Predictors of mortality and median survival time of critically ill patients
Preditores de mortalidade e tempo médio de sobrevivência dos pacientes críticos
Predictores de mortalidad y tiempo promedio de supervivencia de los pacientes críticos

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Conflicts of interest: nothing to declare.

Abstract
Objective: To analyze the predictors of mortality and the average survival time of patients hospitalized in Intensive Care Units.

Methods: This is a prospective cohort, carried out from August 2018 to July 2019, in four adult Intensive Care Units (ICU) from the public and private network of the State of Sergipe. All adult patients were included, provided they had a minimum length of stay of 24 hours in the unit. The primary outcome was death. Secondary outcomes were dialysis, pressure injury, Acute Kidney Injury, need for invasive mechanical ventilation for more than 48 hours, infection, and length of hospital stay.

Results: Of the 432 patients, there was a predominance of death in male patients, older and coming from the emergency unit. The presence of heart failure, creatinine values >1.5 mg/dL at admission, diabetes mellitus, liver disease and smoking were also associated with the death outcome. As for the other predictors, the longest hospital stay, higher Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiologic (SAPS 3) and Nursing Activities Score (NAS) scores, in addition to the use of noradrenaline, stand out. The use of fentanyl was associated with increased survival time and the overall median survival time was 28 days.

Conclusion: The mortality predictors of patients admitted to the ICU in Sergipe were longer length of stay; the highest SOFA, SAPS-3 and NAS scores; creatinine >1.5mg/dl on admission; use of vasopressor drugs and the need for dialysis.

Keywords
Mortality; Survival; Critical care; Organ dysfunction scores; Inpatients; Intensive care units

Descritores
Mortalidade; Sobrevida; Cuidados críticos; Escores de disfunção orgânica; Pacientes internados; Unidades de terapia intensiva

Descritores
Mortalidad; Sobrevida; Cuidados críticos; Puntuaciones en la disfunción de órganos; Pacientes internados; Unidades de cuidados intensivos

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Corrige o texto,
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Introduction

Intensive medicine has made great advances in recent decades, making the care provided in Intensive Care Units (ICU) have significant importance in patient survival. Thus, knowing the sociodemographic, clinical and epidemiological characteristics has been shown to be strategic and assisted in the identification of risks and definition of qualitative and quantitative interventions as a goal to improve the care provided. (1)

Even with the large technological apparatus and new care modalities offered in ICUs, mortality is still high, ranging from 25 to 33%. (2–4) In Brazil, this percentage is more expressive, between 9.6 and 58%. (5–7) These data show the need for early analysis and interventions on predictors of mortality in ICUs.

Both mortality predictors and clinical characteristics of patients in intensive care already indicate that advanced age; the severity of the disease; length of stay in the ICU; hospital interventions, such as the use of mechanical ventilation and vasoactive drugs prior to ICU admission are risk factors for mortality. (8) In addition, the number of associated comorbidities, higher baseline Simplified Acute Physiology (SAPS 2) and Sequential Organ Failure Assessment (SOFA) scores were also associated with worse outcomes. (9) Sepsis from ICU admission and male gender are also associated with mortality. (10) It is worth noting that the SAPS II-adjusted risk of death increases by 5% for each additional point of this score. (10) The assessment of the clinical profile of patients using SAPS and SOFA scores is crucial for implementing strategies to reduce mortality, through continuous assessment of these scores by the ICU care and management staff.

To assist in predicting ICU mortality, different severity and prognosis scores are available: those of organ dysfunction, such as the SOFA, which assesses the extent of the severity of organ dysfunction and the prognostic model of disease severity, which proposes to estimate the chance of death. (11) Assessment of these scores contributes to better management of ICU so that identifying predictors of ICU mortality associated with risk stratification, through the results of the scores, are crucial for the implementation of measures and for assessing quality of care. (12)

The relevance of this study consists in the assessment of variables that impact mortality in ICUs in Sergipe, which contributes to the implementation of strategies to reduce outcomes by the management of the respective sector, in order to cause positive impacts in the reduction of hospital mortality and in the management of quality of health services. Thus, the objective of this study was to analyze the predictors of mortality and the mean survival time of patients hospitalized in ICUs.
Methods

This is a prospective cohort carried out between August 2018 and July 2019, with 430 patients from four ICUs located in the state of Sergipe, in northeastern Brazil, three of which are public referrals and one is private.

