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Liver Inflammation Parameters in Relation to Survival in Patients with Hepatocellular Carcinoma Tumor of differing Sizes

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Abstract

Introduction: Survival in patients with Hepatocellular Carcinoma (HCC) has been previously found to be worse with increase in tumor size, but also with increase in inflammation. To examine these issues separately, we aimed to study the influences on survival of various liver inflammation parameters in the whole cohort, and separately in patients with HCCs of defined Maximum Tumor Diameter (MTD).

Methods: A prospectively collected large database of Turkish HCC patients with documented survival was interrogated. Patients had baseline liver function tests and CT scans for tumor characteristics. Liver function and inflammation parameters included blood tests for levels of albumin, AST, GGT, ALKP, CRP, ESR and WBC.

Results: Survival was worse for patients with larger HCCs, including those with low or high serum AFP levels. Highest hazard ratios were found for patients with abnormal blood albumin (low) or AST (high) levels, regardless of AFP status. When patients were separately examined according to tumor size, only albumin and AST were significant for survival in patients with small <3cm tumors; whereas albumin, AST and ALKP were significant in patients with >3cm HCCs. Abnormal albumin or AST levels in different HCC size cohorts significantly related to percent patients with PVT, higher AFP or increased tumor focality, regardless of tumor size.

Conclusion: Survival in non-surgical HCC patients related to tumor size, but also to abnormal levels of liver parameters albumin and AST, regardless of tumor size. A likely explanation is that these parameters related to more aggressive HCC characteristics.

Keywords: HCC • MTD • Survival • AST • Albumin

Abbreviations: HCC: Hepatocellular Carcinoma; MTD: Maximum Tumor Diameter; AFP: Alpha-Fetoprotein; PVT: Macroscopic Portal Vein Thrombosis; WBC: White Blood Count; T-bill: Total Bilirubin; AST: Aspartate Amino Transferase; ALT: Alanine Aminotransferase; ALKP: Alkaline Phosphatase; GGT: Gamma Glutamyl Transferase; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; CT: Computed Axial Tomography; HR: Hazard Ratio.

Introduction

Survival in patients with Hepatocellular Carcinoma (HCC) is considered to be the product of several factors, including residual liver function (host factors), gender, tumor factors, such as HCC size tumor number, portal vein invasion, serum alpha-fetoprotein levels, therapy and more recently, of inflammatory factors [1-4]. Cirrhosis-associated liver inflammation factors have become increasingly appreciated as contributing to HCC clinical behaviour, possibly as mediators of HCC growth [5-18]. We recently showed that large HCCs with or without associated inflammation have differences in survival as well as tumor characteristics [19].

In the current work, the relationships of liver inflammation indices to survival have been examined across the spectrum of tumor size and we show that liver inflammation parameters are associated with survival in patients with both small and large HCC sizes.

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Materials and Methods

Clinical

A prospectively collected database was examined, containing 1889 non transplant Turkish HCC patients who had survival data, baseline CT-based tumor parameter data as well as baseline serum Alpha-Fetoprotein (AFP) levels, complete blood counts and routine blood liver function tests, including albumin, AST, GGTP, ALKP, C-reactive protein and ESR levels. Diagnosis was made either via tumor biopsy or according to AASLD/EASL guidelines. Statement of Ethics: This work complies with the guidelines of the World Medical Association, Declaration of Helsinki. This work was approved by our institution's IRB as documented in the methods section. Database management conformed to legislation on privacy and this study conforms to the ethical guidelines of the Declaration of Helsinki and the need for approval for this retrospective study on de-identified and deceased HCC patients was waived by our Institutional Ethics Committee. This work has been reported in line with the STROCSS criteria.

Statistical

Data are reported as Mean ± Standard Deviations (M ± SD) for continuous measures, and frequency and percentages for all categorical variables. Normal distributions of quantitative variables using the Kolmogorov-Smirnov test were tested.

For testing the associations among groups, the Chi-square test for categorical variables was used. When the variables not distributed normally,

the Wilcoxon rank-sum (Mann-Whitney) test was used for continuous variables.

