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Significance of Biomarkers of Liver Fibrosis and Cirrhosis Progression in Chronic Viral Hepatitis C in Patients with HIV Infection

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ABSTRACT

This paper presents the results of a study of liver density and an assessment of liver fibrosis markers in 137 patients with HIV infection associated with chronic viral hepatitis C. Activation of the production of interleukin-6 (IL-6), increased regeneration in hepatocytes, which predetermine the outcome of chronic viral hepatitis C into cirrhosis, were revealed. Significant pathogenetic factors that mark liver density were APRI index, albumin, platelets and IL-6. Normal liver density was established at APRI ≤0.50. 1 and 2-degree of fibrosis - F1-2 = with APRI > 0.50 and ≤0.91, 3-degree of liver fibrosis - F3 - with > 0.91 and ≤1.02, liver cirrhosis of HCV etiology with APRI > 1.02. The IL-6 index showed a high correlation with the degrees of liver fibrosis. IL-6 allowed to exclude liver fibrosis in chronic hepatitis C at ≤3.6 pg/ml. A rapid rate of progression of liver fibrosis was detected at APRI>0.74 and AFP>3.25 IU/ml. A good predictive value for the diagnosis of the transition of chronic hepatitis C to liver cirrhosis was shown by IL-6 at > 7.12 pg/ml (sensitivity 72.5% and specificity 92.2%).

KEYWORDS: Chronic viral hepatitis C, HIV infection, fibrosis, cirrhosis of the liver, APRI, alpha-fetoprotein, interleukin-6.

INTRODUCTION

According to the World Health Organization (WHO), there are more than 35 million people infected with HIV in the world. Among injection drug addicts with a positive HIV status, the prevalence of viral hepatitis reaches 80-85%, with a sexual route of infection - up to 30%. The frequency of newly diagnosed cases of hepatitis C in the world is from 1 to 5 cases per 100 thousand populations, and it is believed that the true figure is 5-8 times higher [5]. Parenteral transmission is 10 times more likely to transmit HCV than HIV. One of the main factors that can accelerate the progression of CHV is HIV/HCV co-infection [4, 1, 2, 7, 12, 20, 23]. There are direct and indirect non-invasive markers of liver fibrosis and instrumental diagnostic methods. They are more accessible, quite sensitive and specific and can be used repeatedly, allowing you to assess the stage of fibrosis at various stages of its progression [3, 8, 10, 11, 21]. 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 the diagnosis of severe fibrosis and cirrhosis of the liver [6, 9, 13, 22]. A number of studies show that a violation of the liver architectonics with the formation of fibrotic changes is associated with the degree of activation of the production of interleukin-6 (IL-6), and other studies provide data that a change in the content of this cytokine is associated with acute diseases of the liver and other organs [14, 18, 19]. Alpha-fetoprotein (AFP), a serum marker for hepatocarcinoma, may be elevated 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. Monitoring of AFP, both during the initial examination of patients with liver cirrhosis, and in the dynamics of the disease, allows us to assess the stage of liver cirrhosis [15, 16, 17].

THE AIM OF THE RESEARCH

The aim of the research was to study the stage of fibrosis and cirrhosis of the liver with the assessment of the factors of progression of the pathological process in the liver in chronic viral hepatitis C in patients with HIV infection.

OBJECT AND METHODS OF RESEARCH

Liver density and evaluation of fibrosis markers were studied in 137 patients with HIV infection associated with chronic viral hepatitis C. There were 70 (51.1%) men and 67 (48.9%) women, aged 19 to 60 years (mean age 37.3±6.49 years).

According to the classification of the World Health Organization (2012), patients with I-clinical stage were 21 (15.3%), II-clinical stage - 33 (24.1%), with III - 64 (46.7%) and with IV -clinical stage of HIV infection was 19 (13.9%) patients.

The diagnosis of "HIV infection" was verified in the laboratory complex of the Republican AIDS Center based on the detection of antibodies to HIV in the blood serum by ELISA and IB.

The diagnosis of "Viral hepatitis C" was confirmed based on the detection of anti-HCV by ELISA and the detection of HCV RNA in the blood by PCR.

Liver elastometry using Fibroscan (France) was used as a method for assessing the severity of liver fibrosis in patients with chronic hepatitis C.

