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# The New Cutoff Value of the Hepatic Venous Pressure Gradient on Predicting Long-Term Survival in Cirrhotic Patients

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## ABSTRACT





**Background:** This study aimed to determine the prognostic role of the categorized hemodynamic stage (HS) based on the hepatic venous pressure gradient (HVPG) in patients with portal hypertension.

**Methods:** Of 1,025 cirrhotic patients who underwent HVPG measurement, data on 572 non-critically-ill patients were collected retrospectively between 2008 and 2013. The following two HS categorizations were used: HS-1 (6–9, 10–12, 13–16, 17–20, and > 20 mmHg; designated as groups 1–5, respectively) and HS-2 (6–12, 13–20, and > 20 mmHg). Clinical characteristics, mortality rates, and prognostic predictors were analyzed according to the categorized HS.

**Results:** During the mean follow-up period of 25 months, 86 (15.0%) patients died. The numbers of deaths in HS-1 groups were 7 (6.3%), 7 (6.9%), 30 (18.0%), 20 (15.6%), and 22 (34.4%), respectively ( $P < 0.001$ ). However, the traditional HVPG cutoffs of 10 and 16 mmHg did not improve the discrimination of mortality. In contrast, the mortality rates did differ significantly between the three HS-2 groups ( $P < 0.05$ ). In the multivariate analysis, all models revealed that HS-2 was a common prognostic factor in predicting mortality. The mortality rates increased significantly according to HS-2 in patients with hypoalbuminemia (HVPG, 13–20 mmHg; hazard ratio [HR], 2.54 and HVPG > 20 mmHg; HR, 5.45) and intermediate model for end-stage liver disease (MELD) score (HVPG, 13–20 mmHg; HR, 3.86 and HVPG > 20 mmHg; HR, 8.77;  $P < 0.05$ ).

**Conclusion:** Categorizing HVPG values according to HS-2 is a useful prognostic modality in patients with portal hypertension and can play an independent role in predicting the prognosis in patients with hypoalbuminemia and an intermediate MELD score.

**Keywords:** Cirrhosis; Hemodynamics; Portal Hypertension; Prognosis

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**Disclosure**

The authors have no potential conflicts of interest to disclose.

**Author Contributions**

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**INTRODUCTION**

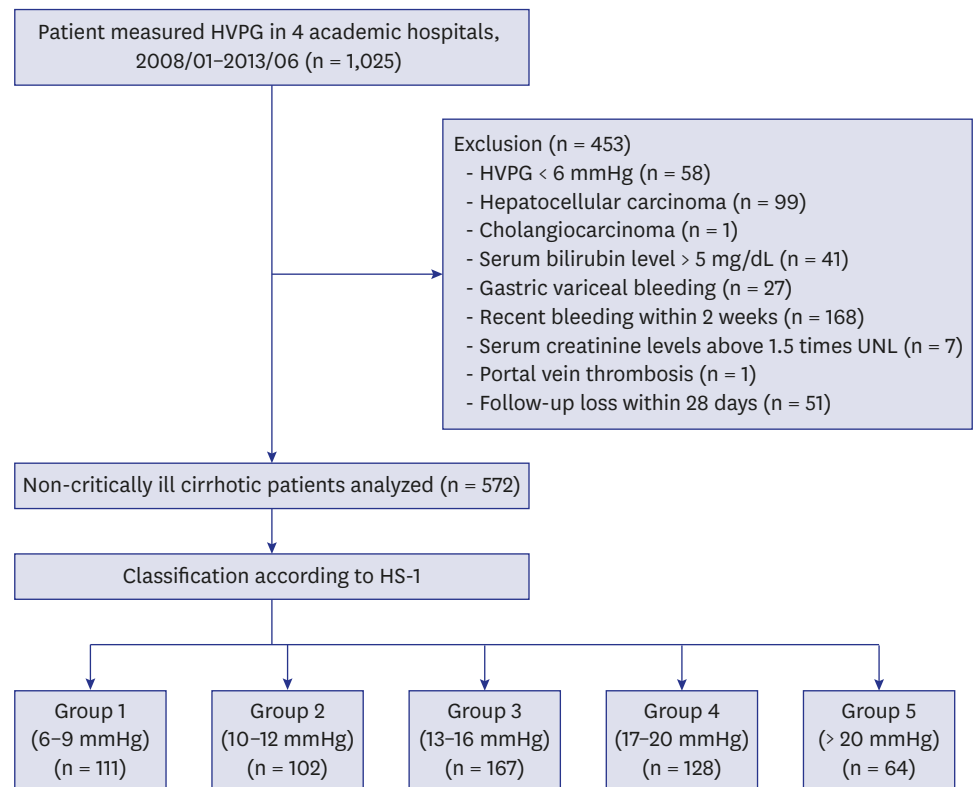
The natural history of cirrhosis is related to elevated portal pressure.<sup>1</sup> Portal hypertension (PHT) is a clinical syndrome characterized by a pathologically elevated portal perfusion gradient.<sup>2,3</sup> Measuring the hepatic venous pressure gradient (HVPG) is safe and has been found to be useful in the diagnosis of PHT and for risk stratification, assessment of prognosis, monitoring of treatment, and identification of patients with hepatocellular carcinoma (HCC) who are candidates for liver resection.<sup>4-10</sup> An HVPG of > 20 mmHg in acute variceal hemorrhage is indicative of a high probability of 1-year mortality.<sup>11</sup> The HVPG has been shown to have an independent role in survival in addition to the model for end-stage liver disease (MELD) score, with each 1-mmHg increase contributing to a 3% increase in mortality.<sup>9</sup>

A previous report suggested that specific stages within the classification of chronic liver disease can be associated with histological, clinical, hemodynamic, and biological stages.<sup>6,12,13</sup> For example, a hemodynamic stage (HS) with HVPG  $\geq$  6 mmHg indicates PHT (stage 1), while HVPG  $\geq$  10 mmHg represents clinically significant PHT (stages 2–4).<sup>6,14,15</sup> Previous reports have suggested that HS utilizing the HVPG score is closely associated with the clinical stage according to the presence of clinical complications.<sup>16,17</sup> However, considering that there are various causes of cirrhosis, regional and gender differences, and dynamic disease progression such as acute-on-chronic liver failure, few studies have evaluated survival prediction according to clinical characteristics and HS using the HVPG score in patients with PHT.<sup>18</sup>

The present study investigated the current real-life setting in which patients with cirrhosis receive standard therapies for the different complications, with the aim of quantifying survival according to the HVPG grade and the prognostic value of HVPG grades and other prognostic factors.

