



# Significance of Serum Biomarkers in Early Diagnosis of Hepatocellular Carcinoma in Patient with Fisher Groups

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## Abstract

**Introduction:** This study investigates the relationship between serum biomarkers and the detection of hepatocellular carcinoma (HCC) in different fisher groups in Bangladesh. The research adopts a descriptive and experimental approach to demonstrate the health risks faced by fishermen, including tobacco consumption, polluted drinking water, and insufficient sunlight exposure. **Method:** We used serum biomarkers such as vitamin D, alpha-fetoprotein (AFP), creatinine (Cr), and hemoglobin A1C (HbA1c) to evaluate their significance in distinguishing between different categories and sexes. **Result:** We determined a strong and direct correlation between insufficient vitamin D levels and an increased risk of liver cancer. The combination of AFP, vitamin D, and Cr (AFP+Vit-D+Cr) emerges as a highly predictive tool, enhancing diagnostic accuracy and providing a reliable means of identifying hepatocellular carcinoma. **Conclusion:** The identified correlation showed the significance of addressing lifestyle factors and promoting nutritional support to mitigate the risk of liver cancer

**Significance** | The research addresses a crucial gap by linking the unique lifestyle and stressors in fisher groups to hepatocellular carcinoma.

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among fisher groups. The AFP+Vit-D+Cr combination is a promising diagnostic tool for hepatocellular carcinoma, offering an improved early detection and intervention approach.

**Keywords:** Liver Cancer Detection, Fisher groups, Serum Biomarkers, Vitamin D Insufficiency, Health Risk Factors

## 1. Introduction

Hepatocellular carcinoma (HCC) is a significant global health challenge, ranking as the third leading cause of cancer mortality worldwide with a low 5-year survival rate of 7.0% (Henriques et al., 1993; Rohlfing et al., 2012). In Bangladesh, HCC is the third-leading cause of cancer incidence and death, particularly affecting the fishing community, which relies heavily on fishing for survival (Li et al., 2015). Fishermen face stressors like disputes over fishing grounds and loans, leading to coping mechanisms such as smoking, further fueled by high-interest rates from local money lenders (Kuddus et al., 2020; Kuddus et al., 2021; Sunny et al., 2021b; Islam et al., 2023). This unhealthy lifestyle persists post-fishing, contributing to the risk of HCC. Additionally,

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inadequate sanitation and lack of clean drinking water in fishing communities contribute to hepatitis and other waterborne illnesses, escalating HCC risk (Henriques et al., 1993).

Various technologies exist for HCC detection, with marker investigation proving to be a reliable, early diagnosis, and cost-effective approach (Adelani et al., 1993; Lee et al., 2013; Edoo et al., 2019). Biomarkers like alpha-fetoprotein (AFP), heat shock protein (HSP), glypicans-3 (GPC3), and others play a crucial role in HCC detection (Lai et al., 2018). Vitamin D, hemoglobin A1C (HbA1c), and creatinine also show significant correlations with HCC (Lai et al., 2018; Lee et al., 2019; Markotic et al., 2022).

This study aims to investigate the correlation between various biomarkers, including AFP, vitamin D, HbA1c, and creatinine, for the diagnosis of HCC among fishing communities. The unique lifestyle and stressors in fishing communities were not been clearly linked to HCC, and this research addresses this gap, providing insights into cost-effective approaches for patient investigations. Understanding the complex relationship between lifestyle factors and HCC is crucial for effective prevention and early detection, and the findings of this study are expected to contribute valuable insights for developing targeted prevention and intervention strategies.

## Materials and Methods

### Study Design

This study encompassed two distinct phases conducted at Ibn Sina Diagnostic and Imaging Center in Dhaka, Bangladesh, from January 2021 to December 2022. The initial stage involved a descriptive study employing a non-random sample, while the subsequent phase comprised a laboratory-based cross-sectional study.

### Descriptive Study:

The study utilized purposive sampling, yielding 1238 participants, with 1183 diagnosed with hepatocellular carcinoma (HCC) and 55 forming the control group. Inclusion criteria encompassed individuals aged 15 to 90 with confirmed HCC diagnosis through histological examination, excluding those who had initiated HCC treatment. Data collection followed the guidelines of the Immunology and Histopathology Department at Ibn Sina Diagnostic and Imaging Center for patients' information.

