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FREQUENCY OF HEPATOMA IN PATIENTS WITH CIRRHOSIS ON THE BASIS OF ALPHA FETOPROTEIN AND ULTRASOUND ABDOMEN

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Abstract

BACKGROUND: *The most common form of primary tumour in the liver is hepatoma, a severe high-grade tumour with fast infiltrative development. It mainly affects those with long-term liver conditions, especially those who have cirrhosis brought on by an infection with hepatitis B or C.*

OBJECTIVE: *To determine the frequency of hepatoma in patients with liver cirrhosis based on alpha-fetoprotein and ultrasound abdomen.*

Study design: *Cross sectional descriptive study*

Duration of study: *20th-Nov-2024 to 19th-Jan-2025*

Setting: *Department of Gastroenterology and Medicine, Liaquat University Hospital, Hyderabad*

Sample Size: *Total 280 patients with liver cirrhosis*

Sample technique: *Non probability consecutive sampling.*

PATIENTS AND METHODS: *Patients with cirrhosis of the liver, aged 18 to 60, of either gender, were gathered and tested for hepatoma using alpha-fetoprotein and ultrasonography abdomen. Data was gathered using a pre-designed proforma, with frequency (%) and mean ± SD computed for both qualitative and quantitative factors.*

RESULTS: *The mean ± SD values for age (years), duration of liver cirrhosis (months), BMI (kg/m²), and alpha-fetoprotein levels were 52.95 ± 8.54, 18.65 ± 7.92, 30.21 ± 3.63, and 1185.72 ± 98.85, respectively. The study population comprised 161 males (57.5%) and 119 females (42.5%). Additionally, 142 participants (50.7%) were from rural areas, while 138 (49.3%) were from urban areas. The prevalence of obesity, smoking, diabetes mellitus, hypertension, and a family history of malignancy was 49.3%, 48.2%, 54.6%, 55.7%, and 46.1%, respectively. The distribution of etiological factors included hepatitis B virus (26.7%), hepatitis C virus (53.5%), HBV + HCV co-infection (10.7%), and non-viral causes (8.9%). Hepatoma was diagnosed in 178 patients (63.5%) with statistical significance based on alpha-fetoprotein levels ($p<0.01$) and radiological assessment ($p=0.04$).*

CONCLUSION: *Hepatoma has been seen in cirrhotic individuals. Thus, patients with chronic liver illness should be regularly followed for liver cancer.*

INTRODUCTION: One of the leading causes of death for people with chronic liver disease is cirrhosis.[1] Hepatocellular carcinoma, hepatic encephalopathy, ascites, and hepatorenal syndrome are among the issues linked to cirrhosis.[2-5]Hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol, and nonalcoholic steatohepatitis (NASH) are the main causes of cirrhosis.[6-8] But throughout the last ten years, the worldwide epidemiology of cirrhosis has evolved.[7]

The most frequent primary liver cancer and a major cause of mortality for cirrhosis patients is hepatoma/hepatocellular carcinoma (HCC).[9]Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are linked to over 80% of HCC cases. Cirrhosis is caused by HCB and HCV and affects 80-90% of people with HCC.[10] With an average lifespan of less than a year for individuals with advanced illness; HCC has a typically bad prognosis. However, with curative therapy, people with early-stage HCC might have a 70% 5-year survival rate.[11] In order to standardise the management of HCC, a number of national and international recommendations have been developed.[11-13]

Although guidelines vary somewhat in their recommendations, patients with persistent HBV and HCV infections and those with cirrhosis of any aetiology are considered the target group for monitoring. Ultrasonography (US) at 6-month intervals is the main surveillance test, whether or not alpha-fetoprotein (AFP) is present, according to the majority of recommendations.[12, 13, 9]For the US identification of early HCC, a number of studies produced inconsistent findings. Furthermore, the AFP's monitoring function remains contentious, with conflicting reports of its effectiveness.[14-16]

According to a research by Abduljabbar et al 4.77% of patients with cirrhosis had hepatomas on ultrasonography (16/335).[17] However, 16.71% (56 / 335) of all cirrhotic patients had abnormal AFP (>20 ng/ml). According to a research done at the Hayatabad Medical Complex in Peshawar, 10.5% of patients with cirrhosis had hepatomas based on AFP and ultrasonography.[18]

