Clinical Chemistry 54:9
000–000 (2008)

Prognostic Value of Chromogranin A at Admission in Critically Ill Patients: A Cohort Study in a Medical Intensive Care Unit

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BACKGROUND: Risk assessments of patients should be based on objective variables, such as biological markers that can be measured routinely. The acute response to stress causes the release of catecholamines from the adrenal medulla accompanied by chromogranin A (CGA). To date, no study has evaluated the prognostic value of CGA in critically ill intensive care unit patients.

METHODS: We conducted a prospective study of intensive care unit patients by measuring serum procalcitonin (PCT), C-reactive protein (CRP), and CGA at the time of admission. Univariate and multivariate analyses were performed to evaluate the ability of these biomarkers to predict mortality.

RESULTS: In 120 consecutive patients, we found positive correlations between CGA and the following: CRP ($r^2 = 0.216$; $P = 0.02$), PCT ($r^2 = 0.396$; $P < 0.001$), Simplified Acute Physiologic Score II (SAPS II) ($r^2 = 0.438$; $P < 0.001$), and the Logistic Organ Dysfunction System (LODS) score ($r^2 = 0.374$; $P < 0.001$). Nonsurvivors had significantly higher CGA and PCT concentrations than survivors [median (interquartile range): 293.0 μg/L (163.5–699.5 μg/L) vs 86.0 μg/L (53.8–175.3 μg/L) for CGA, and 6.78 μg/L (2.39–22.92 μg/L) vs 0.54 μg/L (0.16–6.28 μg/L) for PCT; $P < 0.001$ for both comparisons]. In a multivariable linear regression analysis, creatinine ($P < 0.001$), age ($P < 0.001$), and SAPS II ($P = 0.002$) were the only significant independent variables predicting CGA concentration ($r^2 = 0.352$). A multivariate Cox regression analysis identified 3 independent factors predicting death: log-normalized CGA concentration [hazard ratio (HR), 7.248; 95% confidence interval (CI), 3.004–17.487], SAPS II (HR, 1.046; 95% CI, 1.026–1.067), and cardiogenic shock (HR, 3.920; 95% CI, 1.731–8.880).

CONCLUSIONS: CGA is a strong and independent indicator of prognosis in critically ill nonsurgical patients.

Chromogranin A (CGA),[6] a glycoprotein of 48–52 kDa and the first member of the chromogranin/secretogranin family *(1)*, is released primarily by stimulated chromaffin cells *(2)*. This multifunctional protein is capable of influencing cardiovascular function *(3)*, which is often altered in critically ill patients *(4)*. CGA is also considered a reliable indicator of the activation of sympathetic tone *(5)*.

In clinical practice, CGA has been used as a marker of pheochromocytomas *(6)*, carcinoid tumors *(7, 8)*, neuroblastomas *(9)*, neuroendocrine tumors *(10)*, and neurodegenerative diseases *(11)*. Recent data have shown CGA to be a useful prognostic indicator in patients with chronic heart failure *(4)*, suggesting that CGA may have some association with cardiovascular diseases. Furthermore, a pilot study *(12)* has shown CGA to be a predictor of mortality in patients with acute myocardial infarction. The findings of this study have been confirmed in a subsequent study by the same authors, who showed that CGA is a strong and independent prognostic indicator in patients with complicated myocardial infarction *(13)*. Although CGA is generally regarded as a major protein released with catecholamines from the adrenal medulla under conditions of acute stress *(5)*, no study has been carried out

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Received December 20, 2007; accepted June 20, 2008.
Previously published online at DOI: 10.1373/clinchem.2007.102442
[6] Nonstandard abbreviations: CGA, chromogranin A; MOF, multiple organ failure; CRP, C-reactive protein; PCT, procalcitonin; SAPS II, Simplified Acute Physiological Score II; LODS, Logistic Organ Dysfunction System; CI, confidence interval; HR, hazard ratio; AUC, area under the ROC curve.

to evaluate the value of CGA measurement in the context of patients at risk of multiple organ failure (MOF) subsequent to a single acute nonsurgical stress.

