DR. VINCENZO LA MURA (Orcid ID : 0000-0003-4685-7184)
DR. JUAN CARLOS GARCIA-PAGAN (Orcid ID : 0000-0001-9032-4954)
PROF. JAIME BOSCH (Orcid ID : 0000-0003-3414-0055)

Article type : Original

A new prognostic algorithm based on stage of cirrhosis and HVPG to improve risk-stratification after variceal bleeding

Short title: stage of cirrhosis, HVPG and risk stratification

Vincenzo La Mura[1,2,3], Marta Garcia-Guix[4], Annalisa Berzigotti[1,5], Juan G Abraldes[1,6], Juan Carlos García-Pagán[1], Candid Villanueva[4], and Jaime Bosch[1,5].

[1]Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic-IDIBAPS, University of Barcelona and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd).

[2]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Medicina Generale - Emostasi e Trombosi, Milano, Italy

[3]CRC "A.M. e A. Migliavacca" per lo Studio e la Cura delle malattie del Fegato and Dipartimento di scienze Biomediche per la Salute, Università degli studi di Milano, Milano, Italy

[4]Gastrointestinal BleedingUnit, Department of Gastroenterology, Hospital de Sant Pau, AutonomousUniversity, Barcelona, and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd)

[5]Swiss Liver, Hepatology, University Clinic for Visceral Medicine and Surgery, Inselspital, University of Bern, Switzerland

[6]Division of Gastroenterology, University of Alberta, CEGIIR, Edmonton, AB, T6G 2X8, Canada

email-address:

Vincenzo La Mura: vincenzo.lamura@unimi.it;
Marta Garcia-Guix: mgarciagui@santpau.cat;
Annalisa Berzigotti: Annalisa.Berzigotti@insel.ch;
Juan G Abraldes: juan.g.abraldes@ualberta.ca
Juan Carlos García-Pagán: JCGARCIA@clinic.cat
CandidVillanueva: CVillanueva@santpau.cat

Correspondence: Prof. Jaime Bosch, Maurice Müller Haus F 805; Murtenstrasse 35, 3010 Bern, Switzerland. e-mail: jaime.bosch@dbmr.unibe.ch
Phone +34 608110193

Disclosures: the authors have nothing to disclose with regards to this study.

Author Contributions: Study concept and design: JB, VLM. Acquisition of data: VLM, MGG. Analysis and interpretation of data: VLM, JGA, AB, JCGP, CV, JB. Writing of the manuscript: VLM, JB. Critical revision of the manuscript for important intellectual content: JB, CV, JCGP, AB, JGA. Statistical analysis: VLM, JGA, AB. Obtained funding and study supervision: JB.

Word count: 5303 (main text; references; table and figure legends)
Number of Figures: 4
Number of Supplementary Figures: 1
Number of Tables: 2
Number of Supplementary Tables: 3

Abstract *(word count 250)*

Background & Aims: HVPG decrease ≥20% or ≤12mmHg ("responders") indicates good prognosis during propranolol/nadolol treatment but requires two HVPG measurements. We aimed at simplifying risk-stratification after variceal bleeding using clinical data and HVPG. ***Methods:*** 193 cirrhotic patients (62% with ascites and/or hepatic encephalopathy, HE) included within 7-days of bleeding had HVPG measured before and at 1-3 months of treatment with propranolol/nadolol plus endoscopic band ligation. End-points: Rebleeding and

rebleeding/transplantation-free survival for 4-years. Another cohort (n=231) served as validation set.

Results: During follow-up 45 patients had variceal bleeding and 61 died. HVPG-responders (n=71) had lower rebleeding-risk (10% vs 34%, p=0.001) and better survival than 122 non-responders (61% vs 39%, p=0.001). Patients with/HE (n=120) had lower survival than patients without (40% vs 63%, p=0.005). Among patients with ascites/HE, those with baseline HVPG≤16mmHg (n=16) had low rebleeding-risk (13%). By contrast, among patients with ascites/HE and baseline HVPG>16mmHg, only HVPG-responders (n=32) had good prognosis, with lower rebleeding-risk and better survival than non-responders (n=72) (respective proportions: 7% vs 39%,p=0.018; 56% vs 30% p=0.010). These findings allowed developing a new algorithm for risk-stratification in which HVPG-response was only measured in patients with ascites and/or HE and baseline HVPG>16mmHg. This algorithm reduced the grey-zone (high-risk patients not dying on follow-up) from 46% to 35% and decreased by 42% the HVPG measurements required. The validation cohort confirmed these results.

Conclusion: Restricting HVPG measurements to patients with ascites/HE and measuring HVPG-response only if baseline HVPG>16mmHg improves detection of high-risk patients while markedly reducing the number of HVPG measurements required.

Keywords: Portal hypertension; bleeding; Survival; Cirrhosis

Abbreviations: EBL: endoscopic band ligation; FHVP: Free Hepatic Venous Pressure; HE: hepatic encephalopathy; HVPG: Hepatic Venous Pressure Gradient; NSBBs: non-selective beta-adrenergic blockers; WHVP: Wedged Hepatic Venous Pressure; OLT: orthotopic liver transplantation; TIPS: transjugular intrahepatic porto-systemic shunt.

Grant Support: **s**upported by Grants from the Instituto de Salud Carlos III, Ministerio de Economia y Competitividad (PI 13/341, PI10/1552,PI10/01552, PI13/02535 and PI16/01992). The CIBERehd is funded by the Instituto de Salud Carlos III.

INTRODUCTION

Variceal bleeding is a major complication of cirrhosis, with a high risk of rebleeding and high mortality in untreated patients. This makes mandatory to implement effective therapy, which nowadays consists in the combination of non-selective beta-blockers (NSBBs) and repeat endoscopic band ligation sessions (1,2). The hepatic venous pressure gradient (HVPG) provides valuable prognostic information in patients with cirrhosis during the prevention of recurrent variceal bleeding (3,4). Many studies (5-8) and meta-analysis (9,10) have consistently shown that a HVPG reduction ≥20% of baseline or to values ≤12mmHg during long-term treatment is associated with a reduced risk of recurrent variceal bleeding, of other portal hypertension related complications, and improved survival.

However, the high specificity of the hemodynamic response indicating a good prognosis is not associated with a high sensitivity, since up to 48% of patients who are HVPG non-responders to NSBBs will not rebleed during the follow-up, representing what has been named as a "grey zone" (11). Such relatively low sensitivity hampers risk stratification and diminishes the cost-effectiveness of HVPG-guided therapy.

Baseline HVPG in cirrhosis bears prognostic significance (3,4,7,8,12-22). A baseline HVPG equal or above 10 mmHg is strongly predictive of the risk of

developing varices, decompensation, hepatocellular carcinoma and decompensation after liver resection for hepatocellular carcinoma. Furthermore, several studies have shown that a baseline HVPG over 16 mmHg identifies patients with reduced survival (23-26).

