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Original Article

Predictors of post-hepatectomy liver failure in patients undergoing extensive liver resections for hepatocellular carcinoma

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Backgrounds/Aims: To determine the prevalence of post-hepatectomy liver failure/insufficiency (PHLF/I) in patients undergoing extensive hepatic resections for hepatocellular carcinoma (HCC) and to assess the predictive value of preoperative factors for post-hepatectomy liver failure or insufficiency (PHLF/I). **Methods:** A retrospective review of patients who underwent liver resections for HCC between 2001 and 2013 was conducted. Preoperative parameters were assessed and analyzed for their predictive value of PHLF/I. Definitions used included the 50-50, International Study Group of Liver Surgery (ISGLS) and Memorial Sloan Kettering Cancer Centre (MSKCC) criteria. **Results:** Among the 848 patients who underwent liver resections for HCC between 2001 and 2013, 157 underwent right hepatectomy (RH) and extended right hepatectomy (ERH). The prevalence of PHLF/I was 7%, 41% and 28% based on the 50-50, ISGLS and MSKCC criteria, respectively. There were no significant differences in PHLF/I between RH and ERH. Model for End-Stage Liver Disease (MELD) score and bilirubin were the strongest independent predictors of PHLF/I based on the 50-50 and ISGLS/MSKCC criteria, respectively. Predictive models were developed for each of the criteria with multiple logistic regression. **Conclusions:** MELD score, bilirubin, alpha-fetoprotein and platelet count showed significant predictive value for PHLF/I (all $p<0.05$). A composite score based on these factors serves as guideline for physicians to better select patients undergoing extensive resections to minimize PHLF. **(Ann Hepatobiliary Pancreat Surg 2018;22: 185-196)**

Key Words: Liver; Resection; Cirrhosis; Liver failure; Predictors

INTRODUCTION

Hepatocellular carcinoma (HCC) is the six most common type of cancer worldwide. It is a leading cause of cancer-related death, accounting for up to 1 million deaths annually worldwide.[1,2] Risk factors include chronic viral hepatitis, alcohol-induced cirrhosis and non-alcoholic fatty liver disease. Majority of the disease burden is reported in hepatitis B endemic regions such as Southeast Asia and sub-Saharan Africa.[3]

Liver resection is curative for HCC when patients fail to qualify for liver transplantation. The recurrence rates post-hepatectomy have been reported at 70-85%.[4] Even in high-volume centers, liver resection is associated with significant morbidity and mortality rates, mostly due to hemorrhage, bile leaks, infection and post-hepatectomy liver failure or insufficiency (PHLF/I). PHLF is the most dreaded and least reversible, with incidence rates reported at approximately 8% in previous studies.[5] Sequelae and manifestations of PHLF/PHLI range from mild biochemical derangements to irreversible liver failure and death.

In addition to quantitative assessment of the future liver remnant (FLR), qualitative assessment is also important for preoperative prediction of PHLF. Currently, no vali-

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dated predictive models exist for PHLF/I particularly in the Asian population.

MATERIALS AND METHODS

This study aims to determine the prevalence of PHLF/I in patients diagnosed with HCC undergoing extensive hepatic resections, and investigate the predictive value of preoperative parameters for PHLF/I based on the pertinent criteria. Extensive hepatic resections are defined in this study as right hepatectomy (RH) and extended right hepatectomies (ERH), given that these procedures involve the most extensive liver volume resected, exposing patients to great risk for PHLF/I.

Study population

All patients derived from a single tertiary institution undergoing potentially curative liver resections for HCC between the years of 2001and 2013 were reviewed from a prospectively maintained clinical database. Clinical and operative data of 130 patients who underwent right hepatectomy (RH) and 27 patients who underwent extended right hepatectomies (ERH) were analyzed. Patients were evaluated for extended liver resections based on comorbidities, qualitative function of future liver remnant (FLR), the stage of disease and the presence of portal hypertension. The majority of these patients did not undergo definitive volumetric assessment, which was available in our institution until 2012. Currently, such assessments are not routinely performed in our institution and only selectively carried out according to the surgeon's discretion. Similarity Indocyanine Green Retention test at 15 min (ICG_{R15}) is done selectively and was only introduced in our institution in 2004. All patients in the final study cohort of 157 patients underwent single-stage hepatic resections. We excluded 2-stage surgeries as they are not common in our center for HCC cases, and to potentially eliminate unnecessary confounders in our study.

Criteria for post-hepatectomy liver failure/ insufficiency

The criteria for PHLF/I were based on three internationally well-established models. These include the 50-50 criteria, International Study Group for Liver Surgery (ISGLS) criteria and Memorial Sloan Kettering Cancer Centre (MSKCC) criteria.[6-8]

Preoperative parameters

Based on physiological factors and a literature review of similar studies, the parameters considered as possible predictors for risk of postoperative hepatic failure were selected and divided into 4 categories.[9-16]

The first category consisted of demographic factors including age, weight, height, body mass index, race, and gender of the patient. The second category consisted of biochemical factors such as pre-operative albumin, bilirubin, prothrombin time, creatinine, platelet count, alpha-fetoprotein (AFP), total white blood cells, lymphocyte counts, neutrophil counts and ICG_{R15}.[9-15] The third category consisted of composite scores including Child-Turcotte-Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) score, both of which were calculated pre-operatively based on the closest set of values prior to surgery.[16] The fourth category consisted of perioperative factors including operative, time, intra-operative blood loss, extent of surgery, tumor size and tumor rupture.

Statistical analysis

All variables were assessed using univariate logistic regression. Those significant at $p<0.20$ were analyzed using a stepwise selection algorithm in a multivariate logistic regression model. Variables significant at $p<0.20$ in multivariate logistic regression analysis were then selected as the optimal subset of independent predictors for PHLF/I. These variables were used to form a predictive equation ($y=b_0+\sum_{i=1}^{k} b_i x_i$) from which the probability of PHLF/I was calculated ($p=e^y/(1+e^y)$). Receiver operating characteristic (ROC) curves were plotted for each of the above models, where area under curve (AUC) was calculated to determine their validity as a predictive model.

