JHEP|Reports

Persistent varices in cured patients: Understanding the role of hepatic venous pressure gradient

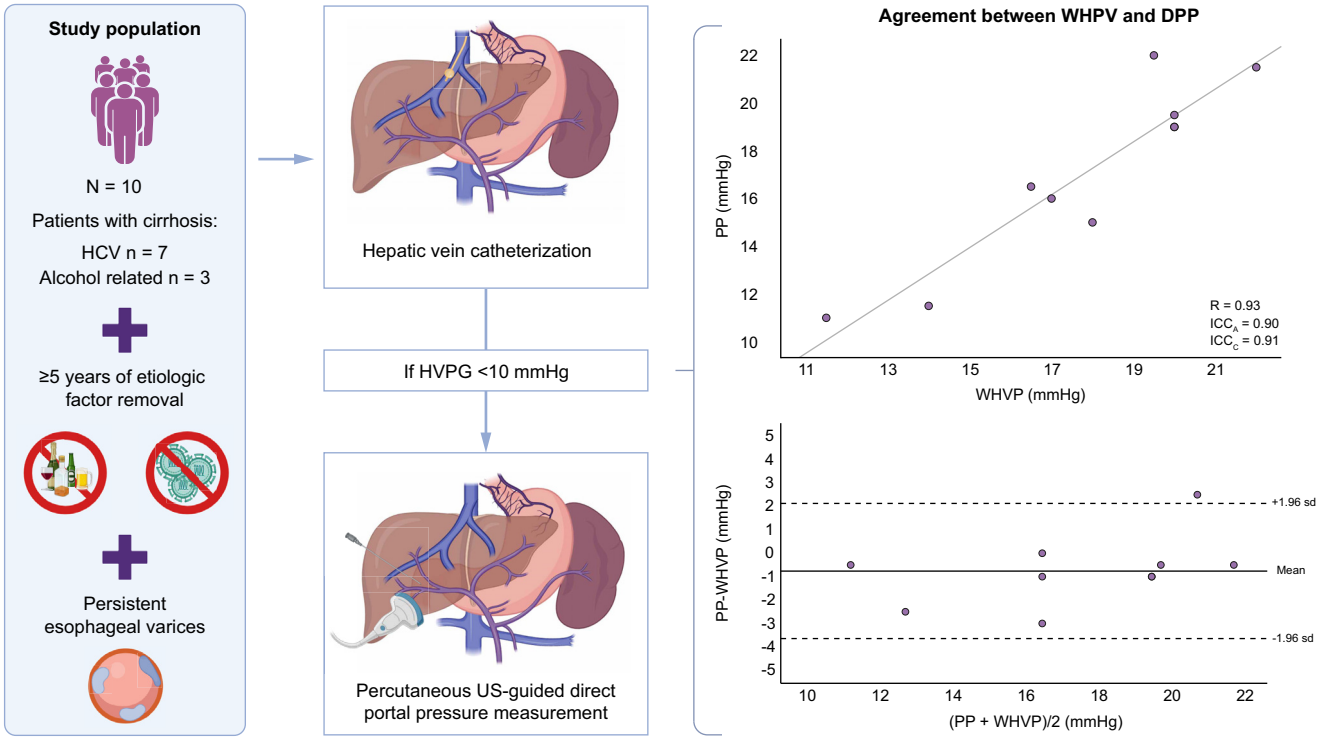
Authors

Pol Olivas, Alexandre Soler-Perromat, Luis Tellez, …, Juan Carlos García-Pagán, Ángeles García-Criado, Virginia Hernández-Gea

Correspondence

vihernandez@clinic.cat (V. Hernández-Gea).

Graphical abstract



Highlights:

- Varices can persist after etiologic factor removal despite low HVPG.
- HVPG has an excellent correlation with portal pressure in cirrhosis regression.
- Esophageal varices and portosystemic shunts may not be unequivocal signs of clinically significant portal hypertension after cirrhosis etiologic factor removal.

Impact and implications:

Despite a favorable evolution after the removal of the etiologic factor, varices persist in some patients, and there is a lack of concise guidelines for the evaluation and management of portal hypertension in this population. Our research underscores the persistence of varices in the absence of clinically significant portal hypertension and significantly demonstrates the accuracy of hepatic venous pressure gradient (HVPG) in reflecting portal vein pressure in this specific patient group. These findings emphasize the crucial role of HVPG in the assessment of portal hypertension after etiologic factor removal and lay the groundwork for further investigation into clinical outcomes and the necessity of non-selective beta-blockers in individuals with persistent varices after the removal of etiologic factor.

https://doi.org/10.1016/j.jhepr.2024.101170

JHEP|Reports

Persistent varices in cured patients: Understanding the role of hepatic venous pressure gradient☆

Pol Olivas[1,2,3,4], Alexandre Soler-Perromat[5], Luis Tellez[2,6], José Antonio Carrión[7], Edilmar Alvarado-Tapias[2,8], José Ferrusquía-Acosta[2,9], Sabela Lens[1,2,4], Antonio Guerrero[2,6], Ángeles Falgà[1,3], Pamela Vizcarra[1,3], Lara Orts[1,2,3], Valeria Perez-Campuzano[1,2,3], Sarah Shalaby[1,2,3], Sonia Torres[1], Anna Baiges[1,2], Fanny Turon[1,2,3], Juan Carlos García-Pagán[1,2,3,4], Ángeles García-Criado[5], Virginia Hernández-Gea[1,2,3,4,*]

JHEP Reports **2024**. vol. 6 | 1–8

Background & Aims: Etiologic factor removal (ER) drives recompensation and improves portal hypertension in cirrhosis. Esophageal varices (EV) and portosystemic shunts (PSS) have been found in patients despite hepatic venous pressure gradient (HVPG) dropping below 10 mmHg after ER, questioning HVPG accuracy in reflecting true portal pressure in the setting of ER. We aim to evaluate the correlation of HVPG with direct portal pressure (DPP) in patients with persistence of EV after ER despite HVPG <10 mmHg.

