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Predictors of unresectability after portal vein embolization for centrally-located cholangiocarcinoma

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Key words: cholangiocarcinoma; portal vein embolization; sarcopenia; score; resection; complications

Abbreviations:

AUC: area under the curve
BD: biliary drainage
BMI: body mass index
BSA: body surface area
BWR: body weight ratio
CC: cholangiocarcinoma
CLCC: centrally-located cholangiocarcinoma
ERCP: endoscopic retrograde cholangio-pancreatography
FLR: future liver remnant
IHCC: intrahepatic cholangiocarcinoma
MDCT: multidetector computed tomography
MRI: magnetic resonance imaging
NLR: neutrophil-to-lymphocyte ratio
OS: Overall survival
PET: positron emission tomography
PHCC: perihilar cholangiocarcinoma
PLR: platelet-to-lymphocyte ratio
PMA: psoas muscle area
PMI: psoas muscle index
PVE: portal vein embolization
ROC: receiver operator characteristic

ABSTRACT

Background. The curative treatment of perihilar cholangiocarcinomas (PHCC) and centrally-located intrahepatic cholangiocarcinomas (IHCC) often requires major hepatectomy preceded by portal vein embolization (PVE). this strategy, however, is associated with a high rate of drop-outs before operation or failure of resection at the time of operative exploration. We aimed to identify predictors of unresectability (dropout or failure of resection) after PVE for centrally-located cholangiocarcinoma (CLCC), including PHCC and IHCC.

Method. All patients undergoing PVE for a planned resection of CLCC between 2000 and 2018 in our center were evaluated retrospectively. Predictors of unresectability were determined under intention-to-treat conditions, based on clinical, biologic, and radiologic data collected before PVE.

Results. Eighty-eight consecutive patients scheduled for PVE before operative exploration were included, 56 of whom (64%) underwent curative resection and 32 (36%) were not resected, including those who did not undergo exploration(n=11) and those operated on but not resected (n=21). The most common cause of unresectability was tumor progression (62%). A psoas muscle index <500mm^2/m^2 (p=0.04), high BMI (p=0.023) and low serum albumin level (p=0.007) were associated with unresectabilty on multivariate analysis. A composite score including these variables (cut-offs determined after ROC curve analysis) was proposed and achieved accurate discrimination regarding unresectability (AUC=0.82, p<0.001).

Conclusion. Predictors of unresectability after PVE for CLCC were identified, with sarcopenic overweight patients having a greater risk of unresectability. This preoperative score enables a fairly accurate prediction of unresectability in a given patient. These simple, objective, and

inexpensive parameters should be considered in all patients with CLCC scheduled to undergo PVE.

INTRODUCTION

Cholangiocarcinoma (CC) is a malignancy originating from the epithelial lining of the biliary ducts, representing 3% of all gastrointestinal malignancies[1,2]. Centrally-located cholangiocarcinomas (CLCC) include both perihilar cholangiocarcinoma (PHCC) and centrally-located intrahepatic cholangiocarcinomas (IHCC). PHCC, the most common subtype accounting for 60-70% of CC[3], develops from the right and/or left hepatic ducts or common bile duct near the hilum[4]. These neoplasms remain a challenging entity with a poor prognosis[4]. Radical resection is the only possible chance to achieve long-term survival[5], but, at the time of laparotomy, only 40-70% of patients have resectable disease[6]. Resection of PHCC often requires a major hepatectomy with extrahepatic bile duct resection, hepatic pedicle lymphadenectomy, and sometimes vascular reconstruction[7] to obtain negative surgical margins[8]. These procedures, however, remain associated with a substantial risk of postoperative morbidity and mortality[9].

The major concern with radical resection in potentially resectable CLCC is the small future liver remnant (FLR), increasing the risk of post-hepatectomy liver failure which is the most common cause of postoperative mortality[10]. For this reason, Makuuchi et al.[11] were the first to introduce portal vein embolization (PVE) before hepatic resection. PVE is the gold standard strategy to increase FLR volume, because the hyertrophy after PVE permits safer major liver resection with a decreased risk of liver failure and death[12]. PVE is indicated when the FLR volume is less than 20-30% of the total liver volume or less than 0.5% of the body weight ratio (BWR) in normal liver[13,14]. Specific cut-offs in case of cholestatic livers, however, are not clearly defined. Resectability rates after PVE before major hepatectomy ranging from 58% to

100% have been reported in the literature, [15,16]. Many studies reported the reasons for unresectability after PVE under an intention-to-treat analysis, but predictors of unresectability after PVE for CLCC have not been clarified in the literature. These predictors could have a major impact on the decision-making process, particularly in borderline patients.

The aim of this study was therefore, to assess predictors of unresectability after PVE for CLCC in an intention-to treat analysis.

METHODS

Study design and population

We reviewed all patients who underwent PVE before planned major hepatectomy (≥3 segments) for potentially resectable CLCC between January 2000 and December 2018, whether the the patients finally underwent hepatectomy or not. CLCC included PHCC and IHCC extending to the first-order portal pedicle branches and requiring major hepatectomy. We merged both entities, because patients with centrally-located IHCC usually require a major hepatectomy with biliary reconstruction (± vascular reconstruction) as for PHCC. Patients with gallbladder carcinoma, IHCC not extending to the hilum, and distal CC (not requiring hepatectomy) were excluded. All patients were evaluated by our institutional multidisciplinary tumor board. Patients were scheduled for PVE if they had insufficient FLR volume, in normal liver, <30% of total liver volume and/or <0.5% of BWR[14], and empirically in cholestatic liver, <40% of TLV or <0.8% of BWR[10].

Preoperative radiologic assessment of resectability

Comprehensive radiologic assessment was done for all patients before any biliary drainage. Before 2010, all patients were evaluated by multi-detector, computed tomography (MDCT) and CT angiography to evaluate the relation of the tumor to the hepatic artery and portal vein, and *on demand* in few cases, with magnetic resonance imaging (MRI) and a positron emission tomography (PET) scan for detection of extrahepatic disease (because MRI and PET scan were not available in our center). Starting from the year 2010, all patients were assessed by MDCT, MRI, magnetic resonance cholangiopancreatography (MRCP), and PET scan.

