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TITLE PAGE

Abdominal surgery in patients with idiopathic noncirrhotic portal hypertension: a multicenter retrospective study

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FOOTNOTE PAGE

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List of abbreviations:

ASA, American Society of Anesthesiology; CI, Confidence Interval; HR, Hazard ratio ratio; HIV, Human Immunodeficiency virus; INCPH, Idiopathic noncirrhotic portal hypertension; IQR, interquartile range; PVT, Portal Vein Thrombosis TIPSS, Transjugular Intrahepatic portosystemic shunt;

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Abstract

In patients with idiopathic noncirrhotic portal hypertension (INCPH), data on morbi-mortality of abdominal surgery are scarce We retrospectively analyzed the charts of patients with INCPH undergoing abdominal surgery within the VALDIG network. Forty-four patients with biopsy-proven INCPH were included. Twenty-five (57%) patients had ≥1 extrahepatic conditions related with INCPH and 16 (36%) had a history of ascites. Forty-five procedures were performed, including 30 minor and 15 major. Nine (20%) patients had ≥1 Dindo-Clavien grade ≥3 complication within 1 month after surgery. Sixteen (33%) patients had ≥1

portal hypertension related complication within 3 months after surgery. Extrahepatic conditions related with INCPH (p=0.03) and history of ascites (p=0.02) were associated with portal hypertension related complications within 3 months after surgery. Splenectomy was associated with development of portal vein thrombosis after surgery (p=0.01). Four (9%) patients died within 6 months after surgery. Six-month cumulative risk of death was higher in patients with serum creatinine ≥100 μmol/L at surgery (33%, *vs.* 0%, p<0.001). An unfavorable outcome (*i.e.* either liver or surgical complication or death) occurred in 22 (50%) patients and was associated with presence of extra-hepatic conditions related with INCPH, history of ascites and serum creatinine ≥100 μmol/L: Five percent of the patients with none of these features had an unfavorable outcome, *vs.* 32% and 64% when one or ≥ 2 features were present, respectively. Portal decompression procedures prior to surgery (n=10) were not associated with post-operative outcome. **Conclusion**. Patients with INCPH are at high-risk of major surgical and portal hypertension related complications when they harbor extrahepatic conditions related with INCPH, history of ascites or increased serum creatinine.

Idiopathic noncirrhotic portal hypertension (INCPH) is a heterogeneous group of rare diseases causing portal hypertension and characterized by the absence of cirrhotic modification of the liver parenchyma and the patency of portal and hepatic veins. In Europe, INCPH accounts for less than 2% of the indications for liver biopsies (1,2). Liver histological lesions found in patients with INCPH include obliterative portal venopathy, hepatoportal sclerosis, nodular regenerative hyperplasia and incomplete septal cirrhosis (3). INCPH has been associated with various conditions including thrombophilia, hematologic malignancies, human immunodeficiency virus (HIV) infection, genetic and immunological disorders (4,5). Patients with INCPH may develop portal hypertension related complications, but usually have preserved liver function.

Patients with chronic liver diseases may require abdominal surgery for indications related to their liver disease (*e.g.* splenectomy or parietal surgery), or unrelated. Most available data on the risk of surgery in patients with liver disease pertains to cirrhosis, where post-operative morbidity and mortality are influenced by liver dysfunction and degree of portal hypertension (6–9), type of surgery (10,11) and comorbidities (9). Given the link between portal hypertension and post-operative outcome (11), portal decompression has been proposed to facilitate abdominal surgery and improve outcome, although reported results are contrasted (12–17).

Experience regarding abdominal surgery in patients with INCPH is mostly limited to portosystemic shunt and/or splenectomy performed in adults or children from Eastern countries (5,18–20). The present study thus aimed at evaluating the outcome of patients with INCPH undergoing abdominal surgery and at assessing the impact of preoperative portal decompression procedures.

Patients and Methods

Patients

Between April 2017 and November 2017, we contacted all the centers participating in the Vascular Liver Disease Interest Group (VALDIG) or the French network for vascular liver diseases to retrospectively identify all patients with INCPH having had ≥1 abdominal surgery. Surgeries were considered only if INCPH 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 2017-01219) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Definitions

Diagnosis of INCPH was based on the criteria proposed by the VALDIG group, after exclusion of cirrhosis (Supplementary Table 1). Histologic diagnosis of INCPH was confirmed by pathologists experts in liver diseases. Patients with portal vein thrombosis were included in this study if this thrombosis occurred after INCPH diagnosis. Patients with chemotherapy-induced non-cirrhotic portal hypertension, and/or who underwent liver resection for colorectal liver metastasis were not included, since the main liver lesion in these patients is sinusoidal obstruction syndrome, *i.e.* a distinct entity from INCPH (21).

Date of diagnosis of INCPH was the date the first liver biopsy demonstrating the absence of cirrhosis while signs of portal hypertension were already present, as detailed in supplementary Table 1. According to the previous reports, extra-hepatic conditions associated with INCPH were classified into the following categories (22–25): immunological disorders (autoimmune conditions, common variable immune deficiency, history of solid organ transplantation, Crohn's disease, human immunodeficiency virus infection), recurrent abdominal infections, medication or toxins, prothrombotic state (myeloproliferative syndrome, heterozygous factor II or V Leiden, or familial history of venous thromboembolism), genetic disorders.

