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Original Research

# Association between Liver Stiffness and Gastro-Esophageal Varices in Chronic Liver Diseases

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**Abstract**

***Objective:*** Elastography is a non-invasive method used to estimate the extent of liver fibrosis, measured as liver stiffness (LS). We examined the relationship between gastro-esophageal varices and LS and the value of LS for prediction of esophageal varices and varices bleeding.

***Methods:*** From 2014 to 2016, we conducted a retrospective study of 138 patients with chronic liver diseases, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, primary biliary cholangitis, and viral hepatitis. LS was measured by transient elastography, with the median values being considered the final result.

***Results:*** In 63 cirrhosis cases, LS was highest in alcoholic cirrhosis. In the 89 cases who underwent endoscopy, a significant correlation between LS and the presence or absence of esophageal varices was confirmed (present, 38.2 ± 22.6 kPa; absent, 14.3 ± 11.2 kPa; $P < 0.0001$), while there were no significant differences between the two groups in terms of the form and red color sign of varicose veins. LS was significantly higher in patients with a history

of bleeding compared to those without (bleeding, 42.1 ± 26.7 kPa; no bleeding, 23.0 ± 19.0 kPa; *P* = 0.0047). In addition, LS of multiple bleeding varices tended to be higher than that of a single bleeding varicose vein, although this difference was not statistically significant.

***Conclusion:*** The LS index is useful for diagnosing gastro-esophageal varices and as an indicator of the risk of bleeding or intractability. However, the cut-off values differed among the various liver diseases, so it is important to determine cut-off values for each separate etiology.

**Keywords**

Liver stiffness; gastro-esophageal varices; bleeding; platelet count

## 1. Introduction

In chronic liver disease, the diagnosis of hepatic fibrosis grade is important for predicting the risk of liver cancer, and determining the treatment methodology. Liver biopsy is currently the gold standard for the assessment of liver fibrosis; however, this is a high-risk examination, especially for liver diseases with reduced platelet counts and prolonged prothrombin time. Transient elastography (TE) utilizing liver elastography principles is a simple and non-invasive technique for the measurement of liver stiffness (LS). LS determined by TE has been reported to show correlations with histopathologic liver fibrosis in various liver diseases, such as viral liver disease and nonalcoholic fatty liver disease (NAFLD) [1-3], making it possible to estimate fibrosis based on liver elasticity. TE measures elasticity in terms of the elastic modulus (kPa), with higher kPa values indicating greater progression of fibrosis. Although the elasticity cut-off reported in the literature varies, 7 kPa or higher is considered to indicate significant fibrosis, and 10.1–17.6 kPa or higher is considered to indicate liver cirrhosis [1, 4].

Gastro-esophageal varices are among the three major complications of cirrhosis, resulting largely from portal hypertension, a key factor in the prognosis of liver cirrhosis. Therefore, in patients with chronic liver disease, regular use of upper gastrointestinal endoscopy is necessary to check for the presence of varicose veins, their size (form; F) and red color (RC) sign [5]. Management of varices that present the possibility of bleeding requires the use of drugs or endoscopic treatment. However, upper gastrointestinal endoscopy imposes a burden, and its optimal usage frequency is unclear. In addition, there are some uncertainties regarding the stage at which an endoscopic examination is needed and the risk factors of varices bleeding. The RC sign is insufficient for predicting risk markers. Recently, the European Liver Congress issued a statement that the combination of LS and blood platelet counts was a useful criterion for endoscopic assessment of gastro-esophageal varices [6].

In the present study, we examined the relationship between gastro-esophageal varices and LS by TE. Specifically, we investigated the potential of LS as a predictive marker of the presence of

varices and bleeding risk.

## 2. Material and Methods

We conducted a retrospective study of 138 patients who underwent TE evaluations at our hospital (Tokyo Women's Medical University Hospital, Tokyo, Japan) between November 2014 and October 2016 for the following liver diseases: NAFLD (n = 48); alcoholic liver disease (n = 34); primary biliary cholangitis (PBC) (n = 170; viral hepatitis (n = 21 comprising hepatitis C [n = 16] and hepatitis B [n = 5 patients]; other (n = 18; idiopathic portal hypertension, autoimmune hepatitis, etc.). We had performed a liver biopsy in 97 of these patients to confirm the degree of fibrosis. The diagnosis of liver cirrhosis was determined by liver biopsy F4 or clinical diagnosis (varicose veins, computed tomography signs of liver atrophy and surface imperfection) [7, 8].

