CHEST

Prognostication of Mortality in Critically Ill Patients With Severe Infections

Yok-Ai Que, MD, PhD; Idris Guessous, MD, PhD; Elise Dupuis-Lozeron, MSc; Clara Rodrigues Alves de Oliveira, MD, PhD; Carolina Ferreira Oliveira, MD, PhD; Rolf Graf, PhD; Gérald Seematter, MD; Jean-Pierre Revelly, MD; Jean-Luc Pagani, MD; Lucas Liaudet, MD; Vandack Nobre, MD, PhD; and Philippe Eggimann, MD

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

Manuscript received January 17, 2015; revision accepted May 15, 2015; originally published Online First June 11, 2015.

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

AFFILIATIONS: From the Department of Adult Intensive Care Medicine (Drs Que, Revelly, Pagani, Liaudet, and Eggimann), the Community Prevention Unit (Dr Guessous), Institute of Social and Preventive Medicine, and the Infectious Diseases Service (Drs Alves de Oliveira and Ferreira Oliveira), University Hospital Medical Center and University of Lausanne, Lausanne, Switzerland; the Unit of Population Epidemiology (Dr Guessous and Ms Dupuis-Lozeron), Division of Primary Care Medicine, Department of Community Medicine, Primary Care, and Emergency Medicine, Geneva University Hospitals, Geneva, Switzerland; the Research Center for Statistics (Ms Dupuis-Lozeron), University of Geneva, Geneva, Switzerland; the Swiss Hepato-Pancreatico-Biliary Center (Dr Graf), Department of Visceral and Transplant Surgery, University Hospital, Zürich, Switzerland; the Service d'Anesthésiologie (Dr Seematter), Hôpital Riviera, Montreux, Switzerland; and the Graduate Program in Infectious Diseases and Tropical Medicine (Dr Nobre), Department of Internal Medicine, School of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

Drs Que, Guessous, Nobre, and Eggimann contributed equally to this work.

FUNDING/SUPPORT: This study was funded by an unrestricted grant from the Loterie Romande and the Fondation pour la Recherche en Soins Intensifs and a grant from the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (Fapemig). Dr Que is funded by the

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]

European Commission Research [Grant FP7-Health-2013-Innovation-2-PHAGOBURN], the Swiss Initiative in System Biology (SystemsX-MicroscapesX-51RTP0-151038), the Swiss platforms for translational medicine (SwissTransMed B5-platform), and Swiss National Research Foundation [Grants SNF CRAGP3-151512 and IZ73Z0-152319]. Dr Liaudet is supported by the Swiss National Research Foundation [Grant 32000-118174/1]. Dr Guessous is supported by the Swiss National Science Foundation [Grant SNF 33CM30-124087/1].

CORRESPONDENCE TO: Philippe Eggimann, MD, BH 08-622, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, 1011 Lausanne, Switzerland; e-mail: Philippe.Eggimann@chuv.ch

DOI: 10.1378/chest.15-0123

To derive a predictive model for in-hospital mortality, we performed model selection on several logistic regression models using data from the derivation cohort. The rationale for this was to improve the prediction of outcomes of patients in the ICU with severe sepsis or septic shock by combining universally used severity scores (APACHE II or SAPS II) and circulating biomarkers (CRP, PCT, and PSP). APACHE II and SAPS II scores represent the most used severity scores to describe the characteristics of patients in the ICU in the United States and Europe, respectively. We ran independent models with APACHE II and SAPS II, as they include approximately the same sets of parameters. We estimated the prediction errors of all possible models by combining one of the two scores with at least one circulating biomarker. PCT and PSP variables were log-transformed because of their highly skewed distribution and the presence of large extreme values. The linearity of the relationship between the outcome and the different predictors was empirically verified using nonlinear models. Two kinds of prediction errors were computed from the probability of death as predicted by each model: (1) The squared prediction error (SPE), which is the mean of the squared differences between the predicted probabilities and the actual outcome, and (2) the misclassification error (MCE), which is the proportion of subjects misclassified by the model. The latter was obtained by dichotomizing the estimated probabilities with a cutoff of 0.5.[29] We selected the model with the smallest prediction error corrected for prediction optimism in order that it corresponded to the error that is expected to be obtained for future outcomes.[29] Receiver operating characteristic curves and AUCs of the best models were reported. We also illustrated the predicted probability of death as a function of PSP. The probabilities of death as functions of PSP were plotted using the median of PCT and severity scores of the derivation and validation cohorts, respectively, as fixed values.

