Check for updates

Received: 12 May 2020 | Accepted: 18 June 2020

DOI: 10.1111/ijcp.13593

ORIGINAL PAPER

ONCOLOGY

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Serum levels of inflammatory markers CRP, ESR and albumin in relation to survival for patients with hepatocellular carcinoma

Hikmet Akkiz[1] | Brian I. Carr[2] | Harika G. Bag[2] | Ümit Karaoğullarından[1] | Kendal Yalçın[3] | Nazim Ekin[3] | Ayşegül Özakyol[4] | Engin Altıntaş[5] | Hatice Y. Balaban[6] | Halis Şimşek[6] | Ahmet Uyanıkoğlu[7] | Ayhan Balkan[8] | Sedef Kuran[1] | Oğuz Üsküdar[1] | Yakup Ülger[1] | Burak Güney[1] | Anil Delik[1]

[1]Çukurova University, Adana, Turkey

[2]İnönü University, Malatya, Turkey

[3]Dikle University, Diyarbakır, Turkey

[4]Eskişehir Osmangazi University, Eskişehir, Turkey

[5]Mersin University, Mersin, Turkey

[6]Hacettepe University, Ankara, Turkey

[7]Harran University, Şanlıurfa, Turkey

[8]Gaziantep University, Gazientep, Turkey

Correspondence
Brian I. Carr, Liver Transplant Institute, Inonu University, Bulgurlu Mah, Elazig Yolu 15 km, 44289 Merkez Battalgazi, Malatya, Turkey.
Email: brianicarr@hotmail.com

Funding information
This work is supported in part by NIH grant CA 82723 (B.I.C)

Abstract

Introduction: Hepatocellular carcinoma is associated with several chronic inflammatory conditions. It is increasingly understood that the inflammation may be part of the carcinogenic process and prognostically important.

Objective: To evaluate the serum levels of three inflammation markers in relation to survival in HCC patients.

Methods: We retrospectively examined the serum levels of CRP, albumin and ESR, both singly and in combination, in relation to patient survival.

Results: Survival worsened with increase in CRP or ESR or decrease in albumin levels. Combinations of CRP plus albumin or CRP plus ESR were associated with an even greater range of survival (3-fold), together with significant differences in maximum tumor diameter (PVT) and percent of patients with portal vein thrombosis (PVT). The triplet of CRP plus albumin plus ESR was associated with a sevenfold difference in survival, comparing low vs high parameter levels. These significant differences were found in patients with small or large tumors.

Conclusions: Combinations of CRP with albumin or ESR or all three parameters together significantly related to differences in survival and to differences in MTD and percent PVT, in patients with both small and large size HCCs.

1 | INTRODUCTION

Inflammation has increasingly been recognised as an important associated factor for several tumor types of the gastrointestinal tract,[1-6] including hepatocellular carcinoma (HCC).[6-8] It has been increasingly recognised that inflammation may be prognostically important and may even define tumor types within the same diagnosis[9-13] and several reviews have been published on the likely hepatocarcinogenic mechanisms within the inflammatory tumor microenvironment, especially for HCC.[8] Amongst the clinically useful semi-quantitative indices of tumor-associated inflammation are the Glasgow Index for GI tumors in general,[14] and HCC,[15-20] using combination serum C-reactive protein (CRP) and albumin levels, as well as several variant indices.[21]

Abbreviations: AFP, alpha-fetoprotein; Alb, albumin; ALKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CT, computerised axial tomography; ESR, erythrocyte sedimentation rate; GGTP, gamma glutamyl transpeptidase; Hb, haemoglobin; HCC, hepatocellular carcinoma; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; MRI, magnetic resonance imaging; MTD, maximum tumor diameter; Plt, platelets; PVT, portal vein thrombosis; T. bili, total bilirubin.

Hikmet Akkiz, Brian I. Carr and Harika G. Bag have authors contributed equally.

 © 2020 John Wiley & Sons Ltd

In the current study, we have made use of previously available survival data from a new large Turkish multi-institutional HCC collaborative,[22] to examine the contributions of serum CRP or albumin, singly or together, for evaluation of survival in our HCC patients, and to introduce for the first time, to our knowledge, the usefulness of erythrocyte sedimentation rate (ESR) data to the prognostic model. We found that combination of CRP plus albumin or CRP plus ESR levels are associated between threefold and sevenfold the survival, between groups. A triplet combination of CRP plus albumin plus ESR was even more discriminatory for survival.

What's known?

- Most important HCC marker is AFP (alpha-fetoprotein), but less than 50% of patients have elevated AFP levels.
- Additional or substitute markers are needed for prognosis.

What new

- Our data draw attention to the role of inflammatory markers in HCC aggressiveness and survival and show that without considering AFP, the blood levels of the inflammatory parameters C-reactive protein, Erythrocyte Sedimentation Rate and albumin can predict both prognosis and tumor aggressiveness factors, especially tumor size and presence of portal vein thrombosis (PVT).

2 | METHODS

2.1 | Patient data

We retrospectively analysed a database of 785 prospectively accrued HCC patients who had full baseline tumor parameter data, including CT scan information on HCC maximum tumor diameter (MTD), number of tumor nodules and presence or absence of macroscopic portal vein thrombosis (PVT) and serum AFP levels; complete blood count; routine serum liver function tests, (total bilirubin, GGTP, ALKP, albumin, transaminases, CRP levels and where available, ESR levels), as well as patient demographics. Diagnosis was made either via tumor biopsy or according to international guidelines. The study group were patients aged 18 years or over, who were diagnosed with HCC and who were not eligible for surgical curative therapies. Patients were followed up every 3-4 months until death. Full blood count, AFP and liver functions were obtained at each follow-up visit, as well as CT scans as appropriate. 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 of each participating institution.

