Research Article

AFP, albumin, tumor characteristics

HEPATOLOGY FORUM

doi: 10.14744/hf.2023.2023.0023

Alpha-fetoprotein and albumin inversely relate to each other and to tumor parameters in patients with hepatocellular carcinoma

Brian Carr[1], Vito Guerra[2], Volkan Ince[1,3], Burak Isik[1,3], Sezai Yilmaz[1,3]

[1]Liver Transplant Institute, Inonu University School of Medicine, Malatya, Turkiye; [2]National Institute of Gastroenterology, S. de Bellis Research Hospital, Bari, Italy; [3]Department of Surgery, Inonu University School of Medicine, Malatya, Turkiye

Abstract

Background and Aim: Alpha-fetoprotein (AFP), an oncofetal protein and biomarker in hepatocellular carcinoma (HCC), has unclear roles and actions.To evaluate the relationships between AFP, liver function tests, and HCC aggressiveness.

Materials and Methods: A retrospective analysis of an HCC patient database was conducted to examine the relationships between baseline serum AFP values, liver function tests, and tumor characteristics.

Results: Statistically significant positive trends were observed between AFP levels and both AST and bilirubin, along with negative trends between AFP and albumin. Significant correlations were also found between AFP and MTD, multifocality, and PVT. Increases in MTD, multifocality, and PVT were noted even at low AFP levels, indicating both AFP-independent and AFP-dependent processes. However, these parameter changes were minimal compared to the substantial changes in AFP levels. Relationships between AFP-related liver and tumor characteristics were found to be similar but inverse to those for albumin, with normal albumin levels associated with more favorable tumor characteristics. Additionally, serum levels of albumin and AFP were inversely related.

Conclusion: AFP and albumin levels significantly, but inversely, correlate with tumor parameters, suggesting that albumin may suppress HCC functions and could serve as a potential prognostic marker.

Keywords: AFP; HCC; PVT; tumor size.

Introduction

Hepatocellular carcinoma (HCC) prognostic factors are broadly grouped into liver factors and tumor factors. Unlike most other tumors, a high percentage of HCC patients die from their underlying liver disease, which predisposes them to HCC.[1] This was first formally recognized in the staging system developed by Okuda.[2] Tumor factors include three radiologically observed parameters: maximum tumor dimension (MTD), tumor multifocality, and macroscopic portal vein thrombosis by the tumor (PVT), as well as serum levels of alpha-fetoprotein (AFP).[3,4] Although AFP levels have been extensively studied in HCC and are considered a useful prognostic marker when elevated,[5–7] the connection between high AFP levels and poor prognosis is unclear, despite the known correlation of increasing AFP levels with HCC size.[8] Considering that survival in HCC patients depends on liver function, tumor characteristics, or both, this report examines the relationships between AFP and liver function tests (LFTs), and between AFP and tumor characteristics such as MTD, multifocality, and PVT.

We found a significant, yet weak, correlation between AFP levels and all three tumor factors. However, there is an inverse relationship between AFP and albumin serum levels, with albumin also significantly relating to all three tumor characteristics.

Materials and Methods

Clinical

A database containing 6,488 adult HCC patients, previously discussed in our publications,[9–11] was examined for baseline tumor characteristics. These included MTD, number of tumor nodules, macroscopic PVT, baseline serum AFP levels, and standard serum LFTs. Diagnosis was made either through tumor biopsy or in accordance with AASLD/EASL guidelines. All patients were classified as Child Pugh class A or B and received locoregional therapy, except for some who received only best supportive care. The majority of these patients had chronic hepatitis B (75%), a minority with hepatitis C, virtually no cases of alcoholism, and a very small number of NASH patients.

Database management adhered to privacy legislation, and this study conforms to the ethical guidelines of the Declaration of Helsinki. Approval for this retrospective study on deceased and de-identified HCC patients was granted by our Institutional Ethics Committee, IRB Approval No. 2022-3905 (Oct 4, 2022). The approval included a waiver from written informed consent for these deceased and de-identified patients, in line with local guidelines.

How to cite this article: Carr B, Guerra V, Ince V, Isik B, Yilmaz S. Alpha-fetoprotein and albumin inversely relate to each other and to tumor parameters in patients with hepatocellular carcinoma. Hepatology Forum 2024; 5(1):11–17.

Received: May 24, 2023; **Revised:** Jul 20, 2023; **Accepted:** Jul 25, 2023; **Available online:** January 16, 2024

Corresponding author: Brian Carr; Inonu Universitesi Tip Fakultesi, Karaciger Nakli Enstitusu, Malatya, Turkiye
Phone: +1 412 980 4518; **e-mail:** brianicarr@hotmail.com

