Research Article
Cirrhosis

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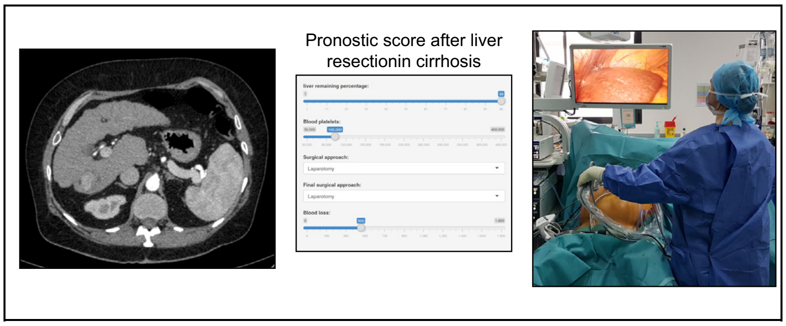
An ordinal model to predict the risk of symptomatic liver failure in patients with cirrhosis undergoing hepatectomy

Graphical abstract



Highlights

- Laparoscopy reduces the risk of liver failure after resection in a cirrhotic liver.
- Remnant to total liver volume and platelets are other predictors of liver failure.
- Intraoperative blood loss is a postoperative predictor of liver failure.
- Predictive models are available at: https://prodeau.shinyapps.io/shiny/.

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Lay summary

In patients with liver cirrhosis, the risk of a hepatectomy is difficult to appreciate. We propose a statistical tool to estimate this risk, preoperatively and immediately after surgery, using readily available parameters and on online calculator. This model could help to improve the selection of patients with the best risk-benefit profiles for hepatectomy.

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An ordinal model to predict the risk of symptomatic liver failure in patients with cirrhosis undergoing hepatectomy

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Background & Aims: Selection criteria for hepatectomy in patients with cirrhosis are controversial. In this study we aimed to build prognostic models of symptomatic post-hepatectomy liver failure (PHLF) in patients with cirrhosis.

Methods: This was a cohort study of patients with histologically proven cirrhosis undergoing hepatectomy in 6 French tertiary care hepato-biliary-pancreatic centres. The primary endpoint was symptomatic (grade B or C) PHLF, according to the International Study Group of Liver Surgery's definition. Twenty-six preoperative and 5 intraoperative variables were considered. An ordered ordinal logistic regression model with proportional odds ratio was used with 3 classes: O/A (No PHLF or grade A PHLF), B (grade B PHLF) and C (grade C PHLF).

Results: Of the 343 patients included, the main indication was hepatocellular carcinoma (88%). Laparoscopic liver resection was performed in 112 patients. Three-month mortality was 5.25%. The observed grades of PHLF were: 0/A: 61%, B: 28%, C: 11%. Based on the results of univariate analyses, 3 preoperative variables (platelet count, liver remnant volume ratio and intent-to-treat laparoscopy) were retained in a preoperative model and 2 intraoperative variables (per protocol laparoscopy and intraoperative blood loss) were added to the latter in a postoperative model. The preoperative model estimated the probabilities of PHLF grades with acceptable discrimination (area under the receiver-operating characteristic curve [AUC] 0.73, B/C *vs.* 0/A; AUC 0.75, C *vs.* 0/A/B) and the performance of the postoperative model was even better (AUC 0.77, B/C *vs.* 0/A; AUC 0.81, C *vs.* 0/A/B; p <0.001).

Conclusions: By accurately predicting the risk of symptomatic PHLF in patients with cirrhosis, the preoperative model should be useful at the selection stage. Prediction can be adjusted at the end of surgery by also considering blood loss and conversion to laparotomy in a postoperative model, which might influence postoperative management.

Lay summary: In patients with liver cirrhosis, the risk of a hepatectomy is difficult to appreciate. We propose a statistical tool to estimate this risk, preoperatively and immediately after surgery, using readily available parameters and on online calculator. This model could help to improve the selection of patients with the best risk-benefit profiles for hepatectomy.

Introduction

The safety of elective hepatectomies in cirrhotic patients has increased significantly during the last decades but mortality of such procedures is still estimated between 3 and 14%.[1] Post-hepatectomy liver failure (PHLF) is the most worrisome complication, with a reported mortality as high as 50%.[2,3] Moreover, it is the leading cause of prolonged hospitalization, increased costs, and poor long-term outcomes in patients undergoing this surgical procedure.

The need to predict the risk of PHLF should be a major concern before performing a liver resection in a patient with cirrhosis, especially since the main indication is represented by hepatocellular carcinoma (HCC), which may be treated by other options, such as liver transplantation, thermo-ablation or transarterial chemo-embolization. However, given the shortage of liver grafts, primary surgical resection is increasingly considered in patients with HCC and could even be an acceptable treatment in selected patients beyond the Barcelona Clinic Liver Cancer (BCLC) criteria,[4] provided that the estimated morbidity

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and mortality rates remain similar to those in the so-called "ideal" patients.[5] Moreover, associating liver resection and liver transplantation, with the use of liver resection as a down-staging or bridging approach,[6] or considering liver transplantation as a salvage therapy in case of HCC recurrence[7] may represent a curative strategy.

Several predictors of PHLF have been reported in patients with cirrhosis, such as model for end-stage liver disease (MELD) score,[8,9] hepatic venous pressure gradient (HVPG),[10–12] indocyanine green (ICG) clearance[13,14] and liver stiffness (LS).[15] In addition, multivariable models or decisional algorithms have been proposed to predict the risk of liver failure and mortality after HCC resection.[2,14,16] However, neither the European Association for the Study of the Liver (EASL) nor the American Association for the Study of the Liver Diseases (AASLD) have retained these models in the current international guidelines for the management of HCC[17] and none of these models has been routinely adopted by other authors. The following may explain the lack of consideration of these tools in clinical practice: (i) some are based on expert opinions rather than statistical methods; (ii) some rely on biological or haemodynamic measurements, such as ICG clearance or HVPG, that are not routinely performed worldwide; (iii) some are derived from studies with heterogeneous inclusion criteria, *e.g.* regarding the proportion of cirrhotic patients[2] or the proportion of HCC;[18] (iv) few of them have been externally validated and a lack of reproducibility has been observed. In addition, several intraoperative variables, such as blood loss and duration of surgery,[19] are not included in these models even though they have been shown to be correlated with PHLF.

The aim of the present study was therefore to determine predictors of symptomatic PHLF, including intraoperative variables, and to build pre- and postoperative models of PHLF in patients with cirrhosis.

Patients and methods

Study design and participants

This study was derived from a larger, prospectively designed, registered (clinicaltrials.gov: NCT01715402), multicentre, non-interventional observational study investigating determinants of the postoperative course following hepatectomy. This trial complies with the TRIPOD statement,[20] and was deemed non-interventional by the ethics committees of participating institutions, approved by the French Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and the agency for data protection. Informed consent was obtained from participating patients.

