

THE RISK OF HEPATOCELLULAR CARCINOMA ON PATIENTS DIAGNOSED WITH HEPATITIS B AND HEPATITIS D (2012-2015)

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ABSTRACT

Introduction. Hepatocellular carcinoma is the most common primary liver cancer (90%), the 5th neoplasia in terms of incidence and the 3rd mortality cause worldwide (1). This increased mortality is the consequence of diagnosis in an advanced state and of the fact that most HCC develop based on a chronic hepatic pathology. In Romania, around 7% of the population is affected by chronic hepatitis B, the incidence of this disease being increased in urban areas (2). The sooner the hepatitis B virus infection occurs in life, the higher the probability is, for this to become chronic and to lead to cirrhosis or liver cancer. Hepatitis D only occurs among people who are infected with the Hepatitis B virus because HDV is an incomplete virus that requires the helper function of HBV to replicate.

Objective of the study. The main purpose of the surveillance and/or screening is to decrease mortality and morbidity by means of liver cancer for patients diagnosed with hepatitis B and hepatitis D.

Material and methods. The study was conducted on a number of 102 patients diagnosed with viral hepatitis (HBV, HDV+HBV) admitted at the “Fundeni” Hospital, Bucharest, between 2012-2015. Two batches of patients were taken into account (patients with hepatitis B and hepatitis D). The viral load and chosen treatment were clinically, biochemically and imagistically evaluated.

Results. We have noticed a significant increase in patients diagnosed with hepatitis B and D. The existence of the hepatitis D infection in patients diagnosed with hepatitis B significantly increases the occurrence potential of liver cancer. The hepatic destruction degree by means of cirrhotic liver occurrence respectively hepatic cirrhosis much higher for patients diagnosed with hepatitis D.

Conclusions. The close monitoring of the patients in this research program brings real benefit for the prevention of liver cancer and diagnosing it early, having a much better prognosis on the quality of life.

Keywords: hepatic virus B, liver cancer, hepatic virus D

INTRODUCTION

Most patients diagnosed with hepatocarcinoma in Romania are admitted with tumors in an advanced state. HCC incidence is in a constant increase, whilst general survival rate of 5 years is still under 10%, which is caused by the impossibility of applying an efficient screening on patients with an HCC risk factor. Hepatitis B is a serious liver infection caused by the hepatitis B virus (HBV) (1,2). The infection with hepatitis B virus represents the 10th mortality cause in the world, causing 80% of the liver cancer cases. Often these symptoms last a few weeks and rarely does the initial infection result in death. It may take 30 to 180 days for symptoms to begin. In those who get infected around the time of birth 90% develop chronic hepatitis B while less than 10% of those infected after the age of five

do. Most of those with chronic disease have no symptoms; however, cirrhosis and liver cancer may eventually develop (2-4). These complications result in the death of 15 to 25% of those with chronic disease. A vaccine can prevent hepatitis B, but there's no cure if you have it. Progression to cirrhosis usually takes 5-10 years, but it can appear 2 years after onset of infection (5,6). About 60 to 70% of patients with chronic hepatitis D develop cirrhosis. A high proportion of these patients die of hepatic failure. Hepatocellular carcinoma (HCC) occurs in chronically infected HDV patients with advanced liver disease with the same frequency as in patients with ordinary hepatitis B. HCC may actually be more a secondary effect of the associated cirrhosis than a direct carcinogenic effect of the virus (7,8). The mortality rate for HDV infections lies

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between 2% and 20%, values that are ten times higher than for hepatitis B (9). Pathologic changes in hepatitis D are limited to the liver, the only organ in which HDV has been shown to replicate (10,11). The histologic changes consist of hepatocellular necrosis and inflammation (12). There is no vaccine for Hepatitis D, but it can be prevented in persons who are not already HBV-infected by Hepatitis B vaccination.

