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# C-reactive protein and hepatocellular carcinoma: analysis of its relationships to tumor factors

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## Abstract

C-reactive protein (CRP) is a blood marker for inflammation and is an independent prognostic factor for many human cancers. Combined with albumin levels, it forms the basis of the Glasgow Index for cancer prognosis. We reviewed the literature on CRP and HCC and also evaluated blood CRP levels and combination CRP plus albumin levels in a large HCC cohort. In order to understand the prognostic significance of CRP, we retrospectively examined a large HCC cohort and examined the relationship of CRP levels to tumor parameters. We report, that CRP alone and CRP plus albumin combined as well, significantly correlated with parameters of HCC aggressiveness, such as maximum tumor dimension (MTD), portal vein thrombosis (PVT) and blood alpha-fetoprotein (AFP) levels, both as individual parameters and all parameters together (Aggressiveness Index). This extends current thinking, to suggest a possible explanation for the usefulness of blood CRP levels in HCC prognostication.

### Keywords

C-reactive protein; HCC; aggressiveness

## Abbreviations

C-reactive protein (CRP) has long been recognized to be part of the acute phase response and to be associated with chronic inflammatory diseases [1], and is synthesized in the liver and is secreted into the plasma as a pentamer, belonging to the family of pentraxins, together with serum amyloid protein [2]. It is also considered to be a marker both of inflammation as well as of cancer [3,4]. Although it is secreted in the presence of HCC, it is not considered to be a diagnostic marker for HCC [5], but it has nevertheless been reported to have significant prognostic value [6-8]. More recently, CRP has come to be seen in the context of systemic inflammation and cancer. The Glasgow score, consisting only of the 2 parameters, CRP and albumin, has been found to be an important and independent prognosticator for several cancer types, including HCC [9-18]. Furthermore, there is evidence that CRP is produced not just by hepatocytes, but also by HCC cells [19]. However, the function, biological role and significance in determining HCC prognosis are still unclear. The reason behind the prognostic significance of CRP for HCC has not been clearly explored. This study was undertaken to examine whether there might be any relationship between blood CRP levels and indices of HCC clinical biology. We report an association between blood CRP levels and clinical indices of HCC aggressiveness, namely MTD, PVT, AFP and tumor multifocality. This forms the basis for considering in future that CRP itself might be a target for new therapies.

# Methods

## Patient data

We retrospectively analyzed a database of 995 prospectively-accrued HCC patients who had full baseline tumor parameter data, including CT scan information on HCC size, number of tumor nodules and presence or absence of PVT and plasma AFP levels; complete blood count; routine blood liver function tests, (total bilirubin, GGTP, ALKP, albumin, transaminases) and patient demographics. Diagnosis was made either via tumor biopsy or according to international guidelines. Inclusion criteria included patients with a known HCC diagnosis and had CRP data at baseline. Patients were excluded who did not have CRP data. Database management conformed to legislation on privacy and this study conforms to the ethical guidelines of the Declaration of Helsinki and approval for this retrospective study on de-identified HCC patients was obtained by the Institutional Review Board. Survival information was not available for this analysis.

Aggressiveness Index was calculated as the sum of scores [20,21]: MTD (cm, in tertiles): MTD<4.5; 4.5 ≤ MTD ≤ 9.6; MTD>9.6; scores 1, 2, 3 respectively; AFP ng/ml (cut-off): AFP<100; 100 ≤ AFP ≤ 1000; AFP>1000; scores 1, 2, 3 respectively; PVT (No/Yes): PVT(No); PVT(Yes); scores 1, 3 respectively; Number of Tumor Nodules: Nodules ≤ 3; Nodules>3; scores 1, 3 respectively.

## Statistical analysis

Mean and SD for continuous variables, and relative frequency for categorical variables, were used as indices of centrality and dispersion of the distribution. For categorical variables, the Chi-square and z test for proportions were used. The Wilcoxon rank-sum (Mann-Whitney) test was to test the difference between two categories, and the Kruskal-Wallis rank test to test the difference among categories.