Data collection

The demographic and preoperative nutritional parameters of patients, as well as laboratory investigations including a complete blood count, liver function tests, and tumor markers were all collected prior to PVE. Patients with jaundice underwent biliary drainage of FLR by endoscopic retrograde cholangio-pancreatography (ERCP) as first-line treatment, and it was usually accompanied by endoscopic biopsy (brush cytology) of the tumor, or percutaneous transhepatic drainage in the event of failure. The total number of drainage procedures, the side of the liver drained, post-drainage complications, and the degree to which serum bilirubin levels decreased after drainage were also recorded.

We also studied markers of the inflammatory response. i.e. the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and focusing specifically on previously reported cut-off values for NLR and PLR[17-22]. Preoperative parameters of nutritional assessment were analyzed using previously published cut-off values that included markers for muscle mass depletion (sarcopenia):

- Psoas muscle index (PMI): psoas muscle area (PMA) measured on the axial section of a CT through the third lumbar vertebra, normalized by height squared[23] with cut-off value of 500 mm^2/m^2 [24].
- PMA normalized by body surface area (BSA)[25].

All these variables were evaluated before PVE.

Technical details regarding the PVE procedure and post-PVE assessment

All PVE procedures were performed by experienced hepatobiliary surgeons. Different approaches were used (either percutaneous transhepatic or ileocolic **(ELSEVIER HAVE THEM EXPLAIN WHAT THEY MEAN BY ILEOCOLIC)**, depending on technical feasibility and the surgeon's preference. A control portal venography was performed, then the portal branches supplying the diseased side of liver were catheterized selectively, a guidewire was introduced, and embolization was initiated. The embolic agents used included n-butyl-cyanoacrylate mixed with ethiodized oil or absolute ethanol. We did not embolize the portal branch of segment IV in cases of planned extended right hepatectomy. Total venous deprivation (PVE and hepatic vein occlusion) was not performed during this study.

Daily clinical evaluations and liver function tests were ensured to enable the rapid detection of post-PVE complications. Volumetric assessments were made regarding total liver volume and FLR, both before and then 3 or 4 weeks after PVE, based on volumetric CT reconstructions. If the FLR reached a sufficient volume, the patient was scheduled for liver surgery. Otherwise, provided that all branches of the portal vein supplying the part of liver to be resected were correctly occluded on CT images, a further volumetric assessment was performed after 4 weeks. When the targeted branches of the portal vein were still permeable or partially embolized, a supplementary PVE was scheduled. PVE was considered to have failed when there was an insufficient increase in FLR volume or contralateral embolization of non-targeted portal vein branches in the FLR. Post-PVE follow-up also included subsequent CTs enabling evaluation of the tumor and potential detection of any local progression or distant metastases.

Operative exploration and assessment of resectability

During operative exploration by laparotomy or laparoscopy, all patients were evaluated for distant metastases in the form of peritoneal nodules, malignant ascites, liver metastases, distant

lymph node metastases or locally advanced tumor which precluded resection. In the event of non-resectability (defined as non-radical resection or insufficient FLR), patients were referred for palliative chemotherapy or were assessed for their eligibility for liver transplantation according to the Mayo clinic protocol[26] (and included in the non-resected group for our study because of the intention-to-treat analysis). No further procedures were performed during this exploratory surgery.

The whole cohort was divided into two groups: a resected group which included patients who underwent liver resection, and an unresected group including the patients who did not undergo operative exploration or underwent exploration alone (no resection). Overall survival (OS) was calculated as the interval between the first outpatient visit and death or the last follow-up visit. The primary endpoint was the detection of predictors of unresectability after PVE for CLCC in an intention-to-treat analysis based on pre-PVE parameters whatever the reasons of unresectability.

This study was approved by the Institutional Review Board for our institution.

Statistical analysis

Categorical variables are described using absolute numbers with percentages. Continuous variables are expressed as medians and ranges. The Chi-square or Fisher exact test was used to compare categorical variables, with Student's *t* test or the Mann-Whitney *U* test for continuous variables. A stepwise logistic regression test was used to detect predictors of unresectability. After univariate analysis, variables with P value <0.1 were included in the multivariate analysis. A P value ≤0.05 was considered to be statistically significant. A prognostic model based on the predictors thus identified (multivariate analysis) was built, and the probability of unresectability was calculated. For each variable considered in the composite model, a receiver operator characteristic (ROC) curve enabled identification of the best cut-off value (Youden index). The

discriminatory power of this model (+1 point when the cut-off point was reached) in predicting unresectability was presented as an AUROC (area under the ROC) and its associated 95% confidence interval. The Kaplan-Meier test was applied for survival analysis and the difference in survival between the groups was compared using a log rank test. All statistical analyses were performed using SPSS statistical software, version 23.0 (SPSS, Inc., Chicago, IL).

RESULTS

Patient characteristics

A total 88 patients were included, 56 (64%) who underwent liver resection after PVE (resected group) and 32 (36%) in the unresected group. Eleven patients (13%) did not undergo operati e l exploration because of the failure of PVE (n=6; 55%), tumor progression detected on post-PVE CT images (n=3; 27%), severe septicemia, septic shock after ERCP leading to multi-organ failure and death (n=1; 9%), and a contraindication to anesthesia (n=1; 9%) (Fig 1). Seventy-seven patients (88%) underwent operative exploration to assess resectability, 21 of whom (24%) were considered to be unresectable. The most frequent reason for unresectability was tumor progression (86%), whether it was intrahepatic or extrahepatic, followed by cirrhotic liver with early signs of portal hypertension and ascites that were not detected in the preoperative imaging (10%); finally, no mass found in the hilar region with a negative frozen section and normal cholangiogram in one patient. The tumor progression was most often found intra-operatively (n=18), mainly in patients diagnosed before 2010 (n=12) due to limited availability of modern imaging in this period.

