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Opinion paper

Combining nutrition and exercise to optimize survival and recovery from critical illness: Conceptual and methodological issues

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SUMMARY

Survivors of critical illness commonly experience neuromuscular abnormalities, including muscle weakness known as ICU-acquired weakness (ICU-AW). ICU-AW is associated with delayed weaning from mechanical ventilation, extended ICU and hospital stays, more healthcare-related hospital costs, a higher risk of death, and impaired physical functioning and quality of life in the months after ICU admission. These observations speak to the importance of developing new strategies to aid in the physical recovery of acute respiratory failure patients.

We posit that to maintain optimal muscle mass, strength and physical function, the combination of nutrition and exercise may have the greatest impact on physical recovery of survivors of critical illness. Randomized trials testing this and related hypotheses are needed. We discussed key methodological issues and proposed a common evaluation framework to stimulate work in this area and standardize our approach to outcome assessments across future studies.

1. Introduction

Critically ill patients receiving mechanical ventilation are at high risk of developing ICU-acquired complications. Survivors of critical illness commonly experience neuromuscular abnormalities, including muscle weakness known as ICU-acquired weakness (ICU-AW) [1]. The incidence of neuromuscular abnormalities ranges from 25% to 100% of critically ill patients depending on definitions used and populations studied [1]. Patients who develop sepsis, multi-organ failure, or prolonged mechanical ventilation or immobility are at particular risk for developing neuromuscular abnormalities [1–3]. ICU-AW is associated with delayed weaning from mechanical ventilation, extended ICU and hospital stays, more healthcare-related hospital costs, a higher risk of death, and impaired physical functioning and quality of life in the months after ICU admission [1,2,4]. These observations speak to the importance of developing new strategies to aid in the physical recovery of acute respiratory failure patients.

Conceptually, nutrition and exercise may be potential strategies to prevent or attenuate ICU-acquired weakness and associated physical impairments; however, further evidence is needed [5]. The objective of this paper is to discuss the concept of early implementation, during critical illness, of a combined nutrition and exercise intervention to improve survival and recovery from critical illness. Herein, we provide rationale for a combined intervention

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and some conceptual and methodological issues to consider for research evaluating this hypothesis.

2. Concepts in support of a combined intervention

2.1. Nutritional intervention

Prior large-scale observational studies of critically ill patients suggest that optimal amounts and timely provision of nutritional intake is associated with reduced infectious complications, duration of mechanical ventilation, and mortality [6–8], along with perceptions of faster physical recovery [9]. Further examination of the data suggests that optimizing daily protein intake, rather than total daily caloric intake, may more positively affect ICU patient outcomes [10,11]. Large, randomized controlled trials (RCT) evaluating the potential benefit of enhanced protein intake on clinically important endpoints are lacking. However, small trials demonstrate that greater protein intake is associated with improved weaning from mechanical ventilation [12] while larger trials show non-significant improvements in long-term physical functional performance (6 min walk test at 12 months) [13] and a significant improvement in 60-day quality of life [14]. In contrast, some observational studies have suggested that greater versus lesser protein intake is associated with greater muscle wasting [15] and lower likelihood of an early discharge from ICU [16]. However, these observational studies have methodological flaws that limit the validity of their findings [8,17].

Overall, controversy exists regarding optimal protein and amino acid doses in critically ill patients. Some advocate that doses as high as 2.5 g/kg/day are effective and safe [18]. A recent prospectively defined subgroup analysis of a large RCT infusing amino acids up to 2.0 g/kg/day demonstrated a significant survival advantage (6% absolute risk reduction in mortality) in a subgroup of patients with no renal impairment at baseline (unpublished data). Controlled prospective randomized trials could help resolve this controversy and confirm this subgroup effect.

2.2. Exercise interventions

With increasing recognition of ICU-AW and related physical impairments, there has been an increasing interest in early ICU-based exercise/rehabilitation strategies. These interventions have shown reductions in durations of mechanical ventilation and ICU stay as well as improved physical function [19]. However, existing studies have not reported nutrition intake or have grossly underfed their patients [20–23]. Hence, there may be an opportunity to simultaneously optimize the ICU delivery of nutrition and early ICU rehabilitation.