Characterization of the severity of organ failures and prediction of patient outcome are of major importance for physicians who care for critically ill patients. MOF remains the main problem in intensive care because of its impact on morbidity, mortality, and resources *(14)*. MOF can develop as a consequence of multiple causes, such as infection, systemic inflammatory response syndrome, myocardial infarction, septic shock, and so on, which can lead to the activation of various endogenous cascades that can cause cellular dysfunction and death *(15)*.

This study was designed to evaluate whether unselected critically ill patients at admission demonstrate increased plasma CGA concentrations and whether CGA can be of any interest in the care of patients at high risk of death.

Materials and Methods

STUDY POPULATION

The protocol for this study was approved by our institutional review board for human experimentation; written informed consent was obtained from each participant or authorized representative before enrollment. Patients older than 18 years were recruited consecutively over 3 months between July and September 2007. Exclusion criteria included *(1)* a duration of stay <24 h and *(2)* conditions known to increase CGA concentrations independently of acute stress [i.e., a history of documented neuroendocrine tumors *(7)* or chronic treatment with proton pump inhibitors before admission *(16)*]. Patients who required surgical interventions were also excluded. Of the 120 participants included in the study, 70 patients had a primary diagnosis of severe infection (sepsis, 44; severe sepsis. 9; septic shock, 17), 17 patients had circulatory failure without infection (cardiogenic shock, 6; others, 11), 26 patients had self-poisoning with coma and/or respiratory failure, and 7 patients experienced out-of-hospital cardiac arrest (without previous documented heart failure).

PROCESSING OF BLOOD SAMPLES

Blood samples were collected at admission by venipuncture into serum-separator tubes without anticoagulant (BD Medical Systems). The tubes were immersed in ice and immediately transported to the laboratory for processing. Serum was separated by centrifugation at 1500*g* for 15 min at 4 °C and stored in 200-μL aliquots at −80 °C until analysis. All samples were stored and processed identically to ensure uniformity of measurements.

MEASUREMENTS

Serum C-reactive protein (CRP) was measured by an immunoturbidimetric assay, and serum creatinine was measured with the Jaffe method as specified by the manufacturer of the test kit (Behring Diagnostics). Serum CGA concentrations were measured with a commercial sandwich RIA kit (a gift of CISBIO, Marcoule, France), with ^{125}I-labeled bioactive CGA as a tracer molecule and 2 monoclonal antibodies against human CGA amino acid sequences 145–197 and 198–245. Intraassay and interassay CVs for the CGA assay were 5.9% and 7.7%, respectively (15 replicates of a human serum pool; mean, 32 μg/L). In the central 95% of the healthy population, serum CGA concentrations range from 19 μg/L to 98 μg/L. In neuroendocrine system tumors, the CGA serum concentration varies from the typical range up to 1 200 μg/L, depending on the biological and structural characteristics of the tumor, as well as on the extent of tumor spread *(17)*. Procalcitonin (PCT) concentrations were measured on the Kryptor system (Brahms Diagnostic) with the time-resolved amplified cryptate emission methodology in accordance with the assay manufacturer's recommendations. Leukocytes were counted with an LH 700 automated blood cell counter (Beckman Coulter).

CLINICAL DATA

Patient diagnoses were determined at admission. We defined septic shock and severe sepsis according to the criteria set by the International Sepsis Definition Conference *(18)*. Cardiogenic shock was diagnosed after documentation of myocardial dysfunction, and factors such as hypovolemia, hypoxia, and acidosis were excluded or corrected according to the definition of Forrester et al. *(19)*. The Simplified Acute Physiological Score II (SAPS II) and the Logistic Organ Dysfunction System (LODS) score were calculated at admission according to published standards *(20, 21)*.

