

## C-reactive protein and bacterial infection in cirrhosis

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### Abstract

In the general population, C-reactive protein (CRP) level increases in the presence of acute or chronic inflammation and infections. In patients with cirrhosis, the basal level is higher than in patients without cirrhosis, due to chronic hepatic and other inflammation, but when infection occurs the more severe the underlying liver dysfunction, the lower the increase in CRP. Therefore, the predictive power of CRP for infection and prognosis is weak in patients with decompensated/advanced cirrhosis and in the intensive care setting. However, higher CRP and also persistently elevated CRP levels can help identify patients with a higher short-term risk of mortality.

**Keywords** C-reactive protein, bacterial infections, cirrhosis, Intensive Care Unit, mortality, prognosis

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### Introduction

Bacterial infections are a common cause of morbidity and mortality in patients with cirrhosis. In about 30% of patients, infections are present at admission or develop during hospitalization [1]. Moreover, bacterial infections are known to be a potential trigger factor for many complications of cirrhosis, including variceal bleeding, hepatic encephalopathy, renal failure and impairment in hemostasis [2].

Sixty percent of bacterial infections are community-acquired, where the causative organisms are Gram negative bacilli (GNB) in about 60% (especially *Escherichia coli*) and Gram positive cocci (GPC) in about 30-35%, and forty percent are nosocomial infections, with 60% of GPC and 30% GNB, as result of the use of therapeutic procedures and previous antibiotic therapy. The most frequent infections are spontaneous bacterial peritonitis (SBP), urinary tract infections, pneumonia, cellulitis and bacteremia [3,4].

A major problem is that "traditional" culture methods under diagnose sepsis in these patients, only being positive in 50-70% of cases, and culture methods take time; therefore

surrogate markers, such as C-reactive protein (CRP), may be useful to identify an infection early on.

Patients with cirrhosis have an increased risk to develop bacterial infection, sepsis, sepsis-induced organ failure and sepsis-related death [3]; on the other hand, infections significantly increase the mortality rate, which reaches 38% [3]. These patients are twice as likely to die from sepsis than individuals without cirrhosis [5]. Hospital mortality with septic shock may exceed 70%, related to the development of multiorgan failure [6]. In particular, renal failure occurs in 33% of patients with cirrhosis who have SBP and in 27% of those with sepsis unrelated to SBP: this is initially the hepatorenal syndrome, which in presence of shock rapidly develops into ischemic acute tubular necrosis.

### Methods

MEDLINE was searched, in the international literature, using the textwords "C-reactive protein or CRP", "acute phase proteins", "liver cirrhosis", "bacterial infections", "critically ill patients", "Systemic Inflammatory Response Syndrome" or "SIRS", "hepatocellular carcinoma or HCC".

### Pathogenesis of sepsis in cirrhosis

The particular susceptibility of patients with cirrhosis to infections is related to an immunodeficient state due to the concomitant presence of various facilitating mechanisms. In cirrhosis there are changes in the intestinal flora and intestinal barrier, reduced reticuloendothelial function,

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deficiencies in C3 and C4, decreased opsonic activity of the ascitic fluid and neutrophils leukocyte dysfunction [4]. The above mechanisms lead to a reduced bacterial clearance, which also facilitate bacterial translocation induced by increased intestinal permeability and bacterial overgrowth [4,7]; patients with alcoholic cirrhosis have depressed neutrophil phagocytic activity and intracellular killing (of *Staphylococcus aureus* and *Escherichia coli*).

In the early phase of bacterial sepsis, there is an excessive pro-inflammatory response, with significantly higher circulating levels of the pro-inflammatory cytokines tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-6 in infected patients with cirrhosis than in those without. The activation of Toll-like receptors 4 (TLR4), one of the pathogen recognition receptors (PRRs), used by the immune system to recognize macromolecules expressed by microbes (microorganisms-associated molecular patterns, MAMPs) and stimulated by lipopolysaccharide (LPS), induces higher production of TNF- $\alpha$  and IL-6 in cirrhotic rats than in normal rats. This has been confirmed *ex vivo*, demonstrating a higher production of TNF- $\alpha$  and IL-6 by monocytes from Child C than from Child B patients. Monocytes in patients with cirrhosis are also defective in LPS-induced production of anti-inflammatory IL-10. Genetic immune defects, i.e. TLR2 polymorphisms, could also contribute to the high risk of bacterial infection in cirrhosis [8].

This bacteria-induced “cytokine storm” contributes to sepsis-related organ failure [7,9,10]. In addition, the pro-inflammatory phase is followed by a prolonged “immunoparalysis”, called compensatory anti-inflammatory response syndrome (CARS), contributing to repeated secondary nosocomial infection and death [11].

### Clinical risk factors and current diagnosis of bacterial infections

Clinical risk factors associated with the occurrence of bacterial infections in cirrhosis are low ascitic protein levels ( $<1.5$  g/dL), a prior episode of SBP, variceal bleeding and high Child-Pugh score [12-15].

