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Clinical and Laboratory Characteristics of Patients with Hepatocellular Carcinoma Associated with Viral Hepatitis B

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Abstract The presence of cirrhosis increases the risk of developing hepatocellular carcinoma by more than 30 times compared with patients without cirrhosis. Such a high risk of developing primary liver cancer is due to the fact that cirrhosis is the final stage in the progression of a large number of lesions and liver diseases. It should be borne in mind that in most patients, cirrhosis of the liver is compensated in nature and, accordingly, is asymptomatic. In such cases, the onset of symptoms and, accordingly, the diagnosis of the disease occurs either at the onset of the decompensation phase of liver cirrhosis, or when signs of neoplasm appear. The work included data from a retrospective and prospective analysis of case histories of patients diagnosed with hepatocellular carcinoma who were hospitalized at the Republican Specialized Scientific and Practical Medical Center for Oncology and Radiology of the Republic of Uzbekistan from 2016 to 2019. 68 Patients were divided into 2 groups. The main group consisted of patients with hepatocellular carcinoma and positive tests for HBsAg. The control group included patients with hepatocellular carcinoma, in which serological markers for viral hepatitis were negative**.** This is due to the direct participation of the hepatitis B virus itself in the development of oncogenesis of hepatocellular carcinoma. In addition, the clinical picture consists of the symptoms of the oncological process on the one hand and the clinical picture of a prolonged viral liver damage, on the other hand.

Keywords Hepatocellular carcinoma, Viral hepatitis B, Cirrhosis

1. Introduction

According to the International Organization for Research on Cancer, liver cancer is in 5th place among the most common malignant neoplasms in men (523,000 cases per year; 7.9%) and 17th place in women (226,000 cases per year; 6.5%) in the world [1]. Unlike other more common neoplasms, which tend to decrease in incidence, the incidence of liver cancer increases [2]. Hepatocellular carcinoma is the sixth most common type of cancer in the world, accounting for 7% of all cancers. The incidence of hepatocellular carcinoma is about 749,000 new cases each year. The highest incidence rates of hepatocellular carcinoma (about 85% of cases) are observed in East Asia and Africa [3]. Hepatocellular carcinoma is the fourth leading cause of death among oncological diseases in the world. About 33% of all deaths from hepatocellular carcinoma are associated with chronic viral hepatitis B infection, while 30% are associated with alcohol abuse, 21% with chronic viral hepatitis C infection, and 16% with the rest of the etiology [4]. With chronic carriage of viral hepatitis B, the risk of hepatocellular carcinoma increases by 5–15 times compared with patients not suffering from chronic viral hepatitis [5].

The introduction of vaccination programs at birth significantly reduced the frequency and prevalence of viral hepatitis B in several areas with high endemicity, which had a serious impact on the incidence of the liver, especially hepatocellular carcinoma [6,7]. Despite the fact that the prevalence of viral hepatitis B infection in the world is decreasing, the absolute number of infected people continues to grow as a result of global population growth [8]. Since chronic viral hepatitis B, as a rule, is asymptomatic until progressive liver disease develops, up to approximately 80% of infected patients are not aware of their infection and concomitant liver disease [9].

Hepatocellular carcinoma associated with viral hepatitis B is mainly observed among men (203,000 new cases in 2015 versus 70,000 in women), while the ratio of men to women

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is about 3: 1, and also causes one third of deaths from hepatocellular carcinoma [10]. An additional factor associated with an increased risk of hepatocellular carcinoma is the duration of the disease [11]. Chronic inflammatory condition and hepatic oxidative stress caused by chronic hepatitis B accelerate cell aging processes. Aging processes are at the genomic level and are associated with the shortening of telomeres, the length of which is inversely proportional to the degree of fibrosis and reaches the lowest values for hepatocellular carcinoma [12].

The presence of cirrhosis increases the risk of developing hepatocellular carcinoma by more than 30 times compared with patients without cirrhosis [13]. Such a high risk of developing primary liver cancer is due to the fact that cirrhosis is the final stage in the progression of a large number of lesions and liver diseases. It should be borne in mind that in most patients, cirrhosis of the liver is compensated in nature and, accordingly, is asymptomatic. In such cases, the onset of symptoms and, accordingly, the diagnosis of the disease occurs either at the onset of the decompensation phase of liver cirrhosis, or when signs of neoplasm appear.

