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Prognostic value of procalcitonin in patients with cirrhosis hospitalized for acute infection ☆

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ABSTRACT

Background: In patients with cirrhosis, infections significantly increase the risk of short and long-term mortality. During infection, the levels of procalcitonin increase, but it has not yet been clarified its prognostic value in subjects with cirrhosis. Therefore, the aim of this study was to evaluate the prognostic role of procalcitonin in patients with liver cirrhosis hospitalized for acute infection, and to compare it with other markers of infection. *Patients*: We included 279 patients hospitalized because of infection, 133 with liver cirrhosis. At admission the levels of the main biochemical parameters of infection, i.e. leukocytes, procalcitonin, C reactive protein and lactate, were considered. *Results*: The duration of hospitalization and antibiotic therapy were longer in patients with cirrhosis, while no difference was observed for mortality. In both groups, a correlation with the duration of hospitalization and antibiotic therapy was observed for high levels of procalcitonin. In the cirrhotic population, in particular, higher procalcitonin values were associated with an increase in the length of hospitalization and antibiotic therapy, suggesting an even greater predictive value for those patients. High levels of leucocytes and lactate were positively associated with the duration of hospitalization, but not with the duration of antibiotic therapy. For mortality, the strongest correlation was found for high serum lactate levels, regardless of the presence of cirrhosis. *Conclusion*: In patients with cirrhosis and acute infection, the value of procalcitonin at admission is a good prognostic indicator for the course of hospitalization, and could be useful for guiding the management and treatment of hospitalized patients.

1. Introduction

Patients with liver cirrhosis have an up to three-fold higher risk of developing infections than the general population. According to a recent hypothesis, systemic inflammation occurring during infection can promote the transition from a compensated to a decompensated condition [1]. Moreover, in these patients, infections significantly increase the risk of short and long-term mortality [2]. Therefore, in patients with cirrhosis, an early diagnosis and prognostic evaluation during infection are crucial to reduce the risk of morbidity and mortality.

Plasma concentrations of procalcitonin (PCT) in subjects without infection are very low, but in presence of infection, especially of bacterial origin, its production significantly increases in several tissues [3,4]. Although the specific biological functions of PCT have not been fully clarified, it seems to act as a modulator of inflammatory responses [5]. PCT, besides being a good indicator of infection, has been shown to be a useful marker for predicting mortality and guiding antibiotic therapy in the general population with ongoing infections [6].

The liver plays a central role in the production of PCT during infection, therefore it could be expected that in liver diseases the synthesis and blood concentration of PCT are decreased. However, in patients with advanced liver disease, the basal levels of PCT are even increased, suggesting a complex relationship between liver and PCT levels [7]. Studies conducted in patients with liver cirrhosis have led to conflicting results and the prognostic role of PCT in subjects with cirrhosis has not been clarified yet [8–10].

The aim of this study is to evaluate the prognostic role of PCT in patients with liver cirrhosis hospitalized for acute infection, and to compare it with other markers of infection.

☆ The authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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2. Patients and methods

This is a retrospective study including patients hospitalized for acute infection in the Unit of Internal Medicine and Hepatology, University and General Hospital of Padova, Italy, from 2018 to 2020. Patients were divided into two groups based on the diagnosis of liver cirrhosis. Inclusion criteria were as follows: (a) age >18 years; (b) hospitalization due to an acute infection. The diagnosis of infections was made according to international guidelines. The severity of the infection was stratified based on the presence or not of sepsis, according to Sepsis-1 criteria (defined by the American College of Chest Physicians and the Society of Critical Care Medicine), and on the qSOFA score. Based on the data available, it was not possible to calculate SOFA and CLIF score.

Demographics, clinical, and laboratory data from patients included in the study were recorded. The laboratory data recorded were the first obtained within 48 h after the admission. In patients with cirrhosis, acute-on-chronic liver failure (ACLF) presence was assessed at admission and the grade was calculated according to the diagnostic criteria of the European Foundation for the study of chronic liver failure (EF-CLIF) [11]. ACLF grade 1 was characterized by the presence of kidney failure (serum creatinine ≥2 mg/dl) or by other single organ/system failure (liver: serum bilirubin ≥12 mg/dl; brain: grade III-IV hepatic encephalopathy based on West Haven criteria7; coagulation: international normalized ratio [INR] ≥2.5 or platelet count ≤20 × 10^9/L; circulation: treatment with vasoconstrictors to maintain arterial pressure or inotropes to improve cardiac output; lungs: PaO2/FiO2 ≤200 or SpO2/FiO2 ≤214), if associated with kidney dysfunction (serum creatinine ranging from 1.5 to 1.9 mg/dl) and/or with mild-to-moderate (grade I-II) HE. ACLF grade 2 and ACLF grade 3 were defined by the presence of 2 or ≥3 organ/system failures, respectively.

Patients were followed-up till the end of the hospitalization or death. The primary endpoints of the study were the duration of hospitalization and antibiotic therapy. The secondary endpoint was in-hospital mortality. The study was approved by the Ethics Committee of the University and General Hospital of Padova.

2.1. Statistical analysis

Data characteristics were summarized by frequency and percentage if categorical variables, and by the median and the interquartile range (IQR) due to the non-normal distribution of some continuous variables of interest. The comparison of the characteristics between two groups was performed using the Wilcoxon rank sum test and Pearson Chi-square test for qualitative and quantitative variables, respectively. A Kruskal-Wallis test was used if the comparison by quantitative variables involved more than two strata.

