Profile of the Risk of Death After Septic Shock in the Present Era: An Epidemiologic Study

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All authors conceived and designed the study. Drs. Pavon, Binquet, and Quenot analyzed and interpreted the study. All authors drafted the manuscript for important intellectual content and approved for submission.

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Objectives: To investigate mortality of ICU patients over a 3-month period after an initial episode of septic shock and to identify factors associated with mortality.

Design: Prospective multicenter observational cohort study.

Setting: Fourteen ICUs from 10 French nonacademic and university teaching hospitals.

Patients: All consecutive adult patients with septic shock admitted between October 2009 and September 2011 were eligible.

Intervention: None.

Measurements and Main Results: Multivariable analyses were performed using a Cox proportional hazard model and a flexible extension of the Cox model. In total, 1,495 of 10,941 patients (13.7%) had septic shock and 1,488 patients (99.5%) were included. Median age was 68 years (range, 58–78 yr). The majority of admissions (84%) were medical. Median (interquartile range) Simplified Acute Physiological Score II and Sequential Organ Failure Assessment were, respectively, 56 (45–70) and 11 (9–14). ICU and hospital mortality were, respectively, 39.4% and 48.6%. At 3 months, 776 patients (52.2%) had died. Factors significantly associated with increased risk of death in the multivariable Cox model were older age, male sex, comorbidities (immune deficiency, cirrhosis), Knaus C/D score,

and high Sequential Organ Failure Assessment score. Flexible analyses indicated that the impact of Sequential Organ Failure Assessment score was greatest early after septic shock, while the onset of the effect of age, nosocomial infection, and cirrhosis was later.

Conclusions: This is the most recent large-scale epidemiological study to investigate medium-term mortality in nonselected patients hospitalized in the ICU for septic shock. Advances in early management have improved survival at the initial phase, but risk of death persists in the medium term. Flexible modeling techniques yield insights into the profile of the risk of death in the first 3 months. (*Crit Care Med* 2013; 41:2600–2609)

Key Words: epidemiology; intensive care; medium-term outcome; sepsis

Septic shock, defined as a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes, despite adequate fluid resuscitation (1), affects between 10% and 30% of patients managed in ICU (2–9), and the incidence is increasing (3). Septic shock is associated with an increased risk of in-hospital morbidity and death (2). Mortality from septic shock in the ICU is estimated to range between 45% and 63% in observational studies (3, 10), but it is reportedly declining over time (3, 6, 10). Septic shock incurs considerable economic costs and represents a major public health challenge (2). Furthermore, it has a negative impact on quality of life and on medium- and long-term prognosis (5, 11–13).

Several risk factors have been shown to be associated with short-term septic shock-related mortality (ICU or in hospital), namely late ICU admission, age, previously existing comorbidities, infection characteristics, and inappropriate antimicrobial therapy (3, 5, 14–16). The severity of sepsis is another important determinant of prognosis in septic shock and is estimated by scores such as Sequential Organ Failure Assessment (SOFA) or the Multiple Organ Dysfunction Score (17, 18). However, apart from age and severity of shock, which are persistently identified as risk factors for mortality, there are conflicting data between studies regarding the importance of other prognostic factors. This could partially be explained by the fact that populations vary between studies, often reporting results from randomized clinical trials (14–17) where the populations are highly selected and not representative of patients encountered in routine practice: for example, in two main interventional studies, 28-day mortality ranged from 24% to 61% in the control group and from 24.7% to 55% in the treatment group (14, 17). These discrepancies were mainly explained by differences in the severity at inclusion. In addition, exclusion criteria in these studies led to study populations that did not completely reflect real-life patients.

Since the publication of the Surviving Sepsis Campaign in 2004 (18) and its update in 2008 (19), few epidemiological studies have been published with recent data regarding the incidence of septic shock and characteristics and prognosis of patients (10). In particular, there is a paucity of very recent data that take into account the profound changes in management since the publication of these guidelines. The most recent studies have focused on ICU and in-hospital mortality rates and showed a positive impact of guidelines (20–22).

