Hepatic venous pressure gradient and rebleeding risk of patients with nonalcoholic steatohepatitis cirrhosis after variceal bleeding

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Research Article

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Abstract

Background & Aims

Hepatic venous pressure gradient (HVPG) has a strong predictive value for variceal rebleeding in cirrhotic patients, but the accuracy of an HVPG may be compromised in nonalcoholic steatohepatitis (NASH) cirrhosis. This study aimed to evaluate the accuracy of an HVPG for predicting rebleeding in NASH cirrhosis after initial variceal bleeding.

Patients and Methods

Thirty-eight NASH cirrhosis patients and 82 hepatitis B virus (HBV) cirrhosis patients who experienced variceal bleeding for the first time were included in this study. We compared the HVPG levels in NASH cirrhosis and HBV cirrhosis. The prognostic value of an HVPG for variceal rebleeding was evaluated.

Results

Compared with HBV cirrhosis, NASH cirrhosis demonstrated a lower portal pressure (26.3 ± 6.1 vs. 30.1 ± 4.7; P<0.001), lower wedge hepatic venous pressure (24.1 ± 5.3 vs. 27.6 ± 5.5; P = 0.001) and lower HVPG (15.3 ± 3.8 vs. 18.0 ± 4.8; P = 0.003). HVPG was proven to have promising prognostic value among NASH cirrhosis patients (AUC = 0.82; P = 0.002). The optimal baseline HVPG threshold for predicting rebleeding in NASH cirrhosis was 17 mmHg. Multivariate analysis also indicated that an HVPG ≥17 mmHg was a significant predictor of variceal bleeding (HR 9.40; 95% CI 1.85-47.70; P = 0.007).

Conclusions

Patients with NASH cirrhosis had lower HVPG than those with HBV cirrhosis. However, the prevalence of rebleeding was similar between the two groups. HVPG measurement is still an accurate way to assess the risk of variceal rebleeding in NASH cirrhosis.

Introduction

Nonalcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated fatty liver disease, has become an important public health concern and has a global prevalence of 25% [1]. Nonalcoholic steatohepatitis (NASH) (a severe form of NAFLD typically characterized by lobular inflammation, ballooning degeneration and fibrosis) can progress to end-stage liver disease (such as cirrhosis and hepatocellular carcinoma) and eventually liver-related mortality [2,3,29]. Approximately 20% of patients with NASH will progress to cirrhosis and encounter cirrhosis-associated decompensation outcomes (e.g., variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, and ascites) [4,5]. Therefore, early identification of patients at high risk for cirrhosis-related complications is beneficial for prognosis in NASH cirrhosis.

Hepatic venous pressure gradient (HVPG) has a strong predictive value for staging cirrhotic portal hypertension and is the strongest predictor of complications of portal hypertension in cirrhosis [6,7,23]. An HVPG value >5 mmHg indicates portal hypertension, and a value >10 mmHg indicates clinically significant portal hypertension (CSPH), while an HVPG value of 20 mmHg or higher predicts a high incidence of active variceal hemorrhage at endoscopy and a high mortality [8,9]. Several studies have evaluated the capacity of an HVPG to correspond to liver-related complications, especially in viral and alcoholic cirrhosis, but few studies have focused on HVPG measurement in clinically decompensated NASH cirrhosis and its correlation with variceal rebleeding. The predictive value of an HVPG in previous investigations was controversial, and NASH patients had similar portal hypertensive complications at lower HVPG compared with other liver disease etiologies [6,24]. Under normal conditions, an HVPG greater than 10 mmHg predisposes patients to esophageal varical bleeding and other portal hypertension-related complications. However, an HVPG of no more than 10 mmHg in NASH may lead to the above-described complications [10,11]. On the other hand, a reduction in an HVPG in each stage of NASH fibrosis was observed compared to hepatitis C virus (HCV) disease [12,13], which raises the concern of whether an HVPG is accurate in predicting evaluating portal hypertensive complications in NASH cirrhosis.

Variceal bleeding is a life-threatening complication with a high rebleeding rate and mortality among portal hypertension-related events. Even if the first variceal bleeding is controlled, stricter means are needed to monitor and prevent rebleeding. Within the first days following an initial hemorrhage episode, the mortality rate reaches 20%, and the rebleeding rate is as high as 30-50% [30,31]. Therefore, we applied this study to compare portal and hepatic venous pressure among patients with NASH cirrhosis and HBV cirrhosis and to evaluate the accuracy of an HVPG for predicting variceal rebleeding and other clinical decompensation events.