RESULTS

Patient characteristics

The study population comprised 848 patients who underwent potentially curative liver resections for HCC. Of these, 157 patients who underwent one-stage extensive hepatic resections (RH and ERH) were identified including 130 who underwent RH and 27 treated with ERH. All

the patients in the study cohort presented with varying degrees of liver cirrhosis based on a combination of pre-operative scans and/or postoperative histopathology. A total of 134 (85%) patients were classified under CTP class A and the remaining 23 (15%) patients under CTP class B. The median MELD score was 8.97 (range 3-23 points). No significant differences existed between RH and ERH across all parameters (Table 1). Pre-operative CT volumetry and ICGR15 were performed in only 2 and 48 cases, respectively. Notably, pre-operatively, 2 patients underwent portal vein embolization (PVE) and 7 patients underwent selective internal radiation therapy (SIRT) with Yttrium-90 (Y-90), both of which resulted in varying degrees of contralateral FLR hypertrophy prior to surgery.

The 90-day mortality was 5.1% (8 patients) involving 6 patients who underwent RH and 2 cases treated with ERH. One patient was categorized under CTP class B (underwent RH) while the remainder were CTP class A. The cause of death was attributed to PHLF and/or multi-system organ failure associated with PHLF in 3 patients, acute myocardial infarction in 3 patients and severe intra-abdominal sepsis not associated with PHLF in 2 patients. The median time to PHLF-related death was 26 days (range, 9-45).

Prevalence of post-hepatectomy liver failure/insufficiency and associated mortality

A total of 11 (7%), 44 (28%) and 65 (41%) patients fulfilled the 50-50, MSKCC and ISGLS criteria for PHLF/I respectively.

Patients fulfilling the various criteria for PHLF/I were at a higher risk of 90-day mortality when compared with patients who did not; the results were only significant based on the 50-50 criteria (OR 20.3, $p<0.01$ in 50-50; OR 2.47, $p=0.23$ in ISGLS; OR 2.73, $p=0.17$ in MSKCC). Patients undergoing ERH were associated with a higher risk of PHLF/I when compared with RH (10% vs. 6% in 50-50, 45% vs. 41% in ISGLS, 29% vs. 27% in MSKCC), although it failed to reach statistical significance across all 3 criteria (OR 1.58, $p=0.52$ for 50-50; OR 1.06, $p=0.89$ for MSKCC; OR 1.21, $p=0.64$ for ISGLS) (Table 2).

Predictors of post-hepatectomy liver failure/insufficiency

This study identified 4 significant independent predictors of PHLF/PHLI across the three criteria after multivariate analysis: pre-operative MELD score ($p=0.03$ for 50-50), platelet count ($p=0.03$ for 50-50), AFP ($p=0.01$ for 50-50), and bilirubin ($p=0.03$ for ISGLS and $p=0.01$ for MSKCC).

MELD score was a significant independent predictor for PHLF only under the 50-50 criteria ($p=0.03$). Association between MELD score and risk of PHLF was strongest at a cut-off of 8 under ISGLS and MSKCC criteria (OR 2.56, $p<0.01$ for ISGLS; OR 3.16 $p<0.01$ for MSKCC), and at a cut-off of 13 under 50-50 criteria (OR 6.27, $p=0.04$). Across all the 3 criteria, patients with a MELD score in excess of 11 (n=20) consistently presented with higher rates of PHLF when compared with their counterparts reporting a MELD score of less than 11 (14% vs. 6% in 50-50, 65% vs. 38% in ISGLS, 60% vs. 23% in MSKCC). In addition, all patients with MELD score greater than 20 (n=3) had PHLF/I.

Preoperative thrombocytopenia was a significant independent predictor for PHLF only under the 50-50 criteria ($p=0.03$). The association was strongest at a cut-off level of $120\times10^3/\mu L$ (OR 10.58, $p<0.01$). Patients with preoperative platelet counts of $<120\times10^3/\mu L$ (n=8) presented with significantly higher rates of PHLF when compared with those reporting platelet counts $>120\times10^3/\mu L$ (38% vs 5%).

Preoperative hyperbilirubinemia was a significant independent predictor for PHLF in both the ISGLS and MSKCC criteria (OR=2.99; $p=0.03$ for ISGLS; OR=2.39; $p=0.01$ for MSKCC). Association between preoperative bilirubin and risk of PHLF was strongest at a cut-off of 1.15 mg/dL in the ISGLS criteria (OR 2.60, $p<0.01$). The cut-off was 1.9 mg/dL in the MSKCC criteria (OR 3.67, $p=0.01$). Patients with a preoperative bilirubin in excess of 2 mg/dL (n=7) all had PHLF according to the ISGLS and MSKCC criteria.

Preoperative AFP was a significant independent predictor for PHLF only in the 50-50 criteria (OR 1.000, $p=0.01$). Association between AFP and risk of PHLF was strongest at a cut-off of 50,000 ng/mL and 2,500 ng/mL in 50-50 (OR 3.40, $p=0.01$) and MSKCC (OR 3.40, $p=0.01$) criteria respectively.

