MEDDOCS Open Access Publisher

ISSN: 2637-4501

Annals of Gastroenterology and the Digestive System

Open Access | Research Article

The Weak Relationship between Elevated Serum Alpha-Fetoprotein Levels and Tumor Characteristics, but strong Relationship to Survival in Hepatocellular Carcinoma Patients

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Received: Dec 07, 2023

Accepted: Dec 28, 2023

Published Online: Jan 04, 2024

Journal: Annals of Gastroenterology and the Digestive System

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: HCC; PVT; Multifocality; AFP; Relationships.

Abbreviations: HCC: Hepatocellular Carcinoma; MTD: Maximum Tumor Diameter; PVT: Portal Vein Thrombosis; CT: Computed Axial Tomography; AFP: Alpha-Fetoprotein; Ep CAM: Epithelial Cell Adhesion Molecule.

Abstract

Background: Alpha-Fetoprotein (AFP) is an oncofetal-protein that is an important prognostic biomarker in Hepato Cellular Carcinoma (HCC) patients, yet the reasons for this importance are unclear.

Aims: We aimed to evaluate the relationships between AFP and Maximum Tumor Diameter (MTD), multifocality, Portal Vein Thrombosis (PVT) and survival.

Methods: A retrospective analysis was made of a large HCC patient database to evaluate the relationships between baseline serum AFP values and both baseline liver function tests and tumor characteristics.

Results: Statistically significant trends were found between levels of AFP and MTD, multifocality, PVT and survival. However, the range of AFP changes was 100-fold compared to the maximum 3-fold parameter changes. Similar findings were obtained for the AFP changes in relation to both liver function parameters. A survival model was constructed, combining both serum albumin and GGT values and produced a significant HR of 10.86 in patients with high AFP levels.

Conclusions: AFP is prognostically important, and significantly, but only weakly related to tumor characteristics and liver function. Tumor parameter and liver function changes seem insufficient to explain the prognostic value of AFP. Other, unmeasured factors must likelybe involved.

Cite this article: Carr BI, Guerra V, Ince V, Isik B, Yilmaz S. The Weak Relationship between Elevated Serum Alpha-Fetoprotein Levels and Tumor Characteristics, but strong Relationship to Survival in Hepatocellular Carcinoma Patients. Ann Gastroenterol Dig Syst. 2024: 7(1): 1080.

Introduction

AFP is a mammalian tumor-associated fetal glycoprotein, with molecular weight 68–72 k Da which was first discovered in human fetal serum in 1956 [1]. It is normally produced by the fetal liver and yolk sac during the first trimester of pregnancy and rapidly declines after birth and remains at low levels thereafter. The association of AFP with HCC was described in the 1960s by Abelev et al. And Tatarinov separately [2,3] and has been used as a clinical HCC biomarker to diagnose HCC since then.

Between 30 and 50% of HCC patients in various series of HCC patients have normal serum AFP levels [4-10] especially in small HCCs. Elevated serum AFP levels in patients at risk for HCC are typically associated with an increased risk of HCC development and with poorer prognosis once diagnosed [11]. The tumor aggressiveness and poor prognosis parameters of Maximum Tumor Diameter (MTD) and Portal Vein Thrombosis (PVT) have been shown to be associated with elevated AFP levels previously, but PVT can be found with low AFP levels [12-14]. We therefore investigated a large HCC clinical database containing patients having serum AFP levels over a 100-fold range, to evaluate the relationship between AFP levels and tumor markers and with survival. We found that AFP levels significantly but only weakly related to tumor aggressiveness characteristics. However, a much stronger relationship was found between AFP levels and survival. The mechanisms underlying it prognostic significance are yet to be clarified.

Methods

Clinical

A database containing 6158 previously published [9,12,14] adult HCC patients was examined for AFP-related survival and baseline radiological tumor characteristics of Maximum Tumor Diameter (MTD), number of tumor nodules, macroscopic Portal Vein Thrombosis (PVT) from CT scans, as well as baseline serum Alpha-Fetoprotein (AFP) levels and standard liver function tests and hematology. Diagnosis was made either from tumor biopsy or according to AASLD/EASL guidelines. All patients were non-surgical and received systemic therapy, locoregional therapy, or best supportive care. This work was approved for a waiver by Inonu University Ethics Committee, IRB Approval No: 2022- 3905, for a waiver from written informed consent for these deceased and de-identified patients, in accordance with local guidelines.

