

Hepatocellular Carcinoma in Albania: Incidence and Risk Factors

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Abstract: *Background:* Hepatocellular carcinoma represent a challenging malignancy of worldwide importance. *Aim:* To assess the incidence and the potential impact of the risk factors. *Methods:* It was a hospital-based case-control study of 648 HCC patients between January 2000 and November 2014. The age-adjusted incidence rates were calculated for 5-years period. Liver cirrhosis was designed by biopsy or in the presence of unequivocal clinico-biochemical and ultrasonographic data. HCC was defined in cirrhotic subjects by CT or MRI. For subjects without cirrhosis cytological confirmation was mandatory. *Results:* Study population comprised 527 (77.1%) males and 157 (22.9%) female, given M:F ratio of 3.4:1. The mean age of all patients was 60.4 years, with majority of them (70%) between 50 and 70 years. Underlying cirrhosis was present in 89.3% of cases, and 68% of them were Child-Pugh class A. The overall age-adjusted incidence rates started to increase in 2010, from 6.6 and 7.4 per 100 000 population in 2000 and 2005 respectively, to 8.9 in 2010 and 9.3 in 2014, nearly 4 times higher in man than in women. The greater incidence occurred in patients 60 and 70 years of age. 50.9% of all cases were associated with HBV infection, 21.8% with concomitant HBV infection and alcoholism, 13.8% with alcoholic alone, 8% with HCV infection, and 4.9% were HCC patients with not a reliable risk factor. *Conclusions:* The incidence rates of HCC has almost doubled in Albania between 2000 and 2014. HBV infection and heavy alcohol consumption significantly influenced for the increased incidence of HCC in our country.

Keywords: Hepatocellular carcinoma, HBV infection, HCV infection, alcoholism, incidence

1. Introduction

Hepatocellular carcinoma (HCCC) is the fifth most common neoplasm worldwide (1), with over a million new cases diagnosed annually (2, 3). Its incidence differs considerably in different geographical regions, with more than 80% of cases occurring in resource-poor countries (3, 4). Several epidemiological studies have documented a dramatic increase in the incidence of HCC; it doubled during the last 20 years and is expected to peak between 2015 and 2020 (5). In addition, the incidence of the tumor is increasing in a number of countries in which it previously had low or an intermediate occurrence rate (6, 7). The number of death per year, attributed to the liver cancer is almost identical to its incidence (1), making it the second cause of cancer related mortality in the world, and the ninth leading cause of cancer death in United States (8).

HCC is unusual among human cancers because of the causative agent is often clear. However, there are multiple etiologic factors affecting HCC, making HCC an extremely complex condition associated with poor prognosis (9). The commonest and geographically most widely distribution of the recognized causes of HCC are chronic HBV and HCV infection, and cirrhosis whatever its cause (10). The relative risk of HCC in patients with chronic hepatitis B or chronic hepatitis C infection is about 25-30 times higher than that of those without the infection (11). Changes in the time trends of HCC and variations in its age, sex and race-specific rates among different regions are likely to be related to differences in hepatitis viruses that are most prevalent in a population, the timing of their spread, and the ages of the individuals the viruses infect (12).

HCC is one of the major consequences of chronic hepatitis B, and variety of viral load and host factors contribute to its development. It is now well documented that 70-90%

individuals who develop HCC in the setting of HBV infection have cirrhosis (13). In hepatitis B virus-related cirrhosis, the 5-year cumulative risk for HCC is 15% in high endemic areas and 10% in the West (6).

Chronic HCV infection is another important global cause of HCC, especially in developed countries. Significant increase in the incidence of HCC that have been observed over the past two decades in the United States has been mainly attributed to the large reservoir of long-standing chronic hepatitis C (5, 14). The rate of HCC among HCV infected persons ranges from 1% to 3% over 30 years (12).

Heavy alcohol intake has been definitely recognized as a cause of chronic liver disease, including HCC (15). In the USA and Austrian cohorts, alcoholic liver disease appears to account for 24-35% of cases of HCC (16). The annual incidence of HCC was reported at around 2.5% among Child-Pugh class A or B alcoholic cirrhosis (15). In the absence of HBV and HCV infections, and alcohol abuse, dietary aflatoxin exposure (17), non-alcoholic steatohepatitis (18), and iron overload (19) have been robustly associated with the risk of developing HCC.

The aim of the present study was to investigate the incidence rates and the potential impact of the risk factors of HCC in Albania.

