Journal of Critical Care 30 (2015) 654.e1–654.e7

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Evolution and prognosis of long intensive care unit stay patients suffering a deterioration: A multicenter study☆

Alberto Hernández-Tejedor, MD, PhD [a,*], Lluís Cabré-Pericas, MD, PhD [b], María Cruz Martín-Delgado, MD, PhD [c], Ana María Leal-Micharet, MD [a], Alejandro Algora-Weber, MD [a]EPIPUSE study group

[a] Unidad de Cuidados Críticos, Hospital Universitario Fundación Alcorcón, 28922 Alcorcón, Madrid, Spain
[b] Unidad de Cuidados Intensivos, Hospital de Barcelona SCIAS, 08034 Barcelona, Spain
[c] Unidad de Cuidados Intensivos, Hospital Universitario de Torrejón, 28850 Torrejón de Ardoz, Madrid, Spain

ARTICLE INFO

Keywords:
Bioethics
Decision making
Life-sustaining treatment
Multiple organ dysfunction syndrome
Organ dysfunction scores

ABSTRACT

Purpose: The prognosis of a patient who deteriorates during a prolonged intensive care unit (ICU) stay is difficult to predict. We analyze the prognostic value of the serialized Sequential Organ Failure Assessment (SOFA) score and other variables in the early days after a complication and to build a new predictive score.
Materials and methods: EPIPUSE (Evolución y pronóstico de los pacientes con ingreso prolongado en UCI que sufren un empeoramiento, *Evolution and prognosis of long intensive care unit stay patients suffering a deterioration*) study is a prospective, observational study during a 3-month recruitment period in 75 Spanish ICUs. We focused on patients admitted in the ICU for 7 days or more with complications of adverse events that involve organ dysfunction impairment. Demographics, clinical variables, and serialized SOFA after a supervening clinical deterioration were recorded. Univariate and multivariate analyses were performed, and a predictive model was created with the most discriminating variables.
Results: We included 589 patients who experienced 777 cases of severe complication or adverse event. The entire sample was randomly divided into 2 subsamples, one for development purposes (528 cases) and the other for validation (249 cases). The predictive model maximizing specificity is calculated by minimum SOFA + 2 * cardiovascular risk factors + 2 * history of any oncologic disease or immunosuppressive treatment + 3 * dependence for basic activities of daily living. The area under the receiver operating characteristic curve is 0.82. A 14-point cutoff has a positive predictive value of 100% (92.7%-100%) and negative predictive value of 51% (46.4%-55.5%) for death.
Conclusions: EPIPUSE model can predict mortality with a specificity and positive predictive value of 99% in some groups of patients.

1. Introduction

Intensive care units (ICUs) and life-sustaining treatments (LSTs) have helped increase the survival of many diseases but can also result in a useless prolongation of the dying process, which leads to an emotional and difficult-to-estimate economic burden [1,2]. Symmers [3] wondered whether new technology really sustained life or simply interfered with the process of dying, and Blackhall [4] proposed that cardiopulmonary resuscitation maneuvers were selectively applied, as it is still recommended [5]. Thirty-five years ago, most patients dying in the ICU underwent cardiopulmonary resuscitation [6]; knowing the limited utility of its indiscriminate use, it has given way to LST decisions [7]. In many cases, it is not possible to establish an accurate prognosis, and this leads to the application of intensive measures to the patient, even beyond what physicians would choose for themselves [8,9], and this is also described in the Appropriateness of Care in the ICUs study [10]. To predict the outcome, several scores and algorithms have been developed, most of them designed to be used upon ICU admission. However, we did not find any study specifically designed to assess the course after a complication or adverse event of patients already admitted in an ICU.

The prognosis of a patient who deteriorates after a prolonged ICU stay is not easy to predict, as many variables can influence it upon admission to the ICU: basal situation before ICU admission, prognosis of chronic diseases, reason for admission, length of stay in the ICU, and many others. We designed the present study on the assumption that the serialized calculation of the Sequential Organ Failure Assessment (SOFA) during the following days after a complication can guide the prognosis and, therefore, the decisions to take and can be the basis of an algorithm valid in some circumstances to predict mortality

☆ Conflict of interest: The authors declare no conflict of interest. There were no sources of support.

