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Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy ☆,☆☆

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***Background/Aims*: In acute variceal bleeding (AVB) hepatic venous pressure gradient (HVPG) is associated with prognosis. However, this has not been studied in patients receiving the currently recommended therapy. We evaluate here the performance of early HVPG measurement as a predictor of treatment failure in patients with acute variceal bleeding managed with the current standard treatment and whether clinical variables might be of similar predictive accuracy.**

***Methods*: We included 117 patients with AVB in whom HVPG was measured within 48 h of admission. The main endpoint was 5-day failure, a composite of uncontrolled bleeding, early rebleeding or death within 5 days.**

***Results*: Eighteen patients (15%) had 5-day failure. Multivariate analysis identified three variables independently associated with 5-day failure: HVPG $\geqslant$20, systolic blood pressure at admission <100 mm Hg and non-alcoholic cause of cirrhosis. The discriminative capacity of this model was good (*c* statistic: 0.79). When only clinical variables were included in the analysis, Child–Pugh class, systolic blood pressure at admission and etiology were the independent predictors. This model had also a good discriminative ability (*c* statistic: 0.80).**

***Conclusions*: HVPG independently predicts short-term prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy, but similar predictive accuracy can be achieved using only simple clinical variables that have universal applicability.**

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***Keywords*: Portal hypertension; Endoscopy; Prognostic models**

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1. Introduction

Acute variceal bleeding is a major complication of cirrhosis. Despite the improvement in prognosis in the last decades [1–3], mortality from the acute bleeding episode is still high, of about 15–20% [1–4]. Several studies have defined a number of factors associated with a poor outcome in acute variceal bleeding [4–6]. Theoretically, these factors could be used to stratify patients in different risk groups [5] and, thus, to tailor management to the underlying risk of treatment failure. However, in most centers all patients are treated in the same way regardless of the likelihood of a good or a bad outcome [7].

Previous studies have shown that in patients with acute variceal bleeding a HVPG $\geqslant$20 mm Hg, measured in the first 48 h of admission for bleeding, is associated with a poor outcome [5,8,9]. In a recent randomized trial it was suggested that HVPG could be used to select those patients that could benefit from the early initiation of more aggressive treatments, such as TIPS [9]. However, the previous studies establishing the poor prognosis of patients with acute variceal bleeding and HVPG $\geqslant$20 mm Hg were done at a time when the standard therapy for variceal bleeding was monotherapy (vasoactive drugs or sclerotherapy), which was associated with a rate of treatment failure of 30–40% [5,6,9], while with current recommended treatment (vasoactive drugs from admission to the hospital + endoscopic therapy at the time of diagnostic endoscopy + prophylactic antibiotics) the risk of failure is much lower, of 15–20% [1–3,10,11]. On the other hand, HVPG is a simple technique but it is not available in every center and, therefore, its applicability in patients with acute variceal bleeding would be presumably low. Therefore, whether the risk of failure in these patients could be predicted with similar accuracy by using clinical, easily-obtained variables is of obvious relevance.

The aims of this study were to evaluate the performance of early HVPG measurement as a predictor of treatment failure in a large multicenter cohort of patients with acute variceal bleeding managed with the current standard treatment and to evaluate whether clinical variables may be of similar predictive accuracy as the measurement of HVPG.

2. Methods

2.1. Study cohort

We retrospectively reviewed the data of cirrhotic patients with portal hypertension admitted to four Spanish hospitals with acute variceal bleeding between January 1996 and March 2003. These four centers have been co-operating in a series of studies on portal hypertension and variceal bleeding [12–17] and applying uniform criteria for diagnosis, treatment and measurements of HVPG. Inclusion criteria for the present study were: diagnosis of cirrhosis (based on liver biopsy and/or unequivocal clinical data and compatible findings on imaging techniques); acute bleeding from esophageal varices confirmed by emergency endoscopy according to Baveno II–IV definitions; treatment of the acute bleeding episode with a combination of vasoactive drugs from admission (somatostatin or octreotide), early endoscopic therapy (band ligation or sclerotherapy within 12 h from admission at the time of diagnostic endoscopy) and antibiotic prophylaxis; and HVPG measurement within 48 h from admission to the hospital. Patients with advanced hepatocellular carcinoma at baseline (a single nodule of more than 5 cm or more than three nodules >3 cm), cholestatic liver disease, portal vein thrombosis and those in whom the outcome could not be assessed were not considered for the study. The time of admission to hospital was considered the time zero for the follow-up. Prognostic variables were recorded at admission. The diagram in Fig. 1 shows the flow of patients included in the study cohort.

