Abdominal surgery in patients with chronic noncirrhotic extra hepatic portal vein obstruction : A multicenter retrospective study

Elkrief, Laure; Denecheau-Girard, Corentin; Magaz, Marta; Praktiknjo, Michael; Colucci, Nicola; Ollivier-Hourmand, Isabelle; Dumortier, Jérôme; Simon Talero, Macarena; Tellez, Luis; Artru, Florent; Meszaros, Magdalena; Verhelst, Xavier; Tabchouri, Nicolas; Beires, Francisca [**and 10 more**]

How to cite

ELKRIEF, Laure et al. Abdominal surgery in patients with chronic noncirrhotic extra hepatic portal vein obstruction : A multicenter retrospective study. In: Hepatology, 2024. doi: 10.1097/HEP.0000000000000901

This publication URL: https://archive-ouverte.unige.ch/unige:177761

Publication DOI: 10.1097/HEP.0000000000000901

Hepatology Publish Ahead of Print
DOI:10.1097/HEP.0000000000000901

Abdominal surgery in patients with chronic noncirrhotic extra hepatic portal vein obstruction: a multicenter retrospective study

Laure Elkrief [1,2], Corentin Denecheau-Girard [1], Marta Magaz [3], Michael Praktiknjo [4], Nicola Colucci[5], Isabelle Ollivier-Hourmand [6], Jérôme Dumortier[7], Macarena Simon Talero[8], Luis Tellez[9], Florent Artru[10], Magdalena Meszaros[11], Xavier Verhelst[12], Nicolas Tabchouri[13], Francisca Beires [14], Irene Andaluz[3] , Massimo Leo[14], Mara Diekhöner[15], Safi Dokmak[16], Yliam Fundora[17], Judit Vidal-Gonzalez[8], Christian Toso[5], Aurélie Plessier [2,14], Juan Carlos Garcia Pagan[3], Pierre-Emmanuel Rautou [2,14] , on behalf of the ERN RARE-LIVER; a study of VALDIG, an EASL consortium

1 Faculté de médecine et service d'hépato-gastroentérologie, CHRU de Tours, ERN RARE-LIVER France

2 Inserm, Centre de recherche sur l'inflammation, UMR 1149, Paris, France

3 Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic, Institut de Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). CIBEREHD (Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas). Health Care Provider of the European Reference Network on Rare Liver Disorders (ERN-Liver). Departament de Medicina i Ciències de la Salut. Universitat de Barcelona.

4 Department of Medicine B, University Hospital Münster, Münster, Germany

5 Service de chirurgie viscérale, Hôpitaux Universitaires de Genève, Geneva, Switzerland

6 Service d'hépato-gastroentérologie, CHU de Caen, ERN RARE-LIVER France

7 Service d'Hépatogastroentérologie, Hôpital Edouard Herriot, Lyon
8 Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain
9 Departamento de Gastroenterología y Hepatología Hospital Universitario Ramon y Cajal, Madrid, Spain
10 Service d'hépato-gastroentérologie, CHUV, Lausanne, Switzerland
11 Service d'Hépato-gastroentérologie, CHU de Montpellier, France
12 Department of Gastroenterology and Hepatology, Ghent University Hospital, Belgium
13 Service de chirurgie digestive et de transplantation hépatique, CHRU de Tours, France
14 AP-HP, Service d'Hépatologie, Hôpital Beaujon, DMU DIGEST, Centre de Référence des Maladies Vasculaires du Foie, FILFOIE, ERN RARE-LIVER, Clichy, France
15 Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany
16 AP-HP, Service de chirurgie hépato-biliaire et pancréatique, Hôpital Beaujon, DMU DIGEST, Clichy, France

17 Department of General & Digestive Surgery, Institut de Malalties Digestives I Metabòliques , Hospital Clínic, University of Barcelona, IDIBAPS, Spain.

Authors' contribution

Conception and design of the study: LE, PER

Generation, collection, assembly, analysis and/or interpretation of data: CDG, MM, MP, NC, IO, JD, MT, LT, FA, MM, XV, NT, FB, IA, ML, MD,

Drafting or revision of the manuscript: LE, CDG, JC-GP, PER, MP, IO

Approval of the final version of the manuscript: CDG, MM, MP, NC, IO, JD, MT, LT, FA, MM, XV, NT, FB, IA, ML, MD SD, JVG, CT

Corresponding author:
Dr Laure Elkrief
Service d'hépatogastroentérologie Hôpital Trousseau, Faculté de médecine de Tours
l.elkrief@chu-tours.fr

Financial support

None

Conflicts of Interest

Laure Elkrief is on the speakers' bureau received grants from AbbVie and Gilead. Isabelle Ollivier-Hourmand received grants from AbbVie and Gilead. Macarena Simon Talero consults for Grifols. Juan Carlos Garcia Pagan consults and is on the speakers' bureau for Cook. He is on the speakers' bureau Gore. He received grants from AstraZeneca and Mallinckrodt. Pierre-Emmanuel Rautou consults for Abbelight, Boehringer Ingelheim, GENFIT, HemostOD, and Mursla Bio. He is on the speakers' bureau for AbbVie and Tillots. He received grants from Terrafirma. The remaining authors have no conflicts to report.

Key words: cavernoma, portal vein thrombosis, TIPS, portal stent, anticoagulation

List of abbreviations

EHPVO, extrahepatic portal vein obstruction
PVT, portal vein thrombosis
PSVD, Porto sinusoïdal vascular disorder
VKA, vitamin K antagonist
DOAC, direct oral anticoagulant
VALDIG, Vascular Disease Interest Group
TIPS, transjugular intrahepatic portosystemic shunt
IQR, interquartile range
CI, confidence interval

Graphical Abstract

GA1

Abstract

Background & aims: In patients with noncirrhotic chronic extra-hepatic portal vein obstruction (EHPVO), data on morbimortality of abdominal surgery are scarce.

Approach & results: We retrospectively analyzed the charts of 76 patients (78 interventions) with EHPVO undergoing abdominal surgery within the VALDIG network. Fourteen percent of the patients had ≥1 major bleeding (unrelated to portal hypertension) and 21% had ≥1 Dindo-Clavien grade ≥3

postoperative complication within 1 month after surgery. Fifteen percent had ≥1 portal hypertension related complication within 3 months after surgery. Three patients died within 12 months after surgery. An unfavorable outcome (*i.e.* ≥ 1 above-mentioned complications or death) occurred in 37% of the patients and was associated with a history of ascites and with non-wall, non-cholecystectomy surgical intervention: 17% of the patients with none of these features had an unfavorable outcome, *vs.* 48% and 100% when one or both features were present, respectively. We then compared 63/76 EHPVO patients with 126 matched (2:1) control patients without EHPVO but with similar surgical interventions. As compared with control patients, incidence of major bleeding ($p<0.001$) and portal-hypertension related complication ($p<0.001$) was significantly higher in patients with EHPVO, but not that of grade ≥ 3 postoperative complication nor of death. The incidence of unfavorable post-operative outcome was significantly higher in patients with EHPVO than in those without (33% vs. 18%, $p=0.01$)

Conclusion. Patients with EHPVO are at high-risk of major peri- or postoperative bleeding and postoperative complications, especially in those with ascites or undergoing surgery other than wall surgery or cholecystectomy.

Chronic non cirrhotic extra hepatic portal vein obstruction (EHPVO) refers to the chronic occlusion of the main portal vein, with or without extension to superior mesenteric vein and splenic vein, in patients without underlying cirrhosis. In the majority of the patients, EHPVO is associated with the development of porto-portal collaterals leading to the formation of a portal cavernoma (1). In Europe, EHPVO is considered a rare disease, with a prevalence ranging from 0.35 to 2.5 per 100 000 inhabitants (2,3). Nevertheless, it remains the second leading cause of portal hypertension (3). Although EHPVO usually refers to patients with portal vein thrombosis (PVT) in the absence of underlying liver disease, it can occur in patients with pre-existing porto-sinusoidal vascular liver disorder (PSVD)(4). EHPVO has been associated with local and/or general risk factors for thrombosis, found in around 20% and 70% of the patients, respectively (1). Patients with EHPVO may develop severe portal hypertension, but usually have preserved liver function (5–7). Long-term anticoagulation has been generally recommended in patients with EHPVO, either using vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) (8,9).