In order to provide anonymity, hospitals were coded as: H1, a medium-complexity hospital located in the central region of the state, is a reference in emergency care in the non-metropolitan region of Sergipe, which has 11 ICU beds. H2, located in the central-south region of Sergipe, consists of a teaching hospital linked to the Universidade Federal de Sergipe, with care on spontaneous demand and 22 ICU beds. H3, located in the capital, has access through regulation, with care organized by referenced demand, with 05 ICU beds. H4 is a private institution, located in the capital, classified as large, with access by spontaneous demand, with 22 ICU beds. The ICUs were listed for the study due to the possibility of greater access for patients, both because they have a reference ICU in Sergipe, and because they have the main ICUs in the non-metropolitan region of the state.

Patients aged 18 years or older and with a minimum stay of 24 hours in the ICU were included. Patients without creatinine results, which made it impossible to classify Acute Kidney Injury (AKI) according to the criterion “Kidney Diseases: Improving Global Outcomes” (KDIGO) and those with missing or incomplete study variables, were excluded.

Data were collected by a trained team, in which at least two researchers, on a shift basis, made daily visits to the four ICUs, distributed throughout the state, for seven consecutive days, after the inclusion of patients in the study. The data collection instrument was developed by the authors themselves and was organized in the following domains: demographic data; clinical features; ICU admission support; and clinical outcomes.

Variables of interest were age, sex, race, origin and presence of comorbidities, according to the International Classification of Diseases (ICD-10). Primary outcomes were death and survival. Secondary outcomes were discharge, dialysis, pressure injury (PI), AKI, need for invasive mechanical ventilation for more than 48 hours, cardiovascular and neurological complications (stroke), infection, length of hospital stay.

Mortality was defined as death from any cause during the ICU and hospital follow-up period and patients who survived until discharge or their transfer to another institution were classified as survivors.

The laboratory tests collected (urea, serum creatinine, electrolytes and liver profile) in the ICU routine, available in the medical records, were followed up to record the outcomes. After the seventh day of hospitalization, if patients were still hospitalized in the unit, researchers continued to monitor them until they left the ICU, either by discharge, death or transfer to another institution. However, the test records were no longer performed after the first seven days of hospitalization.

SAPS 3 and SOFA were calculated in the first 24 hours of ICU admission. The SAPS is a score used as a predictive index of mortality, in which SAPS 2 assesses clinical characteristics associated with the current context of patients in the ICU, while SAPS 3 makes an assessment with greater emphasis on the flow of patients until admission to the ICU, such as the in-hospital location of patients before admission to the ICU, length of hospital stay and the like.(13) SOFA is the gold standard score for assessing mortality from sepsis.(13) The Nursing Activities Score (NAS), the score used to assess the nursing workload, was calculated from the consultation of nursing records, medical prescription and patients’ water balance in the last 24 hours. All NAS variables (basic activities, ventilatory support, cardiovascular, renal, neurological, metabolic and specific interventions) were of interest for this study.

Comorbidities were assessed using the Charlson Comorbidity Index, adjusted for age. This index assesses in-hospital mortality by measuring patients’ clinical profile and comorbidities, such as the presence of diabetes mellitus, heart failure, history of acute myocardial infarction, stroke, and the like.(14)
Categorical variables were described by absolute and relative frequencies. Continuous variables were presented as mean and standard deviation, median and interquartile range. The hypothesis of independence between categorical variables was tested by the chi-square test. Differences in measures of central tendency were verified by the Mann-Whitney test. Mean survival times were estimated using Cox regression. The significance level adopted was 5% and the software used was R Core Team 2020.

The study was previously approved by the Research Ethics Committee of the Universidade Federal de Sergipe (UFS), with favorable opinion under number 2,830,187 and CAEE (Certificado de Apresentação para Apreciação Ética - Certificate of Presentation for Ethical Consideration) 92517018.0.0000.5546.