Regarding the diagnosis of underlying liver diseases, NAFLD was identified utilizing the established practice guidelines for the diagnosis of NASH/NAFLD [9]. Alcoholic liver disorder was diagnosed according to the diagnostic criteria [10] of the Japanese Society for Biomedical Research on Alcohol. Viral hepatitis was diagnosed on the basis of HBs antigen-positive or HCV RNA-positive tests (HBs QT abbot and Abbott RealTime HCV (ART) assay. Abbott Laboratories, North Chicago, IL, USA). PBC was diagnosed if at least two of the following internationally accepted criteria were met: biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation, presence of serum anti-mitochondrial antibodies, histological evidence of nonsuppurative destructive cholangitis, and destruction of interlobular bile ducts [11].

We performed upper gastrointestinal endoscopy in 89 patients and examined the presence or absence of gastro-esophageal varices and endoscopic findings of varices (form, RC sign). Endoscopic treatment of varicose veins was conducted in 31 patients. Of these, 15 patients received treatment for bleeding of varicose veins, and 16 underwent hemostatic therapy because of RC without bleeding.

TE was performed on all 138 patients using a FibroScan (Echosens, Paris, France) and an ultrasound transducer probe mounted on the axis of a vibrator. The tip of the transducer probe was placed in the intercostal space at the level of the right midaxillary line and at the center of the right liver lobe. The vibration transmitted from the vibrator toward the tissue induces an elastic shear wave that is propagated through the tissue. These propagations are followed by pulse-echo ultrasound acquisitions, and their velocity, which is directly related to tissue stiffness, is measured [12]. Ten successive images were acquired for each patient and the results were expressed as kPa, using the median of 10 valid acquisitions. The success rate was calculated as the ratio of the number of successful acquisitions to the total number of acquisitions, and a success rate of at least 60% or interquartile range of less than 30% was considered reliable. In this study, the two examinations, LS measurements by TE and upper GI endoscopy, were performed within 6 months.

For each patient, a complete history was obtained, and physical examination was performed, followed by measurement of the following laboratory parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, hepatitis B serology (hepatitis B surface

antigen, antibodies to hepatitis B surface antigen), hepatitis C serology (hepatitis C virus antibody and/or HCV RNA), and autoantibodies (anti-nuclear and anti-mitochondrial antibodies). All liver biopsy specimens were examined by the same pathologist (EH).

Informed consent was obtained from all participants before enrollment in the study. The study protocol conformed to the ethical guidelines of the 2008 Declaration of Helsinki and was approved by our institution's research committee (approval number 4200).

### *2.1 Statistical analysis*

Statistical analysis was conducted using SPSS 12.0 software (SPSS, Chicago, IL, USA). Mean LS for various disease categories was expressed as mean ± standard deviations (SD), and the values were compared using the Mann–Whitney test. The diagnostic performance of the LS index was assessed using receiver-operating characteristic (ROC) curves. The probability of true positive (sensitivity) and true negative (specificity) assessment was determined for selected cut-off values, and the area under the ROC curve (AUROC) was calculated. *P*-values <0.05 were considered to indicate statistical significance.

## 3. Results

According to the underlying cause of liver disease causes, 138 patients were classified into the following five groups: NAFLD, alcoholic, viral hepatitis, PBC, and other liver diseases. Table 1 shows the overall LS, age, sex, blood data, and liver cirrhosis complication rate for each group. LS, including non-cirrhotic, was significantly higher in alcoholic liver disease and lower in NAFLD.