It is important to emphasize that infected patients with cirrhosis can be asymptomatic at initial stages [16,17]. Therefore, a complete work-up should be carried out at admission and whenever a hospitalized patient clinically deteriorates in order to detect and treat a possible infection as soon as possible.

The diagnosis of SBP is based on ascitic fluid analysis: polymorphonuclear (PMN) count  $\geq 250$  cells/mm<sup>3</sup> is considered diagnostic and constitutes an indication to initiate an empirical antibiotic treatment, as the ascitic fluid culture is positive only in 40-60% of cases. Leukocyte reagent strips have been proposed as a rapid screening test for the diagnosis of SBP, but its variable sensitivity (45-100%) makes this method suboptimal.

Infection is easier to diagnose in the presence of sepsis, the first stage of severity of the inflammatory host response

to infection. Two or more of the following criteria, and the presence of infection, are required to make the diagnosis of sepsis in the general population: 1) a heart rate  $\geq 90$  beats/min; 2) tachypnea  $\geq 20$  breaths/min or partial carbon monoxide pressure (PaCO<sub>2</sub>)  $\leq 32$  mmHg or the need of mechanical ventilation; 3) a core temperature  $\geq 38^\circ\text{C}$  or  $\leq 36^\circ\text{C}$ ; 4) a white blood cell count  $\geq 12 \times 10^9/\text{L}$  or  $\leq 4 \times 10^9/\text{L}$  or  $>10\%$  of immature neutrophils [18]. Unfortunately, these criteria are also found due to chronic liver disease per se. In cirrhosis, the hyperdynamic circulation leads to tachycardia in the absence of infection, and conversely patients receiving  $\beta$ -blockers for prophylaxis of variceal bleeding have a reduced heart rate; hepatic encephalopathy may lead to tachypnea; hypersplenism decreases white blood cell count. For these reasons, the diagnostic accuracy of these criteria (Systemic Inflammatory Response Syndrome, SIRS, criteria) for the detection of sepsis is much lower in patients with cirrhosis: they are present in 10-30% of decompensated patients with cirrhosis without infection and in only 55-70% of infected patients. However, the presence of SIRS at admission or during hospitalization constitutes a useful prognostic parameter since it is associated with a higher probability of portal hypertension-related complications and death during acute liver failure or decompensated cirrhosis [8,19,20].

### CRP

CRP, named for its capacity to precipitate C-polysaccharide of *Streptococcus pneumoniae*, is a well-known marker of inflammation and is also used as a marker of infection in different settings. It is synthesized in the acute phase of inflammation mainly in response to IL-6, but also IL-1 and IL-17 [21]. Serum CRP concentrations increase in situations responsible for a SIRS (with or without documented infection) in patients without cirrhosis (AUROC in the diagnosis of sepsis versus SIRS: 0.794, for CRP  $>90$  mg/L) and is strongly associated with mortality in different populations of patients without cirrhosis in intensive care [22,23]. However, although CRP is a sensitive but nonspecific systemic marker of inflammation, it also rises dramatically in other situations, including trauma, burns, myocardial infarction and cancer [24], i.e. potential reasons for admission to intensive care.

### Production of CRP

Despite the widespread use of CRP in clinical practice, the site of production and the metabolism of CRP are not well defined. It was thought that CRP was produced exclusively by hepatocytes, but recent studies suggest other sites of production including coronary-artery smooth-muscle cells, inflamed kidneys, human neurons and alveolar macrophages, adipose tissue and also due to external stimuli such as smoking, alcohol and coffee intake [25-28]. The plasma half-life of CRP is about 18.8 h, determined mainly by plasma clearance, while the renal clearance is negligible, both in patients with severe

renal disease and in healthy subjects: CRP can be filtrated, but like other proteins it is reabsorbed by the tubulus [29,30].

### Methods for detection of CRP

The main methods for detecting serum CRP include turbidimetric immunoassay, latex photometric immunoassay and ELISA, giving a result which can range from 10 to 1000 mg/L. Moreover, a high-sensitive method exists, used in particular in the cardiovascular disease setting (high-sensitive CRP level, hs-CRP, ranges from 0.5 to 10 mg/L).

### CRP in acute alcoholic hepatitis (AH)

In alcoholic hepatitis, Vanbiervliet *et al* found that CRP levels (n=29/101 active drinkers) increase significantly with the severity of disease ( $P<0.001$ ), having excluded infections, inflammatory disease or antibiotic therapy. CRP was an independent factor for predicting alcoholic hepatitis (OR 1.1 CI, 95% 1.02–1.19,  $P=0.01$ ; AUROC 0.78, cut-off values of CRP >19 mg/L, diagnostic accuracy 82%, sensitivity 41%, specificity 99%, positive and negative predictive value 92% and 81% respectively) [31] and for prognosis, in patients with and without cirrhosis [32]. It was not useful to distinguish sepsis from patients without sepsis.

