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ARÁN

Nutrición Hospitalaria

Trabajo Original

Valoración nutricional

Do nutritional assessment scores have a relationship with transthyretin levels?

¿Las puntuaciones de la evaluación nutricional tienen relación con los niveles de transtiretina?

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Abstract

Background and aims: nutritional screening tools assess factors like weight loss, BMI, food intake, and disease severity to determine a patient's nutritional risk and needed care. Plasma transthyretin is a practical measurement used to assess nutritional evolution due to its rapid response to food intake. This study examines the relationship between nutritional scores, transthyretin protein levels, and the possibility of death.

Methods: the sample consisted of 302 patients hospitalized in the wards or intensive care unit of a public teaching hospital, using parenteral nutrition as the primary source of nutrition. Five nutritional screening tools were applied, and patient charts were verified for transthyretin levels.

Results: from the sample, 260 were adults, and 42 were children, with a mean age of 48.3 years. When evaluating the patient's outcome in relation to the scores, the Malnutrition Universal Screening Tool proved to be better at predicting death (p-value = 0.02). None of the scores were related to transthyretin levels, showing that lower transthyretin values did not influence nutritional risk.

Conclusion: we believe early identification of nutritional risk through nutritional scores is necessary for better nutritional monitoring to minimize unfavorable outcomes. This study corroborates the more recent concept that transthyretin is not useful for determining unfavorable outcomes in hospitalized patients with a severe inflammatory process. In clinical practice, identifying a patient at nutritional risk according to the Malnutrition Universal Screening Tool and promoting adequate nutritional monitoring may reduce mortality.

Keywords:

Transthyretin. Nutrition assessment. Nutritional scores.

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Resumen

Antecedentes y objetivos: las herramientas de detección nutricional evalúan factores de riesgo como: pérdida de peso, índice de masa corporal, ingesta de alimentos y gravedad de la enfermedad. Así, estos factores establecen el riesgo nutricional del paciente y, en consecuencia, definen el nivel de atención requerido. Una medida práctica, con una vida media de 48-72 horas, es la transtiretina plasmática, que se ha utilizado para evaluar la evolución nutricional de los pacientes, debido a su rápida respuesta a la ingesta de alimentos. El objetivo de este estudio fue evaluar si los puntajes nutricionales están relacionados con los niveles de proteínas del paciente, en este caso evaluados por transtiretina y su asociación con la posibilidad de muerte.

Métodos: la muestra consistió en 302 pacientes hospitalizados en las salas o la unidad de cuidados intensivos de un hospital público docente, utilizando nutrición parenteral como fuente primaria de nutrición. Se aplicaron cinco herramientas de detección nutricional y se verificaron los registros de los pacientes para determinar los niveles de transtiretina.

Resultados: de la muestra, 260 eran adultos y 42 eran niños, con una edad media de 48,3 años. Al evaluar el resultado del paciente en relación con las puntuaciones, la Herramienta de detección universal de desnutrición demostró ser mejor para predecir la muerte (valor p = 0,02). Ninguna de las puntuaciones se relacionó con los niveles de transtiretina, lo que demuestra que los valores más bajos de transtiretina no influyeron en el riesgo nutricional.

Conclusión: creemos que la identificación temprana del riesgo nutricional a través de puntajes nutricionales es necesaria para un mejor seguimiento nutricional, con miras a minimizar los resultados desfavorables. Sobre todo, este estudio corrobora el concepto más reciente de que la transtiretina no es útil para determinar resultados desfavorables en pacientes hospitalizados con un proceso inflamatorio severo. Por lo tanto, identificar al paciente en riesgo nutricional según la Malnutrition Universal Screening Tool y promover un seguimiento nutricional adecuado puede reducir potencialmente la mortalidad.

Palabras clave:

Transtiretina. Evaluación nutricional. Puntajes nutricionales.

INTRODUCTION

Malnutrition will bring changes in body composition, damaging physical and mental functions and worsening the patient's clinical outcome. One of the greatest difficulties in nutritional assessment is performing it on hospitalized patients. Identifying nutritional risk early through nutritional scores is necessary for better nutritional monitoring, adequate nutritional action, and potentially reducing unfavorable outcomes in this population, especially critically ill patients (1).

Nutritional screening tools assess risk factors such as weight loss, Body Mass Index (BMI), low dietary intake, and severity of the underlying disease. These factors are necessary for establishing the patient's nutritional risk and, subsequently, defining the level of attention they will need (2). There are several scores proposed for this purpose, and the most used are the Malnutrition Universal Screening Tool (MUST), the Mini Nutritional Assessment (MNA), Nutrition Screening 2002 (NRS 2002), Nutrition Risk in the Critically Ill Score (NUTRIC Score), and Strong Kids — for pediatric patients.

