Original Article

A novel scoring system for conversion and complication in laparoscopic liver resection

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Background: Although laparoscopic liver resection (LLR) has been increasingly popular worldwide, there is lack of predictive model to evaluate the feasibility and safety of LLR. The aim of this study was to establish a scoring system for predicting the possibility of conversion and complication, which could facilitate the patient selection for clinicians and communication with patients and their relatives during the informed consent process.

Methods: Consecutively 696 patients between August 1998 and December 2016 underwent LLR were recruited. The entire cohort was divided randomly into development and validation cohorts. The scoring system for conversion and complication were established according to risk factors identified from multiple logistic analysis. Subgroup analysis was performed to assess the clinical application. And the C-index and decision curve analysis (DCA) were conducted to evaluate the discrimination in comparison with other predictive models.

Results: Six hundred and ninety-six patients were enrolled eventually. The rate of conversion in the development and validation cohorts was 8.3% and 10.3%, respectively. Compared with 12.6% complication rate in the development cohort, 12.9% was concluded in the validation cohort. Upon on the identified risk factors, the risk stratification model was established and validated. Subsequent subgroup analysis indicated low risk patients presented superior surgical outcomes compared with high risk patients. Besides, the C-index and DCA implied our models had better capacities of predicting conversion and complication in comparison with previous scoring systems.

Conclusions: This novel scoring system presents the remarkable capacities of predicting conversion, complication in LLR. And thereby, it could be a useful instrument to facilitate the patient selection for clinicians and communication with patients and their relatives during the informed consent process.

Keywords: Laparoscopic liver resection (LLR); conversion; complication; predictive model

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Introduction

Given its superiority of faster recovery, shorter length of stay, less blood loss, lower postoperative morbidity without compromising the survival, there has been an increasing trend toward laparoscopic liver resection (LLR) worldwide (1-4). With advances in laparoscopic

Table 1 Review of scoring systems for laparoscopic liver resection in recent years

Authors	Year	No. of LLR	Inclusion criteria	Risk factors	Event of interest
Troisi *et al.* (10)	2014	265	Hepatectomy	Tumor location	Conversion
Cauchy *et al.* (11)	2015	223	Major hepatectomy	Age; diabetes; BMI; tumour size; biliary reconstruction	Conversion
Ban *et al.* (12)	2014	90	Hepatectomy	Tumor location; extent of liver resection; tumor size; proximity of major vessel; liver function	Degrees of difficulty
Lee *et al.* (13)	2015	–	Hepatectomy	Tumor location; extent of liver resection	Degrees of difficulty
Hasegawa *et al.* (14)	2017	187	Hepatectomy	Extent of liver resection; tumor location; BMI; platelet count	Degrees of difficulty
Silva *et al.* (15)	2018	541	Hepatectomy	Hypertension; extent of liver resection; operative time	Conversion
Kawaguchi *et al.* (16)	2018	452	Hepatectomy	Extent of liver resection	Degrees of difficulty

LLR, laparoscopic liver resection; BMI, body mass index, kilogram per square metre. Lee *et al.* reported the risk model according to the experts' assessments.

equipment and technologies, indications of LLR have been extended to major and complicated hepatectomies, such as standard hemihepatectomy, extended hemihepatectomy, mesohepatectomy, and the associating liver partition and portal vein ligation for staged hepatectomy (5-7). Even for patients with colorectal cancer with liver metastases, LLR is an appropriate option offering benefits in short-term outcomes based on the Southampton Consensus (8).

Of note, according to the report from Second International Consensus Conference on laparoscopic hepatectomy, minor LLR is still in stage of reassessment while the major LLR remains in exploration stage (9). For a safe dissemination of LLR, several predictive models for conversion or scoring systems for degrees of difficulty have been established (10-16) (*Table 1*). Nevertheless, there is evidence that bias generated from the indirect relevance are sophisticated statistically, as the conversion and complication are not determined by surgical difficulty alone. In addition, thorough discussion of the incidence of conversion and complication is the key point during the informed consent process. A novel scoring system for conversion and complication is more efficient to make patients and their families understand the cost to benefit in LLR, which could prevent the subsequent dispute and compliant in case conversion and complication rate arise. And more experienced surgeon is recommended for skillful LLR in patients with high risk of complication or conversion.