### CRP in chronic inflammation (patients with and without cirrhosis)

Systemic changes of the acute-phase response accompany not only acute but also chronic inflammatory disorders. Patients with cirrhosis without infection have elevated circulating IL-6 concentration and also increased expression of TNF-receptors [33,34]. In cirrhosis, several factors independent of infection, such as hepatocellular carcinoma (HCC), necrosis or the ongoing local inflammatory reaction in liver tissue and bacterial translocation (BT), are potentially able to induce the synthesis of these markers limiting their clinical utility [26,35,36].

In a study assessing the relationship of serum leptin level to sex, nutritional status and energy metabolism in patients with

alcoholic liver cirrhosis, Campillo and co-workers found that CRP concentrations were higher in patients with cirrhosis than in those without ( $12.1\pm 14.4$  mg/L vs  $5.9\pm 4.9$  mg/L) [37]. This difference was also observed by Tilg *et al* [33] in their study of serum cytokines in chronic liver disease (136 cirrhosis vs. 128 non-cirrhotic stage: CRP was  $1.2\pm 0.2$  vs.  $0.4\pm 0.1$  mg/dL).

Two studies have documented increased concentrations of CRP in non-infected patients with cirrhosis, regardless of the etiology: increased serum CRP levels were found to be lower in autoimmune than alcoholic or viral cirrhosis [33,38].

### CRP in advanced liver disease (Table 1)

The relationship between CRP and the severity of liver cirrhosis has been assessed, using Child-Pugh score. In two series (n=105 [39] and n=79 [26]) no significant difference was found between patients classified with different Child Pugh scores (data not reported,  $P=0.33$  [39]), with and without infection (Child C vs. A:  $10.3\pm 5.8$  mg/dL vs.  $11.2\pm 3.3$  mg/dL and  $2.6\pm 2.3$  mg/dL vs.  $2.9\pm 1.9$  mg/dL, respectively [26]).

In contrast, another two studies demonstrated that the accuracy of CRP for identifying patients with infection decreased in advanced liver disease (n=368, CRP cut off 9.2 mg/L: AUROC for detection of infection Child A 0.97; Child B 0.91; Child C 0.87 [40]) or in presence of ascites (AUROC 0.95 without vs. 0.88 with ascites [40]). In a case-control study (n=30 infected vs. 30 non infected patients), despite the increased basal CRP concentrations in patients with advanced liver dysfunction, the more severe the underlying liver dysfunction, the lower the CRP response to bacteremia [41].

Therefore CRP has a weak predictive power for infection in patients with decompensated cirrhosis, as confirmed also by Le Moine *et al* [34] who showed that CRP correlated weakly with IL-6 levels in infected patients (where IL-6 was >200 pg/mL), indicating a defective acute phase response in cirrhosis.

### CRP in patients with cirrhosis admitted to Intensive Care Units (ICU)

In critically ill patients, there is evidence that CRP levels adequately reflect systemic immune activation [42,43] and it is independently associated with post-ICU survival [44]. In

**Table 1** C-reactive protein (mg/dL) and advanced liver disease. In parentheses, the number of patients

	Total patients	Child A	Child B	Child C	In relation to the severity of cirrhosis
Bota [26]	39 infected	(15) $11.2\pm 3.3$	(14) $10.8\pm 4.9$	(10) $10.3\pm 5.8$	No significant difference
	40 non infected	(13) $2.9\pm 1.9$	(13) $2.7\pm 1.1$	(14) $2.6\pm 2.3$	No significant difference
Janum [39]	105	(5)	(41)	(59)	$P=0.33$
Papp [40]	368	(113) AUROC 0.97	(142) AUROC 0.91	(103) AUROC 0.87	
Park [41]	30 infected			5.0 (0.2-12.1) infected	$P<0.001$
	30 non infected			0.5 (0.1-1.2) non infected	

this setting, patients with cirrhosis have higher mortality rate, greater disease severity, assessed on the basis of the APACHE II score, a greater degree of organ dysfunction, as defined by the SOFA score, and higher rate of infection than patients without cirrhosis [45-47]. However, in a study (79 patients with cirrhosis from 864 patients) [26], there was no significant difference in the accuracy of basal CRP for detection of infection in patients with and without cirrhosis (AUROC 0.64 and 0.69 respectively), perhaps because most intensive-care patients have a certain degree of inflammation, which is not always the case in other hospital settings.

### CRP as marker of SIRS and infection in cirrhosis (Table 2)

The occurrence of a systemic inflammatory response syndrome can influence survival: SIRS increases the risk of encephalopathy, renal failure, infections and death during acute or chronic decompensated cirrhosis. Therefore, SIRS can be an additive prognostic factor to severity of liver disease. However, it can be difficult to diagnose SIRS in cirrhosis, thus new markers would be particularly useful in this population.

CRP has been evaluated both for the diagnosis of SIRS and for prediction of short-term mortality in cirrhosis.