On the other hand, it has recently been emphasized that prognosis of cirrhosis is markedly dependent on the stage of the disease. Prognosis is good while patients are compensated, and worsens dramatically upon clinical decompensation – defined by the development of ascites, variceal bleeding or hepatic encephalopathy (HE) (27). Within the decompensated stage, prognosis is in turn different if the decompensation is due to variceal bleeding alone or if this occurs in the form of, or associated with ascites and/or HE, in which case prognosis is much worse. Patients with ascites and/or HE on top of bleeding have a high mortality risk, which has led to recommend that the main goal of therapy in such cases should be survival (2,28-29). Current recommended therapy for the prevention of variceal rebleeding is the combination of NSBBs plus endoscopic band ligation (EBL) (2), both for patients with or without ascites/HE. This study explores in a large series of patients receiving recommended treatment for the prevention of variceal rebleeding whether considering the presence/absence of ascites and/or HE and adding the finding of a baseline HVPG below or over 16mmHg to the traditional criteria of hemodynamic response may improve risk stratification and simplify the use of HVPG-based therapeutic decisions.

PATIENTS AND METHODS

Study cohorts

The study cohort comprises n=193 patients with cirrhosis receiving NSBBs and EBL for preventing variceal rebleeding at the Liver Unit, Hospital Clínic, Barcelona

and at the Gastroenterology Division, Hospital de Sant Pau, Barcelona in whom HVPG response to NSBBs (after 1-3 months on NSBBs) was evaluated and who were included in previously published studies (29-33). The study is a nested retrospective analysis using the initial database. 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); admission for variceal bleeding within the previous 7 days; baseline HVPG values of at least 12 mmHg; subsequent long-term treatment with NSBBs (propranolol or nadolol) combined with repeated EBL sessions; and a second HVPG measurement after 1 to 3 months of continued pharmacological therapy. Patients with hepatocellular carcinoma at baseline, portal vein thrombosis, contraindications to beta-blockers, previous TIPS or surgical shunts or cholestatic liver disease were excluded. Two-hundred and thirty-one patients who received NSBBs without concomitant EBL included in previous studies from the same institutions (30, 35-36) and who had baseline and repeat HVPG measurements served as a validation cohort of the proposed algorithm for risk-stratification. Both in the training and validation cohorts, patients were considered positive for ascites if they presented clinical evidence of ascites at inclusion or if they had clinically evident ascites confirmed by paracentesis in the previous 12-months. HE was considered to be present when clinically evident (grade $\geq$ 2 in the West Haven scale) and diagnosed by a physician during hospital admission or at an outpatient visit. All included patients have given their informed consent to the initial studies. The retrospective collection of clinical and hemodynamic data for the current study was approved by the ethical committee for clinical investigation of the Hospital Clinic in Barcelona.

Hemodynamic Measurements

Baseline hemodynamic studies were performed before starting NSBBs for preventing variceal rebleeding. The study was performed once the patients were in stable conditions, at days 4-7 after admission for variceal bleeding. In brief, under local anaesthesia, a venous introducer was placed in the right internal jugular vein by the Seldinger technique. Under fluoroscopy, a 7F balloon-tipped catheter was advanced into the main right hepatic vein for measuring wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) as previously described (4). WHVP was measured after verifying adequate occlusion of the hepatic vein by the inflated balloon, while FHVP was measured at 2-3 cm of the outlet of the hepatic vein into the inferior vena cava. All measurements were taken in triplicate. Permanent tracings were obtained in a multichannel recorder (Mac-Lab®, GE Healthcare, Freiburg, Germany, for Hospital Clinic; PowerLab 8SP, AD Instruments, for Hospital Sant Pau), and were reviewed specifically for this study by experienced investigators (VLM, JGA, JCGP, JB, CV) unaware of the clinical data of the patients.

HVPG was calculated as the mean of triplicate measurements of WHVP and FHVP. The second hemodynamic study to evaluate the hemodynamic response to NSBBs was performed 1 to 3 months later, once the patient had reached a stable dose of the NSBB for at least two weeks.

Titration of NSBBs and Follow-Up

After the hemodynamic evaluation, all patients were started on oral propranolol (20 mg b.i.d.) or nadolol (20 to 80 mg o.i.d), that were increased stepwise, if clinically tolerated, until heart rate had fallen to 50-55/minute, while systolic blood pressure was > 90 mmHg up to a maximum of 320 mg/day for propranolol or 240 mg/day for nadolol.

The first EBL session was performed at admission for the control of acute variceal bleeding. Sessions were repeated every 3-4 weeks until variceal eradication (29). Follow-up endoscopies were scheduled at 3 months, 6 months and every 12 months thereafter. In case of variceal recurrence, additional EBL sessions were performed. All patients were followed-up in the outpatient clinic at 1, 3, and 6 months, and every 3-6 months thereafter. Medical history, physical examination, biochemistry, hematologic tests and abdominal ultrasound were performed every six-months. Follow-up data were collected for up to 4 years (follow-up was extended for those patients censored at two-year in the original studies), or until death or liver transplantation (OLT). Patients who stopped NSBBs were censored the day of drug withdrawal (per treatment received analysis). Clinical events assessed were rebleeding, death or liver transplantation defined according to Baveno criteria (2). Patients who discontinued propranolol/nadolol were censored at the time of treatment discontinuation; the same was done for patients who received TIPS during the follow-up.

Statistical Analysis

Statistical analysis was performed with SPSS 19.0 package (SPSS, Chicago, IL) and R (http://www.r-project.org). Data are reported as frequencies or means with standard deviation. Comparisons for continuous and categorical data were performed with unpaired Student t test, Mann–Whitney test, or Fisher exact test as appropriate. For the survival analysis, we considered two clinical end-points: rebleeding and rebleeding/OLT-free survival. Rebleeding risk was tested as cumulative incidence function which takes into account death or liver transplantation as competing risks (37). Rebleeding and OLT-free survival on follow-up are depicted using Kaplan-Meier curves. The log-rank test was used to compare the groups considered in this analysis. The hazard ratios (HR) of

association with rebleeding and survival were adjusted by introducing independent variables in the Fine Gray model for competing risk analysis (38) and the multivariable Cox proportional hazards model, respectively. Redundant variables were not introduced in the final analysis. The contribution of each variable was estimated by the HR with its 95% confidence intervals (CIs). Comparison of the number of patients misclassified as belonging to a high-risk category by traditional criteria and by the new criteria derived from the study was done with the McNemar test. Algorithms for risk stratification based on baseline HVPG, presence/absence of ascites/HE and HVPG response were constructed. Significance was established at $p<0.05$.

RESULTS

Clinical and hemodynamic characteristics of patients included in the study.

