

## AWARENESS IN CIRRHOTIC PATIENTS REGARDING SURVEILLANCE OF HEPATOCELLULAR CARCINOMA

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### ABSTRACT

**Objective:** To assess the awareness and correlate factors among cirrhotic patients for the surveillance of Hepatocellular Carcinoma (HCC).

**Study Design:** Prospective correlational study.

**Place and Duration of Study:** Gastroenterology Outpatient Department, Pak Emirates Military Hospital, from Nov 2017 to Jun 2018.

**Methodology:** An aggregate of 300 patients within the age range of 16-80 years, diagnosed with liver cirrhosis were included in the study through non-probability consecutive sampling. The data was collected by the self-administered questionnaire including age, gender, educational level, socio-economic status, cause of cirrhosis, Child Pugh Class, awareness regarding method and interval of surveillance and source of information. Effectiveness of the procedures was noted on a pre-designed Performa. Data was analyzed by using SPSS version 19.

**Results:** Of total participants, 194 (64.7%) were males while 106 (35.3%) were females with mean age of  $38 \pm 2.5$  years with no statistical difference observed in age, hepatocellular carcinoma related cirrhosis account for 192 (64%). Of total, 184 (61.3%) belonged to middle class and high schooling as highest educational level in 132(44%). Two hundred and ten (70%) participants were unaware about hepatocellular carcinoma surveillance and were not informed by doctors while 90 (30%) had some idea.

**Conclusion:** Health care professionals and community leaders ought to advise patients about the advantages of hepatocellular carcinoma surveillance through designed educational projects to enhance adherence to surveillance program, early diagnosis and treatment.

**Keywords:** Hepatocellular carcinoma, Hepatitis C virus, Surveillance.

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### INTRODUCTION

Liver cancer is the second driving reason for growing demise around the world; it is additionally the fifth most common malignancy in men and the ninth in women. Asia and Africa account for 85% of global liver malignancy load<sup>1</sup>. In Pakistan, the estimated age standardized rate for hepatocellular carcinoma (HCC) in men is 7.6 per 100,000 persons per year and 2.8 per 100,000 persons per year in women<sup>1,2</sup>. In 2012, an estimated 782000 new cases of liver cancer occurred in the world, with reported deaths of 745000<sup>3</sup>. Among the liver malignancies, HCC represents 70-85% of cases, and 70-90% of these are cirrhosis related<sup>4</sup>. HCC is an immense threat worldwide and its occurrence is relied upon to increase not only in western world but also eastern countries because of unending and evolving hepatitis C infection (HCV) infection and other etiological factors<sup>5</sup>.

Despite difference in etiology of HCC around the globe, it is currently the main cause of death of patients with compensated liver cirrhosis<sup>6</sup>. Vital, the occurrence

and death rates of HCC are fundamentally the same throughout the world, accordingly underscoring the high lethality rate of this tumor for the time being, particularly when it is analyzed at late stages blocking any powerful curative treatment<sup>7</sup>, in spite of the fact that a great mortality drift has late been observed in Europe<sup>8</sup>.

Over 90% of HCC occur in a cirrhotic liver, and the fundamental driver is chronic HCV or HBV infections, alcohol consumption and non-alcoholic fatty liver disease<sup>9</sup>. In Pakistan hepatitis C accounts for 60-70% HCC<sup>1</sup>. A surveillance test is required which has high effectivity, affordability, acceptability and a sufficient specificity.

There is an inclusive understanding that US is the imaging test to be utilized for surveillance of HCC along serum alpha fetoprotein levels recommended by APASL. A meta-analysis suggests the effectivity of US, as a surveillance test for HCC, at 94% for asymptomatic tumors and 63% for early HCC, with a specificity of >90%<sup>10</sup>.

Lately European Association for the study of the liver (EASL) and American Association for the study of Liver Diseases (AASLD) have suggested the Barcelona

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Clinic of Liver Cancer (BCLC) organizing framework for the administration of treatment for HCC. Active surveillance of high risk is needed with alpha-fetoproteins and ultrasound abdomen 6monthly. A restorative calculation was created dependent on the BCLC arrangement with four phases (0/A, B, C, and D) with curative treatment (resection, liver transplantation (LT), and ablative therapies) is utilized for patients with early stage disease (BCLC 0/A). Curative therapies by and large improve 3 year survival rate to 80%<sup>10</sup>. For intermediate stage disease (BCLC B) with transarterial chemoembolization, 3 year survival rate is 30%. Sorafenib and regorafenib are the main cutting edge remedial choice for patients with advanced HCC (BCLC-C)<sup>11</sup>.