Logistic regression model was to evaluate the associations between PVT (No/Yes) on single variables examined.

Final multiple linear or logistic regression models were obtained with the backward stepwise method and the variables that showed associations with $p<0.10$ were left in the models.

When testing the null hypothesis of no association, the probability level of $\alpha$ error, two tailed, was 0.05. All the statistical computations were made using STATA 12.1 Statistical Software (StataCorp) 2014, release 12 (College Station, TX).

# Results

## CRP in relation to HCC patient demographics, liver and tumor parameters

The total cohort was initially dichotomized according to normal and abnormal (>10 mg/dL) serum levels of CRP (Table 1). Demographic features such as age, gender, percent HBV and HCV were similar in the 2 groups. However, percent cirrhosis and alcohol consumption were significantly higher in the high CRP group, as were ALKP, AST and total bilirubin levels, but blood albumin levels were significantly lower. There were 4 tumor parameters,

namely maximum tumor diameter (MTD), tumor multifocality, portal vein thrombosis (PVT) and blood alpha-fetoprotein (AFP) levels and they were each significantly higher in the high CRP group, except for tumor multifocality. The trends in the tumor parameters of MTD, percent PVT and alpha-fetoprotein (and their combination, expressed as a Tumor Aggressiveness Index) were then plotted as a function of blood CRP values (Figure 1). In each case, there was a significant relationship (for PVT, $p<0.0001$); for MTD and AFP, $p<0.001$). The high and low CRP groups were then dichotomized according to small or large (>5 cm MTD) tumor size (Table 2). The differences between high and low CRP groups were found to be confined mainly to the patients with larger tumors, although an increase in MTD and percent PVT and a decrease in blood albumin was found in the high CRP groups for both small and large size tumors.

### Tumor parameters in relation to blood CRP +/- albumin groupings

Although the Glasgow tumor inflammation index is based on <10> mg/L CRP values, we found that a more detailed tumor parameter picture was obtained using 2 CRP cutoffs, namely, <10, 10-50 and >50 mg/L blood CRP values (Table 3). We found as significant trend for increase in each of AFP, MTD and percent PVT parameters, with increase in CRP grouping. Actual values for AFP, MTD and percent PVT were significantly different when patients with CRP <10 mg/L were compared to patients with CRP 10-50 mg/L, as well as to patients with CRP >50 mg/L. When patients with CRP 10-50 mg/l were compared with patients with CRP >50 mg/L, only AFP and PVT were significantly different.

Each of the 3 CRP groups was then subdivided by addition of either high (>3.5 g/dL) or low (<3.5 g/dL) blood Albumin values, as done in the Glasgow Index [9-16] and as shown in Table 4. Patients with low albumin plus highest CRP >50 had the largest MTDs of mean 7.8cm and the highest mean AFP values (group [c]). Groups [c] and [f] with highest CRP of >50 also had the highest percent of patients with PVT (48.21 and 58.33 percent, respectively). By contrast, group [d] with the combined highest albumin and lowest CRP levels, had the lowest levels of AFP, smallest MTDs and lowest prevent of patients with PVT. The significant inverse relationship of blood albumin to CRP levels is further shown in Figure 2, which is a Scatterplot between blood albumin and CRP levels (Pearson correlation coefficient $r=-0.2994$, $p<.0001$).

### Logistic regression model of CRP and CRP relationship to AFP

A logistic regression model of CRP on single variables was then calculated (Table 5A). Significant OR values were found for several parameters, but the highest ORs were found for PVT (OR 1.88) and the Tumor Aggressiveness Index (OR 1.71) [20,21]. In a final multiple logistic regression model of CRP, only blood total bilirubin and high Tumor Aggressiveness Index score were found to be significant (Table 5B).

