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Trabajo Original

Paciente crítico

Prognostic value of severity by various visceral proteins in critically ill patients with SIRS during 7 days of stay

Pronóstico de gravedad mediante niveles de proteínas viscerales en paciente crítico con SIRS

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Abstract

Introduction: Critically ill patients typically develop a catabolic stress state as a result of a systemic inflammatory response (SIRS) that alters clinical-nutritional biomarkers, increasing energy demands and nutritional requirements.

Objective: To evaluate the status of albumin, prealbumin and transferrin in critically ill patients and the association between these clinical-nutritional parameters with the severity during a seven day stay in intensive care unit (ICU).

Method: Multicenter, prospective, observational and analytical follow-up study. A total of 115 subjects in critical condition were included in this study. Clinical and nutritional parameters and severity were monitored at admission and at the seventh day of the ICU stay.

Results: A significant decrease in APACHE II and SOFA ($p < 0.05$) throughout the evolution of critically ill patients in ICU. In general, patients showed an alteration of most of the parameters analyzed. The status of albumin, prealbumin and transferrin were below reference levels both at admission and the 7th day in ICU. A high percentage of patients presented an unbalanced status of albumin (71.3%), prealbumin (84.3%) and transferrin (69.0%). At admission, 27% to 47% of patients with altered protein parameters had APACHE II above 18. The number of patients with altered protein parameters and APACHE II below 18 were significantly higher than severe ones throughout the ICU stay ($p < 0.01$). Regarding the multivariate analysis, low prealbumin status was the best predictor of severity critical ($p < 0.05$) both at admission and 7th day of the ICU stay.

Conclusion: The results of the present study support the idea of including low prealbumin status as a severity predictor in APACHE II scale, due to the association found between severity and poor status of prealbumin.

Key words:

Critically ill. SIRS. APACHE. Protein metabolism. Prealbumin. Transferrin.

Resumen

Antecedentes: los pacientes críticos suelen desarrollar un estado de estrés catabólico que se traduce en una respuesta inflamatoria sistémica (RIS) que altera los biomarcadores clínico-nutricionales, aumentando las necesidades de nutrientes y de energía.

Objetivo: evaluar el estatus de albúmina, prealbúmina y transferrina en pacientes críticamente enfermos y la asociación entre estos parámetros clínico-nutricionales con la severidad del paciente durante siete días de estancia en la unidad de cuidados intensivos (UCI).

Método: estudio multicéntrico, de seguimiento, prospectivo, observacional y analítico. Un total de 115 sujetos en estado crítico fueron incluidos en el estudio. Los parámetros clínico-nutricionales y la gravedad clínica fueron controlados al ingreso y al séptimo día de estancia en UCI.

Resultados: una disminución significativa en la gravedad del paciente ($p < 0.05$) fue registrada a lo largo de la evolución de la estancia en la UCI. En general, los pacientes mostraron una alteración de la mayoría de los parámetros analizados. El estatus de albúmina, prealbúmina y transferrina se situaron por debajo de los niveles de referencia tanto en la admisión como a los 7 días en UCI. Un alto porcentaje de pacientes presentó una alteración de los niveles de albúmina (71.3%), prealbúmina (84.3%) y transferrina (69.0%). Al ingreso, entre el 27 y 47 por ciento de pacientes con parámetros proteicos alterados presentaron un APACHE II por encima de 18. Los pacientes con parámetros proteicos alterados y APACHE II por debajo de 18 fueron significativamente más altos que los más graves y aumentaron a lo largo de la estancia en UCI ($p < 0.01$). En cuanto al análisis multivariado, niveles bajos de prealbúmina fueron el mejor predictor de severidad crítica ($p < 0.05$) tanto en la admisión como a los 7 días de estancia en la UCI.

Conclusión: los resultados del presente estudio apoyan la idea de incluir la prealbúmina como predictor de la gravedad dentro de la escala APACHE II debido a la asociación encontrada entre la gravedad y un estatus pobre de prealbúmina.

