# CRP is a superior and prognostically significant inflammation biomarker for hepatocellular cancer patients treated by liver transplantation

ClinicalPractice

## Abstract

**Background:** Inflammation and its markers are considered prognostically important for many cancers, including Hepatocellular Carcinoma (HCC). However, it is not really clear which markers are the best.

**Aims:** To assess in a cohort of prospectively-evaluated HCC patients who were treated with liver transplant and whose survival was known, multiple commonly used inflammatory markers in relation to survival and to both clinical and tumor aggressiveness parameters.

**Results:** Amongst 330 transplanted HCC patients, CRP was found to be the only significant inflammatory marker for survival, on multivariate Cox regression analysis. NLR, PLR, GGT, AST, ALT and the Glasgow inflammation score were also found to be significant, but on univariate analysis only. CRP was significant in patients with both small (< 5 cm) and large HCCs and in patients with elevated or low Alpha-Fetoprotein (AFP) levels. Comparison of HCC patients with high (>2.5 mg/dL) compared low serum CRP levels showed significant differences for blood levels of NLR, LMR, Hb, total bilirubin and liver transaminases, as well as Maximum Tumor Diameter (MTD) and percent of patients with Portal Vein Thrombosis (PVT).

**Conclusions:** Elevated serum CRP levels were associated with significantly increased MTD and percent of patients with PVT and significantly worse overall survival in HCC patients who were treated by liver transplantation.

**Keywords:** HCC, CRP, survival, cox

**Abbreviations:** CRP: C-Reactive Protein; AFP: Alpha-Fetoprotein; ALKP: Alkaline Phosphatase; AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: Gamma Glutamyl Transpeptidase; HCC: Hepatocellular Carcinoma; MTD: Maximum Tumor Diameter; OS: Overall Survival; PVT: Portal Vein Invasion; HR: Hazard Ratio; Hb: Hemoglobin; Glasgow: Glasgow Index; NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; LMR: Lymphocyte to Monocyte Ratio; AUC; Area Under the Curve

## Introduction

Rudolf Virchow first proposed that there might be an association between chronic inflammation and development of cancer in 1863 [1]. A quarter of all human cancers may be associated with inflammation related to infections; which likely depends on the presence of tumor micro environmental inflammatory cells [2,3]. In Hepatocellular Carcinoma (HCC) patients; chronic hepatitis B or C or alcoholism or metabolic syndrome/Non-Alcoholic Steatohepatitis (NASH) cause chronic inflammation and subsequent HCC development; usually with multiple intermediate steps in an altered tumor microenvironment [4,5].

The acute phase reactant C-Reactive Protein (CRP) is a non-specific index of inflammatory activity; which is cheap and has been in clinical use for years [6] and is a useful blood-based biomarker of both disease extent and prognosis in several cancers; especially of the GI tract and for HCC [7-9]. It is synthesized in the liver and in HCC cells [10,11] and is thought to reflect both systemic and local inflammation. Several other indices of systemic inflammation have been proposed; most notably the combination of blood CRP and albumin levels (Glasgow index) [12,13]; blood ESR levels [14]; and ratios of Neutrophils To Lymphocytes (NLR) and Platelets To Lymphocytes (PLR) [15-18]; in addition to liver inflammation enzymes AST; ALT; GGT in relation to HCC.

In the current study; a number of commonly

**Brian I Carr[1*], Volkan Ince[1], Harika Gozukara Bag[2], Sertac Usta[1], Veysel Ersan[1], Burak Isik[1] and Sezai Yilmaz[1]**

[1]Department of Surgery, Liver Transplantation Institute, Inonu University, Turkey

[2]Department of Biostatistics, Medical School, Inonu University, Turkey .

*Author for correspondence:
brianicarr@hotmail.com

clinically used inflammation markers were compared for their prognostic usefulness in a large HCC dataset; but only CRP was found to be significant for survival in both small and large size tumor patients; as well as in those with elevated or low AFP levels.

