Original Article

Early detection of liver damage in Mexican patients with chronic liver disease

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ABSTRACT

Background and Objective: Liver cirrhosis is usually detected at the later stages of disease. This study is aimed to detect liver damage in patients with chronic liver disease using transitional elastography (TE) and to assess the biochemical parameters associated with liver damage. **Methods:** In 578 patients, chronic liver disease based on etiology was diagnosed by clinical and laboratory tests. Liver damage was evaluated with TE (FibroScan®), while its association with biochemical parameters was performed using the logistic regression tests. **Results:** Overall, the main etiologies of liver damage were hepatitis C virus (HCV) (37%), alcoholic liver disease (ALD) (33%) and non-alcoholic steatohepatitis (NASH) (26%). Patients were 40 to 50 years of age. ALD and hepatitis B prevailed in men, whereas HCV and NASH in women. The stages of fibrosis were F0 (*n* = 121, 21%), F1 (*n* = 122, 21%), F2 (*n* = 58, 10%), F3 (*n* = 46, 8%) and F4 (*n* = 87, 15%). In patients with liver cirrhosis, ALD (*n* = 96/217, 45%), HCV (*n* = 94/217, 43%) and NASH (*n* = 21/217, 10%) were the leading etiologies. Platelets count (OR=3.31, 95%CI 1.61-6.78), glucose (OR=3.07, 95%CI 1.50-6.26), gamma-glutamyl-transferase (OR=3.60, 95%CI 1.79-7.25), albumin (OR=3.89, 95%CI 1.61-9.36), and total bilirubin (OR=3.93, 95%CI 1.41-10.91) were associated to advanced stages of fibrosis (F3-F4) regardless of etiology. The concordance and positive predictive values of these parameters were higher as compared to other scores. **Conclusion:** Asymptomatic liver disease due to HCV, ALD and NASH prevailed in young adults. Advanced liver damage assessed by TE was associated with five biochemical parameters. In conjunction, both methodologies may be useful for the early detection of fibrosis and cirrhosis in Latin America.

Key words: chronic liver disease, transient elastography, liver fibrosis, cirrhosis, risk factors.

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INTRODUCTION

Liver cirrhosis (LC) is a health problem worldwide. The Global Burden Study 2010 ranks LC as the 23rd cause of disease burden worldwide causing 31 million global disability-adjusted life years (DALYs), and it is the 12th cause of mortality with more than one million deaths per year.[1,2] The most common etiologies leading to chronic damage and LC are excessive alcohol consumption, hepatitis C virus (HCV) infection or hepatitis B virus (HBV) infection, and most recently the non-alcoholic steatohepatitis (NASH) due to the global obesity pandemic. [2]

Nonetheless, differences in the prevalence of each etiology have been identified according to geographies. For example, in the developed countries, LC caused by alcohol consumption seems to be declining, while HCV infection may be soon under control.[2, 3] In contrast, in Latin America, the prevalence of alcoholic liver disease (ALD) has remained stable or might have increased; whereas viral hepatitis infection is underestimated, and the prevalence of NASH is unknown or scarcely considered as an emerging health problem.[3-5]

Particularly in Mexico, LC is the fourth largest cause of mortality, causing more than 30,000 deaths per year, a rate that is

considered as one of the highest in Latin America.[6] Also, nearly six million people have alcohol abuse,[4,7] more than two million are infected with HCV,[3] and HBV infection has been reported with high prevalence in vulnerable risk groups.[8] Furthermore, 70% of the adult population in the country have excessive weight, which is a known risk factor for chronic liver damage.[5]

In Latin America, few studies have been performed for the detection of liver damage by different etiologies. This situation results in the underestimation of the burden of this condition and a lack of awareness at earlier stages of liver damage that could prevent its progression. Besides, in health institutions, LC is often diagnosed at end stages when clinical complications are already present, such as variceal bleeding, encephalopathy, and ascites.[9] Since the course of disease may be influenced by genetic and environmental risk factors,[10] it is important that the causes and degree of liver damage be detected at early stages.