Patient with EHPVO may require abdominal surgery for indications related to EHPVO, such as the treatment of the underlying local risk factor (*e.g.* gallstones or Crohn's disease) or symptomatic portal cavernoma cholangiopathy (10–12). The indication for surgery may also be unrelated to EHPVO.

In patients with cirrhosis, as well as in those with PSVD, morbidity and mortality after abdominal surgery has been associated with the severity of portal hypertension (13,14), but also with the degree of liver dysfunction (14,15), the type of surgery (15,16) and comorbidities (13,17,18). EHPVO, especially if a cavernoma is present, has long been regarded as a contraindication to surgery due to the high risk of bleeding and mortality (19). Currently available data evaluating post-operative outcomes in patients with EHPVO is limited to single-center, retrospective uncontrolled studies, including a limited number of patients, almost exclusively undergoing surgery for the treatment of portal cavernoma cholangiopathy (10,20,21). Moreover, although perioperative bleeding is, at least theoretically, a major concern in patients with EHPVO (mainly due to severe portal hypertension and anticoagulation), perioperative bleedings have never been carefully evaluated in patients with EHPVO. The aim of the present study was thus to evaluate post-operative outcome in a large multicenter cohort of patients with EHPVO compared with patients without EHPVO.

Methods

Patients

Between January 2019 and February 2022, we contacted all the centres of the Vascular Liver Disease Interest Group (VALDIG) and of the French networks for vascular liver diseases to retrospectively identify all patients with EHPVO having had ≥1 abdominal surgery between 2002 and 2020. Surgeries were considered only if EHPVO was known prior to the procedure. Patients' identification was based on local databases. For patients who underwent more than one procedure during the study period, general clinical characteristics are presented at the time of the first procedure and each procedure was analysed separately. The study was approved by our institutional review board (CCER 2019-01254) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Then, patients with EHPVO undergoing surgery (EHPVO group) were matched 1:2 with patients without EHPVO undergoing surgery (control group). Matching criteria included surgical intervention, age at surgery (± 10 years), date of surgery (± 5 years) and the centre. When one centre could not find controls without EHPVO, we used the database of Tours University Hospital (France) to search for an appropriate control. If more than 2 patients met the matching criteria, 2 controls were randomly selected by the local investigators.

Definition

Diagnosis of EHPVO was based on abdominal imaging (contrast enhanced computed tomography or magnetic resonance imaging) showing complete obstruction of the main portal vein 6 months or more before surgery, with or without portal cavernoma. Cirrhosis was excluded based either on liver biopsy or the absence of morphological signs of cirrhosis or by liver stiffness measurement (22,23).

Causal factors for EHPVO were classified, as recommended (24,25), into general risk factors for thrombosis and local risk factors. The following risk factors for thrombosis were classified as "strong risk factor for thrombosis": myeloproliferative neoplasm, antiphospholipid syndrome, and a personal or first-degree family history of unprovoked venous thrombosis (9).

History of ascites was defined as either a previous episode of ascites, or ascites controlled with diuretics at the time of surgery, or clinically detectable ascites at surgery. High-risk varices were defined by the presence of medium or large varices at endoscopy and/or by a history of variceal band ligation. Endoscopic data were recorded on an upper gastrointestinal endoscopy performed within 3 years before surgery in patients without varices and within 1-2 years in those with small varices (according to Baveno VI recommendations), except for patients treated with non-selective beta blockers (26).

Portal decompression intervention before surgery included either portal vein recanalization (PVR) with or without transjugular intra hepatic portosystemic shunt (TIPS) placement or surgical portosystemic shunt. Patients in whom surgical portosystemic shunt was the unique indication for surgery were not included into this study.

The following data were collected at surgery: (a) clinical features before surgery, including age, gender, American Society of Anesthesiology (ASA) class, age-adjusted Charlson comorbidity index (the Charlson Comorbidity index is a weighted index that takes into account the number and the seriousness of comorbid diseases by assigning points for certain illnesses; the age-adjusted Charlson comorbidity index assigns an additional point for each decade of life after 50 years of age) (27), clinical, laboratory, imaging and endoscopic features; (b) surgical data, including indication, type of surgery, planned or emergency procedure, laparoscopy or open surgery. According to the results of a recent Delphi survey, patients were not classified into major or minor surgeries, because our aim was to identify predictive factors of poor outcome after surgery (28).

Study endpoints

Duration of follow-up was calculated from the date of surgery to the last visit. Study endpoints were prespecified before data collection and are detailed in Supplementary Table 1, http://links.lww.com/HEP/I426. Bleeding complications unrelated to gastroesophageal varices, occurring either during or within 1 month after surgery, were classified into minor and major bleeding according to recommendations of the International Society on Thrombosis and Haemostasis (29). Postoperative complications were defined as any event occurring within 1 month after surgical intervention and categorized according to the Dindo-Clavien classification (30). Portal hypertension–related complications were defined as any of the following events: decompensation of ascites, overt hepatic encephalopathy, portal hypertension–related bleeding, within 3 months after surgical intervention. Decompensation of ascites was defined as follows: (i) in patients without ascites, onset of clinically detectable ascites, confirmed by ultrasonography; (ii) in patients with previous ascites not requiring paracentesis, ascites requiring paracenteses within 3 months following surgery or requiring a TIPS. Recurrence of thrombosis was defined as occurrence of a symptomatic or asymptomatic venous thromboembolic event at any site within 3 months after surgery (9). Postoperative death was defined as death occurring within 12 months after surgical intervention. Finally, an unfavorable outcome was *a priori* defined as the occurrence of ≥1 of the following events: major bleeding and/or postoperative complication grade ≥ 3 according to the Dindo-Clavien classification within 1 month after surgery, portal hypertension–related complications within 3 months after surgery, or death within 12 months after surgery (13).

Statistical analysis

Results are presented as median (interquartile range [IQR]) or absolute number (percentage). Comparisons between quantitative variable were performed using the Mann Whitney U test. Comparison between categorical variables were performed using the Chi-square or Fisher exact test, as appropriate. Cox regression analyses were performed to determine features associated with bleeding unrelated to study endpoints in patients with EHPVO. Since the outcomes of interest were rare, we applied the Firth's penalized maximum likelihood bias reduction approach for Cox regression, using the R Project "coxphf" software package (31). Features included into univariable analyses were prespecified based on their previous identification as prognostic factors either in patients with portal hypertension (cirrhosis or PVSD) undergoing abdominal surgery, or in patients with EHPVO, namely age adjusted Charlson comorbidity index (18), strong risk factor for thrombosis (32), serum creatinine at surgery (13,14,18), serum bilirubin at surgery (18,33,34), history of ascites at surgery (13,35,36), high-risk varices (37,38), the type of intervention (15), and emergency procedure (15,35). The thresholds for serum creatinine (≥100 μmol/L) and age adjusted Charlson comorbidity index (≥6) were chosen according to previous publications (13,39). Regarding serum bilirubin, the threshold of 50 μmol/L was chosen in agreement with Child-Pugh classification. Although MELD and Child-Pugh scores are associated with post-operative outcome after abdominal surgery in patients with cirrhosis (15,40), we deliberately chose to include serum creatinine and bilirubin rather than MELD, since INR is typically normal in patient with EHPVO, and since a significant proportion of the patients were treated with VKAs. We did not include Child-Pugh score in the analysis of the factors associated with post operative outcomes, since serum albumin concentration was available in only 55 out of the 81 patients. Regarding major bleeding, we included into univariable analyses surgery performed under anticoagulant therapy and platelet count on top of the above mentioned features (41). Variables achieving a *P* value below 0.10 in univariable analyses were included into a multivariable analysis. In order to evaluate the influence of portal decompression on postoperative outcome, we performed additional analyses including portal decompression in the multivariable analysis. In order to evaluate whether EHPVO is associated with an increased risk of complications or death after surgery, we compared patients with EHPVO with matched control patients without EHPVO. We also performed Cox regression analysis including EHPVO as a potential factor for postoperative outcomes. Hazard ratios (HRs) for Cox analyses were provided with their 95% confidence interval (CI). Cumulative risk of complications or death was assessed according to the Kaplan-Meier method and compared using the log-rank test. All tests were two-sided, and $P \leq 0.05$ was considered to be significant. Data handling analysis were performed with SPSS 28.0 (SPSS

Inc., Chicago, IL) and RStudio (2023.12.0+369). Figures were performed using GraphPad Prism 10.0.