## Discussion

Blood CRP levels are being used increasingly in inflammation-based indices for several cancers, including HCC, such as the Glasgow Index and several of its variations [22-24]. It is described as an ‘independent’ marker for prognosis, meaning that it is seemingly

unrelated to accepted tumor-based prognostication parameters, such as tumor size (MTD), tumor number and metastasis (TNM) or the combination of tumor and liver damage classification schemes that are now considered to be important for HCC [25,26]. It is increasingly clear that non-tumor factors are also important in HCC prognosis [27-29] including tumor microenvironment [30,31]. Despite the significant association of CRP-based inflammation indices and tumor survival, the mechanisms have so far been elusive, but are thought to relate to systemic inflammation as cause or consequence of growing tumors. The current study was undertaken in this context. Although this database is from a large new Turkish multi-institution collaboration, giving it power of patient numbers, survival data is not available for this cohort and thus for this study.

Despite the weakness in this study of an absence of survival data, we have been able to discern significant associations between blood CRP levels and parameters of HCC aggressiveness, namely MTD, percent patients with PVT and blood AFP levels (Tables 1, 3 and 4 and Figure 1). In addition to the Glasgow inflammation index that dichotomizes patients according to blood CRP levels or <10 or >10 mg/L, we found further refinement for subset analysis in using 3 CRP cutoffs of CRP <10, 10<CRP ≤ 50 and >50 mg/L. A logistic regression model for CRP showed several significant factors, but especially for the HCC Aggressiveness Index score in a final multiple logistic regression model of CRP (Table 5). We also examined the possibility that elevated CRP levels might provide a useful marker in AFP-negative HCC [22]. CRP is produced in the liver. However, although its best-documented significance is a refection of the systemic inflammatory response [1,3], since it is also produced by HCC cells [3,4,32-34,36], it likely has additional roles. Thus, our finding of significant relationships between blood CRP levels and several parameters of tumor growth and aggressiveness, suggest that either the systemic inflammatory response may play a role in HCC biology, or that CRP may actually be involved in stimulation of HCC growth and invasion. The fact that CRP not only is produced in non-cancerous liver in response to the presence of various tumors and HCC, but is actually produced by HCCs, suggests some direct involvement in HCC biology.

Several cytokines and other factors have been shown to influence CRP production, including IL-1, IL-6 and STAT-3 [32-37]. Furthermore, as well as being a reflection of an inflammatory response, CRP has also been shown to inhibit expression of N-Cadherin and can activate human monocyte tumoricidal activity [38,39]. The pentraxin family includes CRP, and the soluble pattern recognition receptor long petraxin 3 can antagonize FGF and can inhibit FGF-dependent angiogenesis and tumor growth [40], and also can alter tumor matrix and microenvironment [41,42]. Furthermore, a new generation of IL-6 inhibitors has potential in cancer therapy, by disrupting the IL-6/CRP interactions [43-45]. Thus, several mechanisms exist to not only explain a putative role for CRP in HCC biology, but several agents such as IL-6 inhibitors are already being evaluated to directly antagonize CRP or to inhibit factors that are known to stimulate its production.

CRP is one of the best known amongst several inflammatory cytokines that are thought to be important in cancer [17,18,28]. They include both interleukins, interferons and Tumor necrosis factor-α [46-57]. More recently, the neutrophil to lymphocyte (NLR) ratio has also been shown to also be a useful reflection of the inflammatory environment and clinical HCC

survival prognosticator [24,58-64]. It has recently been incorporated in various ways in modern HCC classification systems [60,63], as well as in combination with CRP [65].

## Conclusion

Our results show, an association between clinical CRP levels and parameters of human HCC growth and aggressiveness. New work on control of CRP suggests the possibility that inhibitors of IL-6 and of other inflammatory mediators, working through CRP, may have potential as novel cancer therapy agents. This extends current thinking, to suggest a possible explanation for the usefulness of blood CRP levels in HCC prognostication and that CRP might also be a therapeutic target.