To the best of our knowledge, no observational study has yet addressed the issue of medium-term prognosis in unselected ICU patients with septic shock. Yet, this issue becomes increasingly important, as more and more patients survive the initial episode of shock, only to die soon thereafter, often from comorbidities. Prognostic studies and clinical trials in other similarly severe pathologies, such as acute lung injury, often consider 3-month survival to be equivalent to full patient recovery, but it has been shown that negative repercussions actually persist for several years after the initial episode (23). In the context of septic shock, the dynamics of mortality are of particular interest and should be explored using time-to-event techniques. Most published studies use statistical models, such as the very popular Cox proportional hazard (PH) model (24), which are based on the hypothesis that the effects of prognostic factors are constant over time. However, this is rarely the case in routine practice (25). In addition, the Cox model relies on the assumption of log-linearity, which requires the estimated risk (log hazard) to be a linear function of a continuous prognostic factor. Accurate assessment of the role of quantitative prognostic factors, such as age or SOFA score, requires simultaneous modeling of both 1) potential changes over time in their effects and 2) the dose-risk relationships that describe how the risk changes with increasing value of the factor (26–28). Flexible extensions of the Cox model allowing simultaneous assessment of both time-dependent and non–log-linear effects of continuous covariates have recently been developed (29, 30) and have yielded new insights into the role of prognostic factors in many diseases (27, 28, 30).

In this context, we hypothesized that mortality from septic shock in the ICU remains high in France after the first month of follow-up, despite improvements in patient management. Therefore, we aimed to investigate mortality of patients over a period of 3 months after an initial episode of septic shock and to identify factors associated with this mortality, using appropriate modeling techniques.

METHODS

Study Population

This prospective cohort included all consecutive adult patients with a diagnosis of septic shock admitted to 14 ICUs in 10 public hospitals (five academic teaching hospitals and five nonacademic hospitals) in the northeast of France, between October 2009 and September 2011. Septic shock was defined based on the PROWESS-SHOCK study (16), namely documented or suspected infection requiring initiation of vasopressors despite adequate vascular filling, with at least one of the following hypoperfusion criteria: 1) metabolic acidosis (base excess $\geq$ 5 mEq/L, alkaline reserve $<$ 18 mEq/L, or lactate $\geq$ 2.5 mmol/L), 2)

oliguria/renal insufficiency (< 0.5 mL/kg/hr for 3 hr or elevation > 50% of baseline creatinine), or 3) hepatic dysfunction (aspartate transaminase or alanine transaminase > 500 IU/L or bilirubin > 34 μmol/L).

Data Collection

Data collection included sociodemographic characteristics; chronic health status as evaluated by the Knaus score; comorbidities; Simplified Acute Physiological Score (SAPS) II at ICU admission (31); SOFA score (32) over the 24 first hours following vasopressor initiation; infection site and germ(s), when identified; life-support therapy in ICU and in hospital; and length of ICU and hospital stay (among survivors and nonsurvivors). The Knaus Chronic Health Status score consists of class A, normal health status; class B, moderate activity limitation; class C, severe activity limitation due to chronic disease; and class D, bedridden patient (33). Antimicrobial therapy was classified as appropriate if the prescribed antimicrobial regimen was active against the identified pathogen. Vital status and World Health Organization performance status (34) at ICU and hospital discharge and 3 months after the initial shock episode, as well as place of residence at 3 months (home, institution, hospital), were recorded from patient medical files or by direct phone contact with the patient, family, or treating physician.

Patients with a second episode of shock in hospital or who were later readmitted for recurrent shock were not included a second time.

All data were collected using a standardized electronic case report form by dedicated clinical research assistants. Automatic checks were generated for missing or incoherent data. According to French legislation, patients (or their legal representative) were informed that their data were collected for research purposes unless they specifically refused. Collection of nominative data was approved by the national authority for the protection of privacy and personal data and by the ethics committee of the French Society of Intensive Care.

Statistical Analysis

Quantitative variables are reported using mean (± SD) or, in case of nonnormal distributions, median (interquartile range [IQR]) and qualitative variables as number (percentage).

To evaluate the dynamics of mortality and to identify prognostic factors associated with 3-month mortality, time-to-event techniques were used. Initiation of vasopressors in response to septic shock was considered the "time zero" (beginning of follow-up). Time-to-event was defined as time to death of any cause and measured in days. Patients who remained alive at 90 days of follow-up were censored at that time. In simple unadjusted bivariate analyses, the probability of death was estimated using the Kaplan-Meier method and compared using the log-rank test. At an expected mortality rate of 50%, we calculated that 1,400 patients would be necessary to ensure high statistical power of 90% to detect a minimum clinically important relative risk increase of 25% (hazard ratio [HR], 1.25) for a binary variable with 30% incidence at a two-tailed test ($\alpha = 0.05$). Based on conservative estimates of the expected recruitment rates in participating centers, we expected that a time window of 24 months would be necessary to accrue an adequate number of patients.

