

Frequency and Predisposing Factors of Hepatocellular Carcinoma in a Hepatology Outpatient Unit

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Abstract

Background: Patients with chronic viral hepatitis are at high risk of developing hepatocellular carcinoma (HCC). Various predisposing factors have been described for the occurrence of HCC in these patients. The aim of the present study was to identify these risk factors.

Method and Material: A retrospective descriptive epidemiological study, of 549 patients with chronic viral hepatitis was conducted. Patients were examined from January 1st 2007 to September 31st 2013 at the Hepatology outpatient unit of a General Hospital of Athens-Greece. Demographic, clinical characteristics of patients and laboratory test results were gathered from the registry of the outpatient unit. Statistical analysis was performed with the PASW18 software, using Pearson's chi-square test. P values of less than 0.05 were considered significant.

Results: Files of 549 examined patients in the outpatient unit were reviewed and 253 (46.1%) were diagnosed with chronic hepatitis B (CHB) and 296 (53.9%) with chronic hepatitis C (CHC). The majority of patients (57.2%) were men and less than 65 years old (87.4%). The frequency of HCC was 4.4% (24 patients). Fifteen patients were diagnosed with CHB and 9 with CHC ($P=0.039$). The factors found to be associated with the development of HCC in our study were age ≥ 65 years ($P<0.001$), diabetes mellitus ($P=0.003$), chronicity (≥ 10 years) of viral infection ($P=0.007$) and liver cirrhosis ($P<0.001$).

Conclusions: The prevalence of HCC was significantly higher in patients with CHB compared with CHC patients. Age ≥ 65 years, diabetes mellitus, chronicity of viral infection and liver cirrhosis were the main predisposing factors for the occurrence of HCC. The early diagnosis of diabetes and the early treatment of viral hepatitis could contribute to the prevention of HCC.

Keywords: HBV; HCV; Hepatocellular carcinoma; Predisposing factors; Viral Hepatitis

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Introduction

Chronic viral hepatitis is a major health problem worldwide. It is a chronic inflammation of the liver parenchyma caused by hepatitis B virus (HBV) or hepatitis C virus (HCV). Almost two billion people are infected with HBV worldwide, while the number of virus vectors is estimated at over 360 million. Infection with HBV is the tenth leading cause of death worldwide and causes more than 600,000 deaths each year [1]. Prevalence of chronic HBV infection in Greece ranges from 0.41% to 0.85% in voluntary blood donors and reaches 22% in immigrants from Albania [2].

It is also estimated that 170-200 million people worldwide are infected with HCV, while each year 3-4 million people are newly diagnosed while HCV is responsible for 350,000 deaths per year [3] In Greece the exact prevalence of HCV infection is unknown and it is believed that 2% of the general population suffers from chronic HCV infection, with a geographical distribution of 0.5% to 7.5%. [4].

Chronic viral hepatitis is a major causative factor for the development of hepatocellular carcinoma (HCC), the fifth most common cancer worldwide and the second most common

cause of death from neoplastic disease. Specifically, each year 250,000 to 1,000,000 deaths are caused by HCC worldwide [5]. Chronic hepatitis B (CHB) accounts for 50% of all HCC cases and chronic hepatitis C (CHC) for 25% of them [6]. Literature suggests that male subjects, chronic alcohol consumption, obesity, and diabetes mellitus (DM) are among the main predisposing factors of HCC [7-20].

In a country with poor epidemiological registry, the purpose of the present study was to estimate the frequency of HCC in patients with chronic viral hepatitis, and separately in patients with CHB and in those with CHC. Also, we attempted to highlight the predisposing factors of HCC in these patients. The importance of this study lies in the fact that in Greece there are significant deficits in epidemiological data that will allow the design and implementation of a long-term strategy to prevent HCC, especially in patients with chronic viral hepatitis.

