ORIGINAL ARTICLE

Concordance of non-invasive serology-based scoring indices and transient elastography for liver fibrosis and cirrhosis in chronic hepatitis C

Emir Trnačević[1], Nermin Salkić[2], Alma Trnačević[3], Anja Divković[1], Fatima Hukić[1], Nusret Butković[1], Amra Serak[4], Amer Mujkanović[5]

[1]Department for Laboratory Diagnostics, University Clinical Centre Tuzla, [2]Department of Gastroenterology and Hepatology, Internal Medicine Hospital, University Clinical Centre Tuzla, [3]Infectious Disease Hospital, University Clinical Centre Tuzla, [4]Department of Family Medicine, Public Health Centre Tuzla, [5]University Clinical Centre Tuzla, Surgery Hospital, Department for Plastic Surgery; Tuzla, Bosnia and Herzegovina

ABSTRACT

Aim To assess concordance of eight frequently used serology-based scoring indices for liver fibrosis and cirrhosis with transient elastography (TE) in chronic hepatitis C (CHC) patients in order to determine serum indices with the highest concordance and clinical usability in clinical practice.

Methods In this prospective study, 63 CHC patients were included and TE results were compared with eight non-invasive indices. The diagnostic performance of these tests was assessed using receiver operating characteristic curves with kappa index calculated for the concordance analysis.

Results Median age of 63 patients was 54 years (interquartile range: 42 to 63); 27 (42.9%) were females. According to areas under the Receiver Operating Characteristics (AUROC), the best performing serum markers for significant liver fibrosis (METAVIR ≥F2), advanced liver fibrosis (≥F3) and cirrhosis (F4) determined by TE measurements (≥7.1kPa, ≥9.5kPa and ≥12kPa, respectively) were Fibrotest (AUROC=0.727 for ≥F2) and FIB-4 score (AUROC=0.779 for ≥F3 and AUROC=0.889 for F4). Fibrotest cut-off at >0.50 was concordant with TE for presence of significant fibrosis in 30 (out of 45; 66.7%), FIB-4 cut-off at <1.45 was concordant for absence of significant fibrosis in 13 (out of 18; 72.2%) and Goeteborg University Cirrhosis Index (GUCI) cut-off at >1 was concordant for presence of cirrhosis in 16 (out of 22; 72.7%) patients, but not for exclusion of cirrhosis.

Conclusion Serology-based scoring indices had moderate overall concordance with TE. We propose that FIB-4 score, Fibrotest and GUCI be used in routine practice to exclude and diagnose significant fibrosis and diagnose cirrhosis, respectively.

Key words: diagnosis, hepatic cirrhosis, hepatic fibrosis, non-invasive markers, vibration controlled transient elastography

Corresponding author:
Nermin Salkić
Department of Gastroenterology and Hepatology, University Clinical Centre Tuzla
Prof. Ibre Pašića bb, 75000 Tuzla, Bosnia and Herzegovina
E-mail: snermin@gmail.com
Phone: +387 35 303 358;
Fax: +387 35 250 474;
ORCID: https://orcid.org/0000-0003-4727-9267

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INTRODUCTION

Chronic hepatitis C (CHC) is one of the most frequent causes of liver cirrhosis and its complications- (1). Despite recent advances in the treatment, epidemiological data from Bosnia and Herzegovina (B&H) show that there is up to 1% prevalence of CHC in general population, and the most of the patients are with advanced liver fibrosis (2,3).

The stage of liver fibrosis in CHC patients has a huge impact on prognosis, treatment strategy and follow-up, with or without treatment (4). Liver biopsy is a traditional method of reference used to assess fibrosis stage in CHC (4); however, it is an invasive procedure with serious complications in up to 0.5% of procedures, biopsy samples <15mm in length are not reliable and its accuracy is limited by heterogeneity of samples and inter-observer and intra-observer variability (4–7).

Due to inherent limitations of liver biopsy as a diagnostic procedure, several serology based non-invasive methods (indices) for assessments of liver fibrosis and cirrhosis have been developed with variable clinical accuracy and applicability (8-15). Fibrotest, aspartate aminotransferase (AST)-to- alanine aminotransferase (ALT) ratio (AAR score), AST to Platelet Ratio Index (APRI score), FIB-4 test, Goteborg University Cirrhosis Index (GUCI), Forns score, Lok score, Hui score are all serological clinical indices combining several biochemical and clinical variables into mathematical formula, and were extensively evaluated and validated for various aetiologies of chronic liver disease (8–15). Yet, all these serological indices have limitations as blood tests can be influenced by other associated diseases, comorbidities or even laboratory equipment and/or technique (16).

