Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.10.597 2020;27(1):194-8

Original Article

Assesment of serum alkaline phosphatase levels on the risk of presence hepatocelluler carcinoma in the liver transplantation patients

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Abstract

Aim: Multivarious serum biomarkers have been investigated for their potential prognostic value in HCC. This aim of study evaluate the effects of Alkaline phosphatase levels on the risk of presence Hepathocelluler canser (HCC) among the liver transplantation patients.

Material and Methods: Between 2004 and 2018 878 consecutive adult Liver Tranplantation patients in our center was reviewed These patients were divided into two groups according to presence of HCC [(n=208) HCC positive (Group A) and (n=670) HCC negative (Group B)].Data collection included, We evaluated the predictive values of liver fonctions tested liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and gamma-glutamyltransferase [GGT], Hemoglobine (Hb), international normalized ratio (INR). The independent sample t test, Mann Whitney U test, chi-square test and Fisher exact test were used. to compare data. P-value of < 0.05 was considered statistically significant.

Results: A total 878 patients included in this study. 670 patients had HCC negative (Group A) 208 had HCC positive(Grup B). The mean age in each group were 57.06 ± 11.27 years in group A and 50.46 ± 13.7 years in group B. (p=0.032). HOMA IR [5.2 (0.6-36) in group A, 4.2 (0.2-85.0) in group B] were lower in group B(p= 0.001). Serum ALP levels [184.39 ± 159.72 U/L in Group A, 159.7 2± 159.72 U/L in group B] were lower in group B (p = 0.046).

Conclusion: Serum Alkaline phosphatase levels can be use as predictive component of the HCC. Follow-up studies are needed.

Keywords: Hepatocelluler carcinoma; alkaline phosphatase; liver transplantation

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death in men worldwide (1). Liver function tests and hepatobiliary system enzymes are easily accessible and economic tests for the evaluation of liver diseases. In recent studies, serum albumin (ALB) and alkaline phosphatase (ALP) levels were found related with HCC (2). Alpha feto protein (AFP) and ALP are also known as determinant markers for HCC (3,4) . HCC accounts for about 80% of malignant liver cancers. HCC is most commonly developed due to chronic hepatitis B (CHB) infection or chronic hepatitis C virus (CHC) infection (5). Numerous studies have reported the association of elevated liver enzymes and liver function tests with various types of cancer (6). Liver enzymes and function tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), direct bilirubin (DB), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), prothrombine time (PT) and International normalized ratio (INR). Liver enzymes and function tests are routine tests used in the diagnosis of liver diseases. These enzymes usually increase in patients with liver diseases and therefore may reflect the stage of liver disease. (7,8). The aim of this study was to investigate whether serum ALP levels are a predictive marker of HCC in patients with chronic liver disease.

MATERIAL and METHODS

Laboratory tests and clinical characteristics of patients who underwent liver transplantation between 2004 and 2018 in our center were retrospectively reviewed and

Received: 14.10.2019 **Accepted:** 30.01.2020 **Available online:** 18.02.2020

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recorded from hospital central records. Data collection included demographic variables, MELD scores, body mass index (BMI), Homeostatic Model Assessment Insulin Resistance (HOMA-IR), ALP, ALT, AST, GGT and TB in the study. In addition total cholesterol, triglycerides (TG), ALB, glucose, creatinine (Cr), thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxin (fT4), AFP, CA 19-9, hemoglobin (Hgb), platelet (PLT), white blood cells (WBC) and INR were also examined. Radiological images of all patients were evaluated by computed tomography (CT) or magnetic resonance imaging (MRI). Radiologically, patients with HCC were classified as group A and patients without HCC were classified as group B. Mann-Whitney U test, Chi Square test, Student's t-test and Independent sample t test were used as statistical tests. P-value lower than 0.05 was considered as statistically significant. A total of 878 patients had a liver transplantation included in our study. Two hundred and eight patients with HCC were classified as HCC positive (Group A) and six hundred and seventy patients were classified as HCC negative (Group B).