All *P* values were two-sided, and statistical significance was set at a *P* value of .05. All analyses were performed using R for Windows (version 3.0.1)[30] with the mgcv,[31] pROC,[32] ROCR, and ggplot2 packages.[33]

Results

Patient Characteristics of the Derivation and Validation Cohorts

The characteristics of patients included in both the derivation and the validation cohorts are presented in Table 1. Overall, 103 of 158 (65%) and 53 of 91 (58%) patients included in the derivation and validation cohorts, respectively, had septic shock. Most patients had at least one comorbid condition. Compared with patients from the validation cohort, those included in the derivation cohort presented with more severe infections with the following severity scores: APACHE II (28; IQR, 13.5 vs 21; IQR, 12; $P < .001$), SAPS II (68; IQR, 24.5 vs 42; IQR, 23.5; $P < .001$), and Sequential Organ Failure Assessment (SOFA) (11; IQR, 4 vs 7; IQR, 6; $P < .001$). Overall hospital mortality was lower in the derivation cohort (42 of 158 [27%] vs 39 of 91 [43%]; $P = .012$). This held true for both cases of severe sepsis (four of 55 [7.2%] vs nine of 38 [24%]; $P = .052$) and patients with septic shock (38 of 103 [37%] vs 30 of 53 [57%]; $P = .029$). Pulmonary, abdominal, or both origins accounted for more than two-thirds of all cases in both cohorts.

Severity Scores and Biomarkers for Sepsis Severity and Survival Status

Plasma levels of the circulating biomarkers are presented for both cohorts in Tables 2 and 3 for sepsis severity and are grouped according to survival status in Table 4. APACHE II and SAPS II scores, as well as PCT and PSP levels, were significantly more elevated in patients with septic shock compared with those with severe sepsis in both cohorts. APACHE II and PSP were both significantly lower in surviving patients in both cohorts.

Prediction of In-Hospital Mortality by Severity Scores and Biomarkers

The accuracy of the severity scores and biomarkers to predict in-hospital mortality for both cohorts is presented in e-Table 1. APACHE II (AUC derivation cohort, 0.638 [0.543-0.733]; AUC validation cohort, 0.636 [0.521-752]) had moderate accuracy for the prediction of death in both cohorts. Similar results were observed for circulating PSP (AUC, 0.665 [0.571-0.758]) and SAPS II (AUC, 0.598 [0.499-0.698]) in the derivation cohort only.

Development and Validation of a Sepsis Model to Predict In-Hospital Mortality

The performance of in-hospital mortality prediction models including only acute-phase proteins in the derivation cohort is presented in e-Table 2. Table 5 and e-Tables 3 and 4 describe the incremental effect of adding CRP, PCT, and PSP alone or in combination to the predictive performances of APACHE II or SAPS II severity scores. The models that combined PSP with either APACHE II or SAPS II predicted mortality better than those based on the addition of CRP or PCT. A combination of both PSP and PCT with APACHE II, or with SAPS II, further improved the performance of scores. The best models were APACHE II + log(PCT) + log(PSP) (AUC, 0.721; 95% CI, 0.632-0.812; MCE, 0.236; SPE, 0.202) and SAPS II + log(PCT) + log(PSP) (AUC, 0.710; 95% CI, 0.617-0.802; MCE, 0.236; SPE 0.205).

The performance of these models in the validation cohort were APACHE II + log(PCT) + log(PSP) (AUC = 0.629; 95% CI, 0.502-0.576; MCE, 0.416; SPE, 0.266) and SAPS II + log(PCT) + log(PSP) (AUC = 0.637; 95% CI, 0.510-0.764; MCE, 0.429; SPE, 0.267) (Fig 1). Figure 2 illustrates the predicted probability of death as a function

TABLE 1] Patient Characteristics of Development and Validation Cohorts According to Sepsis Severity