Therefore, such a scoring system for predicting conversion and complication has been long of interest. Based on our over ten-year experience of LLR, predictive models for conversion and complication were therefore conducted, which could facilitate the patient selection, avoiding excessive conversion and complication in clinical settings.

Methods

Patients and methods

This is a retrospective study approved by the Ethical Committees for Human Subjects at Sir Run Run Shaw Hospital (SRRSH), School of Medicine, Zhejiang University, China. In this study, those patients who underwent concomitant extrahepatic procedures (except cholecystectomy), vascular or biliary reconstruction, or two-staged hepatectomy were excluded. The indication for patients with laparoscopic hepatectomy was summarized as below: (I) American society of anesthesiologists (ASA) grade ≤ III; (II) Child-Pugh grade A or B; (III) symptomatic benign tumors or suspicious malignancies on preoperative image examinations; (IV) for malignancies, no distant metastasis was indicated, the number of lesions was ≤3 with each lesion less than ≤5 cm, restricted in hemihepatic lobe.

We started to perform LLR since August 1998. Initially, the laparoscopic peripheral wedge resection procedure was performed. With the accumulation of experience, the

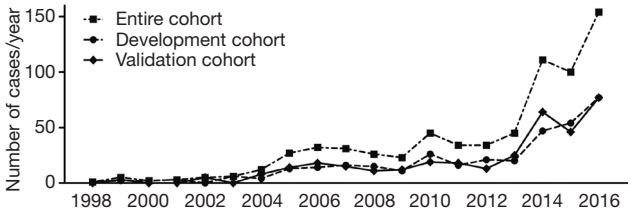

Figure 1 Chronological distribution of laparoscopic liver resection in our center. The development of laparoscopic hepatectomy in our center. The year is plotted on the x-axis and the number of cases is plotted on the y-axis.

extent of resection was extended to major and complicated hepatectomy step by step. Between August 1998 and December 2016, 696 informed patients with pure LLR were reviewed eventually (*Figure 1*). Clinical information including demographic characteristics, pathological features, and surgical outcomes, was collected by independent investigators. Then, the entire cohort was randomly divided into development and validation cohorts with ratio of 1:1. In the development cohort (n=348), a multivariate logistic analysis with step-down elimination process was conducted. Based on the identified risk factors, predictive models for conversion and complication were established, respectively. Next, subgroup analysis of surgical outcomes followed by a comparison between the different models was performed.

Surgical technique

For laparoscopic hepatectomy, which was defined as pure laparoscopy. The operative details of laparoscopic hepatectomy have been previously described (3). In brief, after general anesthesia, a 10 mm camera trocar was inserted at the level of the umbilicus. Pneumoperitoneum was established using carbon dioxide to a pressure of 10–14 mmHg in general. Then three more ports were established with the navigation of laparoscopy: a 10 mm main port in the xiphoid for surgical manipulation and two 5 mm accessory ports on the right side of the abdomen. The position of trocars was altered appropriately according to the location of tumor. Ultrasound was used for intraoperative detection of lesion, if needed. The liver parenchymal transection was carried out using a Peng's multifunctional operative dissector (Hangzhou Shuyou Medical Instrument Co., Ltd., Hangzhou, China) along with ischemia line. Meanwhile, the central venous pressure was maintained at 4–5 cmH_2O. Vascular clips or polypropylene sutures were applied to control the divided biliary and vascular structures. The Pringle maneuver was carried out as a salvage measure for bleeding control. The specimen of the liver was retrieved and placed in a plastic bag. Drainage tubes were left if bleeding or bile leakage was suspected.

