Anesthesiology 2007; 107:15–23

Protein C Concentrations Correlate with Organ Dysfunction and Predict Outcome Independent of the Presence of Sepsis

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Background: **Characterizing the evolution of protein C concentrations in critically ill patients may help in identifying high risk groups and potential therapeutic targets. The authors investigated the time courses of protein C concentrations and their relation to the presence of sepsis, organ dysfunction/failure, and outcome.**

Methods: **This observational cohort study, in a university hospital surgical intensive care unit (ICU), included 312 consecutive patients with an estimated ICU length of stay more than 48 h. Plasma protein C concentrations and parameters of organ dysfunction were measured daily until discharge or death.**

Results: **Protein C concentrations were below the lower limit of normal in 50.6% of patients (n = 158) on admission and decreased to a nadir within 3–4 days after admission before almost normalizing by 2 weeks thereafter, irrespective of the presence of sepsis, sex, source and type of admission, and type of surgery. The minimum protein C concentration was lower in patients with severe sepsis/septic shock (n = 54) than in those with sepsis (n = 63) and those who never had sepsis (n = 195), and was negatively correlated to the maximum Sequential Organ Failure Assessment score ($R^2 = 0.345$, $P < 0.001$). Protein C levels were lower in nonsurvivors (n = 46; 14.7%) than in survivors, especially in the first 4 days after admission. In a multivariable analysis with ICU mortality as the dependent variable, a minimum protein C concentration less than 45% was an independent risk factor for ICU death.**

Conclusions: **In critically ill surgical patients, protein C concentrations were generally low, associated with organ dysfunction/failure, and independently associated with a higher risk of ICU mortality.**

THE protein C pathway represents one of the major natural anticoagulant systems, exhibiting antithrombotic, profibrinolytic, and antiinflammatory properties.[1] Under physiologic conditions, this pathway inhibits the conversion of prothrombin to thrombin, thus preventing clot formation. Activation of the clotting system and microvascular coagulopathy are part of the host response to infection.[2]

Several studies[3–7] have reported decreased protein C concentrations in patients with sepsis syndromes. Moreover, a strong correlation between lower protein C levels and worse outcome has been reported.[8] Continuation or worsening of coagulopathy during the first days of severe sepsis has also been found to be associated with subsequent development of new organ dysfunction and worse outcome.[9]

Activation of inflammatory pathways can, however, occur in a variety of clinical conditions in the intensive care unit (ICU), including after surgical interventions and traumatic injury.[10] Boldt *et al.*[10] reported considerable alterations in the hemostatic network in patients with severe trauma and those admitted to the ICU after neurosurgical procedures. Protein C concentrations were more markedly decreased in patients with sepsis compared to those with severe trauma and neurosurgery, but this observation[10] was limited by the small number of patients in this study. Characterizing the evolution of protein C concentrations and their possible relationship to morbidity and mortality may help in identifying high-risk groups and potential therapeutic targets.

Therefore, the aim of our study was to investigate the time course of protein C concentrations and their relation to the presence of sepsis, organ dysfunction/failure, and ICU mortality in a cohort of surgical ICU patients.

This article is accompanied by an Editorial View. Please see: Gropper MA: Multisystem organ failure: Predicting the future. ANESTHESIOLOGY 2007; 107:6–7.

Materials and Methods

All patients admitted to the surgical ICU between January and October 2001 and who had an estimated ICU length of stay of more than 48 h were screened for eligibility. Exclusion criteria were age younger than 18 yr, advanced malignancy or other conditions with shortened life expectancy (< 4 weeks), pregnancy, and previous inclusion in the study; patients were also excluded if decisions to withhold or withdraw life-sustaining treatments were established within the first 24 h of ICU admission. Patients were followed up until ICU discharge. The study was approved by the institutional review board of Friedrich Schiller University hospital (Jena, Germany), and written informed consent was obtained from all patients or their next of kin.

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Received from the Department of Anesthesiology and Intensive Care, Friedrich Schiller University, Jena, Germany. Submitted for publication November 15, 2006. Accepted for publication February 6, 2007. Supported by competitive, peer-reviewed grants from the Thuringian Ministry of Science, Thueringen, Germany.

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Data Collection

The Acute Physiology and Chronic Health Evaluation II score[11] and the Simplified Acute Physiology Score II[12] were obtained within 24 h of admission. The Sequential Organ Failure Assessment (SOFA) score, a system that assesses the summary function of 6 organ systems (respiratory, cardiovascular, neurologic, renal, hepatic, and coagulation) using a scale of 0 (normal) to 4 (most abnormal) for each,[13] was calculated daily. The maximum SOFA score (SOFAmax) was defined as the highest SOFA score reached during the ICU stay and was used to express the worst organ dysfunction status attained during the ICU stay. Data recorded on admission included age, sex, referring facility, primary and secondary admission diagnoses, associated comorbidities, and surgical procedures preceding admission. The McCabe classification,[14] which classes underlying disease in terms of the likely outcome as rapidly fatal, ultimately fatal, or nonfatal, was used to assess the severity of underlying comorbidity. The presence of systemic inflammatory response syndrome criteria, organ failure, and/or infection was recorded daily together with the laboratory indices of organ dysfunction/failure (including platelet count, serum total bilirubin, serum creatinine, and serum lactate concentration).

