years, a BMI of 32.3 kg/m^2 and five patients (33.3 %) were male (Table 1). Admission diagnoses were medical reasons for ten patients and surgical reasons for five patients. Both groups exhibited deficiencies in meeting their protein and energy requirements during their ICU stay, with a median protein deficit of 18 g/day and a median energy deficit of 451 kcal/day. During the study period, one patient in the protein supplementation group withdrew from follow-up without providing a rationale following hospital discharge. Additionally, two patients in the isocaloric carbohydrate group were lost to follow-up.

3.1. Physical functioning

In total, 14 out of 15 patients had at least one of the four composite score values (one missing in the isocaloric carbohydrate control group), with 11 out of 15 patients having a composite score at ICU discharge, hospital discharge and at least one measurement

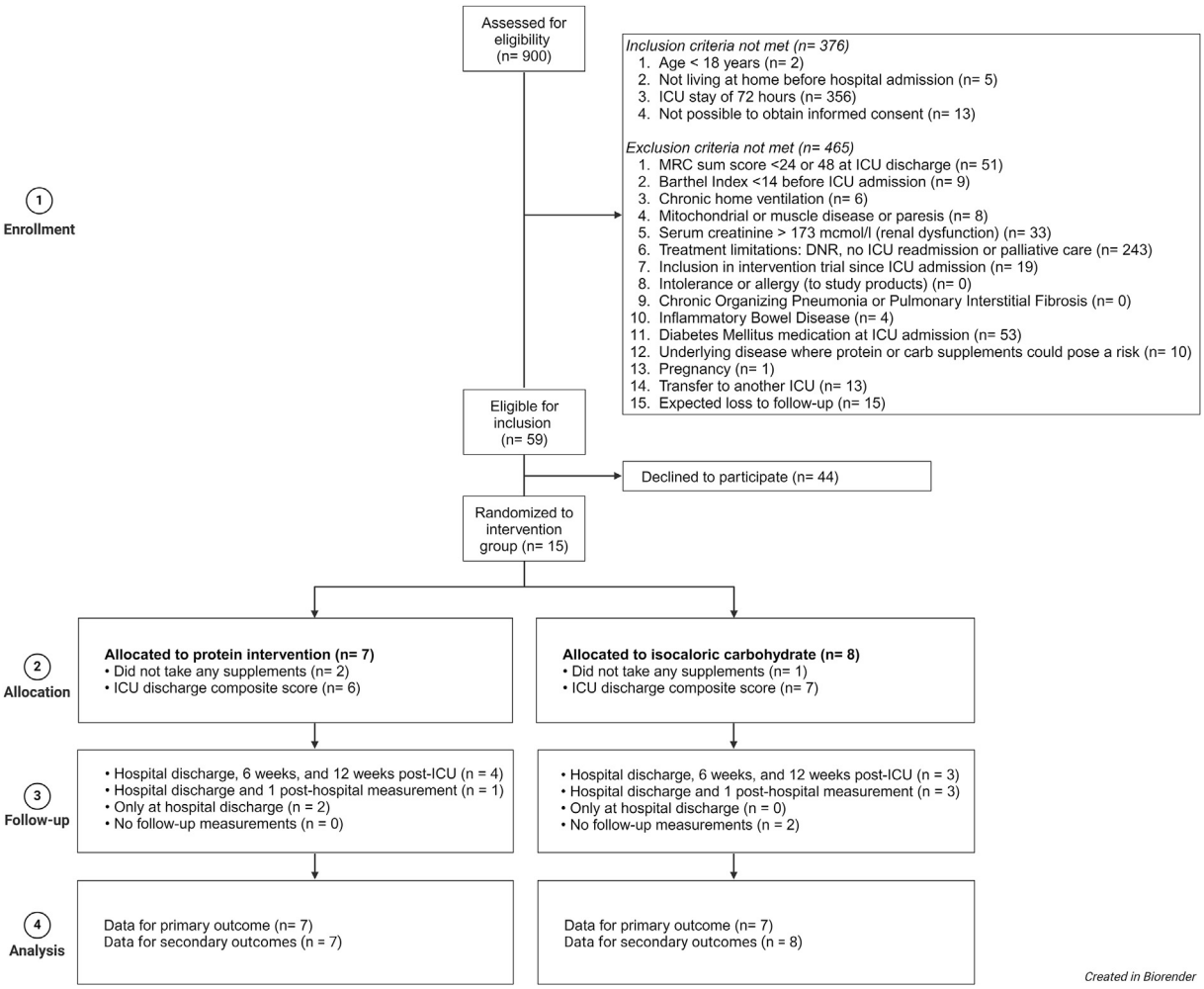

Fig. 2. Flow diagram of screened patients.