**Results**

During the study period, 430 patients were included. The comparative analysis between clinical and demographic characteristics of individuals shows that patients in the AKI group were older (67 [56-79] years vs. 57 [45-70] years, <0.001) and, for the most part, from the emergency unit (p<0.001). The mortality found among the patients assessed was 32.1%. When comparing clinical and demographic characteristics, a statistically significant difference was observed for the variables age, unit of origin before admission to the ICU, diagnosis of heart failure, diabetes and liver disease, baseline creatinine > 1.5 mg/dl and a previous cerebral ischemic event, being higher among patients who died when compared with survivors. Moreover, in support of ICU admission, patients in the death group were more severe, demonstrated by greater need for vasoactive drugs, invasive procedures and worse SAPS III scores and Charlson comorbidity index (Table 1).

Table 2 shows the comparison between the assessed groups, where worse outcomes are observed among those who died, including the need for dialysis (26.6% vs. 7.9%, p<0.001), development of PI (22.5% vs. 6.3%, p<0.001) and AKI (48.9% vs. 16.2%, p<0.001), acute myocardial infarction (8.0% vs. 2.1%, p=0.003), stroke (10.9% vs. 2.1%, p<0.001), use of mechanical ventilation for more than 48 hours after admission (71.7% vs. 21.2%, p<0.001) and infection (60.6% vs. 19%, p<0.001) (Table 2).

During daily follow-up of patients for seven days in the ICU, it was possible to observe that in the death group, water balance, diuresis, serum creatinine, hemoglobin and lactate levels, as well as workload (measured by NAS) and SOFA score were worse when

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**Table 1. Clinical-demographic characterization and admission support of assessed patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Death (n, %)</th>
<th>Surviving (n, %)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70 (50.7)</td>
<td>146 (50)</td>
<td>0.888</td>
</tr>
<tr>
<td>Female</td>
<td>68 (49.3)</td>
<td>146 (50)</td>
<td></td>
</tr>
<tr>
<td>Age in years, med (IQR)</td>
<td>67 (56-79)</td>
<td>57 (45-70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight in kg, med (IQR)</td>
<td>61 (51-70)</td>
<td>60.8 (52.2-68.9)</td>
<td>0.788</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>74 (54)</td>
<td>111 (38.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical center</td>
<td>17 (12.4)</td>
<td>136 (46.9)</td>
<td></td>
</tr>
<tr>
<td>Medical clinic</td>
<td>41 (29.9)</td>
<td>33 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Surgical clinic</td>
<td>5 (3.6)</td>
<td>103 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>23 (17.4)</td>
<td>24 (8.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Previous acute myocardial infarction</td>
<td>20 (14.9)</td>
<td>25 (8.7)</td>
<td>0.055</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73 (54.1)</td>
<td>139 (48.1)</td>
<td>0.251</td>
</tr>
<tr>
<td>Current smoker</td>
<td>16 (11.9)</td>
<td>27 (9.4)</td>
<td>0.417</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>41 (30.6)</td>
<td>69 (23.9)</td>
<td>0.143</td>
</tr>
<tr>
<td>Baseline creatinine &gt; 1.5 mg/dl</td>
<td>39 (29.5)</td>
<td>39 (13.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>49 (36)</td>
<td>62 (21.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Liver disease</td>
<td>18 (13.4)</td>
<td>16 (5.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>31 (23.1)</td>
<td>25 (8.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ICU admission support

| Use of dobutamine | 6 (4.4) | 3 (1) | 0.024   |
| Use of noradrenaline | 53 (38.4) | 37 (12.7) | <0.001   |
| Use of fentanyl   | 79 (56.8) | 80 (27.5) | <0.001   |
| Use of midazolam  | 52 (37.7) | 41 (14.1) | <0.001   |
| Nasoenteral tube  | 82 (59.4) | 99 (34.4) | <0.001   |
| Orotracheal tube  | 82 (59.4) | 87 (30.1) | <0.001   |
| Central venous catheter | 68 (49.3) | 111 (38.4) | 0.033   |
| Indwelling urinary catheter | 102 (73.9) | 223 (77.4) | 0.424   |
| Nasogastric intubation | 24 (17.4) | 34 (11.8) | 0.112   |
| Admission SAPS 3, med (IQR) | 34 (27-64) | 21 (13-31) | <0.001   |
| Charlson, med (IQR) | 43 (6) | 30 (4) | <0.001   |