The database had some missing values of the lactate variable (83, 29.7%) and since there was a correlation with other covariates, we imputed the missing values using a MICE (Multiple Imputations by Chained Equation; Van Buuren and Groothuis-Oudshoorn, 2011) procedure based on 30 iterations using a CART (Classification and Regression Tree) algorithm. The analyses to determine the prognostic value of lactate have been repeated also with only non-imputed data, confirming the results, just with slightly lower statistical significance, due to the reduction of the sample size.

We used a binomial logistic regression model to evaluate which variables were associated with increased mortality. We considered the following starting variables: leukocyte, C-reactive protein (CRP), procalcitonin (PCT), lactate, diagnostic group, gender, age, presence of comorbidities (heart disease of different aetiology, diabetes mellitus, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and neoplasms), presence of sepsis, and identification of multidrug-resistant organism (MDRO). Continuous variables as leukocyte, CRP, PCT, and lactate were categorized in tertiles, considering the empirical distribution, in order to estimate potential non-linear relationships. With a backward approach, the variables were selected minimizing the Akaike Information Criterion (AIC) index. Results were reported by means of Odds Ratio (OR) and the relative 95% Interval Confidence (95% IC).

The outcomes of the length of hospitalization and the duration of the antibiotic therapy were analyzed using the Cox regression model. However, since the presence of deaths influenced the reported outcomes, as suggested by Brock et al. (2011), we employed a Fine and Gray model (Fine and Gray, 1999), commonly used in survival analysis considering the presence of competing risk. In this case the competing risk is death, which is competitive with the hospital discharge or the end of the antibiotic therapy. In addition, the results of the Fine and Gray model have a prognostic meaning since the use of a subdistribution hazard function (Wolbers et al., 2009). The initial model incorporated the same covariate of the logistic model, and a backward variable selection approach was employed minimizing the AIC index. The model results were reported by means of Hazard Ratio (HR) and the relative 95% Interval Confidence (95% IC). The regression model related to the duration of the antibiotic therapy was restricted to the subgroup of patients affected by bacterial infection. We tested the presence of a significant interaction between PCT and the diagnostic group by a Wald test. An additional sensitivity analysis was conducted estimating the two previous regression models on the basis of complete set of data without imputation.

In order to establish a cut-off value for the PCT concentration which most correlates with an increment of the length of stay and the duration of the antibiotic therapy we followed an approach in which the previous Fine and Gray model was estimated using only the PCT value in binary form (≤ cut-off, > cut-off) as the only predictor and the best value of cut-off was chosen minimizing the AIC index following a similar procedure adopted in other studies (Chang et al., 2017).

The limit of the first type error for test was set to 0.05. All calculations were performed with R program (version 4.2) and the packages *mice, survival, cmprsk*, and *survminer*.

3. Results

A total of 279 patients admitted to hospital for acute infection were included: 133 with and 146 without liver cirrhosis. The aetiology of liver cirrhosis was 43.8% alcoholic, 16.3% viral, 14.8% combined alcoholic and viral, and 25.1% due to other causes. In the group of patients with cirrhosis, the MELD-Na and the Child-Pugh average score was 23.1 and 9.1, respectively.

Patients with cirrhosis were younger than patients without cirrhosis ($p < 0.001$), more often males ($p = 0.01$). In comparison with cirrhotic patients, those non cirrhotic reported a higher presence of comorbidities, in particular the presence of heart diseases (51% vs 35%, $p = 0.007$) and COPD (26% vs. 13%, $p = 0.005$). The levels of leukocytes and CRP were higher in the non-cirrhotic population ($p < 0.001$), while lactates were higher in patients with cirrhosis ($p < 0.001$). The PCT levels did not differ between the two groups. A higher prevalence of sepsis was reported among non-cirrhotic patients vs those cirrhotic (59% vs. 38%, $p < 0.001$), while there was no difference in the prevalence of multidrug-resistant organisms. The duration of hospitalization and antibiotic therapy were longer in the group with cirrhosis ($p < 0.001$ and $p = 0.001$, respectively). The in-hospital mortality rate was similar in the two groups (11.3% in patients with cirrhosis and 8.9% in patients without cirrhosis; $p > 0.05$; Table 1).

In the group of patients with cirrhosis, in most cases (92%) the diagnosis of chronic liver disease was made before admission, and

Table 1
Demographic, clinical and laboratory features of patients at admission according to group. Data are expressed as median (IQR).