Currently, liver biopsy has limited use in the clinical practice due to sampling error, high cost and potentially serious health complications.[11] Therefore, the use of non-invasive diagnostic tools of liver damage has increased in the last years. For instance, transient elastography (TE) with a high diagnostic accuracy in assessing and staging liver fibrosis has been validated by several studies.[12-14] At present, the practice guidelines emitted by the American and European Associations for the Study of the Liver recommend the use of TE as the first-line methodology tool for diagnosis and management of liver damage.[15,16] TE (FibroScan®) measures liver tissue stiffness and classifies the degree of fibrosis into four categories: initial stage of fibrosis (F1), intermediate (F2), advanced (F3) and cirrhosis (F4), before ascites is present.

Besides TE, multiple studies have proposed several biochemical parameters for the detection of liver fibrosis.[17] However, the usefulness of a majority of these may be limited in clinical practice and they have not been tested in our population. This study is aimed to detect liver damage in patients with chronic liver disease using transitional elastography (TE) and to assess the biochemical parameters associated with liver damage.

MATERIALS AND METHODS

Study population

This cross-sectional study was conducted at the Department of Molecular Biology in Medicine, Hospital Civil de Guadalajara, "Fray Antonio Alcalde" in Guadalajara, Jalisco, Mexico. This Department has been a referral center to provide medical attention to patients with different hepatopathies over the last 20 years. Patients with a preliminary diagnosis or with risk factors for liver damage are referred for confirmatory clinical and molecular diagnosis. A qualified medical staff interviewed each patient to register demographic data, medical history, clinical and laboratory data. The patients who were attended from January 2012 to August 2015 were included in this study. Individuals who were positive for anti-HIV antibodies were excluded. The etiology of liver damage was established according to the clinical criteria mentioned below.

Clinical criteria

ALD was diagnosed based on significant alcohol consumption (>40 g/d) for at least five years, and the drinking pattern of alcohol in West Mexico as previously published.[4,7]

Both chronic HCV and HBV infections were diagnosed by serological, molecular and clinical assessment, as previously reported.[8,18]

Diagnosis of NASH was performed in individuals who were (1) negative for HCV and HBV and consumed less than 40 g/d of alcohol; and (2) had any of the following biochemical alterations: aspartate aminotransferase (AST) ≥ 54 IU/L, alanine aminotransferase (ALT) ≥ 42 IU/L, glucose ≥ 100 mg/dL, triglycerides (TG) ≥ 150 mg/dL or homeostasis model assessment of insulin resistance (HOMA) ≥ 2.5. Liver damage was assessed by TE, and NASH was confirmed by liver biopsy.

Other etiologies of liver damage such as autoimmune hepatitis, primary biliary cirrhosis, drug-induced hepatotoxicity and primary sclerosing cholangitis were diagnosed using the standard criteria.

Laboratory tests

Blood samples (10 mL) were obtained by venipuncture after a 12 h overnight fast. Biochemical tests, including glucose, insulin, platelets count, albumin (ALB), total bilirubin (TB), ALT, AST, gamma-glutamyl-transferase (GGT), total cholesterol (TC), TG and high-density lipoprotein cholesterol (HDL-c), were determined by an AU5800 Clinical Chemistry System (Beckman Coulter´s Inc. USA). Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation.[19] The very low-density lipoprotein cholesterol (VLDL-c) was estimated as Total Cholesterol - (LDL-c + HDL-c). The HOMA was calculated as: fasting plasma glucose (mg/d L) x fasting serum insulin (mU/L)/405. Insulin resistance (IR) was defined as an HOMA of 2.5 or above.