2.2. Hemodynamic measurements

All four centers have wide experience in HVPG measurements that were conducted according to published recommendations [18–20]. All studies were performed after the initial resuscitation, and with the patient in hemodynamically stable conditions (absence of signs of hypoperfusion, heart rate <120 bpm and systolic blood pressure >90 mm Hg), a median of 30 h after admission (range 2–48). Seven patients (6%) were admitted more than 24 h after the initial manifestation of bleeding. HVPG was measured as previously described [18]. In brief, under local anesthesia, a venous introducer was placed in the right femoral vein or internal jugular vein by the Seldinger technique. Under fluoroscopy, a 7F balloon-tipped catheter (Boston Scientific Medi-Tech, Natick, MA, USA) was guided into the main right hepatic vein for measurements of wedged (occluded) and free hepatic venous pressures (WHVP and FHVP). Portal pressure was measured as the HVPG – the difference between WHVP and FHVP [18,19], while off vasoactive drug-therapy for at least 30 min. Permanent tracings of the hemodynamic studies were reviewed under blind conditions specifically for this study.

2.3. Definitions

According to the Baveno consensus workshops, failure to control bleeding was defined as the inability to achieve a 24-h bleeding-free period in the first 48 h of admission [21]. Early rebleeding was defined as any further significant bleeding within the first 5 days of admission [21]. Bleeding related mortality was defined as any death occurring within 42 days of admission [21].

The primary endpoint analyzed was 5-day failure, a composite of uncontrolled bleeding, early rebleeding or death within 5 days, whichever occurs first [21]. Secondary endpoint was bleeding related mortality.

2.4. Statistical analysis

The discriminative ability of HVPG to predict 5-day failure was assessed by ROC analysis. The HVPG value that maximized the sum of sensitivity and specificity (i.e. that with highest Youden's index) was considered as the best cut-off. The relationship between the different variables and the risk of developing the events was analyzed by logistic regression. The contribution of each variable to the risk of developing the endpoint is reported as the odds ratio (OR) with 90% confidence intervals [22]. Tested variables included HVPG $\geqslant$20 mm Hg, demographic data [age, gender, etiology of cirrhosis (alcoholic *vs* non-alcoholic), presence of active alcoholism], liver function (Child class and MELD score), data related to the severity of the bleeding (active bleeding at endoscopy, systolic blood pressure at admission, hematocrit at admission) and presence of infection at admission. For the purpose of the analysis, patients with both viral infection and a history of alcohol consumption were considered to have cirrhosis of viral etiology [23].

The independent predictive value of HVPG was tested in multivariable analysis. Due to the expected correlation between variables and the low number of events, a pre-planned hierarchic multivariable analysis was conducted [24]. In this analysis, HVPG $\geqslant$20 mm Hg was entered in a first block, since the primary aim of the study was to eval-

