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Can tissue perfusion be used for predicting mortality in an intensive care unit?

Perfusão tecidual pode ser utilizada para predição de mortalidade em unidade de terapia intensiva?

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RESUMO: *Objetivo*: Comparar a acurácia para predição de mortalidade dos indicadores de perfusão tecidual e APACHE II nas primeiras 24 horas de internação em uma unidade de terapia intensiva (UTI) do sul do Brasil. *Métodos*: coorte prospectiva. Foram avaliados o diagnóstico de internação, idade, sexo, casos cirúrgicos ou não-cirúrgicos, APACHE II, índice de perfusão tecidual (IP), lactato sérico, saturação venosa central de oxigênio (SvcO2) e a diferença venosa-arterial de dióxido de carbono (ΔPCO2) nas primeiras 24 horas de internação. Os participantes foram acompanhados até o desfecho na UTI: alta ou óbito. *Resultados*: Participaram do estudo 126 indivíduos com média de idade de 62,2±16,8 anos e principal causa de internação cardiovascular (37,3%). As variáveis que estiverem relacionadas ao óbito foram apenas a maior idade (p=0,015), casos não-cirúrgicos (p=0,001), maior pontuação no APACHE II (p=0,001) e maior tempo de internação (p=0,004). O estudo elaborou um modelo de avaliação prognóstica utilizando os casos não-cirúrgicos e a SvcO2<65% que, quando comparado com o APACHE II, se mostrou mais acurado para previsão de mortalidade em UTI (área sob a curva ROC 0,727 (IC 95% 0,616 – 0,838 versus 0,802 (IC 95% 0,701 – 0,904). *Conclusão*: Os indicadores de perfusão tecidual analisados não apresentaram relevância estatística como preditores de mortalidade nas primeiras 24 horas quando analisados de forma independente no estudo. O escore APACHE II apresentou-se como uma boa forma de avaliação prognostica para os pacientes, assim como o modelo proposto no presente estudo para previsão de mortalidade, que quando comparado ao escore APACHE II, apresentou um índice de confiabilidade e uma área sob a curva ROC mais elevada.

Descritores: Mortalidade; Cuidados críticos; Unidade de terapia intensiva; APACHE; Ácido láctico; Fotopletismografia; Prognóstico.

ABSTRACT: *Objective*: To compare the accuracy of tissue perfusion indicators with APACHE II for predicting mortality in the first 24 hours of hospitalization in an intensive care unit (ICU) in southern Brazil. *Methods*: A prospective cohort study. The evaluated variables were: hospitalization diagnosis, age, gender, surgical or non-surgical cases, APACHE II, tissue perfusion index (PI), serum lactate, central venous oxygen saturation ($SvcO_2$) and arterial-venous carbon dioxide difference (ΔPCO_2) in the first 24 hours of hospitalization. Participants were followed-up until the ICU outcomes of discharge or death. *Results*: A total of 126 subjects with a mean age of 62.2 ± 16.8 years having the main cause of cardiovascular hospitalization (37.3%) participated in the study. The variables which were related to death were only the greater age (p = 0.015), non-surgical cases (p = 0.001), higher APACHE II score (p = 0.001) and longer hospitalization time (p = 0.004). The study developed a prognostic evaluation model using non-surgical cases and $SvcO_2$ <65%, which was more accurate for predicting ICU mortality when compared to APACHE II (area under the ROC curve 0.727 (95% CI) 0.616-0.838 versus 0.802 (95% CI 0.701-0.904). *Conclusion*: The analyzed tissue perfusion indicators were not statistically significant as predictors of mortality in the first 24 hours when analyzed independently in the study. The APACHE II score showed to be a good form of prognostic evaluation for the patients, as well as the model proposed in the present study for mortality prediction, presenting a higher reliability index and area under the ROC curve when compared to the APACHE II score.

Keywords: Mortality; Critical care; Intensive care units; APACHE; Lactic acid; Photoplethysmography; Prognosis.

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INTRODUCTION

Intensive care units (ICUs) stand out for providing care to critically ill patients, being high complexity and having a high service cost. In this sense, the use of prognostic indicators enables evaluating the epidemiological profile of each ICU, as well as tracking the likelihood of the worst outcomes. The Acute Physiology and Chronic Health Evaluation II (APACHE II), the Sepsis Related Organ Failure Assessment (SOFA), the Simplified Acute Physiology Score II (SAPS II) and the Logistic Organ Dysfunction System (LODS) can all be cited amongst the most used sciences[1-5]. These scores are calculated using a sum of numerical values corresponding to clinical and laboratory changes presented by the patient.