after hospital discharge. The reasons for incomplete physical assessments included loss to follow-up and the necessity of conducting some follow-up outside the hospital, where not all necessary equipment was available. In both groups, the composite score demonstrated an increase from the time of ICU discharge to three months post-ICU discharge, with the median score rising from 195 % (range 108–230 %) to 322 % (range 207–395 %) in the protein supplementation group and from 101 % (range 24–257 %) to 281 % (range 203–379 %) in the isocaloric carbohydrate control group (Fig. 3). Moreover, the individual physical performance scores exhibited a general improvement over time in both groups and nearly all individuals (Table 2).

3.2. Other PICS domains

Furthermore, post-ICU patients exhibited improvement in other domains over time (Supplementary Table 3). These included enhanced cognition (MMSE), reduced anxiety and depression (HADS), and fewer post traumatic stress disorder (PTSD) symptoms (TSQ). Moreover, patients also showed augmented quality of life and health status (EQ-5D-5L, NHP, and SF-36).

3.3. Other outcome measures

The median duration of hospitalisation was 26 days for the protein supplementation group and 41 days for the isocaloric carbohydrate control group. The six-month mortality rate was 0 % in both groups. One patient in the protein supplementation group and two patients in the isocaloric carbohydrate control group were lost to follow-up. Additionally, at the six-week follow-up, some measurements were missing due to re-hospitalisations in the ICU or patients being too frail in rehabilitation centres to perform measurements. The protein supplementation group collectively missed a median of 24 supplement packets (adherence ~71 %), whereas the isocaloric carbohydrate control group missed 56 packets (adherence ~33 %). Supplementary Tables 4A–4B and Supplementary Fig. 1 present laboratory values and plasma amino acid concentrations. The median increase in total amino acid concentrations was higher in the protein supplementation group (2,540 to 2,928 μmol/L) than in the isocaloric carbohydrate control group (3,025 to 3,076 μmol/L), primarily due to a more considerable rise in non-essential amino acid levels in the protein group. No major adverse events were reported. The adverse effects reported were nausea ($n = 2$), loss of appetite ($n = 2$), diarrhoea ($n = 1$), and abdominal discomfort ($n = 1$).

4. Discussion

In this single-centre, parallel, two-arm, randomised, double-blind, investigator-initiated trial, we compared protein supplementation (40 g protein daily, during breakfast and lunch) with an isocaloric carbohydrate control (maltodextrin) over six weeks post-

Table 1
Baseline characteristics.

	Protein supplementation	*n*	Isocaloric carbohydrate control (maltodextrin)	*n*
Demographics				
Age, y	63 [44–75]	7	53 [31–73]	8
Male sex, no. (%)	2 (28.6)	7	3 (37.5)	8
Weight, kg	89.5 [67.0–143.0]	7	97.3 [74.0–126.5]	8
Height, cm	175 [160–186]	7	175 [163–197]	8
BMI, kg/m^2	32.3 [26.2–44.1]	7	32.0 [19.5–43.4]	8
Type of admission, no. (%)				
Medical	5 (71.4)	7	5 (62.5)	8
Surgical	2 (28.6)	7	3 (37.5)	8
Clinical scores				
Barthel score[a]	20 [19–20]	7	20 [19–20]	7
Clinical Frailty score[b]	3 [2–5]	5	2 [2–6]	5
mNUTRIC score[c]	4 [1–6]	7	3 [1–6]	8
NRS-2002 score[d]	7 [3–8]	6	1 [0–5]	6
APACHE-II score[e]	18 [14–30]	7	22 [17–26]	8
SOFA score[f]	7 [3–15]	7	9 [5–10]	8
ICU stay duration				
ICU length of stay, days	6 [4–18]	7	8 [5–20]	8
Invasive mechanical ventilation, no. (%)	5 (71.4)	7	7 (87.5)	8
Duration of invasive mechanical ventilation, days	4 [1–13]	5	7 [3–14]	7
Nutritional intake				
Received enteral nutrition during ICU stay (%)	5 (71.4)	7	7 (87.5)	8
Received enteral nutrition at ICU discharge (%)	3 (42.9)	7	5 (62.5)	8
Received parenteral nutrition during ICU stay, (%)	2 (28.6)	7	2 (25.0)	8
Refeeding syndrome during ICU stay, yes (%)	5 (71.4)	7	1 (12.5)	8
Cumulative protein deficit during ICU stay, g	110 [-264-554]	7	225 [-220-1233]	8
Protein deficit in g/kg/day	0.2 [-0,4–0.7]	7	0.3 [-0.1–0.8]	8
Cumulative energy deficit during ICU stay, kcal	2174 [-3408-13341]	7	5909 [-7150-22104]	8
Energy deficit in kcal/kg/day	3 [-5-12]	7	7 [-5-14]	8

