Annals of Gastroenterology (2020) **33,** 1-8

The significance of C-reactive protein to albumin ratio in patients with decompensated cirrhosis

Theodora Oikonomou[a], Ioannis Goulis[a], Stefania Kiapidou[a], Nikoletta Tagkou[b], Evangelos Akriviadis[a], George Papatheodoridis[b], Evangelos Cholongitas[b]

Hippokration General Hospital, Medical School of Aristotle University of Thessaloniki; Laiko General Hospital, Medical School of National and Kapodistrian University of Athens, Greece

Abstract

Background Prognostic indicators in patients with decompensated cirrhosis are vital for the estimation of death risk. The ratio of C-reactive protein to albumin (CAR) has been verified as a prognostic marker in patients with hepatocellular carcinoma and decompensated cirrhosis related to hepatitis B virus. Neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and gamma globulins have been separately studied in cirrhosis. We evaluated the predictive role of CAR and other inflammatory markers in decompensated patients.

Methods We prospectively studied 159 patients with stable decompensated cirrhosis, calculating the following indexes: CAR, NLR, LMR, Child-Turcotte-Pugh (CTP), and model for end-stage liver disease (MELD).

Results MELD (area under the curve [AUC] 0.814) and CTP score (AUC 0.752) were superior to the other markers above in predicting patients' mortality (P<0.05). Patients with CAR<2.17 (median value) presented better times of survival: 20 months (12-27) vs. 14 months (10-17) (log rank P=0.015). NLR and LMR barely discriminated patients' prognosis. In multivariate analysis, only MELD and CTP scores were significant risk factors, whether using the proposed cutoff of 1.3 (hazard ratio [HR] 1.17 [1.106-2.44], P<0.001) or the median 2.17 CAR categorical variable (HR 1.17 [1.104-1.243], P<0.001). When patients who underwent liver transplantation were excluded, apart from the MELD and CTP scores CAR 2.17 was the only significant factor associated with the outcome (HR 3.61 [0.96-13.6], P=0.05) and detected different survival times: 10 (1-48) vs. 11 (2-38) months, log rank P=0.003. Patients with LMR≥1.9 presented significantly better renal function, in terms of true glomerular filtration rate (80±34 vs. 64±33 mL/min, P=0.004) and creatinine levels: 0.84 (0.1-1.8) vs. 0.98 (0.59-3.3) mg/dL (P=0.001).

Conclusion Our findings demonstrate the significance of CAR and LMR in the outcome and renal function of decompensated patients.

Keywords CRP-to-albumin ratio, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, gamma globulins, decompensated cirrhosis

Ann Gastroenterol 2020; 33 (6): 1-8

[a]Fourth Department of Internal Medicine, Hippokration General Hospital, Medical School of Aristotle University of Thessaloniki (Theodora Oikonomou, Ioannis Goulis, Stefania Kiapidou, Evangelos Akriviadis); [b]First Department of Internal Medicine, Laiko General Hospital, Medical School of National and Kapodistrian University of Athens (Nikoletta Tagkou, George Papatheodoridis, Evangelos Cholongitas), Greece

Conflict of Interest: None

Correspondence to: Evangelos Cholongitas, MD, PhD, Associate Professor, First Department of Internal Medicine, Medical School of National and Kapodistrian University of Athens, Laiko General Hospital, Agiou Thoma 17, 11527 Athens, Greece, e-mail: cholongitas@yahoo.gr

Received 14 December 2019; accepted 9 July 2020; published online 16 September 2020

DOI: https://doi.org/10.20524/aog.2020.0534

Introduction

Cirrhosis reflects the end stage of every chronic liver disease. Its natural history is characterized by an asymptomatic phase, termed "compensated" cirrhosis followed by a rapidly progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction, termed "decompensated cirrhosis" [1]. Survival is much lower in patients with decompensated cirrhosis, and signs of decompensation seem to be accurate predictors of death risk [2]. Research in coming years could focus on the primary prevention and treatment of cirrhosis, including the use of noninvasive tests to screen for earlier stages of the disease [3].

Traditionally, classification using the Child-Turcotte-Pugh (CTP) model is most widely used to determine prognosis in patients with chronic liver disease, and has been shown to be useful in the assessment of patients with cirrhosis. In addition, the model for end-stage liver disease (MELD) is a reliable measure of short-term mortality risk in patients with end-stage liver disease of diverse etiology and severity [4]. In 2006, D'Amico *et al*, in a large systematic review, pointed out the need to make suggestions for future studies of prognostic indicators of cirrhosis, so that the information can be used in clinical practice [1].

A recent study reported the predictive value of high C-reactive protein (CRP) levels in patients with decompensated cirrhosis regarding short-term mortality, independently of relevant predictive factors such as MELD score [5]. CRP may be considered a surrogate marker for the early identification of infection in hospitalized cirrhotic patients [6], or subclinical inflammation related to bacterial translocation, and has true prognostic significance in cirrhotic patients with advanced liver failure, enabling the identification of those patients with a poor short-term prognosis [7].

