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Combination of transient elastography with serum-based non-invasive tests improves prediction of liver fibrosis in patients with chronic hepatitis C: a prospective cohort study

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Background. To date, there is not enough data to conclude whether the combination of different non-invasive liver fibrosis tests could improve the accuracy in prediction of liver fibrosis. The aim of this study was to assess correlation between transient elastography (TE), aspartate aminotransferase to platelet ratio index (APRI), fibrosis 4 score (FIB4) and histological stage of fibrosis (F).

Materials and methods. In this prospective study the correlation of TE, APRI and FIB4 with the stage of fibrosis was assessed in 140 patients with chronic HCV hepatitis. TE, APRI and FIB4 were measured the same day before biopsy. Fibrosis was evaluated using the METAVIR score. Cut-off values were established by applying the ROC curve analysis. All non-invasive tests were combined into pairs in order to evaluate the accuracy of fibrosis prediction.

Results. The stage of fibrosis correlated with TE (R-0.74), FIB4 (R-0.67) and APRI (R-0.58). To detect F4 TE cut-off value 12.1 kPa had 93.8% sensitivity and 85% specificity; APRI cut-off value 1.42 (84.4/81.1) and FIB4 cut-off value 2.89 (84.4/84.0) were established. To determine F ≥ 3 – 10.3 kPa (91.1/83.9), 1.28 (77.8/78.5), 2.28 (84.4/81.7); F ≥ 2 8.5 kPa (80.9/74.3), 1.12 (72.1/78.6), 1.63 (82.4/75.7); F ≥ 1 5.35 kPa (85.4/100), 0.45 (89.2/87.5), 0.89 (87.7/75). Significant increase of accuracy was observed in TE/APRI (p – 0.008) and FIB4/APRI (p – 0.02) groups to predict F ≥ 1, and TE/FIB4 to predict F ≥ 2 (p – 0.04) and F ≥ 1 (p – 0.04).

Conclusions. Combined use of TE/APRI, FIB4/APRI increased the accuracy to predict F ≥ 1, and TE/FIB4 combination increased the accuracy to predict F ≥ 2 and F ≥ 1.

Key words: transient elastograhy, APRI, FIB4, liver fibrosis, combinations

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INTRODUCTION

According to the guidelines of European Association for the Study of the Liver (EASL) treatment of hepatitis C virus (HCV) infection should be prioritized in patients with advanced fibrosis (METAVIR score F3-F4) and is justified in patients with moderate fibrosis (METAVIR score F2) (1). In patients with minimal or no fibrosis (METAVIR score F0-F1), the timing of therapy is debatable (1). The staging of liver fibrosis is important in patients with HCV infection not only for establishment of treatment indications, but also serves to predict the response to the treatment, or to plan the surveillance if cirrhosis is present. Despite of certain limitations including invasiveness, sampling variability (2), inter-observer variability (3), liver biopsy is still a primary standard to evaluate liver fibrosis in patients with HCV infection. In order to overcome these limitations non-invasive fibrosis tests are developed and gradually introduced into clinical practice. The last HCV treatment guidelines by EASL recommend to assess the stage of liver fibrosis by non-invasive tests initially, with liver biopsy reserved for uncertain cases or additional aetiologies (1). There are many non-invasive direct and indirect liver fibrosis tests with different specificity and sensitivity. Some of them are easy applicable in daily practice (aspartate aminotransferase to platelet ratio index (APRI), fibrosis 4 score (FIB4)), while some of them are more complex (Fibrotest) or require dedicated devices (transient elastography). The best non-invasive tests suggested by the World Health Organization to assess the stage of fibrosis due to excellent viability, easy reproducibility and low cost are APRI and FIB4, but transient elastography is also recommended were it is available (4). Transient elastography is based on the measurement of physical properties of the liver, while APRI, FIB4 or other serum based tests are based on the measurement of biochemical processes in patients with liver disease. A lot of studies have been done to investigate the diagnostic value of transient elastography and other non-invasive tests (5–9); however, there is still not enough data to conclude whether the combination of different methods could improve accuracy in prediction of fibrosis. Therefore, we performed a prospective study which was aimed to evaluate the diagnostic value of the most common non-invasive liver fibrosis tests (APRI, FIB4 and elastography) and their combinations in patients with HCV.