2.2 | Statistical analysis

Continuous variables were summarised by median, minimum and maximum values. Comparisons between two groups were performed by Mann-Whitney *U* test. Categorical variables were expressed as count and percentage, comparisons according to these variables were made by Pearson's chi-square, continuity corrected chi-square or Fisher's exact test where appropriate. Kaplan-Meier method and Log-Rank test were used for survival analysis. In all analysis two-tailed significance level was considered as 0.05. IBM SPSS Statistics for Windows version 22.0 (NY, USA) was used for statistical analysis.

3 | RESULTS

3.1 | Survival for single blood inflammation markers, CRP, albumin or ESR

This study group comprised patients aged 18 years or over, who were diagnosed with HCC as in the Methods section and who were not eligible for surgical curative therapies. Patients were followed up every 3-4 months until death. Serum levels of the inflammation indices CRP, albumin and blood ESR were examined at baseline presentation, in relation to HCC patient survival. CRP levels were chosen from terciles of the total cohort, with the lowest level ≤10 mg/dL being the Glasgow score cut-off value.[14-18] The lowest CRP serum level (≤10 mg/dL) was associated with the longest survival of 71.5 months and was statistically significant from the lower survivals associated with serum levels of CRP

TABLE 1 Kaplan-Meier analysis for differing serum CRP levels (mg/dL) in the total cohort

		Survival time		Log-Rank
		Mean ± SE	95% CI	*P*-value
CRP	≤10 (n = 625)	71.514 ± 5.144[a]	61.432-81.596	.001
	10-25 (n = 69)	32.091 ± 4.761[b]	22.759-41.424	
	>25 (n = 91)	40.647 ± 6.244[b]	28.410-52.885	

Note: The difference between the groups with different superscript letters was found to be statistically significant. CRP ≤ 10 group has a longer survival than the others. CRP, C-reactive protein; CRP units: mg/dL.

TABLE 2 Kaplan-Meier analysis for differing albumin blood levels (g/dL) in the total cohort

		Survival time		Log-Rank
		Mean ± SE	95% CI	*P*-value
ALB	<2.5 (n = 282)	51.173 ± 5.358[a]	40.671-61.675	<.001
	2.5-3.5 (n = 333)	45.052 ± 3.883[a]	37.441-52.662	
	>3.5 (n = 170)	83.569 ± 8.008[b]	67.873-99.265	

Note: The difference between the groups with different superscript letters found to be statistically significant. There is no difference between the ALB < 2.5 and ALB = 2.5-3.5 groups, but ALB > 3.5 group has a longer survival than the others. ALB, albumin. Albumin units: g/dL.

TABLE 3 Kaplan-Meier analysis for differing ESR levels (mm/h) in the total cohort

		Survival time		Log-Rank
		Mean ± SE	95% CI	*P*-value
ESR	<15 (n = 115)	102.927 ± 11.437[a]	80.510-125.344	<.001
	15-50 (n = 234)	46.559 ± 3.966[b]	38.785-54.333	
	>50 (n = 80)	31.075 ± 5.042[c]	21.193-40.958	

Note: The difference between the groups with different superscript letters was found to be statistically significant. All groups' survivals are significantly different from each other. ESR, erythrocyte sedimentation rate; ESR units: mm/h.

10-25 or >25 mg/dL (Table 1). Albumin levels were also chosen from the highest level of the Glasgow score (>3.5 g/dL) being normal.[14] The highest value was associated with the longest survival of 83.5 months and was statistically longer than the survival associated with the other 2 albumin serum levels (Table 2). ESR levels were also just by tercile analysis of the total cohort, with ESR 15 mm/h being the upper limit of the normal serum range and thus the lowest point for this analysis (<15 mm/h). We found be far the largest range for survival, of 31-102.9 months for the ESR values (Table 3) and each ESR group was associated with a statistically significant survival difference from each other ESR group.

3.2 | Significance of parameter background for CRP and ESR significance

The survival of patients with different CRP levels was assessed in the presence of normal or low serum albumin levels (Tables 4 and 5). Significant differences were found, regardless of albumin background. However, for patients with low serum CRP ≤10 mg/dL levels, survival was significantly longer in patients with normal albumin levels >3.5 g/dL than in patients with low albumin levels. Thus, the level of CRP alone gives an incomplete picture of the prognostic significance, without simultaneously considering albumin (and doubtless other parameter) levels. Similarly, when differing ESR levels were considered in the context of elevated or low serum CRP levels (Tables 6 and 7), survival at each ESR level was significantly higher in the context of low CRP (Table 7) than in elevated CRP serum levels (Table 6). For differing ESR levels in the context of elevated CRP (Table 6), each ESR level was associated with significantly different survival compared with each other ESR level.

3.3 | Survival for the combination of two inflammation markers

The Glasgow Inflammation prognostic score for GI cancers was based upon the combination of the two parameters, serum CRP and albumin levels. The three possible combinations of our three inflammation parameters were therefore next separately examined. The combination of serum CRP with albumin levels, showed an almost threefold survival difference of 34 vs 90 months, between high CRP/low albumin compared with low CRP/high albumin in the total cohort (Table 8). Significant differences were also found when patients with small tumors (≤5 cm) or large tumors (>5 cm) were examined separately (Tables 9 and 10). Thus, this two parameter combination seems to be useful in both small and large HCC patients. In order to try to understand the possible explanation of these survival differences between the two CRP/albumin groups, we examined their related clinical characteristics. We found that for the shorter survival group, every single parameter was significantly worse than the longer survival group, especially having higher levels of GGT, ALKP, transaminases, total bilirubin, AFP and lower Hb (Table 11). When the radiological tumor characteristics were examined, significantly larger tumors (higher MTD) and increased percent of patients with PVT was found, but not tumor numbers in the shorter survival group compared to the longer survival group (Table 12).