Baseline characteristics of post-ICU patients before commencing six-week protein supplementation (n = 7) compared to isocaloric carbohydrate control (n = 8) with a follow-up of 12 weeks after ICU discharge. Data are presented as median [range]. BMI = body mass index.

[a] Barthel score assesses activities of daily living, with scores ranging from 0 (indicating dependence) to 20 (indicating independence).

[b] Clinical Frailty score is a seven-point scale employed to assess the level of fitness or frailty, with higher scores indicating a higher degree of frailty.

[c] The modified Nutrition Risk in Critically Ill (mNUTRIC) score measures the risk of adverse events in critically ill patients that can be modified by aggressive nutritional therapy, with higher scores (ranging from 1 to 9) indicating a greater risk.

[d] The Nutritional Risk Screening 2002 (NRS-2002) ranges from 0 to 7, with higher scores indicating a higher risk of malnutrition.

[e] The Acute Physiology and Chronic Health Evaluation II (APACHE II) score ranges from 0 to 71, with higher scores indicating greater disease severity and an increased risk of mortality.

[f] The Sequential Organ Failure Assessment (SOFA) scores range from 0 to 20, with higher scores indicating more severe organ failure. During ICU stay, nutritional requirements (for energy and protein) were calculated using a step-up protocol and adjusted targets for refeeding syndrome, with targets set at 1.3 g/kg BW/day of protein and 25 kcal/kg BW/day of energy. Refeeding syndrome is defined as a drop in blood phosphate levels below 0.65 mmol/L within 72 h of starting feeding, with an initial normal level, and a decrease of at least 0.16 mmol/L required for diagnosis.

ICU. It is acknowledged that the study did not attain the stipulated sample size for statistical power, thus classifying it as exploratory. Notwithstanding this limitation, we observed an overall improvement in the composite score for physical function during the three-month recovery period among all post-ICU patients. Comparable physical tests were performed in a previous cohort of ICU survivors, and, similar to our findings, an improvement over time was also observed in that study [42]. Notably, during the ICU and post-ICU phases, the achieved protein and energy values were below the ESPEN target [32]. This finding is similar to that of a recent review by Moisey and colleagues [18]. The small sample size (due to premature termination from slow recruitment) limited the ability to detect significant intergroup differences and precluded definitive conclusions regarding the primary and secondary endpoints. Nonetheless, this study highlights critical barriers influencing the feasibility of nutritional intervention studies in post-ICU patients. We identify key challenges and barriers across three phases: patient recruitment, intervention adherence, and follow-up assessment retention (Fig. 4).

4.1. Patient recruitment

Over 20 months, 900 patients were screened for the study. Of these, 6.6 % met the inclusion criteria and only 1.7 % provided consent to participate. Many patients were excluded during the recruitment phase due to the inclusion and exclusion criteria. These criteria were set to be rigorous, to retain a group with moderate ICU-acquired weakness and to minimise loss to follow-up by excluding treatment restrictions, while also ensuring safety by excluding patients with severe renal dysfunction due to the protein load (collagen peptides) and patients on diabetes medications due to the isocaloric carbohydrate control (maltodextrin). Previous research involving ICU survivors has also demonstrated that the exclusion criteria employed to measure physiological nutrition-impacting symptoms objectively have the potential to impede participation significantly and may serve as independent barriers to food intake [43]. Patient recruitment was also influenced by study visits in the hospital, which was essential for participation in the trial. This fact is in line with a recent systematic review on refusal rates of patients during ICU follow-up, indicating that recruitment rates are lower when patients are asked to return to the index hospital [44]. The timing of recruitment had a negligible impact on recruitment rates, with comparable rates observed for patients approached in the ICU, in the acute ward, or after hospital discharge [44]. Furthermore, the intervention, daily protein supplementation and the time investment associated with study participation, in conjunction with health conditions and individual characteristics (including age and length of ICU stay), may influence the