Multivariable analyses were performed using a Cox PH model (24). The initial multivariable model included all patient characteristics that were found to be at least marginally associated ($p < 0.25$ for the log-rank test) with 3-month mortality in bivariate analyses. However, bivariate correlations between potential predictor variables were first estimated, and in the case of near collinearity, only the most informative among collinear variables was selected for inclusion in the initial multivariable model. A backward elimination procedure was then applied to identify factors that had independent statistically significant associations with the hazard of all-cause 3-month death ($p \leq 0.05$).

Cox PH model imposes a priori the conventional PH and log-linearity assumptions that may not be valid if the effect of the prognostic factor varies depending on, respectively, the follow-up time and/or the observed value. To verify if these assumptions are consistent with our data and to account for their possible violations, we also applied a flexible extension of the Cox model previously validated through simulations and clinical applications (29). In particular, the flexible model allowed us to account for potential time-dependent (i.e., nonproportional) and/or non–log-linear effects of variables selected for the multivariable Cox model. This flexible model uses regression splines (35, 36) to jointly estimate time-dependent and non–log-linear effects of continuous covariates, as well as time-dependent effects of categorical factors (29). Likelihood ratio tests are used to test statistical significance of the violation of the PH and/or log-linearity hypotheses. To account for possible type I error inflation, due to our reliance on the backward elimination procedure, we considered only *p* values below 0.04 as "statistically significant." The statistically significant time-dependent and/or non–log-linear effects identified in the final multivariable flexible model were then estimated and plotted, together with the bootstrap-based 95% confidence bands (29). The fit of the flexible model was compared with the conventional Cox model based on the Akaike Information Criterion (AIC) (37) with a reduction of AIC by 10 or more indicating a very considerable improvement (38, 39). Additional information on the flexible model and its interpretation is available in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/A707).

Appropriate antimicrobial therapy was considered a time-updated covariate, and its effect was estimated after adjustment for the other covariates, including their statistically significant non–log-linear and/or time-dependent effects.

Most analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC), whereas flexible analyses were implemented using a customized program in the C programming language (29).

RESULTS

Study Population

Patients admitted to the ICUs of participating hospitals were systematically screened between October 2009 and September

2011. A total of 10,941 patients were admitted to the participating ICUs during the study period. Among these, 1,495 patients (13.7%) presented a septic shock and were included in the study. Complete follow-up was obtained for 1,488 patients (99.5%); seven patients were lost to follow-up.

The baseline characteristics of the study population are shown in **Table 1**. Median age was 68 years (range, 58–78), almost two thirds were men. The majority of admissions were of medical origin (84%). The most common comorbidities were immune deficiency in 31% of patients ($n = 459$), and 23% of patients had least two comorbidities. The median (IQR) SAPS II and SOFA scores were, respectively, 56 (45–70) and 11 (9–14). Approximately two thirds of patients presented community-acquired infection, and more than half (53.6%) had respiratory tract infection as the primary site of infection at the origin of septic shock. The infectious organism was identified in 873 patients (58.7%) who presented septic shock. Gram-negative bacilli were the most frequent pathogens on the positive isolate microorganism in 38.8%, whereas Gram-positive cocci microorganisms were identified in 31.1%. Patients with nosocomial infection more frequently had Gram-negative bacilli as the infectious agent ($p = 0.001$) and were mainly transferred patients ($p < 0.0001$), in particular from other university hospitals ($p < 0.0001$). They also had more frequent Knaus C or D score ($p < 0.0001$), immunosuppression ($p < 0.0001$), and chronic renal failure ($p < 0.016$).

Outcomes and Treatments

ICU and hospital mortality rates were, respectively, 39.5% and 48.6%, and at 3 months, 776 patients (52.2%) had died. Patient outcomes are described in **Table 2**. Overall 30-day and 90-day probabilities of death were, respectively, 43.2% (95% CI, 40.7–45.8%) and 52.7% (95% CI, 50.2–55.3%). Thus, almost 18% of the 3-month probability of death occurred after the end of the first month following the shock.

The median (IQR) duration of vasopressor therapy was 4 days (2–6 d) (**Table 3**). Invasive mechanical ventilation was required in most patients (83.9%) at the start of the septic shock. Continuous renal replacement therapy and intermittent hemodialysis were used in 32.5% and 19.6%, respectively. Among the 873 of 1,232 patients (70.9%) in whom the germ responsible for infection was identified, only 55 patients (6.3%) had inappropriate antimicrobial therapy, and among these, 60% of the patients died in a median of 5 days (IQR, 1–17).

