Perspective directions of non-invasive diagnostics of fibrosive changes in the liver upon non-alcoholic fatty liver disease

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Key words: non-alcoholic fatty liver disease, liver fibrosis, diagnosis, informative value, metabolic syndrome, evaluation

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the x sama extension x liver disease second in the world, with the highest frequency of occurrence among residents of Western countries [20, 28].The results of a retrospective analysis published in 2014 showed a 10-fold increase in the incidence of hepatocellular carcinoma (HCC), associated specifically with NAZHBP, for the period from 2000 to 2010, which amounted to 34.8% of all cases of hepatocellular carcinoma [22].

According to the calculations, NAFLD creates serious economic and public health problem, due to the fact that the direct medical costs of doing of the patient with NAPP in the United States is approximately $ 1,613, and in Europe € 1 163 per patient per year, which is a very disturbing precedent given the rapidly growing prevalence of the disease in the world [15].

In recent years, it has been proven that it is a marked fibrosis of liver tissue in NAJBP is more associated with an increased risk of developing cirrhosis of the liver, fcc and mortality of patients, regardless of the presence or severity of other identified histological signs of the disease [19, 26]. Currently, the active conduct of a morphological study for the diagnosis of liver fibrosis in patients with NAJBP is often limited by the presence of comorbid pathology and, as a consequence, a high risk of complications during biopsy, the invasiveness of the procedure itself, the small size of the biopsy that does not reflect the complete picture of the liver, and other significant factors. That is why there is a question about finding noninvasive markers for predicting the development and progression of fibrosis changes in the liver, which are the subject presented a literature review.

BAAT Evaluation System

The BAAT evaluation system is one of the very first predictive panels designed specifically to assess the risk of formation Liver fibrosis in patients with excessive body weight and NAZHBP. In this diagnostic panel, four variables are used (body mass index, age, AST level and triglycerides in the blood serum), the increase of which independently correlates with the presence of septal fibrosis confirmed with liver biopsy, as was shown by the retrospective analysis of the cohort of 93 of patients [25].

The BAAT assessment system is a weighted score for each of the indicators: BMI (≥28=1, <28=0), the age of the patient at the time of liver biopsy (≥50 years=1, <50=0), AST level (≥ 2N=1, ≤2N=0) and the serum triglyceride index (≤ 1.7 mmol / L=1, <1.7=0). The total score can range from 0 to 4. The score of 0 is associated with a 100% absence of signs of septal liver fibrosis, with the area under the ROC curve being 0.84 [25].

BARD evaluation system

This system has been developed for the first time S. A. Harrison c group of researchers [11] based on the results of a retrospective logistic regression analysis of 827 patients with NAZHBP. Thus were identified three variables taken into account in calculating the amount of mathematical points: B: body mass index ≥28 kg / m ^{2}=1 point, AAR: ratio of AST / ALT ≥ 0,8=2 points and DM — if the patient has diabetes diabetes=1 point. When assessing the validity of this system of accounts, it was noted that the total score from 2 to 4 points had a ratio 17 (95% CI: 9.2 — 39.9) for fibrosis (F3 — F4) stages expressed, with negative th predictor its value was obtained in 96% of cases to eliminate the initial manifestations of fibrosis in the liver (F 0 — F 1).

At present, the results of the practical application of this system of accounts are highly contradictory. In several minutes and was shown esearch high prognostic Separated Separated Separated the negatively values s of the prediction method, from 81 to 97% [8, 36, 37]. On the contrary, in the study G. Ruffillo and colleagues [36] it was demonstrated that BARD evaluation system has a sensitivity of only 51.4% and specificity — 77.2% and only expressed fibrosis stages. Moreover, there are suggestions that the BARD system can lead to an overestimation of the body mass index and diabetes mellitus when performing the final count of the results [24].

FibroTest System

FibroTest System or Fibrosure are the same test, sold under different commercial names in the states of Europe. This system is a diagnostic panel that includes assessment of indicators of total bilirubin, GGTP, a2-macroglobulin, haptoglobin and apolipoprotein, taking into account the age and sex of the patient. This system is designed to predict the development of significant stages of fibrosis in patients with chronic viral hepatitis B and C [33, 34], as well as NAZHBP [13].

The predictive value of the FibroTest panel It was confirmed in V study. Ratziu and colleagues, under supervision of which were 267 patients with a morphologically confirmed diagnosis of NAJBP [1]. The control group included 954 healthy donors, comparable in sex and age with patients in the main group. According to the results of this study it was noted that FibroTest panel demonstrated AUROC 0.86 and 0.92 for the prediction of fibrosis F2 — 4 and fibrosis F3 — 4, respectively, which indicates a high prognostic significance of the predictive models. Wherein Sensitivity panel "meaningful" prediction of fibrosis was 77% and specificity — 98% [1].