Measurements and Sampling

Blood samples were collected daily; routine parameters of organ dysfunction/failure were measured in our laboratories using automated measures. Arterial lactate concentrations were measured using an automated blood gas analyzer (ABL700 Radiometer®; Copenhagen, Denmark). Plasma protein C concentrations were determined chromogenically by the Coamatic®-Test (Chromogenix, Mölndal, Sweden) on citrated fresh blood. Detection of protein C was validated to a lower detection limit of 5%. Values of protein C higher than 70% were considered as normal. The initial protein C measurement was performed within 24 h of ICU admission.

Definitions

Sepsis, severe sepsis, and septic shock were defined according to the American College of Chest Physicians–Society of Critical Care Medicine consensus conference criteria[15] by the attending senior intensivist. Central nervous system failure was defined as disturbed consciousness, irritability, disorientation, and/or delirium without evidence of drug induced manifestations; thrombocytopenia was defined as platelet count less than $100 \times 10^3/\mu l$ or greater than 30% decline within 24 h without evidence of blood loss as an etiologic factor; respiratory failure was defined as arterial partial pressure of oxygen less than 75 mmHg in room air, ratio of arterial partial pressure of oxygen to inspired fraction of oxygen less than 250 mmHg; cardiovascular failure was defined as systolic blood pressure less than 90 mmHg or mean arterial pressure less than 70 mmHg for at least 1 h despite adequate fluid resuscitation; renal failure was defined as urinary output less than 0.5 ml/kg/h for at least 1 h in the absence of hypovolemia or a twofold increase in serum creatinine; and metabolic acidosis was defined as base excess less than −5 mEq/l or a plasma lactate concentration 1.5 times above the reference value.

Statistical Analysis

Data were analyzed using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL). A Kolmogorov–Smirnov test was used to verify the normality of distribution of continuous variables. A Friedman test was used to assess the evolution of protein C activity within groups over time and differences between groups were assessed using the multifactorial analysis of variance. A Wilcoxon test was used to compare initial and minimum protein C concentrations. A Kruskal–Wallis H test was used to compare differences between groups with subsequent pairwise comparisons using a Mann–Whitney U test with Bonferroni correction for multiple comparisons. The predictive value of protein C activity on ICU outcome was calculated using a receiver operator characteristic curve, and the area under the curve was computed. The best cutoff point was defined using the Youdin index, and sensitivity, specificity, negative predictive value, and positive predictive value were calculated. We conducted a multivariable analysis with ICU mortality as the dependent variable to determine the predictive value of protein C concentrations after adjusting for the possible confounding factors. Variables considered for the multivariable analysis included age, sex, source of admission, type of surgery, occurrence of sepsis syndromes during the ICU stay, and SOFAmax. The multivariable analysis was preceded by a univariate selection of potential prognostic variables ($P < 0.2$). Colinearity between variables was ruled out before covariates were introduced in the model. A forward, stepwise approach was used for multivariable modeling, and the minimum protein C concentration was introduced at the final step as a categorical variable, according to the cutoff point determined by the receiver operator characteristic curve. Variables were retained in the multivariable model with $P < 0.1$. Goodness of fit was tested using the Hosmer and Lemeshow test, and odds ratios were computed.

A P value less than 0.05 was considered significant. Data are presented as mean ± SD unless otherwise indicated.

Results

Characteristics of the Study Group

Of 1,095 patients admitted to our surgical ICU during the study period, 312 patients (199 male and 113 female;

Table 1. Characteristics of the Study Group on Admission to the ICU (n = 312)

Age, mean ± SD, yr	63 ± 15
Sex, male/female	199/113
APACHE II score, mean ± SD	15.1 ± 6.5
SAPS II score, mean ± SD	38.7 ± 12.6
SOFA score, mean ± SD	7.6 ± 3.1
McCabe classification, n (%)	
Nonfatal	299 (95.8)
Rapidly fatal	12 (3.8)
Ultimately fatal	1 (0.3)
Source of admission, n (%)	
OR/recovery	202 (64.7)
Shock room	39 (12.5)
Other hospital	35 (11.2)
Hospital floor	27 (8.7)
Other ICU	9 (2.9)
Type of admission, n (%)	
No surgery	70 (22.4)
Elective surgery	129 (41.3)
Emergency surgery	113 (36.2)
Type of surgery, n (%)	
Cardiothoracic surgery	154 (49.4)
Neurosurgery	29 (9.3)
Vascular surgery	21 (6.7)
Trauma surgery	22 (7.1)
Others*	16 (5.1)
ICU mortality, n (%)	46 (14.7)
ICU length of stay, median [IQR], days	6 [4–14]

* 10 gastrointestinal, 3 urogenital, and 3 oropharyngeal

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; IQR = interquartile range; OR = operating room; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

mean age, 63 yr) met the inclusion criteria and were enrolled in the study. The characteristics of the study group are presented in table 1. One hundred twenty-nine patients (41.3%) were admitted after elective surgical intervention, and 113 patients (36.2%) were admitted after emergency surgical procedures. Cardiothoracic surgery was performed in 154 of the study patients (49.4%). Seventy patients were referred from other facilities and did not undergo any surgical procedure in the 48 h preceding ICU admission because of respiratory failure (n = 22), severe sepsis without a surgical focus (n = 9), deterioration in the level of consciousness (n = 13), trauma (n = 5), successful cardiopulmonary resuscitation (n = 4), acute renal failure (n = 5), congestive heart failure or myocardial ischemia (n = 5), gastrointestinal bleeding (n = 4), seizures (n = 2), and arrhythmia (n = 1). The median ICU length of stay for all patients was 6 days (25–75% interquartile range, 4–14 days), and the overall ICU mortality rate was 14.7% (n = 46).