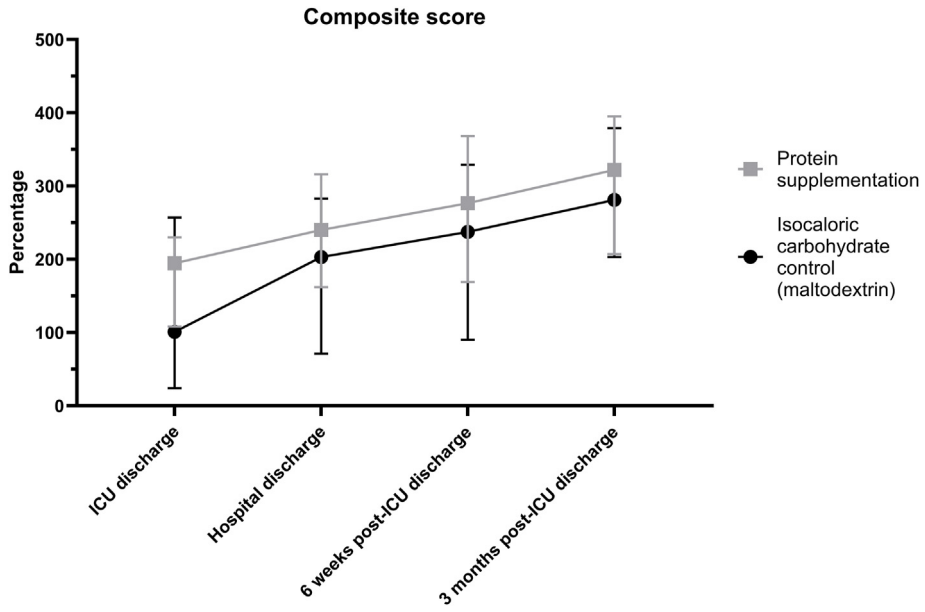

Fig. 3. Composite score of physical functioning.
Composite score of physical function expressed as a percentage relative to reference values following six-week protein supplementation (grey squares, n = 7) compared to isocaloric carbohydrate control (black circles, n = 7) with a follow-up of 12 weeks after ICU discharge in post-ICU patients. This composite score was composed of the maximum handgrip strength, arm and leg muscle strength, and exercise capacity outcomes. Data are presented as median and range. Data represent n = 13 patients at ICU discharge, n = 13 at hospital discharge, n = 8 at 6 weeks post-ICU discharge and n = 10 at 12-weeks post-ICU discharge.

willingness to participate in follow-up procedures [44,45]. Notably, the patient cohort in this study was, on average, younger, had a higher proportion of females, and were more frequently admitted with a medical indication than the general ICU population [46]. The sex distribution of patients who did not give consent was equal.

4.2. Intervention adherence

Many missed doses were observed in both the protein intervention and isocaloric carbohydrate control group (maltodextrin), with the median number of missed supplements in the latter group nearly twice as high (46 vs 24). Of all patients, seven missed more than half of their doses, including three who did not take any supplements at all. Patients reported that this was partly due to their perceived side effects, the most common being nausea and loss of appetite. However, no significant differences between the groups could explain the higher number of missed doses in the isocaloric carbohydrate group. Reduced appetite, taste, and increased feelings of fullness have been reported by ICU survivors in other studies [47–49]. One study identified the loss of appetite as the most prevalent physiological alteration following an ICU stay, with the potential to persist for up to three months following ICU discharge [49]. Furthermore, additional factors may also contribute to compliance with the intervention. The participants were instructed to consume the supplements orally or have them administered via an enteral feeding tube, with 10 out of 15 patients in our cohort still having a nasogastric tube at the start of the intervention. However, for patients consuming the supplements orally, factors such as post-extubation dysphagia, which can persist well beyond ICU discharge [50], and the altered swallowing physiology due to the presence of a nasogastric tube, may influence consumption [51]. Cognitive function might also affect compliance, as patients may have difficulty remembering to take supplements due to impaired cognitive functions after ICU discharge [52]. Additionally, the frequency and timing of the instructions for taking the supplements may also have been a contributing factor to missing supplements. Previous research in post-ICU patients indicates that sleep disturbances are common, and that the intake of supplements is missed due to increased daytime sleeping patterns [49,53]. A recent feasibility study assessed the efficacy of amino acid supplements in ICU patients [54]. The supplements were administered five times a day, a dosage that was deemed feasible given the patients' ICU status. Nevertheless, the authors suggested reducing the number of doses from five times a day to twice a day to enhance delivery. In our study, improvements in adherence may have been achieved by telephone reminders and the provision of supplements by healthcare professionals. Additionally, post ICU-patients may experience delirium, which can result in an inability to recall what they have eaten and whether they have already consumed a meal. This recall problem can also manifest as a lack of requests for assistance during mealtimes [49]. Furthermore, some patients cannot feed themselves independently. One study reported that 26 % of post-ICU patients exhibited this inability due to factors such as critical illness polyneuropathy or neurological deficits [55].

