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Individual prognostic assessment in the intensive care unit: can therapeutic persistence be distinguished from therapeutic obstinacy?

Avaliação prognóstica individual na UTI: é possível diferenciar insistência terapêutica de obstinação terapêutica?

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ABSTRACT

Objectives: Availability of state-of-the-art technology at intensive care units has often turned into a tool aggravating suffering by prolonging the end-of-life process. Distinguishing therapeutic persistence from therapeutic obstinacy has become a great challenge for present-day medicine. The aim of this study was to assess the benefit-harm relation in the use of life-sustaining therapies by means of an evolutionary system of individual prognostic assessment.

Methods: A cohort, prospective, observational study at the intensive care unit of the São Francisco De Paula University Hospital of UCPel, Pelotas RS from March 2006 to August 31, 2007. Individual prognostic assessments were recorded by using an evolutionary system, the UNICAMP II index, associated with albumin transferrin and lymphocytes serum levels, life- sustaining therapies and the outcome. Statistical analysis was carried out by the Student's t-test, ANOVA test, Chi-square test, Fisher's exact test, Spearman's correlation test and area under the receiver-operating characteristic curve. A p value < 0.05 was considered statistically significant.

Results: Four hundred forty seven patients were assessed during the study. Prevalence of death was significantly higher among those who received life-sustaining therapies at a later stage of the intervention, and those whose prognostic index and nutritional status worsened at an early stage of intervention.

Conclusion: Assessment of individual evolutionary prognostic proved to be a useful method to objectively subsidize ethical decisions related to therapeutic persistence and therapeutic obstinacy.

Keywords: Intensive care units; Medical ethics; Palliative care/ethics; Right to die

INTRODUCTION

In today's medical context, especially regarding intensive care units (ICU), stage-of-the-art technology available has not always achieved a better quality of life for patients. Often, the capability to prolong time of life of these persons has become an instrument that potentializes pain, suffering and prolongs the end-of-life. Patients admitted to the ICU due to severity of their pathology, present limitations in their capacity to take decisions. Sometimes they become vulnerable to therapeutic applications that go beyond the possible recovery of the clinical condition becoming a therapeutic obstacle. According to Elio Sgreccia, therapeutic obstinacy

takes place when: a) treatment inefficacy shows their uselessness, b) there is a remote possibility, that severity of treatment, will modify the outcome of the disease; c) therapeutic means become exceptional, no longer proportional to the objective, sought by the physician. This is different from therapeutic insistence, that relates to an ethically positive attitude by the physician committed to maintain life-sustaining therapies over long periods when facing a situation of prognostic unpredictability of some pathologies.[1]

Over the last thirty years, predictive systems have been sought to accurately discern a fairer allocation of the finite resources of the ICU. In this sense, within the scope of medical ethics, the threshold for use o life-sustaining therapy has been extensively discussed. Such actions may surpass the limits of therapeutic insistence and become futile therapies. Studies state that the objective mechanism to reach such a perception should present high specificity in the determination of who will die, when few patients would survive if treatment were continued.[2]

The predictive systems found in literature attempt to identify what is the probability of death as an outcome for groups of patients based on diagnoses and organic changes. However, they are of no avail to asses prognoses of individuals. In 2002, Terzi et al.[3] developed a model for individual prognostic assessment for patients in intensive care units, the UNICAMP model. It was the result of analysis of a data bank from a Brazilian university hospital and compared to other models found in literature. In addition to checking validity and portraying Brazilian reality, one of its merits was to attribute to risk estimation a single score for all patients, regardless of the cause for admission in the ICU. Nevertheless the UNICAMP model like the others also does not uses objective variables related to the nutritional status, which by itself is known to be a relevant factor for the outcome death.

This study sought to record the prognostic evolution of critically ill patients in the ICU of a university hospital, using the UNICAMP II, associated to objective variables related to the nutritional status (albumin, transferrin and lymphocyte count). The purpose was to verify the predictive capacity of the test in relation to the outcome death. In addition efforts were made to assess the relation between onset of life-sustaining therapies and prognostic evolution of patients, for the purpose of supporting ethical decisions related to offer these therapies.