Body composition

In all the patients, body composition and body mass index (BMI) was assessed by electrical bioimpedance using an

InBody 3.0 instrument (Analyzer Body Composition, Biospace, Korea). The BMI index was based on the criteria of World Health Organization.[20]

Liver stiffness measurement and fibrosis staging

The stage of liver damage (fibrosis) was assessed by TE (FibroScan® Echosens, Paris, France). The average value of the readings expressed in kilopascals (kPa) was used as an indicator of liver fibrosis. The success rate (SR) was calculated as the ratio of valid to total number of measurements. As an indicator of variability, the ratio of the interquartile range (IQR) of liver stiffness values to the median (IQR/M) was calculated. TE examinations with more than ten valid measurements, an SR of more than 80% and an IQR/M less than 30% were considered to be reliable.[12] Liver stiffness and liver damage stages were classified according to the specific cut-off values by each etiology according to the manufacturer's instructions. For this study, F1-F2 stages were classified as mild liver damage, whereas F3-F4 stages were classified as advanced liver damage.

Clinical diagnosis of liver cirrhosis

Clinical diagnosis of LC was established if the patient showed clinical complication of cirrhosis (ascites, esophageal varices or encephalopathy) and had an absence of other pathologies at the time of entry to the study.

Statistical analysis

Kolmogorov-Smirnov test was used to analyze the normal distribution of all variables. Quantitative variables were expressed as mean ± Standard Deviation (SD). Statistical differences for quantitative variables were determined by student´s *t*-test and one-way ANOVA. When necessary, post hoc tests were run to define intergroup differences according to the homogeneity of the variances. Bonferroni's test for equal variances and Dunnett's T3 test for unequal variances were used. Qualitative variables were expressed in frequencies and percentage. Chi-square test evaluated the statistical differences for qualitative variables.

The cases evaluated with TE were grouped into two categories: mild liver damage (F1-F2) and advanced liver damage (F3-F4). Thus, the variables with a *P*-value <0.2 were included in the univariate and multivariate logistic regression test to analyze their association with liver fibrosis. Areas under the curve (AUC) plots were constructed for the selected variables in the multivariate logistic regression. Concordance was determined using Kappa test and Fleiss criteria. Statistical analyses were performed in the SPSS software (version 20.0). A *P*-value <0.05 was considered to be significant.

Ethical guidelines

The study complied with the ethical guidelines of the 2013 Declaration of Helsinki. This study was revised and approved by the Institutional Review Broad. All patients signed a written informed consent.

RESULTS

Clinical characteristics of patients with liver disease

As shown in Table 1, 578 adult patients (335 males and 243 females over 18 years of age) were diagnosed with chronic liver damage. Overall, the foremost etiologies of chronic liver damage were HCV infection (*n*=212/578, 37%), ALD (*n*=191/578, 33%) and NASH (*n*=148/578, 26%), while HBV infection and AIH were less frequent. Others etiologies were primary biliary cirrhosis (2 cases), drug-induced hepatotoxicity (2 cases) and primary sclerosing cholangitis (1 case). Most patients were young, and in the economically productive age group (40-50 years). NASH and AIH were mainly prevalent in women, whereas a higher proportion of men had ALD and HBV. All patients had excess weight and those with NASH had the highest BMI of all groups.

Also, a differential metabolic profile by etiology was found. HCV patients had a higher frequency of IR (*n*=102/212, 48%) and diabetes (*n*=30/212, 14%) and lower platelets values compared to the rest of the study groups ($P=1 \times 10^{-6}$). ALD patients had higher levels of liver enzymes AST, ALT, and GGT, and lower levels of ALB and HDL-c ($P=4\times10^{-5}$). NASH patients showed higher TC, TG, LDL-c and VLDL-c levels than those with HBV infection and ALD ($P=2\times10^{-4}$).

Detection of liver damage using TE and diagnosis of liver cirrhosis

Table 2 shows the different stages of fibrosis by TE as per the etiology of liver damage. Among these, 21% (*n*=121/578) patients did not have liver damage (F0). Liver fibrosis was detected in 39% of patients. Of these, 21% (*n*=122/578) were in the F1 stage, 10% (*n*=58/578) in F2, and 8% (*n*=46/578) in F3. Also, asymptomatic cirrhosis (F4) was detected in 15% (*n*=87/578) of the cases. 23% (*n*=130/578) of cases were clinically diagnosed with liver cirrhosis, and 2% (*n*=14/578) were invalidated.

