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DUAS VARIANTES DO *NUTRITIONAL RISK IN THE CRITICALLY ILL* (NUTRIC) COMO PREDITORAS DE MORTALIDADE HOSPITALAR EM PACIENTES CRITICOS.

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Trabalho de Conclusão de Curso de Graduação apresentado como requisito parcial para obtenção de grau em bacharel em Nutrição, à Universidade Federal do Rio Grande do Sul, Faculdade de Medicina.

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1. Resumo estruturado (conforme as normas vigentes da biblioteca);
2. Revisão da literatura e lista de referências (conforme as normas vigentes da biblioteca);
3. Artigo original (no formato da revista de interesse);
4. Anexos necessários e normas da revista de interesse de submissão.

RESUMO

Introdução: A desnutrição é uma situação comum em pacientes hospitalizados e é altamente frequente em pacientes críticos e está associada a um maior risco de mortalidade. O *Nutritional Risk in the Critically Ill* (NUTRIC) é um instrumento para identificação do risco nutricional especifica para pacientes criticamente doentes e sugere a utilização da interleucina-6 (IL-6) como marcador de inflamação aguda, parâmetro nem sempre disponível nas Unidades de Tratamento Intensivo (UTIs). Já a proteína C-reativa (PCR) também é marcador inflamatório sensível, estável e de mais fácil dosagem. O objetivo deste estudo foi avaliar a concordância entre a versão modificada do escore NUTRIC (sem IL-6) (NUTRIC-1) e uma variante composta de PCR (NUTRIC-2) e sua capacidade de predizer mortalidade hospitalar em pacientes críticos.

Métodos: Estudo de coorte prospectivo em 315 pacientes admitidos na UTI do Hospital de Clinicas de Porto Alegre (HCPA) no período de outubro de 2017 a abril de 2018. Os pacientes foram classificados como de alto risco nutricional (NUTRIC-1) quando apresentaram pontuação ≥5-9 pontos e para avaliação do NUTRIC-2 quando pontuação ≥6-10 pontos (1 ponto foi acrescentado quando PCR ≥10 mg/l). A concordância entre os instrumentos foi avaliada pelo teste *Kappa*. A capacidade preditiva de mortalidade foi avaliada pela curva *Receiver Operating Characteristic* (ROC).

Resultados: Os pacientes apresentaram idade média de 60,8 ± 16,3 anos e 53,5% eram mulheres. A maioria dos pacientes apresentaram níveis de PCR ≥10mg/dl (n = 263; 83,5%) e admissão na UTI do tipo clinica (n = 219; 69,5%). A prevalência da mortalidade hospitalar foi observada em 41% dos pacientes avaliados. O alto risco nutricional, avaliado pelo NUTRIC 1 e 2 foi demonstrado em 57,5% e 55,6% dos pacientes críticos. Os instrumentos demostraram concordância forte e significativa (*Kappa* = 0,935; p = 0,020) e desempenho satisfatório para predizer mortalidade [AUC 0,695 (0,636-0,774) e 0,699 (0,640-0,758), NUTRIC-1 e NUTRIC-2, respectivamente].

Conclusão: Ambas as versões do instrumento NUTRIC apresentaram boa concordância e desempenho satisfatório como preditores de mortalidade hospitalar em pacientes críticos. Uma análise mais aprofundada desta variante e associação entre adequação nutricional e mortalidade é necessária.

Descritores: Risco nutricional, NUTRIC, Pacientes críticos, Unidade de terapia intensiva.

ABREVIAÇÕES

Revisão da Literatura

UTI Unidade de Terapia Intensiva

ASPEN Sociedade Americana de Nutrição Enteral e Parenteral

ESPEN Sociedade Europeia de Nutrição Parenteral e Enteral

IMC Índice de massa corporal

NUTRIC Nutrition Risk in the Critically Ill

SOFA Sequential Organ Failure Assessment

APACHE II Acute Physiology and Chronic Health Evaluation II

IL-6 Interleucina-6

PCR Proteína C- Reativa

ROC Receiver Operating Characteristic

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1. REVISÃO DA LITERATURA

1.1 Desnutrição

A desnutrição é definida como uma condição crônica resultante da falta de alimentos, calorias adequadas, proteínas e/ou outros nutrientes necessários para a manutenção e reparo de tecidos (POWERS; SAMAAN, 2014). Ainda é uma situação na qual se aumenta o risco de desenvolvimento de eventos clínicos negativos, como morbidade e mortalidade (OZBILGIN et al., 2016).

A prevalência de desnutrição em pacientes hospitalizados é de aproximadamente 30% (LIM et al., 2012), sendo que grande parte desses doentes desenvolve essa condição durante o período de internação (WAITZBERG; CAIAFFA; CORREIA, 2001). Mais recentemente, a literatura demonstrou que aproximadamente 50% dos pacientes podem em algum momento da hospitalização apresentar desnutrição (CORREIA; PERMAN; WAITZBERG, 2017; RABITO et al., 2017). E no cenário das UTIs esta prevalência pode alcançar até 54% (CORREIA, 2018).

Esta elevada prevalência se deve ao fato de que mesmo os pacientes que apresentam estado bem nutrido quando admitidos nas UTIs demonstram rápido declínio em seu estado nutricional (KRONDUP, 2014)

A desnutrição nestes indivíduos está associada à anorexia, à presença de infecções hospitalares e ao tratamento intensivo, visto que alguns suportes terapêuticos, como a ventilação mecânica e a hemodiálise, estão relacionados à lesão muscular e à depleção proteica (BARR et al., 2004; YOUSEFZADEH et al., 2007).

Além disso, esses pacientes desenvolvem desnutrição em decorrência da resposta inflamatória sistêmica associada à doença crítica e do estado de catabolismo severo causado pelo aumento das citocinas e hormônios relacionados ao estresse (JENSEN et al., 2009; MCCLAVE et al., 2016). Resultados de um estudo clássico realizado em pacientes críticos demonstrou que esses pacientes apresentam perda de aproximadamente 1-2 kg de proteína corporal (aproximadamente 10-15% do teor inicial de proteína total) durante 10 dias de

internação, apesar do bom estado nutricional prévio e do suporte energético e proteico adequado (ISHIBASHI et al., 1998). Essas condições hipermetabólicas diferenciam os pacientes críticos dos demais pacientes hospitalizados e evidencia a relevância em identificar de forma correta a presença da desnutrição.

Sendo assim a identificação do risco nutricional de forma mais precoce possível se torna de grande importância para uma melhora nutricional e evolução clínica podendo assim reduzir o risco de desfechos clínicos desfavoráveis nesse grupo de pacientes.

1.2 Instrumentos de risco nutricional

O termo risco nutricional é definido como o aumento da morbidade e mortalidade da doença base do paciente devido à presença concomitante de determinado grau de desnutrição (MORETTI et al., 2014). Ou seja, significa o risco do paciente adquirir complicações e/ou resultados adversos que poderiam ter sido prevenidos através de um adequado suporte nutricional (KONDRUP, 2014).

A triagem nutricional é o processo utilizado para a identificação dos pacientes que estão em risco nutricional e, portanto, necessitam de uma avaliação nutricional mais detalhada e uma conduta dietoterápica mais agressiva e específica (JASEN et al 2013) com o objetivo de diminuir resultados clínicos desfavoráveis como ocorrência de infecções, hospitalização prolongada e mortalidade (MCCLAVE et al., 2009).