Evolution of Protein C Concentrations during the ICU Stay

The initial protein C concentration was below the lower limit of normal in 50.6% of patients (n = 158). None of the study patients received protein C concentrates or activated protein C. However, 147 patients, mostly after cardiovascular surgery (n = 89), received fresh frozen plasma (1–4 units in 67 patients, 5–8 units in 29 patients, and > 8 units in 51 patients); 9 of these patients also received prothrombin complex (1,000–3,000 units) during the ICU stay.

The evolution of protein C levels over the 2 weeks after admission to the ICU, stratified by the presence of various sepsis syndromes, is presented in figure 1. Protein C concentrations decreased over time, reaching a nadir within 3–4 days after ICU admission and almost normalizing by 2 weeks thereafter, irrespective of the presence of sepsis syndromes. Initial protein C concentrations were lower in patients with severe sepsis (n = 54; including 48 patients with septic shock) compared with those who never had sepsis during the ICU stay

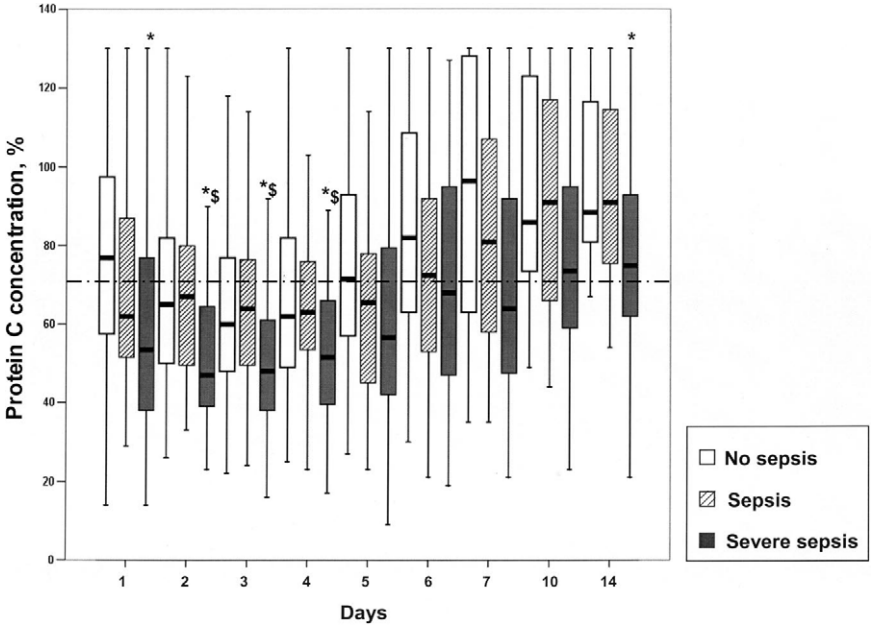

Fig. 1. Box plot representing the time course of protein C concentrations (%) over the 2 weeks after admission to the intensive care unit in patients who never had sepsis in the intensive care unit (*open boxes*), those with sepsis (*hatched boxes*), and those with severe sepsis (including septic shock; *closed boxes*). The *dashed line* represents the lower limit of normal for protein C activity (70%). Friedman test: $P < 0.05$ in each group over time. Multifactorial analysis of variance; $P < 0.05$ between groups. * $P < 0.05$ compared with no-sepsis group (Mann–Whitney U test with Bonferroni correction). $ $P < 0.05$ compared with sepsis group (Mann–Whitney U test with Bonferroni correction)

Table 2. Severity Scores on ICU Admission, ICU Length of Stay, and Initial and Minimal Protein C Concentrations According to the Source of Admission, Occurrence of Sepsis Syndromes over the ICU Stay, Type and Site of Surgery, and ICU Outcome

