DOI: 10.15386/cjmed-554

HYALURONIC ACID AS A BIOMARKER OF FIBROSIS IN CHRONIC LIVER DISEASES OF DIFFERENT ETIOLOGIES

OLGA HILDA ORASAN[1], GEORGE CIULEI[1], ANGELA COZMA[1], MADALINA SAVA[1], DAN LUCIAN DUMITRASCU[2]

[1]4th Medical Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2]2nd Medical Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

Chronic liver diseases represent a significant public health problem worldwide. The degree of liver fibrosis secondary to these diseases is important, because it is the main predictor of their evolution and prognosis.

Hyaluronic acid is studied as a non-invasive marker of liver fibrosis in chronic liver diseases, in an attempt to avoid the complications of liver puncture biopsy, considered the gold standard in the evaluation of fibrosis. We review the advantages and limitations of hyaluronc acid, a biomarker, used to manage patients with chronic viral hepatitis B or C infection, non-alcoholic fatty liver disease, HIV-HCV coinfection, alcoholic liver disease, primary biliary cirrhosis, biliary atresia, hereditary hemochromatosis and cystic fibrosis.

Keywords: hyaluronic acid, liver fibrosis, chronic liver diseases

Chronic liver diseases may cause inflammation and progressive scarring, over time leading to irreversible hepatic damage (cirrhosis). Hyaluronic acid (HA), an essential component of the extracellular matrix in virtually every tissue of the body, mostly synthesized by hepatic stellate cells and degraded by sinusoidal endothelial cells [1], has been found to correlate with the histological stages of liver fibrosis (F) in chronic liver diseases [2]. HA has shown very good diagnostic accuracy for the non-invasive assessment of fibrosis and cirrhosis [3,4]. The aim of this paper is a systematic literature review regarding HA for the assessment of liver fibrosis in chronic liver diseases: chronic viral C and B infections (CHC and CHB), non-alcoholic fatty liver disease (NAFLD), Human immunodeficiency virus/hepatitis C virus (HIV/HCV) coinfection, alcoholic liver disease (ALD), autoimmune disease and genetic disorders.

Manuscript received: 02.09.2015
Accepted: 17.09.2015
Address for correspondence: olgaorasan@yahoo.com

Hyaluronic acid and chronic viral C infection

In chronic hepatitis C (CHC), most studies showed that measuring serum hyaluronic acid (HA) levels had value in distinguishing advanced fibrosis/cirrhosis from absent or mild fibrosis [5,6,7,8-9]. Values for the area under the curve (AUC) were higher for differentiating patients with cirrhosis than the values for differentiating patients with advanced fibrosis (Table I). AUC values between 0.850 and 0.90 are considered to be as good as liver biopsies for staging fibrosis by many fibrosis experts [10].

Regarding the diagnosis of the exact stages of fibrosis, results were mixed, with few studies finding that it could differentiate between them. El-Kamaryet et al. found particularly that serum HA significantly differed across fibrosis stages ($P<0.05$) [12] but generally measuring HA was effective in differentiating between F0/F1 and F2/F2/F4 [4,9]. HA performed better or was similar in detecting cirrhosis when compared with other direct serum markers such as amino-terminal peptide of type III procollagen (PIIIP) [2,4], type IV collagen [4],YKL-40 [4], tissue inhibitor of metalloproteinases-1 (TIMP-1) [6].

Table I. HA cut-off values for diagnosing different fibrosis stages in CHC.

	HA (ng/mL)	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUC
F≥2	>75.7 [4]	75	81	79	76	0.805
	>103.1 [11]	66.7	90	89	62.2	0.783
	>121 [7]	14	99	94	57	0.73
F≥3	>60 [8]	88	59	47	93	NA
	>85 [2]	64.5	91.2	NA	NA	0.864
	>109.7 [11]	100	82.3	62.5	100	0.929
	>110 [8]	73	83	63	89	NA
	>160 [7]	22	100	100	81	0.77
F≥4	>60 [8]	98	54	30	99	NA
	>110 [8]	88	78	44	97	NA
	>110 [2]	79.2	89.4	NA	NA	0.924
	>183.5 [4]	80	80	80	80	0.854
	>237 [7]	31	99	57	96	0.97

AUC- area under the curve; CHC- chronic viral hepatitis C; F- liver fibrosis; HA- serum hyaluronic acid; NA- not available; NPV- negative predictive value; PPV- positive predictive value; Se- sensitivity; Sp- specificity.

In a study that compared 4 direct serum markers (blood platelets count, type IV collagen, HA and serum osteopontin) only serum osteopontin demonstrated a sequential increase from F0 through F4 with a significant difference (P<0.001) between each group that coincided with the degree of fibrosis. There was a marked increase in the case of serum HA in groups F3 and F4 compared to F0, but the difference was not significant between F1 and F2 [9].

Values for transforming growth factor beta 1 (TGF-ß1), TIMP-1, HA and PIIIP were also compared for pediatric and adult HCV chronic infections. The difference among fibrosis stages was significant for HA and PIIIP in adults and for TIMP-1 in children. In the pediatric cohort, the highest AUC was that of TIMP-1, which discriminated advanced fibrosis from other stages, but it was also noted that HA showed 100% specificity for advanced fibrosis. In adults, the best AUC was that of HA (0.929). In the same study the aspartate transaminase/platelet ratio index (APRI) and aspartate transaminase/alanine transaminase (AST/ALT) ratio (AAR) were compared, and regarding the adult cohort, they did not perform better than HA [11].