Ethical Committee Approved: Demiroğlu Bilim University, İstanbul, 04.10.2019/4343

RESULTS

A total 878 liver transplant recipients included in this study. This was a retrospective study and 208 patients had HCC and cirrhosis (Group A) and 670 patients had cirrhosis without HCC (Group B). The mean age was 57.06 ± 11.27 years in group A and 50.46 ± 13.7 years in group B (p=0.032). Mean HOMA-IR levels were 5.2 (0.6-36) in group A, and 4.2 (0.2-85.0) in group B. Mean HOMA-IR level was significantly lower in group B (p=0.001). Serum ALP levels were 184.39 ± 159.72 U/L in Group A, and 159.32± 159.53 U/L in group B. ALP levels were also lower in group B (p=0.046). The mean BMI was 27.35 ± 5.09 in the group A and 25.45 ± 4.45 in the group B, and the mean

Table 1. Comparison of clinical features and laboratory results of liver transplant patients between HCC and non-HCC patients

	HCC positive	HCC negative	p
n	208	670	**0.002**
Age (year)	50.06±11.27	50.46± 13.7	0.788
BMI	27.35±5.09	25.45±4.45	**0.012**
MELD-Na	18,5385±5.07	15.71±6.09	**0.015**
GGT (U/L)	91,10±92.94	118.34±182.29	0.062
ALP(U/L)	184,39±159.72	159.32±159.53	**0.046**
ALBUMIN (gr/dl)	2.75±0.60	3.23±1.44	**0.008**
HOMA-IR	5.2(0.6-36)	4.2(0.2-85.0)	0.001
Triglycerides (mg/dL)	113.00±42.49	138.92±76.23	**0.023**
LDL (mg/dL)	33.49±4.99	88.29±53.17	0.073
TSH microIU/ml	2.4144±1.65	2.50±2.84	0.086
FT3 picomol/L	2.95±0.99	3.45±1.00	**0.004**
FT4 pmol/L	10.24±8.38	11.39±9.2	0.384
Hba1c	5.78±1.80	5.66±3.74	0.722
Ca-19.9 u/mL	**49.82±57.56**	**81.53±288.02**	**0.039**
AFP ng/mL	**52.28±109.23**	**11.48±33.41**	**0.028**
AST (U/L)	**76.80±54.45**	**103.65±230.85**	**0.020**
ALT (U/L)	44.88±31.77	69.18±118.78	0.096
INR	**1.92±0.65**	**1,59±0.55**	**0.008**
T BIL mg/dL	**6.07±6.81**	**5.12±7.58**	**0.007**
CREATININ mg/dL	**0.87±0.43**	**1.00±1.78**	**0.135**
PLT (1000x/µL)	**115969.69±100097.94**	**109473.28±90043.70**	**0.211**
HB (g/dL)	**10.92±2.96**	**12.27±5.09**	**0.034**
WBC (1000x/µL)	**3.32**±4.20	**5.05**±1.63	**0.052**

HCC: Hepatocellular carcinoma, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, TB: Total bilirubin, TG: triglycerides, TSH: Thyroid stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxin, AFP: Alfa feto protein, Ca-19.9: Karbonhydrate antigen 19-9, Hgb: hemoglobin, PLT: Platelets, WBC: White blood cells, INR: International Normalized Ratio, HbA1c: Hemoglobin A1C