Hepatology Forum - Available online at www.hepatologyforum.org

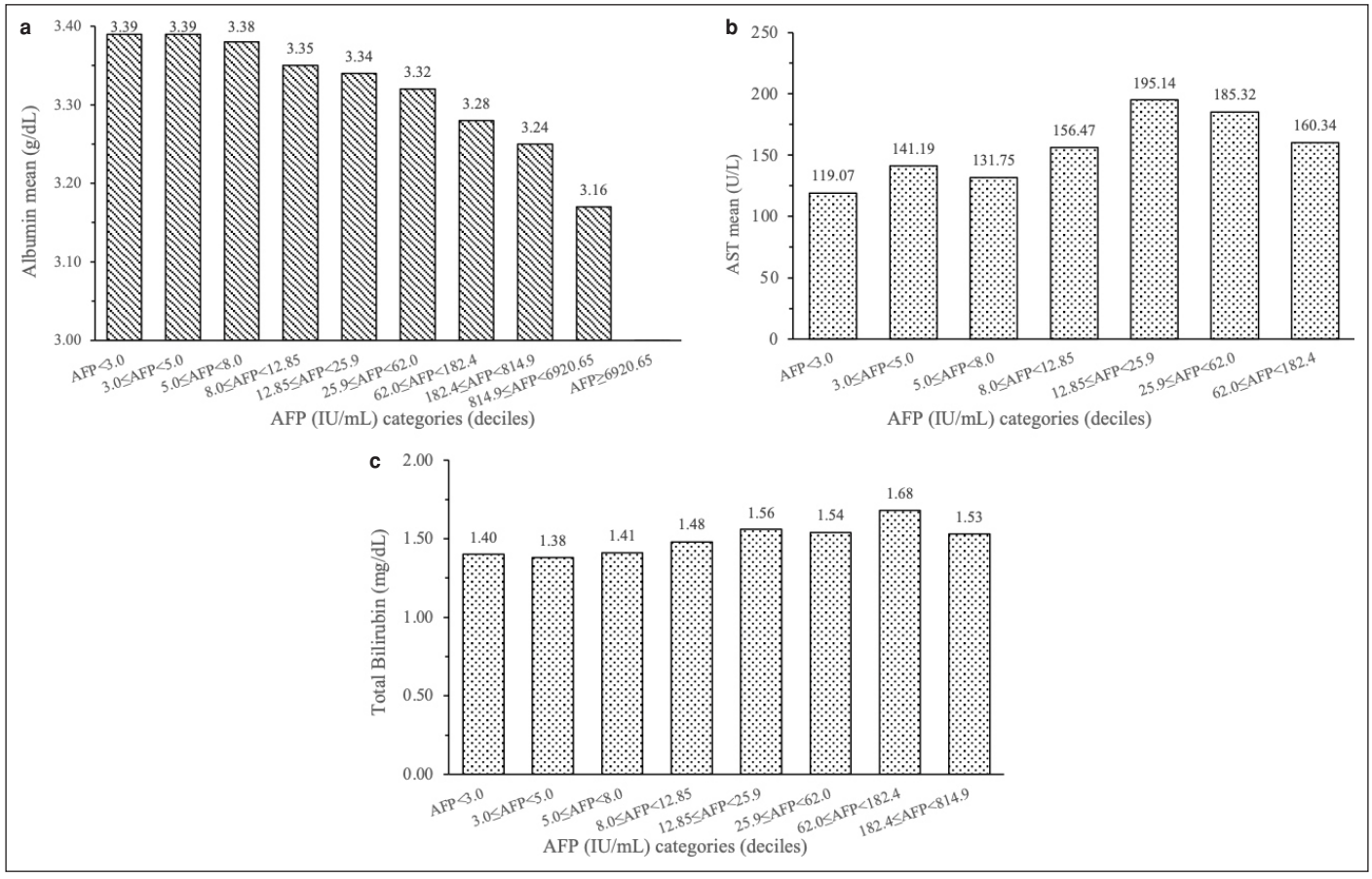

Figure 1. Relationships between serum AFP and liver function values. Histogram between: **(a)** Albumin and AFP in categories (deciles), (r=-0.1064*, p<0.0001), together with a linear regression line of Albumin on AFP as categories (deciles), in total cohort, **(b)** AST AFP in categories (deciles), (r=0.0365*, p=0.0015), in total cohort; **(c)** Total bilirubin and AFP in categories (deciles), (r=0.0520*, p<0.0001), in total cohort.

*r, Pearson's correlation coefficent; AFP: Alpha-fetoprotein; AST: Aspartate aminotransaminase.

Statistical Analysis

Patient parameters were reported as mean±standard deviation (M±SD) for continuous variables, and as frequencies and percentages (%) for categorical variables.

Normal distributions of quantitative variables were tested using the Kolmogorov-Smirnov test.

To test associations among groups, the Chi-square test was used for categorical variables. For continuous variables not normally distributed, the Kruskal-Wallis rank test and the Wilcoxon rank-sum (Mann-Whitney) test were used to evaluate differences between groups.

The χ^2 method for trend was performed to evaluate the trend between categorical levels for PVT positive (PVT (+)) and Focality (foci 1, 2, ≥3). For continuous variables, the non-parametric test for trend across ordered groups was employed.

The proportion test was applied to evaluate statistical differences between each level of Albumin (g/dL) as a category in the parameters examined.

