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Efeitos da Terapia Nutricional Especializada na Redução da Mortalidade em Idosos Críticos e da Nutrição Parenteral na Supressão da Fome em Adultos Hospitalizados

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Efeitos da Terapia Nutricional Especializada na Redução da Mortalidade em Idosos Críticos e da Nutrição Parenteral na Supressão da Fome em Adultos Hospitalizados

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“O papel da ciência é substituir a complexidade visível por uma simplicidade invisível”
(Jean Baptiste Perrin)

SINOPSE

Desnutrição hospitalar sabidamente se associa a piores desfechos. O reconhecimento de déficits nutricionais, sua mitigação e tratamento, especialmente a pacientes frágeis, coloca o suporte nutricional como um componente essencial nas estratégias terapêuticas a doentes hospitalizados.

O paciente idoso frequentemente é excluído de estudos que versam sobre os efeitos da terapia nutricional em desfechos, especialmente no contexto da terapia intensiva. Sabidamente esta fatia de pacientes cursa com evidente fragilidade e maior mortalidade. A primeira parte deste projeto de doutorado visou específica e objetivamente avaliar o impacto da terapia nutricional em idosos. Foram avaliados 533 pacientes idosos com idade igual ou superior a 65 anos críticos e constatado que a pausa nutricional dentro da primeira semana se associa independentemente a maior mortalidade. Este resultado é de extrema importância pois torna explícito o impacto do balanço energético e proteico negativos dentro da primeira semana de terapia intensiva na mortalidade e a necessidade de permanente atenção por parte da equipe assistencial em relação a este parâmetro.

Pacientes hospitalizados que são submetidos a terapia nutricional parenteral costumam ser mais graves e exigir tratamentos de maior complexidade. Uma vez estabilizados a transição da nutrição parenteral à nutrição oral é a regra. Entretanto, uma parcela destes pacientes apresenta inapetência tornando esta transição mais difícil. Muitas vezes a equipe assistencial cogita de que a nutrição parenteral seja a causa da inapetência e procede com a suspenção da terapia nutricional para estimular o consumo de alimentos por via oral. Esta transição foi estudada na segunda parte deste projeto de doutorado e demonstrou que nutrição parenteral não suprime a fome. Os pacientes que costumam cursar com inapetência são os mais idosos, inflamados ou mais doentes (sobremaneira por câncer metastático).

Assim, as duas partes deste doutorado trazem a importância da construção de um planejamento nutricional que atenda as características de específicas populações visando otimizar o tratamento nutricional.

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IMC – índice de massa corporal

NP – Nutrição parenteral

UTI – Unidade de terapia intensiva

ARTIGO 1: Nutrition as a risk for mortality and functionality in critically ill older adults

BMI – body mass index

CRP – C-reactive protein

HCPA – Hospital de Clínicas de Porto Alegre

ICU – Intensive care unit

SAPS 3 – Simplified Acute Physiology Score 3

ARTIGO 2: Does parenteral nutrition suppress hunger? A prospective cohort study

AIC – Akaike information criterion

ASPEN – American Society for Parenteral and Enteral Nutrition

BIC – Bayesian information criterion

BRASPEN – Brazilian Society for Parenteral and Enteral Nutrition

CCI – Charlson comorbidity index

CCK – Cholecystokinin

CRP – C-reactive protein

ESPEN – European Society for Parenteral and Enteral Nutrition

GIP - Gastric inhibitory peptide

GLP-1 – Glucagon-like peptide-1

HCPA – Hospital de Clínicas de Porto Alegre

ICU – Intensive care unit

NRS-2002 – Nutritional risk screening 2002

PN – Parenteral nutrition

PYY – Peptide YY

ROC – Receiver operating characteristic

SAPS 3 – Simplified Acute Physiology Score 3

SOFA – Sequential organ failure assessment

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CAPÍTULO 1
INTRODUÇÃO

Desnutrição é frequentemente observado no doente hospitalizado, podendo estar presente na internação ou se desenvolver durante este período e acometer aproximadamente metade dos doentes[1]. Desnutrição também está associada a aumento de custos e de morbimortalidade[2]. Práticas de jejum desnecessárias e prescrições inapropriadas de nutrição resultam em subalimentação dos pacientes que podem estar associada ou ser a causa direta da desnutrição hospitalar, independente da doença de base ou do estado inflamatório do paciente[2]. Entretanto, a quantidade ótima de nutrição para pacientes hospitalizados ainda não está claramente definida[2].

Cerca de 60-65% dos pacientes hospitalizados apresentam um estado nutricional pior em comparação com indivíduos saudáveis. Na verdade, a hospitalização está associada a mudanças importantes na ingestão nutricional regular devido a vários fatores, como horário restrito de fornecimento de alimentos, diminuição do apetite, efeitos adversos da medicação e períodos prescritos de jejum[3]. Outrossim, estes pacientes não costumam consumir a quantidade de proteína ou suplementos prescritos, o que foi demonstrado por Weijzen e colegas[4] a partir da comparação entre o prescrito e ingerido. Falta de apetite, recusa de refeições hospitalares e jejum relacionado a procedimentos são as causas mais frequentes de desnutrição hospitalar evitável[5].

Quanto a via de nutrição, pacientes com impossibilidade de uso do trato gastrointestinal se beneficiam de nutrição parenteral (NP), que deve ser descontinuada e migrada para nutrição enteral/oral assim que possível[6-8]. NP é uma importante modalidade de nutrição para pacientes incapazes de serem adequadamente alimentados pelo trato digestório, favorecendo desfechos especialmente em doentes desnutridos[9] ou naqueles de alto risco que não atingem meta de calorias e proteína[10]. Entretanto, a transição da dieta parenteral para dieta oral com aceitação plena do paciente requer muitas vezes, além de readaptações estruturais, o retorno de sensações fisiológica como fome e saciedade.

Saciação e saciedade são controladas por uma cascata de fatores que começam quando um alimento é consumido e continuam à medida que o mesmo é digerido e absorvido. O alimento ingerido estimula áreas específicas do cérebro que estão envolvidas na regulação da ingestão de energia, em resposta às percepções sensoriais e cognitivas do alimento consumido e à distensão do estômago. Esses sinais são integrados pelo cérebro e a saciedade é estimulada. Quando os nutrientes chegam ao intestino e são absorvidos, são liberados vários sinais hormonais que são novamente integrados no cérebro para induzir a saciedade. Além desses sinais episódicos, a saciedade também é afetada por flutuações nos hormônios, como a leptina e a insulina[11]. A Figura 1 esquematiza as fases em que os fatores que afetam a saciedade e a saciedade atuam, desde o início da alimentação até a saciedade tardia.

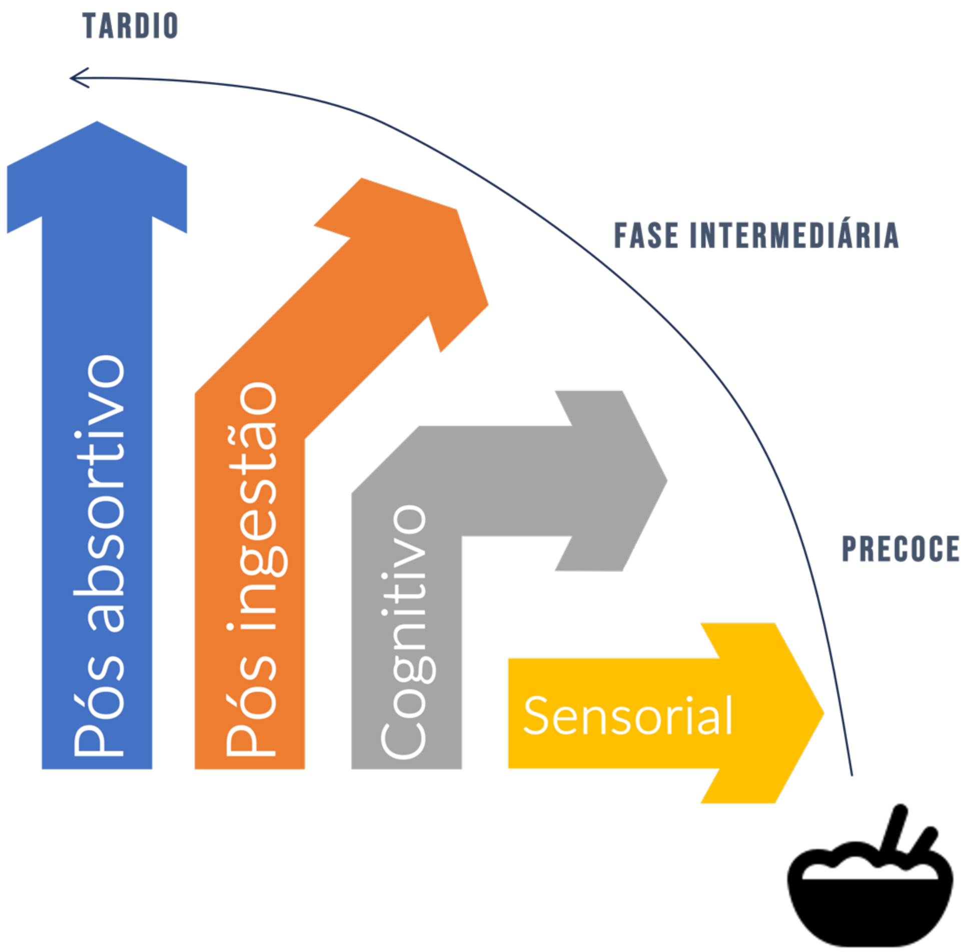

Figura 1- A cascata da saciedade

Como esta figura demonstra, a saciação e a saciedade são inicialmente afetadas por fatores sensoriais e cognitivos, incluindo expectativas sobre o que deve ser consumido, o sabor, textura e cheiro da comida ou bebida e quaisquer associações que surjam com experiências anteriores. Assim que a comida ou bebida chega ao estômago, os fatores pós ingestão começam a fazer efeito. Inicialmente, a distensão do estômago envia sinais ao cérebro, iniciando a saciedade. À medida que a digestão continua nos intestinos, os hormônios que promovem a saciedade e a saciedade são liberados do intestino. por receptores especializados em vários locais do organismo, incluindo o cérebro, fornecendo informações sobre o estado nutricional que também afeta a saciedade. A longo prazo, a saciedade também pode ser afetada por sinais como a leptina, que transmitem informações sobre o nível de armazenamento de gordura no corpo[11]. Este é um processo complexo que vem evoluindo a milhões de anos.

Alguns pacientes parecem demorar mais para o restabelecimento da fome e consequente adequada ingestão oral[12]. Não há consenso em relação a um padrão de nutrição parenteral, tempo ou cenário clínico que prediga ocorrência de anorexia, hiporexia ou saciedade precoce. Nem mesmo há consenso se há ou não alterações de fome e/ou saciedade em indivíduos submetidos a nutrição parenteral. A maioria dos estudos que abordam a questão são antigos, geralmente com pequenas amostras, em humanos e modelos experimentais e avaliam basicamente o efeito da quantidade de calorias ofertadas e se algum dos substratos administrados (lipídio, glicose ou proteína) tem um papel mais relevante.

