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Role of Serum Alpha-fetoprotein in Assessing the Resectability of Hepatocellular Carcinoma

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Abstract **Original Research Article**

Background: Serum AFP is a well-established tumor marker of hepatocellular carcinoma (HCC) which has already proved its acceptability in confirming the diagnosis and predicting the prognosis of HCC. ***Objective:*** The current study is aimed to evaluate the role of serum alpha-fetoprotein in assessing the resectability of HCC. ***Methods:*** This was a single-center, cross-sectional study done from September 2020 to August 2021 at the department of Hepatobiliary, pancreatic, and liver transplantation surgery at BSMMU. A total of 27 HCC patients who met the inclusion criteria were enrolled in the study. Clinical, laboratory, and imaging findings were obtained using a standardized data collecting sheet with the patients' informed agreement. AFP was measured by automated chemiluminescence analyzer (LIAISON XL, DiaSorin, Italy) in the Department of Biochemistry & Molecular Biology, BSMMU. Based on the ROC curve of this study, the patients were divided into group 1 with AFP levels 38.45 ng/ml and group 2 with AFP levels >38.45 ng/ml. According to the resectable criteria (TNM stage: I, II, BCLC stage: 0, A, B, CTP grade: A, B, ECOG PS: 0) established for the study, each AFP group was further subdivided into resectable and unresectable subgroups. Finally, the parameters (tumor size, number, location, CTP grade, fibrosis score, performance status, HBV positive, HBV DNA, BCLC and TNM stage) of the resectable and unresectable patients in each AFP group were evaluated. Statistical analyses were performed using SPSS version 22. Quantitative variables were expressed as mean±standard deviation and examined using an unpaired t-test. The qualitative data were represented by frequencies and percentages, and the Chi-Square test and Fisher exact test (where applicable) were used to determine any correlation. The statistical tests were conducted with a 95% confidence interval, and P0.05 was deemed statistically significant. ***Results:*** In this study, thirty seven percent (37%) patients were resectable. In group 1, most (72.3%) of the patients were resectable whereas, in group 2 majority (87.5%) of the patients were unresectable. The difference of resectability was statistically significant (p = 0.002) between two groups. No patients were resectable at AFP level above 700 ng/ml. The mean tumor size (cm) of our study was 8.17±4.02 and that of resectable patients in group 1 and unresectable patients in group 2 were 7.4±3.8 and 9.5±4.1 respectively. Majority of the tumors were single and located in the right lobe. Local extension and distant metastasis were preset in unresectable patients of group 2. Among the total patients 63% patients had CTP grade A and the remaining had CTP grade B and C, no patients had CTP B or C in group 1. Majority of the patients had grade 2 to 4 fibrosis in unresectable patients of group 2. Among 27 patients, 20 (74.1%) patients had good performance status (PS 0) and remaining had PS 1 or 2. Hepatitis B virus was positive in 16 (59.3%) patients and DNA was detectable in 8 (29.6%) patients. Hepatitis C virus was positive in only 1 (3.7%) patient which was inactive. HBV positivity and detectable HBV DNA was significantly associated with poor resectable status in group 2 but insignificant in group 1. In group 1, 63.6% patients had TNM stage I and BCLC stage A whereas in group 2, 62.5% and 87.5% patients had TNM stage III and advanced BCLC stage (stage B, C& D) respectively, and were unresectable. The differences in both groups were statistically significant in both stages. ***Conclusions:*** The overall resectability was 37%. Preoperative serum AFP level is a good predictor of resectability of HCC. The value of AFP above 700 ng/ml indicates 100% unresectability of HCC.

Keywords: Hepatocellular Carcinoma, Alpha-Fetoprotein, Resectability, Child-Turcotte-Pugh, Tumor Stage.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for about 90% of all liver malignancies. It is the fifth most prevalent cancer [1], and the second largest cause of cancer death globally [2]. Half of all instances of HCC are related with hepatitis B virus infection and 25% are associated with hepatitis C virus infection [2], while the rest are due to non-viral causes [3, 4]. Curative hepatic resection (HR) predominates in the treatment for hepatocellular carcinoma (HCC) with a satisfactory survival outcome [5-7], although less than 30% of patients are eligible candidates for liver resection (LR) at

present [8, 9]. The exceedingly low resectability rate and dismal results observed with conservative treatment emphasize the critical need to discover these tumors at an early stage when they are amenable to surgical removal [10].

