Original Article

Evaluation of time to death after admission to an intensive care unit and factors associated with mortality: A retrospective longitudinal study

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ABSTRACT

Background: Among nonsurvivors admitted to the intensive care unit (ICU), some present early mortality while other patients, despite having a favorable evolution regarding the initial disease, die later due to complications related to hospitalization. This study aims to identify factors associated with the time until death after admission to an ICU of a university hospital.

Methods: Retrospective longitudinal study that included adult patients admitted to the ICU between January 1, 2008, and December 31, 2017. Nonsurviving patients were divided into groups according to the length of time from admission to the ICU until death: Early (0–5 days), intermediate (6–28 days), and late (>28 days). Patients were considered septic if they had this diagnosis on admission to the ICU. Simple linear regression analysis was performed to evaluate the association between time to death over the years of the study. Multivariate cox regression was used to assess risk factors for the outcome in the ICU.

Results: In total, 6596 patients were analyzed. Mortality rate was 32.9% in the ICU. Most deaths occurred in the early (42.8%) and intermediate periods (47.9%). Patients with three or more dysfunctions on admission were more likely to die early \((P < 0.001)\). The diagnosis of sepsis was associated with a higher mortality rate. The multivariate analysis identified age >60 years (hazard ratio [HR] 1.009), male (HR 1.192), mechanical ventilation (HR 1.476), dialysis (HR 2.297), and sequential organ failure assessment >6 (HR 1.319) as risk factors for mortality.

Conclusion: We found a higher proportion of early and intermediate deaths in the study period. The presence of three or more organ dysfunctions at ICU admission was associated with early death. The diagnosis of sepsis evident on ICU admission was associated with higher mortality.

Key Words: Intensive care units, in-hospital mortality, multiple organ failure, university hospitals

Cite this article as: Mezzaroba AL, Larangeira AS, Morakami FK, Junior JJ, Vieira AA, Costa MM, et al. Evaluation of time to death after admission to an intensive care unit and factors associated with mortality: A retrospective longitudinal study. Int J Crit Illn Inj Sci 2022;12:121-6.

Received: 23.11.2021; Revision: 14.01.2022; Accepted: 26.01.2022; Published: 20.09.2022.
INTRODUCTION

Despite technological, laboratorial, and drug advances, mortality rates in intensive care units (ICUs) are still quite variable and dependent on the patient population evaluated, severity of the disease, reasons for hospitalization, and quality of the service offered, with the rates ranging from 6.4% to 40%.\(^1\)\(^-\)\(^3\)

Among nonsurvivors admitted to the ICU, some present early mortality, which is generally related to the severity of the initial diagnosis at hospitalization, while other patients have a favorable evolution regarding the initial disease, but die later due to complications related to hospitalization. Among these complications, sepsis stands out as one of the main causes of multiple organ dysfunction and is determinant of increased early and late mortality in critically ill patients.\(^1\)\(^-\)\(^5\)

Few studies in the literature show the factors associated with the time to death in patients hospitalized in ICUs.\(^6\)\(^-\)\(^9\) In addition, definitions of “early death” and “late death,” according to the time between the patient’s admission to the ICU and their death, are inconsistent since there is no consensus on the definitions and ICUs diverge widely according to their epidemiological profiles in relation to median time to death.\(^8\)

It has been suggested that gross national income is a major determinant of time to death.\(^7\) Knowledge of the factors associated with the time to death of patients admitted to the ICU has organizational and ethical implications. Recognition of these factors could improve the prognostic assessment of patients and assist in the treatment and optimization of resources, with more aggressive and direct action being focused on specific factors more commonly related to death.\(^1\)\(^,\)\(^6\)\(^,\)\(^8\) This understanding could also contribute to the optimization of the flow of ICU beds: The possible transfer of patients without the prospect of clinical recovery to palliative care units would increase the availability of ICU beds and, therefore, reduce access time for critical patients.

The aim of this study was to analyze the factors associated with the time to death of critically ill patients in a general ICU of a public university hospital.