In the setting of bacterial infection the median CRP level was significantly lower in patients with cirrhosis than without cirrhosis (105 with cirrhosis vs. 202 without: median CRP level 81 mg/L vs. 139 mg/L [39]; 33 vs. 93: median CRP level 103 mg/L vs. 146 mg/L,  $P=0.03$  [48].

However, in a cohort of 148 patients with decompensated

cirrhosis admitted to a single Hepatology unit, Cervoni *et al* [49] found baseline CRP levels to be higher in patients with infection (46 mg/L vs 27 mg/L in patients without infection;  $P<0.001$ ), SIRS (53 mg/L vs. 27 mg/L in patients who did not fit SIRS criteria;  $P<0.001$ ) and in alcoholic hepatitis (44 mg/L vs. 32 mg/L for different etiology,  $P=0.049$ ). Moreover, CRP was positively correlated with the bilirubin concentration, heart rate and leukocyte count. The AUROC of CRP for the diagnosis of SIRS was 0.73 (95%CI 0.62-0.81) and was significantly higher than the AUROC of procalcitonin (PCT) (0.65, with 95%CI 0.50-0.75) for the same diagnosis. The best predictive value of CRP for SIRS, given by the Youden index, was 26 mg/L, with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 76.2%, 63.8%, 45.7% and 87.0% respectively.

Another study [50] reported AUROC for sepsis of 0.81 (95%CI 0.72-0.89), based on 98 patients with cirrhosis admitted in an emergency department.

In a prospective study [51] on decompensated cirrhosis ( $n=64$ ), significantly higher median CRP and PCT levels were observed among infected patients ( $P<0.001$ ). The AUROC for CRP for the diagnosis of infection was  $0.835\pm 0.052$ . CRP level  $>29.5$  mg/L exhibited sensitivity 82% and specificity 81%; for PCT it was  $0.860\pm 0.047$ , ( $P=0.273$ , with sensitivity 67% and specificity 90%).

### CRP and mortality in cirrhosis

In a study of 148 patients with cirrhosis admitted in a Hepatology Department, the 6-month mortality was associated with

**Table 2** CRP and SIRS/infection

	Patients (with cirrhosis)	Infected/non infected	Median CRP level in patients with cirrhosis and infection (mg/L)	Median CRP level in patients without cirrhosis and infection (mg/L)	AUROC for infection	CRP cut off (mg/L)	Sensitivity - specificity	Notes
Janum [39]	307 (105)		81	139				
Mackenzie 48]	146 (33)		103	146				
Cervoni [49]	(148)				0.73 (for SIRS)	26	76%-64%	Decompensated pts
Li [50]	(98)	27.6%			0.81 (for sepsis)	24.7	80%-80%	Emerg. unit
Lazzarotto [51]	(64)	-			0.835 (for infection)	29.5	82%-81%	Decompensated pts
Lin [53]	(94)					20	80%-81%	
Tsiakalos [55]	(88)	19/69			0.91	55.8	79%-96%	
Papp [40]	(368)	139/229			0.93	9.2	88%-88%	
Bota [26]	864 (79)	48%/-			0.64			ITU patients
Viallon [54]	(61)	21/40			79%	80	62%-92%	SBP. Emerg. unit

CRP, c-reactive protein; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome; ITU, intensive therapy unit

high baseline CRP levels (47 mg/L vs. 29 mg/L, respectively in non-survivors and survivors  $P=0.003$ , univariate analysis), and also high MELD score, high INR, elevated blood lactate and presence of extrahepatic co-morbidities. Considering the 29 mg/L cut-off value of CRP at baseline and at day 15, patients with CRP levels persistently higher than 29 mg/L (group A, 32 patients) had worse 3-month and 6-month survival compared with patients who had baseline CRP level 29 mg/L with subsequent decrease below 29 mg/L (group B, 29 patients) and compared to patients with baseline CRP level <29 mg/L (group C, 84 patients). The 3-month and 6-month survival rates were 48.1% and 45.1%, 86.1% and 77.6%, 84.0% and 78.4% in group A, group B and group C patients respectively ( $P<0.001$ ) [25]. These results can be interpreted as decreases in CRP levels preceding clinical improvement, whereas the failure of CRP concentrations to fall could predict a poor outcome in infected patients with cirrhosis. The multivariate analysis using Cox modeling, corrected for age, identified three predictors of short-term mortality: MELD score, presence of at least one extrahepatic co-morbidity and belonging to group A (HR 2.73; 95%CI 1.41-5.26;  $P=0.003$ ). Moreover, the performance of these three variables taken together in a multiple logistic regression analysis for predicting 6-month mortality was 0.80 (AUROC; 95%CI 0.73-0.87), suggesting the possible use of a "MELD-CRP" score [49].

