UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM ALIMENTAÇÃO, NUTRIÇÃO E SAÚDE

RELAÇÃO DA INADEQUAÇÃO NUTRICIONAL COM A MORTALIDADE EM PACIENTES CRITICAMENTE DOENTES

ALUNA: NUTR. MARIANE KUBISZEWSKI CORUJA

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Formato da dissertação

Essa dissertação segue o formato proposto pelo Programa de Pós-Graduação em Alimentação, Nutrição e Saúde da Universidade Federal do Rio Grande do Sul:

1. Revisão da literatura sobre o tema

2. Artigo Original

Sumário

Lista de abreviaturas

APACHE II: Acute Physiology and Chronic Health Disease Classification System II

AUC: Área Sob a Curva

CTI: Centro de Tratamento Intensivo

ESPEN: European Society for Clinical Nutrition and Metabolism

IC: Intervalo de Confiança de 95%

NUTRIC: Nutrition Risk in the Critically ill

NUTRIC-m: Nutrition Risk in the Critically ill modificado

OR: Odds Ratio

SOFA: Sequential Organ Failure Assessment

TNE: Terapia Nutricional Enteral

VM: Ventilação Mecânica

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Resumo

A doença crítica representa um estado de estresse catabólico, o qual é produzido pela resposta inflamatória sistemica. A doença crítica é entendida em diferentes estágios: (1) fase aguda que é composta por dois períodos: período inicial (1-3 dias), que se caracteriza por instabilidade metabólica e aumento severo do catabolismo, e período tardio (2-4dias), que reflete em perda muscular significativa e estabilização dos distúrbios metabólicos. E a fase tardia (pós-aguda) segue com a melhora da inflamação, estado catabólico e internação prolongada e reabilitação.

Todo esse processo resulta pode resultar em piores desfechos como maior tempo de internação no Centro de Tratamento Intensivo (CTI), riscos de infecções, tempo de uso de ventilação mecânica, óbito entre outros. Neste sentido, a importância da nutrição no doente crítico é cada vez mais reconhecida, principalmente em pacientes com longa permanência em CTIs que requerem suporte especial por este estado de catabolismo severo. De fato, a desnutrição é uma manifestação clínica frequente neste grupo de pacientes e, esse quadro pode ser agravado pela presença do risco nutricional e da inadequação da terapia nutricional.

O risco nutricional deve ser avaliado para realização de intervenções nutricionais precoces. O *Nutrition Risk in the Critically ill* (NUTRIC) é um instrumento de triagem nutricional desenvolvida especificamente para pacientes críticos e avalia critérios como idade, escores de gravidade de doença - *Acute Physiology and Chronic Health Disease Classification System II (*APACHE II) e *Sequential Organ Failure Assessment* (SOFA), número de comorbidades, dias de internação prévios à admissão no CTI e níveis séricos de interleucina 6 (IL-6). O instrumento foi revalidado retirando do escore final as medidas da IL-6, denominada então de NUTRIC modificado (NUTRIC-m). Diversos estudos já vêm demonstrando que o alto risco nutricional, identificado pelo NUTRIC, está associado ao maior risco de desfechos clinicos desfavoráveis, dentre eles, a mortalidade.

Em relação a terapia nutricional, o fornecimento adequado de nutrientes, conforme o quadro clínico e fase da doença crítica, evita complicações, reduz perda de massa magra e pode melhorar desfechos negativos. A tolerância

metabólica deve ser considerada, onde a inflamação na fase aguda ou anabolismo na fase pós- aguda podem incluir riscos dependendo do aporte calórico- proteico ofertado. O início precoce, entre 24 e 48 horas de internação é indicado, sendo um dos principais motivos a integridade funcional e trofismo do trato gastrointestinal. A recomendação ideal de calorias e proteínas na doença crítica ainda é bastante discutida, principalmente em relação as fases da doença. As diretrizes internacionais e nacionais, sugerem, em geral, um aumento lento e progressivo das metas calóricas e proteicas, levando em consideração sempre o quadro clínico e tolerância do paciente. No entando, as recomendações ideais das ofertas de calorias e proteínas durante as fases da doença crítica ainda são bastante discutidas, seus riscos, benefícios bem como a importância da adequação da terapia nutricional.

Neste sentido, realizamos um estudo de coorte prospectivo em pacientes críticos com suporte nutricional exclusivo por via enteral, nos primeiros 10 dias de admissão em uma CTI. Os principais objetivos foram avaliar a relação, na fase aguda (período inicial e tardio) do consumo calorias e proteínas e sua adequação nutricional com: (1) o risco nutricional, identificado pelo NUTRIC-m, e, (2) com a mortalidade em um período de 30 dias.

Palavras- chave: doença crítica, calorias, proteína, enteral nutrição enteral, mortalidade.

CAPÍTULO I

REVISÃO DA LITERATURA

1. Centro de Tratamento Intensivo: o paciente e a doença crítica

Pacientes de Centro de Tratamento Intensivo (CTI) alteram seu estado nutricional rapidamente, e em um grau ainda maior naqueles que são malnutridos previamente à internação, o que resulta em desfechos clínicos desfavoráveis (1). Os pacientes críticos, em sua grande maioria, apresentam um estado de estresse catabólico induzido pela resposta inflamatória sistêmica, o que gera aumento da demanda metabólica (2).

A doença crítica está associada à resposta inflamatória sistêmica, que causa complicações como aumento da morbidade, mortalidade, e tempo de hospitalização dos pacientes (2). As fases da doença crítica geralmente são descritas como *"ebb*" e "*flow".* A fase *ebb* compreende a fase inicial, hiperaguda, geralmente com a característica da instabilidade hemodinâmica, a fase *flow* é o período subsequente, com instabilidade metabólica e catabolismo que pode ser mais ou menos prolongado após o período de anabolismo (3). A fase aguda é composta por dois períodos: período inicial, de instabilidade metabólica e aumento severo no catabolismo, e período tardio, de perda muscular significativa e estabilização dos distúrbios metabólicos. A fase tardia (pós-aguda) segue com a melhora da inflamação, estado catabólico e internação prolongada e reabilitação / ou fase crônica. Nesta fase pode-se observar a tendência de retorno ao estado clínico prévio, com melhora clínica que é observada pela dispensa de métodos de suporte avançado (3).