OUTCOME

The primary outcome measure was 3-month mortality.

STATISTICAL ANALYSES

Continuous data are reported as the median (interquartile range), and group differences were evaluated with the Mann–Whitney *U*-test or the Kruskal–Wallis test. The Kolmogorov–Smirnov test was used to test whether variables were normally distributed. Categorical variables are reported as the percentage (frequency), and χ^2 tests were used to evaluate frequency differences between groups. Relationships between variables were evaluated with Spearman rank correlation tests. Multiple linear regression analysis equations were built by means of backward stepwise selection

Table 1. Comparison of clinical characteristics and biological markers for survivors and nonsurvivors.[a]

	Survivors (n = 87)	Nonsurvivors (n = 33)	*P*
A. Clinical characteristics			
Age, years	70 (57–79)	70 (62–80)	0.554
Male sex, % (n)	62 (54)	70 (23)	0.288
SAPS II score	41 (32–53)	70 (55–79)	<0.001
LODS score	4 (2–7)	8 (6–12)	<0.001
Sepsis, % (n)	51 (44)	61 (20)	0.219
Severe sepsis, % (n)	21 (9)	12 (4)	0.503
Septic shock, % (n)	20 (17)	42 (14)	0.011
Cardiogenic shock, % (n)	7 (6)	30 (10)	0.002
Time from first organ dysfunction to admission, h	24 (6–48)	24 (6–72)	0.372
ICU stay, days	8 (4–16)	8 (3–13)	0.415
B. Biological markers			
CGA, μg/L	86 (53–175)	293 (163–699)	<0.001
CRP, mg/L	74 (24–151)	72 (18–145)	0.975
PCT, μg/L	1 (0–6)	7 (2–23)	<0.001
Leukocytes, $\times 10^6$/L	13 100 (9400–16 000)	12 000 (5850–18 750)	0.459
Creatinine, μmol/L	131 (86–220)	186 (112–329)	0.007

[a] The primary outcome measure was 3-month mortality. Data are presented as the median (interquartile range) or as the percentage (frequency).

procedures that excluded variables with *P* values >0.05; *P* values were calculated with the Wald test. A Kaplan–Meier survival analysis was performed for the most significant variables. A Cox proportional hazards regression model was used to evaluate the effect of the logarithmically transformed CGA concentration on the endpoint and to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). To assess the independent prognostic value of CGA concentration, we first used a backward stepwise elimination procedure. In all cases, a *P* value <0.05 was considered statistically significant. We computed ROC curves to characterize both the prognostic accuracy of the biomarkers and their diagnostic accuracy in separating sepsis patients and nonsepsis patients, i.e., infection vs inflammation. All statistical analyses were performed with the SPSS statistical package (SPSS for Windows version 11.5).

Results

We excluded 35 of the 155 patients screened for this study (32 patients because of a duration of stay <24 h, 1 patient because of chronic proton pump inhibitor treatment, and 3 patients because of a history of neuroendocrine tumors).

ADMISSION CHARACTERISTICS OF PARTICIPANTS

The clinical characteristics of the final study population of 120 participants are summarized in Table 1. Nonsurvivors (n = 33) had significantly higher LODS and SAPS II scores than survivors (n = 87), and septic shock and cardiogenic shock were significantly more frequent in the nonsurvivor group than in the survivor group (Table 1A). Nonsurvivors had significantly higher concentrations of creatinine, PCT, and CGA (Table 1B; Fig. 1); however, there were no statistically significant differences between survivors and nonsurvivors with respect to age, leukocyte count, and CRP concentration.