Results

Patients

Between November 2002 and December 2020, 95 surgeries were performed in 93 patients selected from 12 University tertiary centers (Supplementary Table 2, http://links.lww.com/HEP/I426). Seventeen patients were excluded for reasons shown in Figure 1. Finally, 76 patients were included into the study, of whom one had 3 surgical interventions. The main characteristics of the 76 included patients are presented in the Table 1. Median interval between EHPVO diagnosis and surgery was 36 (7-113) months. A general risk factor for thrombosis was found in 32 (42%) patients, including 23 (30%) patients with a myeloproliferative neoplasm (22/23 with *JAK2*^{V617F} mutation). In addition, 11(15%) patients had a personal history of venous thrombosis. Thus, 34 (45%) patients were considered as having a strong risk factor for thrombosis. A local risk factor for thrombosis was found in 42 (55%) patients. Among them, ≥1 general risk factor was also found in 11 (15%) patients. Finally, no risk factor for PVT was found in 12 (16%) patients. Twenty-three (30%) patients had a history of ascites, among whom 11 (15%) patients were treated with diuretics at the time of surgery.
Fifty (66%) patients were treated with long-term anticoagulation therapy. Six (8%) patients were treated by antiplatelet agents, including 4 with a dual therapy of anticoagulant and antiplatelet agents. In 9 patients, surgery was performed without interruption of anticoagulation therapy (n=8) or of antiplatelet agents (n=1). Among the 42 patients in whom anticoagulation was interrupted before surgery, the interval between surgery and resumption of anticoagulation was 2 (1-10) days. Data on routine low dose prophylactic anticoagulant therapy after surgery were not available.

Type of, and indications, for surgery are detailed on Table 2. The patient who had three surgical interventions underwent cholecystectomy in 2009, treatment of post-surgery hernia in 2014 and treatment of umbilical hernia in 2016. Surgery was performed using open route in 62 (80%) patients, whereas 16 (21%) had laparoscopy. Five out of 62 open surgeries corresponded to conversion from laparoscopy to open surgery. Twelve (15%) interventions were emergency procedures.

Complications and death after surgery in patients with EHPVO

Major peri and post-operative bleeding unrelated to gastroesophageal varices

Bleeding complications occurred in 18 (23%) of the 78 interventions, including 9 (12%) during and 12 (14%) after surgery. Three patients had both bleeding during and after the surgery. Bleeding was major in 14 (18%) cases, all of them requiring unplanned red blood cell transfusion. By Cox univariable analysis, features associated with major bleeding complication included serum creatinine ≥ 100 µmol/L, emergency surgery, and intervention other than cholecystectomy or abdominal wall surgery. Neither platelet count nor surgery performed under anticoagulation were associated with major bleeding (Supplementary Table 3, http://links.lww.com/HEP/I426). Interval between surgery and reintroduction of anticoagulation was neither associated with major bleeding (HR (95% CI) 0.99 (0.96-1.103, p = 0.71). By Cox multivariable regression analysis, only emergency surgery (p=0.06), and intervention other than cholecystectomy or wall surgery (p=0.054) tended to remain associated with major bleeding, although the association did not reach statistical significance (Supplementary Table 3, http://links.lww.com/HEP/I426).

Post operative complications unrelated to portal hypertension within one month after surgery

Thirty-three (44%) patients had ≥1 complication within one month after surgery. The type and severity of postoperative complications are presented in **Table 3**. Infections were the most common, since 20 infections occurred in 17 (22%) patients. Sixteen (21%) patients had ≥1 grade ≥ 3 postoperative complications according to Dindo-Clavien classification. By Cox univariable regression analysis, features associated with the occurrence of ≥1 grade ≥ 3 complication included serum bilirubin ≥ 50 µmol/L, serum creatinine ≥ 100 µmol/L, emergency surgery, and intervention other than cholecystectomy or abdominal wall surgery (**Figure 2 and** Supplementary Table 3, http://links.lww.com/HEP/I426). By Cox multivariable regression analysis, the only feature that remained significantly associated with a lower incidence of ≥1 grade ≥ 3 complication was the type of surgery (other than cholecystectomy or wall surgery) (HR [95% CI] 0.17 [0.02 – 0.73], p = 0.01). (Supplementary Table 3, http://links.lww.com/HEP/I426). As shown in **Figure 2A**, cumulative incidence of ≥1 grade ≥ 3 complication was similar in patients with either cholecystectomy or wall surgery, but was significantly lower than in other patients.

Portal hypertension-related complications within 3 months after surgery

Fourteen portal hypertension related complication occurred in 12 (15%) patients. Ten (13%) had post operative ascites, of whom 9 (12%) were successfully treated with diuretics. Median interval between occurrence of ascites and its resolution was 11 (6-45) days. The last patient who developed postoperative ascites presented a septic shock complicating an intra-abdominal fungal infection and

died 12 days after surgery (Supplementary Table 4, http://links.lww.com/HEP/I426; Patient 36). Two (3%) patients developed hepatic encephalopathy. One had a favourable outcome under medical therapy (lactulose) within 24 hours. The second one developed hepatic encephalopathy during a septic shock and died 12 days after surgery (Supplementary Table 4, http://links.lww.com/HEP/I426; Patient 36). Two (2%) patients had variceal bleeding. The interval between surgery and variceal bleeding was 5 and 11 days respectively. The first patient had large varices but was not treated neither with beta-blockers nor endoscopic band ligation. In the second, endoscopy had not been performed before surgery. Both were successfully treated with endoscopic band ligation. By Cox univariable regression analysis, a strong risk factor for thrombosis was the only factor associated with the occurrence of portal hypertension related complication (p=0.03) (Supplementary Table 3, http://links.lww.com/HEP/I426).

Recurrence of thrombosis within 3 months after surgery

Recurrence of thrombosis within 3 months after surgery occurred in only 1 (1%) patient. Extension of thrombosis was diagnosed 42 days after a cephalic duodeno-pancreatectomy for an ampulloma. Surgery had been complicated by intra-abdominal collection and delayed wound healing. Extension of thrombosis (from the portal vein only, to intra hepatic portal vein branches) was diagnosed at the occasion of a systematic imaging procedure, in the absence of symptoms. Extension of thrombosis occurred under anticoagulant therapy (enoxaparin 6000 IU twice a day), without recanalization during follow-up. No patient developed extra-splanchnic venous thrombosis.

Death within 12 months after surgery

Three (4%) patients died within 12 months after surgery, with an interval of 12, 38 and 77 days after surgery, respectively. The individual data of these 3 patients are presented in Supplementary Table 4, http://links.lww.com/HEP/I426.

Overall unfavorable outcome after surgery within 12 months after surgery

Twenty-three (30%) patients were admitted in intensive care unit after surgery. Overall, median length of hospital stay was 10 (4-18) days. Median follow-up duration after surgery was of 103 days (interquartile range 63-247 days). Twenty-seven (35%) patients had an unfavorable outcome after surgery, as defined above **(Figure 3A)**. By Cox univariable regression analysis, history of ascites and type of intervention (other than cholecystectomy or wall surgery) were significantly associated with an unfavorable outcome after surgery (**Figure 3B and Table 4)**. By Cox multivariable regression analysis, type of intervention (other than cholecystectomy or wall surgery) remained significantly

associated with an unfavorable outcome after surgery (p = 0.007). History of ascites was also associated with an unfavorable outcome although the association did not reach statistical significance (p=0.08) (**Table 3**). We then classified patients according to the type of intervention and history of ascites and observed that 15% of the patients with none of these items had an unfavorable outcome, while 46% of the patients with one of these features and 2/2 patients with these 2 features had an unfavorable outcome **(Figure 3C).**

Influence of portal decompression on post-operative outcome

Nine (12%) patients had portal decompression before surgery. The indication for portal decompression was preparation for surgery, portal hypertension related bleeding and treatment of portal biliopathy in 5, 2, and 1 patient, respectively. Two patients underwent surgical portal decompression with 1 superior mesenteric vein jump graft and 1 spleno-renal shunt, 5.9 and 3.7 years before surgery, respectively. Seven patients underwent portal vein recanalization without (n=5) or with TIPS (n=2) (Supplementary Figure 1, http://links.lww.com/HEP/I426). The median interval between portal vein recanalization and surgery was 58 (IQR 12-180) days.