Prognostic Factors of 3-Month Mortality

Factors identified by multivariable Cox regression analysis as significantly associated with increased risk of death were older age, presence of comorbidities (especially immune deficiency and cirrhosis), a Knaus score of C or D, higher SOFA score, and nosocomial infection (**Table 4**). Urinary tract infection was associated with a 35% reduction in the 3-month risk of death (95% CI, 18–48%). In multivariable analyses, bloodstream infection was no longer associated with 3-month risk of death ($p = 0.230$).

The flexible model substantially improved the goodness of fit compared with the Cox model (AIC = 6,720.46 vs AIC = 6,770.82 for the Cox PH model). This improvement in the predictive ability of the flexible model was mainly due to the fact that the PH hypothesis was rejected for both age ($p = 0.009$) and SOFA score ($p < 0.0001$), indicating that the effects of these two factors on the hazard of death changed very significantly during the 3-month follow-up. On the other hand, the flexible analyses confirmed that after accounting for their time-dependent effects, both age and the SOFA score had linear effects on the logarithm of the mortality hazard ($p = 0.370$ and $p = 0.980$ for tests of log-linearity for age and SOFA score, respectively).

Overall, the results of the flexible analyses indicated that although the risk of all-cause mortality in the 3 months after septic shock increased steadily with increasing age and increasing baseline SOFA score, the impact of both factors changed significantly over the follow-up period. **Figure 1**, ***A*** and ***B*** describe the time-dependent effects of these two factors. In both figures, the horizontal axis represents the follow-up time, and the vertical axis shows how the HR associated with, respectively, a 10-year increase in age or one-point increase in the SOFA score changes over time. The impact of older age increases during the first month of follow-up and remains high thereafter (Fig. 1*A*), when the risk of death was increased by at least 50% for every 10 additional years of age. In contrast, the effect of increasing initial SOFA score was especially high right after the shock and decreased steeply over the first week, with slower decreases thereafter (Fig. 1*B*). Right after the shock, an increase of one point on the SOFA scale was associated with an almost two-fold increase in risk of death (HR, 1.93 [95% CI, 1.77–2.09]). This indicates that the short-term risk of immediate death associated with higher SOFA scores is much higher than suggested by the conventional Cox PH model (HR, 1.20 [95% CI, 1.17–1.22]), which (incorrectly) forces this effect to remain constant over the entire follow-up period. In contrast, after the shock, the effect of the initial SOFA score becomes only marginally significant (HR, 1.18 [95% CI, 1.02–1.36]), and it has no predictive ability at 3 months of follow-up (HR, 0.96 [95% CI, 0.64–1.45]).

Flexible analyses also revealed statistically significant time-dependent effects of nosocomial versus community-acquired infections ($p = 0.016$) and preexisting cirrhosis ($p = 10^{-3}$). The associations of both factors with a higher risk of death became apparent 1 week after the initial shock (Figs. 1, *C* and *D*). On the other hand, the impact of immune deficiency, previous chronic health status (Knaus score), and urinary tract infection remained constant over the 3 months of follow-up, as for all three factors, the PH hypothesis was not rejected ($p > 0.19$ for the corresponding PH tests in Table 4). Finally, we did not observe any effect of inappropriate antimicrobial treatment ($p = 0.52$).

DISCUSSION

Our study is the first to estimate medium-term prognosis (3-mo mortality) in a real-life cohort of septic shock patients since the publication of updated guidelines (19). Our data both highlight the major impact of age and initial SOFA score on prognosis in this population and provide new insights

TABLE 1. Baseline Characteristics of the Study Population of 1,488 ICU Patients With Septic Shock and Probability of Death at 1 and 3 Months (EPIdemiology of Septic Shock Study 2009–2011)