The MUST evaluates three pillars for diagnosis: BMI, unintentional weight loss, and the effect of acute illness on nutritional intake.3 The MNA (Guigoz *et al.*, 1996) is a nutritional screening tool designed for older adults over 65 years old. It comprises 18 questions: weight loss, BMI, number of meals a day, mobility, presence of neurological disease, and even the older adults' perception of their health (4).

Another widely used tool in the hospital environment is the NRS 2002, which analyzes the severity of the patient's disease. It has been validated for use in all adult hospitalized patients, including older adults, as it considers an age greater than 70 years old relevant for nutritional risk. Nutritional intervention is then established according to the score obtained (5).

One of the greatest nutritional assessment difficulties is performing it on critically ill patients; therefore, the NUTRIC score was developed. The criteria for this tool are age, severity scores (The Acute Physiology and Chronic Health Evaluation II - APACHE II and The Sequential Organ Failure Assessment — SOFA), number of comorbidities, days of hospitalization before admission to the ICU, and interleukin-6 (IL-6) levels (if available) (6).

In children and adolescents, the Strong Kids tool can be used and is composed of objective questions, such as the presence of serious illness or major surgery, food intake, diarrhea or vomiting, and weight stability (7).

One biomarker that is very practical to measure due to its short half-life (48-72 hours) is plasma transthyretin (TTR). It has been used to assess the nutritional evolution of patients due to its rapid response to food intake. However, its applicability in relation to the prognosis of hospitalized patients has not been reported (8).

Considering that clinical nutritional evaluation and assessment are essential for the management of hospitalized patients and that death is undoubtedly an inverse outcome, the present study aimed to assess whether patients at nutritional risk classified according to nutritional scores would have lower levels of protein plasma levels, assessed by TTR levels and whether there were any associations with the possibility of death (9).

MATERIALS AND METHODS

STUDY DESIGN

A cross-sectional prospective study was developed. The total sample consisted of 338 patients, of which 36 were excluded due to not signing the Informed Consent Form (ICF), an ethical criterion indispensable for the development of studies involving human beings, leaving a total of 302 patients included in the study at a public teaching hospital, which is a quaternary care hospital. Data were collected in the first 72 hours after starting Parenteral Nutrition (PN). Specific studies in this population are essential because it is a frequently used type of nutrition among critically ill patients.

The use of PN as the primary source of nutrition was the criterion for inclusion in the sample. Not filling out the ICF by the patient or their legal guardian (in cases of unconscious and pediatric patients) was the exclusion criterion for this sample. Those under 18 years of age who could sign were asked to fill out an Assent Form.

ETHICAL ASPECTS

This study was approved by the Research Ethics Committee of the State University of Campinas under number 2.676.452.

ASSESSMENT OF NUTRITIONAL STATUS

Weight and height were used to calculate the BMI in adults, according to the World Health Organization (WHO) 2000 classification (10). Weight was measured using a Plena® digital scale with a maximum capacity of 150 kg, and height was measured with a vertical metal stadiometer ranging from 20 cm to 220 cm. When it was impossible to weigh or measure the patient, the data obtained from reading the medical records or from that reported by them or their family member were used. If a patient was older than six years and was restricted to bed, the height estimated by the formula of Chumlea *et al.* was employed, where the knee height (KH) in centimeters is used in the predetermined equations (11). For restricted children, those under six years of age, height/length was measured using a horizontal wooden stadiometer.

For children and adolescents, the WHO (2006 and 2007) curves were used to classify the nutritional status, where the Z-score values were adopted. The Z-score was calculated using the WHO Anthro and WHO Anthro plus software (12).

For the nutritional classification of older adults, those with a BMI between 23 and 28 kg/m^2 were considered eutrophic. Those below 23 kg/m^2 were considered malnourished, and those above 28 kg/m^2 were considered obese (13).

NUTRITIONAL RISK ASSESSMENT

To determine nutritional risk, the researchers applied nutritional screening tools, and the questions were directed to the patients themselves when they had health conditions to answer or to a family member if the patients were unconscious or were from the pediatric population. The screening tools were applied according to the target population, as described below:

In eligible patients, the following tools were applied:

– Adults: MUST (3), NRS 2002 (5).
– Critical adults: MUST, NRS 2002 and NUTRIC (6).
– Older adults: MUST, NRS 2002 and MNA (4).
– Critical older adults: MUST, NRS 2002, MNA and NUTRIC.
– Children: Strong Kids (14).