It is essential to consider the nature of the nutritional intervention, such as the macronutrient composition, dietary protein source, amino acid content, and/or protein quality. The present study provided collagen protein which is considered a low-quality protein source but characterized by a distinct amino acid profile (high in proline, glycine, and hydroxyproline) compared to high quality protein sources, high in essential amino acid content, considered important for muscle mass support. Dietary collagen protein has been suggested the preferred source to support connective tissue synthesis/renewal and functional performance [28,56–59], and previous research has shown that collagen peptides, in combination with resistance training, can positively increase lean body mass and muscle strength in sarcopenic older men [27] and premenopausal women [60]. To date, there is limited evidence for the optimal protein source or amino acid composition for clinical populations suffering from muscle weakness, such as ICU survivors. Research has shown greater

Table 2
Study outcomes on physical domain, discharge data, and feasibility.

	Protein supplementation	*n*	Isocaloric carbohydrate control (maltodextrin)	*n*
Physical health				
Composite score[a], %				
ICU discharge	195 [108–230]	6	101 [24–257]	7
Hospital discharge	240 [162–316]	7	203 [71–283]	6
6 weeks post-ICU discharge	277 [169–368]	4	238 [90–329]	4
12 weeks post-ICU discharge	322 [207–395]	5	281 [203–379]	5
Handgrip strength[b], %				
ICU discharge	72 [30–88]	7	38 [15–122]	7
Hospital discharge	82 [47–136]	7	50 [19–117]	7
6 weeks post-ICU discharge	89 [60–100]	4	65 [42–115]	6
12 weeks post-ICU discharge	97 [25–125]	6	73 [39–128]	5
Leg muscle strength[c], %				
ICU discharge	49 [22–82]	6	27 [1–65]	7
Hospital discharge	57 [33–75]	7	45 [17–84]	6
6 weeks post-ICU discharge	55 [39–80]	4	53 [7–78]	4
12 weeks post-ICU discharge	79 [17–91]	6	60 [24–83]	5
Arm muscle strength[c], %				
ICU discharge	67 [27–100]	7	34 [13–65]	7
Hospital discharge	81 [47–124]	7	51 [31–68]	6
6 weeks post-ICU discharge	86 [47–105]	4	69 [33–72]	5
12 weeks post-ICU discharge	81 [31–144]	6	89 [43–127]	5
6m walking distance[d], %				
Hospital discharge	9 [0–32]	7	36 [0–57]	7
6 weeks follow-up	58 [0–83]	4	44 [0–70]	6
12 weeks follow-up	71 [62–101]	5	60 [24–83]	5
Timed chair-stand-test[e], sec				
Hospital discharge	51.02 [13.35–120.00]	5	16.17 [10.50–120.00]	5
6 weeks post-ICU discharge	16.16 [10.78–51.02]	4	16.36 [12.80–120.00]	6
12 weeks post-ICU discharge	12.19 [9.81–14.31]	5	13.74 [11.88–15.41]	4
CPAx[f]				
ICU discharge	27 [23–45]	7	23 [15–32]	7
Hospital discharge	43 [38–47]	7	43 [18–45]	7
6 weeks post-ICU discharge	48 [43–50]	4	45 [22–50]	5
12 weeks post-ICU discharge	50 [50-50]	3	46 [36–50]	4
MRC sum score[g]				
ICU discharge	37 [32–46]	6	35 [26–46]	7
Hospital discharge	48 [42–57]	7	47 [30–50]	7
6 weeks post-ICU discharge	57 [48–60]	4	50 [40–60]	6
12 weeks post-ICU discharge	58 [54–60]	6	53 [48–60]	5
Discharge data				
Hospital length of stay	26 [11–52]	7	41 [14–57]	8
ICU readmission, %	2 (28.6)	7	2 (25.0)	8
Hospital readmission, %	2 (28.6)	7	2 (25.0)	8
Discharge destination, %				
Home	4 (57.1)	7	2 (25.0)	8
Rehabilitation centre	3 (42.9)	7	5 (62.5)	8
Nursing home	0 (0.0)	7	1 (12.5)	8
6-month mortality, %	0 (0.0)	7	0 (0.0)	8
Feasibility				
Missed supplements	24 [0–84]	7	46 [0–84]	8
24h recall data nutritional intake (excluding study supplements)				
Energy intake, kcal				
Week 4 daily energy intake	2141 [1995–2880]	3	1590 [1363–3218]	3
Week 4 daily energy intake in kcal/kg/day	25 [21–43]	3	21 [13–30]	3
Week 6 daily energy intake	1768 [1187–2202]	5	2636 [1807–3464]	2
Week 6 daily energy intake in kcal/kg/day	21 [8–26]	5	24 [17–32]	2
Week 8 daily energy intake	1633 [1041–1820]	4	2276 [1902–2650]	2
Week 8 daily energy intake in kcal/kg/day	17 [7–27]	4	21 [17–25]	2
Week 10 daily energy intake	1601 [1553–2881]	4	2555 [2307–2804]	2
Week 10 daily energy intake in kcal/kg/day	20 [11–28]	4	24 [22–26]	2
Protein intake, g				
Week 4 daily protein intake	96 [92–98]	3	80 [68–188]	3
Week 4 daily protein intake in g/kg/day	1.2 [0.9–1.4]	3	1.0 [0.6–1.8]	3
Week 6 daily protein intake	78 [55–110]	5	158 [90–225]	2
Week 6 daily protein intake in g/kg/day	0.9 [0.5–1.2]	5	1.5 [0.8–2.1]	2
Week 8 daily protein intake	76 [44–91]	4	126 [108–144]	2
Week 8 daily protein intake in g/kg/day	0.9 [0.3–1.2]	4	1.2 [1.0–1.3]	2
Week 10 daily protein intake	72 [67–116]	4	118 [94–142]	2
Week 10 daily protein intake in g/kg/day	0.9 [0.5–1.1]	4	1.1 [0.9–1.3]	2
Serious adverse events, %	0 (0.0)	7	0 (0.0)	8
Reported side effects, %				