2. Methods

We conducted a hospital-based case-control study in which a total of 648 HCC patients routinely attending the liver unit and oncologic service of the University Hospital Center "Mother Theresa" in Tirana between January 2000 and November 2014. We defined as incident cases all new cases of HCC diagnosed during the enrolment period. The age-adjusted incidence rates for HCC were calculated for 5-years

period between 2000 and 2014. The data concerning each case were collected only once, at the first contact with the patients during the study period.

Liver cirrhosis was diagnosed by liver biopsy or in the presence of unequivocal clinical, biochemical and ultrasound signs (20). The Child-Pugh criteria were used for the grading of cirrhosis. Heavy alcohol consumption was defined as consumption of > 80 mL of ethanol per day for the least 10 years before development of the liver disease. HCC was defined in cirrhotic subjects by one imaging technique (CT scan and MRI) showing a nodule larger than 2 cm with contrast uptake in the arterial phase and contrast washout in venous or late phases or two techniques showing this radiological behavior for nodules 1-2 cm in diameter. Cytohistological confirmation was required for subjects who do not fulfilled this accepted criteria (21). For subjects without cirrhosis histological confirmation was mandatory. Tumor characteristics included staging (based on Barcelona Center for Liver Cancer classification) and vascular involvement (22).

Serum hepatitis B surface antigen (HBsAg), HBeAg and anti-HDV were tested using a radioimmunoassay kit (Abott Laboratories). Anti-HCV was measured by means of second generation enzyme immunoassay (Abott Laboratories). Serum biochemical tests were performed by a systemic multiautoanalyser(Technicon SMAC). Serum alpha-fetoprotein (AFP) level was measured by ELISA, and an AFP value greater than 20 ng/ml was considered abnormal.

The study protocol was approved by the ethical committee.

The mean and standard deviation was used to present continuous variables. The discrete variables were presented in absolute number and percentage. T-test and Hi-square test was used to see the differences between two groups (for continuous variables). A P-value < 5% was considered statistically significant.

3. Results

Between 2000 and 2014 there were 648 cases of HCCs. The mean age of all patients was 60.4 years, with majority of them (70%) between 50 and 70 years. HCC was rare among individuals younger than 40 years of age. Study population comprised 527 (77,1%) males and 157 (22,9%) female, given M:F ratio of 3,4:1. Underlying cirrhosis was present in 89,3% of cases, and 68% of these cases were Child-Pugh class A.

Among 648 cases tested for hepatitis virus markers, 74,1% were HBsAg positive, 8,1% anti-HCV positive and many as 18,2% were negative for both viral markers. Thirty five percent of the subjects were heavy drinkers, 21,5% of them were alcoholic cirrhotic patients with concomitant HBV infection.

The age-adjusted incidence rates of liver cancer among Albanian man and women for consecutive 5 years period between 2000 and 2014 is shown in Fig 1a. The overall age-adjusted incidence rates of HCC started to increase in 2010, from 6,6 and 7.4 per 100 000 population in 2000 and 2005, respectively, to 8.9 in 2010 and 9.3 in 2014. The age-adjusted incidence rates of HCC were nearly 4 times higher in man than women.

The age distribution of new cases with HCC for consecutive 5-years period from 2000 and 2014 is shown in Fig 1b. The incidence has increased in most age group older than 50 years, with the exception of age group 70 to 80 years. The greatest incidence occurred in patients 60 and 70 years of age. Concomitant with the increase in incidence, the age distribution of patients with HCC progressively shifted towards younger persons (32% of the patients with HCC were included in age-group of 50 and 60 years).