Overall, 38% (*n*=217/578) patients had LC detected either by TE with an asymptomatic F4 stage, together with those clinically diagnosed. Among this subgroup, the most frequent cause was ALD (*n*=96/217, 45%), followed by HCV infection (*n*=94/217, 43%) and NASH (*n*= 21/217, 10%), whereas HBV and AIH were found in a lower proportion (Figure 1).

Table 1. Demographic and clinic characteristics of patients by etiology of liver disease (n=578)

Variable	HCV	ALD	NASH	HBV	AIH	OTHERS
Number of patients, *n* (%)	212 (37)	191 (33)	148 (26)	14 (2)	8 (1.4)	5 (0.6)
Age (years)	49.9 ± 13*	46 ± 13.7	41.5 ± 12.5	46.5 ± 15.1	50.7 ± 20.8	40.4 ± 17.3
Gender (F/M)	107/105	21/170[§]	100/48	4/10	8/0	3/2
BMI (Kg/m^2)	26.9 ± 4.4	26.4 ± 4.6	30.5 ± 6.3[†]	25.2 ± 4.1	27.1 ± 2.5	31.1 ± 6.8
Platelets(x10^3/µL)	171 ± 86*	225 ± 55	247 ± 60	182 ± 70	ND	ND
Glucose(mg/dL)	108 ± 46	105 ± 40	99 ± 32	96 ± 14	94 ± 18	ND
HOMA	3.7 ± 3.5	5.5 ± 18.2	3 ± 3.1	ND	ND	ND
IR, *n* (%)	102 (48)*	8 (4)	31 (21)	ND	ND	ND
Diabetes, *n* (%)	30 (14)*	19 (10)	8 (5)	1 (8)	0 (0)	ND
TC (mg/dL)	160 ± 44	161 ± 64	203 ± 48[†]	169 ± 22	192 ± 37	ND
TG (mg/dL)	142 ± 71	167 ± 103	188 ± 98[‡]	156 ± 84	118 ± 47	ND
LDL-c (mg/dL)	92 ± 41	96 ± 45	122 ± 43[†]	94 ± 23	124 ± 39	ND
VLDL-c (mg/dL)	28 ± 14	32 ± 21	37 ± 22[‡]	28 ± 11	ND	ND
HDL-c (mg/dL)	42 ± 17	32 ± 18[§]	42 ± 18	40 ± 8	43 ± 8	ND
AST (IU/L)	61 ± 52[‖]	57 ± 53[‖]	32 ± 23	26 ± 11	86 ± 45	ND
ALT (IU/L)	63 ± 61[‖]	42 ± 39[‖]	36 ± 36	23 ± 9	73 ± 30	ND
GGT (IU/L)	68 ± 78[‖]	91 ± 110[‖]	33 ± 41	30 ± 24	ND	ND
ALB (g/dL)	3.7 ± 0.6	3.2 ± 1[§]	3.9 ± 0.5	3.9 ± 0.4	ND	ND
ALP (IU/L)	105 ± 53	101 ± 71	83 ± 32[‡]	82 ± 29	ND	ND
TB (mg/dL)	1.1 ± 1	3.8 ± 6.8[§]	0.7 ± 0.4	0.8 ± 0.2	ND	ND

Average values are expressed as mean ± SD. Gender is expressed as number of cases. HCV: hepatitis C virus; ALD: alcoholic liver disease; NASH: non-alcoholic steatohepatitis; HBV: hepatitis B virus; AIH: autoimmune hepatitis; F: female; M: male; BMI: body mass index. HOMA: homeostasis model assessment; IR: Insulin Resistance; TC: total cholesterol; TG: triglycerides; LDL-c: low density lipoprotein cholesterol; VLDL-c: very low density lipoprotein cholesterol; HDL: high density lipoprotein cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl-transferase; ALB: albumin; ALP: alkaline phosphatase; TB: total bilirubin. (*HCV *vs.* ALD and NASH, $P=1x10^{-8}$). ([†]NASH *vs.* HCV and ALD, $P=1x10^{-7}$). ([‡]NASH *vs.* HCV, $P=<1x10^{-3}$) ([§]ALD *vs.* HCV and NASH, $P=2x10^{-4}$) ([‖]HCV and ALD *vs.* NASH and HBV, $P=4x10^{-5}$). One-way ANOVA, Dunnett´s T3, Bonerroni´s test.

