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## ORIGINAL ARTICLE

# MAJOR RISK FACTORS, CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH HEPATOCELLULAR CARCINOMA; A RETROSPECTIVE STUDY AT TIKUR ANBASSA HOSPITAL, ADDIS ABABA UNIVERSITY, ADDIS ABABA, ETHIOPIA

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## ABSTRACT

**Background:** Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide, accounting for over half a million deaths per year. Hepatocellular carcinoma can occur secondary to viral hepatitis, HBV or HCV. It can also occur secondary to other causes of Cirrhosis (alcoholism being the other most common cause).

**Objectives:** To describe clinical and laboratory characteristics of Hepatocellular carcinoma in a tertiary care hospital in Addis Ababa, Ethiopia

**Methods:** A retrospective study was conducted in patients admitted to Tikur Anbassa specialized Hospital with a diagnosis of Hepatocellular carcinoma during the period of January 1, 2013 to Dec. 31, 2015. Data were collected using structured questionnaire on basic demographic factors, behavioral risks, laboratory profiles and imaging reports. Descriptive analysis was performed on the data collected.

**Results:** Fifty one patients fulfilled the criteria for Hepatocellular carcinoma in the study period. Thirty nine were males and 12 were females. Hepatitis B and C viruses were found to be the causes for HCC in 48% of the cases. History of alcohol abuse was documented in 45% of the individuals.

About 26% of the patients had Ascites, 35 % were found to have portal vein thrombosis, The child-Pugh score for patients who had complete profile were Child A 46%, Child B an equal percentage of 46% and for Child C 0.7%.

**Conclusion:** The contribution of Hepatitis virus is high with equivalent proportion of HBV and HCV. Alcohol intake and unidentified risk factors have also played for another half of the causes. Almost a third of patients have Portal vein thrombosis and 96% were either Child Pugh A or B. Enhancing immunization coverage frequent use of infection prevention and availability of treatment for viral hepatitis will help to reduce Hepatocellular carcinoma.

**Key words :-** Hepatocellular carcinoma, risk factors, Ethiopia

## INTRODUCTION

Hepatocellular carcinoma is considered a notorious disease for its insidious onset and silent clinical course which renders early diagnosis extremely difficult. It is the fifth most common malignancy in the world and is estimated to cause approximately half a million deaths annually. Primary Hepatocellular carcinoma (PHC) accounts for 85-90% of all primary liver Cancers, with a median survival of less than one year [1,2]. PHC incidence during the past two decades has more than tripled in the United States (US),

where it is the fastest increasing cause of cancer related deaths (3-5).

PHC is a rapidly fatal cancer, even though an increasing prevalence observed in developed nations, it mostly affects persons in developing countries, this could be due to the high incidence of Hepatitis B virus in these regions (6-11). The incidence of Primary Hepatocellular Carcinoma in developed countries accounts for 7.64 and 2.65 /100,000 populations in male and females respectively. These values are lower compared to developing countries which comprises for 17.8 and 6.17/100,000 populations in male

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and females (12,13). The incidence is especially high in Asia and Sub-Saharan Africa (5, 14-16).

Major risk factors for primary hepatocellular carcinoma include infection with HBV or HCV, alcoholic liver disease, and nonalcoholic fatty liver disease (3, 17, 18). The distribution of these risk factors among patients with hepatocellular carcinoma is highly variable, depending on geographic region and race or ethnic group (17,19). Worldwide, chronic HBV infection accounts for approximately 50% of all cases of primary Hepatocellular carcinoma and virtually all childhood cases. The other virus that is associated is HCV and the estimated risk of primary Hepatocellular carcinoma is 15 to 20 times as high among persons infected with HCV as it is among those who are not infected (2, 20,21). The other endocrine disease that has shown epidemiological association is Type 2 Diabetes mellitus (DM). Several case-control and a few cohort studies have shown that on average, primary Hepatocellular carcinoma is twice as likely to develop in persons with type 2 diabetes as compared with those who do not have diabetes (18).