MATERIALS AND METHODS

Study design

We performed a single centre prospective study in the Hospital of Lithuanian University of Health Sciences. Our study included patients with HCV who were referred to our clinic for liver biopsy during 2013. HCV was diagnosed by conventional tests – presence of HCV antibodies and HCV-RNR. Exclusion criteria were acute hepatitis, focal liver lesions, other liver comorbidity or patient refusal to participate in this study. Patients were naive to antiviral treatment before inclusion. The study was approved by the regional Bioethical Committee. All patients have signed an informed consent form before inclusion.

Investigations

The routine haematological (complete blood count) and biochemical (alanine transaminase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), bilirubin) investigations were performed at the same day before biopsy. Abdominal ultrasonography was performed to exclude focal liver lesions.

Non-invasive liver fibrosis tests

Liver stiffness using a FIBROSCAN® (Echosens, Paris, France) device was measured the same day before liver biopsy. Patients were in the fasting state. The procedure was performed according to manufacturers' recommendations. The interquartile range/median <30% and success rate >60% were considered as good quality criteria during transient elastography. We made 10 successful measurements for each patient.

APRI was calculated using the following formula: (AST/upper limit of normal AST)/platelet count (10^9) × 100 (10) and FIB4 using the following: age ([yr] × AST [U/L])/((PLT [10(9)/L]) × (ALT [U/L])^(1/2)) (11). Upper limits for ALT and AST were 45 U/l, 35 U/l, respectively.

Liver biopsy

Liver biopsy was performed using a spring-loaded core biopsy instrument with the 22 mm shooting length. We used a 14G biopsy needle to acquire liver tissue. The liver biopsy specimen was fixed in formalin and processed routinely by pathologists. The biopsy specimen included mean 14.5 ± 5.1 portal tracts (range 4–29). The histological fibrosis

grade was evaluated using the METAVIR score by an expert pathologist. The pathologist was blinded to the results of non-invasive tests. According to the METAVIR score the following fibrosis stages were established: F0 – no fibrosis; F1 – portal fibrosis, without septa; F2 – few septa; F3 – numerous septa without cirrhosis; F4 – cirrhosis (12).

Statistical analysis

The statistical analysis was performed using SPSS 20.0. The Kolmogorov–Smirnov test was used to check data normality. For descriptive statistics frequencies, means and standard deviations were calculated. METAVIR scores were compared with the APRI, FIB4 and liver stiffness expressed in kPa using the non-parametric Spearman correlation. According to the METAVIR score patients were categorised into F0 versus F1/F2/F3/F4, F0/F1 vs F2/F3/F4, F0/F1/F2 vs F3/F4 and F0/F1/F2/F3 vs F4. Areas under the receiver operating characteristic (AUROC) curve were calculated and points for the best specificity and sensitivity were established, the positive predictive value (PPV) and the negative predictive value (NPV) were calculated. P value less than 0.05 was considered statistically significant. The Z test was applied to compare the accuracies of different tests and their combinations.

RESULTS

Baseline demographic and biochemical characteristics are represented in Table 1.

The spearman correlation analysis revealed that all non-invasive tests correlated with the stage of fibrosis. A strong correlation with the stage of fibrosis was found for TE (R-0.74, $p < 0.01$) and for FIB4 (R-0.67, $p < 0.01$) and a moderate correlation for APRI (R-0.58, $p < 0.01$). Comparisons of the mean scores of TE, FIB4 and APRI in different stages of fibrosis are presented in Fig. 1. We found significant differences between all stages of liver fibrosis except for F1 vs F2 ($p = 0.05$) in the transient elastography group, F2 vs F3 ($p = 0.19$) in the FIB4 group and F2 vs F3 ($p = 0.34$), F3 vs F4 ($p = 0.05$) in the APRI group.

The AUROC curves for each category of fibrosis are presented in Fig. 2. AUROC for F4 versus F0/F1/F2/F3 was 0.941, 0.904 and 0.839 for TE, FIB4 and APRI, respectively; for F3/F4 vs F0/F1/F2 0.954, 0.882, 0.820; for F2/F3/F4 vs F0/F1 0.871, 0.852, 0.790; F1/F2/F3/F4 vs F0 0.974, 0.833 and 0.888.

