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Determinants of the Outcome in Liver Cirrhosis Patients Admitted in Intensive Care Unit for Severe Sepsis or Septic Shock: An Unselected Cohort Study

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Keywords:

Sepsis; Septic Shock; Mortality; Outcome; Cirrhosis; Risk Factors

1. Abstract

1.1. Introduction: Determinants of mortality of patients with liver cirrhosis and septic shock are poorly known.

1.2. Methods: Multicenter observational study including all patients with liver cirrhosis admitted in ICU for severe sepsis/septic shock in 1997-2014 from the OUTCOMEREA® database. Patients with liver transplantation were excluded. Risk factors of 28-day and 90-day mortality were identified using a Cox model.

1.3. Results: 228 patients with liver cirrhosis were included. Cirrhosis was newly diagnosed in 66 patients (29%) while 91 patients (42%) were already followed by hepatologists. Lungs were the main source of infection (86, 38%). Patients were mostly transferred from Emergency department (118, 52%); only 36 (16%) from hepatology. The mortality estimated by the Kaplan-Meier method was 51% (95%CI 45-58) for the 28-day mortality and 63% (95%CI 56-70) for the 90-day mortality. Decision to forego life-sustaining therapies (DFLST) was taken for 79 patients (35%) during the ICU stay resulting in 68 (86%) ICU death. DFLST was decided 2 days [IQR:1-9] after admission. In multivariate analysis, acute and chronic organ failure, serum lactate level, and inappropriate initial antibiotic remained associated with the 28-day mortality. Relevant adverse prognostic factors were also identified: women (HR: 1.72; 95%CI:1.12-2.6, p=0.01), unknown Child-Pugh score previous ICU admission (HR: 2.28; 95%CI:1.33-5.37, p<.01), and transfer from hepatology ward (HR: 2.11, 95%CI :1.30-3.45, p<.01).

1.4. Conclusion: The prognosis of cirrhotic patients admitted to intensive care for severe sepsis/septic shock remains poor. Absence of previous medical follow-up and status worsening despite initial care in specialized area were associated with mortality, independently of female gender, severity of shock and early inadequate antimicrobial therapy.

2. Introduction

Cirrhotic patients with acute decompensation (ascites, gastrointestinal bleeding, hepatic encephalopathy or bacterial infections) frequently require to be managed in intensive care unit (ICU). Their associated morbidity and mortality is very high, mainly related to infection and infection–related complications [1]. The risk of bacterial infections, of sepsis and of sepsis-related death is increased by more than 2-fold in these patients [2], and any bacterial infection on admission is an important risk factor for in-hospital mortality [3]. The most recent studies showed an ICU mortality rate up to 70% for patients with septic shock [4]. Furthermore, ICU mortality underestimates the medium-term mortality. Thus, identifying patients eligible for intensive care appears eagerly needed [5]. However, only few studies evaluated the risks factors of death in liver cirrhosis patients with sepsis. Secondary admission from non-emergency wards, spontaneous bacterial peritonitis, positive blood culture, inappropriate initial antimicrobial therapy, timing of initial antimicrobial therapy and organ dysfunction including acute-on-chronic liver failure seemed to be the best predictors of short-term mortality [4, 6, 7]. The Child-Pugh score has also been associated with mortality; however, it was only based on data from admission, during decompensation [8]. In cirrhotic patients admitted in hospital, some characteristics of the cirrhosis and patient's lifestyle may also influence survival [9, 10]. The assessment of severity of organ failures in cirrhosis requires specific tools [11]. The Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA score) appeared as a better predictor of the in-hospital mortality than the Sequential Organ Failure Assessment (SOFA) score or the Model for End Stage Liver Disease (MELD) [12, 13]. The aim of our study was to determine risk factors of short and intermediate-term death of patients with liver cirrhosis admitted in general ICU for severe sepsis or septic shock, taking into account the severity of underlying illness, habits and sepsis characteristics.