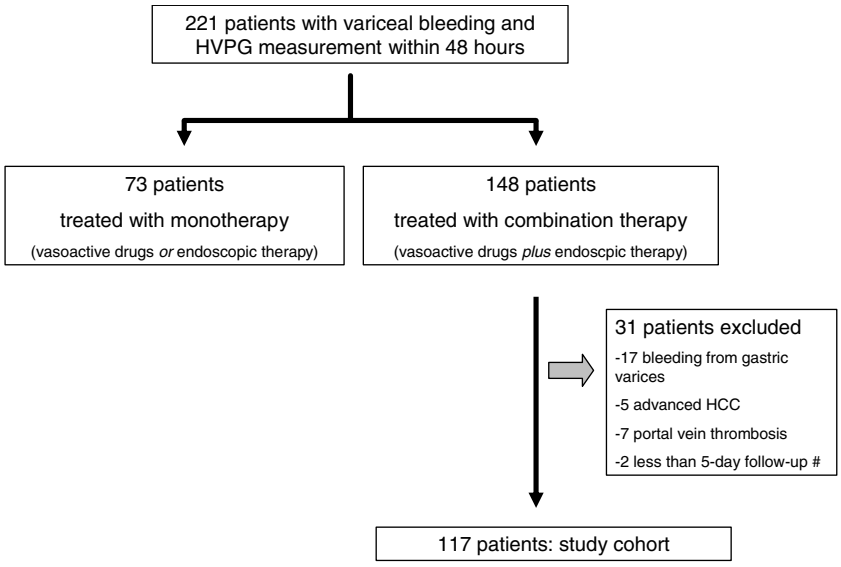

Fig. 1. Flow diagram showing the disposition of the patients. #1 patient transferred to another hospital, 1 patient voluntary discharged.

uate the predictive value of HVPG. Parameters of liver function were entered in a second block, presence of infection at admission in a third block, severity of bleeding in a fourth block and demographic data in a fifth block. Backward stepwise regression was performed after the incorporation of every new block, and variables explaining a statistically significant proportion of the variance ($p < 0.1$) were maintained in the model. A similar analysis was conducted without the first block (HVPG) to check the predictive ability of clinical variables. Finally, to check the validity of our hierarchic approach and the robustness of our final predictors, we conducted non-hierarchic, unrestricted bootstrapping logistic regression analysis [25,26]. In this analysis 500 samples of 117 patients were randomly selected with replacement [25,26]. For each sample, we conducted stepwise regression analysis, and the number of times each variable appeared on the final models was tabulated. Variables that appear in 50% or more of the models can be considered reliable predictors of the outcome [27].

All reported p values are two-sided. Statistical analysis was performed with SPSS 12.0 package (SPSS, Chicago, IL). Bootstrapping analysis was performed with the macro *regressionbootstrap* provided with the SPSS 12 package, modified by the investigators for the performance of logistic regression.

3. Results

3.1. HVPG and 5-day failure

Eighteen patients (15%) developed the primary endpoint (5-day failure). ROC curve confirmed 20 mm Hg as the best cut-off to predict 5-day failure. A HVPG between 16 and 20 mm Hg was not associated with an increased risk of failure as compared with a HVPG between 12 and 16 mm Hg. Table 1 shows the baseline characteristics of the patients according to HVPG. Patients with HVPG $\geqslant$20 mm Hg were younger, more frequently alcoholics and had more frequently ascites, higher bilirubin, Child–Pugh and MELD scores, and lower albumin and systolic blood pressure at admission than patients with HVPG <20 mm Hg. There was a strong relationship between the presence of HVPG $\geqslant$20 mm Hg and Child–Pugh class (Fig. 2).

Three out of 50 patients with a HVPG less than 20 mm Hg developed 5-day failure, while this occurred in 15 out of 67 patients with a HVPG $\geqslant$20 mm Hg (OR: 4.52; 90% CI: 1.52–13.46; $p = 0.015$). The finding of a HVPG $\geqslant$20 mm Hg had a sensitivity of 83% (90% CI: 65–93), specificity of 48% (90% CI: 39–56), positive predictive value of 22% (90% CI: 14–31), negative predictive value of 94% (90% CI: 89–100), positive likelihood ratio of 1.59 (90% CI: 1.26–2.01) and negative likelihood ratio of 0.35 (90% CI: 0.15–0.85) to predict 5-day failure. In addition, patients with a HVPG $\geqslant$20 mm Hg had significantly greater transfusion needs, significantly longer ICU stay and needed more frequently derivative treatment (Table 2).