On the other hand, serum albumin, a laboratory component of CTP score and a marker of liver insufficiency, lies among the most frequent predictors, indicating that even subtle abnormalities are predictive of death in cirrhotic patients [1]. Combining these data, a novel inflammation-based prognostic score was investigated in patients with hepatocellular carcinoma (HCC) [8]. The CRP-to-albumin ratio (CAR) was first introduced in patients with acute medical admissions and sepsis [9,10]. In 2015, Kinoshita *et al* [8] tried to verify its utility in liver disease, suggesting that the ratio might constitute an independent prognostic marker in patients with HCC in particular. Even more recently, Huang *et al* [11] introduced the marker in liver cirrhosis. They implied that CAR as a simple marker of inflammation could predict the long-term prognosis of patients with decompensated cirrhosis related to hepatitis B virus (HBV) [11].

In the same context, neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation, has been considered a useful predictor of short-term mortality in hospitalized cirrhotic patients [6]. Lymphocyte-to-monocyte ratio (LMR) has also been developed as an inflammation-based prognostic factor in liver cirrhosis, and is associated with the prognosis of HBV-related decompensated cirrhosis [11]. Similarly, in decompensated disease, elevated gamma globulins were also significant indicators of death risk [2], reflecting persistent intrahepatic inflammation.

The aim of our study was to evaluate the predictive role of CAR and other complementary, simple inflammatory markers in patients with stable decompensated cirrhosis. We attempted to determine their prognostic significance in patients with decompensated cirrhosis related to various liver diseases. Furthermore, our analysis focused on presenting a new biomarker with proposed cutoff values that could discriminate decompensated patients' outcomes.

Patients and methods

This was a prospective study of consecutive patients with stable decompensated cirrhosis who presented for pre-liver transplantation (LT) evaluation in our Department between 2010 and 2019. Decompensated cirrhosis was defined as a history of ascites, variceal bleeding and encephalopathy in patients with known cirrhosis. Patients were stable regarding their chronic liver disease: i.e., they had no active variceal bleeding, encephalopathy or infection, such as spontaneous bacterial peritonitis (SBP), during the last month before admission. Detailed clinical evaluation, laboratory measurements (including procalcitonin, blood cultures and ascitic fluid paracentesis) and radiological exams (chest x-ray, upper abdominal ultrasound), when necessary, were performed in order to exclude patients with clinical infection.

We examined our patients carefully and recorded their demographic, clinical and laboratory characteristics: age, sex, cause and duration of liver disease, previous complications of cirrhosis (i.e., variceal bleeding, encephalopathy or SBP), medication administered for the liver disease (duration and dosage), and vital signs (blood pressure, pulse rate). We estimated basic serum laboratory variables: albumin, protein, gamma globulins, bilirubin (total and direct), clotting profile, creatinine, electrolytes (e.g., sodium and potassium), aminotransferases (aspartate and alanine), alkaline phosphatase, γ-glutamyl transpeptidase, and lactate dehydrogenase. We evaluated our patients' prognosis by calculating their MELD [4] and CTP [12] scores. Finally, we calculated the CAR for our patients, as well as NLR and LMR. Based on our hospital's hematology and biochemical department, CRP has an upper limit of normal of 6 mg/L, the normal range for albumin is 3.5-5.2 g/dL and for gamma-globulins 2.3-3.4 g/dL. Normal range for neutrophil proportion is 45-75%, for monocytes 2-11% and for lymphocytes 20-51%.

According to our Department's protocol, patients underwent further evaluation before becoming placed on the LT list. In particular, their renal function ("true" glomerular filtration rate [GFR]) was assessed using ^{51}chromium-EDTA [13] along with estimated GFR using the creatinine-based 4-variable Modification of Diet in Renal Disease formula [14].

Only patients with full demographic and laboratory data were included in the study. All our patients were followed up prospectively, and their outcome was recorded and their features analyzed, whether they remained under supervision or underwent LT or died.

The study protocol was approved by our Institutional Review Board and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis

Continuous variables in our cohort were presented as mean±standard deviation (normally distributed) or median with interquartile range (non-normally distributed). Categorical variables were expressed as frequencies or percentages. Cox regression analysis was carried out to identify factors associated with our patients' outcomes and the association of inflammatory markers (CAR, NLR, LMR, and gamma globulins) with patients' characteristics. Survival analysis and Kaplan-Meier curves were used to estimate

the association of inflammatory markers with the clinical outcome. The discriminative ability of these markers to predict the outcome (alive vs. death or LT) of patients with decompensated cirrhosis was evaluated using the area under the receiver operating characteristic curve (ROC). This has the true-positive and false-positive rates on the vertical and horizontal axes, respectively. As the area under the curve (AUC) approaches 1.0, the model approaches 100% sensitivity and specificity. [15] Correlations between inflammatory markers and patients' characteristics were studied using the non-parametric Spearman's rho test or the parametric Pearson's r test. A P-value <0.05 was considered statistically significant. Statistical analysis was conducted using SPSS (version 25.0 IBM) and MedCalc Statistical software (version 19.1).