Definition of end points

Demographic characteristics, tumor features and surgical outcomes were collected retrospectively. The primary end points of this study were the feasibility (conversion) and safety (complication). While operative time, blood loss, the rate of transfusion and hepatic inflow occlusion with Pringle maneuver, and postoperative hospital stay were regarded as second end points. The extent of liver resection was defined by the Brisbane 2000 terminology (17). Among, the major hepatectomy contained equal or more than three segmentectomy according to the Couinaud segment. In this setting, anterolateral segment was defined as 2, 3, 4b, 5, 6 segment, posterosuperior segment was defined as 1, 4a, 7, 8 segment. For tumor located both in anterolateral and posterosuperior segments, the tumor position was defined as junction area. The severe of complication was classified according to the Clavien-Dindo classification (18). The 90-day mortality was defined as any death occurring within 90 days after liver resection.

Statistical analysis

The continuous variables were expressed as medians with ranges, while categorical data were presented as numbers with proportions. Correspondingly, the Mann-Whitney U test was used to compare continuous variables, while the Pearson Chi-square test or corrected Chi-square test, was used to compare categorical data as appropriate. The clinical variables of development cohort were analyzed with multiple logistic regression. Subsequently, risk models were established based on the risk factors with P values less than 0.05 in above-mentioned regression model. Concordance index (C-index) and Decision curve analysis (DCA) were calculated for the evaluation of discrimination by R software (version 3.3.3). Significance was considered when two-tailed P values were less than 0.05 by SPSS, version 22.0 for Windows (IBM Corporation, Armonk, NY, USA).

Results

Clinical characteristics

Totally, 696 patients who met the criterion were enrolled. All clinical variables, including demographic characteristics, pathological features and surgical outcomes, were summarized in *Table 2*. The rates of conversion in the development and validation cohorts were 8.3% and 10.3%, respectively. Additionally, compared with 12.6% of complication in the development cohort, a comparable rate of 12.9% was concluded in the validation cohort (n=348). The major complication (Clavien-Dindo grade ≥ III) was only 4.6% (32/696) in the entire cohort. With respect to the 90-day mortality, only one patient of validation cohort died at 45 days after hepatectomy.

Establishment of risk models

The risk factors identified by logistic regression analyses for conversion, complication were presented in *Table 3*. In detail, the preoperative potential risk factors including age, gender, body mass index (BMI), ASA classification, liver cirrhosis, serum biochemical values, Child-Pugh grade, pathology, tumor size, lesion and location, magnitude of resection, were entered into the multiple logistic regression with step-down process. Alanine transaminase (ALT), ASA grade, and tumor location were related to conversion. While ALT, pathology, liver cirrhosis, tumor location, and magnitude of resection were associated with complication.

On this basis, the score in the present risk model (SRRSH risk model) was defined as follows. For conversion, ASA (I, score of '0'; II/III, score of '1'), ALT (<2 fold of normal upper limit, score of '0'; ≥2 fold of normal upper limit, score of '3'), tumor location (anterolateral segment, score of '0'; junction area, score of '1'; posterosuperior segment, score of '2'). For complication, ALT (<2 fold of normal upper limit, score of '0'; ≥2 fold of normal upper limit, score of '3'), pathology (benign, score of '0'; malignant, score of '3'), tumor location (anterolateral segment, score of '0'; junction area, score of '1'; posterosuperior segment, score of '2'), magnitude of resection (minor, score of '0'; major, score of '3') and cirrhosis (absent, score of '0'; present, score of '2'). In total, the SRRSH risk models were classified into three levels: low risk, score ≤1; medium risk, score 2; and high risk, score ≥3 in conversion-derived risk model; while low risk, score ≤1; medium risk, score 2–4; and high risk, score ≥5 in complication-derived risk model, respectively (*Table 3*).