Table 2. Detection of liver damage using TE and clinical cirrhosis by etiology of liver disease

			Stages of liver damage *n* (%)					
Etiology of liver disease	Number of patients	Invalid cases	F0	F1	F2	F3	F4	Clinical cirrhosis
HCV	212	5 (2)	0 (0)	76 (36)	26 (12)	11 (5)	44 (21)	50 (24)
ALD	191	1 (0.5)	51 (27)	22 (12)	10 (5)	11 (6)	18 (9.5)	78 (41)
NASH	148	7 (5)	66 (45)	18 (12)	19 (13)	17 (11)	20 (13)	1 (1)
HBV	14	1 (7)	0 (0)	4 (29)	1 (7)	5 (36)	2 (14)	1 (7)
AIH	8	0 (0)	3 (37.5)	0 (0)	0 (0)	2 (25)	3 (37.5)	0 (0)
Others	5	0 (0)	1 (20)	2 (40)	2 (40)	0 (0)	0 (0)	0 (0)
Total	578	14 (2)	121 (21)	122 (21)	58 (10)	46 (8)	87 (15)	130 (23)

HCV: hepatitis C virus; ALD: alcoholic liver disease; NASH: non-alcoholic steatohepatitis; HBV: hepatitis B virus; AIH: autoimmune hepatitis

Biochemical parameters associated with advanced liver damage regardless of etiology

Table 3 shows the analysis to assess the relationship between clinical and biochemical parameters with the degree of liver damage regardless of etiology. The result of the TE by study group was classified into mild liver damage (F1-F2 stages) and advanced liver damage (F3-F4 stages). Eight parameters were significantly different between both subgroups: age, platelets count, AST, GGT, ALB, TB, glucose and TC. Subsequently, platelets count (OR=3.31 95%CI, 1.62-6.78, *P*=0.001), glucose (OR=3.07, 95%CI, 1.50-6.26, *P*=0.002), GGT (OR=3.60 95%CI, 1.79-7.25, $P=1\times10^{-4}$), ALB (OR=3.89, 95%CI, 1.61-9.36, *P*=0.002) and TB (OR=3.93, 95%CI, 1.42-10.91, *P*=0.009) were associated with advanced liver damage by univariate and multivariate logistic regression analyses as shown in Table 4.

In Table 5, optimal cut-off values and receiver operating characteristic curves (ROC´s) of these five biochemical parameters are shown. Overall, the mean value of AUC was 0.69, with a sensitivity of 66%, specificity of 69%, a PPV of 72%, an NPV of 66% and concordance of 0.43. Based