Different teams measured HA during antiviral therapy and the responder (sustained virological response or SVR) and non-responder (null virological response or NVR) patient values were compared. Trocmeet et al. found a significant decrease of serum HA concentration at the end of follow-up compared with baseline values in responder patients in interferon α-2a (INF-α-2a) plus ribavirin therapy, which was also reported by other teams [13,14]. However, Patel et al. have shown that the drop of HA levels in responder patients did not always correlate with improvement of hepatic fibrosis [15]. Also Trocme et al. did not find HA to decrease during the treatment period whatever the virological response was, a result also reported by others[16,17]. Even so, other studies showed that HA could increase during antiviral treatment both in responder and non-responder patients, even if in the follow-up after treatment HA levels decrease [18,19].

In CHC patients on hemodialysis, one study found that the AUC of HA for differentiating absent or mild fibrosis (F0-1) from marked fibrosis was significantly lower (AUC=0.65) [20] than that observed for HA in CHC patients with normal renal function [4]. In contrast, another study found that HA was a good marker to discriminate significant fibrosis (F≥2) for CHC patients with end-stage renal disease (ESRD) on hemodialysis. The AUC for patients with ESDR and HCV, 0.808, was higher than the AUC for HCV only patients (0.745). Also, the length of time on hemodialysis did not correlate to HA levels in this study, however it should be considered that women with ESRD had lower levels of HA (decrease in bone metabolism resulted from the presence of estrogen) and that the mean time on hemodialysis was 9.7 years, when a significant difference in HA levels could take more than 10 years to be detected. Patients with ESDR and CHC had much higher values of HA compared to CHC only patients (P<0.001) [21]. Yet one team found HA levels to be significantly higher in the group with HCV only infection compared with the group of patients that had HCV infection and was on hemodialysis (p<0.05) [22].

When compared against APRI, AAR or the FIB-4 index in patients with ESRD and hepatitis C or B infection, HA was the most efficient for fibrosis diagnosis (highest AUC values for predicting each stage). In particular, HA was the only non-invasive test that could determine F2 fibrosis (cut-off value at 80.24 ng/mL, AUC=0.76), F3 fibrosis (cut-off value at 88.54ng/mL, AUC=0.74). For F1, no test stood out as significantly better than the others (cut-off value for HA was 33.46 ng/mL, AUC=0.73). None of the tests could determine the F4 score (AUC for HA was 0.67). Patients with ESRD and hepatitis B or C had

higher HA levels than patients without viral hepatitis but with ESDR, yet this difference did not reach statistical significance (P=0.314) [23]. Furusyo et al. also reported lower serum HA in patients on dialysis compared with patients on dialysis and with HCV, yet their difference was much higher and significant [24].

HA concentrations were measured in patients with CHC that underwent liver transplantation (LT) to see if they can predict rapid fibrosis progression (RFP, an increase in the fibrosis score ≥2 from biopsy 1 to biopsy 2 in a mean interval of 33±6 months). No significant difference was noted between those with and without RFP before LT. Serum concentrations for HA were significantly higher at the time of the first biopsy in those who developed RFP in comparison with those who did not. Serum HA, with an AUC of 0.89 was better at predicting RFP than conventional histological and biochemical markers such as hepatic stellate cell activity (HSCA). HA concentration of ≥90 μg/l at initial biopsy had a sensitivity and specificity of 80% in predicting subjects who would develop RFP by the second biopsy. Serum HA levels lowered by the time of the second biopsy [25].

Hyaluronic acid and chronic viral B infection

Montazeri et al. studied liver fibrosis in HBeAg-negative patients in relation with serum HA levels. Normal volunteers had a significantly lower mean value of HA when compared against chronic hepatitis B (CHB) patients. A cut-off point of 126.4 ng/ml could discriminate extensive fibrosis (Ishak fibrosis stage 3-5) from milder ones (stage 0-2) with a sensitivity of 90.9% and a specificity of 98.1%. Serum HA was found to be an independent factor in predicting fibrosis for HBeAg-negative patients [26], as it was in HBeAg-positive patients [27]. When comparing mean HA in HBeAg-positive patients with HBeAg-negative ones, HA levels were higher in the HBeAg-positive group (1207.65 ng/mL versus 819.866 ng/mL, p<0.01) [28]. As in CHC, HA levels increased with fibrosis level from mild to extensive fibrosis, with studies finding that it could differentiate reliably between mild and extensive fibrosis (Table II).

Table II. HA cut-off values for diagnosing different fibrosis stages in CHB.

	HA (ng/mL)	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUC
S0-S2	113< [29]	92	95	94	89	NA
	126.4< [26]	90.9	98.1	90.9	98.1	0.98
S5-6	>181 [29]	100	95	78	100	NA
F≥2	>185.3 [30]	84.2	83.3	90.6	73.5	0.909
	>203.53 [32]	63.1	78.4	84.4	52.4	0.735

AUC - area under the curve; CHB - chronic viral hepatitis B; F - liver fibrosis; HA - serum hyaluronic acid; NA - not available; NPV - negative predictive value; PPV - positive predictive value; S - Ishak fibrosis stage; Se - sensitivity; Sp - specificity.

HA had the most significant levels of correlation with fibrosis level compared to markers such as AST, ALT, alkaline phosphatase, platelet count, albumin, total bilirubin and prothrombin time [26].