The present study included all consecutive adult patients from the main cohort, with either suspected or proven liver cirrhosis, undergoing an elective hepatectomy whatever the indications. These included, but were not limited to, HCC. Confirmation of liver cirrhosis was secondarily obtained by pathological examination of the surgical specimen and was defined as the F4-stage of the METAVIR classification.[21] Patients without F4-stage fibrosis were excluded. Other exclusion criteria were: repeat hepatectomy, incomplete data recording of postoperative outcomes and liver cirrhosis caused by obstructive jaundice.

The study duration was 4 years, starting from September 2012 and ending in August 2016. Inclusions were completed in June 2016 to respect a minimum follow-up of 3 months. In all patients, the preoperative work-up was based on either computed tomography (CT) scanning or magnetic resonance imaging, platelet count, liver and kidney function tests, measurement of serum levels of alpha-fetoprotein (AFP) and upper gastrointestinal endoscopy. The decision to extend this work-up by performing ICG clearance measurement, transjugular HVPG measurement and/or LS measurement by Fibroscan™ (Echosens, Paris) was left at each centre's discretion. All cases were discussed at a multidisciplinary oncological board and the decision to proceed with surgery was made on a case-by-case basis. Overall, the main factors that were considered indications for surgery in patients with HCC were a single nodule of any size, without macrovascular invasion, with preserved hepatic function (up to Child-Pugh A6), and provided that sufficient remnant liver volume could be maintained. These criteria correspond more or less to a strong recommendation of the 2018 EASL Clinical Practice Guidelines,[17] which were published posteriorly to the inclusion period of the present study. However, when tumour size was up to 3 cm, percutaneous ablation was considered first. Portal vein embolization (PVE)[22] and/or transarterial chemo-embolization (TACE)[23] were performed prior to surgery in patients with insufficient remnant liver volume (*i.e.* less than 40 to 50% ratio to total liver volume). The indication for a laparoscopic liver resection complied with the recommendations from the first international consensus conference.[24] From May 2015 on, the recommendations from the second international consensus conference[25] were followed. Overall, laparoscopy was considered in all patients without a history of abdominal surgery, with a single nodule of up to 5 cm, located in segments 2 to 6 and resectable by a minor hepatectomy. Intraoperative packed red blood cell transfusions were provided in cases of significant haemorrhage (≥1,500 cc), a drop of intraoperative Hb value under 75 g/L, or ST segment changes. For Hb values between 75 g/L and 95 g/L, packed red blood cell transfusion was discussed in cases of low mean arterial pressure or in patients with a history of coronary artery disease.

Data collection and study endpoints

Twenty-two preoperative variables, which were identified in literature reports as being predictors of postoperative outcome after liver resection in patients with HCC and/or liver cirrhosis, were recorded (Table 1 and Tables S1 and S6).

Intraoperative variables that have been shown to be correlated to postoperative morbidity were also recorded (Table 1 and Tables S1 and S6). Blood loss was estimated by measuring the volume of the suctioned blood in the suction containers and by subtracting the volume of saline irrigation. Additionally, in open liver resections, sponges were weighted at the end of the surgery. The use of a laparoscopic approach was examined either on an intent-to-treat basis (ITT-laparoscopy) or per protocol (PP-laparoscopy), *i.e.* after exclusion of conversion to an open approach.

The primary endpoint was the occurrence of PHLF defined as a 3-class ordinal variable adapted from the International Study Group of Liver Surgery (ISGLS) definition:[26] 0/A for either the absence of PHLF or grade A PHLF; B for grade B PHLF and C for grade C PHLF. In summary, PHLF was defined as an increased international normalized ratio and concomitant hyperbilirubinemia (according to the normal limits of the local laboratory) on or after postoperative day 5; grade A PHLF requires no change of the patient's clinical management; the clinical management of patients with grade B PHLF deviates from the regular course but does not require invasive therapy; the need for

Table 1. Baseline characteristics and intraoperative data in the 343 patients according to ISGLS grades.

Variables	N	ISGLS Grades[1] O/A n = 211	B n = 95	C n = 37	OR (95% CI)	p value
General Variables						
Age* (years)	343	66.0 (10.3)	65.7 (10.2)	65.4 (9.4)	0.96 (0.78–1.19)	0.73
Sex (male)	343	180 (77.9%)	80 (84.2%)	29 (78.4%)	0.78 (0.44–1.38)	0.57
BMI (kg/m^2)	332	26.8 (5.17)	25.7 (4.60)	26.9 (5.10)	0.98 (0.94–1.02)	0.30
Diabetes	343	87 (41.2%)	38 (40.0%)	8 (21.6%)	0.70 (0.45–1.10)	0.12
HCC tumour	343	186 (88.1%)	84 (88.4%)	31 (83.7%)	0.87 (0.46–1.63)	0.67
Preoperative treatment	343	28 (13.3%)	16 (16.8%)	6 (16.2%)	1.28 (0.71–2.30)	0.41
Aetiology of cirrhosis						
Alcohol	343	108 (51.2%)	46 (48.4%)	24 (64.9%)	1.16 (0.76–1.78)	0.49
NASH	343	67 (31.8%)	22 (23.2%)	10 (27.0%)	0.71 (0.44–1.15)	0.22
Viral hepatitis	343	83 (39.3%)	38 (40.0%)	12 (32.4%)	0.91(0.59–1.41)	0.66
Surgical approach[2]						
ITT-laparoscopy	343	89 (42.2%)	18 (18.9%)	5 (13.5%)	0.29 (0.17–0.49)	<0.001
PP-laparoscopy	343	76 (36.0%)	10 (10.5%)	2 (5.4%)	0.18 (0.09–0.34)	<0.001
Variables assessing PHLF						
Ascites	343	5 (2.4%)	2 (2.1%)	1 (2.7%)	0.99 (0.24–4.10)	0.99
Child-Pugh	343	5.36 (0.81)	5.26 (0.50)	5.27 (0.51)	0.80 (0.56–1.12)	0.21
MELD score	329	8.54 (2.29)	8.25 (1.83)	8.21 (2.05)	0.93 (0.84–1.04)	0.21
I-MELD score	321	150 (3.88)	150 (3.85)	149 (4.65)	0.96 (0.90–1.02)	0.24
MELD-Na score	318	9.98 (2.88)	9.60 (2.86)	10.1 (3.36)	0.98 (0.91–1.06)	0.58
ICG-15#	187	14.0 (11.5)	14.8 (10.0)	12.9 (6.91)	1.00 (0.74–1.35)	0.99
AST$	322	52.0 (37.8)	52.5 (34.6)	59.5 (38.1)	1.05 (0.93–1.18)	0.43
ALT$	316	47.2 (38.4)	52.4 (42.4)	61.2 (47.6)	1.10 (0.99–1.22)	0.14
GGT/ALT	314	3.90 (3.40)	3.72 (2.77)	4.89 (5.13)	1.03 (0.97–1.09)	0.39
RTLV†	269	86.8 (16.9)	77.6 (20.8)	71.0 (22.5)	2.10 (1.54–2.86)	<0.001
Variables assessing PHT						
Oesophageal varices	343	14 (6.63%)	11 (11.6%)	1 (2.70%)	1.18 (0.53–2.59)	0.68
Platelet count&	323	17.4 (7.18)	16.0 (7.03)	15.8 (7.00)	0.97 (0.93–1.00)	0.0752
CSPH criteria	343	41 (19.4%)	20 (21.1%)	6 (16.2%)	0.98(0.57–1.68)	0.94
HVPG@ (mmHg)	88	7.19 (3.67)	8.27 (3.00)	8.08 (1.98)	1.52 (0.81–2.82)	0.19
Liver stiffness* (kPa)	143	21.1 (14.2)	24.0 (15.1)	17.4 (13.1)	0.99 (0.78–1.25)	0.92
Spleen volume§ (mm^3)	222	394 (242)	448 (294)	419 (252)	1.11 (0.91–1.36)	0.28
Total liver–spleen volume ratio	222	0.237 (0.172)	0.246 (0.145)	0.248 (0.154)	0.99 (0.98–1.01)	0.80
Remnant liver–spleen volume ratio	214	0.299 (0.209)	0.242 (0.154)	0.218 (0.121)	0.23 (0.069–0.76)	0.013
Intra-operative variables						
Blood loss (ml)	259	437 (397)	642 (428)	895 (478)		<0.001
Linear term					$7.2*10^4$ ($1.1*10^3$ –$4.6*10^6$)	<0.001
Quadratic term					$3.6*10^{-3}$ ($6.5*10^{-5}$-0.20)	0.006
Duration of surgery¥ (min.)	286	220 (86.5)	265 (93.8)	305 (101)	2.27 (1.66–3.11)	<0.001
Liver ischemia time# (min.)	286	8.66 (11.7)	11.3 (15.9)	14.7 (20.1)	1.32 (1.06–1.63)	0.0124
PBRC	184	4 (4.12%)	5 (7.94%)	8 (33.3%)	6.37 (2.41–16.85)	<0.001

