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Original Research

Evaluation of total alpha-fetoprotein, alpha-fetoprotein-L3, haptoglobin, and asprosin concentration in hepatocellular carcinoma

HCC and AFP, AFPL3, haptoglobin, asprosin

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Abstract

Aim: Serum alpha-fetoprotein (AFP) is a widely used indicator in the diagnosis and follow-up of HCC. New and simple biomarkers seem to be necessary for their ease of screening and accessibility. This study aims to evaluate the AFP, AFP-L3, haptoglobin (Hp), and asprosin levels as well as the AFPL-3/AFP ratio in HCC cases.

Methods: Descriptive statistics were presented as numbers, percentages, mean, standard deviation, and median. The Kolmogorov-Smirnov test was used to check the normal distribution of the data. The data were not normally distributed. The Mann–Whitney U test was used to compare non-normally distributed data between the two groups. Categorical data were expressed as n (%) and compared using the Chi-square test. Spearman's correlation test was used to assess the relationship between the data.

Results: AFP, AFP-L3, and Hp concentrations and AFP-L3/AFP ratio were significantly higher in the HCC group than in the control group ($p<0.001$ for AFP, AFP-L3, and Hp; $p=0.010$ for AFP-L3/AFP ratio). Asprosin concentration was significantly lower in the HCC group than in the control group ($p<0.001$). A very good negative correlation was found between Asprosin and Hp and AFP ($r=-0.84$, $p<0.001$, and $r=-0.75$, $p<0.001$, respectively), and a very good positive correlation was found between AFP and Hp ($r=0.79$, $p<0.001$).

Conclusion: Our results indicate that the AFP, AFP-L3, Hp, and asprosin concentrations and the AFP-L3/AFP ratio might well be beneficial biomarkers in the diagnosis of HCC. The clinical significance of varying levels of these biomarkers requires further investigation.

Keywords

HCC, alpha-fetoprotein, alpha fetoprotein-L3, haptoglobin, asprosin

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Introduction

Hepatocellular Carcinoma (HCC) is one of the most common malignancies, and the main risk factor for the development of HCC is cirrhosis, especially in patients with underlying hepatitis B and C infection. HCC accounts for 7% of all cancers. In the present, HCC diagnosis is dependent on the serum markers, one or more imaging methods, and histological verification. According to both the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) clinical guidelines, the diagnosis of HCC in cirrhotic patients should be based on non-invasive criteria and/ or pathology. CT or MRI should be used first due to its high sensitivity and examination of the whole liver.[1,2]

Early screening methods may reduce HCC mortality. Alpha-fetoprotein (AFP) is one of the most commonly used biomarkers for HCC screening.[3] However, AFP concentration may also increase in benign liver diseases, as well as in some non-liver diseases. AFP is a group of heterogeneous glycoproteins comprising three different glycoforms. On the other hand, AFP-L3 binds with lens culinaris agglutinin and appears to be produced only by cancer cells. It is one of the glycolized forms of AFP, and studies on its clinical role in early HCC diagnosis are ongoing. Recent studies have shown that the ratio of AFP-L3 to total AFP (%AFP-L3) increases its potential value in the diagnosis of early liver cancer. Therefore, novel and simple biomarkers are required to improve screening efficiency.[4,5] Haptoglobin (Hp) is an acute-phase glycoprotein, and there are studies showing that it increases significantly in many cancers, including breast, lung, ovarian cancer, and oral squamous cell carcinoma. Abnormal glycosylation of serum Hp has attracted the attention of researchers because of its potential as a reporter molecule for various liver diseases, including HCC.[6,7] The glucogenic hormone asprosin is associated with metabolic disorders, has been demonstrated; the role tumors play in energy metabolism in the tumor microenvironment has yet to be investigated.[8,9] Asprosin has been shown to induce insulin resistance and systemic inflammation, which may indirectly increase IGF-1 levels and promote cellular proliferation, thereby contributing to carcinogenesis. In patients with chronic viral hepatitis, inflammation, fibrosis, and angiogenesis are significantly elevated in liver tissue, leading to disruptions in energy and lipid metabolism. However, such metabolic disturbances are increasingly being reported in hepatocellular carcinoma (HCC) as well.[10,11,12] We used asprosin, a hormone that is triggered by fasting and supports hepatic glucose secretion, in HCC patients to compare it with control subjects. In order to confirm our hypothesis that the serum concentration of AFP, AFP-L3, Hp, and asprosin is different between HCC and healthy patients, we aimed to investigate these markers and the AFP-L3/AFP ratio in patients with HCC and healthy controls.