TABLE 4 Kaplan-Meier analysis for quantitative CRP levels at constant normal albumin >3.5 levels

		Survival time		Log-Rank
		Mean ± SE (Median)	95% CI	*P*-value
ALB > 3.5	CRP ≤ 10	90.016 ± 8.997a	72.382-107.649	.019
	CRP 10-25	49.744 ± 10.834b	28.509-70.978	
	CRP > 25	28.495 ± 8.258b	12.309-44.680	

Note: CRP ≤ 10 group only has a significantly longer survival than the others; with no significant differences between CRP > 10-25 and >25 groups.

TABLE 5 Kaplan-Meier analysis for quantitative CRP levels at constant normal albumin ≤ 3.5 levels

		Survival time		Log-Rank
		Mean ± SE (Median)	95% CI	*P*-value
ALB ≤ 3.5	CRP ≤ 10	52.133 ± 4.116a	44.067-60.200	.008
	CRP 10-25	26.713 ± 5.012b	16.889-36.538	
	CRP > 25	41.276 ± 6.898b	27.755-54.796	

Note: CRP ≤ 10 group only has a significantly longer survival than the others; with no significant differences between CRP > 10-25 and >25 groups.

TABLE 6 Kaplan-Meier analysis for ESR levels at constant CRP > 10

		Survival time		
		Mean ± SE	95% CI	*P*
CRP > 10	ESR < 15	83.400 ± 18.425[a]	47.284-119.513	
	ESR 15-50	41.480 ± 10.003[b]	21.874-61.086	.011
	ESR > 50	14.640 ± 5.104[c]	4.635-24.645	

Note: Survival differences between all ESR levels are statistically significant.

TABLE 7 Kaplan-Meier analysis for ESR levels at constant CRP ≤ 10

		Survival time		
		Mean ± SE	95% CI	*P*
CRP ≤ 10	ESR < 15	101.093 ± 11.727[a]	78.109-124.077	
	ESR 15-50	47.616 ± 4.341[b]	39.107-56.125	.004
	ESR > 50	34.740 ± 5.969[b]	23.041-46.440	

Note: Only ESR < 15 group has a longer survival, no difference between ESR = 15-50 and ESR > 50.

TABLE 8 Kaplan-Meier analysis for total cohort

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
CRP > 10 & ALB ≤ 3.5	34.460 ± 4.577	25.490-43.431	<.001
CRP ≤ 10 & ALB > 3.5	90.016 ± 8.997	72.382-107.649	

Abbreviations: ALB, albumin (g/dL); CRP, C-reactive protein (mg/dL).

A survival analysis was also performed for those patients with combination high serum CRP plus high blood ESR, vs low levels of the same combination (Table 13). A threefold difference in survival was found between patients having low vs high combination CRP plus ESR. Significant differences were also maintained whether patients with small (<5 cm) or large ≥ 5 cm) HCC s were considered (Tables 14 and 15). The associated clinical characteristics were also compared (Table 16) and significant differences were found for GGT, ALKP, albumin, AST and Hb, but not for ALT or AFP values. Similarly, for radiological tumor characteristics (Table 17), significantly elevated MTD and increased percent of patients with PVT was found for patients with high CRP plus ESR compared to those with low CRP plus ESR.

3.4 | Survival for the combination of three blood inflammation markers

We next examined whether addition of ESR to the CRP plus albumin combination of the Glasgow index might result in any extra discrimination between groups (Tables 18-22). We found a sevenfold difference in survival between high CRP, high ESR and low albumin triplet (abnormal) as compared with low CRP, low ESR,

TABLE 9 Kaplan-Meier analysis for HCC patients with MTD ≤ 5 cm

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
CRP > 10 & ALB ≤ 3.5	31.501 ± 7.676	16.456-46.547	<.001
CRP ≤ 10 & ALB > 3.5	70.563 ± 6.982	56.879-84.248	

Abbreviations: ALB, albumin (g/dL); CRP, C-reactive protein (mg/dL).

TABLE 10 Kaplan-Meier analysis for HCC patients with MTD > 5 cm

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
CRP > 10 & ALB ≤ 3.5	25.023 ± 5.020	15.184-34.862	.001
CRP ≤ 10 & ALB > 3.5	46.021 ± 7.014	32.275-59.768	

Abbreviations: ALB, albumin (g/dL); CRP, C-reactive protein (mg/dL).

TABLE 11 Laboratory values for combination of albumin and CRP

	ALB ≤ 3.5 & CRP > 10	ALB > 3.5 & CRP ≤ 10	
	Median (min.-max.)	Median (min.-max.)	*P*-value
Hb, g/dL	10.8 (5-22.84)	13.8 (8.1-18)	<.001
Plt, 10^3/μL	139 (10-571)	159 (31-532)	.048
HDL, mg/dL	28 (5-89)	38.5 (13.1-96)	.001
LDL, mg/dL	90 (10-208)	94 (39-237)	.193
AFP, ng/mL	196 (1.02-918 965)	18.5 (0.5-300 000)	.004
ALKP, IU/L	207 (16-564)	99.5 (36-653)	<.001
GGTP, IU/L	113 (13-770)	62 (12-1034)	<.001
AST, IU/L	95 (0-952)	44.5 (13-1748)	<.001
T.bili, mg/dL	2.73 (0.3-33.99)	1.005 (0.22-14.07)	<.001
Cholesterol, mg/dL	1.32 (0.9-6.06)	1.14 (0.9-2.29)	<.001
ALT IU/L	46 (5.5-1855)	35 (11-2240)	.033

Abbreviations: see front page.