Jordan e colaboradores[13] aplicaram um questionário sobre fome e saciedade e avaliaram 52 pacientes com nutrição parenteral. Eles observaram que pacientes referiam fome mesmo quando recebiam mais de 4000kcal/dia (uma prática corrente nos anos 70). Entretanto, no subgrupo que recebia lipídio intravenoso, ocorria ausência de fome até 24h após cessação da infusão. Sriram e colegas[12], após 10 anos, também notaram que a maioria dos doentes submetidos a nutrição parenteral não tiveram problemas em iniciar alimentação oral e retirar a solução intravenosa de nutrientes. Uma minoria (10 pacientes) que não conseguiram evoluir adequadamente a ingestão oral de alimentos foram avaliados. Uma redução mais gradual da nutrição parenteral se associou com maior interesse destes pacientes por alimentos, independente de receberem lipídios intravenosos ou não. Muito provavelmente a infusão parenteral de nutrientes não gere um ambiente hormonal local no trato digestório e sistêmico normalmente observado quando da alimentação oral, o que justificaria alterações de motilidade, percepção de fome e saciedade em animais e humanos[13-15]. Talvez esta seja uma das explicações para a observação de doentes recebendo quase 5000kcal e ainda referirem fome[13], ou apresentarem forte desejo por itens salgados, temperados, crocantes, além de pensamentos direcionados a certos alimentos e água[16]. Possivelmente, uma vez que o paciente submetido a suporte nutricional parenteral tenha seu processo patológico resolvido ou em resolução e o trato digestório esteja apto para receber e digerir alimentos, fome e saciedade retornarão a uma condição estável mesmo que estes doentes continuem sendo alimentados por via intravenosa[16].

Independente da via de escolha (parenteral, enteral ou oral), a situação de jejum/hipoalimentação é especialmente pouco explorada na população idosa hospitalizada. Não existe recomendações específicas para prescrição de dietas em pacientes idosos hospitalizados com sarcopenia[17]. Pacientes idosos podem ser inadvertidamente submetidos a períodos de inadequada repleção nutricional, de maneira que o baixo aporte proteico nesta população pode ter um efeito devastador[2]. Além disto, parecem estar em maior risco nutricional que seus pares mais jovens[18]. A vulnerabilidade é maior nos idosos com baixo peso (índice de massa corporal (IMC) ≤ 20 kg/cm2) e costuma se associar a um cenário de pior prognóstico[19].

Como desnutrição em idosos se associa a longa estadia hospitalar e piores desfechos, incluindo elevada mortalidade[20,21], e indivíduos com idade superior a 80 anos parecem ter um risco ainda maior[22,23], atingir as metas de nutrição através de protocolos que evitem pausas de alimentação inadequadamente ou injustificadamente prolongadas parece ser muito importante. Por outro lado, ainda não há dados robustos que explorem o desfecho da população de idosos na unidade de terapia intensiva (UTI) com IMC em faixa de sobrepeso ou obesidade, condição que poderia conferir proteção em um ambiente de defina inflamação e catabolismo (paradoxo da obesidade[24]).

Pacientes idosos submetidos a nutrição parenteral possivelmente constituam um grupo de muito alto risco para o surgimento de desnutrição no curso da hospitalização, uma vez que inflamação tem uma potente ação anorexígena que determina uma evolução com inapetência e dificuldade de transição adequada do período de suporte nutricional parenteral para enteral[25].

As consequências em termos das alterações da composição corporal são catastróficas nesta população, com repercussão nas funções de outros sistemas e imunidade, determinando fragilidade[26]. Um estudo observacional prospectivo demonstrou que o declínio no estado nutricional e a perda de peso estavam significativamente associados ao tempo de internação prolongado, independentemente das características demográficas e da gravidade da doença[20], o que aumenta o custo da hospitalização[27]. A figura 2 esquematiza as principais características do idoso hospitalizado

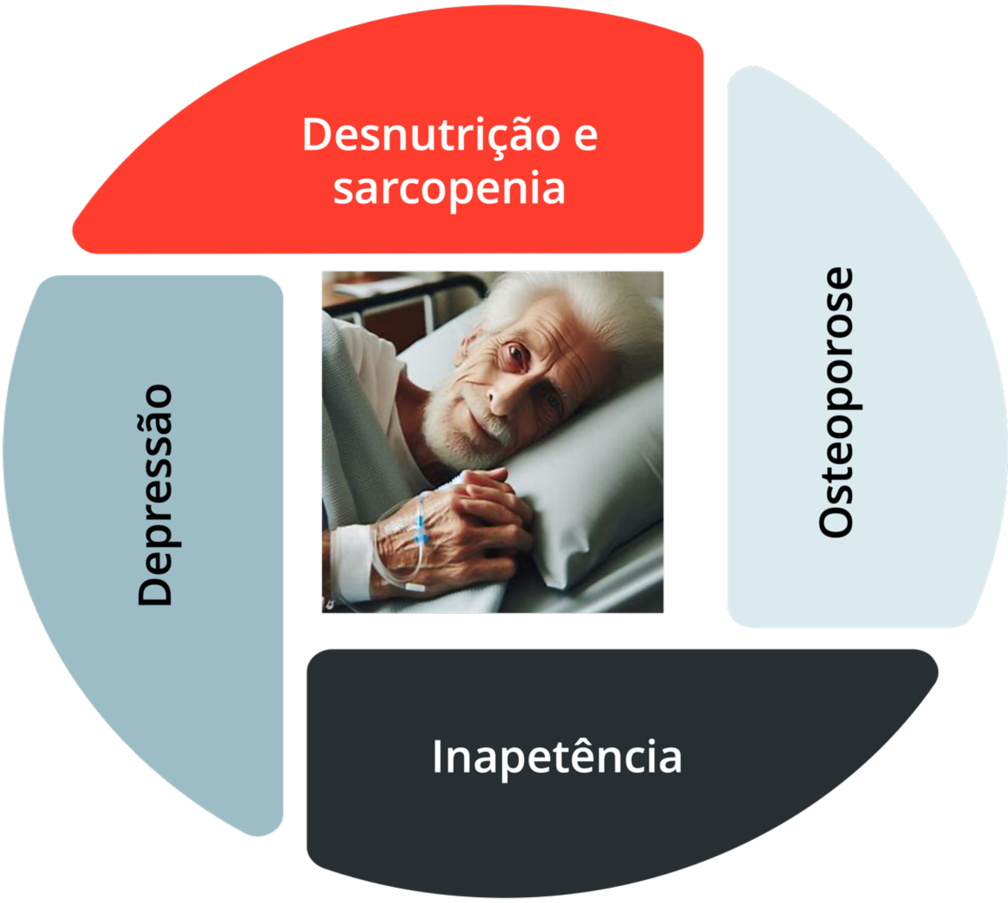

Figura 2 – Características de pacientes idosos hospitalizados frágeis

Estas são questões importantes para a equipe assistencial planejar e definir o término da alimentação parenteral e reinstituição da alimentação oral, planejamento adequado de metas calórico-proteicas em diferentes faixas etárias, e contextos prévios de nutrição (baixo peso, eutrofia, sobrepeso/obesidade), particularmente no idoso e possivelmente aqueles com passagem em UTI.

A presente proposta de doutorado está dividida em dois projetos independentes, que seguem o racional teórico de que a desnutrição hospitalar é deletéria ao paciente e que deve ser ativamente pesquisada e tratada:

Projeto 1 - Impacto a curto e longo prazo da prescrição nutricional em pacientes idosos críticos

Projeto 2 – Impacto da nutrição parenteral total sobre fome e saciedade de pacientes hospitalizados

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CAPÍTULO 2

PROJETO 1

Nutrition as a risk for mortality and functionality in critically ill older adults

ABSTRACT

Background & Aims: There is no specific recommendation for nutrition therapy for critically ill older adults. However, targeting caloric and protein balance and avoiding fasting could improve outcomes in this high-risk nutritional population. This study aimed to evaluate the associations between nutrition and mortality/functionality in critically ill older patients.

Methods: Single-center retrospective observational study of critically ill patients aged 65 years or older. We extracted data from the dietician evaluations about calories, proteins, and the type of diet (fasting, oral, enteral, parenteral) prescribed in the first week of intensive care unit admission. Primary outcomes were intrahospital mortality and independence and functional capacity evaluated after hospital discharge.

Results: Out of the 2,043 patients screened, 533 were included in the study. Most patients were men (52.1%), with a median age of 73 (68–78) years. Overall, the intrahospital mortality rate was 53.8%. SAPS-3, albumin, C-reactive protein, and surgical patients were independently associated with fasting in a multivariate analysis. The multivariate regression analyses showed that SAPS-3, albumin, and fasting were independently associated with mortality. Each fasting day increases the risk of mortality by 16.7%. Also, independence and functional capacity were not related to nutritional prescription.

Conclusion: Older adults (65 years or older) constitute a fragile population in which nutritional breaks were associated with increased hospital mortality. Furthermore, a prospective clinical trial is necessary to establish the best strategy to feed this population.

Keywords

Older adult; Critical care; Nutritional support

INTRODUCTION

Malnutrition is often observed in hospitalized patients, affecting approximately half of the individuals; it may be present at admission or developed during hospitalization[1]. It is associated with increased costs, morbidity, and mortality[2]. Unnecessary fasting and inappropriate nutritional prescriptions can result in the undernutrition of patients, which may be related to, or be the direct cause of, hospital malnutrition, regardless of the patient's underlying disease or inflammatory state[2]. However, the optimal amount of nutrition for hospitalized patients is not yet clearly defined[2].

The prevalence of sarcopenia is high in the older population (≥ 65 years of age)[3] and this characteristic may be accentuated during hospitalization; occupying an essential portion of beds in intensive care unit (ICU). The presence of sarcopenia and frailty are an additional element of interest to the intensivist[4], since the combination of sarcopenia and critical illness is related to a worse prognosis[5-7]. Older patients may be inadvertently subjected to periods of inadequate protein intake, which can have a devastating effect[2]. Fasting also contributes to nutritional deficits during hospitalization and it is a frequent practice in ICU patients. Serum albumin less than 3.5 mg/dL at admission and body mass index (BMI) below 20 kg/m^2 at hospital discharge have been related as factors that predict mortality within the year following hospital discharge[8-10]. There are no robust data that explore the outcome of the older adult population in the ICU with BMI in the range of overweight or obesity, a condition that theoretically could provide a protective effect in an environment of inflammation and catabolism (obesity paradox[11]).