3. Methods

All patients recorded for severe sepsis or septic shock between 1997 and 2014 in one of the 12 participating ICUs of the OUTCOMEREA® database were included. One of the centers had a specific liver transplant activity. Cirrhosis was prospectively recorded in the database by local physicians according to Knaus chronic liver disease definition [14]. Severe sepsis was defined as a systemic inflammatory response syndrome (SIRS) combined with a microbiologically proven or clinically suspected infection and a dysfunction of at least one organ. Septic shock was defined as a severe sepsis associated with acute circulatory failure requiring vasoactive support despite adequate fluid resuscitation. At least two of the following criteria were required for the diagnosis of SIRS: core temperature of 38°C or above or 36°C or less, heart rate of 90 beats/min or above, respiratory rate of 20 breaths/min or above, partial pressure of carbon dioxide (PCO2) of 32 mmHg or less or use of mechanical ventilation, and peripheral leukocyte count of 12,000/mm3 or above or of 4,000/mm3 or less. The organ failure at admission in ICU were recorded using the organ SOFA score. Patients who were admitted for liver transplantation or who had a past history of liver transplantation or readmitted in ICU for a second episode in the same period were not included in the analysis.

3.1. The Following Variables Were Prospectively Collected: date of admission, date of ICU discharge, mortality, site, pathogen involved in the initial infection and its resistance profile, age (years), sex, nutritional status, chronic heart failure, chronic kidney disease, chronic respiratory failure, immunosuppression, sodium (mmol/L), lactate (mmol/L) and Simplified Acute Physiology Score II (SAPS II). An hypoglycemic episode, use of vasopressor, invasive mechanical ventilation, renal replacement therapy, albumin infusion, corticosteroid therapy, red blood cells (RBCs) transfusion, fresh frozen plasma (FFP) infusion, decision to not forego life sustaining therapy (DFLST)(15), and any episode of bacteremia were collected during the first days of ICU stay. SAPS II, SOFA score, CLIF-SOFA score and MELD were calculated using the highest values during the first days of ICU stay. Infection occurring from 48 hours after hospital admission qualified for nosocomial. Retrospective data coming from charts review were: when missing in the prospectively collected database, the following data were sought in the patients anonymized text of the charts: etiology of cirrhosis, persistent alcohol intoxication, beta-blocker prophylaxis, quinolone prophylaxis, hepatocellular carcinoma, Child-Pugh score at previous ICU admission, whether the patient was monitored by a gastroenterologist, the marital status (married, single, divorced, widowed), the professional activity (active, unemployment, disability or retired), the admission origin (Emergency, hepatogastroenterology ward or other ward), the infection site and its pathogen. Data which remained missing were recorded as "Unreferenced". Antibiotic therapy was considered appropriate when at least one antibiotic administered within the first days of ICU stay was active in vitro against the isolated pathogen. When samples were negative, antibiotic therapy was considered appropriate when it met French national guidelines [16].

3.2. Statistical Methods: Categorical variables were described as number and percentage (%), quantitative variables as median and interquartile range [IQR]. Missing data lower than 10% were imputed to the median. A center effect and period effect was tested. Patients transferred at home or in rehabilitation without rehospitalization before Day 28 were considered alive at 28 days. A univariate Cox model censored at 28 days was used to identify the risk factor of mortality. After excluding variables that were clinically correlated, the variables statistically significant at p value of 0.20 or less in univariate analysis were used in the multivariate Cox model. The proportion-

al hazards were checked using graphical methods. The multivariate analyses were stratified by center. The variables were selected in the final model by a stepwise procedure with 0.10 threshold. As the 4 severity scores, SAPS II, SOFA, CLIF-SOFA and MELD, are highly correlated, they were tested successively in non-nested models. The model maximizing the likelihood ratio was retained. The results were given in Hazard ratio (HR) with 95% confidence interval (95%CI). In sensitivity analysis, a secondary model was conducted similarly, using the 90-day mortality. The clinical and demographic parameters associated with DFLST in ICU were compared using Chi2 or Mann Whitney test. All analyses were performed using SAS 9.4® software package.