According to the answers given, each of these nutritional scores generates a nutritional risk classification, which are: low risk, moderate/medium risk, high risk.

LABORATORY EVALUATION

Laboratory tests were collected by health professionals responsible for the patient and sent to the Laboratory of Clinical Pathology at *Hospital de Clínicas* (HC), where the samples were processed according to the standards required for each test. To determine TTR levels, nephelometry was used. The reference value adopted as suitable for TTR was greater than 20 mg/dL, the HC standard (15).

STATISTICAL ANALYSIS

An evaluation of the normality of the sample variables was carried out to determine the tests that would be applicable. With this, it was established that the chi-square test or the Fisher's exact and Fisher-Freeman-Halton tests would be used when indicated to assess the association between two qualitative variables. Data were processed using the Statistical Package for the Social Sciences 16.0 software (SPSS Inc., Chicago, IL, USA). The significance level adopted was 5 %.

RESULTS

The sample consisted of 302 patients, 260 of whom were adults and 42 children, aged between 0.7 and 93.7 years, with a mean age of 48.3 years old; the characterization of the sample is described in table I. NRS 2002 presented the highest percentage of high nutritional risk, followed by MUST (Table II). When assessing the patient's outcome in relation to the scores, MUST proved to be better at predicting death, p-value = 0.02 (Table III). None of the scores were related to TTR, showing that lower TTR values did not influence nutritional risk (Table IV).

Table I. Characterization of the sample

Variables (n = 302)	Frequency	Percentage
Sex		
Female	116	38.4
Male	186	61.6
Age		
0 to 19 years	42	13.9
Above 19 years	260	86.1
Outcome		
Discharged	235	77.8
Death	67	22.2
Hospitalization unit		
ICU	96	31.8
Ward	206	68.2
Reason for PN referral		
GIT surgery	187	61.9
BMT	16	5.3
ILEO	99	32.8

GIT: gastrointestinal tract; BMT: bone marrow transplantation; ILEO: includes abdominal distention, metabolic disorders, and systemic infectious response syndrome.

Table II. Nutritional classification of the sample in relation to BMI and distribution of high nutritional risk according to NRS 2002, MUST, MNA for the older adults, NUTRIC, and Strong Kids

Variables	*n*	%
Nutritional status according to BMI		
Malnourished	82	27.7 %
Eutrophic	122	41.2 %
Overweight/Obese	92	31.1 %
Total	296	100 %
Nutritional classification scores – High risk		
NRS 2002 (*n* = 233)	208	89.3
MUST (*n* = 260)	189	72.7
NUTRIC (*n* = 50)	9	18
MNA (*n* = 51)	18	35.3
Strong Kids (*n* = 39)	28	71.8

NRS 2002: Nutrition Risk in the Critically Ill Score; MUST: Malnutrition Universal Screening Tool; NUTRIC: Nutrition Risk in the Critically ill Score; MNA: Mini Nutritional Assessment.

Table III. Outcome in relation to the NRS 2002, MUST, MNA of the older adults, NUTRIC, and Strong Kids scores

		Death (*n*/%)	Discharged (*n*/%)	*p*-value*
Nutritional risk				
MUST (*n* = 260)	High risk	54/28.6	135/71.4	*0.002*
	Intermediate risk	3/6.3	45/93.8	
	Low risk	3/13	20/87	
Nutritional risk				
NRS 2002 (*n* = 233)	Serious risk	46/22.1	162/77.9	0.809
	Moderate risk	5/20	20/80	
	Low risk	0	0	
Nutritional risk				
Strong Kids (*n* = 39)	High risk	4/14.3	24/85.7	1.0
	Intermediate risk	1/9.1	10/90.9	
Nutritional risk				
NUTRIC (*n* = 50)	High risk	3/33.3	6/66.7	0.429
	Low risk	10/24.4	31/75.6	
Nutritional risk				
MNA (*n* = 51)	Malnourished	9/50	9/50	0.188
	Risk of malnutrition	7/26.9	19/73.1	
	Normal nutritional status	1/14.3	6/85.7	

*NRS 2002: Nutrition Risk in the Critically ill Score; MUST: Malnutrition Universal Screening Tool; NUTRIC: Nutrition Risk in the Critically ill Score; MNA: Mini Nutritional Assessment. *Chi-squared test for probability.*

Table IV. Transthyretin level in relation to NRS 2002, MUST, MNA for the older adults, NUTRIC, and Strong Kids