**Table 1** Clinical and laboratory findings in the study population.

| | All Patients (n=138) | NAFLD (n=48) | ALD (n=34) | HCV/HBV (n=16/5) | PBC (n=17) | Others (n=18) |
|---|---|---|---|---|---|---|
| **Age,y** | 56.7±16.7 | 50.2±17.8 | 60.9±12.4 | 67.1±13.1 | 61.7±12.1 | 49.1±19.2 |
| **Male gender,n(%)** | 71(51.4%) | 20(41.7%) | 24(70.6%) | 11(52.4%) | 5(29.4%) | 10(55.6%) |
| **Bilirubin,mg/dl** | 1.66±2.61 | 0.86±0.38 | 2.20±3.58 | 1.40±0.84 | 3.02±4.33 | 1.83±2.63 |
| **Albumin,g/dl** | 3.81±0.77 | 4.42±0.49 | 3.51±0.70 | 3.32±0.65 | 3.49±0.81 | 3.61±0.67 |
| **Platelet,$10^4$/μl** | 15.9±8.5 | 20.7±6.9 | 13.9±7.2 | 7.9±4.4 | 17.0±9.5 | 15.0±9.2 |
| **PT-INR** | 1.15±0.23 | 1.09±0.20 | 1.20±0.28 | 1.20±0.20 | 1.10±0.15 | 1.20±0.27 |
| **AST,U/l** | 51.9±36.3 | 51.3±34.0 | 54.3±38.2 | 57.0±33.1 | 46.6±30.7 | 48.1±48.1 |
| **ALT,U/l** | 53.9±50.1 | 69.8±52.8 | 45.0±38.9 | 47.1±46.8 | 33.8±19.0 | 54.8±73.2 |
| **ALP,U/l** | 316±214 | 236±74.2 | 299±204 | 353±176 | 539±337 | 305±217 |
| **γ-GTP,U/l** | 109±149 | 68.5±66.3 | 187±231 | 141±38.8 | 141±133 | 106±136 |
| **LC,n(%)** | 63(45.7%) | 8(16.7%) | 21(65.2%) | 17(85.7%) | 8(47.1%) | 9(50.0%) |
| **Child-Pugh A** | 34(24.6%) | 7(14.6%) | 10(29.4%) | 9(47.6%) | 3(17.6%) | 5(27.8%) |
| **B** | 22(15.9%) | 1(2.08%) | 7(20.6%) | 8(38.1%) | 3(17.6%) | 3(16.7%) |
| **C** | 7(5.07%) | 0(0.00%) | 4(11.8%) | 0(0.00%) | 2(11.8%) | 1(5.56%) |
| **Variceal bleeding history** | 20(14.5%) | 1(2.08%) | 10(29.4%) | 1(7.14%) | 2(11.8%) | 5(27.8%) |

Data are expressed as mean ± SD; NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease; PBC, primary biliary cholangitis.

However, since these data are affected by the complication rates of liver cirrhosis, we limited our analysis to the 63 patients with cirrhosis (23 patients diagnosed by liver biopsy, 40 patients by clinical data). Figure 1 shows the mean LS of each etiology group of patients with cirrhosis; alcoholic (n = 21) 48.1 ± 25.4 kPa; viral hepatitis (n = 17) 32.8 ± 18.6 kPa; NAFLD (n = 8) 28.0 ± 14.4 kPa; PBC (n = 8) 27.9 ± 15.0 kPa. LS was highest in the alcoholic cirrhosis group (Figure 1).