3.3. Ethics Committee Approval and Informed Consent: According to French law on non-interventional studies, the study was approved by institutional review board and hospital ethics committee, which waived the need for informed consent of patients included in the database. The database was disclosed to the French Data Protection Authority (CNIL 1675804 v 0).

4. Results

The description of the 228 patients included in the study between 1997 and 2014 are described (Table 1). Patients were aged 61 (52-66) in median, and mostly male (71%). Interestingly, despite a definite diagnosis of liver cirrhosis, patients were followed by a gastro-enterologist before ICU admission in only 31.5% of the cases. Furthermore, the patient Child-Pugh classification was known at ICU admission for only 31.1% of the cases. At ICU admission, their median SAPS II was 56 [43-70] and median SOFA score was 11 [8-14]. Data describing sepsis and clinical and biological characteristics are presented in (Table 2), while data describing therapeutic care are presented in (Table 3). For the 47 patients (21%) who have received some Fresh Frozen Plasma at ICU admission, only two had hemorrhagic events. Initial antimicrobial therapy was based on combination therapy in 122 cases (53%). It included one aminoglycoside in 77 cases (63%) whose 51 patients (66%) were in septic shock. The main beta-lactams used were a 3rd generation cephalosporin (n=94, 41%), piperacillin-tazobactam (n=45, 20%), amoxicillin-clavulanic acid (n=45, 20%) or a carbapenem (n=2, 0.8%). Overall, 81 patients (35%) had a nosocomial infection. The initial antibiotherapy was inappropriate for 26 patients, among whom 11 did not receive any antibiotics because of a misdiagnosis of the infection in the first 24 hours. In the remaining 15 patients, the bacteria involved in the infection were (1) with 3rd or 4th generation cephalosporin use, methicillin susceptible S. aureus (n=7), Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBL-PE) (n=1), Enterococcus faecalis (n=3), and Clostridium difficile (n=1); (2) with amoxicillin-clavulanic acid use, Enterococcus faecium (n=1); and (3) for two cases, only 1st generation cephalosporin for prophylaxis of surgical infections.

The mortality estimated by the Kaplan Meier method was 51% (95%CI 45-58) for the 28-day mortality (Figure 1), and 63% (95%CI 56-70) for the 90-day mortality (Figure 1) and was significantly higher for septic shock than for severe sepsis. There was no difference in the 28-day mortality between patients admitted before or after 2008, median of admission date (p=0.70) or according to the center (p=0.98). Out of 126 patients (55%) still alive after ICU discharge, 27 (21%) died at hospital during their post-ICU stay. None received any liver transplant during the follow-up, and only one was transplanted after 18 months. For 79 patients (35%) a DFLST has been made during their ICU stay. In median, these decisions were made two days [1-9] after admission. On DFLST day, the patients had a median SOFA score of 12 [9-16], 69 (n=87%) had three or more organ failure and 55 (n=70%) were under mechanical ventilation. The clinical and demographic parameters associated with DFLST were an admission to ICU before 2008, a septic shock, the SOFA score at admission and the infection site. Details are provided in Table 2. Among these 79 patients, 68 (86%) died in the ICU and, overall, 75 (95%) died in the hospital. The other causes of in-ICU death were the initial septic shock (23, 19%), cardiac arrest (6, 5%), hemorrhagic shock (3, 2%), multiple organ failure without proven infectious cause (5, 4%), and ventilatory-acquired pneumonia (4, 3%). The multivariate analysis yielded that the 28-day mortality was better explained by the SOFA score than by the other scores (comparisons of non-nested models). The final prognostic variables retained were female gender, unknown Child-Pugh score prior to the ICU admission, chronic heart failure, chronic kidney disease, transfer from hepatology and gastroenterology ward, high serum lactate level, inappropriate initial antibiotic therapy, FFP infusion and DFLST in the first days of ICU stay (Table 4). The prognosis determinants of the 90-day mortality were similar (Table 1).