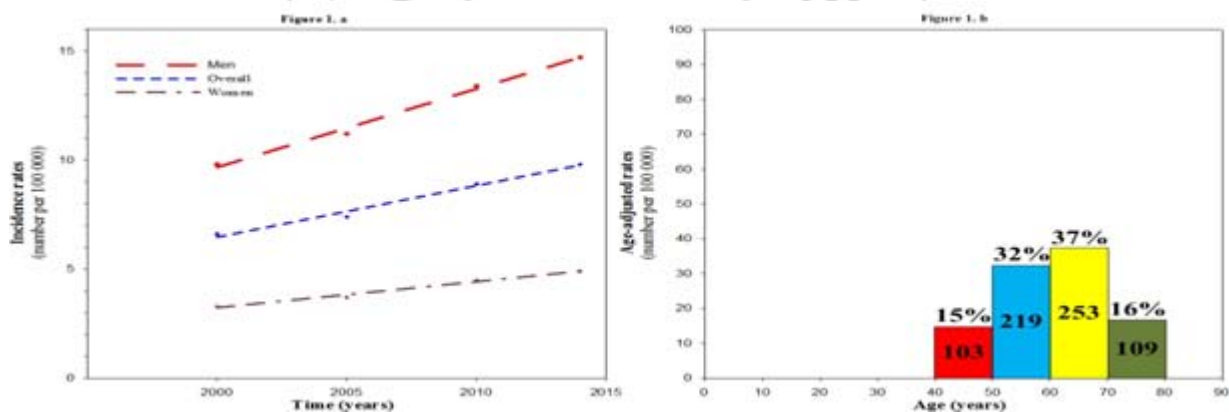


Figure 1: a. Trends in HCC incidence rates over time in Albania (expressed as the number per 100 000 population) b. Age adjusted incidence rates of HCC in 2014 in Albania (expressed as the number per 100 000 population)

The proportion of HCC cases positive for the main risk factors are shown in Tab 1. Half of all cases of HCC were associated with hepatitis B virus infection, with a further 21,5% associated with heavy alcohol consumption and only 0,9% with diabetes mellitus. Other risk factors for developing HCC include alcoholic cirrhosis (13,8% of the cases) and hepatitis C virus infection, in 8% of all subjects

with HCC enrolled in this study, differently to other countries. In 4,9% of the patients with HCC there were not a reliable risk factor.

Table 1: Risk Factors of HCC

Risk Factors	No.	%
HBV	348	50.9
HBV+ALCOHOL	147	21.5
ALCOHOL	94	13.8
HCV	55	8
DIABETUS+HBV	6	0.9
CRYPTOGENIC	34	4.9

The baseline characteristics of cirrhotic patients with concomitant HBV infection and alcoholism, HBV infection alone and alcoholism alone are shown in Tab 2. The rate was 21.4%, 50.9% and 13.8% in cirrhotic patients with concomitant HBV infection and alcoholism, HBV infection alone and alcoholism alone, respectively.

Table 2: Demographic data of cirrhotic patients with concomitant HBV infection and alcohol, HBV infection alone and alcoholism alone

Characteristics	HBV + Alcohol (n=130)	HBV (n=310)	Alcohol (n=84)
Age (y) [Mean±(SD)]	42.8 ± 9.7 (a, b)	46.7 ± 8.9	47.2 ± 10.1
AST [Mean±(SD)]	95 ± 32.6 (a, b)	60 ± 34 (c)	120 ± 80
ALT [Mean±(SD)]	60 ± 48 (a, b)	80 ± 40 (c)	45 ± 28
Bilirubin [Mean±(SD)]	2.2 ± 0.8 (a)	1.4 ± 0.6 (c)	2.4 ± 0.8
Alkaline phosphatase [Mean±(SD)]	280 ± 120 (a)	210 ± 135 (c)	260 ± 120
Platelet count [Mean±(SD)]	80 ± 24 a, (b)	135 ± 45 (c)	125 ± 45
Albumin [Mean±(SD)]	3.4 ± 0.6 (a)	3.6 ± 0.7 (c)	3.4 ± 0.4
A-feto < 20 mg/ml (%)	76 (58%)	155 (50%)	44 (54%)
A-feto 21÷200 mg/ml (%)	42 (32%)	103 (33%)	31 (36%)
A-feto> 200 mg/ml (%)	14 (10%)	52 (17%)	25 (18%)
Child-Pugh A (%)	73 (56%) (a, b)	227 (73%)	58 (69%)
Child-Pugh B (%)	31 (24%)	52 (17%)	16 (19%)
Child-Pugh C (%)	26 (20%) (a, b)	31 (10%)	10 (12%)

- Data shown as median (range) or number (%);
- ^ap value < 0.05 HBV + ALCOHOL vs HBV
- ^bp value < 0.05 HBV + ALCOHOL vs ALCOHOL
- ^cp value < 0.05 HBV vs ALCOHOL

The mean age of patients with concomitant HBV infection and alcoholism was significantly higher than that in subjects with HBV infection alone or alcoholism alone, 42.8 ± 9.7 vs 46.7±8.9 vs 47.2±10.1, p=0.013 and p<0.001, respectively. The mean of AST level of patients with alcoholic cirrhosis was much higher than that in patients with HBV infection and those with concomitant HBV infection and HBV infection alone, 120±80 vs 60±34 vs 95±32, p<0.001, while the mean of ALT level of subjects with HBV infection alone was significantly higher than that in subjects with alcoholism, 80±40 vs 45±28, p< 0.001. Concerning the Child-Pugh class, the rate of A class of patients with concomitant HBV infection and alcoholism was significantly less than the rate in patients with HBV infection and alcoholism and alone, 56% vs 73% vs 69%, p< 0.001.