Patients And Methods

Patients

Eighty-six NASH cirrhosis patients and 176 HBV (HBV) cirrhosis patients underwent transjugular intrahepatic portosystemic shunt (TIPS) due to variceal bleeding for the first time in three tertiary medical centers (Yuzhong Hospital of the Second Affiliated Hospital of Chongqing Medical University, Jiangnan Hospital of the Second Affiliated Hospital of Chongqing Medical University and Chongqing Fuling Central Hospital of Chongqing University) from February 2017 to March 2021 were enrolled. All patients were followed up until September 2021. NASH cirrhosis was diagnosed in patients with fatty liver who developed cirrhotic signs confirmed via histological and imaging evidence and at least one metabolic risk factor without a history of alcohol abuse and other known causes of chronic liver disease. The metabolic risk factors included being overweight or obese (body mass index (BMI) ≥25 kg/m²), hypertension, diabetes mellitus and hyperlipidemia. All HBV patients had evidence of HBV infection (HBV surface antigen and HBV DNA positive).

The inclusion criteria were as follows: (1) decompensated NASH cirrhosis or HBV cirrhosis (histological or/and radiological criteria); (2) clinical manifestations of hematemesis and/or melena; (3) first episode of variceal bleeding confirmed using endoscopy with signs of active bleeding or recent bleeding; (4) age > 18
years and < 80 years; (5) absence of liver transplantation; and (6) no significant alcohol abuse.

The exclusion criteria were as follows: (1) advanced hepatocellular carcinoma according to Milan criteria; (2) absence of hemodynamic measurement; (3) previous treatment of portal hypertension and its complications, such as TIPS placement and endoscopic treatment for variceal bleeding; (4) Child–Pugh score > 13; (5) portal vein thrombosis; (6) bleeding from ectopic varices; and (7) comorbidities and medications that may affect portal hypertension and gastrointestinal bleeding, such as heart failure, peptic ulcer, beta-blocker, and antithrombotic therapy.

Interventions

After admission, clinical history, physical examination, laboratory tests, and radiological imaging (hepatic portal vein computed tomography angiography) were performed. All patients admitted for variceal bleeding were first treated with proton pump inhibitors and vasoactive drugs (terlipressin and octreotide). Blood and glucose-electrolyte solutions were transfused to maintain hemodynamic stability. They received early endoscopic treatment within 24 hours after admission. Endoscopic treatment for esophageal and gastric varices included endoscopic variceal ligation (multiband ligation device [Wilson-Cook Medical]) and histoacryl injection. TIPS placement was performed, and portal hypertension was evaluated during the first 48 hours after initial bleeding when patients were under a stable hemodynamic condition.

Measurement of HVPG

An HVPG measurement was performed during the TIPS procedure and adherence to standard operating procedures. Strict quality control standards were established to ensure the reliability of pressure measurement during the procedures. Using the transjugular approach, a transjugular liver access set (Cook, Bloomington, IN, USA) was guided into the inferior vena cave, right hepatic vein and portal vein. Viatorr® PTFE-covered stents (Gore, Flagstaff, AZ, USA) were implanted following balloon dilation. Embolization of the gastric coronary vein was considered when portography clearly showed dilatation of the gastric coronary vein. The HVPG was obtained by calculating the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP).

Outcomes and Follow-up

The primary endpoint was variceal rebleeding, defined as hematemesis and/or melena according to the Baveno Consensus [14]. Variceal rebleeding was diagnosed using endoscopy when varices were actively bleeding, or signs of recent bleeding were observed, and varices were the only potential source of bleeding. The secondary endpoints were other liver-related morbidities (hepatic encephalopathy, ascites, liver failure, hepatocellular carcinoma) and death from any cause.

Patients were followed up using endoscopy, biochemical assessment and Doppler ultrasonography every 1, 3 and 6 months after TIPS and every year after that. Survival was calculated from the date after surgery to mortality or the latest follow-up. Patients were encouraged to quit smoking and alcohol and maintain a low-fat and low-carbohydrate diet during the follow-ups. Liver-protective treatment was conducted, and antiviral therapy was administered to patients with viral etiology.

Statistical analysis

SPSS version 26.0 was used for statistical analysis. Continuous variables are expressed as the mean and standard deviation, and an unpaired Student’s t test or the Mann–Whitney test was used to compare groups. Count variables are expressed as constituent ratios or rates, and Pearson’s χ² or Fisher’s exact test was used to comparing groups. Cumulative probabilities of clinical outcomes were analyzed using the Kaplan–Meier method and log-rank test. Both univariate and multivariate analyses were used to assess the risk factors associated with variceal rebleeding using the Cox proportional hazard regression model. Discrimination of predictive variables for rebleeding was performed using logistic regression models. Moreover, we identified the optimal cutoff values using logistic regression by calculating the area under the receiver operating characteristic curve (AUC). P ≤ 0.05 was considered statistically significant.

