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Non-invasive serum markers and transient elastography in staging advanced chronic hepatitis C

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Objectives. In the past decade researchers are presenting indirect non-invasive serum markers for liver fibrosis and cirrhosis evaluation. Our aim was to evaluate effectiveness in staging advanced liver disease when using transient elastography and nine non-invasive serum markers: APRI, FIB-4, ASPRI, LSPS, P2/MS, FibroQ, Fibro-α, Pohl, CDR.

Methods. 162 patients with hepatitis C infection were included in this study. Patients were divided in two groups, regarding histopathologic results: advanced liver fibrosis and cirrhosis. The following laboratory measures were obtained in all patients: ALT, AST, albumin, total bilirubin, alkaline phosphatase, gamma glutamyl transferase, INR, hemoglobin, platelet count, alfa fetoprotein, segmented neutrophils count and percentage and monocytes percentage. Transient elastography and nine non-invasive serum markers – APRI, FIB-4, ASPRI, LSPS, P2/MS, FibroQ, Fibro-α, Pohl, CDR – were compared with the results of the histopathological examination. A statistical analysis was done using the Student t-test, the Spearman's rank correlation and the area under receiver-operating characteristic curves (AUROCs).

Results. All nine non-invasive markers correlated significantly with the liver fibrosis stage ($P < 0.001$). Patients with liver cirrhosis had significantly higher ASPRI, LSPS, FIB-4, FibroQ, APRI, Fibro-α, Pohl and transient elastography scores in comparison with significant fibrosis ($P < 0.05$). The Pohl score indicated cirrhosis in 45.6% of cirrhotic patients, whereas it was positive in only 5.7% of non-cirrhotic patients ($P < 0.05$). P2/MS and CDR markers showed no significant difference between fibrosis and cirrhosis groups. The LSPS non-invasive marker showed the highest diagnostic efficiency for liver cirrhosis diagnosis, when using the cutoff score ≥0.99 (sensitivity 86.96%, specificity 85.71%, positive predictive value 88.9%, negative predictive value 83.3%). Transient elastography also showed high efficiency for liver cirrhosis diagnosis: using a cutoff value of ≥12 (kPa), sensitivity, specificity, positive and negative predictive values were 84.78, 80.00, 84.8 and 80.0%, respectively.

Conclusions. In our study the most efficient for liver cirrhosis diagnosis were the LSPS non-invasive serum marker and transient elastography.

Key words: non-invasive serum markers, liver fibrosis, liver cirrhosis, transient elastography, hepatitis C

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INTRODUCTION

Chronic hepatitis C is a major cause of liver cirrhosis, hepatocellular cancer, liver failure and death (1). Over the last 15 years the hepatitis C seroprevalence has increased from 2.3 to 2.8% or more than 185 million infections worldwide (2). In Lithuania anti-HCV rates are high, with 2.78% prevalence (3). Liver fibrosis is the main disease pathway leading to liver cirrhosis. Precise staging of liver fibrosis is essential for patient management because advanced fibrosis and cirrhosis requires an adequate antiviral therapy and a specific follow-up. Until recently liver biopsy was the only one diagnostic and staging method for assessment of liver fibrosis and is still considered as a gold standard. However, liver biopsy is an invasive procedure and is associated with such complications as pain, bleeding, and death (4). Moreover, recent studies showed that liver biopsy has many limitations due to dependency on the size of biopsy and intra- and interobserver variability (5, 6). For this reason, researchers focus on non-invasive alternatives for liver biopsy: in the past decade non-invasive liver fibrosis evaluation methods were presented, such as ultrasound based transient elastography, direct (representing components of extracellular matrix) and indirect (reflecting hepatic inflammation and function) markers for liver fibrosis (7). Most widely accepted are transient elastography (Fibroscan) and indirect markers – APRI and FIB-4, because they are simple to calculate and available in many hospital laboratories during usual patient care. Nevertheless, many other indirect non-invasive markers are available. Our aim was to evaluate transient elastography, APRI, FIB-4 effectiveness in staging advanced liver disease as well as other non-invasive markers – ASPRI, LSPS, P2/MS, FibroQ, Fibro-α, Pohl and CDR.

