

## ORIGINAL ARTICLE

# CORRELATION BETWEEN SERUM ALPHA-FETOPROTEIN LEVEL WITH ULTRASOUND GUIDED FNAC FINDINGS OF LIVER SPACE-OCCUPYING LESIONS IN PATIENTS WITH CHRONIC HBV INFECTION

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### Abstract:

**Background:** Worldwide, 350 million people are chronically infected with HBV, and >50% of HCCs are attributable to HBV infection. Among them, a significant portion presents with a space-occupying lesion (SOL) in the liver and is detected incidentally. Alpha-fetoprotein (AFP) has long been considered the ideal serological marker for detecting hepatocellular carcinoma (HCC). However, limited studies were conducted to reveal the correlation between serum alpha-fetoprotein level & FNAC findings of liver SOL in patients with chronic HBV infection. Therefore, this study aimed to assess the relation between serum alpha-fetoprotein level & ultrasound-guided FNAC findings of liver SOL in patients with chronic HBV infection. **Methods:** The study was a cross-sectional study conducted at the Department of Hepatology & Medicine in Dhaka Medical College Hospital. The study duration was six months. Formal ethical approval was taken before the commencement of the study. Adult patients of chronic HBV infection with newly diagnosed liver SOL through USG admitted to the DMCH were approached and selected according to the selection criteria. Following the description of the study's purpose, methods, benefits, and hazards, informed written consent was taken from each subject. All patients were subjected to a detailed history, clinical examination, and relevant investigations. Data were collected using qualitative and quantitative methods, using a questionnaire designed for the researcher's study. After collection, the data were edited manually and prepared for data entry. The final analysis was done by using SPSS 23. **Results:** Out of 70 SOL in the liver with chronic HBV patients, the mean age was 49.11±12.78 SD (years) [age range 25-72 years] with 80% male and 20% female representation. The majority of the patients (48.6%) had AFP levels were 1 – 10 ng/ml, and 39% had above 400 ng/ml, followed by 7.1% between 11 – 100 ng/ml and 5.7% between 101 – 400 ng/ml. The mean serum AFP level was 5611.94±14861.24 SD (ng/ml). FNAC showed that 42% had well-differentiated carcinoma, 20% had moderately differentiated carcinoma, and 38% had poorly differentiated carcinoma. Rising of alpha-fetoprotein is significantly correlated with cytopathologic grading ( $p < .05$ ). **Conclusion:** Serum alpha-fetoprotein level is significantly correlated with the findings of histological grading of liver SOL in patients with chronic HBV infection.

**Keywords:** alpha-fetoprotein level, FNAC, histological stages, Liver SOL, Chronic Hepatitis B

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## Introduction

Hepatitis B is a viral infection that affects the liver and can result in acute and chronic diseases. Worldwide, 350 million people are chronically infected with HBV, and >50% of HCC cases worldwide are attributable to HBV infection<sup>1</sup>. The consequence of viral hepatitis can also lead to the formation of liver SOL that may or may not be manifested with symptoms and is often diagnosed incidentally. Liver cancer is the sixth most common cancer in the world, with 782,000 new cases diagnosed in 2012<sup>2</sup>. These figures have remained steady despite substantial progress in the diagnostic and therapeutic arena of HCC. This is mainly because of the late diagnosis of this disease, especially in developing countries like Bangladesh. Therefore, the focus of much research revolves around diagnostic strategies to identify early HCC, including alpha-fetoprotein, radiographic imaging, FNAC, and liver biopsy.