high albumin triplet (normal) as shown in Tables 18-20 and figure. The patient numbers required for three different parameters together, did not permit separate evaluation of large vs small tumor patients. However, the clinical characteristics of the two groups was again interesting. Statistically significant differences were again found for GGT, ALKP, AST and Hb, but not for ALT or AFP values (Table 21). A comparison of the tumor characteristic between the 2 groups also showed differences, especially for the

TABLE 12 Tumor characteristics for combination of albumin and CRP

	ALB ≤ 3.5 & CRP > 10	ALB > 3.5 & CRP ≤ 10	
	Median (min.-max.)	Median (min.-max.)	*P*
MTD size (cm)	7 (1-20.5)	5 (1.3-22.5)	.002
	%	%	
Tumor # ≤ 2	59.1	64.7	.407
Tumor # > 2	40.9	35.3	
PVT (–)	57.6	79.8	.001
PVT (+)	42.4	20.1	

Abbreviations: – (absent), + (present); MTD, maximum tumor diameter (cm); PVT, portal vein thrombosis (macroscopic).

TABLE 13 Kaplan-Meier analysis for total cohort

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
CRP > 10 & ESR > 15	29.471 ± 6.742	16.257-42.685	.003
CRP ≤ 10 & ESR ≤ 15	95.193 ± 11.757	72.150-118.235	

Abbreviations: CRP, C-reactive protein (mg/dL); ESR, erythrocyte sedimentation rate (mm/h).

TABLE 14 Kaplan-Meier analysis for HCC patients with MTD < 5 cm

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
CRP > 10 & ESR > 15	19.00 ± 5.451	11.15-17.84	.021
CRP ≤ 10 & ESR ≤ 15	73.41 ± 9.73	54.34-92.48	

Abbreviations: CRP, C-reactive protein (mg/dL); ESR, erythrocyte sedimentation rate (mm/h).

TABLE 15 Kaplan-Meier analysis for HCC patients with MTD ≥ 5 cm

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
CRP > 10 & ESR > 15	23.45 ± 5.91	11.86-35.04	.028
CRP ≤ 10 & ESR ≤ 15	52.64 ± 9.69	33.66-71.63	

Abbreviations: CRP, C-reactive protein (mg/dL); ESR, erythrocyte sedimentation rate (mm/h).

percent of patients with PVT, and almost for MTD, but not for tumor numbers. Thus, an even greater spread was observed for survival between the two triplet groups than between the doublet groups. similar differences between the tumor characteristics were also observed between the two triplet groups as between the two doublet groups.

TABLE 16 Laboratory values for the combination of CRP and ESR

	CRP > 10 & ESR > 15	CRP ≤ 10 & ESR ≤ 15	
	Median (min.-max.)	Median (min.-max.)	*P*-value
Hb, g/dL	11.1 (8.1-14.7)	13.4 (7.15-17.4)	<.001
Plt, $10^3/\mu L$	166 (20-442)	133 (35-2 700 000)	.067
Albumin, g/dL	2.525 (1.4-4.52)	3.3 (1.7-4.88)	<.001
HDL,mg/dL	28 (10-154)	33 (6.3-74.1)	.130
LDL, mg/dL	98 (10-208)	84.5 (30-237)	.714
AFP, ng/mL	282 (1.1-64 448)	15.65 (0.5-97 410)	.208
ALKP, IU/L	234 (67-981)	104 (36-957)	<.001
GGTP, IU/L	121 (16-474)	54 (12-595)	<.001
AST, IU/L	81 (16-505)	53 (20-361)	.045
ALT, IU/L	50 (11-1586)	44 (12-251)	.556
T.bil, mg/dL	1.41 (0.43-21.49)	1.26 (0.45-26.67)	.208
Cholesterol, mg/dL	1.215 (0.92-1.91)	1.2 (0.95-2.29)	.384

Note: Units as in Table 11. Abbreviations on front page.

TABLE 17 Tumor characteristics for the combination of CRP and ESR

	CRP > 10 & ESR > 15	CRP ≤ 10 & ESR ≤ 15	
	Median (min.-max.)	Median (min.-max.)	*P*
MTD size	8 (1.5-20.5)	5 (1-22.5)	.003
	%	%	
Tumor # ≤ 2	60.7	69.6	.530
Tumor # > 2	39.3	30.4	
PVT (–)	46.4	81.7	.001
PVT (+)	53.6	18.3	

Abbreviations: – (absent), + (present); MTD, maximum tumor diameter (cm); PVT, portal vein thrombosis (macroscopic).

4 | DISCUSSION

All three parameters that were studied here showed a significant worsening of survival with increase in serum factor levels, but only for ESR was each factor level significantly different from every other factor level (Tables 1-3). This is a first demonstration, to our knowledge, of a relationship between ESR levels and survival for HCC, or indeed for any cancer.

We explored further the clinical significance of combining CRP and albumin levels for prognostication, as reported by others[14-19] and initially examined the relationship between increasing CRP levels and survival, in the context of either normal or low (abnormal) serum albumin levels (Tables 4-7). Increased CRP levels were associated with decreased survival, regardless of albumin level, but the survival was always lower in the context of lower albumin levels. Thus, environment is important in interpreting CRP levels, in this case serum albumin, but doubtless also in the total context of all other parameters, that were not individually evaluated here. Similarly, when ESR levels were evaluated for their relationship to survival, the survival was always lower for each ESR level in the context of high vs low CRP levels.

