

**UNIVERSIDADE FEDERAL DE UBERLÂNDIA
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE**

**INDICADORES BIOQUÍMICOS E TERAPIA NUTRICIONAL ENTERAL COMO
PREDITORES DE MORTALIDADE EM HOSPITAL UNIVERSITÁRIO DE MINAS
GERAIS**

NAYARA CRISTINA DA SILVA

**UBERLÂNDIA
2019**

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para obtenção do título de Mestre em Ciências da Saúde.

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Orientadora: Geórgia das Graças Pena

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NAYARA CRISTINA DA SILVA

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Presidente da banca (orientador): Profa. Dra. Geórgia das Graças Pena

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*À Deus, a minha família, amigos e a todos aqueles
que fazem parte da minha vida e que
compartilharam comigo cada passo desta
caminhada.*

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À Deus, que além de me conceder o dom da vida, é o responsável por tudo o que tenho e por tudo o que sou. “Sei que podes tudo e que nada te é impossível” (Jó 42,2) e, verdadeiramente, tenho visto Teus planos se cumprirem na minha vida.

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*“O que ninguém nunca viu nem ouviu, e o que jamais alguém pensou
que podia acontecer, foi isso o que Deus preparou para
aqueles que o amam”*

Bíblia Sagrada (1 Coríntios 2:9)

RESUMO

Introdução: O declínio do estado nutricional, o longo tempo de internação e as elevadas taxas de mortalidade hospitalar ainda são realidade em muitos hospitais. Estudos tem mostrado que a desnutrição, estado inflamatório, imunológico, multimorbidade e a terapia nutricional tem sido associados à mortalidade. **Objetivo:** Avaliar preditores de mortalidade hospitalar em pacientes não críticos internados em hospital universitário. **Material e Métodos:** Estudo retrospectivo foi realizado entre 2014 e 2016, incluindo pacientes com maiores de 18 anos admitidos nas unidades Cirúrgicas e de Clínica Médica. Dados demográficos, diagnóstico médico, internação hospitalar, avaliação nutricional e resultados dos primeiros exames bioquímicos solicitados, foram obtidos de bases de dados eletrônicas a partir da admissão hospitalar. Dois artigos foram desenvolvidos, o primeiro avaliando os pacientes submetidos a avaliação nutricional e solicitação de exames bioquímicos, cuja hipótese era que a elevada distribuição de amplitude de distribuição de glóbulos vermelhos (*Red blood cell distribution width* - RDW) na internação hospitalar poderia ser preditora de mortalidade hospitalar. Para o segundo artigo foi hipotetizado que nos pacientes submetidos à terapia nutricional enteral exclusiva com oferta calórica e proteica menores que a recomendação poderiam também estar associados à mortalidade hospitalar. Regressão de Cox foi usada para determinar as associações com mortalidade hospitalar. **Resultados:** Artigo 1: Dos 2923 pacientes, 46,1% eram maiores de 60 anos e 58,7% eram do sexo masculino, 55,7% eram desnutridos e 4,7% morreram. A acurácia do RDW na predição da mortalidade hospitalar foi caracterizada pela área sob a curva ROC ajustada por covariáveis de 0,577 (IC95%: 0,525, 0,629). O RDW foi associado a um risco de mortalidade hospitalar para todas as causas (HR 1,11 - IC 95%: 1,01-1,21), independentemente da idade, sexo, enfermidade, estado nutricional, estado imunológico e multimorbidade. Cada 1% no valor RDW aumentou 17% o risco de morte hospitalar por todas as causas nos pacientes cirúrgicos. Artigo 2: Dos 240 pacientes, 58,3% tinham mais de 60 anos e 60,0% eram do sexo masculino. As frequências de mortalidade hospitalar (19,2%) e desnutrição (78,8%) foram elevadas. As médias de proteína (0,75 g/kg/dia) e energia (17,60 kcal/kg/dia) ficaram abaixo das recomendações gerais e 37,8% não alcançaram a média de 20 kcal/kg/dia em todo o período de internação. A nutrição hipocalórica (HR: 5,78; IC 95%: 1,59-21,04) e a nutrição hipoprotéica (HR: 3,69; IC95%: 1,25–10,93) foram preditores de mortalidade hospitalar por todas as causas em modelos multivariados ajustados. No entanto, a nutrição hipoprotéica quando ajustada por calorias não proteicas/gramas de nitrogênio aumentou o risco de morte (HR: 3,15; IC95%: 1,04–9,53). **Conclusão:** O indicador bioquímico RDW e a baixa oferta de proteína estão associados com o risco de mortalidade hospitalar. Sendo assim, recomenda-se a utilização do RDW na prática para identificação dos pacientes cirúrgicos com maior risco de morte, sendo recomendado a inclusão na avaliação clínica, bem como a maior vigilância nutricional do paciente não crítico em terapia nutricional enteral exclusiva realizando o balanço diário e evolução da dieta minimamente acima de 20kcal/kg/dia de calorias e de 0,8kg/kg/dia considerando que os pacientes tem maior chance de morte quando estes parâmetros estão inadequados.

Palavras-chave: Mortalidade hospitalar; terapia nutricional; hospitalização; prognóstico

ABSTRACT

Introduction: The decline in nutritional status, long hospital stay and high hospital mortality rates are still a reality in many hospitals. Studies have shown that malnutrition, inflammatory, immune, multimorbidity and nutritional therapy have been associated with mortality.

Objective: To evaluate predictors of hospital mortality in patients admitted to a university hospital.

Material and Methods: A retrospective study was conducted between 2014 and 2016, including patients over the age of 18 admitted to the Clinical and Surgical Clinic wards. Two articles were developed, the first one evaluating patients submitted to nutritional evaluation and requesting biochemical tests, whose hypothesis was the high distribution of red blood cell distribution (RDW) distribution in hospital admission could be a predictor of hospital mortality. For the second article, it was hypothesized that in patients undergoing exclusive enteral nutritional therapy with caloric and protein supply lower than the recommendation could also predict in-hospital mortality. Cox regression was used to determine the predictors of in-hospital mortality.

Results: Article 1: Of the 2923 patients, 46.1% were older than 60 years and 58.7% were male, 55.7% were malnourished and 4.7% died. The accuracy of the RDW in predicting hospital mortality was characterized by the area under the ROC curve adjusted by covariates of 0.577 (95% CI: 0.525, 0.629). RDW was associated with an hospital mortality risk for all causes (HR 1.11 - 95% CI: 1.01-1.21), regardless of age, type of ward, nutritional status, immunological status, and multimorbidity. Each 1% in the RDW value increased the risk of all-cause hospital death by 17% in surgical patients.

Article 2: Of the 240 patients, 58.3% were older than 60 years and 60.0% were males. The frequencies of hospital mortality (19.2%) and malnutrition (78.8%) were high. The mean values of protein (0.75g/kg/day) and energy (17.60kcal/kg/day) were below the general recommendations and 37.8% did not reach the mean of 20 kcal/kg/day period of hospitalization. Hypocaloric nutrition (HR: 5.78; 95% CI: 1.59-21.04) and hypoprotein nutrition (HR: 3.69; 95% CI: 1.25-10.93) were predictors of in-hospital mortality by all causes in adjusted multivariate models. However, hypoprotein nutrition when adjusted for non-protein calories/g of nitrogen increased the risk of death (HR: 3.15; 95% CI: 1.04-9.53).

Conclusion: The biochemical indicator RDW and the low supply of protein are associated with the risk of hospital mortality. Therefore, it is recommended to use the RDW in practice for the identification of surgical patients with a higher risk of death, and it is recommended to include them in the clinical evaluation, as well as the greater nutritional surveillance of the non-critical patient in exclusive enteral nutritional therapy, and dietary evolution at a minimum of 20 kcal/kg/day of calories and 0.8kg/ kg/day considering that patients have a greater chance of death when these parameters are inadequate.

Keywords: In-hospital mortality; Nutrition therapy; Hospitalization; Prognosis.

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LISTA DE ABREVIATURAS E SÍMBOLOS

ANOVA	Analysis of variance
ASPEN	<i>American Society for Parenteral and Enteral Nutrition</i>
AUROC	Area under the covariate-adjusted ROC curve
CI	Confidence intervals
CRP	C-reactive protein
ESPEN	<i>European Society of Clinical Nutrition and Metabolism</i>
ICD	International Statistical Classification of Diseases
Kcal	calorie
PTN	Protein
ROC	Receiver operating characteristic
RDW	Red Blood Cell Distribution Width
SGA	Subjective Global Assessment
STATA	Software for Statistics and Data Science
TNE	Prescription enteral therapy
TNO	Prescription oral therapy
TNP	Prescription parenteral therapy
UTI	Unidade de terapia intensiva

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APRESENTAÇÃO

Essa tese está estruturada no formato alternativo aprovado pelo Colegiado do Programa de Pós-graduação em Ciências da Saúde da Universidade Federal de Uberlândia, que prevê a inserção de cópias de artigos.

A tese está organizada nas seguintes seções: (1) Introdução, que destaca a importância do estudo; (2) Fundamentação teórica que norteia as hipóteses do presente trabalho; (3) Objetivos, em que são expostos os propósitos do estudo; (4) Resultados, que contempla os manuscritos elaborados; (5) Considerações finais, que discorre sobre a síntese dos principais resultados do estudo.

O primeiro manuscrito original intitulado **“High Red Blood Cell Distribution Width was Associated with a Risk for Short-Term Mortality in Hospitalized Surgical Patients”** teve como objetivo avaliar a associação do red blood cell distribution (RDW) com a mortalidade hospitalar. O RDW está associado com o risco de mortalidade hospitalar por todas as causas, independentemente da idade, nível de hemoglobina, multimorbidade, estado nutricional e características imunológicas do paciente, e pode ser incluída na rotina de avaliação médica em conjunto com outros fatores de risco para mortalidade. O segundo artigo intitulado **“ Hypoprotetic Enteral Nutritional Therapy Predicts Hospital Mortality in Non-critical ill Patients”** teve como objetivo avaliar a associação da prescrição nutricional com a mortalidade por todas as causas em pacientes hospitalizados. Observou-se que a prescrição hipoproteica (<0,8g/kg/dia) e hipocalórica (<20kcal/kg/dia) foi preditor de mortalidade hospitalar por todas as causas, independentemente da multimorbidade, enfermidade, estado nutricional, imunológico e inflamatório em pacientes não críticos. Além disso, para pacientes não críticos, a prescrição média de proteínas e calorias foi baixa, sendo 0,75g/kg/dia e 17,60 kcal/kg/dia, respectivamente. E em 37,80% dos pacientes a prescrição calórica ficou abaixo de 20kcal/kg/dia durante todo o período de internação, sinalizando dificuldade em evoluir e/ou alcançar as metas totais estabelecidas.

Os artigos serão submetidos para publicação posteriormente, podendo sofrer modificações de acordo com a solicitação dos revisores.

1. INTRODUÇÃO

A mortalidade hospitalar é um importante e tradicional indicador de qualidade hospitalar (TRAVASSOS; NORONHA; MARTINS, 1999). Embora, seja de conhecimento que outros fatores podem afetar a mortalidade hospitalar, vários países, em particular o Brasil, têm avaliado o desempenho de seus hospitais utilizando indicadores de mortalidade hospitalar, como um indicador de problemas na qualidade do cuidado prestado (CORDEIRO; MARTINS, 2018; MCCORMICK; PEARSON; WHITE, 2015). As elevadas taxas de hospitalização e morte hospitalar, bem como, o declínio do estado nutricional e a tendência a internações mais frequentes e prolongadas, suscitam a importância do monitoramento, visando a melhoria da qualidade do cuidado hospitalar prestado (CORREIA; PERMAN; WAITZBERG, 2017). Diante disso, a busca por ferramentas capazes de prever desfechos clínicos, de baixo custo, facilmente mensuradas e rotineiramente obtidas na prática clínica, tem sido alvo de estudos na tentativa de modificar o cenário clínico desfavorável.

Dentre as ferramentas capazes de prever desfechos clínicos, temos alguns indicadores bioquímicos (AKIROV et al., 2017; ARAIN et al., 2010; CORREIA; WAITZBERG, 2003; DANESE; LIPPI; MONTAGNANA, 2015; HUANG et al., 2014; KABAT et al., 2017; MARSIK et al., 2008; PINEDA et al., 2016; TURCATO et al., 2016; YOSHINAGA et al., 2017), sistemas de pontuações (OKAZAKI; SHIRAKABE; HATA, 2014; WANG et al., 2017), além do estado nutricional (BARKER; GOUT; CROWE, 2011; CORREIA; WAITZBERG, 2003; HIESMAYR et al., 2009; PIRLICH et al., 2006; SULLIVAN; SUN; WALLS, 1999; THIBAUT et al., 2011; WANG et al., 2018).

No tocante ao estado nutricional, a desnutrição mesmo há décadas elucidada continua se configurando como um problema de saúde pública, além de estar associada à pior evolução dos pacientes, bem como maior tempo de internação, custos e mortalidade hospitalar (AMARAL et al., 2007; AQUINO; PHILIPPI, 2011; BARKER; GOUT; CROWE, 2011; BURGOS et al., 2012; CORREIA; CAMPOS, 2003; CORREIA; WAITZBERG, 2003; EDINGTON et al., 2000; FONTES; GENEROSO; CORREIA, 2014; O'FLYNN et al., 2005; OCÓN BRETÓN et al., 2012; ORDOÑEZ et al., 2013; PIRLICH et al., 2006; RASLAN et al., 2011; REZENDE et al., 2004; WAITZBERG; CAIAFFA; CORREIA, 2001; WYSZYNSKI; PERMAN; CRIVELLI, 2003).