Os instrumentos de triagem nutricional *Nutrition Risk Screening-2002* (NRS-2002) e *Nutritional Risk in the Critically Ill* (NUTRIC) são ferramentas utilizadas na prática clínica que possuem capacidade satisfatória para determinar risco nutricional em conjunto com a severidade da doença em pacientes hospitalizados. O escore NRS-2002 foi desenvolvido no ano de 2002 baseado em 128 estudos de ensaios clínicos randomizados, realizados com pacientes hospitalizados (KONDRUP et al., 2003) O rastreamento inicial do risco nutricional desse instrumento é baseado nas seguintes variáveis: índice de massa corporal (IMC) <20,5 Kg/m², perda de peso nos últimos três meses, redução na ingestão alimentar na última semana e presença de severidade da doença. Já o rastreamento final é avaliado pela pontuação do estado

nutricional e ao aumento das necessidades devido a severidade da doença (KONDRUP et al., 2003). A pontuação varia de 0 – 7 pontos, sendo necessário somar 1 ponto quando idade ≥ 70 anos (KONDRUP et al., 2003). Ainda, pacientes graves são prontamente categorizados em risco nutricional quando *Acute Physiology and Chronic Health disease Classification System II* (APACHE II) >10 pontos (KONDRUP et al., 2003). Desta forma, quando a avaliação pontuar ≥ 3 pontos, se classifica como presença de risco nutricional (KONDRUP et al., 2003). Já o NUTRIC foi o primeiro instrumento desenvolvido para avaliar o risco nutricional em pacientes internados em UTI (HEYLAND et al., 2011). Ele engloba variáveis como escores de gravidade de doença: APACHE II e *Sequential Organ Failure Assessment* (SOFA), idade, número de comorbidades, dias da admissão hospitalar prévios à admissão na UTI e níveis séricos de interleucina 6 (IL-6). NUTRIC é considerado uma fácil ferramenta a ser utilizada, pois contém variáveis rotineiramente utilizadas na maioria das UTIs, exceção para a IL-6, que não é frequentemente solicitada devido ao seu alto custo (HEYLAND et al., 2011). Assim, outra versão do NUTRIC foi criada posteriormente, retirando do escore final as medidas da IL-6 (HEYLAND et al., 2011). Sendo esta nova proposta denominada de NUTRIC modificado (NUTRIC-m) (HEYLAND et al., 2011). Para avaliação são considerados pacientes com maior risco nutricional os que apresentarem escore ≥ 6 (para a versão original) ou ≥5 (para a versão modificada).

Atualmente o consenso entre a *European Society of Parenteral and Enteral Nutrition* (ESPEN) e a *American Society of Parenteral and Enteral Nutrition* (ASPEN) é de que a aplicação da triagem nutricional deve ser realizada na admissão dentro das primeiras 24 a 72 horas para todos os pacientes hospitalizados (MEIER; STRATTON, 2008; MUELLER, 2011). Porém embora existam recomendações para que o rastreamento nutricional seja rotina na admissão hospitalar, infelizmente, este não é um processo obrigatório na maioria das Instituições de Saúde (CORREIA, 2018).

1.3 Risco nutricional: desfechos clínicos e terapia nutricional adequada

O risco nutricional está associado com desfechos clínicos desfavoráveis como maior taxa de mortalidade e tempo de internação hospitalar em estudos

desenvolvidos em pacientes críticos (VRIES et al., 2018; MARCHETTI et al., 2019) e de emergência (RABITO et al., 2017). Em pacientes críticos foi demonstrado que o alto risco nutricional foi associado à maior taxa de mortalidade em um período de 28 dias quando comparados aos pacientes com menor risco nutricional (VRIES et al., 2018). Mais recentemente, estudo transversal em 200 pacientes gravemente doentes, demonstrou que o alto risco nutricional foi positivamente associado a um risco aumentado de desfechos clínicos, incluindo morte hospitalar (MARCHETTI et al., 2019).

Em pacientes admitidos em uma Emergência onde foram comparados diferentes instrumentos de triagem nutricional também foi obervado associações positivas e significativas entre o alto risco nutricional com mortalidade e o maior tempo de internação hospitalar (RABITO et al., 2017).

Além disso, uma triagem nutricional completa pode beneficar o paciente reduzindo o risco de desenvolvimento de complicações e/ou resultados adversos, pois este poderá ser beneficiado através de suporte nutricional adequado (KONDRUP, 2014). Em uma metanálise de 8 ensaios clínicos randomizados, Heyland et al. (2003) demonstrou uma tendência para redução das taxas de mortalidade quando o suporte nutricional foi iniciado dentro das primeiras 48 horas de internação na UTI. Já na metanálise realizada por Doig et al. (2009) uma redução significativa das taxas de mortalidade foi relatada quando a terapia enteral foi iniciada nas primeiras 24h de admissão na UTI. Além disso, a oferta precoce de terapia nutricional reduziu os custos gerais hospitalares (DOIG; CHEVROU-SEVERAC; SIMPSON, 2013).

Já em um estudo de coorte prospectivo realizado na China, 1085 pacientes com cirurgia abdominal foram triados quanto ao risco nutricional. Dentre eles, 120 foram classificados como pacientes de alto risco. Observou-se que os indivíduos de alto risco que receberam suporte nutricional especializado antes da operação apresentaram menor período de permanência hospitalar e menor ocorrência de complicações pós-operatórias em relação ao grupo de alto risco sem suporte nutricional agressivo. Essa associação não foi encontrada nos 965 pacientes classificados com baixo risco nutricional (JIE et al., 2012).

Rahman et al. (2016), em um estudo observacional, encontrou associação significativa entre adequação nutricional e sobrevivência de 28 dias após admissão na UTI em pacientes com alto risco nutricional. Nos pacientes de baixo risco, porém, não foi observada essa relação.

Esses estudos sugerem que pacientes com alto risco nutricional são mais propensos a se beneficiar de terapia de nutrição especializada do que aqueles com baixo risco. Também demonstram que o suporte nutricional precoce (até 24-48h após a admissão na UTI) está associado a um melhor prognóstico clínico. Sendo assim, identificar o risco nutricional com acurácia e ofertar de forma precoce uma terapia de nutrição agressiva apresenta-se, portanto, como uma estratégia para redução da severidade das doenças e complicações, diminuição no tempo de permanência hospitalar e melhora do prognóstico dos pacientes com alto risco nutricional.

1.4 Avaliação do risco nutricional em pacientes críticos

Identificar o risco nutricional em pacientes criticamente doentes, no entanto, permanece como um desafio para os profissionais da saúde, visto que não é uma população homogênea e não cumprem com os parâmetros de desnutrição tradicionais (MCCLAVE et al., 2009). Os critérios comumente usados para identificar risco nutricional, como exames laboratoriais, exame físico, dados antropométricos, ingestão alimentar e avaliação funcional (KRUIZENGA et al., 2005; FERGUSON et al., 1999; DETSKY et al., 1987; BUZBY et al., 1980), podem não estar disponíveis ou refletir informações errôneas sobre a condição nutricional desses indivíduos.

Isso ocorre porque os pacientes de UTI estão frequentemente sob ventilação mecânica, sedados ou com estado mental alterado, dificultando a obtenção de informações sobre história de ingestão alimentar, estado funcional e sintomas gastrointestinais antes da admissão hospitalar. Já os parâmetros antropométricos, como peso corporal, IMC e circunferência da cintura e do braço, podem refletir mais alterações no balanço hídrico do que fornecer informações fidedignas sobre a composição corporal do paciente, uma vez que muitos desses enfermos recebem

grandes volumes de fluido com objetivo de manter estabilidade hemodinâmica (MCCLAVE et al., 2009). Com relação ao uso de proteínas séricas como marcadores tradicionais, estas são utilizadas como um reflexo da resposta da fase aguda da doença, não representando com precisão o estado nutricional do indivíduo criticamente doente (JENSEN; WHEELER, 2012, HIESMAYR, 2012).

Além disso, nesses pacientes a gravidade da doença aguda e estresse metabólico contribuem tanto para o risco nutricional quanto o estado nutricional de base (KONDRUP, 2014). As ferramentas tradicionais de avaliação nutricional perdem essencialmente essa interação podendo levar a uma classificação equivocada do risco nutricional e ocasionar falhas e atrasos na terapia dessa população (HEYLAND et al., 2011).