Result

Baseline characteristics of patients

Between February 2017 and March 2021, 262 patients with NASH cirrhosis or HBV cirrhosis with first-time variceal bleeding were enrolled. A total of 104 patients were excluded due to incomplete information, 14 due to portal vein thrombosis, 10 due to previous TIPS treatment, 8 due to hepatocellular carcinoma, 4 due to obviously impaired liver function with a Child–Pugh score >13, and 2 due to ectopic variceal bleeding. Among the 120 included patients, 38 (31.7%) had NASH cirrhosis, and 82 (68.3%) had HBV cirrhosis.

The baseline characteristics of all patients with NASH cirrhosis and HBV cirrhosis are shown in Table 1. The mean age of NASH cirrhosis was 56.7 (interquartile range [IQR], 50-65) years, the mean follow-up time was 27.6 months, and that of HBV cirrhosis was 49.2 years (IQR 44-56) and 24.7 months, respectively. Among patients with NASH cirrhosis, the proportion of females was 55.3%, which was significantly higher than that of patients with HBV cirrhosis (17%, P<0.001). Nineteen patients (50%) with NASH cirrhosis had metabolic syndrome, 18 patients (47.4%) were overweight or obese, 28 patients (73.7%) had diabetes mellitus, 10 patients (26.3%) had hypertriglyceridemia, and 8 patients (21%) had hypertension.
<table>
<thead>
<tr>
<th></th>
<th>NASH (n = 38)</th>
<th>HBV (n = 82)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.7 ± 8.8</td>
<td>49.2 ± 9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>21 (55.3)</td>
<td>17 (20.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI (kg/ )</td>
<td>24.7 ± 4.1</td>
<td>21.7 ± 2.6</td>
<td>0.032</td>
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<tr>
<td>Overweight/Obese</td>
<td>18 (47.4)</td>
<td>9 (11.0)</td>
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<td>Ascites</td>
<td></td>
<td></td>
<td>0.319</td>
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<tr>
<td>Mild</td>
<td>15 (39.5)</td>
<td>33 (40.2)</td>
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</tr>
<tr>
<td>Moderate/Excessive</td>
<td>4 (10.5)</td>
<td>17 (20.7)</td>
<td></td>
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<tr>
<td>HCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>3 (7.9)</td>
<td>10 (12.2)</td>
<td>0.481</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>19 (50.0)</td>
<td>6 (7.3)</td>
<td>&lt;0.001</td>
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<tr>
<td>Esophageal varices</td>
<td>34 (89.5)</td>
<td>77 (93.9)</td>
<td>0.392</td>
</tr>
<tr>
<td>Gastric varices</td>
<td>30 (78.9)</td>
<td>66 (80.5)</td>
<td>0.844</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>19 (50.0)</td>
<td>46 (56.1)</td>
<td>0.533</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (21.0)</td>
<td>5 (6.1)</td>
<td>0.014</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28 (73.7)</td>
<td>27 (32.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypertriglyceridemia</td>
<td>10 (26.3)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Child–Pugh class</td>
<td></td>
<td></td>
<td>0.124</td>
</tr>
<tr>
<td>Child class A</td>
<td>22 (57.9)</td>
<td>33 (40.2)</td>
<td></td>
</tr>
<tr>
<td>Child class B</td>
<td>15 (39.5)</td>
<td>40 (48.9)</td>
<td></td>
</tr>
<tr>
<td>Child class C</td>
<td>1 (2.6)</td>
<td>9 (11.0)</td>
<td></td>
</tr>
<tr>
<td>MELD</td>
<td>10.5 ± 2.4</td>
<td>11.8 ± 3.2</td>
<td>0.034</td>
</tr>
<tr>
<td>Platelets (x10^12/L)</td>
<td>83.5 ± 41.2</td>
<td>67.0 ± 49.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.4 ± 0.6</td>
<td>3.3 ± 0.6</td>
<td>0.520</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.4 ± 0.9</td>
<td>1.6 ± 1.3</td>
<td>0.254</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>27.4 ± 17.8</td>
<td>42.3 ± 55.8</td>
<td>0.031</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>38.1 ± 27.9</td>
<td>42.5 ± 41.1</td>
<td>0.492</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>64.2 ± 71.4</td>
<td>43.4 ± 35.4</td>
<td>0.034</td>
</tr>
<tr>
<td>AP (U/L)</td>
<td>92.7 ± 56.6</td>
<td>80.5 ± 28.3</td>
<td>0.118</td>
</tr>
<tr>
<td>INR</td>
<td>1.3 ± 0.2</td>
<td>1.4 ± 0.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>68.2 ± 19.4</td>
<td>66.3 ± 17.5</td>
<td>0.602</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>138.9 ± 3.6</td>
<td>138.0 ± 4.3</td>
<td>0.247</td>
</tr>
<tr>
<td>Portal vein diameter (mm)</td>
<td>15.6 ± 3.1</td>
<td>16.8 ± 3.3</td>
<td>0.030</td>
</tr>
</tbody>
</table>