When testing the null hypothesis of no association, the probability level of error, two-tailed, was set at 0.05. All statistical computations were conducted using StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

Results

Relationships between AFP Concentrations and Liver Function Test Values

The relationships between serum levels of AFP and various serum liver function parameters were initially examined. AFP intervals were derived from dividing AFP levels into deciles. The relationship between AFP and albumin levels was significant and inverse, with the lowest AFP levels corresponding to the highest (most normal) albumin levels (Fig. 1a). Albumin levels began to decline as AFP levels rose above 8 IU/mL (upper limit of normal in our clinical lab). When AFP levels approached 6000 IU/mL (200-fold increase), albumin levels decreased to 3.1 g/dL. The dynamic range of albumin is clearly much smaller compared to that of AFP. Despite this, albumin levels decreased as AFP levels increased in the abnormal range. The association between AFP and Albumin was inverse, as indicated by their Spearman's correlation value, rho = -0.1787 (p<0.0001). The relationship between serum AFP and aspartate aminotransaminase (AST) levels was also examined. AST levels significantly increased with increases in AFP levels (Fig. 1b) but decreased again at the highest AFP levels. Similar trends were observed for AFP and serum total bilirubin levels (Fig. 1c). These trends in levels of albumin, AST, and bilirubin with increasing AFP levels likely reflect liver damage or inflammation.

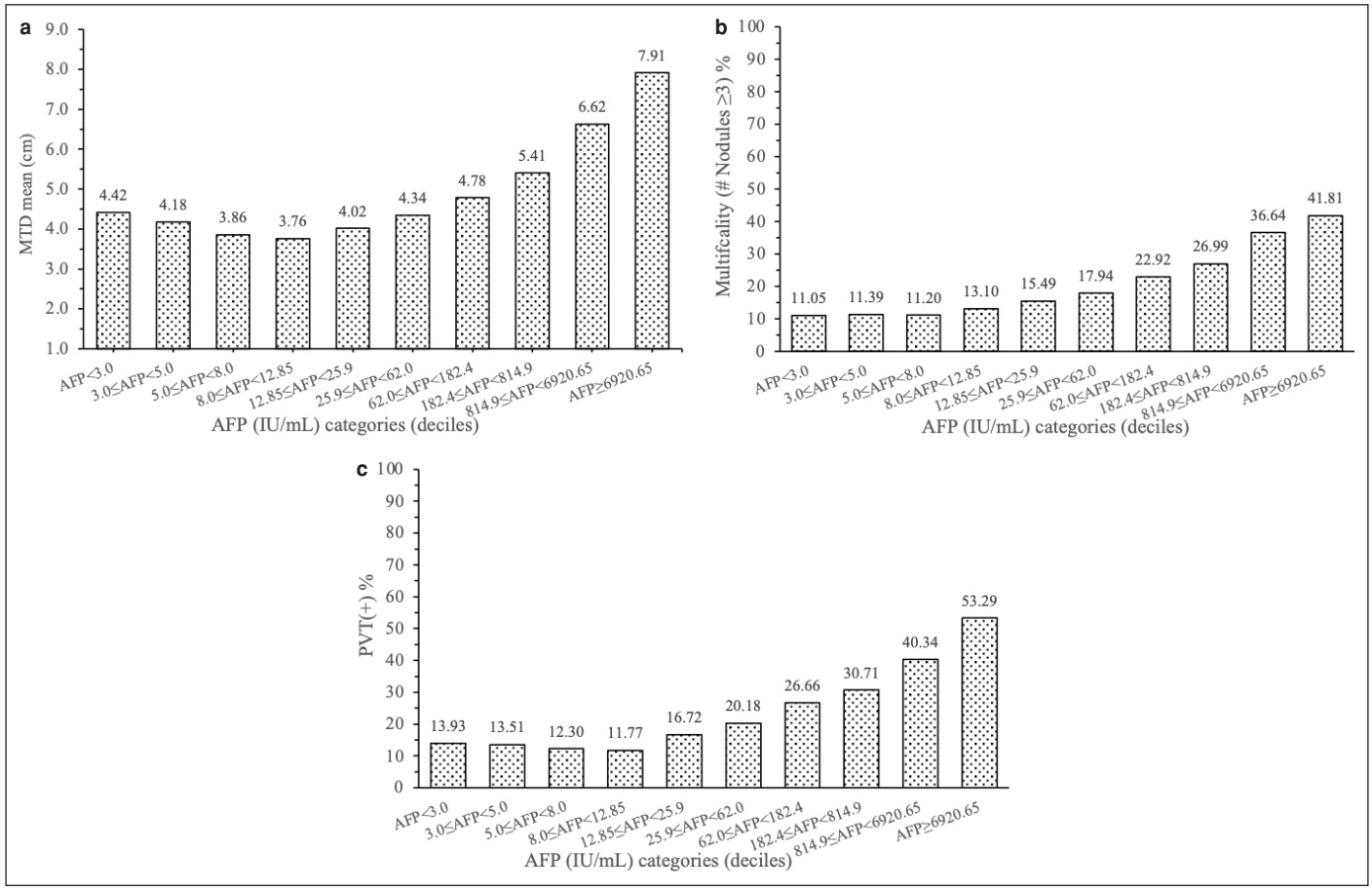

Figure 2. Relationships between serum AFP levels and tumor characteristics. Histogram between: **(a)** MTD and AFP in categories (deciles), (r=0.1933¥, p<0.0001). In total cohort. **(b)** % Multifcality (number nodules ≥3) and AFP in categories (deciles), (p<0.0001*), All patients with AFP ≤10.000 (IU/mL). **(c)** % PVT (+) and AFP in categories (deciles), (p<0.0001*). All patients with AFP ≤10.000 (IU/mL).

