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A Simple System to Predict Mortality in Medical Intensive Care Unit

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Authors' contributions

This work was carried out in collaboration between all authors. Author BPMR designed the study, collected data, and wrote the manuscript. Authors BFP, RMTI, LNS, KS, and PCG collected data. Author SARP did statistical analysis. Authors LAMZ, MPO, PSA, and DRD interpreted data. Author MFM designed the study, interpreted data, and corrected the manuscript. All authors read and approved the final manuscript.

Article Information

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Original Research Article

ABSTRACT

Background: Advances in critical care have increased survival chances and the demand for a scientific approach to outcome prediction. The present study aimed to investigate the associations of clinical information, demographic and laboratory data with mortality; and to elaborate and validate a regression equation for mortality prediction in a medical intensive care unit (ICU). **Methods:** This study included 202 patients and took place in a medical ICU at the Botucatu Medical School Hospital, Brazil. In Phase 1, 123 patients admitted to ICU between September 2003 and October 2004 was retrospectively analyzed and allowed equation elaboration. In Phase 2, the mortality equation was prospectively applied in 79 patients consecutively admitted to ICU between August and December 2006.

___ **Results:** Among Phase 1 patients, 55% were males and mean age was 58±19 years. Mortality

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rate was 29%. Multivariate analysis revealed that shock (p=0.002) and hypoalbuminemia (p=0.024) were associated with higher mortality rate. When regression equation was applied in Phase 2 patients, higher equation values were shown for nonsurvivors (0.512; -1.008 -0.512) than for survivors (-1.008; -1.290 -1.008) (p=0.03). The equation also had good precision, 1.8% (IC95%; 1.1-4.7), and low bias, -3.1% (IC95%; -27.1 -20.8). Areas under the receiver operating characteristic (ROC) curve showed no statistical differences between APACHE II (0.75 \pm 0.06) and the equation (0.66 ± 0.07) (p=0.27).

Conclusions: Our data suggest that a simple and accurate prognostic equation can be used to predict ICU mortality.

Keywords: Outcome; ICU; shock; hypoalbuminemia; mortality; APACHE II.

1. INTRODUCTION

Predicting outcomes in clinical care has always been complex. Advances in critical care medicine have increased survival chances for patients with severe illnesses, as well as the demand for a scientific approach to outcome prediction.

Numerous prognostic predictive models have been developed for critically ill patients [1], and they have become useful tools in interpreting crude mortality rates, potentially allowing interhospital and international comparison of clinical performance and quality of care [2]. APACHE II (Acute Physiology and Chronic Health Evaluation) is one of the most commonly used illness severity score system in intensive care units [3,4]. However, the appropriate use has not always been observed [5]. APACHE II has been very well validated, but may be more cumbersome to use than a simpler prediction model with less variables.

Serum albumin is also considered to be a powerful predictor of longer hospital stay, increased rate of complications, and all-cause mortality [6,7]. However, there is a paucity of information on serum albumin admission values, and, those results are conflicting.

Given that validated biomarkers and mathematical models can offer potential guidance for outcome evaluation, the aim of the present study was to investigate the associations of clinical information, demographic and laboratory data with mortality; and to elaborate and validate a regression equation for the prediction of mortality in a medical ICU.

2. MATERIALS AND METHODS

This study included 202 patients, and took place in a medical ICU in the Botucatu Medical School Hospital, Sao Paulo, Brazil. The study protocol was approved by the hospital Research Ethics Committee.

2.1 Study Design

The study was divided in two phases. In the first phase of the study, 123 patients were retrospectively analyzed. A multiple logistic regression model was employed and permitted elaboration of a regression equation for mortality prediction during ICU stay. The equation was validated in the second phase, when the equation was applied prospectively in 79 patients, and the results were compared with APACHE II.

