The usefulness of non-invasive liver stiffness measurements in predicting clinically significant portal hypertension in cirrhotic patients: Korean data

Won Ki Hong¹, Moon Young Kim¹, Soon Koo Baik¹, Seung Yong Shin¹, Jung Min Kim¹, Yong Seok Kang¹, Yoo Li Lim¹, Young Ju Kim¹, Youn Zoo Cho¹, Hye Won Hwang¹, Jin Hyung Lee¹, Myeong Hun Chae¹, Hyoun A Kim¹, Hye Won Kang¹, and Sang Ok Kwon¹

¹Departments of Internal Medicine and ²Radiology, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Korea

Background/Aims: Liver stiffness measurement (LSM) has been proposed as a non-invasive method for estimating the severity of fibrosis and the complications of cirrhosis. Measurement of the hepatic venous pressure gradient (HVPG) is the gold standard for assessing the presence of portal hypertension, but its invasiveness limits its clinical application. In this study we evaluated the relationship between LSM and HVPG, and the predictive value of LSM for clinically significant portal hypertension (CSPH) and severe portal hypertension in cirrhosis.

Methods: LSM was performed with transient elastography in 59 consecutive cirrhotic patients who underwent hemodynamic HVPG investigations. CSPH and severe portal hypertension were defined as HVPG ≥10 and ≥12 mmHg, respectively. Linear regression analysis was performed to evaluate the relationship between LSM and HVPG. Diagnostic values were analyzed based on receiver operating characteristic (ROC) curves.

Results: A strong positive correlation between LSM and HVPG was observed in the overall population ($r^2=0.496$, $P<0.0001$). The area under the ROC curve (AUROC) for the prediction of CSPH (HVPG ≥10 mmHg) was 0.851, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for an LSM cutoff value of 21.95 kPa were 82.5%, 73.7%, 86.8%, and 66.7%, respectively. The AUROC at prediction of severe portal hypertension (HVPG ≥12 mmHg) was 0.877, and the sensitivity, specificity, PPV, and NPV at LSM cutoff value of 24.25 kPa were 82.9%, 70.8%, 80.6%, and 73.9%, respectively.

Conclusions: LSM exhibited a significant correlation with HVPG in patients with cirrhosis. LSM could be a non-invasive method for predicting CSPH and severe portal hypertension in Korean patients with liver cirrhosis. (Clin Mol Hepatol 2013;19:370-375)

Keywords: Portal hypertension; Liver stiffness measurement; Cirrhosis

Abbreviations:

AUROC, areas under ROC curves; CSPH, Clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value; TE, transient elastography

Corresponding author: Moon Young Kim

Department of Internal Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 220-701, Korea

Tel. +82-33-741-1225, Fax. +82-33-741-1228

E-mail; drkimmy@yonsei.ac.kr

Received: Aug. 16, 2013 / Revised: Aug. 21, 2013 / Accepted: Aug. 29, 2013

Copyright © 2013 by The Korean Association for the Study of the Liver

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
INTRODUCTION

The prognosis and management of chronic liver diseases strongly depend on the severity of portal hypertension. Measurement of the hepatic venous pressure gradient (HVPG) is the gold standard for the assessment of the presence of portal hypertension and correlates with the occurrence of its complications in patients with cirrhosis. However, HVPG measurements are invasive, relatively expensive and available only in specialized centers with well-trained operators. Transient elastography (TE, Fibroscan®, Echosens, France) is a method that allows the measurement of liver stiffness. TE can be performed in the outpatient clinic with immediate results and excellent reproducibility. TE has been proposed as a non-invasive method for the prediction of the severity of fibrosis and the complication of cirrhosis. An liver stiffness measurement (LSM) value above 14.6 kPa diagnosed cirrhosis with 0.79 sensitivity and 0.95 specificity in a large cohort of patients with various causes of chronic liver diseases. Several studies have demonstrated that TE may represent a rapid and non-invasive method for predicting the presence of clinically significant (HVPG ≥10 mmHg) or severe (HVPG ≥12 mmHg) portal hypertension. However, LSM exhibited a relatively weak correlation with HVPG ≥12 mmHg, likely because of the increasing relevance of extrahepatic factors in the progression of portal hypertension such as increases in portal blood flow. However, a similar study of Korean data are lacking. In this study, we evaluated the relationship between LSM and HVPG, and the predictive value of LSM for clinical significant portal hypertension and severe portal hypertension in cirrhosis.