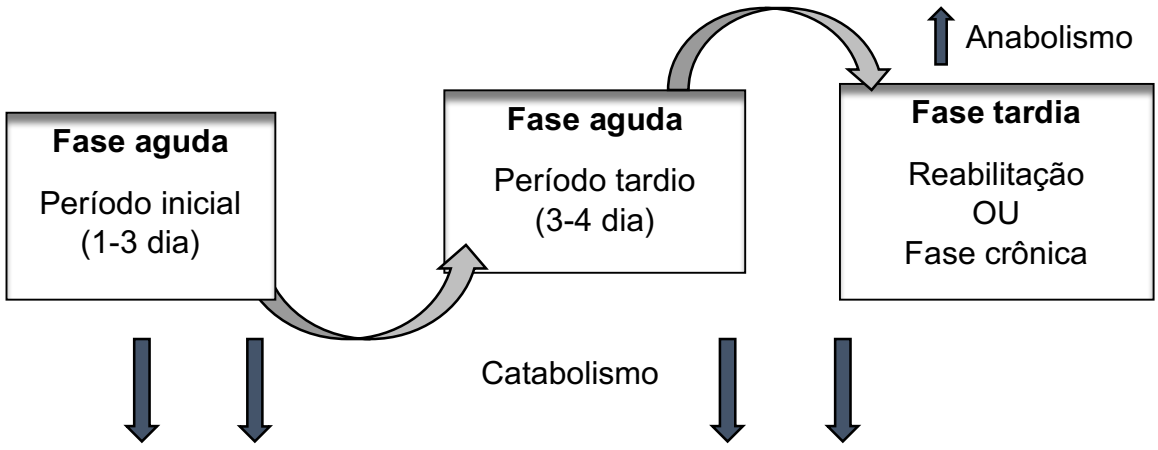

Figura 1. Progressão da doença crítica. Adaptada de Singer et al., 2018 (3)

2. Desnutrição no paciente crítico

A desnutrição pode ser definida como um estado no qual uma deficiência, excesso ou desequilíbrio de energia, proteínas e/ou outros nutrientes causam efeitos adversos sobre a funções do corpo (4). Entretanto, os critérios para identificação de desnutrição, em pacientes críticos, muitas vezes, se torna complexo, alterações de balanço hídrico, relacionados a dados antropométricos, por exemplo, podem ser confundidores na interpretação. Também dados objetivos, como peso atual/ usual e histórico nutricional, nem sempre estão disponíveis (3, 4).

O tratamento intensivo em si ocasiona o desenvolvimento de desnutrição nos pacientes (5). Uma metaanálise, que incluiu 20 estudos com 1,168 pacientes demonstrou que a prevalência de desnutrição em pacientes críticos pode alcançar taxas de 38% a 78% (6). A alta taxa de desnutrição no CTI, e a inadequação da oferta de nutrientes e os processos catabólicos, intensificados durante a doença crítica, aceleram a perda de massa magra (7,8).

De fato, a perda da massa total da proteína do corpo, principalmente dos músculos esqueléticos é frequentemente observada nos pacientes criticamente doentes (9). Um balanço nitrogenado negativo e perda de massa muscular é refletido devido ao aumento da degradação de proteínas e consequentemente um saldo total negativo (9). Dessa forma, a resposta metabólica propicia o suprimento de aminoácidos para outros órgãos e assim serve de substrato para a gliconeogênese e síntese de proteínas, como as de fase aguda, necessárias para defesa imune e reparação de feridas (9). Ainda, o uso de ventilação mecânica (VM) e a terapia de substituição renal são condições que estão relacionadas a lesão muscular e a depleção proteica, logo, a presença da desnutrição pode dificultar a retirada desses suportes (5). Neste sentido, a provisão adequada de nutrientes pode ser um fator de risco modificável para os resultados dos pacientes reduzindo as chances de um quadro grave de desnutrição e de desfechos negativos, como a mortalidade (10).

3. Avaliação do risco nutricional em pacientes criticamente doentes

O risco nutricional se refere ao risco aumentado de morbimortalidade em decorrência do estado nutricional. Tão importante quanto diagnosticar desnutrição é avaliar o risco de deterioração nutricional naqueles pacientes em situações que podem estar associadas a problemas nutricionais (11). No âmbito hospitalar e no cenário de unidades de tratamento intensivo é necessário detectar os pacientes em risco nutricional, pois, dessa forma, pode-se realizar intervenção nutricional primária, evitando-se a instalação da desnutrição por meio de medidas preventivas (11).

O *Nutrition Risk in the Critically ill* (NUTRIC) é um instrumento desenvolvido para avaliar o risco nutricional em pacientes admtidos em CTI (12). Ele engloba variáveis, como escores de gravidade de doença - *Acute Physiology and Chronic Health Disease Classification System II (*APACHE II) e *Sequential Organ Failure Assessment* (SOFA), idade, número de comorbidades, dias de internação prévios à admissão no CTI e níveis séricos de interleucina 6 (IL-6) (12). NUTRIC é considerado uma fácil ferramenta a ser utilizada, pois contém variáveis rotineiramente utilizadas na maioria dos CTIs, exceção para a IL-6, que não é frequentemente solicitada devido ao seu alto custo. Assim, outra versão do NUTRIC foi criada posteriormente, retirando do escore final as medidas da IL-6 (13). Sendo esta nova proposta denominada de NUTRIC modificado (NUTRIC-m) (13). Para avaliação são considerados pacientes com maior risco nutricional os que apresentarem escore ≥6 (para a versão original) ou ≥5 (para a versão modificada) (13).

Estudos em pacientes críticos vêm analisando o desempenho do NUTRIC em suas duas versões na avaliação de risco nutricional e na predição de desfechos clínicos (14). Estudo retrospectivo realizado em 482 pacientes críticos com sepse admitidos em um hospital terciário avaliou o desempenho de ambos os escores, NUTRIC e NUTRIC-m (Jeong). Neste estudo os instrumentos demonstraram associação do alto risco nutricional com maior tempo de internação no CTI e uso de VM (14). Na avaliação de desempenho, a área sob a curva (AUC) dos escores NUTRIC e NUTRIC-m para predição de mortalidade em um período de 28 dias foi AUC 0,762 [Intervalo de Confiança (IC) 0,718 - 0,806] e AUC 0,757 (IC 0,713 - 0,801), respectivamente (14). Também, em um

estudo prospectivo em 384 pacientes criticamente doentes foi observado uma associação positiva entre o risco nutricional, avaliado pelo NUTRIC, e o maior risco de mortalidade (15). Ainda nesse contexto, em estudo retrospectivo com 208 pacientes críticos, duas ferramentas de triagem nutricional, recomendadas para ambientes de CTI, NUTRIC e o *Nutritional Risk Screening* -2002 (NRS-2002), foram comparadas. A análise entre os instrumentos resultou em concordância fraca (Kappa < 0,40). Na amostra total quase metade dos pacientes foram classificados como alto risco pelo NUTRIC e apenas um terço pelo NRS-2202 (16).

4. Terapia nutricional do paciente crítico

Na doença crítica, os objetivos da oferta da terapia nutricional são fornecer nutrientes/ dieta adequada a condição clínica, prevenir deficiências nutricionais, atenuar a perda de massa magra corporal, evitar complicações e melhorar desfechos clínicos (3). A terapia nutricional previne lesão celular oxidativa, modula favoravelmente e atenua respostas imunológicas (2). Enquanto a tolerância metabólica pode ser extremamente limitada pela grave inflamação durante a fase aguda da doença crítica, levando ao risco de "superalimentação", durante a fase pós- aguda, com a inflamação crônica ou início da recuperação/ reabilitação, essa mudança para o anabolismo, pode incluir o risco de "subalimentação" (17). A produção de energia endógena no início da doença crítica não pode ser anulada pela terapia nutricional, assim, recomenda-se um aumento lento e progressivo da oferta de nutrientes (18).

É importante considerar que o suporte nutricional deve ser diferente entre as fases da doença crítica, e a duração delas pode ser variável entre indivíduos pelas diferentes injúrias que levaram a doença (trauma, pacientes cirúrgicos ou clínicos, por exemplo) ou idade e peso corporal que devem ser ajustados individualmente de acordo perfil metabólico e fase (3, 19). Em termos catabólicos, a resposta metabólica ao estresse, pode produzir 50-75% das necessidades de glicose (20).