METHODS

A retrospective longitudinal study was carried out with a convenience sample of adult patients admitted to the ICU of a public university hospital from January 1, 2008, to December 31, 2017. The number of beds in the adult ICU at this hospital ranged from 17 to 20 beds during the study and clinical and surgical patients were admitted to the ICU.

The study was approved by the institutional review board/ethics committee. Written consent requirement was waived by the ethics committee for the purpose of the present study. This manuscript adheres to the strobe guidelines.

Patients were screened using a list generated by the hospital statistical sector of all ICU admissions that occurred in the study period. Patients under 18 or with an unknown age, those with missing data, and ICU readmissions were excluded from the analysis. Missing data were handled by listwise deletion, and all data from any participant with missing values were deleted.

Complete data were collected from all patients included in the study until the hospital outcome. The primary outcome considered was death on ICU discharge.

The general data collected for all admissions to the ICU were age, sex, date of admission to the hospital and the ICU, main diagnosis on admission to the ICU, sector of origin, date of discharge from the ICU and the hospital, and outcome at discharge from the ICU and the hospital.

The data collected for all patients during the ICU stay were the presence of a chronic disease, need for mechanical ventilation, need for dialysis, use of vasoactive drugs, and scores on the acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA) on the 1st day of admission to the ICU, and therapeutic intervention scoring system 28 (TISS 28). Other important variables collected were length of hospital stay and length of stay in the ICU.

The patient’s medical records and the hospital’s electronic database were used as sources for data collection (MedView by Dedalus HealthCare Systems Group Brasil, Barueri, Brazil). All data for the calculation of scores were collected as raw data, using the extremes of abnormality during the first 24 h of ICU stay. Score calculations were performed according to the definitions of the respective systems. For the APACHE II score, the missing data were assigned normal values, as originally described by Knaus et al.\(^9\)

Patients admitted to the ICU during the study period were divided into survivors and nonsurvivors based on the outcome of the ICU admission.

Nonsurvivors in the ICU were divided into three study groups according to the time to death after admission to the ICU: Early group (up to 5 days), intermediate group (6–28 days), and late group (more than 28 days). This division was based on a post hoc analysis performed in 2016 of an international database that included 10,069 patients, which was chosen so that the results could be comparable.\(^7\)
In addition, patients who did not survive in the ICU and the hospital were also divided into septic and nonseptic patients; according to the current consensus definition, septic patients were those who had the diagnosis of sepsis noted on admission to the ICU. Organ dysfunction was defined as a SOFA score >2 for the organ in question on ICU admission; when the patients did not have previous known diseases, the basal SOFA score was considered zero.

The results of continuous variables are described as means, medians, and interquartile ranges (IQR). Categorical data are presented as frequency and presented in tables and graphs. The association between categorical variables was assessed using the Chi-square test.

Simple linear regression analysis was performed to evaluate the association between time to death over the years of the study. Multivariate cox regression was used to assess risk factors for the outcome in the ICU, and the results are expressed as hazard ratio and 95% confidence interval.

The significance level used was 5% and the analyses were performed using SPSS Statistics for Windows, version 19.0 (Armonk, NY, USA: IBM Corp.).

RESULTS

Data were collected from 7,158 patients admitted to the adult ICU of the HU/UEL during the study period. After the exclusion of 159 patients under the age of 18 or with an unknown age, five patients with missing data, and 398 patients who were readmitted to the ICU, totaling 562 exclusions (7.8%), data from 6,596 patients were included in the statistical analysis [Figure 1].

There was a mean of 660 ICU admissions per year over the 10 years of the study. The median age of hospitalized patients was 60 (IQR 45–73) years, with a predominance of males (56.9%). Most patients were admitted from the emergency department (56.2%), and, when classified according to the type of admission, 62.4% had a surgical diagnosis (37.6% of the total patients after elective surgery and 24.8% after emergency surgery) and 37.6% had a clinical diagnosis. Regarding the use of invasive intensive support measures during the ICU stay, 3,877 (58.8%) patients required mechanical ventilation, 1,164 (17.6%) used hemodialysis, and 2,277 required vasoactive drugs while in the ICU.