PATIENTS AND METHODS

Patients

Fifty-nine consecutive patients with cirrhosis (48 men and 11 women, mean age 49.5±8.9; age range 29-69 years) underwent HVPG measurement between February 1, 2009 and February 1, 2010 upon referral to the hemodynamic laboratory of our institution. All patients had previous histopathological confirmation of cirrhosis (METAVIR F4) or a diagnosis of cirrhosis suspected on the basis of standard clinical, ultrasonographic, and biochemical parameters. Exclusion criteria were an age younger than 19 or older than 75 years, shock status requiring a vasopressor, active infection (e.g., spontaneous bacterial peritonitis), acute renal failure of any cause, hepatocellular carcinoma or a history of another primary malignancy within 3 years, clinically relevant coronary artery disease (NYHA functional angina classification III/IV), congestive heart failure NYHA III/IV, clinically relevant cardiomyopathy, history of myocardial infarction in the past 1 year, poorly controlled hypertension (blood pressure >150/100) mmHg, transaminases above tenfold the upper limit of normal, ongoing antiviral therapy, the use of vasoactive drugs, including beta-blockers, diuretics, and anti-inflammatory drugs, pregnancy or lactation, involvement in another study within 90 days, and medical or psychological conditions that would not permit the subject to complete the study or sign informed consent. The study protocol was approved by the Institutional Review Board for Human Research at the Yonsei University Wonju Severance Christian Hospital (Wonju, Republic of Korea). The nature of the study was explained to all patients, each of whom provided written informed consent before the beginning of the study, in accordance with the principles of the Declaration of Helsinki (revision of Edinburgh, 2000).

Transient elastography

After an overnight fasting, all patients underwent a complete abdominal ultrasonography examination in the morning. Immediately following the examination, TE was performed by two experienced operators. The Fibroscan device (Fibroscan®, Echosens, France) consists of a 3.5 MHz ultrasound transducer M probe mounted on the axis of a vibrator. Mild amplitude and low-frequency vibrations (50 Hz) are transmitted to the liver tissue, inducing an elastic shear wave that propagates through the underlying liver tissue. TE was performed as previously described on the right lobe of the liver; in the intercostal space with the patient lying in dorsal decubitus with the right arm at maximal abduction. The operator, assisted by an ultrasonic time-motion image, located a liver portion at least 6 cm thick and free of large vascular structures and the gallbladder. Ten successful measurements were performed on each patient. The success rate was calculated as the ratio of the number of successful measurements over the total number of acquisitions. Only LSM with an interquartile range ≤30% of the median value and a success rate of at least 60% were considered reliable. Results are expressed in kilopascals (kPa) and the median value was used a representative of LSM.

http://www.e-cmh.org http://dx.doi.org/10.3350/cmh.2013.19.4.370
Measurements of HVPG

After an overnight fast, the HVPG was measured. The right hepatic vein was catheterized percutaneously through the femoral vein, and the pressures in both the wedged and the free positions were recorded with a 7-F balloon-tipped catheter (Arrow Deutschland, Postfach Erding, Germany). In case that shunt was observed in right hepatic vein, HVPG was measured in middle hepatic vein. All measurements were performed at least in triplicate, and permanent tracings were obtained on a multichannel recorder. HVPG was determined by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure. An examiner (Y.J.K.) with 12 years of experience with HVPG measurement performed all HVPG procedures. Clinically significant portal hypertension (CSPH) was defined as an HVPG ≥10 mmHg according a consensus definition. Severe portal hypertension was defined as an HVPG ≥12 mmHg.

Laboratory parameters

Laboratory Parameters were obtained in all patients on the day of HVPG measurement and included serum albumin, bilirubin, alanine aminotransferase, aspartate aminotransferase, platelet count, hemoglobin, hematocrit, white blood cell, International Normalized Ratio (INR), blood urea nitrogen, creatinine, electrolyte, and C-reactive protein. The model for end-stage liver disease (MELD) and the Child-Pugh score were calculated.

Statistical analysis

Statistical analyses performed using SPSS 18.0 for Windows. All results are expressed as mean±standard deviation (SD). Linear regression analyses were calculated according to the least squares methods. P-values less than 0.05 were considered statistically significant. The statistical significance of inter-group differences was evaluated by the means of the spearman rank correlation coefficient. The relationship between sensitivity and specificity of LSM at different cutoff points; as a predictor of patients with HVPG ≥10 mmHg or patients with HVPG ≥12 mmHg was evaluated by receiver operating characteristic (ROC) curves. Optimal liver stiffness cutoff values were selected on the basis of sensitivity, specificity, and positive and negative predictive values.

RESULTS

General characteristics of the patients

The characteristics of the patients are summarized in Table 1. The etiology of cirrhosis was classified as alcohol (36, 61.0%), hepatitis B virus (13, 22.0%), alcohol with hepatitis B virus (5, 8.5%), alcohol with hepatitis C virus (2, 3.4%), and cryptogenic cirrhosis (3, 5.1%). The mean Child-Pugh and MELD scores were 6.5±1.8 and 9.6±3.7 (range 6-21), respectively. Mean HVPG and LSM were 13.1±5.2 mmHg (range 5-24) and 26.5±23.6 kPa (range 5.4-75.0), respectively.