¥r, Pearson's correlation coefficent; * Chi-square for trend. MTD: Maximum tumor diameter; AFP: Alpha-fetoprotein; PVT: Portal vein thrombosis.

Relationships between AFP Concentrations and Tumor Characteristics

The relationships between serum AFP levels and the three main tumor characteristics—MTD, percentage of patients with PVT, and percentage of patients with tumor multifocality—were then examined (Fig. 2). We found that MTD significantly increased with increases in AFP values above 62 IU/mL (Fig. 2a). The mean MTD at the lowest AFP levels was 4 cm, suggesting that effects of AFP on MTD might only occur after reaching a certain minimum tumor size. A similar significant trend was observed for the relationship between AFP levels and the percentage of patients with multifocality (Fig. 2b). Notably, about 11% of patients had multifocality even at the lowest AFP levels. A similar pattern was found for the relationship between AFP values and the percentage of patients with PVT (Fig. 2c). A small percentage (13%) of patients had PVT even at the lowest AFP levels (<3.0), but this did not start to increase until AFP levels reached around 12.85 IU/mL or more. This suggests the existence of both AFP-related and non-AFP-related PVT patient groups.

To further evaluate whether the individual increments of the three tumor characteristics might be related to increases in AFP, AFP values were subdivided into three groups: (<100), (101/<1600), and (>1600) IU/mL, respectively. These were then analyzed to determine if the increases in mean MTD (cm), percentage of multifocality, and percentage of patients with PVT differed across the new AFP categories (Fig. 3a–c). Although the parameters in each of the three AFP groupings significantly differed from each other, the tumor parameter changes were relatively small compared to the substantial changes in the three AFP categories (Fig. 3a–c). Therefore, the effects of AFP on each parameter appeared to be small, albeit statistically significant.

Comparisons of Tumor Characteristics Among Albumin Categories:

AFP, a fetal form of albumin, decreases rapidly at birth with a concomitant increase in albumin levels. We examined the relationship between serum albumin levels and the three tumor characteristics in patients with either high or low AFP levels, and those with high or low serum albumin levels (Table 1).

Table 1a indicates that in the total cohort, as serum albumin levels decrease, there is a concomitant and statistically significant increase in MTD, a doubling in the percentage of patients with PVT, and a significant increase in the percentage of patients with tumor multifocality. Table 1b presents the same trends in patients with low serum AFP levels (<100 IU/mL). Similar trends were observed in patients with elevated serum AFP levels (Table 1c). For each MTD value in the low AFP (<100 IU/mL) group, the MTD was smaller compared to patients in the higher AFP (100<AFP≤6400 IU/mL) group (Table