Ha and colleagues [52] also tried to evaluate the value of baseline CRP at admission to hospital as a predictor of clinical outcome and to investigate whether follow-up CRP measurement (at admission and at day 4 or 5) was useful for predicting the 30-day mortality in patients with cirrhosis and bacteremia. They found that the overall 30-day mortality rate was 23.8% (48/154) and there was no association between initial CRP level and mortality. They also observed that 43 of the 78 survivors showed decreased CRP levels below 70% of the initial level at day 4 or 5 (11% vs. 55%;  $P=0.015$ ), and found that a CRP ratio of  $\geq 0.7$  was associated with increased mortality ( $P<0.05$ ). Therefore a decrease in CRP level after the initiation of antimicrobial therapy was significantly associated with a better outcome, although no association between initial CRP level and outcome was found.

Significantly higher levels of CRP ( $P=0.026$ ) and PCT ( $P=0.001$ ) were observed among those who died within 3 months after admission (64 decompensated patients) [51].

### CRP cut-off for infections (Table 2 and 3)

Data are not homogeneous about the optimal cut-off for CRP, to differentiate patients with infection from those without.

Lin *et al* [53] suggested 20 mg/L (with sensitivity 80.39%, specificity 80.77% and accuracy 80.62%), others 24.7 mg/L [50] (se 80.0%, sp 80.3%) or 80.0 mg/L [54] (se 62% sp 92%).

Tsiakalos *et al* [55] analysed the diagnostic value of several acute-phase proteins (CRP, ferritin,  $\beta_2$  microglobulin and others) as indicators of bacterial infection in 88 patients with cirrhosis and found that CRP was the best test for detecting bacterial infection (AUROC 0.91). He proposed a cut-off value of 55.8 mg/L, which showed high sensitivity (79%) and specificity (96%), with the best diagnostic accuracy (92%).

Papp *et al* [40] confirmed that the best marker for infection was CRP (n=368; AUROC 0.93, 95%CI versus AUROC for procalcitonin 0.84, 95%CI), but with the best accuracy detected at 9.2 mg/L (sensitivity 88.1% and specificity 87.8%). Moreover, patients without infection but with CRP above 10 mg/L at baseline developed clinically significant episodes of bacterial infection at a significantly higher rate than patients with CRP <10 mg/L (univariate analysis: OR 3.78, 95%CI 1.21-11.83) and earlier within a 3 month period (Kaplan Mayer analysis: HR 12.12, 95%CI 2.30-63.80,  $P$  Breslow 0.0032,  $P$  LogRank 0.0027) or 12 month follow up period (HR 4.43, 95%CI 1.35-14.54,  $P$  Breslow 0.014,  $P$  LogRank 0.010).

In a cohort of 183 patients with decompensated cirrhosis, a baseline CRP level higher than >12 mg/dL was a significant factor for the diagnosis of infection (OR 4.191, 95%CI 2.203-7.971,  $P=0.000$ ), but in a Child Pugh C group the combination of CRP (>12 mg/dL) and neutrophils-to-lymphocyte ratio (>3.2) (NLR) enhanced diagnostic accuracy of infection [56].

**Table 3** C-reactive protein (CRP) versus procalcitonin (PCT)

	CRP AUROC	Sensitivity %	Specificity %	Cut off	PCT	Sensitivity %	Specificity %	Cut off
Cervoni [49]	AUROC for SIRS 0.73 (95%CI 0.62-0.81)	76	64	26 mg/L	AUROC for SIRS 0.65 (95%CI 0.50-0.75)	na	na	na
Li [50]	AUROC for sepsis 0.81 (95%CI: 0.72-0.89)	80	80	24.7 mg/L	AUROC for sepsis 0.85 (95%CI 0.77-0.92)	81.5	87.3	0.49 ng/mL
Viallon [54]	AUROC for SBP 79% (serum CRP)	62	92	80 mg/L	AUROC for SBP 98% (ascitic PCT)	95	98	0.76 ng/mL
Papp [40]	AUROC 0.93 (95%CI 0.90-0.95)	88	88	9.2 mg/L	AUROC 0.84 (95%CI 0.79-0.88)	na	na	na
Bota [26]	AUROC for SBP 0.64	na	na	na	AUROC 0.68	na	na	na

na, not available

## CRP and HCC

A strong association of CRP with prognosis has been demonstrated in gastrointestinal, pancreatic, renal and ovarian cancers, lymphoma, myeloma bone disease and melanoma. However, the current opinion on the prognostic role of CRP in HCC is still controversial, due to contradictory results but also small sample sizes in individual studies.

A meta-analysis [57] including 11 cohorts (from 10 studies: 7 from Asia) and 1,885 patients with HCC, showed that high serum CRP expression is significantly associated with poor overall survival (OS) (HR 2.15, 95%CI 1.76-2.63) and recurrence-free survival (RFS) (HR 2.66, 95%CI 1.54-4.58) in HCC. Moreover, a pooled analysis concluded that high serum CRP was significantly related to the presence of microvascular invasion [58] (based on five studies: OR 3.05, 95%CI 1.79-5.23,  $P=0.000$ , with no significant heterogeneity between the five studies), multiple tumors (based on five studies: OR 2.36, 95%CI 1.36-4.10,  $P=0.002$ , and substantial heterogeneity), larger tumor size (based on two studies: OR 3.41, 95%CI 1.04-11.18,  $P=0.043$ , with significant heterogeneity), advanced TNM stage (based on two studies: OR 3.23, 95%CI 2.29-4.57,  $P=0.000$ , with no heterogeneity). However, the cut-off values and detection methods for serum CRP were different among the included studies: most set a cut-off value of 10 mg/mL, while two studies relevant to high-sensitive CRP set a cut-off value of 3 mg/L.