Table 1. Patient characteristics. SD = standard deviation, BMI = body mass index, AST = aspartate aminotransaminase, ALT = alanine aminotransaminase, INR = international normalized ratio

	Patients (n = 140)
Gender, n (%)	
Females	50 (35.7)
Males	90 (64.3)
Age, years, mean ± SD	47.0 (±11.2)
BMI, kg/m^2, mean ± SD	25.9 (±4)
Portal tarcts, N, mean ± SD	14.5 (±5.1)
Liver fibrosis stage, N (%)	
F0	8 (5.7)
F1	62 (44.3)
F2	24 (17.1)
F3	14 (10.0)
F4	32 (22.9)
Platelet count, /L × 10^9, mean ± SD	176.5 (±69.2)
ALT, IU/L, mean ± SD	110.6 (±87.3)
AST, IU/L, mean ± SD	87.7 (±75.7)
INR, mean ± SD	1.01 (±0.1)
Bilirubin, μmol/l, mean ± SD	21 (±23.5)

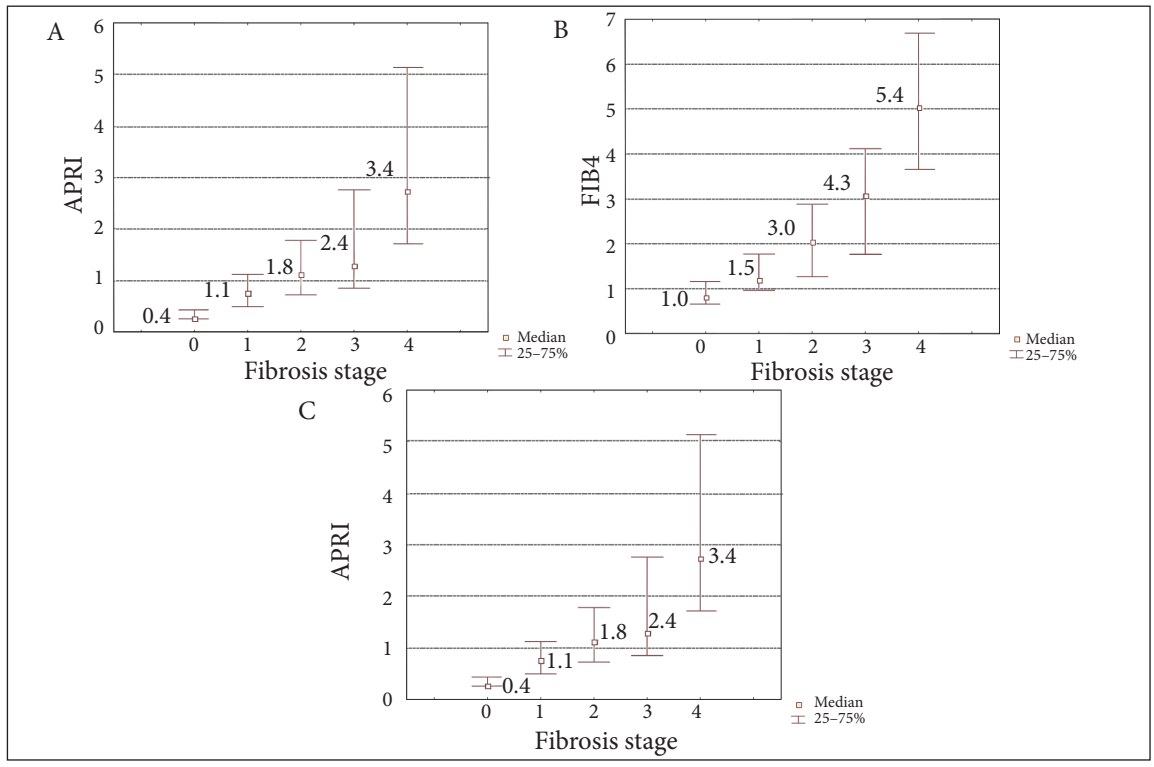

Fig. 1. Comparison of mean scores in different liver fibrosis stages of transient elastography, FIB4 and APRI.