## Methods

Patients who underwent LT for HCC at our Liver Transplantation Institute between March 2006 and October 2020 were the subjects of this study. The data were collected prospectively and were analyzed retrospectively. This study has been approved by Inonu University Institutional Review Board (Approval no: 2020/1275).

The clinical parameters and tumor characteristics of 330 de-identified HCC patients were analyzed according to CRP levels; the cut-off of which was found by ROC analysis (**FIGURE 1**) and were significantly associated with survival post liver transplant 12. Categorical (qualitative) variables were expressed as count and percentage. Comparisons of groups were made by Pearson's chi-square test; continuity corrected chi-square test or Fisher's exact test where appropriate for categorical variables. Quantitative variables were summarized by median; first quartile and third quartile values. Two group comparisons were performed by Mann-Whitney U test. For more than two groups Kruskal-Wallis test and Conover pairwise comparison method were used. Kaplan-Meier survival estimate was used to determine overall survival of the patients. Hazard Ratio (HR) estimations were obtained by either univariate or multivariate Cox regression analysis. Follow-up period was defined as the interval between LT until the date of last visit to the outpatient department for living patients or until the date of death of the patient. Statistical tests were considered significant when the corresponding p value was less than 5%. All statistical analyses were performed using IBM SPSS Statistics for Windows version 25.0 (New York; USA).
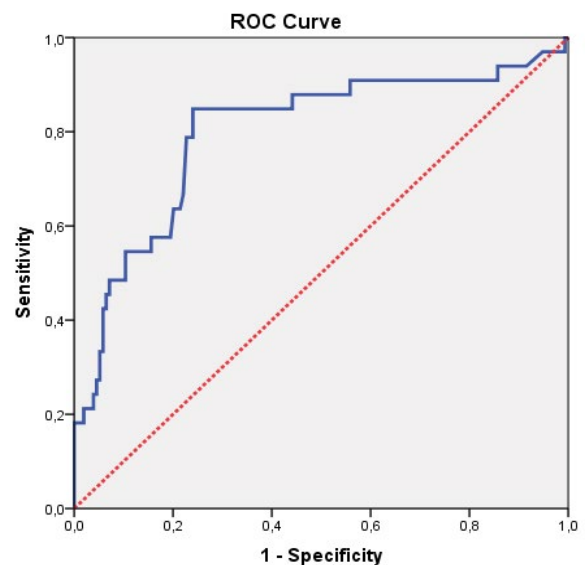
## Results

### ■ Comparison of inflammation indices for survival

A univariate Cox regression analysis was calculated for multiple parameters that have been considered to reflect hepatic inflammation; including NLR; PLR and Lymphocyte to Monocyte Ratio (LMR); the Glasgow inflammation index and blood levels of GGT; CRP; albumin; the liver enzymes AST; ALT; ALKP; GGT; as well as CRP; Hb and platelets (**TABLE 1**). Only NLR; PLR; GGT; CRP and Glasgow index had significant HR p-values. A subsequent multivariate analysis of those parameters with significant p-values showed that only CRP was significant; HR p-value <0.001 (**TABLE 1**). Glasgow index could not be analyzed this way; as its components were already separately part of the analysis.

### ■ Only CRP had significance

CRP; considered as a continuous variable; was also significant in Cox univariate and multivariate analyses when patients with small



**FIGURE 1. Receiver Operating Characteristics (ROC) curve for blood CRP values (mg/dL).**

Diagonal segments are produced by ties.

