A 3-Level Prognostic Classification in Septic Shock Based on Cortisol Levels and Cortisol Response to Corticotropin

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Context The hypothalamic-pituitary-adrenal axis is a major determinant of the host response to stress. The relationship between its activation and patient outcome is not known.

Objective To evaluate the prognostic value of cortisol levels and a short corticotropin stimulation test in patients with septic shock.

Design and Setting Prospective inception cohort study conducted between October 1991 and September 1995 in 2 teaching hospital adult intensive care units in France.

Participants A total of 189 consecutive patients who met clinical criteria for septic shock.

Intervention A short corticotropin stimulation test was performed in all patients by intravenously injecting 0.25 mg of tetracosactrin; blood samples were taken immediately before the test (T0) and 30 (T30) and 60 (T60) minutes afterward.

Main Outcome Measures Twenty-eight–day mortality as a function of variables collected at the onset of septic shock, including cortisol levels before the corticotropin test and the cortisol response to corticotropin (Δmax, defined as the difference between T0 and the highest value between T30 and T60).

Results The 28-day mortality was 58% (95% confidence interval [CI], 51%-65%) and median time to death was 17 days (95% CI, 14-27 days). In multivariate analysis, independent predictors of death ($P \leq .001$ for all) were McCabe score greater than 0, organ system failure score greater than 2, arterial lactate level greater than 2.8 mmol/L, ratio of PaO_2 to fraction of inspired oxygen no more than 160 mm Hg, cortisol level at T0 greater than 34 μg/dL and Δmax no more than 9 μg/dL. Three groups of patient prognoses were identified: good (cortisol level at T0 $\leq$34 μg/dL and Δmax $>$9 μg/dL; 28-day mortality rate, 26%), intermediate (cortisol level at T0 34 μg/dL and Δmax $\leq$9 μg/dL or cortisol level at T0 $>$34 μg/dL and Δmax $>$9 μg/dL; 28-day mortality rate, 67%), and poor (cortisol level at T0 $>$34 μg/dL and Δmax $\leq$9 μg/dL; 28-day mortality rate, 82%).

Conclusion Our data suggest that a short corticotropin test has a good prognostic value and could be helpful in identifying patients with septic shock at high risk for death.

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Septic shock remains the most common cause of death in noncoronary intensive care units (ICUs).[1] To tackle this problem, numerous anti-inflammatory therapies have been tested during the past decade, but all of them have been unable to improve survival in patients with severe sepsis.[2] Thus, there is an urgent need to better characterize septic patients with the worst outcome. Several clinical prognostic factors have already been identified (ie, preexisting underlying disease, presence of organ dysfunction, and severity of illness scores).[3] Moreover, the hormonal profile has been suggested to be a valid predictor of outcome in critically ill patients.[4] However, a pathophysiologic derangement that could help identify a group of patients who might benefit from a particular treatment has not been characterized yet.

The integrity of the hypothalamic-pituitary-adrenal (HPA) axis is a major determinant of the host's response to stress.[5,6] During sepsis, the activation of the HPA axis is highlighted by increased corticotropin release from the pituitary gland,[7] enhanced adrenal secretory activity,[8,9] and high plasma cortisol levels.[10-13] However, whether endogenous glucocorticoid levels are adequate or constitute an independent predictor of death remains controversial.[10-15] For instance, several studies showed that the higher the plasma cortisol concentrations, the worse the patient's outcome.[4,7,10,16-18] In contrast, other studies reported lower cortisol levels in

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nonsurvivors compared with survivors.[19-21] For this reason, in severe sepsis, the evaluation of the appropriateness of the activation of the HPA axis requires dynamic testing. In this respect, the most commonly used test is the short corticotropin stimulation test, normal adrenal function being defined by a plasma cortisol level (before or at 30 or 60 minutes after the injection of corticotropin) above 20 µg/dL.[22] However, basal plasma cortisol levels are commonly greater than 20 µg/dL in severe sepsis and the use of the absolute increase in plasma cortisol levels after the intravenous injection of corticotropin may be more useful to evaluate adrenal function.[12,13] Indeed, occult adrenal insufficiency (ie, an absolute increment of cortisol concentrations <9 µg/dL) after corticotropin may be associated with impaired pressor responsiveness to norepinephrine[23] and a high mortality rate.[24,25] Such results must be confirmed since other investigators have not found any relationship between cortisol response to corticotropin and survival from sepsis.[26]

In the context of renewed interest in corticosteroids as therapy for septic shock,[14,15,21,23-25,27-30] we undertook a prospective study to determine the incidence of occult adrenal insufficiency in septic shock patients and to assess the factors associated with mortality, taking special interest in cortisol levels and cortisol response to corticotropin.