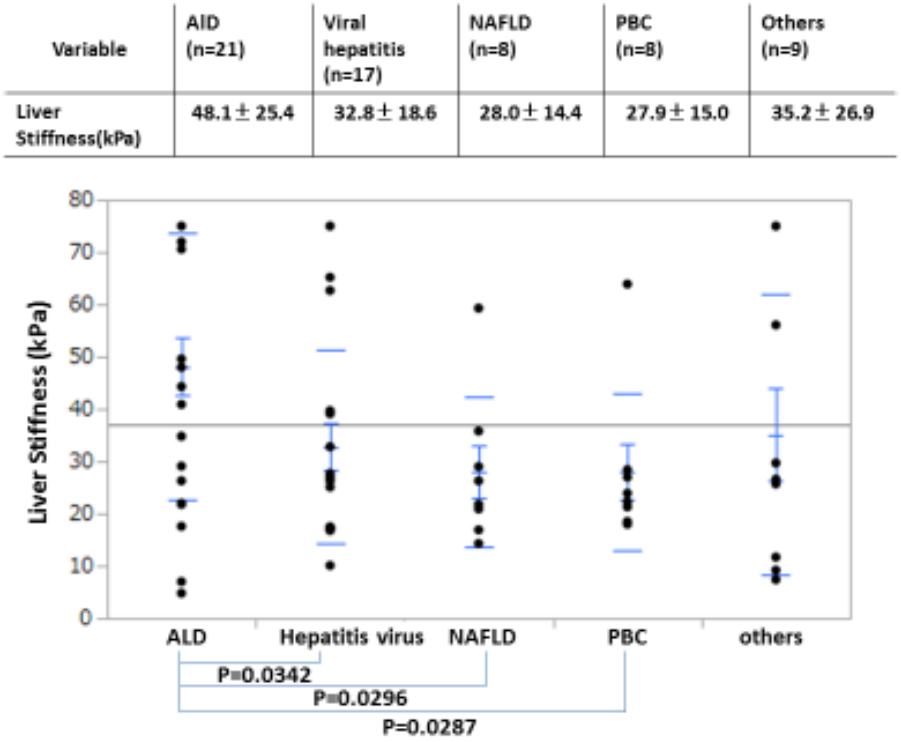


**Figure 1** Liver stiffness (LS) in patients with liver cirrhosis among several liver diseases. LS was highest among patients with alcoholic cirrhosis. Data are expressed as mean ± SD. ALD, alcoholic liver disease; NAFLD, Non-alcoholic fatty liver disease; PBC, primary biliary cholangitis.

There was no association between sex or age and LS. Regarding the relationship between Child–Pugh classification and LS, patients with Child–Pugh grades A, B and C had LS values of 16.8 ± 14.9 kPa, 40.0 ± 23.8 kPa, and 59.8 ± 24.1 kPa, respectively. These results indicated that LS was significantly associated with hepatic reserve function. A significant inverse correlation was observed between LS and platelet counts ($P < 0.0001$, $r = 0.5860$).

In the next study, we analyzed the relationship between endoscopic examination results and LS in the 89 patients who underwent this procedure. LS with gastro-esophageal varices was significantly higher than that in patients without gastro-esophageal varices (present, 38.2 ± 22.6 kPa; absent, 14.3 ± 11.2 kPa; $P < 0.0001$). With an optimal cut-off value for gastro-esophageal

varices of 21.8 kPa and AUROC was 0.849, with a sensitivity of 78.3% and specificity of 79.1% (Figure 2).

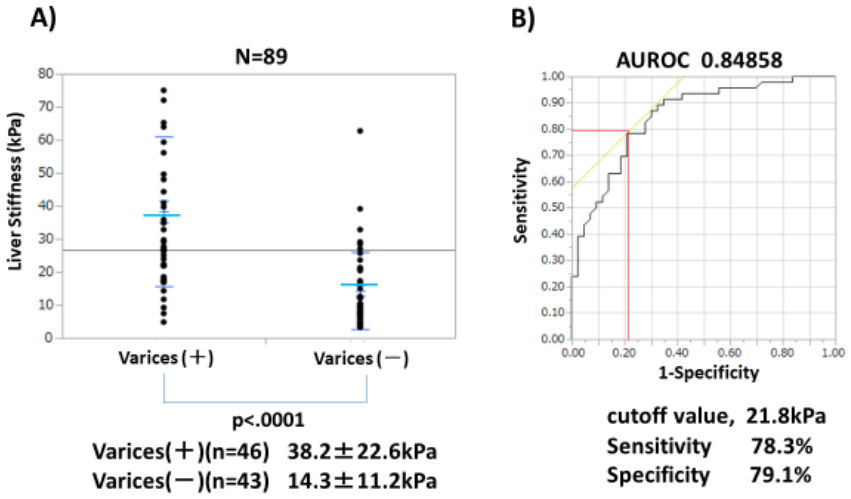


**Figure 2** A) Comparison of LS in patients with chronic liver diseases with and without esophageal varices. Data are expressed as mean ± SD. B) Diagnostic ability of LS for liver cirrhosis. Optimal cut-off value of LS was set at 21.8 kPa, with a sensitivity of 78.3% and specificity of 79.1%.