BMI: body mass index; HCC: hepatocellular carcinoma; MELD: model of end-stage liver disease score; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; AP: alkaline phosphatase; INR: international normalized ratio.

Biochemical analysis of liver function showed that NASH cirrhosis patients had better liver function results and significantly lower Model for End-Stage Liver Disease (MELD) scores ($P = 0.034$). Alanine aminotransferase ($P = 0.031$) and the international normalized ratio ($P = 0.004$) were significantly higher in the HBV group, while the level of gamma-glutamyltransferase (GGT) was significantly higher in the NASH group ($P = 0.034$). In addition, the platelet count was higher in NASH cirrhosis ($P = 0.003$).

Nineteen (50.0%) participants with NASH cirrhosis and 46 (56.1%) participants with HBV cirrhosis experienced active variceal bleeding on endoscopy. Seventeen (26.2%) out of 65 patients experienced active variceal bleeding with an HVPG $\geq$20 mmHg (6 with NASH cirrhosis and 11 with HBV cirrhosis).
Patients with NASH cirrhosis had a lower portal pressure (26.3 ± 6.1 vs. 30.1 ± 4.7; \( P < 0.001 \)), lower WHVP (24.1 ± 5.3 vs. 27.6 ± 5.5; \( P = 0.001 \)) and lower HVPG (15.3 ± 3.8 vs. 18.0 ± 4.8; \( P = 0.003 \)) than those with HBV cirrhosis (Table 2). Among patients who experienced active bleeding, no significant difference in the HVPG levels was observed between NASH cirrhosis and HBV cirrhosis (Fig. 1A). However, significantly lower levels of portal pressure (23.1 ± 5.5 vs. 29.5 ± 5.3; \( P < 0.001 \)), WHVP (21.8 ± 4.8 vs. 27.0 ± 5.3; \( P = 0.001 \)) and HVPG (13.4 ± 2.9 vs. 18.0 ± 4.4; \( P < 0.001 \)) were observed in NASH cirrhosis patients without active bleeding than in HBV cirrhosis patients (Fig. 1B). High HVPG levels were more frequently found in HBV cirrhosis. The HVPG level in 3 (7.9%) NASH patients versus 25 (30.5%) HBV patients was greater than or equal to 20 mmHg (\( P = 0.006 \)). Low HVPG (<10 mmHg) levels were observed in 3 (7.9%) NASH patients and 3 (3.7%) HBV patients. After successful TIPS treatment, the HVPG significantly decreased from 15.3 ± 3.8 mmHg vs. 18.0 ± 4.8 mmHg to 7.7 ± 4.2 mmHg vs. 9.3 ± 3.9 mmHg (NASH cirrhosis vs. HBV cirrhosis, \( P < 0.001 \)). The HVPG level after TIPS treatment of NASH cirrhosis was significantly lower than that after TIPS treatment of HBV cirrhosis (\( P = 0.04 \)). Compared to the baseline, an HVPG value, a mean reduction of 7.6 mmHg was observed in NASH cirrhosis and 8.7 mmHg in HBV cirrhosis. No significant difference was found between them. After TIPS treatment, the HVPG effectively decreased to a level of <20 mmHg in 119 of 120 patients. Among them, 10 (26.3%) NASH patients and 33 (40.2%) HBV patients still had clinically significant portal hypertension (HVPG ≥10 mmHg). The number of acute hemodynamic responders (an HVPG-decrease ≥20% or ≤12 mmHg) was not significantly different.

