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Survival for the Cirrhotic Patient With Septic Shock*

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Cirrhosis is hard: the patients are hard to keep healthy, they are hard to take care of when ill, it is hard to mobilize both financial and institutional resources for their care, and the liver itself is literally hard. Patients with cirrhosis are complex, requiring multidisciplinary care and institutional coordination to adequately care for their needs. Patients with cirrhosis are prone to numerous complications, including refractory gastrointestinal hemorrhage, hepatic encephalopathy, hepatorenal syndrome, and infection (1). Furthermore, they can have hepatic decompensation, sometimes referred to as "acute-on-chronic liver failure," when these events occur. Patients with cirrhosis are often chronically hypotensive, which is often compounded by prophylactic β-blocker use, making shock that much more difficult to manage in this patient set. Septic shock is particularly problematic in this patient population, as patients with cirrhosis are prone to multidrug-resistant infections, renal failure, and adrenal insufficiency (1–3). In addition, infected patients really cannot receive a liver transplant unless adequately treated, although outcomes are reasonable once infections are adequately treated (4). As the recovery rate for septic shock for patients with cirrhosis historically has been quite low (3, 5–7), there is a sense of futility—in particular, for patients who are not a liver transplant candidate at all.

The Collège des Utilisateurs de Bases de données en Reanimation (CUB-Réa) Network was set up as an initiative of the Société de Réanimation de Lagnue Française in 1992 with initial funding from the Assistance Publique-Hôpitaux de Paris (8). The CUB-Réa Network has developed a prospectively maintained database derived from the ICUs of hospitals in Paris and its suburbs. Initially composed of 22 ICU, the group has grown. In this issue of *Critical Care Medicine*, Galbois et al (9) present their analysis of the CUB-Réa database for outcomes of patients with cirrhosis from septic shock. From over 31,000 patients with septic shock, they identified 2,383 patients with cirrhosis in 32 ICUs over a 13-year period. Similar to previous studies (6, 7), they found increased risk of death for the patients with cirrhosis (odds ratio [OR], 2.5; 95% CI, 2.3–2.8). Cirrhotic survivors were less likely to have required mechanical ventilation, renal replacement therapy, or transfusion. They also found that patients with cirrhosis in the second half of the study period had improved survival (OR, 0.7; 95% CI, 0.6–0.9), suggesting that care has improved over time, although the authors mute this conclusion somewhat, as the study is limited by the possibility that both formal and informal intensive care admission policies can change over time. In addition, survival data were censored for all living patients at time of discharge, the degree of cirrhosis could not be assessed from the available data, and the impact of liver transplantation following discharge from the ICU could not be factored into the analysis, as the data collection plan was based around the ICU admission. Despite these limitations, it is encouraging that the authors have shown an improvement in survival over time in a large multicenter study.

For the liver failure community, it is exciting to see improvements in survival. To others, it may seem that even with this improvement, outcomes are still not particularly promising. To help determine who may benefit from intensive care, there have been several attempts to apply scoring systems as predictive models. Childs-Turcotte-Pugh scoring has not been particularly useful prognostically in this setting (6). Although the Model for End-Stage Liver Disease (MELD) scoring may have some predictive value for ICU patients (5), it is not particularly robust for prediction of in-hospital survival when compared with Sequential Organ Failure Assessment (SOFA) scoring (6), despite its predictive value for the severity of underlying cirrhosis. Not surprisingly, concurrent renal failure significantly increases

*See also p. 1666.

Key Words: acute-on-chronic liver failure; cirrhosis; multicenter study; septic shock; transplantation

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mortality in nearly every study of patients with cirrhosis, with the expected rise in MELD and SOFA scoring (1, 5, 6). For the patient who is clearly not going to be a transplant candidate at any time, studies such as the current CUB-Réa analysis (9), coupled with predictive models, provide the team of intensivists and families of the patients realistic expectations of survival.

Liver transplant remains the best option for long-term survival of the patients with cirrhosis. Despite the advantages of SOFA for prediction of ICU survival, the MELD score of the patient remains a vital component of the cirrhotic patient's profile if the patient is a transplant candidate, as once any infection is adequately treated, transplant can occur (4). In the United States, liver allocation is based on MELD score (10). For France, where the CUB-Réa Network functions, the French Liver Allocation Score applies—which overlaps to a fair degree with MELD (11). The recently critically ill patient is likely to have an elevated MELD, with the resulting increase in priority for liver allocation. This last point is critical for the patients with cirrhosis who might be transplantable. Often, liver transplant teams are asked by ICU teams whether a given patient, who is currently infected and decompensated, will ever be a transplant candidate. It is a reasonable question, since both the intensivists and the family must balance the possibility of survival versus futile care and unnecessary suffering. Unfortunately, the answer is not straightforward: while the patient is actively infected, the patient isn't really transplantable—although the patient might be once the infection is cleared and the patient improves somewhat (4). Patients are more likely to be transplanted while hospitalized and in an ICU (12), suggesting that, at least in the United States, decompensation episodes play a role in optimizing a given patient's organ access, although such approach results in significantly higher costs both pre- and postengraftment (13), likely due to the increased level of acuity. As ICUs are becoming more proficient in treating conditions such as septic shock, as shown by the present CUB-Réa Network study, these trends are likely to continue.