Our research used alpha-fetoprotein and abdominal ultrasonography to estimate the prevalence of hepatoma in cirrhosis patients. AFP and abdominal ultrasound are the two most used methods for hepatoma screening. Because hepatoma is a serious health issue, has an early therapeutic stage, and follows a recognized clinical course, screening for it satisfies several screening program standards. The idea behind screening was to find people who were at a high risk of developing HCC, such those who had cirrhosis. However, those with undetected liver cirrhosis often develop HCC.[14] However; the majority of patients will pass away if there is no reliable way to detect those who have an early-stage HCC. According to observational studies, people who underwent screening developed disease at an earlier stage than those who did not. Our study's conclusions will assist gastroenterologists in creating appropriate screening plans to lower related morbidity and death.

PATIENT AND METHODS: From 20th-Nov-2024 to 19th-Jan-2025, the cross-sectional research was conducted in the Gastroenterology and Medicine Department at LUMHS, Jamshoro. The research used a non-probability sequential sample approach to recruit and enroll the patients who were between the ages of 18 and 60, of either gender, and who had liver cirrhosis for at least six months.

LIVER CIRRHOSIS:

Labeled as positive if there is the presence of 3 or more features on abdominal ultrasound:

- On ultrasonography, the left and right lobes of the liver had smaller longitudinal diameters (left lobe <90mm and right lobe <70mm).
- An ultrasound revealed nodules or irregularities in the liver's surface.
- Reduced ultrasonography echogenicity when compared to the right kidney.
- More than 100 millilitres of ascitic fluid are present.
- On ultrasonography, the portal vein's anterior-posterior diameter is more than 13 mm.

HEPATOMA ON ULTRASOUND ABDOMEN:

The presence of at least one of the following features was labeled as hepatoma.

- Compared to a normal liver, it is hypoechoic;
- Fibrosis, fatty changes, necrosis, and calcification

- With localized fatty sparing, a distant halo of hypoechogenicity might be seen.

HEPATOMA ON ALPHA FETOPROTEIN: labeled if AFP is > 400 ng/ml.
The presence of hepatoma was considered positive if either ultrasound findings or AFP levels meet the criteria. The diagnosis does not require both conditions to be fulfilled; a positive result in either test was sufficient for diagnosis.

BODY MASS INDEX: Body mass index (BMI) was calculated using the formula: weight (kg) / height (m^2). Weight was recorded using a digital weighing scale while the individuals wore light clothing and no shoes. Height was measured with a wall-mounted scale; ensuring participants were barefoot and not wearing a cap.

DIABETES MELLITUS: Patients with a documented history of diabetes mellitus (DM) for a minimum of one year who have been receiving oral hypoglycemic agents or insulin for at least the past six months.

HYPERTENSION: Patients who had a documented history of hypertension (HTN) and have been on anti-hypertensive medication for at least six months.
The sample size was determined using the WHO sample size calculator. Based on an ultrasound-detected hepatoma/HCC prevalence of 4.77% in liver cirrhosis, [17] with a 2.5% margin of error and a 95% confidence interval (CI), the required sample size for this study was 280 patients with chronic liver disease (cirrhosis). Individuals on drugs known to impact the function of the liver or alpha-fetoprotein amounts (e.g., steroid medication, antiviral medicines), individuals who have major renal or cardiovascular diseases, pregnant or lactating women, patients with an established record of malignancy, radiation or chemotherapy, active infections, or ongoing inflammatory diseases were excluded.
After receiving clearance from the institute's ethical review committee and the College of Physicians & Surgeons Pakistan (CPSP), data collecting got underway. The research included patients who met the inclusion criteria and presented with gastrointestinal OPD. The patient or carer was given all the information about the trial, including its risks and benefits, prior to enrolment. Written informed permission was obtained after an explanation of the study. At the time of admission, the patient's demographic information and baseline clinical history were obtained after they agreed to participate in the research.
All patients had an abdominal ultrasound performed after their medical histories were taken in order to check for hepatoma. Following the ultrasonography, a phlebotomist used an aseptic procedure to draw a 5 cc blood sample for the measurement of alpha-fetoprotein. On AFP and abdominal ultrasonography, hepatoma was identified as such. In a pre-planned performance evaluation, all qualitative and quantitative characteristics, including gender, age, place of residency, BMI, smoking, diabetes, hypertension, Child-Pugh class, time spent with cirrhosis, family history of cancer, hepatoma on ultrasonography, and AFP, were recorded.
SPSS version 23 was used to analyse the data. The mean ± SD was used to report quantitative factors such age, BMI, AFP, and the length of cirrhosis. Qualitative factors including gender, the place of residency, diabetes mellitus, smoking habits, high blood pressure, child-pugh class, family history of cancer, and hepatoma on AFP and ultrasound were reported in terms of frequency and percentage. Stratification was used to adjust for effect modifiers, including age, gender, location of residence, BMI, diabetes, cigarette smoking status, hypertension, child-pugh class, length of cirrhosis, and family history of cancer. Following stratification, the proper Chi-square/Fischer exact analysis was used, with a p-value of less than 0.05 being considered significant.