Next, the correlation of LS with platelet counts was assessed (Table 2).

**Table 2** Diagnosis of esophageal varices based on liver stiffness and platelet counts.

| | LS**<21.8kPa<br>N=44 | LS≥21.8kPa<br>N=45 |
|---|---|---|
| Plt*≥13.8x10$^4$/μl<br>n=39 | N=33<br>Varices(+ ) 2<br>Varices( - ) 31 | N=6<br>Varices(+ ) 3<br>Varices( - ) 3 |
| Plt<13.8x10$^4$/μl<br>n=50 | N=11<br>Varices(+ ) 8<br>Varices( - ) 3 | N=39<br>Varices(+ ) 33<br>Varices( - ) 6 |

Plt*, platelet count; LS**, liver stiffness

The optimal platelet count cut-off value for the diagnosis of gastro-esophageal varices of was set at 138,000/μl. Of the 33 patients with platelet counts ≥138,000/μl and LS <21.8 kPa, only two (6.1%) had gastro-esophageal varices. In contrast, of the 39 patients with LS ≥21.8 kPa and platelet counts <138,000/μl, gastro-esophageal varices were found in 33 patients (84.6%) (Table 1). These results indicate that the combination of LS and blood platelet counts has a high diagnostic ability for gastro-esophageal varices.

We compared the mean LS according to the presence or absence of varices in each liver disease. In alcoholic patients with varices, LS was significantly higher (49.4 ± 23.8 kPa) than in those without varices (13.8± 8.83 kPa; *P* = 0.0027). In NAFLD patients with varices, LS was higher (32.0 ± 17.2 kPa) than in patients without varices (10.2 ± 6.51 kPa; *P* = 0.0034). While LS was higher in patients with PBC and viral hepatitis, there were no significant differences in the mean index between those patients with and without varices (Figure 3).