A terapia nutricional enteral (TNE) é indicada quando não é possível administrar suas necessidades por via oral por ser impraticável, inadequada ou insegura (21). Os efeitos aprimorados TNE são alcançados fornecendo uma

quantidade ideal (≥80%) do total de energia necessária (22). Em pacientes críticos, o início precoce, entre 24 e 48h de admissão no CTI é recomendado e preconizado (2, 3, 23). Essa orientação visa à manutenção da integridade funcional e trofismo do trato gastrointestinal; mantendo o fluxo sanguíneo local e a liberação de hormônios e agentes endógenos; impedindo a quebra de barreira e o aumento da permeabilidade das células epiteliais; mantendo o funcionamento do tecido linfoide intestinal e a liberação de imunoglobulina A; reduzindo o hiper- metabolismo e catabolismo associados à resposta inflamatória sistêmica e podendo então atenuar a gravidade da doença crítica (23). Ainda, em uma metaanálise que incluiu 21 ensaios clinicos randomizados, demonstrou que o início precoce da TNE em pacientes críticos reduziu o risco de mortalidade em 30% (2).

A recomendação ideal da oferta de calorias e proteínas durante as fases da doença crítica ainda é bastante discutida, seus riscos, benefícios e estratégias nutricionais (24- 26).

As diretrizes nacionais e internacionais de TNE para pacientes críticos sugerem uma menor oferta calórica na fase aguda e inicial da doença crítica (dias 1-3) progredindo durante as fases (3). Na fase aguda (período inicial), quando disponível, a calorimetria indireta (padrão-ouro) é indicada e as necessidades energéticas deve atingir em torno de 50-70%, na sua ausência, a opção é a regra de bolso 15-20 kcal/kg peso atual e/ou 20-25 kcal/kg em pacientes eutróficos; 11-14 kcal/kg peso atual para obesos. Na fase aguda (período tardio- dias 3-4), se sugere aumento do aporte calórico para 80-100% do alvo estipulado pela calorimetria indireta ou 25-30 kcal/kg para eutróficos e 11-14 kcal/kg para obesos (2,3,23).

Em relação ao aporte proteico, baseado nas diretrizes americanas e europeias, recentemente uma revisão sobre nutrição enteral em terapia intensiva, recomenda aporte proteico em dose baixa (até 0,8g/kg) durante a fase inicial da doença crítica, enquanto numa fase reabilitação, uma meta de >1,2g/kg pode ser considerada (25). A interação de alterações metabólicas agudas, inflamação e nutrição no início da doença crítica é complexa. (26). Um guia prático de terapia nutricional na doença crítica, sugere progressão gradual de metas nos primeiros 3 dias (aproximadamente 25% por dia) para atingimento da primeira meta proteica no 4 dia (1,3g/kg). A segunda meta seria atingida durante

a fase já crônica da doença com 1,5 - 2g/kg. Esse aumento considerável é essencial para evitar maior perda de massa e função muscular (26).

O momento ideal para a oferta nutricional proteica ainda é alvo de discussões. O fornecimento de nitrogênio a partir das proteínas por via enteral ou aminoácidos intravenosos tem como um dos principais objetivos o aumento de síntese muscular para a prevenção/ minimização da perda muscular no CTI (25-27). Na fase inicial da doença crítica, são discutidos os prós e contras da maior oferta, o aumento da síntese proteica muscular e infusão intravenosa segura e por outro lado, nenhum efeito na quebra de proteína muscular e aumento da oxidação de aminoácidos (27). É possível que, semelhantes as metas calóricas, as metas proteicas ideais mudem no decorrer da doença crítica, e que uma alta ingestão proteica seja benéfica apenas se não estiver associada a hiperalimentação (3). A *European Society for Clinical Nutrition and Metabolism* (2019) recomenda 1,3 g/kg peso sendo ofertada de forma progressiva (3). Já o guia para nutrição enteral em CTI (2021) indica a oferta nas duas fases da doença crítica: fase aguda inicial - máximo de 0,8 g/kg/dia e na fase tardia de reabilitação esse valor deve ser de > 1,2 g/kg peso (25).

5. Importância da adequação nutricional no paciente crítico

No cenário dos CTIs, no que se refere à adequação nutricional, ou seja, a quantidade ofertada e a meta pretendida os dados ainda são poucos elucidados. Alguns estudos vêm demonstrando os efeitos de diferentes ofertas nutricionais em pacientes criticamente doentes (25- 31).

Um estudo de coorte prospectivo realizado em 252 pacientes críticos demonstrou que a associação entre o risco nutricional, avaliado pelo NUTRIC, e o risco mortalidade foi modificada dependendo do suporte nutricional ofertado (28). Os pacientes com alto risco nutricional (escore ≥ 5 pontos) e com maior tempo de terapia enteral exclusiva (≥ 7 dias), apresentaram um risco 22% menor na mortalidade - em 28 dias- para cada aumento de 10% na meta de ingestão de proteína. Já os pacientes com alto risco nutricional do grupo de terapia exclusiva no período ≤ 6 dias, o risco de mortalidade aumentou aproximadamente em 30% para cada aumento de 10% de ingestão de proteínas e calorias (28).

Estudo retrospectivo em pacientes críticos em uso de VM com distintas composições de área de músculo esquelético avaliou a oferta proteica no 2° e 4° dia na internação (>1,2g /kg/dia e <1,2g /kg/dia, respectivamente) e mortalidade (29). Foi observado que pacientes com baixa área e densidade muscular, identificados por tomografia computadorizada e, com uma maior oferta proteica (>1,2g /kg/dia) a prevalência da mortalidade foi significativamente menor quando comparado aos pacientes com ingesta proteica <1,2g /kg/dia (11% *vs.* 43%, p = 0,001) (29).

Já em um estudo de coorte observacional realizado em 2.853 pacientes críticos admitidos em um CTI por um período > 4 dias e 1.605 pacientes > 12 dias, avaliou a interação da ingestão de proteína e o risco nutricional, segundo NUTRIC, e o impacto na mortalidade em 60 dias (30). Neste estudo foi demonstrado que pacientes com alto risco nutricional, nos períodos > 4 e > 12 dias, o risco de mortalidade para cada aumento de 10% na ingestão proteica reduziu em 6,6% e 10,1%, respectivamente. Não foram observadas diferenças significativas em pacientes com baixo risco nutricional (30).

O estudo *PROTINVENT* avaliou o momento de ingestão de proteína e desfechos clínicos em 455 pacientes adultos críticos em uso de ventilação mecânica prolongada (31). O baixo consumo de proteínas (<0,8 g / kg / dia) antes do 3° dia e alto consumo de proteínas (> 0,8 g / kg / dia) após o 3° dia foi associado a menor mortalidade em 6 meses [Odds Ratio (OR) = 0,609; IC 0,480 - 0,772; p <0,001) em comparação com pacientes com alta ingestão proteica geral. Este estudo também demonstrou um efeito dependente do tempo da ingestão de proteínas neste grupo de pacientes. Um aumento gradual da baixa ingestão de proteínas durante os 2 primeiros dias de permanência no CTI para intermediário no dia 3 e 5 e, alto teor de proteína a ingestão a partir do dia 6 foi associada a menor mortalidade em 6 meses (31). Colaborando com estes resultados, a adequação ≥80% de calorias e proteínas podem diminuir a permanência no CTI /hospitalar e reduzir a mortalidade em 28 dias entre pacientes de alto e baixo risco nutricional (32).