The following data were collected at surgery: (a) clinical features before surgery, including age, gender, American Society of Anesthesiology (ASA) class (26), 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 (27); the age-adjusted Charlson comorbidity index assigns an additional point for each decade of life after 50 years of age), clinical, laboratory, imaging and endoscopic features; (b) surgical data, including indication, type of surgery, planned or emergency procedure, laparoscopy or laparotomy. Major surgery was defined as laparotomy with operative intervention on a visceral organ (9). History of ascites was defined as a previous ascites that was controlled with diuretics at the time of surgery, or clinically

detectable ascites at surgery. Portal decompression intervention before surgery included TIPSS 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. End-points were pre-specified before data collection (Supplementary Table 2). Postoperative complications were defined as any event occurring within one month after surgical intervention, and was categorized according Dindo-Clavien classification. (28). Portal hypertension-related complications were defined as any of decompensation ascites, hepatic encephalopathy, significant portal hypertension related bleeding (29), acute kidney injury, or spontaneous bacterial peritonitis occurring within 3 months after surgical intervention (Supplementary Table 2). 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 two or more paracenteses within 3 months following surgery, or requiring a TIPSS. Post-operative death was defined as death occurring within 6 months after surgical intervention. Finally, an unfavorable outcome was defined either post-operative grade ≥3 complication according to Dindo-Clavien classification within one month after surgery, or portal-hypertension related complications within 3 months after surgery, or death within 6 months after surgery.

In order to evaluate the influence of portal decompression on post-operative outcome, we compared the occurrence of complications between patients who had or not a history of portal decompression procedure, *i.e.* TIPSS placement or surgical portosystemic shunt, performed before abdominal surgery.

Controls

We compared 6-month post-operative cumulative risk of death in patients with INCPH with that of patients with cirrhosis who had abdominal surgery, selected from a recently published cohort (17). Two patients with cirrhosis were matched with one patient with INCPH according to the presence of ascites at surgery (i.e either clinically detectable ascites before TIPS placement or history of ascites at the time of surgery (*i.e.* previous ascites controlled with diuretic therapy at surgery, or clinically detectable ascites at surgery).

We also compared 3-year liver transplantation-free survival of patients with INCPH who had abdominal surgery, *i.e.* patients from the present cohort, with that of patients with INCPH who did not undergo abdominal surgery, prospectively included between January 2011 and June 2018 at the liver hemodynamic unit at Beaujon Hospital (Clichy, France). Diagnosis of INCPH was based on the criteria proposed by the VALDIG group, after exclusion of cirrhosis (Supplementary Table 1). Among the 101 patients meeting these criteria, 7 were excluded because they were referred to the liver hemodynamic unit for evaluation before liver transplantation, 9 because follow-up data were not available, and 3 because they were already included in the present study.

Statistical analysis

Results are presented as median (interquartile range (IQR)) or absolute number (percentage). Comparisons between quantitative variables were performed using the T test or Mann-Whitney test for normally and non-normally distributed variables, respectively. Shapiro–Wilk test was used to determine whether or not the distribution of continuous variable was normal. Comparisons between categorical variables were performed using the Chi-square or Fisher exact test, when appropriate. Univariate Cox regression analyses were performed to determine factors associated with post-operative complication grade ≥3 within one month after surgery, portal-hypertension related complications within 3 months after

surgery, death within 6 months after surgery or unfavorable outcome after surgery. Factors included in the univariate analysis were pre-specified based on their previous identification as prognostic factors in patients with cirrhosis undergoing surgery and/or in patients with INCPH. These factors included age-adjusted Charlson comorbidity index (30), extrahepatic condition associated with INCPH (23–25), history of ascites at the time of surgery (*i.e.* previous ascites controlled with diuretic therapy at surgery, or clinically detectable ascites at surgery) (23–25,31), varices needing treatment (*i.e.* medium/large esophageal and/or gastric varices or history of variceal bleeding or history of endoscopic band ligation and/or glue) (11,31), portal vein thrombosis at surgery (22), serum bilirubin at surgery (8,9,31,32), serum creatinine at surgery (8,9,24,31,33), major surgery (9,10), and emergency procedures (6–8,32). Although MELD and Child-Pugh scores are known to be associated with post-operative outcome after abdominal surgery in patients with cirrhosis (9,32,33), we deliberately chose not to insert these scores, but rather serum creatinine and bilirubin, since 6 patients were treated with vitamin K antagonists and since serum albumin concentration was available in only 34/44 patients. We did not analyze HVPG because HVPG is not a good reflection of portal hypertension in patients with INCPH (25,34).

In order to assess the influence of portal decompression on postoperative outcome, we performed additional analyses including portal decompression in the Cox regression analysis. Hazard ratio (HR) for Cox logistic regression were provided with their 95% confidence interval (CI). Cumulative risk of 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 21.0 (SPSS Inc, Chicago, IL, USA).

Results

Patients' characteristics at surgery

Between 2002 and 2017, 45 surgical interventions were performed in 44 patients from 10 centers participating in the VALDIG network or the French network for vascular liver disease (Supplementary Table 4). Their characteristics at the time of surgery are presented in Table 1. INCPH was diagnosed at the time of surgery in 8 (18%) patients. In the 36 other patients, median time between INCPH diagnosis and surgery was 26 (6-50) months. Prevalence of signs of portal hypertension at INCPH diagnosis, namely ascites and gastroesophageal varices, was similar between the 8 patients in whom INCPH was diagnosed at surgery and the 36 patients with known INCPH at surgery (data not shown). At least one extra-hepatic condition associated with INCPH was present in 25 (57%) patients, including 23 with either immunological disorder or HIV infection. Fourteen (32%) had 2 or more conditions. Age-adjusted Charlson comorbidity index was ≥3 in 35 (80%) patients, indicating that significant comorbidities were common. Liver function was preserved in the majority of the patients, since 32 (73%) patients had serum bilirubin ≤ 34 μmol/L, 32 (73%) had INR < 1.5, none had hepatic encephalopathy and only 7 (16%) patients had clinically detectable ascites, including 2 (5%) with tense ascites at surgery (Table 1). Eleven (25%) patients had serum creatinine ≥100 μmol/L before surgery. HVPG was measured in 28 (64%) patients. Median (IQR) HVPG was 9 (6-15) mm Hg.