Sendo assim Heyland et al. propôs em seu estudo que nem todos os pacientes críticos possuem o mesmo estado nutricional visto que nem todos respondem da mesma maneira a intervenção nutricional agressiva (HEYLAND et al., 2011). Nesse sentido, como antes descrito esse autor elaborou um instrumento de risco nutricional especifico para pacientes críticos, o NUTRIC. Esta ferramenta objetiva quantificar o risco de um paciente desenvolver eventos adversos potencialmente modificáveis por intervenção nutricional precoce e agressiva. Porém, visto que o biomarcador inflamatório (IL-6) nem sempre se encontra disponível no meio hospitalar, estudos em pacientes críticos vem analisando o desempenho do NUTRIC em suas duas versões na avaliação de risco nutricional e na predição de desfechos clínicos (MORETTI et al., 2014; JEONG et al., 2018). Uma variação do NUTRIC-m foi avaliada em um estudo transversal com 368 pacientes críticos em uso de ventilação mecânica (VM) que incluiu o biomarcador Proteína-C Reativa (PCR) na pontuação em substituição à IL-6 (MORETTI et al., 2014). Quando os valores séricos de PCR eram ≥10 mg/dl adicionou-se 1 ponto à pontuação do NUTRIC-m. O NUTRIC-m foi associado positivamente à presença da mortalidade e demonstrou um desempenho não muito satisfatório [Área sob a curva (AUC) de 0,679; IC 0,624 - 0,733]. Mais recentemente, estudo transversal realizado em 482 pacientes críticos admitidos em um hospital terciário avaliou o desempenho de ambos escores, NUTRIC (com IL-6) e NUTRIC-m (sem IL-6) (JEONG et al., 2018). Neste estudo

ambos os instrumentos demonstraram associação do alto risco nutricional com maior tempo de internação na UTI e uso de VM.

1.5 Marcadores inflamatórios

Diante dos conhecimentos atuais sobre a contribuição da resposta inflamatória ao estado nutricional do paciente se torna fundamental o reconhecimento do grau de inflamação em que o paciente se encontra, uma vez que o estado inflamatório vem se associando a um estado imunológico enfraquecido e com maiores chances de infecção e maior permanência hospitalar, sendo assim, alguns marcadores inflamatórios estão sendo estudados e incorporados ao escore NUTRIC (POWERS; SAMAAN, 2014).

A IL-6, biomarcador utilizado na versão original do instrumento NUTRIC, é uma citocina inflamatória sintetizada em resposta a infecções ou lesões teciduais que desloca-se através da corrente sanguínea até o fígado, onde ativa uma resposta imunológica aguda pela indução da síntese de diversas proteínas de fase aguda, entre elas a PCR (TANAKA; NARAZAKI; KISHIMOTO, 2014). Assim a expressão da IL-6 contribui para a defesa do organismo contra infecções e lesões teciduais. Logo que a homeostase tecidual é restaurada, a síntese de IL-6 cessa (TANAKA; NARAZAKI; KISHIMOTO, 2014).

O biomarcador estudado como substituto da IL-6 no escore NUTRIC é a PCR que é uma proteína de fase aguda, que são aquelas as quais aumentam ou diminuem suas concentrações séricas durante o estado inflamatório (AGUIAR et al., 2003). A PCR é produzida principalmente pelos hepatócitos em resposta a estimulação pela Interleucina-6 (IL-6) (LELUBRE et al., 2013). Além disso, a PCR apresenta um custo menor e é considerada um bom marcador clínico por ter uma boa estabilidade, sensibilidade, reprodutibilidade e precisão, além de estar em níveis elevados no sangue apenas quando há estímulo para sua produção, como no caso, um processo inflamatório (RIDKER, 2005). Em adultos saudáveis, a concentração plasmática normal de PCR é em torno de 0,8 mg/l, porém durante a infecção ou inflamação aguda esses valores podem aumentar em até 10.000 vezes (VICENT; DONADELLO; SCHMIT, 2011).

2. JUSTIFICATIVA

A desnutrição é uma manifestação clínica comum em pacientes hospitalizados e está associada com a maior morbidade e mortalidade hospitalar. Condições como elevado risco nutricional e perda progressiva de peso são prevalentes em pacientes críticos de Unidades de Terapia Intensiva (UTIs). Os instrumentos de avaliação de risco nutricional possibilitam identificar previamente o risco da desnutrição, minimizar a perda de peso e beneficiar os pacientes com uma intervenção nutricional precoce e especializada. O principal instrumento em pacientes críticos que considera a condição nutricional concomitantemente ao impacto da doença ou trauma sob o estado nutricional é o sistema de pontuação do *Nutrition Risk in the Critically Ill* (NUTRIC). O instrumento NUTRIC possui ainda um importante diferencial no contexto de UTIs, dado que todos os seus componentes podem ser obtidos através da revisão do prontuário, sem necessidade de uma entrevista com o paciente ou familiar. Além disso, é um sistema de triagem rápido, de baixo custo e de fácil aplicabilidade. O NUTRIC sugere a utilização da interleucina-6 (IL-6) como marcador de inflamação aguda, parâmetro nem sempre disponível nas UTIs. Já a proteína C-reativa (PCR) também é marcador inflamatório sensível, estável e de mais fácil dosagem e que se incorporada juntamente ao instrumento NUTRIC pode avaliar a capacidade preditiva de desfechos clínicos desfavoráveis, em particular, a mortalidade nesse grupo de pacientes. Até o presente, não há estudos que avaliaram o desempenho do NUTRIC e NUTRIC-m em pacientes críticos não ventilados na predição de mortalidade hospitalar. Nesse sentido, os objetivos desse trabalho são: (1) avaliar a concordância entre a versão modificada do escore NUTRIC (sem IL-6) (NUTRIC-1) e uma variante composta de PCR (NUTRIC-2) e (2) a capacidade desses dois instrumentos em predizer mortalidade hospitalar em pacientes críticos admitidos em uma UTI.

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3. ARTIGO ORIGINAL

This original article has been submitted and is under review in the Brazilian Journal of Nutrition (B2).

Two Variants of the Nutritional Risk in the Critically Ill (NUTRIC) score as Predictors of Mortality in Intensive Care Unit Patients at a Brazilian University Hospital.

Duas variantes do instrumento de triagem nutricional Nutritional Risk in the Critically Ill (NUTRIC) como preditoras de mortalidade em pacientes admitidos em uma Unidade de Terapia Intensiva de um Hospital Universitário Brasileiro.

Short title in English: nutritional risk and mortality
Short title in Portuguese: risco nutricional e mortalidade

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Author's contribution

This paper was written by Amanda F. dos Santos, Oellen S. Franzosi and T. Steemburgo. Data were collected, organized and tabulated by A.M. dos Reis and J. Marchetti. The statistical analysis was written by A.M. dos Reis and Amanda F. dos Santos. Data were analyzed by Amanda F. dos Santos, A.M. dos Reis and, reviewed by Oellen S. Franzosi and T. Steemburgo.

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ABSTRACT

Objective: To evaluate the agreement between the modified version of the Nutritional Risk in the Critically Ill score (without Interleukin-6) and a variant composed of C-reactive protein and its capacity to predict mortality.

Methods: A prospective cohort study was carried out in 315 patients in an Intensive Care Unit of a university hospital from October 2017 to April 2018. The agreement between the instruments was evaluated with the Kappa test. The predictive capacity for estimating mortality was assessed with the receiver operating characteristic curve.

Results: The critical patients had a mean age of 60.8 ± 16.3 years and 53.5% were female. Most patients had C-reactive protein levels ≥10mg/dl (n = 263, 83.5%) and the type Intensive Care Unit admission was medical (n = 219, 69.5%). The prevalence of mortality was observed in 41% of the evaluated patients. The proportions at high nutritional risk according to Nutritional Risk in the Critically Ill without Interleukin-6 and with C-reactive protein were 57.5% and 55.6%, respectively. The tools showed strong and significant agreement (Kappa = 0.935; p = 0.020) and satisfactory performance to predict hospital mortality [area under the curve 0.695 (0.636-0.754) and 0.699 (0.640-0.758)].

Conclusion: Both versions of the Nutritional Risk in the Critically Ill tool show a satisfactory agreement and performance as predictors of hospital mortality in critically ill patients. Further analysis of this variant and association between nutrition adequacy and mortality is needed.

Keywords: Nutritional risk, Nutritional Risk in the Critically Ill, Critical patients Intensive care unit.

RESUMO

OBJETIVO: Avaliar a concordância entre a versão modificada do escore do *Nutritional Risk in the Critically Ill* (sem Interleucina-6) e uma variante composta de proteína C-reativa e sua capacidade de predizer mortalidade em pacientes críticos.