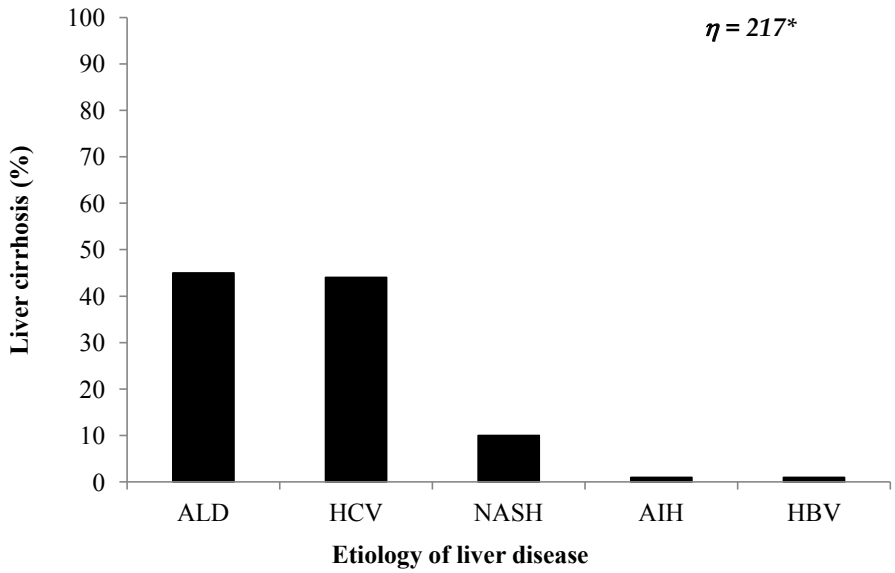

Figure 1: Frequency of cirrhosis by etiology. ALD: alcoholic liver disease; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis; AIH: autoimmune hepatitis; HBV: hepatitis B virus. *Total number of cases= 130 with clinical diagnosis of cirrhosis and 87 in stage F4 using TE.

Table 3. Biochemical profile by grade of liver damage using TE

Variable	Mild liver damage (F1-F2 stages)	Advanced liver damage (F3-F4 stages)	*P*-value
Number of patients	176	133	-
Age (years)	44.9 ± 13.9	48.9 ± 12.9	0.011
BMI (kg/m^2)	27.3 ± 4.8	28.2 ± 5.7	0.214
Platelets (x10^3/μL)	228 ± 71	178 ± 78	1x10^{-5}
Glucose (mg/dL)	99 ± 31	113 ± 54	0.021
HOMA	3.1 ± 2.59	4.3 ± 4.5	0.590
TC (mg/dL)	182 ± 44	168 ± 59	0.036
TG (mg/dL)	165 ± 81	160 ± 79	0.592
LDL-c (mg/dL)	108 ± 43	103 ± 49	0.365
VLDL-c (mg/dL)	33 ± 16	31 ± 15	0.458
HDL-c (mg/dL)	42 ± 18	44 ± 20	0.407
AST (IU/L)	36 ± 24	57 ± 42	1x10^{-5}
ALT (IU/L)	41 ± 31	58 ± 60	0.290
GGT (IU/L)	42 ± 61	87 ± 92	7x10^{-5}
ALB (g/dL)	3.9 ± 0.5	2.8 ± 0.5	0.034
ALP (IU/L)	81 ± 31	92 ± 39	0.206
TB (mg/dL)	0.7 ± 0.4	1.9 ± 0.7	0.019

Average values are expressed as mean ± SD. BMI: body mass index; HOMA: homeostasis model assessment; TC: total cholesterol; TG: triglycerides; LDL-c: low-density lipoprotein cholesterol; VLDL-c: very low-density lipoprotein cholesterol; HDL-c: high density lipoprotein cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl-transferase; ALB: albumin; ALP: alkaline phosphatase; TB: total bilirubin. Student´s *t* test.

Table 4. Biochemical parameters associated with advanced liver damage (F3-F4 stage)

Variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	2.40 (1.70-3.43)	$1x10^{-4}$		
Platelets ($x10^3/\mu L$)	8.90 (5.21-15.48)	$1x10^{-5}$	3.31 (1.62-6.78)	0.001
Glucose (mg/dl)	2.91 (1.96-4.33)	$1x10^{-3}$	3.07 (1.50-6.26)	0.002
TC (mg/dL)	4.09 (2.77-6.04)	$1x10^{-4}$		
AST (IU/L)	5.20 (3.52-7.68)	$1x10^{-4}$		
GGT (IU/L)	5.19 (3.39-7.94)	$1x10^{-5}$	3.60 (1.79-7.25)	$1x10^{-4}$
ALB (g/dL)	13.24 (8.14-21.55)	$1x10^{-6}$	3.89 (1.61-9.36)	0.002
TB (mg/dL)	23.28 (11.93-45.41)	$1x10^{-4}$	3.93 (1.42-10.91)	0.009

TC: total cholesterol; AST: aspartate aminotransferase; GGT: gamma-glutamyl-transferase; ALB: albumin; TB: total bilirubin.