Characteristics	Derivation Cohort			Validation Cohort		
	All Patients (N = 158)	Severe Sepsis (n = 55; 35%)	Septic Shock (n = 103; 65%)	All Patients (N = 91)	Severe Sepsis (n = 38; 42%)	Septic Shock (n = 53; 58%)
Demographics						
Age, mean ± SD	61.2 ± 18.2	57.0 ± 19.8	63.4 ± 17.0	59.9 ± 16.1	56.5 ± 16.7	62.4 ± 15.3
Male (female), No.	93 (65)	30 (25)	63 (40)	54 (37)	24 (14)	30 (23)
Admission categories						
Medical	104 (66)	41 (75)	63 (61)	80 (88)	32 (84)	48 (90)
Scheduled surgery	4 (2)	0 (0)	4 (4)	4 (4)	2 (5)	3 (6)
Unscheduled surgery	50 (32)	14 (25)	36 (35)	7 (8)	4 (11)	2 (4)
Type of infection						
Community (home/ED)	115 (73)	33 (66)	73 (71)	41 (45)	21 (55)	20 (34)
Nosocomial (hospital transfer/during ICU stay)	43 (27)	13 (34)	30 (29)	50 (55)	17 (45)	33 (62)
Severe comorbidities						
COPD	24 (15.2)	8 (14.6)	16 (15.5)	12 (13.2)	5 (13.2)	7 (13.2)
Cardiac insufficiency	21 (13.3)	5 (9.1)	16 (15.5)	21 (23.1)	7 (18.4)	14 (26.4)
Cirrhosis	12 (7.6)	2 (3.6)	10 (9.7)	5 (5.5)	1 (2.6)	4 (7.5)
End-stage renal disease	25 (15.8)	5 (9.1)	20 (19.4)	10 (11.0)	3 (7.9)	7 (13.2)
Immunodeficiency	25 (15.8)	7 (12.7)	18 (17.5)	0 (0.0)	0 (0.0)	0 (0.0)
Insulin-dependent diabetes	10 (6.3)	1 (1.8)	9 (8.7)	11 (12.1)	2 (5.3)	9 (17)
Score, median [IQR]						
APACHE II	28 [13.5]	25 [13]	29 [13.5]	21 [12]	15.5 [9]	23 [13]
SAPS II	68 [24.5]	61 [25.5]	71 [22.5]	42 [23.5]	31.5 [24.8]	50 [27]
SOFA (d 1)	11 [4]	10 [4]	12 [5]	7 [6]	4 [2.8]	9 [5]
Outcome						
Hospital mortality	42 (27)	4 (7)	38 (37)	39 (43)	9 (24)	30 (57)
Infection sites						
Pulmonary	59 (37)	26 (47)	33 (32)	55 (60)	25 (65)	30 (57)
Abdominal	49 (31)	8 (15)	41 (40)	2 (2)	0 (0)	2 (4)
Bloodstream	10 (6)	7 (13)	3 (3)	10 (11)	4 (11)	6 (11)
CNS and ENT	7 (4)	2 (4)	5 (5)	0 (0)	0 (0)	0 (0)
Urinary tract	12 (8)	5 (9)	7 (7)	10 (11)	5 (13)	5 (9)
Soft tissues	19 (12)	9 (16)	14 (14)	4 (5)	0 (0)	4 (8)
Miscellaneous[a]	4 (2)	1 (2)	3 (3)	10 (11)	4 (11)	6 (11)
Microbiology						
Gram positive	56 (35)	24 (43)	32 (31)	16 (17)	5 (13)	11 (21)
Staphylococcus aureus	10	4	3	7	3	4
Streptococcus pyogenes	11	3	8	0	0	0
Streptococcus pneumoniae	26	11	15	2	1	1
Other	9	6	3	7	1	6
Gram negative	55 (35)	17 (31)	38 (37)	26 (28)	13 (34)	13 (24)
Escherichia coli	28	9	19	5	2	3
Pseudomonas aeruginosa	7	2	5	3	2	1
Other	20	6	14	18	9	9

(Continued)

TABLE 1] *(continued)*

Characteristics	Derivation Cohort			Validation Cohort		
	All Patients (N = 158)	Severe Sepsis (n = 55; 35%)	Septic Shock (n = 103; 65%)	All Patients (N = 91)	Severe Sepsis (n = 38; 42%)	Septic Shock (n = 53; 58%)
Fungi	3 (2)	0 (0)	3 (2)	0	0	0
2009 influenza A(H1N1)	1 (1)	0 (0)	1 (1.4)	0	0	0
Undocumented	36 (23)	12 (22)	24 (23)	49 (54)	20 (40)	29 (55)

Data are given as No. (%) unless otherwise indicated. APACHE = Acute Physiology and Chronic Health Evaluation; ENT = ear-nose-throat; IQR = interquartile range; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.
[a]CNS (n = 5), eye and ear-nose-throat (n = 6), infective endocarditis (n = 2), osteomyelitis (n = 1).

of PSP, thereby representing the weight of this marker in the model.