Variable	All (n = 1,488) (%)	Probability of Death		p[a]
		1 Mo (%)	3 Mo (%)	
Age				
< 60 yr	428 (28.8)	32.4	39.0	< 10^{-4}
60 to < 70 yr	277 (25.3)	43.5	52.8	
70 to < 80 yr	437 (29.4)	46.4	59.4	
≥ 80 yr	246 (16.5)	56.0	64.6	
Gender				
Female	537 (36.1)	39.5	48.2	0.018
Male	951 (63.9)	45.3	55.3	
Body mass index (kg/m^2)				
< 20	129 (8.7)	45.1	58.1	0.076
20–25	371 (24.9)	43.9	55.5	
25–30	388 (26.1)	41.9	50.5	
> 30	336 (22.6)	39.4	47.4	
Not available	264 (17.7)	48.2	56.0	
Comorbidities[b]				
Immunosuppression[c]	459 (30.9)	37.6	46.3	< 10^{-4}
Cancer (solid tumors)	226 (49.2)	56.5	69.6	
Hematological cancer	142 (30.9)	62.7	70.6	
Corticoids	109 (23.8)	47.9	58.2	
Transplantation	40 (8.7)	45.0	52.8	
AIDS	10 (2.2)	70.0	70.0	
Other	77 (16.8)	52.0	66.7	
Diabetes mellitus	387 (26.0)	45.3	54.0	0.653
Cirrhosis	133 (8.9)	58.3	68.4	< 10^{-4}
Chronic heart failure (New York Heart Association Class III/IV)	160 (10.8)	54.5	66.2	< 10^{-4}
Chronic respiratory failure[c]	113 (7.6)	41.7	52.9	0.859
Chronic renal failure[d]	171 (11.6)	50.9	57.4	0.152
Number of comorbidities				
None	510 (34.3)	30.7	39.7	< 10^{-4}
1	633 (42.5)	46.7	56.9	
2 or more	339 (23.1)	55.3	64.3	
Knaus[c]				
A/B	853 (57.4)	36.0	44.7	< 10^{-4}
C/D	634 (42.6)	53.0	63.5	
Sequential Organ Failure Assessment				
≥ 11	823 (55.3)	27.5	37.0	< 10^{-4}
< 11	665 (44.7)	55.9	65.4	

(*Continued*)

TABLE 1. (*Continued*). Baseline Characteristics of the Study Population of 1,488 ICU Patients With Septic Shock and Probability of Death at 1 and 3 Months (EPIdemiology of Septic Shock Study 2009–2011)

Variable	All (*n* = 1,488) (%)	Probability of Death		*p*[a]
		1 Mo (%)	3 Mo (%)	
Site of infection[b]				
Respiratory tract	798 (53.6)	44.3	54.3	
Abdominal	285 (19.2)	42.6	52.2	
Renal/urinary tract	209 (14.1)	31.3	41.7	
Bloodstream	196 (13.2)	50.1	59.1	
Other	88 (5.9)	44.6	51.9	
Type of infection				
Community acquired	974 (65.5)	39.0	47.0	$< 10^{-4}$
Nosocomial	514 (34.5)	51.3	63.5	

[a]Log-rank test.
[b]Patients could have more than one comorbidity and/or site of infection.
[c]One missing data.
[d]Two missing data.

about their effects. The decreasing impact of the SOFA score over time suggests that adequate life-support therapy should be envisaged, regardless of the severity of shock. Our flexible analyses revealed that the conventional Cox model largely underestimated the dramatic risk of immediate death, within a few days after the shock, for patients with higher initial SOFA score. It would appear that initial SOFA score cannot be used to reliably predict prognosis after the first week.

This information is important, given that the incidence of septic shock is on the increase, whereas mortality is reportedly decreasing in patients with septic shock (3). Earlier and improved management of septic shock has contributed to decreasing death rates. However, a small proportion of patients with septic shock who are discharged alive, subsequently die within a short timeframe, often from comorbidities. Indeed, in

TABLE 2. Outcomes at ICU Discharge, Hospital Discharge, and 3 Months After Septic Shock (EPIdemiology of Septic Shock Study 2009–2011)

Outcome	All (*n* = 1,488)
ICU mortality, *n* (%)	587 (39.5)
Median (IQR) length of ICU stay, d	9 (3–19)
In-hospital mortality, *n* (%)	724 (48.7)
Median (IQR) length of hospital stay, d	22 (10–43)
3-mo mortality, *n* (%)	776 (52.2)
Place of residence at 3 mo, *n* (%)	
At home	456 (69.1)
Institution	41 (6.2)
Hospital	163 (24.7)
World Health Organization performance status at 3 mo[a]	
0	108 (17.5)
1	115 (18.7%)
2	200 (32.5%)
3	138 (22.4%)
4	55 (8.9%)

IQR = interquartile range.
[a]Ninety-six missing data; 712 survivors.