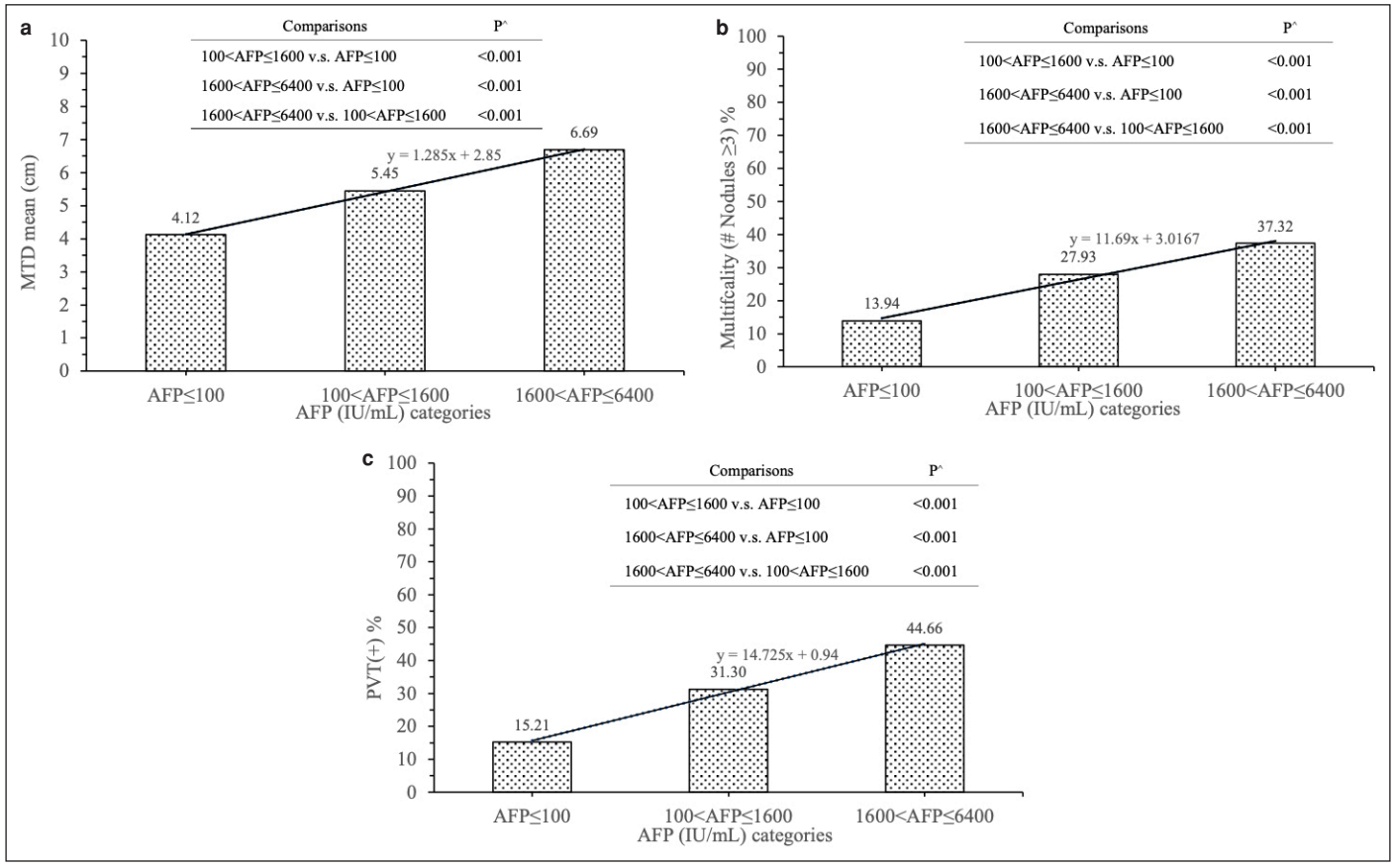

Figure 3. Tumor characteristics in HCC categories. Histogram in all patients with AFP <10.000 (IU/mL) between: **(a)** MTD and AFP in categories (p<0.0001*). The line is the equation of the interpolation values. **(b)** % Multifcality (number nodules ≥3) and AFP in categories, (p<0.0001*). The line is the equation of the interpolation values. **(c)** % PVT (+) and AFP in categories, (p<0.0001*). The line is the equation of the interpolation values.

* Chi-square for trend. ^ Test for pairwise comparisons of proportions. MTD: Maximum tumor diameter; AFP: Alpha-fetoprotein; PVT: Portal vein thrombosis.

1b vs. 1c). This pattern was also evident in both the percentage of PVT and multifocality (Tables 1b vs. 1c). The PVT percentages in the high AFP group were triple those of the low AFP group for the low albumin cohorts (8.83% vs. 24.74%) and more than double in the intermediate albumin cohort (13.44% vs. 33.76%). In both the low AFP (Table 1b) and the high AFP (Table 1c) groups, there was an increase in both percent PVT and multifocality as albumin decreased from left to right across columns (a) to (b) to (c) in Tables 1a, 1b, and 1c. Levels of total serum bilirubin were also analyzed to determine if changes in albumin or AFP might reflect liver failure. Small but significant differences were observed in the levels of total bilirubin, ranging from 0.9 to 1.5 mg/dL.

We then calculated the relationships between increasing serum albumin concentrations in 2cm increments and tumor characteristics (Fig. 4a–d). A significant trend was found for albumin concentration in relation to MTD, percent multifocality, and percent PVT. Notably, for PVT, there was a 3.6-fold difference in the percentage of patients with PVT between the lowest and highest serum albumin levels (36.29% vs. 10.12%). For multifocality, the difference was 1.91-fold, and for MTD, it was 1.42-fold. Using the same serum albumin categories as in Figures 4a, 4b, and 4c on the X-axis, the corresponding serum AFP values were plotted. An inverse relationship was observed between levels of serum AFP and albumin (Fig. 4d). The highest AFP levels, which corresponded with the highest MTD, PVT, and multifocality as shown in Figure 3, were associated with the lowest albumin levels (Fig. 4d). Conversely, the highest albumin levels were associated with the lowest AFP levels (Fig. 4d) and with the lowest MTD, PVT, and multifocality (Fig. 4a–c).

Discussion

This study aimed to examine the correlations between AFP and both liver and tumor factors, as both are altered in HCC patients and believed to contribute to prognosis. The examination of AFP's relationship to liver function revealed a significant negative correlation between AFP and albumin (where low albumin levels are abnormal) and a positive correlation between AFP and both AST and total bilirubin (where high levels are abnormal). We also investigated alanine amino transferase, gamma-glutamyl transpeptidase, and alkaline phosphatase (data not shown), finding results similar to those for AST. Abnormal levels of bilirubin, AST, and albumin all indicate liver damage, likely due to underlying hepatitis or cirrhosis, or from liver parenchyma destruction due to HCC growth. The relationships between rising AFP levels and increases in MTD, multifocality, or PVT were expected. However, several aspects merit attention. First, at the lowest (normal) AFP levels (<3 IU/mL), MTD had already reached 4 cm, multifocality was present in 11% of patients, and PVT in 13.9% (Fig. 2). Therefore, these tumor parameters did not require AFP in the early stages