Além disso, vários estudos tem mostrado que tanto o estado nutricional quanto os indicadores bioquímicos podem ser importantes ferramentas para a predição de condições de saúde, de forma a contribuir com as decisões clínicas, além de viabilizar a intervenção precoce, o tratamento personalizado, minimizando desfechos deletérios, custos hospitalares e otimizando a qualidade do serviço prestado (AI; MU; HU, 2018; AKIROV et al., 2017; AL-KINDI et al., 2017; ARAIN et al., 2010; BARKER; GOUT; CROWE, 2011; CORREIA; WAITZBERG, 2003; DANESE; LIPPI; MONTAGNANA, 2015; GOMES BEGHETTO; KOGLIN; DANIEL DE MELLO, 2010; HSIEH et al., 2017; HUANG et al., 2014; KABAT et al., 2017; KIM et al., 2015, 2016; LIPPI et al., 2017; MARSIK et al., 2008; OMRAN; MORLEY, 2000; ORDOÑEZ et al., 2013; PATEL et al., 2009; PATEL, 2010; PERLSTEIN et al., 2009; PINEDA et al., 2016; PIRLICH et al., 2006; YOSHINAGA et al., 2017).

Dentre eles temos a albumina (AKIROV et al., 2017; BEGHETTO, 2007; CORREIA; WAITZBERG, 2003; PINEDA et al., 2016), a proteína C reativa (MARSIK et al., 2008; YOSHINAGA et al., 2017), a contagem de linfócitos (ARAIN et al., 2010; KABAT et al., 2017; OMRAN; MORLEY, 2000) e mais recentemente a amplitude de distribuição dos glóbulos vermelhos (*Red blood cell distribution width* - RDW) (DANESE; LIPPI; MONTAGNANA, 2015; HUANG et al., 2014; LI; ZHOU; TANG, 2017; TURCATO et al., 2016).

O RDW é um parâmetro laboratorial para quantificar o grau de anisocitose dos eritrócitos (DANESE; LIPPI; MONTAGNANA, 2015; SALVAGNO et al., 2015), usado principalmente, para o diagnóstico diferencial de anemia. Recentemente, emergiu como um forte e consistente preditor de mortalidade e morbidade (AI; MU; HU, 2018; AKIROV et al., 2017; AL-KINDI et al., 2017; HSIEH et al., 2017; KABAT et al., 2017; KIM et al., 2015, 2016; LIPPI et al., 2017; LIPPI; CERVELLIN; SANCHIS-GOMAR, 2016; PINEDA et al., 2016; YOSHINAGA et al., 2017). Todavia, estudos que avaliem a associação do RDW com o risco de mortalidade hospitalar por todas as causas, independente da causa específica de morte, considerando os ajustes necessários dos fatores que corroboram com a mortalidade, em pacientes não críticos, ainda precisam ser realizados.

Um dos pontos que também interferem no estado nutricional é o suporte nutricional, essencial para o sucesso terapêutico, e deve ser parte integrante do manejo clínico do paciente, uma vez que tem estrita relação com desfechos negativos em saúde. Estudos revelam que a ingestão inadequada de alimentos, está associada ao aumento de

complicações, maior tempo de internação hospitalar e mortalidade (CORREIA; WAITZBERG, 2003; HIESMAYR et al., 2009; PIRLICH et al., 2006; SULLIVAN; SUN; WALLS, 1999; WANG et al., 2018). Além disso, contribui para o declínio do estado nutricional, e consequentemente, para o aparecimento e/ou agravamento do quadro de desnutrição hospitalar (BARKER; GOUT; CROWE, 2011; CORREIA; PERMAN; WAITZBERG, 2017; THIBAUT et al., 2011)

Dentre as intervenções nutricionais possíveis, a nutrição enteral, surge como uma possibilidade terapêutica de manutenção ou recuperação do estado nutricional, para aqueles pacientes que não conseguem suprir suas necessidades apenas pela via oral e possuem trato gastrointestinal íntegro (BRASIL, MINISTÉRIO DA SAÚDE, 2000; CAMPANELLA et al., 2008; KREYMANN et al., 2006; MCCLAVE et al., 2009). Entretanto, apesar de ser a via preferencial, em muitos casos, a nutrição enteral pode não atender às necessidades nutricionais dos pacientes, pois muitas vezes a oferta de energia e proteínas são insuficientes, podendo acarretar déficits nutricionais e assim contribuindo para desfechos negativos (ALBERDA; DAY, 2009; CORREIA; WAITZBERG, 2003; PIRLICH et al., 2006; SINGH et al., 2009; SOGUEL et al., 2012; SULLIVAN; SUN; WALLS, 1999; VALIZADE HASANLOEI et al., 2018; VILLET et al., 2005; WANG et al., 2018).

Portanto, assegurar suporte nutricional efetivo, previne déficits calóricos e proteicos, minimizando o impacto no prognóstico clínico. Entretanto, estudos que avaliem a terapia nutricional enteral e a mortalidade hospitalar são mais comuns no paciente crítico (MARIK; HOOPER, 2016; PETROS et al., 2016; RUGELES et al., 2016) bem como estudos que avaliem o não alcance das metas ao longo do tempo de internação e sua associação com o risco de morte, são pouco explorados nos paciente não críticos.

Portanto, estudos que avaliem possíveis fatores associados à a mortalidade hospitalar como o suporte nutricional e os exames bioquímicos ainda precisam ser explorados. Do nosso conhecimento, como o RDW ainda não foi investigado para todas as causas em pacientes não críticos, bem como a associação da nutrição enteral com mortalidade considerando importantes fatores de confusão essenciais para determinação da mortalidade hospitalar, tais como estado nutricional, estado imunológico e multimorbidade. Portanto, o objetivo do estudo foi investigar se o RDW e a terapia nutricional enteral exclusiva podem estar associados à mortalidade em pacientes não críticos hospitalizados.

2. REFERÊNCIAL TEÓRICO

2.1 Preditores bioquímicos de mortalidade hospitalar

Os indicadores bioquímicos são medidas objetivas, de baixo custo, rapidamente mensuradas e rotineiramente obtidos na prática clínica. Usados para indicar processos fisiopatológicos ou respostas farmacológicas à intervenção terapêutica. Podem auxiliar na identificação precoce dos pacientes mais suscetíveis à deterioração da condição clínica e que necessitam de maiores cuidados, além de, serem apontados como bons preditores de morbidade e mortalidade (MAYEUX, 2004; NAYLOR, 2003; REIS et al., 2017).

Dentre eles, a albumina, tem sido amplamente discutida na literatura, como um bom preditor de mortalidade em pacientes hospitalizados (AKIROV et al., 2017; BEGHETTO, 2007; CORREIA; WAITZBERG, 2003; PINEDA et al., 2016), sendo que o risco de morte se eleva progressivamente quando a albumina sérica é inferior a 2,5 g/dL (PINEDA et al., 2016).

Outros indicadores bioquímicos capazes de prever a mortalidade hospitalar citados na literatura são: a proteína C reativa (MARSIK et al., 2008; YOSHINAGA et al., 2017) a contagem de linfócitos (ARAIN et al., 2010; KABAT et al., 2017; OMRAN; MORLEY, 2000) e mais recentemente, o RDW (AI; MU; HU, 2018; AL-KINDI et al., 2017; DANESE; LIPPI; MONTAGNANA, 2015; HSIEH et al., 2017; HUANG et al., 2014; KIM et al., 2015, 2016; LI; ZHOU; TANG, 2017; LIPPI et al., 2017; PATEL et al., 2009; PATEL, 2010; PERLSTEIN et al., 2009; TURCATO et al., 2016; XU et al., 2018).

O RDW é um parâmetro laboratorial que mede a variabilidade no tamanho dos glóbulos vermelhos, ou seja, quantificar o grau de anisocitose dos eritrócitos (DANESE; LIPPI; MONTAGNANA, 2015; SALVAGNO et al., 2015). É um indicador rotineiramente relatado nos exames de hemograma, que são diretamente solicitados pelos clínicos para praticamente todos os pacientes, não representando custos adicionais e cujo valores de referência podem variar de 11,5 a 14,5% (DANESE; LIPPI; MONTAGNANA, 2015; SALVAGNO et al., 2015). É usado principalmente, para o diagnóstico diferencial de anemia, e, quando a possibilidade de anemia é descartada, muitas vezes é completamente ignorado pelos médicos (DANESE; LIPPI; MONTAGNANA, 2015; SALVAGNO et al., 2015).

O RDW emergiu como um forte e consistente preditor de mortalidade e morbidade em uma ampla gama de doenças, incluindo: doenças cardiovasculares (DANESE; LIPPI; MONTAGNANA, 2015; HUANG et al., 2014; LI; ZHOU; TANG, 2017; TURCATO et al., 2016), câncer (AI; MU; HU, 2018; HU et al., 2017; XU et al., 2018), diabetes (AL-KINDI et al., 2017), doença renal (HSIEH et al., 2016, 2017), sepse (KIM et al., 2015), trauma (LIPPI et al., 2017), além de prever a mortalidade em adultos mais velhos (KIM et al., 2016; PATEL et al., 2009) e na comunidade (PERLSTEIN et al., 2009). Entretanto, ao nosso conhecimento, não há estudos sobre a mortalidade hospitalar por todas as causas em amostra representativa de pacientes clínicos e cirúrgicos, a fim de elucidar o RDW como um preditor que poderia ser usado na prática frequentemente como triagem de risco de morte para pacientes hospitalizados independente do diagnóstico clínico.

Por se tratar de um parâmetro simples, incluído rotineiramente na análise automatizada de hemograma completo, portanto, estar disponível sem custo adicional (SALVAGNO et al., 2015), o RDW pode se tornar um marcador prognóstico efetivo e de particular interesse, no ambiente hospitalar, sendo, mais uma ferramenta para auxiliar na prática clínica.

2.2 Terapia nutricional enteral e predição de mortalidade hospitalar

A nutrição é parte essencial no tratamento de pacientes hospitalizados (MCCLAVE et al., 2016a; NICE, 2006). A terapia nutricional é importante para garantir o aporte de nutrientes ao paciente durante o período de internação hospitalar, além de ser indispensável para o sucesso do tratamento e para a boa recuperação do paciente (NICE, 2006).

As intervenções nutricionais incluem modificações na dieta oral, nutrição enteral e nutrição parenteral. A nutrição enteral surge como uma possibilidade terapêutica de manutenção ou recuperação do estado nutricional, naqueles indivíduos que apresentarem o trato gastrointestinal íntegro para o processo digestório, mas com a ingestão oral parcial ou totalmente comprometida (BRASIL, MINISTÉRIO DA SAÚDE, 2000; CAMPANELLA et al., 2008; KREYMANN et al., 2006; MCCLAVE et al., 2009).

Desde de 2001, o IBRANUTRI revelou que apesar da elevada prevalência de desnutrição, apenas 6,1% dos pacientes estavam recebendo nutrição enteral, 1,2% estavam recebendo nutrição parenteral e dos 48,9% de pacientes desnutridos, 10,1% receberam nutrição enteral (WAITZBERG; CAIAFFA; CORREIA, 2001). Por outro lado, 8,9% dos

pacientes recebeu nutrição parenteral e 5,2% receberam nutrição enteral (CORKINS et al., 2014) em estudo nos Estados Unidos. Em pacientes críticos em Unidades de Terapia Intensiva (UTI) canadenses, revelou que 44,6% dos pacientes receberam apenas nutrição enteral, 7,1% receberam nutrição parenteral, e 39,7% não receberam nenhuma forma de suporte nutricional (HEYLAND et al., 2003). Por fim, dos 432 pacientes idosos admitidos em uma enfermaria geriátrica na Malásia, 22% dos pacientes receberam alimentação enteral durante a internação hospitalar (NORDIN et al., 2015).

Portanto, mesmo considerando a variabilidade de serviços e contextos clínicos, são escassos os estudos de prevalência de terapia nutricional. Diante disso, investigar a frequência da terapia nutricional. Quando exploram o tema terapia nutricional, ficam direcionados à visão do prescrito versus infundido (CAMPANELLA et al., 2008; GAMBATO; BOSCAINI, 2015; HEYLAND et al., 2003) ou ainda, explorando a mortalidade da nutrição parenteral *versus* enteral em pacientes críticos (ELKE et al., 2016; LEWIS et al., 2018). Sendo assim, são ainda mais raros estudos que exploram a nutrição enteral e mortalidade hospitalar considerando os ajustes necessários dos fatores que corroboram com a mortalidade.

Embora a nutrição enteral seja o método preferido para fornecer suporte nutricional, (se a via oral estiver impossibilitada), além de estar associada a menores efeitos colaterais e desconfortos, menores taxa de incidência de infecção, tempo de internação hospitalar, custos e mortalidade se comparada com a terapia parenteral (AVELINO-SILVA; JALUUL, 2017; VALIZADE HASANLOEI et al., 2018).