Values are count (percentage) or mean (standard deviation).
Ordinal logistic regression model with proportional odds ratio was used to compare variables across the 3 ISGLS grade. For binary variables (Yes/No), the reference is "No".
[1] Post-hepatectomy liver failure was classified according to the International Study Group of Liver Surgery (Rahbari, Surgery 2011).
[2] The use of a laparoscopic approach was examined either on an ITT basis (ITT-laparoscopy) or PP (PP-laparoscopy), *i.e.* after exclusion of conversion to an open approach.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSPH, clinically significant portal hypertension according to the Barcelona Clinic; GGT, gamma glutamyltransferase; HVPG, hepatic venous portal gradient; ISGLS, International Study Group of Liver Surgery; ITT, intent-to-treat; MELD, model for end-stage liver disease; PHT, portal hypertension; PP, per protocol; PRBC, packed red blood cells; RTLV, remnant to total liver volume.
@ Odds ratio per 5 units increase.
* Odds ratio per 10 units increase.
# Odds ratio per 15 units increase.
$ Odds ratio per 20 units increase.
† Odds ratio per 25 units decrease.
¥ Odds ratio per 120 units increase.
§ Odds ratio per 200 units increase.
& Odds ratio per 10,000 units increase.

invasive treatment defines grade C PHLF. Secondary endpoints were 90-day mortality and 90-day morbidity measured by using both the highest Clavien-Dindo grade[27] and the Comprehensive Complication Index (CCI).[28] Severe morbidity was defined as Clavien-Dindo grade IIIB and higher. In order to detect preventable causes of postoperative death, a root-cause analysis was performed in the patients who died within the first 90 days, using the methods described elsewhere.[29]

Statistical analysis

Categorical variables are expressed as counts and percentages. Continuous variables are expressed as mean ± standard deviation or median (interquartile range [IQR]) in case of non-Gaussian distribution. Normality of distribution was checked graphically and by using the Shapiro–Wilk test.

Pearson correlation coefficients were calculated to evaluate the correlations between RTLV and the number of resected segments and between the liver and spleen volumes. Morbidity and mortality outcomes were compared across the 3 ISGLS grades using Chi-square test except for CCI where ANOVA was used.

Missing data for individual variables ranged from 0% for most categorical variables to 74% for HVPG (Fig. S1). To avoid case deletion in analyses, missing data, whatever the reason, were imputed by multiple imputations using the regression-switching approach (chained equations with m = 20 imputations).[30] The imputation procedure was performed under the missing-at-random assumption using all pre- and intraoperative variables and ISGLS grades with the predictive mean-matching method for continuous variables and logistic regression model for binary variables. Rubin's rules were used to combine the estimates derived from multiple imputed data sets. A visual evaluation of kernel density plots for each variable was performed to check the stability of the imputations.

The associations of pre- and intraoperative variables with ISGLS grade were examined using a bivariate ordinal logistic regression model with proportional odds ratio (OR). The proportional odds hypothesis was tested using the score test. The log-linearity assumption for continuous variables was checked graphically by plotting the observed proportions of grade B/C and grade C according to the deciles of continuous variables. All continuous variables were introduced as a linear term since no evidence of non-log-linear relationship was found, except blood loss, which was modelled by including linear and quadratic terms. Variables associated with ISGLS grade in bivariate analyses (p value <0.20) were included in a backward-stepwise multivariable ordinal logistic regression model with proportional OR using a removal significance level of 0.05. Two multivariate analyses were made: one including only preoperative variables (preoperative model), and a second including pre- and intraoperative variables (postoperative model). Finally, we examined the performance of the 2 models in terms of discrimination and performed an internal validation. The discriminations were evaluated for pre- and postoperative models by calculating the area under ROC curve (AUC) to differentiate B/C *vs.* 0/A grades and C *vs.* 0/A/B grades. An AUC greater than 0.7 was considered as an acceptable discrimination. Comparison in model's performance between AUC was made using the bootstrap test. Internal validation was done by using bootstrap resampling with 1,000 repetitions to estimate the AUC corrected for over-optimism and the shrinkage factors.[31] The shrinkage factor is the estimated shrinking in the regression coefficients to improve the prediction in future patients. Calibration analyses were performed using the Lipsitz and Pulkstenis-Robinson tests,[32] which have been developed to assess the calibration of ordinal logistic models. Statistical testing was done at the 2-sided tailed α level of 0.05. Data were analysed using R software version 3.4.4.