MATERIALS AND METHODS

The retrospective data analysis was conducted at Vilnius University Hospital Santariškių Clinics. The data was collected from 162 patients who were diagnosed with hepatitis C infection between the years 2001–2015 and had significant liver fibrosis or cirrhosis. The following laboratory measures were evaluated: ALT, AST, albumin, total bilirubin, alkaline phosphatase, gamma glutamyl transferase, INR, hemoglobin, platelet count, alfa fetoprotein, segmented neutrophils count and percentage, and monocytes percentage. All patients were negative for other causes of chronic liver disease. The fibrosis and cirrhosis stage was determined using the liver biopsy results and the METAVIR scoring system. Significant fibrosis was considered when the METAVIR score was F3-3.5, liver cirrhosis was considered when the METAVIR score was F4.

The following formulas were used to calculate non-invasive markers scores:

– APRI = [(aspartate aminotransferase (U/L)/upper limit of normal)/platelet count 10^3/μl] × 100. Two separate upper limits of normal were selected: 40 U/l and 35 U/l.

– ASPRI was calculated as the sum of age and SPRI. Age (years): <30 = 0; 30–39 = 1; 40–49 = 2; 50–59 = 3; 60–69 = 4; ≥70 = 5, SPRI calculated as a spleen size (cm)/platelet count (10^3/μl) × 100.

– LSPS = [liver stiffness (kPa) × spleen size (cm)/platelet count (10^3/μl)] × 100.

– P2/MS = [platelet count (10^3/μl)]^2/[monocytes (%) × segmented neutrophils (%)].

– Fib-4 = age (years) × aspartate aminotransferase (U/L)/[platelet count (10^3/μl) × [alanine aminotransferase (U/L)]$^{1/2}$].

– FibroQ = [10 × age (years) × aspartate aminotransferase (U/L) × INR]/[platelet count (10^3/μl) × alanine aminotransferase (U/L)].

– Fibro-α = 1.35 + alfa fetoprotein (kU/L) × 0.009584 + aspartate aminotransferase (U/L)/alanine aminotransferase (U/L) × 0.243 – platelet count (10^3/μl) × 0.001624.

– Pohl was considered positive when ASAT/ALAT ratio ≥1 and platelet count <150 × 10^3/μl.

– CDR (cirrhosis discriminant result) was calculated as the sum of platelet count, ASAT/ALAT ratio and INR. Platelet count (10^3/μl): >340 = 0; 280–339 = 1; 220–279 = 2; 160–219 = 3; 100–159 = 4; 40–99 = 5; <40 = 6. ALT/AST: >1.7 = 0; 1.2–1.7 = 1; 0.6–1.19 = 2; <0.6 = 3. INR: <1.1 = 0; 1.1–1.4 = 1; >1.4 = 2.

A statistical analysis was performed using the Microsoft Excel and SPSS 20.0 programs. *P* value <0.05 was considered statistically significant. Patients were divided into two main groups regarding the liver biopsy results and the METAVIR score. The first group was patients with significant

liver fibrosis (F3-3.5) and the second group was patients with liver cirrhosis (F4). Group differences were determined using the Student t-test. The Spearman's rank correlation was used to assess a significant association between non-invasive markers and liver fibrosis stages. The diagnostic values of non-invasive markers were assessed by calculating the area under the receiver-operating characteristic (AUROC) curves. Diagnostic accuracy was calculated by sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV). The cutoffs selected from the AUROC curve were those that best identified significant fibrosis and cirrhosis.

RESULTS

The mean age of 162 patients (107 males, 55 females) was 53 ± 10 years. Overall, 70 patients had significant liver fibrosis (F3-3.5), 92 patients had liver cirrhosis (F4). The demographic and baseline laboratory data of patients are summarized in Table 1.