PURPOSE

The main purpose of the surveillance and/or screening is to decrease mortality and morbidity by means of liver cancer for patients diagnosed with hepatitis B and hepatitis D. The symptomatic development of the hepatic tumor is closely associated with the hepatic virus B. Even more, the hepatic disease is an important prognosis factor that can significantly influence the survival of the patient, moreover by limiting the therapeutical possibilities with improvement *visa*. Therefore, an exact diagnosis is the key to a successful HCC therapy. Even though in the past 10 years the prophylaxis of acute viral hepatitis B has been an epidemiological priority in Romania, by introduction of vaccination in the National Immunization (in 1995), high media coverage and studies on the population, there was no success in the limitation of acute HBV infections, only noticing a moderate annual decrease. The present thesis has the purpose of studying clinical forms of HBV and HDV infection in patients admitted at the “Fundeni” Hospital, Bucharest, during the time period 15.01.2012 – 10.01.2015. We have tried to determine the connection between age, sex, residence of the patient and the seriousness of the infection, and also the role of the co-infection with HDV and the pathology associated with the evolution of the disease.

The main objectives of the study are:

1. Highlighting the number of patients with an HBV and HDV infection admitted at the “Fundeni” Hospital, Internal Medicine Section, Bucharest, during the time period 15.01.2012 – 10.01.2015.
2. Classifying the patients according to age and sex.
3. Establishing the ground on which the HBV infection evolves with the existence of the HDV.
4. Studying the main biochemical parameters, by highlighting the main laboratory syndromes.

5. Monitoring the patients diagnosed with HBV and HBD by ultrasound and periodically conducted AFP, every 6 months.
6. Establishing an epidemiology plan for the prophylaxis of the HBV infection.

MATERIALS AND METHODS

HCC is mostly an asymptomatic disease. Given the fact that this neoplasia develops on a hepatic pathology, a series of prophylaxis methods have been applied to HBV and HBV+ HDV patients, surveillance by means of abdominal ultrasound, fibroscan, biochemical parameters and by monitoring the α FP is still the basis of an exact diagnosis. The current study is based on a number of 102 patients admitted at the “Fundeni” Hospital, diagnosed with HBV and HDV during the time period 15.01.2012 – 10.01.2015. The study is a retrospective statistical one of the patients admitted with a B and D hepatic virus, using all personal documents presented by them at admission and those obtained from the moment of admission specialty clinical-paraclinical conjunction, taking into account data obtained from other specialists (from gastroenterological, medical, anatomical-pathological services). The evolution of hepatic infections is done by periodically monitoring the ultrasound, α FP, the biochemical parameters and in some cases the carcinoembryonic antigen (CAE) and the carbohydrate antigen CA-125. By determining the oncofetal antigen, respectively the carcinoembryonic antigen (CAE) and the carbohydrate antigen CA-125, we have found significantly increased values only in hepatic metastasis cases, therefore any liver structure modification as well as biochemical modification of the hepatic marker (α FP) is alarming.

The close monitoring of the patients in this research program brings real benefit for the prevention of liver cancer and diagnosing it early, having a much better prognosis on the quality of life.

RESULTS

The study has taken into account 102 patients with viral hepatitis B and D. The composition of the batches is presented in the following table:

TABLE 1. Prevalence of viral hepatitis 2012-2015

BATCH		Frequency	Percent
Valid	VHB	63	61%
	VHB and VHD	39	38%
	Total	102	100%

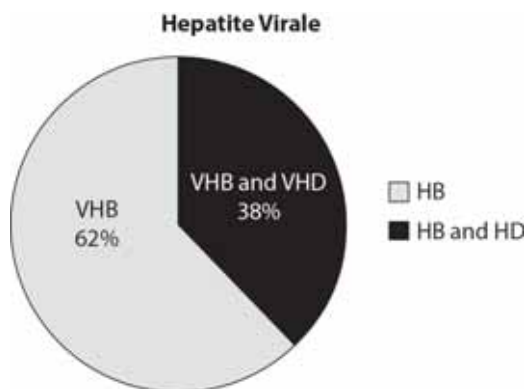


FIGURE 1. Prevalence of viral hepatitis 2012-2015

The most consistent batch is the “HB” batch, in which more than half the cases are included. What is worrying is the very high increase (38%) of patients diagnosed with Hepatitis D and Hepatitis B. An HDV infection absolutely requires an associated HBV infection. Infection with both HBV and HDV is associated with more severe liver injury than HBV infection alone. The outcome of disease largely depends on whether the two viruses infect simultaneously (coinfection), or whether the newly HDV-infected person is a chronically infected HBV carrier (superinfection). Overinfection can worsen the hepatic lesions and, over the course of a few decades, it can lead to cirrhosis and hepatocellular carcinoma. Coinfections of HBV and HDV are usually acute, self-limited infections. The chronic form of hepatitis D is seen in less than 5% of HBV-HDV coinfecting patient. Out of all the patients diagnosed with hepatitis B and hepatitis B+ Hepatitis D, 68 males and 34 females have been identified. The incidence was higher for male patients, which can be seen in Fig. 2. In our study, the M:F comparison was 2,7:1, whilst worldwide it is 3,7:1. Although the cause of incidence difference is unknown, the working environment and also ethanol abuse can be blamed. The high occurrence of hepatocellular carcinoma in male patients can be based on hormonal profile, working environment or life style.

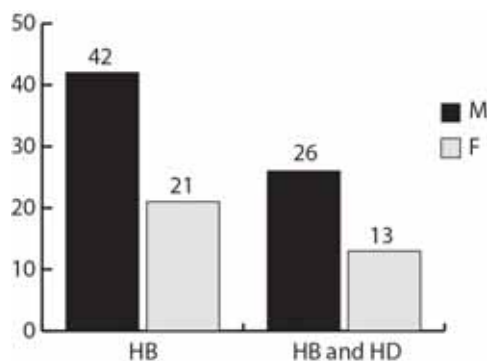


FIGURE 2. Classifying patients according to sex

The evolution of viral hepatitis depends on a variety of factors, such as: diagnosis age, sex, race, viral load, biochemistry, immune response. Because the initial moment of the vital infection is unknown, he is in most cases approximated, in order to calculate the necessary time for the hepatic cirrhosis to develop.

TABEL 2. The presence/absence of cirrhotic liver is presented in batches in the following tables

Cirrhotic liver	VHB		VHB and VHD	
	Yes	48	29	
No	15	10		
Total	63	39		

The structural evolution of the liver is very important. According to Table 2, 76% of the patients diagnosed with hepatitis B have a cirrhotic liver. The study shows that the overinfection of co-infection with hepatitis D is close to that, with a very high percentage (74% of the total). Therefore, patients with hepatitis D develop the cirrhotic syndrome much faster.

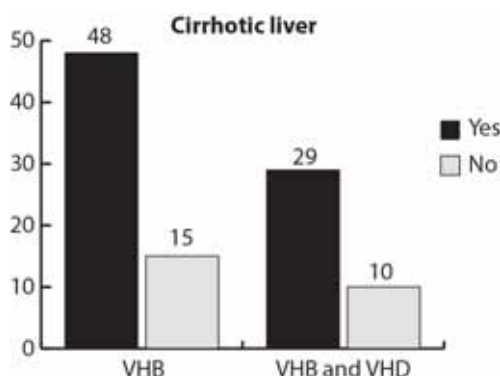


FIGURE 3. The presence/absence of cirrhotic liver is presented in batches in the following tables

The hepatic function was evaluated from a biochemical point of view. The mean AST value was 119 UI/L and the ALT value was 110 UI/L. The mean RBC value in the moment of admission was 11.8 g/dL and the mean hematocrit value was 38.4%. In principle, throughout the monitoring process, there were no This time, all three coefficients are significantly different from 0, indicating the existence of correlations significant hemoglobin decreases identified.

Between each variable pair there is a strong correlation Between each pair of variables exists a strong correlation (Pearson coefficient is over 0.7), also the correlation between the Alanine aminotransferase and the Aspartine aminotransferase values is very strong (Pearson coefficient is 0.914). The following diagram reflects this situation, all

TABLE 3. The correlation coefficients between the ALT, AST and GGT values are presented in the following table

		Correlations Cirrhotic liver		
		ALT	AST	GGT
ALT	Pearson Correlation	1,000	,914**	,723**
	Sig. (2-tailed)		,000	,000
	N	26,000	26	26
AST	Pearson Correlation	,914**	1,000	,703**
	Sig. (2-tailed)	,000		,000
	N	26	26,000	26
GGT	Pearson Correlation	,723**	,703**	1,000
	Sig. (2-tailed)	,000	,000	
	N	26	26	26,000