APACHE II is probably the most well-known and used, being introduced in 1985. It consists of an evaluation of twelve clinical variables, using the worst values presented in the variables in the first 24 hours of admission to the ICU[1,4,5].

Tissue perfusion has also been used as a method of prognostic evaluation and treatment effectiveness in high-risk patients[6-11]. Tissue perfusion can be assessed both by clinical, non-invasive signs, and by laboratory and invasive criteria, which aim at early identification of impaired organ and tissue oxygenation[6-9]. The clinical signs of tissue hypoperfusion include increased heart rate, capillary filling time greater than two seconds, pallor and decreased extremity temperature (among others). However, clinical signs do not always detect hypoperfusion early, nor accurately represent what occurs in peripheral perfusion[1,12].

Laboratory and invasive methods can also be used to assess tissue perfusion, with the main ones being central venous oxygen saturation ($SvcO_2$), serum lactate level, venous-arterial carbon dioxide difference (ΔPCO_2), excess bases and the peripheral perfusion index (PI)[6-8,11,12].

$SvcO_2$ indirectly expresses oxygen consumption by the body, and can therefore be used as a tissue oxygenation index[1,6,13]. The serum lactate level is also used in evaluating tissue perfusion[(6)], because the cell increases anaerobic glucose production when tissue hypoxia occurs in order to maintain its energy production, which is a reaction whose outcome releases lactate in the blood, thus increasing its serum level[6,12,14,15]. ΔPCO_2 is calculated through the difference between the PCO_2 collected in the pulmonary artery and the arterial PCO_2, and in normal conditions it presents values ranging from 2 to 5 mmHg[16,17]. It can be used to evaluate perfusion in patients with suspected hypoperfusion because it presents precocity in its alteration before variations in blood pressure, serum lactate level and heart rate[12].

The PI is derived from the photoelectric photoplethysmography (PPG) signal obtained through pulse oximetry, which is a technique used in most intensive care units due to its ease and performance cost. The inclusion of this index in the pulse oximetry signal is recent, and its use for early assessment of tissue perfusion and its prognostic implication still need further studies[8,9].

In this perspective, the objective of this study was to compare the accuracy of APACHE II with tissue perfusion indicators for predicting mortality in the first 24 hours of hospitalization in an intensive care unit in the south of Santa Catarina State, Brazil.

METHOD

A prospective cohort was carried out in the adult intensive care unit of the Hospital Nossa Senhora da Conceição (*HNSC*), located in Tubarão, SC, Brazil.

Individuals hospitalized between September 2016 and November 2016 and whose family members signed the informed consent form were selected. Exclusion criteria were considered as individuals who were transferred from the ICU, poor PPG signal quality and incorrect medical records or lack of information.

As this is an accuracy study, a prevalence of 25% of mortality (P = 0.25) was considered for the sample calculation, as previously estimated, with an error of 10% (e = 0.1) in the confidence interval of 95% ($Z_{\alpha/2}/2 = 1.96$). Sensitivity was defined as 91% (Sens = 0.91). The equation used is described below[18].

$$n_{sens} = \frac{(Z_{\alpha/2})^2 \, Sens.(1 - Sens)}{e^2 .P}$$

For sensitivity, . Then $n_{sens} \approx 126$.

Data collection included the hospitalization diagnosis, age, gender, PPG pulse curve sign, APACHE II[19] score and tissue perfusion indicators: lactate, ΔPCO_2 and $SvcO_2$ in the first 24 hours. ΔPCO_2 was calculated by the difference in venous and arterial oxygen pressure (PvO_2-$PaCO_2$). Only the PPG signal was collected bedside. The other variables were extracted from the electronic medical record. The individual was followed-up to the outcome of discharge or death, counting the length of stay in the ICU.

