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Portal vein recanalisation alone to treat severe portal hypertension in non-cirrhotic patients with chronic extrahepatic portal vein obstruction

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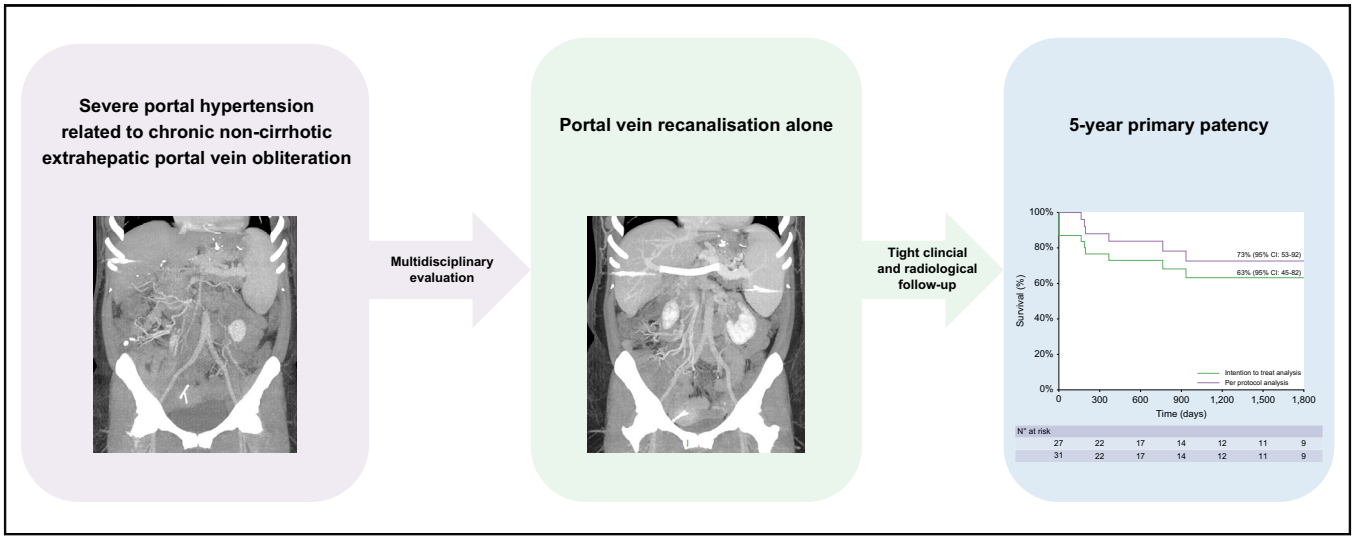
Graphical abstract



Highlights

- CNC-EHPVO with severe portal hypertension can be treated with PVR alone.
- After technical success of PVR, the 5-year primary patency is above 70%.
- After technical success of PVR, 78% of patients had complete resolution of symptoms.
- Intrahepatic extension of obstruction is associated with failure of PVR.
- Indication of PVR for abdominal pain is associated with poorer outcome.

Lay summary

Patients with chronic obstruction of the portal vein and without cirrhosis or malignancy can develop complications related to the high pressure in the venous system. The present study reports long-term favourable outcome of patients in whom the obstruction was treated with stents.

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Research article

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Portal vein recanalisation alone to treat severe portal hypertension in non-cirrhotic patients with chronic extrahepatic portal vein obstruction

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Background & Aims: We aimed to evaluate long-term outcome of patients with chronic non-cirrhotic extrahepatic portal vein obstruction (CNC-EHPVO) who underwent portal vein recanalisation (PVR) without transjugular intrahepatic porto-systemic shunt (TIPS) insertion and to determine factors predicting PVR failure and stent occlusion.
Methods: This retrospective monocentric study included all patients who underwent PVR without TIPS insertion in the context of CNC-EHPVO between the years 2000 and 2019. Primary patency was defined by the absence of a complete stent occlusion on follow-up imaging.
Results: A total of 31 patients underwent PVR with a median follow-up of 52 months (24–82 months). Indications were gastrointestinal bleeding (n = 13), abdominal pain attributed to CNC-EHPVO (n = 7), prior to abdominal surgery (n = 4), and others (n = 7). Technical success was obtained in 27 patients. PVR failure was associated with extension within the intrahepatic portal veins (p = 0.005) and recanalisation for abdominal pain (p = 0.02). Adverse events occurred in 6 patients with no mortality. Anticoagulation was administered in 21 patients after technical success of PVR. In patients with technical success, 5-year primary patency was 73% and was associated with improved muscle mass (p = 0.007) and decreased spleen volume (p = 0.01) at 1 year. Furthermore, 21 (78%) patients with PVR technical success were free of portal hypertension complication at 5 years.
Conclusions: PVR without TIPS insertion was feasible and safe in selected patients with CNC-EHPVO and portal hypertension with past or expected complications. Primary patency at 5 years was obtained in 3 of 4 patients with technical success of PVR and was associated with a control of complications of CNC-EHPVO. PVR was associated with improvement of sarcopenia and decreased spleen volume at 1 year.
Lay summary: Patients with chronic obstruction of the portal vein and without cirrhosis or malignancy can develop complications related to the high pressure in the venous system. The present study reports long-term favourable outcome of patients in whom the obstruction was treated with stents.

Introduction

Chronic non-cirrhotic extrahepatic portal vein obstruction (CNC-EHPVO) is a rare liver disease associated with the risk of developing prehepatic portal hypertension and its associated complications, including gastrointestinal (GI) bleeding, portal cholangiopathy, abdominal pain, ascites, and extension or recurrence of the thrombosis.[1–5] The main causes of CNC-EHPVO are inherited or acquired thrombotic disorders, or local inflammatory causes (acute or chronic pancreatitis, diverticulitis, cholangitis, surgery).[4–6] This condition often affects young adults. Five-year rebleeding rate was around 50% in patients who had experienced a GI bleeding episode.[2] In this population,

Keywords: Chronic non-cirrhotic extrahepatic portal vein obstruction (CNC-EHPVO); Portal vein recanalisation; Portal hypertension; Gastrointestinal bleeding; Portal cholangiopathy; Sarcopenia.
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failure to control bleeding or early rebleeding occurred in 17% of patients, and 21% of them had surgical derivative surgery with the aim to lower portal pressure.[2] In addition, up to 20% of patients with CNC-EHPVO develop symptomatic portal cholangiopathy (cholangitis, symptomatic lithiasis, and jaundice), with endoscopic or radiological biliary stenting as the main therapeutic option,[7–9] which do not treat the underlying pathology. There is paucity of data on the clinical course of patients with other complications such as ascites and abdominal pain. About 40% of patients with CNC-EHPVO have sarcopenia,[10] loss of skeletal muscle mass and strength associated with a poor outcome in a large range of diseases, including cirrhosis, and lacking therapeutic options.[11,12] In patients with cirrhosis, the improvement of portal hypertension secondary to transjugular intrahepatic portosystemic shunt (TIPS) insertion was associated with an improvement of sarcopenia.[11,13,14] Therefore, an efficient approach to treat portal hypertension related to CNC-EHPVO could also improve the loss of muscle mass observed in these patients.

Recanalisation of CNC-EHPVO has long been considered technically challenging and even risky. This was based on the significant adverse events observed when performing portal vein recanalisation (PVR) in patients with acute portal vein thrombosis, possibly because, in that setting, local or systemic thrombolysis was often performed simultaneously with recanalisation.[15–17] In CNC-EHPVO, thrombolysis is not performed because of the nature of the obstruction. In published literature, few articles reported favourable outcomes of extrahepatic portal vein obstruction (EHPVO) recanalisation associated with TIPS placement in patients with or those without cirrhosis,[18–22] confirming the feasibility of the procedure. However, in patients without significant liver fibrosis and with sinusoidal portal hypertension, adjunct TIPS may not be necessary, although it could contribute to hepatic encephalopathy (HE), heart failure, or liver insufficiency.[23]

The aim of this study was to evaluate the short-, medium-, and long-term outcomes of patients with CNC-EHPVO undergoing recanalisation without TIPS placement and determine factors predicting failure of recanalisation and primary and secondary patency.