Patterns of tumor progression

a- Before operative exploration

Three patients (4%) with tumor progression were detected before operative exploration on post-PVE imaging. One patient each developed lung and left suprarenal gland metastases, bone metastasis, and intra-hepatic metastases associated with aorto-caval lymph node metastases diagnosed by PET scan.

b- During operative exploration

Tumor progression was detected intra-operatively in 18 patients (21%) and included local direct extension (n=7), intrahepatic metastases (n=4), and extrahepatic metastases (n=7) in the form of peritoneal metastases (n=5) and LN metastases (n=2).

The demographic, clinical, and pathologic characteristics of both patient groups are summarized in Table 1. Unresected patients displayed a somewhat greater body mass index (BMI) (25.5 vs. 23.7 kg/m^2; p=0.049). As for nutritional parameters (sarcopenia), a greater proportion of patients in the unresected group had a PMI <500 mm^2/m^2 than in the resected group (84% vs 56%; p=0.018, respectively). The PMA/BSA ratio was much less in the unresected group (618 vs. 753 mm^2/m^2; p=0.033). As shown in Table 2, there were more patients with hypoalbuminemia (<35 g/L) and PLR>185 in the unresected group than in the resected group (p=0.046 and p=0.02, respectively).

Preoperative biliary drainage and PVE

There were no differences regarding data on biliary drainage, which were comparable in terms of the number of drainage procedures, the side of the stented bile duct, and post-procedure complications (Table 3). Nine patients (10%) did not undergo biliary drainage before PVE, two of whom were in the unresected group. In relation to PVE, 56 patients (73%) underwent the first biliary drainage (BD) before PVE, 17 patients (22%) underwent biliary drainage and PVE during the same hospitalization, and 3 patients (4%) underwent biliary drainage after PVE before operative exploration. The median interval between the first drainage and the time of operative exploration was greater in unresected patients (90 vs 71 days; p=0.093). Ten patients required a single additional session of PVE to achieve complete occlusion of the targeted branches of the portal vein (seven and three patients in the resected and unresected groups, respectively; p=0.657). The median interval between PVE and operative intervention in the resected group

was 55 days, range (9-323). Note that in one case we observed a long interval between PVE and resection (323 days), because the patient had developed metastases to the hepatic pedicle and celiac LN during the intial post-PVE operative exploration after which he received chemotherapy (GEMOX) and multiple sets of biliary drainage. Then, after re-evaluation, there was a very good response to chemotherapy allowing for complete resection of the tumor and lymphadenectomy. Among the 77 patients who underwent exploration, nine (12%) needed a complementary PVE session due to insufficient FLR leading to a greater interval (> 55 days) until the time of operative exploration.

Complications after PVE

Eighteen of the 88 patients experienced complications after PVE (21%). Major complications (Dindo-lavien ≥ IIIa) occurred in four patients in the resected group and two in the unresected group. In the resected group, two perihepatic collections and one liver abscess required percutaneous drainage, while one case of hematoma in the mesentery of the right colon leading to severe ischemia required right hemicolectomy. In the unresected group, one patient developed liver failure with encephalopathy associated with pneumonia and sepsis which required management on the intensive care unit, and another experienced a pneumothorax requiring the insertion of a pleural catheter.

Failure of PVE

PVE failed in nine patients (28%) in the unresected group: four patients with erratic embolization (two with embolization of the portal branches of the FLR, one with incomplete occlusion of the portal branches in the diseased part of the liver that would be resected, and one who presented with both events), two with portal vein thrombosis of the FLR, one with

insufficient hypertrophy of FLR, one lost to follow-up after PVE, and one with severe portal hypertension contraindicating PVE. Three of these 9 patients achieved unsatisfactory hypertrophy with borderline FLRV and underwent exploration and finally were not resected due to advanced disease (n=2) and cirrhosis with ascites (n=1). In the resected group, two patients presented with erratic embolization; the first was prepared for extended right hepatectomy and developed thrombosis of the proximal part of the left portal vein of the FLR while the right anterior sectorial portal branch was still permeable with insufficient hypertrophy (FLR/BWR=0.4%); therefor this patient underwent an additional PVE; in the second case, accidental embolization of the contralateral side occurred, but sufficient hypertrophy was achieved (FLR/BWR=0.64).

Operative and post-operative outcomes in the resected group

There were 79% and 21% of right (± extended) and left extended hepatectomies, respectively as shown in Table 4. Eighteen patients (32%) underwent portal vein reconstruction, while arterial resection was performed in 5 (9%) cases. Two patients underwent resection under venovenous bypass. The 90-day post-resection mortality rate was 16% (9 patients). The most common cause of mortality was post hepatectomy liver failure(defined according 50/50 criteria[27]) in 6 patients (11%) followed by infectious complications with septicemia and septic shock in 3 patients (5%) due to biliary fistula (n=2), and leakage from distal entero-enteric anastomosis with peritonitis (n=1). There was no difference in the post-PVE FLR volume between survivors and early death patients (p=0.592). Median OS was greater in the resected than in the unresected group (30.2 vs. 17.2 months, respectively; p=0.119).

Management of unresected patients

Three patients (9%) in the unresected group underwent liver transplantation according to the Mayo clinic protocol[26], two of whom had long overall survival (89 and 139 months), 19 patients (59%) received palliative chemotherapy, palliative care (n=8), and 2 patients were lost follow up. Recurrent cholangitis in all patients was managed by repeated biliary stents either by endoscopic (n=26) or percutaneous approaches (n=5); one patient was managed by hepatico-enterostomy (Roux-en-Y). One patient underwent right hemicolectomy due to intestinal obstruction because of of peritoneal carcinomatosis.