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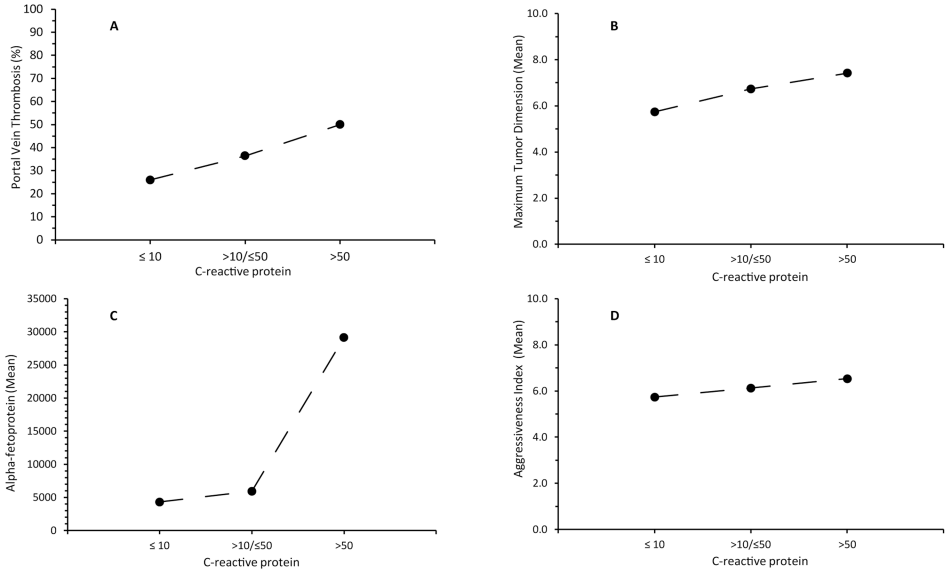


**Figure 1.**

Trends in tumor indices in relationship to C-reactive protein parameter (CRP) in HCC patients. PVT (% of patients) in CRP categories ($p<0.0001$*) (A); MTD means in CRP categories ($p<0.001$*) (B);. AFP (mean) in CRP categories ($p<0.001$*) (C); Aggressiveness Index (mean) in CRP categories ($p<0.001$*) (D). * test for trend.

Abbreviations: CRP, C-reactive protein; AFP, Alpha-fetoprotein; MTD, Maximum Tumor Diameter; PVT, Portal Vein Thrombosis.

Aggressiveness Index is sum of scores:

MTD (in terciles): MTD<4.5; 4.5 ≤ MTD≤9.6; MTD>9.6; scores 1, 2, 3 respectively;

AFP (cut-of): AFP<100; 100 ≤ AFP ≤ 1000; AFP>1000 ng/ml; scores 1, 2, 3 respectively;

PVT (No/Yes): PVT (No); PVT (Yes); scores 1, 3 respectively;

Tumor Nodules (number): Nodules ≤ 3; Nodules>3; scores 1, 3 respectively.