Alpha-fetoprotein (AFP) has been considered for a long time the ideal serological marker for detecting hepatocellular carcinoma (HCC). It is well known that persistently elevated AFP levels are related to the presence of HCC and that their determination can be helpful for a better definition of at-risk patients (i.e., patients with a history of cirrhosis)<sup>3</sup>. Many studies have demonstrated survival benefits using AFP alone for surveillance of HCC in patients with chronic HBV infection. However, it is not considered common practice, as it can arise in other causes of liver pathology like acute viral hepatitis, for that a confirmatory test is needed to diagnose whether a SOL in the liver is HCC and the stage of the disease. The advantages of ultrasound-guided FNAC in the diagnosis of liver diseases cannot be overemphasized. The advantages of this technique are its high diagnostic accuracy and low cost, thereby rendering the older technique of blind percutaneous biopsy using a coarse needle obsolete. The Liver is a common site for various neoplastic and non-neoplastic lesions, such as primary liver tumors (benign or malignant), metastatic deposits, congenital and acquired cysts, abscesses, and granulomas. The appropriate clinical management of liver lesions depends upon accurate diagnosis, which is a dilemma<sup>5</sup>. From the SOL in the liver most common is HCC. Overall, liver cancer is the sixth most common cancer worldwide<sup>6</sup>, accounting for 5.7% of the overall incident cases of cancer<sup>7</sup>. Surprisingly, liver cancer is the third most common cancer in developing countries among men after lung and stomach cancer. It is also two and eight times more common in men than in women. Each year, 500,000 to 1 million individuals are diagnosed with HCC worldwide<sup>10</sup>. Its Incidence varies widely among

different geographical areas (from < 2 to >50 per 100,000 males/year), reaching peak value in some countries of Southeast Asia<sup>9</sup>. In many countries in Southeast Asia, this incidence is reported to have risen in recent years & has resulted in a proportionate increase in mortality rates.

Although the USA is among regions of low incidence, a 70% increase in HCC has been observed over the past two decades, apparently related to the emergence of chronic hepatitis. But in Asia, most particularly in East Asia, the incidence rate of HCC is very high, e.g., 58 per 100,000 in China, 53 per 100,000 in Taiwan, 45 per 100,000 in Korea, 30 per 100,000 in Hong Kong & more than 30 per 100,000 persons in Thailand<sup>9</sup>. It is low in India (less than 3-4 per 100,000 persons). Few studies have been conducted about the incidence and prevalence of HCC in many Asian countries, such as Bangladesh, Pakistan, and the Arabian Peninsula. Due to a lack of data from these countries, incidence and prevalence could not be documented<sup>9</sup>. The life expectancy of patients with HCC is poor, overall median survival of 9 months of untreated HCC & likely reflects the overall ratio of mortality to incidence of 0.95<sup>10</sup>. Patients with persistent HBV infection have a 100 times higher risk of HCC compared to non-infected individuals. Other causes of HCC apart from HBV infection include: HCV, aflatoxin, alcoholism, smoking & hereditary conditions like hemochromatosis, alpha 1-antitrypsin deficiency, and NAFLD<sup>11</sup>. In Bangladesh, HBV infection is the major etiology of HCC. For more than decades, chronic HBV infection has been associated epidemiologically with the development of HCC as there is no good surveillance in our country, we usually get HCC at late presentation.

AFP is a fetal-specific glycoprotein with a molecular weight of around 70 kDa. It is synthesized primarily by cells of the embryonic liver, the vitelline sac & the fetal intestinal tract in the 1st trimester of pregnancy. Serum AFP elevation thereafter suggests underlying pathology, which may be malignant. AFP >400-500 ng/dl is considered diagnostic for HCC, although fewer than half of the patients may generate levels that high<sup>12</sup>. With values of that magnitude, the specificity of AFP is 100% but at a cost, the sensitivity falls below 45%. In a study using 20 ng/ml as the cut-off point, the sensitivity rose to 78.9%, although the specificity declined to 78.1%<sup>13</sup>.

Early diagnosis of HCC is important because of the prognostic implications. A final diagnosis requires pathological confirmation. FNAC is a sufficiently accurate, simple, rapid, safe, relatively painless, and cost-effective technique. FNAC under image guidance has gained increasing acceptance as the diagnostic

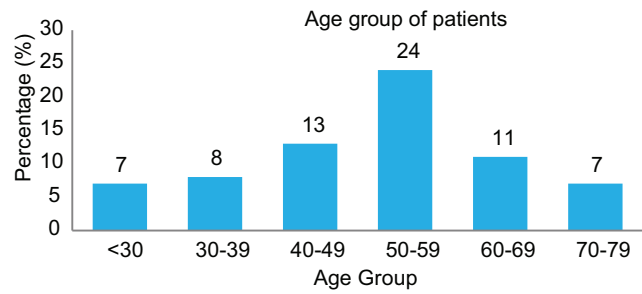
procedure of choice for patients with focal hepatic lesions. The diagnostic sensitivity of ultrasound-guided FNAC ranges between 67%-100% & has a specificity of 93%-100%. The majority (80%) of malignant liver lesions can be diagnosed on cytology combined with clinical correlation<sup>14</sup>. So FNAC was obtained from the SOL of the liver to differentiate primary HCC from metastatic deposits. This study aimed to identify the correlation between serum AFP & FNAC findings of liver SOL in patients with chronic HBV infection.