Methods: This is a bicentric 'proof of concept' study evaluating HVPG and ultrasound-guided percutaneous DPP in patients with HCV or alcohol-related cirrhosis with persistent varices and HVPG <10 mmHg after at least 5 years of ER.

Results: Seven patients with HCV and three with alcohol-related cirrhosis with persistent varices and HVPG <10 mmHg after at least 5 years of ER were included. At evaluation, all patients had a patent portal vein and were compensated. The median platelet count was 129.5 (IQR 95–145) × 10^9/ml, and the median liver stiffness measurement was 16.15 (IQR 14.4–22.3) kPa. In five patients, EV remained the same size (two large and three small), and five downsized to small after ER. Wedge hepatic vein pressure (median 19 [IQR 16.5–20] mmHg) and portal pressure (median 18 [IQR 15–19.5] mmHg) had an excellent correlation (R = 0.93, p <0.0001). Portal pressure gradient (PPG) confirmed the absence of clinically significant portal hypertension as identified by HVPG across all the patients.

Conclusions: HVPG accurately reflects PPG in the context of HCV and alcohol-related cirrhosis regression. After ER, EV may persist despite HVPG <10 mmHg. The benefit of prophylaxis in patients with EV and HVPG <10 mmHg is unknown. Future studies with clinical endpoints are needed to validate our findings.

Introduction

Patients with cirrhosis who have clinically significant portal hypertension (CSPH) are at a higher risk of decompensation,[1] and benefit from prophylaxis with non-selective beta-blockers (NSBBs).[2] Etiologic factor removal (ER) in advanced chronic liver disease represents a pivotal milestone as it is correlated with enhanced liver function, decreased hepatic venous pressure gradient (HVPG), and reduced risk of decompensation.[3–12] However, it is crucial to note that not all patients experience CSPH resolution after etiological cure,[5–8] and how to discriminate which patients are no longer at risk of decompensation and thus could avoid life-long prophylaxis requires further refinement.[13]

Non-invasive tests (NITs) have proven effective in identifying patients at both low and high risk of CSPH after sustained viral response (SVR).[14] However, a substantial gray zone persists, and management of patients with pre-existing esophageal varices (EV) and liver stiffness measurements (LSMs) falling within the ambiguous range (LSM between 12 and 25 kPa) is still controversial.[13,15–17] In the absence of specific data, guidelines suggest endoscopic surveillance in this group of patients to guide management.[13]

Interestingly, EV and portosystemic shunts (PSS) may persist or progress after SVR even when HVPG drops below the conventional CSPH threshold of 10 mmHg, questioning its accuracy in reflecting true portal pressure.[14–24] Furthermore, there is growing awareness that extrahepatic vascular changes, resistant to regression, may persist despite ER and potentially contribute to pre-sinusoidal portal hypertension,[25,26] a phenomenon not entirely captured by HVPG. In light of these challenges, our aim is to comprehensively assess the correlation between HVPG and direct portal pressure (DPP) in patients with HVPG levels below 10 mmHg and the persistence of EV post ER to provide insights into the management of portal

☆ Given its role as Editor, Virginia Hérnandez-Gea had no involvement in the peer-review of this article and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to the Guest Editor Pierre-Emmanuel Rautou.

* Corresponding author. Address: Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic, Villarroel 170, Barcelona 08036, Spain. Tel.: +34932275400 (2209); Fax: +34-932279856.
E-mail address: vihernandez@clinic.cat (V. Hernández-Gea).

https://doi.org/10.1016/j.jhepr.2024.101170

hypertension in cirrhosis regression in a population without available guidance.

Materials and methods

This is an observational, prospective, and 'proof of concept' study, where invasive procedures have been performed at the Hospital Clinic Barcelona and Hospital Ramón y Cajal Madrid by expert personnel.

Selection of patients

From May 2021 to March 2023, all patients with HVC or alcohol-related cirrhosis referred to the hemodynamic laboratory or visited the outpatient clinic were eligible and consecutively considered for inclusion.

Cirrhosis was diagnosed by a previous liver biopsy or by unequivocal clinical, biochemical, and ultrasonographic findings. The evaluation of portal pressure involved hepatic vein catheterization and a simultaneous ultrasound (US)-guided trans-parietal DPP measurement in patients whose HVPG was <10 mmHg. NSBBs were discontinued 4 days before the procedure. In addition, retrospective clinical data were gathered for analysis.

Patients included in the study met the following inclusion criteria: diagnosis of HCV-related or alcohol-related cirrhosis with SVR or abstinence for at least 5 years, EV in gastroscopy evaluation within the past 6 months, and absence of portal vein thrombosis confirmed by US, angio-MRI, or angio-CT during the same timeframe.

Patients meeting any of the following criteria were excluded: age <18 or >80 years, prior orthotopic liver transplant, active hepatocellular carcinoma, HIV infection, or a history of previous liver surgery.

Data on LSM and spleen stiffness measurement (SSM) within the past 6 months were also documented.

Portal hypertension evaluation

EV were classified into small (<5 mm) and large (>5 mm) varices during the endoscopy following internal protocols. All endoscopies were performed under sedation.

Invasive procedures were conducted with the patient fully awake. Hepatic vein catheterization and DPP measurement were performed simultaneously.

In patients on NSBB, the medication was discontinued 4 days before the procedures.

The HVPG measurement was performed by experienced personnel as previously described.[27] Briefly, under fluoroscopy, a 7F catheter balloon was guided into the main right or medium hepatic vein where free hepatic venous pressure (FHVP) and wedge hepatic venous pressure (WHVP) were measured in triplicate. HVPG was defined as the difference between mean WHVP and mean FHVP.

The DPP measurement was conducted by an experienced radiologist. Patients underwent non-invasive vital sign monitoring, including electrocardiography, arterial blood pressure, and pulse oximetry. None of the patients received sedation; however, a paracetamol infusion was started just before the procedure, and local anesthesia with mepivacaine was administered before the puncture.