					Protein Concentration, %	
	n	APACHE II Score	SAPS II Score	ICU LOS	Initial	Minimum
Sex						
Male	199	15.0 ± 6.7	38.3 ± 12.0	7 [4–14]	73.0 ± 30.1	52.8 ± 22.1
Female	113	15.4 ± 6.3	39.3 ± 13.5	6 [4–12]	78.0 ± 30.3	54.8 ± 24.1
Source of admission		‡	‡	‡	‡	
OR/recovery†	202	13.9 ± 5.4	35.0 ± 9.7	6 [4–11]	77.6 ± 29.8	51.9 ± 20.4
Shock room	39	18.1 ± 7.3§	45.8 ± 15.4§	13 [5–21]§	69.1 ± 30.3	53.1 ± 23.1
Other hospital	35	16.1 ± 7.9	44.3 ± 13.7§	8 [4–17]	69.7 ± 32.5	59.5 ± 32.7
Hospital floor	27	16.0 ± 6.8	42.6 ± 10.7§	6 [4–10]	77.9 ± 27.6	63.0 ± 21.8
Other ICU	9	23.7 ± 8.3§	56.7 ± 19.3§	13 [3–18]§	48.2 ± 24.1§	39.4 ± 19.5
Type of admission		‡	‡		‡	
No surgery†	70	18.0 ± 7.8	46.5 ± 15.0	7 [4–14]	66.7 ± 30.1	55.8 ± 25.9
Elective surgery	129	13.9 ± 4.7§	32.5 ± 7.5§	6 [4–10]	81.3 ± 30.8§	50.0 ± 20.3
Emergency surgery	113	14.7 ± 7.0	40.9 ± 12.2§	8 [4–17]	72.4 ± 28.2	56.1 ± 23.1
Type of surgery		‡	‡	‡	‡	‡
Cardiothoracic†	154	14.2 ± 5.1	34.1 ± 8.0	6 [4–11]	78.6 ± 29.7	49.9 ± 20.4
Neurosurgery	29	17.6 ± 8.0	50.3 ± 13.5§	12 [7–21]§	91.2 ± 29.0	70.4 ± 25.0§
Vascular	21	12.9 ± 5.2	34.7 ± 10.7	4 [3–9]	72.3 ± 29.6	58.8 ± 21.5
Trauma	22	12.1 ± 5.9	32.8 ± 9.5	14 [8–23]§	68.5 ± 28.4	44.6 ± 15.9
Others*	16	14.3 ± 7.5	40.3 ± 11.3	5 [3–10]	56.0 ± 21.8§	53.8 ± 21.2
Sepsis syndromes		‡	‡	‡	‡	‡
No sepsis†	195	13.6 ± 5.8	35.9 ± 11.0	5 [3–8]	79.6 ± 28.9	58.9 ± 22.9
Sepsis	63	15.7 ± 5.8§	41.2 ± 11.9§	12 [6–24]§	71.5 ± 29.7	52.7 ± 20.1
Severe sepsis	54	20.1 ± 7.3§	45.7 ± 15.3§	15 [7–25]§	61.4 ± 31.4§	35.1 ± 14.6§
ICU outcome						
Survivors†	266	14.1 ± 5.7	36.8 ± 11.1	6 [4–13]	76.3 ± 28.8	56.6 ± 22.2
Nonsurvivors	46	21.1 ± 7.6§	49.8 ± 15.0§	7 [3–16]	66.5 ± 36.8§	35.7 ± 17.8§

Intensive care unit (ICU) length of stay (LOS) is presented as median [interquartile range]; others are presented as mean ± SD.

* 10 gastrointestinal, 3 urogenital, and 3 oropharyngeal. † Reference group for pairwise comparisons. ‡ $P < 0.05$ between groups (Kruskal–Wallis H test). § $P < 0.05$ compared with the reference group (Mann–Whitney U test with Bonferroni correction for multiple comparisons).

APACHE = Acute Physiology and Chronic Health Evaluation; OR = operating room; SAPS = Simplified Acute Physiology Score.

(n = 195) (table 2). Patients with sepsis (without sepsis-attributable organ failure, n = 63) had initial protein C concentrations that were comparable to those of patients without sepsis. Protein C concentrations decreased significantly in all patients irrespective of sex, source of admission, type of admission, and type of surgery (table 2). The minimal value reached was more pronounced in patients with severe sepsis compared with the other two groups (fig. 2). The minimum protein C concentration was higher in patients admitted after neurosurgical procedures than in those who underwent cardiothoracic surgery (70.4 ± 25.0 *vs.* 49.9 ± 20.4%; $P < 0.05$). Severity scores and ICU length of stay varied widely among the various subgroups (table 2).

Relation between the Evolution of Protein C Concentrations, Organ Dysfunction/Failure, and ICU Outcome

The minimum protein C concentration correlated negatively with the SOFAmax ($R^2 = 0.345$, $P < 0.001$; fig. 3). All patients with a SOFAmax greater than 16 (n = 21) and 91% of those with a SOFAmax between 8 and 16 had a minimum protein C concentration below the lower limit of normal. The minimum protein C concentration was also lower according to the degree of organ dysfunction/failure as assessed by the SOFAmax subscores for the cardiovascular, respiratory, renal, hepatic, and coagulation systems (fig. 4).

Forty-six patients (14.7%) died in the ICU: 27 had severe sepsis, 5 had sepsis, and 14 never had sepsis. Age was similar between nonsurvivors and survivors (66 ± 16 *vs.* 63 ± 15; $P = 0.22$). Simplified Acute Physiology Score II (49.8 ± 15.0 *vs.* 36.8 ± 11.1; $P < 0.01$) and Acute Physiology and Chronic Health Evaluation II scores (21.1 ± 7.6 *vs.* 14.1 ± 5.7; $P < 0.01$) were higher in nonsurvivors compared with survivors. Protein C concentrations decreased in both nonsurvivors and survivors, reaching a nadir 3–4 days after ICU admission (fig. 5) and increasing thereafter, but were lower in nonsurvivors compared with survivors (multifactorial analysis of variance; $P < 0.05$), especially over the first 4 days after admission. The area under the curve for ICU mortality prediction was 0.78 (95% confidence interval [CI], 0.71–0.85; $P < 0.01$) for minimum protein C concentration, 0.78 (95% CI, 0.71–0.85; $P < 0.01$) for Acute Physiology and Chronic Health Evaluation II score; and 0.77 (95% CI, 0.70–0.85; $P < 0.01$) for Simplified Acute Physiology Score II (fig. 6). The best cutoff point for minimum protein C concentration was 45%, and this had a sensitivity of 78%, a specificity of 67%, a negative