Selection of HCC patients for LR requires appropriate preoperative staging [8]. Currently, the determinants of resectability and prognosis for HCC include tumor load, liver functional reserve, and patient performance status [11, 12]. Numerous imaging modalities evaluate the tumor burden, which includes tumor size, number, location, vascular invasion, lymph node involvement, and distant metastasis. Preoperative imaging (CT, MRI) has a sensitivity and diagnostic value of around 80%, but is limited for satellite nodules and lesions smaller than 1 cm. Intraoperative ultrasound is more precise for very early, less than 1 cm HCC, although it is difficult to arrange and extremely dependent on the surgeon. Positron emission tomography (PET) is useful for identifying extrahepatic diseases that significantly impact clinical decision-making, but it is expensive and difficult to obtain. Diagnostic laparoscopy using intraoperative ultrasonography is important to avoid an unnecessary laparotomy, but it is difficult to arrange and largely dependent on the skill of the surgeon [8]. Consequently, the evaluation of tumor burden remains problematic. Child–Turcotte–Pugh (CTP) classification has been used to evaluate the liver functional reserve in HCC patients for a long time and has been incorporated into many HCC staging systems. However, the CTP classification has limitations because some of the variables are subjective and approximately 20% of HCC patients do not have cirrhosis at the time of diagnosis [11]. The assessment of performance status (PS) scale approved by the Eastern Cooperative Oncology Group (ECOG) is extensively used by clinicians to evaluate the functional state of patients with various cancers [13]. However, this scale is nearly entirely subjective.

Although numerous staging systems are utilized to evaluate the resectability and forecast the prognosis of HCC, nearly every staging system has inherent flaws [11-14]. The quest of the ideal staging method for HCC has been the subject of extensive discussion [11-15]. Moreover, the combination of staging system and treatment algorithm may lead to a number of complications in actual clinical situations [16, 17]. To date, however, the most widely acknowledged BCLC staging approach is contested by many facilities that resect HCC beyond BCLC stage A for lack of other effective therapy options [7]. Again, the BCLC staging system is more of an algorithm for treatment than a pure cancer staging system. The Tumor-Node-Metastasis (TNM) staging method is not valid because it is predominately based on pathological findings, despite the fact that it has undergone multiple revisions over time (currently in its 8th edition) [18]. Therefore, it is necessary to design a robust staging system for patients with HCC [11], that will be reasonably simple and practicable for assessing the resectability of HCC.

Alpha-fetoprotein belongs to a group of plasma proteins that are routinely generated by the fetal yolk sac during early embryonic development and later by fetal liver cells, but are produced at a very low level or undetectable levels in healthy adults [19]. It was initially identified by [20] in the serum of some HCC patients [21]. Sixty to seventy percent of individuals with early HCC and eighty to eighty five percent of those with advanced disease were found to have elevated serum levels of AFP [22-19]. Several studies have indicated that an elevated serum AFP level is associated with HBV-related HCC [23-14], increased tumor size [22-24], number [25], poor differentiation [26, 27], advanced BCLC and TNM staging [26][27 and poor prognosis [28, 29] noted that AFP has been regarded as the gold standard in comparison to other serum markers and that its link with the etiological [30], and clinicopathological[31] characteristics of HCC has been demonstrated. However, in recent years, use of serum AFP as a diagnostic and/or prognostic biomarker in HCC surveillance has been questioned in developed countries [23]. However, serum AFP is still recommended as a valuable biomarker to screen, evaluate prognosis, and monitor recurrence following treatment for HCC in clinical practice [32, 33].

The purpose of the current study was to analyze the significance of serum alpha-fetoprotein in determining the resectability of hepatocellular carcinoma in light of the information presented above.

OBJECTIVE

- To evaluate the role of serum alpha-fetoprotein in assessing the resectability of HCC.