According to elastometry data, depending on the degree (stage) of AF, in accordance with the study indicators, the examined patients were divided into the following groups: the group with the absence of liver fibrosis F0 consisted of 30 (21.9%) patients, with the presence of fibrosis with degrees F1-F4 - 107 (78.1%) patients, 1st degree of liver fibrosis (F1) was detected in 42 (30.7%) patients, 2nd degree of fibrosis (F2) was verified in 27 (19.7%) patients, 3rd degree (F3) in 15 (10.9%) patients and 23 (16.8%) patients had grade 4 liver fibrosis (F4), which corresponds to cirrhosis in the outcome of chronic hepatitis C (Fig. 1).

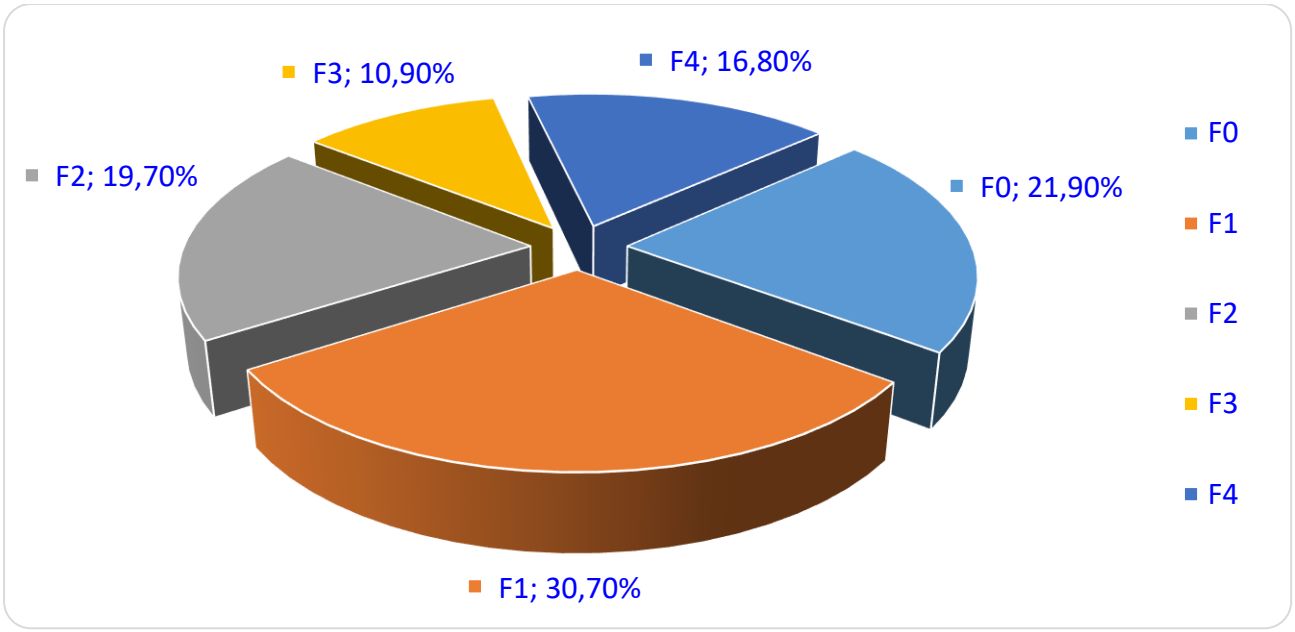

Figure 1. Separation of HIV-infected patients with chronic hepatitis C depending on the severity of liver fibrosis

The examined patients in this work according to the severity of liver fibrosis are shown in Tab. 1.