Métodos: Estudo de coorte prospectivo em 315 pacientes admitidos em uma Unidade de Tratamento Intensivo de um hospital universitário Brasileiro no período de outubro de 2017 a abril de 2018. A concordância entre os instrumentos foi avaliada pelo teste *Kappa*. A capacidade preditiva de mortalidade foi avaliada pela curva *Receiver Operating Characteristic* (ROC).

Resultados: Os pacientes apresentaram idade média de 60,8 ± 16,3 anos e 53,5% eram mulheres. A maioria dos pacientes apresentaram níveis de proteína C-reativa ≥10mg/dl (n = 263; 83,5%) e o tipo de admissão na UTI foi clínica (n = 219; 69,5%). A prevalência da mortalidade foi observada em 41% dos pacientes avaliados. O alto risco nutricional, avaliado pelo *Nutritional Risk in the Critically Ill* sem Interleucina-6 e com proteína C-reativa foi demonstrado em 57,5% e 55,6% dos pacientes críticos. Os instrumentos demostraram concordância forte e significativa (*Kappa* = 0,935; p = 0,020) e desempenho satisfatório para predizer mortalidade [área sob a curva 0,695 (0,636-0,774) e 0,699 (0,640-0,758)].

Conclusão: Ambas as versões do instrumento *Nutritional Risk in the Critically Ill* apresentam boa concordância e desempenho satisfatório como preditores de mortalidade em pacientes críticos. Uma análise mais aprofundada desta variante e associação entre adequação nutricional e mortalidade é necessária.

Descritores: Risco nutricional, *Nutritional Risk in the Critically Ill*, Pacientes críticos, Unidade de Terapia Intensiva.

INTRODUCTION

Malnutrition is a common situation in hospitalized patients and is highly frequent in critically ill patients [1] and is associated with a higher risk of mortality, longer hospital stays and consequently higher financial costs to health services [2]. In critically ill patients, acute disease severity and metabolic stress affect nutritional risk, which is also related to unfavorable outcomes in the patient's prognosis, such as poor healing, increased risk of nosocomial infections, and all-cause mortality [3]. The nutritional status is an important modifiable risk factor for clinical outcomes in critically ill patients [4] and their early identification is of great importance for the reduction of morbidity and mortality in this group of patients [3].

There are many tools created to identify nutritional risk which use a variety of criteria [5,6]. However, these tools were developed for outpatients and / or hospitalized patients and are not specific for patients in the Intensive Care Unit (ICU), since they don’t use ICU markers of disease severity and prognosis and may classify all critically ill patients with high nutritional risk [6,8].

Heyland et al. proposed a specific nutritional risk instrument for critically ill patients the NUTRIC score (Nutrition Risk in Critical Ill) based on conceptual model of malnutrition development [7]. This tool quantifies the risk of a patient developing adverse events that are potentially modifiable by early and aggressive nutrition intervention [7]. In addition, it is a method strongly recommended by the American Society of Parenteral and Enteral Nutrition (ASPEN) [9]. In fact, this tool demonstrated that approximately 50% of patients admitted to the ICU have high nutritional risk [1]. Similar found was describing by a Brazilian study in which the prevalence of high nutritional risk was observed in 46% of critically ill patients [10]. More recently, a retrospective study demonstrated that NUTRIC is superior to Nutritional Risk Screening 2002 (NRS - 2002) protocol for assessing malnutrition risk in ICU patients [4]. Moreover, researchers have demonstrated that the high nutritional risk, identified by NUTRIC, is associated with clinical outcomes and death [1,11]

Inflammatory markers such as Interleukin-6 (IL-6) and C-reactive protein (CRP) are being studied and incorporated into the NUTRIC score [7,8] since inflammation is associated with a weakened immune state with increased chances of infection and longer hospital stay [12]. The studies are still scarce. Heyland et al.

described the importance of the role of inflammation in the presence of malnutrition, expressed by IL-6 [7]. However, this biomarker does not present as a common variable in the medical records and another cutoff was proposed in the absence of IL-6 [7]. On the other hand, a study conducted in critically ill patients using mechanical ventilation has shown that the addition of CRP improves NUTRIC score performance and may be an alternative to IL-6 when it is not available [8].

Considering that nutritional risk in critically ill patients refers to the risk of developing complications associated with poor nutritional status [13] and the presence of malnutrition is high and frequently associated with increased mortality, the aim of this study was to evaluate the agreement between the modified version of the NUTRIC score (without IL-6) (NUTRIC -1) already validated and a variant of CRP (NUTRIC-2) and its ability to predict hospital mortality in critically ill patients.

MATERIALS AND METHODS

Patients

A prospective cohort study was performed with critically ill patients admitted to the ICU of a university hospital in Brazil. The cohort included adult patients (age ≥18 years, of both genders, admitted in the period of October (2017) to April (2018). Patients with advanced terminal illness, neurodegenerative diseases, therapeutic limitations, and pregnant women were excluded from the research.

Patients were identified through daily screening in a maximum period of 72 hours after admittance to the ICU. They were accompanied until the hospital discharge or death. All data used in this research was taken from physical and electronic records, from patient, assistant staff, family and/or companions. No modifications in the patients' treatment were performed during the hospitalization period.

The study was conducted according to the guidelines of the Declaration of Helsinki and all procedures involving patients were approved by the Hospital Ethics Committee (protocol #170524). All patients or their legally responsible person signed an informed consent form.

General evaluation

Clinical e demographic characteristics as diagnosis, age, gender, ethnicity, body mass index (BMI), and C-reactive protein (CRP) values were collected from electronic records. Other outcome measures included length of stay (LOS) in the hospital (days), ICU LOS (days), ICU free-days, readmission at the ICU, infection during hospitalization (according to the medical records), and death. The following infectious complications were considered: urinary, respiratory, and gastrointestinal tract, surgical wounds, central nervous system, and cutaneous infections. All outcomes were obtained from medical records of each participant.

C-reactive protein

The inflammatory biomarker CRP was obtained through the electronic record within 72 hours after hospitalization of the patient in the ICU.

Nutritional Screening

The nutritional screening was performed by a trained nutritionist using Nutrition Risk in the Critically Ill (NUTRIC) in the period of up to 72 hours after admission to the ICU [7].The NUTRIC-1 was calculated based on patient's age, number of comorbidities, number of days at the hospital before ICU admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores [14]. The APACHE II score was obtained through axillary temperature, mean blood pressure, heart rate, respiratory rate, arterial oxygen partial pressure, and serum levels of leukocytes, creatinine, potassium, sodium, and hematocrit, besides age and diagnosis. The SOFA score was obtained with platelet count, serum total bilirubin, serum creatinine, mean blood pressure, vasopressor use, arterial oxygen partial pressure /inspired oxygen fraction ratio (PaO2/FiO2) [14]. For the NUTRIC-2, the same variables were used, adding one point when CRP levels ≥10 mg/dl [8].

Statistical Analyses

Data are presented as mean and standard deviation, median (P25 – P75), or number (%), and compared using t-Student, Mann - Whitney U and, χ^2 tests, respectively. Patients were classified as high risk in the modified version (NUTRIC-1) when score ≥5-9 points and in the proposed variant (NUTRIC-2) ≥6-10 points (1 point added when CRP ≥10 mg/l).

The agreement between the screening tools was calculated through the Kappa coefficient. Kappa varies from 0 - 1: a value <0.2 indicates poor agreement; 0.2 - 0.4 fair agreement; 0.4 - 0.6 moderate agreement; 0.6 - 0.8 substantial agreement; and > 0.8 almost perfect agreement [15]. The Receiver Operating Characteristic (ROC) curve was constructed by calculating the sensitivity and specificity; it was used to evaluate the performance of scores NUTRIC- 1 and 2 to predict mortality.

The calculations were performed with the *Statistical Package for The Social Sciences* (SPSS) 23.0 (Chicago, IL) software, and P- values <0.05 were considered statistically significant.

Ethical aspects

The "*Screening instruments nutrition as outcomes of critical patients in clinical predictor*" was a prospective cohort study, carried out at Hospital de Clínicas de Porto Alegre, approved by its Research Ethics Committee registration number 170524, and it is in accordance with Resolution 466/12 of the National Health Council and the Declaration of Helsinki. All procedures with the participants were performed only after their signing the ICF.