One-hundred-ninety-three patients were included in the study cohort. Clinical characteristics and hemodynamic data of the patients are reported in Table 1. Seventy-one (37%) exhibited a fall in HVPG below 12 mmHg or of at least 20% of the baseline value and were considered "HVPG-responders" to continued administration of NSBB, 122 (63%) were non-responders. As per current recommendations, both responders and non-responders were kept on NSBBs treatment and continued EBL. For 73 patients (38%) bleeding alone was the index manifestation of clinical decompensation, while for 120 patients (62%) bleeding occurred as a further decompensation on top of ascites (n=74; 38%), of HE (n=5; 3%), or of ascites plus HE (n=41; 21%). As patients with HE alone (on top of bleeding) were only 5, these were added to the other 74 patients with ascites alone to make up a group of 79 patients with bleeding+ascites/HE (41%). A comparison of the clinical characteristics and hemodynamics in these different stages of decompensation is summarized in Table 1. As shown, patients presenting only with

bleeding had better liver function, lower portal pressure and were more frequently HVPG-responders to continued administration of NSBB than the other groups.

Prognosis according to HVPG response

During follow-up (median 31 months), 45 patients experienced variceal rebleeding, 61 patients died and 10 were transplanted according with the local transplantation policy based on MELD score and at least 6-month of verified abstinence from alcohol. Rebleeding occurred in 39/122 non-responders *vs* 6/71 HVPG responders (cumulative 4-year rebleeding risk: 34% *vs* 10%; HR: 4.332, 95%-CI: 1.854-10.075; p=0.001) (Fig. 1). According to HVPG response, 83/122 (68%) non-responders (representing 43% of the cohort) were misclassified as high-risk since they did not rebleed on follow-up ("grey zone"). The cumulative 4-year OLT-free survival was 61% in responders vs 39% in non-responders (HR 2.142, 95%-CI: 1.321-3.474; p=0.002).

Prognosis according to presence of ascites/HE and to baseline HVPG >16 mmHg

As expected, presence of other manifestations of clinical decompensation at the moment of bleeding (ascites and/or HE; n=120) markedly influenced 4-year survival (40% vs 63%, p=0.005). The rebleeding-risk increased and survival progressively worsened with increasing number of manifestations of decompensation (e.g. patients with bleeding as the only decompensation event Vs patients with bleeding + ascites/HE Vs patients with bleeding + ascites + HE). Specifically, in the 79 patients presenting with bleeding + ascites/HE, 4-year rebleeding was 21% and survival 48%, which were better than those observed in the 41 patients presenting with bleeding + ascites + HE who had greater rebleeding risk (38%) (p=0.062) and worse survival (24%) (p=0.036).

As for baseline HVPG, 34 patients (18%) had a pre-treatment HVPG ≤16 mmHg. This was associated with a low rebleeding risk even in patients with poor prognostic indicators. Indeed, rebleeding was low and similar in the 16 patients with baseline HVPG ≤16mmHg presenting with bleeding + ascites and/or HE as in the 19 patients HVPG non-responders with baseline HVPG ≤16mmHg (13% and 12% respectively). Corresponding figures for survival were also similar: 47% and 52%.
By the contrary, in patients with a combination of negative prognostic markers, such as patients presenting with bleeding plus ascites and/or HE who had a baseline HVPG >16 mmHg, the HVPG response to NSBBs strongly correlated with the outcomes. In this subgroup, non-responders (n=72) had a 39% rebleeding risk, much higher than the 7% observed in hemodynamic responders (n=32) and the 13% of rebleeding-risk already shown in patients presenting with bleeding plus ascites and/or HE who had baseline HVPG ≤16mmHg (n=16) (p=0.018) (Supplementary Figure 1, panel A). Survival was also worse in patients presenting with bleeding plus ascites and/or HE together with a baseline HVPG >16mmHg and who were non-responders to NSBBs (30%), as compared with patients in the same category who were either HVPG responders (56%) or who had a baseline HVPG ≤16mmHg (47%) (p=0.010) (Supplementary Figure 1, panel B).

Refining risk-stratification in cirrhosis: a new clinical and hemodynamic algorithm

The above data allow establishing a novel algorithm for risk stratification in patients with cirrhosis surviving an episode of variceal bleeding. Given the high survival (63%) of patients with only variceal bleeding, the algorithm takes into account, firstly, the presence of ascites and/or HE in addition to bleeding and, secondly, the baseline HVPG. The new algorithm restricts measurement of the baseline HVPG to patients with ascites and/or HE when admitted for bleeding and restricts the

assessment of the hemodynamic response to those with ascites and/or HE who have a baseline HVPG >16 mmHg (Figure 2, panel A). Using this algorithm, rebleeding occurred in 27/72 of patients classified as "high-risk" (i.e. those with ascites and/or HE, baseline HVPG >16mmHg and absence of hemodynamic response) *Vs* 18/121 of the "low-risk patients" (cumulative 4-year rebleeding risk: 39% *vs* 17%; HR: 2.882, 95%-CI: 1.609-5.164; p<0.001) (Figure 2, panel B).

It is worth noting that a sensitivity analysis demonstrated that a range of baseline HVPG from 15 mmHg to 17 mmHg performed similarly, but 16 mmHg was the best cut-off to use as an additional prognostic criterion on top of ascites/HE. This indicates that our finding is robust, as the variability of HVPG measurements is below 1 mmHg (39). We also performed an exploratory analysis comparing patients with and without active alcohol consumption (patients with active alcohol intake: n=58 in low-risk, n=37 in high-risk; patients without active alcohol consumption: n=63 in low-risk, n=34 in high-risk) and the discriminative ability of the algorithm for survival did not change (data not shown).

The new algorithm decreased the number of patients incorrectly classified as 'high-risk' for rebleeding: the number and relative proportion of patients who did not rebleed on follow up among the group classified as high-risk for the old and new algorithm were, respectively, 83/122 (68%) (corresponding to 43% of the total cohort) and 45/72 (62%) (corresponding to 23% of the total cohort; p<0.001, McNemar test), while the number of patients who rebled among the low-risk group were 6/71 (8.4%) for the old-algorithm and 18/121 (14.8%) for the new algorithm (corresponding respectively to 3% and 9% of the total cohort). This suggests the new algorithm performs better among high-risk patients. Similar findings were observed for survival. Indeed, the number of patients misclassified as high-risk, respectively for the old and the new algorithm, for this end-point was 56/122(46%) (or 29% of the total cohort) vs 25/72 (35%) (or 13% of the total cohort) (p<0.001,

McNemar test). The corresponding numbers of misclassified low-risk patients with regards to mortality were 22/71 (31%) using the initial algorithm and of 41/122 (33%) when using the new algorithm.