Long-term outcomes following PVE

The median follow-up of the entire cohort was 21.2 [0.8 – 142.2] months. Resected patients had better OS than those not resected (1-y, 3-y, 5-y OS=70%, 578%, and 25% vs. 75%, 22%, 18%; p=0.006) as shown in Figure 2. Sarcopenia did not associate with any difference in OS between the resected and unresected groups (median OS of 15.4 months and 21.9 months, respectively; p=0.783). There was no difference in OS between the PHCC and IHCC (p=0.359), while IHCC had worse DFS than PHCC (p=0.018) in the resected group.

Predictors of unresectability after PVE

Univariate and multivariate analyses of the predictors of unresectability after PVE are detailed in Table 5. Univariate analysis found that PMI <500 mm^2/m^2, a low PMA/BSA, a low serum albumin level, and PLR>185 were associated with a greater rate of unresectability. PMI <500 mm^2/m^2 (OR=6.030; p=0.040; 95% CI 1.218–37.981), high BMI (OR=1.346; p=0.023; 95% CI 1.041–1.741), and low serum albumin levels (OR=1.793; p=0.007; 95% CI 0.669–0.939) were independent predictors of unresectabilty after PVE under multivariate analysis.

Using ROC curve analyses to predict unresectability, the best cut-off point for albumin was 33 g/L (AUC=0.723; *p*=0.001; 95% CI 0.605 – 0.841), while for BMI it was 24.8 kg/m^2 (AUC=0.620; *p*=0.020; 95% CI 0.529 – 0.770). In addition, we built a score using these three independent predictors of unresectability (PMI< 500 mm^2/m^2, albumin ≤ 33 mg/L, and BMI ≥ 24.8 kg/m^2). We stratified this score over 0 – 3 points, with one point for each factor present. The incidence of unresectability with scores of 0, 1, 2, and 3, were 0%, 5%, 54%, and 64%, respectively (p <0.001). This score achieved very good discrimination with respect to unresectability (AUC=0.817), as shown in Figure 3.

<u>In univariate analysis of predictive factors of PHLF and 90-day mortality in the resected group, PMI <500 mm^2/m^2, serum albumin ≤33 mg/L, and BMI ≥24.8 kg/^{m2} were not significant predictors.</u>

DISCUSSION

This is the first study to have demonstrated that a low PMI, high BMI, and low serum albumin level are independent predictors of unresectabilty after PVE. These findings highlight the negative impact of sarcopenia as an important risk factor for unresectability after PVE for CLCC. This simple score proposed, available at the first consultation, can discriminate accurately (AUC=0.817) the chance of resectability.

Sarcopenia is defined as a syndrome characterized by a progressive and generalized loss of skeletal muscle mass and strength[28,29] and is associated with several cancers[30,31]. Preoperative sarcopenia is a poor prognostic factor after hepatic, biliary, or pancreatic surgery[32,33].In contrast, obesity represents a substantial risk factor for many health disorders, including cholangiocarcinomas[34,35], and is associated with poor outcomes in patients with hepatocellular carcinoma[36]. The combined condition of sarcopenia and obesity, or sarcopenic obesity, has been described as a prognostic factor for poor outcomes in the case of solid tumors[37], but not until now in the setting of CLCC assessment.

In the present series, we showed that 84% of patients in the unresected group had sarcopenia with PMI <500 mm^2/m^2 and a greater BMI than the resected group. There was no difference in OS between resected and unresected sarcopenic patients (p=0.783), although resected sarcopenic patients tended to present a poorer OS (three unresected patients were transplanted, thus increasing the OS of the whole subgroup). In a retrospective study of Coelen et al.[38] showed that low skeletal muscle mass (<46.8 cm^2/m^2 in males and <39.1 cm^2/m^2 in females) was an independent predictor of early postoperative mortality (p=0.009) and poor OS (HR=2.02; p=0.020; 95% CI 1.12 – 3.65), while in our study, a low PMI (<500 mm^2/m^2) was not a predictor for 90-day mortality and poor OS (p=0.201). Van Vugt et al.[39] showed that low skeletal muscle mass did not indicate a difference in OS in any treatment group (resected, laparotomy without

resection, initially unresectable), and the same finding was shown in the present study. To date, no reports have assessed the predictive effect of sarcopenia on the resectability of patients.

A high PLR has been reported as affecting the development of sarcopenia[40,41] and promoting tumor progression and hematogenous metastases[42,43]. In our study, a PLR >185 was a risk factor for unresectability under univariate analysis (p=0.023) but did not reach a level of significance under multivariate analysis (p=0.072).

Previous studies have reported that lower serum albumin levels were a poor prognostic indicator of survival in several cancers regardless of therapeutic management[44,45]. In the study by Waghray et al.[46], a serum albumin level <30 g/L was identified as an independent predictor of OS after resection of hilar cholangiocarcinoma (HR 0.31; 95% CI 0.14–0.70). During our study, serum albumin levels (≤ 33g/L) were found to be an independent risk factor for unresectability after PVE. This observation could be explained by cancer cachexia and an inflammatory response resulting in an increase in the catabolic state, a loss of vital body proteins, and changes to immune status with tumor progression[46].

The aforementioned results of recent studies have demonstrated the importance of perioperative nutritional therapy and regular exercise in preventing frailty, improving skeletal muscle mass and physical function and achieving an improvement in OS[47,48]. The preoperative immunonutrition was reported to have improved the outcome of liver resection for cancer[49]. Improving nutritional status in icteric patients remains somewhat theoretic and is quite complicated and unreliable. In fact, most CLCC patients in our study presented with jaundice, abdominal pain, and anorexia, resulting in multi-parametric malnutrition with low serum albumin levels. Because we have shown that unresectability after PVE was not affected by biliary drainage before PVE but was only predicted by nutritional parameters, and in the knowledge that

the nutritional status of patients is closely related to biliary excretion in the digestive tract, patients should be drained internally before PVE in order to improve their nutritional parameters.