Sixteen (36%) patients were treated with anticoagulants before surgery, including low molecular weight heparin (n=7), non-fractioned heparin (n=1), fondaparinux (n=1), rivaroxaban (n=1) and vitamin K antagonists (n=6). Among these 16 patients, anticoagulation was stopped before surgical intervention in 8 patients. Thus, 8 (18%) patients were still treated with anticoagulation therapy at the date of surgery. Seven (16%) patients were treated with antiplatelet agents before surgery, including aspirin (n=6) and clopidogrel (n=1). Among these 7 patients, antiplatelet agents had been stopped before

surgical intervention in 2 patients. Thus, 5 (11%) patients were still treated with antiplatelet agents at the date of surgery.

Type of, and indications for abdominal surgery are detailed in Table 2. One patient underwent 2 different operations (emergency surgery for perforated gastric ulcer suture, followed by elective abdominoplasty, 2 years later). There were 15 (33%) major and 30 (67%) minor interventions (including 12 laparoscopic surgeries). Eleven interventions (24%) were emergency surgeries, whereas the 34 (76%) remaining were planned interventions. Among the 7 patients with elevated serum creatinine concentration (*i.e.* serum creatinine ≥100 µmol/L) and a history of ascites at surgery, 3 had major surgery and 2 others had surgery in emergency (Supplementary Table 5). In the peri-operative period, red blood cells and platelets were transfused in 11 (24%) and 8 (18%) patients, respectively.

Post-operative complications within 1 month after surgery

According to the Dindo-Clavien classification, 61 post-operative complications occurred in 31 (70%) patients within 1 month after surgery (Table 3). In median, 2 (1.0-3.0) complications occurred per patient. In 9 (20%) patients, post-operative complications were classified as grade ≥3 or more according to the Dindo-Clavien classification.

Ten (22%) patients developed post-operative bleeding, including 4 classified as grade ≥3 according to the Dindo-Clavien classification. Three patients required an intervention (surgical or radiological), and 2 required transfusion of red blood cells and/or platelet units (Supplementary Table 6). Antiplatelet agents at surgery (3/10 (30%) *vs.* 2/35 (6%), p=0.03), as well as anticoagulation (5/10 (50%) *vs.* 3/35 (9%), p=0.003) were the only factors associated with post-operative bleeding among those tested, as indicated in Table 1. Platelet count at surgery was similar in patients with or without post-operative bleeding (p=0.6).

Nineteen post-operative infections occurred in 15 (33%) patients, including only one classified as grade ≥3 according to Dindo-Clavien classification. No patient developed post-operative liver failure.

As shown in Table 4, none of the pre-specified factors were significantly associated with the development of at least one grade ≥3 complications according to the Dindo-Clavien classification.

Portal hypertension related complications within 3 months after surgery

Twenty-seven portal hypertension related complications occurred in 16 (36%) patients within 3 months after surgery. Median time between surgery and occurrence of such complications was 6 (1-17) days. Decompensation of ascites, occurring in 12 (26%) patients, was the most frequent of such complications. In two patients, a TIPSS was placed for refractory ascites, 5.9 and 7.5 months after surgery, respectively. Hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis and acute kidney injury occurred in 3 (7%), 2 (4%), 3 (7%) and 7 (16%) patients, respectively. One patient had TIPSS placement for refractory variceal bleeding 14 days after surgery. Resolution of portal hypertension related complication occurred in 15 out of the 16 patients, after 26 (10-59) days. One patient died 5.7 months after surgery (Patient 7, Table 5). Length of hospital stay was significantly longer in patients who developed portal hypertension related complications than in those who did not (30 (6-45) days *vs.* 6 (3-16) days, p=0.002).

Factors associated with the occurrence of at least one portal hypertension related complication included a history of ascites and extra-hepatic conditions associated with INCPH. Serum creatinine at surgery was not associated with the occurrence of at least one portal hypertension related complication (Table 4).

Portal vein thrombosis after surgery

Five (11%) patients developed *de novo* portal vein thrombosis (PVT), 28 (range 1-45) days after surgical intervention (Supplementary Table 7). Interestingly, 3 out of these 5 surgeries were splenectomies, whereas 2 had other surgical interventions. PVT occurred in 3 out of the 6 patients (50%) who had splenectomy *vs.* 2 out of the 39 (5%) who had another surgical intervention (p=0.01). Overall, complete recanalization was observed in 3 of 5 patients. Two

out of the 3 patients received anticoagulation, and complete recanalization was observed after 4 and 5.5 months, respectively. The third patient did not receive anticoagulation, since a TIPSS was inserted; complete recanalization was observed after 8 months.

Death after surgery

Thirteen (29%) patients were admitted in intensive care unit after surgery, with a median (IQR) length of stay in intensive care unit of 4 (2-7) days. Median (IQR) overall length of hospital stay was 10 (4-28) days. Four patients died within 6 months after surgery. Their characteristics are presented in Table 5. None of the patients underwent liver transplantation within the observation period.

As shown in Table 4, age-adjusted Charlson comorbidity index and serum creatinine level were associated with death within 6 months after surgery. Patients with age-adjusted Charlson comorbidity index ≥6 before surgery had a 6-month cumulative risk of death of 27% vs. 0% for patients with an index below this threshold (p=0.002). We have previously reported that serum creatinine level higher than 100 μmol/L is associated with a poor outcome after TIPSS in patients with INCPH (25). Using this threshold here, we observed that patients with serum creatinine ≥100 μmol/L had a 6-month cumulative risk of death of 33% *vs.* 0% for patients with serum creatinine below this threshold (Figure 1).

We compared 6-month cumulative risk of death after abdominal surgery of patients with INCPH with that of patients with cirrhosis matched according to the presence of ascites at surgery. One patient with INCPH could not be matched according to the presence of ascites, explaining why 43 patients with INCPH were compared with 86 patients with cirrhosis. Characteristics of the 86 patients with cirrhosis are shown in Supplementary Table 3. As shown in Figure 1B, 6-month cumulative risk of death was similar between the two groups.