Discussion

CRP and PCT represent the two most studied and the most widely used biomarkers in clinical practice.[24] Despite their usefulness in some settings (ie, helping in the diagnosis of sepsis and guiding antibiotic therapy), isolated measurements of these molecules have never been shown to predict outcome among patients in the ICU.[24,34,35] Regarding PSP, we and others showed that this marker can predict the mortality of critically ill patients who present with severe sepsis and septic shock admitted to different ICUs.[16,20] Similar results have been shown for patients with ventilator-associated pneumonia[19] and peritonitis.[21] The present findings confirm the predictive value of PSP in these settings in a larger set of patients with sepsis.

Herein, we developed and validated a sepsis model to predict in-hospital mortality in patients with severe sepsis or septic shock who required intensive care management. Using independent derivation and validation cohorts, we found that combining both PCT and PSP to either standard APACHE II or SAPS II severity scores improved the performance of these scores for the prediction of in-hospital mortality in patients with sepsis.

Despite their proven usefulness for comparing severity and predicting mortality in critically ill patient populations, severity scores such as APACHE II and SAPS II are not able to recognize and discriminate between individual outcomes.[36] Given their usefulness, they have been used to stratify the response to new adjuvant antisepsis therapies, such as recombinant human activated protein C[9] or eritoran.[10]

Models based on the combination of different biomarkers represent a new and interesting strategy to overcome the limited performance of isolated parameters for a given outcome. Data regarding combinations of circulating biomarkers and severity scores to predict mortality in patients with sepsis are scarce in the literature.[37] This strategy has been proposed by Giamarellos-Bourboulis et al[38] and Suberviola et al.[39] Giamarellos-Bourboulis et al[38] combined the APACHE II score with urokinase plasminogen activator receptor (suPAR) levels to predict outcome in patients with sepsis.[38] However, suPAR did not improve the performance

TABLE 2] Plasma Levels of Biomarkers and Severity Scores of Derivation Cohort According to Sepsis Severity

Measure	All Patients (N = 158)	Severe Sepsis (n = 55)	Septic Shock (n = 103)	*P* Value
Severity scores				
APACHE II	28.0 (13.5)	25.0 (13.0)	29.0 (13.5)	.002
SAPS II	68.0 (24.5)	61.0 (25.5)	71.0 (22.5)	.002
Biomarkers				
CRP, mg/L	259.0 (150.8)	229.0 (153.5)	275.0 (148.0)	.204
PCT, ng/mL	24.5 (49.7)	9.7 (23.2)	37.4 (51.1)	< .001
PSP, ng/mL	248.4 (382)	78.8 (230.6)	323 (351.9)	< .001

Data are presented as median (IQR). CRP = C-reactive-protein; PCT = procalcitonin; PSP = pancreatic stone protein. See Table 1 legend for expansion of other abbreviations.

TABLE 3] Plasma Levels of Biomarkers and Severity Scores of Validation Cohort, According to Sepsis Severity

Measure	All Patients (N = 91)	Severe Sepsis (n = 38)	Septic Shock (n = 53)	*P* Value
Severity scores				
APACHE II	21.0 (12)	15.5 (9.0)	23.0 (13.0)	< .001
SAPS II	42.0 (23.5)	31.5 (24.8)	50.0 (27.0)	< .001
Biomarkers				
CRP, mg/L	181.2 (209.3)	176.6 (169.0)	186.1 (227.2)	.702
PCT, ng/mL	4.5 (16.9)	1.5 (8.4)	8.6 (20.3)	.002
PSP, ng/mL	111.2 (365.3)	58.9 (207.8)	184.0 (451.4)	.005

Data are presented as median (IQR). See Table 1 and 2 legends for expansion of abbreviations.

of APACHE II. Similarly, Suberviola et al[39] combined APACHE II and SOFA to CRP, PCT, proadrenomedullin, and suPAR to predict outcome in patients with sepsis; again, the addition of biomarkers did not improve the performance of severity scores.[39] In contrast, by combining two biomarkers, PCT and PSP, with APACHE II or SAPS II, our model effectively resulted in an improved AUC over the AUC of each individual parameter, while providing minimal error prediction. Similarly, combining clinical scores of pneumonia and blood biomarkers measured upon hospital admission in patients with community-acquired pneumonia, the ProHosp study group further improved the prognostic capabilities of the clinical scores.[40]

With the observed rising incidence of sepsis,[41,42] risk stratification is essential for the following reasons: (1) to identify patients who are more likely to benefit from tailored advanced management of sepsis[43-45]; (2) to guide decision-making in institutions with scant resources, such as limited ICU beds or ICU specialists; and (3) to improve the selection of patients before their inclusion in interventional studies, based not only on the severity of infection but also mostly on their predicted outcome.[42,46] However, our study was not designed to determine an absolute threshold from which individual tailored therapy should be prescribed to patients with sepsis. This concept should be validated in a larger controlled trial. As available resources vary among institutions, we suggest that each center defines its own cutoff value of predicted mortality to adapt treatment intensity.