As a consequence, we propose that the early detection and treatment of sarcopenia, obesity, and malnutrition using different strategies may improve the resectability rate. For example, high risk patients (score 3) should receive an effective preoperative rehabilitation program with specific nutritional therapy to improve their nutritional status, sufficient biliary drainage, and re-evaluation of the surgical strategy to gain time before tumor progression without losing the chance of curative resection,although their score predicts high unresectability rate. In the view of shortening the delay before operation and consequently the risk of cancer progression and reducing post-PVE complications (21%), one could propose in the rare cases where both types of hepatectomy are indicated -i.e. right extended or left extended sides- recommending a left-extended hepatectomy without PVE (often possible) rather than a right-extended hepatectomy that requires complex preparation; although this strategy is surgically more demanding, it may offer more rapid surgical exploration.

Finally, the 90-day mortality rate (16%) in the resected group of our series was comparable to that reported in recent western studies (17.6% & 16.2%)[50,51] but was greater than that reported in the meta-analysis by Franken et al.[52] of patients in Western centers. These results were poorer than those reported in the Eastern centers. Note that as a tertiary reference center, we often accept "marginal indication" patients contra-indicated by other teams (Bismuth type IV in 17 patients for example), and that might be the explanation for observed high postoperative mortality observed.

The principal strength of this study was its innovative subject, because it is the first study to have identified predictors of unresectability after PVE for CLCC. Our findings support

previously published variables in comparable situations with clear cut-off points, thus reflecting the validity of our statistical analysis. The identified predictors of unresectability are simple, objective, and easily applicable to in the clinical practice of all teams. We were also able to propose a new score with high predictive value that could have a major impact on detecting high-risk patients in terms of their unresectability after PVE, thus modifying the treatment strategies implemented to improve outcomes.

The present study had several limitations. First, it was retrospective in design. Second, it was conducted at a single center on a relatively small patient cohort, so the results should be interpreted with caution. Third, the patients enrolled in the study were operated on over a long period (2000-2018) which could have introduced some bias, particularly with the high rate of missing data; however, there was no radical change in the perioperative management, and in particular, we did not yet introduce enhanced rehabilitation program routinely. Moreover, no external validation was performed to validate our prognostic score, so additional, multicentric prospective studies are recommended to validate our findings, and also to evaluate the potential benefit of immunonutrition in this setting.

In c0nclusion. sarcopenia, a high BMI, and low serum albumin levels prior to PVE were independent predictors of unresectability after PVE for CLCC under this intention to treat analysis. These are simple, objective, and inexpensive parameters that should be considered in all CLCC patients in whom PVE is planned before operative exploration for resection of CLCC to enable risk stratification and clinical decision-making. The early detection and management of these risk factors could improve resectability rates after PVE as well overall survival. A change

of strategy to avoid PVE, when possible, could also be advocated. The external validation of these results is now required.

COI/ DISCLOSURE

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FIGURE LEGENDS

Figure 1. Treatment flow chart of the study population and the causes of unresectability after PVE

Figure 2. Overall survival curves in resected & unresected groups

Figure 3. Receiver operator characteristic (ROC) curve analysis of our composite risk score to predict the unresectability after PVE

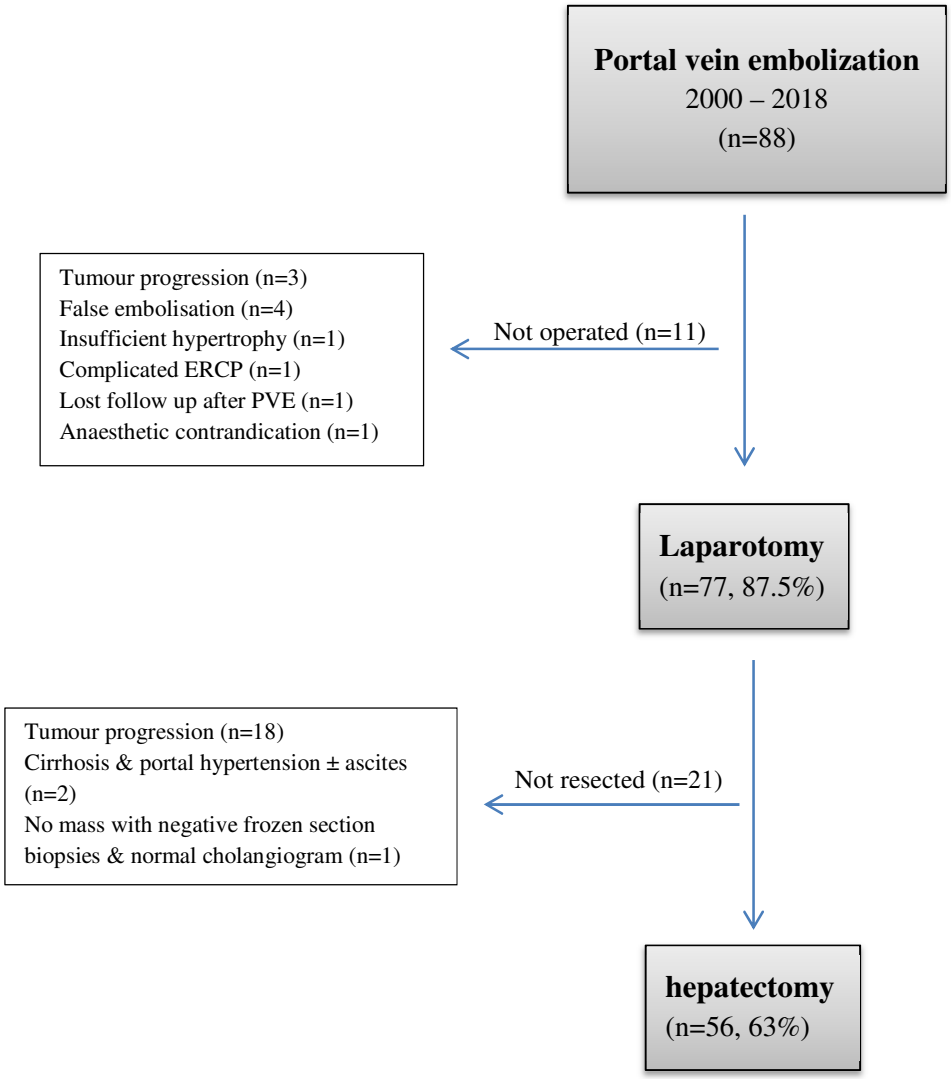
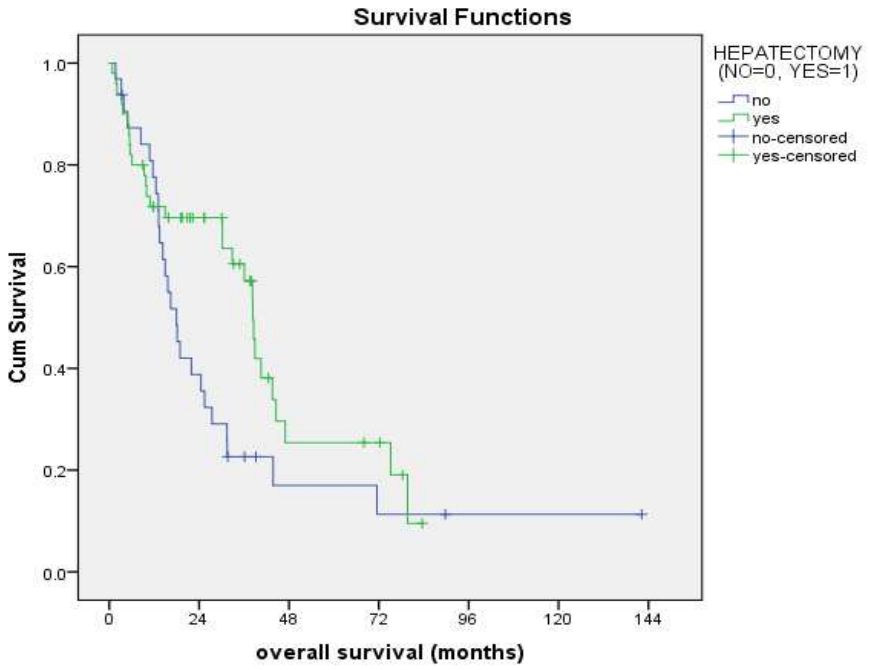