In addition, in order to evaluate the impact of abdominal surgery on overall outcome of patients with INCPH, we compared 3-year liver transplantation-free survival of patients with INCPH who had abdominal surgery within 3 years after diagnosis of INCPH (29 patients

from the present study) with that of patients with INCPH but without abdominal surgery (n= 82). As shown in Figure 1C, 3-year transplant-free survival was similar between the two groups.

Overall post-operative unfavorable outcome

Overall post-operative outcome was unfavorable in 22 (50%) patients. History of ascites was associated with an unfavorable outcome (Table 4). As extra-hepatic conditions related with INCPH and serum creatinine levels fell short of statistical significance and as we have previously reported that these features are associated with a poor outcome after TIPSS in patients with INCPH (25), we classified patients according to these items and to history of ascites at surgery. As shown in Figure 2, 5% of the patients with neither extra-hepatic condition associated with INCPH nor history of ascites at surgery nor serum creatinine ≥100 µmol/L had an unfavorable outcome. Only one patient without these criteria had an unfavorable outcome; this patient had post-operative bleeding after cholecystectomy, requiring reintervention under local anesthesia. By contrast, 64% of the patients with ≥2 features had an unfavorable outcome.

Influence of portal decompression on post-operative outcome

As shown in Figure 3, 11 patients had portal decompression prior to, or at the time of, surgery. In 1 of these patients, portosystemic shunt was the indication for surgery, with concomitant splenectomy (Table 2 and Figure 3). In the 10 remaining patients, median time between portal decompression and surgical intervention was 4.0 (0.3-44.6) months.

In order to assess the effect of portal decompression on the outcome after surgery, we compared the outcome of the 10 patients who had either TIPSS or portosystemic shunt before surgery, to the 33 patients who did not (Supplementary Table 8). Except for beta-blockers, baseline characteristics did not differ between the two groups. Post-operative outcomes did not differ between patients with previous TIPSS or portosystemic shunt and those without. In patients who had a previous TIPSS or surgical portosystemic shunt, one

patient had a grade ≥3 complication within one month after surgery (leakage), and 3 had at least one portal hypertension related complications within 3 months after surgery (1 decompensation of ascites, 1 decompensation of ascites and encephalopathy and 1 acute kidney injury). When included in the univariate Cox regression analysis, portal decompression was not associated with neither portal hypertension related complications (HR (95% CI) 0.746 (0.212-2.618), p=0.647) or death within 6 months after surgery (HR (95% CI) 1.153 (0.120-11.088), p=0.902). Furthermore, portal decompression was not associated with an unfavorable outcome after surgery (HR (95% CI) 0.874 (0.322-2.372), p=0.792).

Discussion

This study focusing on the outcome of patients with INCPH undergoing abdominal surgery shows that 6-month mortality after surgery was 9%, affecting patients with comorbidities and/or serum creatinine level ≥ 100 µmol/L. Patients without extra-hepatic conditions related with INCPH, without increased serum creatinine and without a history of ascites at surgery had a favorable post-operative outcome. Although this study gathered the largest number of patients with INCPH undergoing abdominal surgery reported at present, interpretation of the results should take into account that number of patients included remained limited, that the study was retrospective, and that various surgical interventions were performed. Given the rarity of the disease, conducting a prospective study seems however not realistic.

The main information derived from this study is that mortality of patients with INCPH undergoing abdominal surgery is higher than that reported in the general population. We observed a 6-month mortality rate of 9% (95% CI 1-17%) in patients with INCPH, while in the general population, in-hospital or 1-month mortality after abdominal surgery ranges from 3 % (95% CI 0.4-7%) to 12% (95% CI 7-18 %) (35–37). We observed that 6-month mortality rate of patients with INCPH did not differ from that of patients with cirrhosis, matched for ascites, who underwent abdominal surgery between 2005 and 2016 (17). It should however

be noted that mortality of patients with cirrhosis in this cohort was lower than previously reported (7,10,31–33). Indeed, in patients with cirrhosis, reported mortality after surgery ranges from 7 % (95% CI 2-12%) to 30 % (95% CI 15-44%) (7,8,31,33) at 1 month, is of 30% (24-36) at 3 months and 54% (47-61) at 1 year (32). This lower mortality observed here in patients with cirrhosis may be related to a better selection of candidates for abdominal surgery, and to the fact that these procedures were performed in tertiary centers. This outcome of patients with INCPH after surgery echoes the overall survival of patients with INCPH outside the surgical setting, known to be intermediate between those of the general population and of patients with cirrhosis (23). In the present study, comorbidities were the main drivers of postoperative mortality, as death within six months after surgery was restricted to patients with age-adjusted Charlson comorbidity index ≥ 6 or with serum creatinine ≥100 μmol/L before surgery. This finding is in line with the natural history of INCPH, where half the mortality is accounted for by extrahepatic comorbidities (22–24), as well as with the outcome after TIPSS placement where mortality is associated with serum creatinine and the presence of extra-hepatic conditions associated with INCPH (25). Interestingly, transplant-free survival after INCPH diagnosis was similar in patients who did and did not undergo abdominal surgery during follow-up, suggesting that, in selected patients managed in expert centers, surgery does not have a deleterious impact on the natural history of INCPH. We did not find any association between the type of intervention and post-operative outcomes, but cannot rule out a lack of power due to the limited sample size.

The second major finding of the present study was that portal hypertension related complications, especially ascites, were the most frequent, occurring within 3 months after surgery in 36% and 26% of the patients, respectively. Portal hypertension related complications increased the length of hospital stay, and 3/16 (19%) required a TIPSS after surgery for refractory ascites or variceal bleeding. However, they were transient in most

patients. These results suggest that portal hypertension *per se*, should not be regarded as a definite contra-indication for abdominal surgery in patients with INCPH.