For studying the time between entry to a study and a subsequent event, the non-parametric Kaplan–Meier method was used to explore survival probability, and the log-rank test was applied to evaluate the equality of survival among categories.

The CoX model is a statistical technique for exploring the relationship between the survival of a patient and singular or several explanatory variables, it also allowed us to estimate the Hazard Ratio (HR) of survival for an individual, given their prognostic variables (measured as continuous or categorical). The CoX proportional hazard model was fitted to the data, and the proportional hazard assumption was evaluated by means of Schoenfeld Residuals (SRT).

All models for fitting were evaluated by means of Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC). Risk estimators were expressed as Hazard Ratios (HR) and 95% Confidence Interval (95% CI).

In the models, multicollinearity was evaluated through the Variance Inflation Factor (VIF), using the score of 2 as cut-off for exclusion. When testing the null hypothesis of no association, the probability level of error at two tails, was 0.05. All the statistical computations were made using STATA, StataCorp. 2021. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC.

Results

Maximum tumor diameter and survival in patients with high or low serum AFP levels

The relationship of Maximum Tumor Diameter (MTD) to survival was initially examined. Survival decreased with increase in MTD, as expected, both for patients with low <20 IU/mL serum AFP levels and with elevated >20 IU/mL serum AFP levels. At each MTD level, survival was greater for patients with low versus high AFP levels. Even for patients with the smallest tumors of MTD <2 cm, survival was 50% higher for patients with low compared with high AFP levels (Tables 1A and 1B).

Single liver parameters in relation to survival in the total cohort

Individual indices of inflammation in relation to survival in patients with AFP <20 IU/ml were next examined. Serum levels of albumin (HR 1.83), AST (HR 1.39) and ALKP (HR 1.27) were each significantly related to survival, whereas serum levels of ALT, GGT, C-reactive protein, erythrocyte sedimentation rate (ESR) or total White Blood Counts (WBC) were not significantly related to survival. The same individual indices of inflammation were next examined in patients with serum AFP >20 IU/ml. Serum levels of albumin (HR 1.89), AST (HR 1.46) and ALKP (HR 1.42) were again each found to be significantly related to survival; additionally, as were levels of ALT (HR 1.16) and WBC (HR 0.85). Interestingly, patients with high AFP and elevated WBC had higher survival than those with low WBC (Tables 2 and 3).

Single liver parameters in relation to survival in patients of defined MTD bands

The same single parameters were then examined in the total cohort in relation to survival in patients with small (MTD ≤ 3.0 cm), large (6.1 cm ≤ MTD ≤ 9.0 cm) and intermediate (3.1 cm ≤ MTD ≤ 6.0 cm) tumor size (MTD) bands. We found that in patients with small tumors, only blood albumin and AST levels significantly related to survival. However, in patients with both intermediate size and large size HCCs, blood levels of albumin, AST and ALKP were each significantly related to survival (Table 4).

HCC aggressiveness characteristics in relation to serum Albumin or AST levels

In order to try to identify the reasons for the survival differences in patients with the 2 highest parameter Hazard Ratios of serum albumin or AST levels, the degrees of the HCC aggressiveness indices AFP, tumor multifocality and percent patients with PVT were examined, separately for patients with HCCs of MTD <3 cm and for MTD 3.1 cm-6 cm. In either MTD band of patients, low serum albumin (abnormal) or high serum AST (abnormal) levels were associated with significantly higher serum AFP levels, percent of patients with tumor multifocality or PVT, all 3 being indices of tumor aggressiveness, in comparison with the indices in patients with high serum albumin (normal) or low serum AST (normal) levels (Table 5).

Table 1A. Relationships of maximum tumor diameter to survival in HCC patients. Kaplan-Meier analysis and CoX regression for MTD categories in 874 HCC patients with serum AFP ≤ 20 (IU/mL).