BMI is the body mass index; AST is aspartate aminotransferase; ALT is alanine aminotransferase; ALP is alkaline phosphatase; GGT is gamma glutamyl transferase; INR is the international normalized ratio; AFP is alfa fetoprotein.

There were significant differences between some variables in the significant fibrosis and cirrhosis groups. Albumin was significantly lower in the liver cirrhosis group while total bilirubin, ALP, GGT, INR and AFP laboratory measures were significantly higher in the liver cirrhosis group.

In the liver cirrhosis group the platelet count was lower, the spleen size was bigger, but we have not determined significant differences. Also there were no significant differences in the age, body mass index and AST and ALT measures.

The main goal was to identify patients with significant fibrosis vs those with cirrhosis using non-invasive liver fibrosis serum markers. The relationship between nine serum indexes, liver elastography and liver fibrosis stages was evaluated (Table 2).

Our findings demonstrated a statistically significant differences between patients with significant fibrosis and cirrhosis. The patients with cirrhosis had significantly higher ASPRI, LSPS, FIB-4, FibroQ, APRI, Fibro-α, Pohl and transient elastography scores than those with significant fibrosis. The Pohl score indicated cirrhosis in 45.6%

Table 1. Variables associated with the presence of significant fibrosis (F3-3.5) and cirrhosis (F4)

	Significant fibrosis F3-3.5 (N = 70)	Cirrhosis F4 (N = 92)	*P* value
Age, years	51.61 ± 9.41	53.25 ± 10.75	N. S.
BMI, kg/m^2	28.17 ± 5.56	28.66 ± 5.48	N. S.
AST, U/l	80.64 ± 94.07	115.34 ± 67.43	N. S.
ALT, U/l	109.49 ± 72.29	113.11 ± 76.42	N. S.
Albumin, g/l	42.26 ± 3.87	37.60 ± 37.60	<0.05
Total bilirubin, μmol/l	17.00 ± 30.51	25.45 ± 16.59	<0.05
ALP, U/l	82.7 ± 39.16	117.41 ± 57.62	<0.05
GGT, U/l	108.53 ± 152.89	164.33 ± 195.36	<0.05
INR	1.03 ± 0.11	1.18 ± 0.18	<0.05
Hemoglobin, g/l	145.78 ± 19.92	138.57 ± 18.03	N. S.
Platelet count, 10^3/μl	185.47 ± 57.27	122.87 ± 65.89	N. S.
AFP, kU/l	6.57 ± 7.43	19.81 ± 30.87	<0.05
Segmented neutrophils, 10^9/l	3.26 ± 1.65	3.97 ± 7.03	N. S.
Segmented neutrophils, %	51.38 ± 10.85	51.83 ± 13.03	N. S.
Monocytes, %	9.21 ± 2.61	10.50 ± 3.17	N. S.
Spleen size, cm	11.42 ± 1.98	14.2 ± 2.51	N. S.

Values were expressed as mean ± standard deviation.

N. S. is not significant.

Table 2. Relationship between non-invasive markers, diagnosed significant fibrosis and cirrhosis

	F3-3.5 (n = 70)	F4 (n = 92)	*P* value
ASPRI	3.42 ± 1.02	4.46 ± 1.45	<0.05
LSPS	0.74 ± 0.71	4.28 ± 4.19	<0.05
P2/MS	87.60 ± 56.74	42.78 ± 54.54	N. S.
FIB-4	2.54 ± 3.12	6.20 ± 5.18	<0.05
FibroQ	2.78 ± 2.94	7.74 ± 6.80	<0.05
CDR	4.29 ± 1.57	6.60 ± 1.63	N. S.
APRI, ULN 40 U/l	1.42 ± 2.63	3.26 ± 3.62	<0.05
APRI, ULN 35 U/l	1.63 ± 3.01	3.73 ± 4.14	<0.05
Transient elastography, kPa	10.68 ± 9.12	25.53 ± 14.45	<0.05
Fibro-α	1.30 ± 0.18	1.61 ± 0.35	<0.05
Pohl score	Positive 4 (5.7%) Negative 66 (94.3%)	Positive 42 (45.6%) Negative 50 (54.4%)	<0.05 N. S.