METHODS

This a cohort, prospective, observational study developed in the general Intensive Care Unit (ICU) of the Hospital Universitário São Francisco de Paula, da Universidade Católica de Pelotas (UCPel), Pelotas – RS, Brazil. The study was approved by the Research Ethics Committee of UCPel (CEP-UCPel) and carried out from March 1, 2006 to August 31, 2007. All patients in the ICU during the data collection period were included, regardless of the cause of admission. Exclusion criteria were: patient or legal representative's refusal do sign an informed consent; less than 18 years of age; less than 24 hours length of stay in ICU and readmission of the patient during the study period.

Patients included in the study were followed from the moment of admission to the ICU until outcome: discharge from the unit or death. Registered were: probable risk of death through an evolutionary system during the first 7 days of stay in the ICU, using the UNICAMP II index [Y = - 3.7594 + (APS x 0.1162) + (0.7178 if mechanical ventilation) + (0.7318 if acute renal failure) + (0.8367 if clinical or surgical emergency)] risk of death being = 1/ [1 + exp (- y); serum levels of albumin, transferrin and lymphocytes at time of admission and on the seventh day; life sustaining therapies employed, as well as time of onset. Risk of death was also registered by the *Acute Physiologic Chronic Heatlh Evaluation* II (APACHE II) in the first 24 hours after admission to serve as reference. Two stages for intervention were defined: early stage (first seven days) and late stage (after the seventh day). Life-sustaining therapies were: invasive mechanical ventilation, hemodialysis, vasoactive drugs (dopamine, noradrenaline, dobutamine), parenteral nutrition, blood and blood components transfusion. Parameters for nutritional depletion analysis were: mild: albumin = 3.5 – 3.0 g/dL; transferrin = 180 – 150 mg/dL ; lymphocytes = 1500 – 1200 /mm^3); moderate (albumin = 2.9 – 2. 5 g/dL; transferrin = 149 – 100 mg/dL; lymphocytes = 1200 – 800 /mm^3); severe: (albumin = < 2.4 g/dL; transferrin = < 100 mg/dL lymphocytes = < 800/mm^3). The offer of life-sustaining therapy at the late stage of intervention was considered futile for patients who, notwithstanding therapies, had a progressively worst prognosis during the early stage of intervention. This corroborates that treatment is not beneficial and, therefore is futile to change outcome of disease. Beneficial treatment was considered to be an improved prognosis during the early stage of intervention, with subsequent discharge from the ICU.

For statistical analysis of the numerical variables, the Student's t test and the variance analysis (ANOVA) were used and, whenever appropriate for categorical variables, the Chi-square test and the Fisher exact test. The Spearman correlation test and the receiver operating curve (ROC) were used to assess respectively, the strength of linear relation between quantitative variables and specificity and sensitivity of the probability of death test.

RESULTS

During the study period, 582 clinical and surgical patients were admitted in the ICU of the Hospital São Francisco de Paula. Of these, 447 were included in the study and followed up during length of stay in the ICU until outcome and 189 of them stayed in the unit for seven or more days. Exclusion criteria and demographic characteristics are respectively shown in figure 1 and tables 1 and 2. Regarding prevalence of death, data showed that it was significantly higher among patients over 60 years of age, those admitted because of respiratory disease, renal disease, sepsis and users of life-sustaining therapies. Patients receiving nutrition had lower prevalence of death in comparison to those not receiving.

Among patients with a seven days or more stay in the ICU, a significantly higher prevalence of death was found in those that began life-sustaining therapies in the late stage of intervention. Nutritional state was established by the serum levels of albumin, transferrin and lymphocyte count. Results showed that the level of undernourishment of patients in the ICU ranged from moderate to severe. Serum levels of albumin and transferrin were significantly different between survivors and those who died, but there was no difference in relation to the lymphocyte serum levels. Prevalence of death was higher among patients more undernourished at admission and among those with a worsening of the nutritional status over the first seven days. Data are shown in figures 2-4. Risk of probable death was assessed by the UNICAMP II index, during the first 24 hours of admission, equivalent to the APACHE II index with r=0.95 and perfectly applicable to patients staying in Brazilian intensive care units (Figure 5).