Results

We prospectively studied 159 stable decompensated patients treated in our Department (109 male, age 53±11 years). Table 1 shows their baseline characteristics. We followed our patients for about 10 months (range: 1-48). When the observational study was completed, 101 patients (64%) had survived and 58 patients (36%) had died or undergone LT: n=31 (19%) and n=27 (17%), respectively. In our cohort, CAR had a median value of 2.17 (range: 0.07-62), NLR 2.9 (range: 0.76-15), and LMR 2.1 (0.31-9.6). Based on the scanty data to date, the value of 1 has been proposed as a cutoff for CAR [11]; there were 40 patients (25%) with CAR<1 and 119 patients (75%) with CAR≥1. Moreover, there were 72 (45%) patients with LMR<1.9, the proposed optimal cutoff level, and 87 (55%) with LMR≥1.9 [11].

Finding the ideal cutoff for CAR

Using the proposed cutoff value of 1 for CAR [11], the results were significant regarding predictive scores for disease severity. The 40 patients with CAR<1 had a significantly better median CTP score than the other 119 patients with CAR≥1: 6 (range: 5-13) vs. 8 (range: 5-13), respectively (P<0.001). Median values of MELD score also showed a statistically significant difference: 10 (6-27) vs. 15 (7-33), respectively (P<0.001). Kaplan-Meier analysis found a trend towards different survival among the 2 groups: time of survival (median, range) 26 (13-38) vs. 16 (13-18) months (log rank P=0.05). ROC analysis showed a weak ability of CAR to discriminate patients based on their outcome: AUC 0.615, 95% confidence interval (CI) 0.527-0.704.

In our cohort, the optimal cutoff point for CAR for discriminating patients' outcomes was calculated to be 1.3, showing the best sensitivity along with specificity, 75% and 45%, respectively, Indeed, Kaplan-Meier analysis proved that this CAR value predicted statistically different survival for our patients. Patients with CAR <1.3 had a better median time of survival than those with CAR ≥1.3: 26 months (range: 14-37) vs. 14 months (range: 10-17), respectively (log rank P=0.016) (Fig. 1). Analyzing their characteristics, we found that patients with CAR<1.3 also had significantly lower total bilirubin (1.23 [0.24-14.5] vs. 2.51 [0.4-33], P<0.001) and higher serum albumin (3.89±0.7 vs. 3.2±0.57, P<0.001). They presented better CTP (7 [5-13] vs. 9 [5-13], P<0.001) and MELD score (11 [6-29] vs. 15 [7-33], P<0.001) and significantly higher LMR values (2.45 [1-6.5] vs. 1.8 [0.3-9.6], P=0.008) (Table 2).

Table 1 Baseline clinical and laboratory characteristics of 159 patients with stable decompensated cirrhosis

Variable	Patients, n=159
Age (mean±SD, years)	53±11
Sex, male n, (%)	109 (69)
Etiology of cirrhosis, n, (%)	
Viral hepatitis	51 (32)
Alcohol	43 (27)
NASH/ Other	65 (41)
Hepatocellular carcinoma, n (%)	19 (12%)
History of complications, n, (%)	
GI bleeding	47 (30)
Encephalopathy	55 (35)
SBP	25 (16)
Albumin (median, range, g/dL)	3.4 (1.4-7)
Gamma globulins (median, range, g/dL)	3.6 (0.3-6.5)
Creatinine (median, range, mg/dL)	0.9 (0.1-3.3)
"true" GFR by ^{51}chromium-EDTA (mean±SD, mL/min)	73±34
Serum sodium (mean±SD, mEq/L)	135±11
Neutrophil (mean±SD, %)	62±13
Lymphocyte (mean±SD, %)	22±9
Monocyte (mean±SD, %)	10±4
NLR (median, range)	2.9 (0.76-15.7)
LMR (median, range)	2.1 (0.31-9.6)
CTP score (median, range)	8 (5-13)
MELD score, (mean±SD)	14 (6-33)
CRP (median, range, mg/L)	6.7 (3.14-166)
CAR (median, range)	2.17 (0.07-62)

NASH, non-alcoholic steatohepatitis; GI, gastrointestinal; SBP, spontaneous bacterial peritonitis; GFR, glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; SD, standard deviation

Median value of CAR=2.17

We divided our patients into 2 groups using the median value of CAR 2.17. There were 79 patients with CAR<2.17 and 80 patients with CAR>2.17. Patients with CAR>2.17 had significantly lower serum albumin values (3.15+0.58 vs. 3.7+0.7, P<0.001) and higher CRP values (3.38 [3.14-8.4] vs. 15.4 [6-166], P<0.001), as expected. In addition, they had