The study by Lee et al. found that serum HA was better in predicting significant fibrosis (F≥2) than apolipoprotein A1 (Apo A1), platelet count, prothrombin time, PIIIP, YKL-40, matrix metalloproteinase (MM-) 2 and 9, and TIMP-1. The AUC of HA (0.80) was also close to that of various models used to predict liver fibrosis: PGAA index (combines prothrombin time, GGT, Apo A1, α2-macroglobulin), Forn's fibrosis index (FFI), APRI, age-platelet index (API) [31]. Zhu et al. showed that TIMP-1 was more valuable for diagnosing significant liver fibrosis (F≥2) than HA. In their study, TIMP-1 had an AUC for diagnosing significant fibrosis(F≥2) of 0.918, with HA having a much lower value (Table II) [32].

The diagnostic performance of serum laminin (LN) was found to be no better than that of HA, AUC for serum HA was 0.909 and 0.815 for LN for predicting significant fibrosis (F≥2), but the difference between them was not found to be statistically significant (p=0.743) [30]. Zhang et al. found that APRI ≥1.5 in combination with different HA cut-off points could detect moderate to severe fibrosis (stages 2-4) in CHB patients. APRI alone had a PPV of 41.3% and a specificity of 84.7%. When HA was added, it increased the PPV (93.7%) and specificity (98.9%) significantly, indicating that APRI ≥1.5 in combination with a HA cut-off point >300 ng/mL can detect moderate to severe fibrosis or cirrhosis (stages 2-4) in CHB patients [33].

In a study that monitored liver fibrosis in children during IFNα treatment, HA showed a significant decrease in responders when levels before treatment and 12 months after INF-α treatment were compared. It was also significantly higher in patients with advanced fibrosis, while tenascin, type IV collagen and TIMP-1 did not reach a significant difference [34]. Telbivudine, used in the treatment of CHB, lowered HA levels in patients with cirrhosis [35].

In children with hepatitis B serum HA above 27 ng/mL had a sensitivity of 100% and a specificity of 50% in predicting advanced fibrosis. The combination of laminin-2 above 34.9 ng/mL and/or HA above 27 ng/mL, had an AUC of 0.84, 87.5% sensitivity and 73% specificity. Biopsy could have been potentially avoided in 75.6% of the children [36].

Hyaluronic acid and non-alcoholic fatty liver disease (NAFLD)

In NAFLD patients HA is an indicator of fibrosis presence [37,38].

Lydatakis et al. found that HA levels were significantly higher in patients with non-alcoholic steatohepatitis (NASH) and fibrosis from those with NASH and without fibrosis, while also correlating with each stage of fibrosis. In patients with NASH but without fibrosis HA levels varied within the normal range of healthy population. The best cut-off value was at 148.8 ng/mL for the identification of patients with NAFLD and fibrosis (sensitivity was 95.7%, specificity 96.3%, PPV 95.7%, NPV 96.3% and accuracy of 96% higher than that of LN) [39]. Suzuki et al. also found that HA correlated with the degree of hepatic fibrosis and was useful in detecting moderate (F2), severe (F3) fibrosis and cirrhosis (F4) [40].

Table III. HA cut-off values for differentiating different fibrosis stages in NAFLD.

	HA (ng/mL)	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUC
F≥1	>24.6 [37]	82	68	60	87	NA
F3-4	>25 [41]	90	84	NA	NA	0.94
	>30 [41]	80	91	NA	NA	0.94
	>42 [42]	100	89	77	100	0.97
	>46.1 [40]	85	79.7	51.1	95.5	0.89
F4	>50 [43]	68.8	82.8	75	77.9	0.797

AUC - area under the curve; HA - serum hyaluronic acid; NA - not available; NAFLD - non-alcoholic fatty liver disease; NPV - negative predictive value; PPV - positive predictive value; Se - sensitivity; Sp - specificity; F - liver fibrosis.

In the study by Dorak et al. HA was the most significant single biochemical factor to discriminate mild and moderate fibrosis against significant fibrosis (AUC=0.94) and performed similarly to the original Enhanced Liver Fibrosis (OELF) score (AUC=0.93) and Enhanced Liver Fibrosis (ELF) score (AUC=0.97), with other parameters like AST/ALT ratio, APRI, NAFLD fibrosis score, Fibrosis-4 (FIB-4) score and BARD score (a system that combines body mass index, AAR and the presence of diabetes) not reaching the AUC value of over 0.75 [41]. LN showed a better accuracy for diagnosing fibrosis (87% vs 73% for HA) [37].

Platelet count (AUC=0.83) and HA (AUC=0.8) were found to have similar predictive value for moderate to severe fibrosis (F2-F3) [38], while Kaneda et al. concluded that platelet count was a better marker for cirrhosis than HA levels and considered HA the better marker for diagnosing severe fibrosis [42].

In one study collagen type IV proved to have similar value in distinguishing F0-2 fibrosis from F3-F4 in NAFLD (AUC=0.827, HA had an AUC=0.774). When comparing serum values between CHC and NAFLD patients, HA was higher in CHC patients while type IV collagen did not have a significant difference [44]. In the study by Sakugawa et al. again both markers could differentiate between stage 0-2 fibrosis and stage 3 or 4. Both showed significant different values between NASH and NAFL patients, the AUC values were close for type IV collage and HA (0.828 versus 0.797) [43]. Kaneda et al. found HA and type IV collagen were independent predictors of severe fibrosis (F3-F4) (HA had an AUC of 0.97 and type IV collagen had an AUC of 0.87) [42]. Yoneda et al. measured liver stiffness in NAFLD and showed it was also strongly correlated with the serum levels of type IV collagen and HA [45].

