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EDITORIAL

A critical view on primary and secondary outcome measures in nutrition trials

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In this issue of *Intensive Care Medicine*, Allingstrup et al. report the results of the EAT-ICU trial. In this single-center study, mechanically ventilated ICU patients were randomized to early goal-directed nutrition (guided by indirect calorimetry and 24-h urinary urea measurements) versus standard of care [1]. The primary outcome of the study was the physical component summary score of SF-36 at 6 months. Secondary outcomes included mortality, rates of organ failures, serious adverse reactions, infections in the ICU, length of ICU or hospital stay, and days alive without life support at 90 days. Primary and secondary outcomes did not differ between the intervention and control groups.

Recently, several important randomized controlled trials (RCTs) in critical care nutrition have been conducted. One noticeable observation across these trials is the variation in the used primary and secondary outcome measures. The spectrum of outcome measures has been broad and included mortality endpoints (at different time frames), new infections acquired during the ICU stay, the duration of ICU dependency, days alive after ICU discharge, duration of renal dysfunction, just to name a few [2–4]. These outcome measures are implicitly meant to reflect different domains such as nutrient delivery, biologic response, safety, functional outcomes, and others (Fig. 1). Likewise, a scoping review reported the use of 250 unique measurement instruments of physical, cognitive, mental health, or quality of life outcome used across 425 critical care studies [5]. Unfortunately, detailed definitions of these outcome measures are often not provided, and when provided they varied across studies. Reviews of trials reporting mechanical ventilation-related outcome measures demonstrated that no more than 25% of trials reported a definition for mechanical ventilation duration, and approximately 65% reported a definition of ventilator-free days. When definitions were provided, there was substantial variation in the definition used and the time point of evaluation [6–8]. The relatedness of outcome measures to the intervention is also critical. As an example, 28-day mortality is often required by the regulatory authorities as the primary outcome measure, although its relevance is poor for most therapeutic nutritional interventions in the ICU. A nutritional intervention could be neutral or safe on a short-term basis, while beneficial on a long-term basis.

Such variation in the used outcome measures and in their definitions has several important implications. It threatens the external validity of the generated evidence. With the lack of clear definition, the robustness of several variables may widely differ between centers (e.g., diagnosis of infection, sepsis or weaning from invasive ventilation etc.), potentially affecting the internal validity of the study. In addition, variation creates a major challenge in comparisons across trials and in accurately combining data for meta-analyses [7, 8]. When planning a new trial, sample size calculations are usually based on data from previous studies, so if the outcome measures used are defined differently, then the accuracy of sample size calculation would be questionable.

These observations highlight the urgent need for agreement on developing a minimum core outcome set for critical care nutrition trials to ensure consistency in outcome selection and measurement. Selection of outcome measures should be based on objective criteria, including content validity, validity, structural validity, internal consistency, reliability, cross-cultural validity, and feasibility [9]. In addition, definitions of outcome measures should be detailed and specific [7].

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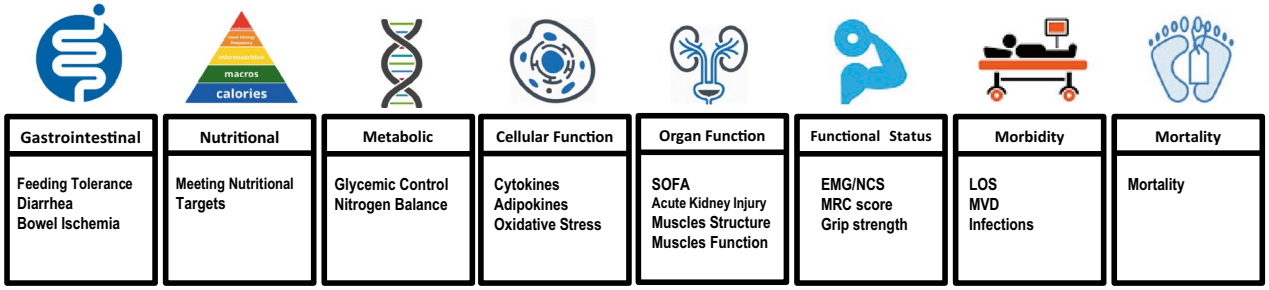

Fig. 1 Examples of outcome measures used in critical care nutrition studies. *SOFA* sequential organ failure assessment, *EMG* electromyography, *NCS* nerve conduction studies, *MRC* Medical Research Council, *LOS* length of stay, *MVD* mechanical ventilation duration

Another important point is the increasing recognition of the effect of nutrition on functional outcomes and the interaction of nutrition and rehabilitation [10]. At present, nutrition and exercise are mostly studied independently. The focus of nutrition studies has largely been on short-term outcomes, such as 28-day mortality, infectious complications, mechanical ventilation duration, and length of stay rather than long-term functional status. When functional outcomes are used, they are assessed as secondary outcomes with different studies using different domains and heterogeneous tools, making comparison very difficult. The investigators of EAT ICU are to be complimented on the use of the physical component summary (PCS) score of SF-36 as recognition of the relationship between nutrition and functional outcome. Evaluating functional outcomes in critical care studies has not been common [5]. Among eligible articles found in the scoping review [5], only 25 measured physical activity limitations (6%), 40 measured cognitive activity limitations (9%), 114 measured mental health impairment (27%), 196 measured participation restriction (46%), and 276 measured quality of life (65%). [5] Like EAT ICU, 55% of critical care studies reporting quality of life used SF-36. However, this was far from being uniform; the same review reported the use of 58 unique instruments to measure quality of life in 196 studies (with an article to instrument ratio = 4.8) [5].

Therefore, there is a need for agreement on including functional outcomes in the core outcome set for studies of critical care nutrition to enable combination and comparison, especially given that measuring these outcomes is resource-intensive. The selection of these outcome measures will require input from relevant stakeholders, and evaluation of properties of different measurement instruments. Such selection may be guided by existing frameworks, e.g., the WHO framework for measuring health and disability (International Classification of Functioning, Disability and Health, ICF) [11].

Finally, there is a need to have a priori plans to combine RCTs, which means that data definitions, including outcome measures, must be standardized and agreed upon. Conducting RCTs is resource-intensive and time-consuming, and systematic reviews and individual patient data meta-analyses would increase the utility of the data but are generally underutilized [12, 13]. In fact, individual patient data meta-analyses are lacking in critical care nutrition at present. An excellent model is the individual patient data meta-analyses of the ProCESS, ARISE, and ProMISe trials of early, goal-directed therapy for septic shock [14]. This is becoming more pressing than ever before, as data sharing plans are now mandated in RCTs [15].

In conclusion, there is a need for a minimum well-defined core outcome set that should be measured and reported in all critical care nutrition trials. This core outcome set will need to include relevant outcome domains, such as functional outcome. Development of such a core outcome set will improve the efficiency of critical care nutrition research by facilitating comparison of studies and combining data in individual patient data meta-analyses and will open additional opportunities for wide-scale collaboration.

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