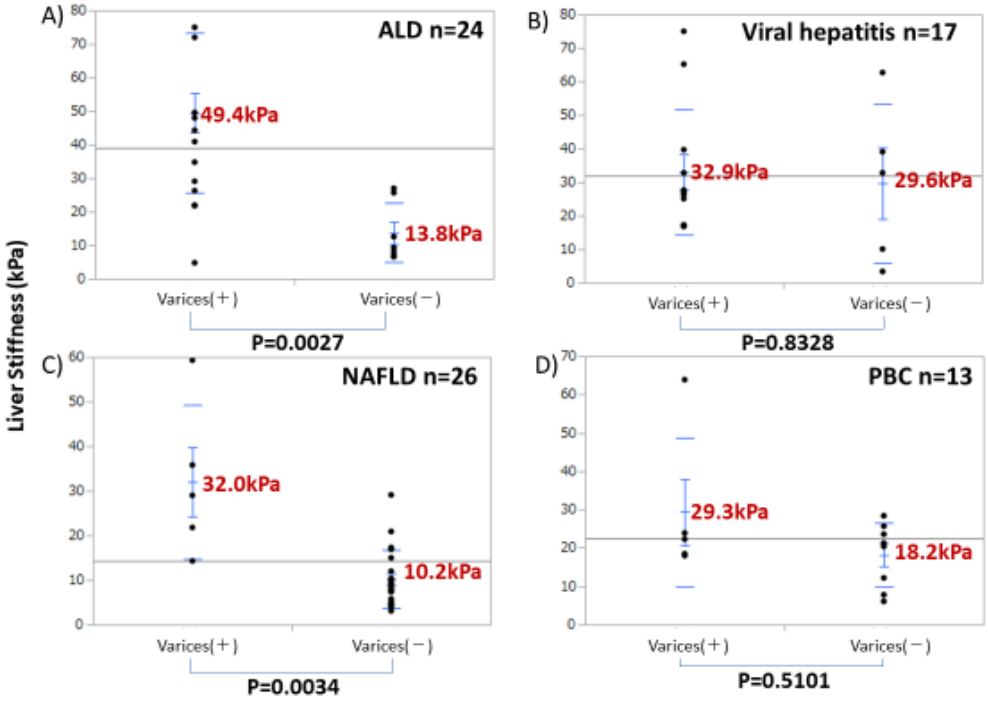


**Figure 3** Comparison of liver stiffness in patients with chronic liver diseases with and without esophageal varices in various liver diseases. A) Alcoholic liver disease (ALD), B) Chronic liver diseases with viral hepatitis, C) Non-alcoholic fatty liver disease (NAFLD), D) Primary biliary cholangitis (PBC).

Of 89 patients, 20 had a prior history of variceal bleeding. LS was significantly higher in those with a history of variceal bleeding (42.1 ± 26.7 kPa) than in those without (23.0 ± 19.0 kPa; *P* = 0.0047; Figure 4).

Using a LS cut-off value for variceal bleeding of 39.7 kPa, AUROC was 0.70870, with a sensitivity of 55.0% and specificity of 87.1%.

Regarding esophageal varices form (F), there were no significant differences among the three groups F1, F2, and F3. LS of the RC-positive group (n = 25) was 37.6 ± 23.3 kPa, while that of the RC-negative group (n = 21) was 38.9 ± 22.3 kPa; the difference was not significant.

A history of multiple variceal bleeding was confirmed in 12 patients (alcoholic liver disease, 6 patients; NAFLD, 1; PBC, 2; primary sclerosing cholangitis, 1; nodular regenerative hyperplasia, 1; idiopathic portal hypertension, 1). When the underlying diseases were limited to alcoholic liver disease, NAFLD, viral hepatitis and PBC, the number of cases of LS with multiple bleeding varices (n = 9) tended to be higher (52.9 kPa) than that of cases with single bleeding varices (n = 6; 31.2 kPa; *P* = 0.0844) (Figure 5).

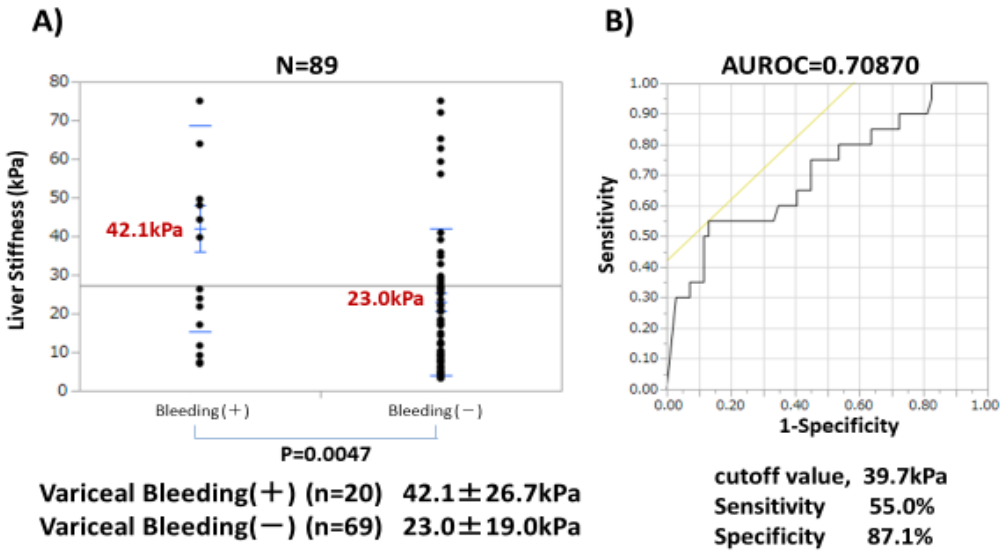


**Figure 4** A) Comparison of liver stiffness in chronic liver diseases with and without esophageal variceal bleeding. B) Diagnostic ability of liver stiffness for variceal bleeding. The optimal cut-off value of liver stiffness was set at 39.7 kPa, with a sensitivity of 55% and specificity of 89%.