MTD (cm)	n	Kaplan-Meier Analysis		Univariate CoX regression	
		Median survival time (95% CI)	Log-Rank p-value	Univariate HR (95% CI)	HR p-value
≤ 2.0	68	61 (56 to 66)	[Ref. category] #	[Ref. category] #	--
(2.1-3.0)	191	52 (47 to 56)	0.0001	1.27 (1.13 to 1.42)	<0.001
(3.1-4.0)	216	47 (41 to 57)	0.0001	1.31 (1.14 to 1.50)	<0.001
(4.1-5.0)	153	35 (31 to 39)	<0.0001	1.82 (1.56 to 2.13)	<0.001
(5.1-6.0)	118	32 (25 to 47)	<0.0001	1.72 (1.38 to 2.14)	<0.001
(6.1-7.0)	73	37 (25 to 48)	<0.0001	1.69 (1.33 to 2.14)	<0.001
(7.1-8.0)	55	36 (22 to 51)	<0.0001	1.77 (1.34 to 2.35)	<0.001

Note: # Reference category for each level of combined parameters.

Abbreviations: MTD: Maximum Tumor Diameter; AFP: Alpha-Fetoprotein; HR: Hazard Ratio Median survival time in months.

Table 1B. Kaplan-Meier analysis and CoX regression for MTD categories in 1015 HCC patients with serum AFP>20 (IU/mL).

MTD (cm)	n	Kaplan-Meier Analysis		Univariate CoX regression	
		Median Survival time (95% CI)	Log-Rank p-value	Univariate HR (95% CI)	HR p-value
≤ 2.0	255	46 (40 to 52)	[Ref. category] #	[Ref. category] #	--
(2.1-3.0)	228	30 (26 to 37)	0.0001	1.30 (1.13 to 1.48)	<0.001
(3.1-4.0)	211	24 (22 to 28)	<0.0001	1.66 (1.45 to 1.91)	<0.001
(4.1-5.0)	154	17 (14 to 21)	<0.0001	2.18 (1.88 to 2.54)	<0.001
(5.1-6.0)	80	14 (12 to 17)	<0.0001	2.41 (2.04 to 2.84)	<0.001
(6.1-7.0)	58	11 (8 to 13)	<0.0001	2.94 (2.46 to 3.51)	<0.001
(7.1-8.0)	29	10 (8 to 12)	<0.0001	3.08 (2.56 to 3.71)	<0.001

Note: # Reference category for each level of combined parameters.

Abbreviations: MTD: Maximum Tumor Diameter; AFP: Alpha-Fetoprotein; HR: Hazard Ratio Median survival time in months.

Table 2. Kaplan-Meier analysis and CoX regression for single parameters in categories in HCC patients with serum AFP>20 (IU/mL).

Kaplan-Meier analysis			Univariate CoX regression	
Parameters	**Median Survival time (95% CI)**	**Log-Rank p-value**	**Univariate HR (95%CI)**	**HR p-value**
Albumin (g/dL)				
≥ 3.5	35 (31 to 37)	[Ref. category]	[Ref. category]	--
<3.5	14 (13 to 16)	<0.0001	1.83 (1.68 to 1.98)	<0.001
AST (IU/L)				
≤ 40	27 (24 to 30)	[Ref. category]	[Ref. category]	--
>40	17 (16 to 18)	<0.0001	1.39 (1.26 to 1.53)	<0.001
ALT (IU/L)				
≤ 40	20 (17 to 22)	[Ref. category]	[Ref. category]	--
>40	19 (18 to 21)	0.96	1.00 (0.92 to 1.08)	0.96
GGTP (IU/L)				
<60	20 (17 to 24)	[Ref. category]	[Ref. category]	--
≥ 60	19 (18 to 20)	0.46	1.07 (0.90 to 1.27)	0.46
ALKP (IU/L)				
<250	22 (20 to 24)	[Ref. category]	[Ref. category]	--
≥ 250	15 (13 to 16)	<0.0001	1.27 (1.17 to 1.37)	<0.001
CRP (mg/L)				
≤ 2.5	16 (9 to 24)	[Ref. category]	[Ref. category]	--
>2.5	15 (11 to 18)	0.85	1.02 (0.80 to 1.31)	0.85
ESR (mm/hr)				
≤ 15	6 (4 to 11)	[Ref. category]	[Ref. category]	--
>15	6 (5 to 7)	0.11	1.25 (0.93 to 1.67)	0.14
WBC (103/µL)				
≤ 3.5	19 (16 to 22)	[Ref. category]	[Ref. category]	--
>3.5	20 (18 to 22)	0.92	0.99 (0.89 to 1.10)	0.92

Note: Median Survival Times In Months.

