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Impact of chronic liver disease in intensive care unit acquired pneumonia: a prospective study

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Abstract *Purpose:* To assess the impact of chronic liver disease (CLD) on ICU-acquired pneumonia. *Methods:* This was a prospective, observational study of the characteristics, microbiology, and outcomes of 343 consecutive patients with ICU-acquired pneumonia clustered according to the presence of CLD. *Results:* Sixty-seven (20 %) patients had CLD (67 % had liver cirrhosis, LC), MELD score 26 ± 9, 20 % Child–Pugh class C). They presented higher severity scores than patients without CLD both on admission to the ICU (APACHE II, LC 19 ± 6 vs. other CLD 18 ± 6 vs. no CLD 16 ± 6; $p < 0.001$; SOFA, 10 ± 3 vs. 8 ± 4 vs. 7 ± 3; $p < 0.001$) and at onset of pneumonia (APACHE II, 19 ± 6 vs. 17 ± 6 vs. 16 ± 5; $p = 0.001$; SOFA, 11 ± 4 vs. 9 ± 4 vs. 7 ± 3; $p < 0.001$). Levels of CRP were lower in patients with LC than in the other two groups (day 1, 6.5 [2.5–11.5] vs. 13 [6–23] vs. 15.5 [8–24], $p < 0.001$, day 3, 6 [3–12] vs. 16 [9–21] vs. 11 [5–20], $p = 0.001$); all the other biomarkers were higher in LC and other CLD patients. LC patients had higher 28- and 90-day mortality (63 vs. 28 %, $p < 0.001$; 72 vs. 38 %, $p < 0.001$, respectively) than non-CLD patients. Presence of LC was independently associated with decreased 28- and 90-day survival (95 % confidence interval [CI], 1.982–17.250; $p = 0.001$; 95 % confidence interval [CI], 2.915–20.699, $p = 0.001$, respectively). *Conclusions:* In critically ill patients with ICU-acquired pneumonia, CLD is associated with a more severe clinical presentation and poor clinical outcomes. Moreover, LC is independently associated with 28- and 90-day mortality. The results of this study are important for future trials focused on mortality.

Keywords Intensive care unit · Lung · Ventilator-acquired pneumonia · Liver cirrhosis · Nosocomial infection · Biomarkers

Introduction

Intensive care unit acquired pneumonia (ICUAP), including ventilator-associated pneumonia (VAP) and non-ventilator ICU-acquired pneumonia (NV-ICUAP), is the leading infection in critically ill patients and a major cause of morbidity and mortality [1–3], despite recent major advances in antimicrobial therapy, supportive care, and the use of a broad range of preventive measures [1, 4, 5]. Several co-factors play a role in the poor outcome of these patients: severity of illness, pre-existing conditions, and host response to infection [5, 6].

Infections in patients with chronic liver disease (CLD) are common [7] and major causes of morbidity and mortality [8, 9]. The high risk of infections in this population is due to abnormalities in natural defense mechanisms, as acquired and progressive defects of the innate immune and reticuloendothelial system, aggravated by alcohol consumption; alterations in the enteric flora; genetic predisposition; intrinsic cellular defects and the increasing use of invasive procedures [10–13]. Common bacterial infections in CLD patients include spontaneous bacterial peritonitis, urinary tract infections, pneumonia, dermatologic infections, and bacteremia associated with invasive procedures [10–13]. Bacterial infections in advanced cirrhosis carry a poor prognosis, mainly due to the increasing prevalence of multidrug-resistant pathogens (MDR), especially extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* [14]. Surprisingly, the American Thoracic Society (ATS) guidelines for the management of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia did not identify CLD as a risk factor for low respiratory tract infections (LRTI) or MDR pathogens [1].

To the best of our knowledge, few studies have evaluated the characteristics of hospital-acquired respiratory infections in the subgroup of CLD patients. Nevertheless, no studies have comprehensively assessed ICUAP in this population.

We hypothesized that CLD was an independent factor associated with poorer mortality in ICUAP. The main aim of this study was to compare ICUAP patients with and without CLD to investigate clinical outcomes. Secondary aims were the microbial etiology and the inflammatory systemic response of CLD patients with ICUAP.

