SCREENING FOR PREVENTION OF HEPATOCELLULAR CARCINOMA IN PATIENTS DIAGNOSED WITH VIRAL HEPATITIS (2012-2015)

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***Keywords**: Hepatitis B virus, Hepatocellular carcinoma, Hepatitis C*

***Abstract:** Hepatocellular carcinoma (HCC) is one of the most common types of cancer worldwide. Over 80% of hepatocellular carcinomas are believed to be closely related to chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV).(1,2) Due to the limited number of treatment options which are now available, HCC is often associated with a poor prognosis and thus it remains the third leading cause of cancer-related deaths. Given the fact that hepatic carcinogenesis is a complex process requiring a long-term development, both the hepatitis B and/or hepatitis C viral infection(s) and the hepatic cirrhosis are the major risk factors that lead to the development of hepatic neoplasm.(3,4) The importance of this pathology derives from several aspects, such as the high number of patients diagnosed with hepatic neoplasm and the liver-related mortality rate that is on the rise, reaching alarming levels, particularly due to the fact that most of the HCC patients present with clinical symptoms when HCC is in a far advanced-stage.(5) This study is conducted over 150 patients treated at "Fundeni" Hospital of Bucharest from 2012 to 2015 and it approaches the screening methods for early detection of hepatocellular carcinoma in patients diagnosed with viral hepatitis infections.*

INTRODUCTION

Liver cancer is one of the most common types of cancer worldwide and its incidence is expected to increase further in the following years.(6,7,8) According to GLOBOCAN estimates for 2012, the liver cancer represents the second leading cause of cancer-related deaths, accounting for nearly 740.000 deaths (9,1% of the total).

Hepatocellular carcinoma (HCC) accounts for 80% of malignant primary liver tumours. This disease tends to affect the liver due to alcohol abuse or chronic HBV and HCV infections in liver cirrhoses-diagnosed patients.(9,10) HCC accounts for more than 70-85% cases of liver cancer worldwide; cirrhoses represents the first factor that has an irreversible and damaging effect upon liver cells.(11,12,13) Besides cirrhosis, we can also talk about several other factors that stimulate the development of liver neoplasm. Thus, chronic HBV infection and HBV + HDV infection generate a high risk of occurrence of hepatocellular carcinoma.(14,15)

PURPOSE

HCC surveillance and/or screening processes aim to decrease the rate of cancer-related mortality and morbidity in patients with pre-existing hepatopathies. At the same time, these are very efficient methods for early detection of liver cancer. This paper attempts to evaluate and survey patients with hepatitis D virus (HDV), HBV and HCV infections, even immediately after the onset of the disease, by means of regular ultrasound and Alpha-fetoprotein (AFP) tests, aiming to detect the occurrence of liver cancer at an early stage and to increase the survival rates.

Clinical experience proved that HCC surveillance by combining ultrasound and AFP tests is a highly efficient preventive method in terms of reduction of mortality rates.

The main objectives of this study are presented below:

1. Prospective evaluation (conducted over a 4-year period, from 01/15/2012 to 01/10/2015) of liver cancer incidence in patients diagnosed with hepatitis virus infections and hospitalized at Fundeni Hospital, Bucharest;

2. Distribution of liver cancer cases depending on age and gender.

3. Identification of hepatic markers in relation to clinical and biochemical parameters, which, according to the researches, have a certain indicative value for HCC diagnosis.

4. AFP development in patients diagnosed with hepatitis virus infections in order to diagnose HCC in its early stage.

5. Assessment of ultrasound efficiency for the screening programs designed to detect and diagnose HCC at an early stage.

MATERIALS AND METHODS

This paper is a retrospective study conducted from 01/15/2012 to 01/10/2015 on a group of 150 patients admitted to Fundeni Hospital, Bucharest. It includes the surveillance of patients diagnosed with HVB, HVC, HVD and post-hepatic cirrhosis.

As regular ultrasound scans and AFP testing are used to keep the disease development under a close surveillance, any changes found in the liver structure as well as any biochemical changes of the AFP tumour marker raise the level of concern. A close surveillance of the patients entering this research program would be more than beneficial for HCC prevention and detection in its early stages, increasing thus the chances for a much better prognosis in terms of the quality of life.