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Improved Prognosis of Septic Shock in Patients With Cirrhosis: A Multicenter Study*

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Objective: To determine the evolution of the outcome of patients with cirrhosis and septic shock.

Design: A 13-year (1998–2010) multicenter retrospective cohort study of prospectively collected data.

Setting: The Collège des Utilisateurs des Bases des données en Réanimation (CUB-Réa) database recording data related to admissions in 32 ICUs in Paris area.

Patients: Thirty-one thousand two hundred fifty-one patients with septic shock were analyzed; 2,383 (7.6%) had cirrhosis.

Interventions: None.

Measurements and Main Results: Compared with noncirrhotic patients, patients with cirrhosis had higher Simplified Acute Physiology Score II (63.1 ± 22.7 vs 58.5 ± 22.8, $p < 0.0001$) and higher prevalence of renal (71.5% vs 54.8%, $p < 0.0001$) and neurological (26.1% vs 19.5%, $p < 0.0001$) dysfunctions. Over the study period, in-ICU and in-hospital mortality was higher in patients with cirrhosis (70.1% and 74.5%) compared with noncirrhotic patients (48.3% and 51.7%, $p < 0.0001$ for both comparisons). Cirrhosis was independently associated with an increased risk of death in ICU (adjusted odds ratio = 2.524 [2.279–2.795]). In patients with cirrhosis, factors independently associated with in-ICU mortality were as follows: admission for a medical reason, Simplified Acute Physiology Score II, mechanical ventilation, renal replacement therapy, spontaneous bacterial peritonitis, positive blood culture, and infection by fungus, whereas direct admission and admission during the most recent midterm period (2004–2010) were associated with a decreased risk of death. From 1998 to 2010, prevalence of septic shock in patients with cirrhosis increased from 8.64 to 15.67 per 1,000 admissions to ICU ($p < 0.0001$) and their in-ICU mortality decreased from 73.8% to 65.5% ($p = 0.01$) despite increasing Simplified Acute Physiology Score II. In-ICU mortality decreased from 84.7% to 68.5% for those patients placed under mechanical ventilation ($p = 0.004$) and from 91.2% to 78.4% for those who received renal replacement therapy ($p = 0.04$).

Conclusions: The outcome of patients with cirrhosis and septic shock has markedly improved over time, akin to the noncirrhotic population. In 2010, the in-ICU survival rate was 35%, which now fully justifies to admit these patients to ICU. (*Crit Care Med* 2014; 42:1666–1675)

Key Words: critical care; humans; liver cirrhosis; prognosis; septic shock

Severe infections represent one of the most dreadful complications of cirrhosis and one of the major causes of mortality in these patients (1). Cirrhosis is associated with the occurrence of severe infections and also with an increased risk of death in infected patients (2, 3).

*See also p. 1737.

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Septic shock is the most severe form of infection, defined by a severe sepsis (acute organ dysfunction secondary to infection) associated with hypotension not reversed by fluid resuscitation (4, 5). In the general population, the prevalence of septic shock is increasing and outcome of patients with septic shock has improved during the past years (6–11). In the last published randomized trials, the mortality at 28 days from septic shock onset was approximately 25–40% (12–14). During the last decade, improved management of different sepsis-induced organ failures include early goal-directed therapy of the circulatory failure (15), protective mechanical ventilation in acute respiratory distress syndrome (ARDS) (16), the modality of renal replacement therapy (17), and earlier effective antimicrobial therapy administration (18, 19). All these improvements have been included in the Surviving Sepsis Campaign guidelines (5). These recommendations were implemented worldwide and were associated with reduced mortality from septic shock (20, 21). Furthermore, this improvement over time in ICU has also been reported in other conditions such as malignancies or chronic obstructive pulmonary disease (22, 23).

Based on former studies, mortality of patients with cirrhosis and septic shock has been estimated as high as 70–100% (24, 25). Recently, it was reported that outcome of patients with cirrhosis admitted to ICUs had improved (26–28). It was confirmed that their mortality in ICU was closely related to different organ failures rather than the severity of underlying liver disease (29–31). This suggested that the improved management of sepsis-induced organ failure in the general population could also benefit to cirrhotic patients. However, patients with cirrhosis are often excluded from the randomized trials aiming to reduce mortality in septic shock (32, 33). This raises the question as to whether the improvement of organ failure management in the general population in ICU in past years has led to a decreased mortality in patients with cirrhosis and septic shock.

The aim of this study was to assess the outcome in a large population of cirrhotic patients admitted to ICU with septic shock. We also aimed to determine if their clinical or microbiological characteristics and the time period impacted the outcome.