For further details regarding the materials used, please refer to the CTAT table and supplementary information.

Results

Descriptive data

The study included 343 patients (see flowchart, Fig. 1). HCC was the main indication for liver resection (87.8% of patients) and alcohol abuse was the main cause of underlying cirrhosis. The liver function was preserved in most patients, with only 20 (5.9%) patients with Child-Pugh B cirrhosis, a mean MELD score of 8.4 ± 0.9 and a mean ICG-R15 of 14.1 ± 10.7. The mean platelet count was 168,000/µl ± 70,000. HVPG and LS were 7.6 ± 3.3 mmHg and 21 ± 14 kPa, respectively. Hepatectomy was anatomical in 211 (61.5%) patients. A laparoscopic approach was performed in 112 patients (32.7% of the whole cohort), and converted to an open approach in 88 (21.5%) of these patients. The mean RTLV ratio was 69% ± 17.4 after anatomical hepatectomy and 97% ± 7.48 after non-anatomical hepatectomy. RTLV ratio was correlated with the number of resected segments (Pearson coefficient: 0.77; 95% CI 0.69–0.83), except in case of major hepatectomy (Pearson coefficient: 0.35; 95% CI 0.07–0.58). The spleen volume was 412 ml ± 259 and was poorly correlated to liver volume (Pearson coefficient:

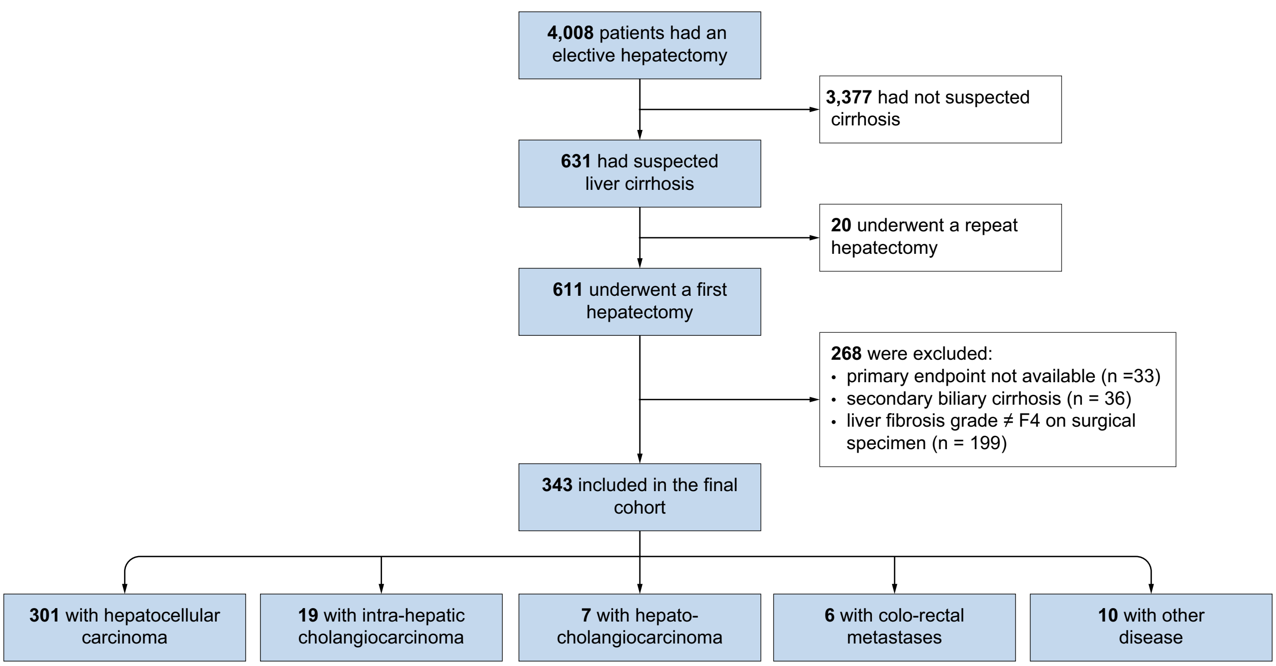

Fig. 1. Flowchart of the cohort used in the study. Three hundred forty-three patients were finally included in the final cohort.

Table 2. Postoperative outcome according to ISGLS grades.

Variable	ISGLS grades[1] O/A	B	C	p value
N	211	95	37	
90-day mortality	4 (1.9%)	4 (4.2%)	10 (27.0%)	<0.001[+]
Dindo-Clavien score				
≥I (*vs.* <I)	117 (34.1%)	94 (98.9%)	37 (100.0%)	<0.001[+]
≥III-B (*vs.* <III-B)	22 (10.4 %)	22 (6.4 %)	19 (51.4 %)	<0.001[+]
CCI	17.4 (21.7)	37.3 (21.1)	62.6 (30.7)	<0.001[¥]

Values are count (percentage) or mean (standard deviation).
ISGLS, International Study Group of Liver Surgery; CCI, Comprehensive Complication Index.
[1] Post-hepatectomy liver failure was classified according to the International Study Group of Liver Surgery (Rahbari, Surgery 2011).
[+] Chi-square test.
[¥] Analysis Of Variance.

0.23; 95% CI 0.10–0.35). The median intraoperative blood loss was 537 ml (IQR 200–775). Baseline patient characteristics and intraoperative data are detailed according to ISGLS grades in Table 1. The same data after multiple imputations are detailed in Table S1.

Overall 90-day mortality was 5.25% and 63 patients (18.4%) suffered from severe morbidity. CCI score was 27.8 ± 27.1. Postoperative outcome is detailed according to ISGLS grades in Table 2. Two hundred and eleven (62%) patients had no symptomatic liver failure (ISGLS 0/A), 95 (28%) patients had moderate symptomatic liver failure (ISGLS B) and 37 (10%) patients had severe symptomatic liver failure (ISGLS C). Morbidity and mortality were significantly different across the 3 groups (Table 2). Eighteen patients died within 3 months after surgery. Four had ISGLS 0/A, 4 had ISGLS B and 10 had ISGLS-C PHLF. The causes of death in patients with ISGLS 0/A/B PHLF were: pulmonary embolism (n = 4), tumour recurrence (n = 2), myocardial infarction (n = 1) and pneumonia (n = 1). A complete root-cause analysis of postoperative deaths in patients with symptomatic PHLF (ISGLS grades B or C) is available in Table S2. This identified a preventable cause of death in 9 patients.

We did not observe any substantial data heterogeneity across the 6 HPB centres for relevant covariates, including age, sex, platelet count, MELD score, RTLV, blood loss and for the main outcomes (Table S3).

