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The significance of biomarkers APRI and AFP in the progression of the pathological process to liver cirrhosis in patients with chronic viral hepatitis C

Bayjanov Allabergan Kadirovich, Khikmatullaeva Aziza Saidullaevna, Abdukadirova Muazzam Alievna, Brigida Krestina Stepanovna

e-mail: drbayjanov@mail.ru, aziza9999@rambler.ru, brigidakrestina@gmail.com

Scientific Research institute of Virology of the Republican specialized scientific-practical medical center of Epidemiology, microbiology, infectious and parasitic diseases

Abstract: This scientific study was carried out on 43 patients with chronic viral hepatitis C. Among the examined patients, there were 23 men (53,5%) and 20 women (46,5%). The age of the patients ranged from 18 to 59 years (the average age of patients was 36,2±5,36 years). The diagnostic significance of the APRI and AFP index in the progression of liver fibrosis to cirrhosis in patients with chronic viral hepatitis C was studied. According to laboratory studies, it was revealed that a significant increase in the value of an indirect marker of liver fibrosis - APRI (AST to platelet ratio index) was detected in patients with chronic viral hepatitis C in the presence of liver fibrosis at stage F1-F4 compared with patients with normal liver density - F0, at p <0,05. There was a twofold increase in the average marker of liver cell regeneration alpha-fetoprotein - AFP in patients with chronic viral hepatitis C in the presence of liver density F1-F4 compared with patients with normal liver density (F0) (p <0,05).

Keywords: biomarker, chronic viral hepatitis C, cirrhosis, APRI, AFP, progression

Introduction. With the parenteral route of infection, the risk of HCV transmission is 10 times higher than HIV [4]. WHO has called chronic hepatitis C virus (CHCV) a “ticking time bomb”, drawing attention to the enormous human, social and economic costs that an epidemic of this viral disease entails? This course often leads to clinical manifestation only in the late stages of the disease, transforming into severe fibrosis and cirrhosis of the liver (LC), which in turn can lead to hepatocellular carcinoma (HCC) [2]. Hepatitis C is a disease caused by an RNA virus (HCV) and belongs to the Flaviviridae family. The disease becomes chronic in 85% of patients and can be asymptomatic in 90% [7, 12]. Today, there are at least 6 main HCV genotypes, which in turn are divided into subtypes [11]. Over the past two decades, great progress has been made in understanding the pathogenesis of fibrosis. Knowledge of the mechanisms underlying fibrosis has made it possible to identify several possible pathways for the diagnosis and prognosis of fibrosis [1, 3, 6, 13]. There are direct and indirect non-invasive markers of liver fibrosis and instrumental diagnostic methods [5, 10]. The APRI index is used as indirect serological markers [9]. An APRI index (aspartate aminotransferase to platelet ratio index) above 0.75 is characteristic of liver cirrhosis. The direct correlation between

the METAVIR scale and the APRI index, according to the literature, is 0,24.

In patients with chronic diseases, this indicator shows high accuracy in diagnosing severe fibrosis and cirrhosis of the liver [15]. Alpha-fetoprotein (AFP), a serum marker of hepatocarcinoma, may be increased in patients with chronic liver disease. It serves as an indicator of tissue regeneration against the background of fibrosis formation. AFP is used as a non-invasive marker of liver fibrosis and cirrhosis, including in the calculation formula along with platelets and transaminases. AFP monitoring, both during the initial examination of patients with liver cirrhosis and in the dynamics of the disease, allows one to assess the stage of liver cirrhosis [8, 14].

These data contribute to research interest in eliminating the factors leading to fibrosis, and subsequently to liver cirrhosis and hepatocarcinoma.

The purpose of the study: To substantiate the diagnostic significance of laboratory parameters - AFP (alpha-fetoprotein) and the APRI index (AST/platelet count ratio index) in the progression of liver fibrosis to cirrhosis in patients with chronic viral hepatitis C.