NAFLD diagnosis was also studied in children, and it was found that HA was significantly higher ($P<0.05$) in NAFLD patients with fibrosis than in controls. HA had the cut-off value at 19.1 ng/mL for differentiatingchildren with NAFLD and fibrosis from those without fibrosis, with an AUC of 0.672. The combination of both HA and cytokeratin-18 (CK-18) was superior to that of HA or CK-18 alone potentially avoiding biopsy in 67.35% of the examined children [46]. For Fitzpatrick et al. HA was not a clinically reliable marker for predicting steatohepatitis or fibrosis in pediatric NAFLD, with CK-18 M30 achieving a better diagnostic value [47].

Hyaluronic acid and HIV/HVC coinfection

Several studies found that HA levels correlating with fibrosis stages in HIV coinfection [48,49,50,51,52] HA levels were higher in co-infected patients [49].

HA had similar diagnostic performances YKL-40, PIIIP [48], APRI, CK-18 [49], FIB-4 index [49,50], and Forns index [50]. TIMP-1 was better at separating fibrosis stages F2/F3/F4 from stages below F2 against HA in HIV-HVC co-infected patients (AUC for TIMP-1 was 0.82 while that of HA was 0.75) [53].

The AUC increased with the stage of fibrosis (Table IV) with the highest value found for diagnosing cirrhosis [48]. Nunes et al. (2005) found that the AUC for diagnosing fibrosis by HA was higher in co-infected patients compared to CHC only patients, with a similar finding for cirrhosis diagnosing. The presence of HIV infection did not affect the levels of any of the markers at the earliest stages of fibrosis (F0-F2) [48]. Resino et al. used a commercial HA-ELISA test (Echelon Biosciences) which was not previously

Table IV. HA cut-off values for differentiating fibrosis stages in HIV-HCV coinfection.

	HA (ng/mL)	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUC
F≥2	>39 [53]	60	88	NA	NA	0.75
F≥3 (Scheuer score)	>48 [52]	87	70	59	91	0.83
F≥3	>59.1 [49]	69	89	NA	NA	0.86
S5-6	>92 [48]	92	83	NA	NA	0.94

AUC - area under the curve; F - liver fibrosis; HA - serum hyaluronic acid; HCV - hepatitis C virus; HIV - human immunodeficiency virus; NA - not available; NPV - negative predictive value; PPV - positive predictive value; S - Ishak fibrosis stage; Se - sensitivity; Sp – specificity.

reported as a fibrosis test, with their HA measurements giving values generally 10 times higher (for significant fibrosis (F≥2) the AUC was 0.671, optimal cut-off point was at 1250 ng/mL, for cirrhosis HA had an AUC of 0.859 with an optimal cut-off point at 1320 ng/mL) [50] than those found in the other studies that used different enzyme-linked protein binding assay or sandwich enzyme binding assay kits [7,48].

Hyaluronic acid and alcoholic liver disease (ALD)

As for the previous liver diseases, serum HA increases in ALD [54] and significantly with advanced stages of fibrosis, and can be an indicator of progression to cirrhosis [55,56]. Studies have found that serum HA does not have a significant difference between F0 and F2 and F0 and F1, with other indexes (FibroTest) performing better. For diagnosing cirrhosis serum HA had an AUC of 0.93 and for differentiating absent/mild fibrosis from significant or higher, the AUC was 0.79 [57]. A threshold for HA at 96 ng/mL had an overall sensitivity for detecting fibrosis, alcoholic hepatitis and cirrhosis of 87% and a specificity of 93%, with an AUC of 0.913. A direct linear correlation was observed between HA and PIIIP [58].

Hyaluronic acid and autoimmune disease

It was observed that in primary biliary cirrhosis (PBC) HA concentrations were significantly increased [59,60,61] and correlated with fibrosis stage [60]. HA was a better marker in predicting development of cirrhosis and symptoms. Furthermore, HA also showed a negative correlation with time of survival and was a more sensitive marker of liver damage in PBC than PIIIP [59].

HA was significantly different between stages I to III of PBC and differentiated mild (F0-F1) from moderate (F2-F3) fibrosis [62] and extensive fibrosis [63]. Liver stiffness measurement with transient elastography (TE) was better than HA in diagnosing cirrhosis [64]. HA concentrations increase significantly over time in all clinical stages of primary biliary cirrhosis ($p<0.01$), whereas the conventional liver function tests only change in the advanced cases [65].

In patients with biliary atresia (BA), severe liver dysfunction was associated with significantly higher HA than the ones with moderate dysfunction or good function [66], with Hasegawa et al. showing that HA correlates with advanced fibrosis score in BA patients [67].

