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RESEARCH ARTICLE

Assessment of risk factors for in-hospital mortality after intensive care unit discharge

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Abstract

Context: Post-intensive care unit (ICU) mortality predictors are unknown.

Objective: To assess post-ICU in-hospital mortality predictors.

Materials and methods: Analysis of 296 patients discharged alive from a medical-surgical ICU during an 18-month period.

Results: Post-ICU in-hospital mortality was 22.6%. Nonsurvivors had significantly higher Charlson comorbidity score and more often had a tracheostomy. C-reactive protein (CRP) "alert measurement", ≥6 mg/dL, independently discriminated survivors from nonsurvivors.

Discussion: A CRP "alert measurement" or the need for tracheostomy may be used to identify patients with high risk of dying after ICU discharge.

Conclusions: Charlson comorbidity score, CRP and tracheostomy predicted post-ICU in-hospital mortality.

Keywords: ICU patient discharge, mortality, C-reactive protein, tracheostomy, Charlson comorbidity score

Introduction

The population of patients admitted to Intensive Care Units (ICU) is predicted to grow in the next years (Adhikari et al., 2010) including a large proportion that will ultimately die. In a recent study, ICU mortality ranged from 10.1 to 27.3%, depending on the case-mix, the country and the continent (Vincent et al., 2009). A great effort has been made to identify risk factors associated with ICU and, in particular, in-hospital mortality. Several scores have been developed, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score (Knaus et al., 1981), the mortality probability models (Lemeshow et al., 1988), the Simplified Acute Physiology Score (SAPS) II (Le Gall et al., 1993), and more recently the SAPS3 (Moreno et al., 2005), among others. Almost all severity scores use a group of demographic, clinical and physiological variables from the first day of ICU stay to obtain an individual patient score and a prediction of in-hospital mortality.

Usually the above mentioned severity scores are used to monitor the performance of a single ICU, to adjust mortality of different ICUs to its case-mix and for helping in guiding resource allocation (Gunning and Rowan, 1999). The currently available models are not useful and were not designed as well as validated for individual patient management (Cullen and Chernow, 1994).

Besides, a substantial percentage of patients, ranging from 4.3 to 31%, die in the wards after ICU discharge (Moreno et al., 1998, Ho et al., 2008). Furthermore, it has been shown that those patients not only had higher ICU lengths of stay (LOS) but also a higher resource consumption (Stricker et al., 2003). Although some patients are discharged from ICU with a plan to limit life support, others die unexpectedly and this seems not to be related

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to treatment deficiencies (Lawrence and Havill, 1999). Discharge of high-risk patients to high-dependency units may theoretically prove to be useful and to reduce mortality.

However, risk factors of post-ICU in-hospital mortality have been scarcely studied. Besides, the above mentioned severity scores were not developed specifically for this evaluation and are not helpful in such assessment. The aim of our study was to assess risk factors easily available at ICU discharge of post-ICU in-hospital mortality.

Methods

We performed a single center, retrospective, observational study with prospectively collected data, conducted during an 18-month period, between January 2008 and June 2009. The local Ethics Committee approved the study design.

All patients discharged alive from the São Francisco Xavier Hospital medical-surgical ICU were included in the study. Patients requiring continuous monitoring and/or intermediate care were discharged to high-dependency units; all other patients were discharged to medical or surgical wards. Only patients discharged home directly from ICU were excluded.

Follow-up was conducted until in-hospital death or hospital discharge. If a patient was readmitted to the ICU during the same hospitalization, only the first ICU admission was considered.

Data collected included demographic characteristics (age, gender); SAPS II; Charlson comorbidity score (Charlson et al., 1987); ICU and hospital LOS; diagnosis of infection during ICU stay; presence and duration of mechanical ventilation, of continuous renal replacement therapy and of central venous catheterization; presence of tracheostomy at the time of ICU discharge; concentration of C-reactive protein (CRP), haemoglobin and platelet count at the day of ICU discharge; discharge period (night – from 8 pm until 8 am; or day – from 8 am until 8 pm).

A comparison between survivors and nonsurvivors at hospital discharge was performed.

