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The CRP level and STATE score predict survival in cirrhotic patients with hepatocellular carcinoma treated by transarterial embolization

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ABSTRACT

Background: Prognostic biomarkers are needed in a heterogeneous population of patients with intermediate hepatocellular carcinoma (HCC) treated by transarterial (chemo)embolization. We aimed to validate the prognostic value of serum CRP levels and the STATE score, combining CRP, albumin and tumor burden.
Methods: All cirrhotic patients with HCC treated by a first transarterial (chemo)embolization (2007–2013) in our institution were included. Overall survival was assessed using the Kaplan–Meier method, log rank, univariate and multivariate Cox analyses.
Results: Among 157 patients included, 87% were men, 86% had Child Pugh A. Etiologies of liver disease included alcohol (57%), hepatitis C (32%), hepatitis B (11%) and/or metabolic syndrome (32%); 89% of patients were classified BCLC B. 33% of the patients had a CRP >1 mg/dl and 33% a STATE score conferring poor prognosis (<18). Patients with CRP <1 mg/dl had better overall survival than patients with CRP >1 mg/dl (20 vs. 8 months, $P = 0.00186$). Median overall survival was 6.73 months for patients with a STATE score <18 vs. 22.23 months for patients with STATE-score ≥18 ($P = 0.0002$). In multivariate analysis, a STATE score <18 was independently associated with increased mortality (HR: 2.06 (CI95%: 1.28–3.34), $P = 0.0031$).
Conclusion: In cirrhotic patients with HCC who underwent transarterial treatment, serum CRP level and STATE score at baseline can predict overall survival.

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and the third cause of cancer-related death worldwide [1]. Around 90% of HCC occurs in patients with chronic liver disease, mainly cirrhosis [2]. Prognosis and treatment are stratified using the BCLC classification, a staging system endorsed by scientific societies in western countries [3]. Most patients are currently diagnosed at advanced stages not accessible to curative treatment [4]. Transarterial chemo-embolization (TACE) is the standard therapy for "intermediate" hepatocellular carcinoma classified BCLC B, including multifocal disease outside Milan criteria without portal thrombosis and metastasis developed on compensated cirrhosis. Transarterial bland embolization (TAE) is sometimes used as an alternative to TACE [3]. However, this population of patients remains highly heterogeneous and some patients are treated outside the guidelines by percutaneous ablation, surgery or yttrium 90 radio-embolization. Moreover, a subset of patients may be downstaged within Milan criteria and thus become eligible for transplantation, thus reaching higher long-term survival [5]. Elsewhere, BCLC C patients with segmental portal invasion, a classical indication for sorafenib treatment, are sometimes treated by TACE or liver surgery [5]. New prognostic factors remain to be identified and should help to optimize treatments of this heterogeneous tumor stage. Several investigators showed that systemic inflammation was associated with poor prognosis in a large range of cancers [6–9]. C-reactive protein (CRP) is a protein of the acute

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phase of inflammation, mainly produced by hepatocytes after stimulation by interleukin-1 (IL-1), IL-6 and IL-17 [10]. It is a widely used biomarker for detecting and monitoring infection, but CRP is also increased in autoimmune diseases and cancers. Several inflammatory parameters, including the level of CRP and the neutrophil/lymphocyte ratio, have been associated with survival in patients with HCC treated by TACE and surgery [11–14]. The STATE score has recently been developed so as to identify patients suitable for the first TACE [15]. The STATE score comprises the serum albumin level (g/l), which is reduced by 12 points if tumor burden exceeds up-to-7 criteria, and by 12 points if C-reactive protein (CRP) levels are ≥1 mg/dl (maximum reduction: 24 points). A STATE score <18 is associated with poor overall survival [15]. However, external validation of the STATE score by an independent steam is still lacking in order to confirm it robustness and reproducibility.

Our aim was to validate the CRP level and STATE score as prognostic tools in cirrhotic patients with HCC classified BCLC B or C and treated by transarterial therapy in a western cohort of patients.

1. Materials and methods

1.1. Inclusion

All HCC developed in cirrhotic patients and classified as Barcelona Clinic Liver Cancer (BCLC) B or BCLC C, with segmented portal thrombosis treated by a first TACE, TAE or DC beads between 2007 and 2013 in a tertiary liver unit at Jean Verdier Hospital in Bondy (France) were included in a retrospective analysis. Patients with HCC that developed on non-cirrhotic liver were excluded from this study. Cirrhosis was diagnosed by biopsy, or using non-invasive methods such as transient elastography or blood tests.