Surgical outcomes of subgroup analysis

The results of subgroup analysis were presented in *Table 4*. In conversion-derived risk model, the conversion rate in the low risk groups (5.4%) was significantly lower than medium and high-risk groups (19.5%, P=0.004 and 17.5%, P=0.015). Compared with high risk group, the low risk group also showed superiority in other surgical outcomes, namely shorter operative time, less blood loss, lower rate of transfusion and complication, and the shorter postoperative hospital stay (P<0.05 for all). In validation cohort, a significant lower rate of conversion in low risk group was clarified in comparison of medium and high-risk groups (P<0.001 for both). Likewise, similar results were confirmed in the entire cohort, which indicated a better feasibility and safety of LLR in low risk patients.

For complication risk model. The rate of complication (2.6%) in the low risk group was significantly less than 9.5% of medium risk group and 28.6% of high-risk group in development cohort (P=0.026 and P<0.001). In validation cohort, despite no significant difference was conducted between low and medium risk groups in terms of complication, an apparently elevated rate of complication in high risk group was presented in comparison with low and medium risk group (23.4% *vs.* 11.3%, P=0.020 and 23.4% *vs.* 6.7%, P<0.001). Generally, a better surgical outcome in low risk group was demonstrated in all cohorts, compared with high risk group (P<0.05 for all). Taken together, high risk patients in complication-derived risk model presented an inferior consequence significantly compared with low risk patients.

Comparison between different risk models

Several risk models in regard to surgical difficulty has been conducted and primary comparison between different risk models has been performed (12-14,16,19,20). In this section, 10 patients in development cohort and 4 patients in validation cohort were excluded as the resection of caudate lobe was not involved in Iwate risk model (14). Therefore, 338 patients in development cohort, 344 patients in validation cohort, and 682 patients in entire cohort were used to assess the clinical application value of this novel model.

For discrimination, the C-index of these models was listed in *Table 5*. In development cohort, the C-index of SRRSH risk model for conversion was 0.650±0.096, which

Table 2 Clinical characteristics and outcomes

Characteristics	Development cohort (n=348)	Validation cohort (n=348)	Entire cohort (n=696)
Age, years			
<60	236 (67.8)	233 (67.0)	469 (67.4)
≥60	112 (32.2)	115 (33.0)	227 (32.6)
Gender			
Female	148 (42.5)	160 (46.0)	308 (44.3)
Male	200 (57.5)	188 (54.0)	388 (55.7)
BMI, Kg/m^2			
<25.0	302 (86.8)	306 (87.9)	608 (87.4)
≥25.0	46 (13.2)	42 (12.1)	88 (12.6)
ASA			
I	107 (30.7)	112 (32.2)	219 (31.5)
II/III	241 (69.3)	236 (67.8)	477 (68.5)
ALT, IU/L			
<2-fold normal upper limit	339 (97.4)	340 (97.7)	679 (97.6)
≥2-fold normal upper limit	9 (2.6)	8 (2.3)	17 (2.4)
AST, IU/L			
<2-fold normal upper limit	336 (96.6)	338 (97.1)	674 (96.8)
≥2-fold normal upper limit	12 (3.4)	10 (2.9)	22 (3.2)
HBsAg			
Negative	222 (63.8)	236 (67.8)	458 (65.8)
Positive	126 (36.2)	112 (32.2)	238 (34.2)
Cirrhosis			
Absent	274 (78.7)	290 (83.3)	564 (81.0)
Present	74 (21.3)	58 (16.7)	132 (19.0)
Child-Pugh grade			
A	334 (96.0)	331 (95.1)	665 (95.5)
B	14 (4.0)	17 (4.9)	31 (4.5)
Pathology			
Benign	157 (45.1)	166 (47.7)	323 (46.4)
Malignant	191 (54.9)	182 (52.3)	373 (53.6)
Histology			
HCC	149 (42.8)	133 (38.2)	282 (40.5)
ICC	18 (5.2)	23 (6.6)	41 (5.9)
HCC&ICC	0 (0.0)	2 (0.6)	2 (0.3)
Intraductal papillary tumor	2 (0.6)	1 (0.3)	3 (0.4)
Metastatic liver cancer	22 (6.3)	23 (6.6)	45 (6.5)
Hemangioma	111 (31.9)	118 (33.9)	229 (32.9)
Focal nodular hyperplasia	21 (6.0)	19 (5.5)	40 (5.7)
Other benign tumors	25 (7.2)	29 (8.3)	54 (7.8)
Tumor size, cm			
<5.0	209 (60.1)	203 (58.3)	412 (59.2)
5.0–10.0	124 (35.6)	23 (6.6)	147 (21.1)
≥10.0	15 (4.3)	22 (6.3)	37 (5.3)
Tumor lesion			
Solitary	307 (88.2)	311 (89.4)	618 (88.8)
Multiple	41 (11.8)	37 (10.6)	78 (11.2)
Tumor location (Couinaud segment)			
I	10 (2.9)	4 (1.1)	14 (2.0)
II	100 (28.7)	119 (34.2)	219 (31.5)
III	101 (29.0)	113 (32.5)	214 (30.7)
IV	61 (17.5)	62 (17.8)	123 (17.7)
V	50 (14.4)	56 (16.1)	106 (15.2)
VI	107 (30.7)	93 (26.7)	200 (28.7)
VII	58 (16.7)	66 (19.0)	124 (17.8)
VIII	42 (12.1)	47 (13.5)	89 (12.8)
Tumor location			
Anterolateral segment	252 (72.4)	248 (71.3)	500 (71.8)
Junction area	40 (11.5)	57 (16.4)	97 (13.9)
Posterosuperior segment	56 (16.1)	43 (12.4)	99 (14.2)