Statistical analysis

Standard descriptive statistics were used. Continuous variables were reported as median [interquartile range (IQR)] or mean ± standard deviation according to data distribution.

Continuous variables were analyzed using the parametric unpaired Student's t test, the nonparametric Mann–Whitney U test or Kruskal–Wallis H test, according to data distribution. Categorical variables were compared using the χ^2 test.

A Receiver Operator Characteristics (ROC) curve was performed to assess the performance of CRP concentration at ICU discharge in the identification of patients with poor outcome. According to the Youden index, a CRP discharge concentration "alert measurement" was defined. The difference in mortality was assessed with Kaplan–Meyer survival curves using a signed log-rank test. To minimize the effect of censored data in the survival analysis, we considered 90-day survival as a target.

We performed a multivariate, backward stepwise, logistic regression analysis with post-ICU in-hospital mortality as the dependent variable. Variables were introduced in the multivariate model if significantly associated with a higher risk of post-ICU in-hospital mortality on a univariate basis at $p < 0.05$. Multicolinearity between all these discrete variables was checked by computing pairwise correlation coefficient (r) between variables taken two by two. An $r < 0.4$ was considered low enough to exclude correlation between the predictors. The adjusted odds ratio (AOR) and the corresponding 95% confidence interval (CI) for each variable were computed.

Tests were performed two-tailed and considered significant when $p < 0.05$. All statistical tests were performed using SPSS for Windows (version 16.0: SPSS, Chicago, IL, USA).

Results

During the study period, a total of 457 patients were admitted to the ICU. The whole population had a mean SAPS II score of 48.1, a standardized mortality ratio of 43.2% and a mean LOS of 7.5 ± 9.8 days. The ICU mortality was 31.5% resulting in 296 patients discharged alive, which constituted our patient population (Figure 1).

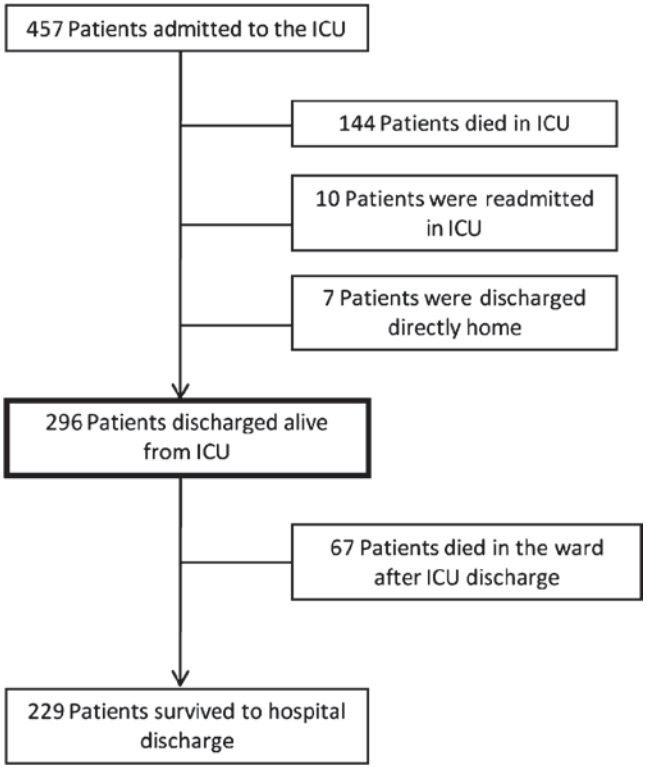

Figure 1. Flow chart showing the number of patients admitted and discharged alive from the ICU during the study period.

Among the patients discharged to the wards/high dependency units, the post-ICU in-hospital mortality rate was 22.6% ($N=67$), corresponding to a cumulative mortality of 46.2%. Half of the deaths in the wards/high-dependency units occurred within 7 days of ICU discharge (median 7 [22] days), and roughly one third in the first 48 h, of which only one after being readmitted to the ICU. Overall the ICU readmission rate was 4.7%.

Clinical and demographic characteristics of the post-ICU in-hospital survivors and nonsurvivors are presented in Table 1.