2.3. Studies in support of combined administration of early nutrition and early exercise

In various non-critically ill populations and in various conditions with muscle atrophy, combining protein and exercise interventions have the largest treatment effects compared with either nutrition or exercise alone. For instance, in older people, exercise along with protein supplementation may promote greater rates of protein synthesis [24,25] and greater improvements in strength compared with exercise alone or nutritional supplements [26–28]. Other studies in patients with obesity [29], HIV/AIDs [30], chronic obstructive pulmonary disease [31] and healthy volunteers undergoing 60 days of bed rest [32,33] suggest that the nutritional intervention, alone, has minimal effect on muscle, but that the combination of exercise and nutritional intervention yields the greatest improvement in muscle mass and strength. In a recent meta-analysis, protein supplementation, when combined with resistance-type exercise training, enhanced gains in strength and muscle mass in both young and elderly non-critically ill adults compared with groups that did not supplement with protein [34]. Accordingly, recent international guidelines recommend 1.0–1.2 g of protein/kg/day protein intake and daily exercise in older adults (resistance training and aerobic exercise) [35].

Although the generalizability of these findings to critically ill patients is unclear, there is biologic plausibility that applying this combined approach may optimize the reduction of muscle atrophy and physical impairments. Patients in the ICU have substantial muscle wasting, which may be related to several postulated factors among which are inflammation, insulin resistance and disuse atrophy [1,36].

2.3.1. Inflammation has a catabolic effect on muscle

Regardless of health status and age, inflammation is associated with muscle atrophy. Pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6, are particularly catabolic and are elevated not only in critically ill patients, but also with prolonged bed rest [37–39]. Interestingly, short-term bed rest (7 days) in older adults was associated with increases in some pro-inflammatory cytokines in muscle despite the absence of change in systemic pro-inflammatory cytokines [40]. Thus, immobility may also contribute to pro-inflammatory processes, which may further exacerbate muscle atrophy when combined with critical illness in an older population.

2.3.2. Insulin resistance has negative implications on muscle mass

Insulin normally prevents muscle protein breakdown [41]. Insulin resistance is a condition in which muscle is resistant to the action of insulin, resulting in reduced insulin-stimulated glucose transport [42] and amino acid delivery into muscle [43]. In an insulin resistant state, there is increased muscle protein catabolism. In ICU patients [44], insulin resistance is generally present and associated with deleterious outcomes [45,46]. Animal models have documented the development of insulin signaling defects in muscle, leading to insulin resistance within muscle [47,48]. In humans, muscle is insulin resistant and can respond to intensive insulin therapy [49]. However, in other clinical populations, insulin sensitivity also can be modified with physical activity [50] and by increased availability of specific amino acids, such as leucine [51].

2.3.3. Disuse atrophy as a result of immobility will modify muscle protein kinetics and strength

With bed rest, associated muscle breakdown is related to functional losses and reduced protein synthesis [52]. Studies in healthy populations using diverse immobilization protocols have all demonstrated accelerated muscle loss within the first 10 days of immobilization [51–53]. With immobility [48] and prolonged bed rest [49,50], as is commonly experienced during critical illness [2,54], muscle develops anabolic resistance, where decreased uptake of amino acids reduces the ability to promote anabolism [55]. Muscle loss is further exacerbated when compounded by hypercortisolemia, which can occur endogenously from the stress response or from common exogenous administration to critically ill patients [56,57].

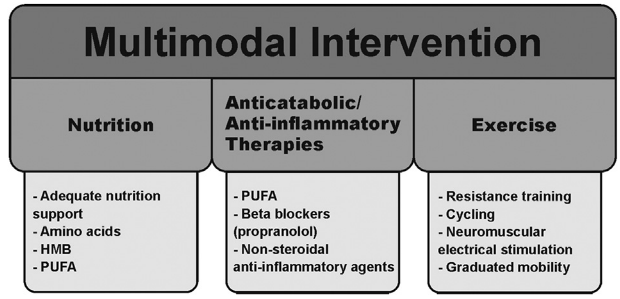
2.4. Exercise stimulates a net positive muscle protein balance

Exercise will not only enhance anti-inflammatory processes and improve muscle insulin sensitivity, but it may reduce insulin requirements. Secondary analysis of an RCT evaluating early versus late physical rehabilitation in ICU patients demonstrated reduced insulin dose for the same measure of glycemic control and reduced

ICU-acquired weakness, despite the early intervention group receiving more corticosteroids [58]. Different types of exercise, particularly resistance exercise, result in positive net muscle protein balance and reduced muscle insulin resistance, by stimulating protein breakdown and synthesis to promote muscle remodeling [57]. Exercise of any type will also enhance exercise-mediated glucose transport and increase blood flow to the muscle, which will ultimately enhance amino acid uptake into muscle to promote protein synthesis [59–62]. This finding is further enhanced with increased amino acid availability from an appropriate nutrition intervention [62,63]. Taken together, this provides the theoretical rationale for bundling the nutritional intervention together with the exercise intervention.