Palabras clave:

Paciente crítico. SIRS. APACHE. Metabolismo proteico. Prealbúmina. Transferrina.

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INTRODUCTION

Assessment of nutritional status in the critically ill continues to be discussed in the literature. There is still a lack of consensus, and no accessible "gold" standard to quantify protein energy malnutrition (1). Once a patient is admitted into the intensive care unit, monitoring of nutritional status becomes important, and this issue has not received as much attention in the critically ill. None of the commonly used nutrition monitoring parameters demonstrated consistent associations with outcome in randomized controlled trials and the development of nutrition indicators, more closely linked to the patient's clinical progress, should be a priority (2). Critically ill patients are typically submitted to develop a catabolic stress state, which results in a systemic inflammatory response. The relative importance of cardiogenic shock, hemodynamic alterations due to sepsis, and catabolic responses, varies according to their initial condition and their responses to treatment (3,4). Either due to gravity, duration of the attack, and the specific conditions of the patient, the inflammatory response is not limited to the injured point, and leads to a number of systemic syndromes such as SIRS (5). In fact, inflammation starts with a quick release of inflammation mediators leading to a multiple organ dysfunction, presenting unfavourable prognosis (6,7). Then, the interaction between nutritional status and critical illness becomes increasingly evident and the impact of nutritional strategies on clinical outcomes, is an area of ongoing research (8). Given the stress condition, the increased metabolic rate, energy expenditure and the increased protein catabolism, could lead to a negative nitrogen balance and high nutritional needs. Hence, protein catabolism is directly associated with elevated metabolic rate (9), related increased mortality rates and the period of time spent in an ICU stay (10). Therefore, the metabolism is not only affected by acute stress and inflammation but also by the nutritional status and comorbidities, the acute disease, and the phase of the acute disease.

Malnutrition is always a strong predictor of unfavourable outcomes, particularly during critical illness (5,11). Nutrition parameters are also used in critical care settings as prealbumin or albumin (12,13). The efficacy of nutritional care needs monitoring, to provide an early indication that patient's requirements are being adequately met. Moreover, variables such as weight change, nitrogen balance, protein turnover measurement, bioelectrical impedance and DXA are too constraining, not sensitive enough and/or too invasive to be used (1). Thus for this purpose, there is a need for a sensitive marker with a short half-life on a day-to-day basis. Prealbumin, with an average life of two days and a carrier protein, thyroxin which depends on the contributions of energy and amino acid, have been proposed as nutritional parameters influenced by inflammatory mediators, acting as biomarkers of inflammation rather than as nutritional parameters (13). During inflammation, mediators released induce hepatic synthesis and rapid elevation of acute phase reactant proteins with decreased synthesis of proteins of short half-life, such as prealbumin. Low prealbumin levels have been documented in both survivors and non-survivors of critical illness being correlated with CRP ratio, severity of disease and mortality (13,14). Albumin is a good nutritional marker that presents a drop in SIRS to hemodynamic changes, increased vascular permeability and to their lower hepatic synthesis. Also, several studies documented an association with higher prealbumin levels and better outcomes in critically ill patients (15).

Because biochemical markers of nutritional status, such as prealbumin and albumin may be unreliable in the setting of critical illness due to confounding effects of disease, inflammation and therapies (16,17), the prognostic value of these two proteins are not still clear. A recent review (2) on outcome prediction by nutrition indicators in the critically ill, reported an association between improved outcome and higher serum prealbumin levels when measured in the ICU on days between 3, 5, 7, or 14. Therefore, nutritional assessment is required in critical care patient during the ICU stay, especially regarding the protein sensible metabolites as prealbumin which needs important attention in that stressing acute situation (18-20). Our aim was to control the changes that occur in the clinical and nutritional parameters, especially albumin, prealbumin and transferrin, and its association with severity during the ICU stay in patients with SIRS.