Table 2 (*continued*)

	Protein supplementation	*n*	Isocaloric carbohydrate control (maltodextrin)	*n*
Diarrhoea	1 (14.3)	7	0 (0.0)	8
Abdominal pain/discomfort	1 (14.3)	7	0 (0.0)	8
Nausea	1 (14.3)	7	1 (12.5)	8
Loss of appetite	1 (14.3)	7	1 (12.5)	8

Physical functioning and feasibility outcomes following six-week protein supplementation compared to isocaloric carbohydrate control (maltodextrin) in post-ICU patients with a follow-up of 12 weeks. Data are presented as median [lowest and highest number].

[a] Composite score: The composite score combines handgrip strength, quadriceps femoris muscle strength, biceps brachii muscle strength, and exercise capacity (6MWD). Scores are adjusted to a reference population based on sex, age, and weight, with lower scores indicating poorer overall performance.

[b] Handgrip strength: The measurement is conducted with the Jamar dynamometer, and the resulting scores are expressed as a percentage of a reference population based on sex, age, and weight. Lower scores indicate reduced handgrip strength.

[c] Muscle strength (leg and arm): The strength of the quadriceps femoris (leg) and biceps brachii (arm) muscles is evaluated through the utilisation of a microFET hand-held dynamometer (Biometrics, Almere, The Netherlands). The scores are expressed as a percentage of a reference population based on sex, age, and weight. A lower score indicates a reduction in muscle strength.

[d] Six-minute walking distance (6MWD): This test assesses an individual's exercise capacity, specifically the distance they can walk in 6 min. The scores are adjusted to a percentage based on a reference population, with adjustments made for sex, age, and weight. Lower scores indicate a reduction in exercise capacity.

[e] Time Chair–Stand Test (TCST): The test assesses lower extremity function by measuring the time taken to perform sit-to-stand movements with the arms folded across the chest. Lower scores indicate superior lower extremity function. If the five sit-stand tests were not completed within the 2-min allotted time, a score of 120 s was assigned.