Table 2 Clinical and laboratory characteristics of patients with CAR lower than the optimal cutoff <1.3 (group 1) and ≥1.3 (group 2)

Variables	Group 1 (n=54, 34%)	Group 2 (n=105, 66%)	P-value
Age (mean±SD, years)	51±10	54±11	0.055
Total bilirubin (median, range, mg/dL)	1.23 (0.24-14.5)	2.51 (0.4-33)	<0.001
Albumin (mean±SD, g/dL)	3.89±0.7	3.2±0.57	<0.001
CRP (median, range, mg/L)	3.28 (3.14-5.31)	12.5 (3.28-166)	<0.001
HCC, n, (%)	10 (18.5)	9 (8.5)	0.054
Creatinine (median, range, mg/dL)	0.84 (0.57-1.46)	0.95 (0.1-3.3)	0.09
"true" GFR by ^{51}chromium-EDTA (mean±SD, mL/min)	80±35	69±34	0.05
Gamma globulins (median, range, g/dL)	3.4 (1.42-6.3)	3.6 (1.1-6.5)	0.055
NLR (median, range)	2.52 (0.79-8.6)	3.14 (0.76-15.2)	0.23
LMR (median, range)	2.45 (1-6.5)	1.8 (0.3-9.6)	0.008
CTP score (median, range)	7 (5-13)	9 (5-13)	<0.001
MELD score (median, range)	11 (6-29)	15 (7-33)	<0.001

CRP, C-reactive protein; CAR, CRP-to-albumin ratio; HCC, hepatocellular carcinoma; GFR, glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; SD, standard deviation

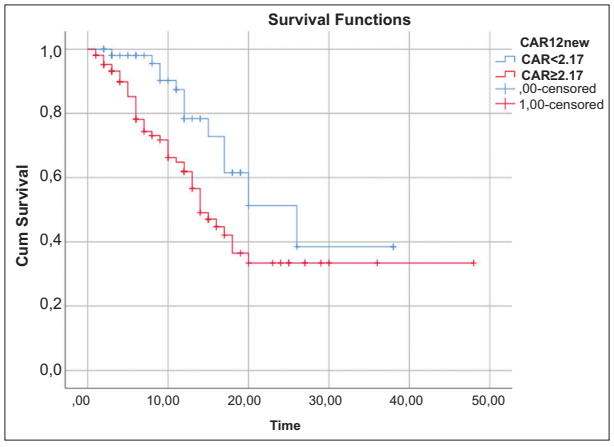

Figure 1 Kaplan-Meier curves showing different survival among decompensated patients based on optimal CAR cutoff value of 1.3 (log rank P=0.016)
CAR, C-reactive protein to albumin ratio

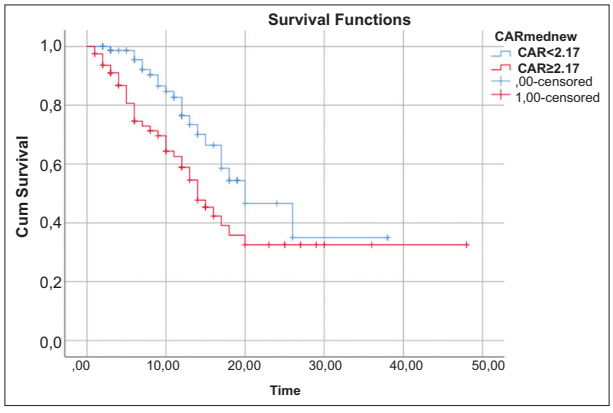

Figure 2 Kaplan-Meier curves showing difference of survival among decompensated patients based on median value of CAR (log rank, P=0.015)
CAR, C-reactive protein to albumin ratio

worse "true"-GFR (67±34 vs. 78±34, P=0.038), NLR (3.34 [0.76-15.2] vs. 2.47 [0.79-15.7], P=0.006), CTP (9 [5-13] vs. 7 [5-13], P<0.001) and MELD score (16 [7-33] vs. 12 [6-29], P<0.001), while presenting lower values of LMR (1.72 [0.31-9.63] vs. 2.47 [0.38-8.26], P<0.001) (Table 3). Kaplan-Meier analysis showed different times of survival, too; 20 months (12-27) vs 14 months (10-17) (log rank P=0.015) (Fig. 2).

Analysis of NLR, LMR, gamma globulins

NLR and LMR could not discriminate patients based on their outcome: ROC analysis for NLR (AUC 0.582, 95%CI 0.493-0.668), LMR (AUC 0.629, 95%CI 0.540-0.712), gamma globulins (AUC 0.509, 95%CI 0.420-0.597). Using the proposed cutoff of 1.9 for LMR we found that patients with LMR>1.9 presented significantly better renal function, based on true GFR (80±34 vs. 64±33 mL/min, P=0.004) and creatinine levels (0.84 [0.1-1.8] vs. 0.98 [0.59-3.3] mg/dL, P=0.001). They had lower CTP score (7 [5-13] vs. 9 [5-13], P<0.001) and MELD score (12 [6-28] vs. 15 [6-33], P=0.006), NLR (2.3 [0.76-6.81] vs. 4.8 [1.44-15], P<0.001) and CAR values (1.52 [0.15-62] vs. 3.9 [0.62-19], P<0.001). Moreover, we verified a positive association between LMR and true GFR (Spearman's ρ: 0.335, P<0.001). Survival analysis did not detect different times (log rank P=0.312).