MATERIAL AND METHODS

STUDY DESIGN

The study design is based on a multicenter, prospective, observational and analytical follow-up study performed in critically ill patients from admission to seventh day in the ICU in different hospitals in southern Spain (Virgen de las Nieves, San Cecilio, General of Baza and Santa Ana de Motril, from Granada). The study was conducted in accordance with the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonization and Good Clinical Practice Standards. Informed consent was obtained from patients or their legal relatives who agreed to participate in the study taking into account the approval of the Ethics Committee and the Committee Research Center.

STUDY POPULATION

A total of 115 subjects in critical condition were included in this study. Critically ill patients inclusion criteria were: to be admitted to the ICU and over 18 years of age; to present a positive SIRS and APACHE II (acute physiology and chronic health evaluation) severity score ≥ 15 points; to have an artificial nutritional support (enteral, parenteral or mixed enteral and parenteral nutrition); not to present neurological, muscle or bone diseases; and to continue in the ICU for at least 7 days. The biochemical, protein, clinical-nutritional and inflammation profile were determined at baseline and on the seventh day of the ICU stay. The scales of severity assessment in critically ill patients SOFA (sequential organ failure assessment) and APACHE II were obtained at admission and at the seventh day in the ICU. Exclusion criteria were: non-acceptance of the patient or their legal representatives to participate in the

study; pregnancy; to present with a highly contagious disease, allergies, Cancer or HIV; food orally ingested before getting blood sample at admission.

NUTRITIONAL ASSESSMENT

Critically ill patient's blood collections were collected by qualified and authorized personnel. The extraction was carried out after fasting in the morning, by vacuum tubes (Venoject). Samples were collected according to hospital protocol, whilst avoiding any extraordinary invasion. Blood samples were taken in ICU patients by venepuncture after hemodynamic stabilization phase at admission and after 7 days of the ICU stay. Biochemical parameters analysed were: total protein, albumin, creatinine, uric acid, triglycerides, lipoprotein (HDL, LDL) cholesterol and the enzyme profile was carried out by the hospital laboratory using standard techniques. Nutritional clinical parameters (albumin, prealbumin), protein (total protein, bilirubin, and uric acid) and inflammation parameters (CRP) were determined by immunoassay colorimetric techniques following quality control and established procedures.

STATISTICAL ANALYSIS

Data was analysed using SPSS statistical software (version 22.0, SPSS Inc., Chicago, USA). Descriptive data was presented as mean (standard deviation) and [percentage of subjects below reference]. Categorical variables were expressed as subjects' frequency percentage. The paired t-student test was used to evaluate the evolutive biological changes throughout the evolution of ICU patients. Pearson bivariate correlation (r) was performed to evaluate the association between protein and clinical-nutritional parameters with the severity in critically ill patients, both at admission and the seventh day of ICU stay. Multiple linear regressions were performed to assess the influence of clinical-nutritional low levels with the severity in critical condition at baseline and on the seventh day of the ICU stay. To evaluate the model goodness Hosmer-Lemeshow test was used.

RESULTS

The general characteristics of the sample are shown in table I. Critically ill patients (n = 115) had a mean age 61.5 (SD 12.7), where 37% were male patients and 78% female patients. All patients had an average stay of 7 days in the ICU. The distribution of the sample corresponding to critically ill patients in different ICUs was 86% from the Virgen de las Nieves, 6% of San Cecilio, 2% General (Baza) and 6% of Santa Ana (Motril). 23.5% of the samples were being treated for lung disorders, 35.7% were receiving treatment for cardiovascular and abdominal disorders, and 5.2% related to other causes. In order to assess the critical situation, the use of APACHE II and SOFA scales, it is essential to precisely adjust the severity of patients and to see to what extent it affects the clinical nutritional status. The comparative analysis of the evolution of critically ill patients throughout the ICU stay showed a significant decrease in APACHE II and SOFA ($p<0.05$) score.