Characteristic	Overall $N = 279$[a]	Non cirrhotic $N = 146$	Cirrhotic $N = 133$	*P*-value[b]
Males, n (%)	182 (65.2%)	85 (58.2%)	97 (72.9%)	0.010
Age, years	73 (62, 81)	78 (70, 85)	65 (58, 74)	<0.001
Heart disease	122 (44%)	75 (51%)	47 (35%)	0.007
Diabetes mellitus	93 (33%)	41 (28%)	52 (39%)	0.051
COPD	55 (20%)	38 (26%)	17 (13%)	0.005
CKD	85 (30%)	43 (29%)	42 (32%)	0.7
Neoplasms	80 (29%)	42 (29%)	38 (29%)	>0.9
Leukocyte (10^9/L)	9.3 (6.0, 14.0)	11.6 (8.0, 15.8)	6.9 (5.2, 11.5)	<0.001
CRP (mg/L)	65 (23, 155)	121 (49, 206)	39 (14, 81)	<0.001
PCT (µg/L)	0.6 (0.2, 2.9)	0.7 (0.2, 5.8)	0.6 (0.2, 1.7)	0.13
Lactate (mmol/L)	1.9 (1.40, 2.75)	1.6 (1.13, 2.70)	2.10 (1.70, 2.80)	<0.001
Sepsis	136 (49%)	86 (59%)	50 (38%)	<0.001
Quick SOFA				0.3
0	135 (48%)	65 (45%)	70 (53%)	
1	121 (43%)	67 (46%)	54 (41%)	
2	20 (7.2%)	11 (7.5%)	9 (6.8%)	
3	3 (1.1%)	3 (2.1%)	0 (0%)	
Hospitalization, days	11 (7, 16)	10 (7, 15)	13 (8, 22)	<0.001
Antibiotic therapy, days	9 (6, 14)	9 (6, 12)	10 (7, 16)	0.001
Deceased, n (%)	28 (10.0%)	13 (8.9%)	15 (11.3%)	0.5
Known cirrhosis diagnosis	–	–	123 (92%)	
Previous cirrhosis decompensation	–	–	99 (74%)	
Beta blocker therapy	–	–	61 (46%)	
Compensated cirrhosis at admission	–	–	78 (59%)	
ACLF Grade				
0	–	–	108 (81%)	
1	–	–	13 (9.8%)	
2	–	–	7 (5.3%)	
3	–	–	5 (3.8%)	

[a] n (%); Median (IQR).
[b] Pearson's Chi-squared test; Wilcoxon rank sum test.COPD= Chronic Obstructive Pulmonary Disease. CKD= Chronic Kideny Disease. CRP= C-Reactive Protein. PCT= Procalcitonin. SOFA= Sequential Organ Failure Assessment. ACLF= Acute-on-chronic liver failure.

Table 2
Aetiology and site of infection according to group.

		Non cirrhotic $N = 146$	Cirrhotic $N = 133$	*P*-value
Aetiology, n (%)	Bacteria	118 (81)	107 (80)	0.78
	Other (fungi, virus)	10 (6.8)	7 (5.3)	
	Unknown	18 (12)	19 (14)	
Site of infection, n (%)	Respiratory	73 (50)	32 (24)	< 0.001
	Urinary	27 (18)	36 (27)	
	Skin	11 (7.5)	11 (8.3)	
	Abdominal	13 (8.9)	28 (21)	
	Unknown	22 (15)	26 (20)	
MDRO (Multidrug-resistant organism)		19 (13%)	18 (14%)	0.9

74% had previous episodes of cirrhosis decompensation. At admission, in 41% of patients, cirrhosis was decompensated, and 19% had ACLF.

Infections were mostly bacterial, with a similar prevalence among cirrhotic and non-cirrhotic patients. We observed a difference in the distribution of the infection sites between the two groups, with a higher percentage of urinary and abdominal infections and a lower percentage of respiratory infections in patients with cirrhosis ($p < 0.001$) (Table 2). Cultures were positive in 54.8% of cases (66.7% Gram negative and 33.3% Gram positive), with similar rates among the two groups. Also the prevalence of MDRO was similar between cirrhotic and non cirrhotic patients.

For all the infection markers considered, the levels observed had a skew distribution with a discrete degree of correlation among them (Fig. 1). In particular for the PCT concentration, we reported a very high value and a strong asymmetry. In order to moderate the influence of the distribution skewness and/or the presence of outliers, the four blood markers were categorized in tertiles, as reported in the method section.

Figs. 2 and 3 reported the marginal distribution (in logarithmic 10 scale) of the duration of the hospitalization and of the antibiotic therapy across tertiles of blood markers and by diagnostic group. As reported in Fig. 2, there was a marginal influence of the PCT tertiles on the hospitalization duration, but only for the cirrhotic group ($p = 0.002$). Considering the length of the antibiotic therapy, both the CRP and PCT tertiles showed a marginal influence on the duration ($p = 0.019$ and $p < 0.001$, respectively), but still only for the cirrhotic group.

The starting model for mortality (Table 3) did not report a significant effect of the PCT as well as the final model, which showed a higher mortality among patients with high lactate levels (first vs third tertile; OR: 4.80, 95%CI: 1.71–15.77). Surprisingly, the presence of CKD was a protective factor (OR:0.20, 95%CI: 0.04–0.64).

In Table 4 the results of the models related to the length of hospitalization and of the antibiotic therapy duration are summarised