Interrupções na dieta e jejum também são variáveis que geram inadequação nutricional e risco para mortalidade no cenário do tratamento intensivo (33,34). Estudo prospectivo em 73 pacientes críticos que tiveram interrupções da nutrição enteral apresentaram uma taxa de subalimentação

maior, sendo as principais causas para pausas, a instabilidade hemodinâmica, seguido pelo alto volume residual gástrico (33). Ainda, mais recentemente, o jejum dentro do CTI foi avaliado em 533 pacientes idosos (> 65 anos) e, cada dia de jejum aumentou o risco de mortalidade em aproximadamente 17% (34).

6. Justificativa e objetivos

A perda progressiva de peso e massa muscular é uma manifestação clínica comum encontrada em pacientes críticos. Além disso, o risco de desnutrição tem elevada prevalência neste grupo de pacientes. O objetivo da avaliação do risco nutricional é identificar precocemente o risco de desnutrição, minimizar a perda de peso e sinalizar os pacientes que terão benefícios com a intervenção nutricional precoce e especializada.

O início precoce da terapia nutricional, em até 48 horas, já é bem estabelecido na literatura, porém, tratando-se de uma população tão heterogênea dentro de um CTI, há muita discussão em relação à oferta nutricional ideal, como a dose, o momento e a taxa de progressão calórica-proteica. De fato, as fases da doença crítica tornam esse oferecimento complexo. Ainda, pacientes com alto risco nutricional, avaliados pelo NUTRIC, são associados de forma significativa a desfechos clínicos desfavoráveis, principalmente mortalidade. Ainda há controvérsias em relação em relação a subgrupos de pacientes críticos que poderiam se beneficiar ou não de oferta nutricional mais agressiva e qual o momento e suporte nutricional ideal nas diferentes fases da doença crítica. É primordial que sejam realizados estudos do efeito da modificação da oferta nutricional durante a internação no CTI. Além do mais, idealmente, a identificação de fatores que definam os estágios de desenvolvimento da doença crítica, seriam de extrema importância para auxílio no planejamento da terapia nutricional.

Sendo assim, os principais objetivos do deste estudo foram avaliar em pacientes adultos críticos em fase aguda (período inicial e tardio) a relação do risco nutricional, identificado pelo NUTRIC, com o consumo calorias e proteínas e sua adequação nutricional; e a relação à ingestão calórica e proteica com a mortalidade em um período de 30 dias.

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CAPÍTULO II

ARTIGO ORIGINAL

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Higher energy and protein intake in the late period of the acute phase may be associated with a lower risk of 30-day mortality in critically ill patients.

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Highlights

- The optimal offer of exclusive nutritional support enterally during the critical illness phases is still controversial.
- We studied the relation during the acute phase (initial and late period) of calorie and protein intake and their nutritional adequacy with mortality.
- In the late period, the higher calories and protein intake were related to lower mortality.
- There was also a relation between protein adequacy and 30-day mortality.

Abstract

Purpose: To investigate whether energy and protein intake in the acute phase (early and late periods) is associated with 30-day mortality in critically ill patients.

Methods: We prospectively collected nutritional and clinical data from critically ill patients receiving exclusive nutritional support (ENS) enterally within the first 10 days of intensive care unit (ICU) stay. The ENS was classified as adequate (≥80% administration) or inadequate (<80% administration). Nutritional risk was assessed using the modified- Nutrition Risk in the Critically Ill (mNUTRIC) score. The relationships between energy and protein intake and 30-day mortality were assessed using Cox regressions adjusted for confounders.

Results: 119 patients were evaluated (71.0 ± 15.4 years; 56.3% male; 68.1% with clinical type admission). A total of 43.7% had a high nutritional risk according to mNUTRIC. The 30-day mortality rate was 22.7%. In both periods, more than 83% patients received ≥80% of ENS administration. In the late period of the acute phase, adequacy of energy (HR = 0.960; 95% CI:0.936 – 0.985) and protein (HR = 0.962; 95% CI:0.939 – 0.985) were independent predictors of 30-day mortality.

Conclusion: In critical patients, higher energy and protein intakes were associated with a lower risk of 30-day mortality during days 5 -10 in the ICU.

Keywords: critical illness, energy, protein, enteral nutrition, intensive care unit, mortality

Introduction

Critical illness is associated with a systemic inflammatory response that causes complications such as increased morbidity, mortality, and length of hospital stay (LOS) [1]. Critical illnesses can be understood at different stages [2]. The 'acute' phase is defined as the 'early acute' period (about 1 to 4 days) and as 'late' acute period (4 days after the initial acute phase). The post-acute phase (>7 days) may merge into a 'chronic' phase (uncertain duration) with persistent organ dysfunction and uncertain prognosis [2].

On average, critical patients lose nearly 2% of skeletal muscle per day during the first week of intensive care unit (ICU) admission [3]. In addition, in this group of patients, malnutrition rates can reach 38%–78% [4]. In this sense, the provision of energy and protein is important for critically ill patients, particularly those staying in the ICU for >48h [5]. In addition, it is essential to identify nutritional risks to benefit patients with early and individualized nutritional therapy [6]. Thus, the NUTRItion Risk in the Critically Ill (NUTRIC) score and/or your version modified (without interleukin-6) is a tool used for screening risk, and was designed to identify critically ill patients who would have the greatest survival benefit relative to energy intake [7].

Data on ideal protein-energy intake and nutritional adequacy during critical illness phases remain controversial [8–11]. Some studies in critically ill patients have demonstrated the effects of different nutritional offers at the acute (early and late periods) and chronic phases and their associations with unfavorable clinical outcomes [12–16]. A prospective cohort study of 252 critical patients showed that

a modifying effect of timing and dose of nutritional support may be present in some high-risk patients, according to NUTRIC, where higher energy intake at the early phase of nutritional support was associated with higher 28-day mortality [12]. In contrast, in a cohort study of critically ill patients hospitalized for periods >4 days and >12 days and at high nutritional risk (NUTRIC), the risk of mortality decreased with an increase in protein intake [13]. In accordance with these results, adults hospitalized for >24h in the ICU demonstrated that an adequacy of ≥80% of energy and proteins can reduce the ICU/hospital stay and 28-day mortality among critically ill patients with high- and low-risk nutritional status [14]. In critical patients on mechanical ventilation (MV), a gradual increase from low protein intake during the first 2 days of ICU stay was associated with lower 6-month mortality [15]. Also, in critical patients on MV with low muscle area and density and higher protein intake (>1.2 g/kg/day) had a significantly lower prevalence of mortality [16].

Considering the importance of the benefit of exclusive nutritional support in phases of critical illness and that data on optimal offer and nutritional adequacy are still controversial, the objectives of this study were to evaluated during the acute phase (early and late period), the relation between calorie and protein intake and its nutritional adequacy with: (1) nutritional risk, identified by m-NUTRIC, and, (2) with mortality within a period of 30 days in critically ill patients.