On the basis of the above considerations, a program of exercise in insulin resistant ICU patients with increased availability and delivery of essential amino acids may promote a more positive muscle protein balance when compared with usual care (predominantly bed rest with no or limited early exercise and underfeeding). In fact, some have proposed that in ICU patients, anabolic resistance may, in part, be due to the insufficient total calories administered to ICU patients as better nourished ICU patients have a more favorable protein balance [64]. Therefore, combining the delivery of these dual interventions may hold greater gains in ICU patient outcomes such as strength and function.

Herein, we discuss various methodological issues that may be of interest to the broader critical care research community evaluating the hypothesis that a combination of increased nutrition intake plus early exercise will result in improved anabolism, decreased muscle wasting and improved physical outcomes of critically ill patients.



Legend: PUFA: Polyunsaturated fatty acids (eicosapentaenoic acid, n-3, fish oil); HMB: β-Hydroxy β-methylbutyric acid. Multimodal interventions can include treatments from all domains. While we have focused on protein and amino acids in the proposed intervention, the potential use of n-3 fatty acids to attenuate inflammation while also promoting anabolism in other clinical scenarios could be investigated.

Fig. 1. Multimodal approach to optimize recovery from critical illness.

3. Methodological issues

3.1. Study design

To test the efficacy of a combined nutrition and exercise intervention, randomized trials are needed. A 4-arm trial might be ideal: nutrition only vs. exercise only vs. combined nutrition and exercise vs. usual care. A factorial design may be efficient if the primary endpoint is mortality as we may not expect a synergistic effect of the nutritional and exercise interventions on mortality. However, this issue is open to debate, and synergy between the nutritional and exercise on muscle and functional outcomes is likely. Thus, the study design, statistical analysis plan and sample size calculation must account for these issues.

A 4-arm Phase III RCT (or 2 × 2 factorial RCT) appropriately powered to test for a statistical interaction may not be feasible given the large sample size requirements. Furthermore, given multifactorial causes of muscle wasting, weakness and physical impairments in these patients, it is reasonable to propose combined interventions to counteract the catabolic environment, especially given strong evidence to support 'multimodal' treatments to prevent and reverse muscle deterioration in other populations [65–67]. Therefore, given the multidimensional causes of catabolism in critical care (Fig. 1), we propose a 2-group study design comparing the effect of a combined nutrition and exercise intervention vs usual care (i.e., no or limited early exercise and underfeeding) would be a reasonable starting point.

3.2. Patient selection

For trials evaluating nutrition and exercise interventions, the design of the eligibility criteria will be based on a number of factors. In general, an approach that defines a "severely ill" patient population at risk of impairment in the study outcomes may allow for the detection of a difference between an intervention and usual care arm with relatively smaller numbers of patients. However, the "severely ill" ICU population also experiences greater mortality, possibly negating the ability to efficiently detect a signal from the intervention. The population to study may best be defined as those ICU patients who suffer adverse effects (e.g. muscle loss, poor physical functioning) as a consequence of their critical illness and yet, still have the potential to benefit from the intervention with a high likelihood of survival. These risks of adverse effects from critical illness may be defined as an actual or anticipated prolonged length of stay or by the presence of organ failure(s). For example, the inclusion criteria might be adults with acute respiratory failure requiring mechanical ventilation with an expected ICU dependency (expected to be alive and needing mechanical ventilation, vasopressor therapy, continuous renal replacement therapy, or mechanical circulatory support) for a minimum of an additional 4 days beyond study enrollment. Alternatively, patients with 2 or more organ failures could be enrolled. This is similar to what was done in a recent Phase III trial of nutritional supplementation [68] which resulted in a patient population with 25–30% mortality, 8–10 days ICU stay, and 4-week hospital stay. Generally speaking, a trial would want to exclude patients with short ICU stay (due to low risk for developing weakness and a low duration of exposure to in-ICU interventions) and those with very long stays (due to differing response to treatment compared with the typical patient).