Methods

Study design and participants

A retrospective descriptive epidemiological study was conducted. The inclusion criteria were: age ≥ 18 years old and certified diagnosis of infection (detection of antibodies against HBV or HCV, determination of HBV-DNA or HCV-RNA). Patients with HBV/HCV co-infection and/or co-infection with the human immunodeficiency virus (HIV) were excluded from the study, because in those patients it is difficult to correlate the development of hepatocellular carcinoma with the presence of HBV or HCV.

Our study population consisted of 574 patients with chronic viral hepatitis (CHB or CHC), who were examined over a seven year period (from 1 January 2007 to 31 September 2013) in the Hepatology outpatient unit of a General Hospital of Athens - Greece. Five hundred and forty nine out of 574 (95.6%) patients met the inclusion criteria and constituted our final study sample.

Data collection

Data collection was conducted in January 2013 by a single member of the research team, who obtained the data based on patient records review, using a short data collection form which was created by the research team specifically for the needs of the present study.

The selected information included demographic patient characteristics (gender, age), the diagnosis of viral hepatitis and HCC, and the potential risk factors for the development of HCC (body mass index -BMI, presence of DM, presence of liver cirrhosis, daily alcohol intake, smoking habits and chronicity of HBV or HCV infection). The chronicity of viral hepatitis was calculated by defining the first exposure of the patient to HBV or HCV. Intravenous drug user's first exposure to the virus was determined by the year of starting using drugs. For the rest of the patients we used the date of laboratory diagnosis of infection.

Ethical issues

The present study was approved by the medical ethics committee of the hospital. The study complied with all ethical principles set by the Declaration of Helsinki. The methods of the study were restricted to recording and analysing patient data related to our

study aim.

Statistical analysis

All variables were categorical and are presented as absolute and relative frequencies. After descriptive statistical analysis, followed bivariate statistical analysis (Pearson's chi-square test) to identify the differences between categorical variables and the presence of HCC. *P* values of less than 0.05 were considered significant. Analysis was performed using the PASW Statistics software.

Results

The study reviewed 549 patient files with chronic viral hepatitis. Almost half, 253 (46%) patients were diagnosed with chronic HBV infection, while 296 (54%) with chronic HCV infection.

Table 1 provides the demographic patient characteristics and the frequency of possible risk factors for HCC. There were more men than women (57.2% vs. 42.8%), while the majority of study participants (87.4%) were aged less than 65 years. The 15.3 % of patients were obese (BMI>30 kg/m²) and 73 (13.3%) were diagnosed with DM. The daily intake of alcohol was reported by 89 (16.2%) patients, while one out of four (23.1%) smoked more than ten cigarettes per day. More than half (312, 56.9%) were diagnosed with chronic viral hepatitis for more than 10 years. Of these, 148 and 164 patients had CHB and CHC respectively. Also,

Table 1 Demographic characteristics and possible predisposing factors for hepatocellular carcinoma of patients with chronic viral hepatitis

	Patients (n)	%
Sex		
Male	314	57.2
Female	235	42.8
Age (years)		
<65	480	87.4
≥ 65	69	12.6
Obesity (BMI>30 kg/m²)		
Yes	84	15.3
No	465	84.7
Diabetes mellitus		
Yes	73	13.3
No	476	86.7
Daily alcohol consumption		
Yes	89	16.2
No	460	83.8
Smoking (>10 cigarettes /day)		
Yes	127	23.1
No	422	76.9
Chronicity of viral infection (years)		
<10	237	43.1
≥ 10	312	56.9
Chronicity of HBV infection (years)		
<10	105	41.5
≥ 10	148	58.5
Chronicity of HCV infection (years)		
<10	132	44.6
≥ 10	164	55.4
Liver cirrhosis		
Yes	106	19.3
No	443	80.7

BMI: Body Mass Index, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus

106 (19.3%) patients were diagnosed with cirrhosis of the liver.

Table 2 summarizes the results of the statistical bivariate analysis between variables of **Table 1** (independent variables) and the occurrence of HCC to patients of the study. HCC found to be more frequent in patients with age ≥ 65 years ($P < 0.001$), patients with diabetes mellitus ($P = 0.003$), those with chronicity of viral infection ≥ 10 years ($P = 0.007$) and those with liver cirrhosis ($P < 0.001$). Also HCC was more frequent in males, obese patients ($BMI > 30 \text{ kg/m}^2$), those with daily alcohol consumption and the cigarette smokers, but not with statistical significance.