De novo PVT occurred in 5 (11%) patients after surgery. Interestingly, PVT following splenectomy was 10-fold more frequent than following other surgeries. Reported rates of PVT following splenectomy range between 17% (95% CI 13-21%) and 36% (95% CI 17-55%) in patients with cirrhosis (38,39), and are of 54% (95% CI 46-61%) in patients with benign hematologic disorders (40). In the present study, the incidence of PVT was similar to that of non-cirrhotic patients, since PVT was observed in 50% (95% CI 9-90%) of the patients with INCPH and splenectomy. Four cases of PVT were diagnosed within one month after surgery. Recanalization occurred in 60% of the patients. These findings suggest that routine ultrasound examination at 1 week, 1 month and 3 months after surgery would allow an early detection of PVT, especially after splenectomy.

Infections within 1 month after surgery were common, being observed in 34% of the patients. This figure is in the same range as estimates of post-operative infections after abdominal surgery in patients with cirrhosis and higher than in the general population [29% (95% CI 21-36%) and 13% (95% CI 12-14%), respectively, $p<0.001$] (41). In cirrhosis, the risk of infection is likely related to altered innate and adaptive immunity and to increased bacterial translocation (42). In patients with INCPH, susceptibility to infection may be related to portal hypertension but also to extrahepatic conditions associated with INCPH, namely immunological disorders and HIV infection. Bleeding occurred within 1 month in 10 (22%) patients and was associated with administration of anticoagulant or antiplatelet agents. This high incidence is reminiscent of the frequent bleeding episodes reported in patients with Budd-Chiari syndrome undergoing invasive procedures while receiving anticoagulation therapy (43).

In the present study, we identified a group of patients having an unfavorable outcome, namely those with extra-hepatic condition associated with INCPH, elevated serum creatinine and/or significant ascites before surgery. By contrast, only 5% of the patients with neither extra-hepatic condition associated with INCPH nor elevated serum creatinine nor significant

ascites before surgery had an unfavorable outcome. These simple features could be helpful in making a decision for abdominal surgery with due information of the patient on the risks of the intervention. Due to the retrospective and uncontrolled design of the study, we could not evaluate the survival benefit of surgery (*vs*. no intervention), taking into account the indication of surgery, the severity of INCPH and extrahepatic comorbidities.

In patients with cirrhosis, the experience of pre-emptive TIPSS placement before surgery is limited to small, retrospective studies (12–17). A limited number of studies compared patients with cirrhosis with preserved or moderately impaired liver function who had pre-operative TIPSS, to patients who underwent elective surgery without preoperative TIPSS. Outcome after surgery was similar between patients who had or not a preoperative TIPSS (15,17). In the present study, portal decompression was not associated with post-operative outcome after surgery. However, present findings are insufficient to draw any firm conclusion for or against preemptive portal decompression before surgery in patients with INCPH. Indeed, TIPSS was placed as a preparation for surgery in only 4 patients; in the 5 remaining patients, TIPSS had been previously inserted for other reasons, with sometimes a broad interval of time between TIPSS insertion and surgery. Larger dedicated studies are thus needed to address this important question.

In conclusion, in this study, we observed that patients with INCPH were at high risk of major surgical and portal hypertension related complications when they harbored extrahepatic conditions related to INCPH, and/or increased serum creatinine and/or a history of ascites. Comorbidities and higher serum creatinine were significantly associated with 6-month mortality. Further studies are needed to evaluate the impact of each type of surgery on the natural history of INCPH and the influence of TIPSS on post-operative outcome.

References

1. Barge S, Grando V, Nault J-C, Broudin C, Beaugrand M, Ganne-Carrié N, et al. Prevalence and clinical significance of nodular regenerative hyperplasia in liver biopsies. Liver Int. Off. J. Int. Assoc. Study Liver. 2016;36:1059–1066.
2. Guido M, Sarcognato S, Sonzogni A, Lucà MG, Senzolo M, Fagiuoli S, et al. Obliterative portal venopathy without portal hypertension: an underestimated condition. Liver Int. Off. J. Int. Assoc. Study Liver. 2016;36:454–460.
3. 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.
4. Schouten JNL, Garcia-Pagan JC, Valla DC, Janssen HLA. Idiopathic noncirrhotic portal hypertension. Hepatol. Baltim. Md. 2011;54:1071–1081.
5. Khanna R, Sarin SK. Non-cirrhotic portal hypertension - diagnosis and management. J. Hepatol. 2014;60:421–441.
6. Mansour A, Watson W, Shayani V, Pickleman J. Abdominal operations in patients with cirrhosis: Still a major surgical challenge. Surgery. 1997;122:730–736.
7. Farnsworth N, Fagan SP, Berger DH, Awad SS. Child-Turcotte-Pugh versus MELD score as a predictor of outcome after elective and emergent surgery in cirrhotic patients. Am. J. Surg. 2004;188:580–583.
8. 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. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 2010;8:451–457, quiz e58.
9. Risk factors for mortality after surgery in patients with cirrhosis. - PubMed - NCBI [Internet]. [cited 2018 Dec 17];Available from: https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pubmed?term=gastroenterology%5BJour%5D+AND+2007%5Bpdat%5D+AND+Teh%5Bauthor%5D&cmd=detailssearch
10. Wong R, Rappaport W, Witte C, Hunter G, Jaffe P, Hall K, et al. Risk of nonshunt abdominal operation in the patient with cirrhosis. J. Am. Coll. Surg. 1994;179:412–416.
11. 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.
12. Azoulay D, Buabse F, Damiano I, Smail A, Ichai P, Dannaoui M, et al. Neoadjuvant transjugular intrahepatic portosystemic shunt: a solution for extrahepatic abdominal operation in cirrhotic patients with severe portal hypertension. J. Am. Coll. Surg. 2001;193:46–51.
13. Gil A, Martínez-Regueira F, Hernández-Lizoain JL, Pardo F, Olea JM, Bastarrika G, et al. The role of transjugular intrahepatic portosystemic shunt prior to abdominal tumoral surgery in cirrhotic patients with portal hypertension. Eur. J. Surg. Oncol. J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol. 2004;30:46–52.
14. Schlenker C, Johnson S, Trotter JF. Preoperative transjugular intrahepatic portosystemic shunt (TIPS) for cirrhotic patients undergoing abdominal and pelvic surgeries. Surg. Endosc. 2009;23:1594–1598.
15. Vinet E, Perreault P, Bouchard L, Bernard D, Wassef R, Richard C, et al. Transjugular intrahepatic portosystemic shunt before abdominal surgery in cirrhotic patients: a retrospective, comparative study. Can. J. Gastroenterol. J. Can. Gastroenterol. 2006;20:401–404.
16. Kim JJ, Dasika NL, Yu E, Fontana RJ. Cirrhotic patients with a transjugular intrahepatic portosystemic shunt undergoing major extrahepatic surgery. J. Clin. Gastroenterol. 2009;43:574–579.
17. Tabchouri N, Barbier L, Menahem B, Perarnau J-M, Muscari F, Fares N, et al. Transjugular Intrahepatic Portosystemic Shunt as a bridge to abdominal surgery in cirrhotic patients. J. Gastrointest. Surg. in press;
18. Sharma BC, Singh RP, Chawla YK, Narasimhan KL, Rao KL, Mitra SK, et al. Effect of shunt surgery on spleen size, portal pressure and oesophageal varices in patients with