The model combines routinely computed severity scores with PCT, a biomarker largely used worldwide, and PSP, a new acute-phase protein that is on the way to being included in automated laboratory procedures in major companies.[47] The simplicity of the model and the fact that it relies on information that is or would be routinely collected in the ICU may facilitate its implementation. The outcome prediction of the model was validated in an independent cohort, despite different observed mortality rates. This suggests that the performances of the model are generalizable to similar, yet different, intensive care settings.

This study has certain limitations. First, owing to organizational constraints, inclusion in the derivation cohort was prospective but could not be strictly

TABLE 4] Plasma Levels of Biomarkers and Severity Scores of Derivation and Validation Cohorts, Stratified According to Survival Status

	Derivation Cohort (N = 158)			Validation Cohort (N = 91)		
Measure	Survival (n = 116)	Death (n = 42)	*P* Value	Survival (n = 52)	Death (n = 39)	*P* Value
Severity scores						
APACHE II	27.0 (13.3)	32.5 (13.5)	.008	18.5 (11.5)	22.0 (14.0)	.027
SAPS II	67.0 (25.3)	71.0 (22.5)	.060	42.0 (22.5)	42.0 (28.5)	.198
Biomarkers						
CRP, mg/L	273.0 (148.5)	225.0 (170.0)	.204	214.3 (181.8)	176.7 (198.1)	.742
PCT, ng/mL	25.7 (52.0)	21.0 (43.1)	.515	3.9 (16.0)	5.6 (15.9)	.494
PSP, ng/mL	209.8 (358.4)	346.7 (456.7)	.002	63.9 (282.8)	185.1 (436.5)	.065

Data are presented as median (IQR). See Table 1 and 2 legends for expansion of abbreviations.

TABLE 5] Performance of In-Hospital Mortality Prediction Models in the Derivation Cohort

Prediction Model	Misclassification Error	Square of Prediction Error	AUC (95% CI)
APACHE II + CRP	0.271	0.214	0.640 (0.548-0.734)
APACHE II + log(PCT)	0.275	0.215	0.656 (0.565-0.747)
APACHE II + log(PSP)	0.232	0.203	0.679 (0.584-0.772)
APACHE II + CRP + log(PCT)	0.275	0.223	0.644 (0.552-0.736)
APACHE II + CRP + log(PSP)	0.234	0.210	0.692 (0.601-0.783)
APACHE II + log(PCT) + log(PSP)[a]	0.236[a]	0.202[a]	0.721 (0.632-0.812)[a]
APACHE II + CRP + log(PCT) + log(PSP)	0.230	0.210	0.719 (0.629-0.810)
SAPS II + CRP	0.270	0.216	0.612 (0.511-0.710)
SAPS II + log(PCT)	0.279	0.216	0.623 (0.527-0.721)
SAPS II + log(PSP)	0.257	0.206	0.659 (0.563-0.755)
SAPS II + CRP + log(PCT)	0.279	0.224	0.621 (0.521-0.721)
SAPS II + CRP + log(PSP)	0.259	0.212	0.684 (0.591-0.775)
SAPS II + log(PCT) + log(PSP)[a]	0.236[a]	0.205[a]	0.710 (0.617-0.802)[a]
SAPS II + CRP + log(PCT) + log(PSP)	0.237	0.213	0.712 (0.619-0.804)

AUC = area under the curve. See Table 1 and 2 legends for expansion of other abbreviations.
[a]Selected models with the smallest prediction error corrected for the optimism of prediction.