MATERIALS AND METHODS

The Database

The database of the Collège des Utilisateurs des Bases des données en Réanimation (CUB-Réa) included prospectively collected data from ICUs in Paris and its suburb and has been described elsewhere (7, 34). According to French regulation, the CUB-Réa project was approved by the Comité National de l'Informatique et des Libertés. CUB-Réa was initially funded by Assistance Publique-Hôpitaux de Paris. CUB-Réa has a steering committee composed of nine medical doctors and a database administrator (P.A.). The steering committee is charged with defining the minimum dataset, item definitions, participation requirements, coding rules, annual activity report, and data audit. Standard information, both administrative and medical in nature, is collected locally. Data are gathered prospectively for all patients hospitalized in the ICUs and are transmitted anonymously to the administrative center to be recorded in a relational database. All ICU stays are referred to the hospital diagnosis-related group. Each hospital controls the completeness of coding, so that there are no missing patients or information regarding ICU stay characteristics. In order to participate in the CUB-Réa, units must meet several criteria: a firm commitment to the study; a physician in charge of collecting and validating the data in each unit; acceptance of external control; and provision of information on staffing and equipment. Coding methods are regularly harmonized among the ICUs. Quality-assurance procedures, including a computer program operating 50 rules designed to check coherence between diagnoses and procedures, are applied to the data in each unit (35). Quality controls were performed during 2000 on 10 stays per ICU and confirmed the overall reliability of the data, as previously shown in 1996 (34). Data were extracted from 1998 (implementation of the 10th revision of the *International Classification of Diseases*) to 2010, corresponding to 237,797 admissions to the 32 ICUs (22 academics) participating in the database during the entire period. Participating centers are listed in the **Appendix 1**.

Data

Data were extracted for "septic shock" (R57.2) or "severe sepsis" (R65.0). In order to focus on septic shock, and according to the international definition, we excluded patients who did not require vasopressors (5). In order to avoid bias induced by readmissions to ICU during the same hospitalization, we only analyzed the first admission to ICU. We classified patients in two groups: with or without cirrhosis. Cirrhosis was diagnosed in patients with the following codes: alcoholic cirrhosis: "alcoholic cirrhosis of liver" (K70.3) or "other and unspecified cirrhosis of liver" (K74.6) + "chronic alcoholism" (F10.2); cirrhosis due to hepatitis B virus: "other and unspecified cirrhosis of liver" (K74.6) + "chronic viral hepatitis B with delta agent" (B18.0) or + "chronic viral hepatitis B without delta agent" (B18.1); cirrhosis due to hepatitis C virus (HCV): "other and unspecified cirrhosis of liver" (K74.6) + "chronic viral hepatitis C" (B18.2); and cirrhosis due to other diseases: "other and unspecified cirrhosis of liver" (K74.6) excluding the previous categories. Liver transplant recipients and patients with acute liver failure and alcoholic hepatitis without cirrhosis were not included. Usual demographic characteristics were collected: age, sex, comorbidities, and modified Charlson comorbidity index (excluding points for liver diseases) (36). Characteristics of the ICU stays were also collected: admission category (medical or surgical), type of admission (direct or from another ward), and length of stay in ICU (LOS-ICU) and in hospital. The severity of illness was assessed by the Simplified Acute Physiology Score (SAPS) II measured 24 hours after ICU admission (37) and organ dysfunctions (respiratory dysfunction: diagnosis, acute respiratory insufficiency [J96.0]; ARDS was defined according to the ancient 1994 American-European consensus conference (38) [J80]; renal dysfunction: diagnosis, acute renal insufficiency [N17.0, N17.1, N17.2, N17.9]; neurologic

dysfunction: diagnosis, coma [R40.2]) (39). Considering the difficult differentiation between disseminated intravascular coagulation (D65) and hemostasis disturbances related to advanced liver diseases, we decided not to collect these data. Sites of infection, pathogens, interventions (duration of vasopressors, placement and duration of mechanical ventilation or renal replacement therapy, and RBC transfusion), and outcome (in-ICU and in-hospital death) were also collected.

Analyses

Categorical variables were compared using the chi-square test, and continuous variables were measured using analysis of variance (ANOVA). Survival curves were estimated by Kaplan-Meier product-limit method. Observations were censored at time of hospital discharge. Survival distributions were compared with the log-rank test. Potential risk factors for death in the ICU and in-hospital were first studied using univariate analyses. Then variables associated with death at a p less than 0.2 level were introduced for multivariate modeling by logistic regression. More generally, each model-building process followed the same steps: univariate test of the relation with death, exploratory analysis of the form of the relationship with death for continuous variables by additive models, development of multivariate models by stepwise procedures, and test of interactions. All tests were two tailed, and p less than 0.01 was considered significant in multivariate models to take into account multiple comparisons. The changes from 1998 to 2010 for relevant variables were analyzed by ANOVA with the contrasts method and by chi-square trend test for continuous and nominal variables, respectively. The in-hospital standardized mortality ratio (SMR) was calculated (observed mortality/mortality predicted by SAPS II) (37). The volume-outcome relationship was explored using funnel plots where targets were the crude ICU and adjusted ICU mortality rates. In order to test volume effect while taking account for differences in patient's characteristics between case-volume categories, an inverse propensity weighting estimator (ipw R package) was used (40). At last, a center effect was estimated by means of intraclass correlation coefficient (ICC) obtained from multilevel mixed logistic model. Data were analyzed using SAS (SAS 9.3 Institute; Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org) statistical software in Unité de Recherche Clinique Paris-Ouest.