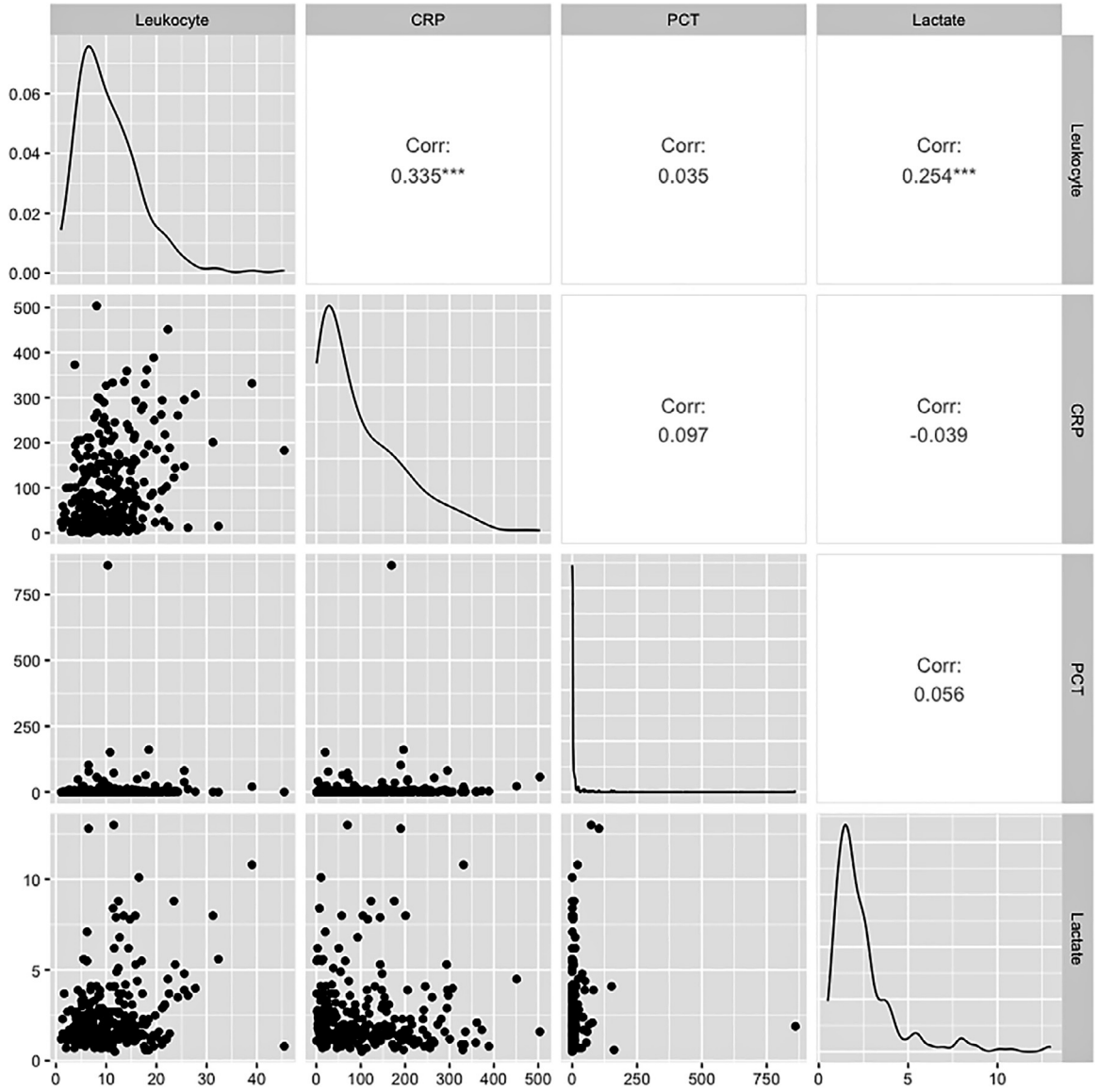

Fig. 1. Pairwise dispersion diagram between values of leukocyte, CRP, PCT, and lactate and Spearman' correlation.

Table 3
Adjusted OR and 95%CI of the logistic regression models for mortality for both the starting model and the final model after the selection variable procedure.

	Starting model (n = 279)			Final model (n = 279)		
Predictors	*Odds Ratios*	95%CI	*P-value*	*Odds Ratios*	*95%CI*	*P-value*
Leukocyte 2nd *tert*. [6.87–12.4]	2.46	0.78–8.61	0.135			
Leukocyte 3rd *tert*. [12.4–45.5]	1.15	0.30–4.64	0.837			
CRP 2nd *tert*. [34.3–119]	1.32	0.40–4.47	0.646			
CRP 3rd *tert*. [119–504]	1.50	0.45–5.19	0.509			
PCT 2nd *tert*. [0.257–1.5]	1.61	0.47–5.97	0.456			
PCT 3rd *tert*. [1.5–860]	1.70	0.50–6.40	0.408			
Lactate 2nd *tert*. [1.4–2.43]	1.78	0.47–7.14	0.396	1.97	0.59–7.03	0.272
Lactate 3rd *tert*. [2.43–13]	4.11	1.19–16.34	**0.032**	4.80	1.71–15.77	**0.005**
Group [Cirrhotic]	1.49	0.51–4.57	0.472			
Gender [F]	0.85	0.31–2.18	0.747			
Age (+1 year)	1.00	0.96–1.05	0.963			
Heart disease	2.40	0.87–7.03	0.098	2.16	0.92–5.13	0.077
Diabetes mellitus	0.93	0.34–2.40	0.886			
COPD	1.62	0.47–4.96	0.414			
CKD	0.17	0.04–0.59	**0.011**	0.20	0.04–0.64	**0.014**
Neoplasms	1.44	0.53–3.80	0.459			
Sepsis	1.48	0.56–4.01	0.429			
MDRO	2.23	0.71–6.61	0.155	2.08	0.75–5.37	0.142

COPD = chronic obstructive pulmonary disease. CKD = chronic kidney disease. CRP = C-reactive protein. PCT = Procalcitonin. MDRO = multidrug-resistant organism.

