Non-invasive liver fibrosis markers: use of serum levels of cytokines IL 1α and TGF-β1 in management of chronic liver diseases

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ABSTRACT

Aim To analyze the usefulness of specified immunological parameters, proinflammatory IL-1α and profibrogenic, antiinflammatory TGF-β1, along with routinely used laboratory tests, in the differential-diagnostic procedure of chronic hepatitis of infectious and noninfectious etiology.

Methods A total of 150 subjects were divided into two groups, depending on the infectious or noninfectious etiology of liver damage, and the control group. Apart from standard laboratory tests, the analysis included serum levels of cytokines: IL-1α and TGF-β1.

Results A high degree of correlation of serum level of IL-1α with viral hepatitis has been found, especially with active replication of genetic material (HBV-DNA or HCV-RNA-PCR positive), p <0.01. The highest mean concentration of TGF-β1 was noted in the group of malignant and toxic hepatitis, p <0.0001. A negative correlation between the concentration of IL-1α and TGF-β1 has been found (-0.18). For IL-1α significant predictive parameters included a previous infection of hepatitis B, lower serum level of TGFβ, age, use of alcohol, lower MELD and Child-Pugh scores. For TGF-β1 significant predictive parameters were age, lower MELD and Child-Pugh scores, history of receiving transfusions, lower serum level of IL-1α, higher serum level of fibrinogen. A predictive model has been delivered: MELD = (TGF-β1) x 0.001 - (IL-1 α) x 0.085 + CTP x 1.771 - 2.052; ( ± 2.04, R2=0.61; p<0.001).

Conclusion Inflammatory and immune parameters, analyzed together could significantly contribute to the understanding of chronic liver damage and thus differential diagnostic procedure. IL-1α and TGF-β1 are important parameters of inflammatory activity and fibrosis evaluation in chronic liver damage.

Key words: Chronic liver disease, hepatocellular carcinoma, inflammation, IL-1α, TGF-β1
Introduction

The assessment of liver fibrosis is a major issue in the management of patients with chronic hepatitis (1). Liver biopsy has traditionally been considered the gold standard for the evaluation of tissue damage, including fibrosis (2). Liver biopsy is, however, an invasive procedure, and its limitations have led to the development of non-invasive methods (3).

Currently available tests rely on a ‘biological’ approach based on the dosage of serum biomarkers of fibrosis and ‘physical’ approach based on the measurement of liver stiffness, using transient elastography (4).

Liver fibrosis is a result of excessive extracellular matrix deposition in the liver in response to chronic inflammatory injury. It is determined by the replication balance between fibrogenesis and fibrosis degradation. Liver fibrosis and its end-point cirrhosis are the main causes of morbidity and mortality in patients with chronic liver disease (5,6). Besides the development of antiviral drugs, there are intensive efforts to develop drugs to effectively target the mechanism of fibrogenesis or to eliminate fibrous tissue once it has accumulated in the liver (7). Therefore, the assessment of liver fibrosis is a major issue in the management of patients with chronic hepatitis (8,9).

Numerous biomarkers have been proposed in chronic hepatitis (10-12) but the most widely used and validated with transient elastography are the aspartate-to-platelet ratio index (APRI) and the FibroTest (13-15).

In order to increase the diagnostic accuracy of these tests, the sequential combination of biomarkers (16, 17) or the concomitant combination of transient elastography and biomarkers has been proposed (18-20).

The focus of recent scientific studies have been cytokines, proven to have a significant role in liver inflammation and fibrogenesis (21, 22, 23). Cytokines are low-molecular-weight mediators of cellular communication produced by multiple cell types in the liver, with the Kupffer cell critically important (21).

IL-1 has a central role in the inflammatory process especially in acute inflammation. It is an indicator of the intensity of inflammatory activity (22). Transforming growth factor beta (TGF-β) enhances collagen synthesis by increasing the proliferative activity of hepatic stellate cells, and has a major role in hepatic fibrosis.

Understanding the mechanism of TGF-β has been the focus of recent studies in unraveling the pathogenesis of many human cancers (23-26).