**METHODS****Patients**

Between January 2008 and June 2013, 1,025 cirrhotic patients were consecutively collected at 4 academic hospitals. All of the patients had a previous histological confirmation of cirrhosis<sup>19</sup> or a diagnosis of cirrhosis suspected on the basis of standard clinical, ultrasonographic, and biochemical parameters.<sup>20</sup> All of the patients had stable hemodynamic parameters and were not active drinkers. Active drinkers were defined as patients who drink alcohol more than 140 grams/week (women), or 210 grams/week (men).<sup>21</sup> HVPG measurements were used to establish the diagnosis of cirrhosis or to assess baseline portal pressure, prior to primary prophylaxis or secondary prophylaxis of variceal bleeding. The patients were enrolled after confirming the presence of an HVPG of  $\geq$  6 mmHg. The exclusion criteria were HVPG < 6 mmHg (58 patients), presence of HCC (99 patients) and cholangiocarcinoma (1 patient), gastric variceal bleeding (27 patients), acute decompensation state such as bilirubin levels > 5 mg/dL (41 patients) and recent esophageal variceal bleeding within 2 weeks (168 patients), serum creatinine levels > 1.5-fold the upper normal limit (7 patients), portal vein thrombosis (1 patient), and loss to follow-up within 28 days (51 patients). Gastric varices are not correlated with HVPG level and patients who have recent esophageal variceal bleeding could be critically ill patients. Finally, 572 non-critically-ill cirrhotic patients were analyzed (**Fig. 1**). Especially in case of alcohol related cirrhosis



**Fig. 1.** Patient enrollment diagram. Clinical data of 1,025 cirrhotic patients with HVPG measurements were collected retrospectively between January 2008 and June 2013. After excluding 453 patients, 572 non-critically-ill cirrhotic patients were analyzed. The severity of HVPG was divided into the following five HS groups according to previously reported cutoffs: group 1, 6–9 mmHg; group 2, 10–12 mmHg; group 3, 13–16 mmHg; group 4, 17–20 mmHg; and group 5, > 20 mmHg. Clinical stages were defined according to the classification by D'Amico et al.<sup>14,17</sup> HVPG = hepatic venous pressure gradient, HS = hemodynamic stage, UNL = upper normal limit.

patients, alcohol abstinence for at least 6 months prior to participating in this study were considered eligible for the study to avoid the influence of inflammation by recent alcohol consumption. The follow-up was performed up to December 31, 2013.

### HVPG measurement

All vasoactive drugs were discontinued at least 72 hours before performing the hemodynamic assessments. The HVPG was measured by operators (hepatologists or interventional radiologists) who had previously performed > 100 HVPG measurements. Under fluoroscopic guidance, a 6-French balloon-tip catheter (Arrow International, Cleveland, OH, USA) was inserted into the right hepatic vein via the internal jugular vein. The free hepatic venous pressure was measured within 5 cm of the junction of the right hepatic vein and inferior vena cava. After balloon inflation, the examiner checked for the absence of a venovenous shunt, then measured the wedged hepatic venous pressure at the same location where the free hepatic venous pressure had been measured. Each measurement was repeated three times, with the results reported as mean values for these three measurements. The HVPG was determined by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure.

### HVPG subgroup, clinical stage, and MELD score

HS-1 was classified as follows according to HVPG grades based on previously reported cutoffs: group 1, 6–9 mmHg; group 2, 10–12 mmHg; group 3, 13–16 mmHg; group 4,

17–20 mmHg; and group 5, > 20 mmHg.<sup>1</sup> The following four clinical stages were defined according to the classification by D'Amico et al.<sup>14</sup>: stage 1, no ascites and varices; stage 2, esophageal varices without hemorrhage and no ascites; stage 3, ascites without a history of esophageal variceal hemorrhage; and stage 4, gastrointestinal bleeding with or without ascites. Decompensated cirrhosis was defined as stage 3 or 4. The MELD score was calculated for each patient on the day of HVPg measurement using the following equation<sup>22</sup>:  $9.57 \times \log_e(\text{creatinine, mg/dL}) + 3.78 \times \log_e(\text{bilirubin, mg/dL}) + 11.2 \times \log_e(\text{prothrombin time, international normalized ratio}) + 6.43$ .

The MELD-Na score was calculated as MELD score – sodium level –  $0.025 \times \text{MELD score} \times (140 - \text{sodium level}) + 140$ .<sup>23</sup> We defined cutoff MELD scores of 10 and 15 with reference to a previous study<sup>24</sup> and the worldwide consensus for those patients who need to receive liver transplantation, thereby categorizing MELD scores into the following three groups: low, 6–9; intermediate, 10–15; and high,  $\geq 16$ .

### Statistical analysis

Statistical analyses and graphic production were performed with SPSS (version 18.0; SPSS, Chicago, IL, USA). Descriptive statistics were produced for the demographic, clinical, and laboratory characteristics of the study patient sample. Continuous and categorical variables were expressed as mean  $\pm$  standard deviation (SD, range) and number (%) values, respectively. The patient characteristics were compared according to HS using the  $\chi^2$  test and one-way analysis of variance with Scheffe's test. To evaluate mortality according to the Child-Pugh (CP) class, clinical stage, and HS, the Kaplan-Meier method with the log-rank test was used to calculate survival, with Bonferroni correction applied to *P* values according to the number of groups.

Based on the results of the survival analysis of our data, we simplified HS-1 into HS-2 as follows: group A, 6–12 mmHg; group B, 13–20 mmHg; and group C, > 20 mmHg. To assess the prognostic predictors of long-term mortality, variables including gender, age, use of beta-blockers, platelet count, albumin, bilirubin, prothrombin time, creatinine, sodium level, CP score, clinical stage, HS-2, MELD score, and MELD-Na score were used in Cox regression models to obtain hazard ratios (HRs) for independent predictive factors. Variables that were significant in the univariate variables were analyzed by stepwise Cox multivariate regression. For the subgroup analyses in the hypoalbuminemia and MELD groups, hypoalbuminemia was defined as a serum albumin level of  $\leq 3.5$  mg/dL, and MELD groups were divided into three groups. *P* values of  $< 0.05$  were considered to be statistically significant.