CRP is a superior and prognostically significant inflammation biomarker for hepatocellular cancer patients treated by liver transplantation

RESEARCH ARTICLE

(<5 cm) or large (>5 cm) HCCs were considered separately (**TABLE 2**). CRP cutoff levels of 2.5 mg/dL; were found by constructing a receiver operating characteristic (ROC) curve AUC=0.798 ± 0.048 (95% C.I=0.703-0.893) p<0.001; with a specificity of 0.76 and sensitivity of 0.85 (**FIGURE 1**). Kaplan-Meier (KM) survival and subsequently Cox analyses were then performed; using these same CRP cutoffs considered as binary; in the whole cohort and separately in patients with small (<5 cm) or large (>5 cm) size HCCs (**TABLE 3**). Patients with

lower CRP levels (<2.5 mg/L) had significantly longer survival that patients with higher levels (>2.5 mg/L) in both the total cohort; as well as when patients with smaller or larger HCCs were considered separately. In **TABLE 4**; the overall mean survival times were calculated according to CRP level; and are shown separately for patients with low (<100 IU/mL) or high (>100 IU/mL) serum AFP levels. The results show the prognostic usefulness of serum CRP levels; independently of patient AFP status.

### TABLE 1. Univariate and multivariate Cox regression analyses for the total cohort, n=330.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Cox regression | | Cox regression | |
| | Univariate HR | HR | Multivariate HR | HR |
| | (95% CI) | p-value | (95% CI) | p-value |
| NLR | 1.057 (1.002-1.115) | 0.043 | 1.015 (0.925-1.113) | 0.753 |
| PLR | 1.004 (1.001-1.007) | 0.009 | 1.004 (0.998-1.010) | 0.182 |
| GGT (IU/L) | 1.003 (1.002-1.004) | <0.001 | 1.001 (0.997-1.005) | 0.615 |
| CRP (mg/L) | 1.012 (1.007-1.018) | <0.001 | 1.013 (1.007-1.019) | <0.001 |
| Albumin (g/L) | 1.014 (0.747-1.377) | 0.928 | | |
| Platelets (10⁹/μL) | 1.002 (0.999-1.004) | 0.148 | | |
| Hemoglobin (g/dL) | 0.983 (0.916-1.056) | 0.645 | | |
| AST (IU/L) | 1.002 (1.000-1.004) | 0.026 | 1.001 (0.996-1.005) | 0.8 |
| ALT (IU/L) | 1.001 (1.000-1.002) | 0.006 | 1.000 (0.998-1.002) | 0.843 |
| ALKP (IU/L) | 1.001 (0.998-1.003) | 0.715 | | |
| Glasgow=0 (n=164) | reference | | | |
| Glasgow=1 (n=20) | 2.412 (1.123-5.180) | 0.024 | | |

Abbreviations: HR: Hazard Ratio: ALKP: Alkaline Phosphatase, GGTP: Gamma Glutamyltranspeptidase, ALT: Alanine Aminotransaminase, AST: Aspartate Aminotransaminase, Hb: Hemoglobin, Glasgow: Glasgow Index, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, LMR: Lymphocyte to Monocyte Ratio, CRP: C-Reactive Protein.

### TABLE 2. Univariate and multivariate Cox regression analyses of CRP in patients with small or large MTD HCCs.

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | Cox regression | | Cox regression | |
| | | Univariate HR | HR | Multivariate HR | HR |
| | | (95% CI) | p-value | (95% CI) | p-value |
| CRP in: | MTD ≤ 5 cm | 1.010 (1.003-1.017) | 0.003 | 1.010 (1.003-1.017) | 0.004 |
| CRP in: | MTD ≤ 5 cm | 1.020 (1.001-1.038) | 0.035 | 1.019 (1.001-1.038) | 0.037 |

Abbreviations: MTD: Maximum Tumor Diameter, CRP: C-Reactive Protein, HR: Hazard Ratio.