Table 2 *(continued)*

Characteristics	Development cohort (n=348)	Validation cohort (n=348)	Entire cohort (n=696)
Type of resection			
Wedge resection	166 (47.7)	157 (45.1)	323 (46.4)
Segmentectomy	57 (16.4)	42 (12.1)	99 (14.2)
Left lateral lobectomy	60 (17.2)	85 (24.4)	145 (20.8)
Extended segmentectomy	22 (6.3)	17 (4.9)	39 (5.6)
Standard/ extended left hepatectomy	25 (7.2)	23 (6.6)	48 (6.9)
Standard/ extended right hepatectomy	18 (5.2)	24 (6.9)	42 (6.0)
Magnitude of resection			
Minor hepatectomy	302 (86.8)	298 (85.6)	600 (86.2)
Major hepatectomy	46 (13.2)	50 (14.4)	96 (13.8)
Operative time, min	140.0 [25–465]	135.0 [30–500]	139.0 [25–500]
Blood loss, mL	270.0 [5–3,500]	200.0 [5–3,500]	200.0 [5–3,500]
Transfusion			
Absent	295 (84.8)	296 (85.1)	591 (84.9)
Present	53 (15.2)	52 (14.9)	105 (15.1)
Hepatic inflow occlusion			
Absent	297 (85.3)	303 (87.1)	606 (87.1)
Present	51 (14.7)	45 (12.9)	90 (12.9)
Conversion			
Absent	319 (91.7)	312 (89.7)	631 (90.7)
Present	29 (8.3)	36 (10.3)	65 (9.3)
Reasons for conversion			
Hemorrhage	9 (2.6)	4 (1.1)	13 (1.9)
Poor vision	15 (4.3)	25 (7.2)	40 (5.7)
Adhesion	5 (1.4)	5 (1.4)	10 (1.4)
Gas embolism	0 (0)	2 (0.6)	2 (0.3)
The rate of complications	44 (12.6)	45 (12.9)	89 (12.8)

Table 2 *(continued)*

Characteristics	Development cohort (n=348)	Validation cohort (n=348)	Entire cohort (n=696)
Type of complications			
Hemorrhage	1 (0.3)	3 (0.9)	4 (0.6)
Bile leakage	0 (0.0)	2 (0.6)	2 (0.3)
Liver insufficiency	2 (0.6)	2 (0.6)	4 (0.6)
Abdominal infection	6 (1.7)	6 (1.7)	12 (1.7)
Pleural effusion/ Ascites	24 (6.9)	18 (5.2)	42 (6.0)
Others	16 (4.6)	17 (4.9)	33 (4.7)
Clavien-Dindo classification			
1	20 (5.7)	20 (5.7)	40 (5.7)
II	12 (3.4)	13 (3.7)	25 (3.6)
III	16 (4.6)	10 (2.9)	26 (3.7)
IV	1 (0.3)	4 (1.1)	5 (0.7)
V	0 (0.0)	1 (0.3)	1 (0.1)
90-day mortality	0 (0.0)	1 (0.3)	1 (0.1)
Postoperative hospital-stay, day	7.0 [1–35]	6.5 [1–49]	7.0 [1–49]