### Laboratory-based Cross-sectional Study:

A lab-based cross-sectional study was conducted at a renowned diagnostic center in Dhaka. HCC patients were categorized based on Alpha-Fetoprotein (AFP) values, with AFP  $\leq$ 400 ng/ml constituting moderately elevated HCC (Group A) and AFP  $>$ 400 ng/ml indicating markedly elevated HCC (Group B). Histological differentiation classified HCC patients into three groups: well-differentiated (AFP  $>$ 20 to 200 ng/ml), moderately differentiated (AFP  $>$ 200 to 400 ng/ml), and poorly differentiated (AFP  $>$ 400

ng/ml). MRI imaging data were collected to confirm the HCC formation in patients group (Figure 1). Exclusion criteria comprised patients with underlying diseases, a history of additional cancers, or concomitant conditions hindering HCC therapy.

### Empirical Data Collection:

Empirical data were collected through a household survey, employing qualitative approaches such as interviews, focus group discussions (FGD), and key informant interviews. The study involved 260 individual interviews, 95 FGDs with 10 participants each, and 15 cross-check interviews with local health complex and NGO staff. A 60-minute semi-structured questionnaire (Supplementary Material) guided the interview process.

### Ethical Considerations:

The study obtained approval from the Scientific Ethical Committee at the University of Anbar, following the guidelines of the Helsinki Declaration. The reporting standards in Our research adhere to the Consolidated Standards of Reporting Trials (CONSORT) standards.

### Blood Biochemistry analysis

AFP, vitamin D, creatinine, and HbA1c were determined with an Advia XPT (USA) and D-10 (USA) provided by Ibn Sina Pathology, Dhaka, Bangladesh. Whole blood samples were collected for HbA1c (Rohlfing et al., 2012). We used widely established Chemiluminescent Immunoassay (CLIA) techniques with an Advia XPT, USA, for measuring -fetoprotein (AFP) and vitamin D. We used HPLC techniques for HbA1c, utilizing D-10 from BioRad in the USA. And we employed enzymatic techniques with Vitros 5600, USA, for serum creatinine. For the experiment, we used a fresh sample.

The reference values of 4 different parameters were following. AFP  $<$ 20 ng/mL was considered as negative and AFP  $>$ 20 ng/mL was considered as positive (Lim et al., 2016). In the case of vitamin D  $<$ 10 ng/mL we considered as severe deficiency, vitamin D 10-24 ng/mL we considered as mild to moderate deficiency, vitamin D= 25-80 ng/mL considered as sufficient and  $>$ 80 ng/mL considered as possible toxic (Kennel et al., 2010). In case of HbA1c $<$ 5.7% considered as normal, HbA1c 5.7% to 6.4% considered as prediabetes and HbA1c $\geq$ 6.5% considered as diabetic (Diabetes overview, 2023), and Creatinine men 0.7 to 1.3 mg/dL considered as negative, creatinine women 0.5 to 1.1 mg/dL considered as negative (Creatinin Blood, 2023)

### Histology analysis

Histological samples were collected by graduate histopathology specialist, and all the samples were collected in a tube and separated by centrifuge diagnosis of AFP, Vitamin D and creatinine and stored at  $-20^{\circ}\text{C}$  for further investigation (Alpha Fetoprotein, 2023).

### Questionnaire

The research involved an extensive literature review to inform the development of a questionnaire targeting socioeconomic factors, anthropometric knowledge, and practices related to water, sanitation, nutrition, and hygiene. The questionnaire included both open-ended and closed-ended items. To enhance its effectiveness, a pre-test was conducted in at least two homes per village, leading to adjustments for coherence and simplicity based on initial data analysis. Recognizing language's significance, the English questionnaire was translated into Bengali to ensure participant and research assistant comprehension. The iterative pre-testing process not only refined language but also improved the interview's structure and content. Households in the pre-testing phase were excluded from the final surveys. This rigorous approach aimed at optimizing the questionnaire's reliability and validity.

### Statistical analysis

The statistical analysis employed Microsoft Excel and IBM SPSS software version 26.0. Results were expressed as frequency, percentage, mean±SD. Mean differences were assessed using the Students t-test, while Pearson Correlation examined relationships between continuous variables. A significance level of  $p < 0.05$  was applied. Additionally, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were analyzed for diverse groups.