### TABLE 3. Kaplan-Meier and Cox regression analysis for single variables.

| | | Kaplan-Meier | | Univariate | |
|---|---|---|---|---|---|
| | | Analysis | | Cox regression | |
| | | Survival time (d) | Log-Rank | HR | HR |
| | | Mean ± SE | p-value | (95% CI) | p-value |
| Total | CRP ≤ 2.5 | 2866.03 ± 90.48 | <0.001 | reference | |
| cohort | CRP>2.5 | 2656.46 ± 253.60 | | 6.941 (2.643-18.229) | <0.001 |
| MTD ≤ 5cm | CRP ≤ 2.5 | 2951.74 ± 60.06 | <0.001 | reference | |
| | CRP>2.5 | 2609.11 ± 287.02 | | 7.670 (2.183-26.942) | 0.001 |
| MTD>5cm | CRP ≤ 2.5 | 2439.82 ± 350.03 | 0.02 | reference | |
| | CRP>2.5 | 1425.16 ± 323.76 | | 4.989 (1.104-22.554) | 0.037 |

Abbreviations: MTD: Maximum Tumor Diameter, CRP: C-Reactive Protein (mg/L), HR: Hazard Ratio, d: Days.

### ■ Clinical and tumor characteristics of patients with high and low blood CRP levels

In order to try to explain the differences in survival based on high or low blood CRP levels; the clinical characteristics for patients with high versus low CRP levels were compared. Patients with higher CRP levels had significantly different levels of NLR and LMR; higher blood levels of total bilirubin and transaminases and lower Hb levels **(TABLE 5).** The tumor characteristics were then compared. Patients with higher CRP levels had significantly larger tumors and a significantly higher percent of these higher CRP patients had PVT; compared to patients with lower CRP levels **(TABLE 6)**. Levels of AFP;

tumor differentiation or percent of patients with multifocality were not significantly different between the 2 CRP groups of patients.

### ■ Serum CRP levels related to both MTD and PVT

Serum CRP levels were then examined in relation to MTD groups. Patients with MTD<5 cm had a significantly lower CRP levels than the other MTD groups **(TABLE 7)**. However; there was no significant difference between MTD 5 cm-7 cm and >7 cm groups in terms of CRP level. Unlike MTD; microscopic PVT (microPVT) could not be expressed quantitatively; but only as the percent of patients with micro PVT **(TABLE 8)**. A significantly lower percent of

**TABLE 4. Kaplan-Meier and Cox regression analysis for low vs. high CRP levels within AFP groups.**

|  |  | Kaplan-Meier | | Univariate | |
|---|---|---|---|---|---|
|  |  | Analysis | | Cox regression | |
|  |  | Survival time | Log-Rank | HR | HR |
|  |  | Mean ± SE | p-value | (95% CI) | p-value |
| AFP ≤ 100 | CRP ≤ 2.5 | 2879.84 ± 113.40 | <0.001 | reference |  |
|  | CRP>2.5 | 2730.16 ± 286.91 |  | 8.093 (2.363-27.720) | 0.001 |
| AFP>100 | CRP ≤ 2.5 | 2564.91 ± 191.18 | 0.041 | reference |  |
|  | CRP>2.5 | 2174.28 ± 544.69 |  | 4.632 (0.926-23.172) | 0.062 |

Abbreviations: CRP: C-Reactive Protein (mg/L), AFP: Alpha-Fetoprotein (IU/mL), HR: Hazard Ratio.

**TABLE 5. Clinical characteristics of HCC patients with low or high serum CRP in the total cohort.**

|  | CRP ≤ 2.5 mg/L | CRP>2.5 mg/L |  |
|---|---|---|---|
|  | Median (1stQ-3rd Q) | Median (1stQ-3rd Q) | p |
| NLR | 2.3 (1.5-3.5) | 3 (1.9-5.9) | 0.008 |
| PLR | 76.6 (55.2-107.9) | 91.3 (52.1-142.4) | 0.189 |
| GGT | 59.5 (38-116) | 73 (39-124.3) | 0.306 |
| Albumin | 2.9 (2.5-3.6) | 2.8 (2.4-3.2) | 0.066 |
| Platelets | 92.5 (61-145) | 83 (60-161) | 0.806 |
| Hemoglobin | 12.9 (10.8-14.3) | 11.4 (9.7-13.3) | 0.021 |
| Total Bilirubin | 1.71 (0.95-2.81) | 1.9 (1.19-5.21) | 0.013 |
| AST | 51 (32-69) | 78.5 (52-106) | <0.001 |
| ALT | 36 (25-50) | 53 (38-80) | <0.001 |
| ALKP | 108.5 (82-152) | 106 (81-158.5) | 0.934 |

*1stQuartile is the 25th percentile-3rdQuartile is the 75th percentile. Abbreviations and units: see legend to Table 1a.