Modelling the risk of symptomatic liver failure

Three preoperative variables were retained in the preoperative model: ITT-laparoscopy (yes *vs.* no), platelet count and RTLV (Table 3). ITT-laparoscopy was associated with a lower risk of PHLF (OR 0.31; 95% CI 0.18–0.53), while low platelet count or low RTLV was associated with a higher risk of PHLF.

In the postoperative model, 4 pre- and intraoperative variables were retained: platelet count, RTLV, PP-laparoscopy and blood loss (Table 3). PP-laparoscopy was associated with a lower risk of PHLF (OR 0.25; 95% CI 0.12–0.51). Increased blood loss was associated with a higher risk of PHLF.

Prediction validity of the 2 models

The preoperative model was considered discriminative with an AUC for P (ISGLS B/C *vs.* 0/A) equal to 0.72 and an AUC for P (ISGLS C *vs.* 0/A/B) equal to 0.73. The AUCs of the postoperative model were 0.77 and 0.81 for P (ISGLS B/C *vs.* 0/A) and P (ISGLS C *vs.* 0/A/B), respectively. The postoperative model yielded significantly better predictions than the preoperative one (p <0.001) (Fig. 2).

After bootstrapping 1,000 datasets with replacement, the corrected AUCs for the preoperative model were 0.69 for the discrimination of P (ISGLS B/C *vs.* 0/A) and 0.70 for the discrimination of P (ISGLS B/C *vs.* 0/A). The corrected AUCs for the postoperative model were 0.74 for P (ISGLS B/C *vs.* 0/A) and 0.78 for P (ISGLS B/C *vs.* 0/A). The shrinkage factors estimated after bootstrapping were 0.77 for the preoperative model and 0.85 for the postoperative model. A good calibration was confirmed for both the preoperative and the postoperative models, using the Lipsitz and Pulkstenis-Robinson tests (p values: 0.51 and 0.27, respectively). Calibration plots are available in Fig. S2. The equations allowing computing predicted probabilities are presented in Fig. S3.

Table 3. Predictors of ISGLS grades[1] after multivariate imputed analysis.

Variables	Odds ratio (95% CI)	p value
Preoperative model		
Intended laparoscopic liver resection	0.31 (0.18–0.53)	<0.001
RTLV[†]	1.45 (1.43–1.47)	<0.001
Platelet count[&]	0.70 (0.56–0.89)	0.003
Postoperative model		
Non converted laparoscopic liver resection	0.25 (0.12–0.51)	<0.001
RTLV[†]	1.47 (1.44–1.49)	<0.001
Platelet count[&]	0.75 (0.59–0.95)	0.012
Blood loss		
Linear term	$1.2*10^3$ ($6.8*10^1$–$2.3*10^3$)	
Quadratic term	$6.7*10^{-2}$ ($3.9*10^{-3}$–1.2)	<0.001

ISGLS, International Study Group of Liver Surgery; RTLV, remnant to total liver volume.
Multivariate analyses were performed using an ordinal logistic regression model with proportional odds ratio after handling missing data by multiple imputations.
[1] Post-hepatectomy liver failure was classified according to the International Study Group of Liver Surgery (Rahbari, Surgery 2011).
[†] Odds ratio per 25 units decrease.
[&] Odds ratio per 10,000 units increase.

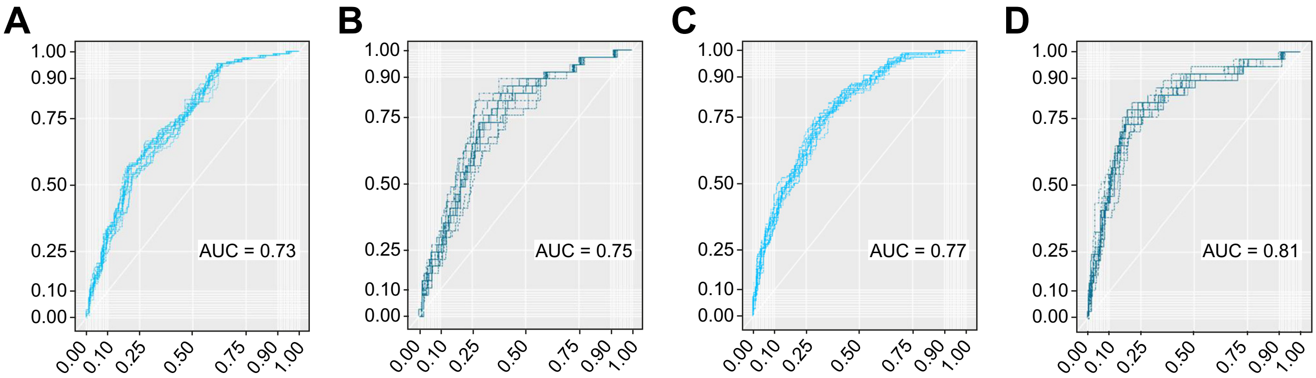

Fig. 2. Receiver-operating characteristic curves and AUC of the 2 predictive models of PHLF. (A) Preoperative model for PHLF grades B/C *vs.* 0/A; (B) preoperative model for PHLF grade C *vs.* 0/A/B; (C) postoperative model for PHLF grades B/C *vs.* 0/A; (D) postoperative model for PHLF grades C *vs.* 0/A/B. PHLF was graded according to the International Study Group of Liver Surgery. Each of the 4 plots represents the 20 receiver-operating characteristic curves corresponding to the 20 imputed datasets. The AUC values summarise the mean of the AUCs from each imputed dataset. AUC, area under the receiver-operating characteristic curve; PHLF, post-hepatectomy liver failure. (This figure appears in colour on the web.)

Predictive ability of the 2 models for secondary endpoints

The AUCs of the preoperative model for the prediction of 90-day mortality and CCI were 0.65 and 0.71, respectively. Those of the postoperative model for the same endpoints were 0.74 and 0.76.

Predictive ability of the 2 models in patients with portal hypertension

Sixty-seven patients (19.5%) presented with clinical signs of portal hypertension (*i.e.* either splenomegaly associated with platelet count <100,000/µl, or oesophageal varices). In those patients, the AUCs of the preoperative model were 0.76 and 0.68 for P (ISGLS B/C *vs.* 0/A) and P (ISGLS C *vs.* 0/A/B), respectively. The AUCs of the postoperative model were 0.77 and 0.69 for P (ISGLS B/C *vs.* 0/A) and P (ISGLS C *vs.* 0/A/B), respectively.