É frequente o achado de que a nutrição enteral não atende às necessidades nutricionais, resultando em oferta insuficiente de energia e proteínas, durante a hospitalização, podendo acarretar déficits nutricionais nos pacientes, contribuindo para desfechos negativos tais como o aumento de complicações, maior permanência hospitalar e mortalidade (ALBERDA; DAY, 2009; CORREIA; WAITZBERG, 2003; HIESMAYR et al., 2009; PIRLICH et al., 2006; SINGH et al., 2009; SOGUEL et al., 2012; SULLIVAN; SUN; WALLS, 1999; VALIZADE HASANLOEI et al., 2018; VALLEJO et al., 2017; VILLET et al., 2005; WANG et al., 2018)

Na prática clínica, sabemos que existem limitações para a evolução da prescrição nutricional, impossibilitando o avanço adequado, tais como fatores relacionados ao paciente (idade, gênero, sintomas gastrointestinais, estado nutricional), fatores relacionados à doença, jejum prolongado, interrupções da terapia nutricional devido a procedimentos

médicos e de enfermagem (ESPARZA; BOIVIN; HARTSHORNE, 2001; IBRAHIM et al., 2002; KRISHNAN et al., 2004; MARTINS et al., 2012; MELO; ALMEIDA; SOUSA, 2017; RIBEIRO et al., 2014).

Além disso, outro ponto que pode influenciar na evolução lenta da prescrição da terapia nutricional é a negligência do cuidado, a falta de avaliação rotineira entre o que foi prescrito e infundido (balanço da dieta), valorizando o alcance da meta no tempo adequado. Com isso o paciente pode receber às vezes, aporte consideravelmente menor do que as suas necessidades nutricionais calculadas. Estudo anterior com pacientes submetidos a terapia nutricional enteral exclusiva, verificou que apenas 31% dos pacientes atingiam a meta calórico-proteica determinada (CAMPANELLA et al., 2008). Estudo em diversas UTI canadenses mostra que pacientes em nutrição enteral recebem, em média, menos de 60% das calorias e proteínas prescritas (HEYLAND et al., 2003). Um estudo em UTI na America Latina, verificou que 40% dos pacientes não atinge a meta (VALLEJO et al., 2017).

Em relação ao tempo de alcance das metas para pacientes críticos, as diretrizes da ESPEN recomendam iniciar a nutrição parenteral suplementar em pacientes que não conseguem atingir o consumo alvo no dia 3, enquanto as diretrizes da ASPEN indicam que a suplementação de NP deve ser considerada após 7 a 10 dias em pacientes que não conseguem atender > 60% das necessidades de energia e proteína (MCCLAVE et al., 2016b; SINGER et al., 2009), no entanto para pacientes não críticos, ao nosso conhecimento, não existe estudos.

A possibilidade de adequação nutricional, se inicia com a prescrição adequada, uma vez que, o valor contido na prescrição é o máximo que o paciente receberá no dia de nutrientes e energia. Outro ponto é a gama de recomendações nutricionais para as diferentes condições clínicas. Assim, a adequada prescrição de nutrientes ainda é um desafio como a primeira etapa do cuidado, devido às dificuldades em determinar a ingestão calórica ideal, pois as necessidades de proteína e energia variam muito entre os indivíduos, além das dificuldades na definição de quando oferecer, qual a melhor via de alimentação (HOFFER, 2018; PATKOVA et al., 2017) e como deve ser feita a evolução da dieta.

O suporte nutricional adequado, focado nas necessidades do paciente, contribui para a diminuição das complicações e perdas musculares, promove a cicatrização das feridas e previne o declínio do estado nutricional, e consequentemente, pode diminuir tempo de internação, morbidade e mortalidade hospitalar (BARBOSA-SILVA, MARIA CRISTINA

GONZALEZ, BARROS, 2002; HIESMAYR et al., 2009; KIM et al., 2012; MARTINS et al., 2012; SOGUEL et al., 2012; VILLET et al., 2005).

Entretanto, apesar das diretrizes, o suporte nutricional insuficiente ainda é um problema (ALBERDA; DAY, 2009; SOGUEL et al., 2012; VILLET et al., 2005). Estudos que avaliem a prescrição nutricional e a mortalidade hospitalar são mais comuns no paciente crítico (MARIK; HOOPER, 2016; PETROS et al., 2016; RUGELES et al., 2016), e ainda assim em uma visão comparativa de vias parenteral e enteral como dito acima ou observam neste caso que dietas hipocalóricas e hiperproteica diminuem o risco de morte pacientes (HOFFER, 2018; PATKOVA et al., 2017).

Portanto, estudos que avaliem a nutricional enteral e a mortalidade hospitalar em pacientes não críticos, ainda são escassos. Por fim, quando levam em consideração essa discussão, muitas vezes não ajustam fatores essenciais para a mortalidade hospitalar, como estado nutricional, estado imunológico e multimorbidade.

2.3 Desnutrição e mortalidade hospitalar

A ingestão alimentar inadequada durante a internação, aliada ao aumento das necessidades energéticas, absorção deficiente ou perda de nutrientes devido a doença ou trauma, são as principais causas da desnutrição hospitalar (BARKER; GOUT; CROWE, 2011; CORREIA; PERMAN; WAITZBERG, 2017; THIBAUT et al., 2011).

Mesmo há décadas elucidada, a prevalência mundial de desnutrição em pacientes hospitalizados continua elevada, podendo variar de 10 a 60 % estando correlacionada com inúmeros fatores, anteriores e posteriores à hospitalização (AQUINO; PHILIPPI, 2011; BARKER; GOUT; CROWE, 2011; CORREIA; WAITZBERG, 2003; GUERRA, 2016; RASMUSSEN; HOLST; KONDRUP, 2010; TAPPENDEN et al., 2013).

A desnutrição está associada negativamente na evolução dos pacientes, geralmente relacionada com desfechos clínicos negativos, tais como diminuição da função muscular, respiratória e imunológica, cicatrização de feridas comprometida, pior qualidade de vida e predisposição a complicações, contribuindo para o aumento da morbimortalidade, tempo de internação prolongado e custos elevados em saúde, além de readmissões mais frequentes (BARKER; GOUT; CROWE, 2011; BURGOS et al., 2012; CORREIA; CAMPOS, 2003; CORREIA; WAITZBERG, 2003; DOMINGUEZ, 2013; ORDOÑEZ et al., 2013; PIRLICH et al., 2006; REZENDE et al., 2004; WAITZBERG; CAIAFFA; CORREIA, 2001).

Diante do exposto, fica evidente a necessidade da otimização dos cuidados nutricionais e implementação de ferramentas para identificação dos indivíduos desnutridos ou em risco nutricional. Nesse sentido, é imprescindível a avaliação do estado nutricional, no momento da admissão, possibilitando antever o resultado clínico, e traçar um plano de intervenção dietoterápica eficiente, a fim de minimizar os efeitos deletérios da desnutrição hospitalar (ARAÚJO et al., 2010; KYLE et al., 2006). Além disso, o estado nutricional deve ser mais valorizado na prática clínica bem como nos estudos em saúde que muitas vezes não o consideram como fator de ajuste para os preditores avaliados.

Os profissionais de saúde devem ser conscientizados, a fim de tornar a avaliação nutricional uma rotina hospitalar, bem como a inclusão do diagnóstico clínico de desnutrição no prontuário, o que possibilitaria um melhor conhecimento e/ou controle das dimensões desse problema de saúde pública (CORREIA; PERMAN; WAITZBERG, 2017; CORREIA; WAITZBERG, 2003; MALAFAIA, 2009; PASQUINI et al., 2012). Além disso, implementar avaliações regulares da ingestão alimentar dos pacientes hospitalizados, com o objetivo de reduzir o risco de desenvolver e/ou agravar a desnutrição e, consequentemente, melhorar os resultados clínicos e reduzir os custos de saúde.

3 OBJETIVOS

3.1 Objetivo Geral

Avaliar indicadores bioquímicos e de terapia nutricional associados com a mortalidade hospitalar em pacientes não críticos internados em hospital universitário de Minas Gerais

3.2 Objetivos Específicos

- Avaliar a prevalência de desnutrição e mortalidade hospitalar;
- Associar o diagnóstico nutricional e exames bioquímicos;
- Estimar a associação dos marcadores bioquímicos com o tempo de internação hospitalar e a mortalidade hospitalar por todas as causas;
- Associar a prevalência de desnutrição com os dados de terapia nutricional enteral prescrita durante o período de coleta de dados;
- Estimar a associação da prescrição de terapia nutricional enteral com o tempo de internação hospitalar e a mortalidade hospitalar.

4 RESULTADOS

4.1 Primeiro manuscrito

High Red Blood Cell Distribution Width was Associated with a Risk for Short-Term Mortality in Hospitalized Surgical Patients

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Background & Aims: Red blood cell distribution width (RDW) is a simple biomarker that reflects the degree of heterogeneity in the volume of erythrocytes and is routinely included in the automated blood count analysis. The aims of this study were to evaluate the association of RDW with in-hospital mortality, based on conceptual adjustment models. **Methods:** A retrospective study from was performed with patients aged 18 years or older in Clinical Medicine and Surgery wards. Cox regression was used to determine the independent predictors of in-hospital mortality. The cutoff value was 13.55%. **Results:** Of the 2923, 46.1% were older than 60 years, 58.7% were male and 4.7% died. The accuracy of RDW in predicting in-hospital mortality was characterized by area under the covariate-adjusted ROC curve of 0.577 (CI95%: 0.525, 0.629). The RDW was associated with a risk for in-hospital mortality for all causes (HR 1.11 – CI 95%: 1.01-1.21), regardless of age, sex, wards, nutrition status, immune status and multimorbidity. Every 1% in RDW value increased 17% the risk of all-cause hospital death the surgical patients. **Conclusions:** High RDW was associated with a risk for in-hospital mortality independent of age, sex, hemoglobin level, multimorbidity, nutritional status and immunological for patients surgical. We recommend the use of RDW as a possible marker of mortality risk in clinical practice.

Keywords: In-hospital mortality; Red blood cell distribution width; Hospitalization; Prognosis.

Introduction

Red blood cell distribution width (RDW) is a laboratory parameter for measuring variability in red blood cell size and the normal value ranges from 11.5 to 14.5% [1,2]. The RDW is an indicator that represents the impaired erythropoiesis and is mainly used for the differential diagnosis of anemia, if the possibility of anemia was ruled out, the RDW was often completely ignored by physicians [1,2].

Recently, RDW has emerged as a strong and consistent predictor of mortality and morbidity in a wide range of diseases, including: cardiovascular disorders [2–5], cancer [6–8], diabetes [9], kidney disease [10,11], sepsis [12], trauma [13]. RDW was also found to predict mortality in older adults [14,15] and in community [16]. Moreover, in the surgical scenario, the increase in RDW was also associated with outcomes, such as mortality [17–19].

Various distinct pathophysiological mechanisms such as ineffective erythropoiesis, nutritional deficiencies, hemodilution, oxidative stress, decreased haemoglobin level, and inflammation have been related to an increased RDW [1,14,16,20,21]. Despite these promising data, its current role in clinical practice still pertains to the differential diagnosis of anemia together with the mean cell volume. In addition, there are few studies in the literature that look at the effect of RDW in surgical and non-surgical patients.

To our knowledge, this is the first study to evaluate RDW as a possible clinical marker for hospitalized patients associated with the risk of all-cause hospital mortality, ie short-term mortality, independent of the specific cause of death, taking into account factors of essential adjustments to determine hospital mortality.

The hospital mortality rate remains high [22] and risk factors and prognoses related to mortality are still not fully understood. Thus, the use of practical predictors of mortality may be useful for early identification of hospitalized patients, especially the surgical patients, requiring intensive care and thus improve survival, especially if it is cheap, rapidly measured and routinely obtained. The RDW meets all these criteria because it is a simple parameter that reflects the degree of heterogeneity in circulating red blood cell volume and is routinely included in the automated analysis of complete blood cell counts along with other hematological indices and is therefore available without additional cost [1], when compared to other markers such as the C-reactive proteins, which has an additional cost and is more time consuming, which makes it an effective prognostic marker and of particular interest.

The objective of our study was to evaluate the association of high RDW with all-cause hospital mortality, based on conceptual adjustment models that include essential elements for the determination of hospital mortality, such as nutritional status, immunological status and multimorbidity.

Materials and Methods

A cross-sectional study was conducted in a University Hospital of the from 1 January 2014 to 31 December 2016 (36 months). We included patients aged 18 years or older hospitalized in Clinical and Surgical wards, who submitted nutritional status evaluation by the Subjective Global Assessment (SGA) being considered their first hospitalization.

Data demographics, diagnosis, hospital stay, nutritional assessment and all blood analysis results, including blood count, leukogram, albumin, and C-reactive proteins (CRP) were obtained from electronic medical databases at hospital admission (some biochemical indicators may have low frequency due to low request). Biochemical tests were performed at a single laboratory and hematological parameters were analyzed using automated Sysmex XN-3000™ Hematology Analyzer, and all were obtained albumin measured by bromocresol green and CRP measured by methods immunoturbidimetry using cobas® 6000 analyzer.

The multimorbidity was defined when the co-occurrence of at least two chronic health conditions in the same person [23–25]. All the diagnosis from each patient were counted following the International Statistical Classification of Diseases (ICD) and Related Health Problems. The multimorbidity was categorized into quartiles: ≤ 3 ; 4 to 5; 6 to 7 and more than 7 ICDs.