Materials and Methods

Subjects and Blood Sampling

A total of 40 healthy volunteers and 40 HCC patients were included in this case-control study. The study was performed at the Department of Internal Medicine and Gastroenterology outpatient clinic of Harran University Hospital between March 2017 and December 2021. Signed informed consent was obtained from all participants.

Patients over the age of 18 who were diagnosed with HCC were included in the study. Patients under the age of 18, pregnant women, or those presenting other systemic malignancies were excluded from the study. Age and gender-matched healthy individuals with normal liver ultrasonography and hepatitis serology panel, over the age of 18, were included in the control group. Individuals with additional diseases, pregnancy, liver diseases (acute hepatitis, chronic hepatitis), or other systemic malignancies were excluded from the control group. The demographic and clinical (such as duration of disease, tumor size, and number) data were obtained at the beginning of the study, and physical examinations were performed. The blood samples of the patients and healthy controls were centrifuged for 10 min at 4000 rpm for the separated aliquots of the serum. The separated serum samples were stored at −80°C. The samples to be studied (i.e., serum samples) were brought to room temperature at least 2 hours before the measurement. The serum samples were used to measure total AFP, AFP-L3, Hp, and asprosin concentrations. Biochemical parameters were obtained from the records of patients and were measured by Roche brand commercial kits and Roche Cobas Integra 800 chemistry analyzer (Roche Diagnostics, Germany).

Imaging Methods

Liver ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI) performed according to the EASL (European Association for the Study of the Liver) guideline were used for the diagnosis of HCC.1 Ultrasonography was used to rule out HCC in the control group. The size and number of lesions should be evaluated using computed tomography (CT) or magnetic resonance imaging (MRI).

Total Afp, Afp-L3, Hp, and Asprosin Concentrations Measurement

Total AFP (Elabscience, Cat. No.E-EL-H0070, Wuhan, China), AFP-L3 (Elabscience, Cat. No.E-EL-H0289, Wuhan, China), Hp (Elabscience, Cat. No.E-EL-H6078, Wuhan, China), and asprosin (BT-LAB, Cat. No.E4095Hu, Shanghai, China) were made according to the commercially purchased ELISA kit method. All ELISA kit CV values (both intra-CV and inter-CV) were <10%.

Ethical Approval

This study was approved by the Ethics Committee of Harran University (Date: 06.08.2019, Decision No: 74059997-050.04.04).

Statistical Analysis

For power analysis, a pilot study was conducted with a control and a patient group consisting of 10 people. An effect size of .68 was obtained in the pilot study. The G power analysis indicated that the sample size should be 40 people for both groups with 85% power and 5% margin of error. Descriptive statistics were presented as numbers, percentages, mean, standard deviation, and median. The Kolmogorov-Smirnov test was used to check the normal distribution of the data. The data was not distributed homogeneously. The Mann–Whitney U test was used to compare non-normally distributed data between the two groups. Categorical data were expressed as n (%) and

compared using the Chi-square test. Spearman's correlation test was used to assess the relationship between the data. A p-value of <0.05 was considered significant. Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Reporting Guidelines

The study was reported in accordance with STROBE guidelines.