Initially, the safest and most suitable intrahepatic branch of the portal tract was selected by ultrasonographic exploration, choosing the branch nearest to the abdominal wall. After administering local anesthesia, the selected portal branch was punctured percutaneously using a thin needle (20G) under continuous ultrasonographic guidance. The correct position for the measurement was confirmed by the sonographic image and by aspirating portal venous blood. Once the needle was properly placed, it was flushed with 3 ml of saline and connected to a digital pressure transducer calibrated to a baseline pressure of 0 mmHg at the midaxillary line and mid-right atrial level. This was then connected to a digital monitoring system capable of transferring the tracing to electronic medical records, providing a permanent tracing of portal vein pressure (PP) using a multichannel recorder. Three independent recordings of the PP were obtained. The portal pressure gradient (PPG) was defined as the difference between PP and FHVP. Pressure was measured for at least 30 s in triplicate.

Gradients (HVPG and PPG) were consistently calculated using FHVP, and not with inferior cava vein pressure (ICVP), in accordance with evidence-based recommendations.[13,27] It has been reported that even when differences between FHVP and ICVP exceed 2 mmHg, gradients measured with FHVP demonstrate a stronger correlation with clinical outcomes.[28]

Data on LSM and SSM were then collected. Measurements were performed after a minimum fasting period of 6 h by an expert nurse using FibroScan® Expert 630 (Echosens, Paris, France). LSM was determined in the right hepatic lobe through the intercostal space with the patient in the supine position and the right arm in maximum abduction. SSM was determined with the patient in the supine position and the left arm in maximum abduction after spleen marking by US. The results were expressed in kilopascals corresponding to the median of 10 determinations. Only valid explorations (success rate >60% and IQR/median ratio <0.3) were included.

Statistical analysis

Continuous variables are expressed as mean (SD) or median (IQR), whenever appropriate. Agreement between WHVP and PP was assessed using Pearson's correlation (R) and the intraclass correlation coefficient (ICC) for both absolute agreement and consistency. ICC values of <0.5 indicate poor agreement, values from 0.75 to 0.90 indicate good agreement, and values of >0.90 indicate excellent agreement. Significance was considered as two-sided p values <0.05. Agreement was also evaluated using the Bland–Altman method, which plots the difference between both pressures (Y axis) over their mean (X axis), showing the 95% limits of the agreement (mean difference ± 1.96 SD). The smaller the range between these two limits, the better the agreement. Agreement between WHVP and PP occurred when both were equal or differed by <10% of the PP value. Disagreement between WHVP and PP occurred when both pressures differed by >10%. Any difference of >5 mmHg was considered a major discrepancy. PP was overestimated by WHVP when the latter was higher than the former by >10% of the PP value. Conversely, PP was underestimated by WHVP when the latter was lower than the former by >10% of the PP value. We defined disagreement as a threshold difference of 10%, as reductions in HVPG of this magnitude have been linked to significant clinical endpoints.[29–32] Statistical

analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA), and a two-sided p value <0.05 was considered statistically significant.

Ethical aspects

This study was conducted in accordance with the International Guidelines for Ethical Review of Epidemiological studies and the principles of the Declaration of Helsinki and has the approval of our institution's ethics committee. The study was initiated in Hospital Clinic Barcelona (ethical approval code: HCB/2021/0614) in December 2023. The protocol was modified to allow the participation of Hospital Ramon y Cajal Madrid (ethical approval code: HRyC/001/24). All patients signed an informed consent form to participate in the study. All authors vouch for the integrity and accuracy of the analysis and its fidelity to the protocol and reviewed and approved the final manuscript.

Results

Patient inclusion and characteristics

Twenty-four eligible patients were recruited for potential participation in the study, of whom 23 provided consent and subsequently underwent hepatic vein catheterization. Following the measurement of HVPG, 12 patients were excluded from further analysis: 11 because of HVPG >10 mmHg and 1 because of the presence of vein-to-vein communications. After abdominal US evaluation, one patient was excluded because of difficult anatomic access to the portal vein puncture. Finally, 10 patients were included in the study (Fig. 1).

Most patients were male (80%), with a median age of 56 (IQR 54–66) years. Cirrhosis was related to HCV chronic infection in seven patients and as a result of alcohol use disorder in three. The median period of SVR and abstinence were 6 (IQR 5–7) and 14 (5–17) years, respectively. Obesity or overweight was present in six (60%) patients, with a median BMI of 25.65 (IQR 24.93–30.40) kg/m^2, and four of them had other metabolic disorders (diabetes mellitus type 2, arterial hypertension, or dyslipidemia) (Table 1).

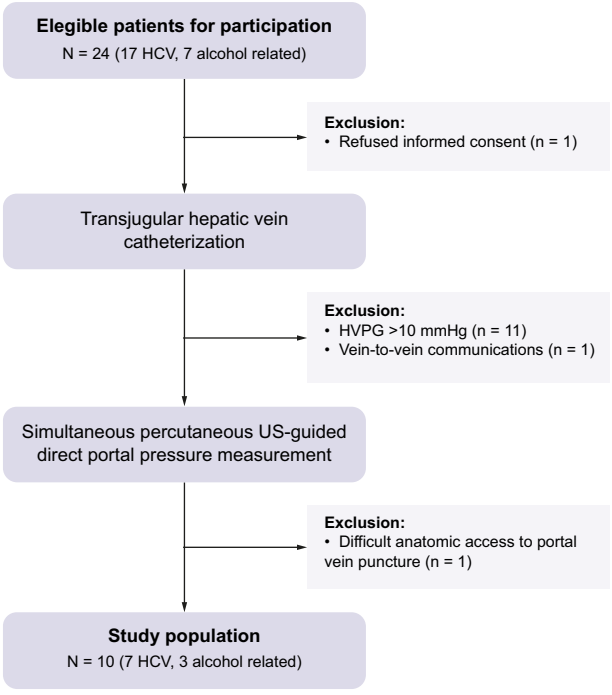


Fig. 1. Flowchart: patient inclusion. HVPG, hepatic venous pressure gradient; US, ultrasound.