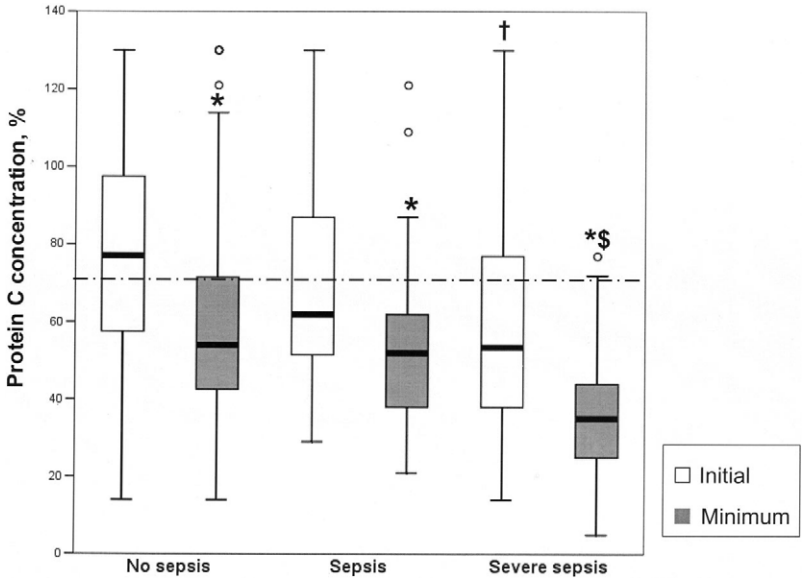

Fig. 2. Box plot representing the initial (*open*) and minimum (*closed*) protein C concentrations (%) over the first 2 weeks after admission to the intensive care unit according to the presence of sepsis or severe sepsis (including septic shock). The *dashed line* represents the lower limit of normal for protein C activity (70%). * $P < 0.05$ compared with initial values (Wilcoxon test). † $P < 0.05$ compared with no sepsis (Mann–Whitney U test with Bonferroni correction). $ $P < 0.05$ pairwise, compared with no-sepsis or sepsis group (Mann–Whitney U test with Bonferroni correction).

predictive value of 95%, and a positive predictive value of 29%.

In the univariate analysis, admission from another hospital or ICU, Simplified Acute Physiology Score II, SOFAmax, severe sepsis, and minimum protein C concentration less than 45% were associated with an increased risk of ICU mortality (table 3). In the multivariable analysis with ICU mortality as the dependent variable, Simplified Acute Physiology Score II (odds ratio, 1.82; 95% CI, 1.27–2.59; $P = 0.001$), SOFAmax (odds ratio, 1.2; 95% CI, 1.02–1.41; $P = 0.028$), and minimum protein C concentration less than 45% (odds ratio, 4.02; 95% CI, 1.43–11.34; $P = 0.008$) were the only independent risk factors for ICU death.

Discussion

The main finding of our study is that protein C concentrations were generally low in patients admitted to the surgical ICU and decreased over time, reaching a nadir within 3–4 days after ICU admission, irrespective of sex, source of admission, type of admission, and type of surgery. Protein C concentrations correlated to the severity of sepsis and to the degree of organ dysfunction and were independently associated with a higher risk of ICU mortality.

Low protein C concentrations have been reported frequently in ICU patients. Previous observations,[3–7] however, have focused mainly on patients with sepsis syndromes, especially those with severe sepsis. The reason

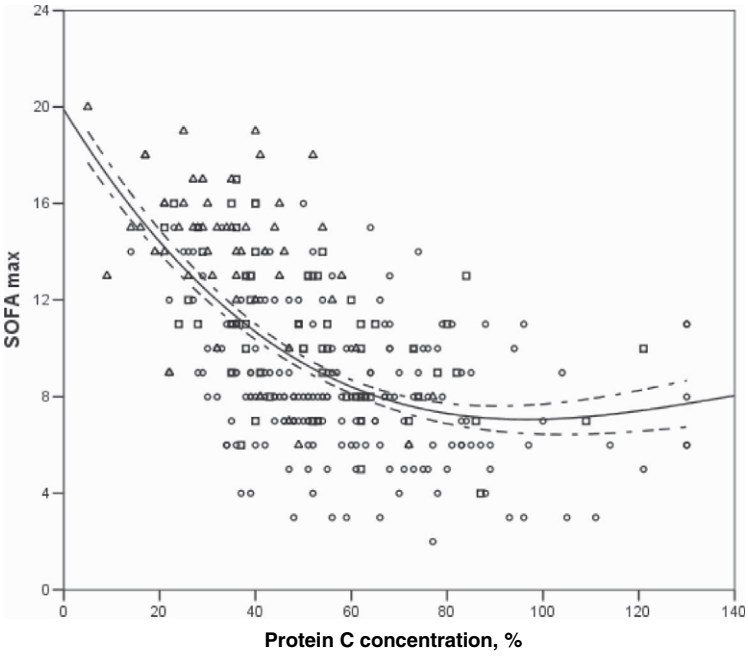

Fig. 3. Scatter plot representing the minimal protein C concentration (%; *x-axis*) and maximum Sequential Organ Failure Assessment (SOFA) score during the intensive care unit stay (*y-axis*) in patients with no sepsis (*open circles*), those with sepsis (*open squares*), and those with severe sepsis (including septic shock; *open triangles*). The *solid line* represents the best fit (quadratic) with 95% confidence interval (*dashed lines*). $R^2 = 0.345$, $P < 0.001$.