Table 3 shows the results of univariable analysis for the prediction of 5-day failure. HVPG $\geqslant$20 mm Hg, sex, active alcoholism, systolic blood pressure at admission <100 mm Hg, hematocrit on admission, albumin, presence of ascites and Child class were significantly associated with the risk of 5-day failure. Hierarchic multivariable analysis (performed as described in methods) identified three variables independently associated with 5-day failure: HVPG $\geqslant$20 mm Hg, systolic blood pressure at admission <100 mm Hg and non-alcoholic etiology of cirrhosis (Table 4). No significant interactions were detected between these variables. A model generated with these three variables had a good discriminative capacity (c statistic: 0.79, 90% CI 0.70–0.88; Fig. 3). The risk of 5-day failure of a non-alcoholic patient with a HVPG $\geqslant$20 mm Hg and a systolic blood pressure at admission <100 mm Hg was 60%. Bootstrapping analysis showed that HVPG was selected in more than 50% of the final models, indicating that it is a robust prognostic predictor. Additional variables selected in more than 50% of the models included Child–Pugh class, systolic blood pressure <100 mm Hg, non-alcoholic etiol-

Table 1
Clinical characteristics of the patients at admission according to baseline HVPG

	HVPG <20 mm Hg ($n = 50$)	HVPG ⩾20 mm Hg ($n = 67$)	p value
Age	60 (13)	56 (13)	0.046
Male sex [n (%)]	33 (66%)	49 (73%)	0.404
Etiology [n alcoholics (%)]	18 (36%)	37 (55%)	0.039
Encephalopathy [n (%)]	4 (8%)	9 (13%)	0.355
Previous variceal bleeding [n (%)]	15 (30%)	17 (25%)	0.676
Ascites [n (%)]	20 (40%)	44 (66%)	0.006
Bilirubin (mg/dL)	2.0 (1.8)	2.7 (2.2)	0.044
Albumin (g/L)	29.2 (4.9)	27.5 (5.0)	0.066
Child–Pugh score (points)	7.3 (1.4)	8.5 (1.8)	0.001
Child–Pugh (%A/B/C)	36/56/8	13/55/31	0.001
MELD score	9.3 (4.1)	12.0 (4.3)	0.001
Systolic blood pressure	118 (23)	111 (22)	0.075
Systolic blood pressure <100 mm Hg [n (%)]	10 (20%)	26 (39%)	0.029
Heart rate (bpm)	97 (18)	101 (17)	0.260
HVPG (mm Hg) (median/range)	16 (12–19)	24 (20–35)	–
Hematocrit (%)	30 (6)	28 (6)	0.199
Active bleeding at endoscopy [n (%)]	10 (20%)	20 (30%)	0.227
Endoscopic therapy [n (%)]			0.793
Sclerotherapy	37 (74%)	52 (78%)	
Band ligation	13 (26%)	15 (22%)	
Vasoactive therapy [n (%)]			0.275
Somatostatin	40 (80%)	60 (90%)	
Octreotide	10 (20%)	7 (10%)	
Infection at admission [n (%)]	4 (8%)	8 (12%)	0.487

All results are expressed in means (SD) unless otherwise stated.

ogy, infection at admission, and hematocrit at admission.

3.2. Clinical predictors of 5-day failure

Using a similar hierarchic strategy, we repeated the analysis of prognostic indicators excluding HVPG, so that only clinical variables were tested. In this analysis Child–Pugh class, systolic blood pressure ⩽100 mm Hg and etiology were independent predictors of 5-day failure (Table 4). These were the variables most frequently selected in bootstrapping-derived clinical models. Again, no significant interactions were detected between these variables. The model had a good discriminative ability (c statistic: 0.81, 90% CI: 0.72–0.90; Fig. 3), very similar to that of the model including HVPG. Based on the regression coefficients of these variables, we derived a simple score in which 1 point was assigned to systolic blood pressure ⩽100 mm Hg, 1 to non-alcoholic cirrhosis, 1 to Child B patients and 2 to Child C patients. This identified three groups of patients with variceal bleeding with different prognosis: low-risk (0–1 points, $n = 44$),