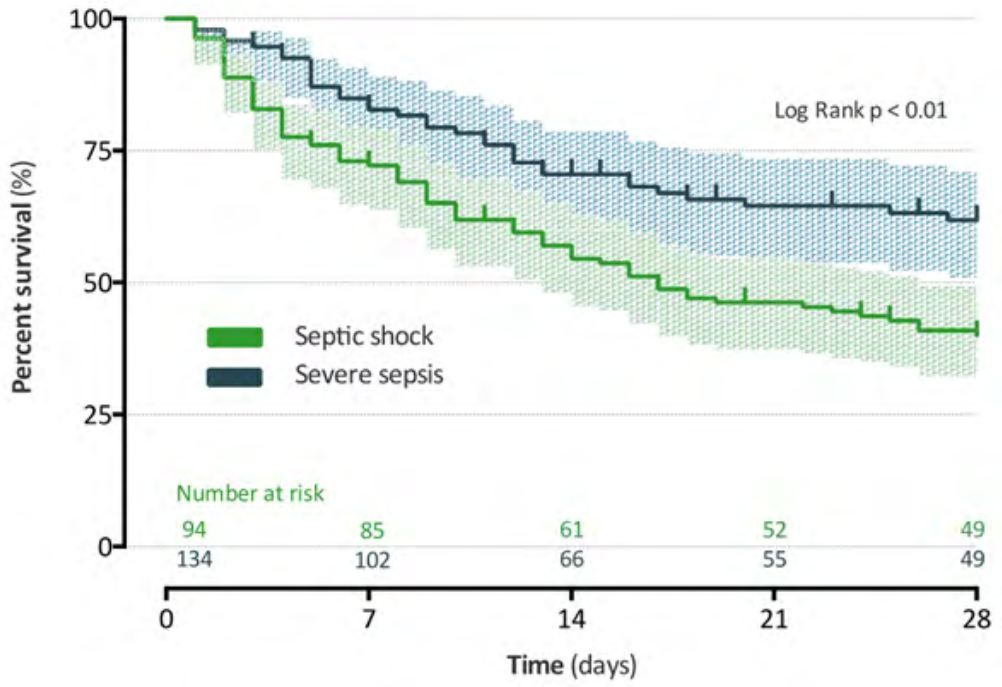

Figure 1: Probability of survival at 28 days of patients with liver cirrhosis admitted in intensive care unit for severe sepsis or septic shock. Survival probability and ± 95% confidence intervals was estimated using Kaplan-Meier methods.

Table 1: Lifestyle and chronic disease characteristics of patients at intensive care unit admission.
Definition of Abbreviations: HR, Hazard Ratio; An univariate Cox model censored at 28 days was used to determine the HR ± 95% confidence intervals and univariate p-Value;