Before ER, three patients had decompensated cirrhosis: one patient had variceal bleeding, another one had ascites and hepatic encephalopathy, and a third one had hepatic encephalopathy. EV were large in seven patients and small in three. Five patients had PSS (Tables 2 and 3).

On hemodynamic evaluation, all patients were compensated and had good hepatic function (Child–Pugh A 5 points, median model for end-stage liver disease [MELD] score 8 [IQR 7–9]). Specifically, the three patients with previous decompensation met the criteria outlined in the Baveno VII definition of recompensation.[13] Liver biopsy after ER was available in four patients, and incomplete septal cirrhosis in the context of cirrhosis regression was observed in two of them. An extensive portal hypertension evaluation was performed, including abdominal US, gastroscopy, laboratory tests, LSM, and SSM (in seven patients). In addition, magnetic resonance or angio-computed tomography evaluating PSS was also available in seven patients. The portal vein was patent in all the patients, and none had a history of previous portal vein thrombosis. Splenomegaly (spleen >13 cm) persisted in five patients, and the median spleen size was 13.2 (IQR 11.6–15) cm. Eight patients had thrombocytopenia with a median platelet count of 129.5 (IQR 95–145) × 10^9/ml, and only two had a platelet count of >150 × 10^9/ml. The median LSM was 16.15 (IQR 14.4–22.3) kPa without any values below 12 kPa or above 25 kPa. Seven patients underwent SSM, and the median value was 35.1 (IQR 29.3–45.6) kPa without any value over 50 kPa. PSS remained present in the five patients with prior history of PSS (Table 1).

EV downsized from large to small in five patients, whereas EV remained unchanged in two patients with large EV and three with small EV. One patient was on secondary prophylaxis (NSBB + isosorbide mononitrate), and six were on primary prophylaxis (two with endoscopic variceal ligation and four with NSBB) (Table 3).

Hepatic hemodynamics evaluation

All patients successfully underwent hepatic hemodynamic evaluation using both transjugular catheterization and direct portal vein puncture approaches. US-guided percutaneous direct portal vein measurement was well tolerated by all patients, and there were no complications related to the procedure.

The median HVPG value was 7 (IQR 6–9) mmHg, and the percutaneous US-guided DPP measurement confirmed the absence of CSPH in all patients, with a median PPG of 6 (IQR 5–8) mmHg (Table 4).

Agreement between WHVP and PP

To evaluate the effectiveness of hepatic vein catheterization as an indirect method for assessing portal hemodynamics in our study population, we analyzed the agreement between WHVP and PP. Given that the two measurements were performed simultaneously, ensuring the same FHVP, WHVP, and PP became the relevant variables. We used the methodology from

Table 1. Patient characteristics at hepatic hemodynamics evaluation.

Patient ID	Sex (M/F)	Age	Etiology	SVR or abstinence (years)	BMI (kg/m^2)	CPT	MELD	Liver biopsy	LSM (kPa)	SSM (kPa)	Platelets (× 10^9/L)	Splenomegaly Y/N (cm)	Portal vein velocity (cm/s)	PSS	Decompensated
1	M	55	HCV	5	25.9	A5	7	–	14.4	–	106	Yes (13.2)	21	No	No
2	M	54	Alcohol	17	33.6	A5	8	–	16.2	35	171	No	15	No	No
3	M	54	HCV	5	30.4	A5	8	Cirrhosis	17.9	29.3	73	Yes (15.4)	20	Yes	No
4	F	55	HCV	7	32.5	A5	6	–	22.3	35.1	133	No	20	Yes	No
5	M	66	HCV	6	24.4	A5	8	Cirrhosis	21	–	95	No	14	No	No
6	F	74	HCV	6	25.5	A5	9	ISC	13.6	–	126	No	10	Yes	No
7	M	56	HCV	7	18.1	A5	9	–	22.7	49.2	145	Yes (15)	15	Yes	No
8	M	60	Alcohol	14	24.7	A5	7	ISC	12.1	45.6	136	Yes (13)	13	Yes	No
9	M	69	HCV	7	22.2	A5	8	–	15.4	36.6	86	No	19	No	No
10	M	53	Alcohol	5	25.3	A5	8	–	16.1	22.9	166	Yes (14)	21	No	No

CPT, Child-Pugh-Turcotte; ISC, incomplete septal cirrhosis; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; PSS, portosystemic shunts; SSM, spleen stiffness measurement; SVR, sustained viral response.

previous studies that compared hepatic vein catheterization with direct portal measurement.[29–32]

The correlation between WHVP and PP was excellent (R = 0.93, p <0.0001). The results of the intra-class correlation coefficient for consistency and absolute agreement confirmed the absence of major proportional and systematic differences between the two measurements (ICC_A = 0.90, p <0.0001; ICC_C = 0.91, p <0.001) (Table 5 and Fig. 2).

Agreement between the two measurements was also assessed using a Bland–Altman plot (Fig. 3). The low range of variation, indicated by a small 95% confidence interval (CI), allowed us to consider a good agreement between the two measurements. Nonetheless, three (30%) patients showed disagreement (with WHVP exhibiting a difference >10% of the PP value), with a majority tendency to overestimate. No major measurement discrepancies (difference >5 mmHg) were observed.

In addition, an agreement analysis between HVPG and PPG was also performed, yielding similar results (Table S1 and Fig. S1).

Discussion

In this study, we aimed to investigate the correlation between HVPG and DPP in cases of cirrhosis with persistent EV for more than 5 years after ER and HVPG <10 mmHg. This 'proof of concept' study involved 10 patients from two hospitals in Spain (Barcelona and Madrid) with proven expertise in portal pressure measurement and management. After confirming HVPG <10 mmHg with liver catheterization, US-guided direct portal vein puncture was performed during the same procedure. Both HVPG and PPG were measured in triplicate for subsequent comparison.