Also, there are no specific diet recommendations for older sarcopenic patients[7]. Malnutrition within the older adult population is associated with prolonged hospital stays, worse outcomes, and high mortality[5,12]. Individuals aged over 80 years seems to be at an even greater risk[13,14]. Therefore, it is important to employ protocols that prevent inadequately prolonged food breaks in order to achieve the nutritional goals of patients. The aims of this study were to evaluate the associations of nutrition and mortality/functionality in critically ill older patients.

MATERIAL & METHODS

Setting and patients

A single- center (Hospital de Clínicas de Porto Alegre - HCPA) retrospective observational study of critically ill older adult patients (≥ 65 years of age) was conducted. From October 2015 to April 2017, all patients admitted to the ICU were screened for study eligibility.

In critically ill patients ≥ 65 years of age, we hypothesized that poor nutrition is associated with increased hospital mortality compared to adequate nourishment. Our exposure of interest was fasting, defined as Nil Per Os (NPO), for at least one day during the first seven days following ICU admission. Our primary outcome was in-hospital mortality determined by hospital records. The secondary outcome was functional independence six months following hospital discharge.

We enrolled all consecutive older adult critical care patients hospitalized in our ICU for 19 months. The HCPA ICU is a 40-bed combined medical/surgical tertiary unit with approximately 2,500 admissions per year. Patients aged 65 years or older were consecutively enrolled. Exclusion criteria were readmission and ICU length of stay less than 24 hours.

For every included patient, the following data at ICU admission were recorded: age, sex, weight, height, hospital/ICU admission category (surgical or medical), comorbidities, Simplified Acute Physiology Score 3 (SAPS 3), and Charlson Comorbidity Index. BMI was calculated using height and weight [weight (kg)/height (m^2)]. BMI ranging 20–27 kg/m^2 was classified as healthy; under 20 kg/m^2, underweight; and over 30 kg/m^2, obese. All patients were in nutritional risk (Nutritional Risk screening 2002 – NRS-2002 – with three or more points). Dietitians performed three evaluations to assess protein and caloric prescription in the first seven days at the ICU, with a minimum time of 24 hours between each one. At each evaluation, the researchers recorded the number of calories and proteins prescribed, infusion volume (when enteral) and patient diet acceptance, and the percentage of calories and protein consumed relative to the planned goal. Also, during the first seven days, the type of prescribed diet (oral, fasting, enteral, and parenteral) was evaluated. All dietary evaluation was extracted from the patient chart (there was no assessment of food intake).

According to the institutional protocol, the staff members prescribed the nutritional support, usually aiming to a targeted energy intake of 20–25 kcal/kg/day and 1.2–1.5 g/kg/day of protein, up to the third day. Fasting, lower caloric/ protein intake than the established goals to the individual patient were considered inadequate nutrition. Additionally, vasopressor use, mechanical ventilation, renal replacement, extracorporeal membrane oxygenation (ECMO), physical therapy practice, the highest C-reactive protein (CRP) value, and the lowest serum albumin value were recorded. Patients were monitored until hospital discharge.

During hospital stay, treatment limitation definition (withdrawing mechanical ventilation, hemodialysis, vasopressor, antibiotics, do not attempt CPR), exclusive palliative treatment (with or without diet suspension) and weight at discharge (minimum 10 days pre-discharge) were assessed. All patients who survived were contacted via phone six months following hospital discharge. For patients (or their relatives) with whom contact was possible, the Katz Index of Independence in Activities of Daily Living and the Lawton-Instrumental Activities of Daily Living were used to evaluate the patient’s functional capacity. Also, understanding of the patient's functional status by the patient or their relative was asked, especially regarding a worsening following the hospital stay. The research team did not have access to the patient functional evaluation prior, during, or soon after hospital discharge.

Ethics

The study protocol was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (CEP/HCPA 180022/2019). When we succeed in contacting the patient or their relative, the researcher read an informed consent form and asked the patient/relative for verbal consent to participate in the study.

Statistics

Statistical analyses were performed using IBM SPSS Statistics 20 and R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive data are reported as the mean ± SD, median (interquartile range) or frequency (percentage). Variables with normal distribution were compared using Student’s t-test, while non-normal distribution were compared using Mann-Whitney U tests. The Chi-square test was used to compare categorical variables. Binary logistic regressions were performed to identify exposure variables associated with the "fasting" and "mortality" outcomes. In the assessment of mortality, we used a model where the most significant variables related to mortality in the univariate analysis were included as controls for the fasting exposure. Kaplan–Meier analysis was used to explore the association between fasting and death of ICU older patients.

RESULTS

Patient's characteristics

Out of the 2,043 patients screened (mean of 193 patients/month), 533 were included in the study **(Figure 1)**. Most patients were men (52.1%), had median age of 73 (68–78) years, and had a length of stay of 21 (13–38) days. The mean SAPS3 score was 66.6 ± 13.9 and Charlson Comorbidity Index was 6 (4-7). Median BMI was 26.4 (22.8-30.1), most individuals received enteral nutrition with a high tolerance and only 2.6% were on parenteral nutrition. In total, 13% of the patients were on palliative care, 67% were discharged alive from ICU, and overall intrahospital mortality rates were 53.8%.

Fasting versus Non-fasting Patients

Fasting was prescribed in 7%, 3%, and 1% in the three consecutive evaluations, respectively. However, in the first week of evaluation, fasting was prescribed for 40% of patients at some point, with a median duration of 0 days (IQR [0–1]). Fasting prescription was associated with the clinical syndrome that led to admission to the ICU. Severe sepsis was significantly associated with fasting and ventilatory failure associated with non-fasting, p<0.001; while neurological and cardiovascular events had no associations with fasting. Surgical patients were more often submitted to fasting (61.6 vs 38.4%, p<0.001). As shown in **Table 1**, patients who underwent at least one day without nutrition during the first week were the most severe (highest SAPS-3 scores, lowest serum albumin levels, and highest CRP), and had the highest mortality. In multivariate analysis **(Table 2**), SAPS-3, albumin, C-reactive protein (CRP), and surgical patients were independently associated with fasting.

Age > 80 years and exclusive palliative care

Patients aged 80 years or older accounted for 22.5% (120 patients) of the sample. Mortality in this subgroup was 56.7%. Compared to the younger population, they had lower BMI (25.4 kg/m^2 [21.7–28.7] vs 26.7 kg/m^2 [23.1–30.4], p=0.025), higher SAPS-3 score (70.4 $\pm$ 12.9 vs 66.2 $\pm$ 14.1, p=0.004), and higher Charlson score (6 [5–8] vs 6 [4–7], p<0.001). There was no difference in caloric and protein prescription between groups nor in total fasting days. Compared to the younger patients, they did not show higher prevalence of palliative care nor mortality (p value of 0.066 and 0.495 respectively).

Patients in exclusive palliative care had a higher Charlson and SAPS score, and higher mortality without statistical differences in fasting, caloric, and protein prescriptions.

BMI

In total, 43.7% of the sample presented overweight and obesity. Most of these individuals were women (57.6%, p<0.001) and it was inversely related to mortality, being higher in survivors (27.1 [23.8–30.6] vs 25.8 [22.2–29.2], p=0.002).

There is no difference in length of staying in the different BMI extracts (BMI less than 20 kg/m2, between 20-29.9 kg/m2, and greater than 29.9 kg/m2). Mortality was higher in the BMI less than 20 kg/m2 (p=0.028; OR 1.84; 95%CI 1.02;3.42). Mortality in the stratum of BMI 20-29.9 and greater than 29.9 was not statistically significant (p=0.927; OR 1.15; 95%CI 0.93;1.43) and (p=0.083; OR 0.76 95%CI 0.50;1.14), respectively. There was no significant association between patients with low BMI who underwent fasting and hospital mortality (39.3% vs. 60.7%, p=0.110).

Mortality

Table 3 shows the characteristics of patients who died during the study. **Figure 2** shows the Kaplan-Meier survival curves. The multivariate regression analyses showed that SAPS-3, albumin, and fasting were independently associated with mortality **(Table 4)**. Each fasting day increased the risk of mortality by 16.7%. The power of the sample was 83% for mortality, considering fasting occurrence.

Follow-up and functioning

Out of the 533 patients included in the study, 246 patients were discharged (45.1%) and follow-up was possible for 118 of them (48%), 86 of whom were alive (76.1%) a year following the discharge. Regarding independence and functional capacity, 14% of the patients were dependent on third parties, 47% were partially dependent, and 39% were independent (Katz index of independence in activities of daily living); while 47% had good functional capacity, 33% slightly reduced, and 20% with significant impairment (Lawton & Brody Instrumental Activities of Daily Living Scale). We did not find an association between these outcomes and BMI, fasting occurrence, total fasting days, nor with caloric and protein prescription along the first week after ICU admission.

Comparing age, BMI, SAPS-3 score, Charlson score, CRP, and albumin between individuals who did and did not answer the follow-up telephone call, we did not find significant differences, except for the Charlson score (5 [4–6] vs. 6 [5–7], p=0.003).

When we stratified to the subpopulation aged 80 or older for the occurrence of fasting, we were unable to observe an improvement in the hospital outcome (51.3% vs. 48.7%, p= 0.693) and in the functional status as determined by the Katz Index of Independence in Activities of Daily Living and Lawton-Instrumental Activities of Daily

Living of survivors (Katz index 6 [5–6] vs. 6 [5–6], p= 0.267; Lawton index 16.3 ± 5.9 vs. 15.5 ± 5.3, p= 0.832).

DISCUSSION

The current study showed that fasting was a better predictor for mortality than caloric/protein prescription in ICU patients. Fasting was independently associated with increased mortality in older adults admitted to the ICU but not with outcomes related to the quality of life three months after discharge. Our data suggest that one day without nutrition increases the risk of death by approximately 15% in the first week of evolution. The population of critically ill older adults has increased[15,16], which implies applying strategies that can reduce or avoid NPO prescription in this population. This study is significant since the older adults are often excluded from this kind of research, resulting in a knowledge gap regarding the effect of nutritional therapy on their outcomes. Furthermore, guidelines and reviews on the nutrition of critically ill older adults date back two or more decades[17-19].

In our study, nutritional breaks (fasting) were frequent in surgical and in more severe patients during the first days of the ICU. Although fasting patients had higher (and statistically significant) SAPS-3, the difference was irrelevant in the clinical setting (65.9 vs. 69.6 points), highlighting fasting as a therapeutic choice by physicians without clinical support for this decision. These data are not surprising once we acknowledge the ICU as a complex environment where the application of nutritional therapy guidelines regarding the timing and achievement of goals is very heterogeneous[20-22]. It is well known that dietary pauses are often prescribed to ICU patients, and they can be responsible for a caloric deficit from 5,000 to 10,000 calories in the first five days of admission[23]. In this study, we were unable to associate the number of calories and protein administered with certain outcomes since these data were not available. However, fasting was associated with mortality, which agrees with several studies that showed an association between mitigation of negative energy balance and favorable outcomes[24,25].