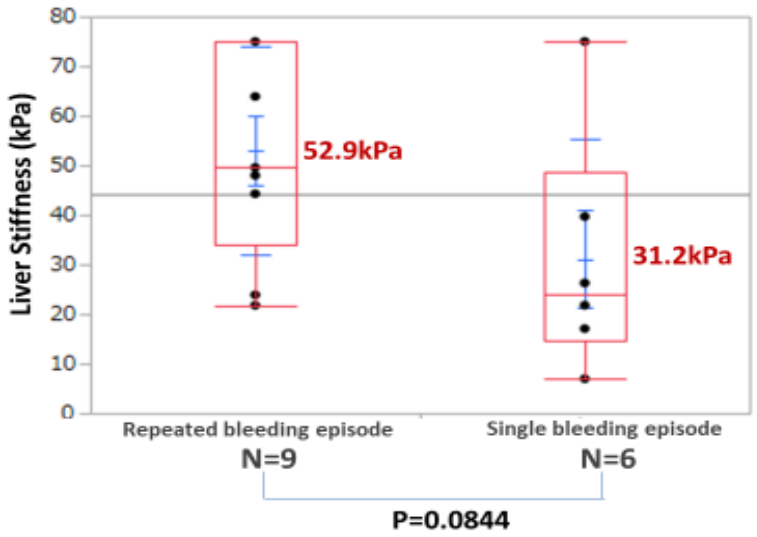


**Figure 5** Comparison of liver stiffness in patients with a single bleeding episode and those with repeated bleeding episodes.

## 4. Discussion

In patients with cirrhosis, bleeding from gastro-esophageal varices is a serious and potentially fatal event. Endoscopic examination is required to diagnose gastro-esophageal varices and determine adaptation to suitable treatment. In this study, we measured LS non-invasively by TE and retrospectively investigated the correlation between gastro-esophageal varices and LS.

First, in patients with cirrhosis, we compared LS among several liver diseases. LS was significantly higher in alcoholic cirrhosis than in other etiologies. The alcoholic cirrhosis group had a higher male ratio and older age. However, there was no correlation between LS and age or sex. Thus, we hypothesize that the differences in LS among etiologies is due to the histopathogenesis underlying the liver disease. Sporea et al. also reported higher LS in alcoholic cirrhosis patients (32.5 kPa) than that in viral cirrhosis patients (24.8 kPa) [13]. The progression of fibrosis in alcoholic cirrhosis exhibits a characteristic pattern that can be affected by increased LS. Alcoholic liver disease and NAFLD have similar pathological features, with small lobular inflammation around the central vein; however, the inflammation is more severe in alcoholic liver disease than in NAFLD. Sclerosing hyaline necrosis disease is a typical pathological change in alcoholic liver [13, 14]. In addition, acetaldehyde, an intermediate metabolite of ethanol, stimulates hepatic stellate cells directly, and the collagen fibers produced accumulate in the Disse space [15]. From these results, we speculate that these pathological differences induce the distinct pattern of fibrosis associated with alcoholic cirrhosis; similarly, differential gastro-esophageal varices development in different liver diseases is likely to be dependent on the pathogenesis.

The results of our study implicate LS as a diagnostic indicator of gastro-esophageal varices, with a sensitivity of 78.3% and specificity of 79.1% when the cut-off value for LS is set at 21.8 kPa. Of 33 patients with platelet counts $\geq$138,000/μl and LS <21.8 kPa, only two patients had esophageal varices (93.9% specificity). Thus, since patients with these conditions have a very low risk of gastro-esophageal varices, unnecessary endoscopy can be avoided. The particular advantage of these criteria is that they are noninvasive; therefore, the cost and complications of endoscopy can be eliminated. In accordance with our data, Franchis et al. (6) demonstrated that patients with platelet counts $\geq$150,000/μl and LS <20 kPa were at very low risk of developing esophageal varices.