As a viable and more accurate alternative, a physical method was developed in form of transient elastography (Fibroscan, Echosens, Paris, France), which is based on liver stiffness measurement with comparable or even improved reliability and clinical accuracy when compared to serum indices (17). Despite the fact that transient elastography (TE) also has its limitation (particularly in obese patients, those with ascites, or more than 5-fold increase in liver transaminase levels), as well as that proprietary equipment is expensive and not widely available, it has become another standard in non-invasive assessment of liver fibrosis and cirrhosis (18).

In countries with limited resources such as B&H, elastography is not widely available, even more, there are only four centres that routinely perform liver biopsy. The need for cheap and widely available method for assessment of liver fibrosis and cirrhosis in routine clinical practice and even primary care is obvious. Although there are numerous papers that compared serology-based indices (or serum markers as this group of tests are also referred to in literature) and elastography against liver biopsy (16,18–20), studies dealing with concordance of serum markers with elastography as newly established standard are sparse.

The aim of this study was to assess concordance of eight of the most frequently used serum markers for liver fibrosis and cirrhosis with TE in population of CHC patients in order to determine serum marker with the highest concordance and clinical usability in routine clinical practice.

METHODS

Patients and study design

This prospective study recruited all consecutive adult patients with chronic hepatitis C that were referred for transient elastography to the Department of Gastroenterology and Hepatology of University Clinical Centre Tuzla from 1 July 2019 to 30 June 2020, as a part of patient's pre-treatment evaluation. Patients were considered for inclusion if they had no treatment during the last 6 months. The CHC was confirmed by HCV–RNA polymerase chain reaction analysis of serum (Cobas Amplicor HCV v2.0, Roche, Switzerland) (21). Cirrhotic patients were compensated and asymptomatic at the time of the inclusion. Patients with co-existing liver diseases other than CHC and post-transplant patients were also excluded. All patients gave consent for the study.

The study was conducted in accordance with the Helsinki Declaration, and it was approved by the institutional Ethics Committee of the University Clinical Centre of Tuzla.

Methods

Serum markers. Demographic and anthropometric data were recorded at the time of TE and fasting blood samples were also collected at the

same time by venepuncture. Standard and identical batches of tubes for all patients were used. All parameters used to calculate non-invasive indices were measured at the Department of Laboratory Diagnostics, University Clinical Centre of Tuzla using serum samples frozen and stored at -80 °C until assayed. All tests were performed on the same day in a single laboratory by operators blinded of clinical and other data about patients. Based on measured serum parameters the following non-invasive serum tests were calculated: AAR (AST/ALT ratio), Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), GUCI, FIB-4, Forns index, Lok score, Hui score and Fibrotest, according to the most recently published formulas (8–15,22).

There are two distinct threshold values for FIB-4 described (10): one threshold set at 1.45, which has an excellent negative predictive value for significant fibrosis (F2 or greater) and other set at 3.25, which has an excellent positive predictive value for cirrhosis. For GUCI score a threshold of 1.0 was described as predictive for cirrhosis and 0.33 as predictive for absence of significant fibrosis (14,23). For Fibrotest, a threshold <0.50 was described as predictive for absence of significant fibrosis, while a threshold of >0.75 was described as predictive for presence of cirrhosis (8,24,25).

Transient elastography. Liver stiffness measurement by transient elastography (Fibroscan, Echosens, Paris, France) was made in a fasting patient on the right lobe of the liver, through the appropriate intercostal space with prone patient and with the right arm in maximal abduction. The tip of the transducer probe was covered with coupling gel and placed on the skin in the appropriate intercostal space, usually in medio-axillary line. At least 10 valid measurements of liver stiffness were considered as technically appropriate; measurement failure was defined as zero valid shots after at least 10 attempts and unreliable measurements were defined as fewer than 10 valid shots or an interquartile range of stiffness median value greater than 30% (26,27). Elastography threshold values corresponding with significant fibrosis (METAVIR F2 or greater; 7.1 kPA), advanced fibrosis (METAVIR F3 or greater; 9.5 kPA) and cirrhosis (METAVIR F4; 12.0 kPA) were used, as previously described for patients with CHC (28).