Hyaluronic acid and genetic disorders

In hereditary hemochromatosis (HH), the concentration of serum HA was found to be increased. This difference was mainly due to increases in HA levels in patients with grade 4 fibrosis compared with subjects with F0-F3 (mean of 137 vs 18.6 ng/mL, p=0.006). A cut-off value of 46.5 provided an AUC of 1.0. The combination of serum ferritin and HA, using cut-off values of 1000 ng/mL and 46.5 ng/mL, respectively, correctly identified all patients with cirrhosis. HA was similar in each grade of fibrosis in non-cirrhotic patients [68]. Another study aimed at evaluating non-invasive alternative means such as HA and TE for the assessment of severe fibrosis in patients with serum ferritin >1000 μg/l or elevated transaminases. HA was higher in patients with severe fibrosis, but did not accurately predict it. TE was significantly higher in patients with severe fibrosis and was able to accurately predict fibrosis stage in 77% of the patients. Efficient assessment of severe fibrosis was not possible in patients with intermediate TE values [69].

In cystic fibrosis with liver disease (CFLD), one study that measured HA levels in children found them to be increased, while HA levels did not correlate with pulmonary fibrosis. The difference in elevation was significant when comparing patients with CFLD against patients with cystic fibrosis without liver disease or even against patients with evidence of liver disease at ultrasound scan but no clinical evidence [70]. Another study found again that HA increased in CFLD patients compared to healthy subjects, but this time the difference was not significant when CFLD patients were compared with patients with cystic fibrosis but no liver disease. Also, HA did not correlate with histological fibrosis [71].

In conclusion, in CHC patients HA was effective in differentiating between F0/F1 and F2/F2/F4, a significant decrease of serum HA concentration being reported at the end of follow-up compared with baseline values in

responder patients to antiviral therapy; also in patients with CHC and ESRD the HA values were significantly lower than those with normal renal function. HA levels where higher in the HBeAg-positive patients compared to HBeAg-negative ones. HA exhibited a significant increase in CHB with fibrosis level from mild to extensive fibrosis. In patients with non-alcoholic fatty liver disease, HIV-HCV coinfection, alcoholic liver disease, primary biliary cirrhosis, biliary atresia, hereditary hemochromatosis HA is an indicator of fibrosis presence, but HA did not correlate with liver fibrosis in cystic fibrosis and duration of alcohol intake.

Acknowledgments

This paper was published under the frame of the European Social Fund, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/138776.

References

1. Guechot J, Loria A, Serfaty L, Giral P, Giboudeau J, Poupon R. Serum hyaluronan as a marker of liver fibrosis in chronic viral hepatitis C: effect of alpha-interferon therapy. J Hepatol. 1995;22(1):22-26.
2. Guechot J, Laudat A, Loria A, Serfaty L, Poupon R, Giboudeau J. Diagnostic accuracy of hyaluronan and type III procollagen amino-terminal peptide serum assays as markers of liver fibrosis in chronic viral hepatitis C evaluated by ROC curve analysis. Clin Chem. 1996;42(4):558-563.
3. Parise ER, Oliveira AC, Figueiredo-Mendes C, Lanzoni V, Martins J, Nader H, et al. Noninvasive serum markers in the diagnosis of structural liver damage in chronic hepatitis C virus infection. Liver Int. 2006;26(9):1095-1099.
4. Saitou Y, Shiraki K, Yamanaka Y, Yamaguchi Y, Kawakita T, Yamamoto N, et al. Noninvasive estimation of liver fibrosis and response to interferon therapy by a serum fibrogenesis marker, YKL-40, in patients with HCV-associated liver disease. World J Gastroenterol. 2005;11:476-481.
5. Isman FK, Kucur M, Baysal B, Ozkan F. Evaluation of serum hyaluronic acid level and hyaluronidase activity in acute and chronic hepatitis C. J Int Med Res. 2007;35(3):346-352.
6. Fontana RJ, Goodman ZD, Dienstag JL, Bonkovsky HL, Naishadham D, Sterling RK, et al. Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C. Hepatology. 2008;47(3):789-798.