n - absolute frequency; % - percentage relative frequency; MED-Median; IQR-Interquartile Range; Q- Pearson’s chi-square test; Pearson’s QM-Ch-Square Test with Montecarlo correction; W- Mann-Whitney test; ICU-Intensive Care Unit; SAPS-Simplified Acute Physiology Score.
increased by 51% with the use of noradrenalin. The risk ratio for death in this time was related to previous smoking (MST=20.31, p=0.010), use of vasopressor (noradrenaline) (MST=23.25, p=0.018), need for dialysis (MST=21.31, p =0.039) and the development of AKI (MST= 20.65, p<0.001). However, the use of fentanyl increased the chance of survival by about 1.42 times. Moreover, the risk ratio for death increased threefold for liver disease, twice for AKI and increased by 51% with the use of noradrenalin.

compared to the survivor group. For the variables serum creatinine and urine output, in all seven days the values were significantly higher in the death group when compared to the non-survivors (Table 3).

The overall median survival time (MST) for the study patients was 28 days. The decrease in this time was related to previous smoking (MST=20.31, p=0.010), use of vasopressor (noradrenaline) (MST=23.25, p=0.018), need for dialysis (MST=21.31, p =0.039) and the development of AKI (MST= 20.65, p<0.001). However, the use of fentanyl increased the chance of survival by about 1.42 times. Moreover, the risk ratio for death increased threefold for liver disease, twice for AKI and increased by 51% with the use of noradrenalin.
Discussion

In this study, it was possible to analyze the predictors of mortality in ICU patients, with emphasis on longer hospital stays; the highest SOFA, SAPS-3 and NAS scores; creatinine >1.5 mg/dl on admission; the use of vasopressor drugs (noradrenaline) and the need for dialysis.

Most patients who had death as an outcome were male, with a mean age of 67 years, coming from the emergency unit. Regarding clinical characteristics, they had a history of heart failure, creatinine above 1.5 mg/dL on admission, diabetes mellitus, liver disease and stroke. The mean overall survival time was estimated at 28 days.

Advanced age represents a predictive factor for death, when associated with multiple comorbidities, especially with regard to diabetes mellitus, arterial hypertension and use of polypharmacy, that contribute to the development of AKI and, consequently, to the higher probability of death among intensive care patients. In addition to age, being a smoker, having liver disease and/or heart failure are predictors of ICU mortality. Therefore, it is necessary to use clinical scores capable of predicting the risk of death in this population, such as the SOFA and SAPS 3.

Another important finding of this study was the correlation between higher SAPS-3 and NAS scores with prolonged hospital stay. The origin of the emergence also contributed to the increase in SAPS 3. This finding is similar to other investigations, which showed higher SAPS 3 scores associated with increased length of stay, higher workloads and admission severity.

The NAS has been configured as an important tool for the nursing team sizing and its attributions in the face of critical patients. According to this measure, a nurse can take care of several patients or more than one nurse can take care of a patient. Therefore, studies that assess the NAS applicability have contributed directly to safety and quality of care. Recently, researchers revealed that the high nursing workload, assessed by the NAS at the time of discharge from the ICU, was associated with the risk of readmission. Thus, nursing professional sizing is related to quality of hospital care, in order to reduce negative clinical outcomes.

Additionally, patients who died had a NAS score 1.23 times higher when compared to survivors. Variables such as the vasoconstrictor effect of noradrenaline, immobility in bed, high NAS score and decrease in the frequency of changes in patients’ decubitus position, can affect worse outcomes, such as increased incidence of pressure injuries and AKI (AKI-KDIGO 2 and 3). It is known that excessive use of norepinephrine can increase serum creatinine levels and result in the need for dialysis. Therefore, noradrenaline has been associated with AKI in the presence of hypovolemia and shock.

Moreover, over time, there was an association between mortality and renal complications. In this study, it was observed that the profile of greater severity of patients, when identified through the NAS or SOFA score, associated with increased creatinine levels, increases the mortality of ICU patients due to AKI, which negatively impacts in patient care quality. Therefore, Vasconcelos et al. agree regarding the use of scales to predict mortality, in addition to associating age, male gender, increased creatinine, PI, high SOFA and NAS scores as greater chances for the development of AKI, also found in the present study.