In order to assess the effect of portal decompression on the outcome after surgery, we compared the outcome of the 9 patients who had either portal vein recanalization (PVR) or portosystemic shunt before surgery, to the 69 patients who did not (Supplementary Table 5, http://links.lww.com/HEP/I426). Post-operative outcomes did not differ between patients with previous PVR or portosystemic shunt and those without. When included in the multivariable Cox regression analysis, portal decompression was not with associated with any of the pre-specified postoperative outcomes (namely major bleeding during or within 1 month after surgery, Dindo-Clavien grade ≥3 postoperative complications, portal hypertension-related outcome within 3 moths after surgery, and death within 12 months after surgery) (data not shown). Furthermore, in the subgroup of 44 patients with an intervention other that wall surgery or cholecystectomy, 6 had a history of portal decompression before surgery. Post-operative outcomes did not differ between patients with history of portal decompression (n=6) and those without (n=38) (data not shown).

Comparison of outcome after surgery between EHPVO and matched controls

Two controls fulfilling the matching criteria could be found for 63 out of 76 patients with EHPVO (**Figure 1**). Characteristics at surgery of the 63 patients with EHPVO and their 126 matched controls included in this analysis are summarized in **Table 1**. Emergency surgery was more frequent among controls than EHPVO patients (36% vs. 18%, p=0.006). The type of interventions included

cholecystectomy, wall surgery and other interventions in 31%, 21% and 49% of the patients, respectively.

Association between EHPVO and pre-specified outcomes after surgery

Incidence of major bleeding (16% *vs*. 2%, p<0.001) was significantly higher in patients with EHPVO (**Figure 4A**). By Cox univariable regression analysis, a strong risk factor for thrombosis, serum creatinine ≥ 100 µmol/L, history of ascites, emergency procedure, cholecystectomy or abdominal wall surgery, and EHPVO were significantly associated with major bleeding after surgery (Supplementary Table 6, http://links.lww.com/HEP/I426). By multivariable analysis, EHPVO remained significantly associated with major bleeding (HR (95% CI) 13.56 (2.65-80.97), p<0.001).

The incidence of grade ≥ 3 post-operative complication did not differ between patients with and without EHPVO (17% *vs.* 14%, p =0.59) (**Figure 4B**). By Cox univariable regression analysis, age-adjusted Charlson comorbidity index ≥6, serum creatinine ≥ 100 µmol/L, history of ascites, emergency procedure, cholecystectomy or abdominal wall surgery, but not EHPVO were significantly associated with the occurrence grade ≥ 3 postoperative complications after surgery (Supplementary Table 6, http://links.lww.com/HEP/I426).

Eleven (17%) patients with EHPVO developed portal-hypertension related complication whereas no control patient without EHPVO did (p<0.001) (**Figure 4B**). By Cox univariable regression analysis, age-adjusted Charlson comorbidity index ≥6, a strong risk factor for thrombosis, history of ascites and EHPVO were significantly associated with the occurrence of portal-hypertension related complication after surgery (Supplementary Table 6, http://links.lww.com/HEP/I426). By multivariable analysis, EHPVO remained significantly associated with portal-hypertension related complication (HR (95% CI) 13.60 (1.01-1919.24), p=0.04).

The incidence of death within 12 months after surgery did not differ between patients with EHPVO and those without (5% *vs*. 3%, p = 0.59)

Finally, the incidence of overall unfavorable post-operative outcome was significantly higher in patients with EHPVO than in those without (Figure 4B). By Cox univariable regression analysis, age-adjusted Charlson comorbidity index ≥6, a strong risk factor for thrombosis, serum creatinine ≥ 100 µmol/L, history of ascites, emergency procedure, cholecystectomy or abdominal wall surgery and EHPVO were significantly associated with an unfavorable outcome after surgery (Table 4). By multivariable analysis, EHPVO remained associated with an overall unfavorable post-operative

outcome, although the association did not reach statistical significance (HR (95% CI) 2.30 (0.94-5.27), p=0.07) (Table 4).

Discussion

Despite the rarity of the disease, the present study was able to gather a large number of patients with noncirrhotic EHPVO undergoing abdominal surgery, as well as of matched control patients without EHPVO. Major bleeding, post-operative complications and portal hypertension-related complications occurred in 23%, 21% and 15% of the patients, respectively. Three (4%) patients died within 12 months after surgery. Patients who had cholecystectomy or wall surgery and who had no history of ascites had a favorable outcome.

The main finding of the present study is that patients with EHPVO are at high-risk of unfavorable outcome after abdominal surgery, as 35% (95% CI 24-45%) developed severe complications. Two previous studies evaluated outcome after surgery in patients with EHPVO. One reported a 40% (95% CI 22-58%) incidence of overall complications among 30 patients with portal cavernoma who underwent planned abdominal surgery (20). By contrast, the other reported no post-operative complications, but out of only 7 patients with EHPVO who had laparoscopic cholecystectomy (42). The monocentric nature of these studies as well as the limited number of patients included likely accounts for these divergent results. Thanks to its multicentric design and the large number of patients included, the present study has been able to overcome these limitations, but also to identify features associated with an unfavorable outcome after surgery, namely history of ascites and surgical interventions other than cholecystectomy or wall surgery. These two simple clinical criteria could be helpful in making bedside decisions for abdominal surgery in patients with EHPVO, with due information of the patient on the risks of the intervention. Due to the retrospective design of the study, we did not perform an intention-to-treat analysis, so that we only included patients who had an intervention, but not those in whom surgery was considered as contra-indicated. Furthermore, the interpretation of the results must take into account that patients recruited in this study were followed in tertiary centres, expert in the management of patients with vascular liver diseases. We thus cannot exclude a potential selection bias. Furthermore, it is important to keep in mind that matching criteria did not take into account some potential prognostic factors, such as emergency surgery or indication for surgery. As patients without EHPVO had more commonly emergency surgery but a similar mortality as patients with EHPVO, we cannot exclude the possibility that EHPVO is in fact associated with higher mortality.

The second major finding of this study is the 16% (95% CI 7-25%) rate of major bleeding not related to gastroesophageal varices; an incidence much higher than that observed in matched control patients

without EHPVO (2% (95% CI 0.3-5)). The only feature associated with both major bleeding and postoperative complication was a non-wall non-cholecystectomy surgical intervention. Low platelet count was not associated with major bleeding, similarly to what is commonly observed with invasive procedures in patients with cirrhosis (41,43). Surgery performed while antiplatelet or anticoagulant therapy was not interrupted was not associated with major bleeding either, but only 9 patients were in this situation so that a lack of power can not be excluded. In addition, given the retrospective nature of the study, data on post-operative anticoagulation, especially routine prophylactic low dose anticoagulation, was not available.

The occurrence of grade ≥3 postoperative complications according to Dindo-Clavien did not differ in patients with EHPVO (21% (95% CI 12-29%) and those without 14% (95% CI 8-20%). The rate of post-operative complications in EHPVO patients was within the range of that previously reported in large registry studies evaluating outcome after surgery in patients with either absence of liver disease or with chronic hepatitis B without cirrhosis (from 8 to 11%) (14,44). Interestingly, although the patients included in this study had surgical interventions that are usually performed by laparoscopic approach (namely cholecystectomy, intestinal resection), open route was chosen in 80% patients. This may reflect that -even when performed by surgeons experts in portal hypertension- surgery in patients with EHPVO is considered more complex.