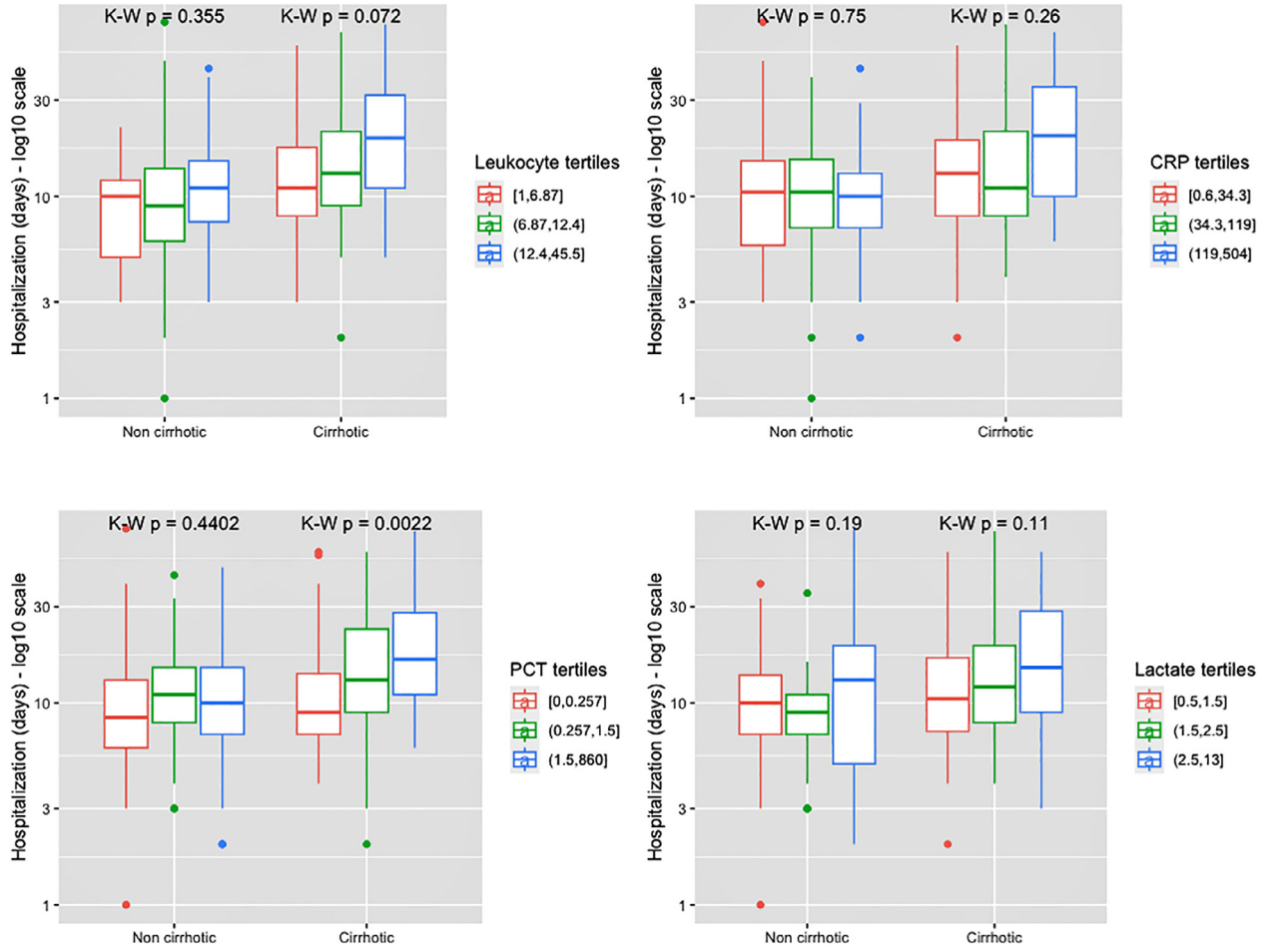

Fig. 2. Distribution of the duration of hospitalization across tertiles of leukocyte, CRP, PCT, and lactate values by diagnostic group. (K–W: Kruskal–Wallis test).

Table 4
HR and 95%CI estimated by the two Fine and Gray model with Hospitalization and Antibiotic therapy as dependent variables.

Predictors	Hospitalization (n = 279)			Antibiotic therapy[a] (n = 225)		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
PCT 2nd *tert.* [0.257–1.5)	0.71	0.52–0.97	**0.031**	0.66	0.46–0.93	**0.018**
PCT 3rd *tert.* [1.5–860]	0.71	0.51–0.99	**0.041**	0.63	0.44–0.90	**0.010**
Leukocyte 2nd *tert.* [6.87–12.4)	0.73	0.52–1.02	0.066	0.98	0.69–1.41	0.926
Leukocyte 3rd *tert.* [12.4–45.5]	0.70	0.50–0.98	**0.040**	0.72	0.50–1.05	0.085
Lactate 2nd *tert.* [1.4–2.43)	0.98	0.70–1.36	0.891			
Lactate 3rd *tert.* [2.43–13]	0.61	0.44–0.86	**0.004**			
Group [Cirrhotic]	0.59	0.43–0.81	**0.001**	0.62	0.44–0.86	**0.004**
Age (+1 year increase)	0.99	0.98–1.00	**0.024**	0.99	0.98–1.00	**0.049**
CKD	1.29	0.96–1.74	0.096	1.31	0.94–1.83	0.108
MDRO	0.52	0.35–0.78	**0.002**	0.47	0.31–0.70	**<0.001**

[a] Analysis restricted to patients with bacterial infection.PCT = procalcitonin. CKD = chronic kidney disease. MDRO = multidrug-resistant organism.

(the starting models are reported in the Supplementary Table 2); both models reported a significant prognostic association with the initial PCT value: the length of stay increased of 29% for the second (p = 0.031) and the third tertile of PCT (p = 0.041) in comparison with the first tertile (concentration <0.257 µg/L); the reported effect appeared stronger considering the duration of antibiotic therapy which resulted in an increase of 34% (p = 0.018) and 37% (p = 0.010) for the second and the third tertile of PCT, respectively (vs. first tertile).