RESULTS

A total of 315 patients were included (60.8 ± 16.3 years old, 53.3% female). A total of 181 (57.5%) and 175 (55.6%) critically ill patients were considered at high risk according to the NUTRIC-1 and NUTRIC-2 scores, respectively. The white ethnicity was reported for 84.0% of the patients and mean BMI was 26.4 ± 6.5 Kg/m². With regard to disease severity, mean APACHE II score was 19.8 ± 7.6 and median SOFA score was 6.0 points (3.0 - 9.0). The median of the CRP was 81.8 mg/dl (22.9 - 175.5) and the majority of patients (83.5%) had CRP ≥10 mg/dl. In addition, more patients were admitted to the ICU with clinical diagnoses (69.5%). The median hospital LOS was 18.0 days (11.0 - 32.0). At the ICU, the median LOS was 6.0 days (3.0 - 11.0), ICU free-days 12.0 days (4.0 – 21.0) and 11.4% were readmitted to the ICU. Around 56.2% of the patients presented infections during the hospitalization period. The following infections were considered: respiratory tract (26%), urinary tract (14.3%), blood (18.5%), cutaneous (7%), surgical wound (2.5%), gastrointestinal

(14.3%), and central nervous system (0.6%). Among the admitted ICU patients, 41% died.

The table **S1** describes the main clinical characteristics of critically ill patient's survivors (n = 186) and non-survivors (n = 129). Patient's non-survivors presented higher APACHE II and CRP levels when compared to surviving patients. Significant differences were also observed regarding hospital LOS among patients. About nutritional risk assessment, we observed that survivors had a lower score according to the NUTRIC evaluation compared to non-survivors. In fact, the higher prevalence of high nutritional risk assessed by NUTRIC 1 and 2 was demonstrated in non-surviving patients (approximately 55%).

Association between high nutritional risk according to NUTRIC (1 and 2) and outcome measures are described in the table **S2**. Patients with high nutritional risk, evaluated by NUTRIC-1, had longer ICU stay and higher prevalence of death when compared to patients who presented nutritional risk <5 points. Patients at high nutritional risk evaluated by NUTRIC- 2 presented similar association with prolonged ICU and death. No significant association was found between high nutritional risk assessed by NUTRIC-1 and 2 and the hospital LOS, ICU free-days, readmission to ICU and presence of infection.

When we constructed the ROC curve, sensitivity and specificity values demonstrated a satisfactory performance to predict mortality using NUTRIC-1 and NUTRIC-2 (**S3; Figure 1**). In addition, the NUTRIC-1 and NUTRIC-2 instruments showed a strong and significant agreement (Kappa = 0.935; p = 0.020).

DISCUSSION

Considering the possible complications associated with poor nutritional status it is very relevant to identify nutritional risk of critically ill patient as soon as possible. Thus, our study aimed to analyze two variants of the NUTRIC tool, one without inflammatory biomarker (NUTRIC-1) and the other using PCR as inflammatory biomarker PCR (NUTRIC-2). We also evaluated the ability of these instruments to predict mortality of these patients.

From 315 patients, 57.5% were classified at high nutritional risk by the NUTRIC-1 tool and 55.6% by the NUTRIC-2 tool where we used PCR as inflammation biomarker. Non-survivors presented higher scores for APACHE II and

SOFA, high CRP levels and length of hospital stay. Non-surviving patients when compared survivors had less weight loss, perhaps because those patients were more severe and therefore died earlier and may have received more fluids. Also, 53% and 55% of patients who died had a higher nutritional risk, according to NUTRIC 1 and 2, respectively. In addition, ICU LOS and death were significantly associated with patients at high nutritional risk.

Some of our results are in agree with those found by Moretti et al. [8] In this cross-sectional study conducted in critically ill patients, it was shown that the highest APACHE II score, length of stay and weight loss were significantly associated with a higher mortality risk [8]. Although, the previous study described by Heyland et al. [7] demonstrated that CRP was not associated with mortality, or did not improve the model of the tool, in the Moretti et al showed that the addition of CRP improves score performance and may be an alternative to IL-6 if not available [8].

These results corroborate with the data found in our study. We also observed a satisfactory NUTRIC performance with CRP to predict mortality in this in critically ill. In addition, the most of our patients (85%) had CRP levels ≥10 mg/dl. Since CRP is a sensitive inflammatory marker in the acute phase of the disease and more accessible in clinical practice, it may be an alternative in the evaluation of critical patients with NUTRIC.

The ability of nutritional screening tools to predict morbidity and mortality was also evaluated in patients at an emergency service [15]. In this study the four tools evaluated, Malnutrition Universal Screening Tool (MUST), Malnutrition Screening Tool (MST) and Simplified Nutrition Appetite Questionnaire (SNAQ) and Nutrition Risk Assessment - 2002 (NRS-2002) demonstrated satisfactory performance to identify patients at nutritional risk. In addition, patients at nutrition risk showed higher risk of very long length of hospital stay as compared with those not at nutrition risk, independent of the tool applied [15].

More recently, Vries et al. applied mNUTRIC (modified NUTRIC, excluding IL-6) and MUST scores in patients in a Dutch ICU, and showed relation between mNUTRIC and mortality and days of mechanical ventilation [3]. A prospective study by Canales et al. showed that the NRS-2002 tool classified all critical patients at high nutritional risk [4]. It is important to point out that the authors did not use the suggested cut-off points for critically ill patients (<3 no risk, ≥3 <5 risk and ≥5 high-

risk) [9] that were recently evaluated and showed ability to distinguish between critically ill patients in terms of clinical characteristics and outcomes [16]. In this way, we can see the importance to perform nutritional screening in this population with suitable scores for critically ill patients.

Our study has some limitations. First, data for both scores were collected by one trained individual, in a study comparing two diagnostic/prognostic models, blinded comparisons would prevent bias. These analyzes were performed only in patients who were admitted to the ICU, and it was not possible to apply them to patients in the ward. More robust results can be provided through a larger number of patients. On the other hand, the clinical outcomes (presence of infection and incidence of death) were evaluated during the entire hospitalization period not censored for 28 days. It is important to note that our analyzes included all patients hospitalized in the ICU, but not only patients with mechanical ventilation. In addition, , patients with different diseases and with a wide age group were included, which makes the results presented relevant. Another limitation of this study is that we do not analyze data on nutritional adequacy, and this is important because the NUTRIC identifies which patients benefit most from earlier and /or aggressive nutritional therapy. And this information is only possible when evaluating nutritional data. The use of the NUTRIC score is taking on large dimensions in the hospital care due to its specificity for the population hospitalized in the ICU, being the only tool created for the screening of these patients. Thus, it is important to produce studies that evaluate this score, as well as studies that test its different variations as alternatives.

CONCLUSION

In this study we conclude that the higher nutritional risk, evaluated by NUTRIC 1 and 2, were associated with an increased risk of worse clinical outcomes during hospitalization, including death and length of stay in the ICU. Furthermore, the both versions of the NUTRIC tools (1 and 2) demonstrated a good agreement and satisfactory performance as predictors of mortality in critically ill patients. Further analysis of this variant and association between nutrition adequacy and mortality is needed.

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S1. Clinical characteristics of critically ill patients' survivors and non-survivors (n = 315).

Clinical characteristics	**Survivors (n = 186)**	**Non - survivors (n = 129)**	***p*-value**
Age (years)[1]	58.1 ± 16.6	64.6 ± 15.0	0.278*
BMI (kg/m²)[1]	27.5 ± 7.0	24.8 ± 5.4	0.133*
APACHE II (score)[1]	18.0 ± 6.3	22.5 ± 7.4	0.001*
SOFA (score)[2]	5.0 (2.0 - 8.0)	7.0 (4.0 - 11.0)	<0.001**
CRP (mg/dl)[2]	68.7 (17.2 - 146.6)	103.4 (38.6 - 205.8)	0.005**
Hospital LOS (days)[2]	20.0 (14.7 - 33.2)	14.0 (8.0 - 30.0)	0.001**
ICU LOS (days)[2]	5.0 (3.0 - 9.0)	6.0 (3.0 - 12.0)	0.114**
ICU FREE-DAYS[2]	11.0 (4.0 – 20.2)	12.0 (4.0 -23.0)	0.486**
Readmission in ICU (yes)[3]	19 (10.2%)	17 (13.2%)	0.416***
Infection (yes)[3]	106 (57.0%)	71 (55.0%)	0.732***
NUTRIC-1[2,a]	4.0 (1.0 – 9.0)	6.0 (2.0 - 13.0)	<0.001**
Score ≥ 5-9 points[3,†]	85 (47.0%)	96 (53.0%)	<0.001***
NUTRIC -2 [2,b]	5.0 (2.0-10.0)	7.0 (2.0 -14.0)	<0.001**
Score ≥6-10 points [3,†]	79 (45.1%)	96 (55.0%)	<0.001***

BMI: Body Mass Index; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; CRP: C-reactive protein; LOS: length of stay; ICU: Intensive Care Unit; NUTRIC: Nutrition Risk in the Critically.