** . Correlation is significant at the 0.01 level (2-tailed).

cases aligning in the trusted reference levels of 95% on one side and the other of the regression line. In conclusion, the subscribed patients had a normal hepatic synthesis function, with no signs of cholestasis, but most of them have increased values of the hepatocellular destruction markers. The study shows that the high viraemia viral infection B is associated with a high degree of fibrosis. Most times the degree of fibrosis is identified by imagistic evaluation, most frequently by FibroScan, FibroTest and abdominal ultrasound. The subscribed patients are, in an overwhelming proportion, cirrhotic. Symptoms are less severe than in acute hepatitis, and while serum ALT and AST levels are elevated, bilirubin and albumin levels and prothrombin time may be normal. In chronic hepatitis D, the HBV markers are usually suppressed. The HCC occurrence in non-cirrhotic patients, although possible through the direct viral carcinogenesis mechanism, is much less common. Most times, as our analysis shows, HCC occurs on a 84.2% cirrhotic liver, after a long evolution of the basic pathology. Alpha-fetoprotein (AFP) is used as a tumor marker to help detect and diagnose cancers of the liver. Though the test is often ordered to monitor people with chronic liver diseases such as cirrhosis, chronic hepatitis B or hepatitis C because they have an increased lifetime risk of developing liver cancer, most current guidelines do not recommend this use. The purpose of the study is to closely monitor patients with hepatitis D, because lately there has been a considerable increase in the transmission of the viral infection. The AFP level in patients with hepatitis D is much higher than in patient diagnosed only with hepatitis B. The use of the alpha feto protein (AFP) as tumor marker consists especially in the detection and monitoring of the evolution of the hepatocellular carcinoma,

which develops alongside hepatic cirrhosis and chronic hepatitis. An AFP serum increase in a patient with hepatitis B or hepatitis D would have to raise awareness that he/she has developed hepatocellular carcinoma. It is generally accepted that the serum levels higher than 500 mcg/l (normally, in most laboratories they are between 10 and 20 mcg/l) in a high risk patient is a matter of HCC diagnosis.

TABLE 3. Distribution of Alpha-fetoprotein on batches has the following descriptive statistical indicators

Alfa feto-protein	N	Mean	Std. Deviation	Minimum	Median	Maximum
HB	63	5.711	4.6697	0.8	4.600	27.9
HB and HD	39	6.289	3.5443	1.4	5.700	18.2
Total	102	6.750	4.4723	0.8	5.500	27.9

The survival of patients was analysed according to AFP values when they subscribed for the study and when the study ended. From our point of view, the data have no importance for initial values (Pearson coefficient=0.17) but have an importance for the final values of the study (progress, death).

Therefore we believe that AFP values don't even have a prognosis impact for the neoplasia that show AFP, except a short-term prognosis. The category with the lowest patient survival rate was the one with patients with values between 100 and 500.

CONCLUSIONS

1. A closer and more careful surveillance of patients entering this research program is highly beneficial for the prevention and detection of liver cancer at its early stages, allowing thus a more favorable prognosis in terms of the patient's quality of life. The most important risk factors that foster the development of liver cancers are represented in this study by the presence of viral hepatic markers.

2. Viral infections with hepatitis B and hepatitis D viruses occur more frequent in men. Consequently, the incidence of developing liver cancer is significantly higher in men than in women.

3. The occurrence of infection with hepatitis D virus in HBV patients increases considerably the potential of liver cancer development. The degree of liver damage caused by the occurrence of cirrhotic liver and cirrhosis respectively is higher in HDV patients.

4. High viraemia Hepatitis B is associated with a high degree of fibrosis, analysed imagistically and by using FibroScan.