In addition, adjusting for the other covariates, leukocyte levels moderately influenced both the considered outcomes, reaching an increase of 30% (p = 0.040), and 28% (p = 0.085) for hospitalization and antibiotic therapy length, respectively, in the comparison between the respective third and first tertile. High levels of lactate were strongly associated with increased hospitalization length (+39% 3rd vs 1st tertile), but not with the duration of antibiotic therapy.

The presence of cirrhosis increased both the length of hospitalization and of the antibiotic therapy duration (41% and 38% increase, respectively). Each 1-year age increase was associate with about 1% duration increment of the two outcomes. The infection by a multi-drug resistant organism increased by 48% the duration of hospitalization and by 53% the duration of antibiotic therapy. We tested the presence of an interaction between PCT in tertiles

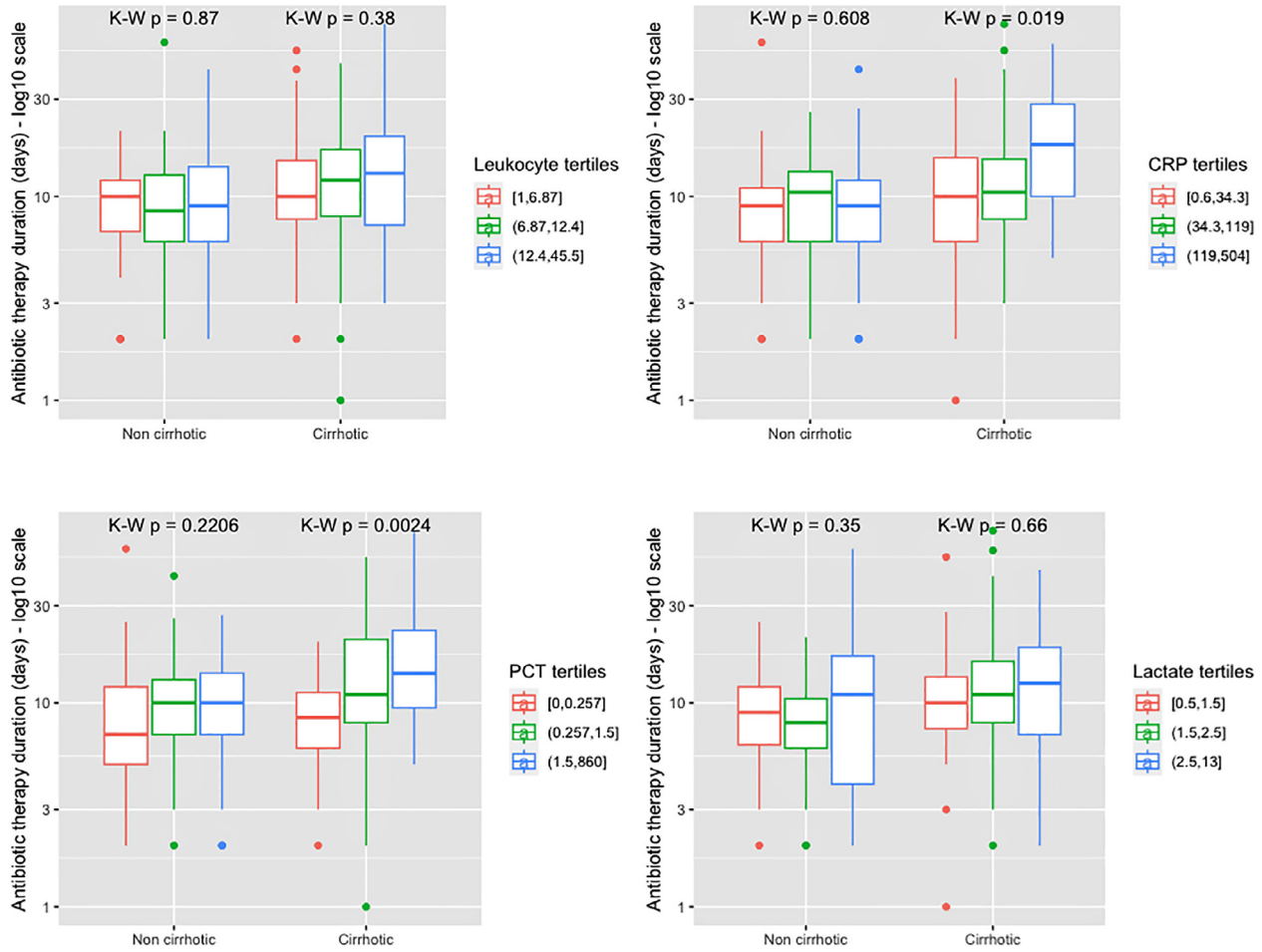

Fig. 3. Distribution of the duration of antibiotic therapy across tertiles of leukocyte, CRP, PCT, and lactate values by diagnostic group. (K–W: Kruskal–Wallis test). Analysis restricted to patients with bacterial infection ($n = 225$).

and diagnostic group, but it was not significant in both models ($p = 0.95$ and $p = 0.51$, respectively). The sensitivity analysis based on complete data confirmed the adverse effects of high PCT levels on the duration of both hospitalization and antibiotic therapy.