The third major finding is that portal hypertension related complications, mostly ascites, occurred in 15% (95% CI 7-23) of the patients, an incidence in the range of that observed in patients with compensated cirrhosis (17% (95% CI 11-23%)(45) or of those with PSVD (21% (95% CI 9-32%) (13). Portal-hypertension related complications happened more frequently in patients with a history of ascites and in those with a strong risk factor for thrombosis, just like in patients with PSVD where portal hypertension related complications after surgery are more common in patients with a history of ascites and with extra-hepatic conditions associated with PSVD (13). However, by contrast to cirrhosis, portal hypertension complications were usually transient, and resolutive either spontaneously or under medical therapy. Furthermore, the 2 patients who had variceal bleeding had no prophylaxis. This result suggests that screening endoscopy should be performed before planned abdominal surgery.

In this study, mortality within 12 months after abdominal surgery was 4% (95% CI 0-8) in patients with EHPVO, a figure lower than that observed in patients with portal hypertension from other causes undergoing abdominal surgery, namely cirrhosis and PSVD. Indeed, in a recent study including 140 patients with compensated cirrhosis and portal hypertension undergoing surgery, 12-months mortality was 19% (95% CI 13-26%) (45). In a study gathering 44 patients with PSVD and portal hypertension

from the VALDIG network, 6-month mortality after surgery was 9% (95% CI 1-17%) (13). In the present study, the rate of death within 12 months after surgery was not higher than that of matched control patients without EHPVO. These results suggest that post-operative mortality in patients with chronic liver disease is more related to the severity of liver dysfunction and to comorbidities than to the degree of portal hypertension. Further prospective studies will be needed to assess the value of the Vocal Penn model to predict postoperative morbidity and mortality in patients with EHPVO (15).

Portal decompression (either surgical or radiological) was not associated with improved post-operative outcome. No study previously evaluated the impact of portal decompression on surgery outcome in patients with EHPVO. Caution is needed when interpreting our results, since only 9 patients had previous portal decompression, including only 5 as a preparation for surgery. However, the relatively rare and, mostly transient, incidence of portal hypertension related complications observed here do not favour portal decompression before surgery in patients with noncirrhotic EHPVO.

In conclusion, patients with EHPVO – and especially those with a history of ascites and/or those who undergo surgery other than cholecystectomy or wall surgery- were at high risk of major bleeding and of portal hypertension related complications after abdominal surgery. However, one year mortality was not higher than that of matched controlled patients.

Aknowledgements

We thank Kamal Zekrini, Thierry Poumaroux, Christelle Jean, and Guillaume Delaval for their help in collecting the data.

PER's research laboratory is supported by the Fondation pour la Recherche Médicale (FRM EQU202303016287), "Institut National de la Santé et de la Recherche Médicale" (ATIP AVENIR), the "Agence Nationale pour la Recherche" (ANR-18-CE14-0006-01, RHU QUID-NASH, ANR-18-IDEX-0001, ANR-22-CE14-0002) by « Émergence, Ville de Paris », by Fondation ARC and by the European Union's Horizon 2020 research and innovation programme under grant agreement No 847949.

MP is funded by the Ernst-und-Berta Grimmke Foundation (No. 5/19) and BONFOR research program of the University of Bonn (grant ID 2020-2A-07 and 2021-2A-07) and by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy – EXC2151 – 390873048.

References

1. Elkrief L, Payancé A, Plessier A, d'Alteroche L, Ronot M, Paradis V, et al. Management of splanchnic vein thrombosis. JHEP Reports. 2023;5:100667.

2. Ageno W, Dentali F, Pomero F, Fenoglio L, Squizzato A, Pagani G, et al. Incidence rates and case fatality rates of portal vein thrombosis and Budd-Chiari Syndrome. Thromb Haemost. 2017;117:794–800.

3. Hernández-Gea V, De Gottardi A, Leebeek FWG, Rautou P-E, Salem R, Garcia-Pagan JC. Current knowledge in pathophysiology and management of Budd-Chiari syndrome and non-cirrhotic non-tumoral splanchnic vein thrombosis. J Hepatol. 2019;71:175–199.

4. De Gottardi A, Sempoux C, Berzigotti A. Porto-sinusoidal vascular disorder. J Hepatol. 2022;77:1124–1135.

5. Bureau C, Laurent J, Robic MA, Christol C, Guillaume M, Ruidavets JB, et al. Central obesity is associated with non-cirrhotic portal vein thrombosis. J Hepatol. 2016;64:427–432.

6. Poisson J, Plessier A, Kiladjian J-J, Turon F, Cassinat B, Andreoli A, et al. Selective testing for calreticulin gene mutations in patients with splanchnic vein thrombosis: A prospective cohort study. J Hepatol. 2017;67:501–507.

7. Turon F, Cervantes F, Colomer D, Baiges A, Hernández-Gea V, Garcia-Pagán JC. Role of calreticulin mutations in the aetiological diagnosis of splanchnic vein thrombosis. J Hepatol. 2015;62:72–74.

8. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. BAVENO VII - RENEWING CONSENSUS IN PORTAL HYPERTENSION. Journal of Hepatology. 2021;S0168827821022996.

9. Plessier A, Goria O, Cervoni JP, Ollivier I, Bureau C, Poujol-Robert A, et al. Rivaroxaban Prophylaxis in Noncirrhotic Portal Vein Thrombosis. NEJM Evidence [Internet]. 2022 [cited 2023 Aug 15];1. Available from: https://evidence.nejm.org/doi/10.1056/EVIDoa2200104

10. Agarwal AK, Sharma D, Singh S, Agarwal S, Girish SP. Portal biliopathy: a study of 39 surgically treated patients. HPB (Oxford). 2011;13:33–39.

11. Khare R, Sikora SS, Srikanth G, Choudhuri G, Saraswat VA, Kumar A, et al. Extrahepatic portal venous obstruction and obstructive jaundice: approach to management. J Gastroenterol Hepatol. 2005;20:56–61.

12. Chattopadhyay S, Govindasamy M, Singla P, Varma V, Mehta N, Kumaran V, et al. Portal biliopathy in patients with non-cirrhotic portal hypertension: does the type of surgery affect outcome? HPB (Oxford). 2012;14:441–447.

13. Elkrief L, Ferrusquia-Acosta J, Payancé A, Moga L, Tellez L, Praktiknjo M, et al. Abdominal Surgery in Patients With Idiopathic Noncirrhotic Portal Hypertension: A Multicenter Retrospective Study. Hepatology. 2019;70:911–924.

14. Johnson KM, Newman KL, Green PK, Berry K, Cornia PB, Wu P, et al. Incidence and Risk Factors of Postoperative Mortality and Morbidity After Elective Versus Emergent Abdominal Surgery in a National Sample of 8193 Patients With Cirrhosis. Ann Surg. 2021;274:e345–e354.

15. Mahmud N, Fricker Z, Hubbard RA, Ioannou GN, Lewis JD, Taddei TH, et al. Risk Prediction Models for Post-Operative Mortality in Patients With Cirrhosis. Hepatology. 2021;73:204–218.

16. Wong M, Busuttil RW. Surgery in Patients with Portal Hypertension. Clin Liver Dis. 2019;23:755–780.

17. Northup PG, Friedman LS, Kamath PS. AGA Clinical Practice Update on Surgical Risk Assessment and Perioperative Management in Cirrhosis: Expert Review. Clin Gastroenterol Hepatol. 2019;17:595–606.

18. Teh SH, Nagorney DM, Stevens SR, Offord KP, Therneau TM, Plevak DJ, et al. Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology. 2007;132:1261–1269.

19. Chaudhary A, Dhar P, Sarin SK, Sachdev A, Agarwal AK, Vij JC, et al. Bile duct obstruction due to portal biliopathy in extrahepatic portal hypertension: surgical management. Br J Surg. 1998;85:326–329.

20. Dokmak S, Aussilhou B, Sauvanet A, Lévy P, Plessier A, Ftériche FS, et al. Safety of supramesocolic surgery in patients with portal cavernoma without portal vein decompression. Large single centre experience. HPB (Oxford). 2016;18:623–629.

21. Varma V, Behera A, Kaman L, Chattopadhyay S, Nundy S. Surgical management of portal cavernoma cholangiopathy. J Clin Exp Hepatol. 2014;4:S77-84.

22. Valainathan SR, Sartoris R, Elkrief L, Magaz M, Betancourt F, Pellegrino S, et al. Contrast-enhanced CT and liver surface nodularity for the diagnosis of porto-sinusoidal vascular disorder: A case-control study. Hepatology. 2022;76:418–428.