RESULTS: Over a research period, a total of 280 patients with liver cirrhosis, aged between 18 and 60 years of either gender, were admitted to the Department of Gastroenterology and Medicine at Liaquat University Hospital Hyderabad. The demographic and clinical data of the study population are shown in Table 1, while the mean ± SD for age (years), the length of liver cirrhosis, the body mass index (kg/m^2), and alpha-fetoprotein (ng/ml) are provided in Table 2. The stratification of hepatoma by gender, alpha-fetoprotein levels, and imaging (ultrasound) with statistical significance is

detailed in Tables 3 and 4, respectively. The observed symptoms were abdominal distention 200 (71.4%), pain 215 (76.7%), anorexia 230 (82.1%), loss of weight 190 (67.8%), jaundice 160 (57.1%), changed mental state 88 (31.4%), and upper gastrointestinal haemorrhage 30 (10.7%).

TABLE 1: THE DEMOGRAPHICAL AND CLINICAL PARAMETERS OF STUDY POPULATION

PARAMETER	FREQUENCY (n = 280)	PERCENTAGE (%)
AGE (yrs)		
18-29	56	20.0
30-39	76	27.1
40-49	75	26.8
50-60	73	26.1
GENDER		
Male	161	57.5
Female	119	42.5
RESIDENCE		
Urban	138	49.3
Rural	142	50.7
DURATION OF LIVER CIRRHOSIS (months)		
6-12	72	25.7
12-24	119	42.5
>24	89	31.8
CHILD-PUGH CLASS		
A	92	32.9
B	82	29.3
C	106	37.9
OBESITY		
Yes	138	49.3
No	142	50.7
SMOKING		
Yes	135	48.2
No	145	51.8
DIABETES MELLITUS		
Yes	153	54.6
No	127	45.4
FAMILY HISTORY OF MALIGNANCY		

Yes	129	46.1
No	151	53.9
HYPERTENSION		
Yes	156	55.7
No	124	44.3
ETIOLOGY		
Hepatitis B virus	75	26.7
Hepatitis C virus	150	53.5
HBV + HCV	30	10.7
Non-viral	25	8.9
HEPATOMA		
Yes	178	63.5
No	102	36.4

TABLE 2: THE MEAN ±SD FOR QUANTITATIVE VARIABLES OF THE STUDY POPULATION

Quantitative variables	**Mean ±SD**
Age (yrs)	52.95 ± 8.54
Duration of liver cirrhosis (months)	18.65 ± 7.92
Body mass index - BMI (kg/m^2)	30.21 ± 3.63
Alpha fetoprotein (ng/ml)	1185.72 ± 98.85
T. Bilirubin (mg/dl)	7.85 ± 3.66
AST(U/L)	64.41 ± 18.63
ALT(U/L)	86.74 ± 12.52
Albumin(gm/dl)	1.99 ± 0.72
INR	1.92 ± 0.35

TABLE 3: THE GENDER DISTRIBUTION FOR HEPATOMA BY ALPHA FETOPROTEIN

		HEPATOMA		
		GENDER		
		Male	Female	Total
ALPHA FETOPROTEIN	Yes	57	48	105
		51.4%	71.6%	59.0%
	No	54	19	73
		48.6%	28.4%	41.0%
Total		111	67	178
		100.0%	100.0%	100.0%