Data are presented as: [1]Mean and standard deviation. [2]Median (P25-P75). [3]Number and prevalence (%).

*t-Student Test; **Mann-Whitney U test; ***χ2test.

[a] Without IL-6; [b] Included CRP (mg/dl).

[†] Result considered as high nutritional risk.

Data were collected in ICU of Hospital de Clinicas de Porto Alegre (2017-2018).

S2. Association between presence of high nutritional risk according to NUTRIC (1 and 2) and outcome measures

Outcomes	NUTRIC- 1[a]			NUTRIC- 2[b]		
	Score <5-9 points	Score ≥5-9 points†	*p*-value	Score <6-10 points	Score ≥6-10 points†	*p*-value
Hospital LOS (days)	18.0 (10.7 - 31.0)[1]	19.0 (11.5 - 32.0)[1]	0.913*	5.0 (3.0 - 9.0)[1]	18.0 (11.0 - 32.0)[1]	0.835*
ICU LOS (days)	5.0 (3.0 - 9.0)[1]	7.0 (4.0 - 11.0)[1]	0.002*	2.7 (1.0 - 7.4)[1]	5.0 (3.0 - 9.0)[1]	0.004*
ICU free-days (days)	10.0 (4.0 – 20.5)[1]	12.0 (4.0 – 22.5)[1]	0.555*	10.5 (4.0 – 21.0)[1]	12.0 (4.0 – 22.0)[1]	0.688*
Readmission ICU (yes)	16 (44.4%)[2]	20 (55.6%)[2]	0.806**	17 (47.2%)[2]	19 (52.8%)[2]	0.722**
Infection (yes)	76 (42.9%)[2]	101 (57.1%)[2]	0.871**	79 (44.6%)[2]	99 (55.4%)[2]	0.939**
Death (yes)	134 (42.5%)[2]	181 (57.5%)[2]	<0.001**	140 (44.4%)[2]	175 (55.6%)[2]	<0.001**

LOS: length of stay; ICU: Intensive Care Unit; NUTRIC: Nutrition Risk in the Critically.

Data are presented as: [1]Median (P25-P75). [2]Number and prevalence (%).

*Mann-Whitney U test; **χ2test.

[a] Without IL-6; [b] Included CRP (mg/dl). † Result considered as high nutritional risk.

Data were collected in ICU of Hospital de Clinicas de Porto Alegre (2017-2018).

S3. Measures of performance of nutrition screening tools to predict mortality in patients in the Intensive Care Unit

Nutrition Screening Tool	Sensitivity, %	Specificity, %	Performance (ROC–AUC)
NUTRIC- 1[a]	74.4	45.7	0.695 (0.636 – 0.754)
NUTRIC- 2[b]	73.6	42.5	0.699 (0.640 – 0.758)

NUTRIC, Nutrition Risk in the Critically; ROC, Receiver Operating Characteristic; AUC, area under the curve.

[a] Without IL-6; [b] Included CRP.

Data were collected in ICU of Hospital de Clínicas de Porto Alegre (2017-2018).

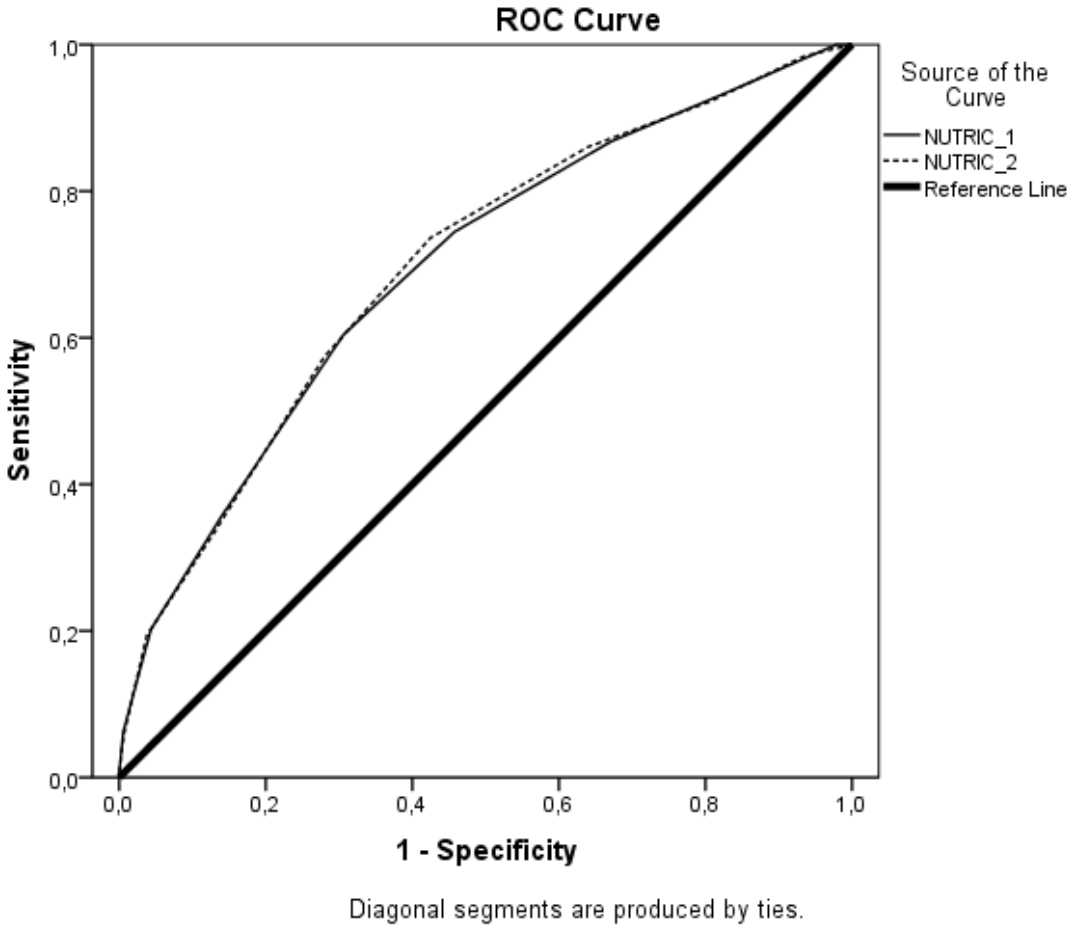

Figure 1. ROC curves to predict hospital mortality of critical patients in the Intensive Care Unit using nutrition screening tools.

NUTRIC, Nutrition Risk in the Critically; ROC, Receiver Operating Characteristic; AUC, area under the curve.

ANEXO A. Normas da revista de interesse de submissão

The *Revista de Nutrição* (Brazilian Journal of Nutrition) (e-ISSN 1678-9865) is a specialized periodical that publishes articles that contribute to the study of Nutrition in its many sub-areas and interfaces. It is published bimonthly and open to contributions of the national and international scientific communities.

There is no fee for submission and review articles.

Submission

All articles must be submitted electronically at <http://mc04.manuscriptcentral.com/rn-scielo>.

Any other form of submission will not be accepted by the editors.

At the time of submission must be attached: (1) The article (complete file in Word format, including cover sheet, abstract, text, references and illustrations); (2) The illustrations (in editable file, in the formats accepted by the magazine); (3) All documentation required by the magazine (duly signed by all authors).