non-cirrhotic portal hypertension. J. Gastroenterol. Hepatol. 1997;12:582–584.
19. Pal S, Radhakrishna P, Sahni P, Pande GK, Nundy S, Chattopadhyay TK. Prophylactic surgery in non-cirrhotic portal fibrosis:is it worthwhile? Indian J. Gastroenterol. Off. J. Indian Soc. Gastroenterol. 2005;24:239–242.
20. Karagul S, Yagci MA, Tardu A, Ertugrul I, Kirmizi S, Sumer F, et al. Portosystemic Shunt Surgery in Patients with Idiopathic Noncirrhotic Portal Hypertension. Ann. Transplant. 2016;21:317–320.
21. Rubbia-Brandt L, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. Histopathology. 2010;56:430–439.
22. Cazals-Hatem D, Hillaire S, Rudler M, Plessier A, Paradis V, Condat B, et al. Obliterative portal venopathy: portal hypertension is not always present at diagnosis. J. Hepatol. 2011;54:455–461.
23. Schouten JNL, Nevens F, Hansen B, Laleman W, van den Born M, Komuta M, et al. Idiopathic noncirrhotic portal hypertension is associated with poor survival: results of a long-term cohort study. Aliment. Pharmacol. Ther. 2012;35:1424–1433.
24. Siramolpiwat S, Seijo S, Miquel R, Berzigotti A, Garcia-Criado A, Darnell A, et al. Idiopathic portal hypertension: natural history and long-term outcome. Hepatol. Baltim. Md. 2014;59:2276–2285.
25. 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. Hepatol. Baltim. Md. 2016;64:224–231.
26. Keats AS. The ASA classification of physical status--a recapitulation. Anesthesiology. 1978;49:233–236.
27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. 1987;40:373–383.
28. 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.
29. de Franchis R, Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J. Hepatol. 2010;53:762–768.
30. 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.
31. 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.
32. 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.
33. 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.
34. Sarin SK, Sethi KK, Nanda R. Measurement and correlation of wedged hepatic, intrahepatic, intrasplenic and intravariceal pressures in patients with cirrhosis of liver and non-cirrhotic portal fibrosis. Gut. 1987;28:260–266.
35. del Olmo JA, Flor-Lorente B, Flor-Civera B, Rodriguez F, Serra MA, Escudero A, et al. Risk factors for nonhepatic surgery in patients with cirrhosis. World J. Surg. 2003;27:647–652.
36. Wilson RJT, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. BJA Br. J.

Anaesth. 2010;105:297–303.
37. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann. Surg. 2012;255:821–829.
38. Li M-X, Zhang X-F, Liu Z-W, Lv Y. Risk factors and clinical characteristics of portal vein thrombosis after splenectomy in patients with liver cirrhosis. Hepatobiliary Pancreat. Dis. Int. HBPD INT. 2013;12:512–519.
39. Kawanaka H, Akahoshi T, Kinjo N, Konishi K, Yoshida D, Anegawa G, et al. Impact of antithrombin III concentrates on portal vein thrombosis after splenectomy in patients with liver cirrhosis and hypersplenism. Ann. Surg. 2010;251:76–83.
40. de'Angelis N, Abdalla S, Lizzi V, Esposito F, Genova P, Roy L, et al. Incidence and predictors of portal and splenic vein thrombosis after pure laparoscopic splenectomy. Surgery. 2017;162:1219–1230.
41. Pessaux P, Msika S, Atalla D, Hay J-M, Flamant Y, French Association for Surgical Research. Risk factors for postoperative infectious complications in noncolorectal abdominal surgery: a multivariate analysis based on a prospective multicenter study of 4718 patients. Arch. Surg. Chic. Ill 1960. 2003;138:314–324.
42. Gustot T, Durand F, Lebrec D, Vincent J-L, Moreau R. Severe sepsis in cirrhosis. Hepatol. Baltim. Md. 2009;50:2022–2033.
43. Rautou P-E, Douarin L, Denninger M-H, Escolano S, Lebrec D, Moreau R, et al. Bleeding in patients with Budd–Chiari syndrome. J. Hepatol. 2011;54:56–63.

Figures' legends.

Figure 1.

Figure 1A: Cumulative incidence of death at 6 months after abdominal surgery, according to serum creatinine before surgery

Figure 1B: Cumulative incidence of death at 6 months after abdominal surgery in 44 patients with INCPH and in 86 patients with cirrhosis matched for ascites at surgery

Figure 1C: Transplant-free survival, from date of diagnosis of INCPH, in patients undergoing or not abdominal surgery during follow-up. Each red arrows indicates an abdominal surgery. For 8/29 patients, INCPH was diagnosed at surgery (red star).