Regarding the scores collected on the 1st day of admission to the ICU, the median of the APACHE II was 19 (IQR 13–28), of the TISS‑28 was 26 (IQR 20–32), and of the SOFA was 6 (IQR 3–11). In relation to the APACHE II, considering serious chronic diseases that receive points in this score, 14.4% of the hospitalized patients presented these comorbidities. When analyzing the SOFA score for admission to the ICU, 40.5% of the patients presented normal organ functions and 59.5% had one or more organ dysfunctions. The median length of stay in the ICU was 4 (IQR 1–10) days, while the median length of hospital stay was 16 (IQR 8–29) days. The evaluated patients had 32.9% mortality in the ICU and 43.3% mortality in the hospital.

Table 1 presents the analysis of the relationship between mortality rates in the ICU and hospital with the number and types of organ dysfunctions presented by patients on the 1st day of ICU admission in the SOFA score. Both ICU and hospital mortality increased progressively according to the number of organ dysfunctions at ICU admission. ICU mortality was from 6.8% for patients with no organ dysfunction to 87.8% for patients with more than three dysfunctions (P < 0.001). In relation to hospital mortality, the variation was from 13.5% for patients without dysfunction to 92% for patients with more than three dysfunctions (P < 0.001).

The presence of any of the six types of organ dysfunction on the SOFA (cardiovascular, respiratory, central nervous system, renal, coagulation, and liver), both alone and in combination, was determinant for increased ICU mortality and hospital mortality (P < 0.001) when compared with patients who did not have any dysfunctions. The association of organ dysfunctions with hospital mortality was similar between the six organ systems analyzed [Table 1].

As shown in Figure 2 and Table 2, the 2,167 patients who died in the ICU were divided into three groups, according to the time since their admission to the ICU: Early group (up to 5 days: 42.8%), intermediate group (6–28 days: 47.9%), and late group (more than 28 days: 9.3%). There was a predominance of deaths in the intermediate group of patients with zero to two organ dysfunctions on the SOFA on admission to the ICU, (P < 0.001). Among...
Table 1: Mortality in the intensive care unit and hospital according to the number and types of organ dysfunctions evaluated by the sequential organ failure assessment score on the first day of hospitalization

| Number of organ dysfunctions* | ICU mortality, n (%) | Hospital mortality, n (%) |
|-------------------------------|----------------------|---------------------------|
| 0                             | 181 (6.8)            | 360 (13.5)                |
| 1                             | 368 (26.7)           | 602 (43.7)                |
| 2                             | 636 (51.5)           | 810 (65.5)                |
| 3                             | 609 (69.0)           | 696 (78.8)                |
| >3                            | 373 (87.8)           | 391 (92.0)                |
| Total                         | 2167 (32.9)          | 2859 (43.3)               |

Table 2: Time to death in the intensive care unit according to the number and types of organ dysfunctions by the sequential organ failure assessment score on the first day of hospitalization

| Type of organ dysfunction** | ICU mortality according to dysfunction | Hospital mortality according to dysfunction |
|-----------------------------|----------------------------------------|--------------------------------------------|
| Cardiovascular*             | 1470 (60.7)/697 (16.7)                 | 1723 (71.1)/1136 (27.2)                    |
| Respiratory*                | 902 (65.6)/1265 (24.2)                 | 1023 (74.3)/1836 (35.2)                    |
| CNS*                       | 1676 (59.0)/491 (13.1)                 | 2032 (72.3)/507 (21.5)                     |
| Renal*                     | 850 (63.8)/1317 (25.0)                 | 991 (74.3)/1868 (35.5)                     |
| Coagulation*               | 114 (68.3)/2053 (31.9)                 | 125 (74.9)/2734 (42.5)                     |
| Liver*                     | 74 (60.7)/2093 (32.3)                  | 85 (69.7)/2774 (42.8)                      |

*ICU mortality and hospital mortality: P < 0.001. **Alone or combined. ICU: Intensive care unit, CNS: Central nervous system

**DISCUSSION**

Patients with three or more dysfunctions on admission, most deaths were in the early group (P < 0.001).

