

Evaluation of relationships between clinical and radiological characteristics and tumor markers in hepatocellular carcinoma

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Abstract

Aim: The aim of this study was to evaluate AFP, CEA and CA 19-9 levels in patients with HCC and non-HCC cirrhosis, and also to investigate the relationship between tumor radiological and clinical characteristics and these markers.

Material and Methods: 572 patients with cirrhosis who were followed for cirrhosis between January 2010 and January 2019 in the gastroenterology outpatient clinic of Demiroglu Bilim University Faculty of Medicine were included in the study. Demographic (age, gender, BMI), laboratory (AFP, CEA, CA 19-9) and imaging findings of the cases were retrospectively screened and recorded. The patients were divided into two main groups as HCC and without HCC.

Results: In the study, 252 patients were HCC and 320 patients were non-HCC. AFP values and male gender ratio were higher in HCC group, whereas CEA and CA 19-9 values were similar between the two groups. (respectively, $p < 0.001$; $p < 0.013$; $p = 0.157$; $p = 0.294$). A significant positive correlation was found between tumor size and AFP levels, but no correlation was found between CEA and CA 19-9 and tumor sizes. (for AFP $r = 0.202$, $p < 0.001$). CEA level was significantly higher in patients with macrovascular invasion ($p = 0.011$).

Conclusion: In our study, positive correlation was found between tumor size and AFP levels in patients with HCC, and a significant correlation was found between CEA and macrovascular invasion. Our study showed that AFP and CEA are valuable markers that can be used to determine prognosis and survival in HCC patients.

Keywords: Hepatocellular carcinoma; AFP; CEA; CA 19-9

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world (1). It is also one of the leading causes of cancer-related deaths (2). There are many factors that play a role in the etiology of HCC such as hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol, diet, smoking and aflatoxin (3,4). In various studies, advanced age, presence of cirrhosis and high alpha fetoprotein (AFP) level were found to be predictive factors for HCC(5). HCC develops on the basis of liver cirrhosis in the majority of cases. Vascular invasion, nodal metastasis and high tumor diameter are among the major poor prognostic factors in HCC (6,7).

Tumor markers are antigens that are secreted by tumor

cells or produced against the tumor. Although the production and secretion mechanisms of these markers are not fully understood, they are generally used to detect metastases and recurrences rather than diagnosis and screening of tumors (8-10). AFP, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are commonly used tumor markers in routine clinical practice. Although AFP is mostly associated with HCC and germinal tumors, it may also be elevated in many other gastrointestinal tumors, cirrhosis and the natural history of viral hepatitis (11). Although CEA is mostly used in the diagnosis and monitoring of colorectal cancer, it can be detected at high levels in many benign and chronic diseases such as pancreatitis, active ulcerative colitis, peptic ulcer, cholecystitis, chronic renal failure

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and pneumonia (12). CA 19-9 is mostly associated with pancreatic and biliary tract cancers, but it may also increase in benign diseases such as pancreatitis, cholangitis and cirrhosis (13). Although many studies have shown that CEA and CA 19-9 are elevated in cases with HCC, there are also some studies that claim otherwise (14, 15). There are also studies evaluating the co-use of CEA, CA 19-9 and AFP in patients with HCC (16). In HCC cases, studies evaluating tumor characteristics and AFP, CEA and CA 19-9 levels together are quite rare. The aim of this study was to evaluate AFP, CEA and CA 19-9 levels in patients with HCC and non-HCC cirrhosis, and also to investigate the relationship between AFP, CEA and CA 19-9 levels and radiological and clinical features of the tumor.

MATERIAL and METHODS

572 patients over the age of 18 who were followed up for liver cirrhosis in the Gastroenterology outpatient clinic of Demiroglu Bilim University Faculty of Medicine between January 2010 and January 2019 were included in the study. Ethics committee approval was given by Demiroglu Bilim University Ethics Committee and the Principles of Helsinki Declaration were followed in the study (approval number 2019-16-04; approved on 18.06.2019). Demographic data (age, sex, height, weight, BMI), laboratory (AFP, CEA, CA 19-9) and imaging (ultrasonography, computed tomography, magnetic resonance and positron emission tomography) findings were retrospectively reviewed from hospital information system. Patients were divided into two groups as HCC and Non-HCC cirrhosis. Patients diagnosed with HCC by liver biopsy were included in the study. Both imaging methods and biopsy results were used to determine tumor characteristics. Patients under the age of 18, without tissue diagnosis for HCC and tumor markers could not be reached were excluded from the study.