TABLE 3. Life-Support Therapy During Hospital Stay in the Study Population of 1,488 Patients With Septic Shock (EPIdemiology of Septic Shock Study 2009–2011)

Treatment	*n* (%)	Median (IQR) Duration (D)
Vasopressors	1,488 (100)	4 (2–6)
Inotropes	412 (27.7)	3 (2–6)
Invasive mechanical ventilation	1,248 (83.9)	7 (3–14)
Noninvasive ventilation	355 (24.2)	2 (1–4)
Continuous renal replacement therapy	484 (32.5)	4 (2–8)
Intermittent hemodialysis	291 (19.6)	3 (1–5)
Hydrocortisone	937 (63.0)	Not available

IQR = interquartile range.

TABLE 4. Factors Affecting 3-Month Survival as Identified by Multivariate Analyses (EPIdemiology of Septic Shock Study 2009–2011)

	Reduced Multivariate Cox Model		Flexible Extension of the Cox Model	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age (per 10 additional yr)	1.31 (1.24–1.40)	$< 10^{-4}$	Figure 1*A*	$< 10^{-4}$
Sequential Organ Failure Assessment (per additional point)	1.20 (1.17–1.22)	$< 10^{-4}$	Figure 1*B*	$< 10^{-4}$
Nosocomial vs community-acquired infection	1.29 (1.11–1.49)	0.001	Figure 1*C*	$< 10^{-3}$
Comorbidities[a]				
Immunosuppression	1.58 (1.37–1.84)	0.001	1.60 (1.34–1.90)	$< 10^{-4}$
Cirrhosis	1.35 (1.07–1.69)	0.011	Figure 1*D*	$< 10^{-4}$
Knaus				
C/D vs A/B	1.39 (1.20–1.60)	$< 10^{-4}$	1.43 (1.23–1.68)	$< 10^{-4}$
Renal/urinary tract site of infection	0.65 (0.52–0.81)	$< 10^{-4}$	0.64 (0.51–0.83)	$< 10^{-4}$

HR = hazard ratio.

[a]Patients could have more than one comorbidity.

The following variables from the full model were not retained in the reduced and flexible models: sex, body mass index, New York Heart Association grade, and number of comorbidities (in categories, 1 vs none, ≥ 2 vs none).

our study, we observed a death rate at 3 months approaching that observed by Annane et al (3) at 1 month in 2000, indicating a potential reduction in mortality over the last decade. This underlines the importance of multidisciplinary management for the medium term, as the risk of death persists after the initial hospital phase. This deferred mortality reflects the fragile state of patients after an episode of septic shock. Knowledge of patient outcomes after discharge is therefore fundamental, to ensure adequate follow-up, in particular through specific rehabilitation programs, for example (40, 41).

The impact of age on mortality in the first month following septic shock is not a novel finding (3). However, through flexible modeling, our analyses revealed that the impact of older age increased over the first month of follow-up and remained very high thereafter. The longer time impact of older age is expected, simply due to the low life expectancy of older patients, who are often particularly frail, with less physiological reserves. Intensive care measures can help elderly patients survive through the first few weeks of their critical illness, but despite this early success, the physiologic effects of advanced age subsequently "catch up with them" in the ensuing weeks. Angus et al (2) demonstrated that aggressive therapy is not futile in the elderly and that beyond an improvement in survival, the quality of life after hospital discharge should also be taken into consideration. On the other hand, our finding that older age has a relatively weaker impact on short-term mortality, in the first few weeks, emphasizes that immediate deaths are mostly associated with specific clinical prognostic factors, such as high SOFA scores.

Indeed, our results confirm the impact of SOFA score on immediate mortality, soon after the septic shock. We chose not to include the SAPS II score in this analysis, because of its large overlap with the information provided by the SOFA score, and the fact that the SAPS II score is not specific to the context of septic shock. The SOFA score is designed specifically to describe a sequence of complications in the critically ill at the time when septic shock occurs (32), whereas the SAPS II score is an overall index of severity, which was calculated at the time of admission in our study and not at the time when the shock actually occurred. The very significant time-dependent effect of the initial SOFA score, revealed by our flexible analyses, indicated that its association with the risk of death decreased steeply during the first week after the shock. This finding underscores that the SOFA score carries a maximum of prognostic information for deaths that will occur within a few days after the shock episode. Our flexible analyses indicated that during this critical period, patients with higher SOFA scores are at a much higher risk than suggested by the conventional Cox regression analyses, which imposed an incorrect assumption that the effect of SOFA remained constant over time. This, together with the fact that our flexible model fit the data much better than the Cox model, suggests that every effort must be made to prevent deaths of patients with high SOFA during the first week after the shock. In contrast, our flexible analyses indicate also that the impact of initial SOFA score becomes weaker after a few weeks of follow-up and disappears by 2–3 months after the shock. Accordingly, sequential assessment of updated SOFA during the follow-up may be useful to improve mid-term prognosis for patients who survive the critical few first days (42). It should be noted that there is no apparent threshold on the continuum of the SOFA score beyond which patients can be considered to be more severely ill. As a consequence, the SOFA score is not suitable for use as a selection criterion for clinical trials, because no obvious categories emerge.