Table 5. Cut-off values and ROC curve of biochemical parameters related to advanced liver damage using TE

Variable	AUCs (95% CI)	*P*-value	Optimal cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Concordance
Platelets ($x10^3/\mu L$)	0.76 (0.68-0.83)	$1x10^{-4}$	192	78.6	71.3	80.2	68.8	0.49
Glucose (mg/dL)	0.64 (0.55-0.72)	$1x10^{-3}$	100.5	55.0	75.2	54.4	71.0	0.25
GGT (IU/L)	0.76 (0.69-0.82)	$1x10^{-5}$	34.5	73.8	65.8	61.5	76.4	0.38
ALB (g/dL)	0.65 (0.57-0.73)	$1x10^{-4}$	3.95	90.6	42.5	75.4	81.2	0.53
TB (mg/dL)	0.65 (0.57-0.73)	$1x10^{-4}$	1.03	33.8	93.2	90.1	33.8	0.50
Total	0.69 (0.61-0.77)	-	-	66.0	69.0	72.0	66.0	0.43

GGT: gamma-glutamyl-transferase; ALB: albumin; TB: total bilirubin; AUC´s: area under curves; PPV: positive predictive value; NPV: negative predictive value. Kappa test.

on these results, patients may have a probability of 98% to present advanced liver damage by having these biochemical parameters altered regardless of etiology. Finally, the diagnostic values of these biochemical parameters were compared with scores for the detection of liver fibrosis in Table 6. In general, the sensitivity and specificity values were similar, fundamentally with the GPRI-Score and the FORNS-Index, but the PPV and concordance values were higher as compared to the other scores.

DISCUSSION

This study shows the frequency of liver fibrosis using TE and the evaluation of five biochemical parameters as independent predictors of advanced liver damage in a Latin American population. Overall, ALD, viral hepatitis C and NASH were the main etiologies of chronic liver damage and LC. These etiologies may be representative of the main risk factors for liver disease nationwide as compared to earlier studies, given the fact that the Hospital attends low and middle-income class populations.[18,21] Also, the study population was young, and each etiology had a particular biochemical profile. Notably, the number of HCV-infected patients was higher than those who had ALD. This difference may be attributed to the fact that more attention is given to the diagnosis of HCV than to ALD or there are more HCV-infected patients than previously estimated.[3,22] Nonetheless, a significant finding was the shift of the 2 to 1 ratio of women versus men previously reported towards an equal relationship of gender. This data is consistent with a recent study that showed a rise in the use of injection drugs among men associated with an increase in HCV infection.[23]

In regards to age, ALD was prevalent mainly in relatively young male adults, as observed in previous studies that showed that patients with ALD and LC were younger as compared to other populations.[24] However, in this study the patients with NASH were the youngest. In fact, a higher BMI, as well as IR and diabetes were more prevalent in this group. Therefore, it is plausible that NASH could increase in the coming years.

Preventive strategies for reducing the incidences of ALD, HCV and HBV have been implemented among the developed countries.[3,4,25] In contrast, among the developing countries, LC is stable or has risen, and the diagnosis is mainly performed in the advanced stages of disease when clinical complications are present.[9,10] Notably, in this study, the early detection of liver fibrosis (F1-F3) using TE

Table 6. Comparison of diagnostic models for detection of advanced liver damage

	AUCs (95% CI)	*P*-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Concordance
5 "HCG" BP (This study)	0.69 (0.61-0.77)	$1X10^{-4}$	66.0	69.0	72.0	66.0	0.43
APRI score	0.69 (0.59-0.76)	$1X10^{-5}$	56.0	80.0	61.0	76.0	0.36
GPRI score	0.74 (0.67-0.82)	$7X10^{-8}$	74.0	62.0	71.0	66.0	0.12
FIB-4 score	0.71 (0.63-0.79)	$2X10^{-6}$	58.0	75.0	56.0	75.0	0.31
FORNS-index	0.72 (0.64-0.80)	$2X10^{-4}$	60.0	77.0	61.0	77.0	0.38

5 "HCG" BP: The five "Hospital Civil de Guadalajara" biochemical parameters; AUC´s: area under curves; PPV: positive predictive value; NPV: negative predictive value.

was possible in one-third of the total cases. Likewise, the diagnosis of LC, both clinically and by TE, was confirmed in one third of the cases and the etiologies were ALD, followed by HCV and NASH.