Data are presented as median [range] and number (percentage). BMI, body mass index; ALT, alanine aminotransferase, IU/L; AST, aspartate transaminase, IU/L; ASA, American Society of Anesthesiologists; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; major hepatectomy, ≥ three segmentectomy; anterolateral segment, 2, 3, 4b, 5, 6 segment; posterosuperior segment, 1, 4a, 7, 8 segment; junction area, junction of anterolateral and posterosuperior segment.

was significant higher than major/minor risk, Complexity Score risk and 10-level index risk models (0.507±0.067, P=0.006, 0.569±0.073, P=0.016 and 0.544±0.102, P=0.031). Contrary to expectations, this study did not find a significant difference of C-index between SRRSH risk and Complexity Score risk, 10-level index risk models in validation cohort. Totally, SRRSH risk model presented a better capacity of predicting conversion than major/minor risk and Complexity Score risk models. Additionally, compared with major/minor risk and Paris risk models, a higher C-index in SRRSH risk model was demonstrated in terms of complication both in development and validation

Table 3 Multiple logistic regression for conversion/complication and definition of risk models

Characteristic	OR (95% CI)	P	Score
Conversion			
ASA grade			
I	Reference	–	0
II/III	2.732 (1.149–6.495)	0.023	1
ALT (≥2-fold)			
Absent	Reference	–	0
Present	17.866 (3.996–79.884)	<0.001	3
Tumor position			
AL	Reference	–	0
Junction area	2.402 (0.763–7.560)	0.134	1
PS	3.468 (1.288–9.338)	0.014	2
Complication			
ALT (≥2-fold)			
Absent	Reference	–	0
Present	8.991 (2.040–39.633)	0.004	3
Pathology			
Benign	Reference	–	0
Malignant	5.149 (1.845–14.369)	0.002	3
Tumor location			
AL	Reference	–	0
Junction area	1.953 (0.710–5.368)	0.195	1
PS	2.482 (1.097–5.618)	0.029	2
Magnitude of resection			
Minor	Reference	–	0
Major	3.523 (1.488–8.342)	0.004	3
Cirrhosis			
Absent	Reference	–	0
Present	2.196 (1.029–4.686)	0.042	2

Risk grade (conversion/complication): low risk, ≤1/0–1; medium risk, 2/2–4; high risk, ≥3/≥5. Data are presented as median with range and number with percentage. OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; ALT, Alanine aminotransferase, IU/L; Tumor position: AL, anterolateral segment, 2, 3, 4b, 5, 6 segment; PS, posterosuperior segment, 1, 4a, 7, 8 segment; junction area, junction of anterolateral and posterosuperior segment; magnitude of resection, major hepatectomy ≥ three segmentectomy.

cohorts. Similarly, an obvious superiority of SRRSH risk model in predicting complication was clarified in the entire cohort.

Given that the proposed SRRSH risk model demonstrated a superior predictive capacity in terms of the C-index, DCA was conducted to ascertain its applicability in clinic. In development cohort, SRRSH risk model had a better net benefit with a wider range of threshold probabilities for both conversion and complication. Furthermore, a non-inferior predictive capacity of SRRSH risk model was indicated in validation cohort. Likewise, our model presented a slight superiority in predicting the conversion compared with major/minor risk, Complexity Score risk, Paris risk, and 10-level index risk models in entire cohort. For complication, the DCA indicated the improved predictive performance at higher threshold probabilities of the SRRSH risk model, as well as its net benefit levels (*Figure 2*).