Statistical analysis

Descriptive results expressed as the mean (standard deviation), median (interquartile range), or as the number (percentage) of patients. An assessment of serological tests vs. TE was made with Pearson or Spearman correlation where appropriate. The diagnostic performance of serum markers was also assessed using Area Under the Receiver Operating Characteristic (AUROC) analysis, with TE as a reference method, albeit imperfect due to indirect nature of TE itself. The comparison of AUROCs was performed according to the method described by DeLong (29). The AUROCs were also used to assess best preforming threshold values of serum markers for the prediction of fibrosis and cirrhosis grades according to TE. Previously published cut-off values for all indices of interest also used to create dichotomous variables in order to calculate concordance coefficient kappa (κ). All statistical tests were 2-tailed, with type I error of 5% ($p<0.05$).

RESULTS

A total of 65 patients with CHC were prospectively recruited with only two (3.1%) unsuccessful measurements by TE, resulting in 63 patients included in the study (Table 1).

Table 1. Baseline characteristics for 63 patients with chronic hepatitis C

Variable	Mean	SD
Gender (females) (No; %)	27 (42.9)	
Age (years)	52.30	13.76
Height (cm)	173	13
Weight (kg)	77	13
Body Mass Index (kg/m2)	25.75	4.20
Platelets (109/L)	184.00	78.32
Prothrombin time (sec)	14.26	12.83
INR	1.30	1.44
Total bilirubin (μmol/L)	16.56	10.01
ALT (IU/L)	116.62	169.93
AST (IU/L)	72.98	96.53
GGT (IU/L)	60.63	52.29
Albumin (g/L)	44.57	4.87
Cholesterol (mmol/L)	4.53	0.90
Haptoglobin	0.78	0.60
Alfa-2 macroglobulin	3.08	1.55
Apolipoprotein A1	1.31	0.40
Transient elastography (No; %)		
Significant fibrosis (≥F2; ≥7.1 kPa)	45 (71.4)	
Advanced fibrosis (≥F3; ≥9.5 kPa)	34 (54.0)	
Cirrhosis (F4; ≥12.0 kPa)	22 (34.9)	

INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase;

In order to test for initial correlation of serum markers, a correlation analysis was performed with matrix table (Table 2). There was a statistically si-

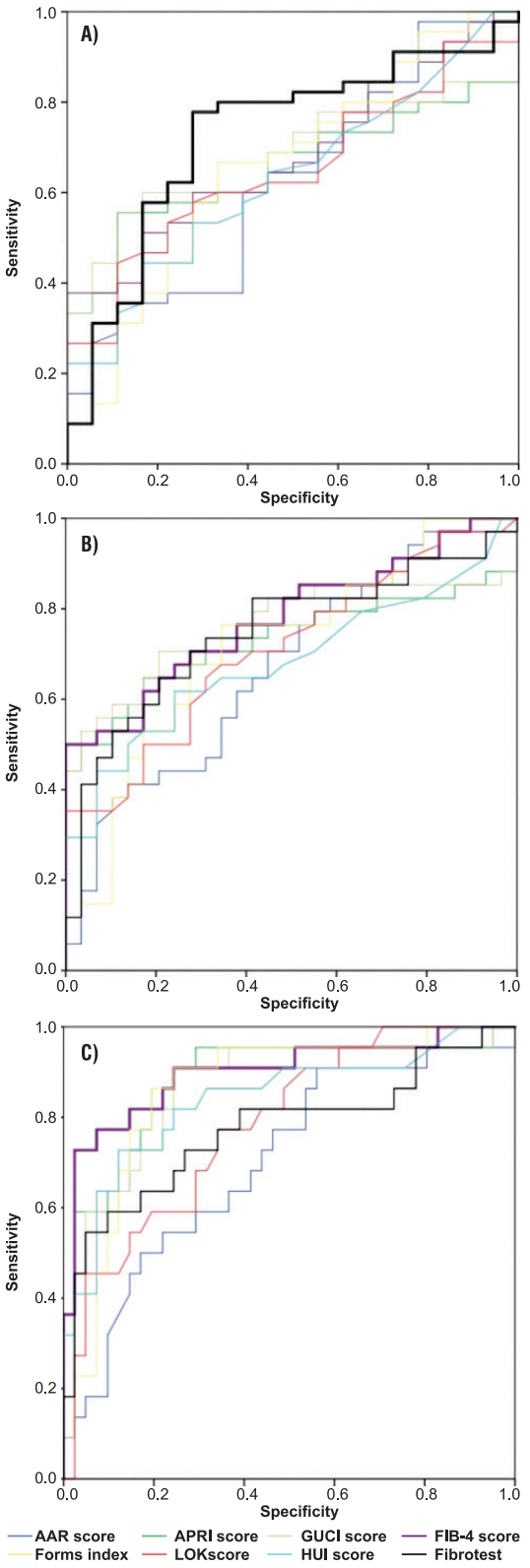

Figure 1. Area under the Receiver Operating Characteristics (AUROC) for serum markers tested against liver fibrosis grades according to transient elastography (TE) measurements. A) significant liver fibrosis (≥F2; ≥7.1 kPa); B) advanced liver fibrosis (≥F3; ≥9.5 kPa); C) liver cirrhosis (F4; ≥12 kPa)

gnificant correlation of all serum markers with TE, with strongest coefficient for FIB-4 and Hui score.

