CHEST

Prognostication of Mortality in Critically Ill Patients With Severe Infections

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BACKGROUND: The purpose of this study was to confirm the prognostic value of pancreatic stone protein (PSP) in patients with severe infections requiring ICU management and to develop and validate a model to enhance mortality prediction by combining severity scores with biomarkers.

METHODS: We enrolled prospectively patients with severe sepsis or septic shock in mixed tertiary ICUs in Switzerland (derivation cohort) and Brazil (validation cohort). Severity scores (APACHE [Acute Physiology and Chronic Health Evaluation] II or Simplified Acute Physiology Score [SAPS] II) were combined with biomarkers obtained at the time of diagnosis of sepsis, including C-reactive-protein, procalcitonin (PCT), and PSP. Logistic regression models with the lowest prediction errors were selected to predict in-hospital mortality.

RESULTS: Mortality rates of patients with septic shock enrolled in the derivation cohort (103 out of 158) and the validation cohort (53 out of 91) were 37% and 57%, respectively. APACHE II and PSP were significantly higher in dying patients. In the derivation cohort, the models combining either APACHE II, PCT, and PSP (area under the receiver operating characteristic curve [AUC], 0.721; 95% CI, 0.632-0.812) or SAPS II, PCT, and PSP (AUC, 0.710; 95% CI, 0.617-0.802) performed better than each individual biomarker (AUC PCT, 0.534; 95% CI, 0.433-0.636; AUC PSP, 0.665; 95% CI, 0.572-0.758) or severity score (AUC APACHE II, 0.638; 95% CI, 0.543-0.733; AUC SAPS II, 0.598; 95% CI, 0.499-0.698). These models were externally confirmed in the independent validation cohort.

CONCLUSIONS: We confirmed the prognostic value of PSP in patients with severe sepsis and septic shock requiring ICU management. A model combining severity scores with PCT and PSP improves mortality prediction in these patients. CHEST 2015; 148(3):674-682

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ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; AUC = area under the curve; CRP = C-reactive protein; IQR = interquartile range; MCE = misclassification error; PCT = procalcitonin; PSP = pancreatic stone protein; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment; SPE = squared prediction error; suPAR = urokinase plasminogen activator receptor

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Severe sepsis and septic shock are leading causes of mortality in patients in the ICU.[1-3] Reported outcome improvements over the last decade have been mostly a consequence of nonspecific supportive management of organ failure and aggressive coordinated treatment protocols.[4] The failure of several promising therapeutic strategies designed to reduce mortality further by specifically targeting pathogen- or host-related mediators[5-7] suggests a considerable degree of heterogeneity in both the microbial agents and host inflammatory response.[8] Future therapeutic strategies should be designed on an individual basis to personalize treatment intensity. Such a customized approach requires rigorous triaging. However, attempts to stratify patients and the decision-making process according to severity scores, such as APACHE (Acute Physiology and Chronic Health Evaluation) II, may not have been sufficiently stringent to tailor new adjunctive therapies and may explain in part the negative results of clinical trials in sepsis.[9-11]

Serum biomarkers, such as C-reactive protein (CRP) and procalcitonin (PCT), routinely assist clinicians in making the diagnosis of bacterial infection and evaluating the severity of sepsis.[12,13] However, their limited performance precludes using these markers for the discrimination of individual prognosis and the personalization of decision-making processes.[12,14] Pancreatic stone protein (PSP), a proinflammatory mediator that binds to polymorphonuclear cells and triggers their activation in vitro,[15] can be used to diagnose sepsis,[16-18] characterize the severity of infection,[17,19,20] and predict the outcome of patients with sepsis requiring ICU management.[19-21] CRP, PCT, and PSP are detectable in most patients with sepsis within a large time window after the onset of sepsis. This contrasts with proinflammatory cytokines, such as tumor necrosis factor-α, IL-1, IL-6, and IL-8, which have good prognostic values for outcome but a short window of expression that limits their clinical usefulness.[20,22-24]

We aimed to confirm the prognostic value of PSP in a larger cohort of patients with severe sepsis and septic shock requiring ICU management. We then hypothesized that a combination of universally used severity scores (APACHE II and Simplified Acute Physiology Score [SAPS] II) with PSP and routinely available biomarkers (CRP and PCT) may improve mortality prediction in these patients.

Materials and Methods

Patient Populations

We used two independent cohorts to validate the prognostic value of PSP in patients with severe infections requiring ICU admission. We then used these cohorts to further develop and validate a sepsis predicitive model.

Derivation Cohort: Patients were prospectively enrolled between February 2008 and February 2012 in a 32-bed adult medico-surgical ICU of a community and referral university hospital in Lausanne, Switzerland. Patients aged ≥ 18 years were included within 24 h of their ICU admission for severe sepsis or septic shock.

Validation Cohort: Patients were prospectively enrolled between September 2009 and May 2012 in two university-based mixed ICUs (18-bed and 30-bed, respectively) in Belo Horizonte, Brazil. Patients aged ≥ 18 years were included if they presented with severe sepsis or septic shock at the time of ICU admission or during ICU stay.

Both cohorts were approved by the institutional review boards of each hospital (Commission Cantonal d'Ethique du Canton de Vaud [173/06] and the Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais [249/09]). All participants or their next of kin provided written informed consent.

Data Collection and Measurement of Plasma Levels of Circulating Biomarkers

Severity scores were computed either 24 h after ICU admission or 24 h after the onset of nosocomial sepsis for patients already staying in the ICU for reasons other than sepsis. Biomarkers were measured within the same time frame. Details of data extraction, calculation of severity scores, and measurement of circulating biomarkers are provided in e-Appendix 1.

Definitions and Characteristics of Infection

Sepsis was defined and classified according to standardized criteria[25] (e-Appendix 1). Infection sites were defined according to criteria published by Garner et al[26] and Calandra et al.[27] Severity of infection was assessed according to both the severity scores and biomarker levels. Patients were followed until death or discharge from the hospital. Hospital mortality was the primary end point.

Statistical Analysis

Continuous variables were reported as the mean and SD or median and interquartile range (IQR), as indicated. Categorical variables were reported as frequencies and percentages. As the distributions of the biomarkers were skewed, comparisons of continuous variables between clinical categories of patients (severe sepsis vs septic shock), or between survivors and nonsurvivors, were performed using nonparametric two-sided Wilcoxon-Mann-Whitney rank sum tests. To assess the discrimination ability of severity scores (APACHE II and SAPS II) and circulating biomarkers (CRP, PCT, and PSP) to predict in-hospital mortality, receiver operating characteristic curves and area under the curves (AUCs) with 95% CI were computed.[28]

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