Moreover, the new algorithm allowed markedly decreasing the number of hemodynamic measurements needed for risk-stratification. Thus, 73 patients without ascites/HE would not need any measurement, 16 patients with ascites and/or HE and a baseline HVPG ≤16 mmHg would need only one measurement, and 104 with ascites and/or HE and a baseline HVPG >16 mmHg would need two measurements, for a total of 224 HVPG measurements *vs* 386 using the traditional HVPG response-based risk-assessment, thus saving 42% of HVPG measurements (Figure 3).

The new algorithm had an excellent prognostic value for survival free of rebleeding or OLT. This was analogous to that obtained by measuring the HVPG-response (Fig. 2, panel C), but saving 42% of the HVPG examinations.

Variables that in univariate analysis were found to be significantly associated with being a high-risk patient (Supplementary Table 1) and with rebleeding and survival on follow-up (Supplementary Table 2) were introduced in a multivariate analysis (Table 2). Belonging to the high-risk group was the only independent predictor of rebleeding (HR: 2.739, 95%-CI: 1.436-5.226; p=0.002) and the strongest predictor of survival free of rebleeding/OLT (HR: 2.539, 95%-CI: 1.546-4.169; p<0.001), followed by low serum sodium levels (HR: 0.943, 95%-CI: 0.899-0.990; p=0.018) and with a residual trend for MELD score (HR:1.042, 95%-CI: 0.993-1.095; p=0.097).

Validation set

Supplementary Table 3 reports the clinical characteristic of the 231 patients included in the validation set. Over the 4-year follow-up, 65 patients experienced variceal rebleeding, 57 patients died and 18 were transplanted.

As depicted in Figure 4, the prognostic performance of the new algorithm was successfully validated both for risk of rebleeding (Figure 4, panel A) and survival (Figure 4, panel B).

DISCUSSION

In this study we present a new algorithm simplifying and improving risk stratification in patients with cirrhosis who receive recommended treatment with NSBBs and EBL to prevent recurrent variceal bleeding. This new strategy, derived from a thorough analysis of two large series of patients (training and validation sets), is based on incorporating data on the stage of decompensation of cirrhosis and results of baseline HVPG measurements. In this new algorithm, HVPG measurements are performed at time of the index bleed only in patients with ascites and/or HE, and assessment of the HVPG response to NSBBs is only done if baseline HVPG is over 16 mmHg. Therefore, it defines as 'low-risk' those patients with variceal bleeding who have no ascites/HE, as well as patients with ascites and/or HE but with baseline HVPG ≤16 mmHg. By contrast, the algorithm considers as 'high-risk' those patients with variceal bleeding who also have all of the following: a) ascites and/or HE, b) HVPG >16 mmHg before starting NSBBs, and c) lack of an adequate hemodynamic response to continued NSBB (failure to decrease HVPG by at least 20% of baseline or ≤12 mmHg).

This new strategy is superior to the traditional in several relevant aspects. First, it would have obviated any hemodynamic measurements in 38% of our patients -those without ascites or HE at time of the index variceal bleeding- and would have restricted measuring the HVPG response to NSBBs to 54% of patients (instead of

100% in the traditional strategy). This represents reducing by almost half the number of hepatic vein catheterisation studies to be performed, thus halving the economic cost, health care burden and patient discomfort required in the previous strategy of risk-stratification. Second, the new strategy is associated with an improved accuracy of the prediction of patients at "high-risk" of rebleeding or death during a four-year follow-up. With regards to rebleeding, the number of patients classified as "high-risk" but who do not bleed during the follow-up (the so called "grey zone") decreased from 83 with the traditional strategy to 45 with the new algorithm (from 43% to 23% of the total cohort). Thirdly, the new algorithm also predicted survival-free of OLT and of rebleeding, an end-point which is more important than rebleeding alone in patients with advanced liver failure, particularly when bleeding occurs in patients with ascites and/or HE, a subgroup in which death is frequent and the most relevant event (2, 28-29).

For all these reasons, it is possible that this new strategy for risk-stratification, with much better cost-effectiveness than the traditional one, might lead to changes in the approach to treatment. This is particularly likely considering that HVPG-guided therapy improved the outcome of therapy in a recent trial (40). High-risk patients are usually referred to be considered for TIPS or liver transplantation to tertiary care centres. It is likely that in these circumstances it would be easier to implement a therapeutic protocol including stratification based on clinical data and HVPG. The practical implication of applying this new algorithm can only be addressed by an adequately designed study. However, the new algorithm has the potential for selecting better the group of high-risk patients, by markedly reducing its number and by having lower "grey-zones" for rebleeding and death (patients included in the high risk group category but who do not bleed or dye on follow-up) (11). It is possible that this high risk patients could benefit from a more aggressive therapeutic approach, for instance by using TIPS. As shown in previous studies both for acute

bleeding (41) and for "difficult ascites" (42), advancing a decision for TIPS (instead of using it as rescue therapy after failure of standard treatment) may be life-saving. Therefore, it may be worth trying this approach in the high-risk population defined by the new algorithm (patients with ascites, HVPG > 16 mmHg, and non-responders to propranolol).

Importantly, the concept that patients with several decompensating events (e.g. bleeding + ascites and/or HE) have the worst prognosis is in line with the recent survival models proposed for the natural history of cirrhosis (27,29). The prognostic information provided by the cut off of 16 mmHg is not entirely new as 5 previous studies showed it to be a predictor of survival (8,23-26). However, none of these studies investigated its prognostic value in the context of the medical treatment of portal hypertension.

Our study has strengths and limitations. A major strength is that it is based in large cohorts of patients, both for the training and the validation cohort, mostly included in prospective clinical trials in two expert centres, so the results are robust. Among the limitations it should be noted that the subgroup of patients with only HE on top of variceal bleeding was quite small (n=5) so its role aggravating the prognosis of patients with bleeding and ascites could not be fully characterized; that's why these were pooled with patients with ascites on top of bleeding. Secondly, from this study we cannot extrapolate if the prognostic value of the new algorithm would extend to patients treated prophylactically, before the first bleeding or clinical decompensation that have a much lower risk of bleeding and death. Finally, the fact that the algorithm still includes HVPG measurements in part of the patients also constitutes a limitation given the cost and invasive nature of the technique. However, non-invasive methods are evolving and may in the future substitute invasive HVPG measurements for risk stratification (43).

In summary, we have demonstrated in a large series of patients with cirrhosis presenting with a recent episode of variceal bleeding that the absence of ascites/HE and the finding of a baseline HVPG ≤16mmHg represent additional criteria of good outcome during subsequent treatment with the standard of care (NSBBs plus EBL). Restricting measurement of the HVPG response to patients presenting with ascites and/or HE at the time of bleeding who have a basal HVPG >16mmHg significantly decreases the "grey" zone, and reduces by 42% the number of HVPG measurements required for risk stratification. Therefore, the new strategy has advantages over the previously defined criteria for a good hemodynamic response to beta-blockers and may facilitate adopting therapeutic decisions based on expected outcomes and risk stratification.