### Results

The fishing community in remote areas of Bangladesh comprises 1238 individuals in approximately 160 households. These households consist of 75.8% nuclear and 24.2% joint families. A significant portion,  $34\% \pm 3\%$ ,  $41\% \pm 6\%$ , and  $13\% \pm 1\%$ , fall into extremely poor, poor, and modest poor categories, respectively. The literacy levels are low, with 50% illiterate, 35% with a signature, 10% primary, and 5% secondary education. Women in these communities were limited decision-making opportunities. About 65% were access to low-interest borrowing through local NGOs. Natural disasters, low earnings, and limited employment opportunities impact nutritional security and livelihood sustainability.

There were 55 respondents inside the control group, 582 in group A, and 601 in group B, respectively. Men (n, 665; 53.7%) comprise the majority of the total (1238) respondents. The current work has provided significant information into the diagnostic ability of serum biomarkers for detecting hepatocellular carcinoma (HCC). Our results contribute to the information on HCC assessment and evaluation by clarifying the relevance of serum vitamin D, alpha-fetoprotein (AFP), creatinine (Cr), and hemoglobin A1c (HbA1c) in distinguishing between categories and sexes. Serum vitamin D is of clinical importance in Group A ( $p = 0.045$ ) showing its potential to act as a diagnostic tool for HCC in this subgroup.

Furthermore, the highly significant ( $p = 0.001$ ) in AFP, vitamin-D, Cr, and HbA1c between Groups A and B (as shown in Table 1) show the potent identifying capacity of these biomarkers in classifying respondent with various HCC groups and difference demonstrates their usefulness in early diagnosis and prognosis monitoring.

Furthermore, the gender-specific analysis found significance of vitamin-D levels between men and women Group-B respondents ( $p = 0.045$ ) and the significance of AFP, vitamin D, Cr, and HbA1c between Group-A and Group-B (as shown in Table 2) for both sexes demonstrate the biomarkers' constant predictive potential, regardless of sex. The high sensitivity (97%), specificity (89%), positive predictive value (PPV) of 98%, and negative predictive value (NPV) of 71% of AFP as a tool for diagnostic purposes show its accuracy.

Fishers, a marginalized group, live hand-to-mouth lives in shabby riverside areas, heavily dependent on fishing. Conflicts arise due to fishing areas, loans, and local money lender pressures. Smoking is prevalent, contributing to HCC. Vitamin-D deficiency is linked to night fishing habits. Lack of hepatitis knowledge, poor lifestyle, and nutrition contribute to the risk. Poor drinking water quality, sanitation issues, and arsenic-contaminated tube wells are prevalent, correlating with kidney diseases and HCC development. The study included 1238 respondents, with men comprising 53.7%. Serum biomarkers, including vitamin D, AFP, creatinine, and HbA1c, were assessed. In Group A, serum vitamin D showed potential diagnostic significance ( $p = 0.045$ ). Significant differences in AFP, vitamin-D, Cr, and HbA1c between Groups A and B suggest diagnostic potential. Gender-specific analysis indicates constant predictive potential, with AFP exhibiting high sensitivity (97%), specificity (89%), PPV (98%), and NPV (71%). The combination of AFP+Vit-D+Cr demonstrates remarkable predictive value with high sensitivity (97%), specificity (95%), PPV (93%), and NPV (89%). No statistically significant associations were found among investigated biomarkers.

### Discussion

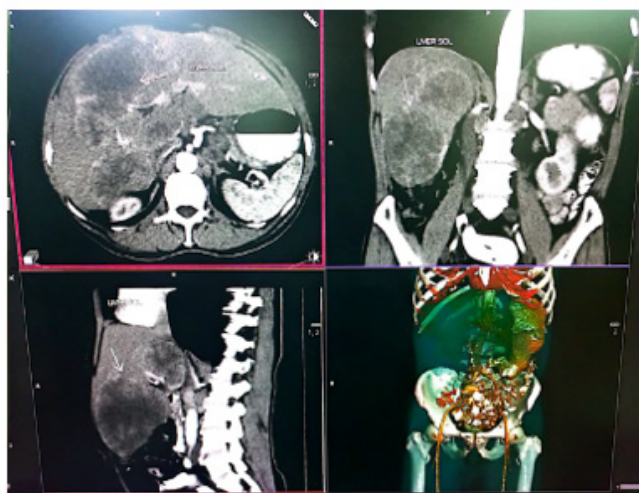
#### Hepatocellular Carcinoma (HCC) and the Fishing Community in Bangladesh