A – Transient elastography: F0 vs F1 $p < 0.01$, F0 vs F2 $p < 0.01$, F0 vs F3 $p < 0.01$, F0 vs F4 $p < 0.01$, **F1 vs F2 p = 0.05**, F1 vs F3 $p < 0.01$, F1 vs F4 $p < 0.01$, F2 vs F3 $p < 0.01$, F2 vs F4 $p < 0.01$, F3 vs F4 $p < 0.01$

B – FIB4: F0 vs F1 $p = 0.04$, F0 vs F2 $p < 0.01$, F0 vs F3 $p < 0.01$, F0 vs F4 $p < 0.01$, F1 vs F2 $p < 0.01$, F1 vs F3 $p < 0.01$, F1 vs F4 $p < 0.01$, **F2 vs F3 p = 0.19**, F2 vs F4 $p < 0.01$, F3 vs F4 $p = 0.02$

C – APRI: F0 vs F1 $p < 0.01$, F0 vs F2 $p < 0.01$, F0 vs F3 $p < 0.01$, F0 vs F4 $p < 0.01$, F1 vs F2 $p = 0.02$, F1 vs F3 $p < 0.01$, F1 vs F4 $p < 0.01$, **F2 vs F3 p = 0.34**, F2 vs F4 $p < 0.01$, **F3 vs F4 p = 0.05**

Table 2. Diagnostic performance of transient elastography in the prediction of liver fibrosis stages. TE = transient elastography in kPa, FIB4 = fibrosis 4 score, APRI = aspartate aminotransferase to platelet ratio index, PPV = positive predictive value, NPV = negative predictive value

Fibrosis stage	Method	Cut-off	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
4	TE	12.15	93.8	85.8	65.2	97.9	87.1
	FIB4	2.89	84.4	84.0	61.4	94.7	84.4
	APRI	1.42	84.4	81.1	57.4	94.5	81.9
≥3	TE	10.35	91.1	83.9	73.7	95.2	86.4
	FIB4	2.28	84.4	81.7	67.8	91.4	81.9
	APRI	1.28	77.8	78.5	62.5	87.8	77.5
≥2	TE	8.55	80.9	74.3	75.7	78.8	77.1
	FIB4	1.63	82.4	75.7	76.7	81.5	79.0
	APRI	1.12	72.1	78.6	74.2	73.6	73.9
≥1	TE	5.35	85.4	100	100	29.6	86.4
	FIB4	0.89	87.7	75.0	97.4	23.8	86.2
	APRI	0.45	89.2	87.5	99.0	33.3	89.1

Cut-off values for different tests were established and specificity, sensitivity, positive predictive value, negative predictive value and accuracy were calculated and are depicted in Table 2. In order to check if a combination of two tests is better to determine the stage of fibrosis we assessed the