7. Halfon P, Bourlière M, Pénaranda G, Deydier R, Renou C, Botta-Fridlund D, et al. Accuracy of hyaluronic acid level for predicting liver fibrosis stages in patients with hepatitis C virus. Comp Hepatol. 2005;4:6.
8. McHutchison JG, Blatt LM, de Medina M, Craig JR, Conrad A, Schiff ER, et al. Measurement of serum hyaluronic acid in patients with chronic hepatitis C and its relationship to liver histology. Consensus Interferon Study Group. J Gastroenterol Hepatol. 2000;15(8):945-951.
9. Matsue Y, Tsutsumi M, Hayashi N, Saito T, Tsuchishima M, Toshikuni N, et al. Serum osteopontin predicts degree of hepatic fibrosis and serves as a biomarker in patients with hepatitis C virus infection. PLoS One. 2015;10(3):e0118744. doi:10.1371/journal.pone.0118744.
10. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol. 2004;99(6):1160-1174.
11. Valva P, Casciato P, Diaz Carrasco JM, Gadano A, Galdame O, Galoppo MC, et al. The role of serum biomarkers in predicting fibrosis progression in pediatric and adult hepatitis C virus chronic infection. PLoS One. 2011;6(8):e23218. doi:10.1371/journal.pone.0023218.
12. El-Kamary SS, Mohamed MM, El-Raziky M, Shardell MD, Shaker OG, ElAkel WA, et al. Liver fibrosis staging through a stepwise analysis of non-invasive markers (FibroSteps) in patients with chronic hepatitis C infection. Liver Int. 2013;33(7):982-990.
13. Ishibashi K, Kashiwagi T, Ito A, Tanaka Y, Nagasawa M, Toyama T, et al. Changes in serum fibrogenesis markers during interferon therapy for chronic hepatitis type C. Hepatology. 1996;24(1):27-31.
14. Yamada M, Fukuda Y, Koyama Y, Nakano I, Urano F, Katano Y, et al. Serum hyaluronic acid reflects the effect of interferon treatment on hepatic fibrosis in patients with chronic hepatitis C. J Gastroenterol Hepatol 1996;11(7):646-651.
15. Patel K, Lajoie A, Heaton S, Pianko S, Behling CA, Bylund D, et al. Clinical use of hyaluronic acid as a predictor of fibrosis change in hepatitis C. J Gastroenterol Hepatol. 2003;18(3):253-257.
16. Leroy V, De Traversay C, Barnoud R, Hartmann JD, Baud M, Ouzan D, et al. Changes in histological lesions and serum fibrogenesis markers in chronic hepatitis C patients non-responders to interferon alpha. J Hepatol. 2001;35(1):120-126.
17. Granot E, Shouval D, Ashur Y. Cell adhesion molecules and hyaluronic acid as markers of inflammation, fibrosis and response to antiviral therapy in chronic hepatitis C patients. Mediators Inflamm. 2001;10(5):253-258.
18. Fontana RJ, Bonkovsky HL, Naishadham D, Dienstag JL, Sterling RK, Lok AS, et al. Serum fibrosis marker levels decrease after successful antiviral treatment in chronic hepatitis C patients with advanced fibrosis. Clin Gastroenterol Hepatol. 2009;7(2):219-226.
19. Fontana RJ, Dienstag JL, Bonkovsky HL, Sterling RK, Naishadham D, Goodman ZD, et al. Serum fibrosis markers are associated with liver disease progression in non-responder patients with chronic hepatitis C. Gut. 2010;59(10):1401-1409.
20. Schiavon LL, Narciso-Schiavon JL, Carvalho Filho RJ, Sampaio JP, Medina-Pestana JO, Lanzoni VP, et al. Serum levels of YKL-40 and hyaluronic acid as noninvasive markers of liver fibrosis in haemodialysis patients with chronic hepatitis C virus infection. J Viral Hepat. 2008;15(9):666-674.
21. Avila RE de, Carmo RA, Farah Kde P, Teixeira AL, Coimbra LV, Antunes CM, et al. Hyaluronic acid in the evaluation of liver fibrosis in patients with hepatitis C on haemodialysis. Braz J Infect Dis. 2010;14(4):335-341.
22. Fouad H, Raziky MS, Aziz RA, Sabry D, Aziz GM, Ewais M, et al. Dendritic cell co-stimulatory and co-inhibitory markers in chronic HCV: an Egyptian study. World J Gastroenterol. 2013;19(43):7711-7718.
23. Orăşan OH, Sava M, Iancu M, Cozma A, Saplonţai-Pop A, Sarlea Ţărmure S, et al. Serum hyaluronic acid in chronic viral hepatitis B and C: a biomarker for assessing liver fibrosis in chronic hemodialysis patients. Int Urol Nephrol. 2015;47(7):1209-1217.
24. Furusyo N, Hayashi J, Kanamoto-Tanaka Y, Ariyama I, Etoh Y, Shigematsu M, et al. Liver damage in hemodialysis patients