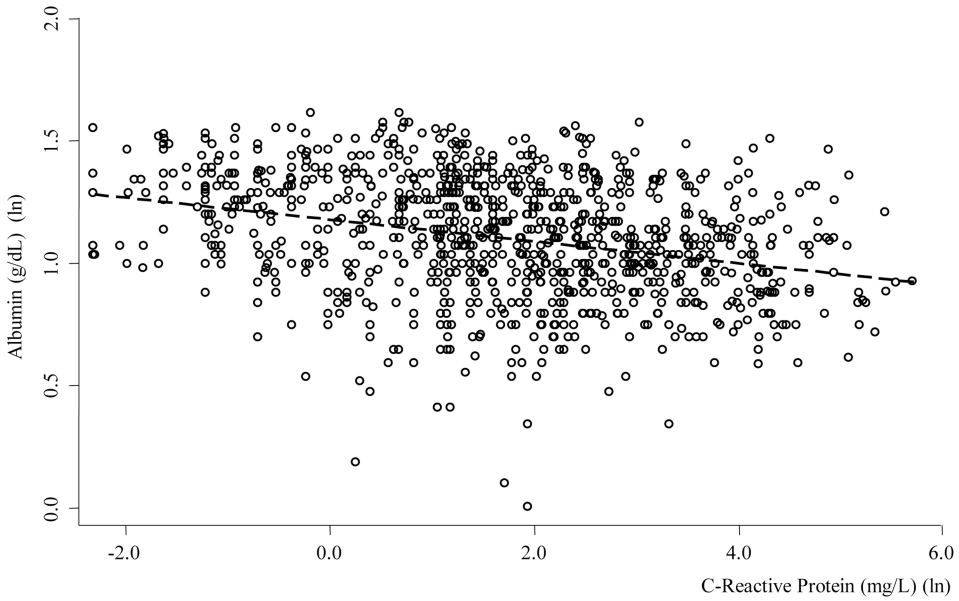


**Figure 2.**

Scatterplot between Albumin (g/dL) and C-Reactive Protein (mg/L), (r=-0.2994*, p<0.0001), together with a linear regression line of Albumin on C-Reactive Protein, in total cohort. All transformed into natural logarithms; fitted values (-------);

* r, Pearson product-moment correlation coefficient.

## Table 1
## HCC patient characteristics, comparing CRP (≤ 10/>10 mg/L) categories

| Variables * | CRP≤10 (mg/L) | CRP>10 (mg/L) | p ψ |
|---|---|---|---|
| Gender (Males) (%) | 512 (80.13) | 292 (81.79) | 0.52 ^ |
| Age (yr) | 63.12 ± 11.15 | 63.28 ± 10.75 | 0.99 |
| Cigarettes smoking (yes) (%) | 178 (47.21) | 89 (47.85) | 0.89 ^ |
| Alcohol (yes) (%) | 57 (14.39) | 56 (22.40) | 0.009 ^ |
| Cirrhosis (yes) (%) | 501 (78.65) | 311 (88.10) | <0.001 ^ |
| HbsAg(+ve) (%) | 371 (59.36) | 204 (61.82) | 0.46 ^ |
| HCV(+ve) (%) | 142 (22.68) | 65 (19.76) | 0.30 ^ |
| Hemoglobin (g/dL) | 12.42 ± 2.23 | 11.44 ± 2.16 | <0.0001 |
| Platelet counts ($10^3$/μL) | 145.42 ± 83.92 | 156.87 ± 107.62 | 0.58 |
| Albumin (g/dL) | 3.22 ± 0.75 | 2.88 ± 0.63 | <0.0001 |
| PT (%) | 14.77 ± 4.93 | 17.31 ± 6.45 | <0.0001 |
| CRP (mg/L) | 3.43 ± 2.78 | 42.74 ± 42.53 | <0.0001 |
| ALKP (U/L) | 191.88 ± 204.48 | 289.80 ± 500.30 | 0.0001 |
| GGTP (U/L) | 137.06 ± 152.11 | 175.53 ± 211.89 | 0.11 |
| AST (U/L) | 142.03 ± 587.81 | 188.41 ± 429.44 | 0.003 |
| Total Bilirubin (mg/dL) | 2.40 ± 3.75 | 5.38 ± 7.47 | 0.0004 |
| Multifocality (n ≥ 2) | 178 (31.23) | 93 (32.40) | 0.73 ^ |
| MTD (cm) | 5.74 ± 3.95 | 6.89 ± 4.53 | 0.0003 |
| Portal Vein Thrombosis (%) | 149 (26.00) | 109 (39.78) | <0.001 ^ |
| AFP (IU/mL) | 4310.48 ± 29213.30 | 12291.33 ± 64664.53 | 0.001 |
| Platelet counts <100 ($10^3$/μL) (%) | 219 (34.49) | 124 (34.93) | 0.89 ^ |
| AFP (IU/mL) (%) | | | 0.01 ^ |
| ≤20 | 296 (47.28) | 128 (37.10) | |
| >20/≤100 | 102 (16.29) | 62 (17.97) | |
| >100/≤1000 | 114 (18.21) | 71 (20.58) | |
| >1000 | 114 (18.21) | 84 (24.35) | |
| MTD (cm) (%) | | | <0.001 ^ |
| <3.5 | 176 (30.72) | 59 (21.69) | |
| ≥3.5/<6.5 | 224 (39.09) | 95 (34.93) | |
| ≥6.5 | 173 (30.19) | 118 (43.38) | |

*All values: Means±Standard Deviation as continuous; Frequences and Percentage (%) as categorical.