METHODS

Study Population

All consecutive patients hospitalized in the ICU of 2 teaching hospitals (Raymond Poincaré hospital, Garches, France, and Antoine Béclère hospital, Clamart, France) between October 1991 and September 1995 were prospectively enrolled in the study if they met the following criteria for septic shock[31]: (1) for less than 7 days, a systemic inflammatory response as defined by 2 or more of the following: temperature higher than 38.5°C or lower than 35.0°C, heart rate of more than 90/min, respiratory rate of more than 20/min or Pa_{CO_2} of less than 32 mm Hg or need for mechanical ventilation, white blood cell count of more than 12.0×10^9/L or less than 4.0×10^9/L or containing more than 10% immature forms; (2) evidence for a nidus of infection; and (3) for less than 24 hours, systolic blood pressure of less than 90 mm Hg (for at least 1 hour) despite adequate fluid replacement and perfusion of 5 µg/kg/min or more of dopamine or dobutamine, and the presence of at least 2 signs of perfusion abnormalities (ie, lactic acidosis, oliguria, or an abrupt alteration in the mental status). Patients were not eligible if they had known previous conditions that may have disrupted the HPA axis.[5,6,13,22] The protocol was approved by our institutional review board and informed consent was obtained from the patient's next of kin.

Data Collection

Clinical Evaluation. At the onset of septic shock, the following variables were recorded: (1) general characteristics including age and sex, date of ICU admission, medical or surgical admission, estimated prognosis of any preexisting underlying disease according to the classification of McCabe and Jackson[32] (nonfatal, ultimately fatal, or rapidly fatal); (2) severity of illness as assessed by the number of organ system failures (OSF score),[33] Simplified Acute Physiology Score II,[34] and vital signs (temperature, mean arterial pressure, heart rate, urinary output); and (3) interventions (at physician discretion) including volume of fluid infusion per 24 hours, antibiotics, type and titration of vasopressors, corticosteroid therapy, need for mechanical ventilation, insertion of a Swan-Ganz catheter, and surgical procedure.

Laboratory Variables. At the onset of septic shock, blood cultures and cultures of specimen drawn from the site of infection, hematologic and chemistry data, and arterial lactate and blood gas determinations were done systematically. A short corticotropin stimulation test was performed with 0.25 mg of tetracosactrin (Synacthène, Ciba, Rueil-Malmaison, France) given intravenously. Blood samples were taken immediately before the test (T0) and 30 (T30) and 60 (T60) minutes afterward. After centrifugation, plasma samples were stored at 4°C and cortisol (normal range, 6-28 µg/dL) was measured by enzyme-linked fluorescent assay (VIDAS Cortisol, Bio Mérieux SA, Lyon, France). The cortisol response (Δmax) was defined as the difference between T0 and the highest of the T30 and T60 concentrations.

Follow-up. All patients were evaluated for 28 days from inclusion in the study. The evaluation of the following variables was performed daily in each patient during the shock: vital signs, hematocrit, total and differential leukocyte counts, platelet count, plasma electrolytes, glucose levels, serum creatinine and liver function test, arterial lactate and blood gases, and interventions, as previously defined.

Statistical Analysis

Statistical analyses were conducted using SAS software package (Version 6.12, SAS Institute, Cary, NC). We investigated the prognostic value for the probability of dying based on patient characteristics collected at the onset of septic shock and on values obtained with the short corticotropin test. We performed univariate analyses in which the data were compared between survivors and nonsurvivors using the *t* test for continuous variables and χ^2 test for categorical variables (or Fisher exact test as appropriate). To perform survival analyses, continuous variables were discretized according to their median value but categorical variables remained unchanged. Survival was estimated by the Kaplan-Meier method and compared between groups with the log-rank test for all the variables. Multivariate analyses were performed using a logistic regression model to estimate the odds ratio of dying (along with the 95% confidence interval [CI]). Calibration of the logistic model was assessed using the Hosmer-Lemeshow goodness-of-fit test[35] to evaluate the importance of the discrepancy between observed and expected mortality. Discrimination was assessed using the area under the receiver operating characteristic (ROC) curve[36] to evaluate how well the model distinguished patients who lived from those who died. A Cox proportional hazards regression model was used to assess variables related to death. This model assumes that the effect of a variable on the instantaneous death rate is constant over time. This assumption was checked for all predictor variables entered in the model.[37] Stepwise and backward selection procedures were used for both regression models (logistic and Cox) to iteratively select the variables that were significantly related to death, as assessed by the likelihood ratio test. For all tests, $P<.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Among the 189 patients admitted during the study period, 96 (51%) were recruited in the Garches center and 93 (49%) in the Clamart center. Of the 189 patients, 109 (58%; 95% CI, 51%-65%) died within the 28-day period following the onset of septic shock, 3 patients died after 28 days (they died after 31, 62, and 66 days, respectively). TABLE 1 shows patient characteristics at the onset of septic shock and results of the univariate analysis between the survivor and nonsurvivor groups. The McCabe and OSF scores and the Simplified Acute Physiology Score II were significantly associated with mortality. Among clinical and biological factors, mean arterial pressure, platelet count, arterial lactate and pH, the ratio of the PaO_2 to the fraction of inspired oxygen (FIO_2) were significantly different between survivors and nonsurvivors. Compared with survivors, nonsurvivors had significantly higher basal plasma cortisol levels (T0) and lower cortisol response to corticotropin (Δmax). The mean maximum [SD] doses of dobutamine during the first 6 hours following the onset of septic shock were significantly lower in survivors compared with nonsurvivors (8.6 [4.5] vs 11.6 [6.4] µg/kg per minute; *P* = .005). Treatment with hydrocortisone during the follow-up was also less frequent in survivors compared with nonsurvivors (12% vs 29%; *P* = .006). The number of patients who had documented infection, sites of infection, and strains diagnosed at the onset of septic shock are shown in TABLE 2. Sites of infection were similar among survivors and nonsurvivors whereas gram-positive microorganisms were more common among nonsurvivors and gram-negative microorganisms were more common among survivors (*P* = .008).