MATERIALS AND METHODS

This cross-sectional study was conducted from September 2020 to August 2021 at the Department of Hepatobiliary, Pancreatic and Liver Transplant Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, after approval of the Institutional Review Board (IRB) of BSMMU, Dhaka. During the study period, all clinically diagnosed HCC patients of any age and gender who were treated at the Department of Hepatobiliary, Pancreatic, and Liver Transplant Surgery at BSMMU were enrolled and HCC patients with undetectable serum alpha-fetoprotein, recurrent case of HCC, HCC patients received neo-adjuvant chemo-radiotherapy or any ablative therapy were excluded. Consecutive sampling method was used and a total of twenty-seven HCC patients were analyzed. Diagnosis of HCC was confirmed by histopathological examination of resected specimen or core-cut biopsy of unresectable HCC. Serum sample for the detection of AFP was taken up on entry into the study before initial treatment and AFP determined by automated chemiluminescence analyzer (LIAISON XL, DiaSorin,

Italy) in the department of Biochemistry and Molecular Biology, BSMMU. The cut off value for normal AFP levels (≤ 20 ng/ml) were chosen on the basis of the EASL guidelines. Optimum AFP threshold was calculated 38.45 ng/ml by a receiver operator characteristic (ROC) curve constructed using AFP to predict resectability of HCC. Based on ROC curve of this study the finally enrolled patients were divided into group 1 having AFP levels ≤ 38.45 ng/ml and group 2 AFP levels > 38.45ng/ml. Each AFP group was further divided into resectable and unresectable groups according to the resectable criteria (TNM stage I II , BCLC stage 0, A B, CTP grade A B and ECOG PS 0 1) set for the study.

Receiver Operating Characteristic (ROC) Curve of AFP for Prediction of Resectability

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	P value	95% Confidence interval (CI)	
						Lower bound	Upper bound
AFP	38.45	82.4	80.0	0.850	0.003	0.705	0.995

Receiver operating characteristic (ROC) curve were constructed using AFP had a best combination of sensitivity and specificity with a cut off value of 38.45 having 82.4% sensitivity and 80.0% specificity for prediction of resectability.

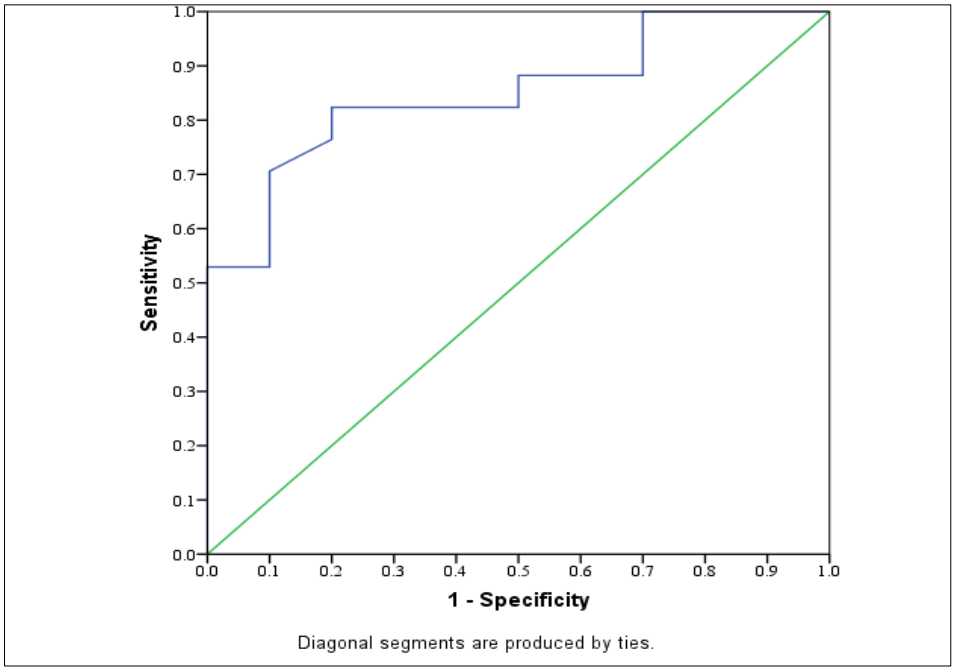

Figure 1: Receiver operating characteristic (ROC) curve of AFP for the prediction of resectability