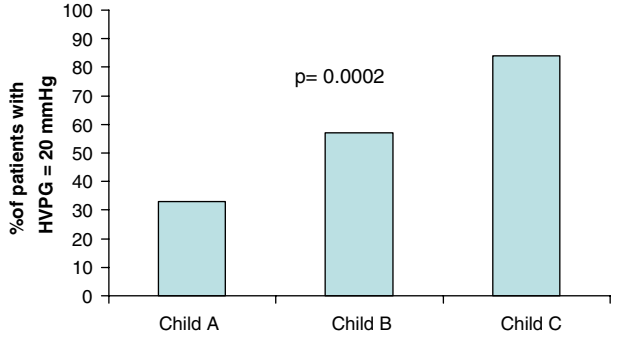

Fig. 2. Relationship between the presence of HVPG ⩾20 mm Hg and Child–Pugh class. p value corresponds to the linear trend. [This figure appears in colour on the web].

Table 2
Outcomes according to HVPG

	HVPG <20 mm Hg ($n = 50$)	HVPG ⩾20 mm Hg ($n = 67$)	p value
5-Day failure	3 (6%)	15 (22%)	0.015
Failure to control bleeding	2 (4%)	4 (6%)	0.663
Early rebleeding (within 5 days)	1 (2%)	15 (22%)	0.001
5-Day mortality	1[a] (2%)	1[a] (2%)	0.834
Need for emergency TIPS or porto-caval shunt	1 (2%)	11 (16%)	0.011
Days of ICU (means ± SD)	4.9 ± 2.4	6.0 ± 3.0	0.034
Days of in-hospital stay (means ± SD)	13.3 ± 7.0	13.1 ± 7.0	0.910
Blood transfusion (units of PRC) (median, range)	2 (0–7)	4 (0–16)	0.003
6-Week mortality	3 (6%)	5 (8%)	0.756

All results expressed in n (%). ICU, intensive care unit; PRC, packed red cells.

[a] Both patients had developed early rebleeding before dying.

Table 3
Univariable analysis: risk of 5-day failure

Variable	OR (90% CI)	*p* value
HVPG ⩾20 mm Hg	4.52 (1.52–13.46)	0.023
Age (per year increase)	1.00 (0.97–1.04)	0.883
Female sex	2.81 (1.19–6.64)	0.049
Non-alcoholic etiology	2.65 (1.05–6.70)	0.076
Active alcoholism	0.29 (0.11–0.73)	0.028
Systolic BP <100	4.65 (1.93–11.23)	0.004
Initial hematocrit (per 1% increase)	0.92 (0.86–0.98)	0.038
Active bleeding at endoscopy	1.56 (0.63–3.88)	0.416
Creatinine (per 1 mg/dl increase)	1.71 (0.63–4.60)	0.375
Albumin (per 1 g/l increase)	0.79 (0.71–0.89)	0.001
Bilirrubin (per 1 mg/dl increase)	1.09 (0.91–1.31)	0.442
Prothrombin ratio (per 1% increase)	0.98 (0.95–1.01)	0.289
Ascites	5.10 (1.71–15.20)	0.014
Encephalopathy	1.00 (0.26–3.82)	1.000
Child–Pugh class		0.040
B vs A	4.73 (0.80–27.70)	
C vs A	10.11 (1.62–62.99)	
MELD (per 1 point increase)	1.06 (0.96–1.17)	0.317
Infection at admission	3.25 (1.07–9.89)	0.081

intermediate risk (2 points, $n = 43$) and high-risk (3–4 points, $n = 30$), with a 2%, 12% and 40% risk of 5-day failure (p value for the linear trend 0.00003). The likelihood ratios associated with each category were 0.128 (0.025–0.643), 0.705 (0.364–1.364) and 3.667 (2.346–5.370), respectively.

3.3. Mortality

Mortality in this study was low (6%) and not different between patients with HVPG higher or lower than 20 mm Hg (Table 2). At univariable analysis mortality was significantly associated with variables reflecting liver function [albumin, bilirubin, presence of ascites, MELD and Child–Pugh class (0% in Child–Pugh A, 5% in Child–Pugh B and 20% in Child–Pugh C)] and with the development of infection during admission. Multivariable analysis was not performed due to the low rate of events.