Patients who will not benefit from the nutrition or exercise interventions, whose response to the intervention may differ from the typical patient, or who may be unable to participate in the planned outcome assessments, also should be excluded from such trials. Such exclusions may include those: (1) expected to die or have life-sustaining treatments withdrawn in the next 7 days; (2) not ambulating independently prior to ICU; (3) with known intracranial or spinal cord process associated with muscle weakness at ICU admission; and (4) with primary neuromuscular disease (e.g., Guillian Barre syndrome). In addition, because there may be unknown adverse events of nutritional interventions in patients with severe end organ damage, we suggest excluding patients with fulminant hepatic failure or severe chronic liver disease (MELD score $\geq$20). Finally, given that the outcome measures described below will require the patient's compliance and understanding, we would recommend excluding patients with known moderate to severe cognitive or communication/language impairment before ICU admission.

In developing these criteria, the issue of ICU patient heterogeneity needs to be considered. Specifically, consideration is needed regarding whether a sarcopenic frail elderly patient with respiratory failure and a projected long ICU stay would benefit more versus less from the intervention than the young former football player involved in a motor vehicle crash who is ventilated for only 4 days. Body mass index, the Nutrition Risk in Critically ill (NUTRIC) score [69], presence of moderate to severe malnutrition, presence of sarcopenia, etc. represent a list of factors that could be considered when determining the potential to benefit from the interventions. In our opinion, we cannot determine with certainty which patient populations would or would not benefit from the proposed intervention based on existing data. Thus, we suggest keeping the eligibility criteria as broad as possible and consider *a priori* subgroup analyses to test specific hypotheses related to the nature of critically ill patients.

3.3. Interventions

3.3.1. The nutritional intervention

Over the past decade, numerous studies have documented that the majority of critically-ill patients do not meet consensus statement nutritional goals [70–76]. Repeated and innovative efforts over the past few years have not significantly increased calories delivered via the enteral route [77]. For an intervention to be successful at increasing calories and protein to ICU patients, additional nutrients via the parenteral route may be necessary. For example, a proposed nutritional intervention could include intravenous amino acid supplementation to achieve an effective dose of 2.0–2.5 g/kg of ideal body weight per day. The total protein dose per day would be inclusive of any protein received from enteral nutrition. This approach is consistent with the methods of administering the study nutrients in the Nephroprotect study [78].

To provide such an intervention, there are practical considerations. Ideally, intravenous amino acids would be delivered as a concentrated solution to minimize volume administration. However, such a concentrated solution would warrant maintenance of central venous access, but ICU patient care has moved to fewer days with central venous access. Alternatively, if a less concentrated solution is selected, administration also could occur via peripheral intravenous access. However, this would require more volume. A pragmatic stance could be considered: use a concentrated solution when a central line is available, use a less concentrated solution when it is not, and consider using oral high protein supplement when intravenous access is not available. There is evidence that high-protein oral nutrition solutions improve grip strength and reduce complications, including readmissions, amongst hospitalized elderly patients [79]. Consideration should be given to continuing the oral nutrition solution throughout hospitalization but at least until the exercise intervention is discontinued.

There is uncertainty whether to administer the IV amino acids as a bolus (over 1–2 h) or a continuous infusion around the clock. For practical reasons, administering the solution over a shorter period of time may be more feasible and optimize adherence. More importantly, from a theoretical point of view, bolus administration may maximize the anabolic effect expected with the therapeutic intervention. Specifically, intermittent feeding (i.e. every 4 h), mimicking typical feeding schedules may stimulate greater muscle protein synthesis than continuous administration in neonatal pigs [80]. This could be done using enteral protein supplements; however, the safety of rapid IV bolus of amino acid solutions requires further investigation. Until then, a continuous infusion would need to be given if intravenous administration is selected for study.

3.4. Timing and duration of the interventions

Optimal timing of starting the nutrition intervention is uncertain and, in a combined intervention, is linked to the timing of the exercise intervention. It would be optimal to start the exercise as soon as possible given the demonstrated benefit of early (i.e. started within 48 h of intubation) versus late (i.e. within approximately 1 week) physical rehabilitation [20]. Moreover, it would be optimal to start both the nutritional and exercise interventions concurrently as previously described. There may be some benefit to early nutritional intervention to attenuate inflammation and muscle loss, but anabolic resistance is a concern. However, exercise is expected to help overcome anabolic resistance. Hence, nutrition and exercise should be bundled and started as early as possible. Consideration could be given to continuing the interventions after ICU discharge; however, issues of feasibility may be a concern and the risk of muscle wasting, weakness and physical impairment may be less after critical illness has resolved, leading to a relatively lower benefit on the hospital ward.