Data Collection and Analysis

Data were collected in a structured data collection sheet only the patients who fulfilled the enrollment criteria. Finally, all the collected data were prepared for statistical analysis. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Quantitative variables (like age, monthly income, BMI, tumor size) were presented as mean±standard deviation and analyzed by the Un-paired t-test. The qualitative variables (gender, education, smoking, pain, jaundice, ascites, CTP grade, performance status, tumor location, single/multiple tumor, TNM stage, BCLC stage, HBV positivity) were indicated by frequencies and percentages and Chi-Square test/Fisher exact test (as appropriate) was used to see any association. Receiver-operator characteristic (ROC) curve were constructed using AFP for the prediction of resectability of HCC. The statistical tests were conducted with the 95% confidence interval and P<0.05 was considered as statistically significant.

RESULTS

Figure 2 shows the distribution of resectable status of the study patients between two groups. It was observed that thirty seven percent (37%) of the studied patients were resectable. Eight (72.3%) patients were resectable in group 1 and 14 (87.5%) patients were unresectable in group 2. The difference of resectability was statistically significant (p = 0.002) between two groups.

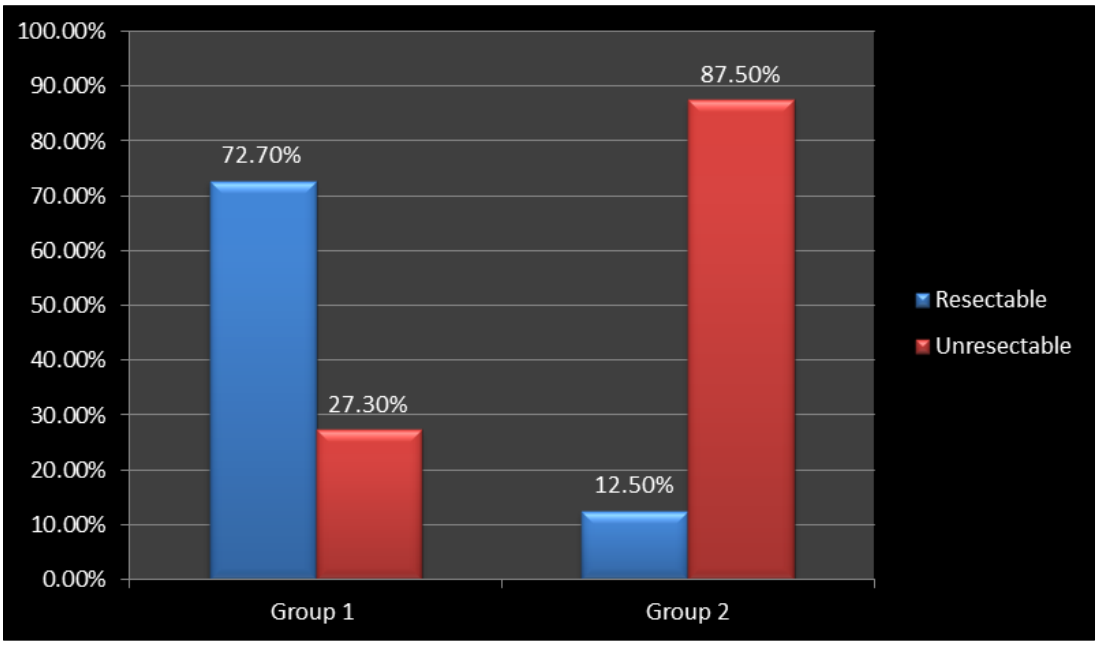

Figure 2: Distribution of resectable status of the study patients in two groups (n=27)