Nonsurvivors were significantly older, had a longer ICU LOS, had a higher comorbidity score (assessed by Charlson comorbidity score) and higher severity scores. In addition, nonsurvivors had longer duration of mechanical ventilation, of renal replacement therapy and of central venous catheterization. The presence of a tracheostomy at the time of ICU discharge was significantly associated with a higher risk of post-ICU in-hospital mortality (36.4% *vs.* 11.0%, $p<0.001$). No influence of the discharge time (day or night) on the mortality rate was found.

The CRP concentration was higher at the day of ICU discharge in nonsurvivors (7.9 [9.6] mg/dL *vs.* 4.9 [7.6] mg/dL), while haemoglobin was significantly lower (9.6 ± 2.2 g/dL *vs.* 10.5 ± 2.1 g/dL), $p=0.006$ and $p=0.008$, respectively (Table 1).

The area under the ROC curve for CRP concentration at the day of ICU discharge was 0.61 (95%CI, 0.53–0.69). A CRP discharge concentration higher than 6 mg/dL was identified as an "alert measurement", better predicting post-ICU in-hospital mortality, with a sensitivity of 0.67 and a specificity of 0.56.

According to this threshold, "alert measurement", a Kaplan–Mayer survival curve was plotted for patients with a CRP ≥ 6 mg/dL or CRP < 6 mg/dL (Figure 2). A higher mortality was noted in patients with CRP ≥ 6 mg/dL, and that became apparent soon after ICU discharge (log rank = 6.75; $p=0.009$).

A multivariate logistic regression analysis was performed with post-ICU in-hospital mortality as the dependent variable. We included six different variables age, ICU LOS, Charlson comorbidity score, CRP "alert measurement", haemoglobin concentration at ICU discharge and the presence of tracheostomy in this model. The duration of mechanical ventilation, of renal replacement therapy and of central venous catheterization

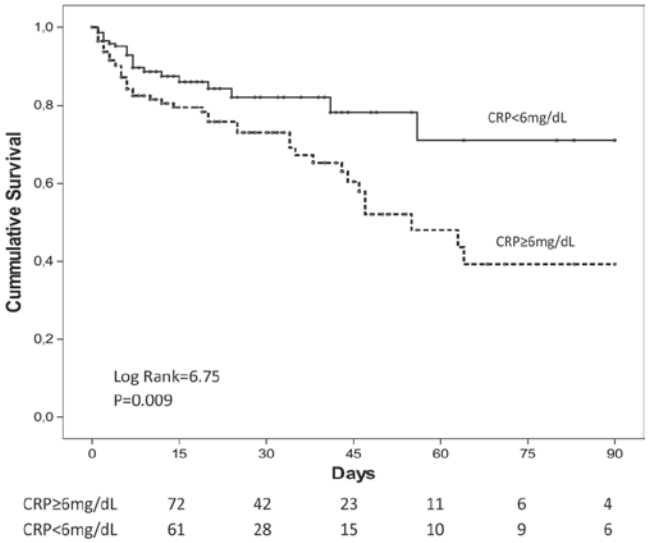

Figure 2. Kaplan–Meyer survival curves according to the presence of the "alert measurement" of CRP concentration (≥6 mg/dL). A significantly higher mortality rate was noted soon after discharge in patients with a CRP concentration of 6 mg/dL or over. Events were censored 90 days after ICU discharge.

Table 1. Comparison of survivors and nonsurvivors characteristics at ICU discharge.