Among patients that stayed in the ICU for seven days or more, prevalence of death was significantly higher in those whose prognostic index worsened along the first seven days, notwithstanding therapies used. Data are shown in figure 6. The UNICAMP II index on the 7th day showed good discrimination with 0.84 of area under the ROC curve. Data are shown in figure 7. When the UNICAMP II index was associated with the nutritional status using serum levels of transferrin, there was a better discrimination with area under the ROC curve of 0.85 (Figure 8). Association of the UINICAMP II index with the serum levels of albumin, alone or together with transferrin did not improve discrimination.

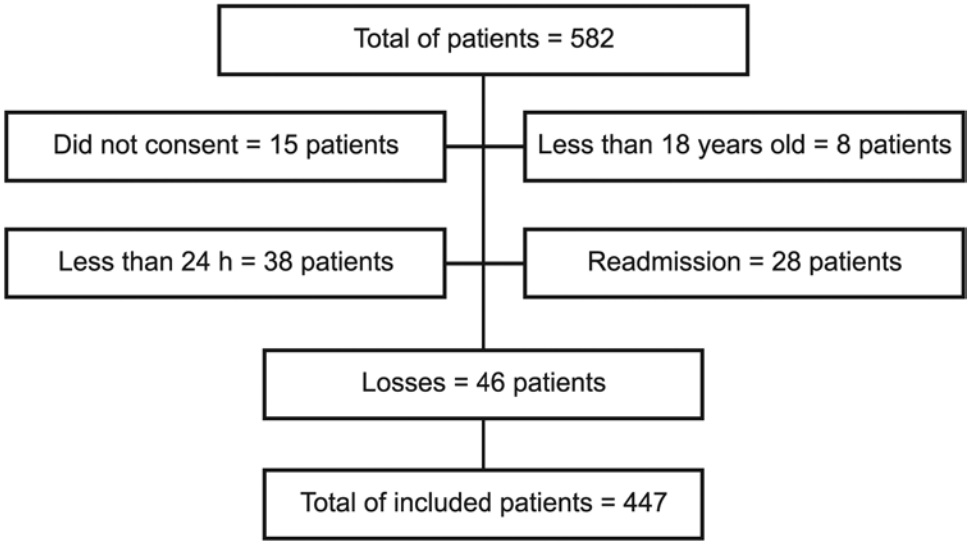

Figure 1 - Exclusion criteria of patients involved in the study.