Patients were divided into two groups according to the diagnosis or not of sepsis on admission to the ICU [Table 3]. Mortality rate in the ICU was higher for septic patients (48.8%) compared to nonseptic patients (12.4%; P < 0.001). The same was observed for hospital mortality (P < 0.001). The differences in mortality rates between groups of septic and nonseptic patients progressively reduced with the increase in the number of organ dysfunctions. In the absence of organ dysfunction, the mortality of the septic group in the ICU was 17.8% and that of the nonseptic group was 2.5%. On the other hand, when there were more than three organ dysfunctions on admission, ICU mortality was 88.6% for septic patients and 81.3% for nonseptic patients (P < 0.001).

The proportion of early, intermediate, and late deaths was not different when comparing the group of patients diagnosed with sepsis on admission to the ICU with the group of patients without sepsis (P = 0.139).

Simple linear regression of the three groups was performed according to the time to death in the ICU over the years of the study. The linear regression of the early group resulted in \( r = 0.49 \) and \( P = 0.152 \), of the intermediate group in \( r = 0.47 \) and \( P = 0.171 \), and of the late group in \( r = 0.19 \) and \( P = 0.590 \).

In the cox regression to analyze risk factors for death in the ICU during the study, age over 60 years, male, use of mechanical ventilation on admission to the ICU, dialysis during the ICU stay, and a SOFA > 6 on admission to the ICU were significant, as shown in Table 4.

Early and intermediate mortality were more frequent in the patients analyzed in the present study and this
Table 3: Mortality rates according to the number and types of organ dysfunctions by the sequential organ failure assessment score on admission and the presence of sepsis on admission

| Variables | ICU mortality | Hospital mortality |
|-----------|---------------|--------------------|
|           | Septic (n=3704), n (%) | Nonseptic (n=2892), n (%) | Septic (n=3704), n (%) | Nonseptic (n=2892), n (%) |
| Total deaths* | 1808 (48.8) | 359 (12.4) | 2282 (61.6) | 576 (19.9) |
| Number of organ dysfunctions* | 0 | 133 (17.8) | 48 (2.5) | 216 (29.0) | 144 (7.5) |
| | 1 | 295 (33.5) | 73 (14.7) | 461 (62.3) | 141 (28.3) |
| | 2 | 517 (64.6) | 119 (41.2) | 651 (68.7) | 159 (65.0) |
| | 3 | 529 (70.3) | 80 (61.5) | 604 (80.2) | 92 (70.8) |
| | >3 | 334 (88.6) | 39 (81.3) | 351 (93.1) | 40 (83.3) |
| Type of organ dysfunction** | Cardiovascular* | 1253 (65.4) | 217 (43.0) | 1450 (75.6) | 273 (64.1) |
| | Respiratory* | 792 (67.5) | 110 (64.2) | 896 (76.4) | 127 (62.6) |
| | CNS* | 1413 (61.5) | 263 (48.4) | 1711 (74.5) | 341 (62.8) |
| | Renal* | 739 (71.4) | 111 (37.2) | 850 (82.1) | 141 (47.3) |
| | Coagulation*** | 106 (74.6) | 8 (32.0) | 113 (79.6) | 12 (48.0) |
| | Liver**** | 69 (67.6) | 5 (25.0) | 77 (75.5) | 8 (40.0) |

*ICU mortality and hospital mortality: P<0.001. **Alone or combined. ***ICU mortality and nonseptic: P=0.003, Others: P<0.001. ****ICU mortality and septic: P<0.001, ICU mortality and nonseptic: P=0.087, hospital mortality and septic: P=0.003, hospital mortality and nonseptic: P=0.024. CNS: Central nervous system, ICU: Intensive care unit.