Figure 1. Treatment flowchart of the study population and the causes of unresectability after PVE



No. at risk	1y	3y	5y	7y	10y
Unresected group (n=32)	24	6	3	2	1
Resected group (n=56)	39	21	7	1	0

Figure 2. Overall survival curves in resected & unresected groups.

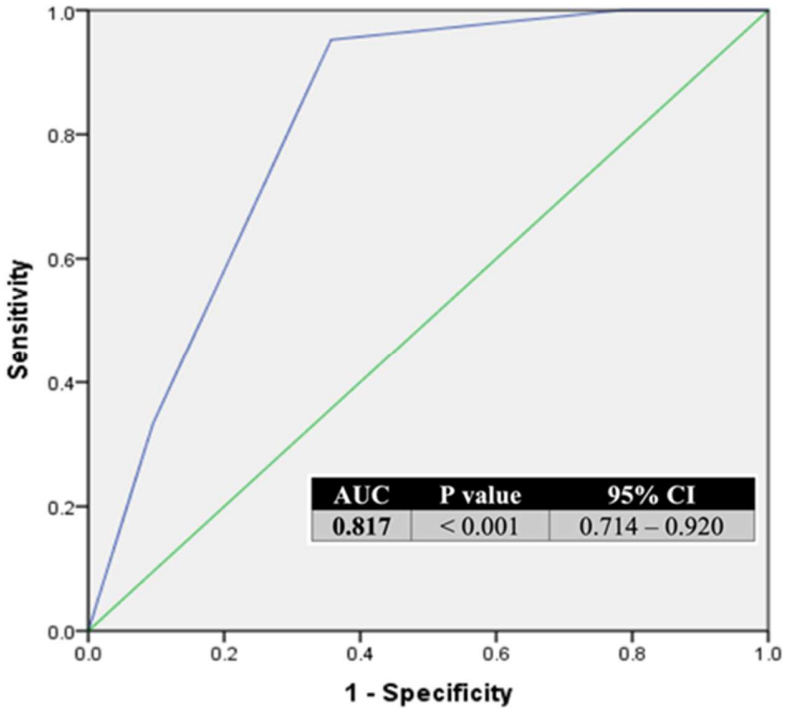


Figure 3. Receiver operator characteristic (ROC) curve analysis of our composite risk score to predict the unresectability after PVE

Table 1. Demographic data and preoperative nutritional and radiologic assessment.