RELATIONSHIP BETWEEN CGA AND CLINICAL SCORES AND BIOMARKERS

CGA concentration was positively but weakly correlated with age, PCT concentration, creatinine concentration, SAPS II, and LODS score ($P < 0.001$ for all variables) and was correlated with CRP concentration in a Spearman correlation analysis ($P = 0.02$; Table 2). When all these variables were entered into a multiple linear regression model and a stepwise backward variable-elimination scheme was followed, only creatinine concentration ($P < 0.001$), age ($P < 0.001$), and SAPS II ($P = 0.002$) remained in the model; these 3

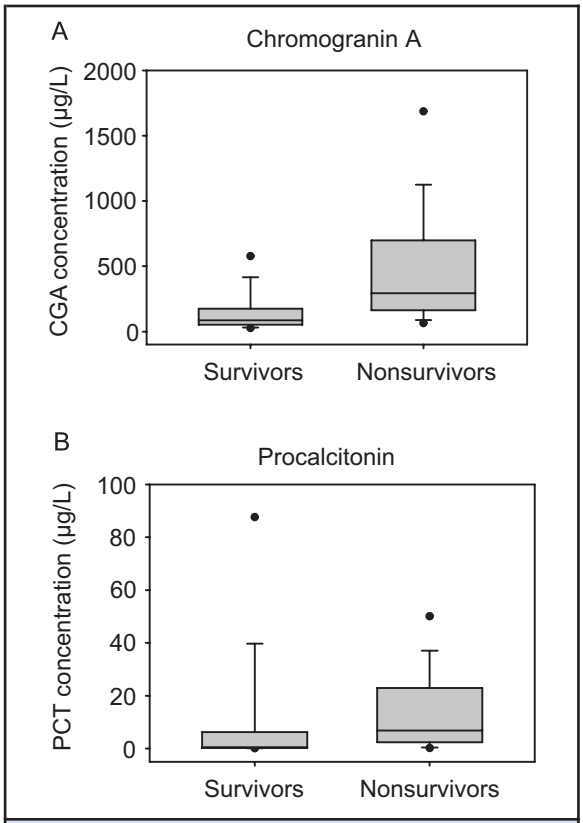

Fig. 1. Comparison of survivors (n = 87) and nonsurvivors (n = 33) with respect to CGA concentration (A) and PCT concentration (B).

Box-and-whisker plots of the median and interquartile range.

variables explained 35.2% (i.e., $r^2 = 0.352$) of the variability in CGA concentration. Identical results were obtained with a stepwise forward variable-selection procedure.

CGA AND DIAGNOSIS

We generated ROC curves to identify the ability of our biomarkers to distinguish between sepsis patients and nonsepsis patients. For this analysis, we chose a cutoff value that optimized sensitivity. For PCT with a cutoff value of 0.34 μg/L, sensitivity and specificity were 0.80 and 0.44, respectively, and the area under the ROC curve (AUC) was 0.70. For CRP with a cutoff value of 44 mg/L, sensitivity and specificity were 0.80 and 0.55, respectively, and the AUC was 0.72. For CGA with a cutoff value of 88 μg/L, sensitivity and specificity were 0.61 and 0.45, and the AUC was 0.56. The differences between the CGA AUC and the AUCs for PCT and CRP were significant ($P < 0.001$ for both comparisons).

CGA AND PROGNOSIS

Thirty-three deaths occurred during the median follow-up time of 23 days. The death rates for CGA and PCT are shown by quartiles in Fig. 2. Statistical analysis revealed a significant difference in death rates between CGA quartile 4 and CGA quartiles 1, 2, and 3 ($P < 0.001$, log-rank test). The death rate for CGA quartile 3 was also significantly different from that of CGA quartile 1 ($P = 0.033$). For PCT, the death rate for quartile 4 was significantly different from the rates for quartiles 1, 2, and 3 ($P < 0.001$), and PCT quartile 2 was significantly different from quartiles 3 and 4 ($P < 0.05$). Table 3 presents the unadjusted HRs and 95% CIs for the association between potential prognostic variables measured at admission and the risk of death. Multivariable Cox proportional hazards regression analysis showed that log CGA concentration, SAPS II, and the diagnosis of cardiogenic shock at admission were significantly associated with outcome. Table 3 shows the adjusted HRs of independent variables for predicting mortality. The adjusted HRs (95% CI) for the independent variables predicting mortality (log CGA concentration, SAPS II, and cardiogenic shock) were, respectively, 7.2 (3.0–17.5), 1.0 (1.0–1.1), and 3.9 (1.7–8.9) (all $P \leq 0.001$).