Materials and Methods

Patients

We conducted a prospective cohort study of critically ill patients in a private hospital in Porto Alegre, RS, Brazil. Patients admitted to the ICU between June 2021 and January 2023 were screened for eligibility. A patient selection flowchart

is presented in **Figure 1**.The cohort comprised adult patients (age ≥18 years) of both sexes, in use of exclusive nutritional support (ENS) enterally, in the first 10 days of ICU admission. Patients with terminal illnesses, neurodegenerative diseases, or therapeutic limitations, and pregnant women were excluded from the study. Patients were selected by daily screening within 96h after admission to the ICU; all were followed through their medical records until hospital discharge or death.

All data used in this study were collected from electronic records and from the patients themselves, the care team, and family and/or chaperones. The study was conducted according to the Declaration of Helsinki guidelines, and all procedures involving patients were approved by the hospital's Ethics Committee (CAEE 45570921.2.0000.5328). Informed consent was obtained from all the patients or their legal guardians.

Data collection

Sociodemographic and clinical data, including age, sex, type of admission (medical, surgical, trauma, and COVID-19), presence of comorbidities (diabetes, hypertension, cardiovascular disease, and cancer), laboratory measurements of C-reactive protein (CRP), treatment such as the use of vasopressor drugs, renal replacement therapy (RRT), MV, and tracheostomy were collected from the electronic records. The patients were followed up using electronic records for data collection regarding the length of stay (LOS) in the ICU, transfer from ICU to hospitalization, and 30-day mortality in the ICU.

Disease severity scores, Acute Physiology and Chronic Health Evaluation II (APACHE II), and Sequential Organ Failure Assessment (SOFA) scores were calculated based on data from the first 24 hours of ICU admission. Nutritional

screening was conducted by a trained nutritionist using the modified NUTRIC (mNUTRIC) within 48 hours of admission to the ICU. The mNUTRIC scale classifies patients according to the following criteria: age, APACHE II score, SOFA score, comorbidities, and number of days of hospitalization before admission to the ICU. Patients were identified as having a high nutritional risk when they scored ≥5 points [17]. Body mass index (BMI) values of the participants were obtained from medical records.

Nutritional therapy data

The current sample was restricted to patients who remained in the ICU for at least four days to obtain more uniform and complete data about ENS enterally. Patients with incomplete nutritional status before day 4 (n = 27), those with therapeutic limitations established in the first 10 days (n = 3), and those who died before the first 4 days (n = 4) were excluded.

For a period of up to 10 days of enteral nutritional therapy in the ICU, data related to the ENS, such as feeding started (up to 24h), time (days), goals, volume, and amount, were monitored through electronic and physical medical records of patients. Energy and protein intake were calculated using enteral formulas and complementary protein modules.

For the calculation of energy and proteins, the actual body weight was measured, reported, or estimated at admission [1,2]. Prescribed energy and protein goals were based on nutritional assessment and nutritional therapy guideline recommendations [1,2]. In patients with obesity (BMI ≥30 kg/m^2), the ideal weight was used to calculate proteins [1].

Statistical Analyses

The sample size was based on the study by Lew et al. [11] and was calculated to detect differences in mean protein adequacy between survivors and non-survivors, with a difference of 6.91% being relevant to the study. Considering 80% power, 5% significance level, a standard deviation of 12.53%, and adding 10% for possible losses and refusals, 119 critically ill patients were necessary. The sample size was calculated using the PSS Health [18].

Data are presented as the mean and standard deviation, median (25^{th} – 75^{th} percentile), or absolute values (%).

Nutritional adequacy was assessed from days 1 to 4 (early acute phase) and days 5 to 10 (late acute phase) of ENS administration and calculated as the percentage of the mean prescription divided by the mean administration values (energy and protein) during the *d* days of hospitalization: [mean administration for *d* days/mean prescription for *d* days × 100]. Energy and protein delivery by the ENS was classified as adequate when patients received ≥80% of the prescribed amount [19].

Nutritional risk was assessed using mNUTRIC, and patients were classified into two groups: low-risk (<5 points) and high-risk (≥5 points). Differences between groups were assessed using the Student's t-test. This was also done to compare survivors and non-survivors.

Cox regression analysis was performed to calculate the hazard ratio (HR) and the respective 95% confidence intervals (CIs) for 30-day mortality. All models were adjusted for the presence of ≥3 comorbidities, MV use, tracheostomy, and RRT.

To assess the adequacy in the first 10 days of ENS among survivors and non-survivors patients was constructed a graph of the mean cumulative percentage of energy and protein intake.

Calculations were performed using the Statistical Package for the Social Sciences (SPSS) 23.0 (Chicago, IL). Statistical significance was set at $P < 0.05$.

Results

Characteristics between survivors (n = 91; 76.5%) and non-survivors (n = 27; 22.7%) is shown in **Table 1**. Of the 119 patients, 56.3% were male, with a mean (± standard deviation) age of 71 ± 15.4 years and 79% were older adults. One patient was transferred from the hospital without evolution on MV, LOS, ENS at ICU in days, and 30-day mortality. Also, when data collection was completed, three patients remained hospitalized in ICU, without evolution of ICU admission hospitalization and, ENS at ICU in days, and two patients were still hospitalized, without outcome for hospital LOS.

Most patients admitted to the ICU were admitted for medical reasons (68.1%), and 45.4% of these patients had ≥3 comorbidities (diabetes, hypertension, cardiovascular disease and/or cancer). The median ICU and in-hospital LOS were 15 (9–25) and 29 (18.5 - 41), respectively. Regarding treatment received in the ICU, 49.5% used vasopressor drugs, 28% received RRT, 87.4% received MV (with a median of 10 days), and 31.1% were tracheostomized. In non-survivors, the proportion of use of these treatments was higher than that of survivors, except for tracheostomy. In the whole sample, the median APACHE II score was 17 (13–20) points, and the median SOFA score was 5 (3–7) points.

According to the mNUTRIC, a high nutritional risk was observed in 43.7% of patients, and among non-survivors, the rate was 55.6%. Regarding nutritional data, the mean BMI was 26.6 ± 4.5 kg/m², 16.8% had BMI ≥30 kg/m² and in older individuals, 12.6% had a BMI <22 kg/m². In addition, 76.5% of patients received ENS within 24 hours of admission in the ICU, and in non-survivors, this onset was observed in 66.7% of patients. Also, more than 83% patients received ≥80% of the ENS goals of calories and proteins. However, in the late period, eleven patients (n = 11) had no ENS data recorded because they were discharged from the ICU between 5 and 10 days.

Table 2 describes nutritional adequacy in the early and late acute phases of critical illness according to nutritional risk (mNUTRIC). In the early acute phase (1 - 4 days), patients with high nutritional risk had higher energy goals when compared to patients with low nutritional risk (17 ± 3.8 *vs.* 15.5 ± 4.0 kcal/kg; p = 0.044). No differences were found between the groups in terms of energy and protein intakes (early and late acute phases). However, we observed that regardless of the phases of critical illness, nutritional adequacy (energy and proteins) was ≥ 80%.

Table 3 shows the nutritional adequacy of survivors and non-survivors at 30 days. In this analysis, in the late period (5-10 days), surviving patients received more energy when compared to non-surviving patients (23.4 ± 4.8 *vs.* 20.9 ± 6.2 Kcal/kg; p = 0.035).