The molecular mechanism of tumor-related CRP elevation in HCC and other solid tumors remains unclear. One possible explanation is the proinflammatory cytokine, IL-6, which is highly expressed in the tumor microenvironment. Recent studies indicate that inflammation, with the interaction between various inflammatory cells and extracellular matrix, plays a crucial role in tumorogenesis. However, Cervoni *et al* [49] found that CRP had a prognostic role in patients with advanced cirrhosis without HCC. So from this study it seems that high serum CRP is a risk factor for cirrhosis related death, independent from HCC.

The prognostic role of serum CRP has been studied also in patients transplanted for HCC ( $n=85$ , 60% met Milan criteria) [59]. The optimum cut-off of CRP was established at 0.9 mg/dL for recurrence free survival (AUROC 0.773, 95%CI 0.640-0.906,  $P=0.001$ ) and 0.64 mg/dL for overall survival (AUROC 0.671, 95%CI 0.570-0.810,  $P=0.005$ ) and patients were divided into low ( $<1$  mg/dL) and high ( $\geq 1$  mg/dL) serum CRP level. The pre-transplant serum CRP level was significantly correlated with the tumor size ( $r=0.445$ ,  $P<0.001$ ), tumor number ( $r=0.375$ ,  $P=0.001$ ), the total bilirubin level ( $r=0.493$ ,  $P<0.001$ ), the albumin level ( $r=-0.355$ ,  $P=0.001$ ), the Child-Pugh score ( $r=0.522$ ,  $P<0.001$ ) and the MELD score ( $r=0.516$ ,  $P<0.001$ ). During follow up, 15 patients (17.5%) developed HCC recurrence at a median time of 5.3 months (median follow-up 28.3 months) and three of them were within the Milan criteria (MC) before transplant. HCC beyond MC, a higher CRP (HR 4.64, 95%CI 1.65-13.95,  $P=0.004$ ) and

microvascular invasion remained significant as independent risk factors for tumor recurrence in the whole population. A high CRP level was also significantly associated with poor RFS (HR 5.96, IC95% 1.41-25.23,  $P=0.02$ ) and decreased OS (HR 9.27, 95% CI 1.73-31.52,  $P<0.001$ ).

## Other markers for infections

PCT, an acute-phase serum protein and precursor of the hormone calcitonin, produced by thyroidal and extra-thyroidal tissues, including the liver, has been validated as marker of infection in non-cirrhotic patients, in particular in critically ill patients [60-62]. Conflicting results exist regarding threshold values and diagnostic accuracy in cirrhosis, using the same cut off value of 0.5 ng/mL (AUC 0.68-0.89) (Table 3).

Bacterial DNA (bactDNA) detection, by polymerase chain reaction, and bacterial products identification, such as endotoxin, in serum or ascitic fluid, has been proposed as a reliable marker of BT which can promote an immunological response similar to that produced by viable bacteria [63]. Some studies have shown molecular evidence of bacterial translocation and suggested that it occurs prior to the development of clinical SBP. However, detection of bacterial products does not imply the viability of bacteria, and therefore the clinical consequences of their presence may be different compared with the presence of viable bacteria. The rates of bactDNA detection in the literature in this setting are different, probably due to the absence of a standard method of detection [64]. Moreover, a routine use is not possible due to cost and difficulties of methodology.

## Conclusion

Basal CRP level is generally higher in patients with cirrhosis than without cirrhosis. During bacterial infections CRP level rises, but in patients with cirrhosis the more severe the underlying liver dysfunction, the lower CRP increases. For this reason, CRP has a weak predictive power for infection and prognosis in patients with decompensated/advanced cirrhosis and in the intensive care setting. Therefore, it is advisable to clinically act on even moderate CRP increases in patients with advanced liver cirrhosis, and initiate empirical antibiotic therapy.

High CRP and also persistently elevated CRP levels (highlighting the existence of systemic inflammation that may be underestimated by SIRS criteria) can help identify patients who have a higher short-term mortality risk. Serial CRP measurements could be useful to establish resolution or persistence of sepsis or inflammation, helping decision making by clinicians when reassessing patients who fail to improve.