TGF-β1 has also been found to be elevated in serum, urine and tissues of patients with hepatocellular carcinoma (HCC) (27,28). Moreover, overexpression of hepatic TGF-β1 was found in HCC tissues and correlated well with carcinogenesis, progression and prognosis of HCC (29, 30).

This increased fibrosis may be due to a super abundance of profibrogenic factors such as transforming growth factor-beta (TGF-β). To assess the degree of fibrosis of liver tissue would be interesting to evaluate serum levels of cytokines involved in this process.

In this study, serum levels of TGF-β1 and IL-1α in patients with chronic liver disease viral hepatitis B or C, alcoholic liver disease, non alcoholic fat liver disease, autoimmune hepatitis or hepatocellular carcinoma were determined to evaluate usefulness of serum TGF-β1 and IL-1α as sensitive molecular markers for the evaluation of chronic liver diseases.

PATIENTS AND METHODS

The study was conducted between January 2010 and January 2011 as an open, randomized, comparative clinical trial.

Before entering the study, each patient reviewed and signed an informed consent. All research described in study, involving human subjects and material derived from human subjects complied with ethical principles. Standards of Good Clinical Practice, Good Laboratory Practice and The declaration of Helsinki were complied with.

The study was conducted at the Department of Gastroenterology and Hepatology, with an approval of the Ethical Committee of the University of Sarajevo Clinical Centre.

Patients

A total of 150 patients 18 - 80 years of age, were recruited. Inclusion criteria were as follows: for viral hepatitis group patients with positive serum anti-HCV or anti- HBV antibodies, polymera-
se chain reaction test where performed; for non viral hepatitis group with previous liver biopsy diagnosis of alcoholic liver disease (ALD), non alcoholic fat liver disease (NAFLD), autoimmune hepatitis (AH) or HCC were needed no more than 6 months before the study.

Exclusion criteria were: the presence of liver disease caused by a hereditary condition, cardiac liver cirrhosis, liver disease which occurred during pregnancy, vascular liver disease, primary biliary cirrhosis and subjects with liver transplant, acute hepatitis, evidence of acute or chronic inflammatory syndrome of other known origin, immunodeficiency states.

Respondents with diagnosis of chronic liver disease (120 patients) were divided in two groups: Viral hepatitis group including chronic viral hepatitis B or C with anti HBV or Anti HCV positive antibodies, HBV-DNA-PCR or HCV-RNA-PCR positive test (1a subgroup), and chronic viral hepatitis B or C with anti HBV or anti HCV positive antibodies, HBV-DNA-PCR or HCV-RNA-PCR negative test (1b subgroup). Non viral hepatitis group included chronic non viral hepatitis (malignant or toxic hepatitis) ALD, NAFLD, HCC (2a subgroup), and autoimmune hepatitis (type 1 or 2) (2b subgroup).

The third group included a control group of 30 healthy subjects.

Methods

A physical examination was carried out and medical history was taken during the pre-study visit. The following data were recorded from all patients: age, gender, body mass index (BMI), history of alcohol and narcotics consumption or receiving transfusion, history of liver disease - liver biopsy, co-morbidity.

Biochemical parameters were recorded: full blood count, international normalized ratio (INR), active partial thromboplastin time (APTT) and routine liver function tests including bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and gamma-glutamyl transferase, proteinogram. Routine biochemical assessment of renal function was performed: urea and creatinine.

Cytokines IL-1α and TGF-β1 where determined and measured in serum by quantitative Sandwich Enzyme Immunoassay technique. Monoclonal antibodies specific for one cytokine (IL-1α or TGF-β1) were coated on microparticles, which come into contact with the sample, and was based on the occurrence of a specific color, measuring the intensity, extent and concentration of cytokine in the sample. The analysis was made from frozen serum samples that were collected in serum separator tube. Values were expressed as pg/ml.

Functional status of the liver was determined by the modified Child Pugh and MELD scores (31, 32).

Statistical analysis

Categorical data were expressed as proportions (%), and continuous data as means ± standard deviation (SD). Statistical methods used in this study included discriminant multivariate analysis, analysis of variance test (ANOVA test), multiple correlation test and Student’s t-test for independent samples. The level of significance was p <0.05.

Charlson comorbidity index was determined for any possible influence of other comorbid conditions on the analysis results (33, 34).