3.5. Exercise interventions

There are several options for an early ICU exercise intervention that is delivered in addition to any “usual care” physical rehabilitation. Delivery of early ICU rehabilitation strategies currently varies greatly across patients and study sites and will evolve over the duration of a trial [81]. Possible interventions include: 1) graduated mobility and/or resistance training with physical and/or occupational therapy [20,23]; 2) in-bed cycle ergometry [22]; or 3) neuromuscular electrical stimulation (NMES) [82] or a variant using thermal NMES [83]. Cycle ergometry and NMES offers the advantages of increasing muscle activity without wakefulness and patient cooperation as described elsewhere [84]. As the field matures, head-to-head comparisons of various rehabilitation interventions may help more fully elucidate the most efficacious interventions; however, as previously mentioned, feasibility is an important consideration for implementation as part of routine clinical practice.

3.6. Co-interventions

In evaluating the effect of a combined nutritional and exercise intervention, other important co-interventions should be standardized to reduce potential confounding of trial outcomes. For example, all study patients should be fed according to a standardized enteral feeding protocol that is consistent with the current clinical practice guidelines [85,86]. As hyperglycemia has adverse effects on protein metabolism, blood glucose should be controlled at less than 10 mmol/L (180 mg/dL) in all groups using standard insulin dosing [87]. As sedation practices will influence the success of active participation in exercise and the delivery of usual care physical rehabilitation, sedation also should be standardized. Ventilation and weaning strategies, and fluid administration and fluid balance may also warrant standardization. It would be important to follow study ICU patients daily documenting adherence with study interventions and key co-interventions.

3.7. Baseline data collection

In order to facilitate a richer understanding of treatment effects in patient subgroups, it is important to carefully characterize baseline status. In studies evaluating nutrition and exercise interventions, we suggest the standard ICU demographic measurements listed in Table 1. Collecting these variables will also enable calculation of the NUTRIC score (a measure of nutrition risk in the ICU) and the opportunity to explore whether patients with high NUTRIC scores benefit more compared with patients with a low NUTRIC score (an *a priori* subgroup analysis) [69]. In addition, to better characterize the baseline health state of enrolled patients,

Table 1
Suggested baseline measures for studies of nutrition and exercise in critically ill patients.

Characteristic/measure	Comments
Age	
Sex	
Height	• To calculate body mass index
Weight	• As above
ICU admission diagnostic category	
Charlson comorbidity index [106]	• Widely-used weighted comorbidity score obtained from review of in-patient medical records, with higher score associated with increased 1-year mortality
Functional comorbidity index [107]	• Comorbidity score that can be obtained from review of in-patient medical records, with higher score associated with worse 1 year functional outcome (not mortality); specifically validated to predict 1 year SF-36 physical function in acute respiratory distress survivors [108]
Additional selected comorbidities, as needed	• Additional comorbidities should be selected and carefully defined for accurate data collection based on the specific research question or study population (e.g., psychiatric comorbidities, including drug and alcohol use disorders).
APACHE score in first 24 h of ICU admission [109]	• Widely used weighted score to quantify severity of illness in critically ill patients
SOFA score [110]	• Widely used organ failure score; can be measured on a daily basis • May correlate with loss of muscle mass [15]
Time from hospital admission to ICU admission	• A potential marker of acute undernourishment and in activity before ICU admission
NUTRIC Score [69]	• Validated measure of nutrition risk that identifies which patients may benefit most from nutrition therapy
Clinical frailty scale [88]	• Score describes baseline functional capacity which predicts for higher short-term and long-term mortality.
Katz activities of daily living (ADL) scale [89]	• Can obtain from multiple sources with some evidence of patient-proxy agreement in ICU patients [95] • Will provide baseline value to compare with post-discharge follow-up measurements
Lawton instrumental activities of daily living (IADL) scale [90]	• As above
Medical Outcomes Study Short Form-36 (SF-36) [91]	• Recommended for, and commonly used, in ICU settings [111] • Has established population norms/utilities [112] • Requires licensing fee • Will provide baseline value to compare with post-discharge follow-up measurements
History of hospitalizations over past year	• To describe the patient's health trajectory prior to the index hospitalization for study enrollment