Table 1 – Description of the demographic variables and prevalence of death

Variable	Result N = 447	Prevalence of death	P value*	RR	Confidence interval
Gender			0.844		
Male	243 (54.4)	36.2		1.00	
Female	204 (45.6)	35.3		0.97	0.76-1.25
Skin color			0.378		
Caucasian	364 (81.4)	34.3		1.00	
Black	62 (13.9)	41.9		1.22	0.88-1.69
Mulatto	21 (4.7)	42.9		1.25	0.75-2.09
Age (years)			0.026		
To 59	177 (39.6)	29.4		1.00	
60 or+	270 (60.4)	40.0		1.36	1.04-1.79
Pathologies			< 0.001		
Cardiovascular	86 (19.2)	24.4			
Surgery abdominal	79 (17.7)	22.8			
Respiratory	118 (26.4)	50.9			
Sepsis	53 (11.9)	54.7			
Neurolological	51 (11.4)	25.5			
Gastrintestinal	23 (5.2)	39.1			
Trauma	13 (2.9)	30.8			
Thoracic surgery	3 (0.7)	0.0			
Endochrine	9 (2.0)	11.1			
Vascular surgery	1 (0.2)	0.0			
Renal	11 (2.5)	45.5			
Mechanical ventilation			< 0.001		
Not used	208 (46.5)	6.3		1.00	
Prior to 7th day	235 (52.6)	60.9		9.74	5.79-16.65
After 7th day	4 (0.9)	100		16.00	9.45-27.10
Dopamine			< 0.001		
Not used	366 (81.9)	28.4		1.00	
Prior to 7th day	62 (13.9)	66.1		2.33	1.83-2.96
After 7th day	19 (4.2)	79		2.78	2.09-3.69
Dobutamine			< 0.001		
Not used	387 (86.6)	31		1.00	
Prior to 7th day	51 (11.4)	62.8		2.02	1.56-2.62
After 7th day	9 (2.0)	88.9		2.87	2.18-3.77
Noradrenaline			< 0.001		
Not used	326 (72.9)	19		1.00	
Prior to 7th day	99 (22.2)	79.8		4.20	3.28-5.36
After 7th day	22 (4.9)	86.4		4.24	3.44-6.00
Hemodialysis			< 0.001		
Not used	402 (89.9)	33.1		1.00	
Prior to 7th day	37 (8.3)	54.1		1.63	1.18-2,27
After 7th day	8 (1.8)	87.5		2.64	1.97-3,56
Nutrition			0.001		
No	78 (17.5)	52.6		1,00	
Yes	369 (82.5)	32.3		0.61	0.47-0.79
Transfusion			< 0.001		<0.001
Not used	299 (67.0)	26.4		1.00	
Prior to 7th day	108 (24.2)	51.9		1.96	1.51-2.55
After 7th day	39 (8.7)	61.5		2.33	1.70-3.18
Death					
No	287 (64.2)				
Yes	160 (35.8)				

RR – relative risk; N - number Results expressed in number(%). Fisher's exact test.

Table 2 – Patient characteristics according to survival status

Variable	Survival	Deaths	P value*
Age |(years)	59.6 ± 17.6	65.1 ± 17.2	0.002
Length of stay ICU (days)	8.2 ± 8.1	10.8 ± 9.4	0.002
Mechanical ventilation (days)	3.0 ± 6.5	8.6 ± 8.8	< 0.001
1st day Albumin	3.0 ± 0.9	2.5 ± 0.7	< 0.001
7th day Albumin	2.4 ± 0.5	2.1 ± 0.6	< 0.001
1st day lymphocytes	1527 ± 1038	1452 ± 1116	0.481
7th day lymphocytes	1591 ± 884	1372 ± 857	0.09
1st day transerrin	176.9 ± 72.6	137.4 ± 61.9	< 0.001
7th day transferrin	139.5 ± 50.9	118.9 ± 56.5	< 0.001
UNICAMP II 1st day	36.3 ± 24.3	67.7 ± 23.7	< 0.001
UNICAMP II 7th day	38.8 ± 23.0	71.6 ± 21.1	< 0.001

ICU intensive care unit. Results expressed in mean±standard deviation. Variance analysis.

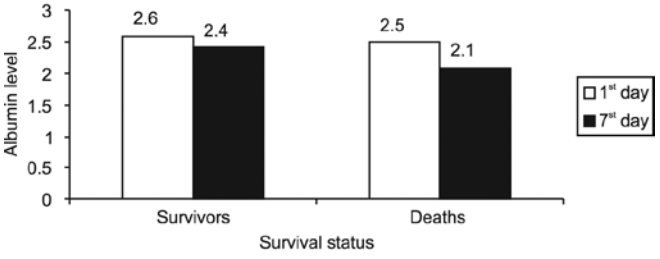

Figure 2 - Albumin serum levels measured on the 1st and 7th day. Although there was a decrease in the serum albumin level in both groups (p<0.001), on the 7th day albumin level was higher among survivors than among deaths (p=0.001)

Figure 3 - Serum levels of lymphocytes measured on the 1st and 7th day. Regardless of the variation there was no significant difference in the level of lymphocytes between deaths and survivors or between the 1st and 7th day

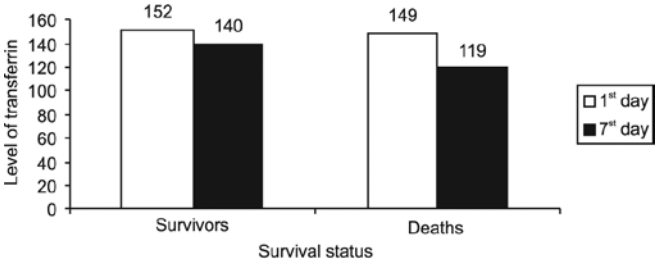

Figure 4 – Serum levels of transferrin measured on the 1st and 7th day. There was a significant decrease in the transferrin level in both groups. However, among survivors on the 7th day the trasnferrin level was higher in relation to those who died. (p= 0.010).

