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par

Corentin DENÉCHEAU-GIRARD

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TITRE

Evolution après chirurgie abdominale chez les patients atteints de thrombose porte chronique non cirrhotique : une étude rétrospective multicentrique cas-témoin.

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Professeur Ephrem SALAMÉ, Chirurgie digestive, Faculté de Médecine -Tours

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Docteur Louis d'ALTEROCHE, Hépatologie – Gastro entérologie, PH, CHU – Tours

Directrice de thèse :

Docteur Laure ELKRIEF, Hépatologie – Gastro entérologie, MCU-PH, Faculté de Médecine – Tours

Résumé

Introduction : la thrombose de la veine porte (TVP) chronique non cirrhotique est une maladie rare. La principale manifestation de la TVP non cirrhotique est l'hypertension portale (HTP). La fonction hépatique est généralement conservée. L'évolution après chirurgie abdominale chez les malades atteints d'une thrombose porte chronique non cirrhotique n'a jamais été évaluée. L'objectif de cette étude était d'évaluer cette évolution après chirurgie abdominale dans une large cohorte de malades atteints de TVP chronique non cirrhotique.

Patients et méthode : étude rétrospective, multicentrique, européenne comportant 81 malades atteints de TVP (âge médian 53 ans, 57% d'hommes) ayant eu une intervention chirurgicale entre novembre 2002 et décembre 2020.

Résultats : une complication post-opératoire sévère (grade ≥3 selon Dindo-Clavien), une complication de l'HTP, ou un décès survenaient dans les 30 jours, 3 mois ou 1 an suivant la chirurgie chez 18 (22%), 23 (28%) et 3 (4%) patients, respectivement. L'insuffisance rénale (créatinine > 100 μmol/L) prédisait le décès à 1 an. Finalement, 26 (30%) patients ont présenté une évolution défavorable (au moins une complication ou un décès). En analyse univariée, les facteurs associés à une évolution défavorable étaient l'antécédent d'ascite et le type d'intervention.

Conclusion : chez les malades atteints de TVP chronique non cirrhotique, le pronostic après chirurgie abdominale est acceptable, surtout en l'absence d'ascite ou d'insuffisance rénale avant la chirurgie.

Mots-clefs : Hypertension portale, cavernome porte, maladies vasculaires du foie

Abstract

Introduction: Chronic non cirrhotic extra hepatic portal vein thrombosis (EHPVO) is defined as the chronic occlusion of the portal vein with or without extension to superior mesenteric vein and splenic vein. EHPVO is the second leading cause of portal hypertension in Europe. Evolution of patient with EHPVO is unclear after abdominal surgery. The goal of this study is to describe evolution after abdominal surgery in a cohort of patient with EHPVO.

Patients and methods: retrospective, controlled, European study including 81 patients with EHPVO (median age 59 years old, 57 % male) undergoing abdominal surgeries between November 2002 and December 2020.

Results: Post operative complication grade ≥ 3 on Dindo-Clavien classification, portal hypertension related complication or death in an interval of 30 days, 3 months and 1 year after surgery happened in 18 (22%à, 23 (28%) and 3 (4%) patients, respectively. Kidney failure was significantly associated with death within 1 year after surgery. Finally, 26 (30%) had unfavorable outcome after surgery (at least on complication grade ≥ 3, portal hypertension related complication or death). By cox univariate analysis, risk factors associated with unfavorable outcome after surgery were history of ascites and the type of surgery.

Conclusion: patients with EHPVO are at higher risk of major postoperative and portal hypertension related complication after surgery. However, one year mortality was comparable in patients without EHPVO

Keywords : Portal hypertension, cavernoma, vascular liver disease

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SERMENT D'HIPPOCRATE

En présence des enseignants et enseignantes
de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
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ABBREVIATIONS

Français

HTP : hypertension portale

IRM : Imagerie par résonnance magnétique

TDM : Tomodensitométrie

TIPS : Shunt trans hépatique porto systémique

TVP : Thrombose chronique de la veine porte

English

ASA : American Society of Anesthesiology

CI : confidence interval

CT : Computed tomography

DOACs : direct oral anticoagulants

EHPVO : extra hepatic portal vein thrombosis

HR : Hazard ratio

ICU : intensive care unit

INR : international normalized ratio

IQR : interquartile range

MRI : magnetic resonance imaging

PSVD : portosinusoïdal vascular liver disease

PVR : portal vein recanalization

PVT : portal vein thrombosis

TIPS : Trans jugular intra hepatic porto systemic shunt

VALDIG : Vascular Liver Disease Interest Group

VKAs : Vitamin K antagonists

PREMIERE PARTIE

Thrombose chronique de la veine porte non cirrhotique

La thrombose chronique de la veine porte (TVP) est définie par une obstruction du flux sanguin portal avec ou sans extension à la veine mésentérique supérieure et/ou à la veine splénique. On estime la prévalence de la TVP, en Europe, entre 0.7 et 3.7 pour 100 000 habitants. [1,2] Elle fait suite à une thrombose aiguë de la veine porte et est considérée comme chronique en cas de persistance au cours d'une durée supérieure à 6 mois ou lors de l'apparition d'un cavernome porte.[3] Ce dernier correspond à l'ensemble des voies de dérivation porto-portale développées suite à la TVP et se localisant préférentiellement au sein du hile hépatique. Le diagnostic de TVP repose sur l'absence de flux sanguin portal visualisée sur un examen radiologique : échographie doppler abdominale et/ou tomodensitométrie (TDM) et/ou Imagerie par Résonnance Magnétique (IRM) avec injection intra-vasculaire de produit de contraste. (Illustration 1).

La thrombose de la veine porte est due à différent facteurs : (i) à un envahissement de la veine porte par un processus néoplasique ; (ii) une compression extrinsèque de la veine porte et (iii) un évènement thrombotique.[4,5] . En raison d'étiologies et de traitements différents, les thromboses de la veine porte d'origine tumorale par invasion vasculaire ou compression externe ne seront pas étudiées

La TVP est également une complication fréquente de la cirrhose avec une prévalence variant entre 0.6% et 26% en fonction des séries. [6] Chez les patients avec cirrhose, la TVP est connue pour entrainer l'apparition ou l'aggravation des signes liés à l'hypertension portale : ascite et encéphalopathie. Cependant, en raison d'une histoire naturelle différente, avec en particulier une amélioration pouvant être spontanée et en raison d'un risque faible d'occlusion totale de la veine porte (17%)[7], les thromboses porte cirrhotiques ne seront pas abordées dans cette étude.

Dans le cadre de la thrombose porte non cirrhotique non tumorale, il existe, dans 60% à 70 % des cas, des facteurs pro-thrombotiques sous-jacents. Dans une récente étude étudiant le bénéfice d'un traitement anticoagulant au long cours chez les patients atteints de TVP, les facteurs de risques de thrombose étaient séparés en risque élevé (syndrome myéloprolifératif, syndrome des anti-phospholipides, mutations homozygotes ou hétérozygotes composites G20210A du facteur II ou G1691A du facteur V Leiden et antécédents personnels ou au premier degré de thrombose veineuse sans facteur déclenchant) et risque faible (mutations hétérozygotes G1691A facteur V Leiden ou G20210A du facteur II, défaut d'activité de l'antithrombine, déficit en protéine C et S en l'absence d'antécédent de thrombose et hyperhomocystéinémie).[8–10]

Outre les facteurs de risques systémiques de thrombose, il a également été décrit des facteurs de risque locaux de TVP : trauma abdominal, maladies inflammatoires chroniques intestinales, antécédent de chirurgie abdominale, infection intra abdominale, néoplasie intra abdominale sans contact avec la veine porte, pancréatites aiguës et chroniques.[11]

Manifestations

La TVP est, en Europe, la seconde cause d'hypertension portale (HTP). Ses principales manifestations cliniques sont la présence de voies de dérivation porto-systémique avec en premier lieu la présence de varices œsophagiennes.[12]

La présence d'un cavernome porte peut être à l'origine d'une biliopathie portale. Cette dernière correspond à l'apparition de sténoses des voies biliaires intra et extra hépatiques dues au développement des collatérales formant le cavernome et des éventuels phénomènes ischémiques associés. La biliopathie portale peut être de sévérité variable allant de perturbations asymptomatiques du bilan biologique (élévation des phosphatases alcalines et Gamma GT) à des tableaux d'angiocholite.[4] (Illustration 2).

Prise en charge

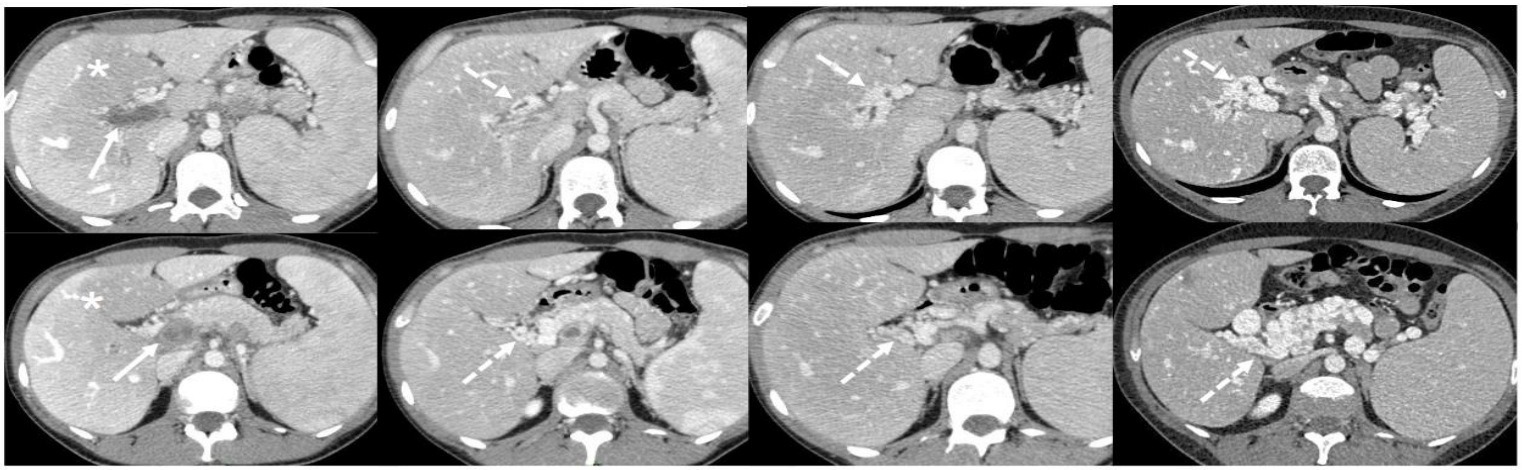
En raison de la présence fréquente d'un facteur de risque de thrombose, les recommandations actuelles sont en faveur d'une anticoagulation prolongée chez les patients avec une TVP et ce malgré le risque hémorragique lié à l'HTP.[13,14] Il a été montré dans une étude française multicentrique, contrôlée, que le maintien d'un traitement anticoagulant par Rivaroxaban chez les patients avec une TVP permet de prévenir le risque de re-thrombose avec un risque hémorragique acceptable. [8]

Les données disponibles semblent être en faveur de la prise en charge des manifestations de l'HTP dans le cadre de la TVP selon les mêmes modalités que dans la cirrhose.[15] Il est donc recommandé de proposer un traitement des varices œsophagiennes par beta bloquant non cardio sélectif ou ligature endoscopique en prévention primaire et par l'association des deux en prévention secondaire. Selon le même schéma que pour les patients atteints de cirrhose, la mise en place d'un shunt porto systémique trans-hépatique (TIPS) peut être une option thérapeutique dans le cadre d'hémorragie par rupture de varices œsophagienne non contrôlée avec un traitement endoscopique par ligatures.[11]