ψWilcoxon rank-sum (Mann-Whitney) test;

^Chi-square test.

Abbreviations: CRP, C-Reactive Protein; PT, Prothrombin Time; AFP, Alpha-fetoprotein; ALKP, Alkaline phosphatase; GGTP, gamma glutamyl transpeptidae; AST, Aspartate aminotransferase; ALT, Alanine transaminase; MTD, Maximum Tumor Diameter.

**Table 2**

**Comparisons amongst HCC patients between CRP (≤10/>10 mg/L) groups in single MTD categories in the total cohort**

| | MTD<5.0 (cm) | | | MTD ≥ 5.0 (cm) | | |
|---|---|---|---|---|---|---|
| **Parameter*** | **CRP ≤ 10 (mg/L)** | **CRP>10 (mg/L)** | **p Ψ** | **CRP ≤ 10 (mg/L)** | **CRP>10 (mg/L)** | **p Ψ** |
| Platelet counts ($10^3$/μl) | 130.00 ± 70.49 | 133.56 ± 85.74 | 0.96 | 166.22 ± 95.42 | 190.55 ± 120.27 | 0.08 |
| Hemoglobin (g/dL) | 12.44 ± 2.29 | 11.51 ± 1.98 | 0.0003 | 12.46 ± 2.16 | 11.84 ± 1.90 | 0.002 |
| CRP (mg/L) | 3.02 ± 2.71 | 35.30 ± 34.05 | <0.0001 | 3.72 ± 2.80 | 39.78 ± 38.78 | <0.0001 |
| GGTP (U/L) | 120.02 ± 150.81 | 199.63 ± 372.32 | 0.51 | 161.78 ± 158.41 | 165.39 ± 156.91 | 0.81 |
| ALKP (U/L) | 162.79 ± 198.47 | 267.44 ± 284.20 | 0.26 | 226.26 ± 217.71 | 249.92 ± 174.48 | 0.09 |
| Total Bilirubin (mg/dL) | 2.13 ± 2.96 | 4.82 ± 6.30 | 0.10 | 2.49 ± 3.94 | 3.49 ± 5.03 | 0.33 |
| Albumin (g/dL) | 3.25 ± 0.76 | 2.88 ± 0.63 | <0.0001 | 3.13 ± 0.73 | 2.94 ± 0.66 | 0.005 |
| AFP (IU/mL) | 1946.10 ± 12949.39 | 3512.07 ± 17519.91 | 0.08 | 7478.00 ± 42279.77 | 12511.47 ± 44520.54 | 0.66 |
| MTD (cm) | 3.01 ± 1.05 | 3.02 ± 1.00 | 0.99 | 8.74 ± 3.78 | 9.48 ± 4.11 | 0.05 |
| Tumor Nodule | | | 0.57 ^ | | | 0.28 ^ |
| % Multyfocality (n≥2) | 79 (26.60) | 26 (23.85) | | 93 (34.83) | 47 (29.75) | |
| PV Thrombosis (%) | 44 (15.02) | 16 (15.69) | 0.87 ^ | 95 (35.58) | 70 (47.95) | 0.01 ^ |
| Cirrhosis (%) | 234 (78.52) | 93 (86.11) | 0.09 ^ | 216 (79.12) | 139 (86.34) | 0.06 ^ |

*All values: Means ± Standard Deviation as continuous; Frequences and Percentage (%) as categorical.

ΨWilcoxon rank-sum (Mann-Whitney) test;

^Chi-square test.

Abbreviations: GGTP, gamma glutamyl transpeptidase; ALKP, Alkaline phosphatase; AFP, Alpha-fetoprotein; MTD, Maximum Tumor Diameter; PVT, Portal Vein Thrombosis; CRP, C-Reactive Protein.