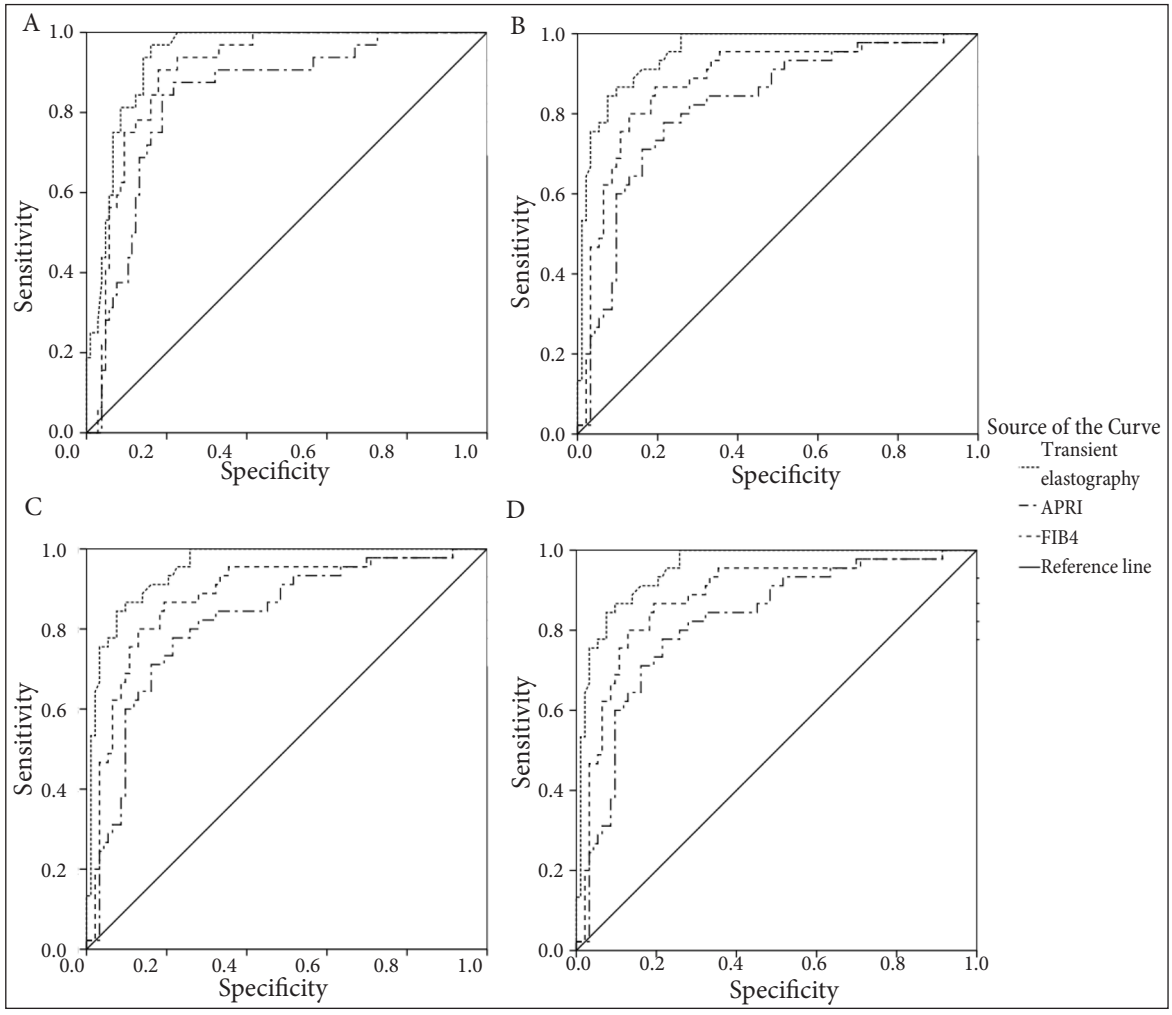

Fig. 2. Receiver-operating characteristic (ROC) curves for transient elastography, APRI and FIB4 for diagnosis of different fibrosis stages. A – fibrosis stage =4, B – fibrosis stage ≥3, C – fibrosis stage ≥2, D – fibrosis stage ≥1. APRI = aspartate aminotransferase to platelet ratio index, FIB4 = FIB4 score

Table 3. Diagnostic performance of non-invasive test combinations in the prediction of liver fibrosis stages. TE = transient elastography in kPa, FIB4 = fibrosis 4 score, APRI = aspartate aminotransferase to platelet ratio index, PPV = positive predictive value, NPV = negative predictive value. P-values for accuracy were calculated for TE/FIB4 and TE/APRI vs TE, FIB4/APRI vs FIB4. Significant differences are marked in bold

Fibrosis stage	Method	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %	p-value
4	TE/FIB4	100	90.2	73.5	100	92.3	0.16
	TE/APRI	96.3	89.9	74.2	98.7	91.4	0.26
	FIB4/APRI	92.3	86.3	64.9	97.6	87.6	0.45
≥3	TE/FIB4	92.5	91.7	86.0	95.7	92.0	0.14
	TE/APRI	94.3	90.1	82.5	97.0	91.5	0.19
	FIB4/APRI	86.8	85.6	75.0	92.9	86.0	0.37
≥2	TE/FIB4	87.7	85.7	87.7	85.7	86.8	**0.04**
	TE/APRI	84.6	87.2	88	83.7	85.8	0.08
	FIB4/APRI	83.6	80.0	79.3	84.2	81.7	0.58
≥1	TE/FIB4	93.6	100	100	41.7	93.9	**0.04**
	TE/APRI	95.3	100	100	58.3	95.6	**0.008**
	FIB4/APRI	94.6	83.3	99.0	45.5	94.0	**0.02**

following combinations: TE/FIB4, TE/APRI and APRI/FIB4. The sensitivity, specificity, PPV, NPV and accuracy for all used combinations were calculated and results are presented in Table 3.