ER has consistently demonstrated its efficacy in improving liver function and reducing portal pressure, leading to recompensation in a significant number of patients.[3–12] The management of patients in the recompensated stage, after the achievement of SVR or long-term abstinence, has emerged as an active area of research, striving for personalized treatment strategies.[13] NITs have proven valuable in identifying patients with varying risks of CSPH following ER.[14] However, challenges persist in the identification and management of CSPH in patients with pre-existing EV, particularly when NIT measurements fall within an ambiguous range.[13,15–17] Recent studies in the context of HCV have indicated the utility of post-treatment NITs in detecting CSPH, with improvements in liver LSM and platelet count associated with negligible risks of portal hypertension decompensation, even if the risk of developing hepatocellular carcinoma still persist. Notably, patients with persistently high LSM values (>25 kPa) are considered at risk of decompensation despite improvements in liver disease, warranting a management approach akin to pre-etiological treatment.[13,14] Recommendations for patients with LSM values between 12 and 25 kPa after the removal/suppression of the primary etiological factor remain less clear, with the last Baveno VII recommendations suggesting repeat endoscopy and potential NSBB withdrawal in the absence of varices. However, specific data have not been generated yet.[13]

Our study unveils a pertinent concern as EV and PSS may persist or progress even when HVPG drops below the conventional threshold of 10 mmHg, raising questions about its accuracy in reflecting true portal pressure.[15–24] This study

Table 2. Patient characteristics before etiologic factor removal.

Patient ID	CPT	MELD	Splenomegaly Yes/No (cm)	Platelets (× 10^9/L)	LSM (kPa)	HVPG (mmHg)	Portosystemic shunts	Decompensation
1	A5	8	Yes	41	37.4	12.5	No	No
2	B9	21	Yes	131	No	16	No	VB
3	A5	9	Yes	73	23.6	–	Yes	No
4	A5	7	Yes	88	46.4	–	Yes	No
5	A5	8	No	98	21	–	No	No
6	A6	10	Yes	94	NA	–	Yes	No
7	B8	15	Yes	76	35.3	19.5	Yes	HE
8	C11	19	Yes	134	NA	17	Yes	HE, A
9	A6	10	Yes	126	20.5	–	No	No
10	A6	10	Yes	119	29.5	–	No	No

A, ascites; CPT, Child-Pugh-Turcotte; HE, hepatic encephalopathy; HVPG; hepatic venous pressure gradient; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; VB, variceal bleeding.

Table 3. Esophageal varices evolution.

	Esophageal varices (small/larges)		
Patient ID	Before etiologic agent removal	After etiologic agent removal	Prophylaxis
1	Small	Small	No
2	Large	Large	NSBBs + IMN
3	Large	Small	NSBBs
4	Large	Small	EVL
5	Large	Large	NSBBs
6	Large	Small	No
7	Small	Small	NSBBs
8	Large	Small	NSBBs
9	Large	Small	NSBBs
10	Small	Small	No

EVL, endoscopic variceal ligation; IMN, isosorbide mononitrate; NSBBs, non-selective beta-blockers.

addresses the unprecedented question of whether HVPG, in the context of regression, accurately reflects actual portal pressure. To explore this, we selected a cohort of patients exhibiting persistence of varices and HVPG <10 mmHg after control of the etiological agent. This cohort, lacking clinical recommendations, provided an optimal scenario to evaluate whether persistent extrahepatic vascular derangements may perpetuate portal hypertension even in the presence of lower intrahepatic resistance.

Our study, for the first time, assessed the correlation of HVPG with DPP in the context of ER. DPP measurements were conducted and correlated with HVPG, demonstrating an excellent correlation. This highlights the utility of HVPG as a reliable tool for excluding CSPH following SVR or alcohol abstinence in patients with cirrhosis associated with HCV or alcohol use disorder. Furthermore, our findings demonstrate the precision of WHVP in capturing portal pressure, with HVPG accurately detecting the absence of CSPH in all patients. Despite minor discrepancies between HVPG and PPG in a few cases, none of these altered the classification of CSPH presence or absence.

Our findings align with existing data reporting the persistence of portocollateral circulation despite liver transplantation and treatment with transjugular intrahepatic portosystemic

Table 4. Hepatic hemodynamics evaluation.

Patient ID	ICVP (mmHg)	FHVP (mmHg)	WHVP (mmHg)	PP (mmHg)	HVPG (mmHg)	PPG (mmHg)
1	11	11	17	16	6	5
2	12	14	20	19	6	5
3	11	12	20	19.5	8	7.5
4	10	10.5	18	15	7.5	4.5
5	9.5	11	20	19	9	8
6	7	7.5	16.5	16.5	9	9
7	14	14	19.5	22	5.5	8
8	8	8	14	11.5	6	3.5
9	10	12.5	22	21.5	9.5	9
10	4.5	6	11.5	11	5.5	5

FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; ICVP, inferior cava vein pressure; PP, portal vein pressure; PPG, portal pressure gradient; WHVP, wedge hepatic venous pressure.

Table 5. Correlation between WHVP and PP.

	R	95% CI	*p* value	ICC_A	95% CI	*p* value	ICC_C	95% CI	*p* value
Study population (n = 10)	0.93	(0.71–0.98)	0.000	0.90	(0.65–0.97)	0.000	0.91	(0.69–0.98)	0.000

This was assessed using Pearson's correlation (R) and the ICC for absolute agreement and consistency. Level of significance p <0.05.
CI, confidence interval; ICC, intra-class correlation coefficient; PP, portal vein pressure; WHVP, wedge hepatic venous pressure.