### Ethics statement

The Institutional Review Board (IRB) of the four academic hospitals approved the study (Soonchunhyang University Seoul Hospital IRB 2013-12-005). Written informed consent to participate in the study procedures was obtained from all of the included patients.

## RESULTS

### Baseline characteristics of patients

The baseline characteristics and the results of biochemical examinations are summarized in **Table 1**. The patients were aged  $53.0 \pm 9.7$  years. The causes of liver cirrhosis were alcohol consumption in 344 (60.1%) patients, viral hepatitis in 157 (27.5%), viral hepatitis and

**Table 1.** Clinical characteristics of enrolled patients

Characteristics	Values (n = 572)
Gender, men	439 (76.7)
Age, yr	53.0 ± 9.7 (25–78)
Cause of liver cirrhosis	
Viral hepatitis	157 (27.5)
Alcohol	344 (60.1)
Mixed (virus + alcohol)	38 (6.6)
Others	33 (5.8)
Use of beta-blocker	267 (46.7)
Presence of ascites	272 (47.6)
Platelet count, × 10 <sup>3</sup> /μL	117 ± 72 (20–562)
Albumin, mg/dL	3.3 ± 0.6 (1.7–5.1)
Bilirubin, mg/dL	1.6 ± 1.1 (0.1–5.0)
AST, U/L	68 ± 76 (13–902)
ALT, U/L	44 ± 86 (3–1,355)
Prothrombin time, INR	1.22 ± 0.26 (0.81–2.67)
Creatinine, mg/dL	0.8 ± 0.2 (0.3–1.7)
Sodium, mEq/L	139 ± 4 (118–148)
CP class	7.0 ± 1.8 (5–13)
A	263 (46.0)
B	245 (42.8)
C	64 (11.2)
Clinical stage	
1	105 (18.4)
2	173 (30.2)
3	253 (44.2)
4	41 (7.2)
MELD score	10.3 ± 3.4 (6–23)
MELD-Na score	11.6 ± 4.2 (6–27)
HVPG, mmHg	14.5 ± 5.2 (6–43)
Death	86 (15.0)
Follow-up duration, mon	25 ± 18 (1–73)

Data are number (%) or mean ± standard deviation (range) values.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CP = Child-Pugh, HVPG = hepatic venous pressure gradient, INR = international normalized ratio, MELD = model for end-stage liver disease.

alcohol consumption in 38 (6.6%), and others in 33 (5.8%). There were 439 (76.8%) men patients, 105 (18.4%) at clinical stage 1, 173 (30.2%) at clinical stage 2, 253 (44.2%) at clinical stage 3, and 41 (7.2%) at clinical stage 4. The overall MELD score and HVPG were 10.3 ± 3.4 and 14.5 ± 5.2 mmHg, respectively (Table 1).

### Patient characteristics according to the severity of PHT

The patient characteristics according to HS-1 are summarized in Table 2. Higher HVPG grades were associated with higher frequency of alcoholic liver disease, serum bilirubin levels, prothrombin time, and prognostic scores such as the CP score, MELD score, MELD-Na score, and decompensated stage, but lower platelet count, serum albumin, and serum sodium (all  $P < 0.001$ ). The CP class and clinical stages were negatively correlated with the HVPG grade (Fig. 2A and B, respectively).

### Cumulative survival according to CP class, clinical stage, and HVPG grade

During the follow-up period of 25 ± 18 months (range, 1–73 months), 86 (15.0%) patients died (Table 1). The causes of death were bleeding (n = 25, 29.1%), hepatic failure (n = 18, 20.9%), hepatorenal syndrome (n = 13, 15.1%), infection including spontaneous bacterial peritonitis (n = 10, 11.6%), hepatic encephalopathy (n = 9, 10.5%), HCC that developed from precancerous lesion such as liver cirrhosis (n = 2, 2.3%), intracranial hemorrhage (n = 5,

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Table 2. Patient characteristics and prognostic stages according to HS-1 groups

Total (n = 572)	Group 1 (n = 111)	Group 2 (n = 102)	Group 3 (n = 167)	Group 4 (n = 128)	Group 5 (n = 64)	P value
Gender, men	91 (82.0)	74 (72.5)	130 (77.8)	95 (74.2)	49 (76.6)	0.400
Age, yr	51.0 ± 9.8	53.0 ± 10.0	53.0 ± 10.3	52.0 ± 9.2	54.0 ± 8.1	0.619
Cause of liver cirrhosis						0.003
Viral hepatitis	41 (36.9)	38 (34.2)	37 (22.2)	27 (21.1)	14 (21.9)	
Alcohol	61 (55.0)	52 (51.0)	108 (64.7)	81 (63.3)	42 (65.6)	
Mixed (virus + alcohol)	5 (4.5)	5 (4.9)	11 (6.6)	15 (11.7)	2 (3.1)	
Others	4 (3.6)	7 (6.9)	11 (6.6)	5 (3.9)	6 (9.4)	
Platelet count, × 10 <sup>3</sup> /μL	149 ± 84	110 ± 70	110 ± 67	105 ± 60	113 ± 79	< 0.001
Albumin, mg/dL	3.7 ± 0.5	3.4 ± 0.5	3.3 ± 0.5	3.2 ± 0.6	3.0 ± 0.6	< 0.001
Bilirubin, mg/dL	1.1 ± 0.8	1.4 ± 1.2	1.6 ± 1.2	2.0 ± 1.2	2.2 ± 1.1	< 0.001
AST, U/L	69 ± 95	60 ± 34	70 ± 79	72 ± 89	65 ± 45	0.800
ALT, U/L	54 ± 111	43 ± 43	47 ± 117	36 ± 38	35 ± 50	0.469
Prothrombin time, INR	1.09 ± 0.15	1.18 ± 0.22	1.19 ± 0.23	1.34 ± 0.31	1.35 ± 0.28	< 0.001
Creatinine, mg/dL	0.80 ± 0.20	0.74 ± 0.21	0.74 ± 0.19	0.78 ± 0.22	0.78 ± 0.23	0.093
Sodium, mEq/L	141.0 ± 3.0	139.0 ± 3.4	139.0 ± 3.8	139.0 ± 3.4	138.0 ± 4.7	< 0.001
CP class	6.0 ± 1.1	7.0 ± 1.6	7.0 ± 1.5	8.0 ± 1.8	8.0 ± 2.0	< 0.001
A	86 (77.5)	55 (53.9)	70 (41.9)	41 (32.0)	11 (17.2)	< 0.001
B	24 (21.6)	42 (41.2)	86 (51.5)	62 (48.4)	31 (48.4)	
C	1 (0.9)	5 (4.9)	11 (6.6)	25 (19.5)	22 (34.4)	
Clinical stage						< 0.001
1	50 (45.0)	25 (24.5)	21 (12.6)	7 (5.5)	2 (3.1)	
2	28 (25.2)	39 (38.2)	68 (40.7)	28 (21.9)	10 (15.6)	
3	26 (23.4)	32 (31.4)	64 (38.3)	85 (66.4)	46 (71.9)	
4	7 (6.3)	6 (5.9)	14 (8.4)	8 (6.3)	6 (9.4)	
MELD score	8.0 ± 2.1	10.0 ± 2.9	10.0 ± 3.2	12.0 ± 3.7	13.0 ± 3.5	< 0.001
MELD-Na score	9.0 ± 2.6	11.0 ± 3.6	11.0 ± 3.9	13.0 ± 4.4	14.0 ± 4.4	< 0.001
Use of beta blocker	30 (27.0)	50 (49.0)	101 (60.5)	59 (45.1)	27 (37.5)	< 0.001
Death	7 (6.3)	7 (6.9)	30 (18.0)	20 (15.6)	22 (34.4)	< 0.001
Follow-up, mon	29 ± 20	25 ± 18	24 ± 17	25 ± 18	22 ± 16	0.069