Table 4: Cox regression model as a function of mortality risk factors in the intensive care unit during the study period

| Variables | Univariate | Multivariate* |
|-----------|------------|---------------|
|           | HR | 95% CI | P | HR | 95% CI | P |
| Age > 60 years | 1.009 | 1.005-1.013 | <0.001 | 1.009 | 1.005-1.013 | <0.001 |
| Male sex | 1.190 | 1.044-1.356 | 0.009 | 1.192 | 1.046-1.358 | 0.009 |
| Type of admission** | | | | | | |
| Elective surgery | 0.966 | 0.817-1.141 | 0.682 | | | |
| Emergency surgery | 1.022 | 0.867-1.206 | 0.795 | | | |
| MV on admission*** | 1.474 | 1.158-1.877 | 0.002 | 1.476 | 1.161-1.876 | <0.001 |
| Dialysis in the ICU | 2.313 | 1.978-2.704 | <0.001 | 2.297 | 1.966-2.684 | <0.001 |
| Sepsis*** | 1.021 | 0.854-1.220 | 0.820 | | | |
| SOFA > 6 *** | 1.320 | 1.293-1.347 | <0.001 | 1.319 | 1.292-1.345 | <0.001 |
| Use of VAD in the ICU | 0.897 | 0.784-1.026 | 0.114 | | | |

*Stepwise forward method, **Reference category for statistical analysis: Admission type: Clinic, ***On admission to the ICU. HR: Hazard ratio, CI: Confidence interval, MV: Mechanical ventilation, ICU: Intensive care unit, SOFA: Sequential organ failure assessment, VAD: Vasoactive drug

pattern was constant over 10 years. The number of organ dysfunctions and a sepsis diagnosis at ICU admission were associated with this pattern.

The demographic profile of the patients analyzed in this study is similar to the national pattern, although the use of invasive support on admission was higher in our sample.[11] This study confirms previous findings in that the greater the number of organ dysfunctions on admission to the ICU, the greater the mortality in the ICU and hospital.[3,7,8] Previous publications have described a greater impact on mortality for the neurological and cardiovascular systems[11] or the hepatic and coagulation systems.[12,17] These associations were not detected in our patients, instead, regardless of which organ was compromised, the number of organ dysfunctions was associated with an increase in deaths, particularly early deaths.

The diagnosis of sepsis on admission to the ICU was associated with a higher mortality rate in the ICU and hospital. However, it was observed that the differences in mortality rates between septic and nonseptic patients decreased according to the number of organ dysfunctions. These data are similar to those found in the literature, since the mortality from multiple organ dysfunction syndrome is very high regardless of its etiology.[3,8]

Early deaths can be considered a quality indicator in intensive care. These deaths are more frequent in low-and middle-income countries and may reflect difficulties in the initial care of critically ill patients.[13,14] Recognizing these difficulties is a fundamental part of a health care improvement plan. Delayed access to a specialized intensive care bed may contribute to the finding of high early mortality, as these patients access the ICU with various organ dysfunctions.[15,16] Difficulty in accessing technology for the essential care of these patients can also lead to worse results.[17] Managing access to intensive care beds and implementing institutional palliative care programs may increase bed availability. The support of rapid response teams could also optimize the initial care of these patients, even outside the ICU environment.[18]
the early prevention and treatment of other organ dysfunctions are important strategies to reduce the risk of death in critically ill patients.[99]

This is one of the few studies to describe the factors associated with time to death in critically ill patients over a long period of observation, however, some limitations should be considered. This is a single-center retrospective cohort study, which reduces its external validity. In addition, the SOFA score analysis was performed only at the time of admission of patients to the ICU, which prevents the sequential assessment of organ dysfunctions. Furthermore, the results related to sepsis should be interpreted with caution, since this diagnosis was considered only on admission to the ICU.

CONCLUSION

We observed a higher proportion of early and intermediate deaths in the study period and the diagnosis of sepsis was not associated with changes in this pattern. The presence of three or more organ dysfunctions at ICU admission was associated with early deaths, with no difference in the impact of this association between the analyzed dysfunctions. The diagnosis of sepsis evident on ICU admission was associated with higher mortality when compared to nonseptic patients.

Research quality and ethics statement

This study was approved by the Institutional Review Board/Ethics Committee at Londrina State University (Approval # 1.791.251; Approval date October 25, 2016). The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the STROBE Guidelines, during the conduct of this research project.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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