Table 1 shows the association of AFP level and CTP scoring system, fibrosis grade and performance status with the resectability. It was observed that in group 1, more than 70% patients were in CTP grade A and were resectable. In contrast, in group 2 more than 60% patients were in CTP grade B & C and were unresectable. It means there is a good association of serum AFP level and CTP grading system with the resectability. In group 1, 55% of the patients had fibrosis grade 0-1 and were resectable. Whereas, 63% patients had fibrosis grade 2-4 and were unresectable in group 2, which indicates that lower AFP level is associated with low grade fibrosis and higher resectable rate and vice versa**.** It was observed that in group I, almost three fourth (72.7%) of the patients were in PS grade 0 and were resectable. In group 2, more than 80% of the patients were in PS grade 0-1 and were unresectable. The difference was statistically not significant (p>0.05) between two groups.

Table 1: Association of AFP level, CTP scoring system, fibrosis grade and ECOG performance status with the resectability (n=27)

	Group 1 (n=11)				***p* value**	**Group 2 (n=16)**				***p* value**
	Resectable		**Unresectable**			**Resectable**		**Unresectable**		
	n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
CTP										
A	8	72.7	3	27.3	0.132^{ns}	2	12.5	4	25.0	0.149^{ns}
B	0	0.0	0	0.0		0	0.0	9	56.3	
C	0	0.0	0	0.0		0	0.0	1	6.2	
Fibrosis Grade										
0-1	6	55.0	1	9.0	0.254^{ns}	1	6.0	4	25.0	0.458^{ns}
2-4	2	18.0	2	18.0		1	6.0	10	63.0	
PS										
0	8	72.7	2	18.2	0.087^{ns}	2	12.5	8	50.0	0.504^{ns}
1	0	0	1	9.1		0	0	5	31.3	
2	0	0	0	0		0	0	1	6.3	

CTP= Child-Turcotte-Pugh, PS= Performance status, n = Number, % = Percent, ns= not significant, p value reached from Chi-square test

Table 2 shows the association of AFP level and the characteristics of tumors with the resectability. It was observed that, the mean tumor size (7.4±3.8) of resectable patients of group 1 was smaller than that (9.5±4.1) of unresectable patients of group 2. More than 60% of the patients had single tumor and were resectable in group 1 whereas, in group 2 almost same percentage of the patients had multiple tumors and were unresectable. Among the resectable patients in group 1 about 70% of the tumors were located in single lobe and no patient had both lobe involvement but in group 2 among the unresectable patients about 56% of the tumors were located in single lobe and more than 30% patients had both lobe involvement. Among the unresectable

patients of group 2, local extension and distant metastasis were present in 31.3% and 12.5% respectively but it was absent among the resectable patients of group 1. These observations indicate that large tumor size, number, location within the liver, local extension and distant metastasis had an association with the AFP level and resectability, but the difference were statistically not significant (p>0.05) between two groups.

Table 2: Association of AFP level and the characteristics of tumors with the resectability (n=27)

	Group 1 (n=11)				***p* value**	**Group 2 (n=16)**				***p* value**
	Resectable		**Unresectable**			**Resectable**		**Unresectable**		
	n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
Tumor Size (cm)										
Mean±SD	7.4±3.8		6.6±4.2		[a]0.768[ns]	4.2±1.3		9.5±4.1		[a]0.099[ns]
T/Number										
Single	7	63.6	1	9.1	[c]0.145[ns]	2	12.5	4	25.0	[c]0.125[ns]
Multiple	1	9.1	2	18.2		0	0.0	10	62.5	
T/Location										
Right lobe	7	63.6	1	9.1	[b]0.037[s]	1	6.3	5	31.3	[b]0.587[ns]
Left lobe	1	9.1	0	0.0		1	6.3	4	25.0	
Both	0	0.0	2	18.2		0	0.0	5	31.3	
Local extension										
Yes	0	0.0	1	9.1	[c]0.272[ns]	0	0.0	5	31.3	[c]0.458[ns]
No	8	72.7	2	18.2		2	12.5	9	56.3	
Metastasis										
Yes	0	0.0	0	0.0	1.000[ns]	0	0.0	2	12.5	[b]0.758[ns]
No	8	72.7	3	27.3		2	12.5	12	75.0	