DISCUSSION

According to our data transient elastography has the best specificity and sensitivity to predict the histological stage of fibrosis, especially in higher stages of fibrosis. For lower stages of fibrosis all non-invasive tests were comparable. The overall accuracy of all tests was better in marginal stages of fibrosis than in intermediate stages. The comparison of biochemical non-invasive tests showed that FIB4 had slightly better correlation and bigger AUROC than APRI. The analysis of combination of two tests showed that accuracy was increased in all analysed groups, but statistical significance was observed just in F ≥ 1 for all combination groups and in F ≥ 2 in the TE/FIB4 group. The last finding could be clinically significant for more accurate liver disease severity assessment (1).

There are many studies that define optimal cut-offs with the best specificity and sensitivity for assessment of liver fibrosis. According to the meta-analysis by Tsochatzis et al. the cut-offs of liver stiffness were 7.6 (5.1–10.1), 10.9 (8.0–15.4), and 15.3 (11.9–26.5) kPa for F ≥ 2, 3, and 4, respectively, in chronic hepatitis C. Sensitivity and specificity in F ≥ 2 and F4 subgroups were 78, 83 and 80, 90%, respectively (13). The cut-offs and sensitivity with specificity in our study are comparable with the results of latter meta-analysis. The wide range of different cut-offs could be explained by different variability in stages of fibrosis across different studies (14). There are less data available regarding the cut-off for F ≥ 1 than other stages of fibrosis, and the cut-offs between 4.8 kPa and 5.3 kPa were observed (15, 16). These data are similar with our findings.

APRI is a simple, easily reproducible non-invasive test for detection of liver fibrosis first described by Wai et al. in 2003 (10). As noted in the last meta-analysis, the range of cut-off values of APRI for different stages of fibrosis are quite wide (17). The range for ≥2 stage of fibrosis varies from 0.5 to 1.5 with the optimal threshold of 0.7 with 77% sensitivity and 72% specificity. The APRI cut-off range for fibrosis stage ≥3 varies from 0.5 to 2 with optimal threshold 1 with 61% sensitivity and 64% specificity. The recommended cut-offs for F4 stage were 1 and 2 with sensitivity and specificity 76, 72 and 46, 91%, respectively. Our cut-off value for predicting significant (F ≥ 2) fibrosis is 1.1 and is comparable with the data of the meta-analysis. The best cut-off points to determine significant and severe fibrosis are far too close to be useful in daily practice and reflects the inability of non-invasive tests to determine intermediate stages of fibrosis. In our study the optimal cut-off for determining cirrhosis (F = 4) is 1.4; however, if taking into consideration the threshold of 1 used by other investigators we obtained sensitivity of 90% with specificity of 62% or sensitivity 72% with specificity 85% for threshold 2.

FIB4 is described as a simple but more complex score to predict liver fibrosis. Few studies were performed in patients with HCV infection to establish the best threshold for liver fibrosis detection. Cut-off of 1.26 for F ≥ 2 showed sensitivity and specificity of 64 and 75%, respectively [18], while lower threshold of 1 had worse sensitivity and specificity (71 and 50%) (19). For F ≥ 3 the optimal threshold varied between 1.45 and 1.81 with sensitivity 74.3, 74% and specificity 80.1, 77%, respectively (5, 19, 20). The cut-off 2.25 had sensitivity and specificity of 82 and 83%, respectively, for discriminating cirrhosis from other fibrosis stages (19). Our data revealed comparable specificities and sensitivities with slightly higher thresholds for all stages.

There is still limited data to conclude if combinations of several non-invasive tests in patients with hepatitis C can improve accuracy for predicting the stage of liver fibrosis. Majority of the studies which analysed combinations of different non-invasive test employed different methodologies; therefore, direct comparison of the results is difficult. The studies differed according to the liver fibrosis classification (METAVIR versus Ishak index) and combination statistics (regression analysis with model construction versus extraction of all cases with the same prediction) (18, 21). The extent of assessed non-invasive tests for different combinations is wide ranging from simple blood tests like APRI [8] to more complex like FIBROTEST, FIBROMETER (22) or including even two non-blood tests like ultrasound-based and acoustic radiation force impulse-based elastography (23).