ACKNOWLEDGMENTS

We thank Drs Eyal Ashkenazi, Andrea Ribeiro de Souza, and Oana Pavel for helping in initial steps of data collection, and Ms Rosa Saez, Angels Baringo and Laura Rocabert for expert technical support.

REFERENCES

1. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N. Engl. J. Med. 2011;364:490.
2. de Franchis R. Expanding Consensus In Portal Hypertension Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J. Hepatol.. 2015;63:743–52.
3. Groszmann RJ, Wongcharatrawee S. The Hepatic Venous Pressure Gradient: Anything Worth Doing Should Be Done Right. Hepatology. 2004;39:280–282.
4. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat. Rev. Gastroenterol. Hepatol. 2009;6:573–582.
5. Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology. 2003;37:902–908.

6. Turnes J, Garcia-Pagan JC, Abraldes JG, Hernandez-Guerra M, Dell'Era A, Bosch J. Pharmacological Reduction of Portal Pressure and Long-Term Risk of First Variceal Bleeding in Patients with Cirrhosis. Am. J. Gastroenterol. 2006;101:506–512.
7. Feu F, García-Pagán JC, Bosch J, Luca A, Terés J, Escorsell A, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet. 1995;346:1056–1059.
8. Merkel C, Bolognesi M, Sacerdoti D, Bombonato G, Bellini B, Bighin R, et al. The hemodynamic response to medical treatment of portal hypertension as a predictor of clinical effectiveness in the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology. 2000;32:930–934.
9. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic Vein Pressure Gradient Reduction and Prevention of Variceal Bleeding in Cirrhosis: A Systematic Review. Gastroenterology. 2006;131:1611–1624.
10. Albillos A1, Bañares R, González M, Ripoll C, Gonzalez R, Catalina MV,et al. Value of the hepatic venous pressure gradient to monitor drug therapy for portal hypertension: a meta-analysis. Am. J. Gastroenterol. 2007;102:1116–26.
11. Thalheimer U, Bosch J, Burroughs AK. How to Prevent Varices From Bleeding: Shades of Grey-The Case for Nonselective β Blockers. Gastroenterology. 2007;133:2029–2036.
12. Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Navasa M, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first varicealhemorrhage. Gastroenterology. 1990;99:1401–7.
13. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic Venous Pressure Gradient Predicts Clinical Decompensation in Patients With Compensated Cirrhosis. Gastroenterology. 2007;133:481–488.
14. Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J. Hepatol. 2009;50:923–928.
15. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N. Engl. J. Med. 2005;353:2254–61.

16. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 1985;5:419–24.
17. García-Tsao G. Further evidence in favor of pharmacological portal pressure reduction in the prevention of variceal hemorrhage. Gastroenterology 1997;112:1770–1.
18. Ripoll C, Bañares R, Rincón D, Catalina MV, Lo Iacono O, Salcedo M, et al. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD Era. Hepatology. 2005;42:793–801.
19. Monescillo A, Martínez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jiménez E, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology. 2004;40:793–801.
20. Moitinho E, Escorsell A, Bandi JC, Salmerón JM, García-Pagán JC, Rodés J, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. Gastroenterology. 1999;117:626–631.
21. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology. 1996;111:1018–22.
22. Turco L, Garcia-Tsao G, Magnani I, Bianchini M, Costetti M, Caporali C, et al. Cardiopulmonary hemodynamics and C-reactive protein as prognostic indicators in compensated and decompensated cirrhosis. J Hepatol. 2018;68:949-958.
23. Berzigotti A, Rossi V, Tiani C, Pierpaoli L, Zappoli P, Riili A, et al. Prognostic value of a single HVPG measurement and Doppler-ultrasound evaluation in patients with cirrhosis and portal hypertension. J. Gastroenterol. 2011;46:687–695.
24. Merkel C, Bolognesi M, Bellon S, Zuin R, Noventa F, Finucci G, et al. Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. Gastroenterology. 1992;102:973–9.
25. Stanley AJ1, Robinson I, Forrest EH, Jones AL, Hayes PC. Haemodynamic parameters predicting variceal haemorrhage and survival in alcoholic cirrhosis. QJM. 1998;91:19–25.
26. Silva-Junior G, Baiges A, Turon F, Torres F, Hernández-Gea V, Bosch J, et al. The prognostic value of hepatic venous pressure gradient in patients with cirrhosis is highly dependent on the accuracy of the technique. Hepatology. 2015;62:1584–92.

27. D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages in cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39:1180–1193

28. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017;65:310-335.

29. Abraldes JG, Trebicka J, Chalasani N, D'Amico G, Rockey DC, Shah VH, et al. Prioritization of Therapeutic Targets and Trial Design in Cirrhotic Portal Hypertension. Hepatology 2019;69:1287-1299.

30. La Mura V, Abraldes JG, Raffa S, Retto O, Berzigotti A, García-Pagán JC, et al. Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. J. Hepatol. 2009;51:279–287.

31. García-Pagán JC, Villanueva C, Albillos A, Bañares R, Morillas R, Abraldes JG, et al. Nadolol plus isosorbidemononitrate alone or associated with band ligation in the prevention of recurrent bleeding: a multicentre randomised controlled trial. Gut. 2009;58:1144–1150.

32. de Souza AR, La Mura V, Reverter E, Seijo S, Berzigotti A, Ashkenazi E, et al. Patients Whose First Episode of Bleeding Occurs While Taking a β-Blocker Have High Long-term Risks of Rebleeding and Death. Clin. Gastroenterol. Hepatol. 2012;10:670–676.

33. Villanueva C, López-Balaguer JM, Aracil C, Kolle L, González B, Miñana J, et al. Maintenance of hemodynamic response to treatment for portal hypertension and influence on complications of cirrhosis. J. Hepatol. 2004;40:757–765.

34. Villanueva C, Aracil C, Colomo A, Lopez-Balaguer JM, Piqueras M, Gonzalez B, et al. Clinical trial: A randomized controlled study on prevention of varicealrebleeding comparing nadolol + ligation vs. hepatic venous pressure gradient-guided pharmacological therapy. Aliment. Pharmacol. Ther. 2009;29:397–408.

35. Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology. 2003;37:902-8.

36. La Mura V, Abraldes JG, Berzigotti A, Erice E, Flores-Arroyo A, García-Pagán JC, et al..Right atrial pressure is not adequate to calculate portal pressure gradient in cirrhosis: a clinical-hemodynamic correlation study. Hepatology. 2010;51:2108-16.