**TABLE 6. Tumor characteristics of HCC patients with low or high serum CRP levels in total cohort.**

|  |  | CRP ≤ 2.5 mg/L | CRP>2.5 mg/L |  |
|---|---|---|---|---|
|  |  | Median (1stQ-3rdQ.) | Median (1stQ-3rdQ.) | p |
| MTD size |  | 2.5 (1.2-3.7) | 3.5 (1.8-5.5) | 0.007 |
| AFP |  | 11.4 (4.4-41.2) | 8.2 (3.2-44.9) | 0.353 |
| # of tumor nodules |  | 1 (1-3) | 1 (1-3) | 0.561 |
|  |  | % | % | p |
| Tumor | Well | 45.1 | 47.7 | 0.733 |
| Differentiation | Moderate+poor | 54.9 | 52.3 |  |
| PVT | None | 67 | 51.6 | 0.043 |
|  | Microscopic | 33 | 48.4 |  |

*1stQuartile is the 25th percentile-3rdQuartile is the 75th percentile.
Abbreviations: MTD: Maximum Tumor Diameter, AFP: Alpha-Fetoprotein (IU/mL), PVT: Microscopic Portal Vein Thrombosis.

CRP is a superior and prognostically significant inflammation biomarker for hepatocellular cancer patients treated by liver transplantation

RESEARCH ARTICLE

| TABLE 7. Serum CRP levels according to HCC size. | | | | |
|---|---|---|---|---|
| MTD | Median | 1stQ | 3rdQ | p |
| <5 cm | 0.84[a] | 0.32 | 3 | |
| 5-7 cm | 2.67[b] | 0.46 | 7.4 | 0.006 |
| >7 cm | 3.25[b] | 1.35 | 11.5 | |

Abbreviations: MTD: Maximum Tumor Diameter, CRP: C-Reactive Protein (mg/L). *The difference between the groups with different superscript letters was found to be statistically significant.

| TABLE 8. Incidence of microPVT according to serum CRP levels in HCC patients with MTD>5 cm. | | | |
|---|---|---|---|
| | microPVT (-) | microPVT (+) | p |
| CRP | (%) | (%)* | |
| <2.5 | 90.6 | 9.4[a] | |
| 2.5-5 | 70.8 | 29.2[b] | 0.004 |
| >5-10 | 75 | 25[a;b] | |
| >10 | 53.8 | 46.2[b] | |

Abbreviations, CRP: C-Reactive Protein (mg/L), microPVT: Microscopic Portal Vein Thrombosis. *The difference between the groups with different superscript letters was found to be statistically significant.

patients (9.4%) with CRP levels of <2.5 mg/L than percent of patients with higher blood CRP levels (>25%) had microPVT. However; the percent of patients with CRP>5 mg/L-10 mg/L level was not statistically different from the others in terms of microPVT positivity.

## Discussion

There is much published evidence for a role of inflammation in many cancers; including hepatocellular carcinoma [19,20]. Inflammation-based prognostic scores have been shown to be associated with survival [21] and with various parameters of tumor aggressiveness [21]. This may be related to the involvement in tumor growth of a variety of easily measurable indices of inflammation such as CRP [21].