A Cox regression model, adjusted for the presence of ≥3 comorbidities, use of MV, RRT, and tracheostomy, was constructed to evaluate the relationship between energy and protein intake and adequacy in the initial and late acute phases with 30-day mortality (**Table 4**). Relations were observed in the late acute

phase with 30-day mortality between energy intake [HR = 0.901 (95% CI:0.831 – 0.978; p = 0.012) and its adequacy [HR = 0.960 [95% CI:0.936 – 0.985; p = 0.002), as well as protein adequacy [HR = 0.962, 95% CI:0.939 – 0.985; p = 0.002).

Figure 2 illustrates the cumulative mean percentage of energy and protein intake in the first 10 days of enteral nutritional therapy in critically ill survivors and non-survivors. In the first 10 days of ENS, non-surviving patients had a cumulative mean (%) lower energy and protein adequacy than surviving patients.

Discussion

The current cohort of ICU patients suggests that greater energy and protein adequacy during 5-10 days of hospitalization is associated with a lower risk of 30-day mortality. Each patient admitted to the ICU had different associated diseases and reasons for the need for intensive care. The ideal nutritional offer for critically ill patients is still much discussed, and the phases of critical illness make this conduct complex.

Several studies have stratified patients according to nutritional risk (by NUTRIC) to evaluate the adequacy of nutritional therapy (particularly protein intake) with clinical outcomes [12–14]. In the present study, when we evaluated the groups of patients according to nutritional risk (mNUTRIC), we observed that the ENS received did not differ between the low and high-risk groups during the early and late phases. However, in the early period, patients with high nutritional risk received a caloric goal compared to patients without risk (17 ± 3.8 *vs*. 15.5 ± 4.0 kcal/kg; p = 0.044). Separating patients according to nutritional risk, but also analyzing the days of hospitalization in the ICU, a prospective cohort study carried out in 252 critically ill patients demonstrated that the association between

NUTRIC and the mortality risk was modified depending on the nutritional support offered [12]. Patients with high nutritional risk (≥ 5 points) and a longer duration of ENS (≥ 7 days) had a 22% lower risk of mortality at 28 days for each 10% increase in target protein intake [12]. In that regard, an observational cohort study evaluated protein intake and nutritional risk according to NUTRIC and the impact on 60-day mortality [13]. In patients with high nutritional risk, in periods of >4 and >12 days, the risk of mortality for each 10% increase in protein intake was reduced by 6.6% and 10.1%, respectively [13]. In 148 critical patients, adequacy of energy and protein ≥80% reduced ICU/hospital LOS and reduced 28 -day mortality among patients with high and low nutritional risk [14].

When comparing survivors and non-survivors, in the late period (5-10 days), surviving patients received more energy compared to non-survivors (23.4 ± 4.8 *vs*. 20.9 ± 6.2 Kcal/kg; p = 0.035). The time to start ENS in the critical illness phase is very important and is associated with mortality [20]. A study of 421 critical patients using MV showed that the highest energy adequacy in 72h was associated with lower mortality [20]. These results are consistent with our findings. In the late phase, were observed that the calories and protein adequacy (%) was related with lower mortality at 30 days (HR = 0.960; HR = 0.962; respectively). On the other hand, in the early period of acute phase no association was found between energy and protein intake or adequacy.

Some studies have specifically analyzed protein intake [15,16]. The PROTINVENT study evaluated the timing of protein intake; low protein intake (<0.8 g / kg / day) before the 3rd day, and high protein intake (>0.8 g / kg / day) after the 3rd day was associated with lower 6-month mortality compared to patients with high overall protein intake [15]. In critically ill patients on MV with

low muscle area and density, and with a higher protein offer (>1.2g /kg/day), the prevalence of mortality was significantly lower than that in patients with protein intake <1.2g /kg/day [16]. In our research, we observed the relation of protein adequacy intake (~94.3%; after the fifth day) with a lower risk of 30-day.

In clinical practice, nutritional therapy guidelines for ICU patients suggest less energy supply in the acute and early phase of critical illness with gradual progression [8]. In the presente study, we evaluated energy and protein intake in the two periods of the acute phase. According to the main recommendations for calories the general goal is around 20 to 30 kcal/kg of current weight in eutrophic patients and 11-14 kcal/kg current weight for patiens with obesity [1,8]. All our patients had an average BMI of 26.6 ± 4.5 kg/m² and ~17% with BMI ≥ 30kg/m². Following the guidelines, the calorie goal was achieved in the late phase, however, we observed that surviving patients had a higher energy intake compared to non-survivors (23.4 ± 4.8 *vs.* 20.9 ± 6.2 Kcal/kg). This result was confirmed in Cox regression, where energy intake (22.7 kcal/kg) was significantly related to 30-day mortality (**Table 4**) and by cumulative mean percentage of energy intake in the first 10 days of enteral nutritional therapy (**Figure 2**).

In relation to protein intake, low-dose protein intake (up to 0.8 g/kg) during the early phase is recommended, while in the rehabilitation phase, a target of >1.2 g/kg can be considered [9]. There is also guidance for progressive supply of up to 1.3 g/kg of weight [8]. In this study, specifically in the late phase, perhaps 1.6 g/kg is too little for a statistically significant protective association with 30-day mortality. In this sense, it is possible to observe the importance of nutritional adequacy, even if the risk of mortality was present above the recommendations.

Our study had some limitations. This sample comprised heterogeneous patients of a wide age range (including adults and older patients) and with different diseases. However, to minimize these effects we adjusted the models for presence of ≥3 comorbidities, use of MV, tracheostomy and RRT. Furthermore, data were collected by only one trained investigator. In a study comparing ENS at different stages of critical illness, perhaps blind comparisons would avoid bias. Also, 11 of our patients were discharged from the ICU between 5-10 days, but we understand that this does not compromise the results found, since most patients (~83%) received nutritional adequacy ≥80% by ENS and this information was related with mortality which was also confirmed by the mean cumulative percentage of energy and protein intake in the first 10 days of ENS. Finally, this study was conducted in a private hospital and its data cannot be extrapolated to public hospitals that have defined characteristics. In this sense, our results need to be validated in other ICU conditions.

Even so, our findings may contribute to clinical practice, as it was demonstrated that in the late acute phase of critical illness, greater protein-energy adequacy was protective for 30-day mortality. These results highlight the importance of reinforcing care protocols to ensure that patients admitted to the ICU receive adequate nutritional therapy. In this sense, in critically ill patients, the benefit of ENS may be more related to an early start and maintenance of the amount of calories and proteins than its aggressive intake.

Conclusion

In the period late of the acute phase (5-10 days of admission in ICU), the higher energy and protein intakes were associated with a lower risk of 30-day in critical patients.

Statement of authorship

All authors were responsible for the study design, writing and revising of manuscript. MKC and VBL were also responsible for the statistical analysis and data interpretation.

Conflict of interest statement

None declared.

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Table 1. Characteristics between survivors and nonsurvivors in a sample of critically Ill patients admitted to a mixed Intensive Care Unit (n = 119).