Materials and methods

Study population

The study was conducted in six medical and surgical ICUs in an 800-bed university hospital in Barcelona. Data were collected prospectively from January 2007 to December 2011. The investigators made daily rounds in the different ICUs. Inclusion criteria were patients older than 18 years, clinical suspicion of pneumonia acquired after 48 h of ICU admission, written informed consent from patient or their next of kin. The only exclusion criterion was severe immunosuppression [15] (neutropenia after chemotherapy or hematopoietic transplant, drug-induced immunosuppression in solid-organ transplant or cytotoxic therapy, and HIV-related disorders). Patients were enrolled consecutively and only the first episode was analyzed. The study was reviewed and approved by the institution's internal review board.

Definition of pneumonia, microbiologic processing, and antimicrobial treatment

Clinical suspicion of pneumonia was based on either (a) clinical criteria (new or progressive radiological pulmonary infiltrate together with at least two of the following: temperature >38 or <36 °C, leukocytosis >12,000/mm^3 or leucopenia <4,000/mm^3, purulent respiratory secretions) [16]; or (b) a simplified clinical pulmonary infectious score (CPIS) ≥6 points [17]. Early-onset pneumonia was defined as occurring within the first 4 days of admission [1].

The microbiologic evaluation, initial empiric antimicrobial treatment, and response to treatment in this population were addressed in a previous study [3]. Polymicrobial pneumonia was defined when more than one potentially pathogenic microorganism (PPM) was identified as causative agent.

Multidrug-resistant pathogens included methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* resistant to beta-lactams, carbapenems, and fluoroquinolones, other MDR non-fermenting gram-negative bacilli (*Stenotrophomonas maltophilia* or *Acinetobacter baumannii* resistant to beta-lactams, aminoglycosides, fluoroquinolones, and carbapenems), and *Enterobacteriaceae* producing extended-spectrum beta-lactamase (ESBL) (resistant to third generation cephalosporins, beta-lactams, and aztreonam) [18].

VAP was considered in patients with previous invasive mechanical ventilation for 48 h or more. Patients were classified as VAP or non-ventilator ICUAP [3].

Definition of chronic liver disease

CLD patients included those with liver cirrhosis, chronic viral hepatitis, alcoholic hepatitis, or non-alcoholic steatohepatitis. Child–Pugh and model for end-stage liver disease (MELD) scores were calculated. We divided the study population into three groups: patients with liver cirrhosis, patients with CLD without cirrhosis, and patients without CLD.

Definition and evaluation of severity scores

We calculated the acute physiology and chronic health evaluation (APACHE)-II [19] and the new simplified acute physiology score (SAPS)-II [20] scores on admission to the ICU and at the onset of pneumonia. The CPIS [17] and the sequential organ failure assessment (SOFA) [21] scores were evaluated on admission to ICU and for the first 9 days after the onset of pneumonia. Septic shock [22] and acute respiratory distress syndrome (ARDS) [23] were defined according to the previously described criteria.

Assessment of systemic inflammatory response

We determined the serum levels of cytokines and other biomarkers within the first 24 h and on the third day after the diagnosis of ICUAP. Mid-regional pro-adrenomedullin (MR-proADM) measurements were performed using a test based on the time-resolved amplified cryptate emission (TRACE) technology (MR-proANP KRYPTOR; BRAHMS AG; Hennigsdorf, Germany). Procalcitonin (PCT) was measured by using TRACE technology (PCT sensitive KRYPTOR; BRAHMS AG). The analytical detection limit and the functional assay sensitivity were as follows: procalcitonin, 0.02 ng/mL, 0.06 ng/mL; proADM, 0.05 nmol/L, 0.25 nmol/L, respectively. C-reactive protein (CRP), interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor alpha (TNF-α) were measured as described elsewhere [24].

Data collection

All relevant data were collected on admission and at the onset of pneumonia from the medical records and bedside flow charts. Patients were followed until death or up to 90 days after the diagnosis of pneumonia.