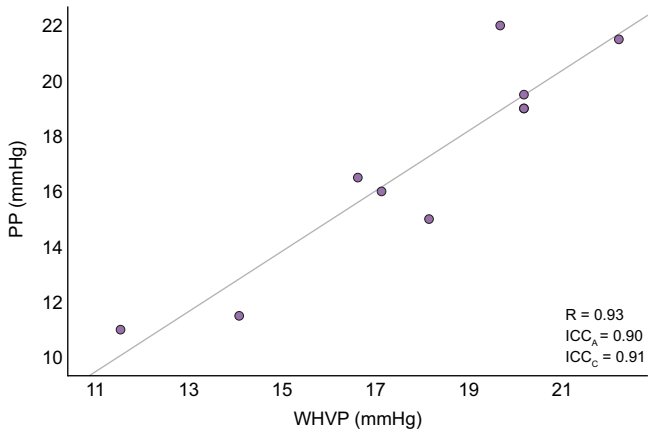


Fig. 2. Correlation between WHVP and PP in patients with alcohol- or HCV-related cirrhosis after >5 years of abstinence or SVR. Values of Pearson's correlation (R) and intra-class correlation coefficient for absolute agreement and consistency are given. Level of significance p <0.05. ICC, intra-class correlation coefficient; PP, portal vein pressure; SVR, sustained viral response; WHVP, wedge hepatic venous pressure.

shunt.[33–40] Notably, EV persistence or enlargement has been observed in patients successfully treated with interferon-based regimens and direct-acting antivirals.[16–23] Previous studies in animal models demonstrated the persistence of extrahepatic vascular alterations after portal hypertension and cirrhosis resolution.[25,41] This persistence is attributed to the viscoelastic mechanical properties of blood vessels, suggesting that once vessels are deformed, they do not return to their original form without compressive stress being applied back.[41] In our study, HVPG accurately reflected portal pressure, demonstrating the persistence of varices even in the absence of high pressure in the splanchnic territory, suggesting that they might be perfused at low pressure. This finding aligns with the low bleeding rate after SVR reported in the study by Lens-Baiges *et al.*[8] in patients with the persistence of EV (even large varices) with HVPG <10 mmHg.

Consistent with our data, animal models of cirrhosis resolution highlighted that mesenteric vascular density is not alleviated despite increased blood flow to the less resistant liver[25,26,41] Moreover, the observation that in a rodent model of portal hypertension by portal vein ligation, the degree of extrahepatic shunts significantly increases after removing the ligation of the portal vein supports the notion that collateral vessels do not disappear but rather collapse during cirrhosis resolution.[41] These findings in animals reinforce our human observations, explaining why PSS persist even after a decrease in intrahepatic vascular resistance and sinusoidal pressure. The specific risk associated with the persistence of vessels at low perfusion pressure in the event of further liver injury remains an unexplored aspect that warrants future investigation.

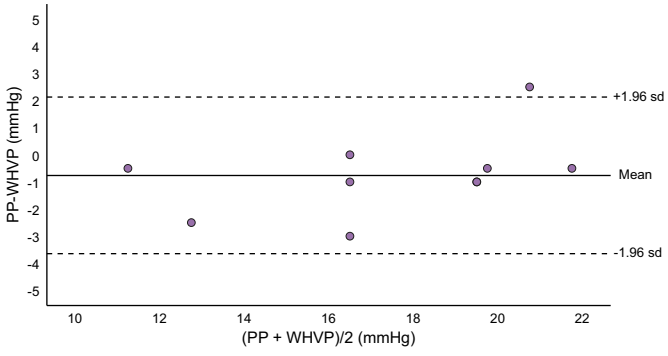


Fig. 3. Bland–Altman plot assessing the agreement between WHVP and PP in patients with alcohol- or HCV-related cirrhosis after >5 years of abstinence or SVR. The plot shows the difference between both pressures (Y axis) over their mean (X). The lines show the 95% limits of the agreement (mean differences ± 1.96 SD). Agreement occurred when both values were equal or differed by <10% of the PP value. Differences of >5 mmHg were considered a major discrepancy. PP, portal vein pressure; SVR, sustained viral response; WHVP, wedge hepatic venous pressure.

In addition, the persistence of vascular changes, including shunts and hyperarterialization (increased splanchnic arterial flow) during regression, may potentially contribute to liver nodule development and the persistence of hepatocellular carcinoma risk even in the absence of portal hypertension.[26]

A notable strength of our study lies in the meticulous evaluation of portal hypertension in expert tertiary centers, using both hepatic vein catheterization and direct US-guided portal pressure measurement. Possible confounding factors, such as the use of NSBBs in the 4 days before portal hypertension evaluation and the presence of vein-to-vein communications after hepatic vein occlusion, were rigorously discarded. However, we acknowledge limitations in our study, primarily the small sample size, which was driven by the invasiveness of the study and its proof of concept design aimed at demonstrating the correlation of HVPG and DPP measurement in the unique scenario of variceal persistence without CSPH. Despite the limited sample size, we contend that this restricted population serves as an ideal model to generate information applicable to diverse clinical scenarios. Nevertheless, we recognize that this approach restricts the generalizability of our findings to the entire population of patients with cirrhosis and ER, especially caused by other etiologies. In addition, this study does not permit the inference of clinical outcomes in patients with EV and the absence of CSPH after ER owing to the lack of prospective follow-up. Furthermore, the potential benefit of NSBBs in this specific population remains questionable. However, our study provides the necessary rationale to explore this question in a larger cohort of patients, focusing on clinical events as the primary endpoint. Finally, it is important to consider that although portal hemodynamics evaluation using HVPG or PPG provides indirect insights into the flow and pressures within the collateral circulation, directly measuring the flow and pressure in varices and shunts could offer a more detailed understanding of the physiopathology. However, such direct measurement techniques are significantly more invasive and risky and have largely been abandoned because of these concerns.

In conclusion, within the context of ER and cirrhosis regression, EV may persist despite HVPG <10 mmHg. Given its excellent correlation with DPP, HVPG is also a valuable tool for evaluating portal hypertension after ER (at least in HCV and alcohol-related cirrhosis), proficiently identifying patients without portal hypertension despite the presence of varices. EV and PSS may not be unequivocal signs of CSPH in the context of cirrhosis regression. However, whether these patients would require prophylaxis remains unknown, necessitating further studies with clinical endpoints to validate our findings in a more extensive population.