The demographic profile of the fishing community in remote areas of Bangladesh reveals a vulnerable population living below the poverty line, with limited access to education and employment opportunities (Islam et al., 2018; Sunny et al., 2020, Sunny et al., 2021a; Sazzad et al., 2023). Fishers' mode of livelihood makes them vulnerable to various fatal diseases like cancer (Chakma et al., 2022; Bari et al., 2023; Hasan et al., 2023). The nexus between Hepatocellular Carcinoma (HCC) and this fishing community becomes evident through various factors.

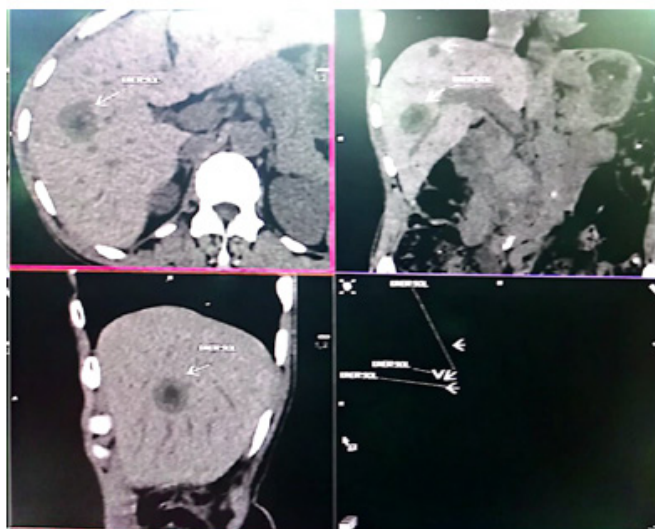
#### Tobacco Consumption and Vitamin-D Deficiency:

**Table 1: Demographic Profile of the fishers**

Variable	Status	Mean ± SD
Family type (%)	Nuclear	75.4± SD
	Joint	29.2± SD
Family size (in number)	Nuclear 4 to 7	6 ±1.3
	Joint 9 to 12	10 ± 1.5
Poverty status (%)	Extremely poor	34±3
	Poor	41±6
	Modest poor	15±1
Education (%)	Illiterate	50±SD
	Signed	35± SD
	0 to 5	10± SD
	5 to 10	5± SD
Occupation (%)	Only Fishing	95 ± 5
	Fishing and other	80 ± 3.5
Access to credit (%)	Yes	65± SD
	No	35± SD



**Figure 1.** High contrast guided MR imaging of hepatocellular carcinoma (FNAC, Liver (SOL)) of an individual patient from the study group A and group B of both sexes. The smears showed many epithelial cells presumably representing hepatocytes. These were arranged single or in sheets and cords. It showed vesicular nucleus with moderate amount of cytoplasm. Moderate degree of nuclear pleomorphism was seen. The data showed positive for malignancy and hepatocellular carcinoma.



**Table 1.** Detection of hepatocellular carcinoma (HCC) with Serum biomarkers in different sex groups. There were 55 respondents inside the control group, 582 in group A, and 601 in group B, respectively. Men (n, 665; 53.7%) comprise the majority of the total (1238) respondents. \*AFP= Alpha-fetoprotein, † Vit-D= Vitamin D, ‡ Cr=Creatinine, § HbA1c= Haemoglobin A1c, ¶ n= Number, # Mean±SD, ♠ Group-A= moderately elevated (AFP >20 to 400), ♥ Group-B= markedly elevated (AFP >400). Independent sample t-test was used as test statistics. p<0.05 has considered as a level of significance, ♦ M, ♣ W