HCC was diagnosed histologically or using non-invasive criteria at imaging, by CT scan and/or MRI according to EASL guidelines [3]. In patients without clinical evidence of infection, several variables were recorded at inclusion, and prior to any treatment: gender, age, Child Pugh score (albumin, prothrombin time, bilirubin, ascites, encephalopathy), transaminases, gamma glutamyl transferase, alkaline phosphatase, creatinine, platelets, CRP, alpha-fetoprotein (AFP), number of tumors, size of the largest nodule and etiology of cirrhosis (hepatitis C or B virus, alcoholic or non-alcoholic steatohepatitis, hemochromatosis).

1.2. Treatment

At our center, patients were treated mainly by TAE, except when included in clinical trials testing TACE or DC-bead treatment. We performed TAE using lipiodol associated with curaspon in order to induce tumor necrosis. TACE was performed using a combination of lipiodol, curaspon and cisplatin, delivered after selective catheterization of arteries feeding the tumor. DC-beads were performed according to the manufacturer's instructions.

After each treatment, patients were evaluated at one month in order to assess lipiodol fixation and radiological response, via abdominal computer tomography and magnetic resonance imaging. For patients with progressive disease or degradation of liver function, no additional treatment by TAE/TACE was performed. For all others patients, additional TAE/TACE/DC-bead treatment was performed on demand, after discussion at a weekly multidisciplinary meeting. If no additional treatment was given, radiological assessment was performed every 3 months.

1.3. Statistical analysis

After the first treatment, all patients were prospectively followed up until death or the last recorded visit until September 1st, 2014. Overall survival was calculated from the date of first treatment to the date of death, date of liver transplantation or last recorded visit. Categorical variables were described as *n* and %, and contiguous variables as median (interquartile range 25–75). Categorical variables were compared using the Fisher exact test and the contiguous variables using the non-parametric Mann–Whitney test. The CRP level was dichotomized at 1 mg/dl as previously described [14]. The STATE score was calculated using the CRP level (mg/dl), the albumin level (g/l) and up-to-7 criteria using the following formula: serum albumin (g/l) – 12 (if up-to-7 out) – 12 (if CRP levels >1 mg/dl). A cut-off of 18 for the STATE score was chosen according to Hucke et al. [15]. The association between the different variables and survival was analyzed using the Kaplan–Meier method with the log rank test. The association of clinical, biological and radiological features with survival was assessed by univariate Cox analysis; then, variables with a *P* value <0.05 were further analyzed using the multivariate Cox analysis. A *P* value <0.05 was considered significant.

2. Results

A total of 157 cirrhotic patients with HCC treated by TAE (*n* = 133, 85%), TACE (*n* = 15, 9%) or DC beads (*n* = 9, 6%) between 2007 and 2013 were included (Table 1). A total of 52 HCC were diagnosed using liver biopsy, and 105 using non-invasive criteria. The median number of transarterial treatments received per patient was 2. 46 patients (29%) received at least one treatment before TA(C)E. 90 patients (58%) received a treatment (excluding new transarterial treatments) post TA(C)E.

Table 1
Description of patients.

Variable	Available data	*N* (%), median (IQR 25–75)
Gender (male)	157	137 (87%)
Age (years)	157	69 (60–77)
Hepatitis C[a]	157	51 (32%)
Alcohol[a]	157	90 (57%)
Hepatitis B[a]	157	18 (11%)
Non-alcoholic steatohepatitis[a]	157	50 (32%)
Hemochromatosis[a]	157	3 (2%)
Mixed etiology[a]	157	52 (33%)
Child Pugh A	151	131 (86%)
Child Pugh B	151	21 (14%)
Prothrombin time (%)	152	76 (66–89)
Total bilirubin (μmol/l)	157	14 (9–21)
CRP (mg/dl)	138	6 (3–14)
CRP >1 mg/dl	138	46 (33%)
STATE score <18 points	128	42 (33%)
Albumin (g/l)	151	35 (31–39)
AST (UI/l)	151	67 (46–108)
ALT (UI/l)	150	48 (34–81)
GGT (UI/l)	149	215 (127–360)
AFP (mg/dl)	157	32 (7–455)
Platelets (/mm^3)	151	121,000 (89,500–181,500)
Single HCC	155	16 (10%)
Multiple HCC	155	139 (90%)
Size of the main nodule (mm)	154	52 (30–80)
Segmental portal thrombosis	148	16 (11%)
BCLC B	148	132 (89%)
BCLC C	148	16 (11%)
Inside up-to-7 criteria	155	38 (24%)
Outside up-to-7 criteria	155	118 (76%)
Bland intra-arterial embolization	157	133 (85%)
Intra-arterial chemo-embolization	157	15 (10%)
DC beads	157	9 (5%)
Death or liver transplantation	157	105 (67%)
Liver transplantation	157	9 (6%)

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; GGT: gamma glutamyl transferase; Alk P: alkaline phosphatase; HCC: hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer.

[a] The sum of etiologies does not square to 100% because some patients have mixed etiologies of cirrhosis.