Surveillance of patients with cirrhosis incorporates tests to identify early stage malignancy and help in utilizing curative treatment. Surveillance adequately assess early stage HCC in randomized controlled trails (RCTs), controlled, and uncontrolled examinations. The advantage of ultrasound (US) in the localization of early-stage HCC has additionally been affirmed in RCTs<sup>12</sup>. Surveillance is used when there is solid proof that it enhances survival. So there is increasing need to utilize easily accessible, acceptable and cost effective measures for surveillance for HCC in patient with cirrhosis. This will help in early diagnosis, better management and improved survival.

## METHODOLOGY

A total of 300 patients who reported in the gastroenterology outpatient department of Pak Emirates Military Hospital Rawalpindi, from November 2017 to June 2018 participated in this cross-sectional study. Patients in the age group of 16-80 years with compensated or decompensated cirrhosis secondary to HCV, HBV, HBV/HDV coinfection, HCV/HBV coinfection, alcoholic liver disease, Nonalcoholic steatohepatitis and metabolic causes (Wilson disease and Hemochromatosis) were included in the study while the patients with HCC and any other malignancy were excluded from the study. Sample size of the study was calculated through WHO sample size calculator at 95% confidence interval, 5%  $\alpha$  and power of study was taken as 80%. The data was collected by the interview based questionnaire in patient's own language.

The study was approved by the ethics review board of the hospital and research department of CPSP. Participants were given full liberty of participating voluntarily and those who chose to be part of

the study signed a written consent form before the study was initiated.

Data was analyzed by using SPSS-19. Mean  $\pm$  SD were presented for quantitative variables like age, duration since diagnosis. Frequency and percentage were computed for qualitative variables like gender, and awareness about surveillance. Chi square test is used to correlate socio-demographic factors with the presence of awareness regarding HCC surveillance in target population. Family income was graded with respect to Poverty and social safety nets. Chapter<sup>15</sup>, Pakistan economic survey 2013-14.

## RESULTS

A total of 300 patients were included in the study. Out of the 300 individuals 194 (64.7%) were male while 106 (35.3%) were females. The mean age of the study participants was  $38 \pm 2.5$  years. No statistically significant difference was observed between age of both groups ( $p \leq 0.05$ ). Socioeconomic status reported with highest frequency one 84 (61%) participants belonged to middle class (those earning between 67-200% of the median income or even those with certain consumption or wealth metrics.) while only 16 (5.3%) belonged to upper class, with one 32 (44%) participants studied till high school as highest education level followed by Middle School 93 (31%) the illiterates were 48 (16%) while 27 (9%) were professionals.

In fig-1 showing the awareness in sample population regarding HCC surveillance methods with alpha-fetoprotein and ultrasound showed the highest surveillance test frequency.

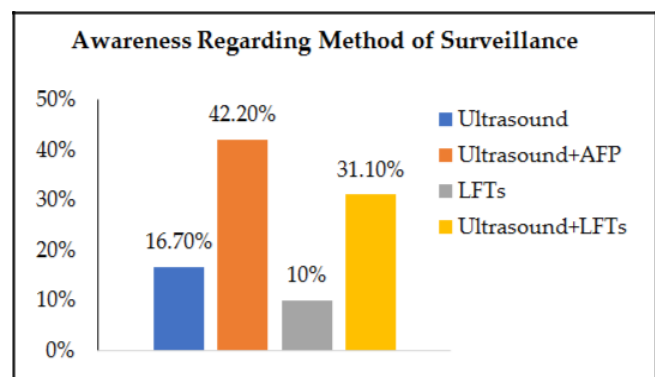


Figure-1: Methods of surveillance.

Out of the 300 participants 210 (70%) participants reported that they have no idea about the screening of HCC while only 90 (30%) were aware about it as shown in the fig-2 .