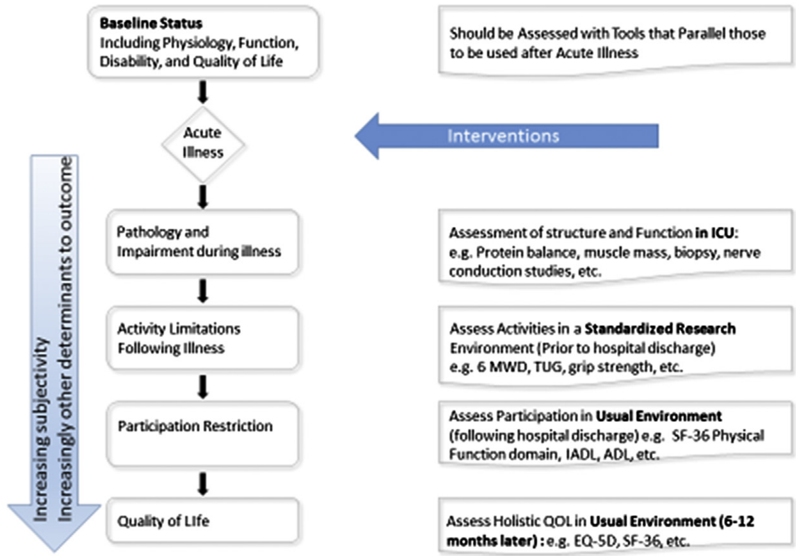
we propose obtaining a proxy assessment of frailty (using the clinical frailty scale) [88], baseline activities of daily living (ADL) [89] and instrumental activities of daily living (IADLS) [90], baseline physical function (using the SF-36 physical function domain) [91], and history of recent hospitalizations (over the past year; to understand the patient's health trajectory). While there are challenges to obtaining valid and reliable baseline measures of quality of life (e.g. balancing bias from patient retrospective recall with disagreement between proxy versus patient-based assessment) [92,93], more objective measures, such as those captured in frailty [94] and functional assessment [95] (including the physical function domain of SF-36 [96]), are reliable in some studies.

3.8. Outcomes

To increase our understanding of clinical trial data, considerable effort is directed to developing standardized approaches to measuring 'core outcome' sets across several clinical domains [97]. These sets represent the minimum that should be measured and reported in all clinical trials of a specific condition, and are also suitable for use in clinical audit or research other than randomized trials [98]. To be useful to the broader ICU research community, we put forth preliminary suggestions for evaluating the outcomes of trials that examine the effect of nutrition and exercise [1]. In doing so, we are not saying a particular trial should be restricted to outcomes specified herein. Rather, there is an expectation that the core outcomes will be collected and reported, making it easier for the results of trials to be compared, contrasted and possibly combined as appropriate while researchers continue to explore other outcomes as well. We stress that this evaluation framework is a starting place and will certainly evolve over time as new evidence accumulates.

There are numerous outcome measures that could be considered when evaluating whether a combined early ICU nutrition and exercise intervention positively affects patient function. A recent systematic review has summarized physical function measures for ICU survivors [99]. Iwashyna and Netzer have created a conceptual framework to organize and describe these possible outcomes and their timing of assessment, based on the World Health Organization's International Classification of Functioning, Disability, and Health [100]. For this program of research, we introduce a modified version of this framework herein (Fig. 2). This framework categorizes the outcomes of survivors of critical illness into 4 domains: 1) Structure and Function; 2) Activity Limitations within a Standardized Setting; 3) Participation Restriction in Usual Environment; and 4) Quality of Life in Usual Environment (see Tables 2–5). This framework distinguishes what a patient can do in a structured research environment (such as a hospital or clinic setting) from what they can do in their usual setting (e.g., home) that may have adaptations. It considers outcomes ranging from those directly related to the harms of critical illness via evaluating the intervention's impact on structure and function to more distal measures, such as patient reported quality of life. This framework acknowledges that patients with similar impairments in structure and function and limitations in activities may have considerable variance in participation outcome measures in their usual setting and in quality of life outcomes due to various modifiers of outcomes, including differences in physical and psychological adaptations and related requirements for participation.

A rigorous program of research will evaluate the impact of the intervention on measures across domains of the framework presented herein. Tables 2–5 contain our suggestions for measures across the domains, recognizing that measures of skeletal muscle mass may have poor correlation with measures of function and measures of function may have poor correlation with measures of participation [54]. Altered physiology, presence of comorbidities, and patient heterogeneity may lead to variations in the nature of the relationship between muscle mass and function [101]. Current evidence from trials of anabolic therapies in patients with cancer cachexia have proven that improvements in muscle mass are not



Legend: Adapted from Iwashnya[100].
ICU- intensive care unit; 6MWD- 6 minute walk distance; TUG- timed up and go; SF-36- short-form 36; IADL- instrumental activities of daily living; ADL- activities of daily living; QOL- quality of life; EQ-5D- Euroqol 5 dimension health status instrument.