Comparing factors in prognosticating patients' mortality

We conducted ROC analysis to compare MELD and CTP score with the herein introduced inflammatory factors CAR,

Table 3 Clinical and laboratory characteristics of patients with CAR<2.17 (group 1) and ≥2.17 (group 2)

Variables	Group 1 (n=79, 49.7%)	Group 2 (n=80, 50.3%)	P-value
Age (mean±SD, years)	52±10	55±11	0.1
Total bilirubin (median, range, mg/dL)	1.45 (0.24-14.5)	3.03 (0.4-33)	<0.001
Albumin (mean±SD, g/dL)	3.7±0.7	3.15±0.58	<0.001
CRP (median, range, mg/L)	3.38 (3.14-8.4)	15.4 (6-166)	<0.001
HCC, n, (%)	11 (14)	8 (10)	0.4
Creatinine (median, range, mg/dL)	0.85 (0.57-1.8)	0.94 (0.3-3.3)	0.14
"true" GFR by ^{51}Chromium-EDTA (mean±SD, mL/min)	78±34	67±34	0.038
Gamma globulins (median, range, g/dL)	3.57 (0.3-6.3)	3.71 (1.1-6.5)	0.1
NLR (median, range)	2.47 (0.79-15.7)	3.34 (0.76-15.2)	0.006
LMR (median, range)	2.47 (0.38-8.26)	1.72 (0.31-9.63)	<0.001
CTP score (median, range)	7 (5-13)	9 (5-13)	<0.001
MELD score (median, range)	12 (6-29)	16 (7-33)	<0.001

CRP, C-reactive protein; CAR, CRP-to-albumin ratio; HCC, hepatocellular carcinoma; GFR, glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; SD, standard deviation

NLR, LMR and gamma globulins. MELD and CTP scores were superior compared to all these new markers in predicting mortality: MELD (AUC 0.814) and CTP (AUC 0.752) (P-values for all comparisons with the other inflammatory markers <0.05) (Fig. 3).

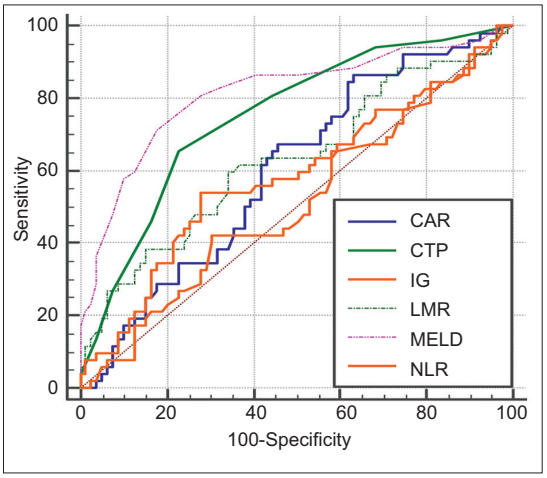

Figure 3 Receiver operating characteristic curves for predictive ability of different markers

Variables associated with our patients' outcome

Univariate and multivariate Cox regression analyses were performed to determine any independent prognostic risk factors in our cohort. Univariate analysis showed that bilirubin (HR 1.066 [1.026-1.108], P=0.001), serum creatinine levels (HR 1.88 [1.16-3.04], P=0.011), CAR as categorical variable using both the optimal cutoff point of 1.3 (HR 2.082 [1.122-3.86], P=0.02) and the median value 2.17 (HR 1.9 [1.11-3.25], P=0.019), CTP (HR 1.308 [1.15-1.482], P<0.001) and MELD score (HR 1.16 [1.115-1.208], P<0.001) were predictive factors associated with patients' outcomes. NLR, LMR and gamma globulins were not found to be significant predictive markers for our patients' outcomes (HR 1.03 [0.953-1.114], P=0.45; HR 0.901 [0.75-1.083], P=0.267; and HR 0.933 [0.704-1.236], P=0.63, respectively). Multivariate analysis showed that only MELD was a significant risk factor in our cohort, whether using the cutoff value of 1.3 (HR 1.17 [1.106-2.44], P<0.001) or 2.17 (HR 1.17 [1.104-1.243], P<0.001) for CAR as a categorical variable (Table 4). When MELD and CTP scores were excluded, none of the inflammatory markers were significantly associated with the outcome.