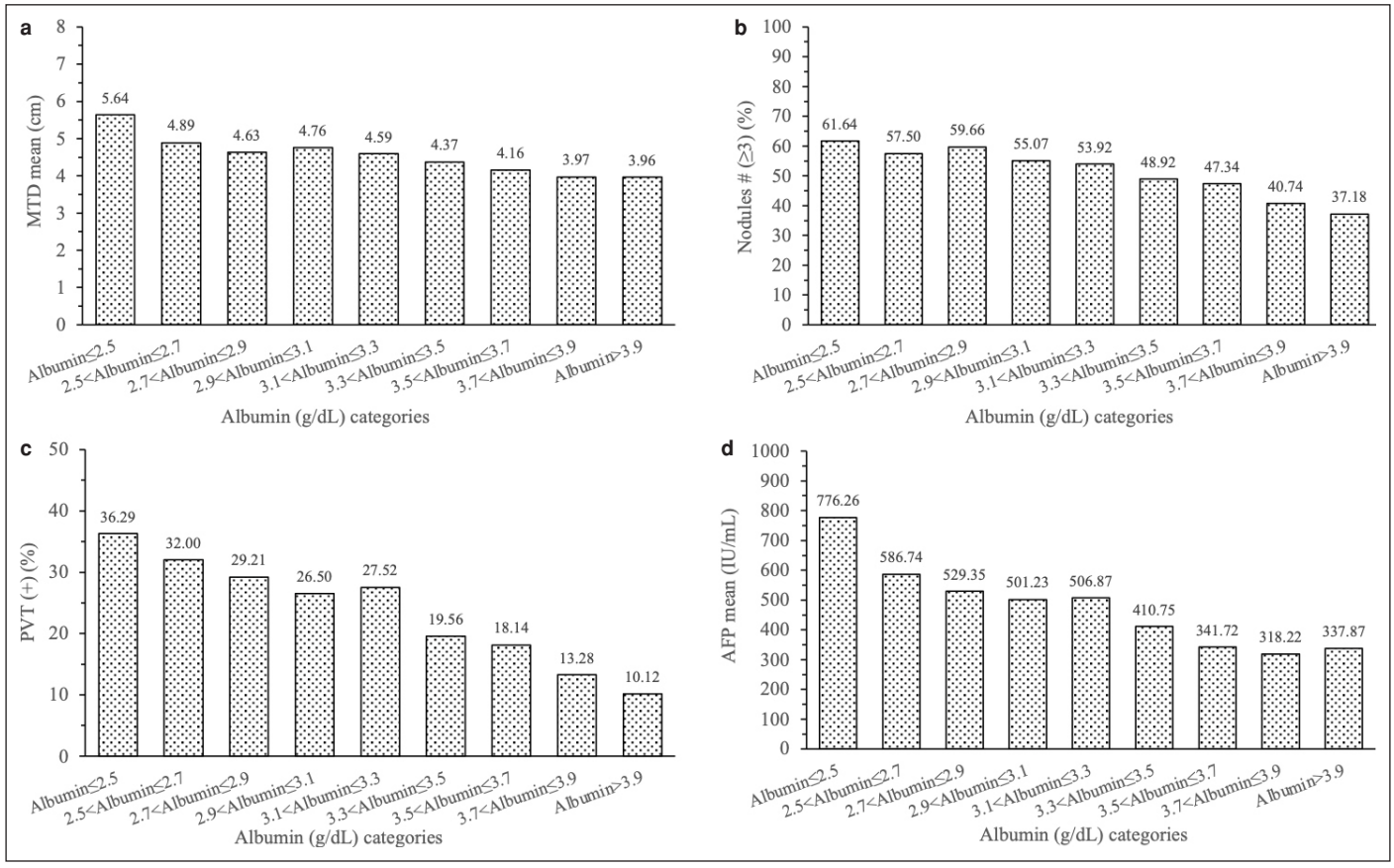

Figure 4. Relationships between serum albumin levels and tumor characteristics. Histogram in all patients with AFP <10.000 (IU/mL) between: **(a)** MTD and Albumin in categories (p<0.0001*). **(b)** Nodules # (≥2) as percentage and Albumin in categories (p<0.0001*). **(c)** PVT (+) percentage and Albumin in categories (p<0.0001*). Comparison Albumin >3.9 v. s. Albumin ≤2.5 p<0.0001¥. **(d)** AFP and Albumin in categories (p<0.0001*). Albumin concentrations in g/dL.

* Test for trend. ¥ Test for pairwise comparisons of proportions. MTD: Maximum tumor diameter; AFP: Alpha-fetoprotein; PVT: Portal vein thrombosis.

of disease progression. This indicates either an AFP-dependent and AFP-independent phase, or a minor role of AFP, as seen in MTD with a dynamic range of 4.42–7.91 cm (less than 2-fold), despite an AFP range of <3–6920 IU/mL (2000-fold). These substantial increases in AFP compared to minimal increases in MTD, percent multifocality, or percent PVT are further illustrated in Figure 3. HCCs are thought to undergo dynamic changes, with increases in MTD associated with nonlinear increases in patients with tumor multifocality and PVT (tumor evolution).[12]