Variable	All patients (n=228)	Survivors at 28 days (n=118)	NoN-survivors at 28 days (n=110)	HR univariate (IC 95%)	p-Value univariate
Age > 60 years	117 (51.3%)	57 (48.3%)	60 (54.5%)	0.85 (0.58-1.23)	0.39
Sex (Male)	163 (71.5%)	89 (75.4)	74 (67.3)	0.73 (0.49-1.08)	0.12
Malnutrition	41 (20.0%)	23 (19.5%)	18 (16.4%)	1.28 (0.77-2.12)	0.34
Marital status					0.71
Married	61 (26.7%)	36 (30.5%)	25 (22.7%)	1	
Single	38 (16.7%)	23 (19.5%)	15 (13.6%)	0.92 (0.48-1.74)	
Divorced	16 (7.0%)	9 (7.6%)	7 (6.4%)	1.13 (0.49-2.61)	
Widowed	12 (5.3%)	5 (4.2%)	7 (6.4%)	1.37 (0.60-3.16)	
Unreferenced	101 (44.3%)	45 (38.2%)	56 (50.9%)	1.29 (0.80-2.06)	
Professional activity					0.27
Active	15 (6.6%)	6 (5.1%)	9 (8.2%)	1	
Unemployed	31 (13.6%)	17 (14.4%)	14 (12.7%)	0.76 (0.33-1.76)	
Disability	19 (8.3%)	15 (12.7%)	4 (3.6%)	0.26 (0.08-0.86)	
Retired	54 (23.7%)	28 (23.7%)	26 (23.6%)	0.78 (0.36-1.66)	
Unreferenced	109 (47.8%)	52 (44.1%)	57 (51.8%)	0.79 (0.39-1.59)	
Followed by a gastroenterologist	90 (39.5%)	44 (37.3%)	46 (41.8%)	1.07 (0.73-1.56)	0.71
Alcoholic cirrhosis	187 (82.0%)	94 (79.7%)	93 (84.5%)	1.21 (0.72-2.04)	0.46
Current persistent alcohol intoxication	134 (58.8%)	63 (53.4%)	71 (64.5%)	1.35 (0.92-2.00)	0.13
Beta-blocker prophylaxis	42 (18.4%)	27 (22.9%)	15 (13.6%)	0.65 (0.38-1.13)	0.13
Quinolone prophylaxis	14 (6.1%)	8 (6.8%)	6 (5.5%)	0.80 (0.35-1.82)	0.59
Hepatocellular carcinoma	17 (7.5%)	12 (10.2%)	5 (4.5%)	0.49 (0.19-1.17)	0.11

Child-Pugh score					0.05
A et B	38 (16.7%)	27 (22.9%)	11 (10.0%)	1	
C	33 (14.5%)	13 (11.0%)	20 (18.2%)	2.63 (1.26-5.49)	
Unreferenced	157 (68.9%)	78 (66.1%)	79 (71.8%)	2.26 (1.20-4.26)	
Chronic heart failure	11 (4.8%)	2 (1.7%)	9 (8.2%)	2.36 (1.19-4.69)	0.01
Chronic kidney disease	8 (3.5%)	3 (2.5%)	5 (4.5%)	1.92 (0.78-4.72)	0.16
Chronic respiratory failure	26 (11.4%)	13 (11.0%)	13 (11.8%)	1.03 (0.58-1.83)	0.93
Immunosuppression	29 (12.7%)	17 (14.4%)	12 (10.9%)	0.88 (0.48-1.61)	0.68
Admission origin					0.01
Emergency	118 (51.7%)	68 (57.6%)	50 (45.5%)	1	
Hepato-gastroenterology ward	36 (15.8%)	10 (8.5%)	26 (23.6%)	1.96 (1.22-3.15)	
Other ward	74 (32.5%)	40 (33.9%)	34 (30.9%)	0.99 (0.64-1.53)	

Table 2: Sepsis and other clinical and biological characteristics within the first days of ICU stay.

Definition of abbreviations: ICU, intensive care unit; HR, Hazard Ratio, ESBL-PE, extended-spectrum β-lactamase-producing Enterobacteriaceae; MRSA, methicillin-resistant Staphylococcus aureus; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment; CLIF-SOFA: chronic liver failure - sequential organ failure assessment; MELD: model of end-stage liver disease. Bacteremia was collected within the first days of ICU stay. An univariate Cox model censored at 28 days was used to determine the HR ± 95% confidence intervals and univariate p-Value;