Relationship between HVPG and LSM

Considering the whole patient population, a statistically significant positive correlation between HVPG and LSM was found (Fig. 1). Figure 1A demonstrates significant linear correlation between
HVPG and LSM ($r^2=0.496$, $P<0.05$). In patients with HVPG ≥10 mmHg or ≥12 mmHg, there was a statistically significant correlation with LSM ($r^2=0.297$, $P<0.05$ and $r^2=0.192$, $P=0.05$, respectively) (Fig. 1B and 1C). However, in case of HVPG ≥12 mmHg, the correlation was relatively weak compared with that of the HVPG ≥10 mmHg group.

**Diagnostic value of LSM for the non-invasive prediction of clinically significant portal hypertension**

Figure 2 presents the ROC curve of LSM for the prediction of CSPH. In case of HVPG ≥10 mmHg, the area under the ROC curves (AUROC) was 0.851 (95% confidence index 0.752-0.949). In cases of HVPG ≥12 mmHg, the AUROC was 0.877 (95% confidence index 0.792-0.962). Based on the ROC curves, different cutoff values for LSM were determined. An LSM ≥21.95 kPa exhibited a positive predictive value (PPV) of 86.8% and a negative predictive value (NPV) of 73.7% for the prediction of patients with HVPG ≥10 mmHg. An LSM ≥24.25 kPa exhibited a PPV of 80.6% and an NPV of 73.9% with a sensitivity of 82.9% and a specificity of 70.8% for the prediction of patients with HVPG ≥12 mmHg.

**DISCUSSION**

The prognosis and management of chronic liver diseases strong-
ly depend on the severity of portal hypertension. Therefore, the assessment of portal hypertension is one of the most important steps in the management of chronic liver disease. The best method to diagnose portal hypertension is the direct measurement of portal pressure. HVPG is currently the gold standard for the diagnosis of intrahepatic portal hypertension. In healthy individuals, HVPG is below 5 mmHg. An HVPG greater than 5 mmHg is suggestive of the presence of portal hypertension, but the complications related to portal hypertension, such as ascites or variceal bleeding, tend to appear if HVPG ≥10 mmHg. Moreover, the presence of severe portal hypertension (HVPG ≥24.25 kPa) could be suspected when a cutoff value is lower, demonstrating that portal hypertension is only partially caused by the amount of fibrosis.

Although HVPG measurement is a safe procedure, it is considered as a relatively invasive method. Therefore, the development of new non-invasive markers of portal hypertension is encouraged. From the initial report of the new technique to quantify the amount of liver fibrosis by LSM using TE, many studies have validated this method in the diagnosis of liver fibrosis and cirrhosis. A few studies demonstrated the good correlation between liver stiffness and HVPG. In these studies, LSM can diagnose clinically significant portal hypertension with an AUROC varying between 0.76 and 0.99. However, the problem is that the cut-off value for clinically significant portal hypertension is variable, between 13.6 kPa and 34.9 kPa. These differences may be due to the heterogeneity of the studied population and different etiologies. Liver stiffness is more elevated in alcoholic liver disease compared to viral liver disease. The optimal cut-off values are higher in the alcoholic group than in the hepatitis C virus infected group (34.9 kPa vs. 20.5 kPa). It suggests that the LSM values must be closely interpreted according to the cause of the liver disease.

Furthermore, liver stiffness is very well correlated with HVPG up to values of 10-12 mmHg, but above these values the correlation is lower, demonstrating that portal hypertension is only partially caused by the amount of fibrosis.

In our study, the main result is that LSM is strongly correlated with HVPG and accurately predicts the presence of clinically significant portal hypertension in patients with cirrhosis in a Korean population. Interestingly, in patients with HVPG ≥10 mmHg or ≥12 mmHg, there was a statistically significant correlation with LSM (r²=0.297, P<0.0001 and r²=0.192, P=0.009, respectively). With a cutoff of LSM ≥21.95 kPa, the NPV and PPV for the diagnosis of CSH (HVPG ≥10 mmHg) were 66.7% and 82.5%, respectively. Moreover, the presence of severe portal hypertension (HVPG ≥12 mmHg) could be suspected when a cutoff value ≥24.25 kPa was reached, with an NPV and PPV of 73.9% and 82.9%, respectively. In our study, the cutoff of LSM for the diagnosis of CSH was different from previous reports indicating cutoff values of 12.5 kPa, 13.6 kPa, and 14.5 kPa. Because most of our study population exhibited alcoholic cirrhosis, the cutoff values may higher than previous reports. As mentioned previously, liver stiffness is more elevated in alcoholic liver disease compared with viral liver disease. The major limitations of this study are the small sample size and the fact that the cirrhosis has not been confirmed by liver biopsy in all the patients. However, this is the first Korean study of a relationship between LSM and HVPG. Based on this study, further carefully designed studies will be conducted in the future.