AFP is part of a gene family closely related to albumin, and their structures are similar. AFP is considered the fetal counterpart of albumin and the primary protein in embryonic plasma.[13] During the neonatal period, plasma AFP levels drop drastically as albumin levels increase, and there is evidence of mutual control of albumin and AFP expression.[14,15] Moreover, albumin can suppress both HCC growth and AFP levels.[16,17] Consequently, we considered albumin as a potential effector protein mediating the relationship between AFP and tumor parameters. This hypothesis is supported by the results in Figures 4a, 4b, and 4c, demonstrating significant suppressive effects of serum albumin concentrations over a 1.56-fold dynamic range (<2.5–3.9 g/dL) versus percent of patients with PVT (36.29% vs. 10.12%, a 3.58-fold range), and lesser suppression of percent of patients with multifocality (1.68-fold range) and MTD (1.42-fold range). The significant inverse relationship between serum AFP and albumin values is depicted in Figure 4d. When patients were categorized into albumin groupings (<2.8, 2.8–3.5, >3.5 g/dL) based on the Child Pugh cirrhosis score,[18] significant decreases in MTD, percent PVT, and percent multifocality were observed as serum albumin levels normalized, in both patients with low and high AFP levels. Our previous work has shown a link between liver dysfunction indices and HCC aggressiveness parameters.[4] Several staining and gene expression studies have demonstrated an inverse relationship between AFP and albumin in HCC tissues and circulating cells.[19–22] Albumin levels were found to be decreased in both tumors and peritumoral tissues.[23] Furthermore, the experimental addition of albumin inhibited HCC invasion and migration *in vitro*, while albumin depletion significantly promoted these processes.[16,17,24] These findings lead to two hypotheses. The first suggests that poorer liver function, associated with more aggressive HCC characteristics,[25] could be a cause or consequence. However, the relatively narrow range of bilirubin levels (Table 1 and Fig. 1c) implies that liver dysfunction may not fully explain these findings. The second hypothesis, which we believe is novel, posits a reciprocal relationship between AFP and albumin levels. Given albumin's previously demonstrated role in modulating HCC growth, the lower albumin (and higher AFP) levels in larger and more aggressive HCCs (with more PVT) might reflect a decrease in albumin, postulated to be an endogenous HCC negative regulator (braking system).

Table 1. Comparisons of MTD, percent multifocality, and PVT in albumin categories

Parameters*	Albumin (g/dL)			p^	Comparisons (p)		
	Albumin ≥3.5 (a)	2.8≤ Albumin <3.5 (b)	Albumin ≤ 2.8 (c)		(b)vs(a)	(c)vs(a)	(c)vs(b)
a)							
MTD (cm) (M±SD)	4.31±3.43	4.67±3.96	5.32±4.09	0.0001	0.007Ψ	<0.0001Ψ	<0.0001Ψ
Median (min–max)	3.00 (0.05–37.00)	3.10 (0.12–50.00)	4.00 (0.17–59.00)				
PVT (+) (%)	699 (15.67)	249 (22.27)	1313 (33.81)	<0.001#	<0.001¥	<0.001¥	<0.001¥
Nodules # (≥3) (%)	2456 (42.00)	754 (50.47)	2876 (58.00)	<0.001#	<0.001¥	<0.001¥	<0.001¥
b)							
MTD (cm) (M±SD)	3.68±2.87	3.99±3.45	4.30±3.59	0.0001	0.09Ψ	<0.0001Ψ	0.01Ψ
Median (min–max)	2.90 (0.10–37.00)	3.00 (0.12–42.00)	3.00 (0.18–54.00)				
PVT (+) (%)	250 (8.83)	88 (13.44)	439 (23.41)	<0.001#	0.001¥	<0.001¥	<0.001¥
Nodules # (≥3) (%)	1435 (37.33)	430 (46.09)	1358 (52.25)	<0.001#	<0.001¥	<0.001¥	0.001¥
c)							
MTD (cm) (M±SD)	5.00±3.65	5.31±3.58	5.94±4.16	0.0001	0.085Ψ	<0.0001Ψ	0.016Ψ
Median (min–max)	3.80 (0.20–25.00)	4.00 (0.70–20.00)	5.00 (0.22–59.00)				
PVT (+) (%)	218 (24.74)	80 (33.76)	399 (39.98)	<0.001#	0.008¥	<0.001¥	0.071¥
Nodules # (≥3) (%)	581 (51.69)	174 (58.19)	822 (66.88)	<0.001#	0.043¥	<0.001¥	0.006¥

*: All values as mean and standard deviation (M±SD) and as Median minimum and maximum (min–max) as continuous; Frequences and Percentage (%). ^: Kruskal-Wallis rank test; Ψ: Wilcoxon rank-sum (Mann-Whitney) test; #: Chi-square test; ¥ test for pairwise comparisons of proportions; MTD: Maximum tumor diameter; PVT: Macroscopic portal vein thrombosis; AFP: Alpha-fetoprotein. Serum Albumin concentrations in g/dL.

Conclusion

Consequently, albumin emerges as a promising candidate for a central role or as a sensor in HCC development, given its significant correlation over a narrow dynamic range with MTD, PVT, and multifocality, both in the presence and absence of elevated AFP levels. Since serum albumin has been shown experimentally to suppress HCC cell growth and invasion *in vitro*,[16,17,24] it may also be a potential therapeutic option for some HCC patient subsets with high AFP levels. These characteristics further suggest that albumin could serve as a useful prognostic biomarker for HCC.

Ethics Committee Approval: The Inonu University Clinical Research Ethics Committee granted approval for this study (date: 04.10.2022, number: 2022-3905).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BC; Design – BC; Supervision – BC; Materials – VI, BI, SY; Data Collection and/or Processing – VI, BI, SY; Analysis and/or Interpretation – VG; Literature Search – BC; Writing – BC; Critical Reviews – VG, VI.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This work was supported in part by NIH grant CA 82723 (B.I.C).