23. Elkrief L, Lazareth M, Chevret S, Paradis V, Magaz M, Blaise L, et al. Liver Stiffness by Transient Elastography to Detect Porto-Sinusoidal Vascular Liver Disease With Portal Hypertension. Hepatology. 2021;74:364–378.

24. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol. 2016;64:179–202.

25. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, et al. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;73:366–413.

26. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J. Hepatol. 2015;63:743–752.

27. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47:1245–1251.

28. Martin D, Mantziari S, Demartines N, Hübner M, ESA Study Group. Defining Major Surgery: A Delphi Consensus Among European Surgical Association (ESA) Members. World J Surg. 2020;44:2211–2219.

29. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8:202–204.

30. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–213.

31. Heinze G, Schemper M. A Solution to the Problem of Monotone Likelihood in Cox Regression. Biometrics. 2001;57:114–119.

32. Condat B, Pessione F, Hillaire S, Denninger MH, Guillin MC, Poliquin M, et al. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology. 2001;120:490–497.

33. Neeff HP, Streule GC, Drognitz O, Tittelbach-Helmrich D, Spangenberg H-C, Hopt UT, et al. Early mortality and long-term survival after abdominal surgery in patients with liver cirrhosis. Surgery. 2014;155:623–632.

34. Orr DW, Harrison PM, Devlin J, Karani JB, Kane PA, Heaton ND, et al. Chronic mesenteric venous thrombosis: evaluation and determinants of survival during long-term follow-up. Clin Gastroenterol Hepatol. 2007;5:80–86.

35. Telem DA, Schiano T, Goldstone R, Han DK, Buch KE, Chin EH, et al. Factors that predict outcome of abdominal operations in patients with advanced cirrhosis. Clin Gastroenterol Hepatol. 2010;8:451–457, quiz e58.

36. Plessier A, Darwish-Murad S, Hernandez-Guerra M, Consigny Y, Fabris F, Trebicka J, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology. 2010;51:210–218.

37. Csikesz NG, Nguyen LN, Tseng JF, Shah SA. Nationwide volume and mortality after elective surgery in cirrhotic patients. J Am Coll Surg. 2009;208:96–103.

38. Ziser A, Plevak DJ, Wiesner RH, Rakela J, Offord KP, Brown DL. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. Anesthesiology. 1999;90:42–53.

39. Bissonnette J, Garcia-Pagán JC, Albillos A, Turon F, Ferreira C, Tellez L, et al. Role of the transjugular intrahepatic portosystemic shunt in the management of severe complications of portal hypertension in idiopathic noncirrhotic portal hypertension. Hepatology. 2016;64:224–231.

40. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. Ann Surg. 2005;242:244–251.

41. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol. 2022;76:1151–1184.

42. Sasturkar SV, Agrawal N, Arora A, Kumar MPS, Kilambi R, Thapar S, et al. Laparoscopic cholecystectomy in patients with portal cavernoma without portal vein decompression. J Minim Access Surg. 2021;17:351–355.

43. Intagliata NM, Rahimi RS, Higuera-de-la-Tijera F, Simonetto DA, Farias AQ, Mazo DF, et al. Procedural-Related Bleeding in Hospitalized Patients With Liver Disease (PROC-BLeeD): An International, Prospective, Multicenter Observational Study. Gastroenterology. 2023;165:717–732.

44. Lin CS, Lin SY, Chang CC, Wang HH, Liao CC, Chen TL. Postoperative adverse outcomes after non-hepatic surgery in patients with liver cirrhosis. Br J Surg. 2013;100:1784–1790.

45. Reverter E, Cirera I, Albillos A, Debernardi-Venon W, Abraldes JG, Llop E, et al. The prognostic role of hepatic venous pressure gradient in cirrhotic patients undergoing elective extrahepatic surgery. J Hepatol. 2019;71:942–950.

Figure 1. Flow chart of the study.

One patient had 3 surgical interventions during the study period.

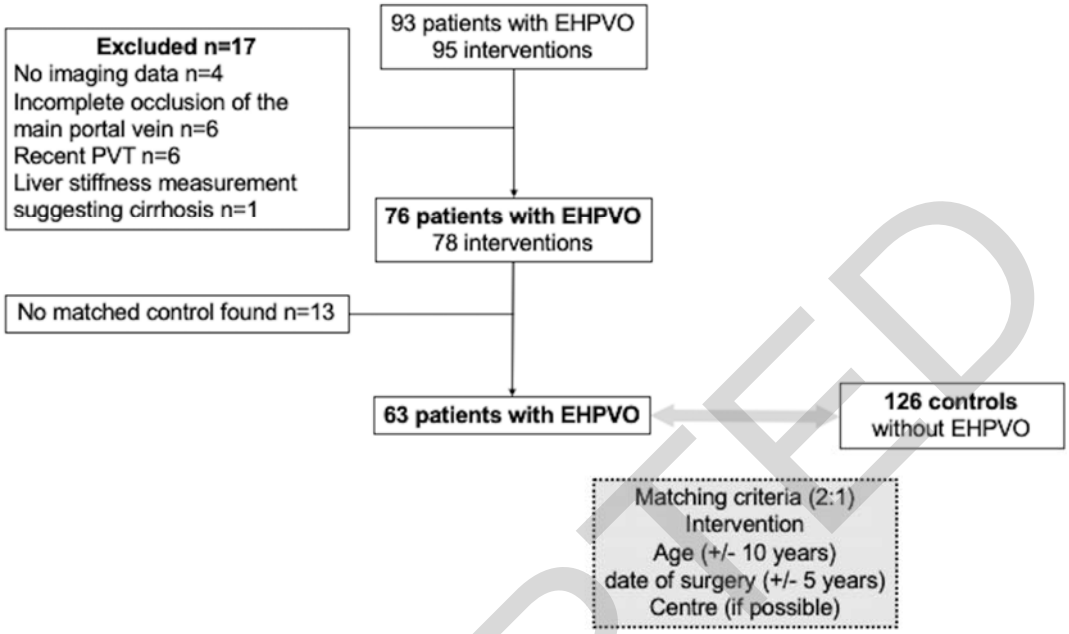
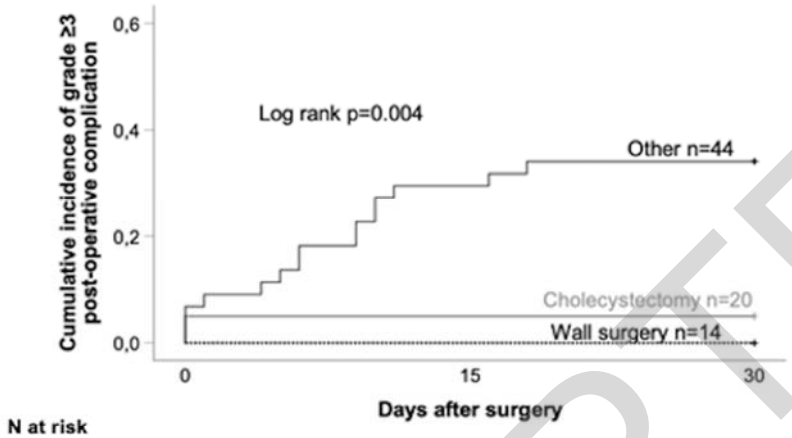


Figure 2. Kaplan-Meier curves. Panel A: Occurrence of grade ≥3 post-operative complication within one month after surgery according to the type of intervention (log rank: wall *vs.* cholecystectomy p=0.4, wall *vs.* other p=0.016, cholecystectomy *vs.* other p=0.18).



N at risk			
Wall surgery	14	14	14
Cholecystectomy	20	19	19
Other	44	29	29

Figure 3. Unfavorable outcome after surgery. An unfavorable outcome was defined as any of major bleeding during or within one month after surgery, post-operative complication grade ≥3 within one month after surgery, portal-hypertension related complications within 3 months after surgery or death within 12 months after surgery.

Panel A: Venn diagram representing the type of complications occurring in the 27 patients with an unfavorable outcome after surgery. Three patients died within 12 months after surgery (red circle).

Panel B: Proportion of the patients with an unfavorable outcome after surgery according to the presence of history of ascites and the type of intervention (other than wall surgery and cholecystectomy).