Patients were classified into the following groups: well-nourished (A), moderate malnutrition (B) and severe malnutrition (C) using the Subjective Global Assessment (SGA) [26], realized by the dietitians and nutrition graduate trainees.

According to the Statistic Sector of the Hospital occurred 11056 hospitalizations in 2014 (3930), 2015 (3610) and 2016(3516), respectively. Of these, we identified 4478 nutritional assessment registered in which 1548 were excluded (51 were under 18 years old, 950 with SGA and without biochemical exams, 446 cases the cases of readmissions and 97 requests for biochemical tests greater than 120 days difference in the application of the

SGA. At the end were include 2930 patient records that had nutritional assessment and biochemical exams (Figure 1).

Descriptive data were summarized using proportions, means ($\pm$ standard deviation, SD) or medians (interquartile range) as appropriate. Categorical variables were compared with Chi-square test and continuous variables were compared using analysis of variance (ANOVA) or Mann-Whitney test.

To evaluate the association of RDW with mortality outcomes, RDW values were evaluate as a continuous variable, as well as binary categorized as > 13.55 and $\leq 13.55\%$ according to the cutoff point identified by receiver operating characteristic (ROC) curve analysis. We also identified cutoff points for the ROC curve, by sex, > 13.2 and $\leq 13.2\%$ for males and > 12.8 and $\leq 12.8\%$ for females. The primary outcome of the study was in-hospital mortality independent of the cause of death, occurred in that single episode of hospitalization regardless of the length of stay analysed as a binary variable, hospital discharge or death.

To identify the probability of in-hospital mortality according to the Kaplan-Meier method, survival curves were used and the differences between the curves were compared from the Log-Rank Test, in-hospital mortality was considered as failure and hospital discharge censoring. Cox regression was performed to determine the independent predictors of mortality in-hospital. In the Cox regression, our event was in-hospital mortality or hospital discharge, the time was length of hospital stay and the main exposure was RDW. The correlation between RDW and CRP was low ($r=0.161$, $p < 0.001$, Spearman test) in our study. Adjustments for demographic, clinical risk factors, nutritional and immunological status and multimorbidity were included in the models from the conceptual model and univariate analysis (see conceptual model in supplementary material). Before entering the variables into the model, the correlation was verified.

To verify if the sample was sufficient for the estimates of Cox regression, we considered an alpha of 0.05, effect size of 0.15, standard deviation of 0.50 in two-tail. We obtained enough observation power of 0.97. In addition, to verify if the sample was sufficient for the estimates of Cox regression, for medical patients, we considered an alpha of 0.05, effect size of 0.15, standard deviation of 0.50 in two-tail, we obtained enough observation power of 0.79. For surgical patients, we considered an alpha of 0.05, effect size of 0.18, standard deviation of 0.50 in two-tail. We obtained enough observation power of 0.93.

The Software for Statistics and Data Science (STATA), version 13.0 was used for all statistical analyses, and 95% confidence intervals (95% CI) were applied. This study was approved by the Research Ethics Committee (CAAE 66930517.0.0000.5152).

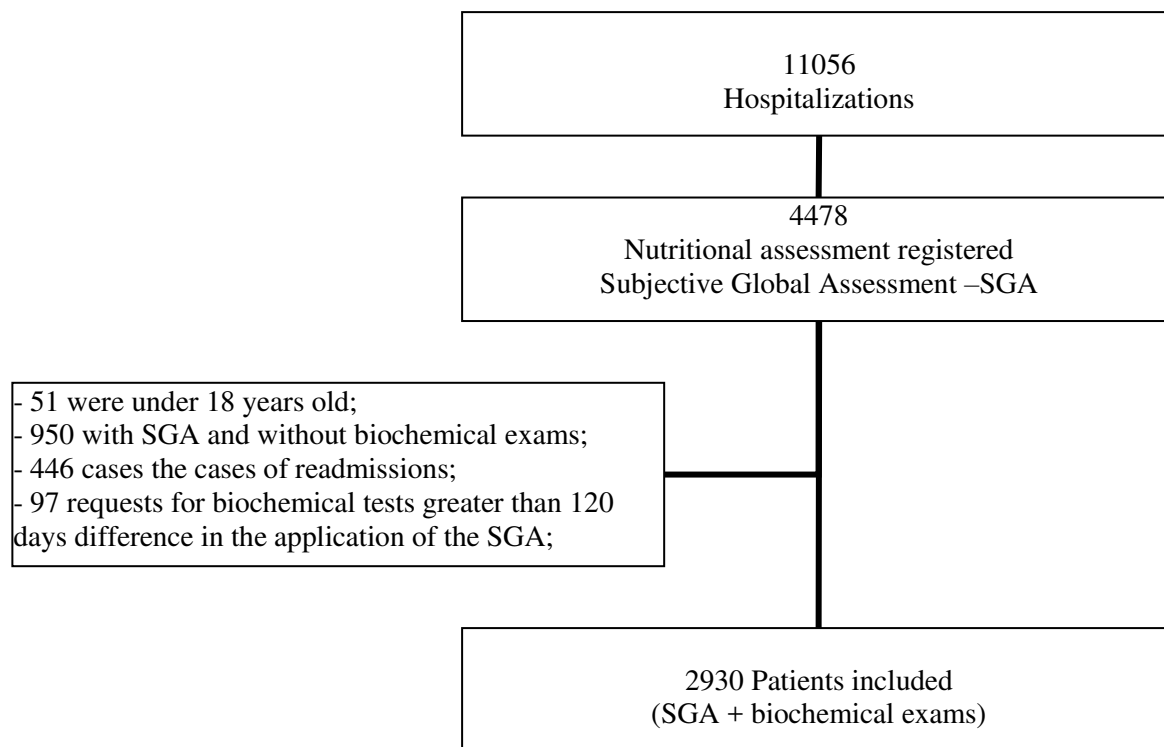


Figure 1: Flow diagram of the process including the patients eligible in the study.

Results

Of the 2923, 46.1% (1497) were older than 60 years and 58.7% (1715) were male aged 18 to 97 years. The prevalence of malnutrition was 55.7% (1629), in which 40.2% (1176) were classified as moderately malnourished and 15.5% (453) as severely malnourished. The prevalence of death was 4.7% (137), in which 87.6% (120) were classified as malnourished and 63.5% (87) were in the group with high RDW. Age, multimorbidity and length of hospital stay were statistically associated with malnutrition, higher RDW and in-hospital mortality for all causes. Most biochemical indicators were significantly associated with malnutrition, higher RDW and mortality in the univariate analysis (**Table 1**).

Table 1. Demographic, clinical and biochemical variables by RDW categories, mortality in-hospital and nutritional status.

Variables	RDW< 13.55% % (n) 60.1(1708)	RDW≥13.55% % (n) 39.9(1136)	p-value	Discharge % (n) 95.3(2786)	Dead % (n) 4.7(137)	p-value	Well nourished % (n) 44.3(1294)	Malnourished % (n) 55.7(1629)	p-value
Age. mean (SD)	54.87(17.72)	57.73(16.79)	<0.001 ^a	55.41(17.39)	67.99(13.80)	<0.001 ^a	51.24(16.26)	59.78(17.42)	<0.001 ^a
Age. older adults % (n)	43.8(748)	49.2(559)	0.005 ^c	44.8(1247)	73.0(100)	<0.001 ^c	32.1(416)	57.2(931)	<0.001 ^c
Sex. male % (n)	60.9(1040)	55.8(634)	0.007 ^c	58.5(1631)	61.3(84)	0.535 ^c	59.2(766)	58.3(949)	0.623 ^c
Anthropometric variables,									
mean (SD)									
Current weight(kg)	69.60(16.35)	66.51(17.50)	<0.001 ^a	68.55(16.86)	64.52(16.37)	0.011 ^a	75.04(16.20)	62.63(15.22)	<0.001 ^a
Usual weight(kg)	72.34(15.92)	71.93(17.84)	0.536 ^a	72.15(16.71)	72.12(17.24)	0.985 ^a	75.91(16.77)	68.99(16.03)	<0.001 ^a
Height(m)	1.65(0.09)	1.64(0.10)	<0.001 ^a	1.65(0.09)	1.64(0.09)	0.284 ^a	1.65(0.09)	1.64(0.10)	<0.001 ^a
Body mass index. kg/m ²	25.29(5.32)	24.66(6.15)	0.005 ^a	25.12(5.68)	23.72(5.07)	0.009 ^a	27.25(5.41)	23.17(5.19)	<0.001 ^a
Usual Body mass index. kg/m ²	26.31(5.22)	26.61(6.19)	0.177 ^a	26.44(5.63)	26.33(5.59)	0.845 ^a	27.55(5.69)	25.50(5.41)	<0.001 ^a
Weight loss (%)	9.46(7.37)	12.16(8.64)	<0.001 ^a	10.59(7.97)	12.60(9.95)	0.034 ^a	6.71(5.17)	12.44(8.52)	<0.001 ^a
Hematological variables.									
mean (SD)									
Erythrocyte(millions/mm ³)	4.35(0.69)	3.90(0.89)	<0.001 ^a	4.18(0.80)	3.78(0.80)	<0.001 ^a	4.36(0.79)	4.02(0.79)	<0.001 ^a
Hemoglobin(g/dL)	12.89(2.08)	10.91(2.40)	<0.001 ^a	12.15(2.40)	11.08(2.45)	<0.001 ^a	12.66(2.34)	11.66(2.37)	<0.001 ^a
Hematocrit (%)	38.53(6.18)	33.58(7.29)	<0.001 ^a	36.69(7.02)	33.67(7.21)	<0.001 ^a	38.03(6.87)	35.39(6.99)	<0.001 ^a
MCV (fL)	89.14(5.38)	86.61(8.73)	<0.001 ^a	88.04(7.07)	89.36(6.78)	0.038 ^a	87.68(6.58)	88.42(7.38)	0.007 ^a
MCH (pg)	29.84(2.02)	28.21(3.45)	<0.001 ^a	29.16(2.83)	29.38(2.55)	0.394 ^a	29.20(2.70)	29.15(2.90)	0.668 ^a
MCHC(g/dL)	33.48(1.28)	32.53(1.71)	<0.001 ^a	33.10(1.54)	32.88(1.54)	0.105 ^a	33.28(1.52)	32.95(1.54)	<0.001 ^a
RDW (%) ⁺	-	-		13(10.0 -29.6)	14(11.0-26.70)	<0.001 ^b	13.00(10.0-27)	13.96(10.0-29.60)	<0.001 ^b
RDW quartis. % (n)									
≤12.0	-	-		31.6(857)	12.7(17)		36.2(450)	26.5(424)	
>12 to ≤13.0	-	-		25.6(693)	20.9(28)	<0.001 ^c	27.1(337)	24.0(384)	<0.001 ^c
>13 to ≤14.5	-	-		19.2(520)	22.4(30)		19.1(238)	19.5(312)	
>14.5	-	-		23.6(640)	44.0(59)		17.5(218)	30.0(481)	
Platelet count(mil/mm ³)	232.89(91.03)	247.79(133.22)	0.001 ^a	239.50(109.94)	229.58(120.52)	0.318 ^a	233.11(100.16)	243.47(117.50)	0.017 ^a
Leucocytes(mil/mm ³)	9.82(4.56)	9.61(5.16)	0.275 ^a	9.71(4.81)	10.25(5.07)	0.218 ^a	9.82(4.55)	9.68(5.01)	0.457 ^a
Lymphocyte (%)	21.45(11.02)	18.96(10.98)	<0.001 ^a	20.71(11.11)	14.91(8.51)	<0.001 ^a	22.11(11.0)	19.17(10.89)	<0.001 ^a
Segmented neutrophils (%)	64.55(12.21)	66.64(12.99)	<0.001 ^a	65.17(12.54)	69.85(12.55)	<0.001 ^a	64.35(12.2)	66.19(12.78)	<0.001 ^a
Band neutrophils (%) ⁺	2.00(1.00-5.00)	3.00(1.00-6.00)	0.018 ^b	4.74(1.00-6.00)	4.00(2.00-7.00)	0.007 ^b	2.00(1.00-6.00)	3.00(1.00-6.00)	0.026 ^b
Eosinophils(mm ³) ⁺	1.00(0.00-3.00)	1.00(0.00-3.00)	0.461 ^b	1.00(0.00-3.00)	1.00(0.00-2.00)	0.041 ^b	1.00(0.00-3.00)	1.00(0.00-3.00)	0.226 ^b