Predictive ability of the 2 models for PHLF after excluding the preventable causes of postoperative death

After excluding 9 patients who died within the first 90 days and in whom a preventable cause of death was detected, the AUCs of the preoperative model for P (ISGLS B/C *vs.* 0/A) and P (ISGLS C *vs.* 0/A/B) were 0.73 and 0.74, respectively. Those of the postoperative model were 0.77 and 0.79.

Discussion

The decision to refer a patient with cirrhosis for an elective hepatectomy is mainly based on a balance between oncologic benefits and perioperative risks with respect to other therapeutic options (liver transplantation or loco-regional therapies). In this study, PHLF in patients with cirrhosis could accurately be predicted before surgery using an ordinal model with no more than 3 usual variables (*i.e.* RTLV, platelet count and ITT-laparoscopy). As PHLF explains most of the postoperative morbidity and mortality in the context of cirrhosis, the probability of PHLF occurrence and the estimation of its severity could be important information during patient selection, either for confirming surgery, choosing the surgical technique or determining the need for dedicated perioperative care. In addition, as soon as surgery was completed, confirming or not the laparoscopic approach and adding intraoperative blood loss to the model significantly improved the predictions. By making the clinician aware of the probability that a patient will develop a symptomatic and/or severe PHLF at the end of surgery, the postoperative model may represent a significant contribution to the postoperative care of those patients.

In the present study, PHLF was the primary endpoint and its definition was based on the ISGLS classification, published in 2011 by Rahbari *et al.*[26]. Skrzypczyk *et al.*[33] showed that the definition of PHLF according to the ISGLS had a better sensitivity compared to the 50–50 and the Peak bilirubin >7 mg/dl criteria to predict major morbidity (35.8% *vs.* 17.4% and 24.8%, respectively) and mortality (56.7 *vs.* 36.7 and 56.7%, respectively). In addition, the ISGLS also proposed a grading of PHLF, which takes into account its clinical impact, with symptomatic PHLF corresponding to classes grades B and C. Therefore, in the present study, patients with grade A PHLF were classified into the same category as those without PHLF, whereas patients with symptomatic PHLF were classified into either grade B or grade C PHLF. Thus, unlike most binary endpoints used in the literature to measure the incidence of PHLF, the main endpoint of the present study was divided into 3 classes of ordered severity. This 3-class endpoint may better reflect the heterogeneity of the postoperative course but needed the use of an ordinal model with proportional odds, producing the probabilities of each class.

In addition to the 26 preoperative variables that were analysed, 5 intraoperative variables were included in the so-called postoperative model. In this study, the risk of PHLF depended not only on preoperative factors but also on intraoperative events, *i.e.* blood loss and full laparoscopic approach. The importance of intraoperative events for the prediction of post-hepatectomy outcomes had been previously speculated[34] but was never clearly demonstrated.

Due to the multicentric design of the study and despite the number of predictors of PHLF that were analysed, some of them were available only for a small proportion of patients. This was the case for ICG-R15, HVPG and LS, which were not performed in all centres. ICG-R15 has been widely adopted in Eastern centres, whereas it is rarely used in Western countries, where the functional liver reserve is mainly evaluated using clinicobiological scores. Moreover, in most French centres, the assessment of portal hypertension before liver resection is usually based on indirect signs (*i.e.* splenomegaly, thrombocytopenia and oesophageal varices), rather than on HVPG or LS, except for major hepatectomy. Thus, more than 50% of data is missing for these 3 variables, so the lack of association between PHLF and either ICG-R15, HVPG or LS should be interpreted with caution. Furthermore, in the centres where HVPG was routinely performed, high HVPG values may have contraindicated liver resection, or led clinicians to use a laparoscopic approach and/or a tumorectomy if feasible. This has obviously introduced a selection bias in the present cohort. However, the preoperative model described herein is based on simple and readily available variables and could be used as a first selection tool for resection in patients with liver cirrhosis, keeping out more sophisticated and/or invasive methods like HVPG measurement as a second step in the selection process. In addition, in the present study, whether ICG-R15, HVPG or LS was routinely used in a centre or performed in a patient did not impact the values of the models' predictors and the main outcomes (Tables S4 and S5).

The relatively high mortality rate observed in the present series (5.25%) deserves some comments: i) its 95% confidence interval is rather large, ranging from 3.14 to 8.17% and the lower limit is close to the value of 3%, which is the expected maximal mortality rate of surgical resection in patients with cirrhosis, recommended in the 2018 EASL guidelines on the management of HCC;[17] ii) this 3% mortality rate is controversial as several recent publications reported higher mortality rates after HCC resection;[5,35–37] iii) in the present study, postoperative mortality was defined as 90-day mortality. In fact, the 30-day mortality rate was 2.3% (8 patients). In several studies, post-hepatectomy mortality is expressed as 30-day or in-hospital mortality. This endpoint does not represent the true mortality since about one-third of all postoperative deaths occur between 1 month and 3 months after liver resection;[38] iv) 4 postoperative deaths occurred in patients with indications other than HCC. In the 14 patients with HCC, the 90-day mortality rate was 4.6% (14 patients); v) all patients included in the present study had histologically proven cirrhosis and this was alcohol-related in more than half of patients. Cirrhosis[36] and alcohol-related liver disease[8,39] had been found to be associated with a higher risk of postoperative mortality; vi) the present study was derived from a multicentre prospectively maintained registry in which unselected consecutive patients undergoing an elective hepatectomy were enrolled. The 30-day mortality rate of 2.3% observed in the present study compares favourably with the 30-day mortality rates of 2.4% and 5.9% which were respectively observed in 2 recent US studies from large national registries, the American College of Surgery National Surgical Quality Improvement Program database and the Veterans Administration Corporate Data Warehouse.[9,37] Furthermore, the 90-day mortality rates were not significantly different across centres. Nevertheless, the models reported in the present series may be used cautiously in centres reporting a very low (near 0%) postoperative mortality.

The complexity of the formulas used in the pre- and the post-operative models may limit their daily applicability. To deal with this difficulty, we developed an R-server website (https://prodeau.shinyapps.io/shiny/), which provides the probabilities of each ISGLS class of PHLF for a given patient. For example, for a patient with 75,000/µl platelet count and a planned laparoscopic resection of 30% of the total liver volume these probabilities are P (ISGLS O/A) = 0.61, P (ISGLS B) = 0.30 and P (ISGLS C) = 0.09. In this patient, if laparoscopy has to be converted to laparotomy with 1,000 ml blood loss, the postoperative probabilities become: P (ISGLS O/A) = 0.21, P (ISGLS B) = 0.44 and P (ISGLS C) = 0.35.