with hepatitis C virus viremia: a prospective 10-year study. Dig Dis Sci. 2000;45(11):2221-2228.
25. Pungpapong S, Nunes DP, Krishna M, Nakhleh R, Chambers K, Ghabril M, et al. Serum fibrosis markers can predict rapid fibrosis progression after liver transplantation for hepatitis C. Liver Transpl. 2008;14(9):1294-1302.
26. Montazeri G, Estakhri A, Mohamadnejad M, Nouri N, Montazeri F, Mohammadkani A, et al. Serum hyaluronate as a non-invasive marker of hepatic fibrosis and inflammation in HBeAg-negative chronic hepatitis B. BMC Gastroenterol. 2005;5:32.
27. Zeng MD, Lu LG, Mao YM, Qiu DK, Li JQ, Wan MB, et al. Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model. Hepatology. 2005;42(6):1437-1445.
28. Tang JT, Fang JY, Gu WQ, Li EL. T cell immune response is correlated with fibrosis and inflammatory activity in hepatitis B cirrhotics. World J Gastroenterol. 2006;12(19):3015-3019.
29. Geramizadeh B, Janfeshan K, Saberfiroozi M. Serum hyaluronic acid as a noninvasive marker of hepatic fibrosis in chronic hepatitis B. Saudi J Gastroenterol. 2008;14(4):174-177.
30. Li F, Zhu CL, Zhang H, Huang H, Wei Q, Zhu X, et al. Role of hyaluronic acid and laminin as serum markers for predicting significant fibrosis in patients with chronic hepatitis B. Braz J Infect Dis. 2012;16(1):9-14.
31. Lee HH, Seo YS, Um SH, Won NH, Yoo H, Jung ES, et al. Usefulness of non-invasive markers for predicting significant fibrosis in patients with chronic liver disease. J Korean Med Sci. 2010;25(1):67-74.
32. Zhu CL, Li WT, Li Y, Gao RT. Serum levels of tissue inhibitor of metalloproteinase-1 are correlated with liver fibrosis in patients with chronic hepatitis B. J Dig Dis. 2012;13(11):558-563.
33. Zhang YX, Wu WJ, Zhang YZ, Feng YL, Zhou XX, Pan Q. Noninvasive assessment of liver fibrosis with combined serum aminotransferase/platelet ratio index and hyaluronic acid in patients with chronic hepatitis B. World J Gastroenterol. 2008;14(46):7117-7121.
34. Lebensztejn DM, Sobaniec-Lotowska ME, Kaczmarski M, Voelker M, Schuppan D. Matrix-derived serum markers in monitoring liver fibrosis in children with chronic hepatitis B treated with interferon alpha. World J Gastroenterol. 2006;12(21):3338-3343.
35. Meng N, Gao X, Yan W, Wang M, Liu P, Lu XD, et al. Efficacy of telbivudine in the treatment of chronic hepatitis b and liver cirrhosis and its effect on immunological responses. J Huazhong Univ Sci Technol Med Sci. 2015;35(2):230-234.
36. Lebensztejn DM, Kaczmarski M, Sobaniec-Lotowska M, Bauer M, Voelker M, Schuppan D. Serum laminin-2 and hyaluronan predict severe liver fibrosis in children with chronic hepatitis B. Hepatology. 2004;39(3):868-869.
37. Santos VN, Leite-Mor MM, Kondo M, Martins JR, Nader H, Lanzoni VP, et al. Serum laminin, type IV collagen and hyaluronan as fibrosis markers in non-alcoholic fatty liver disease. Braz J Med Biol Res. 2005;38(5):747-753.
38. Chwist A, Hartleb M, Lekstan A, Kukla M, Gutkowski K, Kajor M. A composite model including visfatin, tissue polypeptide-specific antigen, hyaluronic acid, and hematological variables for the diagnosis of moderate-to-severe fibrosis in nonalcoholic fatty liver disease: a preliminary study. Pol Arch Med Wewn. 2014;124(12):704-712.
39. Lydatakis H, Hager IP, Kostadelou E, Mpousmpoulas S, Pappas S, Diamantis I. Non-invasive markers to predict the liver fibrosis in non-alcoholic fatty liver disease. Liver Int. 2006;26(7):864-871.
40. Suzuki A, Angulo P, Lymp J, Li D, Satomura S, Lindor K. Hyaluronic acid, an accurate serum marker for severe hepatic fibrosis in patients with non-alcoholic fatty liver disease. Liver Int. 2005;25(4):779-786.
41. Dvorak K, Stritesky J, Petrtyl J, Vitek L, Sroubkova R, Lenicek M, et al. Use of non-invasive parameters of non-alcoholic steatohepatitis and liver fibrosis in daily practice--an exploratory case-control study. PLoS One. 2014;9(10):e111551. doi:10.1371/journal.pone.0111551.
42. Kaneda H, Hashimoto E, Yatsuji S, Tokushige K, Shiratori K. Hyaluronic acid levels can predict severe fibrosis and platelet counts can predict cirrhosis in patients with nonalcoholic fatty liver disease. J Gastroenterol Hepatol. 2006;21(9):1459-1465.
43. Sakugawa H, Nakayoshi T, Kobashigawa K, Yamashiro T, Maeshiro T, Miyagi S, et al. Clinical usefulness of biochemical markers of liver fibrosis in patients with nonalcoholic fatty liver disease. World J Gastroenterol. 2005;11(2):255-259.
44. Aida Y, Abe H, Tomita Y, Nagano T, Seki N, Sugita T, et al. Serum immunoreactive collagen IV detected by monoclonal antibodies as a marker of severe fibrosis in patients with non-alcoholic fatty liver disease. J Gastrointestin Liver Dis. 2015;24(1):61-68.
45. Yoneda M, Yoneda M, Mawatari H, Fujita K, Endo H, Iida H, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Dig Liver Dis. 2008;40(5):371-378.
46. Lebensztejn DM, Wierzbicka A, Socha P, Pronicki M, Skiba E, Werpachowska I, et al. Cytokeratin-18 and hyaluronic acid levels predict liver fibrosis in children with non-alcoholic fatty liver disease. Acta Biochim Pol. 2011;58(4):563-566.
47. Fitzpatrick E, Mitry RR, Quaglia A, Hussain MJ, DeBruyne R, Dhawan A. Serum levels of CK18 M30 and leptin are useful predictors of steatohepatitis and fibrosis in paediatric NAFLD. J Pediatr Gastroenterol Nutr. 2010;51(4):500-506.
48. Nunes D, Fleming C, Offner G, O'Brien M, Tumilty S, Fix O, et al. HIV infection does not affect the performance of noninvasive markers of fibrosis for the diagnosis of hepatitis C virus-related liver disease. J Acquir Immune Defic Syndr. 2005;40(5):538-544.
49. Rohrbach J, Stickel F, Schmid P, Thormann W, Kovari H, Scherrer A, et al. Changes in biomarkers of liver disease during successful combination antiretroviral therapy in HIV-HCV-coinfected individuals. Antivir Ther. 2014;19(2):149-159.
50. Resino S, Bellón JM, Asensio C, Micheloud D, Miralles P, Vargas A, et al. Can serum hyaluronic acid replace simple non-invasive indexes to predict liver fibrosis in HIV/Hepatitis C coinfected patients?. BMC Infect Dis. 2010;10:244.
51. Kelleher TB, Mehta SH, Bhaskar R, Sulkowski M, Astemborski J, Thomas DL, et al. Prediction of hepatic fibrosis in HIV/HCV co-infected patients using serum fibrosis markers: the SHASTA index. J Hepatol. 2005;43(1):78-84.
52. Sanvisens A, Serra I, Tural C, Tor J, Ojanguren I, Barluenga E, et al. Hyaluronic acid, transforming growth factor-beta1 and hepatic fibrosis in patients with chronic hepatitis C virus and human immunodeficiency virus co-infection. J Viral Hepat. 2009;16(7):513-518.
53. Larrousse M, Laguno M, Segarra M, De Lazzari E, Martinez E, Blanco JL, et al. Noninvasive diagnosis of hepatic fibrosis in HIV/HCV-coinfected patients. J Acquir Immune Defic Syndr. 2007;46(3):304-311.