Patients and methods

Patients

This retrospective cohort study included all patients who underwent PVR without TIPS insertion in the context of CNC-EHPVO at a tertiary centre in Switzerland (Lausanne University Hospital) between 1 January 2000 and 31 December 2019. Patients with cirrhosis, Budd–Chiari syndrome, active malignancy, and recent EHPVO (<3 months) were excluded. In the absence of local causes for thrombosis, patients were investigated for inherited or acquired prothrombotic disorders. Before recanalisation, a senior radiologist (AD) confirmed diagnosis of CNC-EHPVO, evaluated its extension (and length) within the portal, mesenteric, and splenic veins on imaging (Doppler ultrasound [US], CT, and MRI) and assessed for a cavernomatous transformation of the portal vein. The extension in lateral branches upstream to the main occluded veins was also assessed. The pattern of portal vein obstruction and its extension were classified according to Sarin *et al.*[21] and Marot *et al.*[19] Indication for PVR was collegially confirmed in dedicated multidisciplinary rounds involving gastroenterologists and hepatologists, radiologists, and abdominal surgeons. Of note, some patients were referred for a recanalisation procedure in a context of recurrent abdominal pain. In these cases, patients were assessed and investigated to exclude other usual causes of abdominal pain and particularly related to chronic pancreatitis. All patients gave written consent to the procedure after comprehensive information sharing and counselling on the risk/benefit. The study has been approved by the local ethics committee, commission d'éthique sur la recherche sur l'être humain du canton de Vaud (CER-VD), and is registered under ID number 2019-01409.

Procedure

For the percutaneous transhepatic approach, the procedure of recanalisation was performed as described by Marot *et al.*[19] Briefly, a percutaneous transhepatic access to the portal vein was performed using a Neff® introducer set (Cook Medical). Access to the portal vein was made through segment V or segment VIII. A 5f 40-cm biliary catheter (Soft-vu Berenstein®, Angio Dynamics) was inserted into the intrahepatic portal branches. Recanalisation was performed using a 0.035-inch angulated stiff hydrophilic guidewire (Terumo). When the mesenteric/splenic vein was reached, pressures above and below the obstruction were measured. A portogram was obtained below the obstruction. The occluded segment was first dilated to 6 mm using a 6/40-mm balloon (Passeo®0.035, Biotronik), and a self-expandable nitinol stent (S.M.A.R.T. control®, Cordis) was placed and dilated. Post-stent portography and new portal pressure measurements were obtained. The length of the stent was chosen to cover the whole obstruction. Where necessary, 2 stents were used. Portocaval gradient was not measured.

Where transhepatic access was considered not feasible, transsplenic access was attempted, either as a first attempt or as a revision procedure, using the technique described by Habib *et al.*[23] Briefly a transsplenic access to hilar splenic vein was achieved under US guidance. The recanalisation procedure used an antegrade approach, aiming to recanalise the portal vein to the closest patent intrahepatic vein depending on preprocedure analysis of cross-sectional imaging of intrahepatic portal branches. Stenting and pressure measurements were conducted using the same technique as the transhepatic recanalisation approach. To decrease the risk of bleeding from this access, we limited the access device diameter to 6 Frenchs and occluded the route at the end of the procedure.

At time of patient's evaluation, additional stenting within superior mesenteric vein (SMV) or splenic vein (SV) was decided according to the portal hypertension complication: SMV stenting was considered if patients had mainly SMV territory-related complication such as portal cholangiopathy, GI bleeding caused by duodenal or jejunal varices, and chronic post-prandial abdominal pain; SV stenting was mainly considered in case of GI bleeding caused by gastroesophageal varices. In case of the absence of clear predominant symptoms, additional stenting was decided during the PVR procedure according to the pattern of occlusion.

Antiplatelet agents and/or anticoagulation therapy were prescribed at the discretion of treating physicians and radiologists to minimise the risk of stent thrombosis and/or extension of thrombosis until 2017. In 2017, we collegially decided from our first 15 years of experience to propose the instauration of an anticoagulant therapy in all patients with CNC-EHPVO who underwent PVR with technical success regardless of the presence or absence of a prothrombotic disorder.

Failure of recanalisation was defined by the absence of post-procedure stent opacification (failure to stent insertion or immediate thrombosis of the stent despite maximal dilatation).

After PVR, patients were followed up at 3 months and then every 6 months after the procedure by clinical examination and Doppler US and/or CT and/or MRI. In case of occurrence/recurrence of portal hypertension complication or a suspicion of stent occlusion on Doppler US or MRI, a CT was performed.

Data

Data were retrospectively collected from medical records.

Data at the time of PVR included the following: date of first diagnosis of CNC-EHPVO; presence of oesophageal, gastric, and ectopic varices at endoscopy; clinical and laboratory data at time of recanalisation; β-blocker; indication for recanalisation; splanchnic gradient before and after stent placement; number, length, and diameter of stents; and complication of the procedure. We evaluated by CT scan imaging features of sarcopenia using 2 different measures (total psoas muscle area [TPMA][24] at lumbar 4 [L4] and skeletal muscle index at lumbar 3 [L3; L3SMI][25]) as well as liver and spleen volume at the time of recanalisation ± 1 month. Liver histology was reviewed when available at the time of recanalisation ± 3 months.

Data after PVR included the following: antiplatelet agents and/or anticoagulation therapy administration, clinical data including complications of portal hypertension (GI bleeding, ascites, and portal cholangiopathy), laboratory data, death, and cause of death. Imaging data were also collected including occlusion of the stents as well as TPMA, L3SMI, liver and spleen volumes that were reassessed at 12 ± 3 months by CT scan when available. Where performed, revision procedure of the stent and its outcome data were collected.

Definitions

Primary patency was defined as the absence of a complete stent occlusion on follow-up cross-sectional imaging.

Secondary patency was defined as the absence of a complete stent after a revision procedure on follow-up cross-sectional imaging.

Primary patency and secondary patency were estimated using the date of last CT or MRI where available (n = 29). In the patients without available follow-up CT (n = 2), stent was considered patent when a portal vein flow was identified on US Doppler (with portal velocity ≥10 cm/s).

Sarcopenia

Acquisition of TPMA was made in mm^2 by NVV and FA who were unaware of patients' outcomes. Skeletal muscle index (SMI; cm^2/m^2) was quantified using a semi-automated method from a single axial CT image of the abdomen at the L3 vertebral level.[26,27] The deep learning-based method used in our study followed a traditional U-Net architecture,[27] which was modified by adding a second smaller U-Net to improve its accuracy. These methods have been tested and validated on large CT datasets and are proven to be accurate and reliable.[28,29] All automated muscle segmentations were secondarily reviewed and corrected by an attending musculoskeletal radiologist (FB), blinded to the patient's intervention (as the radiologist had at disposal the unique cross-sectional picture at the L3–L4 level extracted for each patient), using a custom free-hand image segmentation tool.

Sarcopenia was defined by the following previously published L3SMI sex-specific cut-offs: 52.4 cm^2/m^2 in men and 38.5 cm^2/m^2 in women.[30,31]

Liver and spleen volume assessment

3D images of the liver and spleen volumes were built by a radiologist (NVV) and a technologist (NS). Synapse Vincent software (Fujifilm Medical, Tokyo, Japan) was used with the following steps: (1) digital imaging and communications in medicine (DICOM) data of the venous phase were input into the Synapse Vincent; (2) 3D images, including the liver parenchyma, portal vein, hepatic vein, and inferior vena cava, were automatically and manually segmented; and (3) volumes of the entire liver and spleen were calculated automatically.