A prediction model functional status of liver according to MELD score was developed including the following covariates: cytokines IL-1 and TGF-β and Child Pugh score using method of linear regression analysis.

RESULTS

A total of 150 subjects, divided into two groups and two subgroups in each (four groups) with 30 patients in each, as well as a group of 30 healthy subjects as a control group were included (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years) (SD)</th>
<th>Weight (kg) (SD)</th>
<th>Height (cm) (SD)</th>
<th>BMI (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>46,47 (9,72)</td>
<td>79,00 (10,82)</td>
<td>173,00 (7,10)</td>
<td>26,29</td>
</tr>
<tr>
<td>1b</td>
<td>55,93 (13,11)</td>
<td>74,27 (10,23)</td>
<td>170,67 (5,85)</td>
<td>25,58</td>
</tr>
<tr>
<td>2a</td>
<td>57,27 (10,80)</td>
<td>70,57 (10,58)</td>
<td>165,33 (19,31)</td>
<td>24,67</td>
</tr>
<tr>
<td>2b</td>
<td>42,03 (8,44)</td>
<td>69,97 (10,62)</td>
<td>165,07 (19,82)</td>
<td>24,45</td>
</tr>
<tr>
<td>3</td>
<td>35,97 (7,37)</td>
<td>71,93 (11,34)</td>
<td>173,07 (6,29)</td>
<td>23,93</td>
</tr>
</tbody>
</table>

Table 1. Basic demographic and anthropological parameters of subjects per group

Group 1a – HCV RNA or HBV DNA PCR positive; Group 1b – HBV DNA and HCV RNA PCR negative; Group 2a-malignant or toxic hepatitis; Group 2b- autoimmune hepatitis; Group 3 - healthy; SD, standard deviation
Table 2. Average activity values of enzymes, bilirubin, INR and APTT in groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Alpha AT IU/ml (SD)</th>
<th>Asp AT IU/ml (SD)</th>
<th>γ GT IU/ml (SD)</th>
<th>APTI IU/ml (SD)</th>
<th>INR (SD)</th>
<th>APTT (s)</th>
<th>Bil. tot. (µmol/L)</th>
<th>Bil. dir. (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>67.67 (43.91)</td>
<td>63.30 (53.40)</td>
<td>112.40 (92.31)</td>
<td>88.41 (29.44)</td>
<td>1.24 (0.26)</td>
<td>40.89 (4.56)</td>
<td>21.51 (26.46)</td>
<td>8.72 (9.08)</td>
</tr>
<tr>
<td>1b</td>
<td>79.90 (61.96)</td>
<td>78.80 (73.76)</td>
<td>66.43 (37.33)</td>
<td>88.47 (45.47)</td>
<td>1.26 (0.26)</td>
<td>38.69 (4.25)</td>
<td>25.16 (18.61)</td>
<td>8.61 (8.06)</td>
</tr>
<tr>
<td>2a</td>
<td>64.03 (84.86)</td>
<td>105.90 (179.73)</td>
<td>245.33 (246.62)</td>
<td>163.42 (115.40)</td>
<td>1.14 (0.24)</td>
<td>33.87 (5.19)</td>
<td>25.47 (22.10)</td>
<td>10.72 (14.30)</td>
</tr>
<tr>
<td>2b</td>
<td>112.93 (106.49)</td>
<td>96.20 (71.25)</td>
<td>203.17 (183.16)</td>
<td>180.07 (156.61)</td>
<td>1.1 (0.17)</td>
<td>35.7 (4.25)</td>
<td>27.83 (14.20)</td>
<td>9.82 (7.59)</td>
</tr>
<tr>
<td>3</td>
<td>30.63 (7.26)</td>
<td>26.03 (6.18)</td>
<td>36.77 (8.43)</td>
<td>85.73 (21.27)</td>
<td>1.08 (0.15)</td>
<td>38.92 (2.68)</td>
<td>10.65 (3.31)</td>
<td>4.28 (1.27)</td>
</tr>
</tbody>
</table>

Group 1a – HCV RNA or HBV DNA PCR positive; Group 1b – HBV DNA and HCV RNA PCR negative; Group 2a – malignant or toxic hepatitis; Group 2b – autoimmune hepatitis; Group 3 – healthy; SD, standard deviation.