2.1.1 Study phase 1

For sample size estimation, the Fisher–Belle formula was used [8]. The records of 123 patients admitted to the ICU between September 2003 and October 2004 were retrospectively analyzed. Baseline demographic data, clinical information and blood samples were collected, and biochemical tests were performed within 24 hours after admission. Serum levels of potassium, sodium, magnesium, albumin, glycemia, creatinine, and total serum levels of calcium were measured, as well as hematocrit, hemoglobin, and platelets. The following variables were defined: Hyponatremia as serum sodium level < 125 mg/dL, hypomagnesemia as serum magnesium < 1.4 mg/dL, hypokalemia as serum potassium level < 3.5 mg/dL, hypocalcemia as serum calcium level < 8.5 mg/dL, hypoalbuminemia as serum albumin < 3.5 g/dL, renal failure as creatinine > 1.4 mg/dL, hyperglycemia as plasma glucose level > 150 mg/dL, anemia as hemoglobin < 10 g/dL and thrombocytopenia as platelet < 150,000 cells/mm $\rm{^3.}$

Patients were classified into five diagnostic categories: lung diseases (pneumonia, chronic obstructive pulmonary disease (COPD), interstitial lung disease, pulmonary embolism, asthma, acute pulmonary edema and pneumothorax), neurological diseases (acute ischemic stroke, neuromuscular disorders and seizures), heart diseases (acute coronary syndromes (ACS), congestive heart failure, pericarditis and myocarditis), gastrointestinal diseases (upper and lower gastrointestinal bleeding, pancreatitis and cirrhosis) and other diseases. Presence of shock, COPD, upper gastrointestinal bleeding, and ACS were also assessed independently of the diagnostic categories due to their high prevalence in our ICU.

For univariate analysis, all patients with the variable result were included, and all patients were included in multiple logistic regression. Observations containing missing values were ignored by the statistical package. All the patients had the information about shock and albumin.

2.1.2 Study phase 2

The equation constructed in Phase 1 was prospectively applied in 79 patients consecutively admitted to the ICU between August and December 2006.

APACHE II score, serum levels of albumin and presence of shock were recorded on the first day of ICU admission. Hypoalbuminemia was defined as serum albumin < 3.5 g/dL, and shock as lactic acidosis with hemodynamic comprise (systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg).

The equation was applied using the variables shock and hypoalbuminemia according to the regression significance criteria (no=0, yes=1). According to these criteria the patients were classified into four groups.

2.2 Statistical Analysis

Mean \pm SD or medians (lower quartile - upper quartile) for continuous variables and percent for categorical variables were calculated. For areas under the receiver operating characteristic (ROC) curves mean \pm SE was calculated. Chi-square test was performed for comparison of proportions. For comparison of one group, onesample two-tailed Student's t-test was used. For comparison of two groups, the Student's t-test for normal and Mann-Whitney for non-normal distribution were used.

Multiple logistic regression models was performed, allowing construction of the mortality
prediction equation. Mean square error prediction equation. Mean square error (precision) and mean error (bias) were calculated for prediction equation.

One-way analysis of variance (ANOVA), with *post hoc* Tukey multiple comparison test, were conducted to compare mortality prediction equation groups and APACHE II values. For each score, ROC curves were obtained. The comparisons of the areas under the curves (AUC) were performed using the method described by McNeil [9,10]. Significance level was set at $p \le 0.05$. The statistical software SigmaStat for Windows v 2.03 (SPSS) and Medcalc (7.2) were used for statistical analysis*.*

3. RESULTS

This study assessed the associations of clinical information, demographic and laboratory data with mortality in a medical ICU. The characteristics of the patients included in Phase 1 are shown in Table 1.

During Phase 1, 123 patients (55% males), were admitted to the ICU. Mean age was $58±19$ years. Median length of ICU stay was 3 (2-8) days. In our data 20% of the patients had shock, and among them the mortality rate was 56%, which was higher than the non-shock mortality rate of 29% (P<.002). Neurological, endocrine, 29% (P<.002). Neurological, endocrine, gastrointestinal, heart and lung diseases were not associated with mortality. The analysis of laboratory data showed that hypoalbuminemia measured within 24 hours after admission was associated with a higher mortality rate (Table 1). The other variables were not associated with mortality. This was also the case when applied in a multivariate model. Other variables were eliminated and a model using presence or absence of shock and presence or absence of low albumin was implemented.