Predictive models

50-50 criteria: Body mass index, albumin, bilirubin,

Table 1. Population demographics and perioperative variables

Parameters	Whole study population (RH and ERH, n=157)	Right hepatectomy (RH) (n=130)	Extended right hepatectomy (ERH) (n=27)	RH vs. ERH (*p*)
Demographic factors				
Age (years)	61.2±11.7	61.8±12.1	61.1±9.41	0.135
Weight (kg)	63.6±14.0	64.0±14.0	61.9±14.1	0.895
Height (cm)	163±9.53	163±9.96	163±6.95	0.168
Body mass index	23.9±4.70	24.1±4.66	23.0±5.00	0.666
Race,				
Chinese	80.9 (127)	79.2 (103)	88.9 (24)	0.295
Malay	3.82 (6)	4.62 (6)	0 (0)	-
Indian	1.91 (3)	1.54 (2)	3.70 (1)	-
Others	13.4 (21)	14.6 (19)	7.41 (2)	-
Gender, % (n)				
Male	84.1 (132)	82.3 (107)	92.6 (25)	0.252
Pre-operative laboratory investigations				
Hepatitis B positive, % (n)	60.5 (95)	60.0 (78)	63.0 (17)	-
Hepatitis C positive, % (n)	7.01 (11)	6.92 (9)	7.41 (2)	-
Hepatitis B+C positive, % (n)	66.9 (105)	66.2 (86)	70.4 (19)	1.000
Albumin (g/L)	36.1±5.54	35.9±5.79	36.7±4.14	0.892
SB (mg/dL)	1.02±0.620	1.04±0.650	0.920±0.390	0.430
PT (seconds)	11.4±1.41	11.4±1.48	11.1±0.990	0.438
Serum creatinine (mg/dL)	1.05±0.880	1.06±0.960	1.02±0.260	0.128
Platelet count ($\times 10^3/\mu L$)	251±98.1	252±100	246±90.1	0.551
AFP (ng/ml)	4078±13380	3338±11914	7410±18581	0.245
Total white blood cell count ($x10^3/mm^3$)	7.05±2.08	7.06±2.11	6.95±1.99	0.751
Lymphocyte count ($\times 10^3/mm^3$)	1.79±1.57	1.72±0.680	2.16±3.51	0.928
Neutrophil count ($\times 10^3/mm^3$)	8.16±41.5	4.43±1.90	26.1±99.5	0.642
Scoring systems				
CTP score	5.55±0.820	5.57±0.840	5.48±0.70	0.268
CTP Status, % (n)				
CTP A	85.4 (134)	85.4 (111)	85.2 (23)	1.000
CTP B	14.7 (23)	14.6 (19)	14.8 (4)	-
CTP C	0 (0)	0 (0)	0 (0)	-
MELD score	8.97±2.96	9.05±3.14	8.57±1.86	0.556
ICG_{R15}	11.5±5.94	11.3±6.02	12.8±5.67	1.000
Perioperative factors				
Operative time (min)	243±69.6	245±70.9	235±63.7	0.538
Operative blood loss (mL)	924±758	888±678	1080±1040	0.868
Maximum dimension (mL)	87.3±56.3	84.0±50.8	101±75.1	0.415
Number of nodules, % (n)				
1	74.1 (106)	78.5 (91)	55.6 (15)	0.055
2	24.5 (35)	20.7 (24)	40.7 (11)	-
3	1.40 (2)	0.860 (1)	3.70 (1)	-
Tumor rupture, % (n)				
Absent	86.0 (123)	86.2 (100)	85.2 (23)	0.445
Present	14.0 (20)	13.8 (16)	14.8 (4)	-
Mortality				
90-day mortality, % (n)	5.1 (8)	4.6 (6)	7.4 (2)	0.575

Continuous variables are summarized as mean±SD and categorical variables as percent and sample size, i.e., % (n)
SB, Serum bilirubin; PT, Prothrombin time; AFP, Alpha fetoprotein; CTP, Child-Turcotte-Pugh; MELD, Model for End Stage Liver Disease; ICGR15, Indocyanine Green retention rate at 15 minutes

Table 2. Prevalence of post-hepatectomy liver failure/insufficiency across 50-50, ISGLS and MSKCC criteria

Criteria	Definition and Parameters **All values with regards to POD 5* **Criteria for PHLF/PHLI*	Prevalence of PHLF/PHLI in the whole group (n=157)	Patients undergoing RH vs. ERH					Association with 90-day mortality			
			Patients undergoing RH (n=126): Prevalence of PHLF/PHLI	Patients undergoing ERH (n=31): Prevalence of PHLF/PHLI	Odds ratio	95% CI	*p*	90-day mortality in patients with PHLF/PHLI (%)	Odds ratio	95% CI	*p*
50-50 criteria*	PT raised by 50%+SB more than 50 μmol/L (2.92 mg/dL)	11 (7%)	8 (6.3%)	3 (9.7%)	1.58	0.39-6.34	0.519	36.36	20.29	4.18-98.49	0.0002
ISGLS Criteria	INR more than 1.2+SB more than 32 μmol/L (1.87 mg/dL)	65 (41.4%)	51 (40.5%)	14 (45.2%)	1.21	0.55-2.67	0.636	7.69	2.47	0.57-10.73	0.2270
MSKCC criteria	SB more than 70.1 μmol/L (4.1 mg/dL) OR INR more than 2.5 OR Ascites drainage more than 500 mL/day	44 (28%)	35 (27.8%)	9 (29%)	1.06	0.45-2.53	0.889	9.10	2.73	0.65-11.42	0.1702

PT, Prothrombin Time; SB, Serum Bilirubin; RH, Right Hepatectomy; ERH, Extended Right Hepatectomy; PHLF, Post-Hepatectomy Liver Failure; PHLI, Post-Hepatectomy Liver Insufficiency; POD, Post-Operative Day; ISGLS, International Study Group for Liver Surgery; MSKCC, Memorial Sloan Kettering Cancer Centre; INR, International Normalized Ratio

prothrombin time, creatinine, platelet count, AFP, total white cell count, CTP score, MELD score, ICG_{R15} and maximum tumor dimension were the factors most significantly associated with PHLF in univariate analysis. Platelet count (OR=0.99, *p*=0.03), AFP (OR=1.00, *p*=0.01) and MELD score (OR=1.19, *p*=0.03) were selected as the optimal subset of independent predictors for PHLF after multivariate analysis (Table 3).

Platelet count, MELD score and AFP were used to develop a model providing the strongest predictive value for PHLF. Using model coefficients, the model scores for y-intercept cut-offs ($Y^{50\text{-}50}$) were selected at three distinct points (0.038, 0.045, and 0.046). Maximum sensitivity (100%) and specificity (54%) for this model was achieved at cut-offs of 0.038 and 0.046, respectively. (Table 4) The validity of this model was assessed using a ROC curve with an AUC of 0.78.

ISGLS criteria: Bilirubin, prothrombin time, total white cell count and MELD score were the factors most significantly associated with PHLF in univariate analysis. Bilirubin (OR=2.39, p=0.03) and prothrombin time (OR=1.24, p=0.12) were selected as the optimal subset of independent predictors for PHLF after multivariate analysis (Table 3).

Bilirubin and prothrombin time were used to develop a model providing the strongest predictive value for PHLF. Using model coefficients, model scores for y-intercept cut-offs (Y^{ISGLS}) were selected at three distinct points (0.373, 0.351 and 0.297). Maximum sensitivity (91%) and specificity (50%) for this model was achieved at cut-offs of 0.297 and 0.373, respectively (Table 4). The validity of this model was assessed using an ROC curve with an AUC of 0.62.