Statistical analyses

Quantitative variables were expressed as median (IQR). Categorical variables were expressed as frequencies and percentages. Primary endpoints were primary and secondary patency rates at 5 years estimated using the Kaplan–Meier method. Patients with failure of recanalisation at baseline were included in the intention-to-treat analyses but not in the per-protocol analyses.

Secondary endpoints were the technical success rate of PVR and rate of complications, as well as evolution of imaging features of sarcopenia at 1 year after portal recanalisation. Comparisons between patients with technical success and failure of recanalisation and with and without primary patency were performed using the Mann–Whitney *U* test for quantitative variables or the Chi-square test and Fisher exact test for categorical variables. Multivariate analyses were not performed because of the limited sample size. Intracase comparisons of the data were performed using Wilcoxon's signed-rank tests. Correlations were performed with Spearman's rank correlation methods. All statistical analyses were performed using NCSS 2011 (NCSS, LLC) software.

Results

Patients

Of 84 patients who underwent PVR between the years 2000 and 2019, 31 met the inclusion criteria (Fig. S1). Among them, 14 patients were also included in our previous study describing the short-term results of PVR.[19] The median age at PVR was 50 years (IQR 40–60 years). The median follow-up duration was 52 months (24–82 months). Causes for CNC-EHPVO were attributed to acute or chronic pancreatitis in 10 patients (32%), abdominal surgery in 9 patients (29%), and inherited or acquired thrombotic disorder in 12 patients (39%). Indications for recanalisation were severe recurrent or refractory GI bleeding related to portal hypertension in 13 patients (42%), recurrent abdominal pain in 7 patients (23%), planned sus-mesocolic abdominal surgery in 4 patients (13%), portal cholangiopathy in 3 patients (10%), ascites in 1 patient (3%), endoscopic evidence of severe portal hypertension but without history of bleeding in 2 patients (6%), and extension of thrombosis despite anticoagulant therapy in 1 patient (3%). The main characteristics of the patients at recanalisation are provided in Table 1, and detailed characteristics are provided in Supplementary Table S1. A total of 24 patients (77%) had endoscopic signs of portal hypertension: 11 had isolated oesophageal varices (35%), 1 had isolated gastric varices (3%), 7 had both oesophageal and gastric varices (23%), and 13 (42%) had endoscopic portal hypertension gastropathy. Laboratory features

Table 1. Main characteristics of the 31 patients who underwent recanalisation procedure for CNC-EHPVO with PHT.

No.	Age, sex	CNC-EHPVO cause	Indication of recanalisation	Delay between diagnosis and recanalisation (month)	Classification according to Sarin *et al.*[21]/Marot *et al.*[19] types	Extension to mesenteric/ splenic veins	Success	5-year primary patency[a]	PHT complications after successful recanalisation at 5 years
1	45, M	After liver surgery	Recurrent GI bleeding	0	1/1	None	Yes	Yes	No
2	46, M	After pancreatic surgery	Refractory ascites and non-haemorrhagic PHT	1	1/1	Mesenteric	Yes	Yes	No
3[b]	59, M	Chronic pancreatitis	Before surgery	2	1/1	Mesenteric and splenic	Yes	No	No
4	48, M	After pancreatic surgery	Recurrent GI bleeding	0	1/1	Splenic	Yes	Yes	No
5[b]	46, F	After pancreatic surgery	Recurrent GI bleeding	1	1/1	Mesenteric and splenic	Yes	Yes	Yes[c]
6[b]	49, M	Prothrombotic disorder: FII and FV composite heterozygotia	Recurrent GI bleeding and chronic abdominal pain	128	3/2	None	Yes	Yes	No
7[b]	55, M	Chronic pancreatitis	Before surgery	25	1/1	Mesenteric and splenic	Yes	Yes	No
8[b]	50, M	Suspected unidentified prothrombotic disorder	Before surgery	87	3/2	Mesenteric and splenic	Yes	Yes	No
9[b]	62, F	Suspected unidentified prothrombotic disorder	Recurrent GI bleeding	19	1/1	Mesenteric and splenic	Yes	Yes	No
10[b]	55, M	Necrotic pancreatitis	Recurrent GI bleeding	2	1/1	Mesenteric and splenic	Yes	Yes	No
11[b]	58, M	Chronic pancreatitis	Portal cholangiopathy	8	3/2	Mesenteric and splenic	Yes	No	Yes
12[b]	26, M	Prothrombotic disorder: antiphospholipid syndrome	Extension of thrombosis under anticoagulant therapy	49	3/2	Mesenteric and splenic	Yes	Yes	No
13[b]	60, M	Chronic pancreatitis	Recurrent GI bleeding	35	3/3	Mesenteric and splenic	No, owing to intrahepatic extension	N/A	N/A
14	62, F	After pancreatic surgery	Severe GI bleeding	0	1/1	Mesenteric	Yes	Yes	No
15	74, M	Chronic pancreatitis	Portal cholangiopathy	0	3/2	Mesenteric	Yes	Yes	No
16	28, M	After colonic surgery	Chronic abdominal pain	7	3/3	Mesenteric and splenic	No, owing to intrahepatic extension	N/A	N/A
17	31, M	Prothrombotic disorder: antiphospholipid syndrome	Chronic abdominal pain	2	3/3	Mesenteric	Yes	No	Yes
18	53, M	Chronic pancreatitis	Chronic abdominal pain	3	1/1	Mesenteric	Yes	No	Yes
19	78, M	After colonic surgery	Recurrent GI bleeding	3	3/2	Mesenteric	Yes	Yes	No
20	70, F	Thrombotic disorder: paraneoplastic Trousseau syndrome (ENT cancer curatively treated 4 years before GI bleeding)	Severe GI bleeding	48	1/1	Mesenteric	Yes	Yes	No
21	23, M	Thrombotic disorder: antiphospholipid syndrome	Chronic abdominal pain	15	1/1	Mesenteric	Yes	No	Yes
22	71, M	After liver surgery	Chronic abdominal pain and ascites	15	1/2	None	No, owing to intrahepatic extension	N/A	N/A
23	21, F	After pancreatic surgery	Severe endoscopic PHT	73	3/2	Mesenteric and splenic	Yes	Yes	No
24	57, M	Chronic pancreatitis	Severe GI bleeding	1	1/1	Mesenteric and splenic	Yes	Yes	No
25	73, M	Chronic pancreatitis	Before surgery	3	3/1	Mesenteric and splenic	Yes	Yes	No
26[b]	42, F	Suspected unidentified prothrombotic disorder	Severe endoscopic PHT	116	3/1	Mesenteric	Yes	Yes	No

(*continued on next page*)

Table 1 (*continued*)

No.	Age, sex	CNC-EHPVO cause	Indication of recanalisation	Delay between diagnosis and recanalisation (month)	Classification according to Sarin *et al.*[21]/Marot *et al.*[19] types	Extension to mesenteric/ splenic veins	Success	5-year primary patency[a]	PHT complications after successful recanalisation at 5 years
27	58, F	Thrombotic disorder: myeloproliferative syndrome JAK2+	Recurrent abdominal pain and chronic diarrhoea	193	3/2	Mesenteric and splenic	Yes	Yes	No
28	31, F	Thrombotic disorder: myeloproliferative syndrome JAK2-	Chronic abdominal pain	18	3/2	Mesenteric and splenic	No, owing to intrahepatic extension	N/A	N/A
29[b]	40, M	Chronic pancreatitis	Recurrent GI bleeding	9	1/1	Mesenteric	Yes	Yes	No
30[b]	23, M	Thrombotic disorder: paxorysmal nocturnal haemoglobinuria clone and MTHFR homozygotia	Recurrent GI bleeding	101	3/2	Mesenteric	Yes	Yes	No
31[b]	44, M	Thrombotic disorder: antithrombin deficiency	Portal cholangiopathy	130	3/2	Mesenteric	Yes	No	Yes

Classification according to Sarin *et al.*[21] is as follows: type 1, only trunk; type 2, only branch(es); type 3, trunk and branch(es). Classification according to Marot *et al.*[19] is as follows: type 1, occlusion limited to the origin of the main portal vein and/or to the right or left portal branches; type 2, type 1 plus extension to the origin of segmental branches; type 3, type 2 plus extension to distal branches. CNC-EHPVO, chronic non-cirrhotic extra hepatic portal vein obstruction; F, female; GI, gastrointestinal, M, male; N/A, not applicable; PHT, portal hypertension.