Table 3. Statistical analysis of protein parameters in groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Total proteins (g/L) (SD)</th>
<th>Albumin (g/L) (SD)</th>
<th>Globulin (g/L) (SD)</th>
<th>A/G index (SD)</th>
<th>Fibrinogen (g/L) (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>74.03 (7.56)</td>
<td>37.70 (5.92)</td>
<td>36.33 (4.93)</td>
<td>1.05 (0.22)</td>
<td>4.76 (0.78)</td>
</tr>
<tr>
<td>1b</td>
<td>74.80 (6.30)</td>
<td>39.13 (5.10)</td>
<td>36.47 (5.54)</td>
<td>1.10 (0.24)</td>
<td>4.29 (0.76)</td>
</tr>
<tr>
<td>2a</td>
<td>72.90 (9.35)</td>
<td>34.10 (6.58)</td>
<td>38.37 (8.15)</td>
<td>0.95 (0.31)</td>
<td>4.23 (1.48)</td>
</tr>
<tr>
<td>2b</td>
<td>75.67 (8.67)</td>
<td>34.77 (5.22)</td>
<td>39.57 (6.45)</td>
<td>0.90 (0.19)</td>
<td>4.23 (0.71)</td>
</tr>
<tr>
<td>3</td>
<td>73.57 (5.80)</td>
<td>40.67 (3.10)</td>
<td>32.97 (3.37)</td>
<td>1.24 (0.16)</td>
<td>4.26 (0.68)</td>
</tr>
</tbody>
</table>

Group 1a – HCV RNA or HBV DNA PCR positive; Group 1b – HBV DNA and HCV RNA PCR negative; Group 2a – malignant or toxic hepatitis; Group 2b – autoimmune hepatitis; Group 3 – healthy; SD, standard deviation.

Table 4. Statistical analysis of hematological parameters in groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Hb (g/L) (SD)</th>
<th>MCV (fL) (SD)</th>
<th>Le (x109/l) (SD)</th>
<th>Tr (x109/l) (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>144.10 (14.20)</td>
<td>95.03 (3.83)</td>
<td>6.04 (3.42)</td>
<td>161.38 (1.56)</td>
</tr>
<tr>
<td>1b</td>
<td>141.50 (20.16)</td>
<td>94.97 (5.62)</td>
<td>5.99 (8.42)</td>
<td>167.71 (1.81)</td>
</tr>
<tr>
<td>2a</td>
<td>129.77 (16.84)</td>
<td>91.54 (4.55)</td>
<td>7.26 (5.36)</td>
<td>245.25 (2.43)</td>
</tr>
<tr>
<td>2b</td>
<td>136.86 (14.82)</td>
<td>91.80 (4.97)</td>
<td>7.04 (5.41)</td>
<td>194.42 (2.58)</td>
</tr>
<tr>
<td>3</td>
<td>143.73 (7.60)</td>
<td>93.38 (3.02)</td>
<td>6.47 (4.74)</td>
<td>236.17 (1.74)</td>
</tr>
</tbody>
</table>

Group 1a – HCV RNA or HBV DNA PCR positive; Group 1b – HBV DNA and HCV RNA PCR negative; Group 2a – malignant or toxic hepatitis; Group 2b – autoimmune hepatitis; Group 3 – healthy; SD, standard deviation.

IL-1α in the control group (group 3) was different in relation to groups 1a (p <0.001), 1b (p <0.001), and in relation to group 2a (p <0.001), as well as compared to group 2b (p <0.001) (Figure 1).

IL-1α had the highest mean concentration in group 1a with PCR positive test (5.73 pg/mL) and then in group 2b with PCR negative test (5.39 pg/mL).

Statistical significance of IL-1 serum level was observed between groups 1a and 1b (p = 0.026), between groups 1a and 2a (p = 0.001), 1a and 2b (p = 0.0002), 1b and 2b (p = 0.004). Groups 2a and 2b did not significantly differ in the concentration of IL-1α (p >0.05) (Figure 1).

The highest serum level of cytokine IL-1α was in group 2a (malignant and toxic liver diseases).