Variables	All* (n = 119)	Survivors (n = 91; 76.5%)	Non-survivors (n = 27; 22.7%)
Demographics			
Age (years)	71.0 ± 15.4	68.8 ± 15.8	78.4 ±11.6
Older adults (≥ 60 years old)	94 (79.0%)	68 (74.7%)	25 (92.6%)
Sex (male)	67 (56.3%)	53 (58.2%)	13 (48.1%)
Clinics			
Type of admission			
Medical	81 (68.1%)	64 (70.3%)	17 (63.0%)
Surgical	16 (13.4%)	13 (14.3%)	2 (7.4%)
Trauma	5 (4.2%)	5 (5.5%)	0
COVID-19	17 (14.3%)	9 (9.9%)	8 (29.6%)
Comorbidities ≥3**	54 (45.4%)	36 (39.6%)	17 (63%)
ICU LOS (days)***	15 (9 - 25)	14.5 (8 - 26.75)	17 (10 - 24)
Hospital LOS (days)***	29 (18.5 - 41)	33 (20 - 53.25)	24 (14 - 29)

Treatment			
Vasopressor drugs	59 (49.5%)	39 (42.9%)	18 (66.6%)
Use RTT	33 (28%)	21 (23%)	12 (44.4%)
Use of MV	104 (87.4%)	78 (85.7%)	25 (92.6%)
MV in days	10 (5 - 23)	8 (5 - 20.5)	13 (6.5 - 23.5)
Tracheostomy, n (%)	37 (31.1%)	25 (27.5%)	11 (40.7%)
ICU severity scores			
APACHE (points)	17 (13 - 20)	16 (12 - 20)	18 (15 - 22)
SOFA (points)	5 (3 - 7)	5 (3 - 7)	5 (3 - 6)
Nutrition / ENS			
mNUTRIC score			
High (≥ 5)	52 (43.7%)	37 (40.7%)	15 (55.6%)
BMI (kg/m²)	26.6 ± 4.5	26.5 ± 4.4	26.6 ± 5.0
BMI ≥ 30 kg/m²	20 (16.8%)	13 (14.3%)	6 (22.2%)
BMI <22kg/m (older adults)	15 (12.6%)	10 (11%)	5 (18.5%)
Start of ENS (up to 24 hours)	91 (76.5%)	73 (80.2%)	18 (66.7%)
ENS at ICU in days ***	12 (8 - 24)	11.5 (7 - 25)	13 (9 - 24)

Adequacy of ENS (≥80%)			
Early period (1-4 days)			
Energy (kcal/kg)	108 (90.8%)	83 (91.2%)	23 (85.2%)
Protein (g/kg)	109 (91.6%)	85 (93.4%)	23 (85.2%)
Late period (5-10 days)****			
Energy (kcal/kg)	99 (83.2%)	79 (86.8%)	19 (70.4%)
Protein (g/kg)	102 (85.7%)	80 (87.9%)	21 (77.8%)

ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; RRT, renal replacement therapy APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; mNUTRIC, modified Nutrition Risk in the Critically ill; BMI, body mass index; ENS, enteral nutrition support.
Data presented as mean ± standard deviation, n (%), or median (interquartile range).
* One patient was transferred from the hospital without evolution on MV, LOS, ENS at ICU in days and, 30-day mortality.
**Comorbidities included: diabetes, hypertension, cardiovascular disease, and cancer
*** Three patients remained hospitalized in ICU, without evolution of ICU admission, hospitalization, ENS at ICU in days and, two patients were still hospitalized, without outcome for hospital LOS.
**** Eleven patients had no ENS data recorded because they were discharged from the ICU.

Table 2. Nutritional adequacy in the early and late of acute phases of critical illness according to nutritional risk (mNUTRIC).

	Low Risk (< 5 points)	**High Risk (≥ 5 points)**	***P* value***
Early period (1-4 days)	n = 67	n = 52	
Energy			
Goal (kcal/kg)	15.5 ± 4.0	17.0 ± 3.8	**0.044**
Intake (kcal/kg)	14.6 ± 3.9	15.7 ± 3.6	0.100
Adequacy (%)	94.4 ± 10.2	93.7 ± 9.8	0.683
Protein			
Goal (g/kg)	0.9 ± 0.3	1.0 ± 0.3	0.142
Intake (g/kg)	0.9 ± 0.3	0.9 ± 0.3	0.208
Adequacy (%)	94.6 ± 9.8	94.3 ± 9.1	0.842
Late period (5-10 days)	n = 60	n = 48	
Energy			
Goal (kcal/kg)	23.6 ± 4.7	24.7 ± 4.5	0.235
Intake (kcal/kg)	21.9 ± 5.6	23.7 ± 4.9	0.080
Adequacy (%)	92.8 ± 14.6	95.8 ± 8.1	0.194
Protein			
Goal (g/kg)	1.6 ± 0.3	1.6 ± 0.3	0.530
Intake (g/kg)	1.5 ± 0.4	1.6 ± 0.4	0.082
Adequacy (%)	92.8 ± 15.7	96.6 ± 7.0	0.096

Data presented as mean ± standard deviation * Student t test.

Table 3. Nutritional adequacy in the early and late of acute phases of critical illness among survivors and non-survivors at 30 days.

	Survivors	**Non- survivors**	***P* value***
Early period (1-4 days)	n = 91	n = 27	
Energy			
Goal (kcal/kg)	16.3 ± 4.1	15.9 ± 3.6	0.687
Intake (kcal/kg)	15.2 ± 3.9	14.8 ± 3.7	0.652
Adequacy (%)	94.0 ± 10.2	94.2 ± 9.5	0.922
Protein			
Goal (g/kg)	0.9 ± 0.3	1.0 ± 0.3	0.853
Intake (g/kg)	0.9 ± 0.3	0.9 ± 0.3	0.914
Adequacy (%)	94.6 ± 9.4	93.9 ± 9.9	0.737
Late period (5-10 days)	n = 82	n = 25	
Energy			
Goal (kcal/kg)	24.6 ± 4.3	23.2 ± 4.5	0.187
Intake (kcal/kg)	23.4 ± 4.8	20.9 ± 6.2	**0.035**
Adequacy (%)	95.7 ± 7.9	88.8 ± 20.3	0.109
Protein			
Goal (g/kg)	1.6 ± 0.2	1.6 ± 0.3	0.612
Intake (g/kg)	1.6 ± 0.3	1.6 ± 0.6	0.941
Adequacy (%)	96.1 ± 7.9	88.6 ± 21.4	0.098

Data presented as mean ± standard deviation * Student t test.

Table 4. Cox regression: relation between caloric and protein intake and adequacy in the early and late of acute phases with 30-day mortality.

	Mean	HR	CI 95%	*P* value
Early period (1-4 days)				
Energy				
Intake (Kcal/kg)	15.1	0.996	0.891 – 1.113	0.941
Adequacy (%)	94.0	0.999	0.959 – 1.040	0.944
Protein				
Intake (g/kg)	0.9	1.142	0.232 – 5.626	0.870
Adequacy (%)	94.4	0.985	0.945 – 1.028	0.498
Late period (5-10 days)				
Energy				
Intake (Kcal/kg)	22.7	0.901	0.831 - 0.978	**0.012**
Adequacy (%)	94.0	0.960	0.936 – 0.985	**0.002**
Protein				
Intake (g/kg)	1.6	0.894	0.275 – 2.909	0.852
Adequacy (%)	94.3	0.962	0.939 – 0.985	**0.002**

HR: Hazard Ratio, CI: Confiance Interval
All models were adjusted for the presence of ≥3 comorbidities, use of mechanical ventilation, tracheostomy, and renal replacement therapy.