5. In this study, the ALT level has directly influenced the carcinogenetic, evolution, its progression

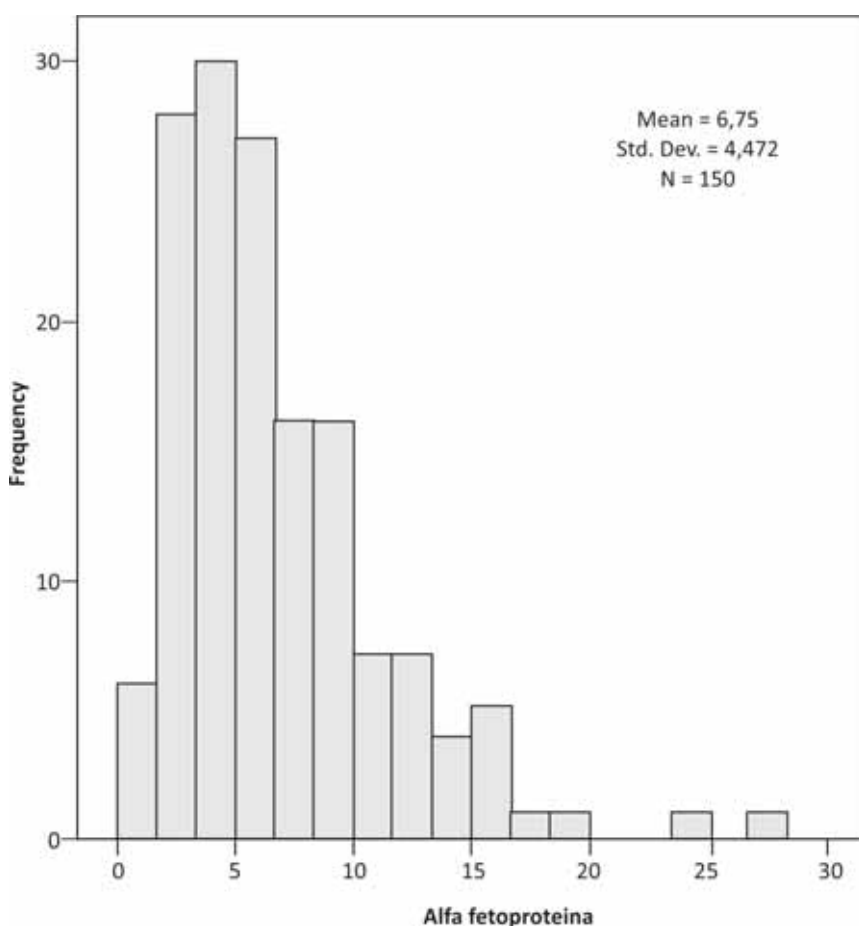


FIGURE 4. The overall distribution of the Alpha-fetoprotein values is presented in the following histogram

being more rapid than in the patients with constant ALT levels. Among all biochemical parameters we have analyzed (albuminemia, bilirubin, coagulation parameters), the reduction of the platelet count was the single variable that accurately and specifically reflected the unfavorable evolution to the worsening stage of the hepatic fibrosis.

6. AFP can temporarily increase whenever the liver is injured and regenerating, and moderate elevations can be seen with a variety of conditions. Because of this, AFP testing cannot be used solely to diagnose cancer. In addition, not every cancer will produce AFP, so a person could still have cancer even when the AFP is normal. For these reasons, the AFP test should not be used to screen the general population for cancer.

7. The AFP diagnosis-related sensibility and specificity highly depend on the admissible threshold value. There has been considered that values exceeding 400 ng/ml indicate the presence of HCC while the values varying from 100 to 400 ng/ml indicate the susceptibility of HCC

8. The biological manifestations highlighted in HCC on the cirrhotic liver have a nonspecific nature and are largely the expression of a the pre-ex-

isting liver disease. The preponderant increase of AST compared to ALT and the unexplained, isolated increase of cholestasis enzymes suggest in a certain clinical context the possibility of developing a HCC. The analysis of hematologic parameters enables the identification of possible paraneoplastic syndromes

9. The importance of ultrasound for the surveillance and early detection of liver cancer and the use of AFP as adjuvant test in diagnosing the liver cancers. Ultrasound imaging is often used due to its accuracy in the early detection of liver nodules (dysplastic regenerative nodules).

10. Ultrasound imaging represents a very efficient method for screening the patients diagnosed with viral hepatitis B and D. If performed regularly, it allows the early detection of the disease in a large number of patients, improving thus the disease prognosis.

11. HCC prevention must become the main concern in Romania, given the ineffective treatment for advanced stages. Primary (vaccination) and secondary (screening) prevention measures as well as the broadening of access to antiviral therapies are necessary measures in our population.

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