	NRS 2002		**Moderate risk**	**Serious risk**		**Total**	***p*-value**
Transthyretin	Adequate	*n* %	0 0.0 %	12 100 %		12 100 %	
	Inadequate	*n* %	16 12.2 %	115 87.8 %		131 100 %	
	Total	*n* %	16 11.2 %	127 88.8 %		143 100 %	0.361*
	MUST		**Low risk**	**Intermediate risk**	**High risk**	**Total**	
Transthyretin	Adequate	*n* %	1 6.3 %	2 12.5 %	13 81.3 %	16 100 %	
	Inadequate	*n* %	11 7.5 %	28 19.2 %	107 73.3 %	146 100 %	
	Total	*n* %	12 7.4 %	30 18.5 %	120 74.2 %	162 100 %	0.896†
	MNA		**Normal**	**Risk of malnutrition**	**Malnourished**	**Total**	
Transthyretin	Adequate	*n* %	0 0.0 %	0 0.0 %	0 0.0 %	0 0,0 %	
	Inadequate	*n* %	3 10 %	15 50 %	12 40 %	30 100 %	
	Total	*n* %	3 10 %	15 50 %	12 40 %	30 100 %	NA
	NUTRIC		**High risk**	**Low risk**		**Total**	
Transthyretin	Adequate	*n* %	0 0.0 %	2 100 %		2 100 %	
	Inadequate	*n* %	6 21.4 %	22 78.6 %		28 100 %	
	Total	*n* %	6 20 %	24 80 %		30 100 %	1.00*
	Strong Kids		**High risk**	**Intermediate risk**		**Total**	
Transthyretin	Adequate	*n* %	2 100 %	0 0.0 %		2 100 %	
	Inadequate	*n* %	14 63.6 %	8 36.4 %		22 100 %	
	Total	*n* %	16 66.7 %	8 33.3 %		24 100 %	0.540*

**Fisher's exact test bilateral probability; †Fisher-Freeman-Halton exact test bilateral probability. NA: not applicable statistical test.*
NRS 2002: Nutrition Risk in the Critically Ill Score; MUST: Malnutrition Universal Screening Tool; NUTRIC: Nutrition Risk in the Critically ill Score; MNA: Mini Nutritional Assessment.

DISCUSSION

Although the scores are not intended to define outcomes, it was observed that those with a higher nutritional risk, according to the MUST, had a higher risk of death (*p*-value = 0.002). Another observation of the present study is that no relationship was identified between TTR levels and nutritional risk. This corroborates new evidence that TTR does not reflect the nutritional status of individuals suffering from an acute inflammatory process (16). This is the reality of many hospitalized patients, especially those needing PN.

The MUST was observed to be more useful in predicting death than the NRS 2002. Rabito *et al.* showed that the risk ratio for mortality was 2.34 times higher in patients classified as at nutritional risk, according to the MUST. Some differences were observed between the MUST and NRS 2002 tools in relation to nutritional risk classification, and can be explained by the lower BMI cutoff point in the MUST

compared to the NRS 2002 (19). Gomes-Neto *et al.* also found an association between high nutritional risk according to MUST and higher mortality, even after adjustments for age, sex, ward, and hospitalization in the six months before baseline ($p = 0.02$) (20).

Vries *et al.,* in their study, identified that NUTRIC was useful in predicting the mortality of patients within 28 days of hospitalization and was superior to MUST when compared (17). As for Strong Kids, NUTRIC, and MNA, the sample was probably too small to determine any difference.

Of the adult assessment scores, MUST is an effective tool for nutritional screening of the patient by identifying weight loss and low food intake. A recent study (N = 430) found that among patients with a BMI ≥ 25 kg/m^2, only 5 % were classified as at nutritional risk according to MUST versus 36 % according to the Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) score. This difference occurred because the PG-SGA SF also considers the functionality of the gastrointestinal tract (nausea, dysphagia, and diarrhea). Therefore, a more comprehensive evaluation of the patient is necessary to consider different criteria aiming at the best nutritional diagnosis (18).

On the other hand, Liu *et al.*, in patients with COVID-19, when comparing the various nutritional assessment scores — NRS 2002, MNA, Nutrition Risk Index (NRI), and MUST — observed that the only score not identified as a good predictor of prognosis was the MUST. The authors attributed this finding to the fact that the cardinal points of MUST are BMI, unintentional weight loss, and acute disease state, unlike other tools that consider other aspects. Another critical issue was that all the patients included in the study were in severe conditions, which already classified them as having high nutritional risk, according to MUST. Patients classified as having a higher nutritional risk were also observed to have significantly worse clinical outcomes (21).