Statistical analysis

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 were evaluated using the Kolmogorov-Smirnov test.

When the variables not distributed normally, the Wilcoxon rank-sum (Mann-Whitney) test was used for continuous variables.

For testing the associations among groups, the Chi-square test for categorical variables was used, furthermore the chi-square test for trend or the non-parametric test for trend, respectively for variables measured on a categorical or continuous scale, were used to evaluate the existence of proportional variations of the parameter examined, in relation to the increase of the AFP categories.

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 probability among the AFP categories; moreover, the log-rank test for trend was used to evaluate the existence of proportional changes in survival probability in relation to the increase in the AFP categories.

As the Cox model is a statistical technique for exploring the relationship between the survival of a patients and singular or several explanatory variables, and also it allows us to estimate the Hazard Risk (HR) of survival for an individual, given their prognostic variables (measured as continuous or categorical), was used.

The Cox proportional hazard model was fitted to the data, and the proportional hazard assumption was evaluated by means of Schoeneld Residuals (SRT).

All models for fitting were evaluated by means of Akaike Information Criteria (AIC) and Bayesian information criterion (BIC).

Risk estimators was expressed as Hazard Ratios (HR) and 95% Confidence Interval (95% CI).

In the models the 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, Stata Corp. 2021. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC.

Results

Relationships between serum AFP levels and tumor characteristics.

Serum AFP levels were found to cover a wide range. In order to examine the relationships between AFP levels and the HCC characteristics of Maximum Tumor Diameter (MTD), multifocality and Portal Vein Thrombosis (PVT), AFP levels were presented in 5 groups, each group being a $\geq$5-fold increase over the previous one (**Figure 1**). **Figure 1A** shows that AFP increased over a 100-fold, from $\leq$200 IU/mL to greater than 25,000 IU/mL, whereas MTD increased from 4.18 cm to 10.09 cm (a 2.4-fold MTD increase). **Figure 1B** shows the increase in percent of patients with multifocality, increasing from 45.9% to 71.45% (a 1.6-fold multifocality increase). Similarly, the changes for percent of patients with PVT are shown in **Figure 1C** and increase from 16.50% to 64.55% (a 3.9-fold PVT increase). All parameter changes were significant, each having a $p< 0.0001$ for trend.

Relationships between serum AFP levels and liver function and blood counts.

The relationships between serum AFP levels and liver function and blood counts are shown in **Table 1**. The largest changes were found for levels of total bilirubin, a median increase from 1.6 to 3.3 g/dL (2-fold increase); AST levelshad a median increase from 58.4 to 120.0 IU/L (a 2-fold increase); platelet counts had a median increase from 121 to 199 cells x $10^3/\mu L$ (a 1.64-fold increase); and WBC counts had a mediandecrease from 4000 to 914 (a 4.37-fold decrease). There was also a small increase in the APRI ratio, from 1.29 to 1.69. All of these param-

eter changes occurred over the same >100-fold range in AFP, as in **Figure 1**.

Table 1: Comparisons among AFP (IU/mL) categories for single parameters analyzed in HCC patients.

	AFP (IU/mL)					
A. Parameter* Median values	**AFP ≤ 200**	**200 < AFP ≤ 1000**	**1000 < AFP ≤ 5000**	**5000 < AFP ≤ 25000**	**AFP > 25000**	p^
	(a)	*(b)*	*(c)*	*(d)*	*(e)*	
Albumin (g/dL), Median	3.6	3.4	3.4	3.3	3.2	0.0001
Total Bilirubin (mg/dL), Median	1.6	1.9	1.99	2.9	3.3	0.0001
AST (IU/L), Median	58.4	72.0	80.0	84.0	120.0	0.0001
ALT (IU/L), Median	48	56	56	56	57	0.0001
GGT (IU/L), Median	150	170	192	200	226.5	0.0001
Total Cholesterol (mg/dL), Median	148	141.5	150	148	149.5	0.12
LDL (mg/dL), Median	83	84	95.4	88	107.5	0.0001
HDL (mg/dL), Median	43	41	39	35	31	0.0001
WBC (cells/mm^3), Median	4000	2800	1385	1030	914	0.0001
Platelets (cells x10^3/µL), Median	121	128	147	151.5	199	0.0001
APRI, Median	1.29	1.47	1.43	1.48	1.69	0.0001
GPR, Median	138.93	144.44	141.60	153.44	124.78	0.37