Table 4
Mutivariable models for 5-day failure

	OR (90% CI)
Model with all variables	
HVPG ⩾20 mm Hg	5.44 (1.67–17.69)
Systolic blood pressure <100	4.94 (1.88–13.02)
Non-alcoholic etiology	4.96 (1.73–14.27)
Model excluding HVPG	
Child class	
Child B vs A	6.41 (1.01–40.75)
Child C vs A	17.61 (2.37–130.89)
Systolic blood pressure <100	5.54 (2.03–15.17)
Non-alcoholic etiology	6.66 (2.00–22.17)

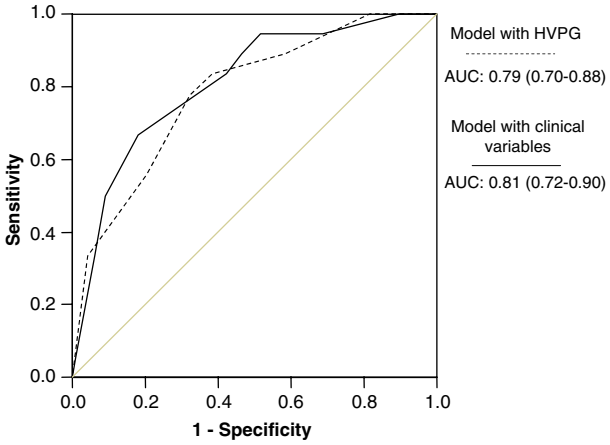

Fig. 3. ROC curves of the models generated with and without hepatic venous pressure gradient (HVPG) (AUC, area under curve). [This figure appears in colour on the web].

4. Discussion

Previous studies have shown that in patients with cirrhosis admitted for acute variceal bleeding the early measurement of HVPG is a strong prognostic indicator, a HVPG value above 20 mm Hg being associated with an increased failure rate, of about 50% [5,9]. This raised the question of whether early measurements of HVPG in variceal bleeding could be used to select patients for a more aggressive initial management. In a study by Monescillo et al. [9], 52 patients with initial HVPG ⩾20 mm Hg were randomized to standard therapy or TIPS. The standard therapy in this study was initial somatostatin treatment followed by endoscopic sclerotherapy and oral norfloxacin. However, somatostatin was stopped after sclerotherapy, which means that patients were under drug therapy for less than 4 h. The failure rate in patients in the standard care arm was 50%, as compared with 12% failure rate in patients randomized to TIPS. However, the probability of 5-day failure in more recent trials using endoscopic treatments in combination with vasoactive drugs maintained for 2–5 days in association with antibiotic prophylaxis was 14–20% [10,11,28], much lower than the 40% failure rate reported for patients treated with either endoscopic or pharmacological therapy alone [28,29]. Therefore, whether the finding of HVPG ⩾20 mm Hg in patients treated according to current recommendations still reflects a high risk of treatment failure remained conjectural.

In the present study, in which all patients received combination therapy for acute variceal bleeding, we show that the risk of 5-day failure in patients with HVPG ⩾20 mm Hg is 4 times greater than in patients with HVPG <20 mm Hg. However, the failure rate in this high-risk group was relatively low. This indicates that the improved prognosis of acute variceal bleeding in patients with cirrhosis observed in recent years is also

observed in the high-risk group, to a point that questions making the decision for an aggressive, expensive therapy such as TIPS on the basis of a HVPG $\geqslant$20 mm Hg, since 78% of patients in this group had an uneventful outcome on combined medical therapy. We concentrated our analysis in a composite endpoint, 5-day failure, since 5 days is, by consensus, the time frame for the acute variceal bleeding episode [7,21]. This is a meaningful endpoint since it has been associated with increased mortality, need of rescue therapies, increased resource consumption and increased hospital stay and has been used in recent trials [10] and recommended at the Baveno IV Consensus Workshop [7].