MSKCC criteria: Body mass index, bilirubin, platelet count, CTP score, MELD score, ICG clearance and operative time were the factors most significantly associated with PHLI on univariate analysis. Bilirubin (OR=2.99, p=0.01), platelet count (OR=0.99, p=0.07), MELD score (OR=1.13, p=0.09), and operative time (OR=1.004, p=0.15) were selected as the optimal subset of in-

Table 3. Results of univariate and multiple logistic regression analyses

Parameters	No post-hepatectomy liver failure/dysfunction (n=146)	Post-hepatectomy liver failure/dysfunction (n=11)	Univariate analysis			Stepwise multiple logistic regression1		
			Odds ratio	95% CI	*p*	Adjusted odds ratio	95% CI	*p*
		50-50 criteria						
Body mass index	23.69±4.44	30.26±8.04	1.27	1.02, 1.58	0.034			
Albumin (g/L)	36.25±5.47	33.64±6.09	0.93	0.84, 1.02	0.119			
Total serum bilirubin (mg/dL)	0.99±0.48	1.41±1.53	1.80	0.94, 3.45	0.075			
Prothrombin time (seconds)	11.31±1.29	12.25±2.43	1.39	1.01, 1.92	0.042			
Serum creatinine (mg/dL)	0.99±0.43	1.85±2.95	1.44	0.95, 2.17	0.085			
Platelet count ($\times10^3/\mu L$)	255.39±98.42	190.00±72.41	0.99	0.98, 1.00	0.037	0.99	0.98,1.00	0.0264
AFP (ng/ml)	3368.79±11794.70	11883.42±24553.62	1.00	1.00, 1.00	0.052	1.00	1.00,1.00	0.0081
Total white blood cell count ($\times10^3/mm^3$)	6.96±1.92	8.23±3.56	1.29	1.00, 1.67	0.051			
Child Pugh Score	5.53±0.77	5.91±1.30	1.62	0.88, 2.95	0.119			
Child Pugh								
Child's A	94.03 (126)	5.97 (8)	2.54	0.66, 9.82	0.176			
Child's B/C	13.04 (3)	27.27 (3)	1.00		1.000			
MELD Score	8.76±2.14	11.78±7.80	1.18	1.03, 1.36	0.017	1.19	1.02,1.38	0.0261
ICG_{R15}	11.92±6.07	8.12±3.44	0.88	0.73, 1.07	0.199			
Maximum dimension (mm)	89.28±57.61	60.80±23.93	0.99	0.97, 1.00	0.157			
		ISGLS criteria						
SB (mg/dL)	0.90±0.34	1.18±0.85	2.44	1.18, 5.08	0.017	2.39	1.11,5.15	0.0254
PT (seconds)	11.16±1.13	11.68±1.70	1.30	1.02, 1.65	0.037	1.24	0.95,1.62	0.1166
Total white blood cell count ($\times10^3/mm^3$)	6.86±1.88	7.31±2.32	1.11	0.95, 1.29	0.197			
MELD Score	8.48±2.15	9.66±3.73	1.16	1.01, 1.34	0.038			
		MSKCC criteria						
Body mass index	23.25±4.48	25.35±4.91	1.10	0.99, 1.22	0.07			
Total serum bilirubin (mg/dL)	0.90±0.35	1.31±0.97	3.61	1.61, 8.10	0.002	2.99	1.28,7.02	0.0118
Platelet count ($\times10^3/\mu L$)	260.42±100.13	226.11±88.97	1.00	0.99, 1.00	0.061	1.00	0.99,1.00	0.0674
CTP Score	5.46±0.71	5.80±1.02	1.59	1.05, 2.39	0.027			
CTP Category								
CTP A	73.88 (99)	26.12 (35)	1.84	0.73, 4.61	0.195			
CTP B/C	60.87 (14)	39.13 (9)	1.00	--	1.000			
MELD Score	8.52±2.11	10.13±4.27	1.20	1.04, 1.38	0.015	1.13	0.98,1.31	0.0888
ICG_{R15}	12.24±5.82	9.13±6.00	0.91	0.79, 1.04	0.166			
Operative time (minutes)	238.02±60.68	255.70±87.64	1.00	1.00, 1.01	0.159	1.00	1.00,1.01	0.1582

Univariate analysis was performed on all parameters under Table 1. Results in Table 3 only include parameters with $p<0.2$ on univariate analysis (only parameters with $p<0.20$ in the univariate analysis were included as candidate predictors in the stepwise multiple logistic regression. Continuous variables are summarized as mean±SD and categorical variables as percent and sample size, i.e., % (n)

[1]Only variables significant at $p<0.20$ in the stepwise regression are listed

SB, Serum bilirubin; PT, Prothrombin time; AFP, Alpha fetoprotein; CTP, Child-Turcotte-Pugh; MELD, Model for End Stage Liver Disease; ICG_{R15}, Indocyanine Green retention rate at 15 minutes

dependent predictors for PHLF after multivariate analysis (Table 3).

Bilirubin, platelet count, MELD score and operative time were used to develop a model providing the strongest predictive value for PHLI. Using model coefficients, the model scores for y-intercept cut-offs (Y^{MSKCC}) were selected at three distinct points (0.129, 0.173 and 0.222). Maximum sensitivity (100%) and specificity (51%) for this model was achieved at a cut-off of 0.129 and 0.222, respectively (Table 4). The validity of this model was as-

Table 4. Models for predicting probability of PHLF/I

Parameter	50-50 criteria			ISGLS criteria			MSKCC criteria		
				Model coefficients					
Intercept	−1.8735			−3.6478			−3.1983		
Total serum bilirubin	-			0.8730			1.0958		
MELD score	0.1701			-			0.1244		
Platelet count	−0.0116			-			−0.00398		
Operative time	-			-			0.00389		
Alpha-fetoprotein	0.000048			-					
Prothrombin time	-			0.2134			-		
Model score analysis parameters				Model score cut-offs					
Model score$^{50\text{-}50/ISGLS/MSKCC}$	0.03834	0.04506	0.04636	0.37265	0.35071	0.29687	0.12853	0.17259	0.22191
Sensitivity (%)	100	90.1	81.1	66.2	75.4	90.8	100	79.5	75
Specificity (%)	44.6	51.2	53.7	50	42.4	15.2	16.2	33.3	51.4
Positive predictive value	0.11977	0.12317	0.11754	0.48315	0.48039	0.43066	0.31729	0.37512	0.31722
Negative predictive value	1	0.98681	0.97513	0.67647	0.70909	0.7	1	0.84064	0.80714