ULN is the upper limit of norm.

of the cirrhotic patients, whereas it was positive in only 5.7% of the non-cirrhotic patients (*P* value <0.05). Only two non-invasive serum markers – CDR and P2/M2 showed no significant difference.

All non-invasive markers correlated significantly with the liver fibrosis stage (all *P* values <0.001). The highest correlation coefficient was found with LSPS, P2/M2 serum marker correlated negatively (Table 3).

The AUROCs, cutoff values, sensitivity, specificity, positive predictive values and negative predictive values of serum non-invasive markers are shown in Table 4.

ULN is the upper limit of norm; PPV is the positive predictive value, NPV is the negative predictive value; AUC is the area under the curve.

AUROCs of LSPS and transient elastography were the highest in comparison with other non-invasive markers when differentiating significant fibrosis and cirrhosis. There were no differences between two separate upper limits of normal when calculating APRI. ASPRI had the lowest AUROCs.

Table 3. The correlation between non-invasive liver fibrosis serum markers and the stage of liver fibrosis

Variable	Correlation coefficient (Spearman's rho)	*P* value
ASPRI	0.589	<0.001
LSPS	0.689	<0.001
P2/MS	–0.504	<0.001
FIB-4	0.585	<0.001
FibroQ	0.612	<0.001
CDR	0.601	<0.001
APRI, ULN 40 U/l	0.508	<0.001
APRI, ULN 35 U/l	0.508	<0.001
Transient elastography	0.643	<0.001
Fibro-α	0.585	<0.001

Table 4. Sensitivity, specificity, positive predictive values, negative predictive values and the area under the curve of non-invasive markers

ASPRI					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% Cl]
≥3.77	68.46	75.71	78.7	64.6	0.728 [0.653–0.795]
P2/MS					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% Cl]
≤43.50	73.91	80.00	82.9	70.0	0.793 [0.723–0.853]
FIB-4					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% Cl]
≥2.63	83.70	74.29	81.1	77.6	0.841 [0.776–0.894]

Table 4 (continued)

FibroQ					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% CI]
≥3.48	75.00	84.29	86.2	72.0	0.857 [0.793–0.907]
CDR					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% CI]
≥5	76.09	87.14	88.6	73.5	0.847 [0.782–0.898]
APRI (UNR 40 U/l)					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% CI]
≥1.59	68.48	85.71	86.3	67.4	0.796 [0.726–0.855]
APRI (ULN 35 U/l)					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% CI]
≥1.81	68.48	85.71	86.3	67.4	0.796 [0.726–0.855]
LSPS					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% CI]
≥0.99	86.96	85.71	88.9	83.3	0.912 [0857–0.951]
Fibro-α					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% CI]
≥1.44	75.00	84.29	86.2	72	0.841 [0.775–0.894]
Transient elastography					
Cutoff value	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC [95% CI]
≥12	84.78	80.00	84.8	80.0	0.876 [0.815–0.923]