In univariate analyses, prior nutritional status—evaluated in our cohort by BMI—was also associated with mortality. The BMI stratified study, regarding the length of stay and mortality, showed that older adults with BMI less than 20 kg/m^2 had higher mortality (and a strong tendency of older adults with BMI greater than 29.9 kg/m^2 to have lower mortality. Yet, we are unable to argue in favor of the obesity paradox phenomenon in older adults. Still, this population reproduces the numerous reports of the association between low weight and worse outcomes[26-28]. Contrary to our expectations, fasting occurrence was not associated with an increase in mortality in low-weight older adults. However, this finding is in accordance with the result of a cohort of critically ill underweight population[29].

Our cohort demonstrates that older adults aged 80 years or over and underweight individuals (BMI less than 20 kg/m^2) have higher mortality than their younger peers and their higher BMI peers, which is not surprising. However, this subpopulation did not seem particularly susceptible to the theoretical harms of fasting, which we expected to happen. Two considerations can explain these findings in this subgroup. Firstly, it is possible that the energy balance was similar between individuals and, therefore, mitigated the influence of fasting. Secondly, basal energy expenditure was not objectively measured in this population, and there are reports that it may be lower[30,31]. In this scenario, even with fasting, the current energy provision would supply the caloric demand. These data suggest that this fragile population may not tolerate fasting periods and the emergence of an extremely negative energy balance, reinforcing the energy and protein recommendations advocated in some guidelines[32,33].

We also covered aspects related to functioning among survivors. We were unable to demonstrate an association between the days of food break or caloric/protein prescription and outcomes after hospital discharge (degree of dependence and quality of life). Beyond the fact that losses of follow-up were very high (52%), it is highly speculative that a certain period of fasting could impact functionality among survivors. However, fasting could be interpreted as a marker of undernutrition in these patients. Otherwise, there was no prior physical capacity, functionality, or independence assessment. In this way, it is not possible to exclude a similar previous limitation. We believe that more studies should be conducted to demonstrate the real behavior of older adults ICU survivors and their relationship with nutritional therapy processes during the hospitalization period.

This study has some limitations. Due to the nature of the study, it was not possible to stratify different doses of vasopressor and the duration of its use, which could offer a more robust analysis of this parameter regarding the outcomes. Likewise, it was not possible to assess the relationship between administered *vs.* planned supply of energy and protein to patients, which did not allow the comparison of different doses of calories and protein with outcomes. We used BMI to categorize previous nutritional status and there was no assessment of body composition by computerized tomography or dual-energy x-ray absorptiometry scan, nor a functional assessment (such as dynamometry), which would allow a realistic estimation of these patients' muscle mass and function. It's essential to keep in mind that using BMI as a prior nutritional categorization increases the chance of assessment errors. Unfortunately, we also do not have indirect calorimetry, which would objectively infer this population's energy expenditure. It was not possible to individually prepare and monitor energy balance measures, considering the insufficient data in these patients' medical records. Finally, there was a considerable loss of data in the follow-up after hospital discharge, which may have significantly compromised the quality of the analyses in survivors. However, except for the Charlson score, we found no significant differences between the patients who responded and who did not respond to the questionnaires. Since those who responded were individuals with fewer comorbidities, the hypothesis that mortality in the overall group was higher is plausible.

CONCLUSION

Older patients (aged 65 and over) constitute a fragile population in which nutritional breaks were associated with increased hospital mortality. Our study shows the significance of avoiding NPO prescription in older adults in ICU. This observation needs to be confirmed by prospective controlled trials.

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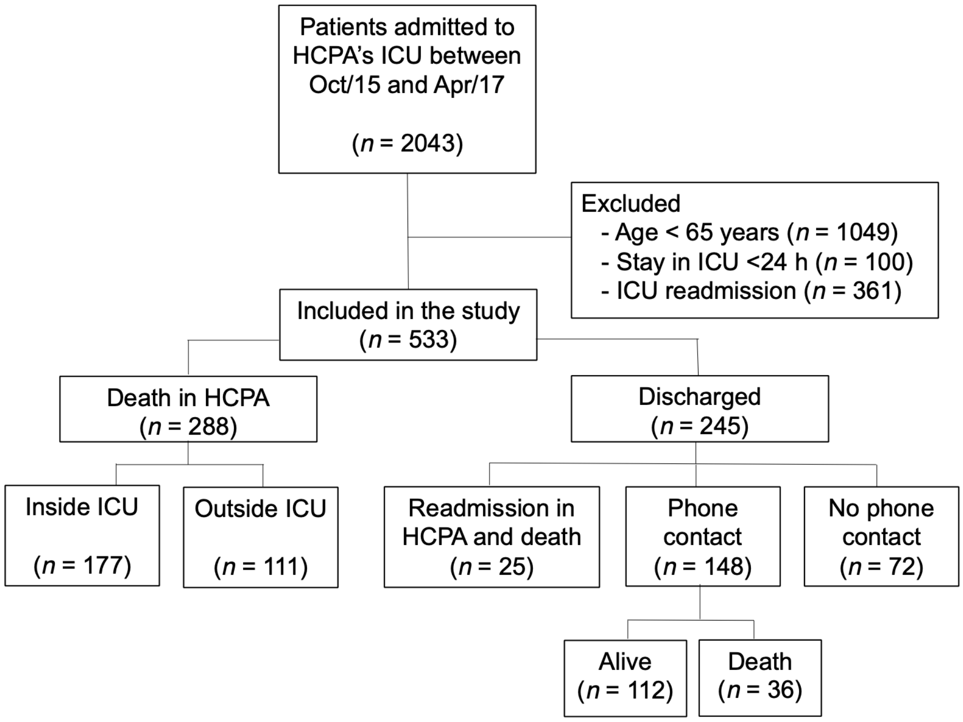

Figura 1. Screenings, assessments, and follow-ups included in the study and the reasons for exclusion. Apr/17, April 2017; HCPA, Hospital de Clínicas de Porto Alegre; ICU, intensive care unit; Oct/15, October 2015

Table 1- Baseline characteristics

Parameters	Overall 533	Fasting No 315 (58.9%)	Fasting Yes 218 (41.1%)	p
Age (median [IQR])	**73 [68-78]**	**73.1 [68.3-78.3]**	**72.8 [68.4-78.2]**	**0.813**
Gender = Male (%)	**278 (52.1)**	**164 (58.7)**	**114 (41.3)**	**0.856**
BMI (median [IQR])	**26.4 [22.8-30.1]**	**26.7 [26-30]**	**26.7 [26.2-30.6]**	**0.857**
Charlson (median [IQR])	**6 [4-7]**	**6 [5-7]**	**6 [4-7]**	**0.051**
SAPS3 (mean (SD))	**66.5 (±13.9)**	**65.5 (±13.7)**	**69.6 (±13.8)**	**0.002**
Albumin (median [IQR])	**2.7 [2.2-3.3]**	**2.8 [2.3-3.3]**	**2.5 [2-3]**	**<0.001**
C-reactive protein (median [IQR])	**179.4 [96-285.1]**	**167.4 [80.2-254.4]**	**212.7 [109-308]**	**0.002**
Clinical scenario = Surgical (%)	**85 (15.9)**	**33 (38.4)**	**52 (61.6)**	**<0.001**
Clinical syndromes at admission (%)				**<0.001**
Respiratory Failure	**173 (32.5)**	**116 (67.1) ***	**57 (32.9)**	
Severe sepsis	**119 (22.5)**	**56 (47.1)**	**63 (52.9) ****	
Cardiologic event	**84 (15.7)**	**55 (65.5)**	**29 (34)**	
Neurologic event	**75 (14)**	**51 (68)**	**24 (32)**	
Mixed parameters	**81 (15.2)**	**37 (45.7)**	**44 (54.3)**	
Mechanical ventilation	**341 (64.2)**	**183 (53.8)**	**158 (46.2)**	**0.001**
Palliative care (%)	**71 (13.3)**	**39 (59.4)**	**32 (40.6)**	**0.430**
Length of stay (days, median [IQR])	**21 [13-38]**	**22 [14-38]**	**21 [12-39]**	**0.572**
Death (%)	**287 (53.8)**	**146 (35.5)**	**141 (64.5)**	**<0.001**

Fasting: Nil Per Os (at least one day during the first seven days following ICU admission); IQR: interquartile range; SD: standard deviation; SAPS-3: Simplified Acute Physiology Score 3; * ventilatory failure associated with the absence of fasting; ** severe sepsis associated with fasting.

Table 2- Multivariate analysis of parameters associated with fasting

	RR (CI)	p value
Charlson score	0.878 (0.799-0.964)	0.007
SAPS-3 score	1.014(0.997-1.032)	0.100
C-reactive protein	1.002 (1.000-1.004)	0.028
Serum albumin	0.768 (0.560-1.054)	0.102
Sepsis	1.300 (0.792-2.134)	0.299
Surgery	3.629 (1.732-7.603)	0.001
Mechanical ventilation	1.604 (0.992-2.595)	0.054

RR: relative risk; CI: confidence interval; SAPS-3: Simplified Acute Physiology Score 3.

Table 3- Univariate analysis and mortality

	Overall	Survival		p value
	533	Yes (246)	No (287)	
Age (years, median [IQR])	73 [68-78]	72 [67-87]	73 [69-78]	0.008
Age ≥ 80 years old No. (%)	120 (22.5)	52 (46.9)	68 (56.1)	0.495
Male No. (%)	278 (52.1)	125 (45)	153 (55)	0.594
BMI (median [IQR])	26.4 [22.8-30.1]	27.1 [23.8-30.6]	25.8 [22.2-29.2]	0.002
Surgical patients No. (%)	86 (16.1)	42 (48.8)	44 (51.2)	0.574
Charlson score (median [IQR])	6[4-7]	6 [4-7]	6 [5-7]	0.024
SAPS-3 score (mean (SD))	66.5 (±13.9)	61.7 (±13.7)	71.8 (±12.6)	<0.001
Vasopressor use No. (%)	297 (55.8)	114 (38.4)	183 (61.6)	<0.001
Sepsis No. (%)	135 (25.3)	53 (39.3)	82 (60.7)	0.063
Serum albumin (median [IQR])	2.7 [2.2-3.30]	2.8 [2.3-3.3]	2.5 [2.0-3.0]	<0.001
C-reactive protein c	179.4 [96.0-285.1]	147[70.3-261.3]	207.9 [114-308]	0.002
Fasting No. (%)	217 (40.8)	77 (35.5)	140 (64.5)	<0.001
Total fasting days (median [IQR])	0 [0-1]	0 [0-1]	0 [0-2]	<0.001
Palliative care No. (%)	71 (13.30)	3 (4.2)	68 (95.8)	<0.001
Length of stay (days, median [IQR])	21 [13-38]	19 (10.5-31)	27 (17-47)	<0.001