Abbreviations: AFP: Alpha-Fetoprotein; AST: Aspartate Aminotransaminase; ALT: Alanine Transaminase; GGTP: Gamma Glutamyltranspeptidase; ALKP: Alkaline Phosphatase; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; WBC: White Blood Cells; HR: Hazard Ratio

Table 3. Kaplan-Meier analysis and Cox regression for single parameters in categories in HCC patients with serum AFP≤20 (IU/mL).

Kaplan-Meier analysis			Univariate CoX regression	
Parameters	**Median Survival time (95% CI)**	**Log-Rank p-value**	**Univariate HR (95% CI)**	**HR p-value**
Albumin (g/dL)				
≥ 3.5	63 (60 to 70)	[Ref. category]	[Ref. category]	--
<3.5	31 (28 to 36)	<0.0001	1.89 (1.73 to 2.06)	<0.001
AST (IU/L)				
≤ 40	58 (52 to 61)	[Ref. category]	[Ref. category]	--
>40	40 (37 to 42)	<0.0001	1.46 (1.30 to 1.55)	<0.001
ALT (IU/L)				
≤ 40	50 (46 to 55)	[Ref. category]	[Ref. category]	--
>40	44 (41 to 47)	0.0008	1.16 (1.06 to 1.26)	0.001
GGTP (IU/L)				
<60	55 (44 to 65)	[Ref. category]	[Ref. category]	--
≥ 60	45 (43 to 48)	0.08	1.15 (0.98 to 1.36)	0.09
ALKP (IU/L)				
<250	53 (49 to 57)	[Ref. category]	[Ref. category]	--
≥ 250	34 (29 to 38)	<0.0001	1.42 (1.33 to 1.60)	<0.001
CRP (mg/L)				
≤ 2.5	59 (25 to 62)	[Ref. category]	[Ref. category]	--
>2.5	65 (55 to 101)	0.94	0.98 (0.56 to 1.70)	0.94
ESR (mm/hr)				
≤ 15	10 (3 to 16)	[Ref. category]	[Ref. category]	--
>15	12 (3 to 41)	0.66	1.26 (0.44 to 3.60)	0.67
WBC (103/μL)				
≤ 3.5	45 (38 to 56)	[Ref. category]	[Ref. category]	--
>3.5	56 (52 to 59)	0.01	0.85 (0.74 to 0.96)	0.01

Note: Median survival times in months.

Abbreviations: AFP: Alpha-Fetoprotein; AST: Aspartate Aminotransaminase; ALT: Alanine Transaminase; GGTP: Gamma Glutamyltranspeptidae; ALKP: Alkaline Phosphatase; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; WBC: White Blood Cells; HR: Hazard Ratio.

Table 4. Kaplan-Meier analysis and Cox regression for single parameters in the total HCC patient cohort in relation to tumor size: MTD≤3.0cm (A), 3.1≤MTD≤6.0cm (B), 6.1≤MTD≤9.0cm (C).

Kaplan-Meier Analysis			Univariate Cox regression	
Parameters	**Median Survival time (95% CI)**	**Log-Rank p-value**	**Univariate HR (95% CI)**	**HR p-value**
A				
Albumin (g/dL)				
≥ 3.5	21 (4 to 38)	[Ref. category]	[Ref. category]	--
<3.5	6 (4 to 11)	0.04	1.99 (1.00 to 3.96)	0.05
AST (IU/L)				
≤ 40	19 (1 to 34)	[Ref. category]	[Ref. category]	--
>40	6 (4 to 8)	0.12	1.86 (0.82 to 4.20)	0.01
ALKP (IU/L)				
<250	8 (5 to 19)	[Ref. category]	[Ref. category]	--
≥ 250	3 (2 to 7)	0.09	1.69 (0.89 to 3.25)	0.11