L'apparition d'ascite est rare dans le cadre de la TVP en raison d'un fonction hépatique conservée.[16]

Un traitement spécifique de la biliopathie portale doit être réservé aux formes symptomatiques : lithiase biliaire symptomatique ou angiocholite.[17]

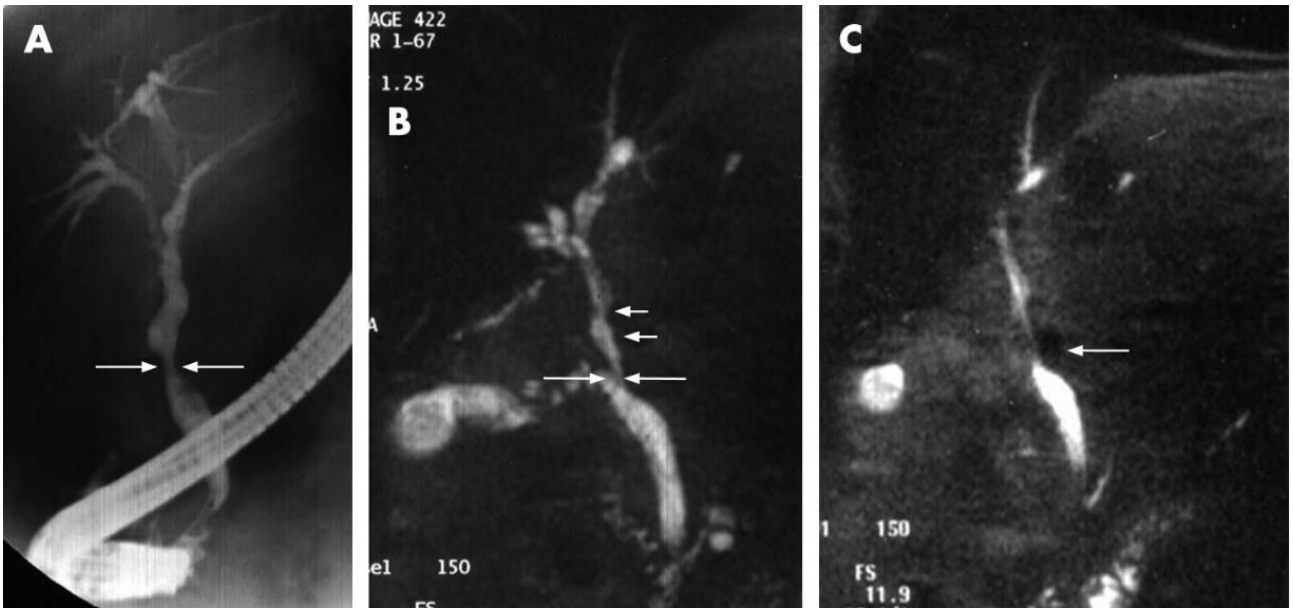
Illustration 1 : ***Exemple de formation d'un cavernome porte à la suite d'une TVP, images TDM en coupe axiale, au temps portal***.



A B C D

A : thrombose aiguë de la veine porte (flèche pleine) et troubles perfusionnels hépatiques associés (*)
B, C et D : apparition progressive au cours du temps d'un réseau de veines collatérales au sein du hile hépatique avec une extension progressive au pancréas (flèche pointillée)
Source : Management of splanchnic vein thrombosis, Elkrief et al. JHEP Reports, 2023

Illustration 2 : Biliopathie portale



A : Cholangiographie rétrograde endoscopique chez un patient avec un TVP mettant en évidence une sténose de la voie biliaire principale, secondaire au cavernome. (Flèche)
B : Même patient, séquence de Bili IRM montrant des sténoses de la voie biliaire principale (flèches longues). Les flèches courtes indiquent l'empreinte des voies de dérivation du cavernome sur la voie biliaire.
C : Bili IRM montrant l'association entre la sténose de la voie biliaire et la veine collatérale marquée par la flèche.

Source : Portal hypertensive biliopathy. Dhiman et al, Gut, 2007

Chirurgie abdominale et hypertension portale

Il est établi que les patients avec une cirrhose ont un risque majoré de morbi-mortalité après chirurgie.[18] Ce surrisque existe aussi bien dans le cas de chirurgie hépatique[19] ou extra hépatique.[20]

Dans une étude rétrospective incluant 8193 patients avec cirrhose opérés d'une chirurgie abdominale non hépatique, et en comparaison à un groupe contrôle sans cirrhose, la mortalité post opératoire était 4 fois supérieure chez les patients avec cirrhose. Dans cette même étude, les patients avec cirrhose avaient également un surrisque significatif de présenter une complication hémorragique ou infectieuse après chirurgie par rapport à des patients sans cirrhose.[20] Il a également été montré que la chirurgie abdominale chez des patients atteints de cirrhose est un facteur de risque d'apparition d'une décompensation de la cirrhose.[21]

Dans une série récente étudiant l'évolution après résection hépatique pour carcinome hépato-cellulaire (CHC) dans une population de 79 patients avec cirrhose et avec une hypertension portale dite significative (gradient porto-systémique > 10 mmHg), 28 (35 %) patients ont présenté une décompensation de la cirrhose en post-opératoire. L'apparition d'une ascite était la décompensation la plus fréquente, intéressant 25 patients. Dans cette même série, le gradient de pression porto-systémique était significativement associé au risque de décompensation post-opératoire de la cirrhose.[22]

Dans une étude rétrospective, multi centrique, il a été montré que chez les patients atteints de maladie vasculaire porto-systémique (MVPS), il existe également une morbi-mortalité accrue après chirurgie. Dans une étude rétrospective incluant 44 patients avec MVPS, la mortalité post opératoire à 6 mois était plus élevée que celle de la population générale (9% contre 3-12%). Dans cette même étude, il n'existait pas de différence significative entre les patients atteints de MVPS et de cirrhose.[23]

L'ensemble des données décrites ci-dessus montre une association entre l'hypertension portale et le risque de complication après chirurgie chez les patients atteints de cirrhose ou d'hypertension portale non cirrhotique. Dans le cadre des patients avec TVP, les données après chirurgie sont peu nombreuses et issues d'une seule cohorte de faible effectif.[24] L'objectif de notre étude est donc d'étudier l'évolution après chirurgie au sein d'une cohorte de patients avec TVP en comparaison à un groupe contrôle.

DEUXIEME PARTIE: ARTICLE ORIGINAL

Abdominal surgery in patient with EHPVO, a retrospective European multicentre case-control study

Introduction

Chronic non cirrhotic extra hepatic portal vein thrombosis (EHPVO) is defined as the chronic occlusion of the portal vein with or without extension to superior mesenteric vein and splenic vein. It is usually associated with the development of porto-portal collaterals leading to the formation of a portal cavernoma. [4,25,26] In Europe, EHPVO is considered a rare disease, with a prevalence ranging from 0.7 to 3.7 per 100 000 inhabitants.[1,2] However, it is considered the second leading cause of portal hypertension in Europe.[12] EHPVO usually refers to patients with portal vein thrombosis in the absence of underlying liver disease. However, PVT can also occur in patients with pre-existing portosinusoïdal vascular liver disease (PSVD).[27] EHPVO has been associated with local and/or general risk factors for thrombosis, found in 20% and 70% of the patients, respectively.[3] Patients with EHPVO may develop severe portal hypertension, but usually have preserved liver function.[28] Long-term anticoagulation has been generally recommended in patients with EHPVO[8,13], either using Vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs).

Patient with EHPVO may require abdominal surgery for indications related to EHPVO, such as the treatment of the underlying local risk factor (e.g. chronic pancreatitis or Crohn's disease). In addition, the indication for surgery may be unrelated to EHPVO. By contrast, bilio-enteric bypass surgery is usually not recommended for treatment of symptomatic portal biliopathy.[29] Portal hypertension has been associated with an increased morbidity and mortality after abdominal surgery, both in patients with cirrhosis but also in those with PSVD.[23,30] However, Both in patients with cirrhosis and PSVD, besides portal hypertension and its severity, post-operative morbidity and mortality are largely influenced by other factors, such as the degree of liver dysfunction [18,20,31,32], the type of surgery [18,33] and comorbidities. [20,31,34] In addition, despite the link between portal hypertension and post-operative outcome [35], studies evaluating portal decompression to facilitate abdominal surgery and improve outcome, reported controversial results. [23,36]

Data evaluating post-operative outcomes in patients with EHPVO is limited to single-centre, small sample, retrospective uncontrolled studies, mainly gathering children or adults undergoing surgery for treatment of portal biliopathy. [37–40] 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 so far in patients with EHPVO.

Therefore, the aim of the present study was to evaluate post-operative outcome in a large cohort of patients with EHPVO as compared to patients without EHPVO, with a special attention to bleeding.

Patients and Methods

Patients

Between January 2019 and February 2022, we contacted all the centres participating in the Vascular Liver Disease Interest Group (VALDIG) or the French network for vascular liver diseases (FILFOIE) 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 or diagnosed at the time of the surgery. Patients' identification was based on local databases. The study was approved by our institutional review board (CCER 2019-01254) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

We compared post-operative outcomes in patients with EHPVO with matched patients without EHPVO who had abdominal surgery. Cases (patients with EHPVO) and controls (patients without EHPVO) were matched (1:2) according to the type of surgical intervention, age at surgery (+/- 10 years), date of surgery (+/- 5 years) and centres. When one centre could not find controls without EHPVO, we tried to find control patients in the database of the Tours University Hospital, France (coordinating centre). We use the same matching criteria as previously mentioned except for the centre. Finally, two matched controls fulfilling the matching criteria could be found for 67/81 patients (Figure 1).

Definition

Diagnosis of EHPVO was based abdominal imaging (Doppler ultrasound and axial CT or MRI imaging using vascular contrast agent) showing complete obstruction of the main portal vein for at least 6 months and or portal cavernoma.[4,3,13] Cirrhosis was excluded either based on liver biopsy or the absence of morphological signs of cirrhosis (namely nodular liver surface and segment IV atrophy)[41] or by liver stiffness measurement <10 kPa.[42] Patients with recent PVT, incomplete occlusion of the main portal vein or isolated superior mesenteric vein or splenic vein thrombosis were excluded.

Causal factors for EHPVO were classified into the following categories : (a) general risk factors for thrombosis, including (i) inherited thrombophilia, e.g. factor V Leiden mutation, prothrombin gene mutation and (ii) acquired general risk factors for thrombosis, namely myeloproliferative neoplasms and other acquired disorders (e.g. antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria); (b) local risk factors: pancreatitis, inflammatory bowel diseases. [3,4,43] According to a recent study, patients with at least one of the following general risk factors for thrombosis were classified as a strong risk factor for thrombosis : myeloproliferative neoplasm, antiphospholipid syndrome, homozygous or composite heterozygous G20210A factor II or G1691A factor V mutations, and a personal or first-degree family history of unprovoked venous thrombosis.[8]

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 by either the presence of medium or large varices at endoscopy and/or history of bleeding or variceal band ligation and/or patient treated with non-selective beta blockers.

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)[44], clinical, laboratory, imaging and endoscopic features; (b) surgical data, including indication, type of surgery, planned or emergency procedure, laparoscopy or laparotomy. According to the results of a recent Delphi consensus, patients were not classified into major or minor surgeries. In fact, according to experts of European Surgical association, this classification needs to acknowledge the complexity of the procedure, its pathophysiological consequences, and consecutive clinical outcomes. A surgery can only be classified as “major” or

"minor" after the complete resolution of the surgical act and its follow-up. Since the aim of this study was to describe factors, pre-existing to surgical intervention, predictive of poor outcome after surgery hence did not use post-operative data for analysis.[45]

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 indication for surgery were not included.