Basophils(mm3) ⁺	0.00(0.00-0.50)	0.00(0.00-0.00)	0.294 ^b	0.00(0.00-4.00)	0.00(0.00-0.00)	0.278 ^b	0.00(0.00-0.50)	0.00(0.00-0.00)	0.275 ^{a,b}
Monocytes (%)	7.15(3.29)	6.90(3.50)	0.062 ^a	7.03(3.37)	7.25(3.53)	0.469 ^a	7.04(3.38)	7.05(3.38)	0.996 ^a
C-Reactive Proteins (mg/d) ⁺	1.8(0.50-9.80)	4.45(1.09-12.48)	<0.001 ^b	2.70(0.70-10.80)	6.60(1.42-14.8)	0.001 ^b	1.90(0.50-9.60)	3.50(0.90-12.20)	<0.001 ^b
C-Reactive Proteins %(n)									
Normal (< 0.5 mg/dL)	27.3(225)	13.7(88)	<0.001 ^c	21.9(315)	11.4(9)	0.024 ^c	27.8(165)	17.2(159)	<0.001 ^c
High (≥0.5 mg/dL)	72.7(598)	86.3(556)		78.1(1122)	88.6(70)		72.2(428)	82.8(764)	
Albumin(g/dL)	3.45(0.80)	3.07(0.72)	<0.001 ^a	3.29(0.80)	2.72(0.61)	<0.001 ^a	3.47(0.77)	3.14(0.79)	<0.001 ^a
Multimorbidity	5.17(3.34)	6.87(4.38)	<0.001 ^a	5.66(3.66)	9.85(5.58)	<0.001 ^a	5.44(3.65)	6.18(4.01)	<0.001 ^a
Nutritional Diagnosis %(n)									
Wellnourish	51.9(529)	39.1(714)		45.8(1277)	12.4(17)		-	-	-
Moderate/ Severe malnutrition	48.1(490)	60.9(1111)	<0.001 ^c	54.2(1509)	87.6(120)	<0.001 ^c	-	-	
Wards %(n)									
Medicine	43.0(735)	56.2(638)	<0.001 ^c	48.6(1354)	42.3(58)	0.162 ^c	51.9(671)	45.5(741)	0.001 ^c
Surgery	57.0(973)	43.8(498)		51.4(1432)	57.7(79)		48.1(623)	54.5(888)	
Duration of hospitalization. %(n)									
< 6 days	26.3(449)	16.5(187)		23.4(653)	8.0(11)		28.7(371)	18(293)	
≥ 6 e < 11 days	26.7(456)	25.4(288)	<0.001 ^c	26.6(742)	16.8(23)	<0.001 ^c	27.7(359)	24.9(406)	<0.001 ^c
≥ 11 e < 21 days	22.9(391)	27.6(313)		24.6(686)	29.9(41)		22.6(293)	26.6(434)	
≥ 21 days	24.1(412)	30.6(348)		25.3(705)	45.3(62)		20.9(271)	30.4(496)	
Outcome. %(n)									
Discharge	97.2(1661)	92.3(1049)	<0.001 ^c	-	-	-	98.7(1277)	92.6(1509)	<0.001 ^c
Dead	2.8(47)	7.7(87)		-	-		1.3(17)	7.4(120)	

MCV: mean corpuscular volume; MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; RDW: red blood cell distribution width; CRP: C-reactive protein.

^aAnova test; ^b U de Mann-Whitney test; ^c Chi-square test; ⁺ Medians (interquartile range).

The accuracy of RDW in predicting in-hospital mortality was characterized by area under the covariate-adjusted ROC curve (AUROC) of 0.577 (CI 95%: 0.525, 0.629), adjusted for immunological status, hemoglobin, length of hospital stay and age (**Figure 2**). The cutoff value is 13.55%, which yielded sensitivity 64.9% and specificity 61.3%.

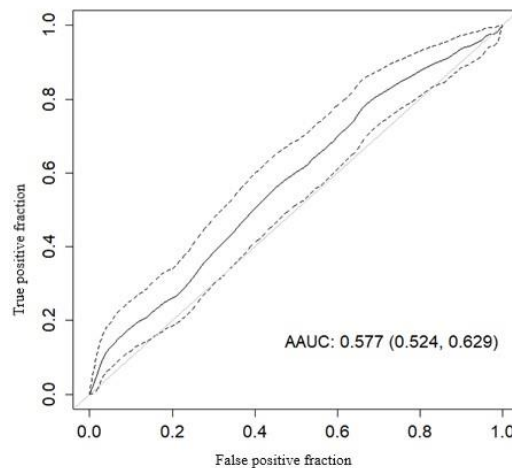


Figure 2. Area under the covariate-adjusted ROC curve of Red Blood Cell Distribution Width (RDW) in predicting in-hospital mortality.

The survival rate of patients with altered values of RDW was significantly lower to all-cause mortality how showed by the log-rank test < 0.001 (**Figure 3**).

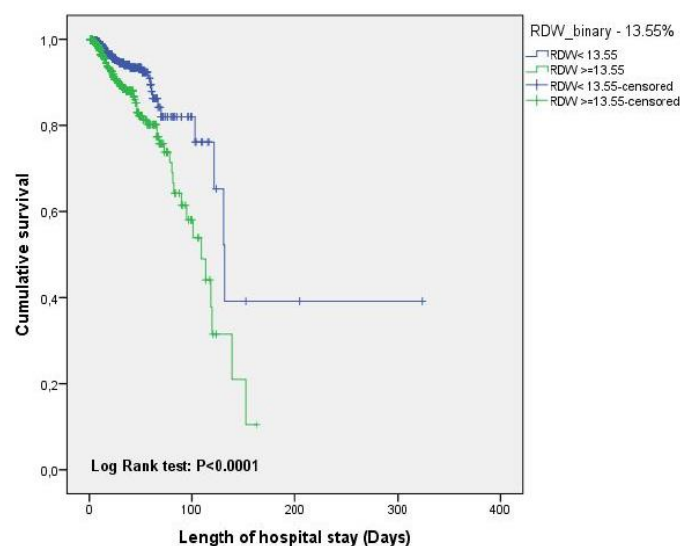


Figure 3. Kaplan–Meier curves for in-hospital mortality according to Red Blood Cell Distribution Width (RDW) values $<13.55\%$ or $\geq 13.55\%$ ($p < 0.001$ by Log rank test).

In the multivariate models, RDW remained a predictor of mortality regardless of age, sex, hemoglobin level, multimorbidity, wards, malnutrition, and the patient's immune and inflammatory status. Every 1% in RDW value increased 11% the risk of all-cause hospital death and among clinical and surgical patients, that 1% increase in RDW increased the risk of all-cause hospital death by 17% the surgical patients (**Table 2**).

Table 2. Cox Regression multivariate for RDW and all cause hospital mortality.

RDW %	Crude model		Adjusted model	
	HR* (CI 95%)	p-value	HR* (CI 95%)	p-value
All patients				
Model 1				
Continuous	1.16 (1.10 - 1.22)	<0.001	1.11 (1.01 - 1.21)	0.020**
Model 2				
<13.55	Ref.		Ref.	
≥13.55	2.14 (1.49 – 3.05)	<0.001	1.88 (1.04 – 3.39)	0.035**
Model 3***				
<12.8 or <13.2	Ref.		Ref.	
≥12.8or ≥ 13.2	2.59 (1.73 – 3.90)	<0.001	2.39 (1.17 – 4.87)	0.016**
Medical Wards - 48.31% (1412)				
Model 1				
Continuous	1.16 (1.07 – 1.26)	<0.001	1.03 (0.87 – 1.22)	0.679***
Model 2				
<13.55	Ref.		Ref.	
≥13.55	1.92 (1.09 – 3.39)	0.023	1.00 (0.39 – 2.54)	0.998***
Model 3****				
<12.8 or <13.2	Ref.		Ref.	
≥12.8or ≥ 13.2	2.09 (1.11 – 3.91)	0.021	0.89 (0.31 – 2.56)	0.835***
Surgical Ward - 51.69% (1511)				
Model 1				
Continuous	1.19 (1.11 – 1.28)	<0.001	1.17 (1.03 – 1.32)	0.010***
Model 2				
<13.55	Ref.		Ref.	
≥13.55	2.82 (1.78 – 4.47)	<0.001	2.65 (1.22 – 5.73)	0.013***
Model 3***				
<12.8 or <13.2	Ref.		Ref.	
≥12.8or ≥ 13.2	3.47 (2.02 – 5.96)	<0.001	4.77 (1.72 – 13.20)	0.003***

*HR: Hazard Ratio.

**Adjusted by nutritional diagnosis, hemoglobin, lymphocyte, multimorbidity, sex, age, wards and CRP.

***Adjusted by nutritional diagnosis, hemoglobin, lymphocyte, multimorbidity, sex, age and CRP.

****RDW 12.8% for female and 13.2% for male.

Discussion

This study showed in a large population of hospitalized patients that a high RDW was associated with a risk for all-cause hospital mortality for surgical patients, regardless of age, sex, hemoglobin level, multimorbidity, wards, condition nutritional and immunological characteristics of the patient, based in conceptual model. In addition, we found a high percentage of malnourished patients as expected and recognized in the literature [27]

By stratifying patients according to the ward, the RDW was associated with the risk of death only in surgical patients, which may be plausible, since surgical patients may have increased oxidative demand and inflammatory load, as well as physiological tolerance, contributing for worse survival [18]. This suggests a role for RDW as a useful, cheap and convenient biomarker associated with short-term mortality in surgical patients. Previous studies in the perioperative setting have revealed that elevated RDW is associated with higher mortality risks after cardiac surgery [28] and in non-cardiac surgery [17–19]. However, to our knowledge this is the first study that observed the effect of RDW in surgical and non-surgical patients, besides having more robust adjustment factors, such as multimorbidity, nutritional status, inflammatory and immunological, based on conceptual model. Since RDW is a marker of inflammation and correlates with nutritional status and hospital mortality, it is important to take these aspects into account.

In addition, our results showed that the association between high RDW and hospital mortality remained even after adjustment for CRP, which is an important and recognized inflammatory marker. In view of this, it seems that the RDW is not influenced only by inflammation, its elevation being mediated by factors other than the inflammatory state. A study, which evaluated the combined effect of CRP and RDW in the prediction of long-term hospital outcomes, showed that RDW, but not CRP, is associated with mortality [29]. In a previous study, adjustment for inflammatory markers, such as CRP, did not substantially reduce the prognostic value of RDW [14,16,30].

RDW is a numerical measure of the size variability of circulating erythrocytes, studies have pointed to RDW as an important inflammatory marker [14,16,30]. Generally, RDW is used as an auxiliary parameter in the diagnosis of anemia, and when there was no suspicion of anemia it is often overlooked by clinicians. Recently, the

RDW was considered as important predictor of prognosis in a wide range of diseases, including: disorders cardiovascular disease [2–5], cancer [6–8], diabetes [9], kidney disease [10,11], sepsis [12], trauma [13], non-selected community-based populations [16,30] and elderly [14,15]. However, studies that observe the effect of RDW in surgical and non-surgical patients are scarce. Previously performed studies have been with surgical patients showing that the increase in RDW is associated with outcomes such as mortality [17–19]. So, it is reasonable that we highlight their valuation in clinical practice.

In addition, we should highlight that RDW is immediate availability and represents no additional cost, because it is routinely reported on the complete blood count. So, the RDW became an interesting marker when compared it to others, such as CRP and interleukin-6, which are costly and time-consuming. Therefore, RDW could be an alternative and useful clinical marker to predict negative health outcomes, since it is a comparatively cheap and readily measured laboratorial marker at no additional cost or examination, calculation, or detailed medical history is required. It can be used in combination with other known prognostic markers, especially in surgical patients, to increase the performance of risk models.

However, the exact pathophysiological mechanisms explaining the relationship between increased values of the RDW and negative outcomes have not yet been fully elucidated. Anisocytosis is conventionally referred to as the heterogeneity of erythrocyte volumes, which may depend on many demographic and clinical variables. Some potential pathophysiological pathways have been suggested to explain why high RDW increases the risk of adverse outcomes, with inflammation [1,20,31–35]. The CRP is also a sensitive marker of inflammation, but the differential performance of these biomarkers can not be explained solely by inflammation. Other plausible explanations for the superiority of RDW as a predictor of risk in our study may be related to the fact that RDW levels are influenced by other pathophysiological mechanisms besides inflammation, specifically oxidative stress and malnutrition [1,14,16,20,21].

The oxidative stress and inflammation leads to ineffective erythropoiesis and the release of large and immature erythrocytes from the bone marrow, as well as altering the half-life of erythrocyte circulation and erythrocyte membrane deformability, factors that may increase anisocytosis [1,16,21,36]. Impaired nutritional status, often present in hospitalized patients, may be associated with anisocytosis due to nutritional deficiencies

(eg iron, vitamin B12 or folate deficiency) [1,33]. In addition, in malnourished patients, the need for protein by the process of haemopoiesis could in itself justify the anisocytosis [37]. In addition to inflammation and malnutrition, some other explanations have been proposed as the cause of anisocytosis, such as aging [14,38,39] physical exercise [40], diseases genetic [33], hemolysis [1] and sex [41,42].

Our study in the univariate analysis shows that there is a significant positive association between sex and RDW. In this sense, RDW values presented better results when analyzed by sex, and we can observe that the strength of association is greater when we respect the particularities of sex. Other studies also found an association between RDW and gender [41,42]. However, our study shows different cutoff points for sex, with impact on the strength of association in surgical patients. So new studies need to be performed respecting the particular sex.

The strengths of our study included the large sample size and the comprehensive dataset, as well as assessing the predictive capacity of RDW to predict in-hospital mortality from all causes, taking into account the length of hospital stay and malnutrition. To our knowledge this is the first study that evaluate hospital mortality in the short-term, from the point of view of hospitalization time and adjusting for malnutrition, observing surgical and non-surgical patients.