### Table 2

<table>
<thead>
<tr>
<th>Portal hemodynamics of patients before and after the treatment</th>
<th>NASH (n = 38)</th>
<th>HBV (n = 82)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein velocity (cm/s)</td>
<td>38.6 ± 16.3</td>
<td>38.8 ± 12.7</td>
<td>0.756</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>26.3 ± 6.1</td>
<td>30.1 ± 4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHVP (mmHg)</td>
<td>24.1 ± 5.3</td>
<td>27.6 ± 5.5</td>
<td>0.001</td>
</tr>
<tr>
<td>FHVP (mmHg)</td>
<td>8.8 ± 3.0</td>
<td>9.7 ± 3.4</td>
<td>0.186</td>
</tr>
<tr>
<td>HVPG before TIPS (mmHg)</td>
<td>15.3 ± 3.8</td>
<td>18.0 ± 4.8</td>
<td>0.003</td>
</tr>
<tr>
<td>HVPG after TIPS (mmHg)</td>
<td>7.7 ± 4.2</td>
<td>9.3 ± 3.9</td>
<td>0.04</td>
</tr>
<tr>
<td>HVPG-decrease ≥20%</td>
<td>35 (92.1)</td>
<td>76 (92.7)</td>
<td>0.911</td>
</tr>
<tr>
<td>HVPG-decrease ≤12 mmHg</td>
<td>34 (89.5)</td>
<td>62 (75.6)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

PP: portal pressure; WHVP: wedged hepatic venous pressure; FHVP: free hepatic venous pressure; HVPG: hepatic venous pressure gradient; TIPS: transjugular intrahepatic portosystemic shunt.

### Rebleeding

During the follow-up, a total of 38 patients (11 NASH patients and 27 HBV patients) had at least one variceal rebleeding. A total of 18 rebleeding events occurred in the NASH group and 51 in the HBV group. There were no significant differences in the cumulative probability of rebleeding at 6 months (5.3% vs. 12.2%), 1 year (15.6% vs. 18.3%) or 2 years (22.7% vs. 32.9%) between the two groups. Furthermore, Kaplan–Meier survival curves indicated no significant difference in the overall rebleeding rate between NASH and HBV cirrhosis. Variceal rebleeding patients had higher baseline HVPG levels than nonrebleeding patients in both groups. Compared to the HBV group, the HVPG of rebleeding patients in the NASH group was significantly higher (18.3 ± 3.9 vs. 14.0 ± 3.0; \( P = 0.001 \)). Among 38 patients with variceal rebleeding, 18 (47.3%) patients had an HVPG ≥20 mmHg. Patients with a higher an HVPG level of ≥20 mmHg had a significantly higher variceal rebleeding rate than those with an HVPG of <20 mmHg (64.3% vs. 21.7%, \( P < 0.001 \)). The observed cumulative probability of variceal rebleeding was significantly higher in those with an HVPG ≥20 mmHg than in those with an HVPG <20 mmHg at the 6-month (25.0% vs. 5.4%) and 1-year (36.2% vs. 11.4%) follow-ups. In logistic regression, an HVPG ≥20 mmHg was associated with an increased risk of variceal rebleeding (HR 6.48; 95% CI 2.59-16.23; \( P < 0.001 \)) compared with an HVPG <20 mmHg. The c-statistic for baseline HVPG for predicting variceal rebleeding was 0.82 in NASH patients (95% CI 0.66-0.97; \( P = 0.002 \)), and the optimal threshold for baseline HVPG was ≥17.0 mmHg (specificity 72.7%, sensitivity 85.2%, [Fig. 2A]). In the HBV group, the c-statistic for baseline HVPG for predicting variceal rebleeding was 0.75 (95% CI 0.36-0.88; \( P < 0.001 \)), and the optimal threshold for baseline HVPG was ≥21.6 mmHg (specificity 48.1%, sensitivity 92.7%, [Fig. 2B]). Elevation of the baseline HVPG level per 1 mmHg increased the rebleeding risk by 1.50 in NASH cirrhosis (95% CI 1.11-2.03; \( P = 0.008 \)) and 1.23 in HBV cirrhosis (95% CI 1.09-1.40; \( P = 0.001 \)). The survival curves of variceal rebleeding in the NASH and HBV groups according to an HVPG are depicted in Fig. 3. The incidence of rebleeding was significantly higher in patients with an HVPG ≥17 mmHg in the NASH group (HR 7.06; 95% CI 1.88-26.56; \( P = 0.001 \)). Multivariate analysis showed that an HVPG ≥17 mmHg (HR 9.40; 95% CI 1.85-47.70; \( P = 0.007 \)), lower albumin (HR 1.25; 95% CI 1.06-1.48; \( P = 0.007 \)), and higher GGT (HR 1.02; 95% CI 1.01-1.03; \( P = 0.002 \)) were independent predictors of variceal rebleeding in the NASH cirrhosis group (Table 3).
and decompensated cirrhosis in NASH cirrhosis, as in other etiologies. The same and strong correlation with the stage of fibrosis has been verified. The measurement of an HVPG in NASH and HCV etiology shared the resistance and portal fibrosis. Portal inflammatory infiltrate leads to a ductular reaction, resulting in progressive fibrosis and thus an increase in portal vascular resistance. HVPG has been clinically significant in the prognosis of cirrhotic complications in compensated and decompensated cirrhosis in NASH cirrhosis, as in other etiologies.