The estimated incidence of liver cancer globally from a study done in 2002 was 600,000 cases of which 82% are from developing countries. Given the poor survival from this disease, the estimated number of deaths is similar to that of new cases (5,15).

In Ethiopia, hospital based study was done 15 years ago showing prevalence of 12% for admission and 31% as a cause of mortality attributed to liver diseases and its complication (22-25). Currently, we are observing an increase in hospital admission and outpatient department visits in the teaching referral hospitals of our country. However, there is lack of systematically conducted studies to assess the incidence and prevalence of chronic liver disease and PHC in our population. Therefore, the objective of this study was to develop records on timely bases, so as to understand the magnitude of the problem. As the major causes of Hepatocellular carcinoma from this study are preventable; we hope the results will help to recommend a plan for policy makers to design essential preventive actions and timely therapeutic interventions for viral hepatitis.

## MATERIALS AND METHODS

A retrospective chart audit was conducted from January 1, 2013 to Dec. 31, 2015 in Tikur Anbassa Hospital, which is a major referral and teaching hospital

in Ethiopia providing specialty follow up service to patients with different disciplines that include patients with Gastrointestinal, Hepatology problems referred from all parts of the country.

The Gastroenterology Unit of Tikur Anbassa Hospital has two senior Gastroenterologists and four fellows working at a time during the specified study period. The service comprises outpatient care, follow-up, inpatient admission and Endoscopy services. The experts who are working in the gastroenterology unit are expected to get involved in the management of patients with different forms of liver disease including malignancy either directly or through consultations. The source populations for the retrospective study were all patient charts who were seen with a diagnosis of liver mass diagnosed to be Hepatocellular carcinoma in accordance with EASL guidelines in the past one year from Tikur Anbassa Hospital.

Improved radiological diagnosis has largely obviated the need for biopsy and now the European Association for Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) recommend noninvasive diagnostic criteria, namely dynamic imaging with CT, to document a lesion with arterial phase enhancement followed by venous phase washout in cirrhotic patients and in high-risk patients without cirrhosis. Biopsy is reserved for lesions that remain indeterminate on 2 imaging modalities. (12,25,26). Hence, we used abdominal CT scan to diagnose Hepatocellular carcinoma in this study.

### Inclusion Criteria

- All patients were are diagnosed with or referred with main impression of Liver mass and diagnosed to have HCC by ultrasound and confirmed by ti-phasic CT scan or liver biopsy will be looked up from the chart and included in the study
- Patients having follow-up in the adult gastroenterology/Hepatology unit of Tikur Anbassa Hospital
- All patients who had been evaluated and diagnosed with HCC in the last one year of the study period

### Exclusion criteria: -

- Extra hepatic primary malignancies
- Intrahepatic cholangiocarcinoma
- Secondaries from other primary sites

A data sheet was prepared to be filled by reviewing the patients chart. The form includes the Socio-demographic characteristics of the patients, medical

history and risk behaviors, Physical examination findings, laboratory data, imaging studies (CT scan)

The clinical stage and grade of the severity of cirrhosis was assessed using the international standards of Child-Pugh and Model for end stage liver disease (MELD). The variables were computed to find the severity of underlying cirrhosis and likely need and potential poor response to liver transplantation. The analyses were done only in individuals who have complete clinical profile.

Collected data was cleaned, entered and analyzed using SPSS windows version 20. Results are summarized in frequency distribution tables, charts and figures. Ethical clearance was enquired and secured from the ethical review board of Addis Ababa University College of Health Sciences. Permission was obtained from Addis Ababa University office of research and graduate studies.

## RESULTS

From the 51 patients included in the study 12 were females (23.5%) and 39 (76.5%) were males giving a sex ratio of 3.25. The age group ranged between 18 to 65 years. Higher proportion of the study participants were in the age group of 55-64yrs (51%) followed by the age group of 45-54 yrs (25 %)(Table 1).