Meanwhile, our results have some limitations. Besides that RDW is a mathematic measure of a biological theme, to be influenced by several factors, the prediction power of AUROC was not so high (0.577, CI 95%: 0.525, 0.629), but our estimates have sufficient power to show the association between RDW and hospital mortality. Besides that, the adjustment for multiple potential confounders in the models, there may still be residual confounding factors that were not accounted for. For example, we do not include data on nutrients such as vitamin B12 or folate. However, these data are not routinely available at the hospital and we have adjusted for hemoglobin level. In addition, we do not have the causes of hospital death, and we did not evaluate the main diagnoses but adjusted for multimorbidity, we did not evaluate the type of surgery. Because it is a cross-sectional study, it is not possible to establish causality.

The results of our study corroborate the relationship between short-term (i.e., in-hospital) mortality in surgical patients with increased RDW values, confirming that anisocytosis should be considered as a clinical marker of negative outcomes in these patients. We suggest the creation of hospital screening protocols that incorporate RDW

as a marker associated with hospital death, making it possible to identify surgical patients with a potential risk of death in order to intervene as early as possible, including clinical interventions to reduce inflammation and improve nutritional status.

Further studies should be developed by monitoring RDW values throughout hospital stay and assessing the predictive capacity of the RDW, observing surgical and non-surgical patients. Additional investigations are needed to elucidate the pathophysiological mechanisms responsible for the relationship between RDW and mortality. In addition, future research taking into account the particularities of sex are necessary, since some evidence suggests a greater magnitude of association between RDW and mortality according to sex.

Conclusions

High red blood cell distribution width (RDW) in surgical patients was associated with a risk for all-cause hospital mortality, regardless of age, sex, hemoglobin level, multimorbidity, wards, condition nutritional and immunological characteristics of the patient, and may be included in the medical evaluation routine in conjunction with other risk factors for mortality. The low cost and near universal availability of RDW enhance its value as an adjunctive to the assessment of the risk of death in hospitalized surgical patients, moreover, it is useful auxiliary tool to decide if a particular patient requires special attention, as well as establish a preventive monitoring, in order to reduce in-hospital mortality.

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Appendix A

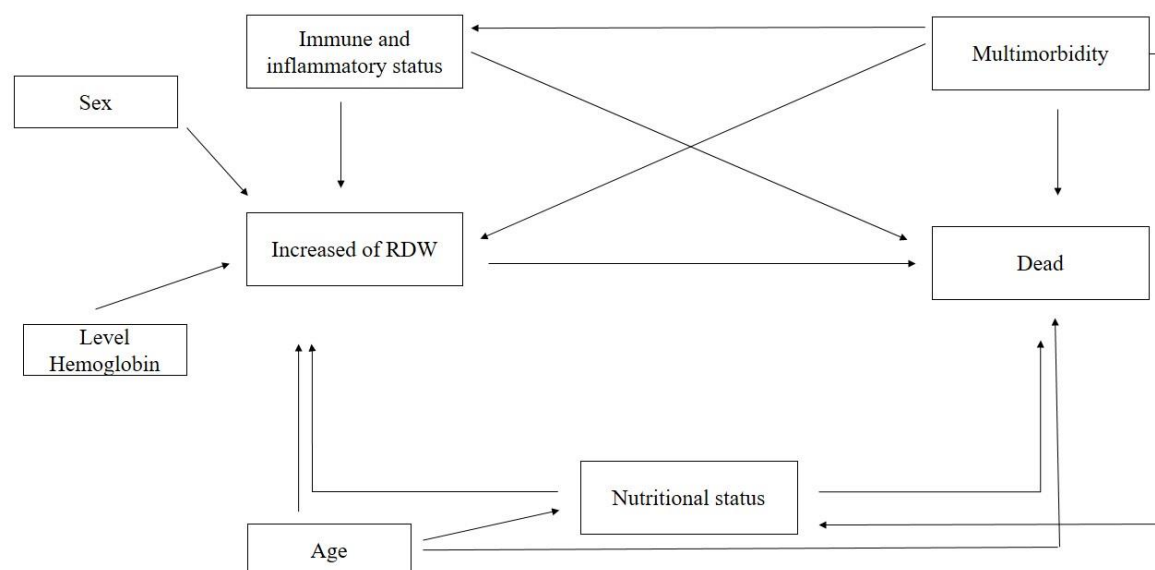


Figure A1: Conceptual model of the study.

A conceptual model is a way of representing a particular concept or set of concepts that support the structure of a research study. The conceptual model shows relationships between factors and the flow of data or processes, that is, it is a representation of the main factors that may be involved with the evaluated outcome (GRAY et al., 2016; VICTORA et al., 1997).

Integrative conceptual models that explain a research study are of paramount importance since they are the best way to establish associations and show the factors involved, taking into account the existing literature. In addition, the use of a conceptual model in research increases the number of well-formed and well-founded research projects (GRAY et al., 2016; VICTORA et al., 1997).

Consistent epidemiological studies should be carried out from the formulation of conceptual models, with evaluation of the variable exposure and outcome and not only by pure mathematics. Our study has this differential when compared to the others, since we use a conceptual model, taking into account the most relevant factors that could alter the RDW, thus reducing the confounding factors.

Pro-inflammatory cytokines inhibit erythropoietin-induced maturation and proliferation of erythrocytes, ie the inflammatory state leads to ineffective

erythropoiesis and the release of large and immature erythrocytes from the bone marrow, in addition to altering the half-life of erythrocyte circulation and erythrocyte membrane deformability, factors that may increase anisocytosis (PERLSTEIN et al., 2009; SALVAGNO et al., 2015).

Impaired nutritional status, often present in hospitalized patients, may be associated with anisocytosis due to nutritional deficiencies (eg iron, vitamin B12 or folate deficiency). The deficiencies of folic acid or vitamin B12, interfere in the normal maturation of all the medullary lineages, mainly in the production of erythrocyte (BUTTARELLO, 2016; SALVAGNO et al., 2015).

Iron deficiency is a common condition that compromises erythropoiesis. Iron deficiency anemia is associated with a decrease in mean corpuscular volume (MCV) and, frequently, an increase in RDW. Iron deficiency anemia involves a decrease in erythropoietic flow, perhaps as a compensation for the decrease in production due to the decrease in iron stores (HIGGINS, 2015).

Lastly, anisocytosis gradually increases with aging as a result of multiple metabolic dysfunctions (LIPPI; SALVAGNO; GUIDI, 2014). With advancing age, pro-inflammatory cytokines are thought to inhibit proliferation of erythroid progenitor cells; and to down-regulate erythropoietin receptor expression (WEISS; GOODNOUGH, 2005). Aging is also closely related to death, since aging, despite being a natural process, subjects the organism to various anatomical, functional, biochemical and psychological changes, with repercussions on the health and nutrition conditions of these individuals (SANTOS; MACHADO; LEITE, 2010).

Multimorbidity, which is an important predictor of complications and unfavorable outcomes, is associated with increased risk of disability, frailty and decreased quality of life, as well as associations with increased risk of death. The biological plausibility of the association between multimorbidity and mortality is analogous to the physiological mechanisms that increase the risk of death in individuals with a specific disease (KADAM et al., 2007; NUNES et al., 2016).

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4.2 Segundo manuscrito

Hypoprotetic Enteral Nutritional Therapy Predicts Hospital Mortality in Non-critical ill Patients

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Abstract

Background & Aims: Providing adequate nutritional support for hospitalized patients is a challenge because of individual variability, disease and treatment. Recent guideline has shown that hypocaloric and hyperproteic diet decreases the risk of complications and death in critically ill patients. However, it is not known whether this is the case with non-critical patients. The objective of the present study was to evaluate the association of energy and protein provision and hospital mortality in non-critically ill patients. **Methods:** A retrospective study was performed with all patients older than 18 years who were admitted to Medical and Surgical Clinic wards on exclusive enteral therapy nutrition and underwent nutritional status evaluation the years 2014 to 2016. The mean of energy and protein was estimated per day and per kilogram body weight from the enteral prescription data considering whole period of hospitalization. A prescription mean was considered hypocaloric or hypoproteic when <20 kcal/kg/day or <0.8 g/kg/day, respectively. **Results:** Of the 240 patients, 58.3% were older than 60 years and 60.0% were male. The frequencies of hospital mortality (19.2%) and malnutrition (78.8%) were high. The mean of protein (0.75 g/kg/day) and energy (17.60 kcal/kg/day) were below the general recommendations and 37.8% did not reach a mean of 20 kcal/kg/day in whole hospitalization period. The hypocaloric (HR: 5.78; 95%CI: 1.59–21.04) and hypoproteic nutrition (HR: 3.69; 95%CI: 1.25–10.93) were predictors of all-cause hospital mortality in adjusted multivariate models. Even in the same model, a hypoproteic nutrition even and energy (non-protein calories to nitrogen ratio) increased the risk of death (HR: 3.15; 95%CI: 1.04–9.53). **Conclusion:** The failure to achieve caloric and protein goals during hospitalization increased the risk of death. Protocols should be implemented to ensure that target caloric and protein levels were reached as quickly as possible in order to optimize patient survival.

Keywords: Hospital mortality; Hospitalization; Nutrition therapy; Energy intake

Introduction

Enteral nutritional therapy is the preferred and most appropriate route for nutritional intervention in individuals who have a usable gastrointestinal tract for the digestive process, after partial or total impairment of oral intake.

It is widely known that the inadequate nutrient supply during hospitalization, the poor absorption or loss of nutrients due to illness, combined with increased metabolic demands may lead to hospital malnutrition and/or its worsening [1–3] and else, the adequate nutritional support, focused on the needs of the patient, contributes to the reduction of complications and muscle losses, promotes wound healing and prevents the decline of nutritional status and, consequently, can reduce length of hospital stay and in-hospital morbi-mortality [4–7]. So, out of doubt, to ensure the provision of adequate nutritional support for hospitalized patients is essential in clinical practice.

In this sense, many studies have compared enteral versus parenteral therapy [8–10] and others have explored the relationship between the prescription and infusion adequacy of enteral nutritional, reporting difficulties in achieving nutritional goals [11–13]. Outside this context, the enteral nutritional therapy is poorly investigated and although often chosen to nutritional support, it does not meet nutritional goals [11,14], and the insufficient nutritional support is still a problem [15–17].

Energy requirements are often calculated using kcal/kg due to the convenience and wide acceptance by clinicians. Many studies debate about energy and protein requirements for critically ill patients and the most recent guidelines of the European Society of Clinical Nutrition and Metabolism (ESPEN) recommend initially 20–25 kcal/kg/day of energy and 1.3–1.5 g/kg/day of protein [18], while the recommendations of the American Society for Parenteral and Enteral Nutrition (ASPEN) recommend 25–30 kcal/kg/day of energy and 1.2–2.0 g/kg/day of protein [19]. In contrast, for non-critically ill patients, the guidelines recommend 20 to 35 kcal/kg/day of energy and 0.80 to 1.2 g/kg/day of protein [20–23].

It is reported in the literature that the critical patient needs to reach their goal within 72 hours after initiation of enteral nutritional therapy [19]. The delay in reaching caloric and protein goals lead to the above-mentioned consequences and may contribute to negative clinical events in hospitalization. Studies that explore the relationship between enteral nutritional therapy time to reach the nutritional goal and its association with clinical events like hospital mortality in non-critically ill patients are scarce.

Thereby, the objective of this study was to evaluate the energetic and protein target attainment time as well as if the mean of energy and protein in exclusive enteral therapy with hospital mortality in non-critically ill patients, considering conceptual adjustment models that include essential elements for the determination of these events, such as nutritional status, immunological status and multimorbidity.

Materials and Methods

A retrospective cohort study was performed in a tertiary-level University Hospital from January 1, 2014 to December 31, 2016. We included hospitalized patients older than 18 years admitted to the Clinical and Surgical wards, in exclusive enteral nutritional therapy and submitted to assessment of nutritional status, considering only their first hospitalization. This study was approved by the Research Ethics Committee (CAAE 66930517.0.0000.5152).

Demographic data (age and sex); clinical diagnoses; length of hospital stay; nutritional status; blood test results, including blood counts, leukogram, albumin and C-reactive protein (CRP) obtained on admission, and the prescription of enteral nutrition therapy were collected from the electronic clinical databases.

All biochemical tests were performed at a single laboratory and hematological parameters were analyzed using automated Sysmex XN-3000 TM Hematology Analyzer, and all were obtained at hospital admission (some biochemical indicators may have low frequency due to low request). Albumin measured by bromocresol green and CRP measured by methods immunoturbidimetry using cobas® 6000 analyzer.

The Subjective Global Assessment (SGA) for assessing nutritional status, patients were classified into the following groups: well-nourished (A) and moderately or severely malnourished (B + C) [24]. The body mass index (BMI; kg/m²) was calculated by dividing the current weight by the square of the height. Multimorbidity was defined as “co-occurrence of at least two chronic health conditions in the same person” [25–27]. To quantify multimorbidity, all the diagnoses of each patient were counted according to the International Statistical Classification of Diseases (ICD) and Health-Related Problems and were later classified into the following quartiles: ≤3.0; 4–5; 6–7 and more than 7 ICDs.