RESULTS

Characteristics

From 1998 to 2010, 31,251 patients with septic shock were identified and 2,383 of them (7.6%) had cirrhosis (**Fig. 1**). Demographic characteristics at the admission to ICU of patients with and without cirrhosis were compared (**Table 1**). Patients with cirrhosis were younger and had less comorbidities with the exception of HIV-related disorders. Their admission to ICU were more frequently related to medical pathology and occurred more often via transfer from other wards. The septic shock was more severe in patients with cirrhosis compared with patients without cirrhosis as evidenced by a higher SAPS II and higher prevalence of renal and neurological dysfunctions (Table 1). The higher frequency of abdominal site of infection in patients with cirrhosis was related to spontaneous bacterial peritonitis, which occurred in 212 patients (8.9%). Positive blood culture was more frequent in patients with cirrhosis. Among the identified pathogens, frequency of Gram-negative and Gram-positive bacteria was similar but patients with cirrhosis were less often infected by *Pseudomonas aeruginosa* but more by Escherichia coli and fungus (Table 1).

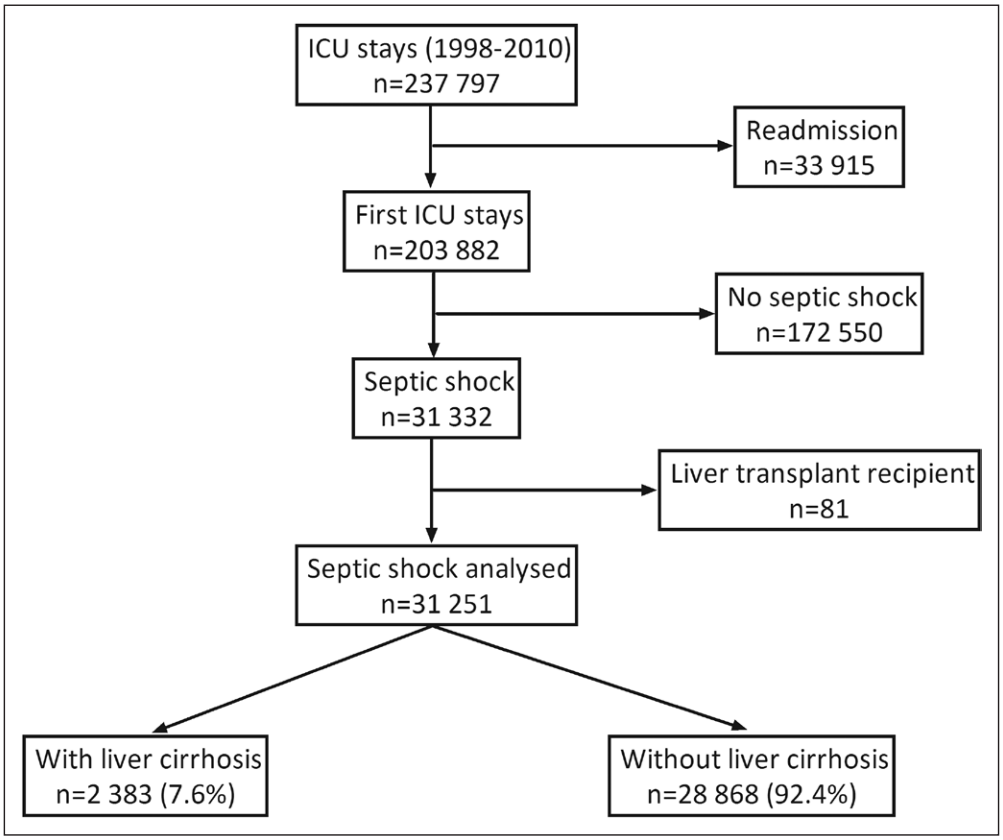

Figure 1. Flowchart.

Effect of Cirrhosis on Outcome and Interventions

Over the study period, in-ICU and in-hospital mortality was higher in patients with

TABLE 1. Demographic Characteristics of Patients With Septic Shock at the Admission to ICU

Variables	Without Cirrhosis (*n* = 28,868)	With Cirrhosis (*n* = 2,383)	*p*
Age, yr	64.1 ± 16.2	58.2 ± 12.2	< 0.0001
Sex, male	62.9%	70%	< 0.0001
Admission category, medical	77.9%	86.2%	< 0.0001
Type of admission, direct	46.1%	41.9%	< 0.0001
Length of stay in hospital before ICU, d	3.6 ± 10.5	4.5 ± 10.8	< 0.0001
Median (quartiles)	0 (0–2)	0 (0–4)	< 0.0001
Comorbidities			
HIV-related disease	3.6%	4.8%	0.002
Cancer/ hematologic malignancy	21.9%	15.5%	< 0.0001
Diabetes mellitus	9.8%	9.8%	0.98
Chronic renal failure	6.4%	6.2%	0.71
Chronic pulmonary disease	15.7%	8.6%	< 0.0001
Modified Charlson's index > 0[a]	67%	49.9%	< 0.0001
Simplified Acute Physiologic Score II	58.5 ± 22.8	63.1 ± 22.7	< 0.0001
Respiratory dysfunction	91.6%	90.9%	0.23
Acute respiratory distress syndrome according to the 1994 criteria	26.6%	26.7%	0.93
Renal dysfunction	54.8%	71.5%	< 0.0001
Neurologic dysfunction	19.5%	26.1%	< 0.0001
Site of infection			
Pulmonary	50.9%	40.3%	< 0.0001
Abdominal	7.5%	15.3%	< 0.0001
Urinary	4.2%	4.1%	0.99
Cardiovascular	4.5%	2.4%	< 0.0001
Neurologic	3.2%	1.8%	< 0.0001
Cutaneous	2.5%	1.7%	0.02
Number of site > 1	6.1%	6.4%	0.02
Positive blood culture	65.1%	75.1%	< 0.0001
Pathogen			
Gram-negative bacteria	51.7%	51.6%	0.94
Escherichia coli	15.9%	22.2%	< 0.0001
Pseudomonas aeruginosa	19.5%	13.8%	< 0.0001
Gram-positive bacteria	34.1%	37.6%	0.003
Anaerobic bacteria	0.4%	0.4%	0.89
Fungus	6.3%	9.9%	< 0.0001