**Methods**

This cross-sectional study was conducted at the Department of Hepatology & Medicine in Dhaka Medical College Hospital from July 2023 to December 2023. Formal ethical approval was taken before the commencement of the study. Adult patients of chronic HBV infection with newly diagnosed liver SOL through USG admitted to the DMCH were approached and selected according to the selection criteria. A total of 70 cases admitted within the study period, fulfilling the inclusion and exclusion criteria, were included in this study by convenient purposive sampling. Study subjects who had cystic lesions in USG, who had contraindications to FNAC such as huge ascites, increased prothrombin time, blood dyscrasias like hemophilia, thrombocytopenia, etc, who had pregnancy, and who were Anti-HCV positive were excluded from the study. Following the description of the study’s purpose, methods, benefits, and hazards, informed written consent was taken from each subject. All patients were subjected to a detailed history, clinical examination, and relevant investigations. After initial management, all patients were advised to perform alpha-fetoprotein levels. Furthermore, FNAC was done by maintaining proper aseptic precautions. Data were collected using qualitative and quantitative methods, using a questionnaire designed for the researcher’s study. After collection, the data were edited manually and prepared for data entry. The final analysis was done by using SPSS 23.

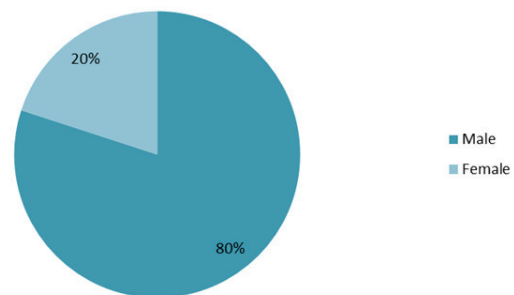
**Results**

A total of 70 cases of SOL in the liver in HBV-positive patients were included in this study. The mean age was 49.11±12.78 years, ranging from 25 to 72 years. The majority of the patients belonged to the age range of 50 to 59 years (34.3%). These followed in decreasing order by age range 40 – 49 years (18.6%), 60 – 69 years (15.7%), 30 – 39 years (11.4%), 70 – 79 years (10%), and <30 years (10%)(Fig.1).The majority of the patients were male (80%). A male-to-female ratio of 4:1 was found (Fig. 2).Occupation of the majority of the patients was farming (47.1%), followed in decreasing order by business (25.7%), homemaking (20%), service (5.7%) and 1% was bed bound (Fig. 3).The majority of the patients had low socioeconomic status (68%). Twenty-three percent were from the middle class, and 9% were from higher socioeconomic status (Fig. 4).



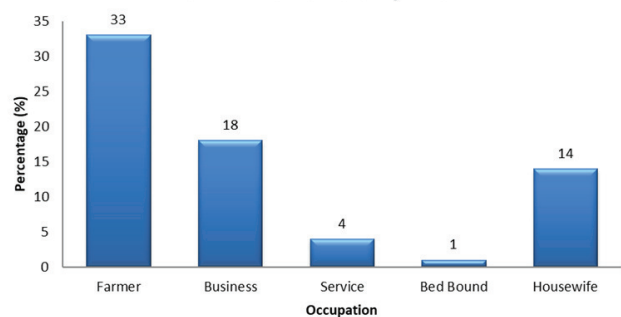
**Fig.-1:** Age group of patients (n=70)