Data are number (%) or mean ± SD values.  $\chi^2$  test and P trend or one-way analysis of variance as appropriate. Hemodynamic stage-1 (HS-1) groups 1–5 were defined as 6–9, 10–12, 13–16, 17–20, and > 20 mmHg, respectively.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CP = Child-Pugh, INR = international normalized ratio, MELD = model for end-stage liver disease.

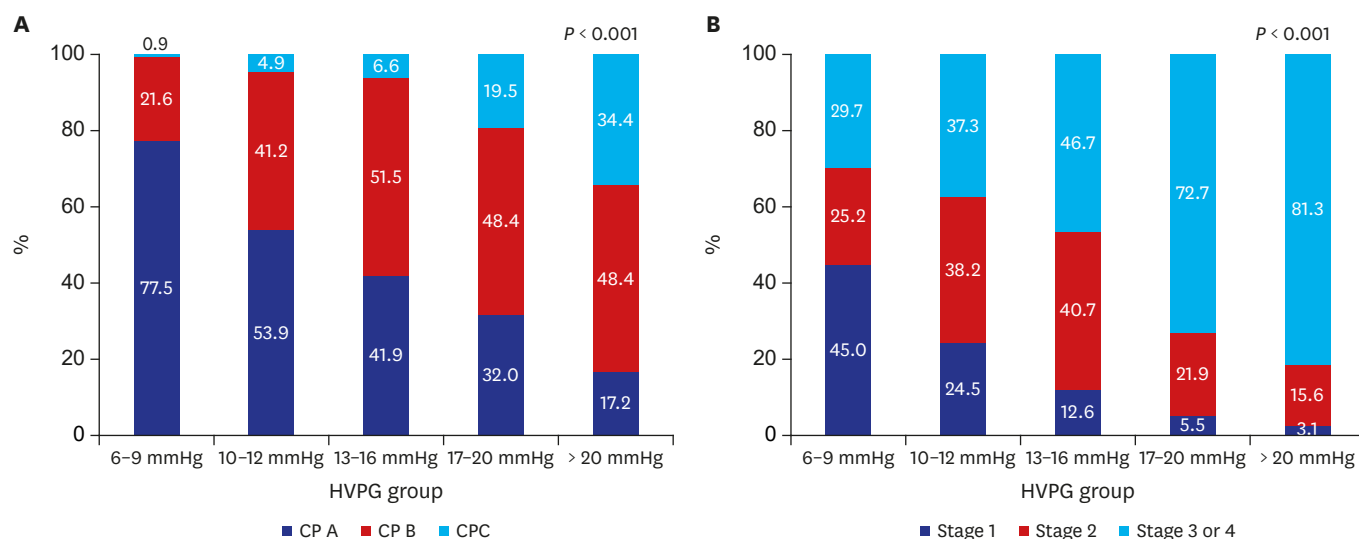


Fig. 2. CP class and clinical stage according to HVPG groups in the enrolled patients. The HVPG group was negatively correlated with (A) CP class and (B) clinical stage.

CP = Child-Pugh, HVPG = hepatic venous pressure gradient.

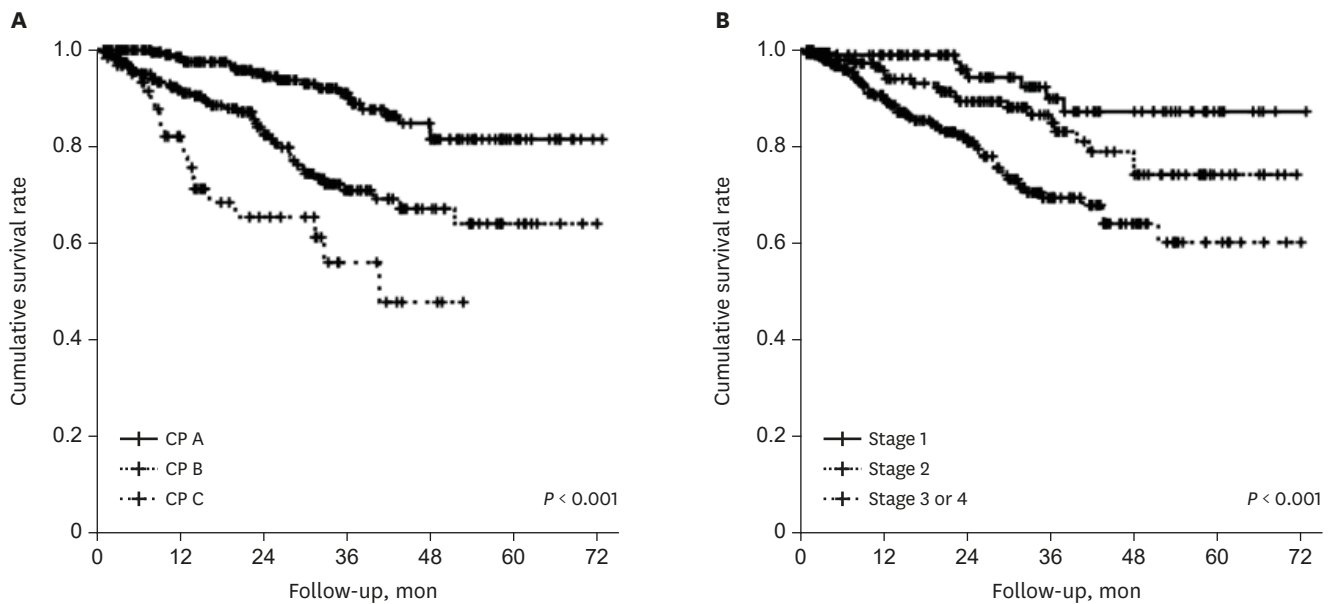
5.8%), and others (n= 4, 4.7%). Two patients underwent liver transplantation due to hepatic encephalopathy (10 months) and hepatic failure (20 months) and were counted as death.