[a]Charlson's comorbidities index was modified to assess comorbidities excluding points for liver disease.

Values are given as mean ± SD except stated otherwise for continuous variables and as percentage for categorical variables.

cirrhosis (70.1% and 74.5%) compared with noncirrhotic patients (48.3% and 51.7%, $p < 0.0001$ for both comparisons). Kaplan-Meier analysis of both groups' survival is reported in **Figure 2** and confirmed a higher mortality in patients with cirrhosis (log-rank test < 0.0001). Median time of survival was 19 days for patients with cirrhosis and 35 days for patients without cirrhosis ($p < 0.0001$). SMR was less than 1 in patients without cirrhosis (0.909 [0.894–0.924]), indicating an in-hospital mortality lower than predicted by SAPS II value, whereas SMR of patients with cirrhosis was higher (1.180 [1.126–1.236]), indicating a mortality higher than predicted by SAPS II value.

To reassess the weight of the association between cirrhosis and in-ICU mortality in septic shock patients, we compared characteristics of all patients according to their survival status at the ICU discharge (data not shown). Multivariate logistic regression analysis identified cirrhosis as an independent risk factor of in-ICU mortality (odds ratio [OR] = 2.524 [2.279–2.795]) (**Table 2**). Admission during the most recent midterm period (2004–2010) was associated with a decrease in mortality (OR = 0.700 [0.665–0.737]).

Interventions during the ICU stay are summarized in **Table 3**. Patients with cirrhosis had a more prolonged duration of vasopressors and a more frequent requirement of renal replacement therapy and RBC transfusion. Mechanical ventilation requirement was similar in both groups. LOS-ICU was decreased in cirrhotic patients due to higher rate of death as LOS-ICU was similar for survivors whatever the cirrhotic status. However, survivors with cirrhosis had an increased LOS in hospital (Table 3).

Characteristics Affecting In-ICU Mortality of Patients With Cirrhosis

We further compared patients with cirrhosis according to their survival status at the ICU discharge to specifically identify

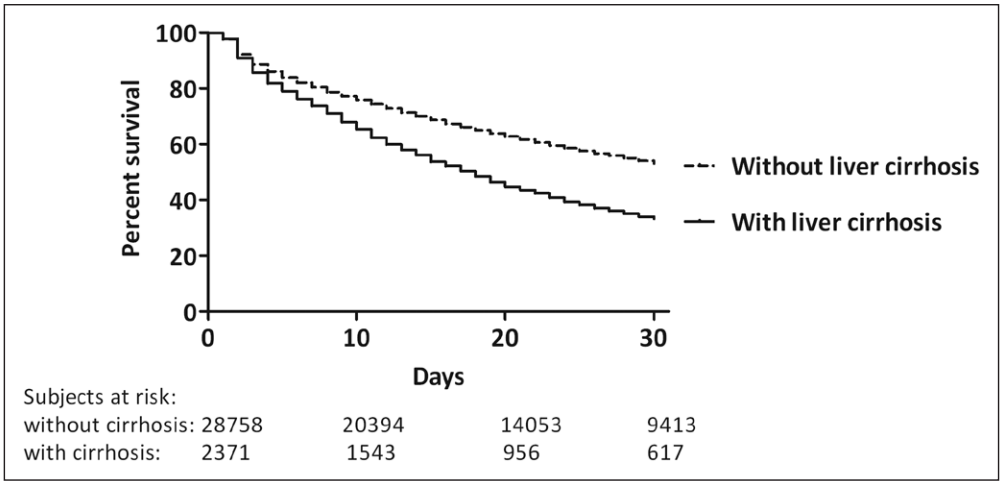

Figure 2. Kaplan-Meier analysis of the probability of survival of patients with septic shock according to the presence of an underlying cirrhosis. The mortality was higher in patients with cirrhosis (log-rank test < 0.0001). Median time to death was 19 days for patients with cirrhosis and 35 days for patients without cirrhosis ($p < 0.0001$).

prognostic factors in this population (**Table 4**). In multivariate analysis, factors independently associated with increased in-ICU mortality were as follows: admission to ICU for a medical reason, SAPS II, mechanical ventilation and renal replacement therapy requirement, septic shock due to spontaneous bacterial peritonitis, positive blood culture, or infection by fungus. Direct admission to ICU and admission during the most recent midterm period (2004–2010) were associated with a decrease in mortality (Table 4). The origin of cirrhosis (alcoholic, HCV, or autoimmune) showed no influence on the outcome.