37. Satagopan JM1, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. Br J Cancer 2004;91:1229–1235)
38. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509
39. **Abraldes JG, Villanueva C**, Aracil C, Turnes J, Hernandez-Guerra M, Genesca J, et al. Addition of Simvastatin to Standard Therapy for the Prevention of VaricealRebleeding Does Not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis. Gastroenterology. 2016;150:1160-1170
40. Villanueva C, Graupera I, Aracil C, Alvarado E, Miñana J, Puente Á, et al. A randomized trial to assess whether portal pressure guided therapy to prevent varicealrebleeding improves survival in cirrhosis. Hepatology. 2017;65:1693–1707
41. García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med. 2010;362:2370-9
42. Bureau C, Thabut D, Oberti F, Dharancy S, Carbonell N, Bouvier A, et al. Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites. Gastroenterology. 2017;152:157-163
43. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. J Hepatol. 2017;67:399-411.

Authors listed in bold shared the first authorship

FIGURE LEGENDS

Figure 1: Classic algorithm of HVPG-response (A) to stratify the rebleeding risk at 4 years (B) and rebleeding/OLT free survival (C).

Figure 2: New algorithm including: ascites and/or HE, basal HVPG of 16mmHg, HVPG-response (A) to stratify the rebleeding risk at 4 years (B) and rebleeding/OLT free survival (C).

Figure 3. Number of HVPG measurement required for risk stratification using the old algorithm (left) and the new algorithm (right).

Figure 4: Validation set (n=231 patients who received NSBBs for rebleeding prophylaxis): The prognostic performance of the proposed stepwise algorithm considering at high risk patients with ascites and/or HE, basal HVPG>16mmHg who were non-responders to NSBBs was excellent.

Supplementary Figure 1: Among patients with ascites and/or HE protective factors for rebleeding (A) and rebleeding/OLT free survival (B) were: having basal HVPG ≤16mmHg or being HVPG-responders if basal HVPG was >16mmHg.

Table 1: Clinical and hemodynamic characteristics of the patients in accordance to the stages of decompensation

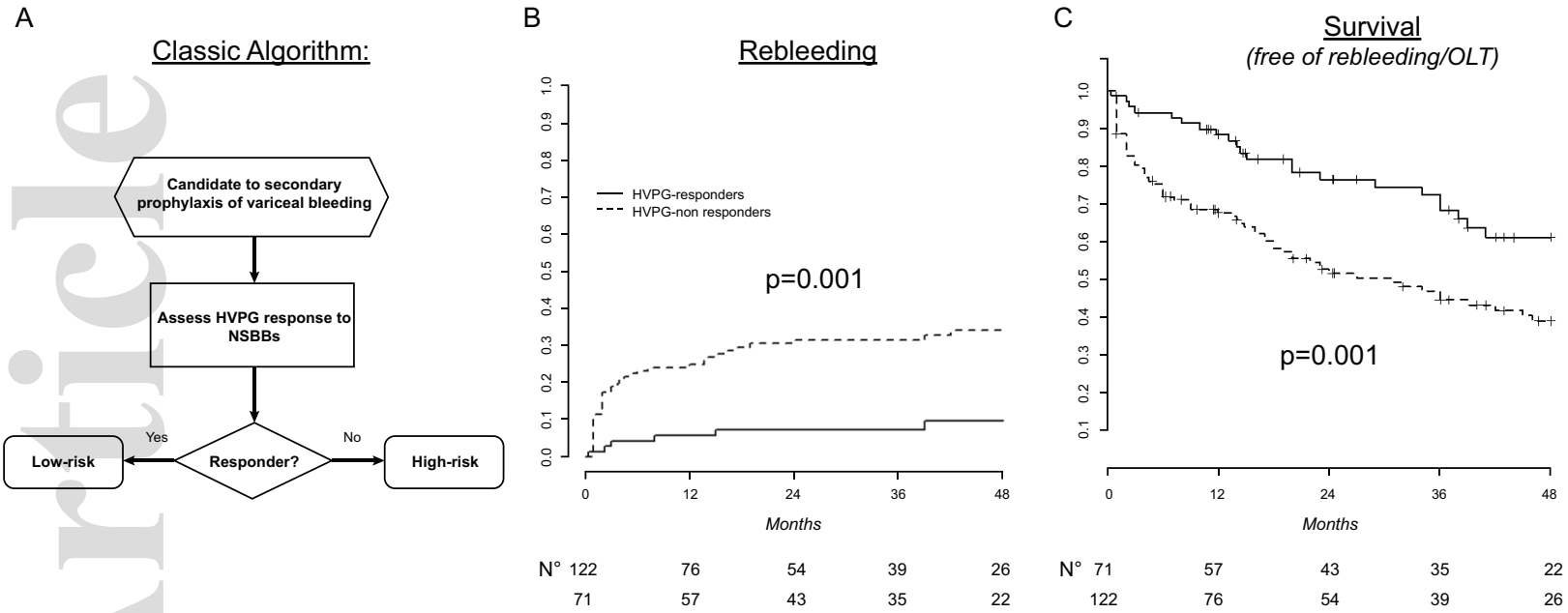
	OVERALL	Bleeding as only decompensation	Bleeding + ascites/HE	Bleeding + ascites+HE	p *linear trend*	Bleeding + ascites and/or HE	p*
Number of patients	193	73	79	41	---	120	---
Age (years)	58(12)	56 (12)	60 (10)	57 (13)	0.447	59 (11)	0.081
Sex (% of male)	75	74	73	78	0.680	75	0.866
Alcohol Etiology (% of patients)	60	52	65	66	0.108	65	0.095
Active alcoholism (% of patients)	50	45	50	56	0.264	52	0.375
MELD score	13.2(4.3)	11.4 (2.5)	13.2 (4.0)	16.7 (5.2)	<0.001	14.4 (4.7)	<0.001
Ascites (% of patients)	60	0	94	100	<0.001	96	<0.001
Hepatic encephalopathy (% of patients)	24	0	6	100	<0.001	38	<0.001
Albumin (g/L)	28.4(5.4)	30.5 (4.9)	28.9(4.6)	23.3(4.5)	<0.001	27.0 (5.2)	<0.001
Bilirubin (mg/dL)	2.5(2.7)	1.9 (1.2)	2.3(1.8)	4.2(4.9)	<0.001	2.9 (3.3)	0.007
Creatinine (mg/dL)	1.00(0.74)	0.83 (0.20)	1.05(0.75)	1.21(1.17)	0.008	1.11 (0.92)	0.002
Hematocrit (%)	27.8(5.4)	29.8 (4.5)	27.2(5.6)	25.3(5.3)	<0.001	26.6 (5.5)	<0.001
Sodium (mEq/L)	137(4)	137 (4)	136(5)	137(6)	0.475	136 (5)	0.154
Platelets (10^3/mm3)	96.9(49.0)	89.7 (46.5)	101.4(45.8)	101.3(57.9)	0.166	101.4 (50.1)	0.109
Prothrombin Activity (%)	62(14)	68.1 (13.0)	62.1(13.6)	54.7(11.7)	<0.001	59.5 (13.4)	<0.001
Small/large varices (% of patients)	6/94	10/90	4/96	5/95	0.225	4/96	0.136
% of patients who stopped NSBBs	7	6	9	5	0.944	8	0.773
Basal HVPG (mmHg)	20.8(4.7)	19.6 (4.9)	21.4(4.4)	22.0(4.8)	0.007	21.6 (4.5)	0.006
Patients with basal HVPG≤16mmHg (%)	18	25	14	12	0.064	13	0.053
HVPG decrease (%) during NSBBs	12.6(17.2)	14.4 (19.1)	13.1(15.6)	8.2(16.5)	0.084	11.5 (16.0)	0.254
HVPG-responders (%)	37	47	37	20	0.005	31	0.032