Affiliations

[1]*Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic, Fundacióde Recerca Clínic Barcelona - Institut de Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), Barcelona, Catalonia, Spain;* [2]*Centro de Investigación Biomédica Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain;* [3]*Health Care Provider of the European Reference Network on Rare Liver Disorders (ERN-RareLiver);* [4]*Depertament de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, Spain;* [5]*Radiology Department, CDI, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain;* [6]*Servicio de Gastroenterología y Hepatología, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Universidad de Alcalá, Madrid, Spain;* [7]*Liver Section, Gastroenterology Department, Hospital del Mar, Institut Hospital del mar D'Investigacions Mèdiques, PSMAR, Universitat Pompeu Fabra, Facultat de ciències de la Salut i de la Vida, Barcelona, Spain;* [8]*Gastroenterology Department, Hospital de la Santa Creu I Sant Pau, Institut d'Investigacions Biomèdiques Sant Pau, Barcelona, Spain;* [9]*Unitat Hepatologia, Servei Aparell Digestiu, Hospital Universitari Parc Taulí, Institut d'Investigació i Innovació Parc Taulí (I3PT), Sabadell, Spain*

Abbreviations

CSPH, clinically significant portal hypertension; DPP, direct portal pressure; ER, etiologic factor removal; EV, esophageal varices; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; ICC, intra-class correlation coefficient; ICVP, inferior cava vein pressure; LSM, liver stiffness measurement; NIT, non-invasive test; NSBB, non-selective beta-blocker; PPG, portal pressure gradient; PP, portal vein pressure; PSS, portosystemic shunts; SSM, spleen stiffness measurement; SVR, sustained viral response; US, ultrasound; WHVP, wedge hepatic venous pressure.

Financial support

This study was supported by: FIS PI20/00569 and FIS 23/00997 funded by "Instituto de Salud Carlos III" and co-funded by the European Union. From "CIBEREHD" funded by "Instituto de Salud Carlos III". From the "Commissioner for Universities and Research from the Department of Economy and Knowledge" of the "Generalitat de Catalunya" (AGAUR SGR2021 01115). P.O. is the recipient of a Rio Hortega Grant. Current contract is funded by the "Instituto de Salud Carlos III" with charges to the European funds of the Recovery, Transformation and Resilience Plan (Plan de recuperacin, transformacin y Resilencia), with file code CM22/00058, pursuant to the Resolution of the Resolution of the Instituto de Salud Carlos II, O.A, M.P. of December, 2023, granting the Rio HOrtega Contracts and "Co-Financed by the European Union". S.S. has a Rio Hortega Grant. Current contract is funded by "Instituto de Salud Carlos III" with charges to the European funds of the Recovery, Transformation, and Resilience Plan (Plan de Recuperacin, Transformacin y resiliencia), with files code CM23/00068, pursuant to the Resolution of the Instituto de Salud Carlos III, O.A., M.P. of December, 2023, granting the Rio Hortega Contracts, and "Co-Financed by the Europena Union". AB is the recipient of a Juan Rodes grant, financed by the "Instituto de Salud Carlos III" with European funds from the Recovery, Transformation and Resilience Plan (file code JR20/00024), by virtue of the Resolution of the "Dirección del Instituto de Salud Carlos II, O.A., M.P." of December 14, 2022, by which the Joan Rodes contracts are granted, and funded by the European Union Next GenerationEU."

Conflicts of interest

The authors declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: VHG, PO. Methodology: VHG, PO, AGC, JCGP. Investigation: PO, LT, ASP, JAC, EAT, JFA, SL, SS, AG, AF, PV, EP, VPC, AB, FT. Formal analysis: PO, FT, AB, VHG, ST. Project administration: VHG, PO. Supervision: VHG, JCGP, AGC. Writing original draft: PO, VHG, JCGP.

Data availability statement

The raw/processed data required to reproduce the above findings cannot be shared at this time because of legal/ethical reasons.

Acknowledgements

We thank Sergio López Durán and María Torres for their support in the direct measurement of portal pressure. We thank BioRender.com for providing some of the images included in the visual abstract. We thank Enric Reverter for his support in statistical interpretation.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101170.

References

Author names in bold designate shared co-first authorship

[1] Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–488.

[2] Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2019;393:1597–1608. Erratum in: Lancet 2019;393:2492.

[3] Akhtar E, Manne V, Saab S. Cirrhosis regression in hepatitis C patients with sustained virological response after antiviral therapy: a meta-analysis. Liver Int 2015;35:30–36.

[4] Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019;393:1453–1464.

[5] Mandorfer M, Kozbial K, Schwabl P, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol 2016;65:692–699.

[6] Lens S, Alvarado-Tapias E, Mariño Z, et al. Effects of all-oral anti-viral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. Gastroenterology 2017;153:1273–12783. e1.

[7] Afdhal N, Everson GT, Calleja JL, et al. Effect of viral suppression on hepatic venous pressure gradient in hepatitis C with cirrhosis and portal hypertension. J Viral Hepat 2017;24:823–831.

[8] **Lens S**, **Baiges A**, Alvarado-Tapias E, et al. Clinical outcome and hemodynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. J Hepatol 2020;73:1415–1424.

[9] Vorobioff J, Groszmann RJ, Picabea E, et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: a 10-year prospective study. Gastroenterology 1996;111:701–709.

[10] Hofer BS, Simbrunner B, Hartl L, et al. Alcohol abstinence improves prognosis across all stages of portal hypertension in alcohol-related cirrhosis. Clin Gastroenterol Hepatol 2023;21. 2308–17.e7.

[11] Pose E, Torrents A, Reverter E, et al. A notable proportion of liver transplant candidates with alcohol-related cirrhosis can be delisted because of clinical improvement. J Hepatol 2021;75:275–283.

[12] Luca A, García-Pagán JC, Bosch J, et al. Effects of ethanol consumption on hepatic hemodynamics in patients with alcoholic cirrhosis. Gastroenterology 1997;112:1284–1289.

[13] de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII—renewing consensus in portal hypertension. J Hepatol 2022;76:959–974. Erratum in: J Hepatol 2022;77:271.

[14] Semmler G, Lens S, Meyer EL, et al. A study by the Baveno Cooperation: an EASL consortium. Non-invasive tests for clinically significant portal hypertension after HCV cure. J Hepatol 2022;77:1573–1585.