The dietary prescription represents the maximum of nutrients could be offer to patients a day. Thus, the mean of energy and protein was estimated per day and per

kilogram body weight, considering the caloric density, volume, and type of each diet prescribed for each whole period of hospitalization. For this, all daily prescriptions were summed and divided by the total days of enteral nutritional therapy, to obtain the daily means of energy (kcal) and protein prescribed. Subsequently, these values were divided by the patient's weight (kg) to obtain the mean prescribed amount of protein (g/kg/day) and calories (kcal/kg/day).

How important is the appropriate nutrition goals also is their time reach time. As there is no specific recommendation in the literature for reach time in the non-critically ill patient, we consider the ASPEN guidelines for critically ill patients should advanced toward goal in 48–72 hours [19,28]. As it was not possible to obtain data of the total energy value, we consider a minimum requirement of 20 kcal/kg/day, in up to the first 72 hours and at the minimum requirement of 20 kcal/kg/day.

According with recommendations that suggest between 20 and 35 kcal/kg/day of energy and 0.80 to 1.2 g/kg/day of protein for non-critically ill patients [20–23], the mean prescribed amount of protein and energy per day and per kilogram (main exposures) were classified as follows: protein <0.8 ; ≥ 0.8 and <1.0 ; ≥ 1.0 and <1.2 ; and ≥ 1.2 g/kg/day and calories <20 ; ≥ 20 and <25 ; ≥ 25 and <30 ; and ≥ 30 kcal/kg/day.

In order to assist in understanding whether the categories of daily mean prescription were associated with clinical variables, as well as to allow comparability with other studies, we considered in our study a hypocaloric diet as <20 kcal/kg/day and a hypoproteic diet as <0.8 g/kg/day. The nonprotein calories-to-nitrogen ratio (NPC: N) were calculated by summing the prescribed carbohydrate and lipid calorie mean divided by the nitrogen content in grams ($N_2 = \text{mean Gm of prescribed protein}/6.25$). The mean of nonprotein calories-to-nitrogen was categorized as <100 : 1, <100 : 1 and > 150 : 1 and ≥ 150 : 1 [29].

For descriptive data, proportions or means ($\pm$ standard deviation, SD) or medians (with interquartile ranges) were used. Categorical variables were compared with the chi-square test, and continuous variables were compared using analysis of variance (ANOVA) or the Mann-Whitney test, as appropriate. The Kaplan-Meier method was used to obtain survival curves and a log-rank test to compare nutritional therapy groups in which hospital mortality was considered as failure and hospital discharge as censoring. Cox regression analysis was performed to determine the association between nutritional therapy and mortality. Mortality (1) or hospital discharge (0) was considered as the event, weighted by the length of hospital stay (days).

Finally, the conceptual model (Supplementary material) was used to define the adjustment factors. To verify if the sample was sufficient for the estimates, we considered a two-sided alpha of 0.05, an effect size of -0.693 and a standard deviation of 0.50 , and we obtained an observation power of 0.99 . As energy (mean kcal) was highly correlated with protein (mean kcal of protein) ($r = 0.97$, $p < 0.001$, Spearman test), therefore, it would not be appropriate for both to be in the same model. Thus, model 1 and 2 demonstrate the effect of energy and protein separately. In order to obtain the effect of both at the same time, it was demonstrated in model 3 the protein prescription (g/Kg/day) and non-protein calories to nitrogen ratio (NPC:N ratio) adjusted[29]. The Software for Statistics and Data Science (STATA), version 13.0 was used for all statistical analyses, and 95% confidence intervals (95% CI) were applied.

Results

Of the 240 patients aged between 21 and 95 years, 58.3% (140) were older than 60 years and 60.0% (144) were male. The prevalence of malnutrition was 78.8% (178), of which 51.3% (116) were moderately malnourished and 27.4% (62) severely malnourished. The frequency of death was 19.2% (46), and of those who died, 86.7% (39) were classified as malnourished. Age, red blood cell distribution (RDW), albumin, multimorbidity and length of hospital stay were statistically associated with death in the univariate analysis (**Table 1**).

The median protein and calorie prescriptions were 0.75 g/kg/day and 17.60 kcal/kg/day. Hypoproteic nutrition was associated with death, and both energy and protein were associated with the length of hospital stay. The median number of days of enteral nutritional therapy and the median length of hospital stay were 8 and 16 days, respectively (Table 1). The mean number of reach time the minimum caloric goal (20 kcal/kg/day) was 4 days, and the percentage of patients who failed to reach ≥ 20 kcal/kg/day in 72 hours was 61.8% (139), of which 37.8% (85) did not reach ≥ 20 kcal/kg/day regarding the length of hospitalization stay. All-cause mortality was significantly higher in patients with hypocaloric (<20 kcal/kg/days) and hypoproteic (<0.8 g/kg/day) diet (log-rank test $p < 0.001$) (**Figure 1 and 2**).

Hypoproteic (<0.8 g/kg/day; HR: 3.69; 95%CI: 1.25–10.93) and hypocaloric (<20 kcal/kg/days; HR: 5.78; 95%CI: 1.59–21.04) nutrition were predictors of all-cause hospital mortality, regardless of multimorbidity, wards or nutritional, immunological and inflammatory status. When the effect of mean protein and protein prescription and

non-protein calories to nitrogen ratio (NPC:N ratio) plus confounding factors, the same it was observed, i.e, the energy and protein are important to in-hospital mortality risk. **(Table 2).**

Table 1. Demographic, clinical and biochemical variables by mortality.

	Total % (n) (240)	Discharge % (n) 80.8 (194)	Dead % (n) 19.2 (46)	p-value
Age. medians (interquartile range)	61.71(51.25-76.00)	61.00(47.00-73.25)	69.72(62.50-79.00)	<0.001 ^c
Age. older adults%(n)	58.3(140)	73.6(103)	26.4(37)	0.001 ^b
Sex. male%(n)	60.0(144)	82.6(119)	17.4(25)	0.384 ^a
Anthropometric variables , medians(interquartile range)				
Weight(kg) ⁺	62.80(51.05-72.00)	62.25(50.03-71.88)	65.00(52.00-76.50)	0.438 ^c
Height(m),mean(SD)	1.63(0.09)	1.64(0.10)	1.62(0.09)	0.247 ^a
Body mass index.kg/m ²⁺	23.11(19.53–26.76)	22.85(19.10–26.53)	23.98(21.16–28.51)	0.149 ^c
Weight loss(%),mean(SD)	9.34(13.17)	9.18(13.38)	10.21(12.16)	0.689 ^a
Hematological variables , mean(SD)				
Erythrocyte(millions/mm ³)	3.98(0.77)	3.99(0.77)	3.95(0.78)	0.742 ^a
Hemoglobin(g/dL)	11.65(237)	11.71(2.56)	11.38(2.26)	0.424 ^a
Hematocrit(%)	35.61(7.42)	35.76(7.56)	34.99(6.88)	0.525 ^a
Mean corpuscular volume(fL)	89.34(7.32)	89.51(7.27)	88.71(7.53)	0.514 ^a
Mean cell hemoglobin(pg)	29.22(2.86)	29.32(2.88)	28.85(2.74)	0.331 ^a
Mean cell hemoglobin concentration(g/dL) ⁺	32.80(31.80-33.70)	32.80(31.80-33.90)	32.70(31.45-33.65)	0.544 ^c
Leucocytes(mil/mm ³) ⁺	9.30(6.40–13.35)	9.20(6.42–12.95)	10.10(6.20–14.00)	0.458 ^c
Lymphocyte(%) ⁺	18.00(10.00–24.00)	18.00(10.25–24.87)	14.00(9.50–20.50)	0.124 ^c
Segmented neutrophils(%) ⁺	69.00(59.00–76.00)	67.00(59.00–75.00)	70.00(60.50–81.00)	0.097 ^c
Band neutrophils(%)	3.00(7.70)	3.00(1.00-7.00)	4.00(2.00-8.00)	0.570 ^c
Eosinophils(mm ³) ⁺	1.00(0.00–2.95)	1.00(0.00–3.00)	0.00(0.00–2.00)	0.004 ^c
Monocytes(%)	6.82(3.37)	6.88(3.42)	6.62(3.20)	0.651 ^a
Platelet count(mil/mm ³) ⁺	229.00(161.00–283.50)	232.00(163.50–284.25)	219.00(151.50–282.00)	0.402 ^c
Red blood cell distribution width(%) ⁺	13.70(12.35–15.00)	13.00(12.00–14.92)	14.00(13.00–16.00)	<0.001 ^c
C-Reactive Proteins(mg/dL) ⁺	6.30(1.25–16.65)	4.89(1.25-16.65)	8.67(1.40-16.50)	0.584 ^c
Albumin(g/dL)	3.03(0.72)	3.11(0.69)	2.70(0.76)	0.050 ^a
Multimorbidity , medians(interquartile range)	7.00(5.00–8.00)	6.00(4.00–8.00)	8.00(7.00-10.25)	<0.001 ^c
Nutritional Diagnosis ,%(n)				
Nourished	21.2(48)	23.2(432)	13.3(6)	0.147 ^b
Moderate/Severe malnutrition	78.8(178)	76.8(139)	86.7(39)	
Wards %(n)				
Clinical	35.4(85)	34.5(67)	39.1(18)	0.558 ^b
Surgical	64.6(155)	65.5(127)	60.9(28)	

Length of hospitalization stay, days Medians(interquartile range)	16.00(9.00-32.75)	16.00(9.00-31.25)	23.50(11.75-60.50)	0.007 ^c
Length of hospitalization stay, days,%(n)				
<6	11.70(28)	100.00(28)	0.00(0)	0.022 ^b
≥6e<11	18.80(45)	77.80(35)	22.2(10)	
≥11e<21	28.30(68)	83.80(57)	16.2(11)	
≥21	41.30(99)	74.70(74)	25.3(25)	
Nutritional therapy , Medians(interquartile range)				
gProtein/kg/d	0.75(0.42-1.08)	0.79(0.47-1.09)	0.64(0.31-1.02)	0.029 ^c
gCarbohydrate/kg/d	1.88(1.23-2.80)	2.00(1.31-2.83)	1.53(0.94-2.33)	0.059 ^c
gLipid/kg/d,mean(SD)	0.75(0.39)	0.77(0.39)	0.65(0.38)	0.084 ^a
Kcal/kg/d	17.60(9.82-25.51)	18.40(11.07-25.64)	14.38(8.26-22.81)	0.068 ^c
Kcal total/d	1120.50(527.16)	1150.75(528.03)	992.92(509.45)	0.06 ^a
Length of nutritional therapy, days	8.00(4.00-16.00)	8.00(4.00-15.00)	8.50(4.00-24.50)	0.422 ^c
Caloric reach time, day,mean(SD)	4.20(4.55)	4.05(4.18)	4.95(6.16)	0.390 ^a
Protein prescription ,g/kg/d,%(n)				
<0.8	53.8(121)	56.60(98)	65.00(26)	0.169 ^b
≥0.8and<1.0	11.60(26)	12.50(23)	7.30(3)	
≥1.0and<1.2	19.10(43)	19.60(36)	17.10(7)	
≥1.2	15.60(35)	17.40(32)	7.3(3)	
Energy prescription ,Kcal/kg/d,%(n)				
<20	58.2(131)	78.60(103)	21.40(28)	0.534 ^b
≥20e<25	15.60(35)	16.30(30)	12.20(5)	
≥25and<30	17.80(40)	19.00(35)	12.20(5)	
≥30	8.400(19)	8.7(16)	7.3(3)	
Caloric minimum range ,%(n)				
Caloric minimum during all hospitalization	37.80(85)	36.40(67)	43.90(18)	0.669 ^b
Energy reach time in up to72 hours	38.20(86)	39.10(72)	34.10(14)	
Energy reach time regarding length of hospitalization >72hours	24.00(54)	24.50(45)	22.00(9)	

^aAnova; ^bChi-square; ^cTestU de Mann-Whitney; ⁺Medians(inter quartile range)

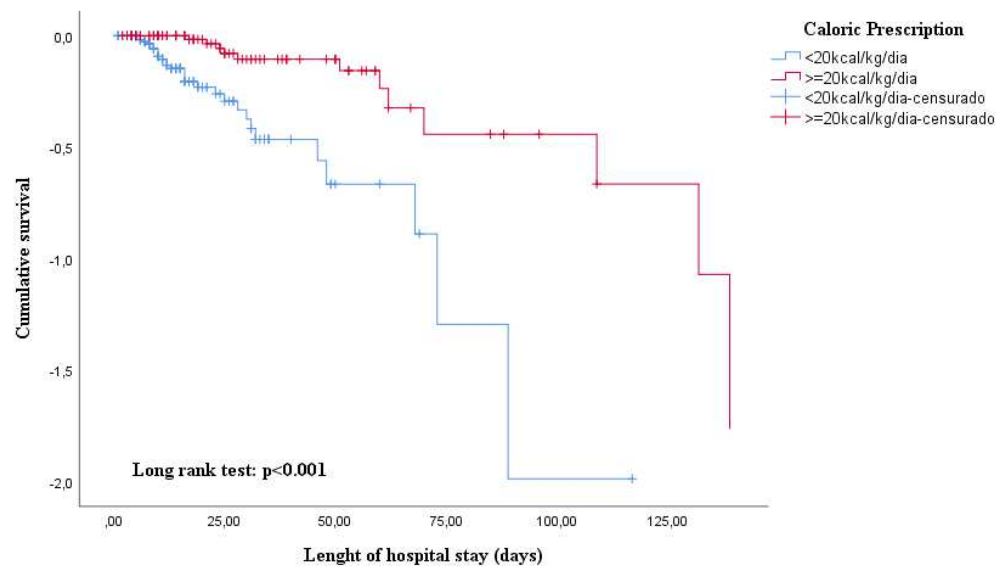


Figure 1. Kaplan-Meier curves for in-hospital mortality according to energy prescription values $<20\text{kcal/kg/day}$ or $\geq 20\text{kcal/kg/day}$ ($p<0.001$ by log-rank test).