consecutive. Second, severity and outcome of patients differed between the derivation and validation cohorts. Severe sepsis and septic shock are syndromes characterized by an undefined and highly variable time between onset of infection, clinical manifestations, and hospital admission. For this reason, the precise interval of time between the onset of infection and the biomarker sampling is difficult to determine, although highly relevant. Delay of hospital/ICU admission may be higher in Brazil than in Switzerland because of a higher density of primary care, infrastructure, and social security coverage. This may have a further major impact on the efficacy of the hospital/ICU management of sepsis. This translated into a lower AUC of both models in the validation cohort. However, the relationship between severity scores and/or biomarkers and mortality were independently supported by the results from both cohorts. Whatever the ICU setting and the potential differences in absolute mortality between the populations of patients with sepsis, the model can identify those at a higher risk of death. Third, severity scores are computed using parameters collected during the first 24 h of ICU stay before being computed. The model can thus only be performed after this delay. Nevertheless, it can still be computed earlier using provisional admission values of severity scores. However, waiting 24 h before applying the model may provide some advantages, such as not considering patients who will die rapidly after ICU admission from multiple organ failure for expensive adjunctive therapies or potential inclusion in clinical trials. Fourth, unfortunately, in our series as well as in others, there are currently not enough data to analyze the PSP value in nonbacterial infections.

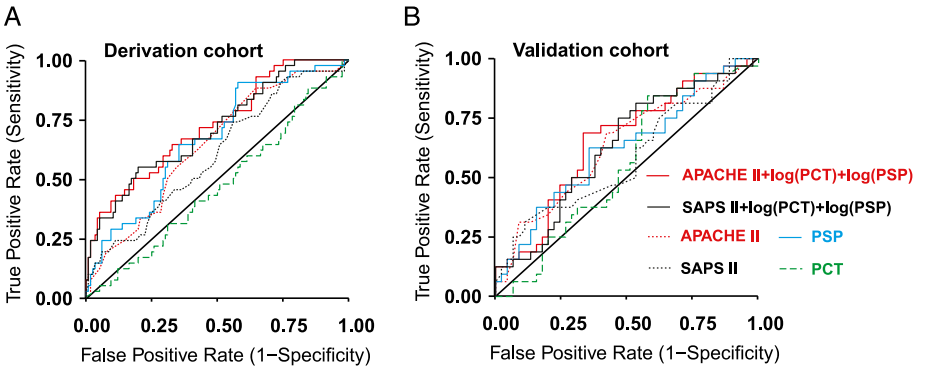

Figure 1 – *A, B, Receiver operating characteristic curves of the best in-hospital mortality predictive models (APACHE II + log[PCT] + log[PSP] and SAPS II + log[PCT] + log[PSP]) and of APACHE II, SAPS II, PCT, and PSP in the derivation (A) and validation (B) cohorts. APACHE = Acute Physiology and Chronic Health Evaluation; PCT = procalcitonin; PSP = pancreatic stone protein; SAPS = Simplified Acute Physiology Score.*

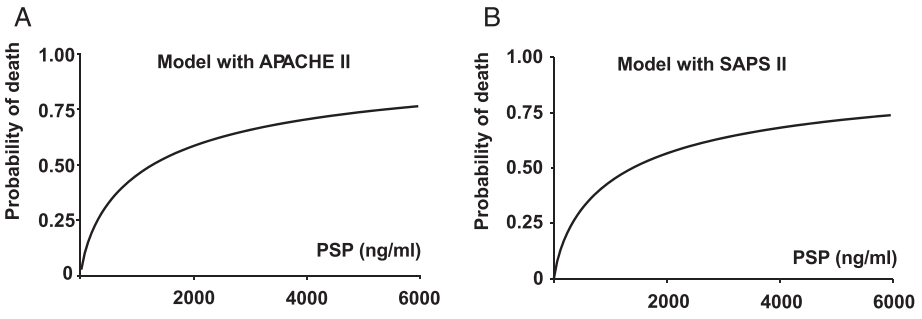

Figure 2 – *A, B, In-hospital mortality predicted by the model in the derivation and validation cohorts of patients with severe sepsis and septic shock. Probability of death as a function of PSP is plotted using the fixed values of the medians of PCT and APACHE II (A) and SAPS II (B) severity scores for the derivation cohort. See Figure 1 legend for expansion of abbreviations.*

Conclusions

Our data confirmed the prognostic value of PSP in outcome prediction of critically ill patients who present with severe sepsis and septic shock admitted to different ICUs. We developed and validated an in-hospital mortality prediction model in two independent cohorts of patients requiring ICU management for severe sepsis or septic shock. This model enhanced in-hospital mortality prediction by combining universally used severity scores (APACHE II or SAPS II), a routinely available biomarker (PCT), and the recently described PSP. We believe that this prediction model may help physicians in the challenging task of improving the care of critically ill patients with sepsis.