Inflammation is thought to induce a microenvironment that is involved in DNA damage; tumor growth and angiogenesis and seems to involve a bidirectional process; in which inflammation can be seen as a response to growing tumor cells; yet is also involved in their growth and invasiveness [19,22]. Various mechanisms appear to be involved; including the presence of tumor growth inducing inflammatory factors and plasma CRP; and the tumors themselves that can produce inflammatory cytokines; including CRP; IL-6 and IL-8. Thus; CRP appears to be elevated both locally (by microenvironment and HCC) and systemically (by the liver; but possibly elsewhere; as in other GI cancers). It can thus be seen as a biomarker for the systemic bodily response to growing cancer; but also as a locally-acting mediator of inflammation-associated cancer growth and invasiveness [23]. It is not just a passive indicator of inflammation; but also has actions of its own; such as modulation of N-cadherin [24] and growth control in some tumor models [25]. Conversely; CRP levels can be depressed with chronic consumption of aspirin [26]; which itself has cancer-prevention properties. However; the precise mechanisms that underlie the relationship of inflammatory markers to tumor biology have not been well defined.

In the current study; we evaluated a range of clinically-used inflammation markers and indices in relation to post-liver transplant HCC survival. Despite several parameters being significant on univariate analysis; only CRP was statistically significant on multivariate analysis. Elevated CRP levels were associated with shorter survival than low serum CRP levels in the total cohort; as well as when patients with smaller or larger tumors were examined separately (**TABLE 3**); as well as for patients with elevated or low levels of alpha-fetoprotein (**TABLE 4**). In order to try to explain these results; the clinical laboratory parameters and tumor characteristics of patients with higher serum CRP levels were compared with those of patients with lower CRP levels (**TABLE 5**). Amongst the clinical laboratory parameters; NLR; hemoglobin; total bilirubin; ALT and AST levels were significantly higher in those patients with higher; compared with lower CRP levels (**TABLE 5**). Thus; indices of inflammation and liver damage were associated with patients having higher CRP levels. When the tumor characteristics were compared; MTD and percent of patients with microscopic PVT were significantly associated with patients having higher serum CRP levels; in comparison to those with low CRP levels.

Thus; serum CRP levels correlated with tumor size and PVT; but not with focality; tumor differentiation or AFP levels **(TABLE 6)**. CRP in this analysis thus correlated with tumor growth (size) and invasiveness. Perhaps that is a sufficient explanation for the prognostic value of serum CRP levels; or perhaps other inflammation-associated factors that were not measured here could contribute. In addition; there was a correlation between serum CRP levels and both MTD and percent of patients having PVT; likely due to the fact that a significant number of these patients were beyond-Milan criteria for liver transplantation for HCC.

## Conclusion

Serum CRP levels are thus a useful prognosticator for patients with HCC undergoing curative liver transplantation and these results reflect the importance of inflammation in the pathophysiology of human HCC.

## Author Contributions

Participated in research design Brian I Carr; Volkan Ince; Sezai Yilmaz; Sezai Yilmaz; Burak Isik. Participated in the writing of the paper Brian I Carr; Volkan Ince; Harika Gozukara Bag; Sezai Yilmaz. Participated in the performance of the research Volkan Ince; Brian I Carr; Sezai Yilmaz; Veysel Ersan; Sertac Usta; Burak Isik. Participated in data analysis Harika Gozukara Bag; Brian I Carr; Volkan Ince; Sertac Usta.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

## Support

CRP is a superior and prognostically significant inflammation biomarker for hepatocellular cancer patients treated by liver transplantation

RESEARCH ARTICLE

## References

Virchow RLK. Die krankhaften Geschwülste. Berlin: August Hirschwald. (1863).

Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. *Int J Cancer*. 121: 2373-2380 (2007).

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 144: 646-674 (2011).

Refolo MG, Messa C, Guerra V, et al. Inflammatory Mechanisms of HCC Development. *Cancers (Basel)*. 12: 641 (2020).

Bishayee A. The role of inflammation and liver cancer. *Adv Exp Med Biol*. 816: 401-435 (2014).

Pepys MB, Belts ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid a protein. *Adv Immunol*. 34: 141-212 (1983).