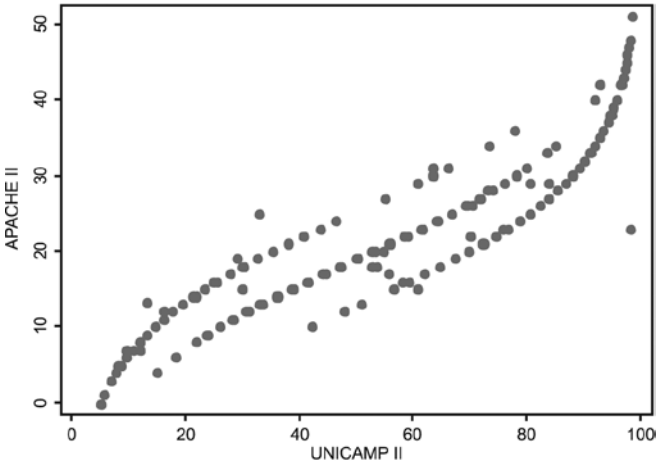

Figure 5 – Correlation between the UNICAMP II and APACHE II indices measured in the first 24 hours of ICU stay. R = 0.95

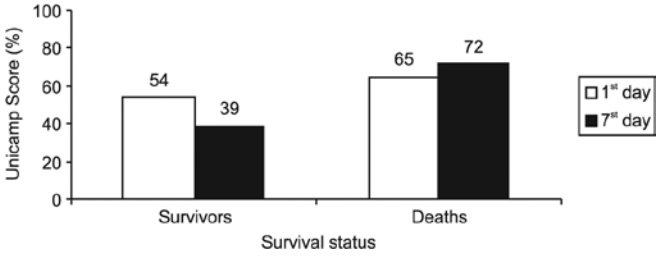

Figure 6 – UNICAMP II index measured on the 1st and 7th day. There was a significant reduction in the UNICAMP II score for survivors (p<0.001) and significant increase among deaths (p=0.014).

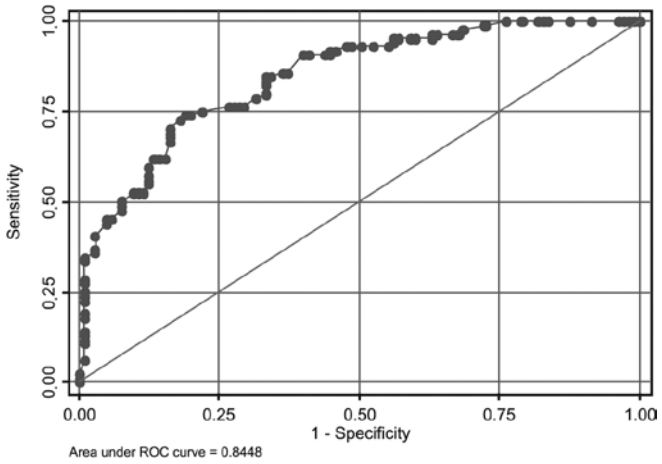

Figure 7 – UNICAMP II System - Performance to discriminate the probability of death for patients that stayed in the ICU for 7 or more days. Indices were measured on the 7th day.