Acknowledgments

Author contributions: P. E. takes responsibility for the content of the manuscript, including the data and analysis. Y.-A. Q., I. G., J.-L. P., L. L., V. N., and P. E. were involved in the conception and the design of the study, analyzed the data, and wrote the paper; C. R. A. d. O. and C. F. O. collected and analyzed data from the Brazilian cohort; R. G. measured PSP/reg in blood samples and contributed to the analysis and interpretation of data; I. G., E. D.-L., and J.-P. R. performed the statistical work; and Y.-A. Q., I. G., E. D.-L., C. R. A. d. O., C. F. O., R. G., G. S., J.-P. R., J.-L. P., L. L., V. N., and P. E. reviewed the paper and agreed with final version of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Graf is the inventor of a patent owned by the University of Zurich for the use of PSP/reg as a marker of sepsis. The remaining authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, data collection and analysis, or in the preparation of the manuscript.

Other contributions: We thank Frederik Delodder, RN, MSc, for data collection; Martha Bain, PhD, for measuring PSP in blood samples; Laurence Leone for his outstanding technical assistance; Najib Maddah for his outstanding IT support; and the members of the Lausanne Sepsis Group (Anne Angelilo-Scherrer, MD, PhD; Jacques Bille, MD, PhD; Philippe Jolliet, MD; Philippe Moreillon, MD, PhD; Thierry Roger, PhD; Pierre-Yves Bochud, MD, PhD; and Thierry Calandra, MD, PhD) for their constructive support. Swaf Sàrl (Lausanne, Switzerland http://www.swaf.ch) developed the e-CRF.

Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Bernard GR, Vincent JL, Laterre PF, et al; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344(10):699-709.
2. Vincent JL, Sakr Y, Sprung CL, et al; Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*. 2006;34(2):344-353.
3. Vincent JL, Rello J, Marshall J, et al; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323-2329.
4. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2):165-228.
5. Calandra T, Glauser MP, Schellekens J, Verhoef J. Treatment of gram-negative septic shock with human IgG antibody to Escherichia coli J5: a prospective, double-blind, randomized trial. *J Infect Dis*. 1988;158(2):312-319.
6. Abraham E, Anzueto A, Gutierrez G, et al; NORASEPT II Study Group. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. *Lancet*. 1998;351(9107):929-933.
7. Opal S, Laterre PF, Abraham E, et al; Controlled Mortality Trial of Platelet-Activating Factor Acetylhydrolase in Severe Sepsis Investigators. Recombinant human platelet-activating factor acetylhydrolase for treatment of severe sepsis: results of a phase III, multicenter, randomized, double-blind, placebo-controlled, clinical trial. *Crit Care Med*. 2004;32(2):332-341.
8. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003;348(2):138-150.
9. Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*. 2012;366(22):2055-2064.
10. Opal SM, Laterre PF, Francois B, et al; ACCESS Study Group. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. *JAMA*. 2013;309(11):1154-1162.
11. Bernard GR, Francois B, Mira JP, et al. Evaluating the efficacy and safety of two doses of the polyclonal anti-tumor necrosis factor-α fragment antibody AZD9773 in adult patients with severe sepsis and/or septic shock: randomized, double-blind, placebo-controlled phase IIb study. *Crit Care Med*. 2014;42(3):504-511.
12. Vincent JL, Donadello K, Schmit X. Biomarkers in the critically ill patient: C-reactive protein. *Crit Care Clin*. 2011;27(2):241-251.
13. Que YA, Virgini V, Lozeron ED, et al. Low C-reactive protein values at admission predict mortality in patients with severe community-acquired pneumonia

caused by *Streptococcus pneumoniae* that require intensive care management. *Infection*. 2015;43(2):193-199.

14. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis*. 2007;7(3):210-217.
15. Keel M, Härter L, Reding T, et al. Pancreatic stone protein is highly increased during posttraumatic sepsis and activates neutrophil granulocytes. *Crit Care Med*. 2009;37(5):1642-1648.
16. Schlapbach LJ, Graf R, Woerner A, et al. Pancreatic stone protein as a novel marker for neonatal sepsis. *Intensive Care Med*. 2013;39(4):754-763.
17. Llewelyn MJ, Berger M, Gregory M, et al. Sepsis biomarkers in unselected patients on admission to intensive or high-dependency care. *Crit Care*. 2013;17(2):R60.
18. Klein HJ, Csordas A, Falk V, et al. Pancreatic stone protein predicts postoperative infection in cardiac surgery patients irrespective of cardiopulmonary bypass or surgical technique. *PLoS ONE*. 2015;10(3):e0120276.
19. Boeck L, Graf R, Eggimann P, et al. Pancreatic stone protein: a marker of organ failure and outcome in ventilator-associated pneumonia. *Chest*. 2011;140(4):925-932.
20. Que YA, Delodder F, Guessous I, et al. Pancreatic stone protein as an early biomarker predicting mortality in a prospective cohort of patients with sepsis requiring ICU management. *Crit Care*. 2012;16(4):R114.
21. Gukasjan R, Raptis DA, Schulz HU, Halangk W, Graf R. Pancreatic stone protein predicts outcome in patients with peritonitis in the ICU. *Crit Care Med*. 2013;41(4):1027-1036.
22. Calandra T, Baumgartner JD, Grau GE, et al. Prognostic values of tumor necrosis factor/cachectin, interleukin-1, interferon-alpha, and interferon-gamma in the serum of patients with septic shock. Swiss-Dutch J5 Immunoglobulin Study Group. *J Infect Dis*. 1990;161(5):982-987.
23. Calandra T, Gerain J, Heumann D, Baumgartner JD, Glauser MP. High circulating levels of interleukin-6 in patients with septic shock: evolution during sepsis, prognostic value, and interplay with other cytokines. The Swiss-Dutch J5 Immunoglobulin Study Group. *Am J Med*. 1991;91(1):23-29.
24. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care*. 2010;14(1):R15.
25. Levy MM, Fink MP, Marshall JC, et al; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256.
26. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control*. 1988;16(3):128-140.
27. Calandra T, Cohen J; International Sepsis Forum Definition of Infection in the ICU Consensus Conference. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med*. 2005;33(7):1538-1548.
28. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.
29. Efron B. How biased is the apparent error rate of a prediction rule? *J Am Stat Assoc*. 1986;81(394):461-470.
30. Sing T, Sander O, Beerenwinkel N, Lengauer T. ROCR: visualizing classifier performance in R. *Bioinformatics*. 2005;21(20):3940-3941.
31. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *J R Stat Soc Series B Stat Methodol*. 2011;73(1):3-36.
32. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12(1):77.
33. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer; 2009.
34. Bouadma L, Luyt CE, Tubach F, et al; PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375(9713):463-474.
35. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(5):426-435.
36. Vincent JL, Opal SM, Marshall JC. Ten reasons why we should NOT use severity scores as entry criteria for clinical trials or in our treatment decisions. *Crit Care Med*. 2010;38(1):283-287.
37. Shapiro NI, Trzeciak S, Hollander JE, et al. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. *Crit Care Med*. 2009;37(1):96-104.
38. Giamarellos-Bourboulis EJ, Norrby-Teglund A, Mylona V, et al. Risk assessment in sepsis: a new prognostication rule by APACHE II score and serum soluble urokinase plasminogen activator receptor. *Crit Care*. 2012;16(4):R149.
39. Suberviola B, Castellanos-Ortega A, Ruiz Ruiz A, Lopez-Hoyos M, Santibañez M. Hospital mortality prognostication in sepsis using the new biomarkers suPAR and proADM in a single determination on ICU admission. *Intensive Care Med*. 2013;39(11):1945-1952.
40. Alan M, Grolimund E, Kutz A, et al; the ProHOSP study group. Clinical risk scores and blood biomarkers as predictors of long-term outcome in patients with community-acquired pneumonia: a 6-year prospective follow-up study [published online ahead of print December 19, 2014]. *J Intern Med*. doi:10.1111/joim.12341.
41. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
42. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840-851.
43. Cruz DN, Antonelli M, Fumagalli R, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. *JAMA*. 2009;301(23):2445-2452.
44. Lu Q, Rouby JJ, Laterre PF, et al. Pharmacokinetics and safety of panobacumab: specific adjunctive immunotherapy in critical patients with nosocomial Pseudomonas aeruginosa O11 pneumonia. *J Antimicrob Chemother*. 2011;66(5):1110-1116.
45. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med*. 2013;39(5):847-856.
46. Calfee CS, Pugin J. The search for diagnostic markers in sepsis: many miles yet to go. *Am J Respir Crit Care Med*. 2012;186(1):2-4.
47. Lascco announces a licensing agreement with Abbott for development and commercialization of pancreatic stone protein biomarker. Lajaunias Science Company website. http://www.lascco.com/News26_11_2012.html. Accessed May 10, 2015.