Table II shows the biochemical parameters, clinical-nutritional, inflammation and cardiovascular in critically ill patients throughout evolution during the ICU stay. Critically ill patients showed an alteration of most of the parameters analyzed by the reference values, at the beginning and throughout the ICU stay. Mainly, the status of albumin, prealbumin and transferrin were below reference levels both at admission and on the 7th days in ICU. Regarding the evolution of critically ill patients during the ICU stay, significant differences ($p < 0.05$) were observed in parameters of renal function (creatinine and uric acid), liver enzymes (AST, ALT and GGT), lipid metabolism (total cholesterol and its fractions), inflammation (CRP), and minerals such as iron. Analyzing the percentage of patients with unbalanced status and regarding the parameters evaluated at the beginning of the ICU stay, a high percentage of patients had low levels of nutritional protein markers such as albumin (71.3%) or prealbumin (84.3%), and markers of anemia and iron metabolism, such as transferrin (69.0%) and seric iron (87.3%).

Figure 1 shows the relationship between the severity of critically ill patients represented by APACHE II and alterations of clinical nutritional protein parameters (albumin, prealbumin and transferrin). According to our results at admission, patients with altered protein parameters and higher severity (APACHE II above 18) showed no significant changes compared to 7th day in ICU stay. The percentage of subjects who had an alteration of these parameters was between 27-47%. On the contrary, patients with altered protein parameters and lower severity (APACHE II < 18) were significantly higher than both, the most severe ($p < 0.01$) and

Table I. General characteristics of the sample

Characteristics	Critical ill (n = 115)	
Age (y)	61.5 (12.7)	
Gender (Female/Male)	37/78	
Diagnostic (%)		
Respiratory (SDRA)	23.5%	
Cardiovascular (IAM)	35.7%	
Abdominal	35.7%	
Others	5.2%	
	Day 0	*Day 7*
APACHE II	21.6 (5.07)	12.6 (3.13)*
SOFA	8.92 (2.76)	6.12 (2.62)*

*n = number of subjects; *Statistically significant differences critical day 0 vs. critical on 7 $p < 0.05$; APACHE: Acute Physiology and Chronic Health disease Classification System; SOFA: Sequential Organ Failure Assessment; ARDS: acute respiratory distress syndrome; AMI: Acute myocardial infarction.*

throughout the ICU stay (from 5-79% and 37-79%, respectively).

The relationship between severity and clinical-nutritional parameters was explored to determine how unbalanced protein status could be described by critically ill patient's severity at admission and after seven days in ICU stay (Table III). In the bivariate analysis, prealbumin and transferrin below reference, were associated with the severity at admission ($p < 0.05$). However, no significant association were found at the 7th day in ICU stay. In order to explore the association between clinical-nutritional parameters and severity, multivariate regression was performed. Prealbumin and transferrin showed to be significantly associated with the severity in critical condition ($p < 0.05$), both at admission and 7th days in ICU stay. No significant association was described between albumin and severity.

DISCUSSION

The main findings of the present study support the idea that severity scales currently used do not reflect the reality of clinical-nutritional status of the patient. The evolution throughout ICU stay, resulted in an increase on the percentage of patients with altered protein levels, despite them presenting a lower severity score. These were significantly more than patients with a worse severity. In addition, the utility of clinical-nutritional proteins as biomarkers to adjust the severity in a critically ill condition might help to adjust with accuracy the severity of patients. In our study, low prealbumin status was associated with the severity as APACHE II score and represented to be the best clinical nutritional-parameter predictor of severity.