The combination of CRP with albumin, as in the Glasgow Index[14] was found to be significantly associated with survival in the total cohort, as expected from the literature, with an almost threefold difference between the low and high survival groups. However, it was also valid for both large and the important small (<5 cm) MTD patients, with an almost twofold survival difference, for whom HCC markers are often not helpful (Tables 9 and 10). To try to explain the prognostic significance of CRP plus albumin combination in HCC, we next examined the clinical characteristics of the poor prognosis group (high CRP plus low albumin) compared to the good prognosis group (low CRP plus high albumin) and found that in the poor prognosis group, multiple lab parameters were significantly worse, including total bilirubin, Hb and the tumor marker AFP and putative tumor markers GGT and ALKP. Interestingly total cholesterol was higher and LDL cholesterol was lower in this poor prognosis group, although different results have been reported for other HCC cohorts.[23] Probably the most important clinical differences were in the tumor characteristics, including AF) as seen in Table 11. The poor prognosis group had significantly larger size (median 7 vs 5 cm) tumors (MTD) and percent of patients with PVT (42% vs 20%). Interestingly, no significant differences were found for numbers of tumor nodules. The same approach was taken for examining the combinations of CRP plus ESR (Tables 13-17). There was a slighter larger range of survival between the good and poor prognosis groups, which also held for the small and large MTD subcohorts. When the clinical characteristics were compared, there were in the poor survival group significantly worse Hb, GGT, ALKP and albumin values, but not for AFP or cholesterol; in the case of AFP, likely due to the huge range in values. When tumor characteristics were compared, there were even greater significant

TABLE 18 Kaplan-Meier analysis for triplet parameters in the total cohort

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
ALB ≤ 3.5 & CRP > 10 & ESR > 30	15.753 ± 4.476	6.980-24.527	<.001
ALB > 3.5 & CRP ≤ 10 & ESR ≤ 30	109.103 ± 13.820	82.015-136.191	

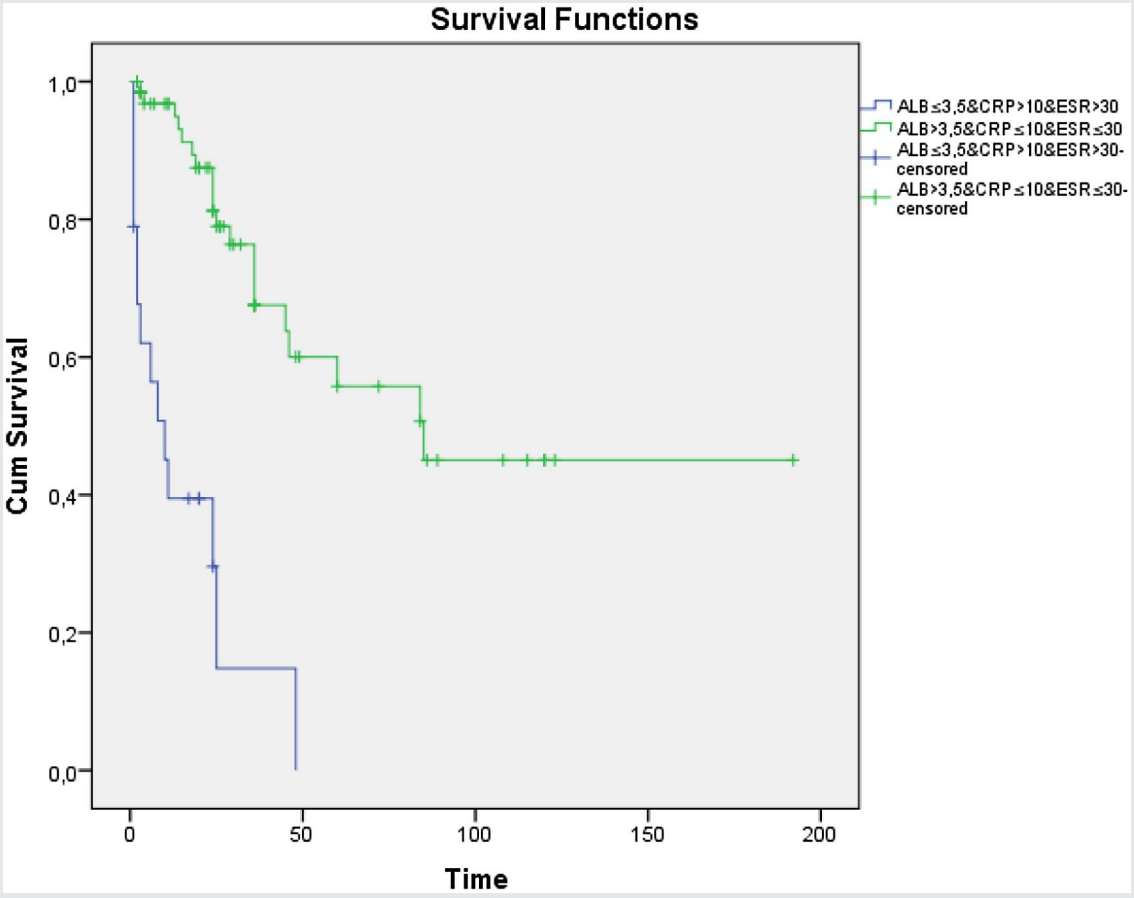


TABLE 19 Kaplan-Meier analysis for triplet parameters in MTD < 5 cm

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
ALB ≤ 3.5 & CRP > 10 & ESR > 30	11.000 ± 5.558	0.107-21.893	.001
ALB > 3.5 & CRP ≤ 10 & ESR ≤ 30	82.337 ± 10.787	61.196-103.479	

TABLE 20 Kaplan-Meier analysis for triplet parameters in MTD ≥ 5 cm

	Survival time		Log-Rank
	Mean ± SE	95% CI	*P*-value
ALB ≤ 3.5 & CRP > 10 & ESR > 30	12.795 ± 4.390	4.190-21.400	<.001
ALB > 3.5 & CRP ≤ 10 & ESR ≤ 30	68.218 ± 11.256	46.156-90.281	

Abbreviations: CRP, C-reactive protein (mg/dL); ESR, erythrocyte sedimentation rate (mm/h); ALB, serum albumim (g/dL).

differences between the better and worse prognosis groups: MTD 8 vs 5 cm, and PVT 53.6% vs 18%.