Follow-up

Duration of follow-up was calculated from the date of surgery. Study endpoints were prespecified before data collection. (Supplementary Table 1) Postoperative complications were defined as any event occurring within 1 month after surgical intervention and categorized according to the Dindo-Clavien classification.[46] In addition, we paid a specific attention to bleeding complications, occurring either during or within 1 month after surgery. Portal hypertension–related complications were defined as any of the following: decompensation of ascites, hepatic encephalopathy, portal hypertension–related bleeding, within 3 months after surgical intervention. Decompensation of ascites was defined as follows: (1) in patients without ascites, onset of clinically detectable ascites, confirmed by ultrasonography; (2) in patients with previous ascites not requiring paracentesis, ascites requiring paracentesis within 3 months following surgery or requiring a TIPS. Postoperative death was defined as death occurring within 12 months after surgical intervention. Finally, an unfavorable outcome was defined as either 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.

Statistical analysis

Results are presented as median (interquartile range [IQR]) or absolute number (percentage).

Comparisons between quantitative variable were performed using the test of Mann Whitney for non-normally distributed variable. Comparison between categorical variables were performed using the Chi-squared test.

Univariate Cox regression analyses were performed to determine factors associated with postoperative complication grade ≥ 3 within 1 month after surgery, bleeding, portal hypertension–related complications within 3 months after surgery, death within 12 months after surgery, or unfavorable outcome after surgery. Factors included in the univariate analysis were prespecified based on their previous identification as prognostic factors in patients with portal hypertension (either cirrhosis or PVSD) undergoing abdominal surgery. These factors included age adjusted Charlson comorbidity index [34], strong risk factor for thrombosis [8], serum creatinine ≥ 100 µmol/L [20,23,34], serum bilirubin ≥ 50 µmol/L, platelet count < 150 G/L [18], history of ascites (previous ascites controlled with diuretic therapy at surgery or clinically detectable ascites at surgery), high-risk varices, the type of surgery (either cholecystectomy or wall surgery versus other) and emergency surgery. [31]

Although MELD and Child-Pugh scores are associated with post-operative outcome after abdominal surgery in patients with cirrhosis,[20,47] we deliberately chose not to insert MELD score rather than serum creatinine and bilirubin, since INR is typically normal in patient with EHPVO, and that a significant proportion of the patients were treated with vitamin K antagonists. In addition, 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 55/81 patients. Finally, we did not include high-risk varices, i.e. presence of medium or large varices at endoscopy and/or history of bleeding or variceal band ligation and/or patient

treated with non-selective beta blockers because endoscopic data was available in only 64/81 patients. Factors associated with bleeding complications included anticoagulant therapy or antiplatelet agents at surgery, platelet count, serum creatinine and serum bilirubin[18,48] Variables with a *P* value below 0.10 in univariate analysis were included in multivariate Cox regression analysis.

In order to evaluate the influence of portal decompression on postoperative outcome, we compared the occurrence of complications between patients who had and those who did not have a history of a portal decompression procedure, i.e., radiologic PVR with or without TIPS or surgical portosystemic shunt, performed before abdominal surgery.

Hazard ratios (HRs) for Cox logistic regression 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 and analysis were performed with SPSS 25 (SPSS Inc., Chicago, IL).

Results

Patients

Between November 2002 and December 2020, 95 surgeries were performed in 93 patients selected from 12 University tertiary centres participating either in VALDIG or FILFOIE network (Supplementary table 2). Twelve patients were excluded as shown on Figure 1. Finally, 81 patients were included in the study, one patient had 3 surgical interventions. The main characteristics of the 81 included patients are presented in the Table 1. Briefly, 46 (57%) patients were men with a median age of 53 (45-62). Twenty-six (32%) patients had overweight (Body Mass Index between 25 kg/m^2 and 30 kg/m^2) and 11 (13%) were obese (BMI > 30 kg/m^2)

A general risk factor for EHPVO was found in 35 (43 %) patients. Nine (11%) patients had an inherited thrombophilia, and 29 (36%) patients had an acquired general risk factor for thrombosis, among them, 27 (33%) patients had myeloproliferative neoplasm. Twenty-two (27%) had only general factor for EHPVO without local factor found. Thirty-five (43%) patients had a strong risk factor for thrombosis.

A local factor for EHPVO was found in 46 (57%) patients, the main causes being previous abdominal surgery and pancreatitis in 16 (20%) and 11 (14%) patients, respectively. Among them, 33 (41%) only had local factor for EHPVO without general factor found. Thirteen (16%) patients presented both local and general risk factor for thrombosis. Finally, no risk factor was found for 13 (16%) patients with EHPVO.

Fifty-five (68%) patients were treated by anticoagulation therapy and among them 53 (65%) were treated at full dose. Ten (12%) patients underwent surgery while still treated with anticoagulation therapy.

Seven (9%) patients were treated by antiplatelet agent with 6 (7%) patients treated with aspirin only and 1 (1%) patient treated with clopidogrel only.

Twenty-six (32%) patients had history of ascites, among whom 13 (16%) patients were treated with diuretics. Thirty-six (44%) patients were treated with non-selective beta-blockers. Among them, 21 (26%) patients received non-selective beta-blockers for primary or secondary prevention of variceal bleeding. Results of endoscopy performed before surgery were available in 64 (79%) patients. Endoscopic data are shown in Table 1. Thirty (37%) patients had high-risk varices. Imaging study performed before surgery showed a portal cavernoma in 72 (89%) patients. Eight (10%) patients had complete occlusion of the portal vein. Additionally, thrombosis extended to the superior mesenteric vein and/or the splenic vein was present in 23 (40%) and 30 (37%) patients, respectively.

Type of, and indications, for surgery are detailed on Table 2. Eighty (99%) patients underwent abdominal surgery. One patient had three surgical interventions: (i) cholecystectomy in 2009 (ii) treatment for post-surgery hernia in 2014 and (iii) treatment for umbilical hernia in 2016. The most common intervention included cholecystectomy, ileal and colorectal resection and abdominal walls surgery in 23 (28%), 16 (19%) and 14 (17%) patients respectively. Only 3 (4%) patients underwent urological surgery including one renal transplantation and two nephrectomies. There were 65 (78%) open and 18 (22%) laparoscopic surgeries. In 5 (6%) cases, laparoscopy was converted into open surgery. Seventeen (21%) intervention were emergency procedures, whereas 66 (80%) were planned intervention.

Post operative complications within one month after surgery

Thirty-six (44%) patients had at least one complication within one month after surgery. The detailed complications are presented in Table 3.

Eighteen (22%) patients had at least one grade ≥ 3 postoperative complications according to Dindo-Clavien classification (Supplementary Table 3). Among grade ≥ 3 postoperative complications according to Dindo-Clavien classification, infections were the most common, observed in 14 (17%) patients.

By Cox univariate regression analysis, factors associated with the development of at least one grade ≥ 3 complication according to Dindo-Clavien classification included serum bilirubin ≥ 50 µmol/L (HR [95% CI] 3.874 [1.210 – 12.048], p = 0.023) an emergency procedure (HR [95% CI] 2.852 [1.105 – 7.362], p = 0.03), and the type of surgery (cholecystectomy or wall surgery) (HR [95% CI] 0.124 [0.028 – 0.538], p = 0.005) (Table 4 and Figure 2). By Cox multivariate regression analysis, the only factor associated that remained significantly associated with a lower incidence of at least one grade ≥ 3 complication according to Dindo-Clavien classification was the type of surgery (cholecystectomy or wall surgery) (HR [95% CI] 0.097 [0.012 – 0.770], p = 0.027). (Table 4)

When we compared 67 patients with EHPVO undergoing 69 surgeries to 138 patients without, cumulative incidence of grade ≥ 3 complication according to Dindo-Clavien classification did not differ between patients with EHPVO and those without (20% vs 15%, p = 0.377) (Figure 3A).

Bleeding

Bleeding occurred in 24 (29%) patients. Eighteen (22%) patients had perioperative bleeding, among whom 17 (20%) needed transfusion. The median number of red blood cell unit was 2 (0-4). Five (6%) patients had post operative bleeding (intra-abdominal bleeding in 4 and

abdominal wall bleeding in 1). Finally, 5 (6%) patients had both perioperative and postoperative bleeding. Bleedings are detailed in Table 3. By Cox univariate regression analysis factors associated with at least one bleeding complication included serum creatinine ≥ 100 µmol/L (HR [95% CI] 2.993 [1.212 – 7.391], p = 0.017) and emergency procedure (HR [95% CI] 2.719 [1.171 – 6.313], p = 0.02). By Cox multivariate regression analysis, no factor remained significantly associated with bleeding complication. (Table 5 and Figure 4).

When we compared 67 patients with EHPVO undergoing 69 surgeries to 138 patients without, cumulative incidence of bleeding was significatively higher in patients with EHPVO and those without (29% vs 12%, p = 0.003) (Figure 3B).

Portal hypertension related complications

Fourteen portal hypertension related complication occurred in 13 (16%) patients. Ten (12%) had post operative ascites, of whom 9 (11%) were successfully treated with diuretics. The median interval between occurrence of ascites and its resolution was 11 (6-45) days. One patient who developed postoperative ascites presented a septic shock and died 12 days after surgery. Two (2%) patients developed hepatic encephalopathy with favorable outcome under medical therapy within 24 hours. Two (2%) patients had variceal bleeding. The interval between surgery and variceal bleeding was 5 and 11 days respectively. Both were successfully treated by endoscopic band ligation. By Cox univariate regression analysis, a strong risk factor for thrombosis and history of ascites was associated with the occurrence of portal hypertension related complication, although the association was not significant (Table 4 and Figure 5). As expected, no control patient without EHPVO developed portal-hypertension related complication. (Figure 3C).

Extension of thrombosis within 12 months after surgery occurred in 1 (1%) patient. Extension of thrombosis was fortuitously diagnosed at imaging, 42 days after surgery. In this patient, thrombosis extended to the intra hepatic portal vein branches, despite ongoing anticoagulant therapy.

Death within 12 months after surgery

Three (4%) patients died within 12 months after surgery, with an interval of 12, 38 et 77 days after surgery, respectively. The individual data of these 3 patients are presented in Table 6. All 3 patients were hospitalized in intensive care unit (ICU) with an interval of 23, 16 and 0 days after surgery, respectively and for a length of ICU stay of 54, 22, and 12 days. By Cox univariate regression analysis serum creatinine ≥ 100 µmol/L was the only factor significantly associated with death within 12 months after surgery (HR [95% CI] 12.592 [1.140 – 139], p=0.039). (Table 4 and Figure 6)

When we compared 67 patients with EHPVO undergoing 69 surgeries to 138 patients without, cumulative incidence of death did not significatively differ between patients with EHPVO and those without (4% vs 4%, p = 0.795) (Figure 3D).

Overall unfavorable outcome after surgery

Overall, 25 (31%) patients had an unfavorable outcome after surgery. By Cox univariate regression analysis, the type of intervention (cholecystectomy or wall surgery) was the only factor significantly associated with an unfavorable outcome after surgery (HR [95% CI] 0.259 [0.097 – 0.691], p = 0.007). (Table 4 and Figure 7). By Cox multivariate regression analysis, the type of surgery (cholecystectomy or wall surgery) remained significantly associated with the absence of an unfavorable outcome after surgery (HR [95% CI] 0.28 [0.104 – 0.751], p = 0.011). (Table 4)

When we compared 67 patients with EHPVO undergoing 69 surgeries to 138 patients without, the cumulative incidence of an unfavorable outcome after surgery was significantly higher in patients with EHPVO and in those without (31% vs 15%, p = 0.012) (Figure 3E).