Table 1. General characteristics of the examined HIV-infected patients with chronic hepatitis C depending on the severity of liver fibrosis

	F_0 (n=30)	F_1 (n=42)	F_2 (n=27)	F_3 (n=15)	F_4 (n=23)
Men	17 (56,7%)	25 (59,5%)	14 (51,9%)	5 (33,3%)	9 (39,1%)
Women	13 (43,3%)	17 (40,5%)	13 (48,1%)	10 (66,7%)	14 (60,9%)
Clinical manifestations					
Asthenovegetative syndrome	2 (6,67%)	11 (26,2%)	8 (29,6%)	12 (80,0%)	22 (95,7%)
Icteric syndrome	0	3 (7,15%)	2 (7,41%)	4 (26,7%)	9 (39,1%)
Pain syndrome	2 (6,67%)	4 (9,53%)	4 (14,8%)	4 (26,7%)	4 (17,4%)
Dyspeptic syndrome	1 (3,34%)	6 (14,3%)	5 (18,5%)	5 (33,3%)	12 (52,2%)
Hemorrhagic syndrome	0	0	0	0	10 (43,5%)

The density of liver tissue according to liver elastometry in patients, depending on the severity of fibrosis, was as follows: no fibrosis F0 (n=30) - 5.57±1.16, 1-grade F1 (n=42) - 7.48±1 .64, 2-grade F2 (n=27) – 9.05±2.18, 3-grade F3 (n=15) – 11.7±3.12 and 4-grade F4 (n=23) – 27.5±4.09 ($p<0.05$).

The density of the liver tissue in patients without cirrhosis averaged 8.45±2.07 kPa.

THE RESULTS OF RESEARCH

Clinical symptoms of HCV increased as the degree of AF increased. A mild degree of fibrosis was manifested by the dominance of clinical symptoms of disease activity, and liver cirrhosis in the outcome of HCV was more often manifested by signs of portal hypertension. Among the clinical syndromes, asthenovegetative 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 hepatitis C in the presence of liver fibrosis in the stage F1-F4 compared with patients with normal liver density - F0 ($p<0.05$).

There was a twofold increase in the mean value of the liver cell regeneration marker alpha-fetoprotein – AFP in HIV-infected patients with chronic viral hepatitis C (HCV) with liver density F1-F4 compared with patients with normal liver density (F0) ($p <0.05$) (Tab. 2).

Table 2. APRI and AFP values in chronic hepatitis C in patients with HIV infection depending on the degree of liver fibrosis

Indicators	Patients with F_0 (n=30)	Patients with F_1-F_4 (n=107)	p
APRI	0,37±0,12	0,75±0,31	<0,05
AFP, IU/ml	2,01±0,57	3,39±1,09	<0,05

Note: p - statistical significance

There were no statistically significant differences between APRI and AFP in men and women ($p>0.05$ and $p>0.05$, respectively). APRI in patients with moderate fibrosis (F1–2) was 1.5 times higher than the level of this indicator in patients without liver fibrosis (F0) ($p <0.05$), 1.6 times higher in patients with severe fibrosis liver (F3) compared with the presence of moderate fibrosis ($p=0.01$).

The value of AFP in chronic hepatitis C in HIV-infected patients with liver fibrosis F1-2 did not have a statistical significance of this value in patients with F0 ($p>0.05$), while it was 1.7 times higher in severe fibrosis (F3) compared with F1-2 ($p <0.05$) and made it possible to distinguish between fibrosis in the F3 stage of liver cirrhosis in the outcome of HCV before the onset of clinical symptoms of the disease ($p <0.05$) (Tab. 3).

Table 3. APRI and AFP indicators for the severity of liver fibrosis in chronic hepatitis C in patients with HIV infection

The degree of liver fibrosis	APRI	AFP, IU/ml
Without fibrosis – F0 (n = 30)	0,37±0,12	2,01±0,57
1- and 2-degree fibrosis – F1-2 (n = 69)	0,56±0,11*	2,43±0,96**
3-degree fibrosis – F3 (n = 15)	0,92±0,29**	4,20±1,41***
4-degree fibrosis – F4 (n = 23)	1,27±0,73***	5,13±1,80

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

CONCLUSIONS

Thus, the following factors are the main pathogenetic mechanisms of fibrogenesis in chronic hepatitis C in patients with HIV infection: activation of interleukin-6 (IL-6) production, increased regeneration processes in the liver, which predetermine the outcome of hepatitis C in liver cirrhosis. APRI, albumin, platelets and IL-6 mark the density of the liver and allow to verify liver cirrhosis in the outcome of hepatitis C, which naturally have scientific and practical significance in the dynamics of the progression of liver fibrosis in chronic viral hepatitis C in patients with HIV infection.

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