Accurate measurement of patients’ fluid balance is also a highly important variable for predicting clinical outcomes in the ICU, since positive fluid balance values were associated with the outcome of death in this study. The importance of constant assessment of direct creatinine, measured through the analysis of creatinine in urine, together with serum creatinine and urinary flow, assessed per hour, is highlighted, as the ideal to adequately identify patients at risk for the development of AKI. The promotion of management strategies for the early diagnosis of this problem is highlighted, in order to improve treatment strategies and then reduce mortality. The risk stratification for AKI is observed as a feasible activity for the nursing team, since both the water balance and the creatinine analysis are routine activities and represent indicators that predict adverse health outcomes.
The risk ratio for death was also associated with liver disease in this study. A retrospective analysis, with patients with liver disease in a Portuguese ICU, identified that alcohol consumption was the most frequent cause of cirrhosis and mortality after ICU admission (53.5%), with sepsis being the main cause of death in that population. In a Portuguese cohort, mortality was also associated with hepatic encephalopathy, renal replacement therapy, use of vasopressors, invasive mechanical ventilation and others.\(^{(29)}\)

In this study, death was associated with the development of PI (22.5% vs. 6.3%, \(p<0.001\)). Corroborating these findings, a study, also developed in Sergipe, identified that, when the risk factors for the development of PI were assessed, patients with AKI had more than 3.5 times the chance of developing PI (95% CI, 1.08 - 11.65; \(p=0.036\)). When assessing the length of ICU stay, it was observed that for each extra day of hospitalization patients is 3.5% more likely to develop a new PI.\(^{(23)}\)

Norepinephrine is also associated with AKI. Such a drug, when used in cases of hypovolemia and shock, can compromise renal function in order to increase mortality.\(^{(27)}\) Therefore, its use should be performed with caution, since such a practice increases the incidence of AKI by 2.92 times, which compromises the prognosis of patients.\(^{(27)}\)

The risk ratio for death was also associated with liver disease in this cohort. A retrospective analysis, with patients with liver disease in a Portuguese ICU, identified that alcohol consumption was the most frequent cause of cirrhosis and mortality after ICU admission (53.5%), with sepsis being the main cause of death in that population. In the Portuguese cohort, mortality was also associated with hepatic encephalopathy, renal replacement therapy, use of vasopressors, invasive mechanical ventilation, and others.\(^{(29)}\)

However, the use of fentanyl increased the chance of survival by about 1.42 times. The relationship between fentanyl use depends on the context of analysis and risk exposure. However, Casault et al. associated fentanyl with higher mortality when compared to propofol and midazolam.\(^{(29)}\)

This study has some limitations. First, be conducted in a single region of the country, which has singularities in relation to material and social structures. Moreover, there was a lack of clinical and demographic data in medical records, which prevented a significant sample of participants. It is suggested to replicate the study, in a multicenter manner, in order to visualize the aforementioned variables in different realities.

It is noteworthy that this is the first study that assessed the severity scores and the nursing workload, through the NAS calculation in four important public and private intensive care units, located in a northeastern Brazilian state. The data presented may contribute to a multidisciplinary care guided by the analysis of specific clinical variables of patients, i.e., advanced age, for example, and also dynamic variables such as SOFA scores, NAS, urinary output, duration of mechanical ventilation, among others, which favors the consolidation of clinical reasoning and promotes the advancement of clinical and managerial practice strategies for managing patient care quality.

**Conclusion**

Mortality predictors of patients admitted to ICUs in the state of Sergipe were longer length of stay; the highest SOFA, SAPS-3 and NAS scores; creatinine >1.5mg/dl on admission; the use of vasopressor drugs (noradrenaline), and the need for dialysis. The use of fentanyl increased the chance of survival by about 1.42 times. The overall MST was 28 days and the risk ratio for death was increased by the presence of liver disease, AKI, and noradrenaline use. Patients who died had a longer hospital stay and higher SOFA, SAPS-3 and NAS scores. The present study contributes to the science of the factors that interfere in the mortality of critically ill patients, providing knowledge of the clinical profile of patients and proposing strategies for management and care interventions, in order to positively impact the survival of critically ill patients.
Predictors of mortality and median survival time of critically ill patients

Collaborations

Oliveira JC, Vasconcelos GMT, Bispo LDG, Magro MCS, Fonseca CD, Pinheiro FGMS and Santana-Santos E contributed to project design, data analysis and interpretation, article writing, relevant critical review of intellectual content and approval of the final version to be published.

References