Influence of portal decompression on post-operative outcome

Nine (11%) patients had portal decompression before surgery. The indication of portal decompression was preparation for surgery, portal hypertension related bleeding and treatment of portal biliopathy in 5 (6%), 2 (2%) and 1 (1%) patient, respectively. Two patients underwent surgical portal decompression with 1 superior mesenteric vein jump graft and 1 spleno-renal shunt. Seven patients underwent radiological portal decompression including 5 portal stents and 2 TIPS. (Figure 9)

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 72 patients who did not (Supplementary Table 4). One patient who had a TIPS before surgery presented a stent thrombosis before surgery. Post-operative outcomes did not differ between patients with previous PVR or portosystemic shunt and those without. When included in the multivariate Cox regression analysis, portal decompression was not associated neither with portal hypertension related complication (p = 0.983) nor with death within 12 months after surgery (p = 0.991).

Discussion

This study is the first to evaluate the outcome after abdominal surgery in a large cohort of European patients with non-cirrhotic EHPVO. We found a high rate of perioperative bleeding, post-operative complications and portal hypertension-related complications, which occurred in, 29% 21% and 16% patients, respectively. Finally, 3 (4%) patients died within 12 months after surgery. The present study has major strengths. First, thanks to the European and French VALDIG and FILFOIE collaborative networks, it is the largest cohort of European patients with EHPVO who underwent abdominal surgery reported so far. In addition, the controlled design of the study allowed us to analyse the influence of EHPVO on post-operative outcomes. Furthermore, control patients were matched according to the centre, to reduce centre-related bias. Importantly, the interpretation of the results must take into account the following limitations: (i) patients recruited in this study were followed in tertiary centers expert in the management of patients with vascular liver diseases; (ii) patients had mixed surgeries, and (iii) patients in whom surgery was not performed were not included. Thus, the present results may not be widely generalizable.

The first major finding of the present study is that mortality within 12 months after abdominal surgery was 4% in this cohort of patients with EHPVO. This is much lower than that observed in patients with intrahepatic portal hypertension from other causes undergoing abdominal surgery, namely cirrhosis and PSVD. In a recent study of 140 patients with compensated cirrhosis and portal hypertension undergoing surgery, one-year mortality was 19%.[21] In addition, in a recent VALDIG study gathering 44 patients with PSVD and portal hypertension, 6-month mortality after surgery was 9%.[23] These results favor that post-operative mortality is not only related to the degree of portal hypertension, but also to the severity of liver dysfunction and comorbidities. We should acknowledge that liver biopsy was not performed in the majority of the patients, therefore we cannot exclude that some patients with PSVD and superimposed PVT were falsely classified as EHPVO.[49]

The second major finding of the present study is that even performed in expert centres, surgery in patients with EHPVO remains a challenge. Although included patients had surgical interventions that are usually performed by laparoscopic approach (namely cholecystectomy, intestinal resection), open route was chosen in 78% patients. In addition, bleeding (either during or after surgical intervention) requiring transfusion occurred in 25% patients. Our results are in line with the 2 existing previous, single-center studies that described the surgical procedures in patients with EHPVO. In the first study, including 30 patients with EHPVO, 7/30 needed transfusion.[24] In the second study including 7 patients who had laparoscopic cholecystectomy, the median operative time was 170 minutes.[50] In addition, postoperative complications occurred in 43% of the patients (and grade ≥3 according to Dindo-Clavien classification in 22% of the patients). Due to the limited number of patients, we could not evaluate the center effect neither for the surgical approach nor for perioperative transfusion.

The third major finding is that portal hypertension related complications, mostly ascites, occurred in 16% of the patients. Again, it is much lower than incidence of portal hypertension related complications after surgery in either patients with cirrhosis or PSVD and portal hypertension.[22] Portal-hypertension related complications more frequently occurred in patients with history of ascites and a strong risk factor for thrombosis. This result echoes factors associated with portal hypertension related complications after surgery in patients with PSVD, namely history of ascites and extra-hepatic conditions associated with INCPH.[21,23,51] However, portal hypertension was usually transient, and resolutive either spontaneously or under medical therapy. This also confirms that ascites is uncommon in patients with EHPVO, and usually triggered by a precipitating factor.[16]

Portal decompression (either surgical or radiological) was not associated with improved post-operative outcomes. The indication of surgery or interventional radiology is usually considered in patients with complications of portal hypertension, mainly bleeding, or portal biliopathy.[52–

[54] No study has specifically evaluated portal decompression as a preparation for surgery in patients with noncirrhotic portal hypertension. In patients with cirrhosis, the experience of TIPS placement as a preparation surgery is limited to small, retrospective studies. [36,55] Although preoperative TIPS is associated with a lower incidence of decompensation after surgery, the impact on survival has not been demonstrated. Caution is needed when interpretating the results since only 9 patients had previous portal decompression, and only 5 as a preparation for surgery. However, with regard to the relatively low, and, moreover not severe, incidence of portal hypertension related complications, our results are not in favor of portal decompression before surgery in patients with EHPVO.

In conclusion, this study shows that patients with EHPVO are at higher risk of major postoperative and portal hypertension related complications after surgery. However, one year mortality was low and not higher than that of matched controlled patients. Surgical procedure is technically challenging. Despite the limitations due to the sample size and the retrospective design of the study, these results support that patients with EHPVO should be performed in expert centers.

Table 1: Main Characteristics of the 81 patients with EHPVO, at surgery

Characteristics	Patient with available data	Number (percentage) or Median (interquartile range)
Clinical Features		
Male gender	81	46 (57)
Age, years	81	53 (45-62)
Charlson comorbidity index	80	2 (1-4)
ASA score	79	2 (2-3)
BMI, kg/m^2	70	24.5 (21-28)
History of ascites	81	26 (32)
Usual treatment before surgery		
Anticoagulation therapy	81	55 (68)
Heparin		27 (33)
Vitamin K antagonist		26 (32)
DOACs		2 (3)
Low dose	55	2 (3)
Full dose	55	53 (65)
Antiplatelet agent	81	7 (9)
Aspirin	81	6 (7)
Clopidogrel	81	1 (1)
Diuretic therapy	81	13 (16)
Beta-blockers	81	36 (44)
For varices treatment	81	21 (26)
Causes of chronic liver disease ¤		
Alcohol	80	13 (16)
Hepatitis B	79	0
Hepatitis C	79	0
Metabolic syndrome	79	6 (7)
Diabetes mellitus	79	10 (12)
Causes of cavernoma		
At least one local factor	81	46 (57)
Abdominal surgery		16 (20)
Pancreatitis §		11 (14)
Infectious disease		7 (9)
Inflammatory disease and tumor		6 (7)
Trauma		3 (4)
Multiple causes		3 (4)
At least one general factor *	79	35 (43)
Inherited thrombophilia	78	9 (11)
Factor V Leiden G1691A mutations		6 (7)
Factor II G20210A mutation		2 (3)
Antithrombin deficiency		1 (1)
Protein S deficiency		2 (3)
Protein C deficiency		1 (1)
Personal or first-degree history of thrombosis	77	10 (12)
Acquired risk factor for thrombosis	75	29 (36)
Myeloproliferative neoplasm	72	27 (33)
Antiphospholipid syndrome	73	1 (1)
Acquired protein S deficiency in HIV infection	1	1 (1)
Strong risk factor for thrombosis	**81**	**35 (43)**

Characteristics	Patient with available data	Number (percentage) or Median (interquartile range)
Laboratory Data		
Haemoglobin, g/dL	80	12.4 (11-14)
Leucocyte count x 10^9/L	78	7.1 (5-12)
Platelet count x 10^9/L	79	180 (120-318)
Prothrombin index, %	76	74 (54-91)
AST, IU/L	71	29 (22-41)
ALT, IU/L	72	29 (18-49)
ALK, IU/L	71	108 (78-172)
GGT, IU/L	74	74 (37-143)
Serum bilirubin, µmol/L	69	13 (8-27)
Serum creatinine, µmol/L	79	73 (56-88)
Serum albumin, g/L	55	37 (33-41)
Endoscopic data at surgery	64	
Gastro-oesophageal varices		
Absent		18 (22)
Small varices		25 (31)
Large varices		21 (26)
High risk varices ‡		30 (37)
Imaging data		
Main portal vein	81	
Complete occlusion		8 (10)
Cavernoma		72 (89)
Portal stent		1 (1)
Superior mesenteric vein	74	
Patent		42 (52)
Partial occlusion		11 (14)
Complete occlusion		13 (16)
Cavernoma		8 (10)
Splenic vein	70	
Patent		39 (48)
Partial occlusion		13 (16)
Complete occlusion		15 (19)
Cavernoma		2 (3)
Spleen size, cm	54	15 (13-17)
Ascites	80	
Minimal		16 (20)
Moderate or abundant		7 (9)
Portosystemic collaterals at imaging	76	53 (65)

Abbreviations : BMI : body mass index ; DOACs : Direct Oral Anticoagulation ; AST : aspartate aminotransferase ; ALT : alanine aminotransferase ; ALK : alkaline phosphatase ; GGT : gamma glutamyl transferase ; IU : International Unit

¤ Some patients can present multiple factors of chronic liver disease.

§ Both acute and chronic pancreatitis

* Some patients can present multiple general risks factors for thrombosis.

‡ High-risk varices were defined by varices medium or large at endoscopic, history of bleeding or history of variceal band ligation or beta-blockers

Table 2: Details of the 83 surgeries performed on 81 patients

	Number
Type of surgery	
Cholecystectomy	23
Ileal and Colorectal surgery *	16
Ileal resection	11
Colic resection	3
Appendicectomy	1
Rectal surgery	1
Abdominal walls surgery	14
Inguinal hernia repair	6
Umbilical hernia repair	4
Incisional hernia repair	4
Bilio-enteric bypass	8
Surgical exploration	7
Liver resection	5
Splenectomy	4
Pancreaticoduodenectomy	3
Urologic surgery	3
Open surgery	65 (78)
Laparoscopic surgery	18 (22)
Planned surgery	66 (80)
Emergency surgery	17 (21)

¤ For 4 (5%) surgeries the main goal was oncologic treatment.