Statistical analysis; numerical data were given as mean-standard deviation. Data with normal distribution were calculated with student-t test and data with non-normal distribution were calculated with Mann-Whitney U test. Categorical data were calculated by Chi-square test. Statistical analysis was performed using SPSS 21.00 program. The confidence interval (CI) was 95% and $P < 0.05$ was accepted as significant.

RESULTS

Of the patients included in the study, 252 had HCC and 350 had non-HCC cirrhosis. While the mean age of the patients was 54.50 ± 9.30 , 52.9% of patients were male and 47.1% of patients were female. Child-Pugh score of HCC group was 7.05 ± 2.13 , while non-HCC group was 9.13 ± 2.21 . The number of tumors, maximum tumor diameter and total tumor diameter of HCC were 2.69 ± 2.89 , 3.44 ± 1.98 cm and 5.06 ± 3.58 cm, respectively. When HCC and Non-HCC groups were compared, age and body mass index (BMI) were similar ($p = 0.054$; $p = 0.413$, respectively). AFP values and male gender ratio were higher in the HCC group. In contrast, CEA and CA 19-9 values were similar

between the two groups ($p < 0.001$; $p < 0.013$; $p = 0.157$; $p = 0.294$, Table 1, respectively).

No statistically significant correlation was found between tumor count and total tumor diameter and AFP, CEA and CA 19-9. There was a significant positive correlation between tumor size and AFP levels, but no correlation was found between tumor size, CEA and CA 19-9 ($r = 0.202$ for AFP, $p < 0.001$). The relationship between tumor markers and radiological and clinical features of HCC is shown in Table 2.

When the relationship between multicentric tumor and tumor markers was examined, there was no significant relationship between tumor markers and whether the tumor was single or multicentric ($p = 0.417$; $p = 0.978$; $p = 0.950$, respectively).

There was no significant correlation between microvascular invasion and AFP, CEA and CA 19-9 ($p = 0.196$, $p = 0.326$; $p = 0.721$, respectively). CEA was significantly higher in HCC patients with macrovascular invasion ($p = 0.011$). AFP and CA 19-9 values were similar between patients with and without macrovascular invasion (Table 3).

Table 1. Laboratory and demographic data of HCC and non-HCC patients

	HCC (n=252)	Non-HCC (n=320)	P*
Age	56.38 ± 9.31	52.30 ± 9.21	0.054
Gender (female / male %)	42.4 / 57.6	52.9 / 47.1	0.013
Body mass index (kg/m ²)	27.37 ± 3.83	27.86 ± 4.76	0.413
AFP (ng/ml)	159.98 ± 877.26	13.27 ± 35.76	<0.001
CEA (ng/ml)	3.88 ± 2.26	3.76 ± 2.47	0.157
CA 19-9 (U/ml)	65.04 ± 156.03	54.09 ± 4.44	0.294

* Mann-Whitney testi

HCC: Hepatocellular carcinoma; AFP: Alfa fetoprotein;
CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen

Table 2. Relationship between tumor markers (tumor number and diameter) and tumor characteristics in HCC

	Tumor Number		Maximum Tumor Diameter (cm)		Total Tumor Diameter (cm)	
	r	P*	r	P*	r	P*
AFP	-0.021	0.743	0.202	<0.001	0.103	0.105
CEA	-0.012	0.849	-0.001	0.849	-0.028	0.657
CA 19-9	0.033	0.607	0.011	0.862	0.026	0.686

* Spearman Correlation

HCC: Hepatocellular carcinoma; AFP: Alfa fetoprotein;
CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen

Table 3. Relationship between tumor markers and type of vascular invasion in HCC

	Macrovascular invasion		P*	Microvascular invasion		P*
	Yes	No		Yes	No	
AFP	162.92 ± 253.86	159.67 ± 918.92	0.126	122.18 ± 196.69	169.10 ± 972.95	0.196
CEA	4.00 ± 2.35	2.77 ± 1.10	0.011	3.67 ± 2.25	3.93 ± 2.30	0.326
CA 19-9	78.58 ± 110.41	63.61 ± 160.19	0.889	74.17 ± 99.51	62.83 ± 166.95	0.721

* Mann-Whitney Testi

HCC: Hepatocellular carcinoma; AFP: Alfa fetoprotein;

CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen

DISCUSSION

Our study is an important study in terms of the relationship between HCC and tumor markers and also the relationships between radiological and clinical features of HCC and tumor markers such as AFP, CEA and CA 19-9. In our study, while AFP levels were higher in HCC patients as expected, CEA and CA 19-9 levels were similar between patients with and without HCC. When the relationship between HCC radiological and clinical features and tumor markers examined, there was no correlation between tumor size and total tumor diameter and tumor markers, but there was a positive correlation between tumor size and AFP. In addition, there was no correlation between multicentric tumor and microvascular invasion and tumor markers, but CEA levels were significantly higher in patients with HCC who had macrovascular invasion. HCC is an aggressive tumor with poor prognosis. The incidence of HCC is increasing all over the world, and according to the latest statistical data, it has become the second most common cause of cancer-related deaths worldwide (17). AFP is still the main tumor marker used in the diagnosis and screening of HCC and may be elevated in a significant proportion of HCC cases. Studies have shown that cirrhosis, advanced age, male gender and high AFP level are predictive factors for HCC (5,18). The relationship between HCC and CEA and CA 19-9 levels is still unclear. Although there are studies showing that CEA and CA 19-9 levels are elevated in patients with HCC, there are some reports claiming that they do not (14-16). In our study, male gender ratio and high AFP were found to be higher in patients with HCC in accordance with the literature. CEA and CA 19-9 levels were similar in both study groups.

Tumor characteristics of HCC are very important in determining prognosis and survival. For example; there are studies showing that vascular invasion, nodal metastasis or high tumor diameter is associated with poor prognosis in HCC (6, 7). Several studies have examined the relationship between tumor markers and tumor characteristics (19-21). In colorectal cancer, there are studies showing relations between remote organ metastasis, lymph node metastasis and local spread of the tumor with CEA and CA 19-9 (19). In addition, there are also studies showing relationship between CEA and histopathological features of the tumor in colorectal cancer

(22). There are a few studies evaluating the relationship between tumor markers and tumor characteristics in HCC (20,21). While there was a positive correlation between remote organ metastasis and tumor markers in a study (20), another study also found a relationship between AFP, CEA and vascular invasion in HCC cases (21).

In our study, no correlation was found between the number of tumors and total tumor diameter and AFP, CEA and CA 19-9. While there was a positive correlation between tumor size and AFP, no correlation was found between tumor size, CEA and CA 19-9. When the relationship between vascular invasion type of tumor and tumor markers was examined, while there was no significant correlation between microvascular invasion and tumor markers, CEA levels were significantly higher in patients with macrovascular invasion. The small number of patients may have been effective. The main differences of our study from other studies are that there is no study examining the relationship between many tumor features and tumor markers in HCC in the literature and our study includes more patients than other studies on this issue.

The main disadvantages of our study were the retrospective nature of our study, the fact that it was a single-center study and that the patient groups in the study consisted of patients with a single ethnic origin.

CONCLUSION

In our study, while AFP was found to be higher in cirrhosis patients with HCC, CEA and CA 19-9 levels were not different between two groups with and without HCC. While tumor size was correlated with AFP levels, no correlation was found between total tumor diameter and tumor markers in HCC cases. In addition, while there was no correlation between tumor markers and multicentric tumor, CEA levels were significantly higher in patients with macrovascular invasion. Despite limiting factors, we believe that our study will make significant contributions to the literature on this issue. More comprehensive data can be obtained through new, multi-center studies.

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