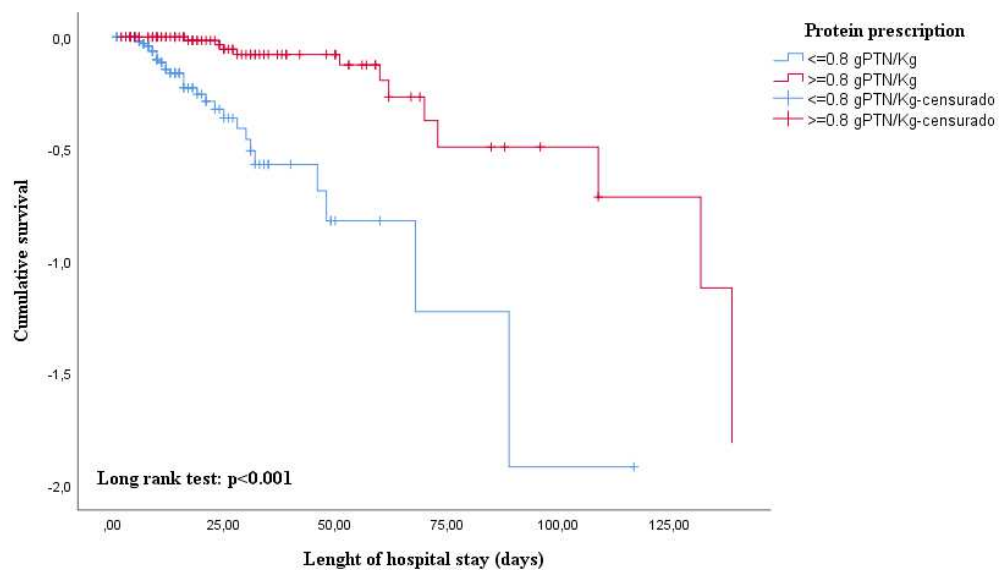


Figure 2. Kaplan-Meier curves for in-hospital mortality according to protein prescription values $\leq 0.8\text{g/kg/day}$ or $\geq 0.8\text{g/kg/day}$ ($p<0.001$ by log-rank test).

Table 2. Cox Regression multivariate for protein and calorie categories and in-hospital mortality

	Crude model	Adjusted model**
	HR* (CI95%)	HR* (CI95%)
Model 1		
Protein(g/Kg/day)		
≥1.0to<1.2	Ref.	Ref.
<0.8	4.57(1.71–12.22)	3.69(1.25–10.93)
≥0.8to<1.0	1.13(0.26–4.84)	1.04(0.24–4.47)
≥1.2	0.50(0.12–2.03)	0.24(0.05–1.08)
Model 2		
Energy(Kcal/kg/day)		
≥25to<30	Ref.	Ref.
<20	6.25(1.96–19.84)	5.78(1.59–21.04)
≥20to<25	2.26(0.55–9.22)	2.68(0.65–11.10)
≥30	1.26(0.27–5.69)	0.84(0.16–4.40)
Model 3		
Protein(g/Kg/day)		
≥1.0to<1.2	Ref.	Ref.
<0.8	4.57(1.71–12.22)	3.15(1.04–9.53)
≥0.8to<1.0	1.13(0.26–4.84)	0.85(0.19–3.78)
≥1.2	0.50(0.12–2.03)	0.25(0.56–1.14)
Non-protein calories to nitrogen ratio(NPC:Nratio)		
<100:1	Ref.	Ref.
>100:1to<150:1	1.43(0.55–3.66)	1.43(0.48–4.21)
≥150:1	14.14(3.26–61.37)	31.02(4.94–194.76)

*HR: Hazard Ratio.

**Adjusted by sex, age, multimorbidity, BMI, RDW, lymphocyte and wards.

Discussion

The present study showed that the inability to reach the minimum protein supply during hospitalization increases the risk of death. Hypoproteic (<0.8 g/kg/day) nutrition appears to be more significant than hypocaloric (<20 kcal/kg/day) nutrition to predict of all-cause hospital mortality, regardless of multimorbidity, wards and nutritional, immunological and inflammatory status in non-critically ill patients.

To our knowledge, there are still no studies that discuss the recommendations for non-critically ill patients and the effects of not achieving established goals on the mortality hospital. The recommendations of energy and protein for non-critically ill patients ranged from 20 to 35 kcal/kg/day and 0.80 to 1.2 g/kg/day, respectively [20,21]. The definitions of hypocaloric and hypoproteic nutrition are still controversial. The ASPEN defines ≤20 kcal/kg/day as goal for critical patients or no more than 80% of estimated energy requirements [28]. It seems to be a consensus that hypoproteic and hypocaloric diets are

defined as <0.8 g/kg/day and <20 kcal/kg/day, respectively. Studies with critically ill patients reported clinical benefits of hypocaloric and hyperproteic nutrition in the early stage of the disease [30,31]. Our study shows that hypoproteic (<0.8 g/kg/day) and hypocaloric (<20 kcal/kg/day) nutrition increased in 3.69 and 5.78 times the risk of in-hospital death.

In addition, even after adjustment for non-protein calories, hypoprotein nutrition increased the risk of death by 3.15 times, which reveals that the amount of protein for non-critically ill patients along with an adequacy in the amount of calories is of utmost importance. Studies with critically ill patients have also found an association between low protein consumption and increased hospital mortality [32–36]; moreover, low protein consumption was associated with worse short- and long-term outcomes [37,38]. Other studies have described an association between low dietary intakes and higher hospital mortality [5,6,16,39,40]. While we recognize that protein seems to be more important, energy also has its physiological importance. As it is known, when the energy supply is insufficient the organism will use lean and lean tissue for deviation of energetic synthesis in order to maintain the supply [31]. Therefore, it is necessary to guarantee minimally the energy supply to prevent the ingested protein from being diverted to energetic synthesis.

Inadequate nutritional support is still a widespread problem [15–17,41–44]. Although guidelines support the use of enteral nutrition to improve clinical outcomes, and enteral nutrition is the preferred route of artificial feeding in patients unable to meet their oral needs, it is often associated with an insufficient supply of energy [16,43,45]. A study with critically ill patients showed that negative energy balance occurs very frequently during critical illness despite nutrition protocols and it is correlated with complications. The authors also highlighted that patients are exposed to caloric deficits that probably cannot be compensated [17]. Our study revealed that patients were exposed to caloric and protein deficits during hospitalization: the median protein and energy requirements found in our study were 0.75 g/kg/day and 17.60 kcal/kg/day, respectively, which were below the recommended values, even with a median 8 days of enteral nutritional therapy.

Another point to consider is the nutritional reached time, which is very important for therapeutic success as well as minimize nutritional deficits. Our study showed that in 61.8% of patients did not reach the goal of 20 kcal/kg/day in the first 72 hours of enteral therapy, and almost 38% of patients failed to achieve this minimum target during the whole hospitalization period. In clinical practice, the necessity of reaching established goals within 72 hours is widely evidenced in critically ill patients [19]; however, to our knowledge, no studies have

demonstrated this values for non-critically ill patients. Goal achievement time is very important clinically, since non-critically ill patients, due to their clinical diversity, could be neglected in this context. Monitoring and reducing reached time to protein and energy is important to patient's clinical evolution.

Nevertheless, we know that there are limitations to the increase caloric and protein of nutritional therapy. First, the individual (age, gender, nutritional status) and disease-related (gastrointestinal symptoms) factors, as also prolonged fasting and frequent interruptions of nutritional therapy due to medical and nursing procedures [11,12,42,46,47]. Secondly, we could observed the lack of daily energy and protein balance of nutritional therapy, i.e, failure to perform routine evaluations of what is being prescribed and infused, a shortage of reassessments of patients and a lack of commitment of the health team to nutritional therapy are the main factors to this neglect of care [17,45].

Finally, failure to meet nutritional requirements during hospitalization, whether due to frequent interruptions or neglect of care, causes slow progression of nutritional therapy and consequently promotes caloric and protein deficits that are accumulated day after day. It may impair the immune response, increase infectious complications and worsen nutritional status, thus contributing to negative outcomes such as increased mortality, prolonged hospital stays and increased costs [4,5,15,17,42].

In addition, protocols should be established in conjunction with all health staff in order to minimize operational factors that may affect the prescription of nutritional therapy and its adequate attendance, as well as to increase monitoring over the goals of nutritional therapies and ensure reached time as quickly as possible. Despite many debates in the literature on nutritional therapy in non-critically ill patients, to our knowledge, this is the first study to evaluate enteral nutritional therapy in non-critically ill patients in this context of reached time, protein and energy prescriptions, and its association with death as well as to adjust for fundamental factors such as nutritional status, taking into account a conceptual model.

Among the limitations of our study, we can highlight that we did not evaluate the adequacy of agreement between the prescribed and infused therapies or the factors involved with non-infusion: we only evaluated the nutritional prescription. Therefore, we could not analyse the causes of underfeeding by providing less than the doses intended (or recommended) by the nutritionist. In view of this, there may be differences between what was prescribed and what was actually infused, and patients may have received even fewer calories and protein if there were clinical problems infusing the prescribed diets. However, our

estimates were more conservative than they would have been if we had evaluated the diet balance directly. Furthermore, we used the patient's weight at admission, and we did not evaluate possible weight loss over the course of hospitalization. Both of these points could have led to underestimation of hospital mortality.

Conclusions

Apparently hypoproteic (<0.8 g/kg/day) nutrition appears to be more significant than the hypocaloric (<20 kcal/kg/day) nutrition in predicting of all-cause hospital mortality, regardless of multimorbidity, wards or nutritional, immunological and inflammatory status in non-critically ill patients. The failure to achieve caloric and protein goals during hospitalization increased the risk of death. In addition, almost 38% not achieved their goals during length of hospital stay. Protocols must be implemented in order to minimize the factors that interfere with the achievement of goals, as well as raise awareness among other health professionals about the importance of nutritional therapy.

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Appendix A

such as age, sex, nutritional state and clinical condition, which are determinants of energy expenditure and impact the calculation of energy and protein requirements [6]. Other factors that may affect nutritional provision are prolonged fasting and frequent interruptions of nutritional therapy due to medical and nursing procedures [7–12].

Studies indicate that nutrient intake is strongly correlated with a number of clinical outcomes, including the risk of death [13–17]. The evaluation of food intake is fundamental for global health care and should be performed regularly in all hospitalized patients. In addition, the evaluation permit earlier identification of malnourished patients who could benefit from nutritional support and/or nutrition team intervention [6].

Aging is also closely related to death, since aging, despite being a natural process, subjects the organism to various anatomical, functional, biochemical and psychological changes, with repercussions on the health and nutritional conditions of these individuals [18]. Furthermore, multimorbidity is an important predictor of complications and unfavourable outcomes and is associated with an increased risk of disability and decreased quality of life, as well as an increased risk of death [19,20]. Finally, malnutrition is associated with negative disease evolution, increased morbidity and mortality, longer hospitalization times, higher health care costs and more frequent readmissions [21–29].

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5 CONSIDERAÇÕES FINAIS

O indicador bioquímico RDW e a baixa oferta de proteína foram associados com a mortalidade hospitalar. Sendo assim, recomenda-se a utilização do RDW na prática como triagem de maior risco de morte em pacientes cirúrgicos, bem como a maior vigilância nutricional do paciente não crítico em terapia nutricional enteral exclusiva realizando o balanço diário e evolução da dieta minimamente acima de 20kcal/kg/dia de calorias e de 0,8kg/kg/dia considerando que os pacientes tem maior chance de morte quando estes parâmetros estão inadequados.

Dois artigos foram desenvolvidos, o primeiro avaliando se o RDW poderia ser preditor de mortalidade hospitalar por todas as causas. Ao nosso conhecimento, foi o primeiro estudo com pacientes hospitalizados, observando os pacientes cirúrgicos e não cirúrgicos, que avaliou a associação entre o RDW e a mortalidade hospitalar por todas as causas, levando em consideração fatores de ajustes essenciais, baseado em modelo conceitual. O segundo artigo avaliando se a terapia nutricional enteral exclusiva, com oferta calórica e proteica menores que a recomendação poderiam também estar associado com a mortalidade hospitalar, ao nosso conhecimento, é o primeiro estudo a avaliar a oferta calórica e proteica e sua associação com a mortalidade em pacientes não críticos.

Nosso resultados sugerem que o indicador bioquímico RDW está associado com o maior risco de morte em pacientes cirúrgicos, recomendamos o uso do RDW como possível marcador de risco de mortalidade na prática clínica, em pacientes cirúrgicos. Além disso, a falha em atingir metas calóricas e proteicas durante a hospitalização aumentou o risco de morte. Protocolos devem ser implementados para garantir que os níveis calóricos e proteicos-alvo sejam atingidos o mais rápido possível, a fim de otimizar a sobrevida do paciente.

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