To date, the only limitation to the wide use of the FibroTest diagnostic panel in actual clinical practice is that a number of evaluation indices such as alpha 2-macroglobulin, haptoglobin, andapolipoprotein A1 are not available for routine testing in most clinical clinics in hospitals and hospitals.

FibroMeter System

FibroMeters system is a set of panels based on serum markers and clinically parameter x s, which are specifically designed to assess the stage of liver fibrosis depending on the etiological factor, in particular FibroMeters for viral hepatitis, alcoholic liver damage and NAJBP [6].

The FibroMeter system for NAJBP includes such indicators as : age, body weight, levels glucose, AST, ALT and ferritin a in serum, as well as the number of platelets. In a large comparative studyevaluating the diagnostic significance of the FibroMeter system for the diagnosis of hepatic fibrosis in NAJBP, compared to other systems (NFS and APRI), FibroMeter showed the highest area under theROC- curve (AUROC) for significant fibrosis (≥ F2)=0.943 (95% CI: 0.91 — 0.98), unlike NFS indicators — 0.855 (95% CI: 0.83 — 0.93) and APRI 0,866 (95% CI: 0.81 — 0.92) [18].

In addition, the FibroMeter system for NAJBP showed high sensitivity in the evaluation of various stages of Fibrosis: F0 / F1 (sensitivity 95%), F0 / F1 / F2 (sensors sensitivity is 75%), F2 / F3 / F4 (sensors sensitivity is 87.9%), with the overall sensitivity by a factor of 91.9%. The assessment as a whole, has shown that diagnostic Cesky reproducibility The FibroMeter for NAPP was the best to detect xth intermediate step fibrosis (F1 / 2) and less important — for the expression of fibrosis and liver stages (F 3/4) [18].

FIB-4 System

The FIB-4 system was originally developed for practical application in assessing liver fibrosis in patients with chronic viral hepatitis C in combination with infection with the human immunodeficiency virus (coinfected population) [9]. This diagnostic panel consists of easy estimated in the routine practice of parameters : age, platelet count, level of AS T and ALT [7].

In a study A. G. Shah and colleagues, an assessment was made of the possibility of using FIB-4 in patients with NAJBP in comparison with other diagnostic systems (FibroTest, Fibroscan, BARD, NFS and NASH) [38]. According to the results of this study, AUROC indicator for FIB-4 panels in identifying patients with severe fibrosis (F3 — F4) yl composition 02 0.8 (95% CI: 0.758 — 0847), whichwas comparable to that of NFS panel, and higher than those AUROC for other comparable systems [38]. Furthermore, in this study yyavlenny NDICATORS ≥ 2.67 for FIB-4 bar was positively associated with them th prognostic value of m in 80% of cases, and the rate of ≤ 1, 0 had a negative prognostic value for the diagnosis of significant stages of liver fibrosis in 90% of cases [38]. Similar results were obtained in several other studies [10, 23, 32], it was noted that the FIB-4, diagnostic panel has the most significant prognostication-terrorist value in the evaluation of the initial and moderate's fibrosisGOVERNMENTAL changes in patients with NAFLD at a value index ≥ 1.43.

The AST / ALT ratio

It was previously demonstrated that the ratio AST / ALT is a rather specific indicator in the diagnosis of liver cirrhosis in patients with chronic viral hepatitis C [4]. In this case, the data confirming the use of the AST / ALT ratio as a system for calculating the risk of developing fibrosis of the liver in NAZHBP, are very limited. In one cohort study of patients with non-alcoholic steatohepatitis,multivariate analysis has established that the AST / ALT ratio can be used as an independent predictor of the expressed stage Fibrosis of the liver (F ≥ 3) / cirrhosis [3].

In operation S. McPherson and co-authors [35], a high predictive value of the AST / ALT ratio was shown in a cohort of 145 patients with morphologically verified NAFLD in the detection of severe liver fibrosis with a sensitivity of 74% and a specificity of 78%, the area under the ROC curve was 0.83.

It is currently believed that the ratio of AST to ALT can be a useful tool to exclude severe hepatic fibrosis as a primary screening [35]. However, when interpreting the results of the AST / ALT ratio,it should be remembered that with age, ALT rates gradually decrease, while the AST level remains stable. This age-related feature can lead to a false increase in the AST / ALT ratio in patients without severe fibrosis [12]. Nevertheless, at present the diagnostic value of the AST / ALT ratio for the detection of severe stages of liver fibrosis is recognized by many researchers, it is no coincidence that this parameter is included in other more complex diagnostic panels — NFS and BARD.

The ratio of AST and platelet count (APRI index)

Evaluation with APRI system is the simplest method, which was originally developed and tested on patients with chronic hepatitis and liver fibrosis (Metavir stage ≥F3 of scale) [5].