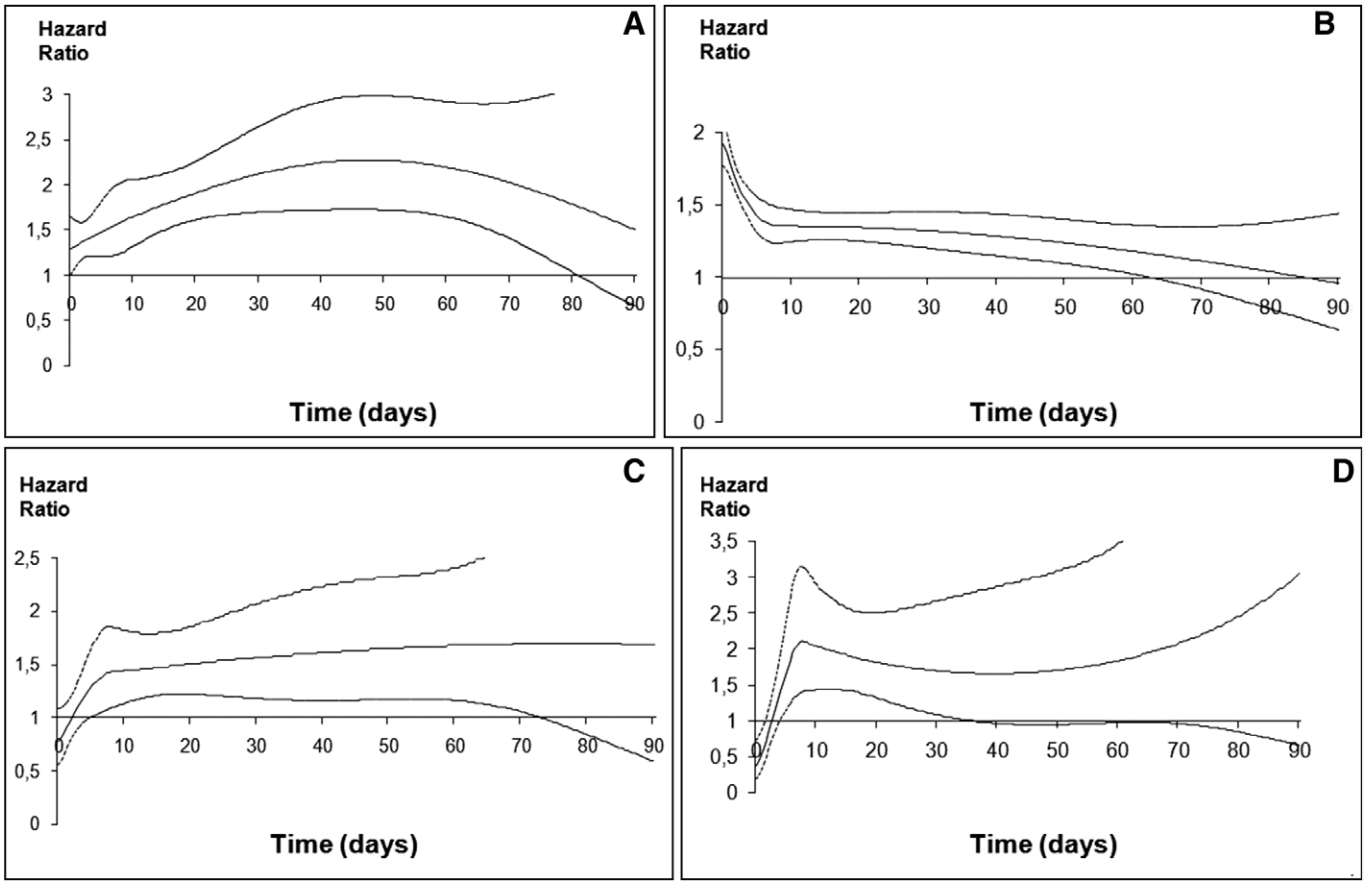

Figure 1. Time-dependent effects of age (for an increase of 10 yr) (**A**), Sequential Organ Failure Assessment score (for an increase of one point) (**B**), nosocomial infection (**C**), and cirrhosis (**D**) on the risk of death over 3 mo after an initial episode of septic shock. *Central lines* indicate the estimated hazard ratio, and the *upper lines* and *lower lines* represent the associated 95% confidence interval.