Table 2. Correlation matrix of serum markers with transient elastography

Serology based index of liver fibrosis/cirrhosis	Transient elastography	
	Correlation coefficient	p
AAR score	0.415	<0.001
APRI score	0.430	<0.001
GUCI score	0.467	<0.001
FIB-4 score	0.740	<0.001
Forns index	0.602	<0.001
Lok score	0.602	<0.001
Hui score	0.758	<0.001
Fibrotest	0.456	<0.001

AAR, AST (aspartate aminotransferase) to ALT (alanine aminotransferase) ratio; APRI, AST to platelets ratio index; GUCI, Goteborg University Cirrhosis Index

The diagnostic performance of serum markers was tested against TE with AUROC (Table 3, Figure 1). For F2 or greater fibrosis, Fibrotest showed the highest AUROC, closely followed by FIB-4 test. For both F3 and F4 fibrosis, FIB-4 showed the highest AUROC when compared with fibrosis grades determined with TE measurements.

Table 3. Area under the receiver operating characteristics (AUROC) for serum markers tested against liver fibrosis grades according to transient elastography (TE) measurements

Serum markers for prediction of F2 or greater according to TE	AUROC	p	95% confidence interval (CI) of AUROC	
			Lower limit of CI	Upper limit of CI
AAR score	0.623	0.130	0.472	0.774
APRI score	0.657	0.053	0.526	0.788
GUCI score	0.680	0.026	0.552	0.809
FIB-4 score	0.684	0.023	0.552	0.816
Forns index	0.657	0.053	0.506	0.808
LOK score	0.650	0.065	0.513	0.787
HUI score	0.633	0.100	0.491	0.776
Fibrotest	0.727	0.005	0.589	0.866
Serum markers for prediction of F3 or greater according to TE				
AAR score	0.668	0.022	0.534	0.801
APRI score	0.729	0.002	0.599	0.860
GUCI score	0.759	<0.001	0.633	0.884
FIB-4 score	0.779	<0.001	0.665	0.892
Forns index	0.716	0.003	0.588	0.844
LOK score	0.710	0.004	0.584	0.836
HUI score	0.683	0.013	0.550	0.816
Fibrotest	0.747	0.001	0.624	0.871
Serum markers for prediction of F4 according to TE				
AAR score	0.702	0.009	0.565	0.839
APRI score	0.877	<0.001	0.777	0.977
GUCI score	0.863	<0.001	0.760	0.965
FIB-4 score	0.899	<0.001	0.808	0.990
Forns index	0.863	<0.001	0.765	0.960
LOK score	0.782	<0.001	0.667	0.898
HUI score	0.840	<0.001	0.728	0.952
Fibrotest	0.774	<0.001	0.639	0.909

AAR, AST (aspartate aminotransferase) to ALT (alanine aminotransferase) ratio; APRI, AST to platelets ratio index; GUCI, Goteborg University Cirrhosis Index

Pairwise comparison of AUROCs did not show significant differences ($p>0.05$) between serum markers for F2 or greater and F3 or greater. A significant difference was detected for F4 where FIB-4 had higher AUROC than Fibrotest, AAR and APRI score ($p<0.05$).

Considering the highest AUROC values for all three clinically significant fibrosis thresholds FIB-4, GUCI and Fibrotest were selected for further analysis, as serum markers with best concordance according to correlation and AUROC analysis.

When compared with TE values, FIB-4 at cut-off point of 1.45 was concordant with TE in 13 (out of 18; 72.2%) patients for exclusion of presence of significant fibrosis with overall $\kappa=0.265$ ($p=0.021$). At the cut-off point of 3.25, FIB-4 was concordant with TE in 14 (out of 22; 63.6%) patients for the prediction of cirrhosis with overall $\kappa=0.661$ ($p<0.001$).

The GUCI score at threshold value of 1.0 was concordant with TE in 16 (out of 22; 72.7%) with overall κ value of 0.551 ($p<0.001$). At the cut-off value of 0.33 GUCI score was concordant with TE in 12 (out of 18; 66.7%) patients for the exclusion of presence of significant fibrosis with κ value of 0.14 ($p=0.262$).