### Table 3

<table>
<thead>
<tr>
<th>Univariate and multivariate analysis for predictors of variceal rebleeding in NASH cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Overweight/Obese</td>
</tr>
<tr>
<td>HVPG ≥17 mmHg</td>
</tr>
<tr>
<td>Albumin</td>
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<tr>
<td>GGT</td>
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<tr>
<td>AP</td>
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</tbody>
</table>

CI, Confidence interval; HR, Hazard ratio; HVPG, hepatic venous pressure gradient; GGT: gamma-glutamyl transpeptidase; AP: alkaline phosphatase

### Other complications of cirrhosis

At enrollment, 19 (50.0%) NASH patients had ascites, 3 (7.9%) had encephalopathy, and 2 (5.3%) had acute-on-chronic liver failure. During a mean follow-up of 27.6 months, 13 (34.2%) patients with NASH cirrhosis developed cirhotic complications other than variceal bleeding, including encephalopathy (7 patients), HCC (1 patient), acute-on-chronic liver failure (7 patients), and ascites (4 patients). Fifty (61.0%) HBV cirrhosis patients had ascites, 10 (12.2%) had encephalopathy, 7 (8.5%) had liver failure, and 4 (4.9%) had HCC at the time of the first visit of the study. Compared with patients with NASH cirrhosis, 42 (51.2%) patients with HBV cirrhosis developed cirhotic complications other than variceal bleeding (22 patients with encephalopathy, 10 patients with HCC, 7 patients with liver failure, 8 patients with ascites) during 2 years of follow-up. Although the NASH group showed a lower total incidence of cirhotic complication outcomes, the occurrence rates of hepatic encephalopathy (26.3% vs. 39%), acute-on-chronic liver failure (23.7% vs. 34.1%), and ascites (60.5% vs. 70.7%) were similar between the two groups. According to the Kaplan–Meier analysis, only the incidence of HCC was significantly higher in HBV cirrhosis (17.1% vs. 2.6%, \( P = 0.008 \)). In the NASH group, the HVPG level was significantly higher in patients with cirhotic complications than in those without complications (16.2 ± 3.9 vs. 13.4 ± 2.8; \( P = 0.026 \)). The prevalence of cirhotic complications increased with the HVPG level. Each 1 mmHg elevation in an HVPG was associated with a 27.8% increase in the risk of clinical events (\( P = 0.035 \)). The c-statistic of an HVPG for the predictive value of cirhotic complications was 0.75 in NASH patients (95% CI 0.59-0.90; \( P = 0.014 \)).

During follow-up, 1 patient with NASH died due to liver failure, and 2 patients with HBV died due to HCC and lethal variceal bleeding. Furthermore, there were no differences in survival between the groups.

### Discussion

HVPG plays an important role in risk stratification and prediction of complications of portal hypertension. In particular, elevated an HVPG correlates with clinical decompensation and poor prognosis of cirrhosis. A previous study on portal hypertension suggested that an HVPG ≥ 12 to 20 mmHg (HR 2.73) and an HVPG ≥ 20 mmHg (HR 4.48) independently predict early and more frequent clinical decompensation. Compensated cirrhosis patients with an HVPG ≥ 20 mmHg are considered “high-risk compensated cirrhosis” [15]. In the study by Monescillo et al. [16], portal pressure estimated by an HVPG could discriminate the high-risk population from the low-risk group. The HVPG cutoff value (20 mmHg) is associated with a higher risk for treatment failure (i.e., failure control of acute bleeding and/or early rebleeding), worse actuarial probability of survival and more complications of portal hypertension. It is clear from these clinical results that an HVPG measurement is a reliable method for cirhotic risk stratification.

Nevertheless, the correlation between an HVPG and cirhotic decompensation has not yet been well documented in NASH cirrhosis. HVPG has been verified to contribute to the progression of cirhotic decompensation in other etiologies. It is suggested that the threshold value of an HVPG for risk stratification is likely to be different in NASH cirrhosis [6, 24]. In this study, we evaluated the correlation between HVPG levels and cirhotic complications in NASH cirrhosis.