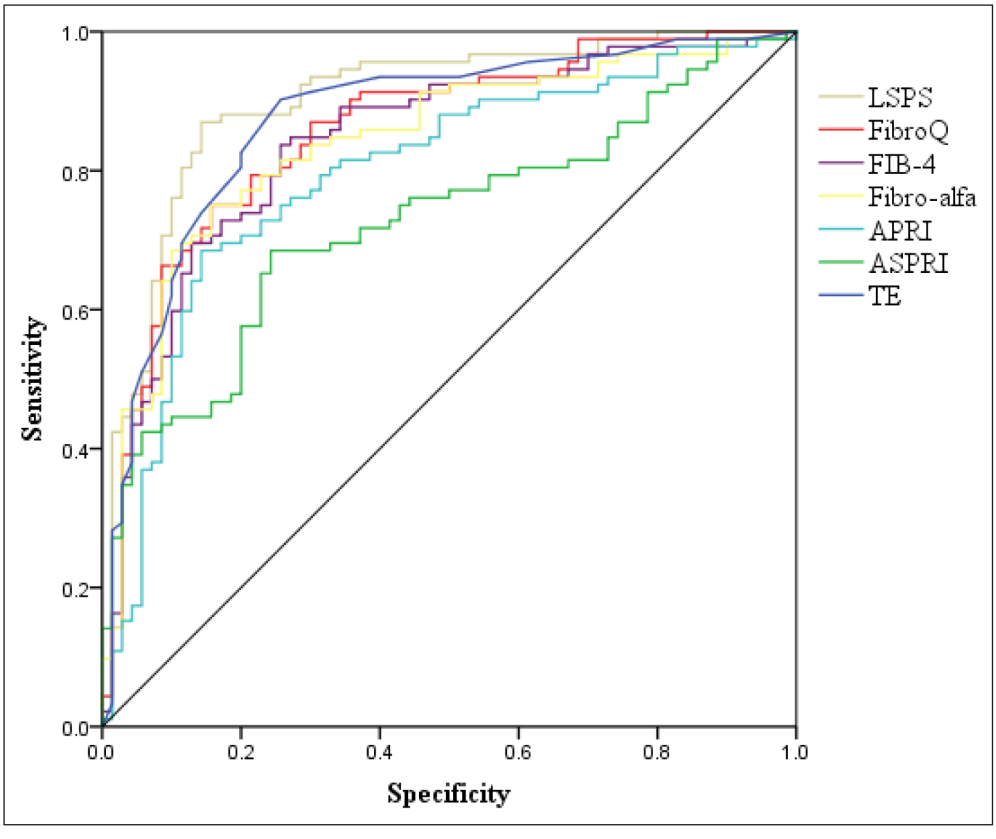

Figure. Curves of the receiver operating characteristics (ROC) of non-invasive tests for prediction of cirrhosis (F4). Only those markers were used, which had significant differences between the significant fibrosis and cirrhosis groups

DISCUSSION

Nowadays, liver biopsy is considered the gold standard for the detection of liver fibrosis, although it is a costly and invasive procedure, which carries a risk of complication and requires hospitalization. Only 1/50 000 of the organ is removed during the procedure and it is great limitation for successful and adequate liver fibrosis staging. Also, liver biopsy is limited by inter- and intraobserver discrepancies. However, patients with advanced stage of liver fibrosis or patients with liver cirrhosis often have contraindications for liver biopsy because of bleeding possibilities and other complications. Based on the European Association for the Study of the Liver recommendations, patients with significant fibrosis and cirrhosis have antiviral treatment priority and requires treatment as soon as possible (8). Non-invasive serum markers could be a great possibility to stage, diagnose advanced liver disease and start immediate treatment.

In this study we found that the optimal ASPRI cutoff value for diagnosing liver cirrhosis was ≥3.77, with a sensitivity of 68.46%, specificity of 75.71% and PPV and NPV of 78.7 and 64.6%, respectively. Our cutoff value when diagnosing hepatitis C caused liver cirrhosis was remarkably lower than the Kim et al. (9) used cutoff value of >12, when diagnosing hepatitis B caused liver cirrhosis.

When evaluating the P2/MS serum marker, we found that the optimal P2/MS cutoff value for diagnosing liver cirrhosis was ≤43.50, with a sensitivity of 73.91%, specificity of 80.00 and PPV and NPV of 82.9 and 70.0%, respectively. But there were no significant differences between the significant liver fibrosis and cirrhosis groups and this marker is non-valuable for differentiation of significant liver fibrosis and cirrhosis.