TABLE 2. Characteristics Affecting In-ICU Mortality of All Patients With Septic Shock (Multivariate Analysis)

Variables	OR	95% CI
Age (per year)	1.013	1.011–1.015
Admission category, medical	1.562	1.465–1.666
Type of admission, direct	0.751	0.712–0.791
Cirrhosis	2.524	2.279–2.795
Modified Charlson's index > 0[a]	1.042	0.988–1.100
Simplified Acute Physiologic Score II (per point)	1.033	1.032–1.035
Mechanical ventilation	3.733	3.416–4.079
Renal replacement therapy	1.860	1.746–1.982
Site of infection		
Pulmonary	0.986	0.934–1.040
Urinary	0.444	0.387–0.510
Neurologic	1.410	1.217–1.634
Cutaneous	0.763	0.646–0.902
Positive blood culture	1.547	1.447–1.654
Pathogen		
Unknown	1.116	1.029–1.210
Fungus	1.853	1.642–2.090
Period, 2004–2010	0.700	0.665–0.737

OR = odds ratio.
[a]Charlson's comorbidities index was modified to assess comorbidities excluding points for liver disease.

Evolution of Prevalence, Severity, and In-ICU Mortality From 1998 to 2010

From 1998 to 2010, prevalence of septic shock per 1,000 admissions to ICU increased and in-ICU mortality decreased despite increasing severity as reflected by an increased SAPS II (**Fig. 3**). These evolutions were similar for patients with and without cirrhosis. Mortality in ICU and in hospital decreased from 73.8% and 77.7% in 1998 to 65.6% and 71.9% in 2010 ($p = 0.01$ and 0.04) for patients with cirrhosis and from 52.4% and 56.4% in 1998 to 42.2% and 46.6% in 2010 ($p < 0.0001$ for both) for patients without cirrhosis.

Placement under mechanical ventilation increased over the time in patients with cirrhosis (from 82.5% in 1998 to 87.7% in 2010, $p = 0.004$) similarly to patients without cirrhosis (from 84.4% in 1998 to 87.2% in 2010, $p < 0.0001$) (**Fig. e1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A947). In-ICU mortality of patients placed under mechanical ventilation decreased over the time in both groups (from 84.7% to 68.5% in patients with cirrhosis [$p = 0.004$] and from 59.4% to 46.3% in patients without cirrhosis [$p < 0.0001$]) (Fig. e1, Supplemental Digital Content 1, http://links.lww.com/CCM/A947).

Placement under renal replacement therapy decreased over the time in patients with cirrhosis (from 33% in 1998 to 20.2% in 2010, $p = 0.0002$) similarly to patients without cirrhosis (from 25.2% in 1998 to 18.5% in 2010, $p < 0.0001$) (**Fig. e2**, Supplemental Digital Content 2, http://links.lww.com/CCM/A948). In-ICU mortality of patients who received renal replacement therapy decreased over the time in both groups (from 91.2% to 78.4% in patients with cirrhosis [$p = 0.04$] and from 71.3% to 57.7% in patients without cirrhosis [$p < 0.0001$]) (Fig. e2, Supplemental Digital Content 2, http://links.lww.com/CCM/A948).

We were not able to document a relationship between volume of patients treated in ICU and outcome in cirrhotic patients. Center effect as estimated by ICC was less than 1% in multivariate multilevel analysis.

DISCUSSION

In this large multicenter study, we report that the outcome of patients with cirrhosis and septic shock has markedly improved

TABLE 3. Interventions Among Patients With Septic Shock According to the Presence of an Underlying Cirrhosis

Variables	Without Cirrhosis (*n* = 28,868)	With Cirrhosis (*n* = 2,383)	*p*
ICU length of stay, d			
All patients	9 (3–19)	8 (3–16)	< 0.0001
ICU survivors	11 (5–22)	11 (5–20)	0.618
ICU nonsurvivors	6 (2–16)	6 (2–14)	0.741
Hospital length of stay, d			
All patients	19 (8–36)	15 (6–31)	< 0.0001
Hospital survivors	26 (14–45)	32 (16–50)	0.0015
Hospital nonsurvivors	12 (4–26)	12 (5–23)	Not significant
Duration of vasopressors, d			
All patients	3 (2–7)	4 (2–9)	< 0.0001
ICU survivors	3 (2–6)	4 (2–7)	< 0.0001
ICU nonsurvivors	3 (2–8)	4 (2–9)	< 0.0001
Mechanical ventilation	86.7%	87.8%	0.11
Duration of mechanical ventilation, d			
All patients with mechanical ventilation	7 (3–16)	6 (3–14)	< 0.0001
ICU survivors	9 (5–18)	9 (4–18)	0.470
ICU nonsurvivors	5 (2–14)	5 (2–12)	0.471
Renal replacement therapy	20.5%	27.2%	< 0.0001
Duration of renal replacement therapy			
All patients with renal replacement therapy	3 (2–6)	3 (2–6)	0.07
ICU survivors	4 (2–7)	5 (2–9)	0.108
ICU nonsurvivors	3 (2–6)	3 (2–5)	0.963
RBC transfusion	6.1%	12.3%	< 0.0001

Values are given as median (quartiles) for continuous variables and as percentage for categorical variables.