Statistical analysis of the data was performed using the Statistical Program for Social Science (SPSS) software, version 19.

For the descriptive analysis of the data, we used frequency tables, measures of central tendency and dispersion in order to determinate the relevant differences between subsets.

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Article received on 29.03.2016 and accepted for publication on 27.05.2016
ACTA MEDICA TRANSILVANICA June 2016;21(2):86-89

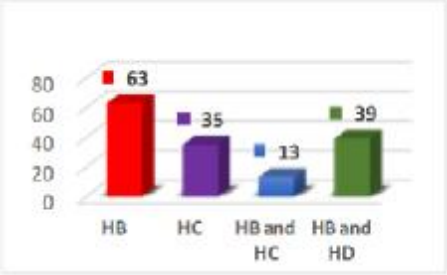
RESULTS AND DISCUSSIONS

This study was focused on 150 patients diagnosed with acute and chronic viral hepatitis. The following table shows the components of the patients' subsets:

Table no. 1.Prevalence of viral hepatitis: 2012-2015

Subset		Frequency	Percent
Valid	HB	63	35.3
	HC	35	23.3
	HB and HC	13	8.7
	HB and HD	39	32.7
	Total	150	100.0

Figure no. 1. Prevalence of viral hepatitis 2012-2015



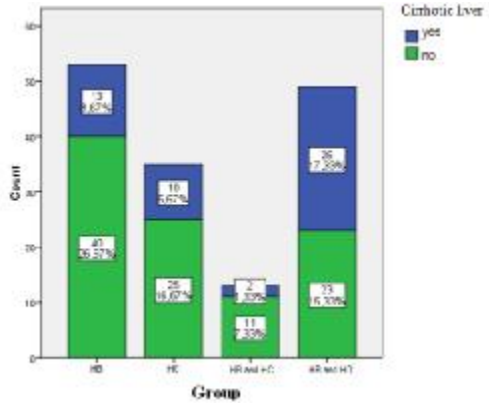
The most significant subset is the "HB" subset which includes over 1/3 of the cases. Fewer cases (13, representing 8.7%) are attributable to the "HB and HC" subset. What is now alarming is the considerable increase in the number of patients diagnosed with HDV and HBV (32%), with a very poor prognosis and a high predisposition to develop liver cancer.

The liver structure was carefully analyzed as it allowed us to properly monitor the degree of liver damage in patients diagnosed with viral hepatitis infections. The regular liver ultrasound performed every 6 months revealed the fact that among all patients infected with hepatitis viruses, those diagnosed with chronic hepatitis D are more predisposed develop cirrhosis more rapidly (see table no. 2).

Table no. 2. Presence/absence of liver cirrhosis, per subsets of patients

Count		Subset				
		HB	HC	HB and HC	HB and HD	Total
Liver cirrhosis	yes	13	10	2	26	51
	no	40	25	11	23	99
	Total	53	35	13	49	150

Figure no. 2. Presence/absence of liver cirrhosis



We clearly notice the high incidence of this fact in the "HB and HD" subset (53.1% cases). The early detection of infections with hepatitis viruses is quite rare; generally, such infections are detected in their chronic phases when the complete recovery is much more difficult to attain. The evolution of viral hepatitis infections into liver cancer or liver cirrhosis takes years (roughly 10 to 20 years). Such evolution to malignancy chiefly depends on a series of factors such as the person's lifestyle, alcohol abuse and other comorbidities which, in time, bring about the irreversible damage of liver cells (hepatocytes). In terms of distribution by age, studies showed that it has a relatively normal distribution, around 50 years of age, except for the interval pertaining to 55-65 years when the frequency of liver cancer cases is much higher.