Variable	**All patients (n=228)**	**Survivors at 28 days (n=118)**	**NoN-survivors at 28 days (n=110)**	**HR univariate (IC 95%)**	**p-Value univariate**
Septic shock	134 (58.8%)	58 (49.1%)	76 (69.1%)	1.87 (1.25-2.80)	<.01
Sites					0.14
Lung	86 (37.7%)	51 (43.2%)	35 (31.8%)	1	
Spontaneous peritonitis and primary bloodstream	36 (15.8%)	15 (12.7)	21 (19.1)	2.06 (1.20-3.54)	
Intra-abdominal	46 (20.2%)	25 (21.2%)	21 (19.1%)	1.22 (0.71-2.10)	
Genito-urinary	20 (8.8%)	9 (7.6%)	11 (10.0%)	1.60 (0.81-3.15)	
Skin and soft tissue	23 (10.1%)	12 (10.2%)	11 (10.0%)	1.14 (0.58-2.25)	
Pathogens					0.17
Enterobacteriaceae	64 (28.1%)	27 (22.9%)	37 (33.6%)	1	
Enterococcus spp. And Streptococcus spp.	41 (17.2%)	26 (22.0%)	15 (13.6%)	0.52 (0.28-0.94)	
Staphylococcus aureus	28 (12.3%)	11 (9.3%)	17 (15.5%)	0.91 (0.51-1.61)	
Pseudomonas spp. And Acinetobacter spp.	12 (5.3%)	6 (5.1%)	6 (5.5%)	0.73 (0.31-1.72)	
Not documented	61 (26.7%)	33 (28.0%)	28 (25.5%)	0.78 (0.48-1.27)	
ESBL-PE or MRSA	6 (2.6%)	2 (1.7%)	4 (3.6%)	1.36 (0.50-3.39)	0.55
Nosocomial infection	81 (35.5%)	36 (44.4%)	45 (55.6%)	1.17 (0.80-1.71)	0.41
Bacteremia	160 (70.2%)	77 (65.3%)	83 (75.5%)	1.55 (1.01-2.40)	0.05
Hypoglycemic episode (< 3 mmol/l)	23 (10.1%)	7 (5.9%)	16 (14.5%)	2.21 (1.30-3.76)	<.01
Hyponatremia (< 135 mmol/l)	91 (39.9%)	48 (40.7%)	43 (39.1%)	1.07 (0.73-1.57)	0.73
Lactate blood level					0.05
≤ 2 mmol/l	52 (22.8%)	37 (31.4%)	43 (39.1%)	1	
2 to 4 mmol/l	90 (39.5%)	52 (44.1%)	38 (34.5%)	1.69 (0.03-3.08)	
> 4 mmol/l	86 (37.7%)	29 (24.6%)	57 (51.8%)	3.46 (1.95-6.11)	
Prognosis scoring system					
SAPS II	56 [43-70]	48 [38-59]	66 [51-82]	1.05 (1.04-1.06)	<.01
SOFA score	11 [8-14]	9 [6-12]	14 [10-17]	1.19 (1.4-1.25)	<.01
CLIF-SOFA score	12 [9-16]	10. [8-13]	15 [12-18]	1.18 (1.13-1.24)	<.01
MELD	22 [15-28]	17 [13-24]	26 [19-32]	1.07 (1.05-1.10)	<.01

Table 3: Therapeutic care within the first days of ICU stay

Definition of abbreviations: ICU, intensive care unit; HR, Hazard Ratio; DFLST, decision to not forego life sustaining therapy; RBCs, red blood cells; FFP, Fresh Frozen Plasma. An univariate Cox model censored at 28 days was used to determine the HR ± 95% confidence intervals and univariate p-Value;

Variable	All patients (n=228)	Survivors at 28 days (n=118)	No-survivors at 28 days (n=110)	HR univariate (IC 95%)	p-Value univariate
Inappropriate intial antibiotic therapy	26 (11.4%)	10 (8.5%)	16 (14.5%)	1.50 (0.88-2.56)	0.13
Corticosteroids therapy	58 (25.4%)	21 (17.8%)	37 (33.6%)	1.79 (1.21-2.67)	<.01
RBCs transfusion	59 (25.9%)	24 (20.3%)	35 (31.8%)	1.55 (1.04-2.32)	0.03
FFP infusion	47 (20.6%)	15 (12.7%)	32 (29.1%)	1.99 (1.32-3.01)	<.01
Albumine infusion	80 (35.1%)	36 (30.5%)	44 (40.0%)	1.31 (0.89-1.92)	0.17
DFLST	24 (10.5%)	4 (3.4%)	20 (18.2%)	3.95 (2.41-6.47)	<.01

Table 4: Risk factors of 28-day mortality in multivariate analysis.