Abbreviation: INCPH, idiopathic noncirrhotic portal hypertension

Figure 2. Proportion of the patients having an unfavorable outcome after surgery according to the presence of extra-hepatic conditions associated with INCPH serum creatinine ≥100 µmol/L and/or history of ascites at surgery.

An unfavorable outcome was defined as any of post-operative complication grade ≥3 within one month after surgery, portal-hypertension related complications within 3 months after surgery or death within 6 months after surgery.

Eleven patients had neither extra-hepatic condition associated with INCPH nor serum creatinine ≥100 µmol/ nor history of ascites at surgery; 17 patients one out of the 3 features among extra-hepatic condition associated with INCPH, serum creatinine ≥100 µmol/ or history of ascites at surgery; 16 patients at least 2 of the 3 features.

Figure 3. Distribution of the patients according to the type and the indication for portal decompression.

Table 1. Characteristics of the 44 patients at surgery

Characteristics	Patients with available data	Number (percentage) or median (interquartile range)
Clinical features		
Male gender	44	30 (68)
Age, years	44	53 (37-65)
Age adjusted - Charlson comorbidity index	44	4 (3-6)
ASA score	44	3 (2-3)
At least one extra-hepatic condition associated with INCPH	44	25 (57)
Immunological disorder		18 (41)
HIV infection		5 (11)
Recurrent abdominal infection		5 (11)
Medication or toxin		5 (11)
Prothrombotic condition		2 (5)
Genetic disorder		2 (5)
At least one other cause of chronic liver disease	44	11 (25)
Excessive alcohol consumption		2 (4)
Metabolic syndrome		5 (11)
Hepatitis C virus infection		4 (9)
Diabetes mellitus	44	13 (30)
Ascites	44	
Absent		28 (64)
Controlled with diuretics		9 (14)
Clinically detected		7 (16)
History of ascites *	44	16 (36)
Hepatic encephalopathy	44	0 (0)
Previous variceal bleeding	43	18 (42)

Treatment before surgery		
Anticoagulation therapy	43	16 (36)
Antiplatelet agents	43	7 (16)
Diuretic therapy	43	15 (34)
Beta-blockers	43	18 (41)
Endoscopic data		
Gastro-esophageal varices	42	
Absent		10 (24)
Small		10 (24)
Medium or large		22 (52)
Varices needing treatment**		30 (71)
Imaging data		
Portosystemic collaterals at imaging	43	25 (58)
Spleen size, cm	35	16 (14-20)
Previous splenectomy	45	3 (7)
Thrombosis of the portal venous axis	43	6 (14)
Partial occlusion		3 (7)
Complete occlusion		3 (7)
Laboratory data		
Hemoglobin, g/dL	42	11.8 (10.0-13.9)
Leucocyte count, x10^9/L	41	5.2 (3.4-10.0)
Platelet count, x10^9/L	42	87 (67-161)
INR	42	1.13 (1.02-1.47)
AST, IU/L	43	32 (25-47)
ALT, IU/L	42	26 (19-37)
ALK, IU/L	41	136 (77-251)
GGT IU/L	42	57 (23-127)
Serum bilirubin, μmol/L	43	17 (12-35)

Serum creatinine, μmol/L	44	79 (61-106)
Serum albumin, g/L	34	37 (31-41)
MELD score	39	9 (7-12)

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

** Medium/large esophageal and/or gastric varices or history of variceal bleeding or history of endoscopic band ligation and/or glue

Abbreviations: ASA, American Society of Anesthesiologists; INCPH, idiopathic noncirrhotic portal hypertension; HIV, human immunodeficiency virus; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ALK, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; IU, international Unit; MELD, Model for End-Stage Liver diseases

Table 2. Type and indications for the 45 surgical interventions

Minor surgeries	**30**
Open surgeries	***18***
Abdominal wall	13
Hernia repair	10
Alfapump® implantation	1
Abdominoplasty	1
Surgical exploration	1
Cholecystectomy	2
Retroperitoneum mass excision	1
Appendicectomy	1
Cesarean section	1
Laparoscopic surgeries	***12***
Abdominal wall	2
Surgical exploration	1
Peritoneal catheter placement	1
Cholecystectomy	4

Splenectomy	1	
Colorectal surgery	4	
Ileal resection (Crohn's disease)	2	
Appendicectomy	2	
Partial liver resection	1	
Major surgeries	**15**	
Urologic or kidney surgery	5	
Renal transplantation	2	
Nephrectomy	2	
Renal carcinoma	1	
Bleeding after renal biopsy	1	
Cystectomy and hysterectomy for urothelial carcinoma	1	
Splenectomy	5	
Splenectomy alone	3	
Splenectomy + caudal pancreatectomy	1	
Splenectomy + porto-caval shunt	1	
Colic resection	2	
Crohn's disease		1
Colorectal cancer		1
Gastric and pancreatic surgery	2	
Gastrectomy for gastric neoplasia	1	
Pancreatectomy for neuroendocrine neoplasia	1	
Partial liver resection	1	

Table 3. Details on 61 surgical or post-operative complications that occurred in 31 patients within 1 month after surgery

Type of complication	
Infection	**19**
Lung	5
Urinary tract infection	3
Skin infection	3
Intra-abdominal infection	3
Cholangitis	1
Clostridium difficile infection	1
No source identified	3
Post-operative bleeding	**10**
Fistula/leak	**5**
Abdominal leak	3
Urinary leak	2
Digestive complications	**5**
Vomiting	2
Ileus	3
Cardiopulmonary	**8**
Respiratory failure	1
Venous thrombosis	2
Pleural effusion	3
Hypotension	1
Tako-Tsubo syndrome	1

Liver Moderate liver failure	**1** 1
Neurologic Confusion	**1** 1
Pain*	**7**
Other Diabetes decompensation Anemia	**5** 4 1