[f] CPAx (Chelsea Critical Care Physical Assessment Tool): Rates physical morbidity in critical care patients using a numeric and pictorial composite score of 10 physical function components graded on a 6-point Guttman Scale. Scores range from 0 (complete dependence) to 5 (independence), with lower scores indicating greater dependence.

[g] MRC sum (Medical Research Council sum score): The MRC sum assesses global muscle strength by evaluating manual strength in six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion) using the MRC scale. The scale ranges from 0 (indicating complete paralysis) to 60 (indicating normal strength), with lower scores indicating weaker muscle strength.

increases in skeletal myofibrillar (contractile) protein synthesis with whey protein supplementation compared to collagen peptide supplementation in healthy older women [61], while muscle connective tissue protein synthesis has been shown to be unresponsive to high quality protein sources [61,62]. In patients exhibiting extreme muscle weakness, enhancing muscle function and connective tissue remodelling within musculoskeletal tissues through dietary collagen peptides might be effective to support recovery after critical illness, however this has never been investigated.

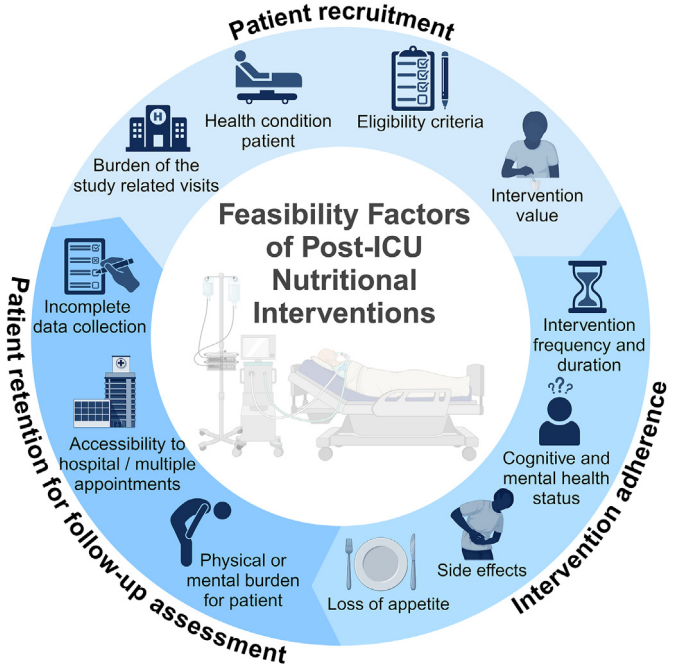

Fig. 4. Factors affecting the feasibility of nutrition research in post-ICU patients. The factors that are proposed to affect the feasibility of post-ICU nutrition supplementation interventions can be categorised into three main areas: patient recruitment, adherence to the intervention, and patient retention for follow-up assessment. Created with Biorender.com.

4.3. Patient retention for follow-up assessment

Furthermore, patients with multiple follow-up appointments, as in our RCT, may encounter more significant difficulties attending follow-up appointments. This follow-up problem is also evident from post-ICU follow-up care; the median rate of retention for the assessment of outcomes associated with hospital-based interventions was 52 % [8.1–82 %] [44]. The most frequently cited reasons for loss to follow-up included appointment cancellation, comorbidities, and incorrectly completed questionnaires [44]. In line, another study of post-ICU patients revealed a refusal rate of 36 % for the three-month follow-up [63]. The group that attended the three-month follow-up exhibited superior quality of life (QoL) three months before ICU admission, and a tendency towards enhanced functional status, although their psychological status at baseline was poorer [63]. It can be surmised that the group attending the follow-up in our study may not represent the entire ICU population. In the present RCT, study visits at each time point entailed ~90 min of questionnaires and assessments, which is a high burden for this specific patient population. The tests were performed in a specific order to minimise the impact on participants' energy levels. It is, however, possible that patients were fatigued during the initial test, thereby affecting the results of the subsequent tests. Therefore, incomplete data or surveys at follow-up can likely be attributed to participants' inability to complete the surveys, mental capacity, fatigue, or logistical challenges. Indeed, fatigue is a common symptom among ICU survivors [64]. Furthermore, a total of eight subjects were admitted to rehabilitation centres for follow-up, who were sometimes unable to undergo all the scheduled tests due to physical or mental limitations. To minimise the burden on patients while ensuring reliable results, carefully weighing the benefits and burdens of each potential outcome is of the utmost importance. The recommendations for instruments to assess PICS in ICU survivors are valuable in this evaluation [40]. Further research is needed to identify the most feasible physical assessments for post-ICU patients, as the composite score employed in this study has not been previously validated, potentially complicating comparisons with other studies. Although the study did not elevate mortality rates, in-hospital mortality following ICU admission can reach approximately 20 % [65,66], influencing patient follow-up and adherence to nutritional intervention studies.