Definition of abbreviations: ICU, intensive care unit; HR, Hazard Ratio; DFLST, decision to not forego life sustaining therapy; FFP, Fresh Frozen Plasma; SOFA: sequential organ failure assessment.

Variable	HR multivariate (IC 95%)	p-Value multivariate
Female gender	1.72 (IC95%:1.12-2.6)	0.01
Child-Pugh score		
A et B	1	
C	1.40 (IC95%:0.64-3.05)	0.39
Unreferenced	2.28 (IC95%:1.33-5.37)	<.01
Chronic heart failure	2.51 (IC95%:1.08-5.84)	0.03
Chronic kidney disease	4.19 (IC95%:1.44-12.17)	<.01
Transfered from of Hepatogastroenterology ward	2.11 (IC95% :1.30-3.45)	<.01
Lactate blood level		
≤ 2mmol/l	1	
2 to 4 mmol/l	1.82 (IC95% :0.96-3.45)	0.07
> 4 mmol/l	3.40 (IC95% :1.78-6.49)	<.01
Inappropriate initial antibiotic therapy	1.78 (IC95% :1.00-3.14)	0.05
FFP infusion	1.63 (IC95% :1.01-2.63)	0.05
DFLST	5.29 (IC95%:2.87-9.72)	<.01
SOFA Score	1.13 (IC95%:1.07-1.19)	<.01

5. Discussion

In a large series of cirrhotic patients with severe sepsis and septic shock admitted in 12 general ICUs in France, the estimated mortality was 51% (95%CI 45-58) after 28 days and 63% (95%CI 56-70) at 90 days out of 126 patients (55%) still alive after ICU discharge, 27 (21%) died before hospital discharge. Only one patient eventually accessed to liver transplantation. The study confirmed the overall poor prognosis of these patients. To the best of our knowledge, our study is the first series of unselected ICU patients with cirrhosis and severe sepsis where DFLST was monitored. The rate is higher than the 50% rate observed in unselected ICU population worldwide and in the Outcomerea database; however, it remains comparable to previous data in cirrhotic patients [17, 18]. Interestingly, death occurred in 95% of the cases after a DFLST. DFLST was mainly related to the severity of organ dysfunction. Yet, the number of DFLST is less important after 2008. This difference can be explained by a change in the medical practices. Indeed, most recent studies have shown that the use of intensive support in cirrhotic patients was not systematically futile. They called for an unrestricted ICU admission, to get enough time to build a therapeutic project based on known previous consultation, actual situation, and organ failures evolution, and a follow-up after a few days with potential revision of treatments in case of persistent high degree of organ dysfunction [3, 19-21]. Indeed, Gusto et al, in a gastro-enterological ICU, reported high survival rates (95% at day 28 and 81% at 6 months) in 21 cirrhotic patients with 2 to 3 organ failures and who underwent urgent liver transplant in a median time of 11 days after ICU admission [22].

Our study also confirmed that the intensity of organ failures and the inadequacy of the initial antimicrobial therapy were both strongly associated with an increased risk of death. New relevant adverse prognostic factors were also identified. First, the absence of known Child-Pugh status was an independent risk factor of death. It may reflect the absence of follow-up of the chronic liver failure. Second, on the opposite, the worsening of patient status during a stay in a

specialized ward before ICU stay is associated with a poor prognosis. This information is similar to the results of Weil et al. They yielded a lower mortality rate for cirrhotic patients admitted to non-specialized ICUs compared to those dedicated to hepatic failure [23]. Indeed, post-hoc analysis of our data showed that these patients were more frequently from the only center with liver transplant activity, with patients who were significantly younger, more severely ill and with a previously more severe chronic hepatic failure, as demonstrated by significantly higher Child-Pugh and MELD scores. They were likely eligible to liver transplant. This negative impact of a previous stay in a gastroenterology unit before ICU admission should encourage an early ICU admission and to a better collaboration with gastroenterologists, with an active screening of survivors accessible to liver transplant, even in septic patients.