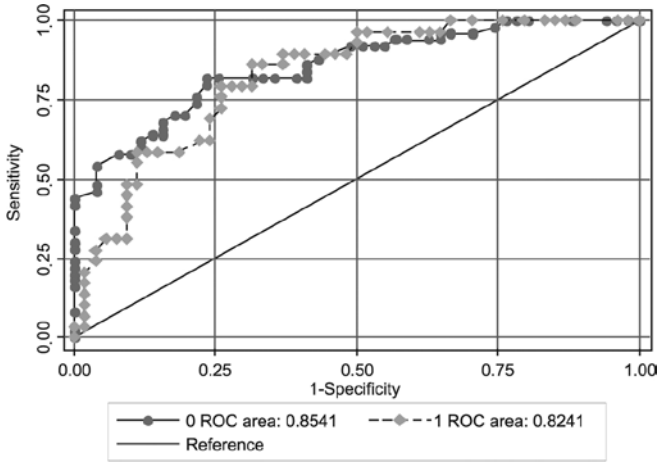

Figure 8 - Diagnostic criteria of death based upon UNICAMP II score on the 7th day according to level of transferrin on the 7th day (dark curve:<130; light curve:>130).

DISCUSSION

This study disclosed that it is possible to accurately discriminate the patients with an unfavorable evolution, regardless of the used therapies by a prognostic evolution system. In bedside clinical practice this assessment is highly relevant to support ethical decision making about the withholding of new life-sustaining therapies. Many studies have tried to use objective data to distinguish patients who will die, from survivors. One of the more used is the APACHE system, whose more recent version the APACHE IV[4] showed good discrimination regarding hospital mortality, with a 0.88 area under the ROC curve. However, it does not intend to be a reference for other countries because of different factors such as admission criteria to the ICU, structure of the ICU and pre and post-admission care.

End-of-life issues, in intensive care medicine, have been prevalent mainly on withdrawing, withholding or not of life support. Arguments that determination of futile care is merely an objective clinical judgment, regarding the efficacy of a particular medical intervention, conflict with reasoning that, even a therapy which positively affects physiology, could be considered futile insofar as it was inconsistent with the patient's goals. Thus, they do not require technological solutions but social and philosophical ones.[5]

This study used an evolutionary prognostic system with objective data associating the UNICAMP II index to the nutritional status with the serum levels of transferrin to assess discrimination during ICU stay, of patients who died or survived, with no intention to verify hospital mortality. Initial reasoning was that a more precise objective assessment will better support therapeutic decisions. The proposed system presented good discrimination with a 0.85 area under the ROC curve. The APACHE II index, in the first 24 hours of ICU stay was used as reference and results showed that the UNICAMP II index was equivalent to the APACHE II. The UNICAMP II index characteristics are that it was based upon data of patients in Brazilian ICU, that it does not use diagnostic category and that it proposes an evolutionary verification of patient's clinical condition. This makes it an interesting tool as a discriminative method for bedside assessment in the ICU.

Another study done in Brazil[6] also showed representativity of the UNICAMP II system regarding Brazilian reality and suggested that it is a prognostic index to be routinely implemented in Brazilian ICU. The prognostic evolutionary system proposed, in this study encompasses objective variables of nutrition, normally not included d in other studies. Verification of other patients in the ICU, already with undernourishment levels, not only portrays Brazilian reality, but also that of Latin America, becoming a relevant factor in prevalence of death. Data also showed that patients with life-sustaining therapies initiated mainly in the late stage of intervention had higher risks and higher prevalence of death. This is also true for those whose prognostic indices and nutritional status worsened over the first seven days and, therefore did not benefit

from treatment. Thus, the importance of systematic monitoring of the prognosis during stay in the ICU is proven. As long as the patient's clinical condition continues to worsen, despite the life-sustaining therapies, during the early stage of admission, as documented by objective data, inefficacy of these therapies is disclosed in relation to the patient's clinical condition. Use of inefficient therapy, unable to change the evolution of a disease is likewise therapeutic futility. On the other hand, the opposite, understood as therapeutic insistence, where benefit of treatment is corroborated by better prognosis over the early stage of intervention and therefore lower prevalence of death.