The PI variable was extracted from the PPG signal using a Reflex Aqwave™ oximeter. It has the capacity to store the pulse curve values at a sampling frequency of 60 Hz and lasts for one minute. The device can export the data in a text file for computational analysis. The data from the PPG pulse curve were entered into MATLAB software (Mathworks Inc., USA) to obtain the tissue perfusion index (PI). The equation PI = (AC/DC)*100% was used, in which AC is the pulsatile component and DC is the non-pulsatile component (Figure 1)[20,21].

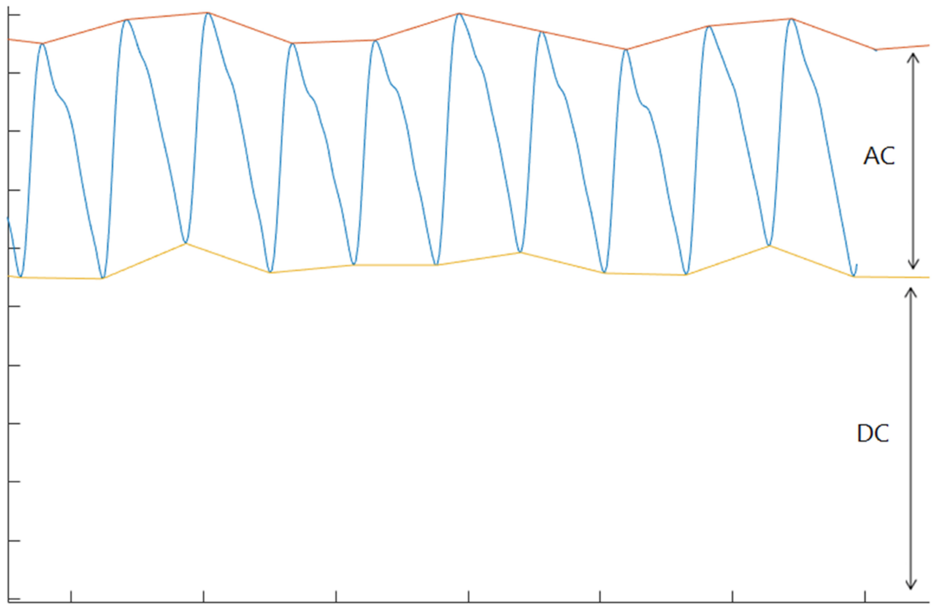

Figure 1 - Identification of AC and DC parameters extracted from the PPG

This work was submitted to the research ethics committee of the University of the South of Santa Catarina (UNISUL), Palhoça, SC, Brazil and was approved under CAAE 50687515.6.0000.5369

The data were stored in a database created with Microsoft Excel® software, and later were exported to SPSS 20.0® software. Data were presented using absolute and percentage numbers, as well as central tendency and dispersion measures. The variables were compared in relation to the outcomes of discharge or death using crude and adjusted logistic regression. Variables with $p<0.2$ were considered for multivariate analysis using the backward method. The $SvcO_2$ variable was dichotomized at the cut-off point $\leq 65\%$ and $> 65\%$. The other tissue perfusion variables were considered continuous in the analysis. The accuracy of multivariate models was compared with APACHE II using the ROC curve. A 95% confidence interval was considered with a level of statistical significance of 5%.

RESULTS

A total of 136 individuals participating in the study were followed-up. Of these, 10 were excluded according to the methodological criteria. Thus, a total of 126 subjects with a median age over 60 years comprised the final sample, with males being more prevalent. Cardiovascular and neurological diseases can be highlighted as the most common diagnoses of ICU admission with just over half of the cases, followed by neoplasms and infections. The median length of stay was 6 days, and approximately ¼ of the monitored participants died (Table 1).

Table 1 – Characteristics of the HNSC ICU sample in Tubarão, SC, Brazil

	Median (IQL)	n(%)
Age (years)	67.0 (51.0 – 75.0)	
Gender		
Male		71 (56.3)
Female		55 (43.7)
Surgery		
No		61 (48.9)
Yes		65 (51.6)
Diagnosis		
Cardiovascular		47 (37.3)
Neurological		21 (16.7)
Neoplasm		14 (11.1)
Infection		13 (10.3)
Gastrointestinal		11 (8.7)
Polytrauma		11 (8.7)
Respiratory		6 (4.8)
Others		3 (2.4)
APACHE II	13.0 (8.0 – 18.0)	
Probability of death (%)	16.5 (8.7 – 29.1)	.
Length of hospitalization (days)	6.0 (3.0 – 15.0)	
Death		
No		95 (75.4)
Yes		31 (24.6)

Others: genitourinary, orthopedic, endocrine

The variables related to tissue perfusion in the first 24 hours of ICU admission are shown in Table 2.