Mahmoud FA, Rivera NI. The role of C-reactive protein as a prognostic indicator in advanced cancer. *Curr Oncol Rep*. 4: 250-255 (2002).

Ma LN, Liu XY, Lu ZH, et al. Assessment of high-sensitivity C-reactive protein tests for the diagnosis of hepatocellular carcinoma in patients with hepatitis B-associated liver cirrhosis. *Oncol Lett*. 13: 3457-3464 (2017).

Fabris C, Pirisi M, Soardo G, et al. Diagnostic usefulness of acute-phase protein measurement in hepatocellular carcinoma. *Cancer Invest*. 14: 103-108 (1996).

Toniatti C, Arcone R, Majello B, et al. Regulation of the human C-reactive protein gene: a major marker of inflammation and cancer. *Mol Biol Med*. 7: 199-212 (1990).

Arcone R, Gualandi G; Ciliberto G. Identification of sequences responsible for acute-phase induction of human C-reactive protein. *Nucleic Acids Res*. 16; 3195-3207 (1988).

Li MX, Bi XY, Li ZY, et al. Prognostic role of glasgow prognostic score in patients with hepatocellular carcinoma: A systematic review and meta-analysis. *Medicine (Baltimore)*. 94: e2133 (2015).

Shiba H, Horiuchi T, Sakamoto T, et al. Glasgow prognostic score predicts therapeutic outcome after hepatic resection for hepatocellular carcinoma. *Oncol Lett*. 14: 293-298 (2017).

Carr BI, Akkiz H, Bag HG, et al. Erythrocyte sedimentation rate and gamma-glutamyl transpeptidase combined are potent predictors of survival and tumor characteristics in hepatocellular carcinoma patients. *J Clin Trials*. 10: 425-432 (2020).

Suner A, Carr BI, Akkiz, H et al. Inflammatory markers CRP and PLR in relation to HCC characteristics. *J Translational Sci*. 5: 10 (2019).

Yamamoto M, Kobayashi T, Kuroda S, et al. Verification of inflammation-based prognostic marker as a prognostic indicator in hepatocellular carcinoma. *Ann Gastroenterol Surg*. 3: 667-675 (2019).

Xu L, Yu S, Zhuang L, et al. Systemic Inflammation Response Index (SIRI) predicts prognosis in hepatocellular carcinoma patients. *Oncotarget*. 8: 34954-34960 (2017).

Rosenblatt RE, Tafesh ZH, Halazun KJ. Role of inflammatory markers as hepatocellular cancer selection tool in the setting of liver transplantation. *Transl Gastroenterol Hepatol*. 2: 95 (2017).

Balkwill F; Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 357; 539-545 (2001).

Hernandez-Gea V; Toffanin S; Friedman SL; et al. Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma. *Gastroenterology*. 144; 512-527 (2013).

Carr BI, Akkiz H, Guerra V, et al. C-reactive protein and hepatocellular carcinoma: analysis of its relationships to tumor factors. *Clin Pract (Lond)*. 15: 625-634 (2018).

Carr BI, Guerra V. A hepatocellular carcinoma aggressiveness index and its relationship to liver enzyme levels. *Oncology*. 90: 215-220 (2016).

Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *J Epidemiol Community Health*. 61: 824-833 (2007).

Kudo S, Saito H, Motoyama S, et al. C-reactive protein inhibits expression of N-cadherin and ZEB-1 in murine colon adenocarcinoma. *Tumour Biol*. 36: 7035-7043 (2015).

Ronca R, Alessi P, Coltrini D, et al. Long pentraxin-3 as an epithelial stromal fibroblast growth factor-targeting inhibitor in prostate cancer. *J Pathol*. 230: 228-238 (2013).

Ho GY, Xue X, Cushman M, et al. Antagonistic effects of aspirin and folic acid on inflammation markers and subsequent risk of recurrent colorectal adenomas. *J Natl Cancer Inst*. 101: 1650-1654 (2009).