All variables found to be significantly different between the survivor and nonsurvivor groups, according to the univariate analysis performed on patient characteristics at the onset of septic shock (apart from physician's interventions, namely the administration of catecholamines or hydrocortisone), were entered into the logistic regression model. Among those variables, the following 5 remained independently associated with death: McCabe and OSF scores, arterial lactate, PaO_2:FIO_2, and Δmax (TABLE 3). Increases in the McCabe and OSF scores were associated with the highest odds of dying with 2.95 (95% CI, 1.56-5.59) and 2.41 (95% CI, 1.51-3.84), respectively. The Hosmer-Lemeshow goodness-of-fit test showed that the model was well calibrated with *P* = .44 (a large *P* value indicating that there is not a large discrepancy between observed and expected mortality). The area under the ROC curve was 0.863, showing that the model discriminated well between patients who lived and those who died.

Survival

The median time to death was 17 days (95% CI, 14-27 days) for all patients.

Table 1. Clinical and Biological Data Collected at the Onset of Septic Shock*

Variable	Total (N = 189)	Survivors (n = 77)	Nonsurvivors (n = 112)	P Value
Age, y	63 (18)	62 (18)	64 (18)	.45
Sex†				
Male	117 (62)	46 (60)	71 (63)	.61
Female	72 (38)	31 (40)	41 (37)	
McCabe†				
0	101 (54)	50 (65)	51 (46)	.02
1	65 (34)	22 (29)	43 (38)	
2	23 (12)	5 (6)	18 (16)	
Organ system failure†				
0	6 (3)	6 (8)	0 (0)	<.001
1	50 (26)	33 (43)	17 (15)	
2	64 (34)	27 (35)	37 (33)	
3	54 (29)	9 (12)	45 (40)	
4	13 (7)	2 (2)	11 (10)	
5	2 (1)	0 (0)	2 (2)	
Simplified Acute Physiology Score II	58 (21)	49 (19)	64 (20)	<.001
Temperature, °C	38.0 (1.9)	38.1 (1.9)	37.9 (1.9)	.51
Mean arterial pressure, mm Hg	59 (20)	65 (21)	55 (18)	<.001
Heart rate, beats/min	120 (28)	118 (27)	122 (29)	.33
Leukocytes, $\times 10^9$/L	15.9 (9.8)	15.9 (8.8)	15.9 (10.5)	.98
Platelets, $\times 10^9$/L	174 (129)	204 (140)	153 (117)	.007
Lactate, mmol/L	4.3 (4.1)	2.6 (2.0)	5.5 (4.7)	<.001
Arterial pH	7.32 (0.13)	7.36 (0.10)	7.29 (0.13)	<.001
PaO_2:FIO_2, mm Hg‡	184 (112)	222 (114)	157 (102)	<.001
Cortisol, µg/dL§				
Level before test	34 (28)	28 (18)	39 (33)	.002
Maximum variation after test‖	11 (17)	14 (12)	8 (19)	.01

*Values are expressed as mean (SD) unless otherwise indicated. *P* values are for comparison of survivors vs nonsurvivors.
†Values are expressed as number (percentage).
‡FIO_2 indicates fraction of inspired oxygen.
§The short corticotropin test was used. To convert values for cortisol to nanomoles per liter, multiply by 27.6.
‖Indicates variation between pretest plasma highest level and the level 30 and 60 minutes after test.

Univariate analysis was performed to compare survival time distributions of all variables collected at the onset of septic shock using the log-rank test. Variables associated with death were McCabe score of more than 0 ($P = .005$), OSF score greater than 2 ($P < .001$), Simplified Acute Physiology Score II greater than 55 ($P < .001$), mean arterial pressure of 60 mm Hg or less ($P < .001$), arterial lactate level greater than 2.8 mmol/L ($P < .001$), arterial pH of 7.33 or less ($P < .001$), $PaO_2:FIO_2$ of 160 mm Hg or less ($P = .002$), T0 greater than 26 µg/dL ($P = .003$), and Δmax of 8 µg/dL or less ($P < .001$). Among variables related to physician interventions, higher doses for dopamine ($P = .04$) and treatment with hydrocortisone ($P = .04$) were significantly associated with death.

Variables identified by the univariate analysis with the log-rank test (apart from physician interventions) were entered in the Cox proportional hazards regression model to identify the variables that have an important effect on mortality. As shown in Table 3, 6 variables were selected as being independently associated with mortality: McCabe score of more than 0, OSF score greater than 2, arterial lactate level greater than 2.8 mmol/L, $PaO_2:FIO_2$ of 160 mm Hg or less, T0 greater than 26 µg/dL, and Δmax of 8 µg/dL or less.