in recent years. Other studies also demonstrated improved outcome of cirrhotic patients admitted to ICU (26, 29, 30), although this is the first large study focusing on septic shock. Prior studies reached 100% mortality for patients with cirrhosis and septic shock questioning the decision-making process of admitting these patients in ICU (24). Using a large database computing 192 ICUs in England, Wales, and Northern Ireland, O'Brien et al (28) recently reported more than 16,000 cirrhotic patients admitted to ICU between 1995 and 2008. Fifteen percent of them had severe sepsis during the first 24-hour admission. Despite an improved in-hospital mortality in the most recent period, the authors reported a very high mortality (> 90%) in patients with sepsis and/or more than one organ support (28). Our results confirm that cirrhosis still represent a strong prognosis factor in patients with septic shock, but the improvement over time and the in-ICU mortality rate reported in 2010 (65.6%) strongly support the admission of these patients to ICU. We observed this encouraging result despite a high level of organ support: all patients received vasopressors (according to inclusion criteria), 87.8% received mechanical ventilation, and 27.2% received renal replacement therapy. We also observed this improvement in patients placed under mechanical ventilation and/or who received renal replacement therapy. Comparison with a previous study based on the same database indicates that cirrhotic patients in septic shock currently have the same mortality rate as the entire cirrhotic and noncirrhotic population had in 1995 (7). We also found that the admission of patients with cirrhosis and septic shock increased over time, with an increasing SAPS II score, suggesting that intensivists are now less reluctant to admit these patients to ICU. This also suggests that this improvement was not related to a more restrictive admission policy.

Outside the ICU setting, the most frequent type of infection is spontaneous bacterial peritonitis (33, 41). However, in our large population of cirrhotic patients with septic shock, lung infection was the most frequent and spontaneous bacterial peritonitis represented only 8.9% of sites. This result is in

TABLE 4. Characteristics of Patients With Cirrhosis and Septic Shock According to Their Survival Status in ICU (Univariate and Multivariate Analyses)

Variables	Survivors in ICU (*n* = 712)	Nonsurvivors in ICU (*n* = 1,671)	*p* in Univariate Analysis	OR (95% CI) in Multivariate Analysis
Period, 2004–2010	63.1%	59.2%	0.076	0.715 (0.580–0.882)
Age, yr	58.2 ± 12.3	58.1 ± 12.1	NS	
Sex, male	71.9%	69.2%	0.193	
Admission category, medical	83.3%	87.4%	0.007	1.562 (1.185–2.061)
Type of admission, direct	43.5%	41.2%	NS	0.754 (0.616–0.923)
Alcoholic liver cirrhosis	65.5%	62.0%	0.110	0.948 (0.768–1.169)
Hepatitis C virus–related cirrhosis	9.8%	10.6%	0.577	
Autoimmune etiologies of cirrhosis	4.8%	5.4%	0.539	
Confusion/coma	19.4%	29%	< 0.0001	
Chronic renal disease	5.5%	6.5%	NS	
Simplified Acute Physiologic Score II	51.7 ± 16.7	67.9 ± 23.1	< 0.0001	1.034 (1.029–1.040)
Mechanical ventilation	76.1%	92.8%	< 0.0001	3.639 (2.728–4.855)
Renal replacement therapy	15%	32.4%	< 0.0001	2.347 (1.831–3.008)
RBC transfusion	7.9%	14.2%	< 0.0001	
Site of infection				
Pulmonary	44.2%	38.6%	0.010	0.801 (0.651–0.986)
Abdominal	15.2%	15.3%	NS	
Spontaneous bacterial peritonitis	7%	9.7%	0.036	1.461 (1.000–2.134)
Other abdominal sites	8.2%	5.6%	0.021	
Urinary	5.3%	3.6%	0.049	0.725 (0.449–1.171)
Cardiovascular	2.4%	2.4%	NS	
Neurologic	1.4%	2%	NS	
Cutaneous	1.8%	1.7%	NS	
Unknown	36.4%	42.7%	0.004	
Positive blood culture	67.6%	78.3%	< 0.0001	1.516 (1.152–1.994)
Pathogen				
Unknown	23.1%	17.7%	0.008	1.158 (0.823–1.628)
No. of pathogens > 1	30.5%	28.6%	0.415	
Gram-negative bacteria	51.9%	51.5%	0.832	
Gram-positive bacteria	35.7%	38.5%	0.270	
Fungus	6.8%	11.3%	0.004	1.632 (1.087–2.448)

OR = odds ratio, NS = not significant.

accordance with other studies that reported a higher frequency of lung infections in cirrhotic patients with septic shock (30, 42). Furthermore, we found that spontaneous bacterial peritonitis was the only infectious site independently associated with in-ICU mortality. Furthermore, our study confirms the higher prevalence and the increased mortality of fungal infections in patients with cirrhosis (42).