**Table 3**

**Comparisons among C-reactive protein groups for tumor characteristics in HCC patients**

| | C-reactive Protein mg/L) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **CRP≤10** | **10<CRP≤50** | **CRP>50** | | **Comparisons** | | |
| **Parameter*** | **(n=639)** | **(n=258)** | **(n=99)** | **p-value Ψ** | | **p-value #** | |
| | ***(a)*** | ***(b)*** | ***(c)*** | | ***(b)vs(a)*** | ***(c)vs(a)*** | ***(c)vs(b)*** |
| AFP (IU/mL) | 4310.48 ± 29213.30 | 5966.78 ± 30776.48 | 29179.23 ± 111.913.40 | 0.0003 | 0.06 | 0.0001 | 0.01 |
| MTD (cm) | 5.74 ± 3.95 | 6.73 ± 4.49 | 7.42 ± 4.69 | 0.0007 | 0.004 | 0.004 | 0.26 |
| PV Thrombosis (%) | 38 (26.00) | 75 (36.41) | 55 (50.50) | <0.001 ^ | 0.007 † | 0.0002 † | 0.05 † |

*All values: Means ± Standard Deviation as continuous; Frequences and percentage (%) as categorical.

ΨKruskal-Wallis rank test;

#Wilcoxon rank-sum (Mann-Whitney) test;

^Chi-square test.

†Test z for proportions. Abbreviations: CRP, C-reactive Protein; AFP, Alpha-fetoprotein; MTD, Maximum Tumor Diameter; PVT, Portal Vein Thrombosis.

**Table 4**

**Comparisons of tumor characteristics amongst HCC patients by Albumin (g/dL) and CRP (mg/L) combined (expanded Glasgow score)**

| | Albumin and CRP combined | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Alb < 3.5 & CRP ≤ 10** | **Alb < 3.5 & 10 < CRP ≤ 50** | **Alb < 3.5 & CRP > 50** | **Alb ≥ 3.5 & CRP ≤ 10** | **Alb ≥ 3.5 & 10 < CRP ≤ 50** | **Alb ≥ 3.5 & CRP > 50** | |
| **Parameter*** | **(n=384)** | **(n=203)** | **(n=85)** | **(n=255)** | **(n=55)** | **(n=14)** | **p-value#** |
| | **(a)** | **(b)** | **(c)** | **(d)** | **(e)** | **(f)** | |
| AFP (lU/mL) | 5448.63 ± 34160.37 | 6467.01 ± 33984.76 | 32747.87 ± 120058.40 | 2651.22 ± 9806.37 | 4098.01 ± 13181.70 | 6943.83 ± 18730.11 | 0.0001 |
| MTD (cm) | 6.09 ± 4.13 | 6.66 ± 4.50 | 7.80 ± 4.92 | 5.16 ± 3.58 | 6.97 ± 4.49 | 5.71 ± 3.12 | 0.0002 |
| PV Thrombosis (%) | 100 (28.09) | 58 (36.02) | 27 (48.21) | 49 (22.69) | 17 (37.78) | 7 (58.33) | <0.001 ^ |

| | (a) vs | | | | | (b) vs | | | | (c)vs | | | (d) vs | | (e) vs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **(b)** | **(c)** | **(d)** | **(e)** | **(f)** | **(c)** | **(d)** | **(e)** | **(f)** | **(d)** | **(e)** | **(f)** | **(e)** | **(f)** | **(f)** |
| AFP | 0.27 | 0.02 | 0.0001 | 0.03 | 0.09 | 0.12 | <0.0001 | 0.009 | 0.19 | <0.0001 | 0.0002 | 0.63 | 0.90 | 0.005 | 0.01 |
| MTD | 0.22 | 0.02 | 0.003 | 0.18 | 0.98 | 0.12 | 0.0004 | 0.58 | 0.69 | 0.0002 | 0.36 | 0.25 | 0.003 | 0.44 | 0.47 |
| PV Thrombosis | 0.08 ϕ | 0.005 ϕ | 0.15 ϕ | 0.21 ϕ | 0.04 ϕ | 0.11 ϕ | 0.005 ϕ | 0.83 ϕ | 0.16 ϕ | 0.0005 ϕ | 0.29 ϕ | 0.53 ϕ | 0.05 ϕ | 0.02 ϕ | 0.21 ϕ |

*All values: Means±Standard Deviation as continuous; Frequences and percentage (%) as categorical.