**Sex distribution of patients**



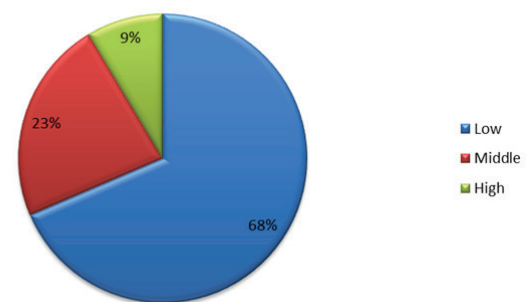
**Fig.-2:** Distribution of patients according to sex (n=70)

**Distribution of Occupation**



**Fig.-3:** Occupation of patients (n=70)

**Socioeconomic status of patients**



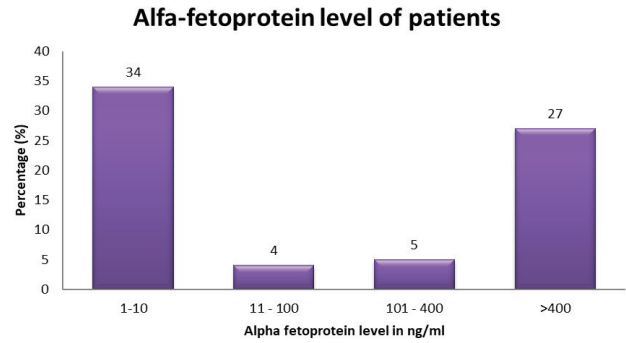
**Fig.-4:** Distribution of patients according to socioeconomic status (n=70)

**Table I**

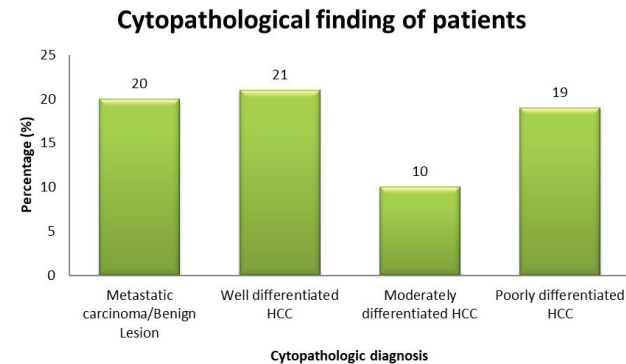
*Clinical features of HBV-positive patients with hepatic SOL (n=70)*

Variable	Frequency	Percentage
Anorexia	51	72.9
Abdominal pain	48	68.6
Weight loss	35	51.5
Abdominal lump	33	47.1
Jaundice	20	28.6

The most common clinical features in HBV-positive patients with hepatic SOL were anorexia (72.9%), followed in decreasing order by abdominal pain (68.6%), weight loss (51.5%), abdominal lump (47.1%), jaundice (28.6%), and ascites (14.3%) (Table I). The mean serum AFP level was 5611.94±14861.24 ng/ml. The Median was 207 ng/ml with a range of 0.70 ng/ml to 98361 ng/ml. The majority of the patients (48.6%) had AFP levels between 1- 10 ng/ml. Approximately 39% of patients had AFP levels above 400 ng/ml, 7.1% had between 11 – 100 ng/ml, and 5.7% had between 101 – 400 ng/ml (Fig. 5). Each patient had undergone FNAC from liver SOL after inclusion. Among them, 71.4% of patients (50) were diagnosed with a case of hepatocellular carcinoma in FNAC, and the other 28.6% consisted of either metastatic carcinoma or benign lesions. Among HCC patients 42% had well-differentiated carcinoma, 20% had moderately differentiated carcinoma, and 38% had poorly differentiated carcinoma (Fig. 6).



**Fig. 5:** AFP level of study population (n=70)



**Fig. 6:** Cytopathologic grading of hepatocellular carcinoma of the study population (n=70)

**Table II**

*Comparison of cytopathologic grading of HCC with serum alpha fetoprotein level (n=70)*

AFP level (ng/ml)	Cytopathologic diagnosis and grading n(%)					P value
	Benign lesion (n=14)	Metastatic Carcinoma (n=6)	Well differentiated (n=21)	Moderately differentiated (n=10)	Poorly differentiated (n=19)	
Normal (1 -10)	8 (57.1)	6 (100%)	13 (61.9)	4(40)	3 (15.8)	
Mildly elevated (11 -100)	0	0	2 (9.5)	2(20)	0	0.012
Moderately elevated (101 -400)	2(14.3)	0	1 (4.8)	1(10)	1 (5.3)	
Markedly elevated (>400)	4 (28.6)	0	5 (23.8)	3 (30)	15 (78.9)	