Outcome measures

The primary outcome was 28-day survival after diagnosis of ICUAP. Secondary outcomes included microbiologic patterns, ICU, in-hospital, and 90-day mortality, length of mechanical ventilation, ventilator-free days (defined as the number of days with no mechanical ventilation between day 1—orotracheal intubation and mechanical ventilation—and day 28), length of ICU and hospital stay, the need for intubation for NV-ICUAP patients, occurrence of septic shock [22], and non-response to treatment [25].

Statistical analysis

All numerical data are reported as mean ± standard deviation (SD), whereas categorical data are reported as percentages. Categorical variables were compared with chi-squared or Fisher exact tests. Quantitative continuous variables were compared using the unpaired *t* test or the Kruskal–Wallis test, based on the normality tests. One-way repeated measures analysis of variance (ANOVA) was used to compare groups of patients.

The predictive value of 28- and 90-day survival of each variable collected in this study was analyzed by using univariate regression logistic analysis, a p value ≤ 0.10 was considered significant. A correlation was then performed to exclude the presence of interactions and co-linearity: the variables with an index (R) ≥ 0.30 were evaluated and filtered. A multivariate model was obtained using a Cox regression backward stepwise analysis to identify independent predictors of survival, using an entry level of ≤ 0.05 and a removal level of ≥ 0.10. Hazard ratios and adjusted analyses were then obtained. In patients with or without CLD a log-rank test with death rates and time to events (survival at 28 and 90 days) were analyzed by using the Kaplan–Meier method. A two-sided p value ≤ 0.05 was considered statistically significant.

Results

Patients characteristics

We prospectively analyzed 343 consecutive patients that met ICUAP criteria, the majority of them recruited in the respiratory ICU (94 patients) and in the hepatic ICU (82 patients). Sixty-seven (20 %) patients had CLD and 46 (67 %) of these had liver cirrhosis (LC). Among cirrhotic patients, MELD score was 26 ± 9, and 20 % were in Child–Pugh class C. Half of the patients with LC had VAP (50 %, $n = 23$); whereas, among patients with other CLD, 11 patients had VAP (52 %) and 10 had NV-ICUAP (48 %). In the group without CLD, 174 (63 %) had VAP and 102 (37 %) had NV-ICUAP. Early nosocomial pneumonia developed in 27 (59 %) patients with LC, in 15 (71 %) patients with other CLD, and 72 (26 %) patients without CLD; whereas, late-onset pneumonia developed in 19 (41 %) LC, in 6 (29 %) patients with other CLD, and 204 (74 %) without CLD patients.

The characteristics of patients at ICU admission and at onset of pneumonia are shown in Table 1. Patients with LC had a lower incidence of cardiac diseases, and those with LC and other CLD had a higher incidence of previous alcohol abuse than those without CLD. Patients with LC were the most severely affected patients; other CLD patients were more severe than non-CLD patients both on admission to ICU and at onset of pneumonia (higher APACHE II and SOFA scores).

Table 1 Baseline characteristics and outcomes of patients on admission to intensive care unit and at onset of pneumonia according to presence or absence of liver cirrhosis and other chronic liver disease ($n = 343$)