Results

The median age of HCC patients was 66.3 (range 32-83). The median age in the control group was 66.0 (range 35-80). There were 32 (80%) males, 8 (20%) females in the HCC group, and 33 (82.5%) males and 7 (17.5%) females in the control group. The groups were similar in terms of demographic characteristics. The etiological distribution of the HCC group included 40 HCC cases developed based on liver cirrhosis, of which 30 had HBV (75%), 6 had HCV (15%), 3 had cryptogenic cirrhosis (7.5%), and 1 had Hepatitis D coinfection (2.5%). The HCC group had higher serum ALP, AFP, AFP-L3, and Hp concentrations (all p<0.001) and the AFP-L3/AFP ratio (p<0.01). The details of the laboratory findings are shown in Table 1.

Liver cirrhosis was observed in all HCC patients. The mean number of HCC lesions in the patient group was 2.8 ± 1.3. The mean HCC lesion size was 5.6 ± 2.7 cm. A very good negative correlation was found between Asprosin and Hp and AFP (r=-0.84, p<0.001, and r=-0.75, p<0.001, respectively), and a very good positive correlation was found between AFP and Hp (r=0.79, p<0.001). The correlations found in laboratory findings are detailed in Table 2.

There were very good positive correlations between disease duration and number of lesions, size of lesions, AFP, AFP-L3, Hp, and asprosin concentrations (r=0.85, r=0.83, r=0.84, r=0.78, r=0.81; all p<0.001). The correlations between AFP, AFP-L3, AFP-L3/AFP, Hp, and asprosin and the number of lesions, lesion size, and disease duration are detailed in Table 3.

Discussion

Although there are a number of potentially curative treatment options for HCC, such as resection or transplantation, only some patients are diagnosed at an early stage and can benefit from such treatments.[13] During the last decade, several promising candidate biomarkers have been identified, but most of these biomarkers have not found clinical use due to limited applicability and high costs.[14,15] AFP concentration and imaging methods (ultrasound and MRI) are the two basic screening methods for HCC diagnosis. AFP concentration is used as a serum marker of HCC, but its sensitivity is low (39- 65%).[16] In the present study, the AFP-L3, Hp, and asprosin concentrations and the AFP-L3/AFP ratio were also measured in addition to the AFP concentration of the HCC patients.

High concentrations of AFP-L3, a glycoform of AFP, have been demonstrated to be associated with poor differentiation and malignant characteristics, liver function decline, and larger tumor mass in HCC. In studies including patients with similar age and gender distribution, AFP, AFP-L3, and ALT concentrations were found to be higher in the HCC group, and it was suggested that these biomarkers could potentially predict HCC development in patients with liver cirrhosis.[17] In addition, a significantly higher AFP-L3 concentration and AFP-L3/AFP ratio in the HCC group suggest that analyzing AFP and AFP-L3 concentrations together can potentially increase HCC diagnosis rates compared with analyzing AFP alone, owing to its low sensitivity. Consistent with previous studies, AFP, AFP-L3, ALT concentrations, and the AFP-L3/AFP ratio were also significantly higher in our HCC group. In a multicenter study conducted in Turkey, the relationship between AFP concentration and tumor size was examined in 1773 patients with HCC; 41.9% of the patients had a serum AFP concentration<20 kIU/L, whereas 16.1% had a serum AFP concentration between 20 and 100 kIU/L. When the tumor diameters of these patients were compared, it was found that 66% of the tumors under 5 cm in diameter had lower AFP concentration than 49% of the tumors over 5 cm in diameter.[18] Similarly, in the present study, the mean tumor size was 5.6 ± 2.7 cm, and a good correlation was found between AFP concentration and tumor size. Furthermore, AFP, AFP-L3, Hp concentrations, and the AFP-L3/AFP ratio increased, and asprosin decreased with both increased duration of the disease, tumor size, and tumor number in our study.