Patients who died or underwent LT (n=58) had significantly higher MELD score (19±6 vs. 12±4, P<0.001), CTP score (9±2 vs. 7±2, P<0.001), bilirubin (4.35 [0.8-33], vs. 1.5 [0.24-16], P<0.001), serum albumin (3.15 [1.9-4.3] vs. 3.4 [1.4-7], P=0.028], CAR (3.15 [0.76-16] vs. 1.48 [0.65-62], P=0.016), GFR (55±34 vs. 74±33, P=0.001) and lower LMR (1.77 [0.56-4.8] vs. 1.99 [0.38-9.6], P=0.05). There were no differences regarding age (53±12 vs. 52±10, P=0.9), serum creatinine (1.01 [0.08-3.3] vs. 0.88 [0.59-1.8], P=0.2), gamma globulins (3.75 [2-5] vs. 3.7 [0.3-6.5], P=0.6), or NLR (4.1 [1.1-8.6] vs. 2.9 [0.76-15], P=0.149).

Excluding patients who underwent LT (n=27), we conducted univariate analysis in the remaining patients (n=132) and found that MELD (HR 1.214 [1.148-1.284], P<0.001), CTP score (HR 1.466 [1.247-1.725], P<0.001), true GFR (HR 0.99 [0.98-0.999], P=0.038), creatinine (HR 1.91 [1.032-3.543], P=0.039), bilirubin (HR 1.072 [1.026-1.121], P=0.002), LMR 1.9 (HR 0.503 [0.242-1.046], P=0.06), CAR 1.3 (HR 3.63 [1.27-10.4], P=0.016) and CAR 2.17 (HR 2.84 [1.27-6.38], P=0.011) were significant factors of survival.

In multivariate analysis, only MELD score (HR 1.18 [1.082-1.29], P<0.001) was a significant factor. However, when MELD

Table 4 Univariate and multivariate Cox regression analysis was performed to acknowledge independent prognostic risk factors in our cohort

Variables	Univariate model			Multivariate model			
	Hazard Ratio	P-value	95%CI	Hazard Ratio	P-value	95%CI	
Sex (n, %)	0.87	0.63	0.508-1.511				
Age (years)	0.98	0.29	0.96-1.011				
HCC (n, %)	1.34	0.46	0.607-2.97				
Albumin (median, range, g/dL)	0.78	0.213	0.535-1.149				
Gamma globulins (median, range, g/dL)	0.933	0.63	0.704-1.236				
Bilirubin (median, range, mg/dL)	1.066	0.001	1.026-1.108				
Creatinine (median, range, mg/dL)	1.88	0.011	1.16-3.04				
GFR (median, range, mL/min)	0.99	0.48	0.99-1.005				
CRP (median, range, mg/L)	1.004	0.53	0.99-1.017				
CAR (median, range)	1.01	0.59	0.97-1.046				
CAR 1.3 (median, range)	2.082	0.02	1.122-3.86				
CAR 2.17 (median, range)	1.9	0.019	1.11-3.25				
CAR 1 (median, range)	1.949	0.066	0.957-3.97				
NLR (median, range)	1.03	0.45	0.953-1.114				
LMR (median, range)	0.901	0.267	0.75-1.083				
LMR 1.9 (median, range)	0.647	0.105	0.381-1.096				
CTP score (mean+SD)	1.308	<0.001	1.15-1.482	0.947	0.56	0.785-1.14	CAR 1.3
				0.945	0.55	0.782-1.14	CAR 2.17
MELD score (median, range)	1.16	<0.001	1.115-1.208	1.17	<0.001	1.106-2.44	CAR 1.3
				1.17	<0.001	1.104-1.243	CAR 2.17

CI, confidence interval; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; HCC, hepatocellular carcinoma; GFR, glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; SD, standard deviation

score and CTP score were excluded, CAR 2.17 was the only significant factor associated with the outcome (HR 3.61 [0.96-13.6], P=0.05) (Table 5). Kaplan-Meier analysis showed that patients with CAR≥2.17 had significantly worse survival (10 [1-48] vs. 11 [2-38] months, log rank P=0.003) (Fig. 4).

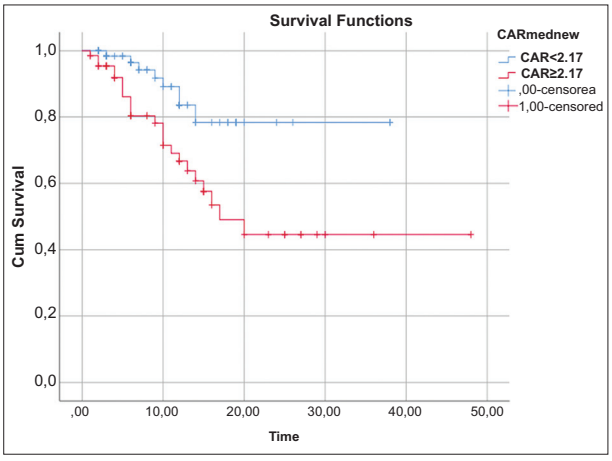

Figure 4 Kaplan-Meier curves showing difference of survival among decompensated patients based on median value of CAR, excluding those who underwent liver transplantation (log rank, P=0.007)
CAR, C-reactive protein to albumin ratio