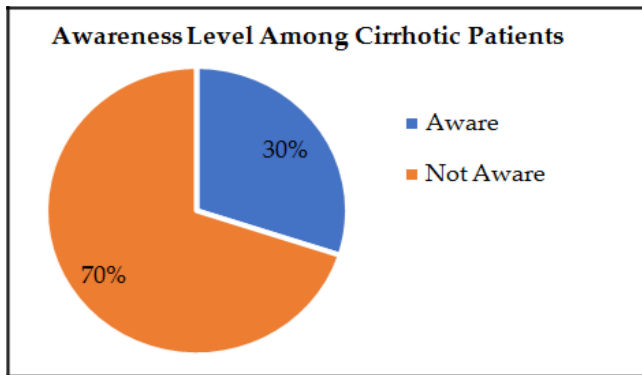


Figure-2: Awareness level about HCC surveillance.

For the awareness of disease since diagnosis 132 (44%) participants reported that they have been diagnosed for <5 years. The highest frequency 192 (64%) for the disease was reported that they had HCV followed by HBV ± HDV 36 (12%) combined the details of each cause shown in table-I.

Table-I: The gender distribution, causes of disease and child class.

Gender, disease frequency and child class in cirrhotics		
	Number	Percentage
<b>Gender</b>		
Male	194	64.7%
Female	106	35.3%
<b>Different Causes of Cirrhosis</b>		
HCV	192	64%
HBV+HDV	36	12%
HCV+HBV	15	5%
Cryptogenic	6	2%
Autoimmune hepatitis	30	10%
Wilson disease	6	2%
NASH	12	4%
Others	3	1%
<b>Child Class</b>		
A	174	58%
B	87	29%
C	39	13%

Regarding awareness about interval of surveillance 219 (73%) participants reported that they have no idea about it while 54 (18%) reported one yearly and 27 (9%) reported 6 monthly assessment. Out of 300 participants only 39 (13%) reported that they were informed by their doctors while 261 (87%) denied.

**DISCUSSION**

The frequency of HCC in developing countries is a few times higher than in developed nations. In Eastern Asia and Middle Africa the Age-Adjusted Incidence Rate (AAIR) ranges from 20-28 cases for every 105 in men, while this is under five for each 105 in Nor

thern Europe, Australia and America<sup>13</sup>. However, a steady increase has been observed in Asian countries like Pakistan<sup>1</sup>. The calculation of the risk associated with any epidemiological or clinical variable is difficult to establish because lack of national data registry for liver cancer and overall lack of proper cancer care which effects the outcome<sup>14</sup>.

Hepatobiliary malignancies are most malignancies according to one reliable Data registry in Pakistan<sup>15</sup>. Most studies on the rate of HCC are uncontrolled and are clinically based, instead of population based. In this way, significant indicators in the overall public may stay undetected. Male sex is related with a higher occurrence in Pakistan<sup>15</sup>, which is in accordance with our study. The occurrence additionally increments with age, likely a surrogate for the term of the hidden liver disease. Presence of liver cirrhosis irrespective of its etiology is greatest risk factor for HCC. Among cirrhotic, viral hepatitis especially chronic hepatitis C

Table-II: Correlation of socio-demographic factors with the presence of awareness regarding surveillance of HCC among the target population.

Socio-demographic factors	Patients without Awareness n (%): 210 (70)	Patients with Awareness n (%): 90 (30)	p-value
<b>Total: n=300</b>			
<b>Age (Year)</b>			
<40	96 (45.7)	42 (46.6)	0.879
>40	114 (54.3)	48 (53.4)	
<b>Gender</b>			
Male	127 (60.5)	67 (74.4)	0.018
Female	83 (39.5)	23 (25.6)	
<b>Education</b>			
<Matric	178 (84.8)	56 (62.2)	0.002
>Matric	32 (15.2)	34 (37.8)	
<b>Background</b>			
Urban	105 (50)	46 (51.1)	0.860
Rural	105 (50)	44 (48.9)	
<b>Family Income</b>			
>Outgoings*	143 (68.1)	53 (58.8)	0.125
<Outgoings*	67 (31.9)	37 (41.2)	

\*Poverty and social safety nets. Chapter 15. Pakistan economic survey 2013-14.

is leading cause of HCC, while other causes such as high alcohol consumption are also on rising trend due to westernization of society<sup>16</sup>. In Pakistan hepatitis C and hepatitis B are most common etiologies for HCC causing upto 58% and 25.3% of cases respectively<sup>17</sup>.