Cortisol Levels and Cortisol Response to Corticotropin

We further investigated the prognostic value of the short corticotropin test using univariate analyses (with χ^2, log-rank tests, and ROC curves) and multivariate analyses (with logistic and Cox models). The 2 variables, T0 and Δmax, were first studied separately. The values of T0 and Δmax were discretized according to their 25th, 50th, and 75th percentiles as well as to their mean value. The reference value of 9 µg/dL[24] was added for Δmax.

As shown in TABLE 4, values of T0 larger than 34 µg/dL (mean) or even 45 µg/dL (75th percentile) were significantly associated with death rates and distribution of survival times, with the smallest P value (χ^2 and log-rank tests) for 34 µg/dL. With T0 greater than 26 µg/dL (50th percentile), the difference in the proportion of deaths was almost significant (χ^2 test) whereas the difference in the distributions of survival times was significant (log-rank test). All the threshold values of T0 are displayed on the ROC curve (FIGURE 1). The area under the ROC curve was 0.620 and the highest value reached for sensitivity and specificity, which is usually close to the intersection point between the ROC curve and the second bisecting line, was the threshold value of 26 µg/dL, which

Table 2. Patients Who Had Documented Infection, Sites of Infection, and Strains Diagnosed at the Onset of Septic Shock*

Variable	Total	Survivors	Nonsurvivors	P Value
Patients	(N = 189)	(n = 77)	(n = 112)	
Who had positive microbial documentation of infection	153 (81)	58 (75)	95 (85)	.10
Who had positive blood culture results	36 (19)	12 (16)	24 (21)	.32
Sites of infection	(N = 223)	(n = 92)	(n = 131)	
Lung	75 (34)	28 (30)	47 (36)	.33
Abdominal	84 (38)	32 (35)	52 (40)	
Cellulitis	21 (9)	9 (10)	12 (9)	
Genitourinary	23 (10)	14 (15)	9 (7)	
Others	20 (9)	9 (10)	11 (8)	
Microorganisms	(N = 210)	(n = 105)	(n = 105)	
Gram-positive	85 (41)	33 (31)	52 (49)	.008
Gram-negative	105 (50)	62 (59)	43 (41)	
Fungi	17 (8)	10 (10)	7 (7)	
Others	3 (1)	0 (0)	3 (3)	

*Values are expressed as number (percentage). A patient could have more than 1 site of infection and microorganism.

Table 3. Multivariate Logistic and Cox Regression Analyses

Variable	Regression Coefficient (β)	SE	Odds Ratio (95% Confidence Interval)	P Value
Logistic Regression*				
Intercept	−1.69	0.66	NA	.01
McCabe	1.08	0.33	2.95 (1.56-5.59)	<.001
Organ system failure	0.88	0.24	2.41 (1.51-3.84)	<.001
Lactate, mmol/L	0.35	0.10	1.42 (1.16-1.73)	<.001
$PaO_2:FIO_2$, mm Hg†	−0.006	0.002	0.99 (0.98-0.99)	.001
Cortisol, µg/dL‡§ Maximum variation after test	−0.03	0.01	0.97 (0.95-0.99)	.01
Cox Regression‖				
McCabe >0	0.61	0.20	1.84 (1.24-2.72)	.003
Organ system failure >2	1.00	0.20	2.73 (1.84-4.06)	<.001
Lactate >2.8 mmol/L	0.60	0.20	1.83 (1.23-2.73)	.003
$PaO_2:FIO_2$ >160 mm Hg†	−0.60	0.20	0.55 (0.37-0.81)	.003
Cortisol, µg/dL‡				
Level before test >26	0.66	0.20	1.93 (1.30-2.85)	.001
Maximum variation after test >8§	−0.89	0.21	0.41 (0.27-0.61)	<.001

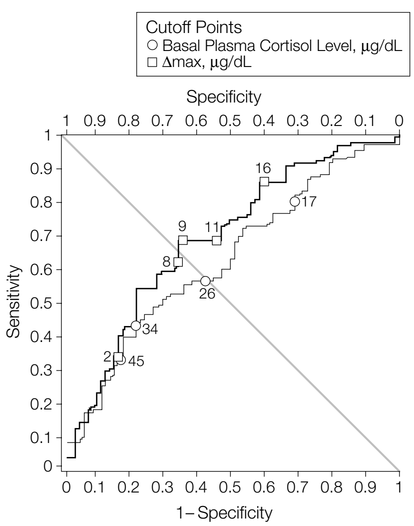
*Results of stepwise and backward selection procedures. Other variables entered in the model were Simplified Acute Physiology Score II, mean arterial pressure, platelets, arterial pH, and cortisol level before test. NA indicates not applicable.
†FIO_2 indicates fraction of inspired oxygen.
‡To convert values for cortisol to nanomoles per liter, multiply by 27.6.
§Indicates variation between pretest plasma level and the level 30 and 60 minutes after test.
‖Results of stepwise and backward selection procedures. All continuous variables are discretized according to their median value. Other variables entered in the model were Simplified Acute Physiology Score II of more than 55, mean arterial pressure of more than 60 mm Hg, and arterial pH of more than 7.33.