Female gender was also identified as a risk factor of death. A similar association was previously reported in two large cohorts of cirrhotic patients suffering from septic shock, but only in univariate analysis [6, 24]. In the general population, women have a better prognosis for septic shock compared to men [25], while for patients with acute alcoholic hepatitis, the poorer prognosis of female patients is shown [26]. Several factors likely contribute to the severity of alcoholic liver disease in women. Experiments in rats suggest that higher endotoxin levels and increased gut permeability to endotoxin likely contribute to more severe liver injury in females, mainly due to estrogen receptor concentrations [27]. A gender disparity was also identified on the risk of hospitalization and mortality in liver transplant waitlist [28, 29]. The reasons for these disparities are not fully understood. This higher mortality could be attributed to the MELD score for graft allocation. In our study there were no differences in terms of causes of liver failure, alcohol abuse or acute hepatitis, or chronic comorbidities that would explain this association.

We found that the risk of infection related to ESBL-E and/or methicillin resistant S. aureus was low, in accordance with one study [6]. Another study recently suggested higher rates in this population of patients exposed to fluoroquinolones or 3rd generation cephalosporins [30]. In a recently published study conducted by Fernandez in 507 cirrhotic patients admitted for infection, among the subset of 117 (23%) patients with septic shock, the rate of infections due to ESBL-PE or MRSA was 44 (8.5%) and 14 (2,8%), respectively [31]. In these patients, prophylaxis with fluoroquinolones or treatment with 3rd generation cephalosporin within the last 3 months, and multidrug-resistant bacteria infection within the previous 6 months were identified as risk factors for infection with multidrug resistant bacteria. Thus, in high ESBL-PE prevalence countries, Fernandez recommended to use carbapenem agents as first line therapy for cirrhotic patients with septic shock [32]. In our study, only 14 patients (6%) had recent history of fluoroquinolone prophylaxis and 62 (27%) had a previous hospital stay within the last 6 months. Thus, the selection of the appropriate antibiotics for probabilistic prescription remains a major issue for these patients with septic shock; it must be based on local epidemiology and risk factors for multidrug resistant pathogens.

Indeed, as previously reported, inadequate antibiotherapy was one of the main risk factors for death in these patients. In the study published by Arabi and colleagues, with similar resistance rates, 24% of the patients had initially inappropriate antibiotherapy compared to 11% in our study [6]. When antibiotic therapy was inadequate, the bacteria was more frequently methicillin susceptible S. aureus. These data confirmed that Gram positive bacteria usually account for a significant number of infections in these cirrhotic patients, possibility related to the increased rate of invasive procedures they underwent [33]. Thus, empirical antibiotherapy should cover Gram positive pathogens, especially S. aureus when skin and soft tissue infection might be the source of sepsis [34]. Our study suffered some limitations. One is the retrospective chart review of the medical history prior to ICU admission. Thus, the collection of data on chronic liver disease and Child Pugh score evaluation may be biased. This lack of data limits the interpretation of the Child score. Nevertheless, these data are in accordance with the low number of patients previously admitted to hepatologic ward or consult. This population probably included patients with severe chronic hepatic failure but not monitored, and patients with a first episode of decompensation of a moderate cirrhosis.. Our cohort may seem smaller than that of previous studies analyzing very large databases; however, our data are more detailed on chronic disease, life habits and ICU care.

6. Conclusion

In conclusion, the prognosis of cirrhotic patients admitted to intensive care for severe sepsis or septic shock remains poor, with a 28-day mortality rate of 51% and a 90-day mortality rate of 63%. Admission criteria are different between ICUs dedicated to liver failure compared to those not specialized. The negative impact of previous stay in a gastroenterology unit before ICU admission should encourage an early ICU admission in case of sepsis and shock to reliably assess the actual prognosis and to evaluate liver transplant feasibility.

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