	Patients with liver cirrhosis ($n = 46$)	Patients with chronic liver disease ($n = 21$)	Patients without chronic liver disease ($n = 276$)	p
Age, years, mean ± SD	58 ± 9	62 ± 12	64 ± 15	0.181
Gender, male/female	31/15	14/7	191/85	0.900
Co-morbid conditions, *n* (%)				
Diabetes mellitus, *n* (%)	11 (24)	8 (40)	57 (21)	0.138
Chronic renal failure, *n* (%)	4 (9)	3 (15)	23 (8)	0.592
Chronic lung disease, *n* (%)	10 (22)	5 (25)	94 (34)	0.188
Chronic heart disorders, *n* (%)	6 (13)	7 (33)	95 (34)	**0.015**
Solid cancer, *n* (%)	4 (9)	4 (19)	50 (18)	0.272
Alcohol abuse (current or former), *n* (%)	29 (63)	12 (60)	45 (16)	**<0.001**
Corticosteroids previous to ICU admission, *n* (%)	8 (19)	4 (20)	33 (13)	0.450
ICU stay before NP days, median (IQR)	4 (2–7)	2.5 (0–6)	4 (2–9)	**0.055**
APACHE II score on admission, mean ± SD	19 ± 6	18 ± 6	16 ± 6	**<0.001**[b]
SOFA score on admission, mean ± SD	10 ± 3	8 ± 4	7 ± 3	**<0.001**[c]
Type of pneumonia, *n* (%)				0.144
VAP	23 (50)	11 (52)	174 (63)	
NV-ICUAP	23 (50)	10 (48)	102 (37)	
Intubation due to pneumonia, *n* (%)[a]	14 (61)	9 (90)	66 (65)	0.086
Hospital stay before pneumonia, days, median (IQR)	8 (5–16)	8 (5–16)	8 (4–15)	0.914
Mechanical ventilation (MV) before VAP, days, median (IQR)	5 (4–7)	5 (4–7)	5 (3–10)	0.243
Early-onset ICUAP, *n* (%)	27 (59)	15 (71)	72 (26)	0.087
Late-onset ICUAP, *n* (%)	19 (41)	6 (29)	204 (74)	0.261
Previous use of antibiotics, *n* (%)	41 (89)	13 (65)	205 (74)	**0.049**
Corticosteroids at diagnosis of ICUAP, *n* (%)	19 (41)	7 (35)	112 (41)	0.881
Bilateral radiological involvement, *n* (%)	19 (41)	8 (40)	74 (27)	0.090
APACHE II score at onset of pneumonia, mean ± SD	19 ± 6	17 ± 6	16 ± 5	**0.001**[b]
Septic shock at onset of pneumonia, *n* (%)	26 (56)	10 (50)	125 (45)	0.381
PaO_2/FiO_2 mmHg at onset of pneumonia, mean ± SD	186 ± 81	188 ± 81	190 ± 78	0.918
CPIS score, mean ± SD	6.7 ± 1.6	6.7 ± 1.6	6.7 ± 1.4	0.889
SOFA score at onset of pneumonia, mean ± SD	11 ± 4	9 ± 4	7 ± 3	**<0.001**[c]
ICU mortality, *n* (%)	18 (39)	5 (25)	88 (32)	0.472
Mortality at day 28, *n* (%)	29 (63)	8 (40)	78 (28)	**<0.001**
Mortality at day 90, *n* (%)	33 (72)	8 (40)	105 (38)	**<0.001**
In-hospital mortality, *n* (%)	32 (70)	8 (40)	98 (36)	**<0.001**
Initial adequate treatment, *n* (%)	21 (75)	7 (87)	157 (88)	0.195
Treatment failure, *n* (%)	35 (76)	12 (60)	141 (51)	**0.007**
Development of septic shock or multiple organ failure, *n* (%)	27 (59)	7 (35)	95 (34)	**0.008**
Ventilator-free days at day 28, median (IQR)	0 (0–13)	13 (0–25)	15 (0–24)	**0.003**
Length of ICU stay, days, median (IQR)				
Among total population	10 (7–22)	10 (8–25)	16 (10–29)	**0.020**
Among survivors	10 (6–25)	10 (6–20)	19 (11–33)	0.087
Length of hospital stay, days, median (IQR)				
Among total population	21 (12–47)	25 (13–51)	39 (20–59)	**0.001**
Among survivors	39 (14–58)	32 (14–52)	45 (25–71)	0.236

Bold values represent statistically significant ($p < 0.05$)

ICU intensive care unit, *IQR* interquartile range, *APACHE* acute physiology and chronic health evaluation, *SOFA* sepsis-related organ failure, *VAP* ventilator-associated pneumonia, *NV-ICUAP* non-ventilator intensive care unit acquired pneumonia, *CPIS* clinical pulmonary infection score

[a] Need for intubation and MV at the onset of pneumonia

[b] Between liver cirrhosis and no chronic liver disease

[c] Between liver cirrhosis and no chronic liver disease and between other chronic liver disease and no chronic liver disease

Microbiological findings

Etiology was determined in 217 (63 %) patients, with no differences in the number of microbiologically confirmed ICUAP between groups. The most frequently isolated pathogens were *Pseudomonas aeruginosa, Enterobacteriaceae*, methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus*, with no significant differences between groups. The incidence of MDR pathogens was similar among groups (Table 2).