ROC curves for CGA, PCT, and SAPS II are shown in Fig. 3. To assess the best positive likelihood ratio, we chose the cutoff value that was associated with the best specificity. For CGA, we chose a cutoff value of 255 μg/L, which produced a sensitivity of 0.63 and a specificity of 0.89 (positive likelihood ratio, 5.73; negative likelihood ratio, 0.42; AUC, 0.82). A cutoff value of 65 for SAPS II produced a sensitivity of 0.61 and a specificity of 0.85 (positive likelihood ratio, 4.07; negative likelihood ratio, 0.46; AUC, 0.87). For a PCT cutoff value of 4.82 μg/L, sensitivity and specificity were

Table 2. Correlation of CGA concentration with clinical scores, clinical variables, and biological markers.

Variable	r^2	P
Age	0.36	<0.001
SAPS II score	0.44	<0.001
LODS score	0.37	<0.001
Time from first organ dysfunction to admission	0.03	0.756
Intensive care unit stay	−0.08	0.390
CRP	0.22	0.020
PCT	0.40	<0.001
Leukocytes	−0.09	0.340
Creatinine	0.56	<0.001

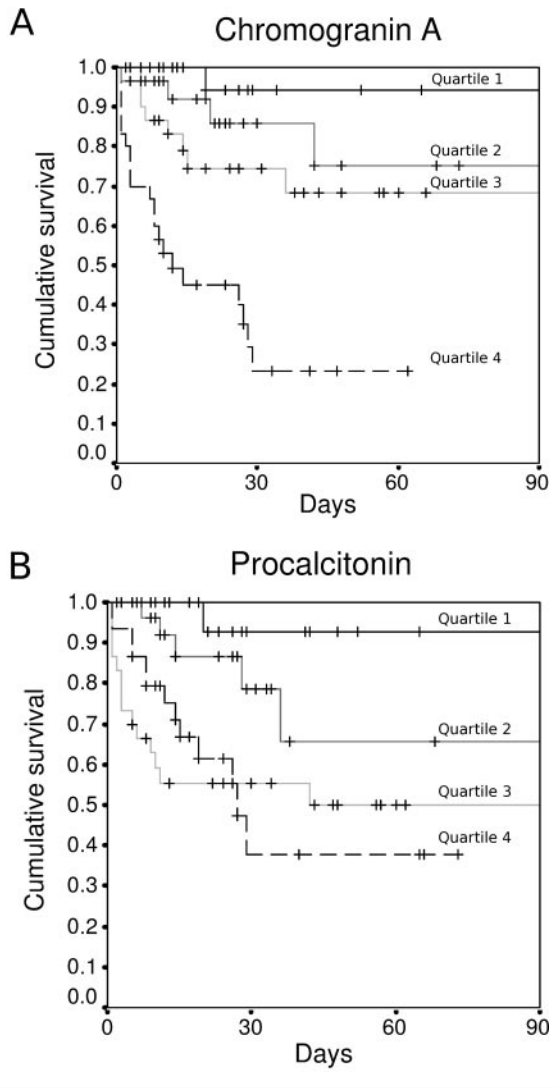

Fig. 2. Kaplan–Meier analysis: cumulative incidence of death by CGA and PCT quartiles.