The cut-off analysis was conducted varying the value of PCT from 0 µg/L to 100 µg/L with steps of 0.1 µg/L. As reported in the Supplementary Fig. 1, we obtained a minimum for a value of PCT equal to 10.5 µg/L both for the hospitalization and the antibiotic therapy duration. The results of the survival regression models applying these cut-off values indicated a doubling both for the length of stay (HR: 0.51, 95%CI: 0.24–1.11) and the antibiotic therapy (HR: 0.46, 95%CI: 0.20–1.06) for concentrations higher than the found cut-off with the respect lower values.

In patients with liver cirrhosis, we also evaluated if markers of infection predict ACLF onset (Table 5). Only PCT was found to be associated with ACLF onset and its grade (Fig. 4).

4. Discussion

Some of the markers of infection commonly used in the general population are not equally reliable diagnostic and prognostic indicators in patients with cirrhosis. In these patients, the use of leukocytes is limited because their levels are often reduced due to the common presence of hypersplenism. CRP is a protein produced only in the liver and its production decreases proportionally with the reduction in liver function [12]. In recent years, the interest in PCT has gained prominence. A decrease in PCT levels during an infection is associated with improved clinical conditions, while increasing values are associated with worse outcomes, including mortality. This is not observed for other biomarkers: CRP shows stable or intermittent serum levels that do not correlate with the severity of the infection [13]. On the other hand, PCT prognostic value in patients with cirrhosis has not been clarified.

In our study, both the length of hospitalization and the duration of antibiotic therapy were longer in the cirrhotic group; this could be a consequence of the condition of immunosuppression that characterizes patients with cirrhosis, with a longer period of treatment needed for recovery [14]. Both durations were also longer in presence of infection by a multidrug-resistant organism: this may be explained by the necessity of further antibiotic treatment, following the first-line empirical therapy, after the identification of the microorganism and the definition of the antibiogram. In-hospital mortality was 10%, without differences between patients with and without cirrhosis. As expected, in patients with cirrhosis, lower levels of leukocytes and CRP were observed. On the contrary, in these patients, the levels of lactate were higher than in patients without cirrhosis, probably as a consequence of a lower hepatic clearance [15]. PCT levels at admission were similar between the two groups, which is in line with a previous study [8]. This could be explained by the fact that hepatocytes maintain the ability to synthesize PCT even in case of cirrhosis and that other organs contribute to the production of PCT during infection.

All the infection markers positively correlate with increased mortality: for values included in the second and third tertile of leukocytes, CRP, PCT, and lactate, the estimated ORs were higher

Table 5
Demographic, clinical and laboratory features of patients with liver cirrhosis by presence of ACLF.

Characteristic	ACLF		*p*-value[b]
	NO, *N* = 108[a]	YES, *N* = 25[a]	
Males, n(%)	80 (74%)	17 (68%)	
Age, years	67 (58, 75)	63 (53, 73)	0.13
Leukocytes (/µL)	6.7 (4.9, 10.4)	9.3 (6.9, 12.9)	**0.016**
CRP (mg/L)	40 (15, 82)	21 (12, 59)	0.3
PCT (µg/L)	0.4 (0.1, 1.2)	1.4 (0.6, 3.3)	**0.005**
Lactate (mmol/L)	2.00 (1.50, 2.70)	2.70 (2.00, 3.60)	**0.009**
Hospitalization, days	12 (8, 21)	16 (11, 28)	0.089
Antibiotic therapy, days	10 (7, 16)	13 (7, 19)	0.3
Deceased, n(%)	13 (12%)	2 (8.0%)	0.7
Known cirrhosis diagnosis	104 (96%)	19 (76%)	**0.003**
Previous cirrhosis decompensation	81 (75%)	18 (72%)	0.8
Beta blocker therapy	51 (47%)	10 (40%)	0.5
Compensated cirrhosis at admission	56 (52%)	23 (92%)	**<0.001**
Quick SOFA			0.3
0	54 (50%)	16 (64%)	
1	45 (42%)	9 (36%)	
2	9 (8.3%)	0 (0%)	
Sepsis	40 (37%)	10 (40%)	0.8
MDRO	15 (14%)	3 (12%)	>0.9

[a] n (%); Median (IQR).
[b] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.CRP = C-reactive protein. PCT = procalcitonin. COPD = Chronic obstructive pulmonary disease. CKD = chronic kidney disease. SOFA = Sequential Organ Failure Assessment. MDRO = multidrug-resistant organism.