Table 3: Details on 55 complications that occurred in 36 patients and 28 bleedings that occurred in 24 patients within 1 month after surgery

Surgical complications	**Number (percentage) or Median (interquartile range)**
Overall postoperative complications	
At least one complication	36 (43)
At least one grade ≥ 3 complication	18 (21)
Most severe complications by patient according to Dindo-Clavien classification	
Grade I	7 (8)
Grade II	11 (13)
Grade IIIa	3 (4)
Grade IIIb	7 (8)
Grade IVa	4 (5)
Grade IVb	1 (1)
Grade V	3 (4)
Detailed complications	
Infection	**25**
No etiology founded	11
Intra-abdominal infection	8
Abdominal wall infection	2
Lung	2
Infectious cholangitis	2
Acute renal failure	**5**
Abdominal complications	**13**
Ileus	5
Cutaneous wound dehiscence	4
Fistula/Leak	2
Constipation	1
Short bowel syndrome	1
Cardiopulmonary	**5**
Dyspnea	2
Hight Blood pressure	1
Pneumothorax	1
Arythmia	1
Anemia	2
Pain	2
Jugular thrombosis	1
Urinary retention	1
Decompensation of diabetes	1

Bleeding	**28**
Per-operative bleeding	18
At least on transfusion	20
Red blood cell transfusion	17
Platelet concentrate transfusion	7
Fresh frozen plasma	5
Post-operative bleeding	10
Operative site bleeding	8
Abdominal wall bleeding	2

Table 4: Univariate and multivariate Cox regression evaluating prespecified factors before surgery associated with occurrence of major endpoint after surgery

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
At least one grade 3 or more complication within one month after surgery						
Age adjusted Charlson comorbidity index ≥ 3	1,461	0,577 - 3,702	0,424			
Strong risk factor for thrombosis	0,79	0,306 - 2,038	0,626			
Serum bilirubin ≥ 50 µmol/L	**3,874**	**1,210 - 12,048**	**0,023**	3,339	0,899 - 12,406	0,072
Serum creatinine ≥ 100 µmol/L	2,789	0,992 - 7,838	0,052	1,055	0,282 - 3,942	0,937
History of ascites	1,68	0,663 - 4,257	0,274			
High risk varices	1,383	0,422 - 4,533	0,593			
Emergency procedure	**2,852**	**1,105 - 7,362**	**0,03**	0,989	0,278 - 3,519	0,987
Cholecystectomy or abdominal wall surgery	**0,124**	**0,028 - 0,538**	**0,005**	**0,097**	**0,012 - 0,770**	**0,027**
Portal hypertension related complication						
Age adjusted Charlson comorbidity index ≥ 3	1,552	0,522 - 4,619	0,429			
Strong risk factor for thrombosis	3,081	0,948 - 10,011	0,061	2,671	0,805 - 8,863	0,108
Serum bilirubin ≥ 50 µmol/L	2,981	0,805 - 11,039	0,102			
Serum creatinine ≥ 100 µmol/L	1,847	0,508 - 6,712	0,351			
History of ascites	2,549	0,856 - 7,592	0,093	2,113	0,696 - 6,415	0,187
High risk varices	1,958	0,573 - 6,690	0,284			
Emergency procedure	1,839	0,566 - 5,974	0,311			
Cholecystectomy or abdominal wall surgery	0,531	0,164 - 1,725	0,292			

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Death within 12 months after surgery						
Age adjusted Charlson comorbidity index ≥ 3	144	0,005 - 3812854	0,338			
Strong risk factor for thrombosis	0,628	0,057 - 6,931	0,704			
Serum bilirubin ≥ 50 µmol/L	8,285	0,517 - 132	0,135			
Serum creatinine ≥ 100 µmol/L	**12,592**	**1,140 - 139**	**0,039**	7,201	0,503 - 103	0,146
History of ascites	4,077	0,370 - 44,96	0,251			
High risk varices	1,08	0,068 - 17,26	0,957			
Emergency procedure	8,264	0,749 - 91	0,085	3,601	0,251 - 51,6	0,346
Cholecystectomy or abdominal wall surgery	0,628	0,057 - 6,931	0,704			
Unfavorable outcome after surgery						
Age adjusted Charlson comorbidity index ≥ 3	1,924	0,892 - 4,151	0,095			
Strong risk factor for thrombosis	1,304	0,604 - 2,814	0,499			
Serum bilirubin ≥ 50 µmol/L	2,197	0,737 - 6,544	0,158			
Serum creatinine ≥ 100 µmol/L	1,668	0,628 - 4,429	0,304			
History of ascites	**2,277**	**1,055 - 4,917**	**0,036**	1,786	0,810 - 3,937	0,151
High risk varices	1,462	0,577 - 3,706	0,424			
Emergency procedure	1,648	0,692 - 3,923	0,259			
Cholecystectomy or abdominal wall surgery	**0,308**	**0,123 - 0,768**	**0,012**	**0,28**	**0,104 - 0,751**	**0,011**

Bold indicate significant association

Table 5: Univariate and multivariate Cox regression analysis evaluating prespecified factors before surgery associated with bleeding

	Univariate Cox analysis			**Multivariate cox analysis**			**Multivariate Cox analysis with portal decompression**		
	HR	95% IC	p	HR	95% IC	p	HR	95% IC	p
Bleeding									
Serum bilirubin ≥ 50 µmol/L	0,414	0,055 - 3,104	0,391						
Serum creatinine ≥ 100 µmol/L	**2,947**	**1,204 - 7,216**	**0,018**	2,163	0,811 - 5,767	0,123	2,533	0,912 - 7,034	0,074
Platelet count < 150 G/L	1,509	0,666 - 3,420	0,325						
History of high-risk varices	2,264	0,849 - 6,040	0,103						
Emergency procedure	**2,66**	**1,158 - 6,110**	**0,021**	2,177	0,864 - 5,482	0,099	2,2	0,874 - 5,540	0,094
Cholecystectomy or abdominal wall surgery	0,591	0,253 - 1,382	0,225						
Surgery performed under anticoagulation therapy	0,619	0,146 - 2,634	0,516						

Bold indicate significant association

Table 6: Characteristics of the 3 patients who died within 12 months after surgery

	Patient 2	Patient 33	Patient 36
Characteristics at surgery			
Age, years	69	79	77
Gender	Female	Male	Female
Age adjust Charlson comorbidity index	4	10	7
Details of medical history	(1) Non metastatic ampullar tumor	(1) Moderate liver disease (2)Diabetes mellitus without organ damage (3)Connective tissue disease	(1) Moderate liver disease (2) Cerebrovascular disease
ASA score	2	4	4
Previous abdominal surgery	Yes	Yes	Yes
Details	Cholecystectomy	Cholecystectomy	Hysterectomy
	Appendicectomy	Splenectomy	
	Hysterectomy	Abdominal collection drainage	
Anticoagulation therapy	Yes	No	Yes
Details	Vitamin K antagonist		Heparin therapy
Laboratory Data			
Serum creatinine, µmol/L	77	238	228
Serum bilirubin, µmol/L		21	321
Platelet, G/L	179	318	191
Prothrombin index, %	39	44	31
Surgery			
Surgical intervention	Pancreaticoduodenectomy	Ileal resection	Cholecystectomy
Indication	Ampullary tumor	Acute peritonitis on perforation on diverticulitis	Acute cholecystis with peritonitis
Emergency procedure	No	Yes	Yes
Open surgery	Yes	Yes	Yes
Per-operative bleeding	No	Yes	Yes
Post operative complication in 30 days after surgery	Hyperosmolar coma	Acute renal failure	Abdominal bleeding
	Septic shock	Anemia	Acute renal failure
		Abdominal leakage with peritonitis	Intra-abdominal candidiasis
		Jugular thrombosis	Septic encephalopathy
Portal hypertension related complication	No	No	Yes
Details			Ascites treated by diuretics
			Variceal bleeding treated by endoscopic ligatures
Interval between surgery and death, days	77	38	12
Cause of death	Haemorrhagic shock on anastomotic ulcer	Intra-abdominal bleeding	Septic shock

Figure 1: Flow chart

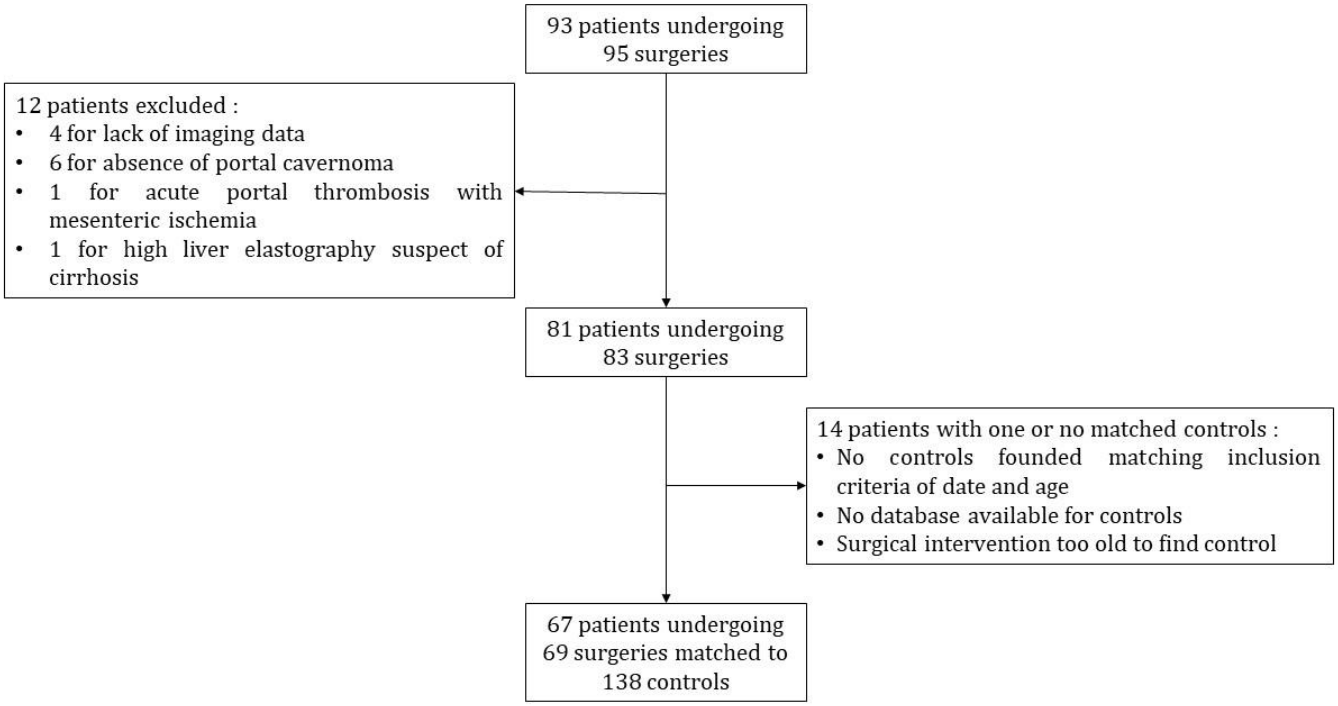
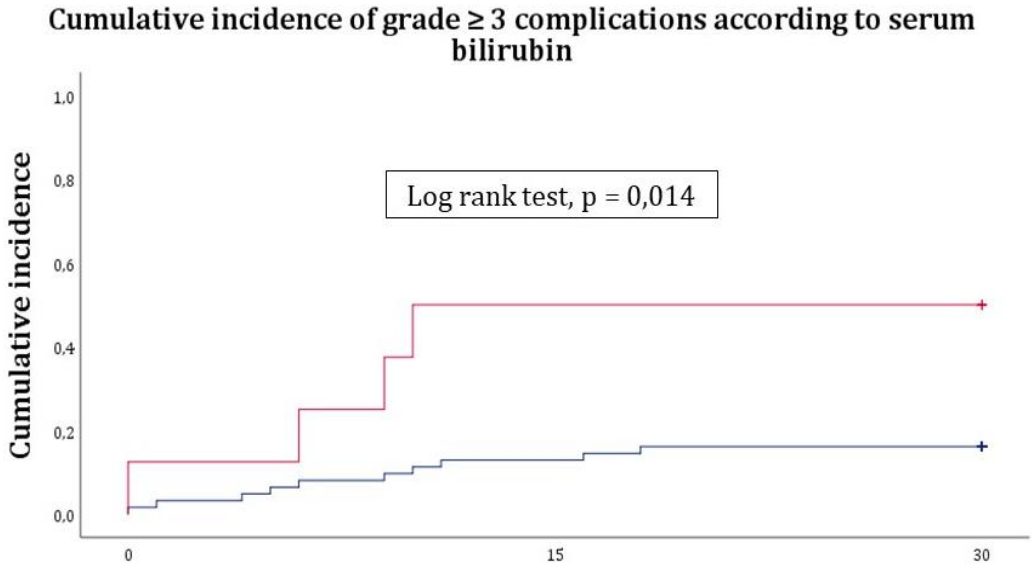