***All the 7 reported complications were classified grade I according to the Dindo-Clavien classifications (i.e any deviation from the normal postoperative course without the need for additional treatment)

Table 4. Univariate Cox regression analysis evaluating pre-specified factors before surgery, associated with the occurrence of major endpoints after surgery

	At least one grade 3 or more complication within 1 month after surgery (n=9)			
	HR	95% CI		*P* value
Age-adjusted comorbidity index	1.103	0.866	1.404	0.427
Extra-hepatic condition associated with INCPH	1.387	0.331	5.810	0.654
History of ascites*	1.340	0.300	5.988	0.702
Varices needing treatment**	2.056	0.240	17.600	0.511
Portal vein thrombosis	2.104	0.363	12.196	0.407
Serum bilirubin	1.012	0.994	1.031	0.189
Serum creatinine	1.002	0.999	1.006	0.188
Major surgery	0.556	0.138	2.242	0.409
Emergency procedure	2.920	0.712	11.981	0.137

	At least one portal hypertension related complication£ within 3 months after surgery (n=16)			
	HR	95% CI		P value
Age-adjusted comorbidity index	1.074	0.913	1.264	0.390
Extra-hepatic condition associated with INCPH	**3.973**	**1.129**	**13.982**	**0.032**
History of ascites*	**3.144**	**1.162**	**8.504**	**0.024**
Varices needing treatment**	0.858	0.298	2.472	0.777
Portal vein thrombosis	0.750	0.170	3.304	0.704
Serum bilirubin	0.991	0.972	1.012	0.401
Serum creatinine	1.002	0.999	1.005	0.112
Major surgery	0.634	0.236	1.704	0.366
Emergency procedure	1.676	0.581	4.830	0.339

	Death within 6 months after surgery (n=4)		
	HR	95% CI	P value

Age-adjusted comorbidity index	**1.372**	**1.040**	**1.810**	**0.025**
Extra-hepatic condition associated with INCPH	0.800	0.113	5.679	0.823
History of ascites*	5.292	0.550	50.919	0.149
Varices needing treatment**	1.116	0.116	10.728	0.925
Portal vein thrombosis	0.039	<0.001	6466.507	0.597
Serum bilirubin	0.797	0.622	1.022	0.074
Serum creatinine	**1.007**	**1.003**	**1.012**	**0.002**
Major surgery	0.487	0.069	3.455	0.471
Emergency procedure	0.992	0.103	9.540	0.994

	Unfavorable outcome after surgery$ (n=23)			
	HR	95% CI		P value
Age-adjusted comorbidity index	1.099	0.963	1.254	0.163
Extra-hepatic condition associated with INCPH	**2.410**	**0.939**	**6.186**	**0.067**
History of ascites*	**3.892**	**1.650**	**9.180**	**0.002**
Varices needing treatment**	1.007	0.390	2.598	0.989
Portal vein thrombosis	1.425	0.479	4.237	0.524
Serum bilirubin	0.999	0.985	1.014	0.901
Serum creatinine	**1.003**	**1.000**	**1.005**	**0.056**
Major surgery	0.851	0.356	2.032	0.716
Emergency procedure	2.136	0.865	5.276	0.100

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

** Medium/large esophageal and/or gastric varices or history of variceal bleeding or history of endoscopic band ligation and/or glue

£Portal hypertension-related complications were defined as any of decompensation ascites, hepatic encephalopathy, significant portal hypertension related bleeding, acute kidney injury, or spontaneous bacterial peritonitis occurring 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 two or more paracentesis within 3 months following surgery, or requiring a TIPSS.

$An unfavorable outcome after surgery was defined as either post-operative complication grade ≥3 within one month after surgery, or portal-hypertension related complications within 3 months after surgery or death within 6 months after surgery.

Abbreviations: HR, Hazard ratio; CI, confidence interval, INCPH, idiopathic noncirrhotic portal hypertension

Bold indicates significant associations.

Table 5. Characteristics of the 4 patients who died within 6 months after surgery

	PATIENT 7	PATIENT 8	PATIENT 20	PATIENT 41
Patient's features at surgery				
Age, years	73	65	51	66
Gender	Male	Male	Male	Male
Age-adjusted Charlson comorbidity index	8	6	9	8
ASA score	3	3	3	4
Extra-hepatic condition associated with INCPH	Previous renal transplantation Azathioprine	None	None	Recurrent abdominal infection *NOD2* mutation
Ascites	None	Tense	Diuretic-sensitive ascites	Tense
History of variceal bleeding	No	No	Yes	Yes
Esophageal varices	Medium-size	Absence	Medium-size	Medium-size
Portal vein thrombosis	No	No	No	No
Platelet count, x10^9/l	99	273	144	52
INR	1	1	0.94	1.16
Serum bilirubin, μmol/l	16	6	8	8
Serum creatinine, μmol/l	533	300	552	143
MELD	14	12	14	9
Surgery				
TIPSS performed before surgery	No	Yes	No	No
Surgical intervention	Renal re-transplantation	Peritoneal catheter placement	Nephrectomy	Alfapump® implantation
Indication	End-stage renal failure	Refractory ascites	Fistula after renal biopsy	Refractory ascites
Post-operative outcome				
Occurrence of portal-hypertension related complication after surgery	**Yes** Ascites	**No**	**Yes** Spontaneous bacterial	**No**

	Variceal bleeding Hepatic encephalopathy Spontaneous bacterial peritonitis		peritonitis	
Other post-operative complication	Leakage	Wound infection	Pleural infection Tako-Tsubo syndrome Acute kidney injury	None
Duration between surgery and death	5.7 months	2.2 months	4.3 months	3.8 months
Cause of death	Variceal bleeding	Cardiac arrest	Pneumonia	Septic shock

Abbreviations: ASA, American Society of Anesthesiologists; INCPH, idiopathic noncirrhotic portal hypertension; MELD, Model for End-Stage Liver Disease