Materials and methods of research: The subjects of the study were 43 patients staying at the Scientific Research Institute of Virology clinic of the Republican specialized scientific-practical medical center of Epidemiology, microbiology, infectious and parasitic diseases, among whom there were 23 (53,5%) men and 20 (46,5%) women aged from 18 to 59 years (average age was 36,2±5,36 years).

The diagnosis of «Viral hepatitis C» was verified based on the detection of specific total antibodies to HCV in the blood serum by enzyme-linked immunosorbent assay (ELISA) using the «Best anti-HCV» kit (Vector-Best, Novosibirsk) and detection of HCV RNA by the molecular genetic method research - polymerase chain reaction (PCR) in the Reference laboratory Scientific Research Institute of Virology of the Republican specialized scientific-practical medical center of Epidemiology, microbiology, infectious and parasitic diseases.

The subject of the study was venous blood, serum and blood plasma, and the genome of the hepatitis C virus from examined patients with chronic viral hepatitis C.

To solve problems and achieve the goal of this study, general clinical, biochemical, immunological, molecular biological, instrumental and statistical research methods were used in the work.

Isolation of HCV RNA from patient blood plasma samples was carried out using the Real Best Delta Mag HBV/HCV kit (set 2), and subsequent reverse transcription by polymerase chain reaction (RT-PCR) in real time using «Real Best HCV kits PCR (set 2)», «Real Best HCV genotype» and amplifier «CFX-96» (Bio-Rad Laboratories, Inc., USA) with determination of the HCV genotype and the level of viral load of the hepatitis C virus (viremia).

All patients underwent comprehensive laboratory and instrumental examination.

Along with general clinical studies, to fulfill the objectives of the study, we used a laboratory diagnostic set of studies, including assessment of the level of an indirect marker of liver fibrosis - the APRI index and a marker of liver cell

regeneration - alpha-fetoprotein - AFP.

Liver elastometry was performed on the basis of liver fibroscanning using the FibroScan device (France).

The rate of liver fibrosis progression (LFP) - the ratio of the severity of liver fibrosis (score) to the duration of infection with the hepatitis C virus - HCV (years) was calculated by the method of Poynard T. (1997).

An indirect marker of fibrosis, the APRI (Aspartate aminotransferase to Platelet Ratio Index) index, the index of the ratio of AST/platelet count, was calculated using the existing special formula for calculating APRI. APRI (aspartate aminotransferase to platelet ratio index) = AST (aspartate aminotransferase) x 100 / (upper limit of AST).n platelets (10^9/l). An index value of <0.5 was considered to correspond to a low risk of severe fibrosis. As the APRI value increased, the risk of developing severe liver fibrosis increased.

Determination of the level of alpha-fetoprotein - AFP in the blood serum of examined patients with chronic hepatitis C virus was carried out using the AFP kit (Siemens) using an immunochemiluminescence assay (CHLA) on an Immulait-1000 analyzer (Germany).

Statistical processing of the obtained data was carried out using the STATISTICA 7.0 computer program, using the Statistica package (Stat Soft) and Microsoft Excel. Differences between samples were considered significant at a p value <0.05.

Results and discussion. The severity of liver density and assessment of indirect biomarkers of liver fibrosis were studied in 43 patients with chronic viral hepatitis C.

Based on the results of elastometry (elastography) of the liver, depending on the degree (stage) of the severity of liver fibrosis in accordance with the indicators of the instrumental study, the examined patients were divided into the following study groups: the group of patients with the absence of liver fibrosis F0 consisted of 9 (20,9%) patients, with the presence of liver fibrosis with degrees F1-F4 – 34 (79,1%) patients.

Among patients with chronic hepatitis C with degrees F1-F4, 1-degree liver fibrosis (F1) was detected in 14 (32,6%) patients, 2-degree fibrosis (F2) was verified in 8 (18,1%) patients, 3 -degree (F3) – 5 (11.6%) patients and 7 (16,3%) patients had 4 degrees of liver fibrosis (F4), which corresponds to liver cirrhosis as a result of chronic viral hepatitis C (Figure 1).