#Kruskal-Wallis rank test;

^Chi-squaretest;

¥Wilcoxon rank-sum (Mann-Whitney) test;

ϕTest z for proportions.

Abbreviations: AFP, Alpha-fetoprotein; MTD, Maximum Tumor Diameter; PVT, Portal Vein Thrombosis, CRP, C-reactive protein; Alb, Albumin.

**Table 5**

**Logistic regression model of CRP (≤ 10/>10 mg/L), on single variables (A). Final multiple logistic regression model of CRP (≤ 10/>10 mg/L), with stepwise method in backward (B)**

| Parameter | OR | se(OR) | p-value | 95% C.I. |
|---|---|---|---|---|
| A) | | | | |
| Platelet counts ($10^3$/μL) | 1.001 | 0.0007 | 0.06 | 1.000 to 1.002 |
| Hemoglobin (g/dL) | 0.82 | 0.03 | <0.001 | 0.77 to 0.87 |
| GGTP (U/L) | 1.001 | 0.0006 | 0.04 | 1.0001 to 1.0023 |
| ALKP (U/L) | 1.001 | 0.0004 | 0.01 | 1.0002 to 1.0020 |
| Total Bilirubin (mg/dL) | 1.10 | 0.02 | <0.001 | 1.06 to 1.15 |
| Albumin (g/dL) | 0.51 | 0.05 | <0.001 | 0.42 to 0.61 |
| AFP (IU/mL) | 1.000005 | 0.000002 | 0.03 | 1.000001 to 1.000009 |
| MTD (cm) | 1.07 | 0.02 | <0.001 | 1.03 to 1.10 |
| Nodules number | 1.06 | 0.16 | 0.73 | 0.78 to 1.43 |
| PV Thrombosis (%) | | | | |
| No (*Ref. category*) | 1 | | | |
| Yes | 1.88 | 0.29 | <0.001 | 1.38 to 2.55 |
| Aggressiveness Index score | | | | |
| Score = 4 (*Ref. category*) | 1 | | | |
| 4<Score ≤ 12 | 1.71 | 0.31 | 0.003 | 1.19 to 2.44 |
| Glycemia (mg/dL) | 0.9998 | 0.0014 | 0.87 | 0.997 to 1.002 |
| HDL(mg/dL) | 0.98 | 0.005 | 0.002 | 0.97 to 0.99 |
| Triglycerides, (mg/dL) | 1.002 | 0.001 | 0.09 | 0.9997 to 1.0049 |
| Total Cholesterol (mg/dL) | 0.998 | 0.002 | 0.40 | 0.995 to 1.002 |
| LDL Cholesterol (mg/dL) | 0.9996 | 0.001 | 0.70 | 0.997 to 1.002 |
| B) | | | | |
| Total Bilirubin (mg/dL) | 1.07 | 0.03 | 0.02 | 1.01 to 1.14 |
| Aggressiveness Index score | | | | |
| Score = 4 (*Ref. category*) | 1 | | | |
| 4<Score ≤ 12 | 2.76 | 1.17 | 0.02 | 1.20 to 6.32 |

Abbreviations: OR, Odds-Ratio; se(O), standard error of Odds-Ratio; CRP, C-reactive protein; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; GGTP, gamma glutamyl transpeptidae; ALKP, Alkaline phosphatase; AFP, Alpha-fetoprotein; MTD, Maximum Tumor Diameter; PVT, Portal Vein Thrombosis; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol.

Aggressiveness Index as sum of scores:
MTD (in terciles): MTD<4.5; 4.5 ≤ MTD ≤ 9.6; MTD>9.6; scores 1, 2, 3 respectively;
AFP (cut-of): AFP<100; 100 ≤ AFP ≤ 1000; AFP>1000 ng/ml; scores 1, 2, 3 respectively;
PVT (No/Yes): PVT (No); PVT (Yes); scores 1, 3 respectively;
Tumor Nodules (number): Nodules ≤ 3; Nodules>3; scores 1, 3 respectively.