Table 2 Etiologic diagnosis of pneumonia

	Patients with liver cirrhosis ($n = 46$)	Patients with chronic liver disease ($n = 21$)	Patients without chronic liver disease ($n = 276$)	p
Etiologic diagnosis, *n* (%)	29 (63)	8 (40)	179 (65)	0.077
Polymicrobial pneumonia, *n* (%)	3 (7)	2 (10)	25 (14)	0.837
P. aeruginosa, n (%)	4 (14)	3 (15)	56 (31)	0.142
Enteric gram-negative bacilli, *n* (%)	10 (34)	1 (5)	54 (30)	0.244
Methicillin-resistant *S. aureus* (*MRSA*), *n* (%)	3 (10)	0 (0)	15 (8)	0.529
Methicillin-sensitive *S. aureus* (*MSSA*), *n* (%)	4 (14)	5 (25)	32 (18)	0.155
Streptococcus pneumoniae, n (%)	2 (7)	0 (0)	9 (5)	0.627
Haemophilus influenziae, n (%)	1 (3)	1 (12)	6 (3)	0.655
Moraxella catharralis, n (%)	1 (3)	0 (0)	2 (1)	0.477
Fungi[a], *n* (%)	1 (3)	0 (0)	7 (4)	0.690
MDR[a] pathogens, *n* (%)	9 (31)	2 (10)	46 (26)	0.634

MDR multidrug-resistant pathogens
[a] Included *Aspergillus* spp., *Candida* spp.

Table 3 Panel of inflammatory response markers

	Patients with liver cirrhosis ($n = 46$)	Patients with chronic liver disease ($n = 21$)	Patients without chronic liver disease ($n = 276$)	p
CRP at day 1, mg/dL ($n = 322$)	6.5 (2.5–11.5)	13 (6–23)	15.5 (8–24)	**<0.001**
CRP at day 3, mg/dL ($n = 301$)	6 (3–12)	16 (9–21)	11 (5–20)	**0.001**
Procalcitonin at day 1, ng/mL ($n = 205$)	1.2 (0.5–1.6)	0.4 (0.2–0.8)	0.32 (0.1–1.4)	**0.003**
Procalcitonin at day 3, ng/mL ($n = 174$)	0.7 (0.3–1.5)	0.3 (0.1–0.9)	0.26 (0.1–0.8)	**0.022**
MR-proADM at day 1, nmol/L ($n = 205$)	2 (1–4)	2 (1–6)	1.1 (0.33–2)	**0.001**
MR-proADM at day 3, nmol/L ($n = 175$)	2 (0.3–4.5)	3 (0.7–8)	1.1 (0.5–1.9)	**0.043**
IL-6 at day 1, pg/mL ($n = 181$)	192 (132–400)	245 (84–334)	106 (36–240)	**0.008**
IL-6 at day 3, pg/mL ($n = 168$)	114 (55–209)	87 (14–364)	72 (18–170)	0.243
IL-8 at day 1, pg/mL ($n = 191$)	164 (77–357)	167 (108–289)	79 (52–134)	**<0.001**
IL-8 at day 3, pg/mL ($n = 171$)	137 (51–253)	85 (49–288)	71 (40–126)	**0.019**
TNF-α, at day 1, pg/mL ($n = 200$)	14 (9–20)	10 (9–22)	7 (5–13)	**<0.001**
TNF- α at day 3, pg/mL ($n = 171$)	10 (6–15)	11 (5–14)	7 (5–12)	0.125
IL-10 at day 1, pg/ml ($n = 37$)	11 (3–17)	2 (1–16)	1.1 (0–2.9)	0.054
IL-10 at day 3, pg/ml ($n = 44$)	3 (0.5–12)	5 (1–8)	0.9 (0–3.1)	0.112

Bold values represent statistically significant ($p < 0.05$)
Values presented as median (interquartile range, IQR)
CRP C-reactive protein, *MR-proADM* mid-regional pro-adrenomedullin, *IL* Interleukin, *TNF-α* tumor necrosis factor alpha

Causative pathogens and rates of MDR were similar in patients with early- or late-onset ICUAP. A causative agent was more frequently isolated in VAP than in NV-ICUAP, although the isolated pathogens were similar.