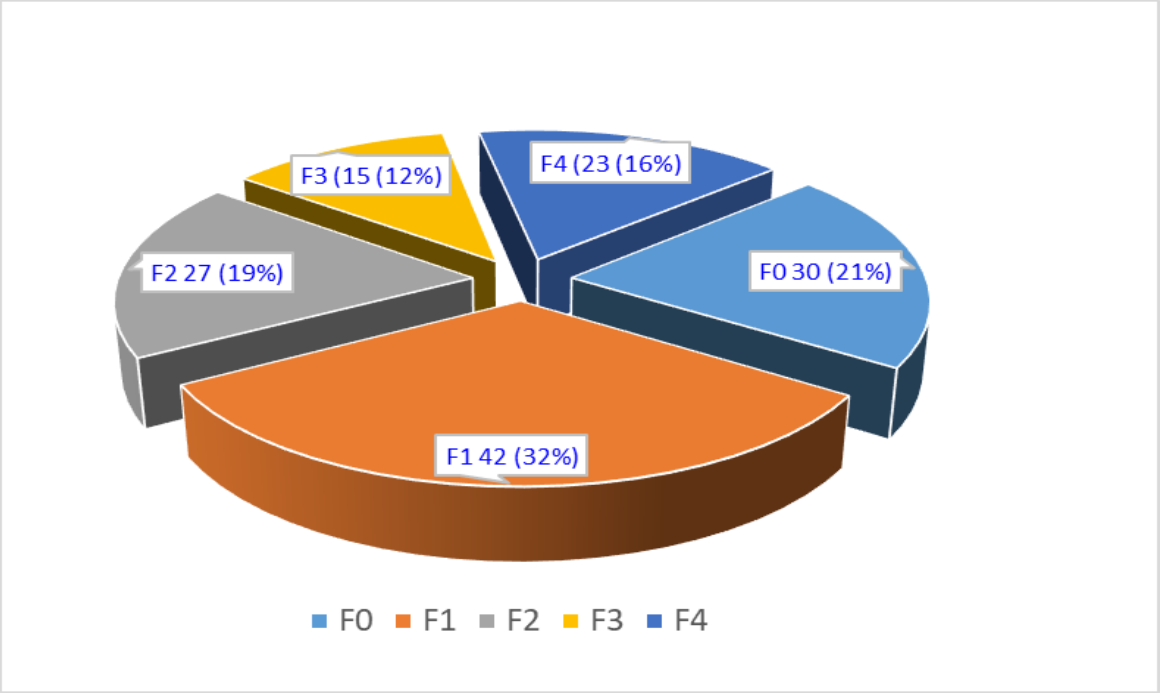

Figure 1. Separation of patients with chronic viral hepatitis C depending on the severity of liver fibrosis

The density of the liver tissue according to liver elastometry in patients, depending on the severity of fibrosis, was as follows: no fibrosis F0 (n=9) – 5,46±1,22, 1-degree F1 (n=14) – 7,39± 1,55, 2-grade F2 (n=8) – 9,03±1.77, 3-grade F3 (n=5) – 11,5±2,89 and 4-grade F4 (n=7) – 27,8±3.65 (p <0,05). The density of liver tissue in patients without cirrhosis averaged 8,39±2,05 kPa.

The examined patients are listed according to the severity of liver fibrosis and the presence of clinical manifestations of the disease in table 1:

Table 1

Characteristics of examined patients with chronic viral hepatitis C depending on the severity of liver fibrosis and clinical manifestations of the disease

Indicators	F_0 (n=9)	F_1 (n=14)	F_2 (n=8)	F_3 (n=5)	F_4 (n=7)
Men	5 (55,6%)	8 (57,1%)	5 (62,5%)	2 (40,0%)	3 (42,9%)
Women	4 (44,4%)	6 (42,9%)	3 (37,5%)	3 (60,0%)	4 (57,1%)
Clinical manifestations					
Asthenovegetative syndrome	1 (11,1%)	4 (28,5%)	2 (25,0%)	4 (80,0%)	6 (85,7%)
Dyspeptic syndrome	1 (11,1%)	2 (14,2%)	2 (25,0%)	2 (40,0%)	4 (57,1%)