Discussion

Although laparoscopic hepatectomy is widely known to have superior short-term outcomes compared with open hepatectomy, the success of LLR cannot not be guaranteed even when it is performed by experienced surgeons (21-24). This is of major importance, since the goal of this study is to help a surgeon to know whether a patient is worth to undergo LLR or not. Previous classifications attempted to predict the likelihood of conversion and complication by grading the surgical difficulty of LLR (12-14,16). Dating back to 1956, Couinaud assessed the complexity of liver resection through defining three or more segmentectomy as major hepatectomy, which has been in use for over 50 years (13). Afterwards, the Complexity Score risk model based on an international survey of experts, 10-level index model, Iwate risk model and Paris risk model were conducted step by step. However, an effective and reliable scoring system to directly predict the rates of conversion and complication with LLR remains indispensable for patient selection and risk stratification.

In the present study, multiple logistic regression was performed to identify the risk factors for conversion and complication, respectively. Generally, the patients with high ASA grade representing an inferior general condition, are prone to occur disturbance of internal environment, and thereby a higher incidence of conversion with various reasons. Intriguingly, previous studies have confirmed that

Table 4 Surgical outcomes of subgroup analysis

Characteristics	Conversion-derived risk stratification						Complication-derived risk stratification					
	Low risk	Medium risk	High risk	P			Low risk	Medium risk	High risk	P		
				L *vs.* M	L *vs.* H	M *vs.* H				L *vs.* M	L *vs.* H	M *vs.* H
Development cohort (n=338)												
Operative time, min	125.0 [25–455]	180.0 [60–445]	187.5 [45–465]	0.001	0.001	0.978	100.0 [25–345]	147.5 [45–445]	180.0 [50–465]	<0.001	<0.001	0.001
Blood loss, mL	200.0 [5–3,500]	400.0 [20–3,500]	400.0 [20–3,000]	0.057	0.018	0.709	100.0 [5–3,000]	300.0 [20–3,500]	200.0 [5–2,100]	0.009	0.020	0.809
Transfusion	32 (12.5%)	9 (22.0%)	11 (27.5%)	0.101	0.012	0.563	6 (5.1%)	15 (12.9%)	31 (29.5%)	0.038	<0.001	0.002
Hepatic inflow occlusion	29 (11.3%)	9 (22.0%)	11 (27.5%)	0.057	0.005	0.563	8 (6.8%)	22 (19.0%)	19 (18.1%)	0.006	0.010	0.868
Conversion	14 (5.4%)	8 (19.5%)	7 (17.5%)	0.004	0.015	0.816	6 (5.1%)	8 (6.9%)	15 (14.3%)	0.570	0.020	0.072
Complication	23 (8.9%)	11 (26.8%)	10 (25.0%)	0.001	0.006	0.851	3 (2.6%)	11 (9.5%)	30 (28.6%)	0.026	<0.001	<0.001
Postoperative hospital-stay	7.0 [1–35]	7.0 [2–17]	9.0 [3–22]	0.232	0.007	0.240	5.0 [1–18]	8.0 [2–35]	8.0 [2–27]	<0.001	<0.001	0.303
Validation cohort (n=344)												
Operative time, min	125.0 [30–385]	170.0 [60–350]	180.0 [35–500]	<0.001	<0.001	0.096	120.0 [40–360]	130.0 [30–385]	180.0 [30–500]	0.029	<0.001	<0.001
Blood loss, mL	200.0 [5–2,500]	300.0 [20–3,500]	400.0 [10–3,000]	<0.001	<0.001	0.517	200.0 [10–2,500]	200.0 [5–2,500]	300.0 [5–3,500]	0.828	0.002	0.005
Transfusion	26 (1.0%)	11 (23.4%)	14 (36.8%)	0.010	<0.001	0.176	13 (9.6%)	10 (8.7%)	28 (29.8%)	0.799	<0.001	<0.001
Hepatic inflow occlusion	18 (6.9%)	15 (31.9%)	11 (28.9%)	<0.001	<0.001	0.768	12 (8.9%)	11 (9.6%)	21 (22.3%)	0.854	0.004	0.011
Conversion	12 (4.6%)	10 (21.3%)	13 (34.2%)	<0.001	<0.001	0.182	7 (5.2%)	7 (6.1%)	21 (22.3%)	0.757	<0.001	0.001
Complication	21 (8.1%)	11 (23.4%)	12 (31.6%)	0.004	<0.001	0.399	9 (6.7%)	13 (11.3%)	22 (23.4%)	0.197	<0.001	0.020
Postoperative hospital-stay	6.0 [2–46]	7.0 [3–45]	8.5 [1–49]	0.073	0.008	0.420	5.00 [2–23]	7.00 [1–46]	8.00 [2–49]	<0.001	<0.001	0.030
Entire cohort (n=682)												
Operative time, min	125.0 [25–455]	180.0 [60–445]	182.5 [35–500]	<0.001	<0.001	0.260	115.0 [25–360]	140.0 [30–445]	180.0 [30–500]	<0.001	<0.001	<0.001
Blood loss, mL	200.0 [5–3,500]	300.0 [20–3,500]	400.0 [10–3,000]	<0.001	<0.001	0.506	150.0 [5–3,000]	200.0 [5–3,500]	300.0 [5–3,500]	0.041	<0.001	0.075
Transfusion	58 (11.2%)	20 (22.7%)	25 (32.1%)	0.003	<0.001	0.177	19 (7.5%)	25 (10.8%)	58 (29.1%)	0.210	<0.001	<0.001
Hepatic inflow occlusion	47 (9.1%)	24 (27.3%)	22 (28.2%)	<0.001	<0.001	0.893	20 (7.9%)	33 (14.3%)	40 (20.1%)	0.026	<0.001	0.109
Conversion	26 (5.0%)	18 (20.5%)	20 (25.6%)	<0.001	<0.001	0.427	13 (5.2%)	15 (6.5%)	36 (18.1%)	0.531	<0.001	<0.001
Complication	44 (8.5%)	22 (25.0%)	22 (28.2%)	<0.001	<0.001	0.641	12 (4.8%)	24 (10.4%)	52 (26.1%)	0.019	<0.001	<0.001
Postoperative hospital-stay	6.0 [1–46]	7.0 [2–45]	9.0 [1–49]	0.029	<0.001	0.185	5.0 [1–23]	8.0 [1–46]	8.0 [2–49]	<0.001	<0.001	0.020