Our results showed lower PP (26.3 ± 6.1 vs. 30.1 ± 4.7; \( P < 0.001 \)), lower WHVP (24.1 ± 5.3 vs. 27.6 ± 5.5; \( P = 0.001 \)) and lower HVPG values (15.3 ± 3.8 vs. 18.0 ± 4.8; \( P = 0.003 \)) in NASH cirrhosis at the time of initial hemorrhage than in HBV cirrhosis. In comparison to patients with HBV cirrhosis, significantly fewer patients had a higher an HVPG (HVPG ≥ 20 mmHg) in NASH cirrhosis (7.9% vs. 30.5%; \( P = 0.006 \)). In the current study, lower HVPG and lower WHVP were found in NASH disease than in HCV disease, and decreases in pressure measurements were observed in different stages of fibrosis, particularly in the lower stage of fibrosis (stage ≤ 3) [13]. Compared with the other etiologies of cirrhosis, these decreased pressure variables of NASH cirrhosis were identical to those in a previous study regarding a similar degree of liver dysfunction [12, 22]. The low level of portal pressure in NAFLD has recently attracted much attention, raising the question of whether HVPG measurements may probably be underestimated in NASH cirrhosis. Previous studies hypothesized that the potential special vasoreactivity mechanism in NAFLD reduces the effect of fibrosis on portal pressure [24]. NASH pathogenesis is correlated with lobular inflammation and portal fibrosis. Portal inflammatory infiltrate leads to a ductular reaction, resulting in progressive fibrosis and thus an increase in portal vascular resistance [21, 32]. It has also been postulated that increased perisinusoidal pressure caused by biliary injury may influence the accuracy of portal pressure in NASH [18, 20]. Moreover, these studies have raised concerns about whether portal hypertension in NASH can be perfectly distinguished by an HVPG measurement. Decreased HVPG values for staging fibrosis in NASH have been verified. The measurement of an HVPG in NASH and HCV etiology shared the same and strong correlation with the stage of fibrosis [13]. HVPG has been clinically significant in the prognosis of cirhotic complications in compensated and decompensated cirrhosis in NASH cirrhosis, as in other etiologies [11, 17].
In this study, the results suggested that the measurement of an HVPG was an accurate predictor of portal hypertension-related decompensations in NASH cirrhosis, such as recurrent variceal bleeding. Although the optimal baseline HVPG threshold for predicting rebleeding of NASH cirrhosis was lower than 20 mmHg, univariate and multivariate analyses revealed that an HVPG $\geq 17$ mmHg was an independent predictor for variceal rebleeding. The median survival time was shorter in NASH patients than in HBV patients when the HVPG was greater than 17 mmHg, although no survival difference was observed. Likewise, our study showed a strong correlation between rebleeding episodes and an HVPG elevation. The risk of variceal rebleeding increased by 50.1% when the baseline HVPG level increased by 1 mmHg. The relationship between high HVPG and complications in NASH cirrhosis has been demonstrated in our study, which can help us corroborate the specific predictive value of an HVPG for predicting the development of variceal bleeding. Previous reports on portal hemodynamics indicated that an HVPG of $\geq 20$ mmHg had been shown to significantly correlate with a high incidence of cirrhotic complications [15, 16]. As mentioned above, the role of the HVPG value in predicting the occurrence of cirrhotic complications in decompensated NASH cirrhosis is controversial. It is difficult to identify NASH patients at high risk for liver-related complications, especially those with an HVPG $< 10$ mmHg [11]. The predictive factors for cirrhotic complications have received much attention in NASH cirrhosis, and identifying independent predictors for portal hypertensive complications is important for patients with NASH cirrhosis [19]. In a study of a large cohort with 475 patients with biopsy-proven NASH from the simtuzumab trials, higher an HVPG, both at baseline levels and elevated levels over time, was associated with a high risk of cirrhosis-related clinical events [11]. With every 1 mmHg increase in an HVPG, the associated risk of decompenation events increased by 15%. We also noticed a difference in the risk estimates of decompenation between our study and a previous study. Perhaps because this study only involves patients with decompensated cirrhosis, the risk of variceal bleeding is likely to be exaggerated. Our findings on the prognostic value of an HVPG for risk stratification in NASH cirrhosis patients are consistent with those of Sanyal et al. [11], which showed the high prognostic value of an HVPG for predicting cirrhotic decompensations and survival.