Figure no. 3. The distribution of patients by age

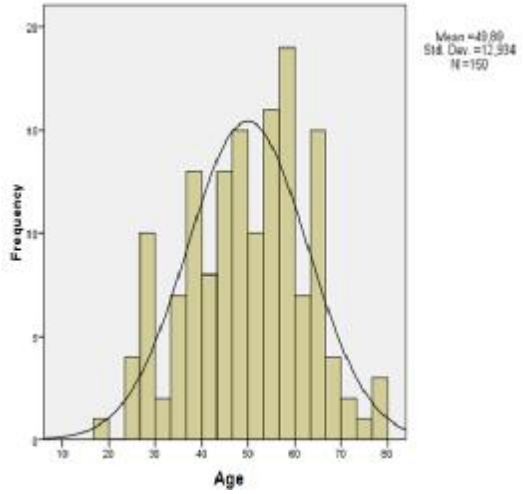
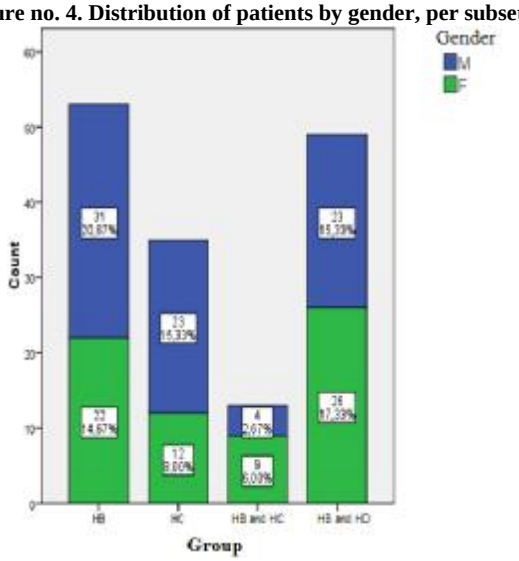


Figure no. 4 shows the patients distribution by sex. The prevalence of liver cancer in male patients is more than obvious in the "HB" and "HC" subsets (men/women ratio = 2.7/1).

Figure no. 4. Distribution of patients by gender, per subsets



The use of Alpha-fetoprotein (AFP) as tumoral marker is particularly important for the detection and surveillance of HCC development which is secondary to viral hepatitis infections (hepatitis B or C) and/or liver cirrhosis. AFP

measurement is of paramount importance for the early detection of liver cancers in these high-risk groups of patients, particularly because it is used as a screening method. Values over 400ng/ml occur more frequently in HCC developed in cirrhotic livers which secrete higher amounts of AFP compared to the non-cirrhotic livers.

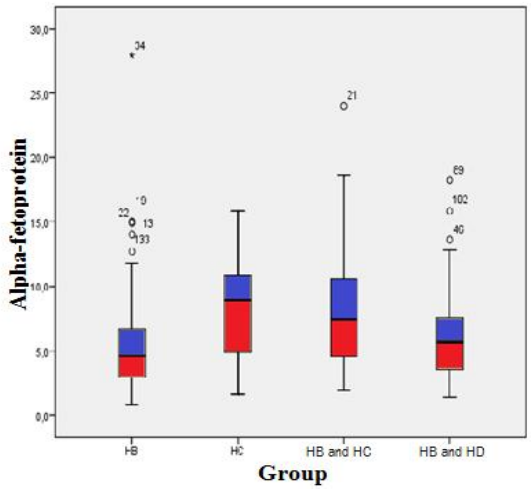
The AFP concentration is in direct correlation with the tumour size. According to this study, the AFP sensibility varies from 50% to 90% while its specificity fluctuates from 20% to 95%.

There is no correlation between the AFP concentration and the tumour growth, stage or degree of malignancy. However, the AFP measurement allows the detection of patients who have the highest risk of developing primary hepatocellular carcinoma.

Table no. 3. The distributions of alpha-fetoprotein values by subsets have the following descriptive statistical indexes

Alpha fetoprotein	N	Mean	Std. Deviation	Minimum	Median	Maximum
HB	53	5.711	4.6697	0.8	4.600	27.9
HC	35	8.163	3.8238	1.6	8.900	15.8
HB and HC	13	8.925	6.7531	1.9	7.400	24.0
HB and HD	49	6.289	3.5443	1.4	5.700	18.2
Total	150	6.750	4.4723	0.8	5.500	27.9

Figure no. 5. AFP values by subsets in patients with viral hepatitis infections



The "HC" subset reveals higher overall values (except for several "exceptional" values). The most frequent AFT may be higher in patients diagnosed with cirrhosis and HBV virus. As documented in a scientific report, the AFP has significantly dropped in patients with HCV-related cirrhosis who underwent treatment with peginterferon and ribavirin.