Table II. Evaluation of biochemical, clinical-nutritional and micronutrient status in critically ill patients during ICU stay

Biochemical parameters	Critical ill patients Mean (SD) [Percentage of subjects below reference values]		
	Day 0	Day 7	Reference
Glucose (mg/dL)	166.1 (78.1) [4.5]	160.8 (53.9)	70-110
Urea (mg/dL)	91.7 (56.6)	97.8 (77.7) [2.4]	10-40
Creatinine (mg/dL)	2.1 (1.80) [6.4]	1.60 (1.43) [13.1]*	0.5-1.3
Uric acid (mg/dL)	5.23 (2.80) [23.8]	4.13 (2.80) [47.4]*	3.0-7.0
AST (U/l)	280.2 (527.6)	61.3 (99.2)*	0-40
ALT (U/l)	122.0 (286.0)	56.8 (127.3)*	0-40
GGT (U/l)	60.4 (63.0) [6.8]	165.3 (154.1) [2]*	10-41
Bilirubin (mg/dL)	1.31 (1.66)	0.96 (0.79)	0-1.0
Alkaline phosphatase (U/l)	95.6 (70.8) [14.4]	123.2 (65.8)*	40-190
CRP (mg/dL)	19.5 (13.6)	13.1 (10.5)*	< 1
Total proteins (mg/dL)	5.13 (1.02) [85.3]	6.07 (7.22) [88.1]	6.0-8.0
Albumin (g/dL)	2.80 (0.63) [71.3]	2.70 (0.62) [67.6]	3.0-5.0
Prealbumin (mg/dL)	12.8 (8.68) [84.3]	14.3 (7.65) [77.3]	19.5-35.8
Iron (mg/dL)	31.5 (33.4) [87.3]	39.9 (32.5) [79.7]*	60- 180
Ferritin (ng/dL)	541.0 (713.0)	450.1 (465.7)	20-250
Transferrin (mg/dL)	135.5 (58.2) [69.0]	133.2 (56.5) [72.5]	170-370
Total cholesterol (mg/dL)	108.5 (38.2) [51]	134.8 (43.7) [27.3]*	110-200
HDL cholesterol (mg/dL)	20.9 (12.7) [84.7]	19.6 (10.7) [96.6]	40-60
LDL cholesterol (mg/dL)	41.0 (24.4) [80.2]	71.6 (46.8) [58.6]*	70-150
Triglycerides (mg/dL)	196.8 (144.3) [5.9]	197.7 (102.0)	50-200
CPK (U/l)	715.5 (1166)	113.3 (162.8)*	0-130
LDH (U/l)	1131 (1651)	710.2 (553.2)*	130-500
Homocysteine (µmol/L)	13.5 (9.90) [14.8]	14.2 (12.0) [15.2]	5.0-15.0
B vitamins			
Folate (ng/mL)	8.11 (4.58)	8.33 (4.63)	2.7-17.0
Cobalamine (pg/mL)	980.0 (672.0)	969.6 (628.3) [5.3]	200-900

*Values are expressed as mean (standard deviation); * = significant differences ($p < 0.05$) in critical ill patient day 0 vs. day 7; [ ] = Percentage of subjects below reference values.*