The addition of ESR to CRP plus albumin (triplet parameters) resulted in a sevenfold increase in the differences in survival between the poor and good survival groups (Tables 18-22), that were almost maintained in the small and large MTD subgroups. Clinical characteristics were similar to the CRP plus ESR groups, as were the tumor characteristics, except for an almost threefold difference in percent of patients with PVT. The explanation for the large sevenfold range of survival for the triplet combination compared with either of the doublets, is not entirely clear, as the differences in both

TABLE 21 Laboratory values for triplet parameter combination of CRP, ESR plus albumin

	ALB ≤ 3.5 & CRP > 10 & ESR > 30	ALB > 3.5 & CRP ≤ 10 & ESR ≤ 30	
	Median (min.-max.)	Median (min.-max.)	*P*-value
Hb, g/dL	11.1 (9.3-14.7)	14.2 (9.7-17.6)	<.001
Plt, 10^3/μL	204 (80-363)	157 (46-382)	.171
HDL,mg/dL	27.1 (16.5-64.5)	39.9 (17.4-74.1)	.011
LDL,mg/dL	91.5 (58-208)	98.15 (39-237)	.312
AFP,ng/m	160 (1.1-64 448)	13.65 (0.5-300 000)	.371
ALKP,IU/L	181 (67-449)	90 (38-351)	.001
GGTP,IU/L	126 (16-431)	57 (12-583)	.003
AST,IU/L	81 (16-505)	37 (20-138)	.006
T.bili,mg/dL	1.31 (0.43-16.62)	1.005 (0.49-3.2)	.088
Cholesterol, mg/dL	1.22 (0.92-1.91)	1.15 (0.9-2.29)	.028
ALT, IU/L	56 (11-238)	35 (13-139)	.077

Note: Units as in Table 11. Abbreviations on front page.

TABLE 22 Tumor characteristics for triplet parameters

	ALB ≤ 3.5 & CRP > 10 & ESR > 30	ALB > 3.5 & CRP ≤ 10 & ESR ≤ 30	
	Median (min.-max.)	Median (min.-max.)	*P*
MTD size	7.25 (2.5-16)	5 (1.4-22.5)	.051
	%	%	
Tumor # ≤ 2	41.2	68.3	.078
Tumor # > 2	58.8	31.7	
PVT (–)	50.0	82.8	.017
PVT (+)	50.0	17.2	

Abbreviations: CRP, C-reactive protein (mg/dL); ESR, erythrocyte sedimentation rate (mm/h); ALB, serum albumim (g/dL).

clinical and tumor characteristics were similar for the doublet and the triplet combinations. Likely, there are other factors that might need to be taken into account.

The main findings reported here are the usefulness in considering blood ESR levels in an HCC prognostic paradigm, which is cheap and ubiquitously available. The addition of two inflammatory markers together requires comment, as they reflect different processes. CRP is synthesised in the liver and in HCC cells and has a reciprocal interaction with interleukins, Il-1 and IL-6, as well as STAT 3 and can influence monocyte tumoricidal activity (see Ref 20 for mechanisms). By contrast, ESR test, using anticoagulated whole blood, has no actual function and is a passive reflection of inflammatory processes that in turn influence blood viscosity, of which fibrinogen levels are a prominent component, which is the basis of the ESR test. Thus, CRP and ESR likely reflect different aspects of the inflammatory processes. Although albumin is widely used as part of several prognostically useful inflammatory indices14-19 and was thought to represent nutritional deficiency in inflammatory diseases and advanced cancer, it has also been reported to directly influence HCC cell growth.[24] Furthermore, evidence has been provided that CRP can directly influence both the myeloid and immune compartments, as well as several aspects of the inflammatory microenvironment.[25-29] Thus, CRP and possibly albumin may be active mediators of both hepatocarcinogenesis and a more aggressive phenotype, and not just passive reflections of the inflammatory processes. CRP levels, however, seem to be a reflection of hepatocarcinogenic mechanisms, either known or to be discovered.

Prognostic markers for HCC are generally found to be in distinct categories. They include: a, tumor-related characteristics, as in most other solid tumors; b, liver function and its impairment; c, semi-specific markers for HCC, such as AFP, des-gamma carboxy prothrombin (DCP) and p-glypican, amongst others; d, inflammation[8-11,13-21] and nutritional based indices,[14,21] including liver inflammation parameters, GGT and ALKP.[30-32] Inflammation, both local (CRP) and systemic (ESR) has recently emerged as an important reflection of HCC aggressiveness and prognosticator. Various other clinical approaches have been taken to its measurement, including peripheral blood neutrophil to lymphocyte (NLR) and platelet to lymphocyte (PLR) ratios.[21,33-49] These novel markers of disease activity are especially needed for that 50% of HCC patients who do not have elevated AFP levels.[30,46,50] However, a central unanswered question is why elevated values of these inflammation markers predict poor survival. This relates to the cause of death in HCC patients. Some die of cachexia from growth of their tumors, as in other tumor types; others die from destruction by tumor growth of liver parenchyma; still others may die from the inflammatory processes themselves, as in many other chronic inflammatory diseases. However, it seems that several of these biomarkers may actively participate in the inflammatory and carcinogenic processes.[26-29,37,38,40] Thus, study of HCC inflammatory biomarkers is likely to lead to new insights into HCC pathogenesis and new approaches to treatment, as IL-6 which controls CRP synthesis, is a recent novel target in tumor therapy.[51,52]

DISCLOSURE

The authors declare no conflict of interest. All authors have read and agree with this paper.