An elevated level of AFP serum found in a patient diagnosed with cirrhosis or HBV virus should raise concerns in respect to a potential development of hepatocellular carcinoma. It is widely recognized that serum levels exceeding 500mcg/l (the reference values of many laboratories varying from 10 to 20mcg/l) in high-risk patients indicate the likelihood of HCC. Nevertheless, liver cancers are frequently diagnosed based on a lower AFP level in patients undergoing screening tests. Furthermore, an elevated AFP level found in HCC patients may be caused by the presence of viral hepatitis infection rather than the existence of alcohol-related liver diseases. We have dosed the levels of alpha-fetoprotein (AFP) and, in some cases, the carcinoembryonic antigen (CEA) and the carbohydrate antigen-125, in patients belonging to the study group. After the measurement of other oncofetal antigens (*i.e.* the carcinoembryonic antigen (CEA) and the carbohydrate antigen-125) we found significantly elevated levels only in patients with liver metastases.

Sensibility, specificity and predictive value for AFP serum in the HCC diagnosis depends on a series of factors such as the characteristics of the individuals subject to various studies and the threshold value chosen for determining and acknowledging the diagnosis.

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 C viruses occur more frequent in men. Consequently, the incidence of developing liver cancer is significantly higher in men than in women.
3. Most cases of liver cancer have been documented in individuals aged 55 to 65.
4. 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.
5. In this study, the ALT level has directly influenced the carcinogenetic evolution, its progression 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 unfavourable evolution to the worsening stage of the hepatic fibrosis. Monitoring the albumin low level and the bilirubin high level, both reflecting an advanced stage of cirrhosis, combined with a reduced functional reserve represent the predictive factors highlighting the risks of developing liver cancer.
6. The biological manifestations highlighted in HCC on the cirrhotic liver have a nonspecific nature and are largely the expression of the pre-existing 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 (polycythemia).
7. 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).
8. The positivity rate is slightly higher in HCC on a cirrhotic liver (37.8%) compared to the non-cirrhotic liver (28.7). Following the study, AFP almost doubles for the viral C etiology as it associates an extended necrotic, inflammatory

and regenerative process.

9. The surveillance program of patients diagnosed with cirrhosis revealed that the ultrasound pattern of multiple hypoechogenic, non – homogeneous nodules is associated with a high risk of evolution of dysplastic nodules into hepatocellular carcinoma.
10. Ultrasound imaging represents a very efficient method for screening the patients diagnosed with viral hepatitis infections. If performed regularly, it allows the early detection of the disease in a large number of patients, improving thus the disease prognosis.
11. There is no doubt that ultrasound is a very useful technique for identifying the occurrence of HCC suspected nodules, and technical improvements to this method (ultrasound with contrast agent) will further increase the acuity of the diagnosis. However, these benefits of the ultrasound constitute at the same time its greatest limits because, being an operator- and equipment performance-dependent technique, may give false negatives.
12. The ideal surveillance interval is not a standard interval. A 6 to 12-month surveillance period, based on the tumour de-doubling time, was put forward.
13. AFP level increases significantly once with the size growth and development of formations, becoming considerably higher in more advanced stages.
14. 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.
15. The quantitative determination of AFP, with setting a threshold value in the context of a suggestive imaging exam, has the value of a definite HCC diagnosis.
16. 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.
17. A quality supportive treatment may prolong the survival of patients with impaired hepatic function in a proportion even higher than systemic antitumor therapy. These data show that, in some cases, the death of patients occurs rather through the decompensation of cirrhosis than the progression of the neoplasia. Therefore, the best approach to these patients is a multidisciplinary one, from their diagnosis to their death.

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