Discussion

LT significantly improves the survival and quality of life of patients with end-stage cirrhosis. However, a large proportion of cirrhotic patients still die while on the transplant list, partly because of the lack of an accurate prediction of life expectancy. Many prognostic models have been proposed in the last 2 decades to predict mortality in cirrhosis [1]. Recently, however, it was shown that the short-term prognosis depends largely on events that temporarily worsen or are superimposed on liver failure, emphasizing the need for powerful prognostic markers able to identify severely cirrhotic patients with the highest short-term mortality risk [5].

Patients with cirrhosis have a high risk of bacterial infections, which burdens their outcome, so early diagnosis and treatment

Table 5 Univariate and multivariate analysis excluding patients who underwent liver transplantation (n=132)

Variables	Univariate model			Multivariate model (excluding MELD & CTP score)		
	Hazard Ratio	P-value	95%CI	Hazard Ratio	P-value	95%CI
Sex (n, %)	0.65	0.237	0.32-1.325			
Age (years)	1.016	0.42	0.978-1.056			
gamma-globulins (median, range, g/dL)	0.98	1.004	0.69-1.46			
Bilirubin (median, range, mg/dL)	1.072	0.002	1.026-1.121			
Creatinine (median, range, mg/dL)	1.91	0.039	1.032-3.54			
GFR (median, range, mL/min)	0.038	0.99	0.98-0.99			
CAR (median, range)	1.013	0.51	0.99-1.054			
CAR 1.3 (median, range)	3.63	0.016	1.27-10.4			
CAR 2.17 (median, range)	2.84	0.011	1.27-6.379	3.61	0.05	0.96-13.6
NLR (median, range)	1.048	0.34	0.95-1.15			
LMR (median, range)	0.8	0.13	0.6-1.06			
CTP score (mean+SD)	1.46	<0.001	1.24-1.72			
MELD score (median, range)	1.21	<0.001	1.148-1.284			

CI, confidence interval; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; GFR, glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; SD, standard deviation

is essential to improve their prognosis [16]. High CRP levels, associated with systemic inflammatory response syndrome and infections, may identify those patients with severe cirrhosis who have a higher short-term risk of mortality [5]. Elevation of serum gamma globulin levels is known to be a frequent occurrence in patients with chronic liver disease [17]. This might reflect systemic inflammation and endotoxemia derived from gut microbiota, associated with the development of the decompensating complications seen in cirrhosis [18]. Hence, inflammation-based prognostic scores such as CAR [8] are worthy of studying in patients with decompensated cirrhosis.

Indeed, CAR has been identified as a prognostic marker in HBV-related decompensated patients and the proposed optimal cutoff of 1 could predict different survival [11]. CAR was first verified as an independent prognostic marker in patients with HCC [8]. Given that cirrhosis is the most common cause of HCC, Huang *et al* proposed that CAR could be a prognostic factor for patients with liver cirrhosis [11]. In Kaplan-Meier analysis CAR>1.0 was a significant risk factor (HR 7.19, [4.69-11.03]); those patients had a 2.43-fold longer survival time and CAR showed the best performance in predicting the mortality of HBV-decompensated cirrhosis, compared with LMR, MELD, and CTP scores.

In our cohort, we studied the marker for the first time in decompensated cirrhosis of different etiologies and searched for the optimal cutoff point. We suggested optimal cutoff points of 1.3 and the median CAR value 2.17 as significant factors for detecting different survival in the univariate Cox regression analysis. However, in multivariate analysis, with or without MELD and CTP scores, we could not demonstrate a significant association with patients' prognosis. Thus, we were not able to confirm the findings of Huang *et al*. However, when those patients who underwent LT were excluded, univariate models for CAR 1.3 (HR 3.63 [1.27-10.4], P=0.016) and CAR 2.17 (HR 2.84 [1.27-6.379], P=0.011) showed significance regarding patients' survival. According to the multivariate analysis, we could propose CAR 2.17 as a significant factor associated with a 3.6 times higher risk for a worse outcome (P=0.05).

Additionally, Huang *et al* investigated the prognostic significance of other inflammatory markers and showed that LMR ≥1.9 is associated with significantly worse survival [11]. Studying our 159 decompensated patients, we found a weak ability of NLR to discriminate patients' outcomes (AUC 0.582, 95%CI 0.493-0.668). LMR also showed similar results (AUC 0.629, 95%CI 0.540-0.712). Interestingly, patients with LMR ≥1.9 presented significantly better renal function, based on true GFR (80±34 vs. 64±33 mL/min, P=0.004) and creatinine levels (0.84 [0.1-1.8] vs. 0.98 [0.59-3.3] mg/dL [P=0.001], with a significant association being found between LMR and GFR (Spearman's ρ: 0.335, P<0.001). They also had worse CTP score (7 [5-13] vs. 9 [5-13], P<0.001) and MELD score (12 [6-28] vs. 15 [6-33], P=0.006]). However, our findings regarding survival analysis (log rank, P=0.312) did not confirm the significance of NLR found by Kwon *et al*, who suggested that NLR could predict one-month survival as the MELD score does in hospitalized cirrhosis patients [6].