[a] Primary patency was defined as the absence of a complete stent occlusion on follow-up cross sectional imaging.

[b] Patients included in our previous study.[19]

[c] This patient has presented 2 early non-severe recurrences of PHT-related GI bleeding with excellent Doppler analyses of the flow concordant with the CT, suggesting a full patency of the stent.

are presented in Table 2. Results of liver biopsy performed before or at the time of recanalisation in 8 patients are presented in Supplementary Tables S1 and S2.

EHPVO

In the majority of the patients, CNC-EHPVO had limited extension within the intrahepatic portal veins, with 14 patients (45%) classified as type 1 according to Sarin *et al.*[21] and 16 (52%) classified as type 1 according to Marot *et al.*[19] Complete occlusion of the portal trunk was observed in 29 patients (94%). A total of 28 patients (90%) presented an extension to SMV with or without extension into the SV (Table 1). All patients had cavernomatous transformation of the portal vein, confirmed by the portography obtained during the procedure. The median duration between diagnosis of CNC-EHPVO and recanalisation was 9 months (2–49 months).

Procedure of recanalisation

The main data regarding the recanalisation procedure are provided in Table 1. As a first attempt, the transhepatic access route was chosen in all but 1 patient (97%). Technical success was achieved in 27 patients (87%). In these patients, the median pressure gradient between SMVs/SVs and portal trunk/branches was 10 mmHg (6–14 mmHg) before and 0 mmHg (0–2 mmHg) after recanalisation (p <0.0001). A total of 16 patients (52%) required 1 stent and the 15 other 2 stents (48%). The median length of total stenting was 100 mm (60–135 mm) with a median diameter of 11 mm (10–12 mm) and dilatation during the procedure was 10 mm (10–10 mm). Adverse events related to the procedure occurred in 6 (20%) patients. These were breach in the right portal vein requiring a second stent to control bleeding, haemoperitoneum requiring a second stent to control bleeding, transient elevation of transaminases up to 5 times the upper limit of normal values with favourable outcome, bleeding from the transhepatic route at Day 2 requiring the transient discontinuation of heparin, ptosis and hypotropia of unknown cause that resolved spontaneously, and puncture of the intestinal tract without complication. In univariate analysis, the 2 factors associated with failure of the procedure were extension within the intrahepatic portal tract assessed by the classification described by Marot *et al.*[19] (p = 0.005) and recurrent abdominal pain as an indication of recanalisation (p = 0.02; Table 3). Of note, in a sensitivity analysis restricted to patients who were not included in our previous study,[18] we observed a trend towards more PVR failure in type 2 (2/6) and 3 (1/2) patients than in type 1 (0/9) patients (p = 0.06) according to the classification described by Marot *et al.*[19]

Regarding anticoagulation, 8 patients (30%) received boluses of non-fractioned heparin (NFH; median of 5,000 IU [5,000–7,250 IU]) during the procedure, and 21 patients (78%) were treated with NFH or low-molecular-weight heparin immediately after the procedure. Three patients (11%) were treated with antiplatelet agent after the procedure, and 3 patients (11%) received neither anticoagulant nor antiplatelet treatment. After hospital discharge, 18 patients (67%) were treated with anticoagulant therapy. The remaining patients were treated with antiplatelet agent (n = 5, 19%), both anticoagulant and antiplatelet therapies (n = 1, 4%) and no long-term treatment (n = 3, 11%).

Five-year primary and secondary patency

Three non-liver related deaths occurred: patient no. 15 died 54 days after surgical repair of abdominal aortic aneurysm rupture; this patient had a known type III endoleak following an endovascular stenting performed 2 year earlier. Patient no. 20 died 698 days after recanalisation of hypoxic cardiac arrest in the context of decompensated chronic respiratory failure. Patient no. 4 died 1,007 days after recurrence of pancreatic adenocarcinoma.

Four PVR failures and 6 complete occlusions of the stent were reported at 5 years (Table 1). In patients with 5-year primary patency, 2 had a partial occlusion without recurrence of portal hypertension complications. Conversely, in patients with technical success of PVR who developed complete occlusion within 5 years, 2 had a partial occlusion (diagnosed 10 days and 6 weeks before the diagnosis of the complete occlusion). Intention-to-treat and per-protocol analyses showed a 5-year primary

Table 2. Biological baseline characteristics of the overall cohort of patients with CNC-EHPVO) who underwent portal vein recanalisation procedure between 1 January 2000 and 31 December 2019.

	Patients with CNC-EHPVO who underwent portal vein recanalisation
Serum albumin, g/L	36 (28–39)
Serum bilirubin, μmol/L	10 (7–17)
Serum ALP, IU/L	96 (61–158)
Serum GGT, IU/L	55 (21–153)
Serum AST, IU/L	28 (21–37)
Serum ALT, IU/L	26 (17–49)
Serum creatinine, μmol/L	71 (60–95)
Prothrombin rate, %	85 (80–100)
Haemoglobin, g/L	112 (96–125)
Total WBC, 10^9/L	7 (4–9)
Platelet counts, G/L	182 (105–257)

Data are expressed in median (IQR). ALP, alkaline phosphatase; ALT, alanine aminotransferase; CNC-EHPVO, chronic non-cirrhotic extra hepatic portal vein obstruction; GGT, gamma-glutamyl transferase; WBC, white blood cell.

patency of 63% (45–82%) and 73% (53–92%), respectively (Fig. 1A), and a 5-year secondary patency of 66% (48–85%) and 76% (58–95%), respectively (Fig. 1B). In univariate analysis, the only factors associated with 5-year primary patency were recurrent abdominal pain attributed to portal hypertension (p = 0.009) and higher haemoglobin level at recanalisation (p = 0.02; Table 4).

Five-year results on portal hypertension complications

A total of 21 of the 31 (68%) patients of intention-to-treat analysis and 21 of 27 (78%) patients of per-protocol analysis had complete resolution of portal hypertension-related symptoms at 5 years (Table 1). At 5 years, patient no. 5 experienced 2 recurrences of non-severe portal hypertension-related bleeding without stent occlusion CT, and conversely, patient no. 3 developed stent occlusion without portal hypertension complication occurrence (Table 1).

Table 3. Univariate analysis of factors associated with technical success of portal vein recanalisation in patients with CNC-EHPVO who underwent recanalisation procedure between 1 January 2000 and 31 December 2019.