Serum levels of TGF-β1 in the control group differed in relation to groups 1a (p = 0.0028), 1b (p = 0.0001) to group 2a (p <0.0001) in relation to the group 2b (p <0.0001) (Figure 2).

The highest mean concentration of TGF-β1 was noted in the group 2a (malignant and toxic hepatitis) (1023.55 pg/mL), then in group 1b (viral hepatitis B or C with PCR negative test (898.80 pg/mL) (p <0.0001).

For IL-1α a significant correlation was found and the stratification of predictive parameters was made as follows: previous infection of hepatitis B, lower serum level of TGF-β, age, use of alcohol, lower MELD and Child-Pugh scores (p < 0.05).
For TGF-β1 a significant correlation was found and the stratification of predictive parameters was made as well: age, lower MELD and Child-Pugh scores, history of receiving transfusions, lower serum level of IL-1α, higher serum level of fibrinogen. (p < 0.05).

A negative correlation between the concentration of IL-1α and TGF-β1 of group 1a has been found (Figure 1). It is evident that the reduction of IL-1α is followed by increasing concentrations of TGF-β. The correlation coefficient was, therefore, negative (-0.18) (Figure 3).

DISCUSSION

In clinical practice, for determining the degree of functional status of liver the Child Turcotte Pugh and MELD scoring systems are used (31, 32). In this study, along with routine laboratory tests, the analysis of serum levels of proinflammatory cytokine IL-1α and antiinflammatory TGF-β1 has been performed for better understanding and monitoring of chronic hepatitis of different etiology.

Measurements of average values of enzyme activity (AST, ALT, γGT and AP) and bilirubin in the groups showed increased activity of these enzymes in groups of patients with chronic hepatitis compared to controls, which was expected due to chronic liver process (1,2,8). The values of total protein were not significantly different, but ratios of the concentration of albumin and globulins were significantly disrupted in groups of malignant and toxic liver damage and autoimmune hepatitis. The analysis of hematological parameters showed no significant discrepancies by groups. Functional indicators of liver damage (Child Pugh and MELD scores) showed a correlation in all groups, but not as a good assessment system for the intensity of inflammation and involvement of the liver fibrosis process. It explains their primary purpose in evaluating the terminal stages of liver damage (32).

Statistical analysis of the cytokines analyzed showed very impressive results for both cytokines. An analysis of serum level of Interleukin-1α showed a high degree of correlation with the activity of viral hepatitis (PCR positive group). The most active inflammatory process occurred in this group, while in other groups inflammatory reaction subsided, and was better controlled. Our result proves a central role of IL-1α in active inflammatory process. It is an indicator of the intensity of inflammation activity (22).

Groups 2a and 2b did not significantly differ in the concentration of IL-1α, which could be explained with “smoldering” inflammation in these two subgroups—“never highly active” (35). McCain et al found elevated levels of this in patients with alcoholic liver disease (36). Gramantieri suggests that elevated levels of IL-1 in samples of liver tissue indicate the pronounced activity of hepatitis C (37).
TGF-β1 had the highest serum level in the group of malignant and toxic liver damage, suggesting the activity of fibrous and malignant process in this group (38).

Significant negative correlations were found in the serum levels of IL-1α and TGF-β1, which proves their antagonistic roles (26). The increase of IL-1α diverts an inflammatory reaction of the predominantly exudative - cellular responses, under the influence of IL-1α, to fibroblast - granulation response, under the influence of TGF-β1 (38).

Histologically speaking, at chronic stage of inflammation significant activity of fibroblasts, fibrous components of reproduction in inflammatory region can be expected (16). If this process is extremely intense generated significant predisposition to replace functional liver tissue with fibrosis, which may have long-term pathological changes in liver structure, and then the functional repercussions (16, 17). At chronic hepatitis it is necessary to evaluate how favorable is the “repair inflammatory reaction” (39). If it is too intense, the stabilization of the formed fibrous tissue could in the long term functionally suppress liver tissue, which leads to liver cirrhosis. Therefore, monitoring of the changes in concentrations of TGF-β1 and IL-1 might be valuable as a “predictor of cirrhosis” in the phase of chronic inflammation. Nagy et al published a study on the elevated TGF-β1 in fibrotic processes in the liver (40). Chen et al associate the values of TGF-β1 mRNA expression and activity of the fibrous process in the liver of patients with alcoholic liver disease (41). Matsuzaki concluded that TGF-β plays a significant role in fibrocarcinogenesis in the liver tissue exposed to chronic inflammation, and signaling pathways of TGF-β provide a general framework for understanding the process of chronic inflammation of the liver parenchyma (42). Murata concluded that in chronic hepatitis B, changes in signaling pathways of TGF-β may be correlated with the evaluation of HCC in the further development of the disease (43). Studies of comparative analysis of serum levels of IL-1α and TGF-β1 in patients with chronic hepatitis have not been found in literature.