Submitted manuscripts may be rejected without detailed comments after initial review by at least two Revista de Nutrição (Brazilian Journal of Nutrition) editors if the manuscripts are considered inappropriate or of insufficient scientific priority for publication in the Journal.

The Revista de Nutrição (Brazilian Journal of Nutrition) does not publish more than 1 (one) article from the same author in the same year (volume) to avoid endogeneity. This procedure aims to increase the number of themes and collaborations made by national and foreign authors.

Open access policy
The Journal provides open access to all its content, which is protected by the Creative Commons license (CC-BY).

Research involving living beings
Results of research involving human beings and animals, must contain a copy of the Research Ethics Committee approval.

Registration of Clinical Trials
Articles with results of clinical researches must present an identification number in one of the Register of Clinical Trials validated by criteria established the World Health Organization (WHO) and International Committee of Medical Journal Editors (ICMJE), whose

addresses are available at the ICMJE site. The identification number must be included at the end of the abstract.

Conflict of interest

Authors: The authors must declare explicitly and individually any potential, direct or indirect, financial or nonfinancial conflict of interest, etc., and any conflict of interest with *ad hoc* referees.

***Ad hoc* referees**: If any of the referees declare a conflict of interest, the Editorial Board will send the manuscript to another *ad hoc* referee.

Plagiarism
All submitted articles will be screened using the plagiarism detection tool CrossCheck before the peer review process.

Social Networks
In order to increase its dissemination, the Revista de Nutrição (Brazilian Journal of Nutrition) asks the authors to disseminate their articles published at the SciELO site at the social networks below, among others:
Academia.edu – https://www.academia.edu/
Mendeley – https://www.mendeley.com/
ResearchGate – http://www.researchgate.net/
Google Scholar - https://scholar.google.com.br/schhp?hl=pt-BR

Referees

The authors may indicate three referees for assessing the manuscript and their respective e-mails and institutional affiliations. Alternatively, the authors may indicate three referees that should not assess their manuscript.

Manuscript Assessment Process

Original manuscripts will be accepted for review as long as they have not been submitted to any other journal in parallel and/or published previously to preserve the original character of the article. They should be accompanied by: a submission cover letter, a completed submission checklist, and all other documents listed in the item "Documents". **All documents must be signed by all authors**.

All manuscripts will only start undergoing the publication process if they are in agreement with the Instructions to the Authors. If not, **they will be returned for the authors to make the appropriate adjustments**, include a letter or

other documents that may be necessary. See item preparation of the manuscript.

Articles with any of the mistakes mentioned above **will be returned even before they are submitted to assessment** regarding the merit of the work and the convenience of its publication.

Pre-analysis: assessment is made by the Scientific Editors based on the originality, pertinence, academic quality, and relevance of the manuscript for the area of nutrition.

Manuscripts approved in this stage will be sent to ad hoc referees. Each manuscript will be sent to three referees of known competence in the theme. The authors may choose one of them. If there is disagreement, the manuscript will be sent to a fourth referee.

The peer review process used is the blind review, where the identity of the authors and the reviewers is not mutually known. Thus the authors must do everything possible to avoid the identification of the authors of the manuscript.

The opinions of the reviewers are one of the following: (a) approved; (b) new analysis needed; (c) refused. The authors will always be informed of the reviewers' opinion.

The referees' opinions will be analyzed by the associated editors, who will then suggest to the Scientific Editor whether the manuscript should be published. The Editor-in-Chief will make the final decision regarding the publication of the manuscript (Approved or Rejected).

Rejected manuscripts that can be reformulated may be submitted again as a new manuscript and undergo a new assessment process.

When changes are requested by the referees, the manuscript will be returned to the authors along with the referees' opinions and suggestions. The authors have 20 (twenty) days to make the adjustments, respecting the Greenwich (London) time.

Accepted manuscripts: manuscripts accepted for publication may return to the authors for approval of eventual changes made during the editing and formatting processes, according to the Journal's style.

Publication in English: if approved, the articles will be

published in English. For the manuscript to be published, the authors must provide the English translation of the version approved by the Journal. The translation is paid for by the authors.

In order to guarantee the quality and uniformity of the translated manuscripts, the manuscript must be translated by a highly trained translator with proven experience in the translation of scientific texts, indicated and certified by the Journal.

If the manuscript needs reviewing by one of the translators indicated by the Journal, the authors must follow the formatting instructions provided by e-mail by the Journal. The authors are responsible for verifying the entire translation (body of the text, illustrations, tables, charts, etc.).

Preparing the Manuscript

The Journal only publishes original articles in English. However, the authors may submit the articles in Portuguese, and if the article is accepted for publication, the Journal will provide the name and contact information of translators certified by the Journal. The translation is paid for by the authors.

Article Category

Original: contributions that aim to disclose the results of unpublished researches, taking into account the relevance of the theme, the scope and the knowledge generated for the research area (maximum limit of 3,500 thousand words - including resumo, abstract, tables, graphs, figures and references).

Review (by invitation): synthesis of the knowledge available on a given theme, based on analysis and interpretation of the pertinent literature, aiming to make a critical and comparative analysis of the works in the area and discuss the methodological limitations and its scope. It also allows the indication of perspectives of continuing studies in that line of research (maximum limit of 4 thousand words – including resumo, abstract, tables, graphs, figures and references). There will be a maximum of two reviews per issue.

Research note: partial unpublished data of an ongoing research (maximum limit of 1,500 thousand words – including resumo, abstract, tables, graphs, figures and references).

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Articles category and subjet area: Authors should indicate the article's category and subject area, namely: food and social sciences, nutritional assessment, nutritional biochemistry, nutrition, nutrition education, epidemiology and statistics, micronutrients, clinical nutrition, experimental nutrition, nutrition and geriatrics, nutrition, maternal and infant nutrition in meal production, food and nutrition policies and health.

The Journal of Nutrition does not assess studies that have already been presented in national or foreign events and/or translated into other languages in order to preserve the originality of the study.

The text should not exceed the number of words established according to article category.

Text structure

The manuscript text should be prepared as follows:

- 1.5 spacing between the lines;
- Arial 12 pt;
- The total number of words in the manuscript should be within the word limit according to its category (the word count should include the words in the abstract and body of the manuscript but not the cover page, references, and illustrations);
- It should be arranged in the following order, including the items that must be presented on separate pages:
    - Cover page (page 1);
    - Resumo/Abstract (page 2);
    - Text (page 3);
    - References (in a separate page below the text);
    - Illustrations (include each one on a separate page below the references);
- Manuscript should be prepared using a word processor similar to Microsoft Word 2010;
- Use A4 paper; top and bottom margins of 2.5 cm; left and right margins of 3 cm;
- Page numbers must be placed on the lower left-hand corner;
- References format should facilitate manuscript revision and editing. Therefore, they should be written according to the Vancouver style, using 1.5 spacing between the lines and 12-point font size;
- The illustrations (Figures and Tables) must be inserted below the References, each one on a separate page, regardless of their size.

The cover page must contain:

a) Complete title in Portuguese: (i) the title must be concise and avoid unnecessary and/or redundant words, such as "assessment of," "considerations about," "an exploratory study about;" (ii) do not use abbreviations or indicate the geographic location of the study.

b) Suggest a short title in English and Portuguese or Spanish for the header with no more than 40 characters with spaces.

c) Include complete title in English compatible with the title in Portuguese.

d) Include the full name of each author. Do not abbreviate the first names. The list of authors, included below the title, should be limited to 6. The Journal strongly recommends that every author and co-authors keep their CV updated on the Lattes Platform for the submission of articles.

e) Include the authors' academic degree (master's, doctor's, etc.), their current institutional affiliation (only one affiliation per author in 3 levels of affiliation, without abbreviations or acronyms), and city, state, and country.

f) Indicate the full address of the institution of the corresponding author.

g) Inform the telephone number and e-mail address of all authors.

h) Explicitly inform the contribution made by each author. Authorship credit must be based on substantial contributions, such as study conception and design, data analysis and interpretation, article review, and approval of the final version. Including the names of authors who have not made any of the contributions above is not justified. Authors' contribution should be written in the language the article will be published.

i) Inform the ORCID® (Open Researcher and Contributor ID) record number. If you do not have one, register for free at: < https://orcid.org/register>. Learn more here.

j) Inform whether the article is based on a dissertation or thesis, indicating the title, author, university, and year of publication.

k) Indicate the following items:
Article category;
Subject Area;
Total number of illustrations (tables, pictures, and figures);
Total number of words (according to the manuscript category).