However, the mean LS values varied when comparing LS based on the presence of varices in the each of the liver diseases, (Fig. 3). Due to insufficient patient numbers, we were unable to determine optimal cut-off values for the presence of varices in each liver disease; therefore, further investigations with larger study samples are necessary to determine cut-off values for each individual liver disease.

In addition, Ikarashi et al. reported differences in the optimal cut-off values of platelet counts for diagnosing LC between NAFLD and hepatitis C virus [16]. It is expected that further studies will clarify the optimal combination of platelet counts and LS for diagnosing gastro-esophageal varices in each liver disease.

In the PBC and viral hepatitis groups, there was no significant difference in LS in the presence or

absence of varices (Fig. 3). PBC, like idiopathic portal hypertension, is well known as a cause of non-cirrhotic portal hypertension [17]. In cases of non-cirrhotic portal hypertension, the prediction of gastro-esophageal varices by LS is difficult. Colina et al. found nodular regenerative hyperplasia (NRH), which might be associated with non-cirrhotic portal hypertension, in 43% of early-stage PBC patients [18]. In our study, two patients (with LS of 7.4 kPa and 11.7 kPa, respectively) were diagnosed with NRH by liver biopsy. In these two patients, LS was relatively low, although both were not only confirmed to have varices >F2, but also a history of variceal bleeding. Cases of viral hepatitis were few and hepatitis B virus and hepatitis C virus were mixed. Further studies with larger sample sizes are required to evaluate the separate optimal cut-off values for gastro-esophageal varices in patients with different forms of viral hepatitis.

Regarding the history of esophageal variceal bleeding, LS in patients with a history of bleeding was 42.1 ± 26.7 kPa compared to 20.1 ± 18.6 kPa in those without such a history ($P$ = 0.0003), thus indicating that LS is a useful marker of bleeding. If LS ≥40 kPa, endoscopy is required, as well as a short follow-up period. In an investigation of the relationship between LS and history of variceal bleeding, Foucher et al. reported a liver cut-off value of 62.7 kPa and AUROC of 0.88 for identifying a history of variceal bleeding [19].

There was no significant association between esophageal varices form or RC sign and LS. In 26 of 46 patients with esophageal varices, varix form and RC sign were assessed after their endoscopic treatment. Vizzutti et al. also reported a significant association between LS and the existence of esophageal varices; however, there was no correlation with the size (“form”) of the varix [20]. In contrast, Kazemi et al. demonstrated a significant association between LS and esophageal varices form [21].

In refractory cases with multiple bleeding varices, LS tended to be higher in alcoholic, NAFLD, viral, and PBC cases, even after endoscopic treatment. This is the first report regarding the relationship between refractory cases and LS, and our findings suggest that LS measurement might make it possible to identify patients with an increased risk of variceal bleeding that could not be previously determined by endoscopy.

However, there are some problems with this approach. It is difficult to measure LS in patients with ascites or obesity. In particular, in NAFLD patients with a BMI ≥28, LS has wide dispersion [22]. In addition, LS is known to be affected by inflammation, jaundice, and congestion, as well as liver fibrosis [23]. Therefore, these factors must be taken into consideration when analyzing the results of LS measurements.

It should be noted that a the single-center study design and the relatively sample size are limitations of this study. In addition, we focused on the risk of bleeding and repetitive bleeding. As far as we know, there are no reports on the relationship between repetitive bleeding and LS. In future studies, we plan to conduct multi-center trials using much larger samples sizes.

In conclusion, although an endoscopic form (F2 or higher) and RC-positive status are established risks for variceal bleeding and criteria for preventive therapy, evaluation of LS by a non-invasive method is not only effective for the diagnosis of esophageal varices, but also for bleeding risk

evaluation. In addition, patients with LS <21.8 kPa and platelet counts ≥138,000/μl have a low risk of gastro-esophageal varices, allowing endoscopy to be avoided. However, optimal cut-off values for LS and platelet counts for gastro-esophageal varices differ among the various liver diseases; Therefore, it is important to establish optimal cut-off values for each.

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**Author Contributions**

HY and MK thought study design and collected data. EH evaluated liver biopsy. SN and KT totally checked this study and paper.

**Competing Interests**

The authors have declared that no competing interests exist.

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