In conclusion, analysis of cytokines (IL-1α and TGF-β1) and functional status of the liver revealed detailed information about the conditions of chronic hepatitis. IL-1α was significantly elevated in inflammatory conditions of pronounced activity (viral, PCR positive hepatitis) and TGF-β1 in the states of pronounced fibrous processes or malignancy.

IL-1α and TGF-β1 are important parameters of inflammatory activity and fibrosis evaluation in chronic liver damage. Our results suggest that inflammatory and immune parameters, analyzed together can significantly contribute to the understanding of chronic liver damage and thus differential diagnostic procedure. Further research on understanding and future therapeutic control of fibrotic processes in the liver are needed.

FUNDING
No specific funding was received for this study.

TRANSPARENCY DECLARATIONS
Competing interests: none to declare.

REFERENCES


SAŽETAK

Cilj Analizirati serumski nivo proinflamatornog interleukina-1 (IL-1α) i antiinflamatornog TGF-β1, uz rutinske laboratorijske nalaze, radi boljeg praćenja i razumijevanja patogenetskih mehanizama, te diferencijalno dijagnostičkog procesa, kod hroničnih oštećenja jetre infektivne i neinfektivne etiologije.

Metode Uključeno je 150 ispitanika, raspoređenih u dvije skupine, ovisno o infektivnoj ili neinfektivnoj etiologiji jetrenog oštećenja, uz treću kontrolnu grupu. Osim analize standardnih laboratorijskih parametara, mjereni su i serumski nivoi citokina IL-1α i TGF-β1.

Rezultati Najveća serumska vrijednost IL-1α izmjerena je u skupini oboljelih od virusnih B ili C hepatitis s PCR pozitivnim testom (p <0.01), dok je najveća serumska vrijednost TGF-β1 bila u skupini obojlih od neinfektivnog hepatitisa maligne ili toksične etiologije (p <0.0001). Mjereni citokini pokazali su statistički značajnu korelaciju s negativnim predznakom (-0,18), što potkrepljuje proinflamatornu ulogu IL-1α, te, nasuprot njemu, antagonističku antiinflamatornu i profibroblastičnu ulogu TGF-β1. Za veće serumske vrijednosti IL-1α signifikantni prediktivni parametri bili su: prethodna HBV infekcija, niže serumske vrijednosti TGF-β1, dob, upotreba alkohola, niži MELD i Child Pugh skorovi (p<0,05). Za veće serumske vrijednosti TGF-β1 signifikantni prediktivni parametri bili su: dob, niži MELD i Child Pugh skorovi, primanje krvnih derivata, niže vrijednosti IL-1α, fibrinogen (p<0.05). Napravljen je prognostički model MELD = (TGF-β1) x 0,001- (IL-1α) x 0,085 + CTP x 1,771-2,052; (± 2.04; R²=0,61; p<0,001).

Zaključak Navedeni rezultati ukazuju da upalni i imunološki parametri, analizirani uporedo, mogu značajno doprinijeti razumijevanju hroničnih jetrenih oštećenja, a samim time i diferencijalno-dijagnostičkom postupku. IL-1α i TGF-β1 su značajni parametri upalne aktivnosti i ocjene fibrogenze kod hroničnih oštećenja jetre. Potrebna su daljna istraživanja na razumijevanju i budućoj terapijskoj kontroli fibroznih procesa u jetri.

Ključne riječi: hronične bolesti jetre, hepatocelularni karcinom, parametri upala, IL-1α, TGF-β1