Variables	Total n (%)			Control Group n (%) (CG)			♠Group-A n (%) (GA)			♥Group-B n (%) (GB)		
	Male, 665 (53.7)	Women, 573 (46.3)	Overall, 1238	Men, 36 (65.5)	Women, 19 (34.5)	Overall, 55	Men, 299 (51.4)	Women, 383 (48.6)	Overall, 582	Men, 330 (54.9)	Women, 271 (45.1)	Overall, 601
AFP*	9091.2 ±44920.9	6108.5 ±37237.1	7710.6 ±41551.8	3.0 ±1.3	2.8 ±1.6	2.9 ±1.4	140.7 ±128.7	155.1 ±128.6	147.7 ±128.7	18192.3 ±62511.0	12753.6 ±53417.5	15739.9 ±58600.9
p-value(M♦ vs W♣)	0.208			0.541			0.178			0.258		
Vit-D†	29 ±19.3	28.7 ±14.9	28.9 ±17.4	35.9 ±10.1	34.9 ±13.3	35.6 ±11.2	29.2 ±13.6	26.8 ±14.7	28 ±14.2	28.1 ±23.9	30.3 ±15	29.1 ±20.4
p-value(M vs W)	0.771			0.765			0.045			0.196		
Cr‡	3.1 ±4.4	3.1 ±4.3	3.1 ±4.3	0.8 ±0.2	0.7 ±0.2	0.8 ±0.2	3.0 ±4.1	2.9 ±3.8	2.9 ±4	3.5 ±4.7	3.5 ±5	3.5 ±4.8
p-value(M vs W)	0.832			0.095			0.633			0.965		
p-value(M vs W)	0.767			0.446			0.379			0.508		

**Table 2.** The positive and negative rates of HCC among respondents in various groups based on gender. The reference values of 4 different parameters were following. AFP <20 ng/mL was considered as negative and AFP >20 ng/mL was considered as positive (Lim et al., 2016).

Variables	Total, n(%)			Control Group (CG)			Group-A, n(%)			Group-B, n(%)		
	Men	Women	Overall	Men	Women	Overall	Men	Women	Overall	Men	Women	Overall
AFP												
Positive	517 (77.7)	444 (70.5)	961 (70.6)				222 (74.2)	228 (80.6)	450 (77.3)	295 (89.4)	216 (79.7)	511 (85)
Negative	148 (22.3)	129 (22.5)	277 (22.4)	3.0±1.3	2.8±1.6	2.9±1.4	77 (25.8)	55 (19.4)	132 (22.7)	35 (10.6)	55 (20.3)	90 (15)
p-value (M vs W)	0.968			0.541			0.85			0.001		
Vit-D												
Mild to moderate deficiency	208 (31.3)	188 (32.8)	396 (32)				90 (30.1%)	116 (41%)	206 (35.4)	118 (35.8)	72 (26.6)	190 (31.6)
Severe deficiency	46 (6.9)	41 (7.2)	87 (7)				16 (5.4)	20 (7.1)	36 (6.2)	30 (9.1)	21 (7.7)	51 (8.5)
Sufficient	410(61.7)	344(60)	754(60.9)	35.9±10.1	34.9±13.3	35.6±11.2	193(64.5%)	147(51.9%)	340(58.4%)	181(54.8%)	178(65.7%)	359(59.7)
p-value (M vs W)	0.742			0.765			0.009			0.045		
Cr												
Positive	279 (42)	226 (39.4)	505 (40.8)				124 (41.5)	123 (43.5)	247 (42.4)	155 (47)	103 (38)	258 (42.9)
Negative	386 (58)	247 (60.6)	733 (59.2)	0.80±0.2	0.70±0.2	0.80±0.2	175 (58.5)	160 (56.5)	335 (57.6)	175 (53)	168 (62)	343 (57.1)
p-value (M vs W)	0.001			0.095			0.688			0.054		
HbA1c												
Normal	319 (48)	259 (45.3)	578 (46.7)	4.9±0.5	5.0±0.5	4.90±0.5	160 (53.5)	135 (47.7)	295 (50.7)	124 (37.6)	107 (39.6)	231 (38.5)
Prediabetic	84 (12.6)	82 (14.3)	166 (13.4)				31 (10.4)	34 (12)	65 (11.2)	52 (15.8)	46 (17)	98 (16.3)
Diabetic	262 (39.4)	231 (40.4)	493 (39.9)				108 (36.1)	114 (40.0)	222 (38.1)	154 (46.7)	117(43.3%)	271 (45.2)
p-value (M vs W)	0.544			0.446			0.371			0.713		

The study identifies a prevalent habit of smoking among fishermen, particularly during fishing trips and gatherings in market areas, which contributes to a significant number of cases of HCC. Furthermore, the nocturnal fishing habits of hilsa fishermen lead to limited sunlight exposure, causing vitamin-D deficiency, strongly associated with HCC (Lange et al., 2013; Yi et al., 2010; Zhang et al., 2010; Louka et al., 2017; Faruk et al., 2023).