Using model coefficients. $y^{50\text{-}50}$=−1.8735+[(MELD score) (0.1701)]+[(Platelet count) (−0.0116)]+[(AFP) (0.000048)]. y^{ISGLS}=−3.6478+[(Total serum bilirubin) (0.8730)]+[(Prothrombin time) (0.2134)]. y^{MSKCC}=−3.1983+[(Total serum bilirubin) (1.0958)]+[(MELD score) (0.1244)]+[(Platelet count) (−0.00398)]+[(Operative time) (0.00389)]. Model score=$e^y/(1+e^y)$), where e=2.72 (mathematical constant). Model score in excess of cut-off values indicates predicted post-hepatectomy liver failure/insufficiency. Model score below cut-off values indicates no predicted post-hepatectomy liver failure/insufficiency

Table 5. MAP score for clinical prediction of PHLF (50-50 criteria)

Parameter	Points			
	0		1	
Model for End Stage Liver disease score (p=0.05)	≤13		>13	
Preoperative platelet counts (p=0.004)	≥120×10^4 μL		<120×10^4 μL	
Preoperative alpha-fetoprotein (p=0.007)	≤50,000 ng/mL		>50,000 ng/mL	
Predictive model analysis parameters	Composite score on predictive model			
	0	1	2	3
Predicted probability on ROC curve for model	0.04	0.28	0.81	-
Sensitivity (%)	100	55	9	-
Specificity (%)	0	90	100	-
Positive predictive value	0.07	0.3	1	-
Negative predictive value	1	0.96	0.94	-

A score of at least 4 points suggests an increased risk of post-hepatetcomy liver failure based on the 50-50 criteria. Empty cells in table correspond to outcomes not observed in the data set

sessed using an ROC curve with an AUC of 0.69.

Simplified novel predictive model for 50–50 criteria: Based on the above results, the Fisher's scoring algorithm was used to develop a simplified score for clinical prediction of PHLF according to the 50-50 criteria, named the MAP (MELD-AFP-Platelet) score. Using binary categorical cut-offs of MELD score, platelet count and AFP at 13 points, 120×103/μL and 50,000 ng/mL respectively, patients were awarded either 0 or 1 point for each parameter, yielding the minimum score 0 and maximum score 3. An ROC curve was plotted with an AUC of 0.73, indicating that the model was a good predictor. Cut-point of the ROC curve (0.28) corresponded to a MAP score of ≥1. Therefore, any patient with a MAP score of ≥1 was deemed at high risk of PHLF based on the 50-50 criteria. Patients with a MAP score of 0 presented with significantly lower rates of PHLF when compared with those reporting a MAP score of ≥1 (4% vs. 28%, OR=8.53, p<0.01). This score has a sensitivity and specificity of 55% and 90%, and a negative predictive value of 0.96 at a cutoff of 1 point (Table 5, Fig. 1).

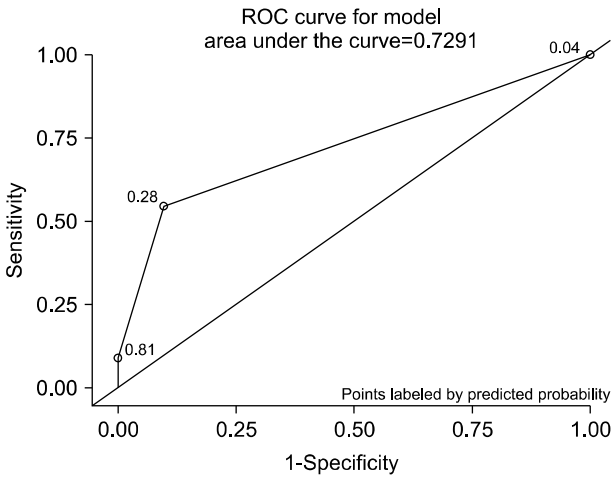

Fig. 1. Receiver operating characteristic curve for predictive model under 50-50 criteria.

DISCUSSION

PHLF/I is the most dreaded complication of liver resection. It is seldom reversible and results in significant post-operative morbidity and mortality. The prediction of PHLF/I today is still a science in evolution, with qualitative and quantitative assessment of FLR representing the basis for most predictive models in previous studies.[17-19]

The relationship between PHLF and 90-day mortality in this study was only significant when the 50-50 criteria were used to define PHLF, which was not unexpected given that only the 50-50 criteria were devised as a predictor of increased risk of post-hepatectomy mortality.[6]

Patients undergoing ERH were consistently at higher risk of PHLF when compared with those undergoing RH, although without statistical significance in our study. Quantitative assessment of the FLR has been a well-established predictor of PHLF. Overly ambitious liver resections can leave a tiny FLR inadequate for compensatory hypertrophy in the critical post-operative period. Resections up to 70-75% of the liver volume are deemed safe in patients with normal hepatic parenchyma. This volume decreases to 40-60% in patients with pre-existing parenchymal disease.[20] This finding is consistent with multiple reports stating that ERH and a diminished FLR were significant and independent predictors for PHLF.[21-25] Kauffmann and Fong.[21] reported that resection of >50% of liver volume, and major hepatectomy including the right hepatic lobe were both independent and significant predictors of PHLF. This study also reported that patients with an FLR <25% had a threefold risk of PHLF when compared with patients reporting an FLR ≥25%. Lee performed a matched cohort comparison between patients undergoing central hepatectomy compared with extended hepatectomy, and found that the extended hepatectomy group carried significantly higher post-operative bilirubin and INR levels compared with the central hepatectomy group. No significant difference was found in our study of patients undergoing RH and ERH in terms of their risk for PHLF/I. This finding could be attributed to the insignificant additional liver volume resected in ERH compared with RH and the small study size.

MELD score was initially developed to determine the risk of 3-month mortality in patients undergoing transjugular intrahepatic portosystemic shunt procedure, and has since been adapted as a prognostic indicator of 90-day survival in chronic liver disease under optimized medical management.[26] It was identified as a significant independent predictor for PHLF (50-50 criteria) in this study. Cucchetti et al.[27] similarly reported a MELD score ≥11 as an excellent cut-off value for predicting PHLF (sensitivity 82% and specificity 89%) and a high MELD score was significantly associated with morbidity (refractory ascites, coagulopathy, and renal impairment) and PHLF-related mortality. Bruix and Llovet[28] and Teh et al.[29] also reported the MELD score was the single most significant independent predictor of PHLF in patients undergoing hepatic resections. These studies further suggest that hepatic resection was only indicated in patients with a MELD score below 9, which is consistent with the findings of our study.