## References

- Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002;**35**:140-148.
- Wong F, Bernardi M, Balk R, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. *Gut* 2005;**54**:718-725.
- Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010;**139**:1246-1256.
- Gustot T, Durand F, Lebrech D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. *Hepatology* 2009;**50**:2022-2033.
- Foreman MG, Mannino D, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. *Chest* 2003;**124**:1016-1020.
- Plessier A, Denninger MH, Consigny Y, et al. Coagulation disorders in patients with cirrhosis and severe sepsis. *Liver Int* 2003;**23**:440-448.
- Wiest R, Garcia-Tsao G. Bacterial translocation in cirrhosis. *Hepatology* 2005;**41**:422-433.
- Fernandez J, Gustot T. Management of bacterial infections in cirrhosis. *Hepatology* 2012;**S2**:S12.
- Deviere J, Content J, Denys C, et al. Excessive in vitro bacterial lipopolysaccharide-induced production of monokines in cirrhosis. *Hepatology* 1990;**11**:628-634.
- Navasa M, Follo A, Fiella X, et al. Tumor necrosis factor and interleukin 6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998;**27**:1227-1232.
- Bone RC, Grodzin C, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest* 1997;**112**:235-243.
- Bernard B, Grangé J, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotics prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999;**29**:1655-1661.
- Yoshida H, Hamada T, Inuzuka S, Ueno T, Sata M, Tanikawa K. Bacterial infection in cirrhosis, with and without hepatocellular carcinoma. *Am J Gastroent* 1993;**88**:2067-2071.
- Llach J, Rimola A, Navara M, et al. Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: relevance of ascitic fluid protein concentration. *Hepatology* 1992;**16**:724-727.
- Ginès P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990;**12**:716-724.
- Rimola A, Garcia-Tao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites club. *J Hepatol* 2000;**32**:142-153.
- Tandon P, Garcia-Tao G. Bacterial infections, sepsis and multiorgan failure in cirrhosis. *Semin Liver Dis* 2008;**28**:26-42.
- American College of Chest Physicians/Society of Critical Care Medicine. Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;**20**:864-874.
- Cazzaniga M, Dionigi E, Gobbo G, Fioretti A, Monti V, Salerno F. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. *J Hepatol* 2009;**51**:475-482.
- Thabut D, Massard J, Gangloff A, et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology* 2007;**46**:1872-1882.
- Eklund CM. Proinflammatory cytokines in CRP baseline regulation. *Adv Clin Chem* 2009;**48**:111-136.
- Castelli GP, Pognani C, Meisner M, Stuanani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care* 2004;**8**:R234-R242.
- Chauveau P, Level C, Lasseur C, et al. C-reactive protein and procalcitonin as markers of mortality in hemodialysis patients: a 2-year prospective study. *J Ren Nutr* 2003;**13**:137-143.
- Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;**340**:448-454.
- Mendall MA, Strachan D, Butland BK, et al. C-reactive protein: Relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. *Eur Heart J* 2000;**21**:1584-1590.
- Bota DP, van Nuffelen M, Zakariah AH, Vincent JL. Serum level of C-reactive protein and procalcitonin in critically ill patients with cirrhosis of the liver. *J Lab Clin Med* 2005;**146**:347-351.
- Imhof A, Froehlich M, Boeing H, et al. Effect of alcohol consumption on systemic markers of inflammation. *Lancet* 2001;**357**:763-767.
- Hirschfield GM, Pepys M. C-reactive protein and cardiovascular disease: new insights from an old molecule. *Q J Med* 2003;**96**:793-807.
- Westhuyzen J, Healy H. Review: Biology and relevance of C-reactive protein in cardiovascular and renal disease. *Ann Clin Lab Sci* 2000;**30**:133-143.
- Vigushin DM, Pepys M, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human c-reactive protein in health and disease. *J Clin Invest* 1993;**91**:1351-1357.
- Vanbiervliet G, Le Breton F, Rosenthal-Allier MA, et al. Serum C-reactive protein: A non-invasive marker of alcoholic hepatitis. *Scand J Gastroent* 2006;**41**:1473-1479.
- Fujimoto M, Uemura M, Kojima H, et al. Prognostic factors in severe alcoholic liver injury. Nara Liver Study Group. *Alcohol Clin Exp Res* 1999;**23**(4 Suppl):33S-38S.
- Tilg H, Wilmer A, Vogel W, et al. Serum levels of cytokines in chronic liver disease. *Gastroenterology* 1992;**103**:264-274.
- Le Moine O, Deviere J, Devaster JM, et al. Interleukin-6: an early marker of bacterial infection in decompensated cirrhosis. *J Hepatol* 1994;**20**:819-824.
- Albillos A, de la Hera A, Gonzales M, et al. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and haemodynamic derangement. *Hepatology* 2003;**37**:208-217.
- Marquez M, Fernandez-Gunerez C, Montes-de Oca M, et al. Chronic antigenic stimuli as a possible explanation for the immunodepression caused by liver cirrhosis. *Clin Exp Immunol* 2009;**158**:219-229.
- Campillo B, Sherman E, Richardet JP, Bories PN. Serum leptin levels in alcoholic liver cirrhosis: relationship with gender, nutritional status, liver function and energy metabolism. *Eur J Clin Nutrition* 2001;**55**:980-988.
- Meliconi R, Parracino O, Facchini A, et al. Acute phase protein in chronic and malignant liver diseases. *Liver* 1988;**8**:65-74.
- Janum SH, Søvsø M, Gradel KO, Schönheyder HC, Nielsen H. C-reactive protein level as a predictor of mortality in liver disease patients with bacteremia. *Scand J Gastroent* 2011;**46**:1478-1483.
- Papp M, Vitalis Z, Altörjay I, et al. Acute phase proteins in the diagnosis and prediction of cirrhosis associated bacterial infection. *Liver Int* 2011;**603**-611.
- Park WB, Lee K, Lee CS, et al. Production of C-reactive protein in Escherichia coli-infected patients with liver dysfunction due to liver cirrhosis. *Diagn Microbiol Infect Dis* 2005;**51**:227-230.
- Pavoa P. C-reactive protein: a valuable marker of sepsis. *Intensive Care Med* 2002;**28**:235-243.
- Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;**340**:448-454.
- Grander W, Dünser M, Stollenwerk B, et al. C-reactive protein