2. Materials and Methods

The work included data from a retrospective and prospective analysis of case histories of patients diagnosed with hepatocellular carcinoma who were hospitalized at the Republican Specialized Scientific and Practical Medical Center for Oncology and Radiology of the Republic of Uzbekistan from 2016 to 2019.

Patients were divided into 2 groups. The main group consisted of patients with hepatocellular carcinoma and positive tests for HBsAg. The control group included patients with hepatocellular carcinoma, in which serological markers for viral hepatitis were negative.

The criteria for inclusion in the main group were the presence of hepatocellular carcinoma, confirmed by ultrasound and computed tomography and / or magnetic resonance imaging and histological confirmation of the diagnosis, as well as the presence of HBsAg. Exclusion criteria were negative markers for HBsAg, the presence of concomitant hepatitis C, human immunodeficiency virus (HIV), under 18 years of age and all other causes of cirrhosis eg. alcoholic, primary biliary cirrhosis.

The criteria for inclusion in the control group were the presence of hepatocellular carcinoma confirmed by ultrasound and computed tomography and / or magnetic resonance imaging and histological confirmation of the diagnosis of negative markers for viral hepatitis and human immunodeficiency virus (HIV), under the age of 18 years.

The average age of patients in group 1 was 46.7 ± 2.18 years. Men were 27 (72.97%), women were 10 (27.03%). The average age of patients in the second group was 54.41 ± 2.63 years. There were 11 men (35.48%), 20 women (64.52%).

The examination of the patients consisted of an assessment of complaints, physical examination, data from general laboratory tests (general and biochemical blood tests), instrumental methods of investigation (ultrasound, computed tomography and / or magnetic resonance imaging), histological data.

Statistical analysis was performed using Excel 16.0 programs. For each series of results, the arithmetic mean (M), the error of the mean (m), were calculated. In the tables, the results are presented as M ± m. Comparison of two samples was carried out using the xi-square. When comparing the average values, the Student t-test was used. For the level of reliability of statistical indicators, $p < 0.05$ was taken.

3. Results

In the analysis, hepatocellular carcinoma was more common in men - 59 people (62.77%) than in women-35 (37.23%) people. The number of men predominated in the group with hepatocellular carcinoma associated with viral hepatitis B, while in the group of patients with hepatocellular carcinoma without viral hepatitis, the numerical advantage was in women. (table 1).

Table 1. Distribution of patients by gender and age in the compared groups

Groups	Sex				Age M±m
	Males		Females		
	n	%	n	%	
Main group n=37	27	72,97	10	27,03	46,7±2.18
Control n=31	11	35,48	20	64,52	54,41±2.63

When analyzing the age composition, the majority of patients in the general group were over the age of 50 years (Fig. 1).

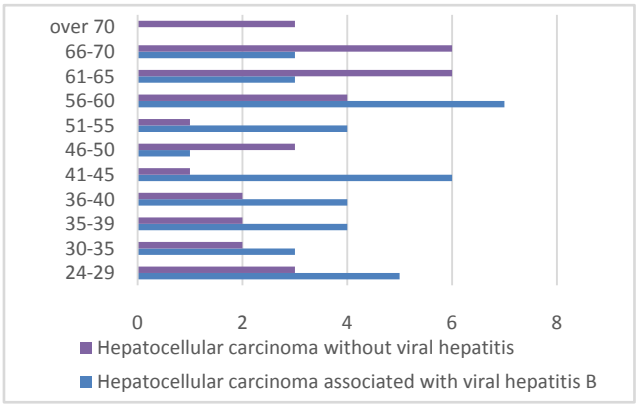

Figure 1. Age distribution in the study groups

In the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B, the number of patients older than 50 years old was only 45.95%, i.e. more than half of the development of hepatocellular carcinoma in this group occurred in the age range of 24-50 years. In the

control group, patients over 50 years old accounted for 64.52%. Thus, hepatocellular carcinoma associated with chronic viral hepatitis B was detected at an earlier age compared to a group of patients with negative markers of viral hepatitis ($p < 0.05$).