Table 4. χ^2 and Log-Rank Tests for Death Rates and Distribution of Survival Times for Different Values of Cortisol Levels Before Test and of Maximum Variation After Test*

Threshold Values (Percentile or Other)	Plasma Level, µg/dL	Total (N = 189)	Survivors (n = 77)	Nonsurvivors (n = 112)	Death Rates χ^2	Death Rates *P* Value	Survival Times Log-Rank	Survival Times *P* Value
Cortisol Level Before Test								
25	>17	141 (75)	53 (69)	88 (79)	2.3	.13	2.3	.13
50	>26	94 (50)	32 (42)	62 (55)	3.5	.06	9.0	.003
Mean	>34	63 (33)	16 (21)	47 (42)	9.2	.002	20.0	<.001
75	>45	48 (25)	12 (16)	36 (32)	6.6	.01	15.9	<.001
Maximum Variation After Test								
25	>2	140 (74)	65 (84)	75 (67)	7.2	.007	12.0	<.001
50	>8	94 (50)	51 (66)	43 (38)	14.1	.001	16.3	<.001
Reference value	>9	86 (46)	50 (65)	36 (32)	19.8	.001	21.8	<.001
Mean	>11	78 (41)	42 (55)	36 (32)	9.4	.002	11.1	<.001
75	>16	47 (25)	31 (40)	16 (14)	16.5	.001	14.5	<.001

*To convert values for cortisol to nanomoles per liter, multiply by 27.6.

Figure 1. Receiver Operating Characteristic (ROC) Curves for Basal Plasma Cortisol Levels (T0) and Maximum Variation of Plasma Cortisol Between T0 and 30 and 60 Minutes After Corticotropin Test (Δmax)



The ROC curves are generated by plotting the sensitivity against 1 minus the specificity for each value of T0 and Δmax. The threshold values that are indicated for T0 and Δmax are the 25th, 50th, and 75th percentiles and the mean values. The reference value of 9 µg/dL also appears for Δmax. The diagonal line represents the second bisecting line. The areas under the ROC curves were 0.620 and 0.686 for T0 and Δmax, respectively. To convert values for cortisol to nanomoles per liter, multiply by 27.6.

was associated with a sensitivity of 0.554 and a specificity of 0.584.

As shown in Table 4, all threshold values chosen for Δmax were significantly associated with death rates and distribution of survival times, with the smallest *P* value (χ^2 and log-rank tests) for 9 µg/dL (reference value). Using this threshold, the estimate of the incidence of occult adrenal insufficiency is 54% (95% CI, 47%-61%) in our septic shock patients. All the threshold values of Δmax are displayed on the ROC curve (Figure 1). The area under the ROC curve was 0.686 and the highest value reached for sensitivity and specificity was the reference value 9 µg/dL, which was associated with a sensitivity of 0.679 and a specificity of 0.649.

The highest values of the χ^2 and log-rank statistics were reached for 34 µg/dL for T0 whereas the highest values for sensitivity and specificity were reached for 26 µg/dL. For Δmax, all results (χ^2 and log-rank tests, and ROC curve) were in close agreement, leading to the same choice for the threshold value, namely 9 µg/dL. Therefore, the following combinations of T0 and Δmax were studied: (1) T0 of 26 or 34 µg/dL or less and Δmax greater than 9 µg/dL; (2) T0 of 26 or 34 µg/dL or less and Δmax of 9 µg/dL or less or a T0 greater than 26 or 34 µg/dL and Δmax greater than 9 µg/dL; (3) T0 greater than 26 or 34 µg/dL and Δmax of 9 µg/dL or less. The information provided by T0 and Δmax together, for both threshold values of T0 (26 and 34 µg/dL), was significantly associated with death rates and distribution of survival times (TABLE 5). However, the value of 34 µg/dL seems to be a more informative cut-off value than 26 µg/dL. By using this threshold value, compared with 26 µg/dL, the proportion of survivors was a bit higher (70% vs 68%) for combination 1 and the proportion of survivors was a bit lower (18% vs 20%) for combination 3. Moreover, the highest values of the χ^2 and log-rank statistics were both reached with 34 µg/dL. Using this threshold, the likelihood ratios for survival were 3.42 for T0 of 34 µg/dL or less and Δmax greater than 9 µg/dL and 0.31 for T0 greater than 34 µg/dL and Δmax of 9 µg/dL or less.

We included, in a multivariate logistic regression model, T0 and Δmax which were respectively discretized according to their mean and reference values (34 µg/dL for T0 and 9 µg/dL for Δmax), the combination of T0 and Δmax, as well as the variables previously identified by the univariate analysis (Table 1). As shown in TABLE 6, high McCabe and OSF scores, high arterial lactate, low PaO_2:FIO_2, T0 greater than 34 µg/dL, and Δmax of 9 µg/dL or less remained independently and significantly associated with death. The Hosmer-Lemeshow goodness-of-fit test showed that the model was well calibrated with *P* = .75. The area under the ROC curve was 0.884, showing that the model discriminated well between patients who lived and those who died.