Table 2 – PI, Lactate, $SvcO_2$ and ΔPCO_2 in the first 24 hours of hospitalization

	Minimum - Maximum	Median (IQL)
PI (%)	47.3 – 231.9	102.9 (83.2 – 134.6)
Lactate (mmol/L)	4.2 – 46.7	14.0 (8.2 – 21.8)
$SvcO_2$ (%)	30.0 – 95.0	67.0 (62.0 – 78.0)
ΔPCO_2 (mmHg)	0.0 – 22.0	9.0 (6.0 – 11.0)

IQL: Interquartile distance

The variables related to death were older age, non-surgical cases, higher APACHE II scores and longer hospital stay (Table 3).

Two models were proposed in the multivariate analysis in which the variables showed a statistical association to predict mortality in the ICU. In comparing model 1 with APACHE II, it can be seen that it is more accurate for predicting mortality in the ICU, showing an area under the ROC curve of 0.802 (95% CI 0.701-0.904, with p<0.001), while APACHE II presented an area under the ROC curve of 0.727 (95% CI 0.616-0.838, with p = 0.002). Model 2 was then proposed in associating APACHE II with model 1, resulting in greater accuracy with an area under the ROC curve of 0.830 (95% CI 0.741-0.918, with p<0.001) (Figure 2).

Table 3 – Bivariate analysis and crude odds ratio for death

	DISCHARGE Median (IQL)	DEATH Median (IQL)	OR (95%CI)	p
Age (years)	65 (48 – 72)	74 (57 – 78)	1.038 (1.007 -1.069)	0.015
Gender*				
Female	55 (77.5)	16 (22.5)	1.000	
Male	39 (72.2)	15 (27.8)	0.756 (0.335-1.709)	0.502
Surgery*				
Yes	57 (89.1)	7 (10.9)	1.000	
No	37 (60.7)	24 (39.3)	5.282 (2.067-13.496)	0.001
APACHE II	11 (7 – 17)	17 (12 – 23)	1.130 (1.055 -1.211)	0.001
Length of hospitalization (days)	4 (3 – 11)	15 (6 – 27)	1.038 (1.012 -1.064)	0.004
PI	109 (84 – 140)	109 (84 – 135)	0.737 (0.236 – 2.304)	0.599
Lactate (mmol/L)	14 (8 – 22)	16 (8 – 21)	0.984 (0.942 -1.028)	0.470
$SvcO_2$ (%)	68 (63 – 77)	65 (58 – 79)	0.986 (0.946 -1.028)	0.500
≤ 65%	30 (61.2)	19 (38.8)	1.00	
> 65%	60 (77.9)	17 (22.1)	0.458 (0.171 – 1.229)	0.121
ΔPCO_2 (mmHg)	8 (6 – 11)	9 (6 – 12)	0.989 (0.877 -1.117)	0.863

* categorical variables expressed in n (%); IQL: interquartile distance.

Model 1	OR (95%CI)	p
Non-Surgical	11.895 (3.332 – 42.473)	<0.001
$SvcO_2$ ≤ 65%	4.229 (1.197 -14.935)	0.025

Model 2	OR (95%CI)	p
Non-Surgical	8.662 (2.278 – 32.938)	0.002
$SvcO_2$ ≤ 65%	4.983 (1.308 -18.976)	0.019
APACHE II	1.110 (1.008 -1.222)	0.034

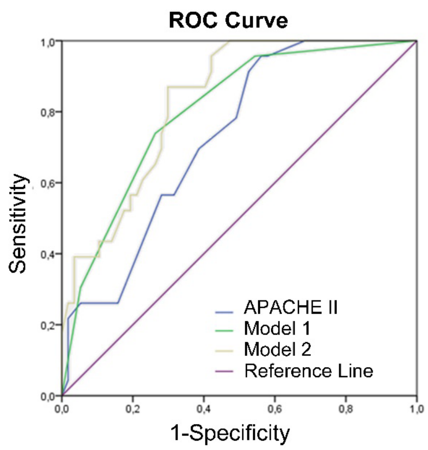

Figure 2 - Mortality prediction models based on epidemiological variables and peripheral perfusion and ROC curve: APACHE II x model 1 and model 2

DISCUSSION

The average age found in the present study represents a profile of older adult patients, and there was a significant difference in the group of patients who died or were discharged during hospitalization. These data are in accordance with the study by Ho et al.[22]. However, the study by Williams et al.[23] carried out with 22,298 patients did not associate age with the risk of death, indicating that it is possible that age may be associated with other factors which contribute to the patient's negative evolution, greater severity of the disease and worse functional status prior to hospitalization.