The mortality rates differed significantly between CP classes A, B, and C (all  $P < 0.017$ , log-rank test with Bonferroni correction) (Fig. 3A), but not between clinical stages 3 and 4 (Supplementary Fig. 1). However, the cumulative survival rate was significantly higher for both clinical stages 1 and 2 than for the decompensated stage (both  $P < 0.017$ ) (Fig. 3B).

The numbers of deaths in HS-1 groups 1–5 during the follow-up period were 7 (6.3%), 7 (6.9%), 30 (18.0%), 20 (15.6%), and 22 (34.4%), respectively ( $P < 0.001$ ). The cumulative survival differed significantly between the following HS-1 groups: group 1 vs. group 3, group 1 vs. group 5, group 2 vs. group 5, and group 4 vs. group 5 (all  $P < 0.005$ , log-rank test with Bonferroni correction) (Fig. 4A). However, the use of the traditional HVPG cutoffs of 10 and 16 mmHg did not improve the discrimination of mortality. Dividing HS into the three groups for HS-2 (Supplementary Table 1) resulted in significant differences in the 1- and 3-year cumulative survival rates between HS-2 groups A, B, and C: 96.6% vs. 94.0% vs. 84.1% for the 1-year cumulative survival, respectively, and 91.4% vs. 75.3% vs. 57.1% for the 3-year cumulative survival ( $P < 0.017$ ) (Fig. 4B).

**Predictors of long-term mortality**

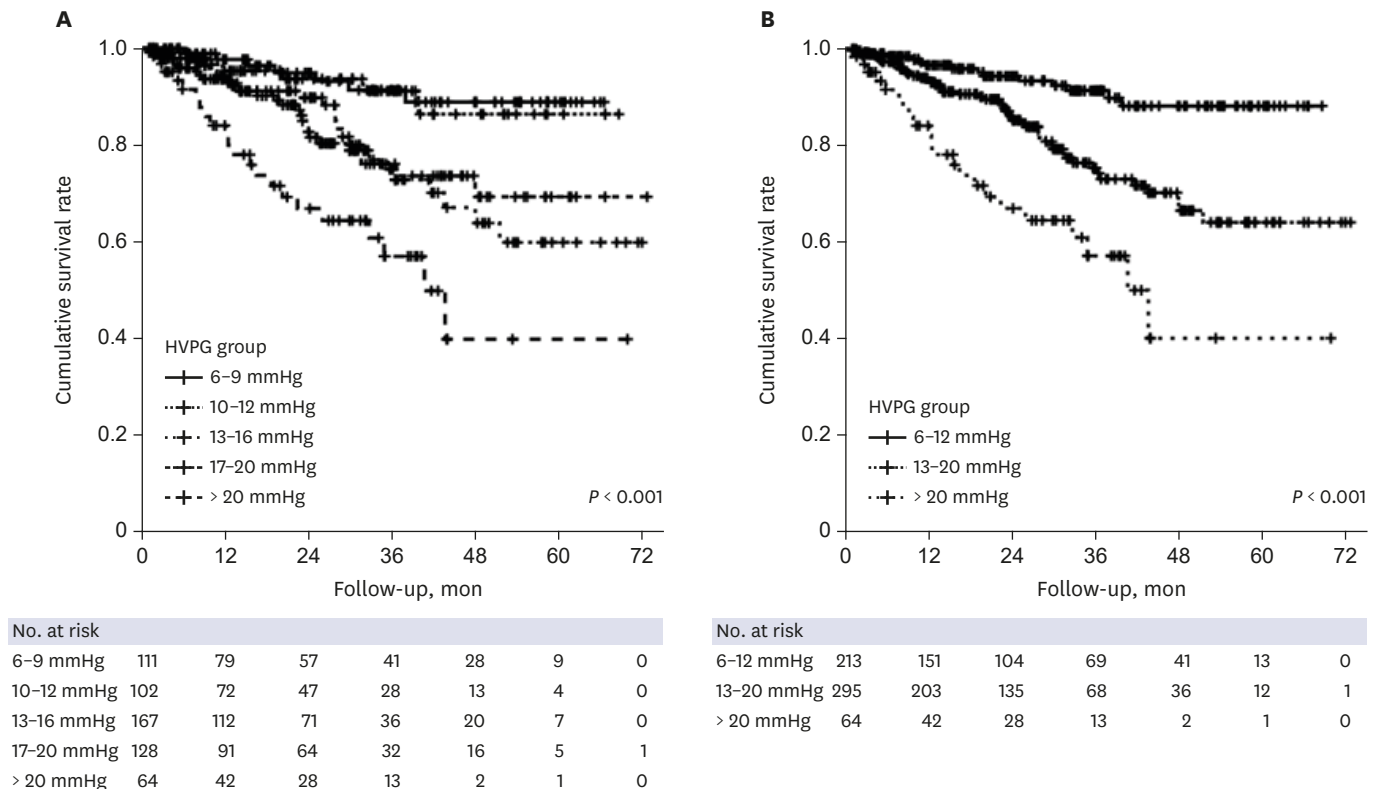
In the univariate analysis for death, the presence of ascites, serum albumin, bilirubin, serum alanine aminotransferase, prothrombin time, sodium level, CP score, CP class, decompensated stage (clinical stage 3 or 4), HVPG 13–20 mmHg or > 20 mmHg, MELD score, and MELD-Na score were related to long-term mortality (all  $P < 0.05$ ). The multivariate