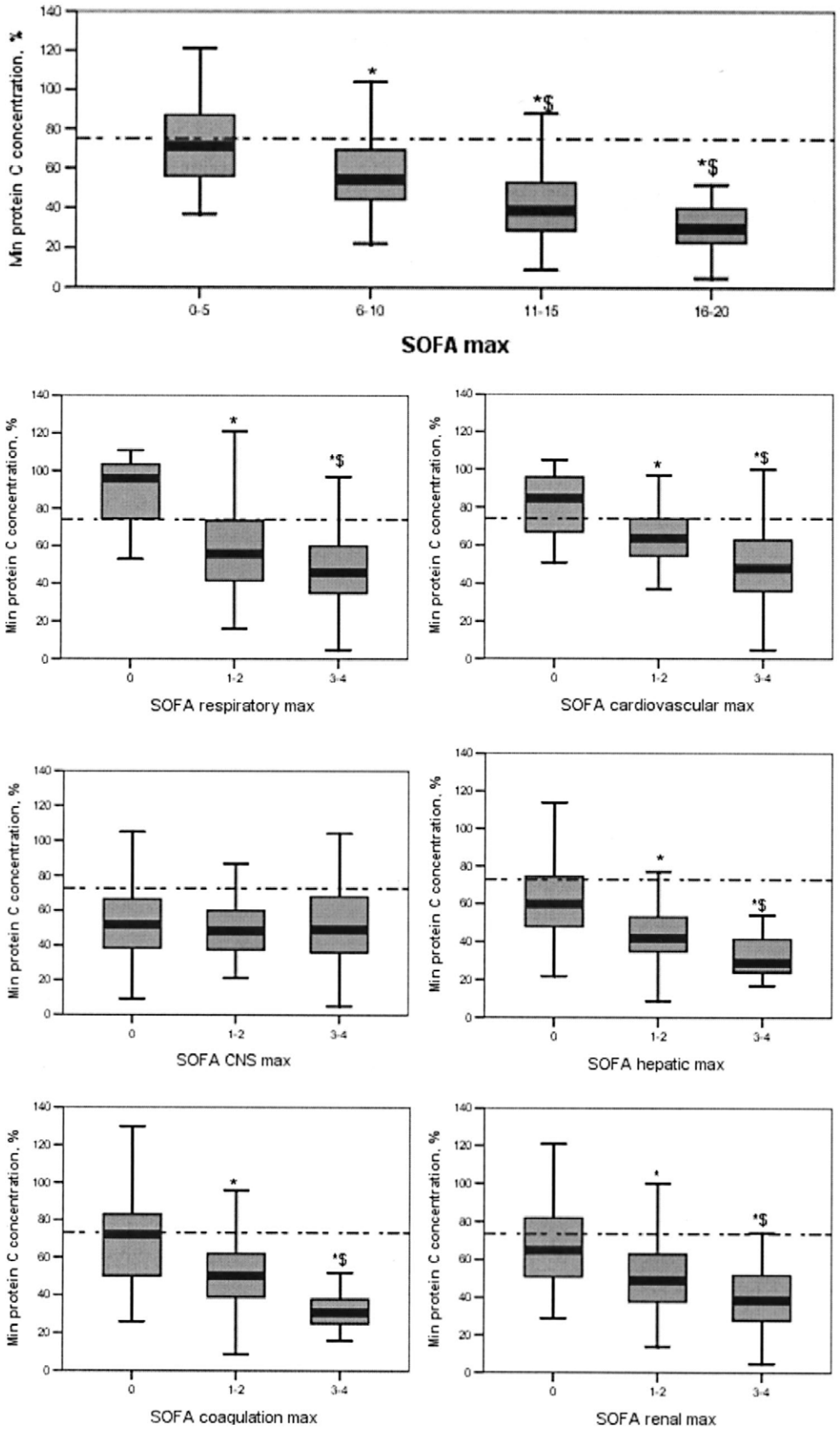

Fig. 4. Box plots representing minimum protein C concentration (%) according to the maximal Sequential Organ Failure Assessment (SOFA) score and maximal organ subscores. The *dashed line* represents the lower limit of normal for protein C activity (70%). * $P < 0.05$ compared with the first category (Mann–Whitney U test with Bonferroni correction). $ $P < 0.05$ compared with the previous category (Mann–Whitney U test with Bonferroni correction).