	Technical success recanalisation (n = 27)	Failure of recanalisation (n = 4)	*p* value
Sarin *et al.*,[21] n (%)			
1	14 (52)	1 (25)	0.07
2	0 (0)	0 (0)	
3	13 (48)	3 (75)	
Marot *et al.*,[19] n (%)			
1	16 (59)	0 (0)	**0.005**
2	10 (37)	2 (50)	
3	1 (4)	2 (50)	
Extension within the main upstream veins, n (%)			
Absence of extension	2 (7)	1 (25)	0.2
Splenic vein alone	(0)	0 (0)	
Mesenteric vein alone	13 (48)	0 (0)	
Both splenic and mesenteric veins	12 (44)	3 (75)	
Length of the extension within the min veins upstream, cm	3 (1–4)	4 (1–5)	0.5
Upstream extension in lateral branches, n (%)			
Absence of lateral branches occlusion	10 (37)	1 (25)	0.1
1 or 2 lateral branches occluded	10 (37)	0 (0)	
>2 lateral branches occluded	7 (26)	3 (75)	
Complete occlusion, n (%)	26 (96)	3 (75)	0.1
CNC-EHPVO related to thrombotic disorder, n (%)	11 (41)	1 (25)	0.5
Indication of recanalisation, n (%)			
GI bleeding	12 (44)	1 (25)	**0.02**
Abdominal pain	4 (15)	3 (75)	
Other	11 (41)	0 (0)	
Delay between diagnosis and recanalisation, month	8 (1–72)	16 (9–31)	0.6
Serum albumin, g/L	36 (26–38)	36 (35–41)	0.5
Serum bilirubin, μmol/L	10 (8–17)	8 (5–18)	0.5
Serum ALP, IU/L	106 (62–186)	73 (42–110)	0.2
Serum GGT, IU/L	56 (21–219)	55 (29–116)	0.9
Serum AST, IU/L	29 (22–38)	23 (20–32)	0.4
Serum ALT, IU/L	27 (16–50)	23 (20–43)	0.8
Serum creatinine, μmol/L	69 (69–80)	76 (70–92)	0.2
Prothrombin rate, %	85 (70–100)	95 (85–100)	0.2
Haemoglobin, g/L	112 (96–123)	124 (95–162)	0.3
Total WBC, 10^9/L	7 (4–9)	7 (4–11)	0.8
Platelet counts, G/L	225 (108–338)	325 (158–353)	0.3

Failure of recanalisation was defined by the absence of post-procedure stent opacification (failure of stent insertion or immediate thrombosis of the stent despite maximal dilatation). Data are expressed in median (IQR) or number and percentage. Comparisons between patients with technical success and failure of recanalisation were performed using the Mann–Whitney *U* test for quantitative variables or the Chi-square test for categorical variables. *p* values in bold denote statistical significance. Classification proposed by Sarin *et al.*[21] is as follows: type 1, only trunk; type 2, only branch(es); type 3, trunk and branch(es). Classification proposed by Marot *et al.*[19] is as follows: type 1, occlusion limited to the origin of the main portal vein and/or to the right or left portal branches; type 2, type 1 plus extension to the origin of segmental branches; type 3, type 2 plus extension to distal branches. ALP, alkaline phosphatase; ALT, alanine aminotransferase; CNC-EHPVO, chronic non-cirrhotic extra hepatic portal vein obstruction; GI, gastrointestinal; GGT, gamma-glutamyl transferase; WBC, white blood cell.

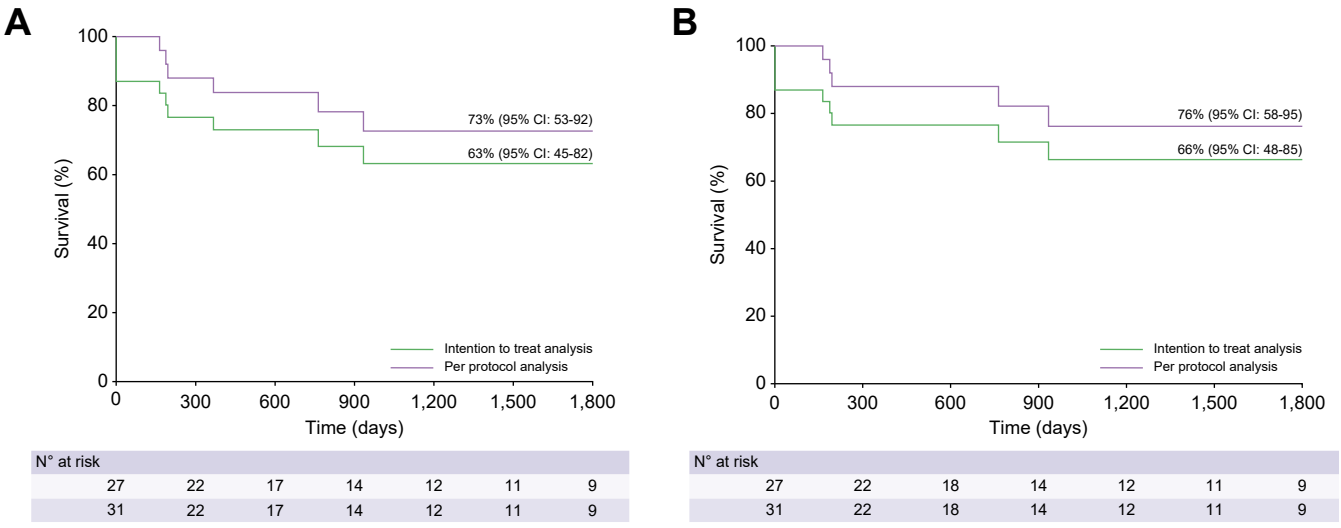

Fig. 1. Five-year primary and secondary patency rates estimated using the Kaplan–Meier method. (A) 5-year primary patency rate. (B) 5-year secondary patency rate. Survival rates were estimated using the Kaplan–Meier method in percentage and 95% CI. Primary patency was defined as the absence of a complete stent occlusion on follow-up cross-sectional imaging. Patients with failure of recanalisation that was defined by the absence of post-procedure stent opacification (failure to stent insertion or immediate thrombosis of the stent despite maximal dilatation) were excluded in per-protocol analyses.

Analyses of patients who underwent PVR with abdominal pain as a primary indication

Of the 7 patients, 6 (86%) with abdominal pain as a primary indication did not reach the 5-year primary patency in intention-to-treat analysis (3 PVR failures and 3 complete occlusions). To investigate the reasons of this outcome, we compared the baseline characteristics of these patients with those of patients with other indications for PVR procedure (Supplementary Table S3). Patients with abdominal pain as a primary indication had higher serum albumin (p = 0.006) and haemoglobin (p = 0.004) concentrations and a trend towards a younger age (p = 0.08), more frequent pro-thrombotic-related CNC-EHPVO (p = 0.09), and type 3 presentation of the classification by Marot *et al.*[19] (p = 0.1). Extension of the occlusion within the lateral branches of the SMV was not associated with abdominal pain as a primary indication for PVR.

Impact of recanalisation on sarcopenia at 1 year

A total of 24 patients had initial CT scan evaluation performed at recanalisation ± 1 month, making it possible to calculate L3SMI. According to the sex-specific cut-offs described in the Patients and Methods section, 88% (n = 21 of 24) of the population had sarcopenia. Among these 24 patients, 15 (10 with primary patency between the 2 CTs and 5 without primary patency between the 2 CTs or with failure of recanalisation) had 1 CT available at Day 0 (±6 days, -2 to +12 days) and 1 at Month 12 (345 days, 312–405 days), enabling the evaluation of the impact of recanalisation on sarcopenia. These patients' features at recanalisation were not different from those without available CTs (data not shown).

In the 10 patients with primary patency between the 2 CTs, both L3SMI and TPMA improved (+8 and 12%, respectively; Fig. 2A and C), whereas in the 5 patients without 1-year primary patency, both L3SMI and TPMA decreased (−2 and −4%, respectively; Fig. 2B and D).

In univariate analysis, the absence of improvement of L3SMI and TPMA was strongly associated with the absence of primary patency or failure of recanalisation (p = 0.0009; Supplementary Table S4).

Impact of recanalisation on liver and spleen volumes at 1 year

We assessed whether the modification of splanchnic haemodynamic and particularly the improvement of perfusion of liver paraenchyma observed after PVR (illustrated in patient no. 27, Fig. S3) was associated with change in liver and spleen volumes.

These analyses were performed in the 15 patients with available CT scan between Day 0 and Month 12. None of these patients had myeloproliferative disorder and/or a history of splenectomy that could have biased the analyses of spleen volumes. In the 10 patients with primary patency at 12 months, liver volume increased by 11%, whereas it decreased by 4% in the 5 patients without primary patency or with failure of recanalisation (p = 0.10). In the 10 patients with primary patency at 12 months, spleen volume decreased by 17%, whereas it increased by 33% in the 5 patients without primary patency or with failure of recanalisation (p = 0.01; Fig. S4).