The number of male patients was higher when compared to female individuals, constituting a similar result to that obtained by Nogueira et al.[24] and Ho et al.[22]. Regarding the average length of stay obtained, there is no consensus regarding the minimum length of stay to be considered a prolonged stay, ranging between 3 days[23], 10 days[23] and 14 days[25,26]. This variation between studies could be explained due to the fact that most of them were performed in intensive care units with a clinical and surgical population, as is the case in the present study. A significant difference was obtained with regard to the length of hospital stay of patients with death outcome (19.6) in relation to cases that evolved to discharge (8.8), as occurred in studies conducted by Nogueira et al.[24] and Santana et al.[25].

The most common hospitalization diagnosis among the patients studied was cardiovascular disease with approximately half of the surgical cases, constituting similar results to those obtained in the study by Ho et al.[22], where cardiovascular diseases were responsible for 33.2% of hospitalized patients in the studied unit, and in the study by Nogueira et al.[24], where 56 of the 148 cases analyzed were due to circulatory system diseases.

The average APACHE II obtained in the present study was similar to the study by Oliveira et al.[27], in which 401 patients admitted to an intensive care unit were analyzed and the average APACHE II presented was 12, showing a statistically significant difference between the patients progressing to death or discharge. These results corroborate the effectiveness of using the APACHE II score as a predictor of mortality in intensive care units, as also happens in several studies[1,2,4,5,22,23].

Non-surgical cases presented a higher mortality risk when compared to surgical cases, being an expected result which was also identified in the work of Hissa et al.[2].

The tissue perfusion markers of PI, ΔPCO_2, $SvcO_2$ and serum lactate used in the present study did not show any significant difference between patients with evolution to discharge or death. This result differs from that presented by the study by Haijar et al.[6], in which lactate and excess bases were analyzed upon admission in 1129 patients with severe sepsis, septic shock or postoperative high-risk surgery in an intensive care unit, in which it was shown that these variables could be used as predictors of death independently. Other studies also corroborate the use of lactate and excess bases as predictors of a worse prognosis in patients admitted to an intensive care unit[11,28,29]. The tissue perfusion markers perhaps did not show a significant difference between the discharge and death groups due to the heterogeneity of the sample.

PI was one of the variables analyzed in the study, and has the advantage of being a way of assessing tissue perfusion, as demonstrated in the studies by He[8] and Lima et al.[9], and can be obtained in a non-invasive way, unlike ΔPCO_2, $SvcO_2$ and serum lactate, and only requiring the use of data obtained through a pulse oximeter; however, there was no statistically significant difference between the groups studied in the present study.

The present study developed a model for predicting mortality in intensive care units using an epidemiological variable, whether surgical or not, together with $SvcO_2$, which was more accurate when compared to the results found using the APACHE II score. This result demonstrates that other predictive tools can be used in the ICU with good precision.

As a limitation of the study, it is possible to describe the possible bias in collecting information in medical records and the sample heterogeneity.

CONCLUSION

The present study demonstrated that the APACHE II score is a good form of prognostic evaluation for patients in an intensive care unit, as well as a proposed model for predicting mortality using epidemiological variables (surgical or non-surgical case) associated with $SvcO_2$, which presented a higher reliability index and an area under the higher ROC curve when compared to the APACHE II score.

The tissue perfusion indicators analyzed in this study, namely PI, ΔPCO_2, $SvcO_2$ and serum lactate, were not statistically significant as predictors of mortality in the first 24 hours when analyzed independently in the study.

Authors participation: *Kock KS*: proposal of the study theme, statistical analysis, description of results, review of the article. *Carvalho CEP*: writing of the article, data collection. *Marques JLB*: statistical analysis, correction and final review of the article.

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