Tobacco use poses a significant global health concern due to its established links to health issues like cardiovascular diseases, respiratory disorders, and cancers. Recent research has highlighted a previously overlooked connection between tobacco consumption and vitamin D deficiency. Our research explores this intricate relationship, examining how tobacco smoke, containing harmful compounds like polycyclic aromatic hydrocarbons and nicotine, can interfere with the absorption and synthesis of vitamin D. Smoking-induced disruptions in metabolic pathways may further impact vitamin D metabolism, contributing to lower circulating levels in smokers. The article also discusses the commonality of chronic inflammation in both tobacco use and vitamin D deficiency, creating a potential vicious cycle. Given that vitamin D deficiency is associated with various chronic diseases, the compounding effect in smokers raises concerns about long-term health outcomes. Recognizing this, public health strategies should address both tobacco use and vitamin D deficiency, integrating interventions like dietary supplementation and increased sun exposure into smoking cessation programs. Routine screening and supplementation for vitamin D deficiencies in smokers should also be considered by healthcare providers. Understanding the interplay between tobacco consumption and vitamin D metabolism is crucial for comprehensive public health strategies and improved overall health outcomes.

#### **Lack of Hepatitis Knowledge and Careless Lifestyles:**

The fishing community's inadequate knowledge about hepatitis, coupled with careless lifestyles and poor nutritional support, increases the risk of HCC. Additionally, the lack of pure drinking water and poor sanitation, along with the consumption of arsenic-affected tube well water, contribute to waterborne diseases and hepatitis, further exacerbating the risk of HCC (Kuddus et al., 2022; Tufael et al., 2023; Banal et al., 2017; Weng et al., 2011).

Hepatitis, a group of viral infections impacting the liver, is a major global health concern. Despite medical advancements, a significant gap persists in public awareness, often worsened by negligent lifestyles. Our research explores the repercussions of limited hepatitis awareness and its connection to lifestyles that can heighten the risk of transmission, progression, and complications associated with hepatitis. With various types like A, B, C, D, and E, studies reveal a widespread lack of knowledge about these infections, leading to ongoing virus spread and delayed medical

care. Stigma surrounding hepatitis, rooted in misconceptions, hampers open discussions and can deter affected individuals from seeking timely medical help. Negligent lifestyles, marked by unsafe practices such as sharing needles and engaging in unprotected sex, significantly increase the risk of transmission, emphasizing the need for targeted education and preventive measures. Vaccination is crucial for hepatitis A and B prevention, but a lack of awareness and a casual attitude toward preventive healthcare result in inadequate vaccine uptake. Hepatitis C, often symptomless for years, can progress unchecked without routine check-ups, underlining the importance of early detection. Public health initiatives should focus on comprehensive education campaigns, destigmatization efforts, and promoting responsible lifestyles to effectively address the global challenge of hepatitis. Empowering individuals with accurate information and fostering a proactive healthcare approach is key to reducing the burden of hepatitis and improving overall public health outcomes.

#### **Cirrhosis and Kidney Diseases:**

The study underscores the close relationship between cirrhosis, a significant risk factor for HCC, and kidney diseases within the fishing community. The complex interaction between liver and kidney functions, exacerbated by cirrhosis, increases the risk of kidney disease, creating a multifaceted health challenge for this population (Lin et al., 2010; Huo et al., 2004; Kumar et al., 2021).