* Corresponding author at: Unidad de Cuidados Críticos, Hospital Universitario Fundación Alcorcón, C/. Budapest, 1, 28922 Alcorcón, Madrid, Spain. Tel.: +34 91 621 95 19; fax: +34 91 621 98 91.
E-mail addresses: albertohmed@hotmail.com (A. Hernández-Tejedor), 10654lcp@comb.cat (L. Cabré-Pericas), mmartin@torrejonsalud.com (M.C. Martín-Delgado), alealmicharet@gmail.com (A.M. Leal-Micharet), aalgora@fhalcorcon.es (A. Algora-Weber).

http://dx.doi.org/10.1016/j.jcrc.2015.01.011
0883-9441/

approaching 100% of probability. The purpose of our study was to analyze the prognostic value of SOFA upon admission and its tendency during the early days after a complication and to generate a mathematical model that predicts a mortality exceeding 99% using the serialized value of the SOFA score in this period.

2. Patients and methods

A prospective, observational, multicenter study was performed in 75 ICUs in Spain. The project was approved (reference 11/96) by the Clinical Research Ethics Committee of the Hospital Universitario Fundación Alcorcón (Madrid, Spain) and classified as "No-Postmarketing Observational Study" by the Spanish Agency of Drugs and Health Products (Agencia Española de Medicamentos y Productos Sanitarios). Scientific support from the Spanish Society of Intensive Care Medicine (Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias) was also requested and granted.

The patient recruitment period lasted 3 months, and afterwards, there was a follow-up period of 4 months. Eligible patients were adults admitted in the ICU for 7 days or more and who experienced a complication or adverse event with organ function impairment (SOFA increased by 1 point or more). We consider complication or adverse event for purposes of this study any supervening clinical entity (infectious, neurologic, hematologic, cardiac, or any other) suffered by the patient and appeared while in the ICU that increases the SOFA score. The progressive worsening of the patient due to a previously diagnosed process was not considered a complication. More than 1 complication may occur in the same patient during the ICU admission. Pneumonia, catheter-related infection, bacterial meningitis, endocarditis, and urinary tract infection were diagnosed according to Infectious Diseases Society of America (IDSA) definitions. Acute coronary syndrome was defined according to European Society of Cardiology guidelines. Renal failure was considered when Acute Kidney Injury Network (AKIN) criteria for stage II or III were met. A deterioration of 2 or more points in Glasgow Coma Scale was considered significant. Other diagnoses were according to medical criteria.

We assess evolution through survival data and length of stay both in the ICU and in the hospital. To assess the course of the complication or adverse event, each researcher calculated the SOFA score on a daily basis from the day before the complication up to 4 days afterwards. We chose the SOFA score due to its ease of use and the fact that it has been used in previous multicenter studies [11].

As previous studies to estimate the sample size are not available, we estimated 500 subjects, adding 250 more cases for external validation, on the basis that a sample size of 404 patients would be required, considering heterogeneity of 50%, a confidence level of 95%, an accuracy of 5%, and 1% of estimated losses.