No. at risk	0	12	24	36	48	60	72
CP A	263	198	142	88	50	18	1
CP B	245	159	105	54	26	8	0
CP C	64	39	20	8	3	0	0

No. at risk	0	12	24	36	48	60	72
Stage 1	105	87	60	37	24	8	1
Stage 2	173	119	87	52	32	11	0
Stage 3 or 4	294	190	120	61	23	7	0

**Fig. 3.** Cumulative survival according to CP class and clinical stage. (A) The mortality rate differed significantly between CP classes A, B, and C (all  $P < 0.001$ , log-rank test). (B) The cumulative survival rate was significantly higher for both clinical stages 1 and 2 than for the decompensated stage (both  $P < 0.001$ , log-rank test). CP = Child-Pugh.



**Fig. 4.** Cumulative survival according to HVPG groups with hemodynamic stage-1 (HS-1) and HS-2. **(A)** The cumulative survival differed between following HS-1 groups: group 1 vs. 3, group 1 vs. 5, group 2 vs. 5, and group 4 vs. 5 (all  $P < 0.001$ , log-rank test). **(B)** However, the use of the traditional HVPG cutoffs of 10 and 16 mmHg did not improve the discrimination of mortality. Dividing HS into three groups for HS-2 (6-12, 13-20, and > 20 mmHg) resulted in significant differences in the 1- and 3-year cumulative survival rates: 96.6%, 94.0%, and 84.1% for the 1-year cumulative survival, respectively, and 91.4%, 75.3%, and 57.1% for the 3-year cumulative survival ( $P < 0.001$ , log-rank test). HVPG = hepatic venous pressure gradient, HS = hemodynamic stage.

analysis used a Cox regression model that considered the serum albumin, serum sodium, CP class, and HS-2. Even when applying multiple models, the long-term mortality risk increased approximately two- and fourfold for HVPG 13-20 and > 20 mmHg, respectively (Table 3).

### Survival analysis in the presence of hypoalbuminemia and MELD groups

According to Cox regression, albumin was an independent risk factor for predicting a poor long-term survival (Table 3). The mortality rates were significantly higher for HVPG = 13-20 mmHg (HR, 2.54; 95% confidence interval [CI], 1.28-5.06;  $P = 0.008$ ) and HVPG > 20 mmHg (HR, 5.45; 95% CI, 2.55-11.62;  $P < 0.001$ ) than for HVPG 6-12 mmHg in patients with hypoalbuminemia (Fig. 5A). In contrast, there were no significant differences in mortality rates between HVPG groups in patients without hypoalbuminemia (Supplementary Fig. 2).

After dividing the patients into three MELD groups, the mortality rates in the intermediate-MELD-score group (score of 10-15) was significantly higher for HVPG 13-20 mmHg (HR, 3.86; 95% CI, 1.16-12.91;  $P = 0.028$ ) and HVPG > 20 mmHg (HR, 8.77; 95% CI, 2.41-31.94;  $P = 0.001$ ) than for HVPG 6-12 mmHg (Fig. 5B).



**Table 3.** Cox regression analysis of variable factors and HVPG grades for mortality

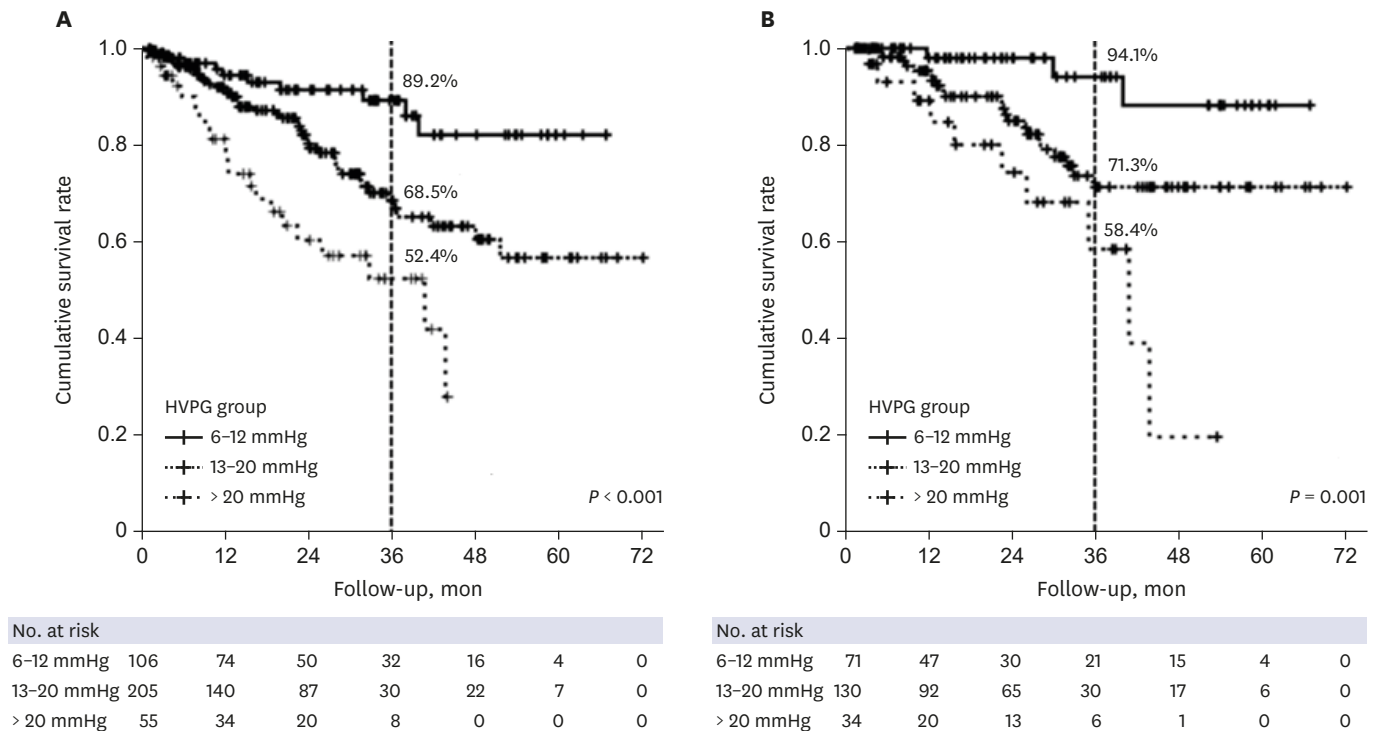
Characteristics	Univariate analysis		Model 1		Model 2		Model 3		Model 4	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Gender, men	1.33 (0.78–2.27)	0.288								
Age, yr	1.01 (0.99–1.03)	0.475								
Use of beta-blocker	1.49 (0.97–2.29)	0.066								
Presence of ascites	2.52 (1.62–3.93)	< 0.001								
Platelet count, 10 <sup>3</sup> /mL	1.00 (0.96–1.03)	0.790								
Albumin, 0.1 mg/dL	0.89 (0.86–0.93)	< 0.001	0.92 (0.88–0.97)	0.001			0.93 (0.88–0.99)	0.003	0.93 (0.88–0.97)	0.002
Bilirubin, mg/dL	1.39 (1.18–1.64)	<0.0001								
AST, U/L	1.00 (0.99–1.00)	0.309								
ALT, U/L	0.99 (0.99–1.00)	0.043								
INR, 0.1 increase	1.11 (1.03–1.19)	0.004								
Creatinine, 0.1 mg/dL	0.99 (0.90–1.10)	0.908								
Sodium, mEq/L	0.88 (0.84–0.93)	< 0.0001	0.94 (0.88–0.99)	0.022	0.93 (0.88–0.99)	0.014	0.93 (0.87–0.99)	0.018		
CP class	1.37 (1.25–1.52)	< 0.0001								
A	1				1					
B	2.87 (1.71–4.83)	< 0.001			1.91 (1.11–3.30)	0.019				
C	5.96 (3.22–11.06)	< 0.001			2.94 (1.46–5.92)	0.003				
Clinical stage										
3/4 vs. 1/2	2.51 (1.60–3.95)	< 0.001								
HVPG, mmHg	1.09 (1.05–1.12)	< 0.001								
6–12	1		1		1		1		1	
13–20	2.91 (1.61–5.27)	< 0.001	2.10 (1.13–3.91)	0.019	2.16 (1.18–3.99)	0.014	2.19 (1.18–4.06)	0.013	2.07 (1.12–3.83)	0.021
> 20	6.48 (3.31–12.7)	< 0.001	3.89 (1.88–8.06)	< 0.001	3.70 (1.79–7.65)	< 0.001	3.99 (1.92–8.28)	< 0.001	3.87 (1.87–8.00)	< 0.001
MELD score	1.12 (1.06–1.18)	< 0.0001								
MELD-Na score	1.12 (1.07–1.18)	< 0.001								