Table 2. Complaints of patients in the compared groups

Groups Indicators in% of n	Hepatocellular carcinoma associated with chronic viral hepatitis B n = 37	Hepatocellular carcinoma with negative hepatitis markers n = 31	Total number of patients n = 68
Weakness	81,08%	71%	75%
Fatigability	62,16%	42 %	53%
Decreased appetite	64,86%	51,61%	59%
Nausea	43,24%	22,58%	34%
Pain in the right hypochondrium	67,57%	45,16%	57,35%
Temperature increase	54%	45%	50%
Losing weight	56,75%	35,48%	47%

Complaints were analyzed at the time of the patient examination. Most often, patients complained of weakness and increased fatigue, decreased appetite, pain in the right hypochondrium, weight loss, fever. Moreover, patients in the group with hepatocellular carcinoma associated with chronic viral hepatitis B complained more about weakness and increased fatigue compared to the control group. There were no statistically significant differences in the groups ($p > 0.05$). 59% of patients complained of a decrease in appetite; no statistically significant differences were revealed between the groups ($p > 0.05$). 34% of patients complained of nausea. Moreover, a higher percentage was in the group with hepatocellular carcinoma associated with chronic viral hepatitis B. However, there were no statistically significant differences ($p > 0.05$). 57.35% of patients complained of pain in the right hypochondrium. In the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B, the frequency of pain was statistically higher than in the control group ($p < 0.05$). Complaints of fever were observed in half of the cases (50%), while this complaint was also more common in the group with hepatocellular carcinoma associated with chronic viral hepatitis B. No statistically significant differences between the groups were found ($p > 0.05$). 47% of patients complained of losing weight. In the group with hepatocellular carcinoma associated with chronic viral hepatitis B, complaints of weight loss were statistically more frequent compared with the group of patients without viral hepatitis ($p < 0.05$).

On examination, ictericity of the skin and sclera was noted in 34% and 35% of cases, respectively. Moreover, ictericity of the skin and sclera during examination was significantly more common in the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B compared with the control group ($p < 0.05$ and $p < 0.05$, respectively).

Liver enlargement occurred in 68% of cases in the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B and in 55% of cases in the group of patients with hepatocellular carcinoma without viral hepatitis. Moreover, despite the fact that the enlarged liver during palpation was slightly smaller in the group of patients with hepatocellular carcinoma without viral hepatitis, no statistically significant differences were detected in the groups ($p > 0.05$). Pain on palpation of the liver was observed in 83.78% of cases in the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B and in 51.61% of cases in the group of patients with hepatocellular carcinoma without viral hepatitis. Pain on palpation was statistically higher in the group with hepatocellular carcinoma associated with chronic viral hepatitis B ($p < 0.05$). Palpable formation occurred in 16.21% of cases in the main group and in 10% of cases in the control group. Despite the fact that the lesions were more often palpated in the group with hepatocellular carcinoma associated with chronic viral hepatitis B, there were no statistically significant differences in the groups ($p > 0.05$).

Spleen enlargement was statistically higher in the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B (41%) compared with the group of patients with hepatocellular carcinoma without viral hepatitis (16%) ($p < 0.05$).

When comparing groups with hepatocellular carcinoma associated with chronic viral hepatitis B and groups with carcinoma without viral hepatitis, ascites was statistically more frequent in the former (13% and 3.23, respectively) ($p < 0.05$).

Table 3. The results of indicators of the general analysis of blood in the studied groups

Groups Indicators M±m	Hepatocellular carcinoma associated with chronic viral hepatitis B n = 37	Hepatocellular carcinoma with negative hepatitis markers n = 31	Norm
Hemoglobin (g / l)	112,92±3,05	110,9±3,13	130-160
Red blood cells (10^{12} / L)	4,01±0,14	4,0±0,11	4,0-5,5
Segmented (%)	4,84±0,33	5,39±0,4	1-6
Stab (%)	67,24±0,99	64,13±1,54	47-72
Eosinophils (%)	3,03±0,25	3,26±0,25	0,5-5
Monocytes (%)	2,81±0,18	2,84±0,18	3-11
Lymphocytes (%)	21,86±1,09	25,61±2,39	19-37
White blood cells (10^{9} / L)	7,69±0,78	7.02±0,65	4,0-9,0
Platelets (10^{9} / L)	221,46±12,32	260,65±9,73	180-320