B. Parameter*	**Comparisons (p-value)**									
	(b)vs(a)	*(c)vs(a)*	*(d)vs(a)*	*(e)vs(a)*	*(c)vs(b)*	*(d)vs(b)*	*(e)vs(b)*	*(d)vs(c)*	*(e)vs(c)*	*(e)vs(d)*
Albumin (g/dL)	<0.0001	<0.0001	<0.0001	<0.0001	0.62	0.001	<0.0001	0.01	0.0008	0.49
Total Bilirubin (mg/dL)	<0.0001	0.007	<0.0001	<0.0001	0.43	0.0005	<0.0001	0.0002	<0.0001	<0.0001
AST (IU/L)	<0.0001	<0.0001	<0.0001	<0.0001	0.02	<0.0001	<0.0001	0.01	<0.0001	<0.0001
ALT (IU/L)	0.0001	0.002	0.02	0.001	0.79	0.52	0.94	0.70	0.76	0.48
GGT (IU/L)	0.03	0.0001	<0.0001	<0.0001	0.07	0.002	<0.0001	0.17	0.002	0.10
Total Cholesterol (mg/dL)	0.03	0.84	0.70	0.14	0.13	0.15	0.03	0.91	0.30	0.28
LDL (mg/dL)	0.20	0.0003	0.07	<0.0001	0.04	0.53	0.0006	0.25	0.06	0.007
HDL (mg/dL)	0.05	<0.0001	<0.0001	<0.0001	0.02	0.0004	<0.0001	0.29	0.02	0.24
Hemoglobin (g/dL)	<0.0001	0.004	0.0002	0.95	0.68	0.44	0.03	0.32	0.10	0.02
WBC (10^3/µL)	<0.0001	<0.0001	<0.0001	<0.0001	0.08	0.02	<0.0001	0.59	0.001	0.006
Lymphocytes	0.47	0.15	0.01	0.76	0.47	0.01	0.81	0.003	0.53	0.07
Platelet counts (10^3/µL)	0.0006	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	<0.0001	0.12	<0.0001	<0.0001
APRI	0.0009	0.005	0.0007	<0.0001	0.95	0.44	0.06	0.43	0.06	0.30
GPR	0.69	0.52	0.45	0.08	0.80	0.41	0.20	0.31	0.32	0.06

* All values are Medians as continuous.

Abbreviations: AFP: Alpha-Fetoprotein; AST: Aspartate Aminotransaminase; ALT: Alanine Aminotransferase; GGT: Gamma Glutamyl Transpeptidae; LDL: Low Density Lipoproteins; HDL: High Density Lipoprotein; WBC: White Blood Cells. APRI was calculated as APRI = 100 × [AST (IU/L)/AST upper limit of normal (ULN)]/[platelet count (PLT) (10^3/µL)]. GPR was calculated as GPR = 100 × GGT (IU/L)/PLT (10^3/µL)].

Serum AFP levels in relation to survival

The relationship between serum AFP levels and patient survival is shown in the Kaplan-Meier plots of **Figure 2.** The median survival for patients with the lowest AFP levels of ≤ 200 IU/mL was 42 months (**Table 2**). This median decreased by nearly 50% for each of the higher AFP groups, respectively, to the lowest level of 5 months for AFP levels of > 250,000 IU/mL. Thus, the median survivals range from 42-5 months (an 8.4-fold change) over the >100-fold range of AFP values. The comparisons for survival between the AFP groups are shown in **Table 2,** with the Kaplan-Meier and Cox model analysis. The Hazard Ratios (HRs) in the model for the risk of death are: 1.94, 2.54, 3.37 and 5.10 for each increase in AFP group compared to the reference group with AFP values of ≤ 200 IU/mL. Thus, as AFP increased, the risk of death increased considerably. The Log-Rank comparison p-values at the bottom of the table show that each AFP group was significantly different to each other AFP group.