54. Sowa J-P, Atmaca Ö, Kahraman A, Schlattjan M, Lindner M, Sydor S, et al. Non-invasive separation of alcoholic and non-alcoholic liver disease with predictive modeling. PLoS One 2014;9(7):e101444. doi:10.1371/journal.pone.0101444.
55. Stickel F, Poeschl G, Schuppan D, Conradt C, Strenge-Hesse A, Fuchs FS, et al. Serum hyaluronate correlates with histological progression in alcoholic liver disease. Eur J Gastroenterol Hepatol. 2003;15(9):945-950.
56. Tran A, Hastier P, Barjoan EM, Demuth N, Pradier C, Saint-Paul MC, et al. Non invasive prediction of severe fibrosis in patients with alcoholic liver disease. Gastroenterol Clin Biol. 2000;24(6-7):626-630.
57. Naveau S, Raynard B, Ratziu V, Abella A, Imbert-Bismut F, Messous D, et al. Biomarkers for the prediction of liver fibrosis in patients with chronic alcoholic liver disease. Clin Gastroenterol Hepatol. 2005;3(2):167-174.
58. Pares A, Deulofeu R, Gimenez A, Caballería L, Bruguera M, Caballería J, et al. Serum hyaluronate reflects hepatic fibrogenesis in alcoholic liver disease and is useful as a marker of fibrosis. Hepatology. 1996;24(6):1399-1403.
59. Nyberg A, Lindqvist U, Engstrom-Laurent A. Serum hyaluronan and aminoterminal propeptide of type III procollagen in primary biliary cirrhosis: relation to clinical symptoms, liver histopathology and outcome. J Intern Med. 1992;231(5):485-491.
60. Guechot J, Poupon RE, Giral P, Balkau B, Giboudeau J, Poupon R. Relationship between procollagen III aminoterminal propeptide and hyaluronan serum levels and histological fibrosis in primary biliary cirrhosis and chronic viral hepatitis C. J Hepatol. 1994;20(3):388-393.
61. Remmel T, Remmel H, Salupere V. Aminoterminal propeptide of type III procollagen and hyaluronan in patients with primary biliary cirrhosis: markers of fibrosis in primary biliary cirrhosis. J Gastroenterol Hepatol. 1996;11(11):1016-1020.
62. Farkkila M, Rautiainen H, Karkkainen P, Karvonen AL, Nurmi H, Niemela O. Serological markers for monitoring disease progression in noncirrhotic primary biliary cirrhosis on ursodeoxycholic acid therapy. Liver Int. 2008;28(6):787-797.
63. Corpechot C, Poujol-Robert A, Wendum D, Galotte M, Chrétien Y, Poupon RE, et al. Biochemical markers of liver fibrosis and lymphocytic piecemeal necrosis in UDCA-treated patients with primary biliary cirrhosis. Liver Int 2004;24(3):187-193.
64. Corpechot C, Carrat F, Poujol-Robert A, Gaouar F, Wendum D, Chazouillères O, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology. 2012;56(1):198-208.
65. Nyberg A, Engstrom-Laurent A, Loof L. Serum hyaluronate in primary biliary cirrhosis--a biochemical marker for progressive liver damage. Hepatology. 1988;8(1):142-146.
66. Kobayashi H, Horikoshi K, Yamataka A, Yamataka T, Okazaki T, Lane GJ, et al. Hyaluronic acid: a specific prognostic indicator of hepatic damage in biliary atresia. J Pediatr Surg. 1999;34(12):1791-1794.
67. Hasegawa T, Sasaki, Kimura T, Hoki M, Okada A, Mushiake S, et al. Measurement of serum hyaluronic acid as a sensitive marker of liver fibrosis in biliary atresia. J Pediatr Surg. 2000;35(11):1643-1646.
68. Crawford DH, Murphy TL, Ramm LE, Fletcher LM, Clouston AD, Anderson GJ, et al. Serum hyaluronic acid with serum ferritin accurately predicts cirrhosis and reduces the need for liver biopsy in C282Y hemochromatosis. Hepatology. 2009;49(2):418-425.
69. Legros L, Bardou-Jacquet E, Latournerie M, Guillygomarc'h A, Turlin B, Le Lan C, et al. Non-invasive assessment of liver fibrosis in C282Y homozygous HFE hemochromatosis. Liver Int. 2015;35(6):1731-1738.
70. Wyatt HA, Dhawan A, Cheeseman P, Mieli-Vergani G, Price JF. Serum hyaluronic acid concentrations are increased in cystic fibrosis patients with liver disease. Arch Dis Child. 2002;86(3):190-193.
71. Pereira TN, Lewindon PJ, Smith JL, Murphy TL, Lincoln DJ, Shepherd RW, et al. Serum markers of hepatic fibrogenesis in cystic fibrosis liver disease. J Hepatol. 2004;41(4):576-583.