Later, attempts were made to use this method to predict the development of liver fibrosis in patients with NAZHBP, but the results of such studies were very ambiguous. Thus, in a retrospectivecohort study of 358 patients with confirmed liver biopsy diagnosed NAFLD, atel showing APRI> 1 has been associated with the probability of the presence of significant fibrosis in the liver, but in this case,this test showed a rather low sensitivity (30%) at a relatively high specificity (92.8%) [14]. In addition, the results of other comparative studies have shown that the APRI panel has the least diagnostic significance in detecting severe stages of fibrosis At NAWA with AUROC from 0.67 to 0.78, compared with BARD and FIB- 4 [6, 34].

Therefore, to date, widespread adoption in the clinical practice of this system assessment for prediction Liver fibrosis in patients with NAJBP is limited by its low prognostic value.

Diagnostic panel for evaluating fibrosis in patients with NUZHBP (NFS)

To date, the NFS counting system is the most studied system for assessing the advanced stages of fibrous changes in the liver, from 2012 recommended for use in clinical practice by the American Association for the Study of Liver Disease [27], in 2015 — by the European Association for the Study of the Liver [29].

Compared with other existing non-invasive fibrosis assessment systems, NFS is one of the most reliable [34]. This diagnostic panel has been developed in the course of the first multicenter study I with 733 patients with NAFLD confirmed by liver biopsy and [16]. The indices of 480 patients were used to develop a counting system, and the remaining 253 patients were taken to test the effectiveness of the administration of this system.

In the NFS system, it is estimated that there are variables — age, the level of glucose in the plasma of venous blood, the body mass index (BMI), the number of platelets, content of albumin and with aratio of AST / ALT as independent predictors x severe fibrosis of the liver [16]. P ri and generate NFS has been applied multiple logistic regression analysis onny with inclusion of the above variables and the allocated two optimal Range and the area, one of which excludes the presence of significant fibrosis Liver (<-1,455), and the other — ascertains its presence in the patient (> 0.766).

The diagnostic value of the NFS system was confirmed in the study McPherson S. and co-authors, comparing a number of non-invasive systems for assessing the presence of severe hepatic fibrosis :FIB-4, BARD, AST / ALT and NFS ratio, where the latter showed better prognostic opportunities with AUROC 0,81 (95% CI 0.71 — 0.91) [34].

Enhanced liver fibrosis test (ELF)

Diagnostic system ELF-test is a simplified algorithm of the Original European test for liver fibrosis [17, 31] and is applicable for various chronic diseases liver. This system includes an evaluation of the content of the amino-terminal propeptide and procollagen type III (PIIINP), tissue inhibitor of matrix metalloproteinases 1 (TIMP-1) and hyaluronic acid.

T he system ELF showed good results in the evaluation of fibrosis in the liver stages (≥F3) in a cohort of 196 patients with the indicator area under the ROC-curve of 0.90 (95% CI: 0.84 — 0.96). W ith p thresholds of this at 0.3576 w points possessed sensitivity 80% and specificity of 90% w d iagnostike pronounced fibrosis [31]. Similar results were obtained in pediatric practice in children with obesity and NAZHBP [31].

There is evidence that ELF test is a good predictor of mortality and from cirrhosis of the liver, which forms in the end their chronic liver disease minutes, including NAFLD [17].

In addition, according to the results of economic analysis, the use of the ELF serum panel proved to be the most cost-effective compared with other diagnostic panels and visualization methods, such aselastography of the liver on the apparatus " Fibroscan " or magneto — o — resonance elastography of the liver [21], which enabled the use of this evaluation system in modern European recommendations the management of patients with diffuse liver diseases and for screening and fibrosis liver. However, in domestic clinical practice, this method was not widely used due to its inaccessibility in most regions of Russia.

Conclusion

Currently, the active Search non-invasive diagnostic systems for assessing the risk of formation and progression of fibrotic changes in the liver in patients with NAZHBP [1]. In our studies, it was shown that the diagnostic significance in assessing liver fibrosis can have both clinical and laboratory indicators. According to the results obtained, the most informative indicators reflecting the risk of progression of the stage of fibrosis F 1 to stage F2, levels of low density lipoproteins, glucose, matrix metalloproteinase- 9 (MMP-9) and serum leptin appeared ; while the increase in liver size duringphysical examination, the level of systolic arterial pressure, the presence of carbohydrate metabolism disorders, the ALT / AST ratio and the waist / hip volume, as well as the serum concentrations of TIM P- 1 and TIMP- 2 were predictors of the progression of fibrosis of stage F 2 into step F 3 [2].

Thus, the problem of searching for non-invasive highly informative systems for predicting fibrotic changes in the liver in patients with NAJBP is very relevant, taking into account The existing restrictions in the everyday using liver biopsy and instrumental methods of

diagnosis of fibrosis that edot to search from the new non-invasive diagnostic systems for the development of the mostvysokovalidnyh and economically reasonable predictive models.

Conflict of interest:

The authors state that there is no conflict of interest.

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The review is devoted to the analysis of currently available non-invasive diagnostic systems for predicting the formation of fibrous changes in the liver of patients with non-alcoholic fatty liver disease. The advantages and possible limitations of each of the available diagnostic systems are analyzed.