Thrombocytopenia was also identified as a significant independent predictor for PHLF (50-50 criteria) in this study. Kaneko et al.[30] reported that preoperative thrombocytopenia was a significant independent predictor of post-operative morbidity and mortality: no patient with a platelet count > 73×10^3 μL died of post-operative complications while 25% of patients with platelet counts < 73×10^3 μL died of postoperative complications. Bennett and Blumgart[31] also reported the need for extra perioperative care with hepatic resections in patients with a platelet count of <100×10^3/μL. More recently, Tomimaru et al.[32] reported a significant correlation between preoperative platelet count and PHLF in both minor and ma-

jor hepatectomies at a cutoff of $<150\times10^3/\mu L$. Thrombocytopenia at the above-mentioned cutoff was a better predictor for PHLF than other parameters such as intraoperative blood loss and ICG_{R15}. Similarly, this study demonstrated thrombocytopenia (at a platelet cutoff of $<120\times10^3/\mu L$) as a significant predictor of PHLF (50-50 criteria).

Hyperbilirubinemia has been widely used as a marker of liver injury and impaired hepatic, metabolic and excretory function. The extent of hyperbilirubinemia was a significant independent predictor of PHLF/I under both the MSKCC and ISGLS criteria in this study. Mullen et al.[33] reported that bilirubin was the most powerful predictor of post-hepatectomy morbidity (refractory ascites and coagulopathy), PHLF, 90-day mortality and 90-day PHLF-related mortality. In addition, other studies by Li et al.[34] and Shen et al.[35] reported that a preoperative serum bilirubin level of $\geq$1.19 mg/dL was a significant independent risk factor for PHLF in patients undergoing liver resection. Motoyama et al.[36] also reported a significant correlation between preoperative serum bilirubin and PHLF using the ISGLS criteria and developed a model for prediction of PHLF incorporating serum bilirubin, INR and the presence of intra-operative packed red blood cell transfusion. This model provide stronger correlation with PHLF when compared with MELD score and ICG_{R15}.

AFP was found to be a significant independent predictor of PHLF (50-50 criteria) in this study. Previous studies have reported the significance of AFP for HCC diagnosis, degree of differentiation of HCC, prediction of recurrence and long-term prognosis in patients undergoing liver resections for HCC.[37-42] Its value as a pre-operative predictor of PHLF has, however, been scarcely reported. Our study is among the few to report the significance of AFP as a predictor for PHLF in a preoperative setting of HCC patients undergoing extensive resections. We postulate that this significant relationship is based on a higher AFP value corresponding to a larger tumor burden, which may require more extensive liver resections, resulting in inadequate FLR. Furthermore, a large proportion of our study cohort manifested underlying cirrhosis (85% CTP A, 15% CTP B), potentially resulting in additional qualitative dysfunction of the above-mentioned FLR. An elevated AFP in this study was indeed associated with increased tumor burden, and was most significant at an AFP cutoff of >1000 ng/mL and its association with a maximum tumor diameter of >10 cm (p=0.0004; OR 4.68). In addition, no patient with an AFP in excess of 50,000 (cutoff used for MAP score) had a maximum tumor diameter <10 cm. Given that only 2 patients in our study population of 157 underwent pre-operative CT volumetry, we used maximum tumor diameter as a surrogate marker for tumor volume. Kohla et al.[41] has reported that a high AFP is an independent predictor of post-transarterial chemoembolization (TACE) hepatic decompensation.

Prothrombin time was only significant in univariate analysis in the 50-50 (p=0.04) and ISGLS (p=0.04) criteria in this study. Among others, reports by Nanashima et al.[43,44] and Motoyama et al.[36] suggested that elevated preoperative prothrombin time (>70-80% of normal ranges) independently predicted PHLF.

ICG_{R15} has been reported as an excellent guide for decision-making in determining a safe threshold of liver volume for resection (popularly known as the Makuuchi decision tree), and has had a great impact on minimizing mortality and morbidity in liver resection.[45] Although ICG_{R15} has been widely used as a predictor of overall survival in patients undergoing hepatectomy, its efficacy as a single pre-operative predictor of PHLF in patients undergoing major hepatic resections has, however, been poorly investigated.[45,46] Studies by Yokoyama et al.[47] and Uchida et al.[48] were amongst the few to demonstrate a statistically significant relationship between ICG_{R15} and PHLF. Results from our study show a poor relationship between ICG clearance and PHLF (p=0.199 for 50-50, p=0.478 for ISGLS, p=0.166 for MSKCC), suggesting that ICG_{R15} alone is not enough to predict PHLF in patients undergoing extensive hepatic resections.

Excessive blood loss is commonly associated with PHLF, PHLI, early morbidity and mortality after liver resections. Operative blood loss was shown to be a poor predictor for PHLF/I across all three criteria (p=0.37 in 50-50, p=0.40 in ISGLS, p=0.41 in MSKCC). Nanashima et al.[43,44] and Stoffels et al.[23] similarly reported a significant relationship between intraoperative blood loss and PHLF.

In addition to the abovementioned parameters (prothrombin time, ICGR15, and intraoperative blood loss), other preoperative factors that have been implicated in PHLF but were not included in our study include serum

laminin,[45] serum hyaluronic acid level[35,45] histopathological activity index,[44] and liver activity at 15 min by technetium-99m galactosyl human serum albumin scinigraphy.[44,45] These investigations are however expensive, not routinely used, and may not be readily available.

The 50-50 criteria were used as the defining criteria for PHLF to create the MAP score based on its significant correlation with 90-day mortality. Furthermore, it is also widely used in clinical practice currently. Although the AUC for the MAP score (0.73) was lower than that of the model generated based on multiple logistic regression (0.78), the binary format of this novel scoring system where patients are awarded either 0 or 1 points based on categorical cutoffs facilitate clinical application. The cut-point of the ROC curve based on the 3 clinical parameters used (MELD score, platelet counts, AFP) corresponded to a MAP score of 1. Any patient with a score of ≥ 1 is thus at high risk of PHLF, and should be closely monitored in the early post-operative period, or have surgical options reconsidered in favor of alternative non-surgical modalities such as ablation, TACE, selective internal radiation therapy and chemotherapeutic agents. Our study found a significant relationship between a MAP score of ≥ 1 and PHLF ($p<0.01$). In patients with a MAP score of 0, our study found a 4% risk of PHLF following extensive hepatic resections compared with the 28% risk of patients with a MAP score of ≥ 1 who had PHLF. A cutoff score of 2 allows 100% specificity but extremely poor sensitivity (9%), with an inferior negative predictive value (0.94). A cutoff score of 1 maximized both sensitivity (55%) and specificity (90%), while ensuring an excellent negative predictive value (0.96). No data may be projected for a cutoff score of 3 based on this model given that no patient in our study cohort fell into this category. Our findings suggest that the individual MELD score, platelet count and AFP at their respective categorical cutoffs used in the model are excellent predictors for PHLF, given that a score of 1 in any of these domains predicts PHLF with a specificity of 90%. Clinical application of the MAP score is thus best utilized in a patient with a score of ≥ 1. In these cases, clinicians can advise patients on the 90% risk of PHLF if extensive hepatic resection is indicated.