Impact of recanalisation on platelet counts at 1 year

This analysis has been performed in the overall cohort excluding 2 patients with myeloproliferative disorders and 2 patients who underwent splenectomy. In patients with primary patency at 1 year, platelet count increased from 175 G/L (106–239 G/L) to 217 G/L (147–292 G/L; p = 0.04) and evolved from 138 G/L (74–284 G/L) to 163 G/L (126–209 G/L; p = 0.3) in patients without primary patency or with failure of recanalisation (Fig. S5). Overall, we observed a median evolution in platelet counts of +22 *vs.* +11% (p = 0.1).

Correlation analyses

Next, we explored the correlation between the evolution of L3SMI and the evolution of liver volume, spleen volume, and liver function tests (Fig. S6). Interestingly, we observed a significant correlation between the L3SMI and spleen volume evolution (Spearman correlation coefficient −0.57, p = 0.03) with a

Table 4. Univariate analysis of factors associated with 5-year primary patency in patients with CNC-EHPVO who underwent technically successful portal vein recanalisation procedure between 1 January 2000 and 31 December 2019.

	Patient with 5-year primary patency (n = 21)	Patients without 5-year primary patency (n = 6)	*p* value
Sarin *et al.*,[21] n (%)			
1	11 (52)	3 (50)	0.9
2	0 (0)	0 (0)	
3	10 (48)	3 (50)	
Marot *et al.*,[19] n (%)			
1	13 (62)	3 (50)	0.2
2	8 (38)	2 (33)	
3	0 (0)	1 (17)	
Extension within the main upstream veins, n (%)			
Absence of extension	2 (10)	0 (0)	0.5
Splenic vein alone	(0)	0 (0)	
Mesenteric vein alone	9 (43)	4 (67)	
Both splenic and mesenteric veins	10 (47)	2 (33)	
Length of the extension within the min veins upstream, cm	3 (1-5)	2 (1-4)	0.5
Upstream extension in lateral branches, n (%)			
Absence of lateral branches occlusion	2 (9)	0 (0)	0.5
1 or 2 lateral branches occluded	13 (62)	5 (83)	
>2 lateral branches occluded	6 (29)	1 (17)	
Complete occlusion, n (%)	20 (95)	6 (100)	0.5
CNC-EHPVO related to thrombotic disorder, n (%)	8 (38)	3 (50)	0.6
Indication of recanalisation, n (%)			
GI bleeding	12 (57)	0 (0)	**0.009**
Abdominal pain	1 (5)	3 (50)	
Other	8 (38)	3 (50)	
Delay between diagnosis and recanalisation, month	9 (1–79)	5 (2–44)	0.9
Feature of porto-sinusoidal vascular liver disease at biopsy, n (%)[a]	3 (60)	3 (100)	0.2
Serum albumin, g/L	35 (23–38)	36 (32–47)	0.2
Serum bilirubin, μmol/L	10 (7–16)	13 (9–40)	0.3
Serum ALP, IU/L	96 (62–169)	131 (61–657)	0.4
Serum GGT, IU/L	39 (19–134)	180 (44–1,073)	0.1
Serum AST, IU/L	29 (22–37)	28 (19–50)	0.6
Serum ALT, IU/L	24 (15–47)	37 (25–88)	0.1
Serum creatinine, μmol/L	69 (58–90)	69 (63–76)	0.5
Prothrombin rate, %	85 (75–90)	95 (69–100)	0.3
Haemoglobin, g/L	104 (94–120)	132 (116–144)	**0.02**
Total WBC, 10^9/L	7 (4–8)	9 (4–10)	0.4
Platelet counts, G/L	243 (102–350)	212 (91–282)	0.5
Long-term anticoagulant/antiplatelet treatment			0.3
None	2 (10)	1 (17)	
Anticoagulant treatment	15 (71)	3 (50)	
Antiplatelet treatment	4 (19)	1 (17)	
Both anticoagulant and antiplatelet treatments	0 (0)	1 (17)	

Primary patency was defined as the absence of a complete stent occlusion on follow-up cross sectional imaging. Data are expressed in median (IQR) or number and percentage. Comparisons between patients with technical success and failure of recanalisation were performed using the Mann–Whitney *U* test for quantitative variables or the Chi-square test for categorical variables. *p* values in bold denote statistical significance. Classification proposed by Sarin *et al.*[21] is as follows: type 1, only trunk; type 2, only branch(es); type 3, trunk and branch(es). Classification proposed by Marot *et al.*[19] is as follows: type 1, occlusion limited to the origin of the main portal vein and/or to the right or left portal branches; type 2, type 1 plus extension to the origin of segmental branches; type 3, type 2 plus extension to distal branches. ALP, alkaline phosphatase; ALT, alanine aminotransferase; CNC-EHPVO, chronic non-cirrhotic extra hepatic portal vein obstruction; GI, gastrointestinal; GGT, gamma-glutamyl transferase; WBC, white blood cell.
[a] Data available for 9 patients.

decrease of spleen size as the size of the muscle increases. The other parameters were not correlated with L3SMI evolution.

Discussion

This study reports the long-term outcome of well-characterised patients who were treated with PVR without TIPS placement in the context of CNC-EHPVO. It shows that in patients with CNC-EHPVO and portal hypertension with past or expected complications who underwent PVR, PVR was associated with a 5-year primary patency at 63% (45–82%) and 73% (53–92%) in intention-to-treat and per-protocol analyses, respectively. Among the indications for recanalisation, patients with recurrent abdominal pain attributed to CNC-EHPVO experienced poorer outcomes, suggesting that performing recanalisation in this situation may not be beneficial and its use evaluated. This study provides original data regarding sarcopenia, an incompletely addressed feature associated with of CNC-EHPVO. Most patients had sarcopenia at the time of recanalisation and technical success of the procedure may improve skeletal muscle mass loss.

The natural history of patients with CNC-EHPVO is in general favourable with a minority of patients developing severe portal hypertension complications over time such as recurrent GI bleeding, portal cholangiopathy, ascites, abdominal pain, or recurrent thrombosis.[4–6] Included patients represent a carefully selected proportion of patients with CNC-EHPVO, as the majority were referred for severe/refractory clinical complication of portal hypertension (n = 27–87%). The 4 others (13%) were referred for recanalisation before abdominal surgery after a multidisciplinary