IQR: interquartile range; SD: standard deviation; SAPS-3: Simplified Acute Physiology Score 3; BMI: body mass index; Statistics: Student’s t-test for parametric comparison, Mann-Whitney U tests for non-parametric comparison, and Chi-square test was used to compare categorical variables

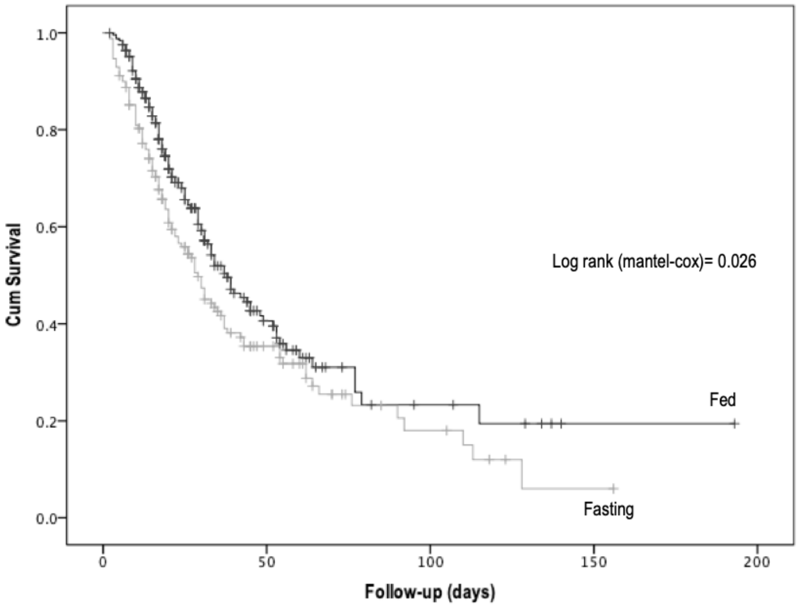

Figura 2. Six-month survival by Kaplan-Meier estimates for time-dependent fed and fasting groups

Table 4- Multivariate analysis of parameters associated with mortality

	RR (CI)	p value
BMI	0.973 (0.938-1.009)	0.135
Charlson score	1.073 (0.973-1.184)	0.158
SAPS-3 score	1.053 (1.033-1.074)	<0.001
Vasopressor use	1.089 (0.648-1.832)	0.747
C-reactive protein	1.001 (0.999-1.003)	0.239
Serum albumin	0.654 (0.469-0.912)	0.012
Sepsis	1.143 (0.674-1.937)	0.621
Fasting	1.695 (1.059-2.713)	0.028
Mechanical Ventilation	0.744 (0.455-1.243)	0.259

RR: relative risk; Fasting: at least NPO one day during 1st week; CI: confidence interval; BMI: body mass index; SAPS-3: Simplified Acute Physiology Score 3.

Nutrition as a risk for mortality and functionality in critically ill older adults

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CAPÍTULO 3

PROJETO 2

Does parenteral nutrition suppress hunger? A prospective cohort study

ABSTRACT

Background: Parenteral nutrition (PN) is commonly used to provide nutrition to patients who cannot be adequately fed through the digestive tract. However, some patients may experience delayed recovery of appetite and oral intake after receiving parenteral nutrition. The factors contributing to this lack of appetite are not well understood and previous studies have provided inconclusive results. This study aimed to investigate whether hospitalized patients receiving parenteral nutrition experienced reduced hunger in a real-life setting.

Methods: This prospective cohort included adult patients who received parental nutrition between April 2022 and July 2023. Patients were evaluated for hunger/satiety during three phases: clinical stability and achievement of calorie and protein targets, transition to oral feeding, and withdrawal from parenteral nutrition. The main clinical and nutritional parameters were obtained from medical records. Statistical analyses were performed to identify the correlations and predictive variables.

Results: Out 231 of the screened patients, 102 were included in the study. Most patients were hungry while receiving parenteral nutrition, with a positive correlation between hunger and successful transition to oral feeding ($r = 0.707$, $p < 0.001$). The presence and dose of lipids in parenteral nutrition did not interfere with hunger and satiety. Gradually reducing energy load as a strategy to increase appetite did not result in increased hunger or interest in food. Poisson regression analysis identified high age, significant inflammation, and metastatic cancer as independent factors associated with the absence of hunger.

Conclusion: This study suggests that parenteral nutrition does not suppress hunger, and that factors other than nutritional therapy should be considered to explain the absence of appetite in these patients. These findings can help guide decision-making regarding the reduction or discontinuation of parenteral nutrition and the initiation of oral feeding, considering the individual patient's condition and needs.

Keywords: parenteral nutrition, hunger, satiety, appetite, cancer, inflammation,

INTRODUCTION

Parenteral nutrition (PN) is a vital method for providing nutrition to patients who cannot be adequately fed through the digestive tract, as demonstrated in a pioneering study by Dudrick and colleagues[1]. It has shown favorable outcomes, particularly for malnourished patients[2] or high-risk patients who fail to meet their calorie and protein targets[3]. However, some patients may experience delayed recovery of appetite and oral intake after receiving parenteral nutrition[4]. The factors contributing to anorexia or early satiety in these patients remain unclear, with limited and inconclusive evidence from previous studies that are often outdated and based on small sample sizes involving both humans and experimental models. These studies attempted to assess the impact of calorie intake and different nutrients (lipids, glucose, or protein) on hunger suppression. However, their findings have been undetermined, with some suggesting that intravenous infusion of calories, particularly without lipids, does not suppress appetite, even at high-calorie levels[5,6].

It is hypothesized that the infusion of nutrients through parenteral nutrition may not generate the same hormonal and systemic responses observed during oral feeding, potentially explaining why individuals receiving high-calorie parenteral nutrition may still experience hunger or food cravings[5,7-9]. Furthermore, hormonal changes associated with intravenous administration of nutrients (such as glucose affecting ghrelin and lipids affecting peptide YY) do not necessarily correlate with the clinical manifestation of satiety[10].The role of lipids in parenteral nutrition and their influence on hunger is also a topic of debate[6,7,11]. Previous studies have described an association between nausea and vomiting, changes in taste (aversion to food), and increased satiety due to excellent energy supply. However, these findings have not been confirmed by recent studies.

It is reasonable to assume that hunger and satiety will return once patients' underlying pathological processes are resolved or improving[9]. Gradually reducing parenteral nutrition in patients transitioning to oral feeding has been shown to increase their interest in food, suggesting this approach for those lacking appetite[4]. To the best of our knowledge, no study has explored this strategy in hospitalized patients. These considerations are crucial for the healthcare team to plan the termination of parenteral feeding and the reintroduction of oral feeding. Caution should be exercised when attributing the lack of appetite to parenteral nutrition, and considering this a reason to reduce or withdraw this kind of therapy, as it may lead to adverse energy balance and potentially negative outcome[12,13].

This study aimed to investigate whether hospitalized patients receiving parenteral nutrition experience reduced hunger in a real-life setting.

MATERIAL AND METHODS

Definitions[14,15]

In this study, appetite was defined as a motivational drive to obtain food. Hunger represents a sensation that translates into a desire or need to eat. Satiety corresponds to the absence of a desire to eat and occurs between two feeding periods. Satiation represents the sensation that leads to the interruption of a feeding session. Successful weaning from PN indicated that the patient had received an adequate amount of energy through the digestive tract.

Setting and patients

This prospective observational study was conducted at a single center at the Hospital de Clínicas de Porto Alegre (HCPA). Adult patients (aged ≥ 18 years) admitted to the hospital between April 2022 and July 2023 were screened for eligibility. The patients were consecutively enrolled in this study. All patients with exclusive parenteral nutrition who were able to communicate were invited to the study (Intensive Care Unit (ICU) or ward). The exclusion criteria were terminal patients (expectation less than three months of life), pregnancy, supplementary parenteral nutrition, psychiatric disease, bariatric surgery, and total or subtotal gastrectomy.

For each included patient, the following data at admission were recorded: age, sex, weight, height, hospital admission category (surgical or medical), comorbidities, Simplified Acute Physiology Score 3 (SAPS 3), sequential organ failure assessment (SOFA) score (in the case of intensive care unit (ICU) admission), nutritional risk screening (NRS-2002), and Charlson Comorbidity Index (CCI)). In addition, the researchers recorded the number of calories and protein given parenterally (at all assessments), Karnofsky score (first and last assessments), handgrip strength measurements, and calf circumference (both at the first assessment).

The following parameters were evaluated: blood count, serum albumin, electrolytes, renal function, and C-reactive protein (CRP) levels. Body Mass Index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. BMI ranging from 20 to 25 kg/m² was classified as healthy, under 20 kg/m² as underweight, and over 30 kg/m² as obese.

Nutritional therapy protocol

The institutional protocol for parenteral nutritional therapy at the hospital is based on guidelines from the European Society for Parenteral and Enteral Nutrition (ESPEN)[16], American Society for Parenteral and Enteral Nutrition (ASPEN)[17], and Brazilian Society for Parenteral and Enteral Nutrition (BRASPEN)[18]. Briefly, the institutional protocol guides the initiation of parenteral nutritional therapy in patients who do not have the enteral route totally or partially, who are metabolically and hemodynamically compensated, early (within 48 hours), and with progression to the goal within 3 days. The calorie target varies depending on whether the patient is critical, 15-25 kcal/kg/day in critical and 25-35 kcal/kg/day in non-critical patients for the first seven days. Parenteral nutrition was prescribed by an intensivist and/or a trained medical team dedicated to medical food in our hospital. Calories, protein, glucose, and lipid loads based on kilograms of weight (in the case of patients with a BMI greater than 30 kg/m², based on ideal weight – height × height × 25) were obtained from the daily prescription of patients.

Hunger and Satiety Evaluation

Hunger and satiety parameters were obtained through a visual scale score based on a study by Holt and Miller[19], whose first half consisted of assessing hunger (famish, hunger, little hunger, neutral: 1, 2, 3, and 4 points, respectively). The second half estimated satiety (slightly satisfied, satisfied, and delighted: 5, 6, and 7 points, respectively) after the patient had ingested food.

Nutritionists performed three evaluations to assess hunger/satiety. When the clinical stability and achievement of the calorie and protein target (phase 1), from the moment the care team started the transition to the oral route (orally offering liquid or pasty foods or a light diet, or eventually through a feeding tube, phase 2), and finally at the time of withdrawal from parenteral nutrition (phase 3). Patients were grouped according to the presence of hunger (preserving appetite according to a specific tool (< 4 points) and no appetite according to a specific tool (≥ 4 points)).

Ethics

The study protocol was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (2021/0232 - CAAE 47605221200005327) and was conducted in compliance with the Declaration of Helsinki.