T= Tumor, cm= Centimeter, SD= Standard deviation, n = Number, % = Percent, s= significant, ns= not significant [a]p value reached from Unpaired t-test, [b]p value reached from Chi-square test, [c]p value reached from Fisher exact test

Table 3 shows the association of AFP level and the hepatitis B virus infection status with the resectability. It was observed that in group I, more than 50% patients were HBV negative and were resectable. In contrast in group 2, seventy five percent patients were HBV positive and among them more than 30% patients had detectable HBV DNA and were unresectable. The difference was statistically significant (p= 0.032) in group 2. It indicates that AFP level is significantly associated with HBV positivity and detectable HBV DNA, and poor resectability.

Table 3: Association of AFP level and the hepatitis B virus infection status with the resectability (n=27)

	Group 1 (n=11)				***p* value**	**Group 2 (n=16)**				***p* value**
	Resectable		**Unresectable**			**Resectable**		**Unresectable**		
	n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
HBV										
Positive	2	18.2	2	18.2	0.201[ns]	0	0	12	75.0	0.009[s]
Negative	6	54.5	1	9.1		2	12.5	2	12.5	
HBV DNA										
Detected	2	18.2	1	9.1	0.190[ns]	0	0	5	31.2	0.032[s]
Undetected	0	0.0	1	9.1		0	0	7	43.8	
NA	6	54.5	1	9.1		2	12.5	2	12.5	

HBV= Hepatitis B virus, DNA= Deoxy ribonucleic acid, n= Number, %= Percent, s= significant, ns= not significant, p value reached from Chi-square test

Table 4 shows the association of AFP level, the TNM staging system and the BCLC staging system of HCC with the resectability. It was observed that in group I, more than 70% patients were in TNM stage I & II, and were resectable. On the other hand in group 2, more than 80% of the patients were in TNM stage III &IV,and were unresectable. The difference was statistically significant in both groups. This indicates that low AFP level is associated with relatively early TNM stage and higher resectability rate and vice versa. In group I, more than 60% patients were in early BCLC stage (stage A), and were resectable. On the other hand in group 2, more than 80% of the patients were in advanced BCLC stage (stage B, C & D), and were unresectable. The difference was statistically significant in both groups. This indicates that low AFP level is associated with early BCLC stage and higher resectability rate and vice versa.

Table 4: Association of AFP level and the TNM staging system of HCC with the resectability (n=27)

	Group 1 (n=11)				*p* value	Group 2 (n=16)				*p* value
	Resectable		Unresectable			Resectable		Unresectable		
	n	%	n	%		n	%	n	%	
TNM										
I	7	63.6	0	0.0	0.004[s]	2	12.5	1	6.2	0.007[s]
II	1	9.1	0	0.0		0	0.0	0	0.0	
III	0	0.0	3	27.3		0	0.0	10	62.5	
IV	0	0.0	0	0.0		0	0.0	3	18.8	
BCLC										
A	7	63.6	0	0.0	0.022[s]	2	12.5	0	0.0	0.001[s]
B	1	9.1	2	18.2		0	0.0	5	31.3	
C	0	0.0	1	9.1		0	0.0	8	50.0	
D	0	0.0	0	0.0		0	0.0	1	6.2	

TNM= Tumor- node-metastasis, BCLC= Barcelona clinic liver cancer, n= Number, %= Percent, s= significant, ns= not significant, p value reached from Chi-square test

Table 5 shows the serum AFP levels and resectable status of the studied patients. It was observed that in group 1 most of the patients (8 patients) were resectable whereas, in group 2 majority of the patients (14 patients) were unresectable. No patients were resectable at AFP level above 700 ng/ml.