The equation may be applied using the variables shock and hypoalbuminemia according to the following regression significance criteria:

Logitp (mortality) = $-2.810 + (1.520 * shock)$ + (1.802 * hypoalbuminemia).

 $(no = 0 \text{ and } yes = 1)$

Risk factors associated with mortality are shown in Table 2. We observed that shock and with hypoalbuminemia were associated with higher mortality risk.

In Phase 2, the equation obtained in Phase 1 was prospectively applied in 79 patients whose characteristics are shown in Table 3. The APACHE II score value was 17 ± 8 .

The calculated logit (p) according to the regression model was higher in nonsurvivors than survivors for the prospective phase of the study (p=0.03), as shown in Fig. 1. This validates the equation*.* According to the regression significance criteria the patients were classified
into four groups: shock (s)=0 and groups: hypoalbuminemia $(h)=0$, -2.18 ; s=1 and h=0, $-$ 1.29; s=0 and h=1, -1.008; s=1 and h=1, 0.512.

Table 1. Univariate analysis for ICU mortality of phase 1

** ICU = intensive care unit*

Table 2. Risk factors associated with mortality from multivariate logistic regression

Table 3. Characteristics of phase 1 and phase 2 patients

n (%), meanSD median, (quartile 1 - quartile 3), n=number, LOS=Length of ICU stay

The predicted and observed mortality, mean error and mean square error for these groups are shown in Table 4. The precision of the mortality equation is 1.8% (IC95%; -1.1 -4.7), and the bias -3.1% (IC95%; -27.1 -20.8). There was no difference between predicted and observed mortality for each equation result, and the mean was not different from zero (P=0.14).

One-way ANOVA showed that there is a statistically significant differences in APACHE scores between the equation groups (P=.006). In the multiple comparison tests, the differences were between the groups: s1h1 vs. s0h0 and s1h0 vs. s0h0.

Table 5 provides data for sensitivity, specificity at the cutoff points, and AUC values. When AUC values were compared, there were no statistical differences between APACHE II and mortality regression equation (p=.27).

Our regression equation for the prediction of mortality, which included shock and hypoalbuminemia, had good precision, accuracy, and low bias in predicting ICU mortality. The presence of each risk factor receives one point, and the total score is 2 (Table 6). A score of 2 was associated with higher mortality in these clinical ICU patients. The best cutoff point for this score was 1, with sensibility of 71.4%, specificity of 50.9%. AUC was 0.6828 and 95%CI 0.5481-0.8176.

Table 4. Mortality regression equation results, predicted and observed mortality, error and error squared

Fig. 1. Calculated predicted probability of death according to the regression model in nonsurvivors and survivors in phase 2 **p<.03*

Score	Best cutoff point	Sensitivity (%)	Specificity (%)	ROC area
APACHE II	15	87.0	58.9	0.75 ± 0.06
Equation	-1.008	52.2	82.1	0.66 ± 0.07

Table 5. Comparisons of the assessment scores in mortality

APACHE II (Acute Physiology and Chronic Health Evaluation, ROC (receiver operating characteristic), p=0.27

Table 6. Mortality for each score for phase 2 patients

4. DISCUSSION

The present study aimed to investigate the associations of clinical information, demographic and laboratory data with mortality; and to elaborate and validate a regression equation for mortality prediction in a medical intensive care unit (ICU). Our regression equation for the prediction of mortality included shock and hypoalbuminemia) [11], and had good precision in predicting ICU mortality. These results reinforce the importance of shock and hypoalbuminemia as predictors of mortality.

The impact of shock on mortality was already expected, as the speed and appropriateness of the therapy administered in the initial hours of shock likely influence outcome [12,13]. Estenssoro et al. observed that shock on admission day is the best predictor of prolonged mechanical ventilation in the ICU [14]. The incidence and prevalence of shock are currently unknown, though septic shock is the leading cause of death in intensive care units [15,16]. In the present study, shock was observed in 20% of our patients, of whom 56% died in the ICU. The presence of shock increased the mortality rate by 4.5 times.