Statistics

Statistical analyses were performed using JAMOVI® 2.3.19.0 and Numbers® 13.0. Descriptive data are reported as mean ± SD, median (interquartile range), or frequency (percentage). Means were compared using t- or Mann-Whitney U tests according to the distribution of variables. Yuen's test was utilized if Levene's test suggested violating the assumption of equal variances. The Chi-square test was used to compare categorical variables. Pearson's linear correlation was used to relate the presence of hunger and success in migrating PN to enteral nutrition. A Poisson regression model was used to estimate the relative risk and 95% confidence interval. Furthermore, a multivariate model was used to identify variables independently associated with the absence of hunger in the transition to oral feeding. The criterion for entering the variable into the multivariate model was that it presented a p-value < 0.10 in the univariate analysis. The final model was chosen based on the best fit to the data, verified through a residual graph, Bayesian Information Criterion (BIC), and Akaike Information Criterion (AIC). A receiver operating characteristic (ROC) curve was constructed based on this analysis.

RESULTS

Of the 231 patients screened, 102 were included in this study (**Figure 1**). **Figure 2** describes the distribution of patients in groups with and without hunger, stratifying each patient according to success or failure in the transition to oral nutrition. **Table 1** provides an overview of the characteristics of patients with and without hunger during the transition from parenteral to oral nutrition. In short, median age was 60.5 (43.5-71), 56.9% were men, CCI was 4 (1-6), BMI was 25.6±5.37 kg/m^2 and 39.2% were admitted to the ICU [SAPS3 score of 65.5±14.3 and SOFA score of 5 (2-7)]. All patients received an all-in-one parenteral nutrition system, with 85.3% being surgical patients (predominance of colectomy (41.4%), stomach-duodenum-jejunum-ileum (33.3%), and complex wall hernias (6.9%)). The average time for progression of parenteral energy supply was 3 [3-4] days and did not differ between the groups. Similarly, the time between parenteral nutrition initiation and transition to oral feeding did not vary between the groups (**Table 1**).

Approximately 37% of the patients did not report hunger during the transition, and 66.7% successfully transitioned to oral feeding. The correlation between hunger and successful transition from parenteral nutrition to digestive tract use was 70.7% ($p<0.001$). Early satiety (feeling of fullness and/or abdominal discomfort after starting to eat) was observed more frequently in patients with no appetite during the transition (85% incidence, $p<0.001$) and in those without successful transition (75% incidence, $p<0.001$). The urea-to-creatinine ratio was higher in those with a higher protein load (> 1.3 g/kg/day) at the transition moment, mainly in patients without hunger (57.4 ± 22 in those with and 71.3 ± 25.4 in those without hunger; $p=0.006$). Among the patients with no correlation between hunger and successful transition (14 patients, 13.7% of the sample), 85% achieved satisfactory migration even without hunger. In comparison, 15% were hungry but could not transition because of structural problems (e.g., fistula and obstruction). Most patients transitioned to oral feeding (81.4%), with dysphagia as the primary cause of enteral nutrition necessity (10.8%).

Calorie, protein, glucose, and lipid doses varied across the three assessment periods **(Table 2)**. We did not observe significant differences between the groups with and without hunger related to the doses of energetic substrates in the different phases of the study or to the gradual reduction of the energy dose during the transition (hunger between patients with and without reduced energy supply, 65% vs. 59.5%, $p= 0.573$).

Table 3 presents the multivariate analysis with the outcome of absence of hunger as the dependent variable. CRP greater than 150 mg/dL, age greater than or equal to 65 years, and metastatic cancer fitted the best model of prediction of hunger absence. An ROC curve was constructed to determine the predictive variables of hunger absence during the transition, demonstrating the area under the curve and accuracy of the parameters obtained from logistic regression (**Figure 3**). The area under the curve was 0.750 (0.660-0.860) with a sensitivity of 84.2% and a specificity of 50.0%). The inclusion of the Karnofsky score in the logistic regression model and its effect on predicting the absence of hunger is shown in **Figure 4**.

DISCUSSION

The findings of this study support previous research indicating that most patients receiving parenteral nutrition experience hunger when transitioning to oral feeding[5,6,10]. The correlation between hunger and successful transitioning was 70.7%, and older age, CRP levels, and metastatic cancer were associated with the absence of hunger. This finding is unsurprising, as eating triggers intricate signaling of hunger and satiety that is potentially lost or modified during parenteral nutrition and disease. Hunger, satiety, and the interactions among postprandial factors are multifaceted and complex. Sensory factors such as taste, smell, and food texture stimulate ingestion. As eating progresses, specific sensory habituation to the ingested food develops, while signals from the gastrointestinal tract (gastric distension, drop in stomach ghrelin, the release of hormones and various peptides) and increased blood glucose reduce food cravings. After food consumption, there are numerous hunger regulators, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide (GIP), and peptide YY (PYY). The regulation of satiety is a fundamental factor in the central nervous system as it receives and integrates several signals from the periphery of the body. The chemical regulators (peptides, hormones) and physical regulators (frequency, volume, weight, and intraluminal pressure) generate the homeostatic adjustment of energy intake and expenditure[9,20-22]. In the absence of these satiating elements provided by food in the digestive tract, hunger may persist (loss of the incretin effect of food) despite an adequate energetic supply[20,23].

Hunger is a subjective feeling[24,25], and it is possible to be fed without the sensation of hunger. This could explain why 12% of our sample without hunger could ingest adequate calories and be successfully weaned from PN. We observed that patients who did not experience hunger had higher levels of inflammation and were older and sicker. In these cases, the lack of appetite or interest in food is likely attributed to uncontrolled illness or poor clinical performance, rather than parenteral nutrition itself.

Contrary to previous reports[7,10], our data suggest that the presence and dose of lipids in parenteral nutrition solutions do not interfere with hunger and satiety. It seems that enteral fat administration causes satiety depending on the lipid droplet size, with the effect being dependent on the intestinal location of fat delivery[26]. Thus, a decrease in ghrelin levels (an incretin hormone) seen after a lipid meal is not secondary to circulating nutrients, but to luminal or neurohumoral factors[10].

Most patients were hungry while receiving parenteral nutrition, and the association between being hungry and successful weaning from PN was significant. We also observed that the gradual reduction in energy load as a therapeutic strategy to increase appetite was not associated with increased hunger or interest in food.

Another interesting observation was that the urea-to-creatinine ratio was higher in the patients without hunger. Furthermore, the urea-to-creatinine ratio was significantly higher in those with a protein load greater than 1.3 g/kg/day. Could these patients be inadvertently subjected to protein overfeeding resulting in unsatisfactory outcomes? If so, echo the recent publications that link the retention of nitrogenous compounds to worse outcomes (in critically ill patients)[27-29]. These observations should be further explored in future studies on patients receiving parenteral nutrition.

Our Poisson regression and prediction model showed that high age (greater than or equal to 65 years), significant inflammation (CRP greater than 150 mg/dL), and metastatic cancer were independently associated with the absence of hunger. The inclusion of the Karnofsky score, which was not significant in the multivariate analyses, provided a better balance between sensitivity and specificity, improving the performance of Poisson regression in detecting patients at the highest risk of not being hungry (AUC 0.800 (95%CI: 0.700-0.890); sensitivity =71.1%; specificity =78.1%; **Figure 4**). This finding confirms our preliminary bedside clinical impressions (the absence of hunger in patients receiving parenteral nutrition is related to the severity of the disease or the presence of inflammation, and not to intravenous nutritional therapy). Furthermore, since leptin is a molecule related to interleukins and is usually elevated in inflammation situations, it could offer an additional explanation for the lack of appetite observed in the most ill or inflamed[30,31]

This study has some limitations. First, it was a unicentric cohort. Second, although patients received treatments guided by our institutional guidelines, therapy guidance was the care team's responsibility and any changes in terms of calorie goals could occur. Third, we did not proceed with plasma measurement of hormones that are potentially involved in appetite regulation. Among the strengths, we highlight that excluding patients with significant stomach resection (or obvious anatomical modification of this region) made the sample more homogeneous. Gastrectomy patients do not express the feeling that we usually understand as a hunger[32]. In addition, we used a specific hunger and satiety scale[19], consistently applied before lunch, which helped reduce intra-patient variability in results. It is important to emphasize that other scales[33] could offer different results.

The regulation of hunger and satiety is a highly complex process that has evolved over millions of years because of interactions between early hominids and food consumed orally for survival. Thus, it is not surprising that patients receive nutrients intravascularly without causing satiety. Humoral and hormonal mechanisms unfolded by food interactions in the digestive tract are necessary for controlling hunger and satiety.

CONCLUSION

Our study offers valuable insights into hunger and satiety among patients receiving parenteral nutrition through bedside observation. This study sheds light on the factors that influence appetite during the transition to oral feeding. Our findings suggest that parenteral nutrition alone does not suppress hunger. Instead, other factors, such as the severity of illness, advanced age, and inflammation, should be considered when attempting to understand the absence of appetite in these patients. These findings could guide clinical decision-making regarding the reduction or discontinuation of parenteral nutrition and initiation of oral feeding.

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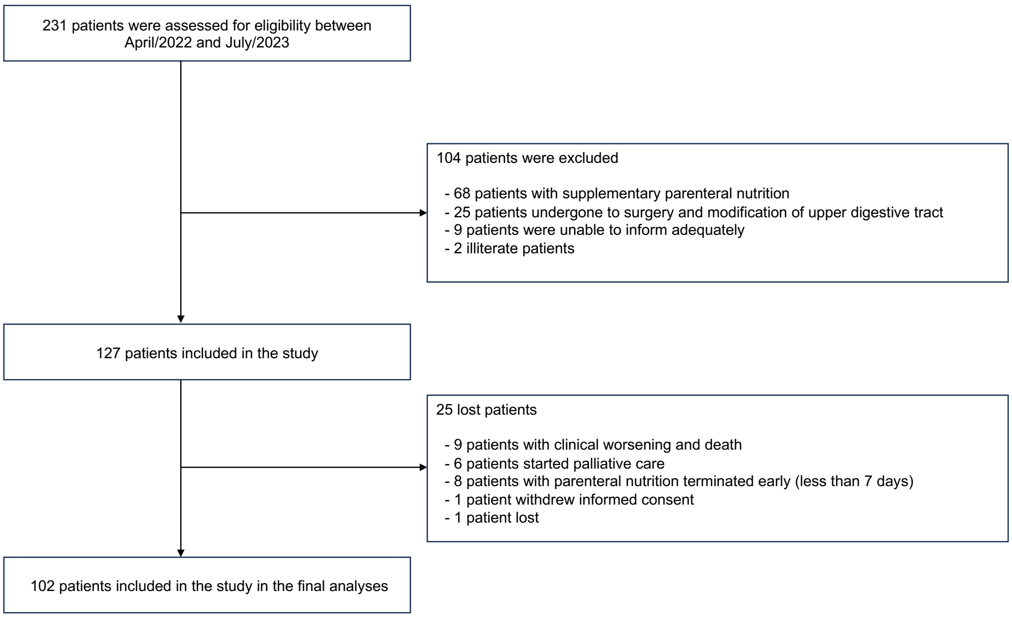