Cirrhosis and kidney diseases are two distinct health challenges that often occur together, creating a complex clinical situation. Cirrhosis, marked by liver scarring and dysfunction, and kidney diseases, affecting kidney filtration and excretion, frequently coexist, intensifying their impact on overall health. Our research explores the relationship between cirrhosis and kidney diseases, examining the underlying mechanisms, common causes, and clinical implications of this dual pathology. Cirrhosis disrupts liver function, leading to complications such as portal hypertension, ascites, and impaired protein synthesis. Kidney diseases involve conditions like chronic kidney disease (CKD) and acute kidney injury (AKI). Hepatorenal syndrome, a serious complication in cirrhosis, involves a rapid decline in kidney function due to changes in blood flow dynamics. Cirrhosis-related complications, like ascites, can worsen kidney function. Excessive alcohol consumption, viral hepatitis, hypertension, and diabetes are common causes of both conditions. Early detection is crucial, with regular kidney monitoring aiding timely intervention. Addressing underlying causes, such as alcohol cessation and managing hypertension and diabetes, is fundamental. In severe cases, liver transplantation or renal replacement therapies may be considered. Managing the coexistence of cirrhosis and kidney diseases requires a multidisciplinary approach, emphasizing understanding, addressing causes, and implementing timely interventions for improved patient outcomes and quality of life. Ongoing research

aims to enhance diagnostic and therapeutic strategies for better management.

#### **Serum Biomarkers for HCC Detection:**

The analysis of serum biomarkers for HCC detection among the fishing community reinforces the link between their lifestyle and the development of HCC. The significant association between vitamin-D levels, alpha-fetoprotein (AFP), creatinine (Cr), and hemoglobin A1c (HbA1c) with HCC categories and sexes underscores the potential of these biomarkers for early diagnosis and prognosis monitoring. The accuracy of AFP as a diagnostic tool, along with the joint AFP+Vit-D+Cr combination, further highlights the relevance of these biomarkers in identifying HCC cases within this community (Fabrizi et al., 2021).

Hepatocellular carcinoma (HCC), the most prevalent liver cancer, poses a global health challenge due to its frequent late-stage diagnosis. Early detection is crucial for better outcomes, prompting increased research into reliable serum biomarkers for HCC. Our research delves into the importance of serum biomarkers in detecting HCC, emphasizing their potential impact on early diagnosis, prognosis, and therapeutic interventions. HCC is often asymptomatic in its early stages, leading to delayed diagnosis and presenting at less treatable stages. Current diagnostic methods, like imaging and alpha-fetoprotein (AFP) levels, were limitations, prompting the search for more sensitive markers. Des-Gamma-Carboxy Prothrombin (DCP), Glypican-3 (GPC3), Lens Culinaris Agglutinin-Reactive Alpha-Fetoprotein (AFP-L3), and Osteopontin (OPN) show promise as complementary markers, enhancing diagnostic accuracy when combined with AFP. Identifying reliable serum biomarkers facilitates early intervention, offering a broader range of therapeutic options and potentially improving patient outcomes. Integration into surveillance programs for high-risk populations and combining with advanced imaging can enhance accuracy, marking an exciting frontier in liver cancer research. The quest for novel biomarkers holds the potential to revolutionize early diagnosis, prognosis, and personalized treatment strategies for HCC.

The fishing community's lifestyle, including smoking habits, limited sunlight exposure, inadequate knowledge about hepatitis, and environmental factors, significantly contributes to the high incidence of HCC. The study's findings emphasize the need for targeted interventions and awareness programs to address these risk factors and improve the overall health and well-being of the fishing community in Bangladesh.

#### **Conclusion**

In conclusion, this study sheds light on the critical issue of late HCC diagnosis and emphasizes the pivotal role of serum biomarkers in early detection. The identified biomarkers,

especially when analyzed with consideration for gender-specific variations, offer promising avenues for improving diagnostic accuracy and ultimately addressing the challenge of late-stage HCC. Further efforts are needed to translate these findings into practical clinical applications to enhance the overall management of HCC patients.

#### **Author contribution**

M.T., A.K., and V.J.U. conceptualized, conducted lab and field works, analysed data, wrote the original draft, reviewed, and edited; A.D., M.R.I., A.S. and M.E.A. conducted research design, validated methodology, analysed, visualized the data, reviewed, and edited; J.A., K.F.B., M.T.S. and P.C.B. validated the methodology, analysed data, investigated, visualized, reviewed, and proof-read; M.S.S.K. and A.R.S. conceptualization, conducted research design, validated methodology, conducted analysis, investigated, visualized the data, reviewed, obtained grant, supervised and edited the paper. All authors read and approved the paper for publication.

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#### **Competing financial interests**

The authors have no conflict of interest.

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