The authors may include a footnote to acknowledge the sponsor and indicate the number of the process and/or notice, and to acknowledge the collaboration of peers and technicians. The paragraph may not exceed three lines. Note: this must be the only part of the text identifying the authors, and other types of notes will not be accepted (except in translation of quotations).

Manuscript assessment will only begin after the inclusion of this information in the title page.

Abstract

All articles submitted in Portuguese or Spanish must contain an abstract in the original language and in English, with at least 150 words and at most 250 words.

The text should not contain citations and abbreviations. Provide from 3 to 6 keywords using Bireme's Health Sciences descriptors.<http://decs.bvs.br>.

The articles submitted in English must contain an abstract in Portuguese in addition to the abstract in English.

Text

Except for the manuscripts presented as Review, Communication, Scientific Note and Assay, the works must follow the formal structure for scientific works:

Introduction

Must contain a current literature review pertinent to the theme and appropriate to the presentation of the problem, also emphasizing its relevance. It should not be extensive except for manuscripts submitted as Review Articles.

Methods

Must contain a clear and brief description of the method, including the corresponding literature: procedures, universe and sample, measurement tools, and validation method and statistical treatment when applicable.

Regarding the statistical analysis, the authors should demonstrate that the procedures were not only appropriate to test the hypotheses

of the study but were also interpreted correctly. The statistical significance levels (e.g. $p<0.05$; $p<0.01$; $p<0.001$) must be mentioned.

Inform that the research was approved by an Ethics Committee certified by the National Council of Health and provide the number of the protocol.

When experiments with animals are reported, indicate if the guidelines of the institutional or national research councils - or if any national law regarding the care and use of laboratory animals - were followed.

Results

Whenever possible, the results must be presented in self-explanatory tables and figures and contain statistical analysis. Avoid repeating the data in the text.

Discussion

The discussion must properly and objectively explore the results under the light of other observations already published in the literature.

Conclusion

Present the relevant conclusions, considering the objectives of the work, and indicate ways to continue the study. **Literature citations will not be accepted in this section**.

Acknowledgments: may be made in a paragraph no bigger than three lines to institutions or individuals who actually collaborated with the work.

Attachments: should be included only when they are essential to the understanding of the text. The editors will decide upon the need of their publication.

Abbreviations and acronyms:should be used in a standardized fashion and restricted to those used conventionally or sanctioned by use, followed by the meaning in full when it is first mentioned in the text. They must not be used in the title and abstract.

References must follow the Vancouver style

References must be numbered consecutively according to the order that they were first mentioned in the text, according to the Vancouver

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In references that have up to 6 authors, display all of the author names. If the reference has more than 6 authors, cite the first 6 authors and then write "et al".

All authors should be cited in references with two to six authors; if more than six authors, only the first six should be cited followed by et al.

The abbreviations of cited journals should be in agreement with the Index Medicus.

At least 80% of the references must have been published within the last five years in indexed journals, and 20% within the last two years.

Citations/references of **undergraduate monographs, works** presented in congresses, symposiums, workshops, meetings, among others, and **unpublished texts** (classes among others) **will not be accepted**.

Citations of a journal article in press, whether it was written by one of the authors or by different sources, **must** be accompanied by a copy of the letter of acceptance (article accepted but not yet published) from the journal it is going to be published. If this requirement is not fulfilled, the citation/reference will be excluded.

If unpublished data obtained by other researchers are cited in the manuscript, it is necessary to include a letter authorizing the use of such data by the original authors.

When the cited document has a DOI (Digital Object Identifier) number, inform the number and exclude the access date (see examples of electronic material). The hyperlink https://doi.org/... must be used.

Reference citations in the text should be presented in numerical order, in Arabic numerals enclosed in square brackets (eg. [1], [2], [3]), after the author's surname, and they must be included in the list of references.

Direct citations translated by the authors must be accompanied by a footnote containing the text in the original language. Indicate that the citation was translated by the author as follows: (Rodgers et al., 2011, our translation).

The accuracy and appropriateness of references to works that have been consulted and mentioned in the text of the article are of the author(s) responsibility. All studies cited in the text must be

listed in the References.

Examples

Journal article in print
Canuto JMP, Canuto VMP, Lima MHA, Omena ALCS, Morais TML, Paiva AM, et al. Fatores de risco associados à hipovitaminose D em indivíduos adultos infectados pelo HIV/aids. Arch Endocrinol Metab. 2015;59(1):34-41.

Article with more than six authors in eletronic media
Fuermaier ABM, Tucha L, Janneke K, Weisbrod M, Lange KW, Aschenbrenner S, et al. Effects of methylphenidate on memory functions of adults with ADHD. Appl Neuropsychol Adult. 2017 [cited 2017 May 15]; 24(3):199-211. Available from: http://www.tandfonline.com/doi/full/10.1080/23279095.2015.1124108

Article that includes a DOI number
Lazarini FM, Barbosa DA. Intervenção educacional na Atenção Básica para prevenção da sífilis congênita. Rev Latino-Am Enfermagem. 2017 [citado 2017 maio 2];25:e2845. https://doi.org/10.1590/1518-8345.1612.2845

Book
Damiani D. Endocrinologia na prática pediátrica. 3ª ed. Barueri: Manole; 2016.

Electronic book
Lomer M. Advanced nutrition and dietetics in gastroenterology. Oxford: Wiley; 2014 [cited 2017 June 6]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/9781118872796.fmatter/pdf

Book chapter
Cominetti CR, Horst MM, Aderuza M. Parte 4: nutrientes, genômica nutricional e relação saúde-doença. In: Cominetti CR, Horst MM, Aderuza M. Genômica Nutricional: dos fundamentos à nutrição molecular. Barueri: Manole; 2015.

Electronic book chapter
Baranoski MCR. Cidadania dos homossexuais. In: Baranoski MCR. A adoção em relações homoafetivas. Ponta Grossa: UEPG; 2016 [citado 2017 maio 25]. Disponível em: http://books.scielo.org/id/ym6qv

Dissertations and Theses
Lee T. Comparing mindfulness-enriched weight management to current standard practices [these]. Lexington: University of Kentucky; 2017.

Electronic texts

Loss S. Nutrição enteral plena vs hipocalórica no paciente crítico. São Paulo: Sociedade Brasileira de Nutrição Parenteral e Enteral; 2017 [acesso 2017 maio 25]. Disponível em: www.sbnpe.com.br/news-braspen/atualizacao-em-tn/nutricao-enteral-plena-vs-hipocalorica-no-paciente-critico.

Software

Brubins Comércio de Alimentos e Supergelados. Dietwin: software de nutrição. Porto Alegre: Brubins Comércio de Alimentos e Supergelados Ltda; 2017.

For other examples please see the norms of the Committee of Medical Journals Editors (Vancouver Group) at <http://www.icmje.org>.

Preparing the illustrations

All types of tables, figures, graphs, drawings, schemes, flowcharts, photographs, maps, organograms, diagrams, blueprints, charts, pictures, etc., are considered illustrations, which serve to illustrate study data. **All empirical studies must include the study location and year**. Figures must not repeat the data in tables or already described in the text.

The maximum number of illustrations accepted per article is 5 (five), regardless of type.

The illustrations must be inserted below the references and should also be submitted as separate files in their original source file through the ScholarOne platform, in Step 6.

The illustrations **must be editable**. The following graphic design software and word processor are accepted: Excel, GraphPrism, SPSS 22, Corel Draw Suite X7, and Word. Therefore, images can be submitted only in the following file extensions: cdr, .pzf, .spv, .jpg, .jpeg, .xls, .xlsx, .doc, .docx, .vsdx, .vst. If a different software is used, use the standard font Frutiger size 7, which is the font used by the Journal during editing.

Images must have a minimum resolution of 600 dpi. Graphs and drawings must be generated in graphic design programs, such as Microsoft Excel, CorelDraw, Adobe Illustrator, etc., and accompanied by their quantitative

parameters in a table. Include the names of all variables.

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