Table 1. Base line characteristics of study participants, AA, Ethiopia ( n=51)

Character	Number	Percent
<b>Age</b>		
18-24	2	4
25-44	10	20
45-54	13	25
55 +	26	51
<b>Sex</b>		
Male	39	76.5
Female	12	23.5
<b>Platelet count</b>		
< 150,000	11	21.6
150,000-450,000	27	52.9
>450,000	06	11.8
<b>Bilirubin (T)</b>		
<2	30	58.8
2-3	3	5.9
>3	6	11.8

The commonest risk factors among those with complete data are Hepatitis B and C virus infections in 48 % of the cases. Significant alcohol intake was found as a risk factor from the history in 45 % of the cases. From 15 patients who were documented to have HIV test (29.4%), co-infection with HBV was found in 3 individuals. Co-infection of HIV and HCV in 2 cases and 2 patients has triple infection with HBV, HCV and HIV.

Table 2. Risk factor distribution of HCC patients at TAH ( n=51)

Characteristics	Number	%
HBsAg +	12	24
HCV Ab +	12	24
Alcohol	23	45

With regards to most common symptoms, signs and imaging characteristics of patients with PHC , most present with right upper abdominal pain (88.2 %) and as cites reported in about 21.6 % of the patients at presentation .About 41.2 % of patients have CT report of portal vein thrombosis. In addition, hepatomegaly and splenomegaly were found in 70.6 % and 19.6 % of the patients respectively (Table 3)

Table 3. Distribution of patients with HCC according to their clinical characteristics at TAH ( n= 51)

Clinical characteristics	Number	Percent
<b>Abdominal Pain</b>		
Yes	45	88.2
No	06	11.8
<b>Ascites</b>		
Yes	11	21.6
No	30	58.8
<b>Hepatomegaly</b>		
Yes	36	70.6
No	15	29.4
<b>Splenomegaly</b>		
Yes	10	19.6
No	41	80.4
<b>Portal vein thrombosis</b>		
Yes	21	41.2
<b>Encephalopathy</b>		
yes - Stage 2	1	2

Twenty seven individuals have completed data to assess the Child pugh stage and MELD score but missed on 24 (47%) of patients. The MELD class were computed and showed a score of < 10 in 48.1% of the cases, while 52% have MELD score >10 (Table4).

Table 4. Distribution of patients based on Child-Pugh Score ( n =27 )

Variables	Number	Percent
Child A	12	44.4
Child B	12	44.4
Child C	3	11.2

Of the 27 patients with complete data, 12 ( 44.4 %) had Child A, 12 (44 %) Child B and only 3 (11.2 %) Child C stages.

Table 5. Distribution of patients based on MELD Classification ( n=27)

MELD Score	Number	Percent
< 10	13	48.1
11-15	7	26.0
16-20	6	22.2
> 21	1	3.7

As shown in table 5, AFP was done for 44 patients of whom 19 (43.2 %) had AFP level of > 500, followed by 11 (25 %) with AFP level of < 20 and 8 (18.2 %) of AFP level 200-500 (Table 5)

**Table 6:** Distribution of Patients who present with imaging diagnosis of HCC with levels of AFP (n=44)

Variables	Number / imaging diagnosis /	Percent
AFP < 20	11	25.0
AFP 20 – 200	6	13.6
AFP 200 – 500	8	18.2
AFP > 500	19	43.2

## DISCUSSION

Over the retrospective study period of one year a total of 51 patients were identified which fulfill the diagnostic criteria for hepatocellular carcinoma. The amount of missing/incomplete information emphasizes the need for proper record-keeping, and to include important checklist information to be included in the chart which comprises back ground information , behavioral risk factors, clinical symptoms, basic laboratory data. Major causes of Hepatocellular carcinoma in our study were infectious causes like hepatitis B and hepatitis C viruses. The other factors are alcohol intake, drug which was also reported by other studies (5).