(A), Median (interquartile range) for CGA concentration data: quartile 1, 35 μg/L (30–53 μg/L); quartile 2, 84 μg/L (77–94 μg/L); quartile 3, 174 μg/L (151–197 μg/L); quartile 4, 563 μg/L (355–974 μg/L). (B), Median (interquartile range) for PCT concentration data: quartile 1, 0.14 μg/L (0.12–0.16 μg/L); quartile 2, 0.48 μg/L (0.36–1.01 μg/L); quartile 3, 4.82 μg/L (3.41–6.67 μg/L); quartile 4, 30.59 μg/L (18.02–43.59 μg/L). Each quartile includes 30 patients.

0.60 and 0.71, respectively (positive likelihood ratio, 2.07; negative likelihood ratio, 0.56; AUC, 0.73).

Discussion

In this study of critically ill nonsurgical patients, we found that significant increases in plasma CGA concentrations were not related to the patients' underlying medical diseases but rather to the severity of disease presentation on admission. To our knowledge, such a finding has not previously been reported. In addition, we found positive correlations between CGA concentration and inflammation markers. Finally, multivariable Cox proportional hazards regression analysis demonstrated CGA concentration to be a strong indicator of outcome in our cohort of patients.

Table 3. Univariate analysis: predictors of mortality (Cox proportional hazards model).

Variable	HR	95% CI	*P*
Age	0.976	0.940–1.014	0.221
Sex	1.304	0.534–3.181	0.560
SAPS II score	1.042	1.017–1.068	0.001
LODS score	0.853	0.701–1.152	0.202
Sepsis	0.987	0.262–3.715	0.985
Cardiogenic shock	4.088	1.011–16.525	0.048
Septic shock	0.867	0.186–4.045	0.856
Time from first organ dysfunction to admission	1.003	0.996–1.010	0.221
Log CGA	9.542	3.364–27.061	<0.001
Log CRP	0.712	0.319–1.586	0.405
Log PCT	1.220	0.634–2.346	0.552
Log leukocytes	1.000	0.999–1.001	0.391
Log creatinine	0.584	0.106–3.232	0.538

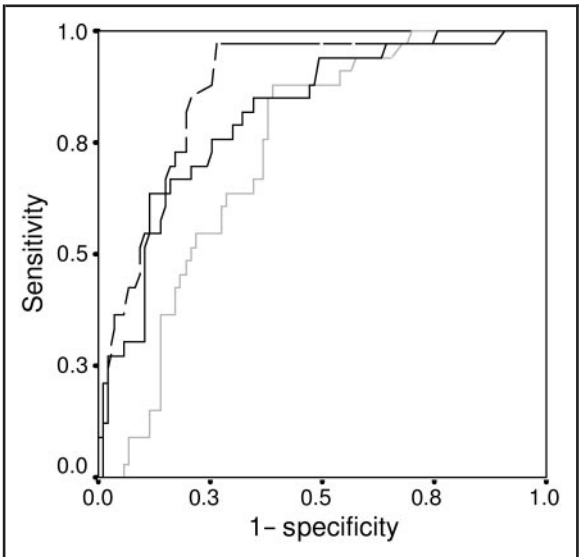

Fig. 3. ROC curve to test the ability of CGA (black line), SAPS II (black dashed line), and PCT (gray dashed line) to predict outcome.

INFLUENCE OF ACUTE RENAL FAILURE ON CGA CONCENTRATION

The accumulation of CGA in end-stage chronic renal disease has previously been reported *(22, 23)*, but the impact of acute renal failure on circulating CGA concentrations in critically ill patients as observed in our study is a new finding. In the work of Estensen et al. *(13)*, a multiple linear regression model was used to show that creatinine clearance and age were independent predictors of log CGA concentration ($r^2 = 0.23$) in patients with complicated myocardial infarction. In our investigation, we obtained an r^2 value of 0.352 when we included the SAPS II score along with creatinine concentration and age in predicting log CGA concentration. Thus, the findings of these 2 studies suggest that acute renal failure influences plasma concentrations of CGA and, perhaps, the mechanisms that control these concentrations.