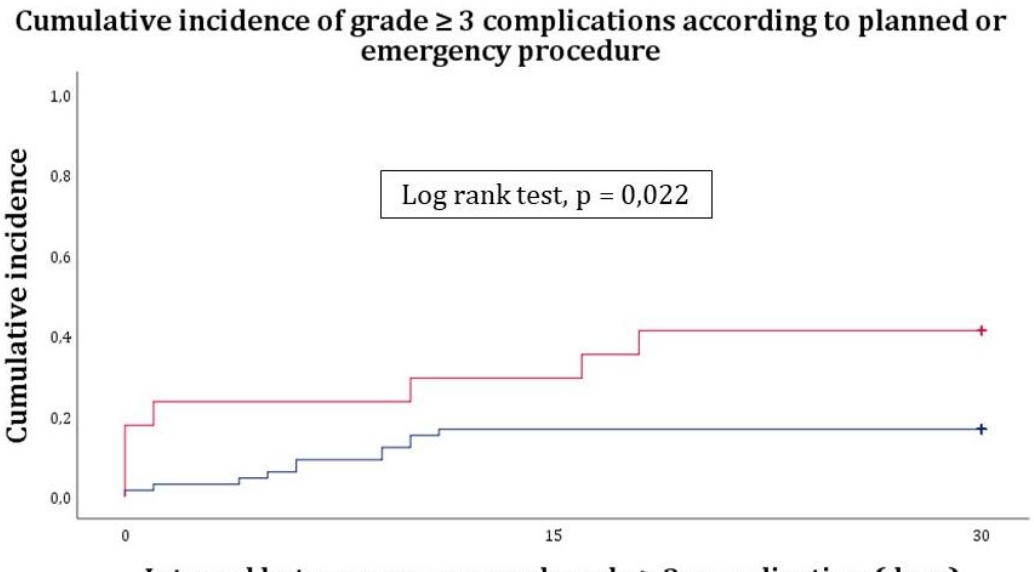
Figure 2: Cumulative incidence of at least on grade ≥ 3 complication according to Dindo-Clavien according to (A) serum bilirubin (B) emergency procedure and (C) type of intervention

A



No. at risk			
Bilirubin < 50 µmol/L	62	54	52
Bilirubin ≥ 50 µmol/L	8	4	4

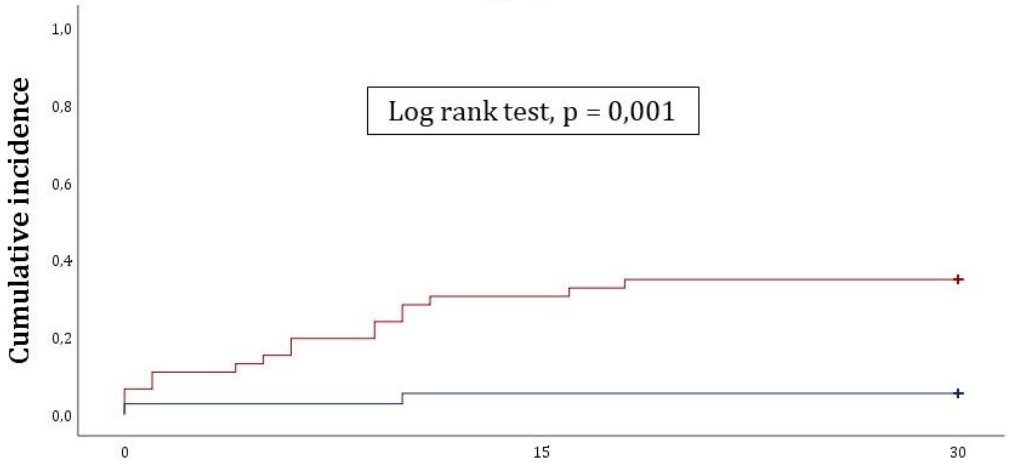
B



No. at risk			
Planned surgeries	66	55	55
Emergency surgeries	17	12	10

C

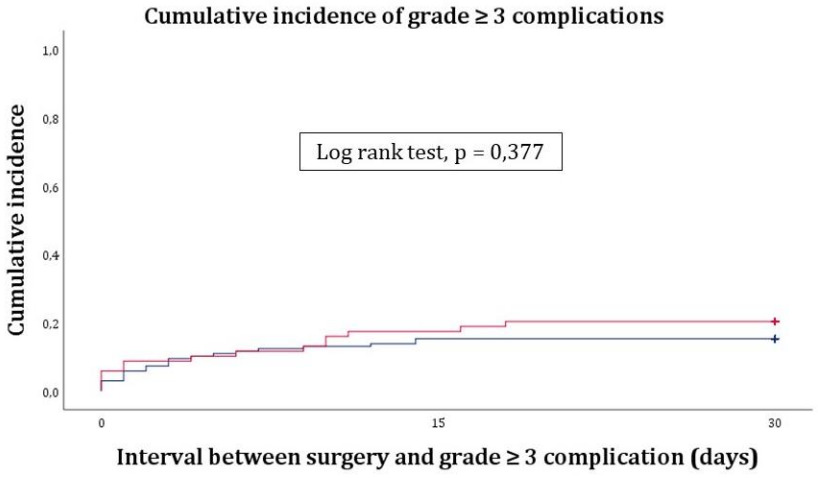
Cumulative incidence of grade ≥ 3 complications according to the type of surgery



No. at risk	Interval between surgery and grade ≥ 3 complication (days)		
Cholecystectomy and wall surgeries	37	35	35
Other surgeries	46	32	30

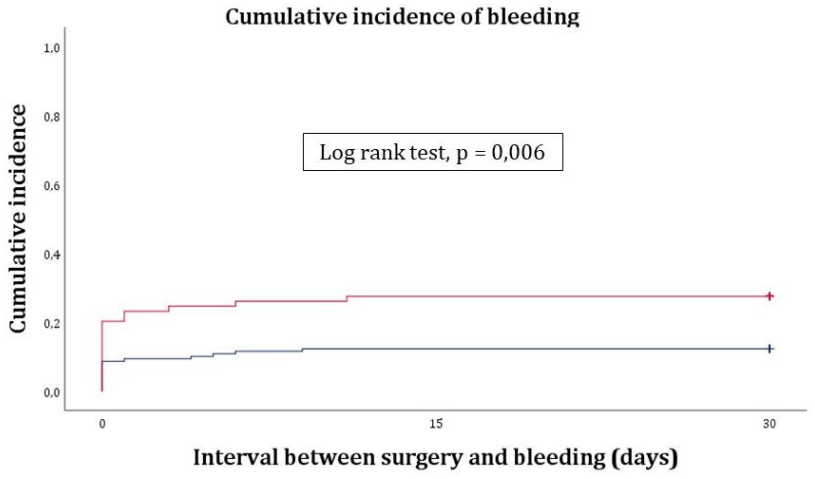
Figure 3: Comparison of cumulative patients with EHPVO, to control without, on post operative outcomes.

A



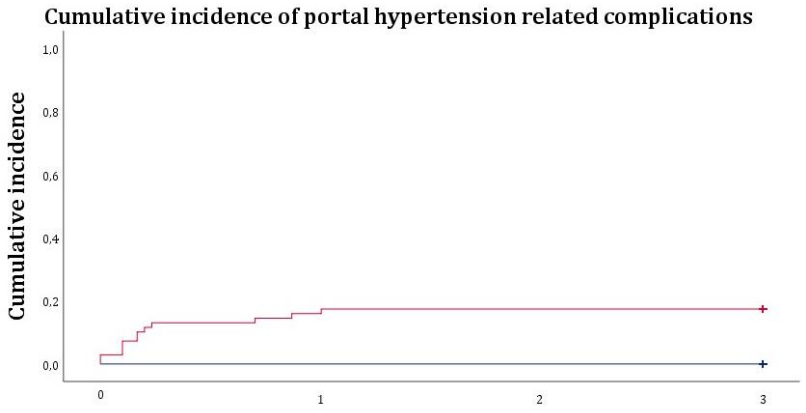
No. at risk			
Controls	138	117	117
EHPVO	69	57	55

B



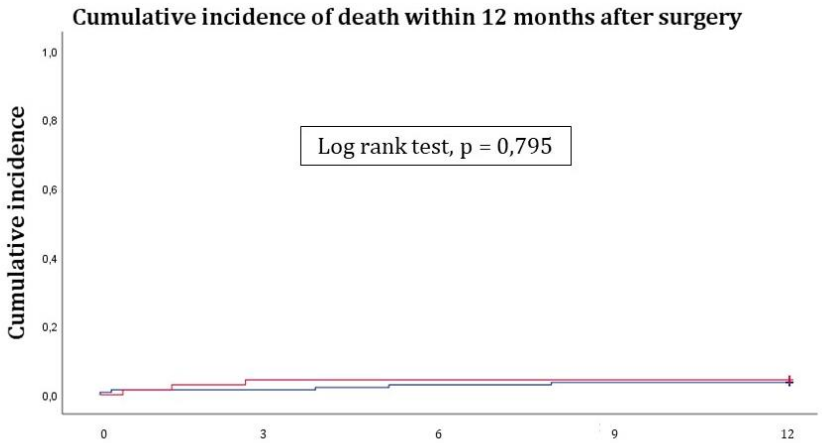
No. at risk			
Controls	138	121	121
EHPVO	69	50	50

C



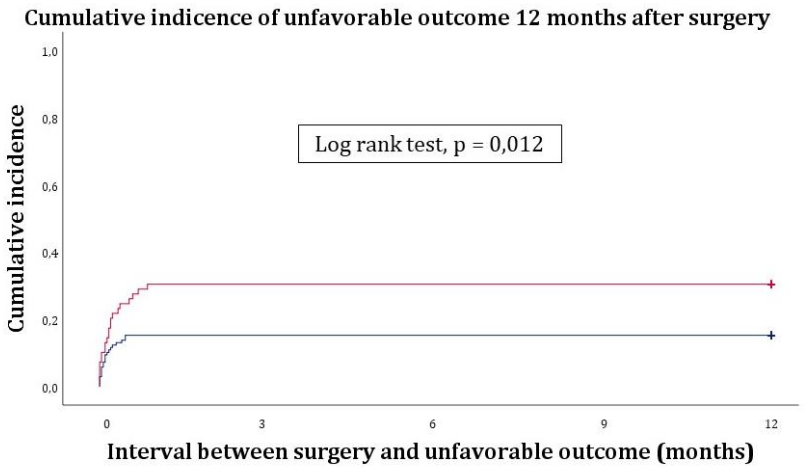
No. at risk				
Controls	138	138	138	138
EHPVO	68	58	57	57