4. Discussion

The most important finding of this study is the evident increase of the incidence rates of HCC from 2000 to 2014. There is no doubt that this conspicuous rising incidence is related to the high prevalence of HBV infection in our country. It is now well documented that HCC is one of the major consequences of chronic hepatitis B and that individuals who develop HCC in the setting of HBV infection have cirrhosis. Meta-analysis of case-control and cross-sectional studies indicated that the lifetime relative risk for HCC was 15-20 time higher among HBsAg-positive individuals, compared with HBsAg-negative individuals and that the incidence rates of HCC in subjects with chronic HBV infection in East Asian countries to be 0.2 per 100 000 persons-years in inactive carriers, 0.6 person-years for those

with chronic HBV infection without cirrhosis, and 3.7 person-years for those with compensated cirrhosis (23). Factors that have been reported to increase HCC risk among HBV carriers are demographic (male sex, older age, ancestry, family history for HCC), viral (higher levels of HBV replication, HBV genotype, longer duration of infection, co-infection with HCV, HIV or HDV virus), clinical (cirrhosis) and environmental (heavy intake of alcohol, exposure to aflatoxin or tobacco) (12).

Hepatitis B is a disease of global distribution. It is estimated that approximately 45% of the world's population live in region endemic for HBV infection, about 30% of the world's population, i.e. nearly 2 billion people show serological evidence of hepatitis B virus (HBV) infection and about 40 million are persistent carriers of HBV (24). Each year over one million people die from HBV-related chronic liver disease, including cirrhosis and HCC (25). The endemicity of HBV infection varies greatly worldwide and is influenced primarily by the age at which infection occurs (26). In fact, almost all infection occur either during the prenatal or early in a childhood, which occurs for the high rates of chronic HBV infection in these populations (27).

Epidemiologic situation of HBV infection in Albania before 1995 has been described as very grave and dangerous, with prevalence rates of HBsAg and Anti-HCV similar to those in hyperendemic countries, 18% and 62% respectively (28, 29). This epidemiologic situation explain very well the fact that half of all our cases of HCC are associated with hepatitis B virus infection, with a further 21.5% and 0.9% associated with alcoholism and diabetes, respectively. Since May 1995, Albania introduced vaccination of new born children against HBV into the National Immunization

Program as the most appropriate immunization strategy to reduce the rates of HBV infection and HBV-related chronic liver disease, including HCC. In 2007, despite the estimated two-fold reduction of HBsAg prevalence (9.5%), Albania remains a highly endemic country (30). Development of HBV vaccine has been a major success in reducing of HBV infection and subsequent development of HCC. In 1884, Taiwan become the first country to vaccinate newborns against HBV infection, and give HB immunoglobulin to infants of high risk (HBsAg-positive and HBeAg-positive) mothers. Since then, HBV carriers rate among children has been decreased to 1.2% and incidence of HCC among vaccinated children decreased by 70% (31). However, the HBV-related incidence of HCC is procepted to increase for several decades because of the high prevalence of chronic HBV infection and prolonged latency to HCC development (32). In parallel with the very high prevalence of HBV infection, the rising incidence of HCC in our country could be also elucidated through improvement in screening programs and diagnosis tools, as well as the increased survival role among patients with cirrhosis allowing time for some of them to develop HCC.

There are striking differences in the incidence of HCC related to age and gender. Variations in different geographic regions are likely to be related to the differences in the prevalence of hepatitis viruses in the population, as well as the timing of the spread of the viral infection and the age of the individuals at the time of the infection. In Albania, the presence of one or more serological markers of HBV infection and the high rate of infection in children 1 to 10 years, confirms that the HBV infection was largely acquired by mother-child transmission or in early childhood. Indeed, our data shown a shift towards younger age case than in low-endemic areas. The high male : female ratio of HCC in our study might be related to the fact that man are at increasing risk for HCC partly because they have a greater incidence of viral hepatitis and alcoholic cirrhosis. On the other hand, high serum level of testosterone have been associated with HCC risk in nested case-control studies of HBV carriers (33).