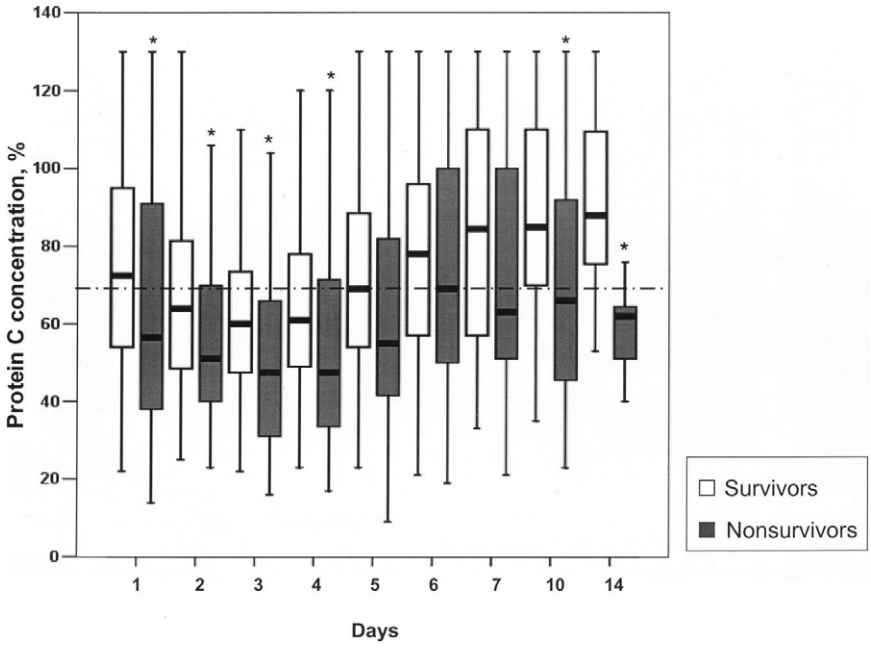

Fig. 5. Box plot representing the evolution of protein C concentration (%) over the first 2 weeks after admission to the intensive care unit according to outcome. Friedman test: $P < 0.05$ in each group over time. Multifactorial analysis of variance: $P < 0.05$. The *dashed line* represents the lower limit of normal for protein C activity (70%). *$P < 0.05$ compared with survivors (Mann–Whitney U test with Bonferroni correction).

for the early decrease in protein C concentrations is probably multifactorial. Acute inflammation, as a response to severe infection or trauma, results in systemic activation of the coagulation system.[16,17] Cytokines have been shown to play an important mediatory role through activation of the tissue factor–factor VIIa (extrinsic) pathway.[18,19] Vascular endothelial cells also play a central role in the mechanisms that contribute to inflammation-induced activation of the coagulation system. Therefore, the subsequent consumption of anticoagulation factors, including protein C, is one possible reason for the decreased protein C levels seen in ICU patients.[16] Impairment of hepatic protein synthesis may also be a contributing factor, due to associated hepatic dysfunction or substrate deficiency.

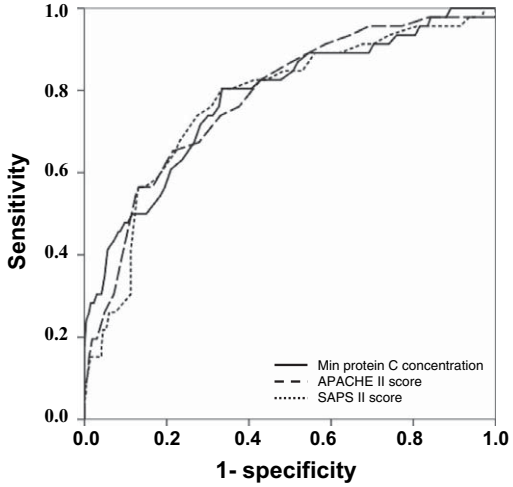

Fig. 6. Receiver operator characteristic curve for intensive care unit mortality prediction. The *solid line* represents the minimum protein C concentration (area under the curve, 0.78; 95% confidence interval, 0.71–0.85; $P < 0.01$), the *dashed line* represents the Acute Physiology and Chronic Health Evaluation (APACHE) II score (area under the curve, 0.78; 95% confidence interval, 0.71–0.85; $P < 0.01$), and the *dotted line* represents the Simplified Acute Physiology Score (SAPS) II (area under the curve, 0.77; 95% confidence interval, 0.70–0.85; $P < 0.01$).

In our study, protein C concentrations decreased significantly regardless of the type of surgery. However, the minimum protein C concentration was lower after cardiothoracic surgery than after neurosurgery. This may not be surprising, because the degree of inflammatory reaction is expected to be associated with the amount of tissue damage. Boldt *et al.*[10] examined several markers of coagulation activation and fibrinolytic activity in 45 patients after severe trauma, neurosurgery, and severe sepsis. Alteration of the hemostatic network was seen in all three groups of critically ill patients. However, this alteration was persistent only in the patients with severe sepsis. Neurosurgical patients had higher protein C concentrations than those with severe posttraumatic injury.

Patients with severe sepsis had lower protein C concentrations than other patients. Nevertheless, our data suggest that the presence of organ failure may be more important in determining protein C concentrations than sepsis itself, because protein C levels were similar in patients who never had sepsis and those who developed sepsis without organ failure. Indeed, in agreement with previous reports,[3,20] we found that protein C concentrations were correlated to the degree of organ dysfunction/failure. Matthay and Ware[21] reported low protein C levels in 45 patients with acute lung injury or acute respiratory distress syndrome due to septic and nonseptic causes. They also found that lower protein C levels were associated with a worse outcome regardless of the presence of sepsis and were correlated to the degree of organ failure.