AUTHOR CONTRIBUTIONS

BIC and HA- concept and ideas. BIC-writing; HGB-statistics; UK, KY, NE, AO, EA, HY, HS, AU, AB, SK, OU, YU, BG and AD- data collection, database formation and quality of data evaluation from original source documents.

STATEMENT OF ETHICS

This work complies with the guidelines of the World Medical Association, Declaration of Helsinki. This work was approved by each institution's IRB as documented in the methods section.

ORCID

Brian I. Carr https://orcid.org/0000-0002-6111-5077
Hatice Y. Balaban https://orcid.org/0000-0002-0901-9192

REFERENCES

1. Tuomisto AE, Mäkinen MJ, Väyrynen JP. Systemic inflammation in colorectal cancer: Underlying factors, effects, and prognostic significance. *World J Gastroenterol*. 2019;25:4383-4404.
2. Zhang S, Cao L, Li Z, Qu D. Metabolic reprogramming links chronic intestinal inflammation and the oncogenic transformation in colorectal tumorigenesis. *Cancer Lett*. 2019;28:123-131.
3. Man SM. Inflammasomes in the gastrointestinal tract: infection, cancer and gut microbiota homeostasis. *Nat Rev Gastroenterol Hepatol*. 2018;15:721-737.
4. Padoan A, Plebani M, Basso D. Inflammation and pancreatic cancer: focus on metabolism, cytokines, and immunity. *Int J Mol Sci*. 2019;20.676.
5. Murata M. Inflammation and cancer. *Environ Health Prev Med*. 2018;23:50.
6. Yang YM, Kim SY, Seki E. Inflammation and liver cancer: molecular mechanisms and therapeutic targets. *Semin Liver Dis*. 2019;39:26-42.
7. Amicone L, Marchetti A. Microenvironment and tumor cells: two targets for new molecular therapies of hepatocellular carcinoma. *Transl Gastroenterol Hepatol*. 2018;2:24.
8. Refolo MA, Messa C, Guerra V, Carr BI, D'Alessandro R. Inflammatory mechanisms of HCC development. *Cancers*. 2020;12:641.
9. Zhao B, Wang Y, Tan X, et al. Inflammatory micro-environment contributes to stemness properties and metastatic potential of HCC via the NF-κB/miR-497/SALL4 axis. *Mol Ther Oncolytics*. 2019;15:79-90.
10. Critelli R, Milosa F, Faillaci F, et al. Microenvironment inflammatory infiltrate drives growth speed and outcome of hepatocellular carcinoma: a prospective clinical study. *Cell Death Dis*. 2017;8:e3017.
11. Garnelo M, Tan A, Her Z, et al. Interaction between tumour-infiltrating B cells and T cells controls the progression of hepatocellular carcinoma. *Gut*. 2017;66:342-351.
12. Carr BI, Pancoska P, Giannini EG, et al. Identification of two clinical hepatocellular carcinoma patient phenotypes from results of standard screening parameters. *Semin Oncol*. 2014;41:406-414.
13. Chew V, Tow C, Teo M, et al. Inflammatory tumour microenvironment is associated with superior survival in hepatocellular carcinoma patients. *J Hepatol*. 2010;52:370-379.
14. McMillan DC, Crozier JE, Canna K, Angerson WJ, McArdle CS. Evaluation of an inflammation-based prognostic score (mGPS) in patients undergoing resection for colon and rectal cancer. *Int J Colorectal Dis*. 2007;22:881-886.
15. Ishizuka M, Kubota K, Kita J, et al. Impact of an inflammation-based prognostic system on patients undergoing surgery for hepatocellular carcinoma: a retrospective study of 398 Japanese patients. *Am J Surg*. 2012;203:101-106.
16. Horino K, Beppu T, Kuroki H, et al. Glasgow Prognostic Score as a useful prognostic factor after hepatectomy f hepatocellular carcinoma. *Int J Clin Oncol*. 2013;18:829-838.
17. 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*. 2015;94:e2133.
18. Shiba H, Horiuchi T, Sakamoto T, et al. Glasgow prognostic score predicts therapeutic outcome after hepatic resection for hepatocellular carcinoma. *Oncol Lett*. 2017;14:293-298.
19. Kinoshita A, Onoda H, Imai N, et al. Comparison of the prognostic value of inflammation-based prognostic score in patients with hepatocellular carcinoma. *Br J Cancer*. 2012;107:988-993.
20. Carr BI, Akkiz H, Guerra V, et al. C-reactive protein and hepatocellular carcinoma: analysis of its relationships to tumor factors. *Clin Pract (Lond)*. 2018;15:625-634.
21. Pinato DJ, Stebbing J, Ishizuka M, et al. A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). *J Hepatol*. 2012;57:1013-1020.
22. Akkiz H, Carr BI, Yalçın KK, et al. Characteristics of hepatocellular carcinoma aggressiveness factors in Turkish patients. *Oncology*. 2018;94:116-124.
23. Carr BI, Giannelli G, Guerra V, et al. Plasma cholesterol and lipoprotein levels in relation to tumor aggressiveness and survival in HCC patients. *Int J Biol Markers*. 2018;33:423-431.
24. Bağırsakçı E, Şahin E, Atabey N, et al. Role of albumin in growth inhibition in hepatocellular carcinoma. *Oncology*. 2017;93:136-142.
25. Lao X, Ren S, Lu Y, et al. Genetic polymorphisms of C-reactive protein increase susceptibility to HBV-related hepatocellular carcinoma in a Guangxi male population. *Int J Clin Exp Pathol*. 2015;2015:16055-16063. eCollection.
26. Han KQ, He XQ, Ma MY, et al. Inflammatory microenvironment and expression of chemokines in hepatocellular carcinoma. *World J Gastroenterol*. 2015;21:4864-4874.
27. Jimenez RV, Kuznetsova V, Connelly AN, Hel Z, Szalai AJ. C-reactive protein promotes the expansion of myeloid derived cells with suppressor functions. *Front Immunol*. 2019;10:2183.
28. Schimmack S, Yang Y, Felix K, et al. C-reactive protein (CRP) promotes malignant properties in pancreatic neuroendocrine neoplasms. *Endocr Connect*. 2019;8:1007-1019.
29. Nakayama T, Saito K, Kumagai J, et al. Higher serum C-reactive protein level represents the immunosuppressive tumor microenvironment in patients with clear cell renal cell carcinoma. *Clin Genitourin Cancer*. 2018;16:e1151-e1158.
30. Carr BI, Akkiz H, Üsküdar O, et al. HCC with low- and normal-serum alpha-fetoprotein levels. *Clin Pract (Lond)*. 2018;15:453-464.
31. Wu SJ, Lin YX, Ye H, et al. Prognostic value of alkaline phosphatase, gamma-glutamyl transpeptidase and lactate dehydrogenase in hepatocellular carcinoma patients treated with liver resection. *Int J Surg*. 2016;36:143-151.
32. Xu XS, Wan Y, Song SD. ,Miao RC et al. Model based on γ-glutamyltransferase and alkaline phosphatase for hepatocellular carcinoma prognosis. *World J Gastroenterol*. 2014;20:10944-10952.
33. Kinoshita A, Onoda H, Imai N, et al. Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. *Br J Cancer*. 2012;107:988-993.
34. Kinoshita A, Onoda H, Imai N, et al. The addition of C-reactive protein to validated staging systems improves their prognostic ability in patients with hepatocellular carcinoma. *Oncology*. 2014;86:308-317.
35. Aino H, Sumie S, Niizeki T, et al. The systemic inflammatory response as a prognostic factor for advanced hepatocellular carcinoma with extrahepatic metastasis. *Mol Clin Oncol*. 2016;5:83-88.