A Brazilian study, published in 2009 reports that curative medicine in the ICU has been obstinate in helping and gaining longer time of life, however says nothing about providing quality at end-of-life.[7] The fundamental issue is to define when one is facing a situation where therapy is merely prolonging life. Precise assessment of prognosis may aid in this sense, as shown here, considering staging of the disease and the need for a new therapy.[8] The evolutionary prognostic system developed in this study, associating the UNICAMP II index with the nutritional status, made an effort to represent Brazilian reality and, possibly that of Latin America, regarding the patient's clinical condition in the ICU, give positive inputs for ethical decision making regarding withholding of life sustaining therapies and avoid implementation of therapeutic obstinacy.

Limitations of the study

This study presents several limitations: first, the fact that it has been carried out in a single center. Although it is a university institution that cares for patients from the public and private sector, it may not represent the reality of other regions in the country. Therefore, other studies are required involving centers of other parts of Brazil to better disclose results. Second, the prognostic index used in this study although based upon a Brazilian data bank and equivalent to international indices, makes more studies essential, Brazilian and international, to substantiate validity. Third, use of classical objective variables to verify the nutritional status such as albumin, transferrin and lymphocyte count may not represent the true nutritional status of critically ill patients, either due to decreased production at the acute stage of the disease, or because of the average long life span. Fourth, therapeutic insistence is represented here by treatment by prognostic unpredictability (improvement or maintenance of the index) during stay in the ICU and therapeutic obstinacy by prognosis worsening, regardless of the treatment used in the early stage of intervention. There never were, at any moment, treatments registered for patients with order for non-resuscitation. As such, this fact could not only be interpreted as objective but also as subjective assessment. Nevertheless, these results stress the need for periodic and systematic monitoring of prognostic evolution of patients in the ICU. This evolution may not only be based upon organic dysfunctions but also together with a nutritional status.

CONCLUSION

This study shows that systematic prognostic monitoring of a patient in the ICU is a useful tool to discern the possibility of implementing the so-called therapeutic futility. This would become clear with worsening of the prognostic indices of patients at the early stage of intervention, regardless of the life-sustaining treatments used. Low basal levels of transferrin, as well as worsening at the early stage of intervention, increase the trial's specificity. As such, it also registers the importance of monitoring the nutritional status. New multicentric studies are mandatory for a better understanding of these results.

RESUMO

Objetivos: A disponibilidade de alta tecnologia na unidade de terapia intensiva tem-se transformado, muitas vezes, em instrumento potencializador de sofrimento ao aumentar o tempo do processo de morrer. Diferenciar insistência terapêutica de obstinação terapêutica tem sido um grande desafio da medicina atual. O objetivo deste estudo foi avaliar a relação benefício versus malefício do uso de terapias que sustentam as funções vitais por meio de um sistema evolutivo de avaliação prognóstica individual.

Métodos: Estudo de coorte, prospectivo, observacional, desenvolvido na unidade de tratamento intensivo do Hospital Universitário São Francisco de Paula da UCPel, Pelotas, RS no período de 1° de março de 2006 a 31 de agosto de 2007. Foram registradas: a avaliação prognóstica individual por meio de um sistema evolutivo, utilizando o índice UNICAMP II associado aos níveis séricos de albumina, transferrina e linfócitos; as terapias mantenedoras das funções vitais; o desfecho. A análise estatística foi realizada utilizando o teste t de Student, a ANOVA, o teste do Qui-quadrado, o teste exato de Fisher, o teste de correlação de Spearman e a curva ROC. Foi consid-

erado estatisticamente significativo um valor p < 0,05.

Resultados: Avaliaram-se 447 pacientes durante o período de estudo. A prevalência de óbito foi significativamente maior entre os que iniciaram as terapias mantenedoras das funções vitais na fase tardia de intervenção e também entre aqueles que pioraram seu índice prognóstico e seu estado nutricional ao longo da fase precoce de intervenção.

Conclusão: A avaliação evolutiva prognóstica individual mostrou-se um método útil para subsidiar, de forma objetiva, tomadas de decisões éticas no referente à diferença entre insistência terapêutica e obstinação terapêutica.

Descritores: Unidades de terapia intensiva; Ética médica; Assistência paliativa/ética; Direito a morrer

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