HCC was detected in 24 of 549 patients (4.4%). As shown in **Table 3**, 15 of the 253 patients with CHB (5.9%) and nine of 296 patients with CHC (3.0%) developed HCC ($P = 0.039$).

Discussion

HCC is a major health problem worldwide. The relationship of chronic viral hepatitis with the pathophysiology of HCC is well known. However, according to the international literature, there are factors other than the infection by HBV and HCV, which have been associated with the occurrence of HCC [7,20]. Our study was

conducted in order to detect these factors. We found that age ≥ 65 years, presence of DM, chronicity (≥ 10 years) of infection and liver cirrhosis were associated with the occurrence of HCC in patients with chronic viral hepatitis.

In addition, our data analysis confirmed the significantly higher prevalence of HCC among CHB patients compared to patients suffered from CHC. This association indicates the strong mutagenic activity of HBV in the liver. HBV is a DNA-virus, whose genome is combined with DNA of hepatic cells during the long stay of the virus in liver parenchyma, leading to various mutations in the genetic material of infected hepatic cells [21,22]. Moreover, the perinatal transmission of HBV is more common than that of HCV, resulting in the existence of HBV on liver parenchyma for more years [22]. In our study, this finding was verified, and a higher proportion of CHB patients had the disease for more than ten years than those who suffered from CHC (58.5% vs. 55.4%).

The age of patients proved to be a strong predisposing factor for the development of HCC in the present study. This obviously relates with the greater length of time the virus (HBV or HCV) stays inside liver parenchyma in people older than 65 years

Table 2 aBivariate analysis between HCC and independent variables

	HCC (yes) n (%)	HCC (no) n (%)	p value
Sex			0.070
Male	18 (5.7)	296 (94.3)	
Female	6 (2.5)	229 (97.5)	
Age (years)			<0.001
<65	9 (1.9)	471 (98.1)	
≥ 65	15 (21.7)	54 (78.3)	
Obesity (BMI>30 kg/m²)			0.870
Yes	5 (5.9)	79 (94.1)	
No	19 (4.1)	446 (95.9)	
Diabetes mellitus			0.003
Yes	8 (10.9)	65 (89.1)	
No	16 (3.3)	460 (96.7)	
Daily alcohol consumption			0.450
Yes	4 (4.5)	85 (95.5)	
No	20 (4.3)	440 (95.7)	
Smoking (>10 cigarettes /day)			0.464
Yes	10 (7.9)	117 (92.1)	
No	14 (3.3)	408 (96.7)	
Chronicity of viral infection (years)			0.007
<10	3 (1.2)	234 (98.8)	
≥ 10	21 (6.7)	291 (93.3)	
Chronicity of HBV infection (years)			0.003
<10	2 (1.9)	104 (98.1)	
≥ 10	13 (8.8)	134 (91.2)	
Chronicity of HCV infection (years)			0.009
<10	1 (0.7)	130 (99.3)	
≥ 10	8 (4.8)	157 (95.2)	
Liver cirrhosis			<0.001
Yes	23 (21.7)	83 (78.3)	
No	1 (0.2)	442 (99.8)	

P value was calculated using Pearson's chi-square test (P value < 0.05 is considered statistically significant)

BMI: Body Mass Index, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, HCC: Hepatocellular Carcinoma

Table 3 Bivariate analysis between chronic viral hepatitis and HCC

	HCC (yes) n (%)	HCC (no) n (%)	p value
Chronic viral hepatitis			0.039
CHB	15 (5.9)	238 (94.1)	
CHC	9 (3.0)	287 (97.0)	

P value was calculated using Pearson's chi-square test (*P* value < 0.05 is considered statistically significant)

HCC: Hepatocellular Carcinoma; CHB: Chronic Hepatitis B; CHC: Chronic Hepatitis C

against younger individuals. As highlighted by Walter et al., [7] in their study the incidence of HCC is significantly increasing over the years, with a higher incidence between the ages of 60-70 years.