Inflammatory biomarkers

At onset of pneumonia, procalcitonin, MR-proADM, IL-6, IL-8, and TNF-α were higher in the LC and other CLD groups. Levels of these biomarkers remained similar on day 3. Data are shown in Table 3. Levels of CRP were lower in patients with LC both at onset of pneumonia (6.5 [2.5–11.5] vs. 13.5 [7–23], $p = 0.012$) and at day 3 (6 [3–12], vs. 15 [8–20], $p = 0.002$) in comparison to the other two groups. Correlation analysis between levels of CRP and IL-6 on day 1 showed a lack of correlation ($p = 0.404$) in patients with LC but a significant correlation in those without CLD ($p = 0.001$).

Outcomes

Following the onset of pneumonia, treatment failure was higher in LC and other CLD patients, whereas development of septic shock was more frequently observed in patients with LC. Initial adequate treatment rates were similar between groups (Table 1).

ICU and hospital stay were shorter in patients with LC and other CLD. However, these differences disappeared when only hospital survivors were analyzed. In addition, LC patients had higher in-hospital, 28-day and 90-day mortality and lower ventilator-free days (VFDs) at day 28; other CLD patients had higher 28-day mortality than non-CLD patients.

Univariate analyses of 28-day mortality showed that presence of CLD, particularly of LC ($p = 0.001$), alcohol abuse ($p = 0.014$), chronic lung disease ($p = 0.026$), or chronic heart disorders ($p = 0.009$), high APACHE-II ($p = 0.023$) score, corticosteroid therapy ($p = 0.042$), or occurrence of septic shock ($p = 0.0175$) at the onset of

Table 4 Stepwise cox multivariate regression model to identify independent predictors of survival at day 28

Variable	β	HR	95 % CI	SE	*p*
Septic shock at the onset of pneumonia	2.233	9.657	1.345–3.705	0.258	**0.002**
Liver cirrhosis	1.813	11.597	1.813–9.096	0.411	**0.001**
Other chronic liver diseases	1.325	0.280	0.467–3.755	0.532	0.597
Chronic lung disease	2.307	9.614	1.360–3.914	0.270	**0.002**
Variable	β†	HR†	95 % CI†	SE†	*p*†
Septic shock at the onset of pneumonia	2.621	5.652	1.184–5.802	0.405	**0.017**
Liver cirrhosis	5.847	10.236	1.982–17.250	0.552	**0.001**
Other chronic liver diseases	1.282	0.136	0.343–4.790	0.673	0.712

Bold values represent statistically significant ($p < 0.05$)
Stepwise model: entry level with $p < 0.05$ and removal level with $p > 0.10$
† Adjusted for age, sex, Apache II, SAPS II, SOFA

pneumonia, high MR-proADM ($p = 0.002$), IL-6 ($p = 0.007$), and TNF ($p = 0.004$) were associated with lower 28-day survival. Multivariate analysis identified LC (but not other CLD), chronic lung disease, and septic shock at onset of pneumonia as independent predictors of 28-day survival (Table 4). After adjusting for age, sex, rate of initial adequate treatment, APACHE II, SAPS II, and SOFA score, LC remained significantly associated with mortality (Table 4).

Univariate analyses of 90-day mortality showed that presence of CLD, particularly of LC ($p = 0.001$), chronic lung disease ($p = 0.001$), high APACHE-II ($p = 0.002$), and SAPS II ($p = 0.049$) scores or occurrence of septic shock ($p = 0.017$) at the onset of pneumonia, high MR-proADM ($p = 0.007$), procalcitonin ($p = 0.055$), TNF ($p = 0.012$), and IL-8 ($p = 0.091$) were associated with lower 90-day survival. Multivariate analysis identified LC (CI 2.915–20.699, $p = 0.001$) [but not other CLD (CI 0.285–3.425, $p = 0.984$)], chronic lung disease (CI 1.511–5.354, $p = 0.001$), and septic shock at onset of pneumonia (CI 1.472–5.134, $p = 0.001$) as independent predictors of 90-day survival. After adjusting for age, sex, rate of initial adequate treatment, APACHE II, SAPS II, and SOFA score, LC remained significantly associated with mortality ($p = 0.005$, CI 1.593–13.361).