Variable	Survivors ($n=229$)	Nonsurvivors ($n=67$)	p value
Male sex, N (%)	126 (55.0)	32 (47.8)	0.295
Age, years (mean ± SD)	62.4 ± 17.9	72.5 ± 14.4	<0.001
ICU length of stay, days (median [IQR])	4 [6]	7 [10]	0.001
Hospital post-ICU length of stay, days (median [IQR])	14 [22]	7 [22]	0.003
Charlson comorbidity score (mean ± SD)	3.5 ± 2.5	4.8 ± 2.5	<0.001
SAPS II (mean ± SD)	40.9 ± 14.4	53.5 ± 12.5	<0.001
Infection on ICU, N (%)	106 (46.3)	39 (58.2)	0.086
Mechanical ventilation, N (%)	156 (69.6)	54 (80.6)	0.079
Mechanical ventilation, days (median [IQR])	4 [5]	6 [8]	0.007
Renal replacement therapy, N (%)	28 (12.4)	14 (20.9)	0.081
Renal replacement therapy, days (median [IQR])	4 [5]	11 [11]	0.002
Central venous catheterization, days (median [IQR])	6 [6]	8 [11]	0.001
Tracheostomy at discharge, N (%)	25 (11.0)	24 (36.4)	<0.001
Discharge haemoglobin, g/dL (mean ± SD)	10.5 ± 2.1	9.6 ± 2.2	0.008
Discharge platelet count, $\times 10^9$/L (median [IQR])	221 [171]	235 [210]	0.679
Discharge CRP ≥ 6 mg/dL[a], N (%)	102 (44.5)	45 (67.2)	0.001
Discharge during nocturnal period (8 pm–8 am), N (%)	13 (5.7)	3 (4.4)	0.536

SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; CRP, C-reactive Protein.

[a]Refer to text for further details.

Table 2. Summary of multivariate analysis with post-ICU in-hospital mortality as the dependent variable..

Variables	AOR	95% CI	*p* value
Presence of tracheostomy	3.8	1.8–8.3	0.001
CRP "alert measurement"	2.8	1.4–5.7	0.003
Charlson comorbidity score[a]	1.2	1.1-1.4	0.005

Variables excluded from the final model: Age, Intensive Care Unit length of stay and haemoglobin. CRP "alert measurement" was defined as a CRP of ≥ 6 mg/dL. AOR, Adjusted odds ratio; CI, Confidence interval; CRP, C-reactive protein.
[a]Per point.

were excluded because they were found to be collinear with ICU LOS.

The SAPS II score were also injected in the model to assess the effect of patient severity. The variables found to be independently associated with post-ICU in-hospital mortality were the presence of tracheostomy, the Charlson comorbidity score and the CRP "alert measurement" at the day of ICU discharge (Table 2).

Discussion

In the present study, we evaluated the performance of several readily evaluable parameters to assess the risk of post-ICU in-hospital mortality. We identified the presence of tracheostomy, higher Charlson comorbidity score and CRP concentration at ICU discharge to be independently associated with post-ICU in-hospital mortality. In fact, a CRP ≥ 6 mg/dL constituted an "alert measurement" signalling a patient with an increased risk of dying while still in the hospital.

Some studies evaluated distinct risk factors of post-ICU in-hospital mortality, essentially patients' demographic and clinical characteristics.

Several authors (Smith et al., 1999, Daly et al., 2001, Azoulay et al., 2005, Campbell et al., 2008, Sakr et al., 2008) found age to be an independent risk factor for post-ICU in-hospital mortality, whilst in our study, age, although also higher in nonsurvivors, was not independently associated with post-ICU in-hospital mortality. Furthermore, contrary to other studies (Smith et al., 1999, Valentin et al., 2003), male gender was not also associated to higher post-ICU in-hospital mortality.

The patients' previous comorbid condition have a significant impact on ICU mortality (Quach et al., 2009) and may also play a role on predicting post-ICU in-hospital survival (Azoulay et al., 2005, Sakr et al., 2008). In our study, we evaluated comorbidities with the Charlson comorbidity score, which proved to be an independent predictor of post-ICU in-hospital mortality. Also patients with a prolonged ICU LOS have been proposed to have a high risk of post-ICU in-hospital death (Daly et al., 2001, Iapichino et al., 2003). We found the same association in our study, although it was not independently associated with mortality.

The ICU admission severity scores, validated for predicting the risk of in-hospital mortality, had also been studied to assess post-ICU in-hospital mortality. As expected, since post-ICU is still part of in-hospital mortality, we and other authors (Smith et al., 1999, Azoulay et al., 2005, Iapichino et al., 2003) found SAPS II to be associated with post-ICU in-hospital mortality. Consequently in this study both ICU and post-ICU mortality were found to be high, in accordance with the high mean SAPS II score.