PATHOPHYSIOLOGICAL ROLE OF CGA IN CRITICALLY ILL PATIENTS

The pathophysiological role that CGA plays in critically ill patients has not yet been clearly defined. Our data have demonstrated that CGA concentration significantly increases in groups of nonsurvivors who had more severe LODS or SAPS II scores. In addition, CGA concentration was inversely related to survival time, a fact that agrees with results of studies of patients in end-stage cardiac failure *(4)* and in myocardial infarction *(13)*. Abnormalities of cellular and tissue energy metabolism are most probably causes of organ dysfunction in critical illnesses (i.e., impaired cellular respiration despite adequate oxygen delivery to tissues). Mitochondrial dysfunction is often blamed for tissue dysoxia and subsequent organ failure during critical conditions *(24)*. In vitro, depolarization-mediated CGA triggers apoptosis in microglial cells *(25–27)*; however, whether CGA participates in the development of MOF by an apoptosis-related mechanism is not yet known .

Increased plasma concentrations of CGA have been reported for various pathophysiological conditions, including enhanced sympathetic tone, production of cytokines in cardiac failure *(4)*, and coronary artery bypass *(28)*. Of note is that the obliteration of chromogranin gene expression in a mouse model leads to a decrease in the size and number of chromaffin granules as well as in arterial hypertension *(29)*. Restoring expression of human CGA or exogenous injection of human catestatin, a potent noncompetitive inhibitor of catecholamine release *(30)*, restores blood pressure *(31)*, further suggesting that CGA and catestatin may play important roles in cardiovascular homeostasis, which is severely altered in critically ill patients.

RELATIONSHIP BETWEEN CGA AND OUTCOME

Our study revealed CGA concentration at admission to be a powerful and early marker of prognosis. Compared with others markers, CGA had the highest positive likelihood ratio (5.72 vs 4.07 for SAPS II and 2.07 for PCT). From an historical point of view, score building was the first step taken to evaluate outcome in critically ill patients, because previous attempts that had used biological variables to evaluate outcome had been unsuccessful *(32)*. Consequently, several clinical scores have been developed to assess the severity of critically ill patients. These scores have been validated with large cohorts of patients through the association of vital-organ dysfunction with mortality *(20, 21)*. For example, physicians routinely use SAPS II to assess the severity of diseases and predict in-hospital mortality, but this score can be calculated only after 24 h of hospitalization and the analysis of 17 biological or clinical variables *(20)*. Ideally, the evaluation of organ dysfunction should be based on a limited number of simple but objective variables that can be measured easily in every institution. CGA concentration measured at admission meets all these criteria and may therefore be helpful to physicians for predicting a poor outcome. When PCT concentration was proposed for such an evaluation of severely ill patients, it rapidly became clear that PCT was a breakthrough in the diagnosis of infection compared with the other available biological tests *(33)*. On the other hand, controversial data exist on the ability of PCT to predict outcome in patients with systemic inflammatory response syndrome (SIRS) *(34–36)*. In our investigation, CGA turned out to be a much better predictor of outcome than PCT but was poorer at distinguishing between inflammation and infection than PCT or CRP.

Conclusions

The present study has demonstrated that plasma CGA concentration is a strong and independent prognostic marker in consecutive critically ill nonsurgical patients. Thus, this biomarker may help physicians to categorize patients for further care and may be useful as a selection criterion for clinical studies.

Grant/Funding Support: This work was supported by Délégation à la Recherche Clinique des Hôpitaux Universitaires de Strasbourg (grant no. 3150, PHRC 2003), Fondation Transplantation (PhD grant to D. Zhang), and the Department of Foreign Affairs (Charcot grant to D. Zhang).

Financial Disclosures: None declared.

Acknowledgments: We thank CIS BIO (Marcoule, France) for the gift of the CGA kits and Nathalie Mela (CNRS, UMR 7191 Institut de Physique Biologique, Strasbourg, France) for careful technical assistance.

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