D



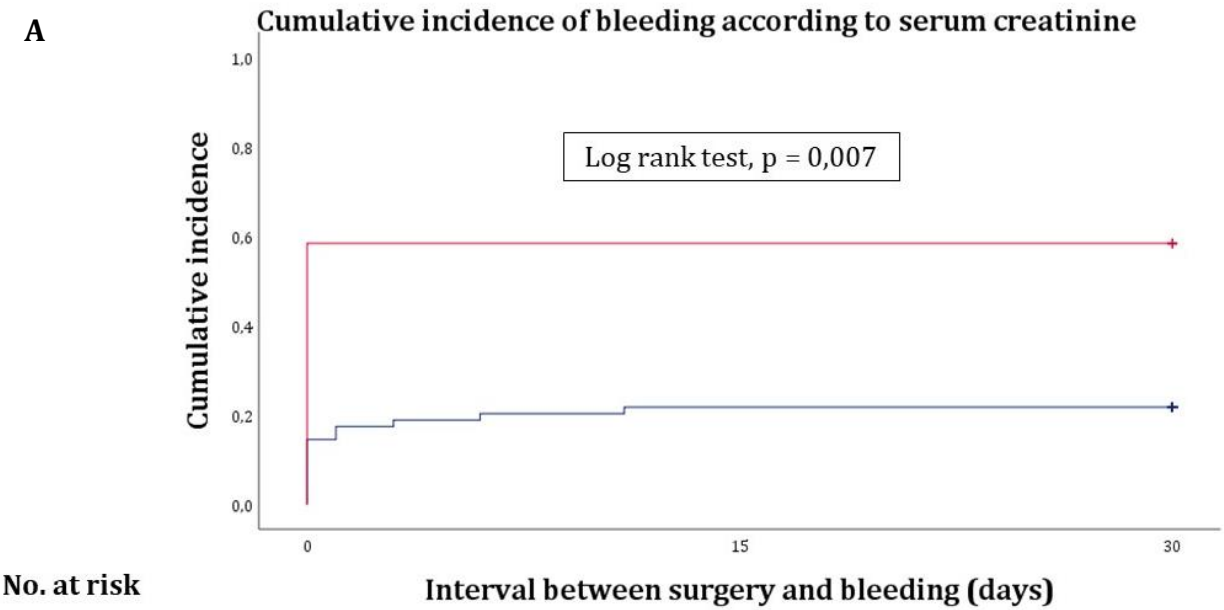
No. at risk					
Controls	138	136	134	133	133
EHPVO	69	66	66	66	66

E

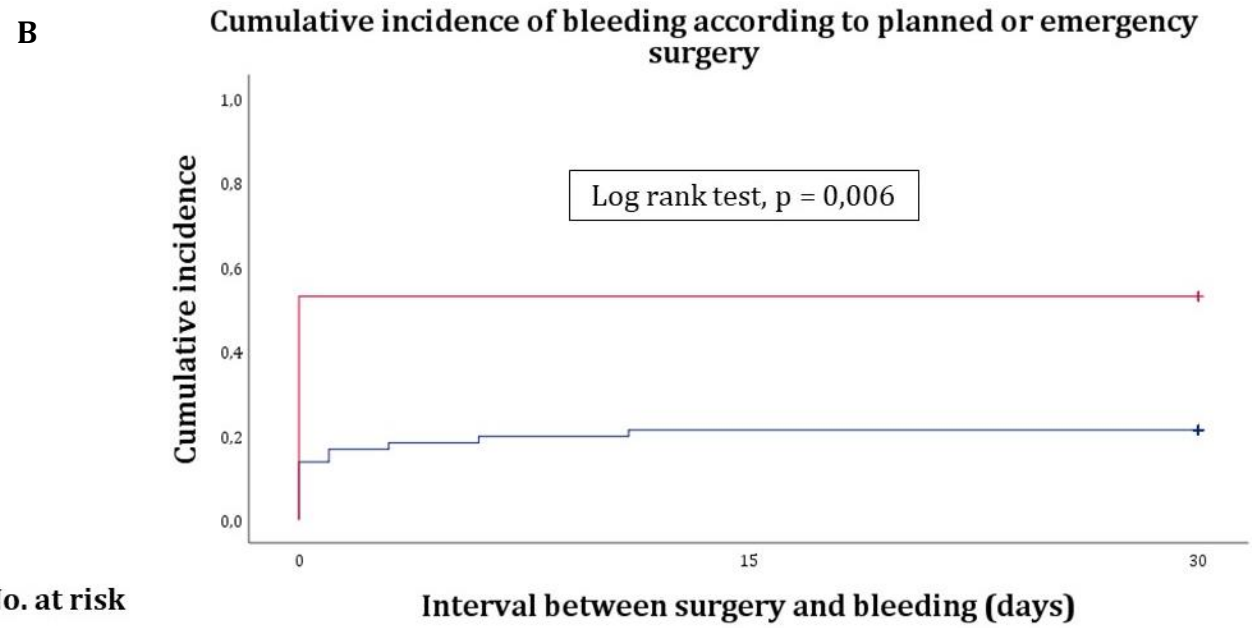


No. at risk					
Controls	138	117	117	117	117
EHPVO	69	48	48	48	48

Figure 4: Cumulative incidence of bleeding according to (A) serum creatinine and (B) emergency procedure



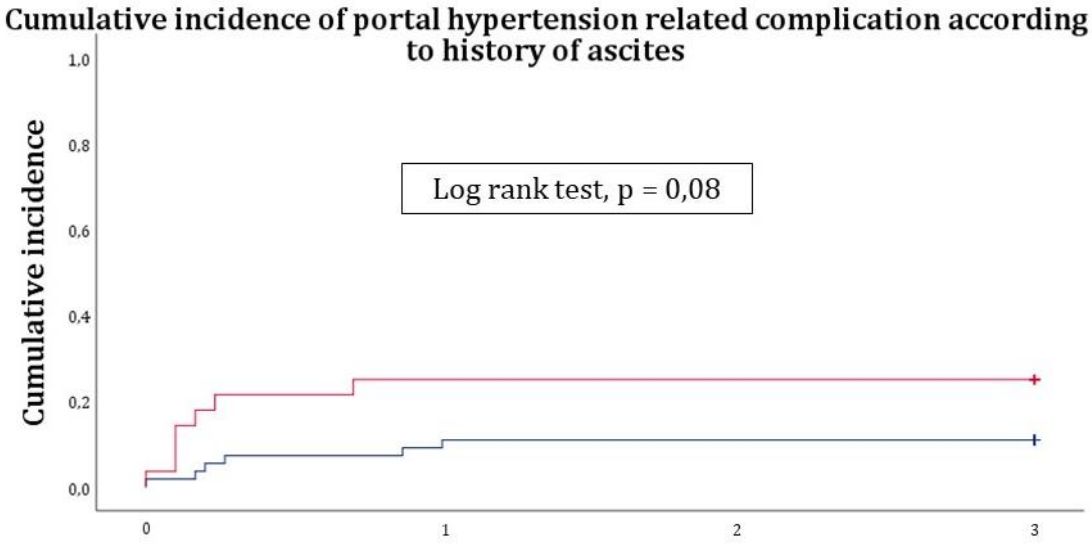
No. at risk			
Creatinine < 100 µmol/L	69	54	54
Creatinine ≥ 100 µmol/L	12	5	5



No. at risk			
Planned surgeries	66	52	52
Emergency surgeries	17	8	8

Figure 5: Cumulative incidence of portal hypertension related complications according to (A) history of ascites and (B) presence of strong risk factor for thrombosis

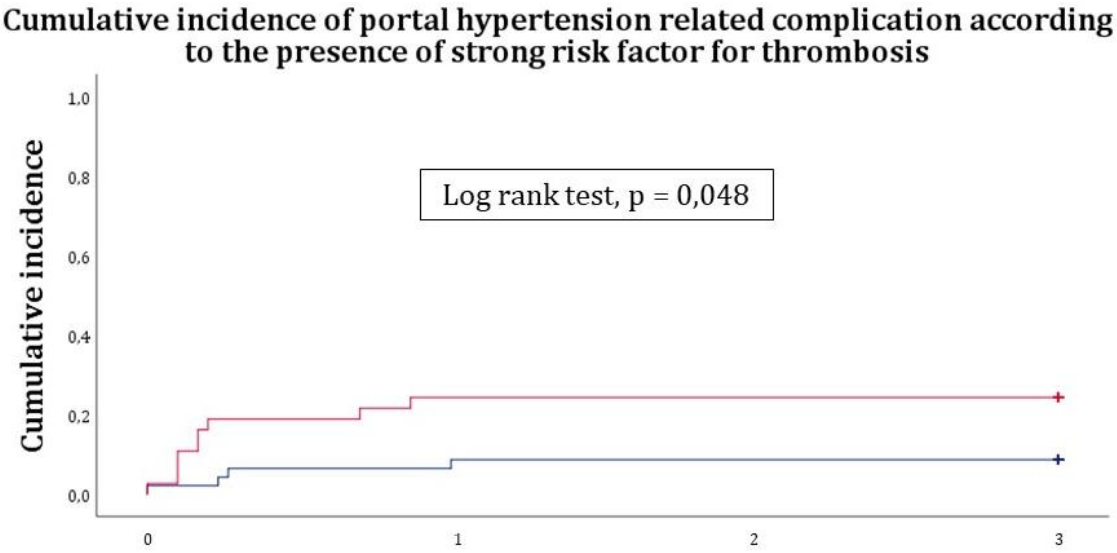
A



No. at risk

No history of ascites	55	50	49	49
History of ascites	28	21	21	21

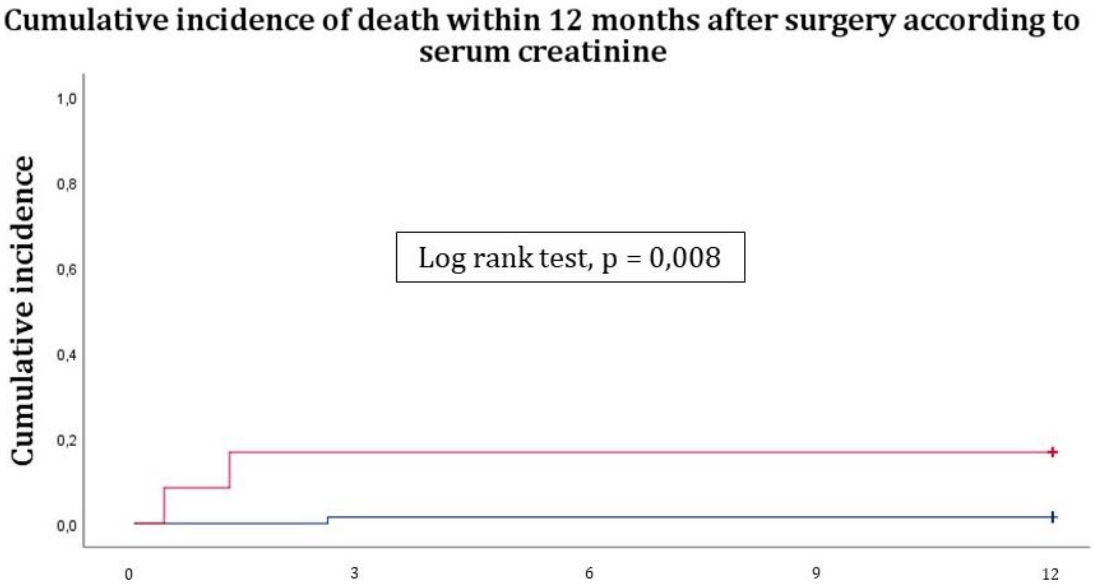
B



No. at risk

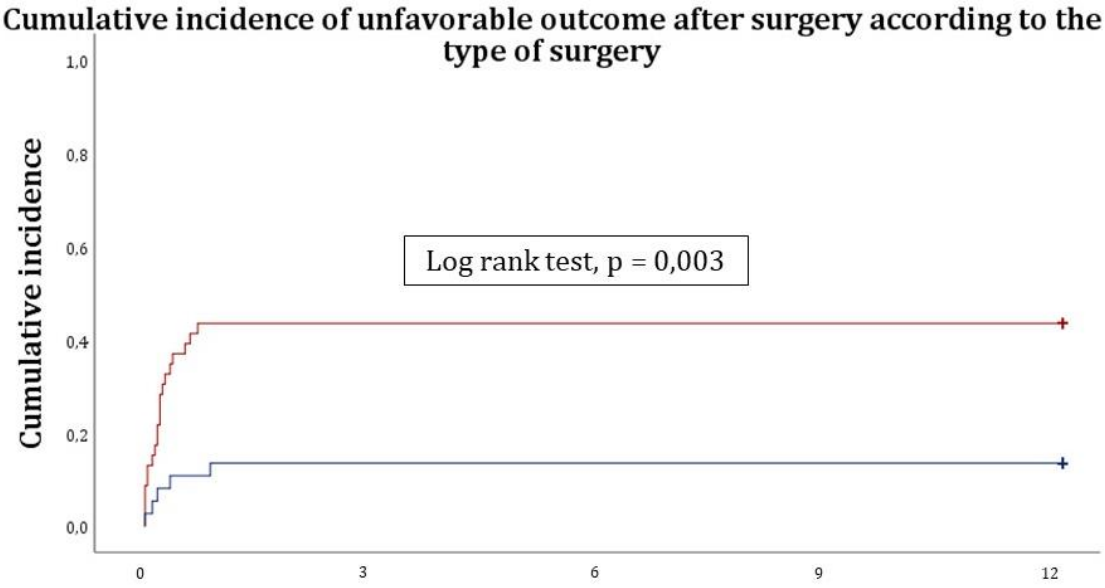
Other risk factor	46	43	42	42
Strong risk factor for thrombosis	37	28	28	28