Figura 1. Trial profile

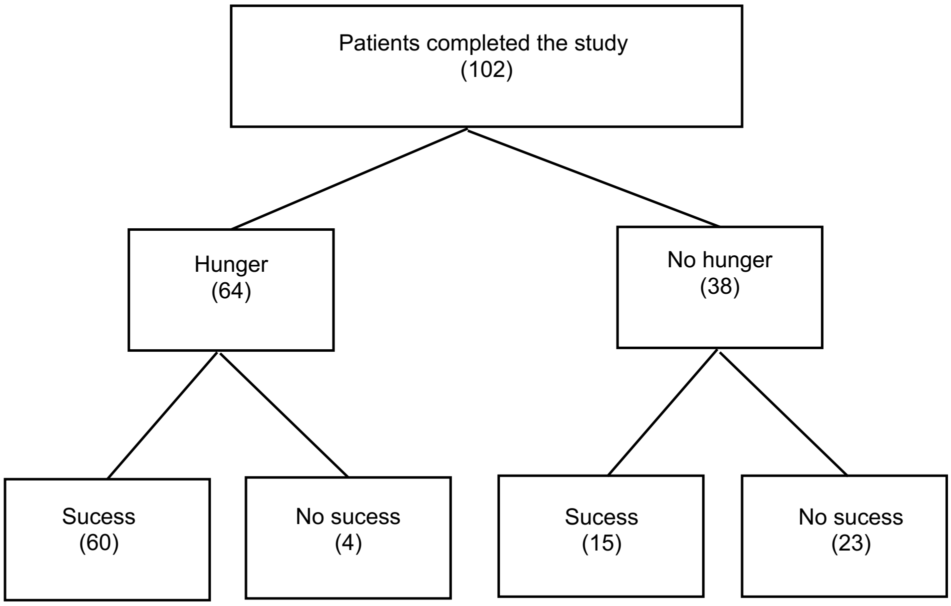


Figura 2. Distribution of patients in groups with and without hunger, stratifying each patient according to success or failure in the transition to oral nutrition

Table 1- Patients with or without hunger in transitioning from parental to oral nutrition

Parameters	Overall 102	Hunger Yes 64 (62.7%)	Hunger No 38 (37.3%)	p-value
Age, median [IQR]	60.5 [43-71]	56 [37.8-67]	67 [52-75]	0.003
Gender = Male, n (%)	58 (56.9%)	40 (39.2%)	18 (17.6%)	0.136
BMI, mean ± SD	25.6 ±5.37	25.4 ±5.6	25.8 ±5	0.879
Charlson, median [IQR]	4 (1-6)	3.5 [0-5]	5 [2.25-6]	0.013
Karnofsky, median [IQR]	50 [50-60]	60 [50-70]	50 [40-50]	<0.001
Hemoglobin, median [IQR]	8.75 [7.6-10.3]	9.1 [7.9-11]	8.1 [7.1-9.4]	0.004
Platelet (*1000), mean ± SD	346.6 ±156.4	353 ±164.4	333 ±143	0.470
Urea (mg/dL), median [IQR]	46 [34.3-72]	42.5 [34-66.5]	59 [39.3-76.8]	0.066
Creatinine (mg/dL), median [IQR]	0.73 [0.56-0.93]	0.72 [0.57-0.91]	0.74 [0.57-0.94]	0.879
Sodium (mg/dL), mean ± SD	139 ±3.85	139 ±3.47	139 ±4.47	0.972
Potassium (mg/dL), median [IQR]	4.4 [3.8-4.6]	4.4 [4.2-4.6]	4.1 [3.6-4.6]	0.035
Magnesium (mg/dL), median [IQR]	1.9 [1.7-2]	1.9 [1.7-2]	1.85 [1.7-2]	0.500
Phosphorus (mg/dL), median [IQR]	3.2 [1.6-3.8]	3.2 [2.8-3.8]	3 [2.3-3.6]	0.108
Calcium (mg/dL), median [IQR]	9 [8.6-9.3]	9.1 [8.9-9.3]	8.9 [8.3-9.3]	0.883
Triglycerides (mg/dL), median [IQR]	157 [113-238]	156 [112-230]	172 [114-256]	0.416
Glucose (mg/dL), median [IQR]	120 [105-141]	117 [103-142]	122 [111-140]	0.272
Hyperglycemia, n (%)	27 (26.4%)	17 (63%)	10 (37%)	0.978
Albumin (g/dL), median [IQR]	2.67 [2.25-3]	2.8 [2.2-3.4]	2.3 [2.2-2.7)	0.001
CRP (mg/dL), median [IQR]	81.1 [40.5-157]	64.3 [34.6-115]	126 [67.8-215]	<0.001
Urea to creatine ratio, mean ± SD	66 ± 25	61.8 ± 21.5	72.9 ± 29	0.030
NPO (days), median [IQR]	6 [3-11]	5.5 {3.75-11.3]	7 [3-10.8]	0.779
Time transition (days), median [IQR]	7 [4.25-11]	6.5 [4-11]	8 [5-11]	0.210
Cancer, n (%)	47 (46%)	27 (54.4%)	20 (42.6%)	0.306
Metastatic cancer, n (%)	14 (13.7%)	5 (35.7%)	9 (64.3%)	0.024
Type 2 Diabetes, n (%)	14 (13.7%)	9 (64.3%)	5 (35.7%)	0.898
Cigarette smoking, n (%)	24 (23.5%)	15 (62.5%)	9 (37.5)	0.977
ICU, n (%)	40 (39.2%)	23 (57.5%)	17 (42.5%)	0.379

SAPS3, mean ± SD	65.5 ±14.3	64.3 ±14.9	67.1 ±13.8	0.545
SOFA, median [IQR]	5 [2-7]	5.5 [2.25-7]	4 [2-8]	0.909
Success PN transition to EN (%)	69 (67.6%)	59 (57.8%)	10 (9.8%)	<0.001

IQR: interquartile range; SD: standard deviation; BMI: body mass index; CRP: C-reactive protein; ICU: Intensive Care Unit; SAPS-3: Simplified Acute Physiology Score 3 (patients with admission at ICU); SOFA: sequential organ failure assessment (patients with admission at ICU); PN: parenteral nutrition; EN: enteral nutrition (oral/enteral nutrition)

Table 2 Calorie and protein doses over time.

Phases	Substrates	Hunger		p-value
		Yes (group A)	No (group B)	
Phase 1	**E-** 23.9 [20-26]	23.6 [20-26]	24.1 [20.5-25.6]	0.766
	P- 1.39 ± 0.25	1.40 ± 0.24	1.37 ± 0.26	0.444
	G- 3.17 ± 0.77	3.18 ± 0.79	3.15 ± 0.73	0.873
	L- 0.67 ± 0.16	0.68 ± 0.16	0.65 ± 0.15	0.360
Phase 2	**E-** 23.6 ± 4.36	24 ± 4.2	23 ± 4.6	0.259
	P- 1.43 ± 0.25	1.4 ± 0.24	1.4 ± 0.26	0.242
	G- 3.25 ± 0.76	3.3 ± 0.75	3.1 ± 0.78	0.246
	L- 0.68 ± 0.16	0.7 ± 0.15	0.65 ± 0.18	0.090
Phase 3	**E-** 16.6 [12.9-23.8]*	16.1 [12.7-22.8]$	17.9 [13.9-24]&	0.491
	P- 1.2 [0.9-2.4]*	1.2 [0.9-1.4]$	1.1 [0.9-1.5]&&	0.710
	G- 2.2 [1.7-2.4]*	2.1 [1.7-3.2]$	2.5 [1.8-3.2]&&&	0.547
	L- 0.48 [0.3-0.7]*	0.4 [0.3-0.7]$	0.5 [0.35-0.65]&&&&	0.757

Phase 1: clinically stable patient with calorie and protein targets met; Phase 2: beginning of the transition phase for using the digestive tract; Phase 3: ending of parenteral nutrition; E: dose of energy (kcal/kg/day); P: protein (g/kg/day); G: glucose (g/kg/day); L: lipid (g/kg/day); * p-value <0.001 along the phases; $ p-value <0.001 within the group of patients in group A through the phases; & p-value = 0.001 within the group of patients in group B through the phases; && p-value= 0.003 within the group of patients in group B through the phases; &&& p = 0.002 within the group of patients in group B through the phases; &&&& p = 0.009 within the group of patients in group B through the phases; data expressed as median and interquartile range or mean and standard deviation.

Table 3- Multivariate analysis of parameters associated with the absence of hunger

	RR (95%CI)	p value
Age (≥ 65)	1.92 (1.17-3.17)	0.010
C-reactant protein (≥ 150)	1.98 (1.29-3.02)	0.002
Metastatic cancer (yes)	1.62 (1.05-2.49)	0.028

RR: relative risk; CI: confidence interval.

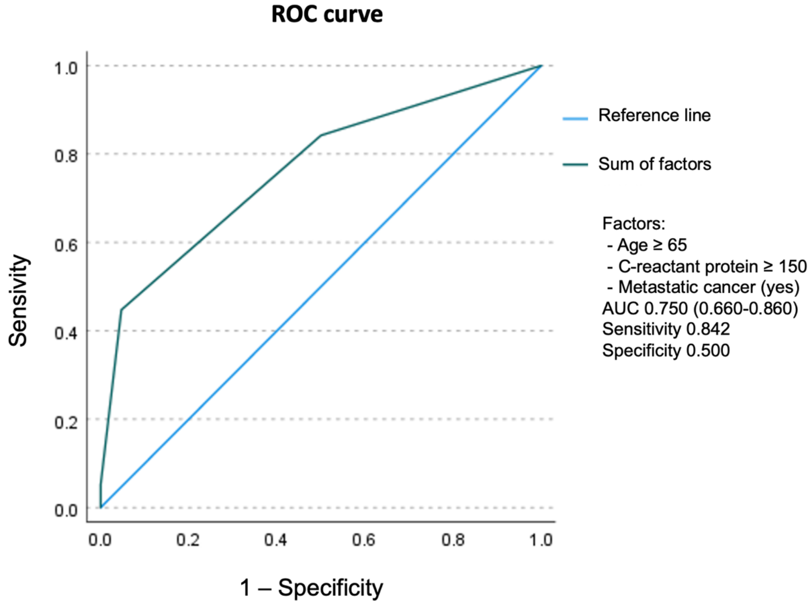
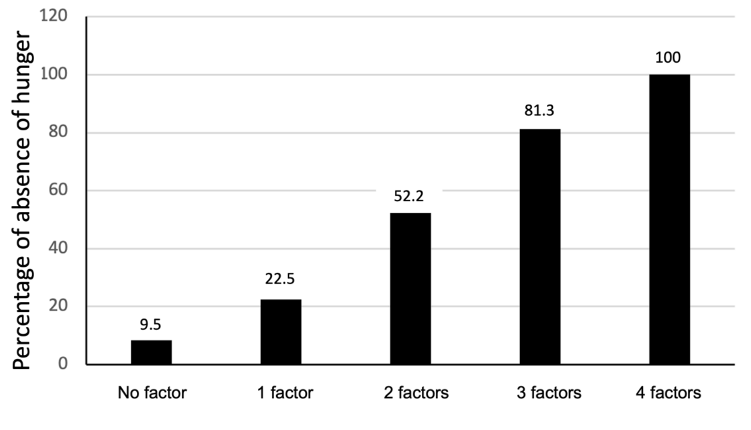