Table 3. Logistic Regression Analysis with ICU Mortality as the Dependent Variable

	Univariate Analysis		Multivariable Analysis*	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Age†	1.16 (0.92–1.45)	0.205	—	—
Sex, female	1.56 (0.61–2.20)	0.656	—	—
Source of admission				
OR/recovery	Reference	NA		
Shock room	2.35 (0.95–5.50)	0.064	—	—
Other hospital	3.15 (1.30–7.65)	0.011	—	—
Hospital floor	2.07 (0.71–6.06)	0.185	—	—
Other ICU	7.28 (1.81–29.33)	0.005	—	—
Emergency surgery‡	2.17 (0.98–4.78)	0.055	—	—
Type of surgery				
No surgery	Reference	NA		
Cardiothoracic	0.45 (0.21–0.94)	0.034	—	—
Neurosurgery	0.88 (0.31–2.54)	0.813	—	—
Vascular	0.36 (0.08–1.69)	0.194	—	—
Trauma	0.53 (0.14–2.03)	0.357	—	—
Others	0.23 (0.63–1.84)	0.194	—	—
SAPS II score§	2.10 (1.63–2.71)	< 0.001	1.82 (1.27–2.59)	0.001
Max. SOFA score‖	1.53 (1.36–1.73)	< 0.001	1.2 (1.02–1.41)	0.028
Sepsis syndromes in the ICU				
No sepsis	Reference	NA	Reference	NA
Sepsis	1.12 (0.39–3.23)	0.842	0.43 (0.13–1.43)	0.168
Severe sepsis	12.93 (6.04–27.69)	< 0.001	2.60 (0.94–7.16)	0.063
Min. protein C < 45%	8.18 (3.78–17.69)	< 0.001	4.02 (1.43–11.34)	0.008

* Forward stepwise. Hosmer and Lemeshow chi-square = 5.11; $P = 0.746$, Nagelkerke pseudo $R^2 = 0.468$. † Per 10 yr. ‡ With elective surgery as a reference. § Per 10 points. ‖ Per point.

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; ICU = intensive care unit; NA = not applicable; OR = operating room; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

Interestingly, the minimum protein C concentrations were independently associated with ICU mortality after adjustment for the degree of organ dysfunction and the presence of sepsis. The exact mechanism behind these associations remains a matter of speculation. In its activated form, protein C inactivates factors Va and VIIIa by proteolytic cleavage, thus slowing down the coagulation cascade. Moreover, activated protein C has antiinflammatory effects on mononuclear cells and granulocytes, which may be distinct from its anticoagulant activity.[22–25] On the other hand, defects in protein C activity enhance vulnerability to inflammatory reactions and the activation of coagulation.[26,27] A wide range of derangements have been described, including diffuse bleeding, hemorrhagic necrosis, and microvascular thrombosis.[28,29] These alterations may trigger organ dysfunction or aggravate preexisting conditions, thus further worsening prognosis. Therefore, the relation between coagulation and inflammation is probably bidirectional and seems to play a pivotal role in the mechanisms leading to organ failure whether or not associated with sepsis.

The tight relation we observed between protein C concentrations and organ dysfunction/failure as assessed by the SOFA score may explain the results of therapeutic studies[30–32] targeting the protein C pathway. A benefit of treatment with recombinant human activated protein C (drotrecogin alfa [activated]) was reported in patients with severe sepsis who had a higher degree of organ dysfunction,[30] and those with overt disseminated intravascular coagulation.[31] However, no beneficial effect was demonstrated in patients with severe sepsis who were at low risk of death, such as those with single-organ failure or an Acute Physiology and Chronic Health Evaluation II score less than 25.[32] These observations support the hypothesis that organ failure, not sepsis *per se*, is the major determinant of protein C deficiency. Whether targeting the protein C pathway could improve outcome in patients with multiorgan failure of nonseptic origin remains an unanswered question. Further studies are needed to confirm or negate this hypothesis.

Although this is the largest report to date exploring the evolution of protein C concentrations in a general ICU population, our study has some limitations. First, our cohort represents a group of surgical ICU patients; therefore, extrapolation of our results to medical ICU patients may not be valid. Second, initial protein C concentrations were measured within 24 h after admission to the ICU and preoperative levels were not determined; therefore, we may have overlooked early changes in plasma concentrations. Dhainaut *et al.*[9] showed that continuing or worsening coagulopathy during the first day of severe sepsis was associated with greater development of new organ failure and increased 28-day mortality. However, we found that the minimum protein C concentration over the first 2 weeks after admission was highly correlated to the admission severity scores and the maximum degree of organ

dysfunction. Third, substitution with coagulation factors may have affected protein C levels. The impact of this substitution is difficult to assess in the clinical setting, but despite having received fewer coagulation factors, neurosurgical patients had higher protein C concentrations than other patients. Fourth, the multivariable analysis is limited to the available covariables and the effect of other unmeasured parameters on the final results is difficult to estimate. Finally, other parameters of coagulation and fibrinolysis were not measured in our study, and possible interactions of these factors with protein C concentrations cannot be excluded.

In conclusion, our study demonstrates that protein C concentrations are generally low in critically ill surgical patients, with a more pronounced decrease during the ICU stay in the presence of severe sepsis/septic shock. Protein C levels were also associated with organ dysfunction/failure and were independently associated with a higher risk of ICU mortality. These findings suggest that targeting the protein C pathway may improve outcomes in patients with multiorgan failure of nonseptic origin. Further studies are needed to confirm or refute this hypothesis.

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