Table 5: Serum AFP levels and resectable status of the study patients in two groups (n= 27)

SL	Group 1 (AFP ≤ 38.45 ng/ml)			Group 2 (AFP > 38.45 ng/ml)		
	AFP (ng/ml)	Resectable	Unresectable	AFP (ng/ml)	Resectable	Unresectable
1	1.38		-	46.9	-	
2	2		-	54		-
3	2.23		-	54	-	
4	2.41	-		256	-	
5	3.74	-		263	-	
6	4.9		-	275	-	
7	5.96		-	374		-
8	6.89	-		**730**	-	
9	17		-	**864**	-	
10	17.9		-	**1000**	-	
11	30		-	**1000**	-	
12	-	-	-	**1350**	-	
13	-	-	-	**1600**	-	
14	-	-	-	**1773**	-	
15	-	-	-	**1780**	-	
16	-	-	-	**1791**	-	
Total	-	**8**	**3**	-	**2**	**14**

AFP= Alpha-fetoprotein, ng= Nano gram, ml= milliliter

DISCUSSION

Alpha-fetoprotein (AFP) is a 591-amino-acid glycoprotein with a half-life of 5-7 days. Foetal yolk sac, liver, and gut generate. 60%-70% of early HCC and 80%-85% advanced cases have highserum AFP levels [22-29], noted that AFP has been utilized internationally as the gold standard for serum indicators and linked it to HCC's etiological [30], and clinicopathological [31], aspects. In clinical practice, AFB is still suggested as a biomarker for HCC screening, prognosis, and recurrence monitoring [32-24]. To determine the HCC resectability, we used AFP, HCC features, liver parenchymal status, and patient condition. Serum AFP correlated with HBV positive, active HBV infection, BCLC, and TNM stages of HCC patients and we found a significant association of serum AFP with HBV positivity, active HBV infection, BCLC and TNM stages of HCC patients.

AFP cutoff values affect HCC surveillance, diagnosis, and prognosis. Given its efficacy, APASL suggested setting the AFP cutoff value at 200 ng/ml instead of 20 ng/ml when used with USG in a surveillance program [22], found that the cutoff value of 20 ng/ml had a 60% sensitivity and 9–50% positive predictive value for HCC detection [23], used a relatively low AFP threshold (11.62 ng/ml) to discriminate HCC in HBV-positive patients from negative. [34], observed that

radiographic hepatic capsular invasion, non-smooth tumor margins on preoperative multiphasic CT, and blood AFP levels greater than 232.2 ng/mL were major predictors of microvascular invasion (MVI), which is linked with early recurrence after liver resection. We observed that, 10 (37%) of 27 patients were resectable, whereas the rest were not. All patients with AFP levels exceeding 374 ng/ml were unresectable. This suggests a serum AFP cutoff for resectability prediction. In this work, an AFP receiver-operator characteristic (ROC) curve with a cutoff value of 38.45 exhibited 82.4% sensitivity and 80.0% specificity for resectability prediction, the best combination of sensitivity and specificity among the literature evaluated.

This study had a mean age of 45 years, similar to [34-35], which had 48 and 49 years, respectively. Most studies showed HCC patients had a mean age above 50. Males outnumbered females 2.85 to 1. Most research patients were urban and had a mean BMI of 22.04±2.75. Anemia, hepatomegaly, and upper abdominal pain were most common.

Liver transplantation can cure HCC, however donor livers are few and selection criterias are very reserved. Thus, curative hepatic resection (HR) is the main treatment for HCC with good survival rates [5-7], however less than 30% of patients are eligible [8-36], showed 35% resectability, greater than other studies. In this study, solitary (52%), unilobar (74%), and reasonably decent liver functional condition may explain why 37% of HCC patients were resectable at diagnosis.

The number of resectable and unresectable patients below and above the AFP threshold value of 38.45 ng/ml was 72.7% in group 1 and 87.5% in group 2, which was statistically significant (p= 0.002). So, we can predict higher resectable rate of HCC in patients with normal AFP level (20 ng/ml) and if raised up to 38.45 ng/ml.