Figura 3. The receiving operating characteristic curve (ROC curve) shows the area under the curve of the sum of factors (age, CPR, and metastatic cancer) with a suggested cutoff point of 1 factor for the absence of hunger



Factors	n(%)	RR (CI95%)	p-value
0	21 (20.6)	1.00	
1	40 (39.2)	2.36 (0.56-9.95)	0.241
2	23 (22.5)	5.48 (1.39-21.7)	0.015
3	16 (15.7)	8.53 (2.24-32.6)	0.002
4	2 (2)	10.5 (2.81-39.2)	<0.001

Figura 4. Percentage of absence of hunger in a Poisson regression model with 4 factors: age (≥ 65), C-reactant protein (≥ 150), metastatic cancer (yes), and Karnofsky score (≤ 50). In this model, Karnofsky score did not reach statistical significance (p= 0.105). However, its inclusion provided a better balance between sensitivity and specificity, improving the performance of Poisson regression in detecting patients at the highest risk of not being hungry (AUC 0.800 (95% CI: 0.700-0.890), with a suggested cutoff point of 2 factors for absence of hunger (≥ 2 factors: Sensitivity=71.1%; Specificity=78.1%)

CAPÍTULO 4

CONSIDERAÇÕES FINAIS

Terapia nutricional atualmente se constitui em um importante elemento do conjunto de terapias aplicadas a pacientes hospitalizados, perfazendo uma gama de procedimentos que engloba o momento de iniciar a repleção nutricional, a velocidade de reposição, as metas energéticas a serem atingidas, a(s) via(s) de administração, a população de pacientes, os diagnósticos que culminam com a indicação do suporte nutricional[1-3]. O planejamento desta terapia está aparentemente associado a melhor cicatrização, reestabelecimento da imunidade e preservação da massa muscular[4], embora a fragilidade da evidência e necessidade de estudos com design adequado e tamanho amostral apropriado[5].

Apesar dos benefícios da terapia nutricional nem sempre é possível cumprir com o planejando, exigindo das equipes assistenciais experiência e expertise para o reconhecimento das dificuldades e as estratégias que podem ser adotadas para garantir uma repleção energética satisfatória. São muitos os obstáculos que desafiam as equipes assistenciais, sobremaneira, inapetência, aumento das demandas metabólicas, disfunção do trato digestório e efeitos colaterais de medicamentos[6].

Pacientes idosos são mais frágeis e, portanto, mais suscetíveis aos efeitos de uma repleção nutricional insuficiente com consequente balanço energético negativo, tema do projeto um deste doutorado, que focou idosos críticos (com 65 anos ou mais). Desnutrição tem elevada prevalência em pacientes hospitalizados e sua associação com aumento de custos, morbidade e mortalidade[7]. Assim, é possível que o impacto nos desfechos nesta população determinado por períodos de jejum (por vezes desnecessários), além de prescrições nutricionais inadequadas, seja negativo. Pausas nutricionais desnecessárias foi um fator de risco independente associado ao surgimento de doença crítica crônica em uma coorte que estudou parâmetros preditivos desta síndrome[8]. Griffiths e colaboradores[9] descreveram há mais de uma década recomendações a respeito da oferta energética e a estreita faixa de calorias que deve ser administrada a doentes críticos, alertando para as consequências desastrosas relacionadas a suboferta (*underfeeding*) quanto para a sobreoferta (*overfeeding*) de energia.

Nada por via oral (NPO- Nil Per Os) foi prescrito para uma parcela significativa dos pacientes idosos críticos durante a primeira semana de internação na UTI, estando o jejum associado à síndrome clínica que motivou a internação. Os pacientes cirúrgicos foram submetidos com mais frequência a pausa nutricional, e os pacientes que passaram pelo jejum apresentaram pontuações SAPS-3 mais altas (escore de gravidade da doença), níveis mais baixos de albumina sérica e taxas de mortalidade mais altas.

Pacientes com 80 anos ou mais apresentaram taxas de mortalidade mais altas, mas, surpreendentemente, a ocorrência de jejum não teve impacto significativo na mortalidade nesta faixa etária. O estudo também constatou que pacientes com IMC inferior a 20 kg/m² apresentaram maior mortalidade, enquanto pacientes com sobrepeso e obesidade apresentaram menores taxas de mortalidade (compatível com o famoso aforismo "paradoxo da obesidade"[10,11]). Entretanto este estudo não tem poder para este tipo de conclusão.

O jejum foi identificado como preditor independente de mortalidade em idosos internados em UTI. Cada dia de jejum aumentou o risco de morte em aproximadamente 15% na primeira semana de internação na UTI. O estudo conclui que os pacientes idosos internados na UTI são vulneráveis aos efeitos negativos do jejum, o que está associado ao aumento da mortalidade hospitalar.

Outro momento importante na terapia nutricional de doentes hospitalizados é a transição da nutrição parenteral para nutrição oral, o que eventualmente é desafiador, podendo ser um gerador de balanço energético negativo e, conforme escrito acima, ser um elemento adicional no desenvolvimento de fragilidade e consequente aumento de risco de morbidades ou mortalidade nesta população. A expectativa dos investigadores era reproduzir neste estudo as observações empíricas que tínhamos de que doentes que recebem nutrição parenteral não apresentam redução de fome secundária a administração intravenosa de nutrientes, desde que tenham controladas as patologias que culminaram nesta modalidade de terapia nutricional. Esta expectativa se desdobra a partir das constatações fisiológicas de que a relação física do indivíduo com alimento ingerido e consequente estímulos em diferentes segmentos do trato digestório em conjunto a respostas aferentes e eferentes por parte do sistema nervoso central regulam a necessidade de se alimentar (fome), a redução deste sentimento (saciação) e a ausência de sinalizações para nova busca de alimento (saciedade)[12-16].

O controle da fome e saciedade envolve a ação de hormônios produzidos no sistema digestório em resposta a expectativa ou presença de alimento, a saber, grelina, produzida no estômago, com secreção aumentada antes das refeições provocando sensação de fome; leptina, produzida por adipócitos, atua como um regulador negativo do apetite a longo prazo; insulina, produzida pelo pâncreas, regula os níveis de glicose no sangue, interferindo indiretamente a fome; peptídeo YY (PYY), liberado pelo sistema digestivo, está associado à sensação de saciedade e reduz o apetite. Além disto, mecanismos de feedback participam deste controle, incluindo colecistoquinina (CCK), liberada em resposta aos alimentos no intestino delgado, sinaliza saciedade e reduz o apetite e receptores de estiramento gástrico e intestinal que sinalizam saciedade à medida que se distendem frente a presença e movimentação do alimento. A sinalização eferente por parte do sistema nervoso central se desdobra de diferentes estruturas, como o hipotálamo, que recebe aferência nervosa e endócrina informado o estado nutricional do paciente, e circuitos neurais que integram sensações olfativas, visuais e centros de recompensa[12-16].

A fome e a saciedade foram avaliadas por meio de uma escala visual em três fases diferentes: durante a estabilidade clínica e o alcance das metas calóricas e proteicas, durante a transição para a alimentação oral e no momento da retirada da NP. Os pacientes foram agrupados com base na presença ou ausência de fome.

O estudo demonstrou que a maioria dos pacientes que receberam nutrição parenteral sentiu fome durante a transição para a alimentação oral. A correlação entre a fome e a transição bem-sucedida foi significativa. Os fatores associados à ausência de fome incluíram idade avançada, níveis elevados de proteína C reativa (PCR) e câncer metastático. Diferente de alguns estudos antigos, o conteúdo lipídico nas soluções de nutrição parenteral não pareceu afetar a fome e a saciedade.

Concluiu-se que os pacientes submetidos a nutrição parenteral não perdem necessariamente o apetite, e fatores como gravidade da doença, inflamação e idade desempenham um papel mais significativo na ausência de fome. Aqui, uma vez mais, fica evidente a fragilidade dos pacientes hospitalizados idosos. Essas informações podem aumentar a compreensão da equipe assistencial, bem como orientar as decisões clínicas quanto à transição da nutrição parenteral para a alimentação oral.

Estes dois estudos, avaliados em conjunto, realçam a importância da terapia nutricional em pacientes hospitalizados. Pacientes idosos estão sujeitos a pausas de nutrição, o que se associam a desfechos desfavoráveis (aumento de mortalidade), além de significativamente terem mais dificuldade de cumprirem com a transição de terapia nutricional parenteral para enteral o que os coloca em risco de balanço energético negativo. A transição difícil de alimentação intravenosa para enteral deve ser um alerta à equipe assistencial para a investigação de outras razões, que não a nutrição parenteral, para justificar esta dificuldade. Não é recomendada a retirada da nutrição parenteral como estratégia para pacientes com inapetência passarem a se alimentar adequadamente através da via oral.

PERSPECTIVAS FUTURAS

Os dois estudos desenvolvidos e apresentados neste projeto de doutorado trazem peculiaridades de específicas populações submetidas a terapia nutricional artificial. Aqui ficou demonstrado a fragilidade de idosos críticos submetidos a terapia nutricional e a dependência desta população de processos por parte do time assistencial que evite a ocorrência de pausa nutricional e mitigue o seu impacto desfavorável na mortalidade. Neste estudo não foi medido o balanço energético cumulativo (tanto o balanço calórico quanto o proteico), o que poderia ser investigado em futuro estudo. Sabemos que o impacto do déficit calórico e, principalmente, o proteico se associam a piores desfechos em populações gerais de pacientes críticos. Possivelmente em idosos críticos o déficit proteico se correlacione positivamente com sarcopenia e consequentemente a fragilidade e possivelmente aumento do risco de mortalidade.

O segundo estudo claramente confirma a impressão que tínhamos a respeito de doentes adultos submetidos a nutrição parenteral, qual seja, esta modalidade de terapia nutricional não suprime a fome desta população. Esta é uma informação importante uma vez que contribui para a elaboração de um plano investigatório e terapêutico adequados por parte da equipe assistencial. Estudos futuros neste contexto poderão explorar as relações destas observações com o perfil hormonal que estes pacientes demonstram. Este painel hormonal poderia contribuir importantemente na compreensão sobre a intrincada relação destes elementos na regulação de fome e saciedade em pacientes hospitalizados submetidos a suporte nutricional parenteral.

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