Fig. 2. A framework for evaluating impact of nutrition and exercise interventions in survivors of critical illness.

Table 2
Suggested measures of body structure and function impairment in the intensive care unit.*

Measure	Comments
Amino acid metabolism/protein synthesis (tracer studies)	• Most proximal endpoint to assess effect of protein supplementation on anabolism • Recent developments have made these studies more practical in the ICU setting [113,114] • Further validation work is needed
Body composition (skeletal muscle mass)	• Ultrasound to measure thickness of quadriceps has good reliability [115] with validation data in the ICU setting evolving; required equipment is available in some ICUs and non-experts can be trained to conduct evaluations • Ultrasound to measure cross-section area of rectus femoris may require equipment not routinely available in some ICUs • CT scan of L3–L4 may be used if available for clinical reasons [104] • Other measures (DXA and BIA) not practical or validated in the ICU setting [101]
Electrophysiology (electromyography/nerve conduction studies – EMG/NCS)	• May provide insight into pathophysiology of nerve and muscle dysfunction [104] • Limited screening evaluation is sensitive and specific for critical illness polyneuropathy/myopathy and ICU-acquired weakness, associated with hospital mortality [116] • Requires expensive equipment and trained expertise to operate and interpret [5]
Upper and lower extremity muscle strength (manual muscle testing with MRC sum-score)	• Commonly-used measure in ICU studies • Requires no measurement equipment or devices • Feasibility and inter-rater reliability varies across studies and time points for assessment (i.e., in-ICU versus out-patient) • Requires rigorous training and standardization [117] • Uses ordinal scale with widely variable differences in muscle force between each 1-unit increase in score [118,119] • Has ceiling effect for stronger patients • Lacks normative/reference values
Strength of specific muscle groups (hand-held dynamometry)	• Less commonly used measure in ICU studies • Requires purchase of equipment • Positive initial data on inter-rater reliability in ICU patients [120] • Measurement dependent on rater strength and experience [119] • Normative/reference values available [121]
Hand-grip strength (hand-grip dynamometry)	• Simple and feasible to conduct • Requires inexpensive equipment and regular calibration • High inter-rater reliability in ICU patients [119] • Conflicting data regarding validity as measure of overall muscle strength in ICU patients • Normative/reference values available [122]

Suggested measures to assess impact of nutrition and exercise interventions on structure and function while patient is in the ICU.
ICU – Intensive Care Unit; CT – Computerized Tomography; DXA – Dual-energy X-ray absorptiometry; BIA – Bio-impedance analysis; MRC – Medical Research Council.
* Given complimentary information obtained, multiple measures of structure and function impairment may be used.

Table 3
Suggested measures of activity limitations in standardized research environment for studies of critically ill patients.

Measure	Selected comments
6 min walk test of functional exercise capacity	• Strong psychometric/clinimetric properties in both acute respiratory failure survivors and chronic respiratory disease patients [123,124] • Requires >20 min to complete a single test given required pre-test rest period [122] • Has modest equipment/set-up requirements • Recommended to perform test twice due to learning effect in chronic respiratory disease patients [122]; but difference with repeat testing may be small in survivors of acute respiratory failure [125] • Difficult to perform in home setting given recommended lap length of ≥30 m

Suggested measures to assess impact of nutrition and exercise interventions on activity limitations after ICU discharge. Other measures to consider include 4 m timed walk [126], timed up and go (TUG) [127,128], physical function ICU rest (scored [129,130]), and the functional independence measure [131], but published evaluation of their psychometric/clinimetric properties is still evolving.

Table 4
Suggested measures of participation restriction in usual environment for studies of critically ill patients.

Measure	Selected comments
Activities of daily living and instrumental activities of daily living [88,89]	• Can obtain from multiple sources with some evidence of patient-proxy agreement in ICU patients [95]
Return to work/prior activity	• Commonly used measure • Patient-centered • Lacks standardized definition but used in many studies [132]
Living location	• Same as above

Suggested measures to assess impact of nutrition and exercise interventions on participant restriction at home or usual care setting after discharge from acute care hospital.

Table 5
Assessment of generic health-related quality of life in usual environment for studies of critically ill patients.