Despite the importance of shock in mortality, laboratory data are also predictive of ICU outcome. The intensity of the acute phase response is associated with many biochemical variables, and could explain the negative impact of hypoalbuminemia.

Hypoalbuminemia is known as a powerful predictor of mortality. Albumin is a circulating plasma protein, accounting for approximately 80% of plasma colloid osmotic pressure. It is also a non-specific carrier protein and a scavenger of oxygen free radicals [17]. Hypoalbuminemia may have a multifactorial origin: inadequate protein intake, protein loss (nephrotic syndrome, proteinlosing enteropathy), liver dysfunction, and inflammatory states [18,19]. Within this context, albumin has been described as a negative acute phase response protein. Serum albumin concentration is known to decrease rapidly in critically ill patients [18,20,21].

However, there is a paucity of data on serum albumin at ICU admission. McCluskey et al. [22] observed that admission serum albumin concentration was an insensitive outcome indicator, but serum albumin measured after 24 hours was accurate. Sung et al. [23] reported that low admission albumin in trauma patients was associated with significantly greater ICU and hospital length of stay, and mortality. In our study, 80% of the patients analyzed presented hypolbuminemia within 24 hours of admission, and 34% of them died at the ICU. The presence of hypoalbuminemia increased the mortality rate by 6.0 times.

In multiple logistic regressions shock and hypoalbuminemia were associated with higher predicted probability of death. The APACHE II score was not used in this model because the frequency of coronary disease in our ICU was very high. The possible risk of biased results due to confounders, that were not included in the regression equation, was dismissed due to higher predicted probability of mortality in nonsurvivors (p=0.03), and the good precision (1.8%) and low bias (-3.1%) of the equation, in Phase 2.

The mean square error (precision) is defined as the average of the square of the difference between the predicted and the observed mortality and the mean error (bias) as the average of the difference between them. Large values indicate a poor prediction score. Moreover, there were no differences between predicted and observed mortality for each equation result, and the mean was not different from zero (p=0.14), showing that the equation is a useful tool in mortality prediction.

To evaluate the performance and compare APACHE II with our equation, ROC analysis was

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used. The ROC curve depicts the relation between true-positive results (number of predicted deaths among those who actually died) and false-positive results (number of predicted deaths among those who actually survived) for each score. The AUC is an overall summary of diagnostic accuracy. AUC equals 0.5 when ROC curve corresponds to random chance and 1.0 indicates perfect accuracy [24]. A good diagnostic tool is usually considered when AUC is higher than 0.8 [22]. The AUC value of our mortality regression equation was 0.66 ± 0.07 . However, this value was not different when compared with APACHE II AUC value $(0.75 \pm 0.06, p=0.27)$ (Table 5). It is also interesting to observe that our scoring model was associated with mortality, with a mortality rate of 54.5% in proteints with shock and 54.5% in patients with shock and hypoalbuminemia.

When the mean APACHE II scores from each equation result were compared to each other, the group with higher equation result presented higher APACHE II values, and lower values in lowest group (p=0.01). Another interesting result is that the presence of shock was associated with higher APACHE II values, reinforcing this diagnostic importance in outcome prediction.

A potential limitation of this study should be noted. Our sample size limited the number of variables that we could statistically analyze in Phase 1. For that reason, other variables or measures may exist that would improve the accuracy of the mortality prediction model. For example: presence of disseminated intravascular coagulation, hypoglycemia, direct admission or transfer from outside facility. Therefore, our model needs to be validated in other ICU settings.

Considering the real advantage of our method in front of the other prognostics tools, our model is equivalent to the more complex APACHE II model at predicting ICU mortality. Other models are more complex and not as easily or appropriately utilized in a busy ICU setting. In addition, our method can be applied, like SAPS (Simplified Acute Physiology Score) 3, at ICU admission. We should take into account that APACHE II, III, IV and SAPS 2 need to be completes 24 hours after admission.

5. CONCLUSION

In conclusion, this simple and accurate prognostic tool can be used to predict the probability of mortality in the ICU.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All procedures were approved by the Research Ethics Committee of Botucatu Medical School, Sao Paulo State University, UNESP. All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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