P value determined by Chi-Square test

Comparison of overall cytopathologic findings as well as cytopathologic grading of HCC with serum AFP shows that poorly differentiated carcinoma was significantly associated with markedly elevated (>400 ng/ml) levels of alpha-fetoprotein (p <0.05). Among well-differentiated HCC, 61.9% had normal AFP levels and 23.8% had markedly elevated AFP. Among moderately differentiated

HCC 40% had normal and 30% had markedly elevated AFP. Among poorly differentiated HCC, 15.8% had normal and 78.9% had markedly elevated AFP. Among metastatic carcinomas, all of the patients (100%) had normal AFP levels. Whereas, among benign lesions, 57.1% had normal, 28.6% had markedly elevated, and 14.3% had moderately elevated AFP (Table II).

## Discussion

In this study, 70 patients infected chronically with HBV with or without cirrhosis and with radiologic evidence of SOL in the liver were evaluated using FNAC. All of the patients except 20 were found to have HCC. The rest of the patients had other benign lesions or metastasis. Patients with HBsAg-positive cirrhosis have a 1000 times higher risk of developing HCC compared to HBsAg-negative individuals<sup>15</sup>.

The mean age of the patients was 49.11±12.78 years. The majority of the patients clustered around this mean, and 34.3% of patients were aged between 50 to 59 years. The maximum age was 72 years, and the minimum age was 25 years. This finding corroborates the findings of Karim et al. (2012)<sup>16</sup>. In their study, they found a mean age of 51 years, ranging from 22 to 75 years. HCC, although rarely occurring during the first 4 decades of life, can occur in populations where HBV is hyperendemic and chronic HBV infection accounts for approximately 50% of the total cases and virtually all of childhood HCC. This explains why HCC is found as early as the third decade of life in this and other studies by Kew et al. (1971)<sup>17</sup> and Chowdhury et al. (2009)<sup>18</sup>.

The present study found a male-to-female ratio of 4:1. Males constituted 80% of the study population. Male predominance was also noted in studies by Chowdhury et al. (2009)<sup>18</sup> who reported a 20.5:1 male-female ratio. Other studies reviewed by Karim et al. (2012)<sup>16</sup> also found a similar high male-female ratio. Male sex is hypothesized to be a risk factor for HCC, causing a 2 to 4 times higher prevalence of HCC in this group. However, several other factors contribute to the sex factor as men are more likely to be infected with viral hepatitis, consume greater quantities of alcohol, smoke cigarettes, and have a higher body mass index than women<sup>32</sup>. Also, it may be the higher testosterone levels that account for the higher incidence in males. It is known that high testosterone levels have been linked to HCC in hepatitis B carriers<sup>19</sup>.

The majority of the patients were farmers (54%), and most of the study population came from a lower socio-economic class. Patients with chronic HBV infection or cirrhosis who come from a lower socio-economic class are less likely to take treatment for HBV and maintain follow-up visits with their physicians or health care centers. As a result, a higher incidence of HCC is a possibility in this group. Mahtab et al. (2014)<sup>9</sup> noted that increased diagnosis and improved treatment of HCC were associated with economic development in China. Treatment of Liver cirrhosis and HCC is given in fewer public medical facilities. There is no national health care insurance system in Bangladesh that

provides full support to therapy even in the terminal stages<sup>20</sup>. Also, early detection of HCC requires screening through serum AFP level and/or USG. But, most healthcare service in the country comes through out-of-pocket expenditure<sup>21</sup>. Combining all those factors, people from lower socio-economic classes are likely to avoid treatment for HBV infection and are more likely to catch HCC from HBV-mediated chronic hepatitis and cirrhosis. This explains the higher proportion of farmers coming from lower socio-economic status in the study.