Combination of two tests increased accuracy to determine F ≥ 2 when TE was combined with APRI (18) (22) or FIB4 (18). There is significant increase

in accuracy to predict F ≥ 3 when TE was combined with APRI or FIB4 (18), but not for the cirrhosis stage in TE/APRI combination (22). Our data show that there is an increase in accuracy in almost all groups; however, a statistically significant improvement in accuracy was observed only in TE/APRI, FIB4/APRI combinations to determine F ≥ 1, and in TE/FIB4 combination to determine F ≥ 2 and F ≥ 1. According to these findings only TE/FIB4 combination could have potential clinical implications if decision for treatment would be based on the presence of significant fibrosis.

CONCLUSIONS

Or study shows that non-invasive tests could be performed to determine liver fibrosis in patients with chronic hepatitis C infection. TE and FIB4 were strongly correlated with liver fibrosis, while APRI showed only moderate correlation. Marginal stages (0 or 4) of fibrosis were determined more accurately than intermediate stages. Our data confirmed that transient elastography is the most accurate non-invasive test to determine liver fibrosis. Although TE/APRI, FIB4/APRI combinations increased accuracy to predict F ≥ 1, only a combined use of TE/FIB4 could be clinically useful to increase the diagnostic accuracy for F ≥ 2 and F ≥ 1 groups.

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FIBROSCAN TYRIMO DERINIMAS SU KITAIS NEINVAZINIAIS KEPENŲ FIBROZĖS NUSTATYMO TESTAIS DIDINA KEPENŲ FIBROZĖS PROGNOZAVIMO TIKSLUMĄ TARP SERGANČIŲJŲ LĖTINIU HEPATITU C

Santrauka

Įžanga. Neinvazinių kepenų fibrozės nustatymo metodų jautrumas ir specifiškumas yra vis dar nepakankamai aukštas. Tyrimų, atliktų siekiant įvertinti, ar skirtingų neinvazinių metodų derinimas padidina tikslumą prognozuojant kepenų fibrozės laipsnį, rezultatai prieštaringi.

Tikslas. Įvertinti kepenų elastografijos (KE), aspartatinės aminotransferazės ir trombocitų santykio (APRI) bei fibrozės 4 indekso (FIB4) koreliaciją su histologiniu kepenų fibrozės laipsniu (F).

Metodai. Šioje prospektyvioje studijoje dalyvavo 140 ligonių, sergančių hepatitu C. KE, APRI ir FIB4 matuoti tą pačią dieną prieš kepenų biopsiją. Kepenų fibrozė vertinta patyrusio patologo pagal METAVIR skalę. Optimalios neinvazinių tyrimų reikšmių vertės buvo apskaičiuotos atlikus ROC analizę. Visi testai buvo suporuoti siekiant įvertinti, ar skirtingos kombinacijos padidina kepenų fibrozės prognozavimo tikslumą.

Rezultatai. Stebėta teigiama KE (R-0,74), FIB (R-0,67) ir APRI (R-0,58) koreliacija su kepenų fibrozės stadija. F4 stadijai prognozuoti KE 12,1 kPa vertės jautrumas – 93,8 %, specifiškumas – 85 %; APRI 1,42 vertės jautrumas – 84,4 %, specifiškumas – 81,1 %; FIB4 2,89 vertės jautrumas – 84,4, specifiškumas – 84,0 %. F ≥ 3 – 10,3 kPa (91,1/83,9), 1,28 (77,8/78,5), 2,28 (84,4/81,7); F ≥ 2 8,5 kPa (80,9/74,3), 1,12 (72,1/78,6), 1,63 (82,4/75,7); F ≥ 1 5,35 kPa (85,4/100), 0,45 (89,2/87,5), 0,89 (87,7/75). Statistiškai reikšmingai padidėjęs tikslumas stebėtas derinant KE su APRI (p – 0,008) ir FIB4 su APRI (p – 0,02) prognozuojant F ≥ 1, taip pat KE derinant su FIB4 prognozuojant F ≥ 2 (p – 0,04) ir F ≥ 1 (p – 0,04).

Išvada. APRI derinant su KE arba FIB4 padidėja tikslumas prognozuojant F ≥ 1, o KE derinant su FIB4 – prognozuojant F ≥ 2 ir F ≥ 1.

Raktažodžiai: kepenų elastografija, APRI, FIB4, fibrozė, kombinacijos