Variables*	Resected (N=56)	Unresected (N=32)	P value
Demographic data			
Sex			
- Male	35 (63%)	23 (72%)	0.372
- Female	21 (38%)	9 (2%)	
Age (y)	64 [38 – 81]	65.5 [35 – 85]	0.677
Past-cholecystectomy			0.341
- Yes	5 (9%)	5 (16%)	
- No	51 (91%)	27 (84%)	
Smoking:			
- Yes	17 (30%)	11 (34%)	0.697
- No	39 (70%)	21 (66%)	
History of other cancers			
- Yes	8(14%)	3 (9%)	0.503
- No	48 (86%)	29 (91%)	
Chronic renal failure			
- Yes	3 (5%)	0 (0%)	0.183
- No	53 (95%)	100 (100%)	
Dyslipidemia			
- Yes	10 (18%)	6 (19%)	0.917
- No	46 (82%)	26 (81%)	
Hypertension			
- Yes	22 (39%)	13 (41%)	0.902
- No	34 (61%)	19 (59%)	
Diabetes mellitus			
- Yes	9 (16%)	4 (13%)	0.650
- No	47 (84%)	28 (88%)	
Preoperative nutritional assessment			
BMI (kg/m^2)	23.7 [17.3 – 32.1]	25.5 [17.9 – 34.8]	0.049
PMA at L3 (mm^2)	1367.4 [561.2 – 2360]	1129 [698.2 – 2430]	0.072
PMI (mm^2/m^2)	449.2 [211.2 – 719.1]	395.3 [220.4 – 750]	0.083
PMI < 500 (mm^2/m^2)			
- Yes	27 (56%)	21 (84%)	
- No	21 (44%)	4 (16%)	0.018
BSA (m$^{2)}$	3.19 (1.93 – 5.89)	3.4 (1.69 – 5.32)	0.223
PMA/BSA (mm^2/m^2)	753.2 [373 – 1203.2]	617.5 [346.8 – 1115]	0.033
Preoperative radiological features			
Tumour site			
- Perihilar	50 (89%)	29(91%)	0.842
- Intrahepatic	6 (11%)	3 (9%)	
Tumour side			
- Right	35 (63%)	19 (59%)	0.714
- Left	4 (7%)	4 (13%)	
- Bilateral (IV)	17 (30%)	9 (28%)	
Bismuth classification of PHCC			
- IIIa	34 (68%)	19 (66%)	0.695
- IIIb	5 (10%)	4 (14%)	
- IV	11 (22%)	6 (21%)	
Tumour size (mm)	21.6 [8 – 62]	22 [7 – 45]	0.935
- ≥30mm	15 (33%)	7 (24%)	0.443
- <30mm	31 (67%)	22 (76%)	
FRV/TLV, pre-PVE	23.8 [11.8 – 47.5]	24.9 [11 – 51.2]	0.425
FRV/BW, pre-PVE	0.54 [0.2 – 0.99]	0.6 [0.24 – 1.08]	0.261
FRV/TLV, post-PVE	34.9 [17 – 61]	35 [17 – 78.7]	0.959
FRV/BW, post-PVE	0.75 [0.4 – 1.6]	0.9 [0.35 – 1.87]	0.086
Hypertrophy (ml), (post FLRV-pre FLRV)	160.5 [-21 – 441]	124.5 [20 – 638]	0.679

Hypertrophy %	39 [-3 – 155]	33.3 [3 – 154]	0.298

** All continuous variables are expressed in median [range]. BMI: body mass index. PMA: psoas muscle area. PMI: psoas muscle index. BSA: body surface area. PHCC: perihilar cholangiocarcinoma. FLRV: future liver remnant volume. TLV: total liver volume. BW: body weight. PVE: portal vein embolization.*

Table 2. Preoperative laboratory assessment

Variables*	Resected (N=56)	Unresected (N=32)	P value
Hemoglobin (g/dl)	12.5 [8.3 – 15.4]	11.9 [8.2 – 14.3]	0.162
Platelets (×1000)	295 [158 – 648]	333 [145 – 803]	0.490
Bilirubin (µmol/L)			
- Total	31.2 [5 – 568]	38 [7 – 390]	0.145
- Direct	18.5 [2 – 185]	28 [1 – 335]	0.366
ALAT (U/L)	66 [12 – 542]	68 [21 – 397]	0.748
ASAT (U/L)	55 [16 – 309]	63 [24 –347]	0.323
GGT (U/L)	345 [26 – 2112]	462.5 [32 – 1910]	0.245
Prothrombin time	91 [60 – 100]	81.5 [58 – 100]	0.016
INR	1.06 [0.89 – 1.47]	1.15 [0.96 – 1.5]	0.014
Albumin (g/L)	34.7 [22.4 – 41.8]	30.2 [20 – 37.8]	0.002
Albumin (g/L)			
< 35	28 (56%)	22 (79%)	0.046
≥ 35	22 (44%)	6 (21%)	
C-reactive protein (mg/L)	9.1 [1 – 163]	33 [4.7 – 87.7]	0.027
Creatinine (µmol/L)	71.5 [46 – 137]	72 [42 – 117]	0.630
CEA (µg/L)	2.4 [0.5 – 45.9]	2.2 [1 – 29.9]	0.862
CA19-9 (kU/L)	75 [0.8 – 10631.2]	176 [2 – 4867]	0.155
ICG %	11 [1.4 – 38.1]	8.9 [3 – 61]	0.308
NLR	2.9 [1.06 – 9.74]	3.12 [0.9 – 13.96]	1.000
NLR			
- > 2.8	29 (56%)	17 (61%)	0.670
- > 3	24 (46%)	14 (50%)	0.742
- ≥ 5	11 (21%)	6 (21%)	0.977
- ≥ 2.49	37 (71%)	18 (64%)	0.527
- > 3.3	22 (42%)	13 (46%)	0.723
PLR	181.38 [79 – 419.7]	217.7 [49 – 863.4]	0.054
PLR			
- > 185	25 (48%)	21 (75%)	0.020
- ≤ 185	27 (52%)	7 (25%)	

**all continuous variables are expressed in median [range]. ALAT: alanine aminotransferase. ASAT: aspartate aminotransferase. GGT:gamma glutamyl transpeptidase. INR:international normalized ratio. CEA: Carcinoembryonic antigen. CA19-9: cancer antigen. ICG: indocyanine green. NLR: neutrophil-to-lymphocyte ratio. PLR: platelet-to-lymphocyte ratio.*

Table 3. Preoperative preparation (biliary drainage and portal vein embolization).