*P-value: <0.01; statistically significant

TABLE 4: THE GENDER DISTRIBUTION FOR HEPATOMA BY IMAGING (ULTRASOUND)

		HEPATOMA		
		GENDER		
		Male	Female	Total
IMAGING (ultrasound)	Yes	68	51	119
		61.3%	76.1%	66.9%
	No	43	16	59
		38.7%	23.9%	33.1%
Total		111	67	178
		100.0%	100.0%	100.0%

*P-value: 0.04; statistically significant

DISCUSSION: The majority of hepatoma cases are discovered at an advanced stage, when effective local ablative therapy or surgical intervention are no longer feasible, making it a serious public health problem.[19] As a result; treatment for these patients is primarily symptomatic. The majority of HCC cases are attributed to chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV), as well as alcohol consumption. While the pathogenesis of HCC varies, most cases develop due to cirrhosis, influenced by the underlying etiological factors.[20]

In this study, 161 (57.5%) of patients with liver cirrhosis were male, and 119 (42.5%) were female, with a mean age ± SD of 52.95 ± 8.54 years. These findings align with previous studies by Zamzam ML,[21] Pande SB et al.,[22] and Kumar R et al.,[23] which suggest that males are more susceptible to HBV or HCV infections, consume alcohol more frequently, smoke cigarettes, and have higher iron levels in their bodies. Additionally, androgenic hormones and genetic predisposition may contribute to the increased risk in males, while female sex hormones may offer a protective effect.[24]

In Europe and the United States, the average age at which HCC is diagnosed is approximately 60 years. In contrast, patients in Asia and Africa typically present with the disease between the ages of 20 and 50. Studies conducted by Das JC et al.,[25] Chowdhury B et al.,[26] and Khokhar N et al.[27] reported mean ages of 49, 48.5, and 58.4 years, respectively.

Based on the Child-Pugh classification, 92 patients (32.9%) were categorized as class A, 82 (29.3%) as class B, and 106 (37.9%) as class C. These findings are consistent with a previous study by Zhao S et al.,[28] which highlighted advanced liver cirrhosis as a major risk factor for HCC development, leading to carcinogenic changes in hepatocytes.

Among the patients, 75 (26.7%) had hepatitis B virus (HBV), 150 (53.5%) had hepatitis C virus (HCV), 30 (10.7%) were co-infected with both HBV and HCV, and 25 (8.9%) had non-viral causes. These findings align with those of Anwar WA et al.,[29] who reported that HCV was the predominant cause of most hepatocellular carcinoma (HCC) cases in Egypt, particularly before widespread access to HCV treatment. Likewise, Zamzam ML found that 6.5% of HCC patients tested positive for HBV, while 91.3% tested positive for HCV. In contrast, Ferenci P et al. found no HCC patients in their study tested positive for HBV. Their research identified hepatitis C cirrhosis as the leading risk factor for HCC, with an annual incidence rate of 2–8%.[30]

Twenty-five individuals (8.9%) with cirrhosis from non-viral sources were included in this research. The research population also included those with diabetes, hypertension, and obesity who had clear hepatic vein Doppler results and tested negative for autoimmune hepatitis, hemochromatosis, and Wilson disease. Nonalcoholic steatohepatitis (NASH) was most likely the cause of the cirrhosis in these cases. It is predicted that people with cirrhosis associated to NASH have a yearly risk of hepatocellular carcinoma (HCC) ranging from 2.4% to 12.8%.[31]

Because they cause chronic inflammation, changes in serum cytokines and modifications to the gut microbiota and bile composition, metabolic syndrome and insulin resistance are important risk factors for the development of HCC in NASH.[32] Sanyal A et al., on the other hand, discovered that NASH was the cause of 59% of HCC cases, with an average incidence rate of 0.3% throughout a six-year evaluation period.[33]

Our patients' clinical appearance of HCC was in line with earlier research. Constitutional signs including fever, weight loss, and anorexia were common complaints. Many patients also complained of discomfort and pain in their abdomens, which might worsen in situations of tumour haemorrhage.[34]These results demonstrate how important HCC development is to the abrupt clinical decline of compensated cirrhosis patients.[35]