In summary, LSM exhibited significant correlation with HVPG in patients with cirrhosis. LSM could be a non-invasive method to predict clinically significant and severe portal hypertension in patients with liver cirrhosis in Korea.

Acknowledgments

This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare, (HI10C2020).

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Suk KT, Baik SK, Yoon JH, Cheong JY, Paik YH, Lee CH, et al. Revision and update on clinical practice guideline for liver cirrhosis. Korean J Hepatol 2012;18:1-21.
2. Kim JN, Sohn KM, Kim MY, Suk KT, Jeong SW, Jung HE, et al. Relationship between the hepatic venous pressure gradient and first variceal hemorrhage in patients with cirrhosis: a multicenter retrospective study in Korea. Clin Mol Hepatol 2012;18:391-396.
3. Kim MY, Baik SK, Yea CJ, Lee IY, Kim HJ, Park KW, et al. Hepatic venous pressure gradient can predict the development of hepatocellular carcinoma and hyponatremia in decompensated alcoholic cirrhosis. Eur J Gastroenterol Hepatol 2009;21:1241-1246.
4. Kim MY, Baik SK. Pathophysiology of portal hypertension, What’s new? Korean J Gastroenterol 2010;56:129-134.
5. Kim MY, Baik SK, Suk KT, Yea CJ, Lee IY, Kim JW, et al. Measurement of hepatic venous pressure gradient in liver cirrhosis: Relationship with the status of cirrhosis, varices, and ascites in Korea. Korean J Hepatol 2008;14:150-158.
6. Kim MY, Baik SK, Lee SS. Hemodynamic alterations in cirrhosis and
portal hypertension. Korean J Hepatol 2010;16:347-352.

7. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48-54.

8. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-350.

9. Foucher J, Chanteloup E, Vergniol J, Castéa L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403-408.

10. Kazemi F, Kettaneh A, N’kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, et al. Liver stiffness measurements selects patients with cirrhosis at risk of bearing large esophageal varices. J Hepatol 2006;45:230-235.

11. Ganne-Carrié N, Ziol M, de Ledinghen V, Douvin C, Marcellin P, Castera L, et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. Hepatology 2006;44:1511-1517.

12. Carrion JA, Navasa M, Bosch J, Bruguera M, Gilabert R, Forns X. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transpl 2006;12:1791-1798.

13. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290-1297.

14. Bureau C, Metivier S, Peron JM, Selves J, Robic MA, Gourraud PA, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment Pharmacol Ther 2008;27:1261-1268.

15. Lemoine M, Katsahian S, Ziol M, Nahon P, Ganne-carrie N, Kazemi F, et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. Aliment Pharmacol Ther 2008;28:1102-1110.

16. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994;20:15-20.

17. Sandrin L, Tanter M, Gennisson JL, Catheline S, Fink M. Shear elasticity probe for soft tissues with 1-D transient elastography. IEEE Trans Ultrason Ferroelectr Freq Control 2002;49:436-446.

18. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705-1713.

19. Bosch J, Mastai R, Kravetz D, Navasa M, Rodés J. Hemodynamic evaluation of the patient with portal hypertension. Semin Liver Dis 1986;6:309-317.

20. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 2004;39:280-282.

21. de Franchis R. Updating consensus in portal hypertension: report of the Baveno III consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension. J Hepatol 2000;33:846-852.

22. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decomposition in patients with compensated cirrhosis. Gastroenterology 2007;133:481-488.

23. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Eng J Med 2005;353:2254-2261.

24. de Franchis R; Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762-768.

25. Choi YJ, Baik SK, Park DH, Kim MY, Kim HS, Lee DK, et al. Comparison of Doppler ultrasonography and the hepatic venous pressure gradient in assessing portal hypertension in liver cirrhosis. J Gastroenterol Hepatol 2003;18:424-429.

26. Sánchez-Conde M, Montes-Ramírez ML, Miralles P, Alvarez JM, Bellón JM, Ramirez M, et al. Comparison of transient elastography and liver biopsy for the assessment of liver fibrosis in HIV/hepatitis C virus-coinfected patients and correlation with noninvasive serum markers. J Viral Hepat 2010;17:280-286.

27. Castera L, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. J Hepatol 2012;56:696-703.

http://www.e-cmh.org  http://dx.doi.org/10.3350/cmh.2013.19.4.370