Variables*	Resected (N=56)	Unresected (N=32)	P value
Bilirubin before drainage (µmol/L)	115 [6 – 493]	204 [16 – 640]	0.149
Bilirubin after drainage (µmol/L)	17 [5 – 150]	21 [7 – 124]	0.333
Decrease in bilirubin (µmol/L)	89 [-22 – 480]	182 [- 30 – 608]	0.154
Biliary drainage			
- Yes	49 (88%)	30 (94%)	0.352
- No	7 (13%)	2 (6%)	
ERCP			
- Yes	40 (71%)	23 (72%)	0.964
- No	16 (29%)	9 (30%)	
Side of stented hepatic duct			
- Right	11 (20%)	2 (6%)	0.246
- Left	18 (32%)	11 (34%)	
- Bilateral	10 (18%)	10 (31%)	
Number of ERCP			
- 1	20 (50%)	12 (52%)	
- 2	10 (25%)	6 (26%)	0.735
- 3	7 (18%)	2 (9%)	
- 4	1 (3%)	2 (9%)	
- 5	2 (5%)	1 (4%)	
Complications after ERCP			
- Yes	14 (35%)	10 (44%)	0.527
- No	26 (65%)	13 (57%)	
PTD			
- Yes	17 (30%)	16 (50%)	0.067
- No	40 (70%)	16 (50%)	
Number of PTD			
- 1	4 (24%)	8 (50%)	
- 2	7 (41%)	6 (38%)	0.146
- 3	4 (9%)	0 (0%)	
- 4	2 (12%)	2 (13%)	
Complications after PTD			
- Yes	4 (24%)	3 (19%)	0.710
- No	13 (77%)	13 (81%)	
Total number of drainage	2 [1 – 7]	1 [1 – 7]	0.799
Interval between 1st drainage & surgery (days)	71.5 [50 – 116]	90 [58 – 167]**	0.093
Interval range between 1st drainage & operation			
- <90 days	20 (36%)	10 (48%)	0.369
- ≥90 days	35 (64%)	11 (52%)	
Side of 1st PVE			
- Right	48 (86%)	25 (78%)	
- Left	1 (2%)	3 (9%)	0.256
- Mixed	7 (13%)	4 (13%)	
Approach of 1st PVE			
- Ileal	22 (41%)	18 (55%)	0.372
- Percutaneous	33 (59%)	14 (46%)	
Embolization material**			
- Histoacryl	28 (58%)	20 (63%)	0.573
- Ethanol	21 (44%)	12 (38%)	
Complementary PVE#	7 (13%)	3 (9%)	0.657
Approach of 2nd PVE			
- Ileal	1 (14%)	2 (67%)	0.098
- Percutaneous	6 (86%)	1 (33%)	
Complication of PVE	12 (21%)	6 (19%)	0.961
- False embolization	3 (25%)	4 (67%)	

a- Portal br. of FLR	1	2	
b- Partial occlusion	2	2	
- PV thrombosis of FLR	0 (0%)	2 (29%)	
a- Left branch	0	1	
b- Right posterior branch	0	1	
- Perihepatic collection	2 (17%)	0 (0%)	
- Liver abscess	1 (8%)	0 (0%)	
- Liver failure	0 (0%)	1 (14%)	
- Fever & cholangitis	4 (33%)	1(14%)	
- Others:##	3 (25%)	1(14%)	
Interval between PVE & surgery (days)	55 [9 – 323]	55 [36 – 105]¥	0.083

** all continuous variables are expressed in median [range]. ¥ these cases were operated but no resected. ** one case in resected group injected by both ethanol & histoacryl. # all cases of complementary PVE are of right posterior portal branch. ## hypotension, right colon ischemia, allergic reaction in resected group, pneumothorax in unresected group. ERCP: endoscopic retrograde cholangiopancreatography. PTD: percutaneous transhepatic drainage. FLR: future liver remnant. PVE: portal vein embolization.*

Table 4. Intra-operative data of the resected group (N=56)

Variable	**Number (%)**
Stages of hepatectomy	
- One stage	55 (98%)
- Two-stage (ALPPS)	1 (2%)
Procedure	
- Right hepatectomy	6 (11%)
- Right extended hepatectomy	38 (68%)
- Left extended hepatectomy	12 (21%)
Vascular resection	
- Portal vein	18 (32%)
- Hepatic artery	5 (9%)
- Inferior vena cava	1 (2%)
Blood loss (ml)	1400 (300 – 8000)
Blood transfusion	26 (46%)
Number of units	3 (1 – 18)
Operative time (min)	485 (267 – 770)

Table 5: Predictors of unresectability after PVE (logistic regression analysis)

	Univariate analysis			**Multivariate analysis**		
	P value	**OR**	**95%CI**	**P value**	**OR**	**95%CI**
Age (y)	0.631	0.990	0.948 – 1.033	-	-	-
BMI (kg/m2)	0.074	1.123	0.989 – 1.276	0.023	1.346	1.041 – 1.741
PMI < 500 (mm2/m2)	0.023	4.083	1.215 – 13.718	0.040	6.030	1.218 – 37.981
PMA/BSA	0.048	0.997	0.995 – 1	0.145	1.006	0.998 – 1.014
FRV/TLV, pre-PVE	0.365	0.978	0.933 – 1.026	-	-	-
FRV/BW, pre-PVE	0.612	1.068	0.829 – 1.375	-	-	-
Tumor size ≥3cm	0.434	1.521	0.532 – 4.348	-	-	-
Bilirubin before drainage (umol/L)	0.121	0.997	0.994 – 1.001	-	-	-
Albumin (g/L)	0.001	0.840	0.755 – 0.936	0.007	1.793	0.669 – 0.939
C-reactive protein (mg/L)	0.290	1.009	0.993 – 1.025	-	-	-
GGT	0.252	1.001	1.000 – 1.001	-	-	-
CA19-9 ≥ 300	0.915	1.056	0390 – 2.854	-	-	-
NLR > 2.49	0.528	1.370	0.515 – 3.646	-	-	-
PLR > 185	0.023	3.240	1.176 – 8.929	0.072	4.780	0.871 – 26.229
ERCP	0.964	0.978	0.373 – 2.566	-	-	-
PTD	0.070	2.294	0.935 – 5.626	0.191	3.174	0.562 – 17.931

BMI: body mass index. PMI: psoas muscle index. PMA: psoas muscle area. BSA: body surface area. FRV: functional residual liver volume. TLV: total liver volume. BW: body weight. PVE: portal vein embolization. GGT: gamma glutamyl transferase. CA: cancer antigen. NLR: neutrophil/lymphocyte ratio. PLR: platelets/lymphocyte ratio. ERCP: endoscopic retrograde cholangio-pancreatography. PTD: percutaneous transhepatic drainage. OR: odds ratio. 95%CI: 95% confidence interval.