A decline in albumin levels was linked to a rise in bilirubin levels, likely due to liver parenchymal damage caused by tumor progression. Similarly, Carr BI et al. reported decreased albumin levels accompanied by elevated AFP levels, particularly in tumors exceeding 5 cm in diameter.[36] Conversely, Mobarak L et al. observed increased albumin levels in HCC patients, suggesting that the heightened synthetic activity of malignant hepatocytes might temporarily offset liver function impairments associated with cirrhosis.[37]

One hundred seventy eight individuals (63.5%) of the cirrhotic individuals in our research had hepatoma. Nonalcoholic steatohepatitis (NASH) and cirrhosis from chronic infection with the hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the main risk factors for the development of HCC. Kanwal F et al. reported that the prevalence of HCC in the United States increased from 9% to 18.5% over a decade.[38] Similarly, Mittal S et al. identified an HCC frequency as high as 65% through database monitoring,[39] while Tariq et al. observed a 5.7% prevalence of HCC in Karachi.[40]

Current research indicates a higher prevalence of HCC in men than in women. El-Serag HB et al. found that HCC was more frequent in dark-skinned men compared to light-skinned women ($p>0.05$).[41]Other studies have similarly reported a higher prevalence of HCC in males than in females.[42]

The present study revealed a significantly higher incidence of hepatoma in individuals over 40 years of age. Tan JT et al. reported that overall survival in HCC patients was notably worse ($p<0.05$) in older individuals (>70 years) compared to younger patients.[43] Similarly, Butt AS et al. found that the incidence of hepatoma was significantly higher in patients aged 50–60 years than in younger individuals ($p=0.00$).[44]

Our research also indicated that a greater proportion of hepatoma patients tested positive for HCV compared to HBV. Yoshizawa H observed that 80% of HCC patients were HCV-positive, highlighting HCV as a key risk factor for hepatoma development.[45] Additionally, Shi J et al. found that individuals with HBV are 15 to 20 times more likely to develop hepatoma than those without infection.[46] In contrast, Donato F et al. reported that HCV-positive individuals are 17 times more likely to develop hepatoma than those infected with HBV.[47]

In this study, among the 25 patients with non-viral etiologies, a history of alcohol consumption was noted in 10 (40%) individuals. Chronic alcohol intake exceeding 80g per day for more than 10 years increases the risk of hepatocellular carcinoma (HCC) fivefold. Furthermore, persistent alcohol use in individuals with HBV or HCV infection doubles the risk of HCC compared to having either infection alone. These findings are consistent with the research conducted by Cho EJ et al.[48]

Alpha-fetoprotein (AFP) has been frequently associated with an increased risk of HCC in cirrhotic patients.[49]Our study identified AFP as a predictor of HCC development in individuals with cirrhosis from various liver disease etiologies. This role differs from its conventional use in monitoring early HCC detection and assessing prognosis following disease onset. Therefore, AFP may be considered a biomarker of the underlying biological state, potentially contributing to HCC risk through yet unidentified mechanisms.[50]

Therefore, individuals with established cirrhosis should undergo regular surveillance for early hepatocellular carcinoma (HCC) detection using alpha-fetoprotein (AFP) testing and imaging techniques to enable timely and effective treatment.

This study has several limitations. It is a cross-sectional study confined to a local population, with a

small sample size and no follow-up, making it impossible to assess long-term outcomes. Additionally, the prevalence of hepatoma may be overestimated, as the study was conducted at a single center that serves as a primary referral facility for an interior region, limiting its generalizability. These factors should be taken into account in future research.

CONCLUSION: In our local population, the incidence of hepatoma is as high as 178 (63.5%) based on alpha-fetoprotein testing and radiographic methods. HBV and HCV remain the primary etiological factors for chronic liver disease (cirrhosis), which progresses to hepatoma. Therefore, timely diagnosis through dynamic imaging is essential for the early detection and accurate characterization of hepatoma.

AUTHOR'S CONTRIBUTION:

Collection and acquisition of data & grammatical corrections	Dr. Mehboob Murtaza
Concept & design of study & proof read	Dr. Imtiaz Hussain
Drafting the article and finalizing the manuscript	Dr. Anand Kumar
Revising critically and make it suitable for final format	Dr. Muhammad Kaleem
Acquisition of data and grammatical review	Dr. Dileep Kumar
Analysis of data and drafting	Dr. Syed zulfiquar Ali Shah
Final Approval of version	By All Authors

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