Fibrotest at threshold value of <0.50 was concordant with TE in 13 (out of 18; 72.2%) patients with overall $\kappa=0.33$ ($p=0.005$). For the threshold value >0.50, Fibrotest was concordant for diagnosing presence of significant fibrosis with TE in 30 (out of 45; 66.7%) patients. At the cut-off point of 0.75, Fibrotest was concordant for presence of cirrhosis with TE in 15 (out of 45; 68.2%) patients with overall $\kappa=0.425$ ($p=0.001$).

DISCUSSION

The results of this study have demonstrated that among eight most frequently used serum markers, FIB-4, GUCI and Fibrotest have shown the best overall concordance with TE. Areas under the ROC curves for those scores do not conflict with previously published results regardless of the reference standard used (TE or liver biopsy) (16,19,30). Yet, the specific concordance for detecting clinically relevant cut-offs is heterogenous and moderate, suggesting the need for utilisation of several serum markers at different cut-offs for various clinically relevant thresholds according to the best detection rate, as proposed previously for chronic hepatitis B patients (31).

According to our results, we propose that for a quick screening in routine clinical use or primary care settings it is the best to use FIB-4 score for excluding significant liver fibrosis (<1.45) thus postponing referral and to use GUCI score (>1.0) for non-invasive detection of cirrhosis and prompt referral to hepatologist. Where available, Fibrotest owing to the highest AUROC (0.727) and concordance rate with TE (66.7%) seems to be appropriate.

Non-invasive staging of liver fibrosis and detection of cirrhosis is incorporated in current guidelines for the diagnosis and management of CHC (18). For a clinician there are two distinct fibrosis thresholds that are clinically relevant: occurrence of significant fibrosis, defined as F2 or higher according to METAVIR classification which signals the need for active treatment and occurrence of liver cirrhosis, defined as F4 according to METAVIR which signals the need for the treatment and prevention of cirrhosis and its complications (32).

Serum markers have been heavily evaluated for different liver pathologies with variable clinical accuracy. As previously reported, all types of serum markers of liver fibrosis have AUCs clustering around the value of 0.85, which is a consequence of inherent insufficiency of liver biopsy to perform at the level of a true gold standard (33,34). When discussing the accuracy of any marker in a case of discordant results, the cause of discordance can be either failure of fibrosis marker or failure of biopsy to detect a true stage, since sensitivity and specificity of liver biopsy are 90% and even in perfect conditions, AUROC for the perfect non-invasive marker would be 0.90 (35,36). This is important to bear in mind when comparing serum marker with TE, as both are derived, developed and compared against imperfect gold standard (LB), so possible causes for discordance are variable.

Transient elastography is one of the most utilized non-invasive tools for evaluation of liver fibrosis in patients with CHC with better diagnostic accuracy as compared to serum tests (37). Still, despite the fact that TE has an excellent overall accuracy, as with all other non-invasive tests, and even liver biopsy (37), it is insufficient in differentiating intermediate stages of fibrosis (i.e., F2 vs F3) (38). Therefore, there are several combination algorithms that advocate combining TE with serum biomarkers, either sequentially or concomitantly in order to increase diagnostic accuracy of clinically relevant thresholds (18,30,39,40). This approach

is very convenient for primary care, as primary care physicians can make initial screening of patients with cheap, available and easy serum markers before referral to a specialized centre for a more advanced procedure such as TE or even biopsy.

There are several limitations of this study that need to be addressed. The sample size is at its lowest limit for statistical analysis, yet it is sufficient for addressing the aim of this study. It would be much better to compare the results against the liver biopsy, but with the availability of TE and current recommendations that most patients with CHC can be evaluated with non-invasive means, we used TE as surrogate reference standard (18,32). For the purpose of this study, concordance of serological tests with TE was the primary aim, we did not attempt to re-evaluate previously established thresholds for TE and serum markers, and we believe that results are sufficiently reliable for derived conclusions, as is the case with previously published studies (19). Further studies including larger sample sizes may attempt to combine serological markers in a combination algorithm, similar to the one we previously developed for chronic hepatitis B (www.chb-lfc.com) (31) that would use best performing threshold points from several serum markers and incorporate them into a single screening tool suitable for everyday clinical practice.

In conclusion, serology based non-invasive indices have moderate overall concordance with transient elastography, with FIB-4, Goteborg University Cirrhosis Index (GUCI) and Fibrotest having the best performance. For CHC patients and in routine clinical practice, even in primary care, we propose that FIB-4 score, Fibrotest and GUCI be used to exclude significant fibrosis, diagnose significant fibrosis and diagnose cirrhosis, respectively.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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