Quantitative data are expressed as mean and SD or median and interquartile range. Qualitative data are expressed as absolute numbers and percentages. Univariate analysis was performed to study the potential predictors of death considered in the study. The Student t test or Mann-Whitney U test and χ^2 test were used to compare quantitative and qualitative data, respectively. Odds ratios with 95% confidence interval were presented as results. The predictive model was constructed with multivariate logistic regression analysis. To confirm the model, an internal validation procedure was made; the sample was split at random into 2 parts: one to develop the model, training set (70%), and another to measure its performance, validation set (30%). In the modeling strategy, a manual elimination of covariates approach was followed, sticking to the rule of thumb: 10 outcome events per predictor variable. First-order interactions were evaluated by a global significance test, chunk test [12], deleting the group of interaction variables from the model, and testing the likelihood ratio. Receiver operating characteristic (ROC) curve was used as predictive performance measure, and sensitivity, specificity, and predictive values were estimated at different cutoff points. We searched for cutoff points for a minimal specificity higher than 95% and maximum sensitivity. Mixed models were adjusted to study SOFA longitudinal data [13]. The model included time (−1, 0, +1, +2, +3, +4) as repeated measure with an unstructured covariance matrix, death as fixed factor, and their interaction. All tests were 2 sided, and $P < .05$ was deemed statistically significant. All statistical analyses were performed using SPSS for Windows, version 18.0 (SPSS, Inc, Chicago, IL).

3. Results

During the 3-month recruitment period, 13 456 patients were admitted in the 75 participating ICUs, which account for a total of 1302 ICU beds. Of those patients, 2594 had an ICU stay of 7 days or longer. During that time, there were 777 complications or adverse events with organ function impairment after the seventh day of admission in 589 patients, and all of them were included. The entire sample (777 cases) was randomly divided into 2 subsamples, the training subsample (528 cases) and the validation subsample (249 cases), to develop a mortality prediction model and thereafter perform its validation.

3.1. Training subsample

Baseline characteristics, severity scores, and evolution of the 528 cases in the training subsample appear in Table 1. Nosocomial infections are the most frequent complication recorded (42%). The most frequent infection was nosocomial pneumonia (79 cases; 15% of included cases). Tables 2 and 3 show the results of the comparison of different variables with survival criterion. Inhospital mortality is associated with older age, higher severity at ICU admission and each day of the complication, and highest SOFA peak value and minor SOFA score reduction in the days after the complication. The presence of previous complications, cardiovascular risk factors, immunosuppresion, and dependence for basic activities of daily living (BADL) were also associated with higher inhospital mortality. The SOFA increase in day 0 has no influence on evolution because the complication leads to a 2.8-point SOFA increase in both survivors and nonsurvivors (Fig. 1).

The discrimination power of variables using SOFA is analyzed using ROC curves (Fig. 2). The discrimination power of SOFA increases on every new day after the complication, reaching an area of 0.799 for the value of the SOFA on the fourth day after the event.

We developed a logistic regression model with the variables that show a greater contribution in the univariate analysis (SOFA, cardiovascular risk factors, immunosuppression, dependence for BADL, previous complication, and no. of treatments for actual complication). Of all the variables considered using the SOFA, we selected the minimum SOFA value of days 0 to +4 for several reasons: (*a*) considering 4 days, we are giving an option to see results of the treatment; (*b*) we did not include SOFA of days −1 and 0 because its discrimination power was inferior to the SOFA score of the days after the complication; and (*c*) for its simplicity.

The model (EPIPUSE 1) includes 4 variables:

0.354 * minimum SOFA of days 0 to +4
+0.556 * hypertension/diabetes/obesity (1, yes; 0, no)
+0.578 * any oncologic disease or being under steroids, immunosuppressors, or chemotherapy (1, yes; 0, no)
+0.907 * dependence for BADL (1, yes; 0, no)

The area under the ROC curve for this model (Fig. 3A) is 0.823 (0.788-0.858, $P = .018$), and the point of maximum sensitivity with a specificity of 100% is 5. Considering a 5-point cutoff, this model has a specificity of 100% (98.4%-100%), sensitivity of 17% (13.1%-21.9%), positive predictive value of 100% (92.4%-100%), and negative predictive value of 50.8% (46.2%-55.3%). Given the excessive loss of sensitivity for a specificity of 100%, we estimate the cutoff for a specificity of 95% getting a value of 4. With this cutoff point, the model shows a specificity of 95.3% (91.8%-97.4%), sensitivity of 40.2% (34.6%-46.1%), positive predictive value of 91% (84.6%-94.9%), and negative predictive value of 57.7% (52.7%-62.5%).