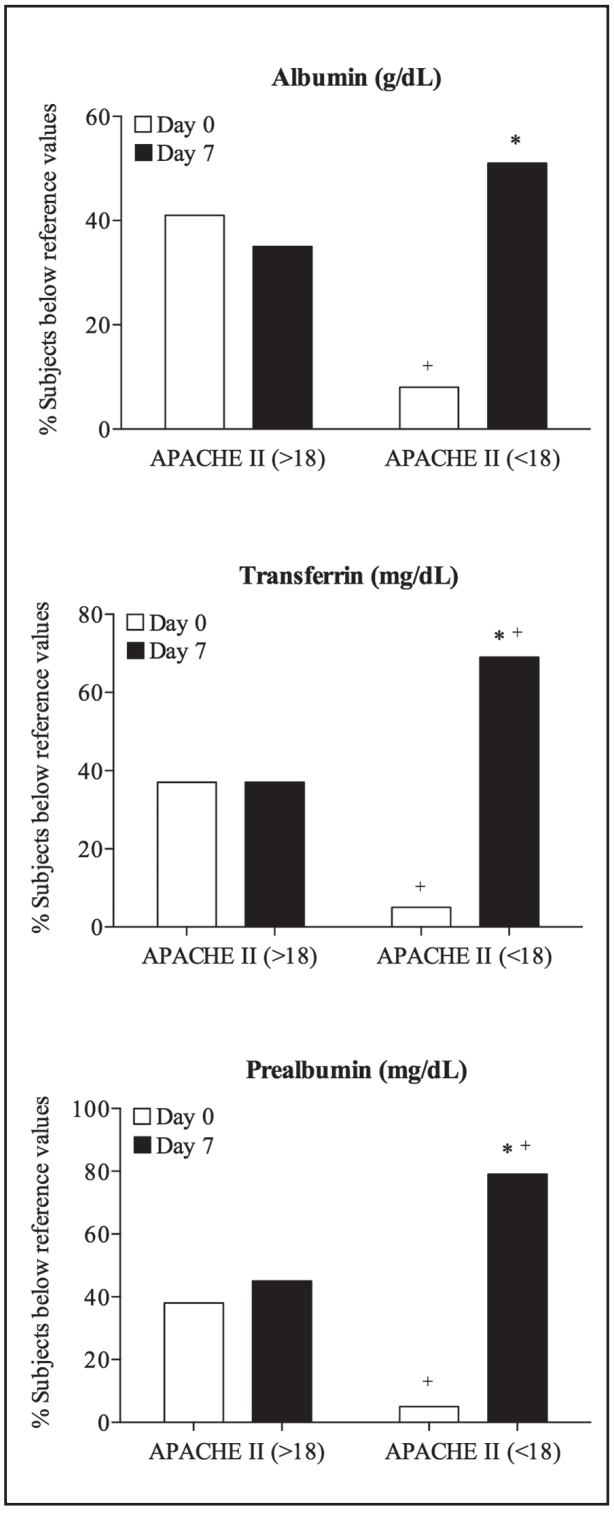

Figure 1.

Relationship between the severity of critically ill patients represented as APACHE II and SOFA, and alteration of clinical-nutritional an proteic parameters at admission and during ICU stay. The APACHE II and SOFA scales were dichotomized according to the median (APACHE II < 18 and ≥ 18; SOFA < 8.5 and ≥ 8.5). Both protein and nutritional clinical parameters were dichotomized as reference values. * = statistically significant changes between day 0 vs. day 7; + = statistically significant changes between APACHE II (> 18) vs. APACHE II (< 18).

Table III. Factors associated to severity in critical ill patient (APACHE II) in multivariate analysis at admission and 7th days in ICU stay (n = 115)

		Factors related to severity in critical ill patient (APACHE II)		
		Adjusted regression coefficient B_1	p value	Adjusted R^2
Day 0				
Model 1				
Prealbumin (mg/dL)	Below reference	-0.555	0.005	13.7
	Normal	Reference	-	-
Model 2				
Prealbumin (mg/dL)	Below reference	-0.407	0.043	18.3
	Normal	Reference	-	
Transferrin (mg/dL)	-	-0-031	0.050	
Model 3				
Prealbumin (mg/dL)	Below reference	-0.391	0.043	17.9
	Normal	Reference	-	
Transferrin (mg/dL)	-	-0.029	0.050	
Albumin (g/dL)	-	-0.892	0.786	
Day 7				
Model 1				
Prealbumin (mg/dL)	Below reference	-0.156	0.526	1.40
	Normal	Reference	-	-
Model 2				
Prealbumin (mg/dL)	Below reference	-0.163	0.515	3.70
	Normal	Reference	-	
Transferrin (mg/dL)	-	-0.300	0.805	
Model 3				
Prealbumin (mg/dL)	Below reference	-0.477	0.049	8.10
	Normal	Reference	-	
Transferrin (mg/dL)	-	-0.049	0.016	
Albumin (g/dL)	-	-1.258	0.300	