In the absence of well-validated scoring systems specific for qualitative assessment of FLR in patients with HCC undergoing extensive liver resections, surgeons have used surrogate markers for hepatic function such as the MELD score, a formula designed more specifically for assessing the severity of chronic liver disease rather than PHLF/I. Although MELD score was found to be an independent and significant predictor of PHLF (50-50 criteria) in multivariate analysis ($p=0.026$, OR=1.19), the MAP score was a better predictor of PHLF ($p=0.0001$ vs $p=0.026$) with a stronger odds ratio (13.4 vs 1.19). Furthermore, the AUC of an ROC presented exclusively for MELD score as a predictor of PHLF according to the 50-50 criteria was far inferior to the MAP score (0.57 vs. 0.73). At the cut-point of the ROC, the sensitivity (54%, MELD score; 55%, MAP score) and specificity (70%, MELD score; 90%, MAP score) of the MELD score was inferior compared with that of the MAP score.

The predictive value of preoperative biochemical parameters for PHLF has been poorly investigated in the literature. Our novel scoring system included routine pre-operative laboratory investigations commonly performed as part of a pre-hepatectomy workup. Pre-existing studies investigating predictive models for PHLF have largely centered around CT volumetric analysis and ICG_{R15}.[17-19] Such an approach is undesirable given that these two investigations may not be readily available for clinical application or routinely carried out. Our results shed light on the strong predictive value of simple biochemical markers that are commonly under-utilized.

This study presents with several limitations. This is a single center retrospective study with a modest sample size with its inherent biases. In this study, only 11 (7%) patients qualify for PHLF based on the 50-50 criteria, which is comparable to other centers worldwide. However additional and larger studies are needed to both internally and externally validate our results and the MAP score.[18,22,23,48-50] Furthermore, current and newer assessment tools that add important information such as scintigraphy, CT volumetry, wedge pressures and ICG_{R15} were not adequately analyzed in our study due to limited data.

In conclusion, preoperative parameters such as MELD score, platelet count, AFP and bilirubin are significant predictors for PHLF in patients diagnosed with HCC undergoing extensive hepatic resections. The MAP score evaluated in this study can be used clinically by physi-

cians in patient selection to minimize PHLF.

REFERENCES

1. Lee SY, Konstantinidis IT, Eaton AA, Gönen M, Kingham TP, D'Angelica MI, et al. Predicting recurrence patterns after resection of hepatocellular cancer. HPB (Oxford) 2014;16:943-953.
2. Goh BK, Teo JY, Chan CY, Lee SY, Jeyaraj P, Cheow PC, et al. Importance of tumor size as a prognostic factor after partial liver resection for solitary hepatocellular carcinoma: implications on the current AJCC staging system. J Surg Oncol 2016;113: 89-93.
3. Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. Gut Liver 2016; 10:332-339.
4. Lu WP, Dong JH. Hepatectomy for hepatocellular carcinoma in the era of liver transplantation. World J Gastroenterol 2014;20: 9237-9244.
5. Golse N, Bucur PO, Adam R, Castaing D, Cunha AS, Vibert E. New paradigms in post-hepatectomy liver failure. J Gastrointest Surg 2013;17:593-605.
6. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg 2005;242:824-829.
7. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). Surgery 2011;149:713-724.
8. Simpson AL, Adams LB, Allen PJ, D'Angelica MI, DeMatteo RP, Fong Y, et al. Texture analysis of preoperative CT images for prediction of postoperative hepatic insufficiency: a preliminary study. J Am Coll Surg 2015;220:339-346.
9. Limdi JK, Hyde GM. Evaluation of abnormal liver function tests. Postgrad Med J 2003;79:307-312.
10. Zakim D, Boyer TD, ed. Hepatology: a textbook of liver disease. 4th ed. Philadelphia: Saunders, 2003:1765.
11. Gibbins JM, Mahaut-Smith MP, ed. Platelets and megakaryocytes. New Jersey: Humana Press, 2004.
12. Behne T, Copur MS. Biomarkers for hepatocellular carcinoma. Int J Hepatol 2012;2012:859076.
13. Kashyap R, Jain A, Nalesnik M, Carr B, Barnes J, Vargas HE, et al. Clinical significance of elevated alpha-fetoprotein in adults and children. Dig Dis Sci 2001;46:1709-1713.
14. Johnson PJ. The role of serum alpha-fetoprotein estimation in the diagnosis and management of hepatocellular carcinoma. Clin Liver Dis 2001;5:145-159.
15. Lee YJ, Lee HR, Shim JY, Moon BS, Lee JH, Kim JK. Relationship between white blood cell count and nonalcoholic fatty liver disease. Dig Liver Dis 2010;42:888-894.
16. Zipprich A, Kuss O, Rogowski S, Kleber G, Lotterer E, Seufferlein T, et al. Incorporating indocyanin green clearance into the model for end stage liver disease (MELD-ICG) improves prognostic accuracy in intermediate to advanced cirrhosis. Gut 2010;59:963-968.
17. Du ZG, Wei YG, Chen KF, Li B. An accurate predictor of liver failure and death after hepatectomy: a single institution's experience with 478 consecutive cases. World J Gastroenterol 2014;20: 274-281.
18. Kim HJ, Kim CY, Park EK, Hur YH, Koh YS, Kim HJ, et al. Volumetric analysis and indocyanine green retention rate at 15 min as predictors of post-hepatectomy liver failure. HPB (Oxford) 2015;17:159-167.
19. Garcea G, Ong SL, Maddern GJ. Predicting liver failure following major hepatectomy. Dig Liver Dis 2009;41:798-806.
20. Dinant S, de Graaf W, Verwer BJ, Bennink RJ, van Lienden KP, Gouma DJ, et al. Risk assessment of posthepatectomy liver failure using hepatobiliary scintigraphy and CT volumetry. J Nucl Med 2007;48:685-692.
21. Kauffmann R, Fong Y. Post-hepatectomy liver failure. Hepatobiliary Surg Nutr 2014;3:238-246.
22. Chapelle T, De Beeck BO, Huyghe I, Francque S, Driessen A, Roeyen G, et al. Future remnant liver function estimated by combining liver volumetry on magnetic resonance imaging with total liver function on 99m tc-mebrofenin hepatobiliary scintigraphy: can this tool predict post-hepatectomy liver failure? HPB (Oxford) 2016;18:494-503.
23. Stoffels B, Enkirch SJ, Websky MW, Vilz TO, Pantelis D, Manekeller S, et al. Posthepatectomy liver failure in extended liver resections: an overview based on a retrospective single-centre analysis. Zentralbl Chir 2016;141:405-414.
24. Lee SY. Central hepatectomy for centrally located malignant liver tumors: a systematic review. World J Hepatol 2014;6:347-357.
25. Shirabe K, Shimada M, Gion T, Hasegawa H, Takenaka K, Utsunomiya T, et al. Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. J Am Coll Surg 1999;188:304-309.
26. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, Ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864-871.
27. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, La Barba G, et al. Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl 2006;12:966-971.
28. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519-524.
29. Teh SH, Christein J, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model of end-stage liver disease (MELD) score predicts perioperative mortality. J Gastrointest Surg 2005; 9:1207-1215.
30. Kaneko K, Shirai Y, Wakai T, Yokoyama N, Akazawa K, Hatakeyama K. Low preoperative platelet counts predict a high mortality after partial hepatectomy in patients with hepatocellular carcinoma. World J Gastroenterol 2005;11:5888-5892.
31. Bennett JJ, Blumgart LH. Assessment of hepatic reserve prior to hepatic resection. J Hepatobiliary Pancreat Surg 2005;12:10-15.
32. Tomimaru Y, Eguchi H, Gotoh K, Kawamoto K, Wada H, Asaoka T, et al. Platelet count is more useful for predicting post-hepatectomy liver failure at surgery for hepatocellular carcinoma than indocyanine green clearance test. J Surg Oncol 2016;113: 565-569.
33. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007; 204:854-862.
34. Li B, Yu Y, He TF, Fan J, Wu ZQ, Zhou J, et al. Value of the conventional liver function tests in the assessment of hepatic reserve. Chinese Journal of Hepatobiliary 2011;17:805-808.
35. Shen Y, Shi G, Huang C, Zhu X, Chen S, Sun H, et al. Prediction of post-operative liver dysfunction by serum markers of liver fibrosis in hepatocellular carcinoma. PLoS One 2015;10: e0140932.