In a previous study conducted with 30 malignant mesothelioma and 30 reactive mesothelial hyperplasia cases, it was found that asprosin concentration was significantly higher in patients with malignancy.[19] Du Cheng et al. compared the albumin, CRP, triglyceride, and asprosin concentrations in 120 patients with pathologically confirmed gastrointestinal or lung cancer and found no significant relationship among them.[20] Some authors hypothesized that asprosin may be a potential therapeutic target in interfering with the development of cancer anorexia, as the asprosin concentrations were found to be significantly lower in the anorexia patients.[21] In the present study, asprosin concentrations were significantly lower in the HCC group than in the control group, and a significant correlation was found between Hp and asprosin concentrations. To the best of our knowledge, no previous studies have been conducted on the relationship between the asprosin concentration and chronic liver disease, such as liver fibrosis, hepatic cirrhosis, and HCC. This significant result suggests that focusing on asprosine in HCC and other liver diseases will contribute to the literature.

Limitations

The limitations of this study are as follows: sample sizes in both groups were small, these results represented only preliminary findings, and therefore, large samples are needed to validate these findings in the future. Benign liver diseases were also not included in the study, so the expression levels of the markers in these patients were unknown, and only the values of healthy individuals and liver cancer patients were compared. Additionally, since the patients were not followed up for a certain period of time, the relationship between the markers and survival could not be evaluated.

Conclusion

The results indicate that the AFP, AFP-L3, Hp, and asprosin concentrations and the AFP-L3/AFP ratio might well be beneficial biomarkers in the diagnosis of HCC. The clinical significance of varying levels of these biomarkers requires further investigation.

Table 1. Comparison of clinical and laboratory data between the HCC and non-HCC groups

	HCC	Non-HCC	p(value)**
Age (year)	66.3(32-83)	66.0(35-80)	0.068
Age of female (year)	73(65-74)	72(66-75)	0.775
Age of male (year)	65(32-83)	66(35-80)	
AST (U/L)	61.2(14-183)	35.0(15-69)	0.030
ALT (U/L)	56.3(15-239)	27.0(17-62)	0.240
ALP (U/L)	123.5(61-408)	87.5(24-202)	**<0.001**
GGT (U/L)	82.0(22-394)	72.5(33-158)	0.321
TG (mmol/L)	5.24(2.7-10.9)	5.74(2.8-11.3)	0.441
AFP (kIU/L)	101.2(24-174.8)	16.8(8.3-45.6)	**<0.001**
AFP-L3 (kIU/L)	33(11.6-41.5)	3.4(1.6-4.1)	**<0.001**
AFP-L3/AFP ratio (%)	33.9	25.2	**0.010**
Hp (g/L)	1.41(0.39-3.05)	0.35(0.10-0.85)	**<0.001**

*AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyltransferase, TG: Triglyceride, AFP: Alphafetoprotein, Hp: Haptoglobin ** Mann-Whitney U Test, Data were shown as median (minimum-maximum).

Table 2. Correlation table between laboratory findings in the HCC group

	ALT	AST	TG	AFP	AFP-L3	Hp	Asprosin
ALT		r=0.87 p<0.001	r =0.02 p=0.857	r=0.15 p=0.176	r=0.07 p=0.497	r=0.18 p=0.097	r=-0.16 p=0.155
AST	r=0.87 p<0.001		r =0.06 p=0.561	r =0.26 p=0.018	r =0.16 p=0.151	r=0.30 p=0.006	r=-0.29 p=0.009
TG	r=0.02 p=0.857	r=0.06 p=0.561		r=-0.09 p=0.422	r=-0.08 p=0.466	r=-0.05 p=0.602	r=0.04 p=0.676
AFP	r=0.15 p=0.176	r=0.26 p=0.018	r=-0.09 p=0.422		r=0.81 p<0.001	r=0.79 p<0.001	r=-0.75 p<0.001
AFP-L3	r=0.07 p=0.497	r=0.16 p=0.151	r=-0.08 p=0.466	r=0.81 p<0.001		r=0.74 p<0.001	r=-0.75 p<0.001
Hp	r=0.18 p=0.097	r=0.30 p=0.006	r=-0.05 p=0.602	r=0.79 p<0.001	r=0.74 p<0.001		r=-0.84 p<0.001
Asprosin	r=-0.16 p=0.155	r=-0.29 p=0.009	r=0.04 p=0.676	r=-0.75 p<0.001	r=-0.75 p<0.001	r=-0.84 p<0.001	