Measure	Selected comments
Medical Outcomes Study Short Form-36 (SF-36)	• Commonly used in ICU and non-ICU settings • Recommended for use in ICU survivors [110] • Has established population norms/utilities [111] • Requires licensing fee
EQ-5D (3-level or 5-level)	• Commonly used in ICU and non-ICU settings • Recommended for use in ICU survivors [110] • Simple and quick to administer • Has established population norms/utility [133] • Requires registration to use, with possible licensing fee

Suggested measures to assess impact of nutrition and exercise interventions on health-related quality of life in the months or years after discharge from acute care hospital.

always translated to improvements in muscle function (e.g. Anamorelin from Helsinn and Enobosarm from GTx Inc.) [102].

As we consider how to apply this framework, given that there are many measures that can be considered, there is a need to prioritize measures to minimize respondent burden, research time, and cost. The choice of primary and secondary outcomes across potential outcome measures will be a function of the research question and candidate intervention. In early stages of evaluating interventions, measures of effect on structure and function, or direct mechanisms of the intervention, may have higher priority, such as measures of anabolism (e.g., protein balance studies using tracers [103], body composition [104] and/or activity level in the ICU or hospital) [98]. These preliminary signals will provide justification for future studies to evaluate patient-centered outcomes at longer-term time points.

We posit that a patient-reported measure of quality of life will be less sensitive to our combined interventions because it has many determinants that will be unaffected by nutrition and exercise (e.g., social support, home environment, adaptability, and coping strategies). Accordingly, given the aim of improving physical performance of surviving patients, the primary outcome should be a measure of activity limitation in the research environment where an objective measure can be obtained. If the intervention is a multifaceted complex healthcare intervention aimed at reintegrating surviving patients into their home environment, then a patient-reported participation measure may be more appropriate.

The optimal timing of assessing the primary outcome is unknown. To evaluate the full effect of the ICU-based intervention, the assessment should be shortly after ICU discharge when the patient has recovered from acute aspects of critical illness. Once the patient leaves hospital, there are practical and logistical challenges to follow patients or to have them come back to hospital and perform standardized testing. Hence, we suggest measurement of activity limitations after ICU discharge and prior to hospital discharge. Given the difficulties inherent in blinding early exercise interventions, it would be important to at least blind the trained outcome assessors.

We also consider it important to measure the following traditional ICU outcomes: duration of mechanical ventilation, ICU-acquired infections, ICU re-admission, re-intubation, length of ICU and hospital stay, hospital discharge location, mortality at different time points, and resumption of prior activities (e.g. return to work).

3.9. Statistical issues

Within RCTs of critically ill patients, high mortality is expected and may vary across the treatment groups. In studies where mortality is not the primary endpoint, researchers must consider how to incorporate mortality into statistical analysis of the primary endpoint. For example, in a trial with the 6-min walk test as the primary endpoint, there will be several categories of subjects: those who die prior to ICU discharge, those who survive the ICU but are unable to complete the 6-min walk test, and those who undertake the 6-min walk test with various distances walked. To adhere to the intention to treat principle (i.e. evaluating all randomized subjects within their original treatment allocation), we recommend the use of a method proposed by Lachin [105] where the above categories of subject outcomes are ranked, such as: 1) ICU death worse than ICU survival; 2) being unable to do the 6-min walk test worse than attempting the 6-min walk test; 3) a shorter 6-min walk distance is worse than a longer distance. The ranked-outcome could then be compared across treatment groups using the rank-based Mann–Whitney *U* test. In this way, we can accommodate the competing risk of mortality along with the functional outcome score measured in survivors. In RCTs where the follow-up period stretches beyond ICU or hospital discharge, within the group of patients who die, patients may be ranked assuming that ICU or hospital death is worse than post-ICU death, and that patients dying after hospital discharge could be ranked according to the when the deaths occurred relative to hospital discharge.

4. Concluding remarks

Survivors of critical illness commonly exhibit muscle weakness, which contributes to impairments in their physical function and quality of life, while increasing healthcare utilization. We posit that to maintain optimal muscle mass, strength and physical function, the combination of nutrition and exercise may have the greatest impact on physical recovery of survivors of critical illness. Randomized trials testing this and related hypotheses are needed. We discussed key methodological issues and proposed a common evaluation framework to stimulate work in this area and standardize our approach to outcome assessments across future studies.

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Contributions

All authors contributed to the drafting of the article and revised the article for important intellectual content, give final approval of the version to be published, and agree to act as guarantor of the work.

Conflict of interest

None of the authors have any competing interests to declare.

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