To date, ALD has been a leading cause of morbidity and mortality in Mexico. In this study, half of the patients with ALD had a diagnosis of cirrhosis. As described before, the pattern of alcohol consumption is habitually comprised of three consecutive stages of increasing alcohol intake.[4,7] This pattern of drinking may explain why the prevalence and mortality rate of cirrhosis due to ALD in Mexico have not significantly declined, remaining as the highest in Latin America.[2,10] Furthermore, these individuals commonly do not seek medical advice until the disease has reached advanced stages of clinical complications.

HCV infection is a global health problem that may soon be eradicated by the introduction of new direct-acting antiviral drugs in certain geographical regions. However, socioeconomic factors, unrighteous attitudes and the lack of HCV screening may impose limitations to combat HCV in developing countries.[3] In this study, HCV patients had a higher frequency of liver fibrosis detected by TE as compared to the other etiologies and was the second cause of LC. The genetic background of the Mexican population, the predominance of HCV genotype 1 and other environmental factors[26] may influence this condition.

Currently, NASH is a growing cause of liver damage in westernized countries. In this study, NASH was the third etiology of liver fibrosis and asymptomatic cirrhosis diagnosed by TE, which may be related to the finding of cryptogenic cirrhosis cases in a study carried out 15 years ago.[9] A significant contribution of this study is the identification of NASH as one of the leading causes of LC in the study population.

On the other hand, HBV-related LC showed a relatively low prevalence rate. However, a high endemicity of HBV infection is prevalent among low-income population groups, and underdiagnosis of infection may occur due to occult hepatitis B.[8] Secondly, in this study population, patients with hepatocellular carcinoma were not detected, which is consistent with the fact that liver cancer is rare in Mexico. This finding may be related to dietary and environmental factors or that patients die prematurely of clinical complications of LC, before liver cancer is diagnosed.[27]

Several biomarker panels have been designed to assess liver fibrosis. The most common are the aminotransferase-to-platelet ratio index (APRI), the Forns index, FIB-4, HepaScore and the FibroTest,[17] which have not been thoroughly validated in the Latin American population including Mexico**.** Furthermore, they have some drawbacks for their use in the clinical practice in developing countries and most scores associated with chronic liver damage only consider one etiology.[28] In contrast with the scores mentioned above, the "HCG" (Hospital Civil de Guadalajara) biochemical parameters used in this study, including glucose and GGT, were associated with advanced liver damage (F3-F4). This data is consistent with several studies that have documented the relation between insulin resistance and the presence of NASH, whereas excessive alcohol intake increases the serum GGT values.[29,30] In consequence, the five HCG biochemical parameters showed a high sensitivity and specificity for the independent prediction of advanced liver damage as well as a higher PPV and concordance as compared to the other scores. Importantly, the alteration of these parameters involved the main etiologies such as HCV/HBV, alcohol and NASH found in the study population. These HCG markers could be undoubtedly available in other institutions similar to our Hospital, where low-resources hinders the plausibility to detect liver disease with high-cost methodologies.

Given the active alcoholism of the Mexican population, the low screening rate of HCV and HBV infection, and the excess weight factor in more than 70% of the adults, the number of cases of chronic liver damage and LC may increase shortly. Therefore, the early recognition of liver damage is necessary to establish prevention strategies, avoid

the progression of fibrosis and improve the quality of life in these patients. This scenario provides the opportunity to establish preventive and intervention strategies based on acts of individualized medicine.[31]

CONCLUSIONS

Asymptomatic liver disease due to HCV, ALD and NASH prevailed in young adults. Advanced liver damage assessed by TE was associated with five biochemical parameters. In conjunction, both methodologies may be useful for the early detection of fibrosis and cirrhosis in Latin America.

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Conflict of Interest

The authors declare no conflict of interest.

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