The parameters of the general blood test of patients on

average were within the range of physiological fluctuations, with the exception of low hemoglobin. So in the group with hepatocellular carcinoma associated with chronic viral hepatitis B, mild anemia (90-110 g / l) was found in 18.92% of cases, moderate anemia (89-70 g / l) in 16.22% of cases. In the group with hepatocellular carcinoma without hepatitis, mild anemia (90-110 g / l) occurred in 25.81% of cases, moderate anemia (89-70 g / l) in 16.13% of cases. A decrease in the number of red blood cells was observed in the group with hepatocellular carcinoma associated with chronic viral hepatitis B in 35.14% and in the group with hepatocellular carcinoma without viral hepatitis in 48.39% of cases, respectively. However, there were no statistically significant differences in the levels of hemoglobin, erythrocytes and color index in the groups ($p > 0.05$).

Despite the fact that the average number of leukocytes and lymphocytes was within the physiological norm, in 24.32% and 29.73% of patients with hepatocellular carcinoma associated with chronic viral hepatitis B, and in 22.58% and 35.48% of patients in the group with hepatocellular carcinoma and negative hepatitis markers, leukocytosis and lymphopenia were observed, which was associated with hypersplenism and bacterial complications. At the same time, there were no statistically significant differences in these indicators in the groups ($p > 0.05$).

Table 4. The results of a biochemical analysis of blood in the studied groups

Groups Indicators M±m	Hepatocellular carcinoma associated with chronic viral hepatitis B n = 37	Hepatocellular carcinoma with negative hepatitis markers n = 31	Norm
Total bilirubin (μmol / L)	25,49±3,2	18,12±1,82	2,0-21,0
Alanine aminotransferase (Unit / L)	93,54±10,5	59,87±6,92	0-64
Aspartate aminotransferase (Unit / L)	131,78±13,89	66,81±7,12	0-62
Creatinine (mmol / L)	44,29±4,15	47,78±7,3	44-80
Urea (mmol / L)	5,06±0,42	4,8±0,35	1,7-8,3
Residual nitrogen (mmol / l)	2,52±0,23	2,28±0,16	0-4
Albumin (g / l)	35,23±1,58	37,85±1,77	30-55
Amylase (Unit / L)	114,93±12,05	91,9±11,82	0-220
Total protein (g / l)	64,35±1,88	67,0±1,3	66-87
Glucose (mmol / L)	5,01±0,27	5,27±0,19	4,2-6,4

In the frequency analysis, thrombocytopenia occurred in 18.92% of cases in the group with hepatocellular carcinoma associated with chronic viral hepatitis B and only 6.62% of cases in the group with hepatocellular carcinoma and negative markers of hepatitis. When comparing the platelet count of patients in the group with negative markers with the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B, the platelet count in the latter was statistically lower ($p < 0.05$).

When analyzing the results of biochemical parameters (Table 3), the level of total bilirubin in patients with hepatocellular carcinoma associated with chronic viral hepatitis B with the control group was statistically higher ($p > 0.05$).

The analysis of cytolytic syndrome data revealed a significantly higher level of Alanine aminotransferase in the group with hepatocellular carcinoma associated with chronic viral hepatitis B, compared with the group with hepatocellular carcinoma without viral hepatitis ($p > 0.05$). When comparing the level of Aspartate aminotransferase in groups of patients with hepatocellular carcinoma associated with chronic viral hepatitis B with the control group, the level of Aspartate aminotransferase in the first group was statistically higher ($p > 0.05$).

Half of the patients showed a decrease in total protein (50%). Average albumin levels were within normal limits. No statistically significant differences in these indicators were observed in the studied groups ($p > 0.05$).

Blood sugar level in all three groups was within the normal range; no statistically significant differences were detected ($p > 0.05$).

The amylase level in the studied groups was within normal limits, no statistically significant differences were found ($p > 0.05$).

The mean urea, creatinine residual nitrogen in the studied groups were within normal limits, there were no statistically significant differences ($p > 0.05$).

At the time of diagnosis of hepatocellular carcinoma, cirrhosis was observed in 59% of cases. It should be noted that liver cirrhosis was more common in the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B (75.68%), while in the group with hepatocellular carcinoma with negative viral markers, cirrhosis accounted for only 38.71% ($p < 0.05$).