The persistent deleterious effect of nosocomial infection on mortality over time, albeit with considerable widening of the 95% CIs, is an interesting finding. In our study, patients with nosocomial infection were more frequently transferred patients, with a higher Knaus score, more frequent immunosuppression, and chronic renal failure. These elements suggest that overall, patients with nosocomial infections likely had underlying frailty, which, in parallel to the presence of cirrhosis, negatively impacted on their prognosis at the acute phase.

In our study, the ICU mortality rate was somewhat lower than that in other reports (39% in our study vs 54% reported by Annane et al [3]), despite the fact that we used a more restrictive definition of septic shock. We based our definition on that of the PROWESS-SHOCK study, which included hypoperfusion criteria (16). This stricter definition was chosen to guarantee that a homogenous definition would be applied in all participating centers. The organizational support for our study with a dedicated team of specifically trained clinical research assistants made it possible to include consecutive patients, with prospective identification of cases by investigators with the aid of the research assistants. Data were monitored regularly for exhaustiveness, and automatic queries were generated in case of inconsistencies. This guaranteed high-quality data with near complete follow-up. In addition, our study was performed over a 2-year period during which there were no major publications of guidelines or clinical trials likely to modify practice. Thus, we believe that the characteristics reported in our study can be considered to be representative of ICU patients in other similar healthcare systems. Our patients presented with more severe disease and a worse general state of health than patients in older studies. This is not unexpected, as the criteria for ICU admission have evolved over time and now cover a larger spectrum of patients, particularly to include older and sicker patients. This corresponds with the profile of the patients included in this study, who were generally older (median, 68 yr), with more comorbidities (23% had least two comorbidities), notably immunosuppression (31%), and deteriorated previous state of health (42.5% were Knaus C/D), as compared with previous reports (2, 3, 5, 6, 10, 43–45).

Other Prognostic Factors Observed in the Literature

Boyd et al (46) recently reported that a positive fluid balance and elevated central venous pressure were associated with increased mortality in septic shock, confirming previous findings (45, 47, 48). In our study, fluid resuscitation was not documented because the reproducibility of the measures is very low. Furthermore, hemodynamic monitoring was not standardized in our study because the techniques are controversial (49). In a recent study, Johnson et al (50) demonstrated that prior antibiotic exposure (for a time period of 90 d) was associated, by

multivariate analysis, with greater hospital mortality in patients with Gram-negative bacteremia complicated by severe sepsis or septic shock. In our study, however, the prior use of antibiotic therapy was not recorded, and therefore, we were unable to replicate these findings. Conversely, our data preclude drawing any firm conclusions regarding the impact of inappropriate antimicrobial therapy in our population, probably because few patients had delayed or inappropriate antimicrobial treatment. Therefore, our data do not allow any conclusions with respect to previous observations by Kumar et al (51), who reported that time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome in 2,731 patients with septic shock.

Limitations

Some limitations of our study have to be recognized. First, no surgical ICUs were included with the result that our conclusions cannot be extrapolated to surgical patients. Second, the duration of hypotension with fluid loading was not available, although the time to introduction of vasopressors was recorded for all patients included in this study. Third, biological variables, such as lactate, cytokine levels, or other markers of inflammation that may influence outcome in septic shock patients, were not measured in our study. Analyses of these variables are planned. Furthermore, there are probably other factors that we did not identify that could also partially explain the observed mortality rate. Finally, we have to emphasize that our goal was not to develop a prognostic score but rather to accurately describe the effects of prognostic factors, including the potential changes over time in their impact. Future research is necessary to validate our findings in an independent study, which should assess both mortality and quality of life over a longer time interval, of at least 1 year.

In conclusion, this is the most recent large-scale epidemiological study to investigate medium-term mortality in nonselected patients hospitalized in the ICU for septic shock. Mortality appears to be declining as compared with previous reports, despite wider ICU admission criteria and an older sicker patient population. Organ failure plays a major role in the early phase, whereas nonmodifiable factors, such as age and comorbidities, play an important role in the medium term. Considerable advances in early management have improved survival at the initial phase, but risk of death persists in the medium term. This information is important and should be taken into account to optimize medium- and long-term management with appropriate rehabilitation programs and regular follow-up.

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