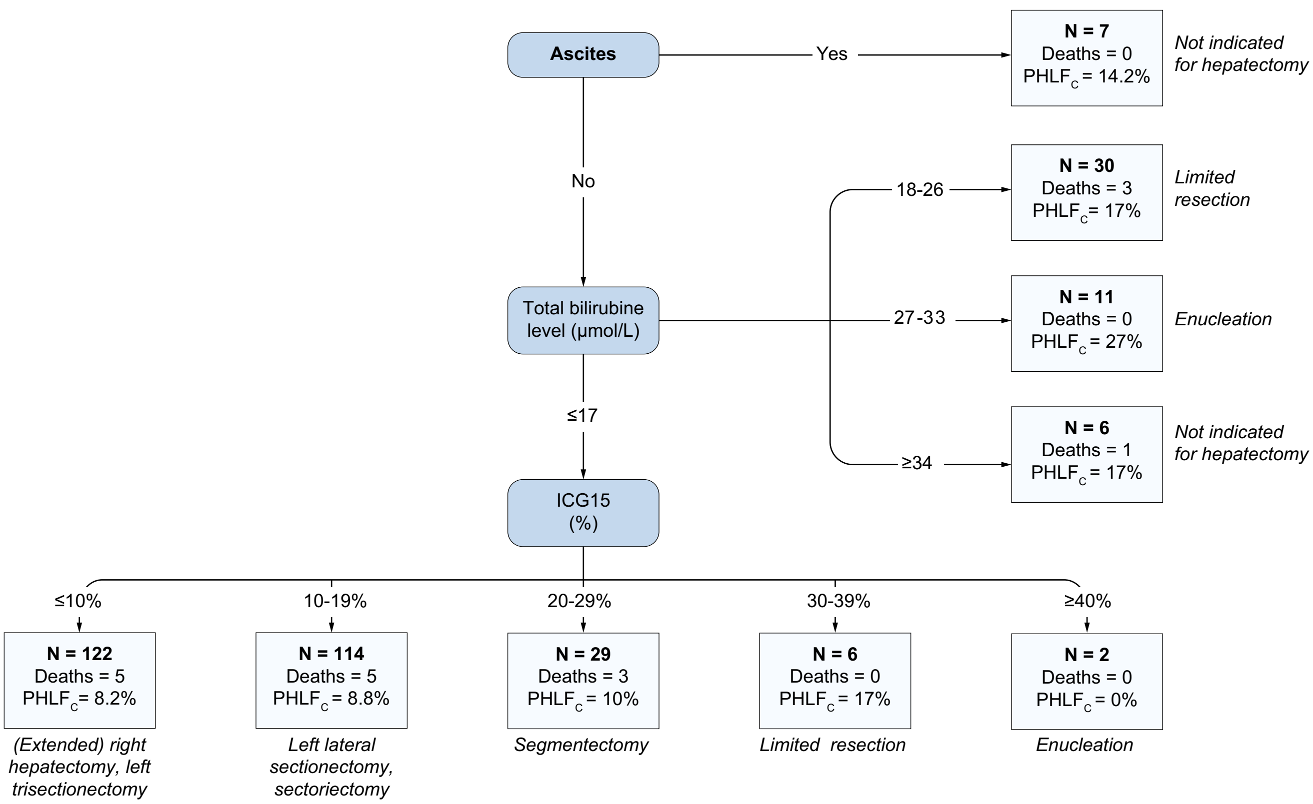

Fig. 3. Application of the Makuuchi's algorithm to the study cohort. Blue boxes indicate the number of patients that would be classified into each of the subgroups, as well as the actual number of postoperative deaths and the actual proportion of grade C post-hepatectomy liver failure according to the International Study Group of Liver Surgery. For each of the subgroups, italic text indicates the maximal extent of liver resection (if any) allowed by the Makuuchi's algorithm. ICG15, indocyanine green clearance at 15 min; $PHLF_C$, grade C post-hepatectomy liver failure.

This study was not designed to predict other clinically relevant outcomes such as 90-day mortality or CCI. Although the AUCs of the models for the prediction of these outcomes were acceptable, this should be interpreted with caution as the variables retained in the models were selected for a different outcome (*i.e.* PHLF grades).

Given the low number of patients with grade C PHLF in the subgroup of patients with portal hypertension, the predictions of the 2 models for P (ISGLS C *vs.* B/A/0) in this subgroup were not accurate. However, for symptomatic PHLF, *i.e.* P (ISGLS B/C *vs.* 0/A) both models had quite high sensitivity and specificity in patients with portal hypertension. The recent AASLD/EASL international guidelines for HCC[17] state that patients with portal hypertension should not undergo liver resection. This recommendation is supported by some studies,[1,40] whereas other studies reported good results of surgery in patients with portal hypertension.[41] Therefore, it is probable that some patients with portal hypertension could undergo liver resection without developing symptomatic PHLF. The preoperative model, by taking into account the remnant liver volume as well as the surgical approach, may offer an additional tool to select candidates for liver resection in this subgroup of patients. However, due to the small number of patients with portal hypertension in this cohort, the robustness of these predictions should be confirmed by additional studies focusing on patients with portal hypertension.

The present findings confirm that the laparoscopic approach reduces postoperative risk in patients with cirrhosis, with a threefold reduction in PHLF. However, it should be noted that laparoscopy was intended in only 33% of the patients. Thus, the weight of laparoscopy found in the present study may be hindered in some centres where it has been reported to be the main surgical approach. The role of platelet count[42] and blood loss[19,43] in the occurrence of PHLF and in postoperative morbidity has also been reported. In addition, platelet count is a well-known determinant of liver fibrosis.[35] Regarding liver volume, the present study is the first to show a linear correlation between PHLF and RTLV in cirrhotic patients. In fact, the well-known cut-offs of RTLV that predict PHLF were only established in cohorts of patients with non-fibrotic liver.[38,44] In the present study, Child-Pugh and MELD scores were not associated with PHLF. This may be explained by the highly selected population with a very low number of patients with decompensated cirrhosis.

Different algorithms have been reported in the literature to assess the perioperative risk of a hepatectomy in patients with cirrhosis. Makuuchi *et al.*[14] developed an algorithm based on the presence of ascites, the bilirubin level, the ICG-R15 and the extent of liver resection. According to this algorithm, 13 patients of our cohort should not have been resected. Actually, only one of these patients died postoperatively and the 12 remaining patients were alive at 3 months. Moreover, the mortality rates were not significantly different across the 9 Makuuchi's groups ($p = 0.55$) in our cohort (Fig. 3). Citterio *et al.*,[2] developed a decision tree based on a cohort of 543 patients with chronic liver disease who underwent hepatic resection for HCC. They used MELD score, the number of resected segments and portal hypertension as determinants of PHLF. In our cohort, only 5 patients would have had a high risk of PHLF according to the Citterio's classification and neither the proportions of patients with ISGLS-C PHLF (10%, 11% and 20%, respectively; $p = 0.56$) nor the mortality rates (6.0%, 4.7% and 0%, respectively; $p = 0.72$) were different across the 3 prognostic groups (Fig. 4). Cescon *et al.*'s algorithm[16] was based on a cohort including 466 patients with cirrhosis undergoing a hepatic resection for HCC and the determinants of liver failure were MELD score, blood sodium level and extent of liver resection. Using Cescon *et al.*'s algorithm in our cohort (Fig. 5), we found that the high-risk group (defined by a predicted risk of death or transplantation >15% and indicating an alternative treatment) comprised 56 patients, of whom, only 5 (8.9%) actually developed an ISGLS class C PHLF, and only 3 (5.4%) died at 3 months. Those rates were comparable with the overall mortality and grade C PHLF rates of the entire cohort. In summary, none of those 3 prognostic classifications was applicable to our cohort, suggesting the need to develop and validate alternative, widely applicable, prognostic models.