Results from the current study revealed that the optimal FIB-4 cutoff value for diagnosing liver cirrhosis was ≥2.63, with a sensitivity of 83.70%, specificity of 74.29% and PPV and NPV of 81.1 and 77.6%, respectively. Our cutoff value was consistent with the published cutoff values of >2.76 (10) for significant fibrosis and 2.89 for liver cirrhosis (11).

In the present study we found that the optimal FibroQ cutoff value for diagnosing liver cirrhosis was ≥3.48, with a sensitivity of 75.00%, specificity of 84.29% and PPV and NPV of 86.2 and 72.0%, respectively. Our cutoff value was higher than that in other studies, where a cutoff value of >1.6 (12–14) was considered optimal for significant fibrosis. Our goal was to evaluate differences between significant fibrosis and liver cirrhosis and higher FibroQ cutoff value for liver cirrhosis suggests that FibroQ might be used to diagnose liver cirrhosis immediately.

In this study we found that the optimal CDR cutoff value for diagnosing liver cirrhosis was ≥5, with a sensitivity of 76.09%, specificity of 87.14% and PPV and NPV of 88.6 and 73.5%, respectively. It was lower than the published cutoff value ≥8 by Lackner et al. (15). Significant differences between the significant liver fibrosis and cirrhosis groups were not determined.

The results from this study showed that the optimal APRI cutoff value (when the aspartate aminotransferase upper limit of norm is 35 U/l or 40 U/l) for diagnosing liver cirrhosis was ≥1.59 (ULN 40 U/l) and ≥1.81 (ULN 35 U/l), with a sensitivity of 68.48%, specificity of 85.71% and PPV and NPV of 86.3 and 67.4%, respectively. The APRI cutoff value of ≥1.59 (ULN 40 U/l) was consistent with the findings by Parise et al., who reported the cutoff value of >1.5 (16).

In our study the optimal LSPS cutoff value for diagnosing liver cirrhosis was ≥0.99, with a sensitivity of 86.96%, specificity of 85.71% and PPV and NPV of 88.9 and 83.3%, respectively. The LSPS non-invasive marker showed the highest efficiency when diagnosing liver cirrhosis. In other studies the LSPS cutoff value of >1.08 (17) was used for hepatitis B caused liver cirrhosis.

Our study agreed with the Attallah et al. recent study (18), where the Fibro-α cutoff value for liver cirrhosis was considered optimal when >1.35. We found a similar optimal Fibro-α cutoff value of ≥1.44 for diagnosing liver cirrhosis, with a sensitivity of 75.00%, specificity of 84.29% and PPV and NPV of 86.2 and 72.0%, respectively.

We evaluated transient elastography significance and found that the optimal transient elastography cutoff value for diagnosing liver cirrhosis was ≥12 (kPa), with a sensitivity of 84.78%, specificity of 80.00% and PPV and NPV of 84.8 and 80.0%, respectively. In various studies cutoff values for liver cirrhosis ranged from 10.1 to 17.6 (19–25).

In the present study, we found a statistically significant difference between the positive Pohl score in the significant fibrosis and liver cirrhosis patient group. This finding supports the results of

Pohl et al. (26) and Lackner et al. (15), who confirmed the diagnostic accuracy of the Pohl score in significant fibrosis and cirrhosis.

In conclusion, all nine non-invasive serum markers (ASPRI, LSPS, P2/MS, FIB-4, FibroQ, CDR, APRI, Pohl and Fibro-α) are efficient when diagnosing advanced liver fibrosis and cirrhosis. In our study the most efficient was the LSPS non-invasive serum marker and transient elastography. All non-invasive markers demonstrated a significant correlation with the liver cirrhosis stage. The combination of these non-invasive markers may replace or reduce the requirement for liver biopsy, particularly for cases with cirrhosis in which liver biopsy has limitations and complications.