The association between length of exposure to invasive devices and post-ICU in-hospital mortality is less well documented. Several studies documented a significantly longer duration of mechanical ventilation in nonsurvivors (Daly et al., 2001, Campbell et al., 2008), similar to our findings. We also found longer periods of renal replacement therapy and central venous catheterization in nonsurvivors. However, the duration of all these procedures were collinear with ICU LOS and therefore not independently associated with post-ICU in-hospital mortality.

The presence of tracheostomy at the time of ICU discharge was independently associated with post-ICU in-hospital mortality, as was shown not only in our study but also by Fernandez et al. (Fernandez et al., 2008). Although tracheostomy may facilitate weaning from mechanical ventilation, ICU discharge and increase ICU survival, some of these patients ultimately die in the wards. Nevertheless, it is not clear whether tracheostomy is a marker of higher illness severity or if it is, by itself, a mortality risk factor. In fact, patients who need a tracheostomy usually have a high burden of neurological or respiratory disease that, by itself, may increase their risk of death.

Night discharge from the ICU was also associated with an increased post-ICU in-hospital mortality, as was shown by Beck et al. (Beck et al., 2002), as well as in a Canadian (Laupland et al., 2008) and in an Australian study (Pilcher et al., 2007). However, we and others (Iapichino et al., 2003, Hanane et al., 2008) were unable to find such an association.

Serum biomarkers associated with increased post-ICU in-hospital mortality would be much useful, especially if easy to measure, simple to interpret and readily available. Several variables have been studied, namely procalcitonin, lactate and CRP (Ho et al., 2008, Castelli et al., 2004, Silvestre et al., 2010). Nevertheless only CRP concentration at the day of ICU discharge had been significantly associated with subsequent post-ICU in-hospital mortality (Ho et al., 2008, Castelli et al., 2004, Litton et al., 2007). In our study an independent association between a CRP concentration "alert measurement" (≥6 mg/dL) and post-ICU mortality was found (AOR of 2.8, 95% CI 1.4–5.7, $p = 0.003$). Therefore, we can speculate that these patients, with CRP concentration at discharge time over this "alert measurement", may potentially benefit from a full workup in order to exclude an ongoing inflammatory or infectious process that may jeopardize their survival probability. A recent study had unveiled a relationship between CRP variation before ICU discharge and mortality. Failure to decrease CRP concentration at least 25% in the last 24 h before ICU discharge was associated with a

significantly higher risk of death (23% vs. 11%, $p = 0.002$) (Ranzani et al., 2011).

CRP is an acute phase protein with a good correlation with the inflammatory response (Póvoa, 2008). An elevated CRP concentration at the time of ICU discharge may be a surrogate marker of a persistent inflammatory process, leading to a higher mortality risk.

Although one recent study (Silvestre et al., 2010) did not found this correlation between CRP concentration at the day of ICU discharge and post-ICU in-hospital mortality, it may have been underpowered to unveil such a relationship.

Most of the authors point out the shortage of ICU beds as the reason for early discharge of patients to the ward. The use of these risk factors to stratify patients' post-ICU in-hospital mortality risk may facilitate the selection of those who would benefit from being discharged to high-dependency units or even from being retained in the ICU (Daly et al., 2001).

Our study has some limitations. It was an observational, retrospective study, although using data prospectively collected in the ICU database, encompassed only one centre and was not controlled to withdrawal of life support decisions or neurological status at ICU discharge. Also there was no written discharge policy and those patients clinically perceived as with a high risk may have been treated differently. Nevertheless, it involved a large population, including all patients discharged to the wards/high dependency units, with complete follow-up and evaluated a large number of variables, which strongly support its conclusions.

Conclusion

An "alert measurement" CRP concentration at the day of ICU discharge (≥6 mg/dL), an elevated Charlson comorbidity score and the presence of tracheostomy were independently associated with an increased risk of post-ICU in-hospital mortality. These parameters may be used for risk stratification and decision making, to facilitate the selection of patients who may safely be early discharged from the ICU and to improve outcomes.

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Declaration of interest

The authors declare that they have no conflicts of interest related to this article.

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