Alcohol intake has been definitely recognized as a cause of chronic liver disease, including HCC. Albania is actually a country where use of alcohol beverages with ethanol content (rakee) is very diffuse habit. Heavy and very heavy drinkers (15-20 % of population), are really at high risk for advanced liver disease (34). This study clearly showed that heavy alcohol intake (daily consumption of more than 80 mL of ethanol) is an important independent risk factors for HCC (13.8% alcoholic alone and 21.5% concomitant of alcoholism with HBV infection). In US and Austria, cohorts study confirmed that alcoholic liver disease appears to account for 24-35% of cases of HCC (35, 36). Recent data showed that the risk of HCC is increased in the alcoholic-related disease (OR 4.06) and represent the second greatest population-attributable fraction (PAF) of risk factors for HCC (16). The annual incidence of HCC was reported at around 2.5% among Child-Pugh class A or B alcoholic cirrhosis in Spain, with higher annual incidence in those 55 years of age and older and platelet count less than 125 000 mm³ (15). On the other hand, this study showed once more the role of association between heavy alcohol consumption

and chronic hepatitis B virus infection in the etiology of HCC (21,5% of the cases). In this occasion, a Japanese study of patients with compensated HBV-liver cirrhosis, showed that heavy alcohol consumption increase the risk for HCC 3-fold (37). Furthermore, a population-based cohort study found that among individuals with chronic HBV infection, the risk for HCC increased significantly among subjects with an alcohol intake of 50 g/g, with a relative risk of 1.2 for 50-99 g/d and 1,5 for greater than 100 g/d (38). These data suggest that hepatitis B virus infection may modify the prognosis for alcoholic liver cirrhosis patients, especially in the developing of carcinogenesis.

Chronic HCV infection is another important risk factor for HCC. Some 180 million people worldwide (approximately 2% of world population) are currently estimated to be chronically infected with the virus (3, 12). The risk of developing HCC for apatient with HCV-related cirrhosis is approximately 2-6% in year (39). In contrast with the trend observed in US and Western European countries, where the proportion of HCV-related HCCs is increasing and will continue to increase due to the rise in HCV infection through continued transmission by drug abusers (40, 41), and in almost in the same way with some other countries (42, 43) we found that 8% of all HCCs were related to the HCV infection. Other risk factors are high viral load, increasing age, male gender and severe degree of hepatic fibrosis (44).

It is well known that the most important clinical risk factor for the development of HCC is cirrhosis. Our findings clearly showed that 89.3% of HCCs developed in cirrhotic liver. The high rate of co-existing cirrhosis in HCC patients have led to the assumption that pre-existing cirrhosis is an important prerequisite for hepatocarcinogenesis, although some HCCs do not arise in the observe of cirrhosis (45). All etiological form of cirrhosis may be complicated by the development of HCC, although not with equal likelihood. Apart from the etiology of the cirrhosis, the major factors predisposing to malignant transformation in cirrhotic patients are increasing age, duration of cirrhosis and male sex (6). The main causes of cirrhosis complicated by malignant transformation in this study were chronic HBV infection, concomitant HBV infection and alcoholism and alcoholism alone, and behind them, chronic HCV infection. Compatible with previous data (46), our study confirmed that HCC occurred at younger age in patients with concomitant HBV infection and alcoholism than those with HBV infection alone (42.8±9.7 vs 46.7±8.9) or alcoholism alone (42.8±9.7 vs 47.2±10.1) and that the rate of Child-Pugh class A with patients with concomitant HBV infection and alcoholism was significantly less that individuals with HBV infection alone (56% vs 73%) or alcoholism alone (56% vs 69%). These data suggest that hepatitis B virus infection may modify the prognosis for alcoholic liver cirrhosis patients, especially in the development of carcinogenesis. So that, alcoholic cirrhotic patients with concomitant HBV infection should be carefully screened for HCC consequently of more severe liver pathology.

One of the limitation that should be underlined is the lack of determination of aflatoxin exposure, particularly of patients with cryptogenic cirrhosis, through the presence of the

aflatoxin metabolites in urine or aflatoxin-albumin adduct in serum.

In conclusions, the incidence of HCC has doubled in Albania between 2000 and 2014 and is likely to continue to increase for the near future consequently to the high prevalence of HBV infection (HBsAg more than 8% in general population) and expected to increase in the future of HCV infection. Apart from the HBV infection, heavy alcohol consumption as well responsible for the observed increase of HCC and that alcohol cirrhotic patients with concomitant HBV infection significantly influenced for the increased incidence of HCC. HBV vaccination of age-specific cohorts (young adolescents) and high risk population for acquiring HBV infection should be the high priority in reducing the incidence of HCC.

5. Conflict of Interest

None declared.

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