Serum AFP and CTP grade of HCC patients were rarely correlated. 63% of our patients had CTP grade A, while the rest had B and C. Though we identified a favorable connection of low AFP levels and high resectable rate in CTP grade A, and higher AFP levels and poor resectability rate in CTP grade B & C, it was statistically not significant, possibly because to limited data. In [19-22], HCC patients were more common in CTP grade A and higher AFP groups, but they did not find that AFP increases with the increasing CTP grade. Poor hepatocytes function in high CTP grade might be the explanation [26], found that serum AFP-positive HCC patients showed higher Ishak fibrosis grade of liver parenchyma than AFP-negative patients (p= 0.001) [37], observed high-grade fibrosis was related with big HCC (>8 cm) (F1– F4). As numerous researches noted, serum AFP is closely connected with HCC size, hence it may be linked to liver parenchyma fibrosis. In this study, serum AFP was not related with high-grade fibrosis, but unresectable patients in AFP group 2 had greater rates of grade 2-4 fibrosis. Serum AFP levels were likewise unrelated to ECOG performance status.

HBV causes up to 80% of HCC worldwide, as everyone knows. 20% of the 400 million chronic HBV patients worldwide may develop HCC [38]. HCC's HBV positive may vary by region and study. HBV infection caused 60% of cases in Africa and East Asia, but just 20% in the West [39], [19], reported 58.1% HBsAg-positive HCC patients, but as high as 81.4% by [29], whereas 59.3% of our patients were HBV positive.

As previously stated, HBV-related HCC has greater AFP than non-HBV-related HCC [40]. HCC-HBV interaction may affect AFP levels [29-41] retrospectively examined the predictive role of baseline AFP value in the long-term risk of HCC in HBV patients. In non-cancer HBV patients, high serum AFP levels were related with a greater risk of HCC. In group 1, HBV positive/negative did not affect resectability, whereas in group 2, HBV positive patients were substantially related with poor resectability. HBV DNA was also negligible in lower AFP groups but significant in higher ones. When blood AFP is elevated, HBV-positive HCC patients have poor resectability, and HBV DNA is even more predictive.

Our study's mean tumor size (cm) was 8.17±4.02, whereas group 1's 7.4±3.8 and group 2's 9.5±4.1 were resectable and unresectable, respectively. Our study indicated that larger tumors are associated with greater AFP and low resectability. In group 2 unresectable patients had even larger tumors. The findings were consistent with prior investigations [24-43], but statistically insignificant. As tumor diameters rose, negative serum AFP concentrations (< 20 µg/L) dropped, according to [29]. This focus on tumor sizes and cutoff values may offer HCC screening and diagnosis criteria [29]. We set our AFP cut-off value to assess HCC resectability, especially in relation to tumor size.

In this investigation, serum AFP did not increase with tumor location in the liver, local extension, or distant metastasis. However, a single tumor had a lower serum AFP level than multiple uni/bilobar tumors.

Several staging systems are available for HCC, such as Okuda, CLIP, BCLC, TNM staging, the French classification etc. In terms of our study, the main function of tumor staging was presented in three main concepts: the malignant characteristics of tumor cells, the degree of liver impairment and the patients' general condition. We used both BCLC and TNM staging. With our data, increasing AFP levels had the dominant advantage that it showed a clear relationship with advanced BCLC and TNM staging. This results might be due to incorporation of CTP grade and ECOG PS of the patients in the study which were in favor of BCLC

staging and relatively large tumor with more multifocal origin might responsible for advanced TNM staging. Our findings matched with several research [29], discovered that increased AFP was substantially linked with BCLC stage but not TNM. AFP levels were associated with hepatic capsule invasion, low grade differentiation, and late BCLC stage, although [44], did not compare AFP levels to TNM staging [26], compared TNM-7 stage I/II and III/IV patients. TNM-7-stage III/IV patients had more AFP-positive tumors than TNM-stage I/II patients (P<0.001). Logistic regression showed that AFP levels >20 ng/ml independently predicted advanced TNM-7 stage [26]. AFP and BCLC staging were not compared.

CONCLUSION

In this study, the overall resectability was 37% and frequency of resectable patients were more in lower AFP level. Preoperative serum AFP level has significant association with HBV positive HCC, detectable HBV DNA, advanced BCLC and TNM stages and it is a good predictor of resectability of HCC. The value of AFP above 700 ng/ml indicates 100% unresectability of HCC. However, surgeons should always aware that neither a normal nor a raised serum AFP may not be the final conclusion of resectability assessment of HCC.

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