We also used Cox proportional hazards regression model by adding T0, Δmax, and their combination in the same manner as previously described to

Table 5. χ^2 and Log-Rank Tests for Death Rates and Distribution of Survival Times for Different Values of Cortisol Levels Before Test and of Maximum Variation After Test*

Plasma Level, µg/dL						Death Rates		Survival Times	
Cortisol Level BeforeTest		Maximum Variation After Test	Total (N = 189)	Survivors (n = 77)	Nonsurvivors (n = 112)	χ^2	*P* Value	Log-Rank	*P* Value
≤26	and	>9	41 (22)	28 (36)	13 (12)	21.4	.001	32.1	<.001
≤26 or >26	and and	≤9 >9	99 (52)	39 (51)	60 (54)				
>26	and	≤9	49 (26)	10 (13)	39 (35)				
≤34	and	>9	57 (30)	40 (52)	17 (15)	31.3	.001	41.6	<.001
≤34 or >34	and and	≤9 >9	98 (52)	31 (40)	67 (60)				
>34	and	≤9	34 (18)	6 (8)	28 (25)				

*To convert values for cortisol to nanomoles per liter, multiply by 27.6.

the variables found to be significant in the univariate analysis to identify the variables that could have an important relationship with mortality. This time, the stepwise and backward selection procedures gave slightly different results. As shown in TABLE 7, the stepwise selection procedure identified the following variables as being independently associated with mortality: McCabe score of more than 0, OSF score greater than 2, arterial lactate level of more than 2.8 mmol/L, PaO_2:FIO_2 of 160 mm Hg or less, T0 greater than 34 µg/dL, and Δmax of 9 µg/dL or less. The backward selection procedure gave slightly different results and identified the following variables as being independently associated with mortality: McCabe score of more than 0, OSF score greater than 2, mean arterial pressure of 60 mm Hg or less, arterial pH of 7.33 or less, PaO_2:FIO_2 of 160 mm Hg or less, T0 greater than 34 µg/dL, and Δmax of 9 µg/dL or less.

FIGURE 2 shows the survival curves for T0 (≤ or >34 µg/dL), Δmax (≤ or >9 µg/dL), and the combination of T0 and Δmax (T0 ≤34 µg/dL and Δmax >9 µg/dL; T0 ≤34 µg/dL and Δmax ≤9 µg/dL or T0 >34 µg/dL and Δmax >9 µg/dL; and T0 >34 µg/dL and Δmax ≤9 µg/dL). A total of 109 deceased patients instead of 112 are taken into account in this figure because, as previously mentioned, 3 patients died after 28 days. Death occurred more rapidly for patients with T0 greater than 34 µg/dL (median time to death, 6 days [95% CI, 4-12 days]), Δmax of 9 µg/dL or less (median time

Table 6. Multivariate Logistic Regression Analysis: Results of Stepwise and Backward Selection Procedures

Variable*	Regression Coefficient (β)	SE	Odds Ratio (95% Confidence Interval)	*P* Value
McCabe	1.07	0.34	2.93 (1.51-5.68)	.002
Organ system failure	0.83	0.25	2.30 (1.41-3.75)	<.001
Lactate, mmol/L	0.30	0.10	1.34 (1.12-1.62)	.002
PaO_2:FIO_2, mm Hg†	−0.008	0.002	0.99 (0.99-0.99)	<.001
Cortisol, µg/dL‡				
Level before test >34§	0.89	0.45	2.43 (1.01-5.87)	.05
Maximum variation after test >9‖	−1.55	0.41	0.21 (0.09-0.47)	<.001

*Other variables entered in the model were Simplified Acute Physiology Score II, mean arterial pressure, platelets, arterial pH, and the combination of cortisol level before test and of maximum variation after test defined in 3 categories: cortisol level before test of 34 µg/dL or less and maximum variation after test of more than 9 µg/dL; cortisol level before test of 34 µg/dL or less and maximum variation after test of 9 µg/dL or less or cortisol level before test of more than 34 µg/dL and maximum variation after test of more than 9 µg/dL; cortisol level before test of more than 34 µg/dL and maximum variation after test of 9 µg/dL or less.
†FIO_2 indicates fraction of inspired oxygen.
‡To convert values for cortisol to nanomoles per liter, multiply by 27.6.
§Discretized according to its mean value.
‖Indicates variation between pretest plasma level and the highest level 30 and 60 minutes after test. Discretized according to the reference value.