36. Motoyama H, Kobayashi A, Yokoyama T, Shimizu A, Furusawa N, Sakai H, et al. Liver failure after hepatocellular carcinoma surgery. Langenbeck Arch Surg 2014;399:1047-1055.
37. An S, Rong W, Wang L, Wu F, Yu W, Feng L, et al Analysis of clinicopathological features and prognosis between alpha-fetoprotein negative and positive hepatocellular carcinoma patients after ro radical hepatectomy. Zhonghua Zhong Liu Za Zhi 2015;37:308-311.
38. Abbasi A, Bhutto AR, Butt N, Munir SM. Corelation of serum alpha fetoprotein and tumor size in hepatocellular carcinoma. J Pak Med Assoc 2012;62:33-36.
39. Lai Q, Melandro F, Pinheiro RS, Donfrancesco A, Fadel BA, Levi Sandri GB, et al. Alpha-fetoprotein and novel tumor biomarkers as predictors of hepatocellular carcinoma recurrence after surgery: a brilliant star raises again. Int J Hepatol 2012;2012:893103.
40. Toro A, Ardiri A, Mannino M, Arcerito MC, Mannino G, Palermo F, et al. Effect of pre-and post-treatment α-fetoprotein levels and tumor size on survival of patients with hepatocellular carcinoma treated by resection, transarterial chemoembolization or radiofrequency ablation: a retrospective study. BMC Surg 2014;14:40.
41. Kohla MA, Zeid MI, Al-Warraky M, Taha H, Gish RG. Predictors of hepatic decompensation after TACE for hepatocellular carcinoma. BMJ Open Gastroenterol 2015;2:e000032.
42. Kadalayil L, Benini R, Pallan L, O'beirne J, Marelli L, Yu D, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol 2013;24:2565-2570.
43. Nanashima A, Sumida Y, Abo T, Tanaka K, Takeshita H, Hidaka S, et al. Clinicopathological and intraoperative parameters associated with postoperative hepatic complications. Hepatogastroenterology 2007;54:839-843.
44. Nanashima A, Tobinaga S, Abo T, Nonaka T, Takeshita H, Hidaka S, et al. Reducing the incidence of post-hepatectomy hepatic complications by preoperatively applying parameters predictive of liver function. J Hepatobiliary Pancreat Sci 2010;17:871-878.
45. Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg 2005;12:16-22.
46. Seyama Y, Kokudo N. Assessment of liver function for safe hepatic resection. Hepatol Res 2009;39:107-116.
47. Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T, Yamaguchi J, et al. The predictive value of indocyanine green clearance in future liver remnant for posthepatectomy liver failure following hepatectomy with extrahepatic bile duct resection. World J Surg 2016;40:1440-1447.
48. Uchida Y, Furuyama H, Yasukawa D, Nishino H, Ando Y, Hata T, et al. Hepatectomy based on future liver remnant plasma clearance rate of indocyanine green. HPB Surg 2016;2016:7637838.
49. Leung U, Simpson AL, Araujo RL, Gönen M, McAuliffe C, Miga MI, et al. Remnant growth rate after portal vein embolization is a good early predictor of post-hepatectomy liver failure. J Am Coll Surg 2014;219:620-630.
50. Narita M, Oussoultzoglou E, Fuchshuber P, Pessaux P, Chenard MP, Rosso E, et al. What is a safe future liver remnant size in patients undergoing major hepatectomy for colorectal liver metastases and treated by intensive preoperative chemotherapy? Ann Surg Oncol 2012;19:2526-2538.