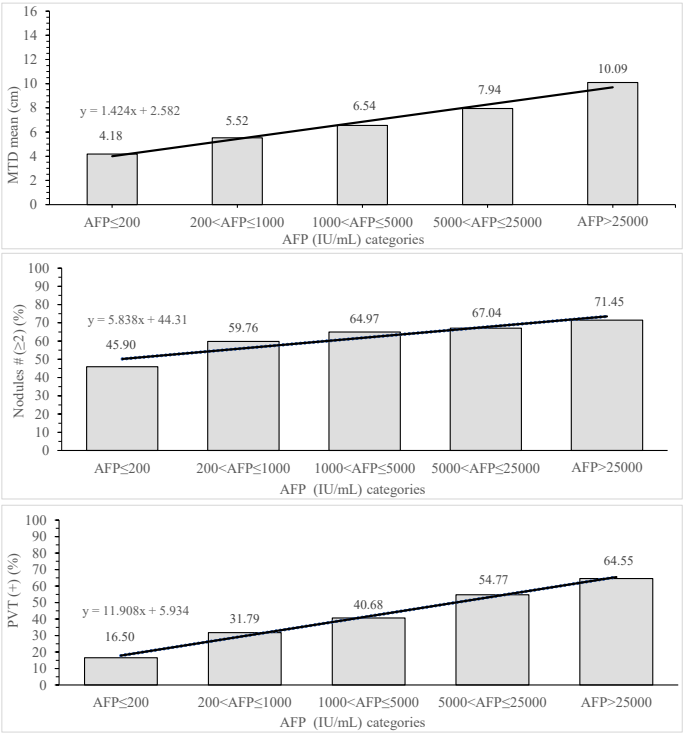

Figure 1: Histogram between: **(A)** MTD and AFP in categories, ($p<0.0001^{*}$); **(B)** Nodules # (≥2) as percentage and AFP in categories ($p<0.0001^{*}$); **(C)** PVT (+) as percentage and AFP in categories ($p<0.0001^{*}$). The line is the equation of the interpolation values. *Test for trend. Abbreviation: MTD: Maximum Tumor Diameter; AFP: Alpha-fetoprotein; PVT: Portal Vein Thrombosis.

Kaplan-Meier analysis and Cox regression for risk parameters.

A Kaplan-Meier analysis and Cox regression for single parameters was then performed, separately in patients with low or high serum AFP levels (**Table 3**). In the high AFP group, only serum albumin and GGT had hazard ratios >2.0, although several parameters had significant Cox p-values. The 2 parameters with HR>2 were then combined to form a model for survival (**Table 4**). Patients with low AFP and without PVT had a significant survival hazard ratio of 2.52 for albumin (< 3.5 (g/dl) plus GGTP (≥60 U/L) compared to the reference of albumin ≥ 3.5 (g/dl) plus GGTP < 60 (U/L). For patients with high AFP levels and without PVT, there was a significant survival hazard ratio of 10.86.

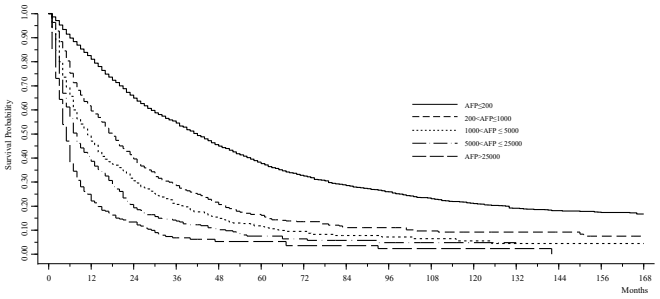

Figure 2: Kaplan-Meier Survival plots for HCC patients, according to different AFP (IU/mL) categories in the total HCC cohort. (log-rank, p<0.0001).
Abbreviations: AFP: Alpha-fetoprotein.

Table 2: Kaplan-Meier and Cox model analysis for HCC patient survival according to AFP (IU/mL) categories.