DM was associated with higher prevalence of HCC among the patients of our study. One out of ten patients with DM developed HCC compared with only 3.3 % of those with free history of DM. This association has also been reported by other researchers [11,15,16,19]. Specifically, Polesel et al., [11] found a strong association between DM and HCC, both in patients with chronic viral hepatitis and patients with non-liver disease. Patients with DM exhibit various metabolic disorders and are often overweight. Increasing levels of insulin-like growth factor in individuals with DM appears to be associated with the stimulation of cell proliferation and carcinogenesis in various tissues, including liver. Also, increased body weight, in many cases leads to a non-alcoholic liver steatosis, which is associated with the development of HCC. Indeed, as shown in our study, obese patients (BMI > 30 kg/m²) were diagnosed with HCC more frequently compared to non-obese patients (5.9% vs. 4.1 %) without, however, this difference to be statistically significant.

Moreover, El-Serag et al., [15] indicated a strong association between DM and HCC, regardless of the existence of other predisposing factors. A meta-analysis by Yang et al., [16] suggested that individuals with DM not only suffer frequently from HCC, but they have a higher mortality from HCC, compared with individuals who do not have DM. Wang et al. [19] in a systematic review and meta-analysis found a high prevalence of HCC in individuals with DM and also indicated the effect of antidiabetic medication in the development of HCC. More specifically, they found that metformin has a potential protective action while the sulphonylureas and insulin associated with the occurrence of HCC. In contrast, Singh et al., [17] found no relationship between antidiabetic agents and the occurrence of HCC.

Chronicity of viral infection by HBV or HCV was another predisposing factor for the development of HCC in patients of this study. For both total population and subpopulations of patients with CHB and CHC, patients with known infection for

more than ten years had a higher prevalence of HCC, compared with those who have the disease for less than ten years. As in the case of the older age (≥ 65 years), HB and HC viruses causes significant damage to the liver parenchyma over the years, which may gradually lead to the development of HCC. It is well known that liver carcinogenesis in individuals with chronic viral hepatitis requires long stay of viruses in liver parenchyma [22].

Liver cirrhosis has proved to be a predisposing factor for the development of HCC, according to the results of our study. It is noteworthy that one in five patients (21.7%) with liver cirrhosis developed HCC compared to only one patient (0.2%) without liver cirrhosis. Many other researchers are in line with this finding. Walter et al., [7] in their research found that liver cirrhosis is the strongest predisposing factor for development of HCC. Also, results found by the studies of Yu et al., [23] and Chu et al., [24] demonstrated the association between liver cirrhosis and HCC.

Finally, in contrary to the findings of our study chronic alcohol consumption has been strongly associated with the occurrence of HCC [7,10,14]. In addition, several studies have highlighted the causal relationship between smoking and HCC [25-27].

Limitations

Our study included only patients with chronic viral hepatitis who were examined at a single Hepatology outpatient unit of a General Hospital of Athens-Greece. The sample size (n=549) was rather small for a period of 7 years and does not allow us to generalize the results of this study to the general population of Greece. Also, our study was retrospective and based on the records of one Hepatology outpatient unit in Athens. We recommend the future conduction of a prospective multicenter study, which will allow the collection of data from a larger population. The data collection from many centers, some of them out of Athens, will allow the generalization of study results for the Greek population.

Conclusions

This study was conducted in a population of patients with chronic viral hepatitis, aiming to indicate the prevalence of HCC among them and to highlight the predisposing factors for HCC. Age ≥ 65 years, DM, chronicity of infection and liver cirrhosis are the main predisposing factors of HCC in these patients. The health professionals, who are involved in the prevention of HCC, should consider these factors. Early diagnosis of DM and the successful regulation of blood glucose levels, mainly through non-medication measures could contribute on reducing the incidence of HCC. Also, both early diagnosis of viral hepatitis and the application of appropriate therapy could reduce the long-term effect of virus on liver parenchyma, which causes the generation of HCC.

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