BMI was significantly higher in the group A (p=0.012). Serum AST levels (76.80 ± 54.45 U/L in group A, 103.6 5 ± 230.85 U/L in group B) were lower in in group A (p = 0.002). When patients were evaluated in terms of MELD Na score, (18.53 ± 5.07 in group A, 15.71± 6.09 in group B) MELD-Na score levels were significantly lower in group B (p = 0.015). Serum ALB levels (2.75 ± 0.60 g/dl in group A, 3.23 ±1.44 g/dl in group B) were lower in group A (p = 0.008). Serum triglyceride levels (113.00 ± 42.49 mg/dL in Group A, 138.92 ± 76.23 mg/dL in group B) were lower in group A (p=0.046). Serum CA- 19.9 levels (49.82 ± 57.56 U/L in group A, 81.53 ± 288.02 U/L in group B) were lower in group A (p=0.039). Serum AFP levels (52.28 ±109.23 ng/mL in group A, 11.48±33.41 ng/mL in group B) were lower in group B (p=0.028). Serum TB levels (6.07±6.81 mg/dL in group A, 5.12±7.58 mg/dL in group B) were lower in group B (p=0.007). When patients examined in terms of INR, [1.92±0.65 in group A, 1.59 ± 0.55 in group B) INR levels were lower in group B (p=0.008) . Serum hemoglobin levels were significantly lower in group A (10.92 ± 2.96 g/dL in group A, 12.27±5.09 g/dL in group B) in this study (p = 0.034) (Table 1).

When HCC patients were evaluated in terms of etiological factors; HBV-induced cirrhosis in 113 patients (53.8%), HCV-induced cirrhosis in 45 patients (10.6%), cryptogenic liver cirrhosis in 23 patients (10.6%), alcoholic cirrhosis in 17 patients (7.7%) and NASH-associated cirrhosis in 11 patients (4.8%) was found. Five patients (4.8%) had liver cirrhosis due to other etiologic factors. When HCC patients in group A were evaluated for etiological factors, no statistically significant difference was detected between ALP values and etiology of cirrhosis (p=0.54) (Table 2).

DISCUSSION

There are many studies showing the effect of liver enzyme elevation on mortality in the literature (7-9). Hann et al. have shown HCC incidence was higher in patients with high liver enzymes and liver function tests (7). Similarly, in this study, serum ALP levels were also significantly higher in the HCC group (Group A) patients (p=0.046).

Liu et al. reported a relationship between AFP/ASTxALT levels and HCC diameter (10). As expected, AFP levels were higher in the HCC patient group in this study. (Group A) (p = 0.028). They also found that serum AFP levels were elevated in HCC patients in their study and same result was similarly obtained in this study. They found that serum AST levels

elevated in HCC positive patients, and this results were also confirmed in this study. Although AST levels were lower in HCC positive group compared to HCC negative group, AST levels were nearly two-fold elevated in HCC group in this study.

Elevation of liver enzymes and liver function tests such as TB, INR and ALB may be associated with the stage of cirrhosis. In our study INR, TB and ALP levels were elevated in the HCC group while ALB levels were reduced. HCC positive patients (group A) had higher MELD scores which mean more advanced level of cirrhosis in this study and this finding may be the main cause of worse results in HCC positive group patients. In a study by Ren M et al., Liver function tests were compared between patients with HBV-induced liver cirrhosis and without HCC. In this study, they found that ALP levels were higher in the HCC group as in our study. (P<0.05) (11).

Table 2. ALP comparison according to etiology

	HBV	HCV	Cryptogenic	Alcohol	NASH	Other	p
n / %	113/53.8	45/21.2	23/10.6	17/7.7	11/4.8	5/1.9	-
ALP (U/L)	157.61±136,46	132.38±61.91	152.22±82.30	196.81±87.72	112.70±52.01	199.25±106.43	0.054

Obesity and insulin resistance are known risk factors for HCC. According to our results, HOMA-IR was lower in HCC negative patients (p= 0.001) and BMI values were higher in HCC positive group patients. Our study confirmed literature knowledge on this issue and this results indicates that obesity is an important risk factor for chronic liver diseases and HCC.

AFP is an important marker for HCC detection (12,13) . In our study AFP levels were lower in HCC negative patients than in HCC patients. Although serum AFP level is an important marker for HCC detection, high serum AFP level is detected in 35% -65% HCC patients (14). In the study of Şahin et al., it was stated that elevation of serum AFP level is an important marker for HCC detection (15). In the study performed by Yu M Ch et al., it was shown that serum ALP levels and serum AFP levels were the determining markers in the detection of HCC recurrence (16). Both AFP and ALP levels were higher in HCC group patients in our study and this findings were consistent with current literature.