			Kaplan-Meier Analysis			Univariate Cox regression	
		N	Median Survival time (mo) (95% C.I.)	Log-Rank p-value	Log-Rank ¥ for trend p-value	HR* (95% CI)	p-value
AFP (IU/mL)				<0.0001	<0.0001	1.52 (1.49 to 1.56)	<0.001
AFP≤200	*(a)*	6079	42 mo. (40-44)			*Reference*	
200<AFP≤1000	*(b)*	831	18 mo. (16-20)			1.94 (1.78 to 2.11)	<0.001
1000<AFP≤5000	*(c)*	559	11 mo. (9-13)			2.54 (2.30 to 2.80)	<0.001
5000<AFP≤25000	*(d)*	397	8 mo. (7-9)			3.37 (3.01 to 3.78)	<0.001
AFP>25000	*(e)*	292	5 mo. (4-6)			5.10 (4.48 to 5.79)	<0.001

Abbreviations: Mo: Months; AFP: Alpha-Fetoprotein.

Table 3: Kaplan-Meier analysis and Cox regression for single parameters in categories in HCC patients with serum AFP≤ 200 (IU/mL) and patients with serum 5000≤ AFP< 25000 (IU/mL).

	AFP≤200 (IU/mL)				5000≤AFP<25000 (IU/mL)			
	Kaplan-Meier Analysis		Univariate Cox regression		Kaplan-Meier Analysis		Univariate Cox regression	
	Median Survival time (95% C.I.)	Log-Rank p-value	HR* (95% CI)	p-value	Median Survival time (95% C.I.)	Log-Rank p-value	HR* (95% CI)	p-value
Albumin (g/dl)		<0.0001				<0.0001		
≥ 3.5	59 (56-62)		[Ref. category]		21 (15-24)		[Ref. category]	
< 3.5	27 (25-29)		1.91 (1.78-2.05)	<0.001	6 (5-7)		2.50 (1.89-3.31)	<0.001
AST (IU/L)		<0.0001				0.006		
≤ 40 (n=122)	52 (47-57)		[Ref. category]		12 (8-23)		[Ref. category]	
> 40 (n=442)	35 (33-37)		1.43 (1.33-1.54)	<0.001	7 (6-8)		1.59 (1.12-2.24)	0.008
GGTP (IU/L)		0.13				0.002		
< 60	45 (40-55)		[Ref. category]		17 (9-56)		[Ref. category]	

≥ 60	41 (39-42)		1.11 (0.97-1.28)	0.13	7 (6-9)		2.13 (1.28-3.55)	0.004
ALKP (IU/L)		<0.0001				0.001		
< 250	45 (43-48)		[Ref. category]		9 (7-13)		[Ref. category]	
≥ 250	30 (27-33)		1.35 (1.25-1.45)	<0.001	7 (4-8)		1.47 (1.15-1.87)	0.002
CRP (mg/L)		0.15				0.40		
≤ 2.5	48 (20-60)		[Ref. category]		9 (6-38)		[Ref. category]	
> 2.5	53 (39-63)		0.78 (0.55-1.10)	0.16	7 (4-15)		1.28 (0.70-2.31)	0.42
ESR (mm/hr)		0.17				0.31		
≤ 15	9 (3-16)		[Ref. category]		6 (3-9)		[Ref. category]	
> 15	7 (4-12)		1.45 (0.82-2.56)	0.19	5 (3-11)		1.40 (0.70-2.79)	0.34
WBC (10^3/μL)		0.007				0.12		
≤ 3.5	39 (34-46)		[Ref. category]		8 (6-15)		[Ref. category]	
>3.5	49 (46-52)		0.87 (0.79-0.96)	0.007	8 (6-10)		1.27 (0.93-1.73)	0.14
Tot. Bil. (mg/dL)		<0.0001				0.001		
< 1.2	52 (49-55)		[Ref. category]		12 (8-16)		[Ref. category]	
≥ 1.2	31 (29-35)		1.50 (1.40-1.60)	<0.001	7 (5-8)		1.44 (1.14-1.82)	0.002
MTD (cm)		<0.0001				0.32		
≤ 5.0	47 (45-50)		[Ref. category]		8 (7-14)		[Ref. category]	
> 5.0	17 (16-20)		2.03 (1.87-2.19)	<0.001	8 (6-9)		1.13 (0.88-1.43)	0.33
Nodule nr. (#) (%)		<0.0001				0.01		
Unifocal (#1)	56 (53-59)		[Ref. category]		11 (6-18)		[Ref. category]	
Multifocal (#≥2)	28 (26-30)		1.75 (1.64-1.87)	<0.001	7 (6-8)		1.39 (1.06-1.81)	0.02
PVT (%)		<0.0001				<0.0001		
Negative	56 (52-59)		[Ref. category]		10 (8-16)		[Ref. category]	
Positive	10 (9-12)		3.52 (3.18-3.90)	<0.001	5 (4-7)		1.65 (1.28-2.13)	<0.001

Note: Median survival times in months. *HR: Hazard Ratio.
Abbreviations: AFP: Alpha-Fetoprotein; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; GGTP: Gamma Glutamyl Transpeptidase; ALKP: Alkaline Phosphatase; AST: Aspartate Aminotransaminase; ALT: Alanine Transaminase; WBC, White Blood Cell; Tot Bil: Total Bilirubin.