[15] Di Marco V, Calvaruso V, Ferraro D, et al. Effects of eradicating hepatitis C virus infection in patients with cirrhosis differ with stage of portal hypertension. Gastroenterology 2016;151. 130–9.e2.

[16] Thabut D, Bureau C, Layese R, et al. Validation of Baveno VI criteria for screening and surveillance of esophageal varices in patients with compensated cirrhosis and a sustained response to antiviral therapy. Gastroenterology 2019;156:997–1009. e5.

[17] Puigvehí M, Londoño MC, Torras X, et al. Impact of sustained virological response with DAAs on gastroesophageal varices and Baveno criteria in HCV-cirrhotic patients. J Gastroenterol 2020;55:205–216.
[18] D'Ambrosio R, Degasperi E, Anolli MP, et al. Incidence of liver- and non-liver-related outcomes in patients with HCV-cirrhosis after SVR. J Hepatol 2022;76:302–310.
[19] Ibrahim ES, Abdel-Samiee M, Youssef MI, et al. Variceal recurrence 4 years post endoscopic band ligation in hepatitis C patients who achieved sustained virological response with oral direct-acting antiviral therapy. J Viral Hepat 2021;28:279–287.
[20] D'Ambrosio R, Aghemo A, Rumi MG, et al. The course of esophageal varices in patients with hepatitis C cirrhosis responding to interferon/ribavirin therapy. Antivir Ther 2011;16:677–684.
[21] Takakusagi S, Saito N, Ueno T, et al. Changes of esophageal varices in hepatitis C patients after achievement of a sustained viral response by direct-acting antivirals. DEN Open 2021;2:e11.
[22] Giannini EG, De Maria C, Crespi M, et al. Course of oesophageal varices and performance of noninvasive predictors following hepatitis C virus clearance in compensated advanced chronic liver disease. Eur J Clin Invest 2020;50:e13231.
[23] Kotani K, Enomoto M, Uchida-Kobayashi S, et al. Short-term hepatocyte function and portal hypertension outcomes of sofosbuvir/velpatasvir for decompensated hepatitis C-related cirrhosis. J Gastroenterol 2023;58:394–404.
[24] Vidal-González J, Martínez J, Mulay A, et al. For the Baveno VI-SPSS group frome the Baven Cooperation. Evolution of spontaneous portosystemic shunts over time and following aetiological intervention in patients with cirrhosis. JHEP Rep 2024;6:100977.
[25] Hsu SJ, Tsai MH, Chang CC, et al. Extrahepatic angiogenesis hinders recovery of portal hypertension and collaterals in rats with cirrhosis resolution. Clin Sci (Lond) 2018;132:669–683.
[26] Payancé A, Rautou PE. Cirrhosis regression: extrahepatic angiogenesis and liver hyperarterialization persist. Clin Sci (Lond) 2018;132:1341–1343.
[27] Ferral H, Schepis F, Gaba RC, et al. Endovascular assessment of liver hemodynamics in patients with cirrhosis complicated by portal hypertension. J Vasc Interv Radiol 2023;34:327–336.
[28] Silva-Junior G, Baiges A, Turon F, 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;62:1584–1592.
[29] Boyer TD, Triger DR, Horisawa M, et al. Direct transhepatic measurement of portal vein pressure using a thin needle. Comparison with wedged hepatic vein pressure. Gastroenterology 1977;72(4 Pt 1):584–589.
[30] Perelló A, Escorsell A, Bru C, et al. Wedged hepatic venous pressure adequately reflects portal pressure in hepatitis C virus-related cirrhosis. Hepatology 1999;30:1393–1397.
[31] Thalheimer U, Leandro G, Samonakis DN, et al. Assessment of the agreement between wedge hepatic vein pressure and portal vein pressure in cirrhotic patients. Dig Liver Dis 2005;37:601–608.
[32] Ferrusquía-Acosta J, Bassegoda O, Turco L, et al. Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis. J Hepatol 2021;74:811–818.
[33] Resnick RH, Iber FL, Ishihara AM, et al. A controlled study of the therapeutic portacaval shunt. Gastroenterology 1974;67:843–857.
[34] Saks K, Jensen KK, McLouth J, et al. Influence of spontaneous splenorenal shunts on clinical outcomes in decompensated cirrhosis and after liver transplantation. Hepatol Commun 2018;2:437–444.
[35] Lim WX, Lin AN, Cheng YF, et al. Portosystemic shunt in pediatric living donor liver transplant. Transpl Proc 2022;54:403–405.
[36] De Carlis L, Del Favero E, Rondinara G, et al. The role of spontaneous portosystemic shunts in the course of orthotopic liver transplantation. Transpl Int 1992;5:9–14.
[37] Borentain P, Soussan J, Resseguier N, et al. The presence of spontaneous portosystemic shunts increases the risk of complications after transjugular intrahepatic portosystemic shunt (TIPS) placement. Diagn Interv Imaging 2016;97:643–650.
[38] He C, Lv Y, Wang Z, et al. Association between non-variceal spontaneous portosystemic shunt and outcomes after TIPS in cirrhosis. Dig Liver Dis 2018;50:1315–1323.
[39] Vidal-González J, Simón-Talero M, Genescà J. Should prophylactic embolization of spontaneous portosystemic shunts be routinely performed during transjugular intrahepatic portosystemic shunt placement? Dig Liver Dis 2018;50:1324–1326.
[40] Tang HH, Zhang ZC, Zhao ZL, et al. Large paraumbilical vein shunts increase the risk of overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt placement. J Clin Med 2022;12:158.
[41] Sikuler E, Groszmann RJ. Interaction of flow and resistance in maintenance of portal hypertension in a rat model. Am J Physiol 1986;250(2 Pt 1):G205–G212.

Keywords: Portal hypertension; Etiologic factor removal; WHVP; Cirrhosis regression; Cirrhosis recompensation.
Received 26 March 2024; received in revised form 4 July 2024; accepted 15 July 2024; Available online 18 July 2024