**p value <0.05 means significant difference between the cohort presented with bleeding as only decompensation event vs bleeding on top of ascites and/or HE*

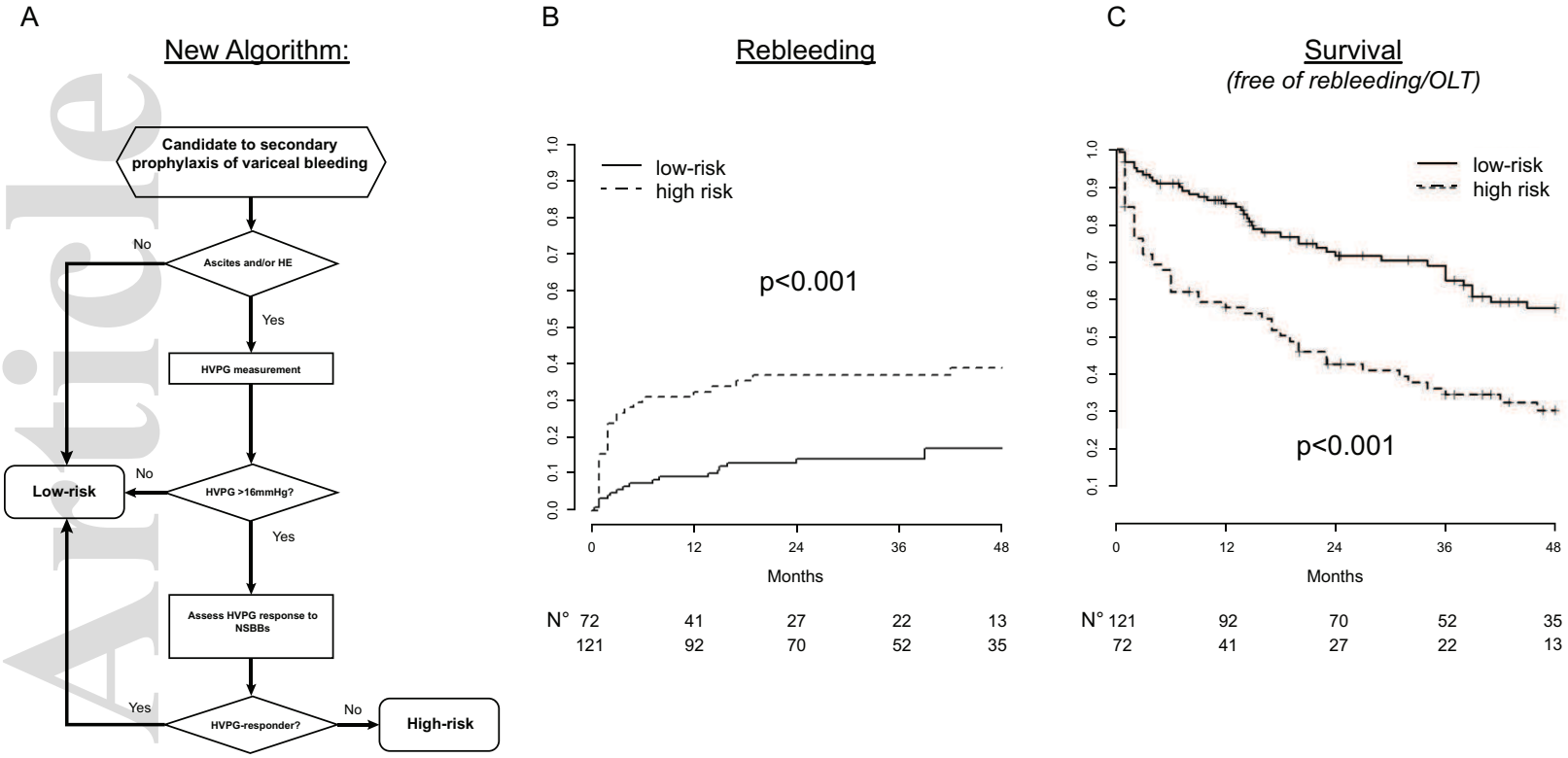
Table 2: Multivariate analysis for rebleeding and rebleeding/OLT-free survival. The Hazard Ratios (HRs) for the condition of "high-risk" proposed by the new algorithm were adjusted for all variables differently distributed in high-risk vs low-risk patients and associated with the event at the univariate analysis with a p<0.1 for each clinical end-point (see supplementary Tables 1-2).

	REBLEEDING *competing risk analysis-FineGray model*			**SURVIVAL Free of rebleeding/OLT** *Cox proportional hazard model*		
INDEPENDENT VARIABLES	HR	95%CI	p	HR	95%CI	p
Age (per year of increase)	NA	NA	NA	0.999	0.979-1.020	0.937
MELD score (per one unit of increase)	1.000	0.934-1.071	1.000	1.042	0.993-1.095	0.097
Hematocrit (per % of increase)	0.984	0.926-1.045	0.623	0.989	0.942-1.038	0.657
Albumin (per g/L of increase)	0.997	0.935-1.063	0.593	1.003	0.957-1.052	0.886
Sodium (per mEq/L of increase)	NA	NA	NA	**0.943**	**0.899-0.990**	**0.018**
High-risk (ascites/HE, HVPG>16mmHg and HVPG non-responders)	**2.739**	**1.436-5.226**	**0.002**	**2.539**	**1.546-4.169**	**<0.001**