Model 1: including sex, age, use of beta-blocker, presence of ascites, albumin, bilirubin, ALT, INR, sodium level, and HVPG grade; Model 2: including sex, age, use of beta-blocker, ALT, sodium level, CP class, and HVPG grade; Model 3: including sex, age, use of beta-blocker, albumin, ALT, sodium level, clinical stage 3 or 4, MELD score, and HVPG grade; Model 4: including sex, age, use of beta-blocker, albumin, ALT, clinical stage 3 or 4, MELD-Na score, and HVPG grade  
 ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, CP = Child-Pugh, HR = hazard ratio, HVPG = hepatic venous pressure gradient, INR = international normalized ratio, MELD = model for end-stage liver disease.

## DISCUSSION

This large-scale retrospective cohort study was designed to evaluate the natural course of various stages of non-critically-ill cirrhotic patients and the clinical implications of HVPG values on the long-term prognosis in real-life situations. Several previous Western studies have found the HVPG to be clinically significant in the prognosis of compensated and decompensated cirrhotic patients,<sup>1,9,14,25</sup> but it had not been determined in a large population study whether this is also the case in Asians. The present study investigated the factors that influence the survival of cirrhotic patients and the clinical value of the HVPG in non-critically-ill Asian cirrhotic patients. We excluded patients in an active state related to hemodynamic instability, and measured the HVPG in the highly stable, non-critically-ill situation to reflect the real baseline PHT condition in each patient.

As we expected, the presence of compensation or decompensation exerted absolutely different effects on the prognosis. In the presence of compensation, survival was significantly better in patients without varices (stage 1) than in patients with varices (stage 2), but it did not differ between clinical stage 3 (ascites with/without variceal hemorrhage) and stage 4 (variceal hemorrhage with/without ascites). This finding is similar to recent Western data,<sup>26</sup> and it suggests that primary treatment and secondary prophylaxis of variceal bleeding and antibiotics improve the outcome of variceal hemorrhage over a timescale of years, whereas the treatments applied to ascites have not changed or improved over a timescale of several decades. This finding is also consistent with the categorical HVPG stages (i.e., HS). As HS increases, the compositions of clinical stage 3 (ascites) also increase, while those of clinical



**Fig. 5.** Cumulative survival according to patients with hypoalbuminemia and an intermediate MELD score. **(A)** The mortality rates was significantly higher for HVPG 13-20 mmHg (HR, 2.54; 95% CI, 1.28-5.06;  $P = 0.008$ ) and HVPG > 20 mmHg (HR, 5.45; 95% CI, 2.55-11.62;  $P < 0.001$ ) than for HVPG 6-12 mmHg in patients with hypoalbuminemia. **(B)** When we divided the MELD scores into three groups (6-9, 10-15, and  $\geq 16$ ), in the intermediate-MELD-score group (score of 10-15), the mortality rates was significantly higher for HVPG 13-20 mmHg (HR, 3.86; 95% CI, 1.16-12.91;  $P = 0.028$ ) and HVPG > 20 mmHg (HR, 8.77; 95% CI, 2.41-31.94;  $P = 0.001$ ) than for HVPG 6-12 mmHg. CI = confidence interval, HR = hazard ratio, HVPG = hepatic venous pressure gradient, MELD = model for end-stage liver disease.

stage 4 do not show any trend with HS. This finding is also consistent with previous data that not only PHT but also hepatic insufficiency and other factors such as infection and low-grade inflammation induced by bacterial translocation might be more important in decompensated cirrhosis.<sup>18</sup> The HVPG therefore appears to have a greater prognostic meaning in compensated cirrhosis than in decompensated cirrhosis.<sup>1</sup>