WBC (103/μL)				
≤ 3.5	10 (3 to 24)	[Ref. category]	[Ref. category]	--
>3.5	6 (1 to 24)	0.34	1.47 (0.64 to 3.38)	0.36
B)				
Albumin (g/dL)				
≥ 3.5	27 (16 to 48)	[Ref. category]	[Ref. category]	--
<3.5	7 (5 to 11)	0.001	2.11 (1.31 to 3.39)	0.002
AST (IU/L)				
≤ 40	20 (8 to 53)	[Ref. category]	[Ref. category]	--
>40	9 (5 to 16)	0.02	1.94 (1.05 to 3.58)	0.01
ALKP (IU/L)				
<250	12 (8 to 24)	[Ref. category]	[Ref. category]	--
≥ 250	5 (3 to 19)	0.007	1.91 (1.16 to 3.15)	0.03
WBC (103/μL)				
≤ 3.5	24 (6 to 35)	[Ref. category]	[Ref. category]	--
>3.5	6 (3 to 12)	0.04	1.64 (0.98 to 2.74)	0.06
C)				
Albumin (g/dL)				
≥ 3.5	15 (3 to 28)	[Ref. category]	[Ref. category]	--
<3.5	6 (3 to 7)	0.04	1.69 (0.98 to 2.91)	0.05
AST (IU/L)				
≤ 40	20 (3 to .)	[Ref. category]	[Ref. category]	--
>40	6 (3 to 8)	0.04	2.49 (0.97 to 6.36)	0.05
ALKP (IU/L)				
<250	8 (5 to 11)	[Ref. category]	[Ref. category]	--
≥ 250	3 (2 to 6)	0.03	1.65 (1.00 to 3.06)	0.05
WBC (103/μL)				
≤ 3.5	6 (3 to 8)	[Ref. category]	[Ref. category]	--
>3.5	8 (1 to 12)	0.41	1.32 (0.65 to 2.69)	0.44

Note: Median survival times in months.

Abbreviation: MTD: Maximum Tumor Diameter; AFP: Alpha-fetoprotein; AST: aspartate aminotransaminase; ALKP: Alkaline phosphatase; WBC: White Blood Cells; Plt: Platelets; HR: Hazard Ratio.

Table 5. Comparisons of HCC aggressiveness characteristics in patients with high or low serum Albumin or AST levels in MTD categories of MTD≤3.0cm (A), or 3.1≤MTD≤6.0cm (B).

Parameters	**Albumin (g/dL)**			**AST (IU/L)**		
	≥ 3.5	**<3.5**	**p Ψ**	**≤ 40**	**>40**	**p Ψ**
A)						
AFP (IU/mL)	260.76 ± 2242.40	1174.55 ± 11465.09	<0.0001	176.49 ± 1706.15	2146.42 ± 34021.30	<0.0001
PVT+ %	6.4	13.8	<0.001^	7.34	13.36	<0.001^
Nodule number >2%	1.41	3.9	<0.001^	2.29	4.37	0.001^
B)						
AFP (IU/mL)	1804.95 ± 11056.96	3699.75 ± 26349.80	<0.0001	2695.04 ± 28739.42	3246.22±15701.11	<0.0001
PVT+ %	17.61	31.31	<0.001^	17.05	29.54	<0.001^
Nodule number >2%	3.99	10.44	<0.001^	5.25	12.3	<0.001^

All values: Mean and Standard Deviation (M±SD) as continuous; Frequencies and Percentage (%) as categorical.

Note: Ψ Wilcoxon rank-sum (Mann-Whitney) test; ^Chi-square test;

Abbreviations: MTD: Maximum Tumor Diameter; AST: Aspartate Aminotransaminase; AFP: Alpha-Fetoprotein; PVT: Macroscopic Portal Vein Thrombosis.