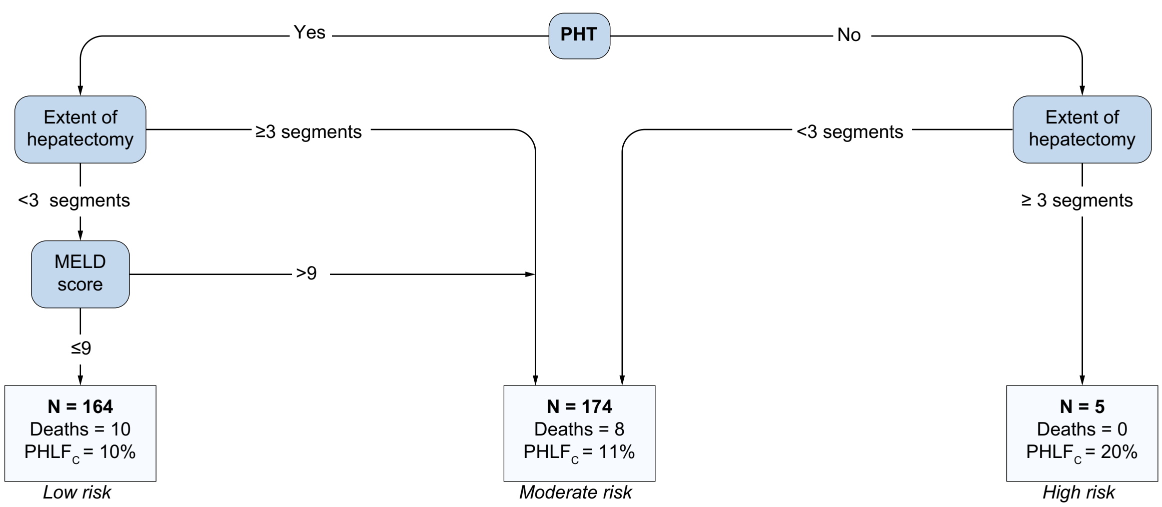

Fig. 4. Application of the Citterio's algorithm to the study cohort. Blue boxes indicate the number of patients that would be classified into each of the subgroups, as well as the actual number of postoperative deaths and the actual proportion of grade C post-hepatectomy liver failure according to the International Study Group of Liver Surgery. For each of the subgroups, italic text indicates the estimated risk of hepatectomy. MELD, model for end-stage liver disease; PHT, portal hypertension; $PHLF_C$, grade C post-hepatectomy liver failure.

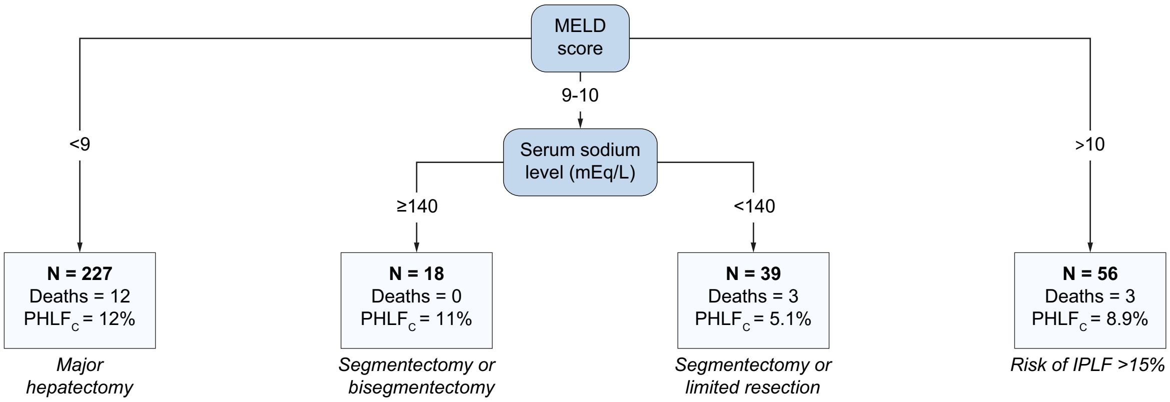

Fig. 5. Application of the Cescon's algorithm to the study cohort. Blue boxes indicate the number of patients that would be classified into each of the subgroups, as well as the actual number of postoperative deaths and the actual proportion of grade C post-hepatectomy liver failure according to the International Study Group of Liver Surgery. For each of the subgroups, italic text indicates either the maximal extent of liver resection allowed by the Cescon's algorithm or the estimated risk of irreversible postoperative liver failure. IPLF, irreversible postoperative liver failure; MELD, model for end-stage liver disease; PHLF$_C$, grade C post-hepatectomy liver failure.

Conclusion

This ordinal model based on 3 simple, plausible and readily available variables (*i.e.* platelet count, RTLV and ITT-laparoscopy) could accurately predict the occurrence of symptomatic PHLF. We suggest using this model as one of the selection tools for hepatectomy in patients with cirrhosis, in order to balance the risk of surgical resection with regards to alternative treatments. Moreover, using the preoperative model, a cut-off of grade C PHLF probability beyond which the risk of PHLF would be considered as prohibitive could be set up by local policies. In addition, the performance of this preoperative model could be significantly improved by adding 2 intraoperative variables (*i.e.* blood loss and PP-laparoscopy). This allows for tweaking PHLF probabilities immediately after surgery. The probabilities of each PHLF grade can be computed from our online calculator, the use of which may facilitate external validation of those models in external independent cohorts.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions

Study concept and design: EB, MP. Acquisition of data: all authors. Analysis and interpretation of data: EB, MP. Drafting of the manuscript: MP, ED, EB. Critical revision of the manuscript for important intellectual content: AD, EV, OF, GL, JYM, JH, JMR, OS, RA, FRP. Statistical analysis: ED, AD. Obtained funding: OF, MP. Administrative, technical, or material support: EB. Study supervision: EB.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.06.003.

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