The present study also found that the traditional HVPG cutoffs of 10 and 16 mmHg did not produce an appropriate discriminative ability for the prognosis. Even though we measured the HVPG in a highly controlled state, hemodynamics can be affected by various factors throughout the lifetime. Therefore, adopting a single critical HVPG cutoff for various clinical situations and etiologies appears to be too strict and less reliable in real clinical practice; for example, the differences between CP scores of 6 and 7 or 9 and 10 are not weighted in a real clinical situation. The HVPG interval between 10 and 12 mmHg is also too narrow to distinguish between compensation with varices formation and decompensation with variceal hemorrhage.<sup>1</sup> Applying the same HVPG cutoff to the risks of variceal hemorrhage and ascites development is also questionable given the differences in their developmental pathophysiologies.<sup>27</sup> For these reasons, we applied categorical values of the HVPG severity as for the CP class. According to HS-2, each of HVPG groups A, B, and group C showed excellent discriminative ability for the long-term mortality in any models, including traditional prognostic factors (Table 3). This categorical model can be helpful for developing more reliable noninvasive surrogate markers for estimating the severity of PHT and the treatment response in future clinical practice.

An HVPG of 10 mmHg has been accepted as an absolute cutoff for clinically significant PHT in many previous studies, especially for the development of varices and the progression from compensated to decompensated cirrhosis. However, we did not use this cutoff of 10 mmHg in the present study for several reasons. First, an HVPG of 10 mmHg did not show prognostic value for long-term mortality in our cohort. An HVPG cutoff of 10 mmHg is based on varix development, and it is relatively low and therefore not appropriate for predicting the long-term mortality in cirrhotic patients. The recent decrease in variceal hemorrhage-related mortality and relative increases in the rates of death and acute decompensation related to ascites such as spontaneous bacterial peritonitis, refractory ascites, or hepatorenal syndrome have also increased the need to increase the HVPG cutoff.

Comparing the usefulness of the HVPG and MELD score for determining the long-term prognosis in cirrhotic patients is controversial.<sup>26,28</sup> The advantage of the HVPG over the CP or MELD score in predicting prognosis is that it reflects PHT and the hemodynamic component directly, and hence the HVPG has been accepted as the most important predictive parameter especially in compensated cirrhosis.<sup>14</sup> In contrast, the prognostic ability of HVPG in decompensated cirrhosis is more controversial because, as mentioned above, extrahemodynamic factors such as hepatic insufficiency and cardiorenal insufficiency have greater influences on the prognosis, and so the MELD or MELD-Na score has been accepted as a more reliable index in this phase. However, combining the use of the HVPG and the MELD/MELD-Na score has been considered to not improve the prognostic accuracy.<sup>9</sup> In general, a MELD score of > 15 is accepted as indicating the need for liver transplantation, but the clinical meaning of an intermediate MELD score (10–15) is not clear, and there have been difficulties in predicting the prognosis and making clinical decisions in this group.

In the present study, the new categorical staging of HS-2 showed an additional discriminative ability in this intermediate-MELD-score group, with the 3-year survival rates for HVPG 13–20 and > 20 mmHg being only 71% and 58%, respectively. This finding suggests that additional information about the HVPG stages can be helpful for identifying patients in the intermediate-MELD-score group who should be considered for early liver transplantation. Additionally, the new HS-2 staging was also helpful in discriminating patients with hypoalbuminemia at risk of early mortality. The combination of the MELD score and HVPG also showed additive prognostic values in the low- and high-MELD-score groups in this study. Patients with an HVPG of > 12 mmHg in the low-MELD-score group (MELD score < 10) and those with an HVPG of > 20 mmHg in the high-MELD-score group (MELD score > 15) also exhibited a trend for poor prognoses (**Supplementary Fig. 3**).

This study was subject to some limitations: 1) the data were collected retrospectively, and the effects of medical treatment such as antiviral therapies could not be analyzed although the proportion of patients who received this treatment was small; 2) only survival data were collected and we did not analyze the development of new acute decompensation during the follow-up; 3) the HVPG was measured by a different operator in each institute and we were unable to calculate the interoperator variability; however, all operators were experts who had sufficient experience in this field and 4) the new HS-2 standard is validated in only specific cohorts and it could not be applied to all the cirrhotic patients. And finally, this study is cross-sectional and only one-time point of HVPG was measured. Therefore, this study could not analyze the prospective effect of other prognostic factors such as ingrowing bacterial translocation as well as treatment of cirrhosis etiology or non-selective beta blocker application as time goes by.

In conclusion, the present study has validated the natural course of cirrhosis and the role of the HVPG in a large Asian population cohort. The presence of compensation or decompensation of cirrhosis showed absolutely different prognoses; however, the stratification of decompensation according to the presence of variceal hemorrhage or ascites was not appropriate for discriminating the prognosis. The new categorized HS staging showed a good prognostic predictive ability, with indeed the combination of the MELD score and HS-2 in the intermediate-MELD-score population providing significant improvements in the prediction of prognosis. These findings suggest that this categorical HS can be helpful in estimating the severity of PHT and treatment responses on the basis of real clinical practice.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Patient characteristics and prognostic stages according to HS-2

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### Supplementary Fig. 1

Cumulative survival rate according to each clinical stage based on the severity of portal hypertension. The cumulative survival rates differed significantly with clinical stage ( $P < 0.001$ ). However, the mortality rate did not differ significantly between clinical stages 3 and 4.

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### Supplementary Fig. 2

Cumulative survival rate according to hemodynamic stage-2 (HS-2) groups in patients without hypoalbuminemia. The cumulative survival rate did not differ significantly between the HVPG groups in patients without hypoalbuminemia.

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### Supplementary Fig. 3

Cumulative survival rate according to HS-2 groups in patients with low MELD scores and high MELD scores. Combining the MELD score and HVPG also showed an additive prognostic value in the groups with (A, B) low and (C, D) high MELD scores in this study. (B) Patients with an HVPG of  $> 12$  mmHg in the low-MELD-score group (MELD score  $< 10$ ) and (D) patients with an HVPG of  $> 20$  mmHg in the high-MELD-score group (MELD score  $> 15$ ) also presented a trend for poor prognoses.

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