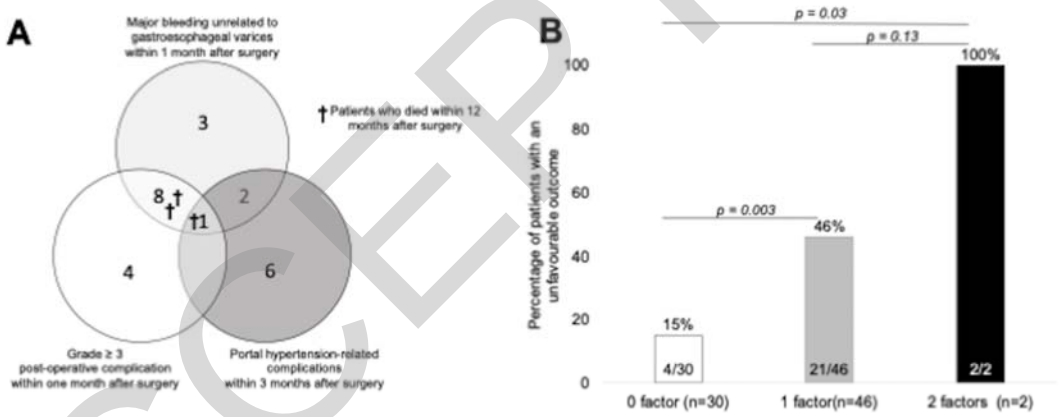


Figure 4. Panel A: Kaplan-Meier curves of peri and post-operative major bleeding in 63 patients with EHPVO and 126 matched control patients without EHPVO (log rank test)**. Panel B: Proportion of postoperative complications after surgery in 63 patients with EHPVO as compared to 126 matched control patients without EHPVO** (Wilconson rank test)

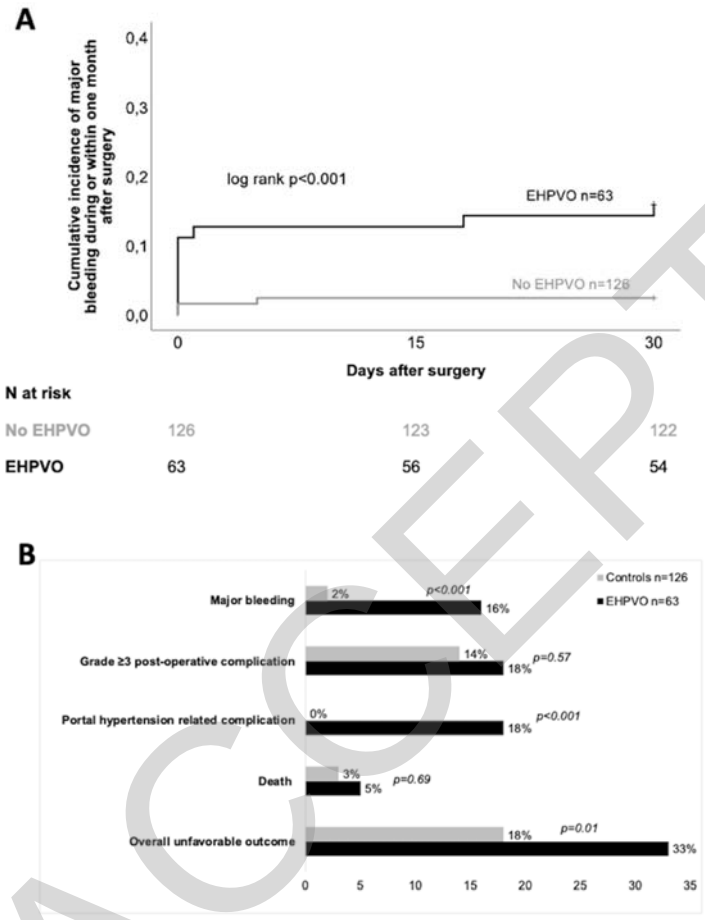


Table 1. Main Characteristics of the included patients at surgery

	Characteristics of the 76 patients with EHPVO§		Characteristics of the 63 patients with EHPVO and their 126 matched controls		P value EHPVO vs no EHPVO
Characteristics	**Number of patients with available data**	**Number (percentage) or Median (interquartile range)**	**Patients without EHPVO N=126**	**Patients with EHPVO N=63**	
Clinical Features					
Male gender	76	44 (58)	49 (40)	35 (56)	0.46
Age, years	76	53 (45-62)	54 (43-65)	53 (39-63)	0.45
Age-adjusted Charlson comorbidity index	76	2 (1-4)	2 (0-4)	2 (1-4)	0.68
ASA score	76	2 (2-3)	2 (2-3)	2 (2-3)	
BMI, kg/m²	70	25 (21-28)	**27 (23-30)**	**26 (22-28)**	**0.04**
History of ascites	76	**23 (30)**		**19 (30)**	
At least one cause of chronic liver disease* Excessive alcohol consumption Metabolic syndrome or diabetes	76	**21 (28)** 12 (16) 10 (13)		**13 (21)** 8 (13) 5 (8)	
Etiologic workup for EHPVO	**76**				
At least one local factor Previous abdominal surgery Pancreatitis § Intra-abdominal inflammation or cancer		**42 (55)** 14 (18) 11 (15) 15 (20) 3 (4)		**30 (48)** 10 (16) 4 (6) 13 (21) 3 (5)	

Trauma					
At least one general risk factor*		**32 (42)**		**32 (51)**	
Inherited thrombophilia		8 (10)		6 (10)	
Factor V Leiden mutation		6 (8)		5 (8)	
Prothrombin gene mutation		2 (3)		1 (2)	
Decreased protein S activity		2 (3)		1 (2)	
Decreased protein C activity		1 (1)		1 (2)	
Decreased antithrombin activity		1 (1)		1 (2)	
Myeloproliferative neoplasm		23 (30)		21 (33)	
Antiphospholipid syndrome		1 (1)		1 (2)	
Personal history of thrombosis		11 (15)		11 (18)	
At least one strong risk factor for thrombosis		**34 (45)**		**33 (52)**	
Usual treatment before surgery	**76**				
Anticoagulation therapy		50 (66)	11 (9)	45 (72)	
Heparin		23 (30)	5 (4)	20 (32)	
Vitamin K antagonist		25 (33)	2 (2)	23 (37)	
DOACs		2 (3)	4 (3)	2 (3)	
Low dose		2 (3)	2 (2)	1 (2)	
Full dose		48 (63)	9 (7)	44 (70)	
Antiplatelet agent		6 (8)	10 (8)	4 (6)	
Aspirin		5 (7)	8 (6)	4 (6)	

Clopidogrel		1 (1)	2 (2)	0 (0)	
Diuretics		11 (15)	14 (11)	13 (21)	
Non selective beta-blockers		**21 (28)**	**23 (18)**	**19 (30)**	
Laboratory data	**76**				
Haemoglobin, g/dL		12.4 (11.2-13.7)	13 (11-14)	13 (11-14)	0.11
Leucocyte count x 10^9/L		6.8 (4.1-10.3)	8 (6-12)	7 (4-10)	0.006
Platelet count x 10^9/L		180 (120-320)	**248 (187-328)**	**164 (99-302)**	**<0.001**
Prothrombin index, %		75 (53-93)	**90 (76-100)**	**73 (50-90)**	**<0.001**
Serum AST, IU/L		29 (22-41)	25 (18-50)	29 (22-40)	0.52
Serum ALT, IU/L		29 (19-49)	26 (18-55)	29 (18-42)	0.85
Serum ALK, IU/L		102 (77-161)	99 (76-165)	97 (74-143)	0.54
Serum GGT, IU/L		71 (37-147)	67 (29-159)	62 (34-117)	0.68
Serum bilirubin, µmol/L		13 (8-26)	11 (7-19)	14 (8-26)	0.08
Serum creatinine, µmol/L		73 (56-87)	74 (59-89)	73 (57-87)	0.77
Serum albumin££, g/L		37 (33-41)	40 (34-43)	38 (35-41)	0.26
Endoscopic data	**63**				
Gastro-oesophageal varices		18 (24)		17 (27)	
Absent		25 (33)		21 (33)	
Small varices		20 (26)		16 (25)	
Medium or large varices					
High risk varices‡	64	30 (40)		26 (49)	
Imaging data					
Main portal vein	75**				
Complete occlusion w/o cavernoma		6 (8)		5 (8)	
Cavernoma		69 (91)		57 (91)	