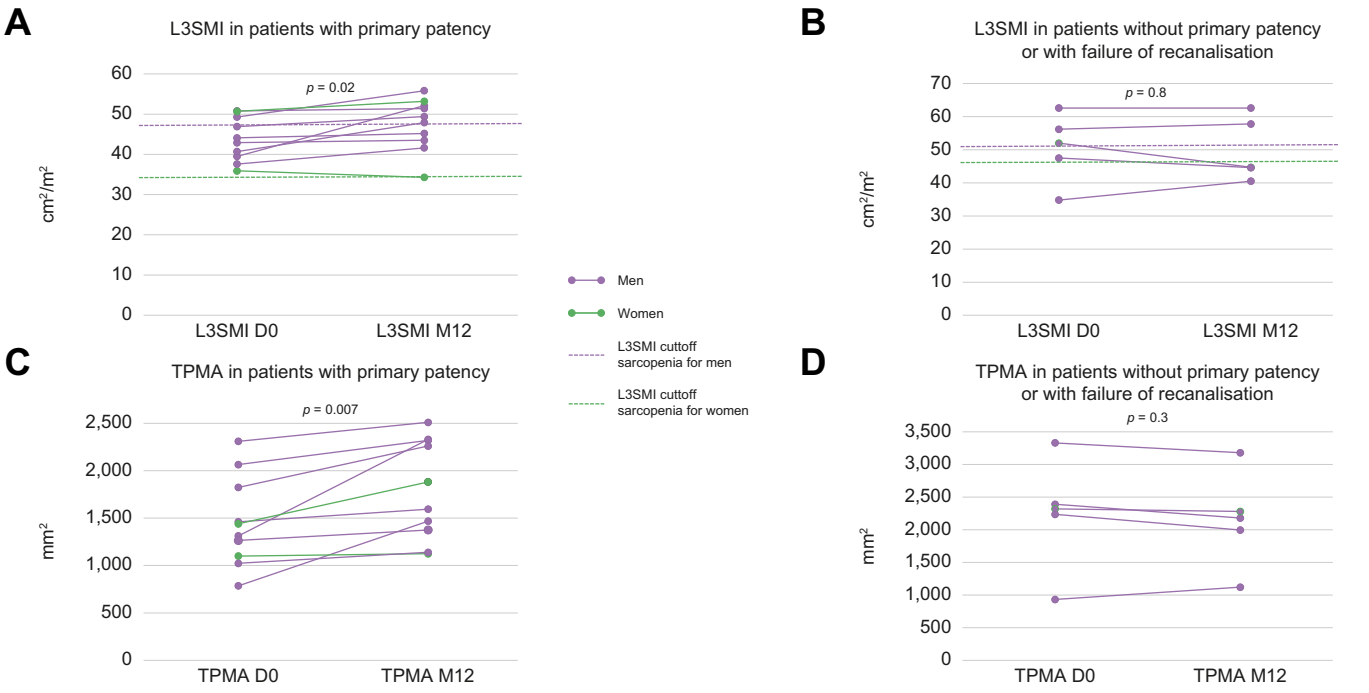

Fig. 2. Evolution of radiological parameters of sarcopenia in patients with available CT scan between recanalisation D0 procedure and M12 post procedure according to primary patency between the 2 CTs and failure of recanalisation. Primary patency was defined as the absence of a complete stent occlusion on follow-up cross-sectional imaging. Failure of recanalisation was defined by the absence of post-procedure stent opacification (failure to stent insertion or immediate thrombosis of the stent despite maximal dilatation). (A) L3SMI evolution between D0 and M12 in patient with primary patency of stent between the 2 CTs (n = 10). (B) L3SMI evolution between D0 and M12 in patients without primary patency between the 2 CTs or with failure of recanalisation (n = 5). (C) TPMA at L4 evolution between D0 and M12 in patients with primary patency of the stent between the 2 CTs (n = 10). (D) TPMA evolution between D0 and M12 in patient without primary patency between the 2 CTs or with failure of recanalisation (n = 5). Intracase analyses performed using Wilcoxon signed rank tests. CT, computed tomography; D0, Day 0; L3, lumbar 3; L3SMI, skeletal muscle index at L3; L4, lumbar 4; M12, Month 12; TPMA, total psoas muscle area.

evaluation. In selected patients with CNC-EHPVO and severe complications of portal hypertension, the surgical derivative approach (*i.e.* portocaval anastomosis) has been used in selected patients with favourable outcomes.[32–34] However, physicians may be reluctant to propose such a high-risk procedure considering the frequent associated comorbidities in these patients. Therefore, the radiological approach is a promising less invasive therapeutic strategy in patients with documented severe portal hypertension without alternative treatment options.

We confirmed the feasibility of the procedure with only 4 recanalisation failures, mainly related to extension of the obstruction to distal portal veins. We have confirmed that intrahepatic extension as defined by Marot *et al.*[19] (type 3) was associated with a higher risk of PVR failure. Importantly, in patients with technical success of PVR, 21 of 27 patients experienced a favourable outcome at 5 years following the procedure with control of portal hypertension-related symptoms and without liver-related events. Of note, 3 of the 4 patients with complete occlusion at 1 year after PVR had prothrombotic disorders, suggesting that a particularly close monitoring of anticoagulant therapy should be performed in this population. Importantly, anticoagulant and/or antiplatelet regimen was not associated with 5-year primary patency in patients with technical success. However, this analysis might be biased by the strategy of anticoagulation we used, namely case by case until 2017 and systematic after 2017.

We also pointed out that, in our experience, 2 of the 4 patients who developed partial occlusion subsequently had a complete occlusion. Considering this, when a partial occlusion is diagnosed, we propose to reassess the portal hypertension severity, optimise the anticoagulant and/or antiplatelet therapy, and discuss collegially the benefit/risk ratio of a revision procedure.

A recent study by Knight *et al.*[22] reported the favourable outcome of 39 patients with CNC-EHPVO who underwent a combined approach (TIPS + PVR) with a primary patency of 63% at 36 months. Patients were mainly referred for variceal bleeding and abdominal pain. In this series, 3 patients developed HE, 1 cardiac failure, and 3 hepatic hematomas likely related to TIPS insertion.[22] In the other available series of the combined approach (PVR + TIPS) in patients with CNC-EHPVO, up to 20% incidence of HE has been reported, whereas no cardiac failure was observed.[18,20,35–41] Although these adverse events were less commonly observed in patients with cirrhosis who undergo TIPS insertion (HE incidence around 40%[42] and cardiac failure around 10%[43]), none of these events were observed in our experience of PVR alone. Theoretically, PVR alone does not expose patients to these complications. In the study by Knight *et al.*,[22] 48.7% of the procedures were performed through transsplenic access. As opposed to the transhepatic approach in which, before PVR, the vein flow is absent, the transsplenic approach requires the puncture of a high-pressure venous system. Hence, the risk of bleeding complication is theoretically higher. However, in recent series gathering more than 1 case of PVR (associated or not with TIPS) via the transsplenic approach in CNC-EHPVO, only 1 of 38 patients experienced a bleeding event (haemoperitoneum).[18,22,36,39–41,44] In our series, none of the 3