- levels and post-ICU mortality in nonsurgical intensive care patients. *Chest* 2010;**38**:856-862.
45. Cholongitas E, Senzolo M, Patch D, et al. Risk factors, sequential organ failure assessment and model for end-stage liver disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. *Aliment Pharmacol Ther* 2006;**23**:883-893.
  46. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;**144**:1426-1437.
  47. Wehler M, Kokoska J, Reulbach U, et al. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. *Hepatology* 2001;**34**:255-261.
  48. Mackenzie I, Woodhouse J. C-reactive protein concentrations during bacteraemia: a comparison between patients with and without liver dysfunction. *Intensive Care Med* 2006;**32**:1344-1351.
  49. Cervoni JP, Thevenot T, Weil D, et al. C-reactive protein predicts short-term mortality in patients with cirrhosis. *J Hepatol* 2012;**6**:1299-1304.
  50. Li CH, Yang R, Pang JH, et al. Procalcitonin as a biomarker for bacterial infection in patients with liver cirrhosis in the emergency department. *Acad Emerg Med* 2011;**18**:121-126.
  51. Lazzarotto C, Ronsoni M, Fayad L, et al. Acute phase proteins for the diagnosis of bacterial infection and prediction of mortality in acute complications of cirrhosis. *Ann Hepatol* 2013;**12**:599-607.
  52. Ha YE, Kang C, Joo EJ, et al. Usefulness of C-reactive protein for evaluating clinical outcomes in cirrhotic patients with bacteremia. *Korean J Intern Med* 2011;**26**:195-200.
  53. Lin ZY, Chuang W, Dai CY, et al. Clinical application of c-reactive protein measurement in the detection of bacterial infection in patients with liver cirrhosis. *Kaohsiung J Med Sci* 2002;**18**:121-126.
  54. Viallon A, Zeni F, Puozet V, et al. Serum and ascitic procalcitonin levels in cirrhotic patients with spontaneous bacterial peritonitis: diagnostic value and relationship to pro-inflammatory cytokines. *Intensive Care Med* 2000;**26**:1082-1088.
  55. Tsiakalos A, Karatzaferis A, Ziakas P, and Hatzis G. Acute phase protein as indicators of bacterial infection in patients with cirrhosis. *Liver Int* 2009;**15**:1538-1542.
  56. Kwon JH, Jang J, Lee S, et al. Diagnostic performance of C-reactive protein and neutrophils-to-lymphocyte ratio for infection in patients with decompensated cirrhosis. Abstract 207, EASL 2013, 2013.
  57. Zheng Z, Zhou L, Gao S, Yang Z, Yao J, Zheng S. Prognostic role of C-reactive protein in hepatocellular carcinoma: a systematic review and meta-analysis. *Int J Med Sci* 2013;**10**:653-664.
  58. Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. *Ann Surg Oncol* 2013;**20**:325-339.
  59. An HJ, Jang J, Bae SH, et al. Serum C-reactive protein is a useful biomarker for predicting outcomes after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2012;**18**:1406-1414.
  60. Tang BM, Eslick G, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis* 2007;**7**:210-217.
  61. O'Grady NP, Barie P, Bartlett JG, et al. American College of Critical Care Medicine; Infectious Diseases Society of America. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med* 2008;**36**:1330-1340.
  62. Meynaar IA, Droog W, Batstra M, Vreede R, Herbrink P. In Critically Ill Patients, Serum Procalcitonin Is More Useful in Differentiating between Sepsis and SIRS than CRP, IL-6, or LBP. *Crit Care Res Pract* 2011;**2011**:594645.
  63. Zapater P, Frances R, Gonzalez-Navajas JM, et al. Serum and ascitic fluid bacterial DNA: a new independent prognostic factor in noninfected patients with cirrhosis. *J Hepatol* 2008;**48**:1924-1931.
  64. Bellot P, Frances R, Such J. Pathological bacterial translocation in cirrhosis: pathophysiology, diagnosis and clinical implications. *Liver Int* 2013;**33**:31-39.