In the absence of clinical-nutritional parameters within the severity scales in the critical patient, we aimed to evaluate the direct relationship between protein status in critically ill patients according their severity and clinical-nutritional outcomes. In a critical condition, this can lead to complications which would be more pronounced due to accelerated proteolysis and inadequate nutritional support, which could compromise their health and survival (21,22). Compared to reference values for healthy people, our critically ill patients showed an alteration of parameters studied, due to protein metabolic disorders derived from the acute inflammatory situation (SIRS) and possibly from the sepsis, worsening overall during the ICU stay.

Malnutrition, characterized by a poor nutritional status and a protein hyper-catabolism was found to be a common situation in patients hospitalized at admission (23), and after a week in ICU (24). In our study, a high percentage of patients presented values below reference in nutritional markers such as albumin (71.3%) or prealbumin (84.3%), and markers of anemia and iron metabolism, such as transferrin (69.0%) and seric iron (87.3%). In 2015, a 2-week study in critically ill patients with a neurological injuries, nutritional and non-nutritional factors were identified to be related with the metabolic response and protein catabolism (25).

Under stress conditions, the alteration of protein metabolism is reflected by an increase in acute phase protein, oxidation of amino acids, and nitrogen losses (26). Several studies (27,28) used APACHE II and SOFA scales of gravity in order to evaluate the clinical situation and predict hospital mortality. In our study, these scales have been linked with clinical-nutritional parameters, finding significant associations between APACHE II and the percentage of subjects with prealbumin, albumin and transferrin values below reference (27-47%) (Fig. 1). It is evident that patients need nutritional monitoring to optimize their care during an ICU stay (20). In our study, at seventh day of admission, we observed that the percentage of patients with protein alteration was significantly higher when they presented less severity. The percentage of patients who presented APACHE II above 18, drastically decreased not exceeding 8% of patients, whereas when the APACHE II was below median, the percentage of subjects with impaired protein and clinical and nutritional parameters, increased to 62.8% (46-79%). For this reason, the main results of our study show that the tool currently used to assess the severity of the patient (APACHE II), does not include nutritional biomarkers that would be useful for a full and accurate assessment and which were a real predictor of the severity of the critical care patient, given the close relationship between the severity and the patient's nutritional status. Our results showed that the percentage of patients with lower APACHE II and altered clinical-nutritional parameters (such as prealbumin, transferrin and albumin), increased during their ICU stay. However, those with greater APACHE II evolve positively thus decreasing the percentage of patients showing altered levels of these parameters (Fig. 1).

The deficit of nutrients is directly associated with mortality (12). In this sense, in addition to albumin, both prealbumin and transferrin, play an important role and are most commonly used parameters to assess the nutritional status of critically ill patients. In our study, the multivariate analysis showed that critical patients who had plasma prealbumin below the reference, presented a better predictor in relation to severity at admission and 7th days in ICU stay. Zhang et al. (29) showed that the APACHE had moderate predictive value but not complete enough to determine hospital mortality among adults with acute lung injury associated with sepsis. In our study, the parameter prealbumin was the best predictor demonstrated in the patient's progress. The percentage of patients with lower APACHE II worsened significantly more than those with higher APACHE II. Given that prealbumin is not included as an item in the scale of APACHE II, it seems not be an optimal way to measure the real severity of the patient's condition.

Our observed changes during ICU stay, mostly in prealbumin levels, predicted the gravity of critical patients measured by APACHE II scale. As previously mentioned, prealbumin is not currently present on the scale as a nutritional biomarker directly associated with severity status. According to the results, APACHE II scale, as it is raised, could be a more useful tool if it included prealbumin levels. This will improve the more realistic view of the severity of the patient where prealbumin was the best predictor of severity, and its assessment throughout ICU would be more effective in terms of sensitivity and specificity, without prejudice to the agility of measurement.

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