NA: not applicable

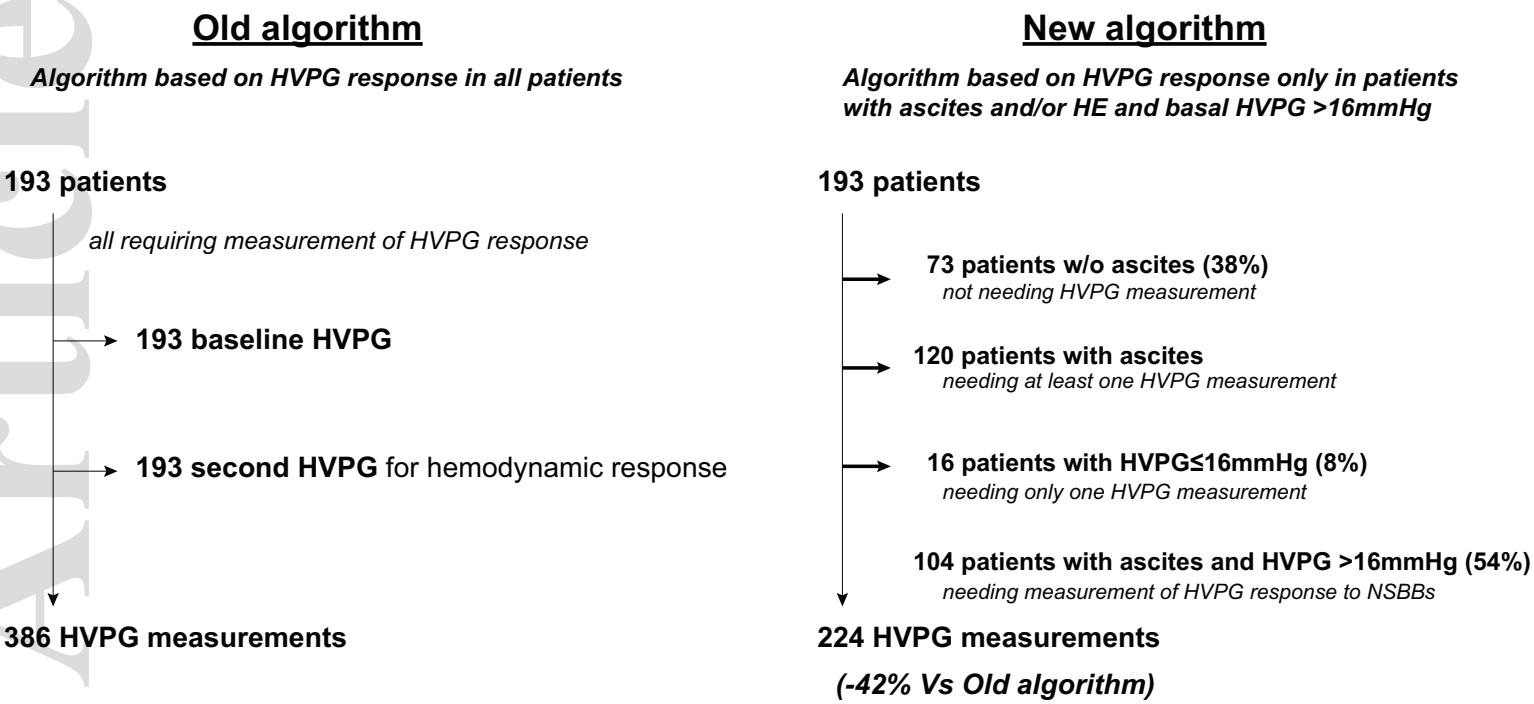


hep_31125_f1.eps

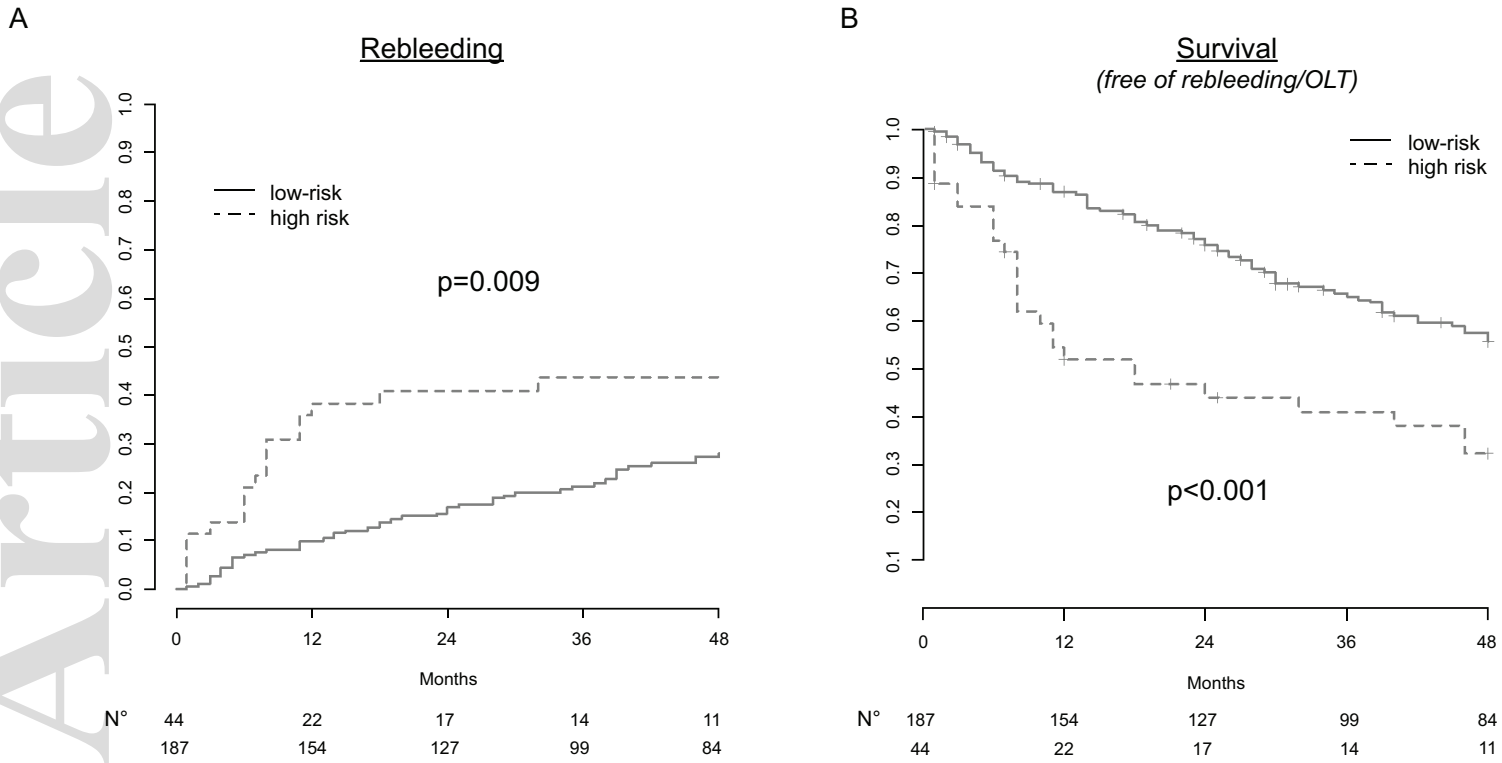


hep_31125_f2.eps

Number of HVPG measurement required for risk stratification



hep_31125_f3.eps



hep_31125_f4.eps