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TG: Triglyceride, AFP: Alphafetoprotein, Hp: Haptoglobin
** Spearman's correlation test

Table 3. Comparison of the number of lesions, lesion size, survival, AFP, AFP-L3, AFPL3/ AFP, haptoglobin, and asprosin

	Number of lesions	Lesion size	Disease duration (mounth)	AFP	AFP-L3	AFP-L3/ AFP	Hp	Asprosin
Number of lesions		r=0.85 p<0.001	r=0.88 p<0.001	r=0.88 p<0.001	r=0.79 p<0.001	r=-0.26 p=0.099	r=0.81 p<0.001	r=-0.83 p<0.001
Lesion size	r=0.85 p<0.001		r=0.83 p<0.001	r=0.89 p<0.001	r=0.77 p<0.001	r=-0.30 p=0.055	r=0.76 p<0.001	r=-0.77 p<0.001
Disease duration (mounth)	r=0.88 p<0.001	r=0.83 p<0.001		r=0.84 p<0.001	r=0.78 p<0.001	r=0.05 p=0.747	r=0.81 p<0.001	r=-0.79 p<0.001
AFP	r=0.88 p<0.001	r=0.89 p<0.001	r=0.84 p<0.001		r=0.81 p<0.001	r=-0.94 p<0.001	r=0.79 p<0.001	r=-0.75 p<0.001
AFP-L3	r=0.79 p<0.001	r=0.77 p<0.001	r=0.78 p<0.001	r=0.81 p<0.001		r=0.16 p=0.301	r=0.74 p<0.001	r=-0.75 p<0.001
AFP-L3/ AFP	r=-0.26 p=0.099	r=-0.30 p=0.055	r=0.05 p=0.747	r=-0.94 p<0.001	r=0.16 p=0.301		r=-0.02 p=0.881	r=-0.29 p=0.065
Hp	r=0.81 p<0.001	r=0.76 p<0.001	r=0.81 p<0.001	r=0.79 p<0.001	r=0.74 p<0.001	r=-0.02 p=0.881		r=-0.84 p<0.001
Asprosin	r=-0.837 p<0.001	r=-0.772 p<0.001	r=-0.799 p<0.001	r=-0.751 p<0.001	r=-0.753 p<0.001	r=-0.294 p=0.065	r=-0.840 p<0.001	

Ethics Declarations
All procedures involving human participants were conducted in accordance with institutional and national ethical standards and the Declaration of Helsinki. Ethical approval was obtained from the Harran University Ethics Committee (Date: 2019-08-06, No: 74059997-050.04.04).

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent
Written informed consent was obtained from all participants.

Data Availability
The data supporting the findings of this article are available from the corresponding author upon reasonable request, due to privacy and ethical restrictions. The corresponding author has committed to share the de-identified data with qualified researchers after confirmation of the necessary ethical or institutional approvals. Requests for data access should be directed to bmp.eqco@gmail.com

Conflict of Interest
The authors declare that there is no conflict of interest.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing, and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

Abbreviations
AFP: Alpha-fetoprotein
AFP-L3: Lens culinaris agglutinin-reactive alpha-fetoprotein
ALP: Alkaline phosphatase
ALT: Alanine aminotransferase
CT: Computed tomography
HCC: Hepatocellular carcinoma
Hp: Haptoglobin
MRI: Magnetic resonance imaging

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