Superior mesenteric vein	**69**				
Patent		42 (55)		33 (52)	
Partial occlusion		9 (12)		8 (13)	
Complete occlusion		10 (13)		9 (14)	
Cavernoma		8 (11)		5 (8)	
Splenic vein	**65**				
Patent		39 (51)		34 (54)	
Partial occlusion		12 (16)		7 11)	
Complete occlusion		11 (15)		10 16)	
Cavernoma		2 (3)		2 (3)	
Spleen size, cm	**51**	15 (13-17)		15 (13-18)	
Ascites at imaging	**76**	**20 (26)**			
Minimal		14 (18)		9 (14)	
Moderate or abundant		6 (8)		7 (11)	
Portosystemic collaterals	**72**	51 (67)		39 (62)	
Intervention					
Cholecystectomy		See Table 2	39 (31)	19 (30)	0.99
Wall surgery			26 (21)	13 (21)	
Other			61 (48)	31 (49)	
Emergency surgery			**45 (36)**	**11 (18)**	**0.006**
Laparoscopic route			21 (17)	14 (22)	0.35

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; DOAC, Direct oral anticoagulant; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALK, alkaline phosphatase; GGT, gamma glutamyl transferase; IU, International Unit

* Several risk factor may be present in the same patient.

A strong risk factor for thrombosis was defined as either factor V Leiden mutation and/or prothrombin gene mutation and/or personal history of thrombosis, and/or myeloproliferative neoplasm and/or antiphospholipid syndrome

History of ascites was defined as a previous ascites that as controlled with diuretics at the time of surgery, or clinically detectable ascites at surgery.

£££Serum albumin was available in 64/126 control patients, and 41/63 patients with EHPVO.

‡ High-risk varices were defined as medium or large varices at endoscopy and/or history of variceal bleeding and/or history of variceal band ligation and/or treatment with nonselective beta-blockers because of portal hypertension.

Endoscopic data were available in 63/76 patients and in 54/63 patients included in the case-control analysis. Endoscopic data were recorded on an upper gastrointestinal endoscopy performed within 3 years before surgery in patients without varices and within 1-2 years in those with small varices (according to Baveno VI recommendations), except for patients treated with non-selective beta blockers (26). .

** One patient had a portal stent before surgery

§One patient had 3 surgical interventions during the study period. The characteristics of this patient are presented at the time of the first surgical intervention.

Table 2: Details on the 78 surgeries performed in 76 patients

	Number	Indication
Type of surgery		
Cholecystectomy	20	
Intestinal resection	12	
Ileal resection	7	Occlusion or stenosis n=3 Infection/inflammation n=2 Perforation n=2
Colorectal resection	4	Neoplasia n=3 Stenosis n=1
Appendectomy	1	Appendicitis n=1
Abdominal wall surgery	14	Eventration n=4 Umbilical hernia n=4 Inguinal hernia n=6
Bilio-enteric bypass	11	Pancreatitis n=7 Cholangiopathy n=4
Surgical exploration	3	Bleeding n=1 Diagnostic workup n=1
Liver resection	5	Neoplasia n=4 Abscess n=1
Splenectomy	4	Bleeding n=4
Gastric or pancreatic surgery	6	Ampulloma/duodenal polyp n=2 Chronic pancreatitis n=2 Stenosis n=1 Devascularisation n=1
Urologic surgery	3	Renal neoplasia n=2 Renal transplantation n=1
Access route		
Open surgery	62 (80)	
Laparoscopic surgery	16 (21)	
Planned or emergency surgery		
Planned surgery	66 (85)	
Emergency surgery	12 (15)	

Table 3: Details on 64 postoperative complications that occurred within one month after 33 interventions

Postoperative complications	**Number (percentage) or Median (interquartile range)**
At least one complication	**33**
Grade of the most severe complications	
Grade I	7
Grade II	11
Grade III	7
Grade IV	5
Grade V	3
At least one grade ≥ 3 complication	**16**
Type of complication	
Infection	**20**
Postoperative bleeding (unrelated to gastroesophageal varices)	**12**
Acute renal failure	**7**
Abdominal complications	
Ileus	5
Delayed wound healing	3
Constipation	1
Cardiopulmonary complications	
Dyspnea	2
Arterial hypertension	1
Pneumothorax	1
Arrhythmia	1
Anemia	2
Fever	3
Jugular thrombosis	1
~~**Metabolic encephalopathy**~~	~~1~~
Pain	2
Decompensation of diabetes (hyperosmolar coma)	1

Table 4: Univariable and multivariable Cox regression (using the Firth's penalized maximum likelihood bias reduction approach) evaluating prespecified factors before surgery associated with the occurrence of an unfavorable occurrence after surgery in 78 patients with EHPVO (upper part), and in 63 patients with EHPVO and 126 matched controls without EHPVO (lower part).

Overall unfavourable outcome after surgery in 78 patients with EHPVO						
	Univariable analysis			**Multivariable analysis**		
	Hazard ratio	**95% CI**	**P value**	**Hazard ratio**	**95% CI**	**P value**
Age adjusted Charlson comorbidity index ≥ 6	1.73	0.70-3.80	0.22			
Strong risk factor for thrombosis	1.29	0.63-2.66	0.49			
Serum bilirubin ≥ 50 µmol/L	1.63	0.44-4.45	0.42			
Serum creatinine ≥ 100 µmol/L	2.28	0.87-5.14	0.09	1.30	0.47-3.13	0.60
History of ascites	2.41	1.16-4.97	0.02	1.96	0.93-4.09	0.08
High risk varices	1.62	0.71-3.84	0.25			
Emergency procedure	2.32	0.86-5.53	0.09	1.66	0.65-3.81	0.27
Cholecystectomy or abdominal wall surgery	**0.31**	**0.12-0.69**	**0.003**	**0.33**	**0.12-0.75**	**0.007**
Overall unfavourable outcome after surgery in 63 patients with EHPVO and 126 matched control patients without						
Age adjusted Charlson comorbidity index ≥ 6	**2.17**	**1.06-4.12**	**0.03**	1.44	0.68-2.86	0.33
Strong risk factor for thrombosis	**2.14**	**1.09-3.95**	**0.03**	0.70	0.30-1.680.42	
Serum bilirubin ≥ 50 µmol/L	1.51	0.59-3.63	0.44			
Serum creatinine ≥ 100 µmol/L	**2.38**	**1.19-4.45**	**0.02**	1.72	0.78-3.57	0.17
History of ascites	**4.45**	**2.24-8.37**	**<0.001**	**2.91**	**1.20-7.04**	**0.02**
High risk varices	1.49	0.62-3.76	0.37			
Emergency procedure	**2.07**	**1.19-3.52**	**0.01**	**2.10**	**1.10-3.98**	**0.03**
Cholecystectomy or abdominal wall surgery	**0.44**	**0.23-0.79**	**0.006**	**0.50**	**0.26-0.92**	**0.02**
EHPVO	2.33	1.30-4.17	0.005	2.30	0.94-5.27	0.07

Bold indicate significant results.

Variables achieving a *P* value below 0.10 in univariate analyses were included into a multivariable analysis.

Overall unfavourable outcome was defined as the occurrence of at least one of the following events: major bleeding and/or postoperative complication grade ≥ 3 according to the Dindo-Clavien classification within 1 month after surgery, portal hypertension–related complications within 3 months after surgery, or death within 12 months after surgery.

A strong risk factor for thrombosis was defined as either factor V Leiden mutation and/or prothrombin gene mutation and/or personal history of thrombosis, and/or myeloproliferative neoplasm and/or antiphospholipid syndrome

History of ascites was defined as a previous ascites that as controlled with diuretics at the time of surgery, or clinically detectable ascites at surgery.

High-risk varices were defined as medium or large varices at endoscopy and/or history of variceal bleeding and/or history of variceal band ligation and/or treatment with nonselective beta-blockers because of portal hypertension.