Recently, Cacciola *et al* studied the role of serum gamma globulins in relation to the clinical outcome in cirrhotic patients [19]. They proved that hypergammaglobulinemia is a strong predictor of disease progression, hepatocellular carcinoma and death in patients with cirrhosis, and that hypergammaglobulinemia may help identify the CTP class A cirrhotics with a poorer prognosis. Our results, however, showed that MELD and CTP score were superior to gamma

globulins in predicting mortality, and that gamma globulins were not significant predictive markers for our patients' outcome in Cox regression analysis.

Our study has several limitations, notably its relatively small sample size. This could downgrade our results. Further and larger studies are needed to verify our findings.

In conclusion, we managed for the first time to investigate the prognostic role of 4 different inflammatory markers in decompensated cirrhotic patients with various etiologies. Our results suggest the significance of CAR and LMR in outcomes and patients' renal function. CAR was associated with the prognosis of patients with decompensated cirrhosis. In general, inflammatory markers appeared to play significant roles in these patients.

Summary Box

What is already known:

- C-reactive protein to albumin ratio (CAR) has been found to predict long-term outcomes in patients with decompensated cirrhosis related to hepatitis B virus
- Neutrophil-to-lymphocyte ratio predicts short-term mortality in hospitalized cirrhotics
- Other inflammatory markers, lymphocyte-to-monocyte ratio (LMR) and gamma globulins, have also emerged as inflammation-based prognostic factors in liver cirrhosis

What the new findings are:

- LMR with a cut-off of 1.9 could predict better renal function in decompensated patients
- Decompensated patients with CAR<2.17 presented better survival
- Excluding model for end-stage liver disease and Child-Turcotte-Pugh scores, CAR≥2.17 was independently associated with death in decompensated patients

References

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006;**44**:217-231.
2. D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci* 1986;**31**:468-475.
3. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet* 2008;**371**:838-851.
4. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;**33**:464-470.
5. Cervoni JP, Thévenot T, Weil D, et al. C-reactive protein predicts short-term mortality in patients with cirrhosis. *J Hepatol* 2012;**56**:1299-1304.
6. Kwon JH, Jang JW, Kim YW, et al. The usefulness of C-reactive protein and neutrophil-to-lymphocyte ratio for predicting the outcome in hospitalized patients with liver cirrhosis. *BMC Gastroenterol* 2015;**15**:146.
7. Cervoni JP, Amorós, Bañares R, et al; EASL-CLIF Consortium. Prognostic value of C-reactive protein in cirrhosis: external validation from the CANONIC cohort. *Eur J Gastroenterol Hepatol* 2016;**28**:1028-1034.
8. Kinoshita A, Onoda H, Imai N, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. *Ann Surg Oncol* 2015;**22**:803-810.
9. Fairclough E, Cairns E, Hamilton J, et al. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. *Clin Med (Lond)* 2009;**9**:30-33.
10. Ranzani OT, Zampieri FG, Forte DN, Cesar L, Azevedo P, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. *PLoS ONE* 2013;**8**:e59321.
11. Huang SS, Xie DM, Cai YJ, et al. C-reactive protein-to-albumin ratio is a predictor of hepatitis B virus related decompensated cirrhosis: time-dependent receiver operating characteristics and decision curve analysis. *Eur J Gastroenterol Hepatol* 2017; **29**:472-480.
12. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;**60**:646-649.
13. Fleming JS, Nunan TO; British Nuclear Medicine Society. The new BNMS guidelines for measurement of glomerular filtration rate. *Nucl Med Commun* 2004;**25**:755-757.
14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461-470.
15. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;**148**:839-843.
16. Piano S, Brocca A, Mareso S, Angeli P. Infections complicating cirrhosis. *Liver Int* 2018;**38** Suppl 1:126-133.
17. Holdstock G, Ershler WB, Krawitt EL. Demonstration of non-specific B-cell stimulation in patients with cirrhosis. *Gut* 1982;**23**:724-728.
18. Patel VC, Shawcross DL. Salivary microbiota-immune profiling in cirrhosis: Could this be the noninvasive strategy that will revolutionize prognostication in hepatology? *Hepatology* 2015;**62**:1001-1003.
19. Cacciola I, Filomia R, Alibrandi A, et al. Hypergammaglobulinemia is a strong predictor of disease progression, hepatocellular carcinoma, and death in patients with compensated cirrhosis. *Liver Int* 2018;**38**:1220-1229.