The retrospective design of this study and the constraints of the database led to some limitations. First, the severity of the liver disease was not assessed. In fact, numerous studies have demonstrated that, when patients with cirrhosis require admission to ICU, the severity of liver disease (assessed by the Child-Pugh or the model for end-stage liver disease scores) was less accurate to predict the outcome than general ICU

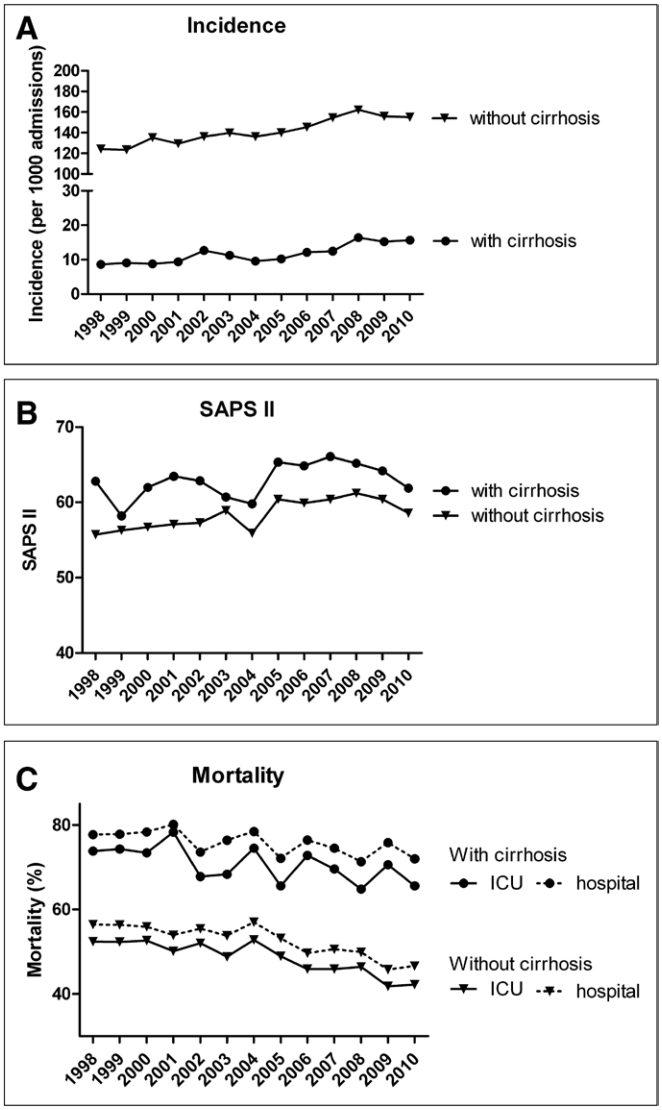

Figure 3. Evolution from 1998 to 2010 for patients with septic shock of the prevalence per 1,000 admissions in ICU (**A**), the Simplified Acute Physiologic Score (SAPS) II (**B**), and the mortality (**C**). The prevalence increased over the time for both groups ($p < 0.0001$ for patients with cirrhosis and for patients without cirrhosis). The SAPS II increased over the time for both groups ($p = 0.02$ for patients with cirrhosis and $p < 0.0001$ for patients without cirrhosis). Mortality in ICU and in hospital decreased over the time for both groups ($p = 0.01$ and 0.04 for patients with cirrhosis and $p < 0.0001$ for patients without cirrhosis).

scores such as the SAPS II or the organ failure scores such as the Sequential Organ Failure Assessment score (26, 29–31). The European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium recently defined the CLIF-SOFA score, redefining the SOFA score dedicated to patients with cirrhosis and acute liver failure (43). We could not discriminate patients who were on the waiting list for liver transplantation at the admission. Patients who are not eligible for transplantation have a worse outcome in ICU (44). Furthermore, we cannot assess the impact of the transplantation on the outcome. In order to not include liver transplant recipients admitted for septic shock, we decided to exclude them from this study. Therefore, none of the reported patients underwent liver transplantation during their ICU stay. As the database is dedicated to data collected during the ICU stays, we cannot precise if any patients underwent transplantation thereafter. Furthermore, even if sepsis-related admissions to ICU are not associated with post-ICU mortality in patients with cirrhosis (26), sepsis occurrence still a watershed in the cirrhosis history associated with a four-fold increased mortality 12 months after and could be used to sort patients on the waiting list for transplantation, which is a curative treatment of cirrhosis and justifies their admission to ICU (1).

The exact cause of this improvement also remains unclear. Despite major advances in the understanding of the septic shock pathophysiology over 4 decades, the basic elements of treatment have not changed since the 1960s (45, 46). Very few studies assessing novel therapy for septic shock have reported a decreased mortality (15, 47, 48). Most of them have been further challenged by negative trials (14, 49, 50). However, numerous large studies have reported that outcome of severe sepsis and septic shock in the general population had improved in last years (6–9, 11). It is widely believed that this recent improvement is related to better knowledge and utilization of the components of the Surviving Sepsis Campaign guidelines as bundles (5), which are also recommended in patients with cirrhosis and septic shock (32, 51). However, a small recent single-center study failed to demonstrate that implementation of recommended bundles improved outcome in patients with cirrhosis and septic shock (52). Our results suggest that cirrhotic patients with septic shock, including those placed under mechanical ventilation or receiving renal replacement therapy, have benefited from progress in septic shock and organ failures management in the general population.

CONCLUSIONS

The outcome of patients with cirrhosis and septic shock has markedly improved over the time akin to the noncirrhotic population. In 2010, the in-ICU survival rate was 35%, indicating that it is well justified to admit these patients to ICU.

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