In a study by Changchien C.S et al., Serum ALP levels were reported to be a predictive marker for HCC (17). In our study serum ALP levels were found significantly elevated in HCC group patients. Yumamato et al. conducted a study showing that ALP production is higher in cancer cells (18). Although ALP isoenzymes were not studied separately in our study, total ALP levels were found to be higher in patients with HCC. This result can be considered as an indicator of higher ALP production of malignant HCC cells.

Rovesti G et al. showed that AST >40 U/L as a prognostic factor for poorer overall survival in 398 advanced HCC patients treated with sorafenib (19). Wang Q et al. showed that GGT/AST ratio may be useful in the diagnosis of

early-stage HBV-related HCC (20). AST is used to evaluate hepatocyte damage in patients with liver disease and AST levels may be slightly elevated in patients with HCC (21). In our study, AST levels were elevated in HCC patients and this result was similar whit previous studies.

We found that MELD Na score was lower in group B (p = 0.015). Serum ALB levels were lower in group A (p = 0.008). In our study serum TB levels were lower in group B (p = 0.007). The albumin-bilirubin (ALBI) score has been established as a novel tool for the assessment of hepatic functional reserve (22) . The ALBI score represents a simple approach to the assessment of liver function in patients with HCC (23). ALBI score reported to assess liver dysfunction and prognosis in patients with HCC (24). In our study ALB levels were lower and serum TB levels were higher in HCC group patients. These results were similarly with previous studies (23-25). HCC group patients had higher MELD score and advanced cirrhosis compared to non-HCC cirrhosis group (group B) in our study and this can be the main cause of these results.

In our study, serum triglyceride levels were lower in group A (p = 0.046). Li Z et al. showed that triacylglycerol (TAGs) with the number of double bond (DB > 2) were significantly.

Down-regulated in HCC tissues (26). Patterson et al. also found that HCC was associated with reduced levels of lysophosphocholines (LPCs), lignoceric acid and nervonic acid (27). Our results can accept similarly with previous studies.

INR levels were higher in HCC group patients in this study (p = 0.008). Similarly Zang H et al. found that increased INR levels were associated with HCC in their study (28). PT is the most frequently used coagulation test in routine laboratory. INR was developed to standardize the PT value in liver diseases and this parameter was included in the Child-Turcotte-Pugh (CTP) score and in the model for end-stage liver disease (MELD) (29). In our study, the MELD scores were higher in the HCC positive group patients, which mean that there were more advanced cirrhosis in this group of patients. The INR elevation in the HCC group was consistent with both the current literature and the degree of cirrhosis.

Serum Hgb levels were significantly lower in group A compared to group B (p = 0.034) in our study. Finkelmeier et al., have invastigated Hgb levels according to the stages of liver cirrhosis and stages of HCC in their study (30). They found low Hgb levels were associated with mortality in HCC patients. In our study Hgb levels were also found lower in HCC patients. Although the data of our study are similar to this study, further studies are needed in the future, as data on the prognostic potential of Hgb levels in HCC patients are limited.

Our study has some own disadvantages. Retrospective design, lack of ALP isoenzyme types and lack of equal distribution between the groups can be listed as the main disadvantages of our study.

CONCLUSION

In our study, the relationship between liver enzymes and liver function tests and HCC detection was investigated among patients with liver cirrhosis. Significant results were obtained in many parameters (AFP, AST, TB, INR, Hgb, ALB, Triglycerid) in HCC patients and these parameters can also be used for future studies. Previous studies on ALP and HCC have focused on several parameters and developing of scoring systems. In this study, we evaluated the direct relationship between HCC and ALP levels. ALP is a cheap, easy and accesible test in daily clinical routine. This study demonstrates that high serum ALP levels may be a predictive marker for early diagnosis of HCC in patients with liver cirrhosis. However, in this study, not only ALP, but also AFP and many other parameters were also found to be significant determinants for the early diagnosis of HCC. New and more comprehensive studies can provide more powerful findings on this issue.

Financial Disclosure: There are no financial supports.
Ethical approval: Demiroğlu Bilim University, İstanbul, 04.10.2019/4343.

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