The NRS 2002 considers weight loss, food intake, BMI, age, and disease severity as criteria for nutritional risk. Luca *et al.* evaluated which of the score components had the most significant influence on mortality and length of stay, that is, the part related to nutrition or the severity of the disease. Findings show that of the 21,855 patients evaluated, both aspects of nutrition and severity were associated with more extended hospital stays and higher odds of all-cause mortality. However, nutrition had a greater impact on length of stay, while severity had a greater association with mortality. Therefore, the potentially modifiable aspect, nutritional aspects, should be addressed since they can influence shorter hospital stays and mortality (22).

In a study that evaluated the use of the NRS 2002 and the implementation of a standardized nutritional policy in hospitalized patients - with surgical sepsis, the length of hospital stay decreased by 17 days compared to the period before the study. However, it is noteworthy that the NRS 2002 is not as sensitive when the patient has chronic malnutrition, where weight loss and decreased food intake have been gradual over several years of the disease (23).

Zhao *et al.* observed in patients infected with SARS-CoV-2 that those with higher scores according to the NRS 2002 score were hospitalized for longer periods and died more. In logistic regression models, for each increase of 1 unit in the NRS 2002 score, there was a 1.23-fold increase in mortality (p-value = 0.026). COVID-19 caused a critical inflammatory state in patients, with changes in procalcitonin, interleukins, CRP, albumin, and TTR. In this case, low levels of TTR correlated negatively with NRS 2002, suggesting the use of TTR as a valuable nutritional marker. Patients at higher nutritional risk benefited from early nutritional therapy (24).

It is noteworthy that once the inflammatory status of critical patients returned to normal, TTR values tended to increase again; however, this is not necessarily associated with nutrition. Adjusting the nutritional offer in this group can reduce oxidative stress and improve the immune response, which could promote their recovery from the clinical situation, but no direct association has been established (16).

Although some authors use TTR as a prognostic marker, our findings indicate its use was ineffective for this purpose. In their systematic review (n = 2104), Akbar *et al.* showed that lower TTR values were associated with worsening of the clinical picture (mortality, ICU admission, or use of mechanical ventilation) in patients with COVID-19. For each 1 mg/dL reduction of TTR, there was a 1 % increase in clinical worsening (OR: 0.992 [0.987, 0.997], $p = 0.004$, I^2: 81.70 %). It is known that in COVID-19, the inflammatory cascade is intensely activated, which causes the disease to worsen. The increase in the release of inflammatory cytokines decreases the production of TTR, and its increase can be used as a negative marker in these patients. The authors corroborated that TTR could be a modest predictor of prognosis in patients with COVID-19. This way, using TTR could be associated with other laboratory parameters to increase its performance (25).

Nutritional risk was high in the population of the present study, which is expected since these are critically ill patients. Maintaining and/or recovering nutritional status is essential for hospitalized patients. Chada *et al.* point out that patients who received inadequate energy and protein supply had higher mortality in 28 days when compared to those with adequate supply. It is clear that a proper nutritional intake, i.e. > 80 % supply of dietary needs, can reduce the length of hospital stay and reduce mortality in patients at high or low nutritional risk (26).

Most evaluated children were classified as high nutritional risk according to the Strong Kids score, and none at low risk. Similar findings were identified in the study by Shaaban *et al.*, where 80.4 % of children < 3 years old were classified as having moderate or severe nutritional risk. It was also observed that those with the worst Strong Kids classification scores had worsened clinical status and longer hospital stays, suggesting that this tool could predict outcomes. Identifying the nutritional risk in children is essential to improve nutritional strategies to prevent and/or treat malnutrition, thus reducing the length of hospital stay and unfavorable outcomes (27).

One limitation of this study was that applying all the score criteria to the entire sample was not always possible. However, this was only the case for a small portion of the sample, so it did not influence the study's general findings. Another point of limitation

is that this study was carried out in a teaching hospital and may not represent the reality of all public hospitals in the country.

CONCLUSION

We believe that early identification of nutritional risk through nutritional scores is necessary for better nutritional monitoring, adequate nutritional action, and, potentially, to minimize the unfavorable outcomes in this population. Above all, this study corroborates the recent concept that TTR is not useful for determining unfavorable outcomes in hospitalized patients with a severe inflammatory process. Furthermore, we identified the MUST score as a valuable tool in predicting the outcome of death among these patients. Therefore, promoting the recovery of nutritional status can potentially reduce mortality. More studies in this area are needed, interventional studies where strategies to promote the recovery of the nutritional status are carried out, and the follow-up of the nutritional score and TTR values, verifying if there is a direct association between them after an intervention period.

Furthermore, when evaluating the score data, the MUST was useful in predicting mortality; however, we believe a multicenter study is welcome to corroborate this conclusion.

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