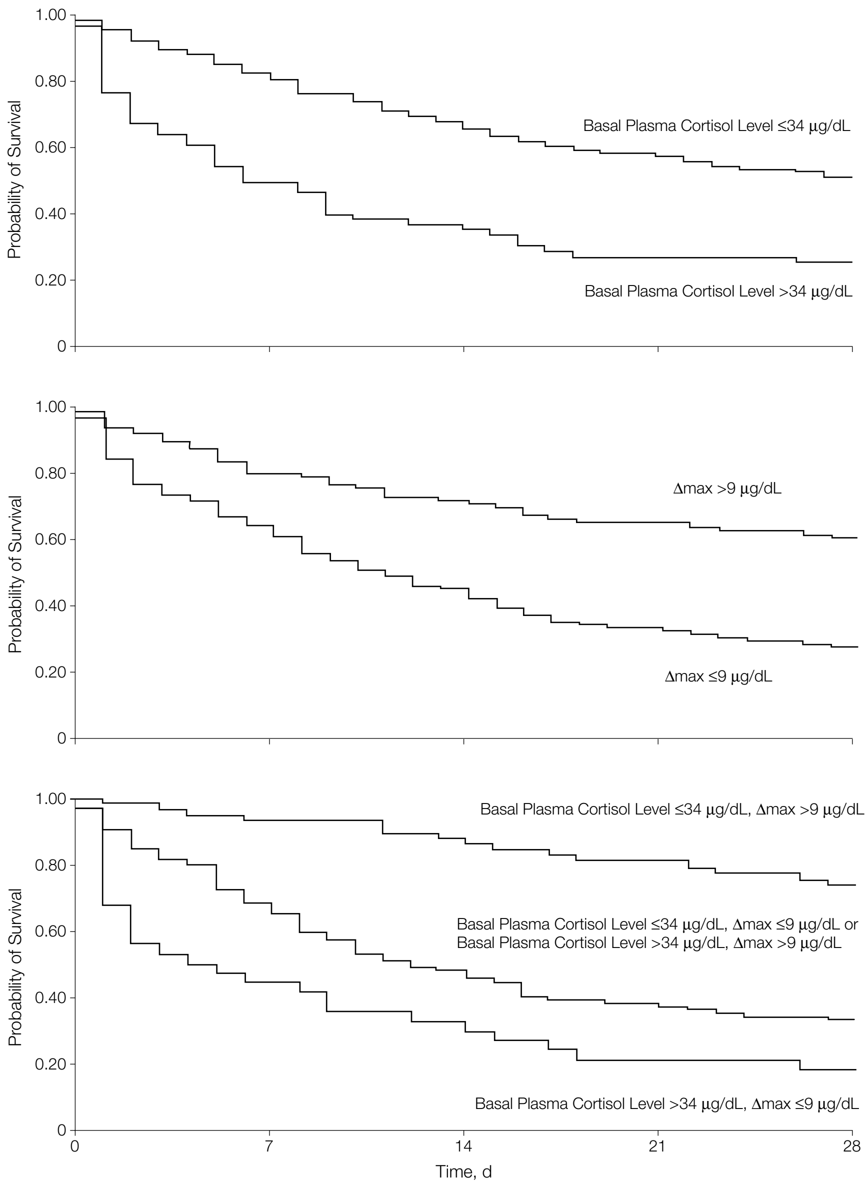
Table 7. Multivariate Cox Regression Analysis: Results of Stepwise Selection Procedure

Variable*	Regression Coefficient (β)	SE	Odds Ratio (95% Confidence Interval)	*P* Value
McCabe >0	0.54	0.20	1.72 (1.16-2.56)	.007
Organ system failure >2	1.12	0.21	3.05 (2.04-4.57)	<.001
Lactate >2.8 mmol/L	0.52	0.21	1.69 (1.13-2.52)	.01
PaO_2:FIO_2 >160 mm Hg†	−0.71	0.21	0.49 (0.33-0.74)	<.001
Cortisol, µg/dL‡				
Level before test >34§	0.97	0.20	2.63 (1.77-3.91)	<.001
Maximum variation after test >9‖	−0.88	0.21	0.41 (0.27-0.63)	<.001

*All continuous variables were discretized according to their median value. Other variables entered in the model were Simplified Acute Physiology Score II of more than 55, mean arterial pressure of more than 60 mm Hg, arterial pH of more than 7.33, and the combination of cortisol level before test and of maximum variation after test defined in 3 categories: cortisol level before test of 34 µg/dL or less and maximum variation after test of more than 9 µg/dL; cortisol level before test of 34 µg/dL or less and maximum variation after test of 9 µg/dL or less or cortisol level before test of more than 34 µg/dL and maximum variation after test of more than 9 µg/dL; cortisol level before test of more than 34 µg/dL and maximum variation after test of 9 µg/dL or less.
†FIO_2 indicates fraction of inspired oxygen.
‡To convert values for cortisol to nanomoles per liter, multiply by 27.6.
§Discretized according to its mean value.
‖Indicates variation between pretest plasma level and the highest level 30 and 60 minutes after test. Discretized according to the reference value.

to death, 11 days [95% CI, 8-15 days]), and for the following combination of T0 and Δmax, a T0 greater than 34 µg/dL and Δmax of 9 µg/dL or less (median time to death, 5 days [95% CI, 2-12 days]). Three different survival patterns appear in Figure 2: (1) high (T0 ≤34 µg/dL and Δmax >9 µg/dL; 28-day mortality rate of 26%); (2) intermediate (T0 ≤34 µg/dL and Δmax ≤9 µg/dL or T0 >34 µg/dL and Δmax >9 µg/dL); 28-day mortality rate of 67%); and (3) low (T0 >34 µg/dL and Δmax ≤9 µg/dL; 28-day mortality rate of 82%).