In patients with hepatocellular carcinoma with cirrhosis of the liver, in most cases there was a Child-Pugh cirrhosis class A and B. Moreover, in the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B, class B was statistically more frequent than in the group with hepatocellular carcinoma against the background of liver cirrhosis without viral markers ($p < 0.05$).

According to the Barcelona clinical classification of liver cancer, patients belonged to stages B and C. There were no statistically significant differences in the studied groups ($p > 0.05$) (Fig. 2).

In all patients, the defeat of the right lobe of the liver prevailed - in 54.41%; hepatocellular carcinoma in the left lobe of the liver was located in 19.12% of cases, and bilobar liver damage was found in 26.47% of patients. The percentage of lesions in the right lobe was statistically higher in the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B ($p < 0.05$). Bilobar lesion was significantly less common in hepatocellular

carcinoma associated with chronic viral hepatitis B compared with the group without viral hepatitis (p< 0.05). No statistically significant differences were found in the lesion of the left lobe in the study groups (p> 0.05).

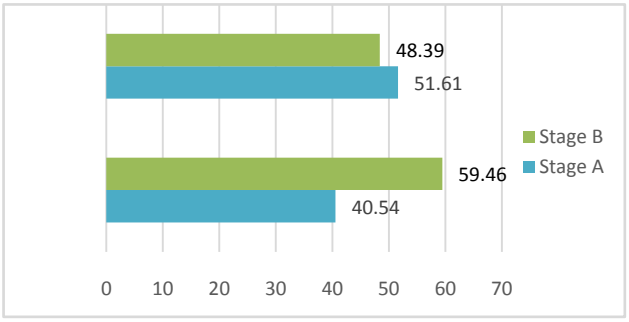

Figure 2. Distribution of patients with hepatocellular carcinoma according to the Barcelona Clinical Classification of Cancer

According to the number of tumor nodes in the liver, the share of the solitary lesion accounted for 69.12% in the general group, 2 nodes were found in 27.94% of cases, 3 or more nodes were noted in 2.94% of cases. No significant differences in the groups were obtained (p> 0.05). The size of the largest tumor formation of more than 5 cm was found in 98.53% of patients, and in only 1.47% of cases the size of the node was 2-5 cm. None of the groups had tumor nodes less than 2 cm. The size of the largest detected tumor node was the group averaged 121.1 ± 39.13 in the group of patients with hepatocellular carcinoma associated with chronic viral hepatitis B, and 98.29 ± 38.23 in the group of hepatocellular carcinoma without hepatitis. Moreover, no significant difference in the groups was revealed (p> 0.05).

Lymph node metastases were observed in 40% of cases. In the group with hepatocellular carcinoma associated with chronic viral hepatitis B, lymph nodes were observed in 37% of cases, in the group with negative viral hepatitis in 41.94% of cases. At the same time, there were no significant differences in the groups (p> 0.05). Organ metastases were observed in 7.35% of cases, statistically more often in group c in the group with hepatocellular carcinoma associated with chronic hepatitis B (10.81% versus 3.23%) (p< 0.05).

4. Discussion

The results of our studies show that hepatocellular carcinoma associated with chronic hepatitis B was statistically more common at a younger age compared with hepatocellular carcinoma without viral hepatitis, which developed mainly after 50 years. Apparently this is due to early infection, leading to malignant transformation of hepatocytes. In our studies, the majority of patients in the group with hepatocellular carcinoma associated with chronic hepatitis B are men, which is consistent with world literature. Patients with hepatocellular carcinoma associated with chronic hepatitis B were statistically more likely to complain of pain in the right hypochondrium and weight loss compared with the control group. Despite the fact that patients in the main group more often complained of weakness, malaise, decreased appetite and nausea, nevertheless, there were no statistically significant differences in the studied groups. On examination, the ictericity of the sclera and skin, splenomegaly and ascites were statistically more common in the group with hepatocellular carcinoma associated with chronic hepatitis B, which is associated as a direct effect of the hepatitis B virus on hepatocytes. In a general blood test in patients with hepatocellular carcinoma associated with chronic hepatitis B, thrombocytopenia was statistically more common, which is associated with the phenomena of hypersplenism characteristic of liver cirrhosis. A detailed examination of the blood chemistry data of patients with hepatocellular carcinoma associated with chronic hepatitis B showed a significantly higher level of total and direct bilirubin, Alanine aminotransferase and Aspartate aminotransferase. Thus, cytolytic syndrome caused by viral liver damage and the immuno-mediated action of viral hepatitis B came to the fore. Patients with hepatocellular carcinoma associated with chronic hepatitis B were more likely to experience cirrhosis, which is also associated with prolonged persistence of viral hepatitis B. In addition, in 24.32% of patients in the main group hepatocellular carcinoma developed without cirrhosis, which is explained by the direct influence of the presence of hepatitis B viruses themselves on the oncogenesis of hepatocellular carcinoma. Tumor nodes in patients with hepatocellular carcinoma associated with chronic hepatitis B were statistically more often located in the right lobe of the liver compared to the control group. Metastases to neighboring organs were also statistically more often observed in patients with hepatocellular carcinoma associated with chronic hepatitis B.