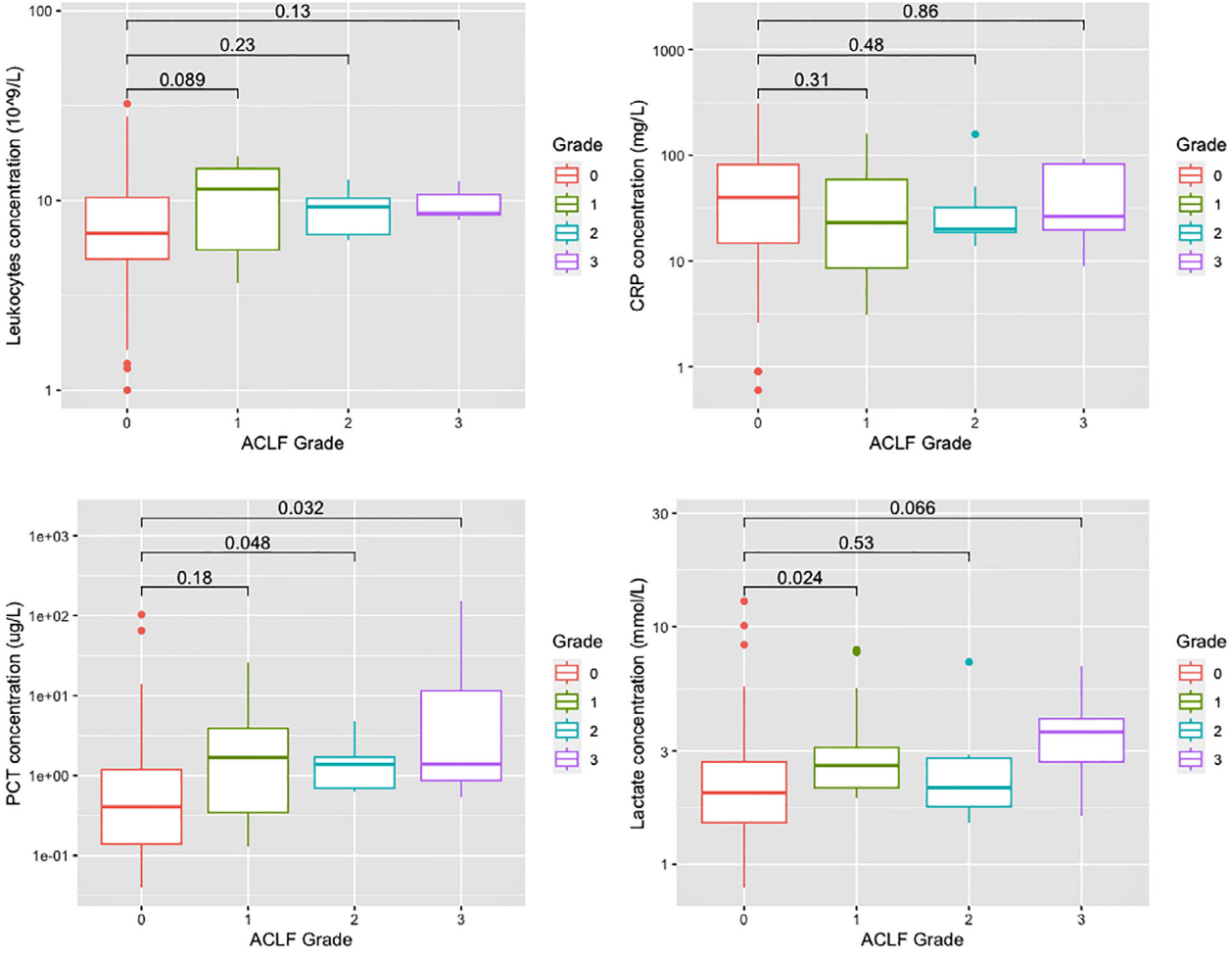

Fig. 4. Distribution of leukocytes, CRP, PCT and Lactate by ACLF grade.

than one. However, because of the limited sample size to analyse this outcome, statistical significance was found only for high serum lactate levels. Surprisingly, CKD was found to be a protective factor for mortality in patients admitted for infection.

With regard to the duration of hospitalization and antibiotic therapy, a positive correlation was observed with high levels of PCT. High levels of lactate and leucocytes had a statistically significant correlation only with the hospitalization duration, probably because the analysis on antibiotic therapy was restricted to the population with a confirmed bacterial infection, reducing the sample size. These data confirm the prognostic value of PCT, lactate and leucocytes in relation to the course of an infection. Subsequently, we evaluated whether there was a difference in the prognostic value of the markers of infection between the two groups. From the descriptive analysis, only in the cirrhotic population, higher PCT values are associated with an increase in the duration of hospitalization and antibiotic therapy, and higher CRP values with an increased duration of antibiotic therapy. This result suggests even greater predictive value of PCT for the cirrhotic population. On the other hand, the ANOVA analysis did not show statistical significance, indicating that PCT is a good prognostic indicator in both cirrhotic and non-cirrhotic populations. Overall, these data indicate that in the cirrhotic population PCT is a good prognostic indicator for the course of the infection, especially if compared to the other markers of inflammation, and this can be explained by the reasons explained above regarding the role of the different markers of infection in patients with cirrhosis. In addition, we showed that, in patients with cirrhosis, PCT was the only marker associated with the grade of ACLF secondary to infection.

One of the limitations of our study is primarily its retrospective design. Furthermore, the decision to include patients presenting non bacterial infection is questionable considering that during viral infections the production of PCT is generally inhibited by IFN-γ; however, the percentage of non bacterial infections was very low and a selection of patients would not be suitable with clinical practice, since generally the aetiology of the infection is not known at admission, but only later during the hospital stay [16]. Moreover, in addition to the single value of the infection markers at admission, it would have been useful to observe their variations over time in relation to the outcomes, but the data were not homogeneous and often missing. Finally, a problem of reverse causality may be present, since the length of antibiotic therapy and hospitalization could have been influenced by the levels of PCT and other markers; on the other hand, more than their levels at admission, their variation during hospitalization and other clinical outcomes are more often considered by clinicians to take decisions about duration of antibiotic therapy and hospitalization.

In conclusion, our study indicates that in patients with cirrhosis and acute infection, PCT is a good prognostic indicator for the course of hospitalization. Studies with a larger number of patients are needed to confirm the potential role of PCT in cirrhosis, as it could guide the most appropriate management and treatment during hospitalization because of infection.

Conflict of Interest

The Authors of this manuscript have no conflicts of interest to declare.

All co-Authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.10.004.

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