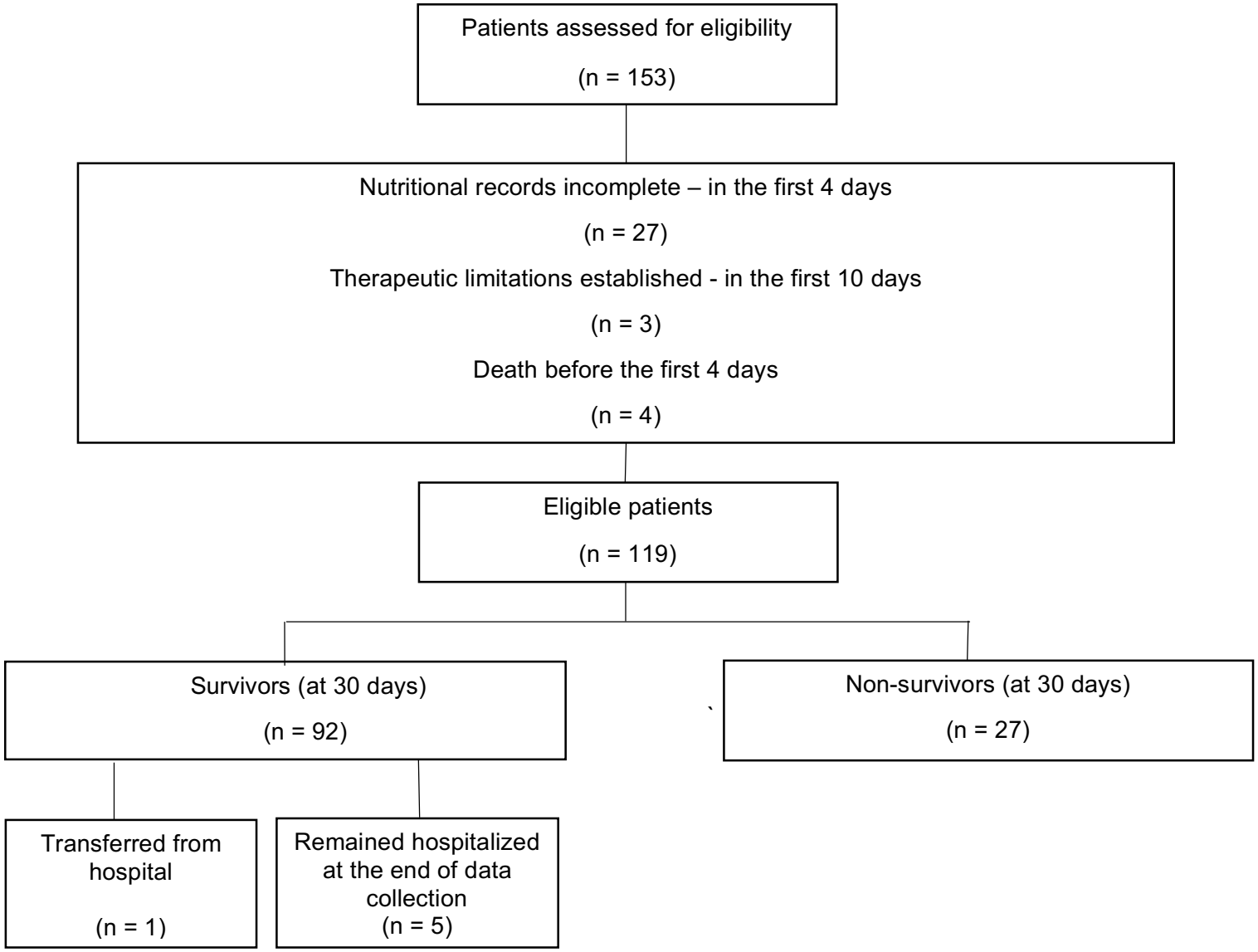

Figure 1. Flowchart of patient selection.

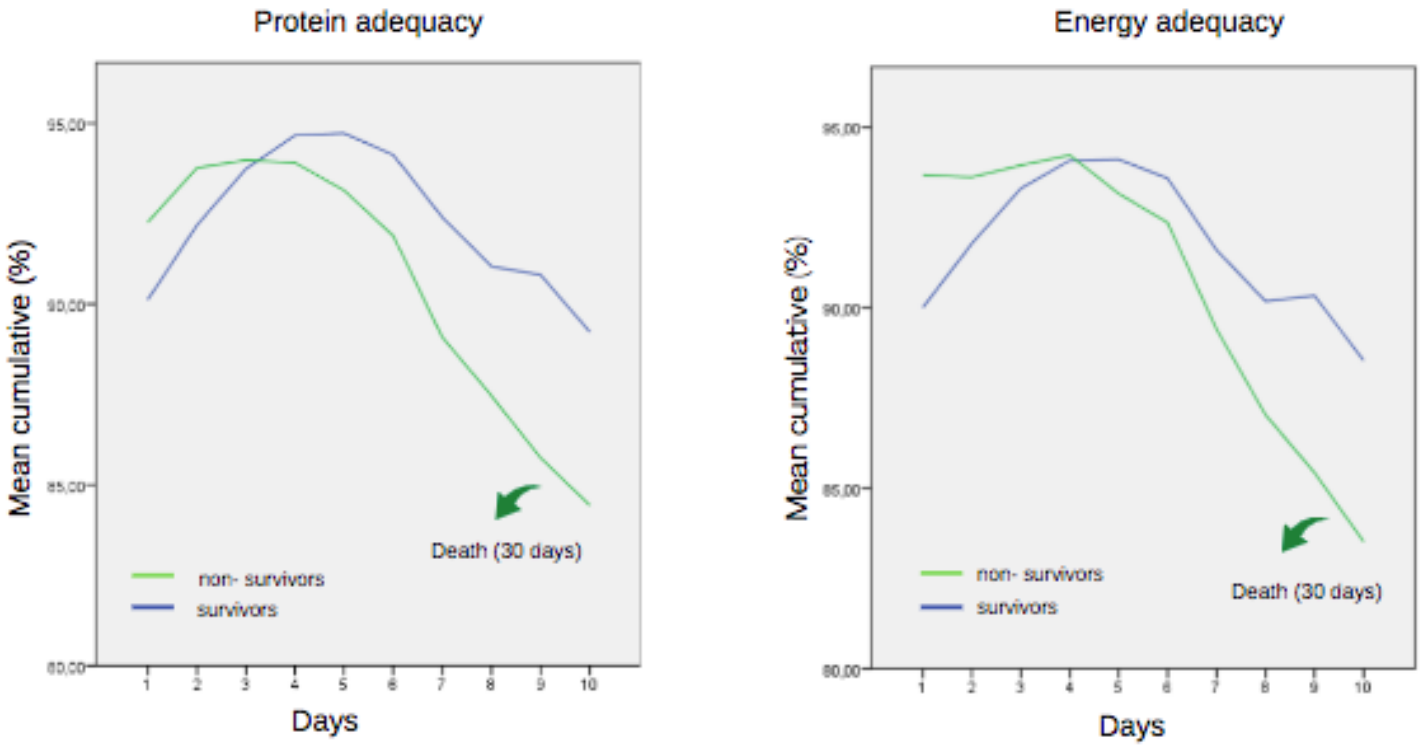

Figure 2. Cumulative mean percentage of energy and protein intake in the first 10 days of enteral nutritional therapy in critically ill survivors and non-survivors.

Anexo

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