The most common clinical feature was found to be anorexia (82%), followed in second and third by abdominal pain (80%) and weight loss (58%). It conforms to the finding reported by Johnson (2001),<sup>22</sup> in his study. He found abdominal pain and weight loss to be the most common presentation of HCC. Abdominal pain and weight loss are some of the first clues of people with chronic HBV infection or HBV-mediated cirrhosis developing HCC, but for earlier detection, AFP level and/or ultrasonography are required.

In the present study, the median serum AFP level was 207ng/ml, ranging from 0.70 to 98361 ng/ml. This is similar to the findings reported by Yuen et al. (2000),<sup>23</sup>. They found that in patients who were screened for HCC median serum AFP was 111ng/ml with a range of 1 – 261500 ng/ml. Serum AFP above 10ng/ml was found in more than 50% of cases, with 39% having an AFP level above 400ng/ml. In the majority of patients (48.6%), AFP was below 10ng/ml.

Among all, 71.4% of patients in this study were found to have HCC on FNAC, and the rest 28.6% had either benign lesions or other metastatic carcinomas. FNAC is an important tool for the initial differentiation and evaluation of SOL in the liver. HCC can be differentiated from other forms of tumors using specific cellular features. In the study by Khanna et al. (2016)<sup>24</sup>, approximately 10% benign lesions, 50% metastatic lesions, and 30% HCC were found. The difference with the present study was that they included all categories of patients having hepatic SOL, in contrast to the inclusion of chronically infected HBV patients only, which was done in the present study. However, Fernandes et al. (2016)<sup>25</sup> noted that a focal liver lesion in a patient with chronic hepatitis B and cirrhosis is not always a hepatocellular carcinoma. A three-tier cytopathologic grading of HCC in the present study found 38% poorly differentiated, 20% moderately differentiated, and 42% highly differentiated HCC. Although biopsy and histopathology are the gold standard for the detection and grading of HCC. FNAC is a useful initial cost-effective tool with fewer hazards<sup>26</sup>.

AFP level was found to correlate with differential immunocytochemistry of primary liver tumors by a study that found raised AFP in HCC and hepatoblastoma<sup>27</sup>. Another study found a positive correlation between AFP level and with size of HCC<sup>28</sup>. Along this line, this study tested the correlation between serum AFP and cytopathologic diagnosis and differentiation of HCC. Serum AFP level was found to be significantly associated with raised AFP level, as benign and metastatic lesions had significantly lower AFP rise than that of HCC. Also, a comparison of cytopathologic grading of HCC with serum AFP showed that poorly differentiated carcinoma was significantly associated with a markedly elevated (>400 ng/ml) level of alpha-fetoprotein ( $p < 0.05$ ). The study by Kondo et al. (1989)<sup>29</sup> has reported that well-differentiated small HCCs (<2 cm) seldom express detectable serum AFP. Brumm et al. (1989) also noted that different histologic grades of tumors influenced the rise of serum AFP level<sup>27</sup>.

Yuen et al. (2000)<sup>23</sup> have shown that early detection of HCC increases the chance of treatment<sup>54</sup>. AFP, if correlated with cytopathologic or histopathologic grading, can be a further addition to the early evaluation of the tumor. So, further large systematic studies should be conducted to corroborate the findings of this study.

### Conclusion

HCC is the sixth most common cancer in the world, with an incidence equal to the death rate. The 5-year survival rate of HCC is very poor, which is mainly due to late diagnosis, tumor biology, and underlying chronic liver disease and cirrhosis. Therefore, a pressing need exists for biomarkers useful for early cancer detection, accurate pretreatment staging, prediction of response to treatment, and monitoring of disease progression. The serological marker currently widely used for the diagnosis of HCC is AFP. In this study, there was a strong correlation between serum AFP level and histopathological findings of HCC in patients with chronic HBV infection.

### Limitations of the study

It was a single-center study with a short duration (6 months). The study population was relatively small. The gold standard technique (biopsy) was not considered.

### Conflict of Interest:

The authors stated that there is no conflict of interest in this study

### Funding:

This research received no external funding.

### Ethical consideration

The study was approved by the Ethical Review Committee of Dhaka Medical College & Hospital,

Dhaka, Bangladesh. Informed consent was obtained from each participant or the caregiver of the patient.

### Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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