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References

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med. 2001; 345: 41–52.
2. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013; 57: 1333–42.
3. Liakina V, Valantinas J. Anti-HCV prevalence in the general population of Lithuania. Med Sci Monit. 2012; 18(3): PH28–35.
4. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med. 2001; 344: 495–500.
5. Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. J Hepatol. 2003; 39(2): 239–44.
6. The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. Hepatology. 1994; 20: 15–20.
7. Nguyen D, Talwalkar JA. Noninvasive assessment of liver fibrosis. Hepatology. 2011; 53: 2107–10.
8. The European Association for the Study of the Liver. Recommendations on Treatment Hepatitis C 2015.
9. Kim BK, Kim SA, Park YN, Cheong JY, Kim HS, Park JY, et al. Noninvasive models to predict liver cirrhosis in patients with chronic hepatitis B. Liver Int. 2007; 27: 969–76.
10. Abdollahi M, Pouri A, Ghojazadeh M, Estakhri R, Somi M. Non-invasive serum fibrosis markers: A study in chronic hepatitis. Bioimpacts. 2015; 5(1): 17–23.
11. Zynkus R, Jonaitis L, Petrenkiene V, Gudinaviciene I, Kupcinskas L. Combination of transient elastography with serum-based noninvasive tests improves prediction of liver fibrosis in patients with chronic hepatitis C: a prospective cohort study. Acta Med Litu. 2015. Vol. 22. No. 2. P. 77–84.
12. Hsieh Y-Y, Tung S-Y, Lee K, Wu CS, Wei KL, Shen CH, et al. Routine blood tests to predict liver fibrosis in chronic hepatitis C. World J Gastroenterol. 2012; 18(8): 746–53.
13. Hsieh YY, Tung SY, Lee IL, Lee K, Shen CH, Wei KL, et al. FibroQ: an easy and useful noninvasive test for predicting liver fibrosis in patients with chronic viral hepatitis. Chang Gung Med J. 2009; 32: 614–22.
14. Attallah AM, Omran MM, Farid K, El-Bendary M, Emran TM, Albannan MS, El-Dosoky I. Development of a novel score for liver fibrosis staging and comparison with eight simple laboratory scores in large numbers of HCV-monoinfected patients. Clin Chim Acta. 2012; 413: 1725–30.
15. Lackner C, Struber G, Liegl B, Leibl S, Ofner P, Bankuti C, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepatology. 2005 June; 41(6): 1376–82.
16. Parise ER, Oliveira AC, Figueiredo-Mendes C, Lanzoni V, Martins J, Nader H, Ferraz ML. Noninvasive serum markers in the diagnosis of structural liver damage in chronic hepatitis C virus infection. Liver Int. 2006; 26: 1095–9.
17. Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology. 2013; 144: 102–11.e1.
18. Attallah AM, El-Far M, Omran MM, Farid K, Albannan MS, El-Dosoky I. Noninvasive diagnosis of liver fibrosis and cirrhosis in chronic hepatitis C patients. J Clin Lab Anal. 2013; 27(2): 121–9.
19. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of

hepatic fibrosis. Ultrasound Med Biol. 2003; 29(12): 1705–13.
20. Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, Bedossa P; FIBROSTIC Study Group. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol. 2010; 53(6): 1013–21.
21. Cross TJ, Calvaruso V, Maimone S, Carey I, Chang TP, Pleguezuelo M, et al. Prospective comparison of Fibroscan, Kings score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. J Viral Hepat. 2010; 17(8): 546–54.
22. Arena U, Vizzutti F, Abraldes JG, Stasi C, Moscarella S, Milani S, et al. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut. 2008; 57(9): 1288–93.
23. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology. 2005; 41(1): 48–54.
24. Kettaneh A, Marcellin P, Douvin C, Poupon R, Ziol M, Beaugrand M, de Lédinghen V. Features associated with success rate and performance of FibroScan measurements for the diagnosis of cirrhosis in HCV patients: a prospective study of 935 patients. J Hepatol. 2007; 46(4): 628–34.
25. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005; 128(2): 343–50.
26. Pohl A, Behling C, Oliver D, Kilani M, Monson P, Hassanein T. Serum aminotransferase levels and platelet counts as predictors of degree of fibrosis in chronic hepatitis C virus infection. Am J Gastroenterol. 2001; 96: 3142–6.