Jaundice syndrome	0	2 (14,2%)	1 (12,5%)	2 (40,0%)	3 (42,8%)
Pain syndrome	1 (11,1%)	1 (7,14%)	2 (25,0%)	2 (40,0%)	2 (28,5%)
Hemorrhage syndrome	0	0	0	0	3 (42,9%)

Clinical symptoms of chronic viral hepatitis C increased as the degree of liver fibrosis increased. A mild degree of liver fibrosis was manifested by the dominance of clinical symptoms of disease activity, and liver cirrhosis in the outcome of chronic viral hepatitis C more often manifested itself as signs of portal hypertension. Among the clinical syndromes, astheno-vegetative syndrome was the most common.

A laboratory study revealed a significant increase in the value of an indirect marker of liver fibrosis - APRI (AST to platelet ratio index) was detected in patients with chronic viral hepatitis C in the presence of liver fibrosis at stage F1-F4 compared with patients with normal liver density – F0 ($p < 0,05$).

There was a twofold increase in the average marker of liver cell regeneration alpha-fetoprotein - AFP in patients with chronic viral hepatitis C with liver density F1-F4 compared to patients with normal liver density (F0) ($p < 0.05$) (Table 3).

Table 3

APRI and AFP in patients with chronic hepatitis C depending on the degree of liver fibrosis

Indicators	Patients with F_0 (n=9)	Patients with F_1-F_4 (n=34)	P
APRI	0,36±0,11	0,73±0,28	<0,05
AFP, IU/ml	2,04±0,61	3,40±1,11	<0,05

Примечание: p – statistical significance

There were no statistically significant differences in the APRI value and the AFP indicator in men and women ($p > 0,05$ and $p > 0,05$, respectively). The APRI index in patients with moderate fibrosis (F1–2) was 1.2 times higher than the level of this indicator in patients without liver fibrosis (F0) ($p < 0,05$), and was 1,7 times higher in patients with severe liver fibrosis (F3) compared with the presence of moderate fibrosis ($p = 0,01$), and also made it possible to distinguish the degrees of liver fibrosis F3 and F4 ($p < 0,05$).

The AFP value for chronic hepatitis C in patients with chronic viral hepatitis C with the presence of liver fibrosis F1-2 did not have statistical significance for this indicator in patients with F0 ($p > 0,05$), while it was 1,69 times higher with a pronounced degree of fibrosis (F3) compared with F1-2 ($p < 0,05$) and made it possible to distinguish fibrosis in the F3 stage of liver cirrhosis in the outcome of

chronic hepatitis C before the manifestation of clinical symptoms of the disease (p <0,05) (Table 4).

Table 4

APRI and AFP indicators for the severity of liver fibrosis in chronic viral hepatitis C

Degree of liver fibrosis	APRI	AFP, IU/ml
Without fibrosis – F0 (n = 9)	0,36±0,11	2,04±0,61
1-st and 2-nd degree fibrosis – F1-2 (n = 22)	0,55±0,12*	2,39±0,92
3-degree fibrosis – F3 (n = 5)	0,93±0,30**	4,18±1,37**
4-degree fibrosis – F4 (n = 7)	1,28±0,69***	5,10±1,75***

*Note: * – significant difference in patients with F1-2 compared to F0;*
*** – significant difference in patients with F3 compared to F1-2;*
**** – significant difference in patients with F4 compared to F3;*

Conclusion: Thus, studying the value of APRI in patients with chronic viral hepatitis C will make it possible to verify all degrees of liver fibrosis, and assessing the liver cell regeneration marker AFP will distinguish between a severe degree of fibrosis from a moderate one and progression to liver cirrhosis.

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