Discussion

Survival in HCC patients has been long understood to be a consequence of tumor factors and liver factors, as well as liver microenvironmental inflammation, and these various influences have been incorporated into almost all modern staging systems [20]. Since HCC arises preponderantly on the basis of chronic liver inflammation, death in HCC patients has also been seen to result from either liver or tumor factors or both [21,22].

The relationship of HCC size to survival has also been much studied, and most investigators have found that prognosis worsens with increase in size [23,24]. Furthermore, several HCC aggressiveness factors, such as serum AFP levels and incidence of PVT have been reported to increase with increase in MTD [24,25] and there may even be a non-linear increase in these factors as MTD increases [26], suggesting that HCCs may evolve and change with increase in size. Thus, large size HCCs might have different tumor biology than small size HCCs. Since larger HCCs tend to have higher AFP levels, one reasonable explanation for the increase in HCC aggressiveness with increasing size might be the roles that AFP has been reported to have in HCC growth, invasiveness, differentiation, metastasis, immunity and as a marker for HCC stem cells [27-29].

We previously reported the identification of 2 large HCC phenotypes, based on liver inflammation factors [19]. The purpose of the current work was to extend that approach to determine if inflammation factors might have a use in the prognosis of patients with small size HCCs as well as for large ones. We found that MTD had an influence on survival, regardless of serum AFP levels. Serum levels of albumin and AST had the highest HR levels for survival, in patients with both high and low serum AFP levels as well as in patients with differing MTDs. To explain this, we examined HCC aggressiveness factors in patients with defined small or larger MTDs and when they were dichotomized according to serum albumin or AST levels, statistically significant differences in percent of patients with multifocality or PVT or levels of AFP suggesting a likely explanation for the relationships of AST and albumin to survival. Whether this is cause or consequence of tumor aggressiveness is not answered in this study. However, since there is a 2-way influence of HCC growth on liver inflammation, as well as a role of liver inflammation on HCC growth, these 2 sets of factors, namely HCC aggressiveness and liver inflammation factors, might be intertwined. Interestingly, small HCCs with normal baseline albumin or AST displayed 6.4% or 7.3% respectively of patients with PVT. This doubled with large tumors to 17.6 or 17.0% respectively of patients with baseline albumin or AST values. Thus, patients with larger HCCs with normal baseline albumin or AST values had more PVT and multifocality than patients with small HCCs, and these percentages doubled for patients with small or large HCCs, when the albumin or AST values were abnormal. Striking trends were seen for AFP values in small versus large tumor patients, and when comparing normal versus abnormal albumin or AST values in patients with either small or large HCCs.

Conclusion

The central findings in this paper are two. Firstly, that abnormal serum albumin or AST levels are significantly related to worse survival in HCC patients who had either small or large tumors. Secondly, that abnormal serum albumin or AST levels also correlate with more aggressive tumor characteristics, in patients having either small or large HCCs. More than one hypothesis might help explain these findings. Possibly, the tumor stem cell that is responsible for HCC growth gives rise to further stem cells per unit volume of tumor, that in turn give rise to invasiveness (PVT or multifocality) producing cells. An alternative hypothesis is that there may be more than one type of stem cell for each HCC mass, giving rise to growth or invasive characteristics.

Strengths of this study include the large sample size and the usefulness of liver parameters in prognostication in patients with small or large size HCCs, whether associated with elevated serum AFP levels or not. Weaknesses of this study include its retrospective nature and the fact that there may be other parameters in addition to those in Table 1 that were not studied and might contribute to prognostication. Despite these reservations, the findings show that liver damage parameters reflect prognosis and HCC aggressiveness and might even be mechanistically involved in their development.

Declarations

Conflicts of interest

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

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Author's contributions

Brian Carr-concept, ideas and writing; Vito Guerra-biostatistics and paper proof reading; Hikmet Akkiz, Ümit Karaoğullarından, Volkan Ince, Burak Isik, Sezai Yilmaz–data collection.

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Strobe statement

The authors have read the STROBE statement–checklist of items, and the manuscript was prepared according to the STROBE statement-checklist of items.

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