5. Conclusions

Despite the similar picture, the clinical picture of hepatocellular carcinoma associated with viral hepatitis B has a number of features compared to hepatocellular carcinoma without viral hepatitis. This is due to the direct participation of the hepatitis B virus itself in the development of oncogenesis of hepatocellular carcinoma. In addition, the clinical picture consists of the symptoms of the oncological process on the one hand and the clinical picture of a prolonged viral liver damage, on the other hand.

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Ethical Approval

The ethical approval for the study was granted by the Committee of Ethical Approval for Researches under the Ministry of Health of the Republic of Uzbekistan.

Consent

Written informed consent was obtained from all participants of the research for publication of this paper and any accompanying information related to this study.

REFERENCES

[1] Hashem B.E. -Epidemiology of viral hepatitis and hepatocellular carcinoma - Gastroenterol. 2012. -Vol. 142. - P. -1264-1273.

[2] Siegel RL, Miller KD, Jemal A.-Cancer statistics, 2018 -CA Cancer J Clin 2018; 68 -P. -7 -30.

[3] International Agency for Research on Cancer, 2011.

[4] Collaboration Global Burden of Disease Liver Cancer. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. - JAMA Oncol -2017 -3 -P. -1683-91.

[5] Tsai WL, Chung RT. -Viral hepatocarcinogenesis. -Oncogene. -2010 -29 (16) -P. 2309 –2324.

[6] Chang MH, Chen CJ, Lai MSHsu HM, Wu TC, Kong MS et al. -Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. -N Engl J Med. -1997 -336 -P. - 1855-1859.

[7] Chiang C.J., Yang Y.W., You S.L., Lai M.S., Chen C.J. -Thirty -year outcomes of the national hepatitis B immunization program in Taiwan. –JAMA -2013 310 -P. - 974-976.

[8] Polaris Observatory Collaborators-Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modeling study. -Lancet Gastroenterol Hepatol. -2018 -3 -P. - 383-403.

[9] Papatheodoridis G. Thomas HC, Golna C., Bernardi M., Carballo M., Cornberg M. et al. - Addressing Barriers to the Prevention, Diagnosis and Treatment of Hepatitis B and C in the Face of Persisting Fiscal Constraints in Europe: Report From a High Level Conference - J Viral Hepat. -2016-23- P.- 1-12.

[10] Collaboration Global Burden of Disease Liver Cancer. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. -JAMA Oncol -2017 -3 -P. -1683 -91 (also corresponds to number 4).

[11] Xie Y. - Hepatitis B virus-associated hepatocellular carcinoma. -Adv Exp Med Biol 2017 -1018 -P. -11-21.

[12] Riccardo Nevola, Luca Rinaldi, Mauro Giordano, Aldo Marrone, Luigi Elio Adinolfi - Mechanisms and clinical behavior of hepatocellular carcinoma in HBV and HCV infection and alcoholic and non-alcoholic fatty liver disease-Hepatoma Res -2018 -4 -P.55.

[13] Thiele M., Gluud L.L., Fialla A.D. et al. - Large variations in risk of hepatocellular carcinoma and mortality in treatment naive hepatitis B patients: systematic review with meta -analyses. - PLoS One. 2014. -Vol. 9. -P.e107177.