Figure 6: Cumulative incidence of death within 12 months after surgery according to serum creatinine



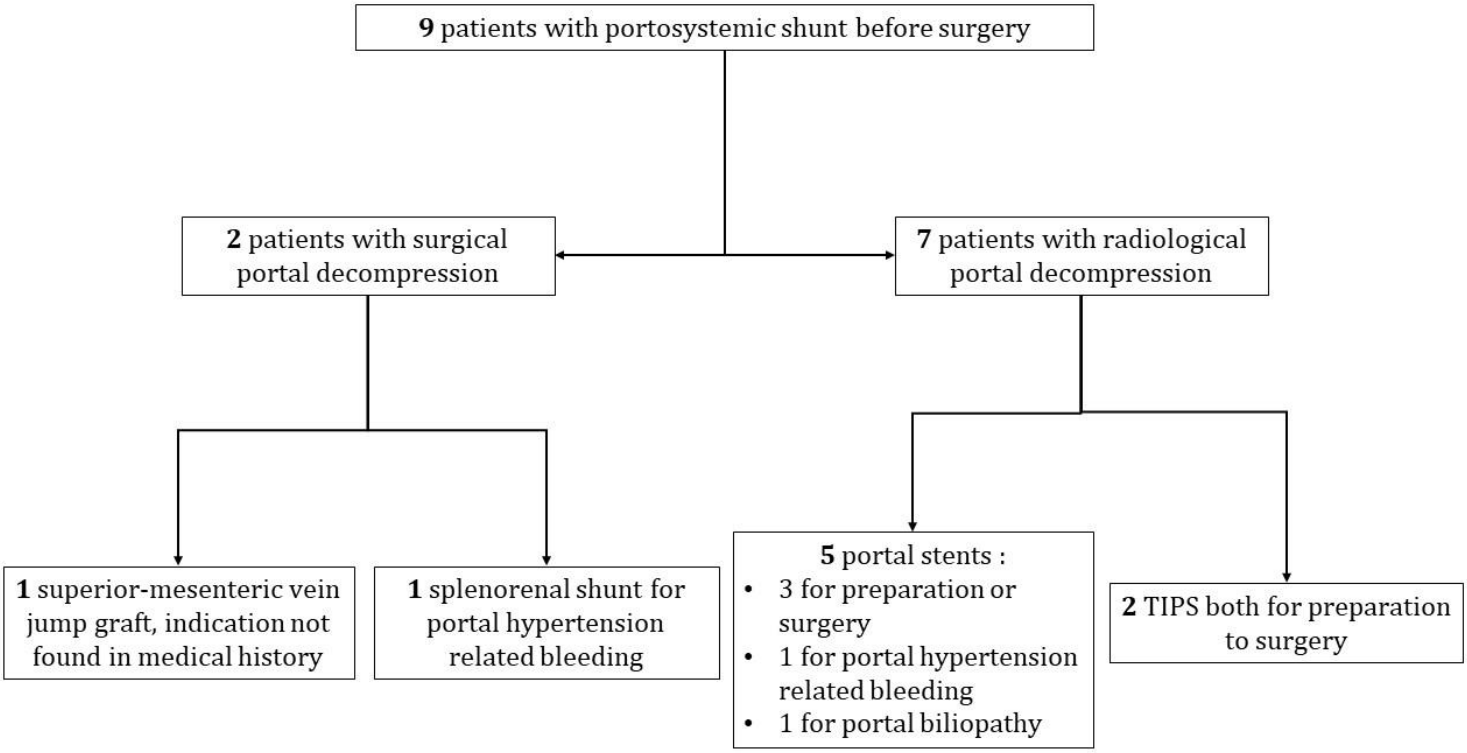
No. at risk					
Creatinine <100 µmol/L	69	68	68	68	68
Creatinine ≥ 100 µmol/L	12	10	10	10	10

Figure 7: Cumulative incidence of unfavorable outcome after surgery according to the type of surgery.



No. at risk					
Cholecystectomy or abdominal wall surgery	37	32	32	32	32
Other surgery	46	26	26	26	26

Figure 8: Detailed of portal decompression before surgery



Abbreviation: TIPS, Transjugular Intrahepatic Portosystemic Shunt

Supplementary data

Supplementary Table 1: Criteria a priori chosen to classify post-operative complications

Post operative complication : complication occurring one month after surgery.	
Post operative complication	Any deviation from the normal postoperative course except portal hypertension related complications : - Decompensation of ascites - Hepatic encephalopathy - Bleeding from gastroesophageal varices
Post operative bleeding	Any bleeding event including per-operative bleeding within 1 month after surgery, except portal hypertension related bleeding.
Classification of post-operative complications according to Dindo-Clavien	Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications Grade III: Requiring surgical, endoscopic or radiological intervention : - Grade IIIa: Intervention not under general anesthesia - Grade IIIb: Intervention under general anesthesia Grade IV: Life-threatening complication (including central nervous system complications) requiring intensive care unit management - Grade IVa: Single organ dysfunction (including dialysis) - Grade IVb: Multiorgan dysfunction Grade V: Death
Portal hypertension related complication within 1 month after surgery	
Decompensation of ascites	In patients without ascites: onset of clinically detectable ascites, confirmed by ultrasonography In patients with previous ascites not requiring paracentesis: ascites requiring two or more paracentesis within 3 months following surgery, or requiring a transjugular intrahepatic portosystemic shunt (TIPS)
Hepatic encephalopathy	Based on West-Haven classification - mild (grade I-II) - severe (grade III-IV)
Variceal bleeding	Any hematemesis or melena in a patient who, on endoscopy, had active bleeding from oesophageal or gastric varices or signs of recent bleeding. Information collected on the necessity of TIPS for variceal bleeding treatment.

Supplementary Table 2: List of inclusion centres and number of patients included

Hospital center	Number of patients with EHPVO	Number of controls without EHPVO
Centre Hospitalier Universitaire de Tours (coordinating center), France	10	36
Hôpital Beaujon, Clichy, France	19	16
Hospital Clinic, Barcelona, Spain	14	24
Universitätsklinikum Bonn, Spain	12	18
Hôpitaux universitaires de Genève, Switzerland	5	10
CHU de Caen, France	5	10
Hôpital Edouard Herriot, Lyon, France	4	8
Vall d'Hebron University Hospital, Barcelona, Spain	4	6
Hôpital universitaire Ramon y Cajal, Madrid, Spain	3	6
Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland	3	0
CHU de Montpellier, France	1	2
Gent university hospital, Gent, Belgium	1	2

Supplementary Table 3: Details on 37 postoperative complications grade ≥ 3 according to Dindo Clavien classification that occurred in 18 patients within 1 month after surgery

Postoperative complication grade ≥ 3 according to Dindo Clavien classification	Number
Infection	14
No etiology founded	4
Intra-abdominal infection	6
Abdominal wall infection	2
Lung	1
Infectious cholangitis	1
Bleeding	
Post-operative bleeding	7
Operative site bleeding	7
Abdominal wall bleeding	0
Acute renal failure	5
Abdominal complications	6
Ileus	1
Cutaneous wound dehiscence	2
Fistula/Leak	2
Short bowel syndrome	1
Cardiopulmonary	0
Anemia	1
Pain	1
Jugular thrombosis	1
Urinary retention	1
Decompensation of diabetes	1

Supplementary Table 4: Comparison of postoperative outcome in patients with portal vein recanalization (PVR) or portosystemic shunt to patients without.

Surgical complications	**Patient with PVR or portosystemic shunt N = 9**	**Patient without PVR or portosystemic shunt N = 72**	**p**
Overall postoperative complications			
At least one complication	4 (44)	32 (44)	0,999
At least one grade ≥ 3 complication*	2 (22)	16 (22)	0,999
Most severe complications according to Dindo Clavien classification			
Grade I	1 (11)	6 (8)	
Grade II	1 (11)	10 (14)	
Grade IIIa	0	3 (4)	
Grade IIIb	1 (11)	6 (8)	
Grade IVa	0	4 (6)	
Grade IVb	1 (11)	0	
Grade V	0	3 (4)	
Major outcome after surgery			
At least one grade 3 or more complication within one month after surgery	2 (22)	16 (22)	0,999
Portal hypertension related complication	0	14 (19)	0,146
Death within 12 months after surgery	0	3 (4)	0,533
Unfavorable outcome after surgery	2 (22)	24 (33)	0,501
Bleeding events	4 (44)	20 (28)	0,302

Abbreviation : PVR, Portal vein recanalization

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Vu, le Directeur de Thèse

Vu, le Doyen
De la Faculté de Médecine de Tours
Tours, le

Denécheau-Girard Corentin

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Résumé : La thrombose de la veine porte (TVP) chronique non cirrhotique est une maladie rare. La principale manifestation de la TVP non cirrhotique est l'hypertension portale (HTP). La fonction hépatique est généralement conservée. L'évolution après chirurgie abdominale chez les malades atteints d'une thrombose porte chronique non cirrhotique n'a jamais été évaluée. L'objectif de cette étude était d'évaluer l'évolution après chirurgie abdominale dans une large cohorte de malades atteints de TVP chronique non cirrhotique. *Patients et méthode* : étude rétrospective, multicentrique, européenne comportant 81 malades atteints de TVP (âge 53 ans, 57% d'hommes) ayant eu une intervention chirurgicale entre novembre 2002 et décembre 2020. *Résultats* : une complication post-opératoire sévère (grade ≥3 selon Dindo-Clavien), une complication de l'HTP, ou un décès survenaient dans les 30 jours, 3 mois ou 1 an suivant la chirurgie chez 18 (22%), 23 (28%) et 3(4%) patients, respectivement. L'insuffisance rénale (créatinine > 100 µmol/L) prédisait le décès à 1 an. Finalement, 26 (30%) patients ont présenté une évolution défavorable (au moins une complication ou décès). En analyse univariée, les facteurs associés à une évolution défavorable étaient l'antécédent d'ascite et le type d'intervention. *Conclusion :* chez les malades atteints TVP chronique non cirrhotique, le pronostic après chirurgie abdominale est acceptable, surtout en l'absence, d'ascite ou d'insuffisance rénale avant la chirurgie.

Mots clés : Hypertension portale, cavernome porte, maladies vasculaires du foie

Jury :

Président du Jury : Professeur Ephrem SALAME

Directrice de thèse : Docteur Laure ELKRIEF
Membres du Jury : Docteur Nicolas TABCHOURI
Docteur Louis d'ALTEROCHE

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