References

1. Couto OF, Dvorchik I, Carr BI. Causes of death in patients with unresectable hepatocellular carcinoma. Dig Dis Sci 2007;52(11):3285-3289.
2. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56(4):918-928.
3. Carr BI, Guerra V. A hepatocellular carcinoma aggressiveness index and its relationship to liver enzyme levels. Oncology 2016;90(4):215-220.
4. Carr BI, Guerra V, Giannini EG, Farinati F, Ciccarese F, Rapaccini GL, Di Marco M, et al. A liver index and its relationship to indices of HCC aggressiveness. J Integr Oncol 2016;5(4):178.
5. Zong J, Fan Z, Zhang Y. Serum tumor markers for early diagnosis of primary hepatocellular carcinoma. J Hepatocell Carcinoma 2020;7:413-422.
6. Pang RW, Joh JW, Johnson PJ, Monden M, Pawlik TM, Poon RT. Biology of hepatocellular carcinoma. Ann Surg Oncol 2008;15(4):962-971.
7. Giannini EG, Marenco S, Borgonovo G, Savarino V, Farinati F, Del Poggio P, et al. Alpha-fetoprotein has no prognostic role in small hepatocellular carcinoma identified during surveillance in compensated cirrhosis. Hepatology 2012;56(4):1371-1379.
8. Carr BI, Guerra V, Donghia R, Farinati F, Giannini EG, Piscaglia F, et al. Changes in hepatocellular carcinoma aggressiveness characteristics with an increase in tumor diameter. Int J Biol Markers 2021;36(1):54-61.
9. Pancoska P, Lu SN, Carr BI. Phenotypic categorization and profiles of small and large hepatocellular carcinomas. J Gastrointest Dig Syst 2013;Suppl 12:001.
10. Carr BI, Pancoska P, Giannini EG, Farinati F, Ciccarese F, Rapaccini GL, et al; Italian Liver Cancer (ITA.LI.CA) group. Identification of two clinical hepatocellular carcinoma patient phenotypes from results of standard screening parameters. Semin Oncol 2014;41(3):406-414.
11. Carr BI, Pancoska P, Branch RA. Tumor and liver determinants of prognosis in unresectable hepatocellular carcinoma: a large case cohort study. Hepatol Int 2009;4(1):396-405.
12. Carr BI, Guerra V, Donghia R, Yilmaz S. Trends in tumor indices in relation to increased hepatocellular carcinoma size: evidence for tumor evolution as a function of growth. J Gastrointest Cancer 2020;51(4):1215-1219.
13. Deutsch HF. Chemistry and biology of alpha-fetoprotein. Adv Cancer Res 1991;56:253-312.
14. Ishikawa H, Nakata K, Tsuruta S, Nakao K, Kato Y, Tamaoki T, et al. Differential regulation of albumin gene expression by heparin-binding epidermal growth factor-like growth factor in alpha-fetoprotein-producing and -non-producing human hepatoma cells. Tumour Biol 1999;20(3):130-138.

15. Nakata K, Motomura M, Nakabayashi H, Ido A, Tamaoki T. A possible mechanism of inverse developmental regulation of alpha-fetoprotein and albumin genes. Studies with epidermal growth factor and phorbol ester. J Biol Chem 1992;267(2):1331-1334.
16. Nojiri S, Joh T. Albumin suppresses human hepatocellular carcinoma proliferation and the cell cycle. Int J Mol Sci 2014;15(3):5163-5174.
17. Bağırsakçı E, Şahin E, Atabey N, Erdal E, Guerra V, Carr BI. Role of Albumin in Growth Inhibition in Hepatocellular Carcinoma. Oncology 2017;93(2):136-142.
18. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(8):646-649.
19. Kojiro M, Kawano Y, Isomura T, Nakashima T. Distribution of albumin- and/or alpha-fetoprotein-positive cells in hepatocellular carcinoma. Lab Invest 1981;44(3):221-326.
20. Luo SM, Tan WM, Deng WX, Zhuang SM, Luo JW. Expression of albumin, IGF-1, IGFBP-3 in tumor tissues and adjacent non-tumor tissues of hepatocellular carcinoma patients with cirrhosis. World J Gastroenterol 2005;11(27):4272-4276.
21. Wong IH, Lau WY, Leung T, Johnson PJ. Quantitative comparison of alpha-fetoprotein and albumin mRNA levels in hepatocellular carcinoma/adenoma, non-tumor liver and blood: implications in cancer detection and monitoring. Cancer Lett 2000;156(2):141-149.
22. Wu GX, Lin YM, Zhou TH, Gao H, Pei G. Significant down-regulation of alpha-albumin in human hepatoma and its implication. Cancer Lett 2000;160(2):229-236.
23. Ljubimova JY, Petrovic LM, Wilson SE, Geller SA, Demetriou AA. Expression of HGF, its receptor c-met, c-myc, and albumin in cirrhotic and neoplastic human liver tissue. J Histochem Cytochem 1997;45(1):79-87.
24. Fu X, Yang Y, Zhang D. Molecular mechanism of albumin in suppressing invasion and metastasis of hepatocellular carcinoma. Liver Int 2022;42(3):696-709.
25. Carr BI, Guerra V. A hepatocellular carcinoma aggressiveness index and its relationship to liver enzyme levels. Oncology 2016;90(4):215-220.