Figure 1 shows survival curves for patients with LC, other CLD, and without CLD. Survival at 28 days was significantly lower in the group with LC. The figure in the Supplementary Material indicates that differences were only associated with the presence of CLD and not with the type of pneumonia (VAP vs. NV-ICUAP). Also survival at 90 days was significantly lower in patients with LC (Log rank = 31.00, $p < 0.001$, data not shown) and associated with the presence of CLD and not with the type of pneumonia (Log rank = 36.48, $p < 0.001$, data not shown).

Discussion

The main findings of this study were that LC was an independent predictor of 28- and 90-day survival in patients with VAP or NV-ICUAP. Microorganisms causing VAP and ICUAP were similar among the three groups. Finally, systemic levels of CRP but not other biomarkers were lower in ICUAP patients with LC.

In the studied population 20 % of patients presented CLD. Most of them had liver cirrhosis, which occasionally was severe enough to be considered an end-stage disease, a condition known to favor infection [26]. As expected [27, 28], patients with CLD had a more severe clinical presentation upon ICU admission, shown by higher APACHE II [19] and SOFA scores [21]. Higher severity of CLD patients was also observed at the onset of pneumonia. These findings agreed with previous studies on other types of infections [14, 29].

The etiology of ICUAP was determined in more than half of the patients [1]. Consistent with previous studies, the most frequently isolated pathogens were *P. aeruginosa, Enterobacteriaceae*, MSSA, and MRSA, with no significant differences between groups [30, 31]. Also the rate of MDR pathogens was not different.

Our microbiology findings concur with previous studies in cirrhotic patients with community- and hospital-acquired infections. Fernandez et al. [29] found that cirrhotic patients with hospital-acquired infections admitted in an ICU or that required invasive procedures had a higher incidence of gram-positive cocci infections. Caly and Strauss [26] showed that hospital-acquired pneumonia in cirrhotic patients was predominantly caused by gram-negative bacilli and staphylococci. A recent study [14] showed that MDR pathogens, particularly ESBL *Enterobacteriaceae*, are commonly isolated among cirrhotic patients affected by community-acquired, healthcare-associated and hospital-acquired infections, with a significantly higher rate in the latter group.

To better characterize ICUAP in patients with CLD, we compared the microbiological etiology of VAP versus NV-ICUAP. The rate of etiologic diagnosis was higher in VAP than in NV-ICUAP, reflecting the facility of obtaining respiratory samples in intubated patients [32]. Nevertheless, we found no differences in the causative agents involved.

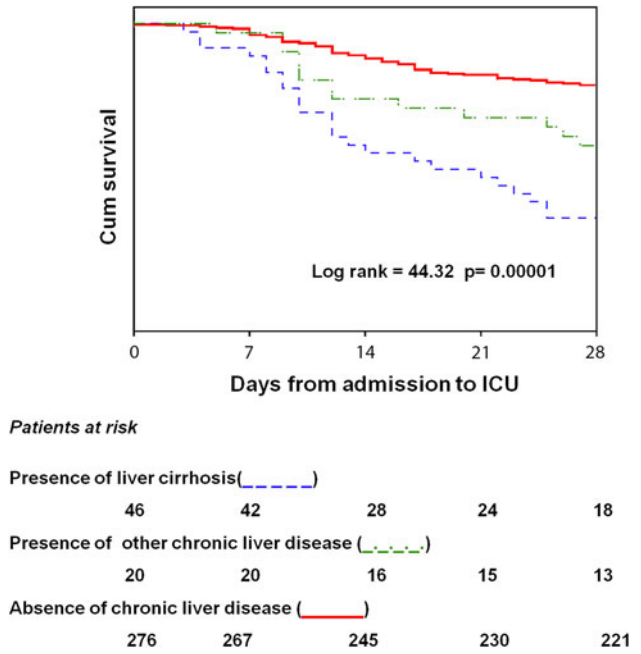

Fig. 1 Kaplan–Meier analysis of study cohort comparing patients with liver cirrhosis, other chronic liver disease, and without chronic liver disease