4.4. Recommendations

The execution of this randomised controlled study has yielded insights that are crucial for conducting subsequent post-ICU research. It is important to note that post-ICU patients may continue to experience symptoms of PICS long after discharge from the ICU. Considering our experience, we propose that researchers consider three key aspects when setting up nutrition intervention in post-ICU patients: patient recruitment, intervention adherence, and patient retention for follow-up assessment. In the context of patient recruitment, it is crucial to acknowledge that the criteria for inclusion and exclusion, which are essential for ensuring a homogeneous cohort in an intervention study, can significantly influence the overall inclusion rate. Improvements may have been achieved in patient adherence through telephone reminders and the provision of supplements by healthcare professionals. To effectively assess study outcomes, the execution of study assessments at patients' homes or rehabilitation centres could have improved the completeness of study measurements. Furthermore, it is essential to assess the significance of each study assessment (both quantitative and qualitative assessments) concerning patient burden, as this influences the probability of incomplete data or loss of follow-up. Conducting research within this patient group presents significant challenges, therefore, we strongly recommended feasibility trials to be conducted in this area, prior to the execution of fully powered randomised efficacy trials. Additionally, it is advisable to involve patient representatives in the design of the study to better overcome some of the barriers related to recruitment, adherence, and retention in post-ICU research. Our findings present the barriers and challenges faced by nutritional intervention studies in post-ICU patients. These findings are essential to understand when developing effective nutritional interventions to mitigate the consequences of ICU-AW or PICS. Individualised nutritional counselling following patients from ICU discharge, on the hospital ward or rehabilitation, to home requires different approaches and might, therefore, present a successful strategy to improve nutritional status, functional recovery, or patient-centred outcomes.

5. Conclusion

This randomised controlled study is the first exploratory study to evaluate the influence of a protein supplement compared to an isocaloric supplement on physical function outcomes in post-ICU patients with ICU-AW. Although the initial sample size was not reached, the results demonstrate that all post-ICU patients demonstrated lower scores than reference values across all domains of PICS at ICU discharge. An overall improvement in physical functioning was observed during the three-month recovery period among all post-ICU patients. This study identifies barriers regarding study feasibility, which can be divided into three categories: patient recruitment, intervention adherence, and patient retention for follow-up assessment. While researching this group of patients presents significant challenges, understanding the limitations and barriers of post-ICU nutrition interventions is crucial to further develop effective strategies to mitigate the consequences of ICU-AW and PICS.

Author contributions

Michelle Paulus: Investigation, formal analysis, data curation, writing – Original Draft, visualisation, writing – Review & Editing. Imre Kouw: writing – Review & Editing. Bert Strookappe: Conceptualization, investigation. Yente Boelens: Conceptualization, investigation. Anoek Hermans: Investigation. Arthur van Zanten: Conceptualisation, funding acquisition, writing – Review & Editing.

Funding statement

This work was supported by an unrestricted research grant by Rousselot, who provided the blinded study feeds but did not play a pivotal role in the design and conduct of the trial, nor did they have access to the data or influence the publication's content.

Conflict of interest

Prof. dr Van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Abbott, AOP Pharma, Baxter, Cardinal Health, Danone-Nutricia, Fresenius Kabi, GE Healthcare, InBody, and Rousselot. The other authors have nothing to declare.

Acknowledgements

The authors thank N. Feisal (Gelderse Vallei Hospital) for her help with data curation, Dr. M.J. Caldas Paulo (Wageningen University & Research, The Netherlands) for her advice on statistical analysis, F. Govers (Gelderse Vallei Hospital) for her help as a specialised physiotherapist in performing physical measurements, Dr. M.G.J. Balvers (Wageningen University & Research, The Netherlands) for supervision of analytical amino acid method development and analysis, and G. de Gier (Wageningen University & Research, The Netherlands) for analysing amino acid concentrations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.01.020.

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