Table 4: Cox regression model for combination parameters in HCC patients with serum AFP ≤ 200 (IU/mL) (A) and 5000 ≤ AFP < 25000 (IU/mL) (B), in presence or absence of PVT.

	PVT(-)		PVT(+)	
	HR* (95% CI)	**HR p-value**	**HR* (95% CI)**	**HR p-value**
A). Albumin (< 3.5 (g/dl) & GGTP (≥60 U/L)	2.52 (1.7-3.6)	<0.001	1.77 (0.8-3.6)	0.111
B). Albumin (< 3.5 (g/dl) & GGTP (≥60 U/L)	10.86 (2.4-47.8)	0.002	1.97 (0.3-14.3)	0.501

Reference category is: Albumin ≥ 3.5 (g/dl) & GGTP < 60 (U/L); *HR: Hazard Ratio.
Abbreviations: PVT: Portal Vein Thrombosis; AFP: Alpha-Fetoprotein; GGTP: Gamma Glutamyl Transpeptidase.

Discussion

AFP was found to be increased over a 100-fold range, from ≤ 200 IU/mL to greater than 25,000 IU/mL, whereas MTD increased from 4.18 cm to 10.09 cm (a 2.4-fold MTD increase) for that AFP range. The increase in percent of patients with multifocality, was from 45.9% to 71.45% (a 1.6-fold multifocality increase) for this 100-fold AFP range, while the percent of patients with PVT increased from 16.50% to 64.55% (a 3.9-fold PVT increase), also over this same range. Thus, while the changes in MTD, multifocality and PVT were all significant in relation to AFP changes, the relationship was weak- a 100-fold increase in AFP compared to a 2.4-fold increase in MTD, a 1.6-fold increase in percent multifocality and a 3.9-fold increase in percent PVT. Similar low single digit increases were found for the various liver function parameters. By contrast, there was an 8.4-fold change in survival in relation to AFP changes (**Figure 2, Table 2**). It is also possible that tumor volume might be a better measure of tumor mass, rather than the commonly-used surrogate of tumor diameter (MTD) as measured on clinical scans. We evaluated this separately for the relationship of tumor volume to AFP, but found essentially similar results (Supplemental **Figure 1)**.

How therefore can the survival changes be explained, as the correlations between AFP levels on the one hand and tumor parameter and liver function parameters on the other hand are so weak? The relationship between MTD and AFP has previously been shown to be non-linear, with changes in AFP accelerating with increases in MTD [15]. But that only occurs with HCCs having a very large size. Since patients with HCC die due to both tumor load and to worsening liver dysfunction [16,17], due either to parenchymal invasion and thus destruction by tumor or to worsening of the causative liver pathology, we wondered

whether liver function parameters might reflect worsening AFP levels, but this relationship was also found to be weak (**Table 1**).

It is possible that constitutional effects of cancer resulting in cancer cachexia might be important, as they are with so many other cancer types and inflammation has been shown to be associated with increasing HCC aggressiveness and poorer prognosis [18,19].

There has been an increased effort to understand the effects of AFP on HCC biology [4,5]. These include the stimulation of HCC cell growth and metastasis, apoptosis and autophagy inhibition and its actions on suppression of the immune system [20-23].

Although this and the work of others assumes there is a causal relationship between increasing AFP levels in HCC patients and worsening tumor factors, perhaps the increasing levels in AFP might even be conversely a consequence of worsening HCC growth or invasion. Most likely, there are other factors that are not being measured in routine clinical practice that mediate worsening survival in HCC patients with elevated AFP levels. Inflammation [26-31] and cancer cachexia [24,25,19] are only 2 amongst several candidate processes that likely reflect the systemic disease nature of HCC.

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