The predictive capacity of HVPG was improved by the use of additional variables reflecting the severity of bleeding (systolic blood pressure at admission <100 mm Hg) and the demographics of the patient (non-alcoholic etiology of liver cirrhosis). It is important to note that in our hierarchic strategy of analysis Child class (one of the most robust prognostic predictors in acute variceal bleeding) was not an independent predictor of 5-day failure in the presence of HVPG. This was probably related to the fact that the presence of a HVPG $\geqslant$20 mm Hg was strongly related to Child–Pugh class, a finding already observed in previous studies [30,31].

Since HVPG is not universally available (especially in emergency situations), the analysis was repeated without including HVPG. In this setting, the Child–Pugh class became a strong independent predictor of failure, together with systolic blood pressure and etiology. It is important to remark that prognosis in acute variceal bleeding could be established with similar accuracy with only these clinical variables (easily obtainable at the bedside) as in the model including HVPG. This finding could be of practical relevance both for establishing decision rules in clinical management and for stratification in future clinical trials.

Child–Pugh class was clearly the most robust predictor of 5-day failure, since it was the variable most frequently present in bootstrapping-derived models. Of note, this was not so for MELD score, which was selected in less than 50% of the models. Regarding the other prognostic predictors, admission systolic blood pressure <100 mm Hg is likely to reflect the severity of bleeding. This cut-off was already found to be of prognostic relevance in previous studies [1,11,28]. It must be noted, however, that systolic blood pressure might reflect not only the severity of bleeding but also the severity of liver disease and concomitant conditions such as infection [30,32,33]. However, its prognostic value was statistically independent of liver function and no significant interactions were observed between this variable and Child–Pugh class. The other independent prognostic indicator of failure was a non-alcoholic etiology of cirrhosis. The presence of a non-alcoholic cause of cirrhosis was a strong predictive factor of failure. The reasons for this finding are unclear, but a better prognosis in alcoholic patients was already observed in the paper by Malinchoc et al., in which the MELD score was originally developed [23]. It could be hypothesized that in alcoholic patients portal hypertension had a greater potential for spontaneous improvement upon abstinence, while cirrhosis from other etiologies requires specific therapy to improve with a concomitant amelioration of portal hypertension [34–36].

A limitation of our study is the low number of events, which might result in low statistical power to detect associations of moderate strength and in limited ability to control for multiple confounding variables in the logistic regression models. Further, the co-lineality between many of the prognostic variables increases the chances of obtaining unstable models with low reproducibility. To overcome these problems, we took two approaches. First, we used a strict pre-planned protocol of hierarchic multivariable analysis that included variables that have been previously shown to robustly predict prognosis in variceal bleeding. Second, we confirmed with bootstrapping analysis the internal validity of our approach. These results, however, would require validation in external, independent cohorts. Finally, it must be noted that this is the largest study to date evaluating the prognostic value of HVPG in acute variceal bleeding, which was the primary aim of this study.

Another limitation of our study is that we could not perform a detailed prognostic analysis for mortality, since this was very low. This might raise concern about a potential bias in the selection of our sample due to its retrospective design. Indeed, a successful initial resuscitation was a prerequisite for HVPG measurements in our study, which could introduce a bias towards the inclusion of less severe patients. However, since patients in whom initial resuscitation fails require by definition a rescue treatment, the focus of prognosis prediction for the early instauration of more aggressive therapies is on those who do not require such emergency procedures. In addition it should be noted that we excluded patients with advanced hepatocellular carcinoma or portal vein thrombosis, which are the factors associated with a worst prognosis in a recent study evaluating the outcome of acute variceal bleeding [4]. On the other hand, in our study patients were homogeneously treated with the most effective scheme at present. In contrast, in recent series reporting higher mortality rates (17%) (1), only 47% of the patients received prophylactic antibiotics, 20% did not receive concomitant drug therapy and 7% of the patients bled from gastric varices.

In summary, this co-operative study shows that the early measurement of HVPG has independent prognostic value in patients with acute variceal bleeding treated

with the current standard of care. However, a similar predictive accuracy can be achieved using only simple clinical variables that have universal applicability. The combination of Child class, etiology and systolic blood pressure on admission might help identifying patients at low and high risk of failure with pharmacologic and endoscopic treatment.

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