Few studies have focused on evaluating the predictive value of an HVPG for rebleeding risk in NASH cirrhosis patients after variceal bleeding. According to our results, the accuracy of an HVPG for predicting variceal rebleeding in NASH cirrhosis is superior to that in HBV cirrhosis. Our observation verifies a significant correlation between increased HVPG and high rebleeding risk. High portal pressure and high variceal pressure are recognized causes of variceal bleeding; hence, an HVPG is a well-known useful predictor for variceal bleeding in cirrhotic patients. An HVPG $\geq 20$ mmHg correlates with grades of varices and increased risk of continued and recurrent variceal bleeding, which has been shown in many experimental and clinical studies [8, 16, 25, 26]. Our findings suggest that an HVPG $\geq 17$ mmHg is a valuable predictor for evaluating the risk of complications in patients with NASH cirrhosis. Thus, early evaluation of an HVPG provides an opportunity for early intervention in these at-risk patients.

The limitation of this study is the relatively small sample size. Another limitation is that the HBV group is not comparable to the NASH group with respect to age and sex ratio, which might be inadequate to accurately describe the predictive value of an HVPG in NASH cirrhosis. NASH cirrhosis has been projected to exceed virus cirrhosis and become the leading cause of cirrhosis worldwide [28]. The number of NASH patients with cirrhosis is still limited due to slow disease progression, which impedes the assessment of long-term survival. Considering that the average follow-up in this study was approximately 2 years, whether an HVPG has a good prognostic value for variceal bleeding in NASH cirrhosis awaits further investigation. We fully anticipate that further studies will explore the predictive value of an HVPG for other complications of advanced cirrhosis due to NASH, including liver failure, hepatic encephalopathy, hepatorenal syndrome and hepatopulmonary syndrome. The hemodynamic measurement of portal pressure is invasive and relatively expensive, which limits its large-scale application. In that instance, a new minimally invasive and cost-effective method is expected to be a replacement for an HVPG, showing a favorable prognostic value for long-term outcomes in NASH patients.

In conclusion, this study showed that patients with NASH cirrhosis had lower HVPG values and a similar prevalence of cirrhosis-related complications after initial variceal bleeding compared with HBV cirrhosis. According to the predictive value for variceal rebleeding, an HVPG is a feasible accurate and valuable means of risk assessment in NASH cirrhosis. The presence of high HVPG contributes to stratifying high-risk patients and leads us to a deeper understanding of the management of NASH patients. Considering the rising trend in the prevalence of NAFLD, regular clinical evaluation and monitoring of liver-related events are recommended in these patients with high HVPG. Early stratification of NAFLD is crucial for early intervention to reduce the risk of recurrent variceal bleeding.

**Abbreviations**

HVPG, hepatic venous pressure gradient; NASH, nonalcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; TIPS, transjugular intrahepatic portosystemic shunt; BMI, body mass index; HCC, hepatocellular carcinoma; FHV, free hepatic venous pressure; WHVP, wedged hepatic venous pressure; ALT, alanine aminotransferase; INR, international normalized ratio; GGT, gamma-glutamyltransferase; HR, hazard ratio; CI, confidence interval; CSPH, clinically significant portal hypertension.

**Declarations**

**Availability of data and materials**

Data for this study is available upon reasonable request by contact to the corresponding author.

**Ethics approval and consent to participate**

The research was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. All patients signed informed consent forms. The research conformed to the Declaration of Helsinki.

**Consent for publication**
Not applicable.

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Author contribution statement
YS and BN conceived and wrote the manuscript. YS, XW, and GX participated in data acquisition and statistical analysis; WS and BN reviewed and edited the manuscript; WS and BN supervised the study. Both authors reviewed and approved the final manuscript.

Competing interests
The authors declare they have nothing to disclose.

References


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Figures

![Figure 1](image-url)

(A) Box plots of hemodynamic measurements in patients with active bleeding. (B) Box plots of hemodynamic measurements in patients without active bleeding. In all box plots, the central lines indicate the median, the boxes indicate the interquartile range, and the whiskers indicate the minimum and maximum values. White and gray boxes represent patients with NASH cirrhosis and HBV cirrhosis, respectively.
Figure 2

(A) ROC curve for the value of HVPG in predicting variceal rebleeding in patients with NASH cirrhosis. (B) ROC curve for the value of HVPG in predicting variceal rebleeding in patients with HBV cirrhosis.
Figure 3

(A) Survival curves of the probability of variceal rebleeding in patients with NASH cirrhosis based on HVPG level. (B) Survival curves of the probability of variceal rebleeding in patients with HBV cirrhosis based on HVPG level.