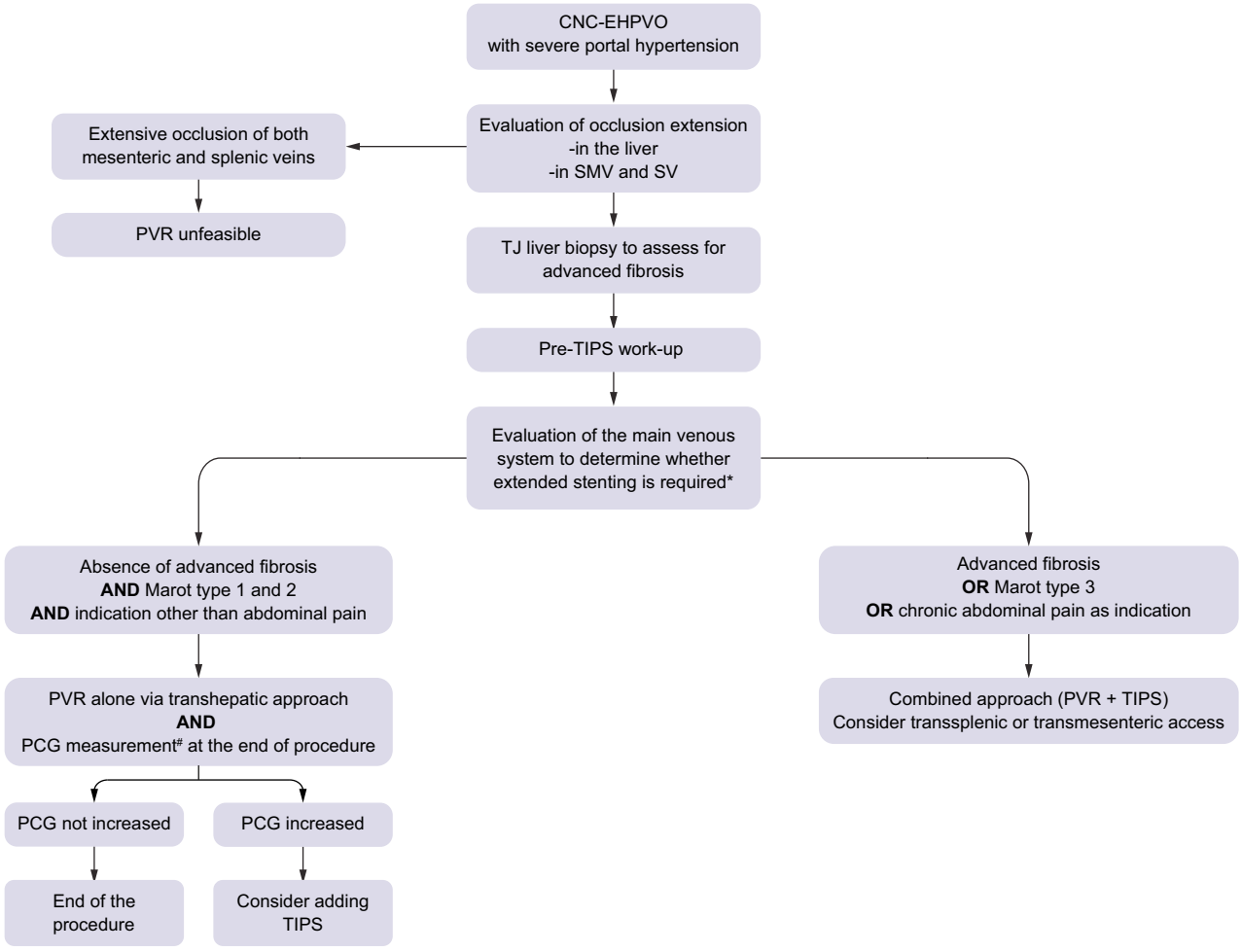

Fig. 3. Proposition of algorithm based on the recent evidence in the field of CNC-EHPVO with severe PHT including the present study. *Target SMV: Portal cholangiopathy, GI bleeding due to duodenal/ileal varices, chronic abdominal pain; target SV: GI bleeding due to gastroesophagal varices; otherwise, per-procedural decision based on occlusion pattern. #PCG measurement: This is a suggestion issued from our experience and the recent evidence from the combined (PVR+TIPS) approach in order to optimize the long-term outcome of the procedure. We propose the threshold for increase to be ≥10 mmHg. CNC-EHPVO, chronic non-cirrhotic extra hepatic portal vein obstruction; GI, gastrointestinal; PCG, portocaval gradient; PHT, portal hypertension; PVR, portal vein recanalisation; SMV, superior mesenteric vein; SV, splenic vein; TIPS, transjugular intrahepatic portosystemic shunt; TJ, transjugular.

patients who underwent PVR through the transsplenic approach had any complication. Of note, when we used the transsplenic route, we limited the access device diameter to 6 Frenchs and occluded the route at the end of the procedure. Therefore, this access appears as a suitable alternative in patients in whom the transhepatic approach failed or with high-risk of failure (Fig. 3).

Six patients (20%) had complications attributed to the technical procedure, among whom 2 required per-procedural additional stenting. As a comparison, excluding a specific complication related to TIPS (HE, liver failure, and cardiac failure) in the largest series of TIPS for idiopathic non-cirrhotic portal hypertension[45–47] and Budd-Chiari syndrome,[48] the incidence of complications ranged from 8% to 29%. The most severe complications were inferior vena cava and portal vein injuries, haemoperitoneum, hepatic hematomas, and stent malposition. In the largest study of the combined approach (PVR + TIPS), 18% of the patients experienced technical procedure-attributable complications (3 patients with hepatic hematomas – with 2 requiring invasive procedure including surgery – and 4 patients with transient fever).

We report favourable long-term primary and secondary patency rates without TIPS placement. This approach has the advantage of avoiding any complications related to TIPS placement and aims to restore normal physiological liver circulation. In our opinion and as illustrated in the proposition of algorithm in Fig. 3, an indication for the combined approach (PVR + TIPS) might be considered in patients with advanced fibrosis and extension of occlusion within the distal intrahepatic portal branches (type 3 according to Marot *et al.*[19]). Another indication for the combined approach (PVR + TIPS) could be patients with chronic abdominal pain as the main indication. Indeed, 6 of the 7 patients (86%) patients who were referred for this indication did not reach the primary outcome. These patients had a particular presentation with a trend towards a younger age, higher haemoglobin level, and increased intrahepatic extension of the occlusion potentially related to an underlying prothrombotic disorder. We therefore would suggest being particularly cautious when indicating PVR in this population and discuss a combined approach (PVR + TIPS) to optimise both technical success and outcome (Fig. 3). Interestingly, we did not find a difference in the

upstream extension characteristics of the occlusion in these patients as compared with patients with other indications. More generally, the latter were also not associated with the 5-year primary patency regardless of the indication. Although extension to small veins is difficult to assess (absence of opacification of occluded segments), we think these features should be cautiously evaluated in future studies to confirm the absence of association with clinical presentation and outcome.

This study provides also original data regarding the improvement of sarcopenia and reduction spleen volume with PVR, likely explained by restoration of physiological hepatic portal blood inflow. However, we cannot exclude that any comorbidities and/or intercurrent events may have impacted the muscle mass evolution in our series. Whether this improves prognosis or the quality of life in these patients needs to be assessed.

This study has several limitations. Retrospective collection of data might have minimized the recurrence of symptoms in patients with subjective symptoms (*i.e.* recurrent abdominal pain). The absence of a validation cohort, caused by the rarity of this condition and the lack of dissemination of this technique, implies that the predictive factors associated with failure of the procedure and 5-year primary patency identified should be considered with caution. Finally, we were not able to accurately retrospectively estimate the number of patients evaluated across the years and excluded for this procedure. A prospective collection of patients is ongoing in this purpose to better identify the process leading to patients' selection. The series reporting a procedure of PVR alone in patents with CNC-EHPVO to treat portal hypertension complications have been gathered in Supplementary Table S5. In the series before ours, the technical success rate was high (ranging from 92% to 100%) with 5% incidence of adverse events related to the procedure. In patients with technical success, resolution of portal hypertension-related symptoms was observed in 100% of patients. However, in a majority of series, the follow-up was limited, and the primary and secondary patency rates were not estimated.

In conclusion, PVR without TIPS insertion in selected patients with CNC-EHPVO and portal hypertension with past or expected complications is feasible and safe and can control complications in the majority of patients at 5 years. Improvement of sarcopenia and reduction in spleen volume is observed following successful PVR. We propose to include this therapeutic option in the multidisciplinary decision process in selected patients with CNC-EHPVO and portal hypertension.

Abbreviations

CNC-EHPVO, chronic noncirrhotic extrahepatic portal vein obstruction; DICOM, digital imaging and communications in medicine; EHPVO, extrahepatic portal vein obstruction; HE, hepatic encephalopathy; L3, lumbar 3; L3SMI, skeletal muscle index at L3; L4, lumbar 4; NFH, non-fractioned heparin; PVR, portal vein recanalisation; SMI, skeletal muscle index; SMV, superior mesenteric vein; SV, splenic vein; TIPS, transjugular intrahepatic portosystemic shunt; TPMA, total psoas muscle area; US, ultrasound.

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Conflicts of interest

None of the contributing authors have disclosures related to this work.

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

Authors' contributions

Design of the study: FA, PER, AD. Acquisition of data: FA, NVV, CS, JVB, FB, NS, AM, PD, EM, MF, AH, RD, DM, PER, AD. Statistical analysis: FA, AD. Drafting of the manuscript and critical review: FA, NVV, CS, JVB, FB, NS, AM, PD, EM, MF, AH, RD, DM, PER, AD.

Data availability statement

The data that support the findings are provided in the main manuscript and in the Supplementary information. Detailed data are not openly available (reasons of sensitivity – human data) and are available from the corresponding author upon reasonable request.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2022.100511.

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