Figure 2. Survival Curves of Patients According to Basal Plasma Cortisol Levels (T0 ≤ or >34 µg/dL), Maximum Variation of Plasma Cortisol Between T0 and 30 and 60 Minutes After Corticotropin Test (Δmax ≤ or >9 µg/dL), and the Combination of T0 and Δmax



Top, 62 of the 126 patients with T0 of 34 µg/dL or less died compared with 47 of the 63 with T0 of more than 34 µg/dL; *P*<.001 (log-rank test). Middle, 75 of the 103 patients with Δmax of 9 µg/dL or less died compared with 34 of the 86 patients with Δmax of more than 9 µg/dL; *P*<.001 (log-rank test). Bottom, 15 of the 57 patients with T0 of 34 µg/dL or less and Δmax of more than 9 µg/dL died compared with 66 of the 98 patients with T0 of 34 µg/dL or less and Δmax of 9 µg/dL or less or T0 of more than 34 µg/dL and Δmax of more than 9 µg/dL and with 28 of the 34 patients with T0 of more than 34 µg/dL and Δmax of 9 µg/dL or less; *P*<.001 (log-rank test). To convert values for cortisol to nanomoles per liter, multiply by 27.6.

COMMENT

In this study, we included ICU patients with well-defined diagnosis of septic shock, complete clinical and physiological data, and a complete follow-up. The study was mainly designed to assess, at the early course of septic shock, the incidence and the prognostic value of occult adrenal insufficiency.

The 28-day mortality from septic shock was 58% (95% CI, 51%-65%). This result is consistent with the 56% rate of ICU mortality at 28 days recently reported.[3] In our patients with septic shock, the incidence of occult adrenal insufficiency was 54% (95% CI, 47%-61%).

Several factors have been suspected to be associated with mortality in severe sepsis and septic shock.[3,38-43] The main prognostic factors reported to date are age, severity of patient's underlying disease, number of organ system dysfunctions, severity of illness scores, hypothermia, neutropenia, thrombocytopenia, lactic acidosis, multisource of infection, positive blood culture, type of infecting organism, blood concentrations of endotoxin, and cytokines. Since the initial reports of Waterhouse[44] and Friderichsen,[45] the implication and prognostic value of a secretory failure of the adrenal glands in patients with severe sepsis is still under debate.*

In the 189 patients with septic shock included in our study, most of the foregoing factors were significantly associated with mortality in the univariate analyses. High basal plasma cortisol levels and weak cortisol response to corticotropin were also associated with mortality. After multivariate analyses, only 6 factors remained independently associated with death: ultimately or rapidly fatal underlying disease, more than 2 OSFs, arterial lactate level greater than 2.8 mmol/L, PaO_2:FIO_2 below 160 mm Hg, basal plasma cortisol levels above 34 µg/dL, and cortisol response to cor-

*References 4, 7-14, 16-21, 24-30, 46, 47 ticotropin below 9 µg/dL. Thus, our study suggests that basal plasma cortisol levels are higher in the patients who have the highest risk of mortality,[4,7,10,16-18] with 34 µg/dL as the best cut-off point to discriminate between survivors and nonsurvivors from septic shock. One third of patients with septic shock had a basal cortisol level above 34 µg/dL. This study also shows that the weaker the cortisol response the higher the risk of death.[10,24,25] A difference of 9 µg/dL between basal cortisol levels and the highest of the 30- and 60-minute concentrations after corticotropin was the best cut-off point to discriminate between survivors and nonsurvivors from septic shock. More than 50% of patients with septic shock had a blunted cortisol response (Δmax $\leq$9 µg/dL). The combination of the value of basal cortisol levels ($\leq$ or $>$34 µg/dL) and the highest value of the cortisol response to corticotropin ($\leq$ or $>$9 µg/dL) allowed us to define 3 different patterns of activation of the HPA axis in septic shock. These patterns were clearly associated with 3 different outcomes. First, 30% of our patients with septic shock had what we consider to be adequate HPA axis activation with a basal cortisol level below 34 µg/dL and a cortisol response to corticotropin above 9 µg/dL. These patients had the lowest risk of death and a median survival time of more than 28 days. Second, almost 20% of our patients with septic shock had a basal cortisol level above 34 µg/dL with an occult adrenal insufficiency (Δmax $\leq$9 µg/dL). These patients had the highest risk of death and a median survival time of 5 days. Finally, more than 50% of our patients with septic shock had a basal cortisol level below 34 µg/dL and a cortisol response to corticotropin below 9 µg/dL or a basal cortisol level above 34 µg/dL and a cortisol response to corticotropin above 9 µg/dL. These patients had an intermediate risk of death and a median survival time of 12 days.

Thus, at onset of septic shock, basal plasma cortisol values and cortisol response to corticotropin appear as independent predictors of 28-day mortality, which allows us to propose a new prognostic classification of 3 groups. This 3-level classification only requires a short corticotropin test and has a good prognostic value. It should therefore be helpful in identifying a group of patients at high risk of death and in planning new randomized trials, particularly to evaluate the effectiveness of corticosteroids.

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