Surveillance for HCC meets some but not all of the standard criteria for assessing the feasibility of instituting a cost-effective surveillance program for the disease. HCC develops frequently in population at risk

and it prompts noteworthy dismalness and mortality. In the Western world, the population at risk promptly acknowledges the requirement for screening, and doctors for the most part do trust that observation is essential, however data from Bharadwaj *et al* study revealed most physicians do screen patient for HCC but they lack in knowledge regarding the appropriate modality for screening<sup>18</sup>, which also reflect on the need for improvement on professional level both on following last guidelines and implicating them in daily routine and also reflect upon poor understanding of participants due to low educational level.

A few agreement meetings and in addition two expert associations have recommended standard HCC surveillance for cirrhotic patients who are at risk group for HCC<sup>19</sup>. Findings from these studies propose that these recommendations have not been very much embraced and followed into clinical practice<sup>20</sup>. In study by Davila *et al*, only 20% of HCC patients who were previously known cirrhotic received HCC surveillance<sup>21</sup>.

Looking at the other side of the coin there are many other factors which come into play and have an important role in delayed or lack of surveillance in cirrhotic patients that include low socio-economic status, low literacy rate, lack of appropriate health services and poor cost effectiveness.

The study of Farinati *et al*, proposed that females have better prognosis and early detection rate for HCC due to better compliance as compared to males<sup>22</sup>. Similarly, patients who are young, literate, living in urban zones with good pay will probably have gotten customary reconnaissance than others.

Patients who were seen by hepatologists were altogether more prone to frequency observation than patients seen by general practitioners and physicians. Explanations behind these observations are not clear however could be due to constrained or obsolete learning, absence of economic motivator, restricted system for regular follow-up updates, lack of proper testing facilities for surveillance (e.g., attractive reverberation imaging), and lack of access to referral facilities for curative therapies. So patients with compensated liver disease should be managed by general physicians with frequent input from hepatologists<sup>19</sup>.

The high prevalence of HCV-3 a genotype in Pakistan as compare to other countries, accounted for the rising rate of HCC<sup>23</sup>. In Contrast to HBV, advancement of HCC in hepatitis C was less connected with ascend in alpha-fetoprotein in Pakistani patients<sup>23</sup>. The patients with viral marker negative cirrhosis are not

under a surveillance program which delay the diagnosis of liver cancer, they have bigger tumor size, shorter interval between establishment of cirrhosis and HCC, and sometimes unattended diabetes mellitus.

Huge numbers of these cases are believed to be identified with non-alcoholic fatty liver infection, which again has a rising pattern in our populace. Surveillance for HCC is prescribed in patients with cirrhosis and in chronic hepatitis B patients as it is practical and survival is enhanced by early evaluation and treatment. Numerous sonologists in Pakistan are skilled to detect early lesions of HCC. Alpha-fetoprotein is presently considered as lacking sensitivity as screening test for HCC. But adding Alpha-fetoprotein to ultrasound increases sensitivity as compared to ultrasound alone in detecting HCC of any stage (97% versus 78%) and for early stage HCC (63% vs 45%) performed every 6 monthly. This is further supported by study of Mittal *et al* that patient receiving surveillance have better chance at treatment than those without it<sup>24</sup>.

Female gender and low education were consistent correlates with lack of awareness regarding surveillance of HCC among the target population. Different findings have been reported in the past on this subject<sup>25</sup>. Reason for this association in our analysis might be limited exposure of women to various health and education facilities in our part of the world. People with less formal education are also usually unable to comprehend even simple health related matters, hence don't indulge much in getting information even regarding their own illness.

TV, Newspaper, Radio and social media need to take initiative in launching awareness campaigns of HCC and implication of surveillance tests. We need to involve personnel's with high stature and influential positions such as teachers, moulan as and clergymen in increasing awareness regarding HCC in their circles, likewise fryer should be distributed in community especially areas of high prevalence of HCV and HBV. Most importantly, we need to establish cirrhosis clinics in our hospitals setting so that all cirrhosis patient should have regular follow up there and clinic should remind patients of their regular surveillance scan by message or call.

## CONCLUSION

Lack of awareness about surveillance is the main cause for increasing HCC risk and complications. Health care professionals and community leaders should effectively advise patients with respect to the advantages of HCC screening through designed educational

programs. Such interventions are relied upon to increase awareness about HCC and HCC screening, and also enhance screening adherence, early diagnosis and possible curative treatment.

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### CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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