36. Li SH, Wang QX, Yang ZY, et al. Prognostic value of the neutrophil-to-lymphocyte ratio for hepatocellular carcinoma patients with portal/hepatic vein tumor thrombosis. *World J Gastroenterol*. 2017;23:3122-3132.
37. Barna BP, James K, Deodhar SD. Activation of human monocyte tumoricidal activity by C-reactive protein. *Cancer Res*. 1987;47:3959-3963.
38. van der Windt DJ, Sud V, Zhang H, et al. Neutrophil extracellular traps promote inflammation and development of hepatocellular carcinoma in nonalcoholic steatohepatitis. *Hepatology*. 2018;68:1347-1360.
39. Li L, Chan SL, Mo F, et al. Status of inflammation in relation to health related quality of life in hepatocellular carcinoma patients. *Qual Life Res*. 2019;28:2597-2607.
40. Bishayee A. The role of inflammation and liver cancer. *Adv Exp Med Biol*. 2014;816:401-435.
41. Ismael MN, Forde J, Milla E, Khan W, Cabrera R. Utility of Inflammatory Markers in Predicting Hepatocellular Carcinoma Survival after Liver Transplantation. *Biomed Res Int*. 2019;14:7284040. PMID: 31737675
42. Suner A, Carr BI, Akkiz H, et al. Inflammatory markers C-reactive protein and PLR in relation to HCC characteristics. *J Transl Sci*. 2019;5.https://doi.org/10.15761/JTS.1000260.
43. Casadei Gardini A, Foschi FG, Conti F, et al. Immune inflammation indicators and ALBI score to predict liver cancer in HCV-patients treated with direct-acting antivirals. *Dig Liver Dis*. 2019;51:681-688.
44. Chu MO, Shen CH, Chang TS, et al. Pretreatment inflammation-based markers predict survival outcomes in patients with early stage hepatocellular carcinoma after radiofrequency ablation. *Sci Rep*. 2018;8:16611. PMID: 30413724.
45. Pang Q, Zhou L, Qu K, Cui RX, Jin H, Liu HC. Validation of inflammation-based prognostic models in patients with hepatitis B-associated hepatocellular carcinoma: a retrospective observational study. *Eur J Gastroenterol Hepatol*. 2018;30:60-70.
46. Suner A, Carr BI, Akkiz H, et al. C-reactive protein and platelet-lymphocyte ratio as potential tumor markers in low-alpha-fetoprotein hepatocellular carcinoma. *Oncology*. 2019;96:25-32.
47. Xu L, Yu S, Zhuang L, et al. Systemic inflammation response index (SIRI) predicts prognosis in hepatocellular carcinoma patients. *Oncotarget*. 2017;8:34954-34960.
48. Yamamoto M, Kobayashi T, Kuroda S, et al. Verification of inflammation-based prognostic marker as a prognostic indicator in hepatocellular carcinoma. *Ann Gastroenterol Surg*. 2019;3:667-675.
49. Wang Y, Sun K, Shen J, et al. Novel prognostic nomograms based on inflammation-related markers for patients with hepatocellular carcinoma underwent hepatectomy. *Cancer Res Treat*. 2019;51:1464-1478.
50. She S, Xiang Y, Yang M, et al. C-reactive protein is a biomarker of AFP-negative HBV-related hepatocellular carcinoma. *Int J Oncol*. 2015;47:543-554.
51. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat Rev Clin Oncol*. 2018;15:234-248.
52. Rossi JF, Lu ZY, Jourdan M, Klein B. Interleukin-6 as a therapeutic target. *Clin Cancer Res*. 2015;21:1248-1257.

How to cite this article: Akkiz H, Carr BI, Bag HG, et al. Serum levels of inflammatory markers CRP, ESR and albumin in relation to survival for patients with hepatocellular carcinoma. *Int J Clin Pract*. 2021;75:e13593. https://doi.org/10.1111/ijcp.13593