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NEINVAZINIAI KEPENŲ ŽYMENYS IR KEPENŲ ELASTOGRAFIJA NUSTATANT PAŽENGUSIOS STADIJOS HEPATITĄ C

Santrauka

Įžanga. Pastarąjį dešimtmetį mokslininkai pristato vis daugiau netiesioginių neinvazinių kepenų fibrozės žymenų, skirtų fibrozės ir cirozės diagnostikai. Mūsų tikslas buvo įvertinti 9 neinvazinių kepenų fibrozės žymenų – APRI, FIB-4, ASPRI, LSPS, P2/MS, FibroQ, Fibro-α, Pohl, CDR ir kepenų elastografijos efektyvumą nustatant pažengusios kepenų ligos stadiją.

Medžiaga ir metodai. Retrospektyviai įvertinti 162 pacientai, kuriems diagnozuota hepatito C infekcija. Pagal kepenų biopsijos rezultatus pacientai buvo padalyti į dvi grupes: su pažengusia kepenų fibroze ir su kepenų ciroze. Vertinti laboratoriniai duomenys: ALT, AST, albuminas, bendras bilirubinas, šarminė fosfatazė, gama-glutamil transferazė, INR, hemaglobinas, trombocitų skaičius, alfa fetoproteinas, segmentuotų neutrofilų skaičius ir procentai, monocitų skaičius ir procentai. Kepenų elastografijos ir 9 neinvazinių kepenų fibrozės žymenų rezultatai buvo palyginti su kepenų biopsijos rezultatais. Statistinė analizė buvo atlikta naudojant *Student t* testą, *Spearman* koreliacijos koeficientą ir plotą po kreive.

Rezultatai. Visi neinvaziniai kepenų fibrozės žymenys reikšmingai koreliavo su kepenų fibrozės stadija ($p < 0{,}001$). Pacientų, kuriems buvo nustatyta kepenų cirozė, ASPRI, LSPS, FIB-4, FibroQ, APRI, Fibro-α, Pohl ir kepenų elastografijos įverčiai buvo gerokai didesni, palyginti su pacientais, kuriems buvo diagnozuota kepenų fibrozė ($p < 0{,}05$). Pohl įvertis patvirtino kepenų cirozę 45,6 % pacientų kepenų cirozės grupėje ir tik 5,7 % pacientų kepenų fibrozės grupėje ($p < 0{,}05$). P2/MS ir CDR žymenys nerodė reikšmingo skirtumo tarp kepenų fibrozės ir cirozės grupių. LSPS žymuo buvo efektyviausias diagnozuojant kepenų cirozę, kai vertės reikšmė – ≥0,99, jautrumas – 86,96 %, specifiškumas – 85,71 %, prognostinė teigiamo testo vertė – 88,9%, prognostinė neigiamo testo vertė – 83,3 %. Kepenų elastografija taip pat buvo efektyvi, kai vertės reikšmė ≥12 (kPa), jautrumas, specifiškumas, prognostinė teigiamo testo vertė, prognostinė neigiamo testo vertė siekė atitinkamai 84,78, 80,00, 84,8 ir 80,0 %.

Išvados. Efektyviausi neinvaziniai kepenų fibrozės metodai pažengusiai kepenų ligai diagnozuoti buvo LSPS serumo žymuo ir kepenų elastografija.

Raktažodžiai: neinvaziniai žymenys, kepenų fibrozė, kepenų cirozė, kepenų elastografija, hepatitas C