In a study done in Zimbabwe at referral hospital, 60 patients with primary Hepatocellular carcinoma were identified of whom 48.3% were seropositive for HBV and 20.0% were Seropositive for HCV, co-infection by HCV and HBV was found in 8% of the patients. Only 13.3% of the healthy controls (blood donors) were positive for HBV. All the controls in this study were negative for HCV(23)

In these current study, most patients are in the productive age group (15-54 years )of age . previous studies have also shown that 79 % individuals are in the age group 41 to 60 yrs. Among the causative viruses, an equal proportion of hepatitis B and C virus (24 % each) were observed. In our patients more cases of hepatitis c infection are identified as compared to previous studies. The risk of increased hepatitis C should be further studied. Some of risk factors could be unsterilized needle stick injuries, traditional tattoos, scarifications.

Comparative studies in our country are older and difficult to compare results. We hope this study will help as a strong basis to further understand the gaps. Previous studies done by E. Tsega had shown that the prevalence of HBV prevalence ranges from 8-12 % with lower incidence of HCV which was around 5 %. The contribution of HCV as a possible risk factor for HCC is higher in these study. These could be due to increased risk of chronicity and complications of HCV compared to HBV.

Another study by E. Tsega in 1994 has shown that HCV infection was significantly more common in patients with chronic liver disease and HCC who had evidence of past HBV infection or no marker for HBV infection. HCV infection appeared to be a more common cause of chronic liver disease and HCC than HBV infection in this population.

Another comprehensive clinical study to assess CLD in Ethiopia to identify common causes was done; in this three year prospective study, 334 inpatients were evaluated, from whom 112 hepatocellular carcinomas were diagnosed. One or more HBV markers were identified in 78 % of HCC patients. Since, study in the controls was not done, it can't be generalized.

These studies have shown variation in the contribution of hepatitis B and C virus as a cause of liver disease. Since the studies have difference in time profile and sample size and no involvement of controls, it cannot lead into generalization, but clearly shows the impact of viral hepatitis. In the current study, we have shown a nearly equivalent proportion in hepatitis B and C viruses. The other result that was obtained from the current study is high number of individuals around 50 % without conventional risk factors. Even though, it is old causes for Hepatocellular carcinoma which are at large modifiable by increased public awareness, universal safety precautions and through vaccination were prevalent in the study. Viral hepatitis B and C comprised almost half of the causative agents. We need to assess the true prevalence of Hepatocellular carcinoma and its risk factors through prospective study. The study should include complete history inquiry, appropriate focused physical examinations, lab tests as to assess the major risk factors and stage of the disease.

This study has identified 51 patients with diagnosis of Hepatocellular carcinoma. Among the identified patients diagnosed with Hepatocellular carcinoma, viral hepatitis comprises 50 % of the causes. Hepatitis B and hepatitis C virus contribute for equivalent

frequency of the causes. The next measure cause identified is alcohol consumption. 5 of the individuals were found to have HIV infection. The degree and stage of hepatitis showed most of the cases are in the early stages of liver injury. Fifty three percent of the individuals diagnosed with Hepatocellular carcinoma have alphafeto-protein (AFP) level which is > 200 IU. This figure supports the lack of sensitivity of alphafetoprotein which is around 41-65 % in the western studies, so, we also shouldn't rely on AFP for diagnosis of PHC.

#### ***Recommendation:***

Public awareness on the burden of Hepatocellular carcinoma is vital. The risk factors can be reduced through health education, Vaccination of at risk individuals for hepatitis B, safe injection practice proper screening of blood before transfusion and caution and post exposure prophylaxis.

The significance of preventive measures to health and national development has to be promoted. A longside primary prevention, disease control efforts should aim to improve the awareness, detection and treatment of hepatitis B, Hepatitis C and early detection of Hepatocellular carcinoma.

Large population based prospective studies with standardized questionnaires and laboratory parameters are recommended to really understand the overall impact as well as its economic costs on the individual and the health system.

## **ACKNOWLEDGEMENT**

The authors would like to express heartfelt gratitude to Tikur Anbassa Hospital Department of Internal Medicine for giving this chance to undertake a study and the collaboration of the staffs of the GI unit. Our appreciation also goes to the Institutional Review Board of the hospital to reply promptly for ethical clearance. Last but not least, we appreciate the external collaborators from University of Toronto who has given a strong support in comments and financing the study.

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