The inflammatory response was different between groups. Serum levels of CRP were especially low in cirrhotic patients in comparison with other CLD and no CLD, both at onset of pneumonia and at day 3. This may be explained by the fact that CRP is mainly synthesized by hepatocytes as part of the acute-phase response, although recent studies suggest other sites of production, including coronary-artery smooth muscle cells [33], kidneys, human neurons [34], and alveolar macrophages. Thus, serum CRP may not be clinically useful in cirrhotic patients upon diagnosis of ICUAP or follow-up. All the other biomarkers analyzed (procalcitonin, MR-proADM, IL-6, IL-8, TNF-α, and IL-10) were higher in the groups of LC and other CLD, reflecting a more severe illness. Higher levels of MR-proADM, as previously described [35], likely related to severe illness, septic shock, and renal failure.

CRP production by hepatocytes is induced by IL-6 [36]. We identified a significant correlation between these two markers in patients without CLD. Interestingly, this correlation was not confirmed among patients with LC. The absence of significant correlation may be due to a lack of hepatocyte production of CRP after IL-6 stimulus. The other inflammatory mediators are also synthesized in the liver, but not predominantly, as they are mainly secreted by circulants activated and by other organs [37, 38].

Finally, this study identified LC as an independent predictor of 28- and 90-day survival in patients with ICUAP. LC patients had poorer clinical outcomes, fewer VFDs at day 28, higher incidence of treatment failure, and more frequent development of septic shock after the onset of pneumonia. This finding is important for future prospective studies of ICUAP focused on mortality.

We also compared 28- and 90-day survival in patients with LC, with other CLD and without CLD according to the type of pneumonia (VAP and NV-ICUAP) and we found worse survival in LC patients, irrespective of the type of pneumonia. These results are in agreement with previous findings by Esperatti et al. [3], who showed that both the causative agents and outcomes were similar in VAP and NV-ICUAP, suggesting that the patient's underlying conditions, rather than intubation, play the most significant role.

Our findings on mortality agree with previous studies on bacterial infections in cirrhotic patients [7, 39]. Arvaniti et al. [7] showed that in patients with cirrhosis infections increase mortality fourfold, 30 % of patients die within 1 month after infection, and another 30 % die by 1 year.

The strengths of our study are its prospective nature, the detailed description of CLD patients, and the accurate study of mortality both at 28 and 90 days. In addition it provides data about non-ventilated and ventilated hospital-acquired pneumonia (HAP) acquired in the ICU.

Nevertheless, some limitations should be addressed. First, this was a single-center study, and therefore the extrapolation of the findings to other settings must be done cautiously. Also, a considerable number of patients came from an hepatic ICU. Research findings generated in highly specialized ICUs are often not generalizable to the vast majority of ICUs.

Second, the number of patients with confirmed etiology in LC and other CLD groups are not sufficient to detect differences in the microbial etiology. Also, ICUAP etiology was not identified in 37 % of the patients. It can be argued that some patients without etiologic diagnosis may not have had pneumonia; however, this is a usual situation in clinical practice and our rate of etiologic diagnosis was similar to ancillary reports in this field. Moreover when only the patients with defined etiology were evaluated, the results were the same. Thirdly, attributable mortality of ICUAP in CLD patients could not be determined with our data. Instead we wanted to describe the associated mortality of CLD patients when affected by VAP/NV-ICUAP. We find it relevant for clinicians in terms of potential prevention of VAP and treatment.

In summary, the findings of our study show that, in critically ill patients affected by ICUAP, CLD is associated with a more severe clinical presentation, worse clinical outcomes, and similar etiology compared with those in patients without liver disease. Most importantly, LC increases 28- and 90-day mortality. For future trials, in ICUAP patients, concomitant liver diseases should be taken into account as an independent prognostic factor.

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Conflicts of interest The authors declare no conflicts of interest.

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