Data are presented as median with range and number with percentage; L, M, and H represent the low, medium and high-risk subgroups derived from our risk models, respectively.

Table 5 Comparison of the C-index in different models

Characteristics	C-index for conversion		C-index for complication	
	Mean ± standard deviation	P	Mean ± standard deviation	P
Development cohort (n=338)				
SRRSH risk	0.650±0.096	–	0.736±0.071	–
Major/minor risk	0.507±0.067	0.006	0.598±0.071	<0.001
Iwate risk	0.606±0.094	0.213	0.642±0.086	0.012
Complexity Score risk	0.569±0.073	0.016	0.625±0.164	<0.001
Paris risk	0.543±0.096	0.051	0.553±0.086	<0.001
10-level index risk	0.544±0.102	0.031	0.560±0.089	<0.001
Validation cohort (n=344)				
SRRSH risk	0.739±0.087	–	0.657±0.083	–
Major/minor risk	0.645±0.085	0.024	0.589±0.071	0.044
Iwate risk	0.802±0.070	0.090	0.655±0.079	0.478
Complexity Score risk	0.713±0.087	0.311	0.598±0.075	0.065
Paris risk	0.762±0.086	0.329	0.579±0.083	0.039
10-level index risk	0.726±0.089	0.399	0.622±0.083	0.195
Entire cohort (n=682)				
SRRSH risk	0.698±0.065	–	0.696±0.056	–
Major/minor risk	0.582±0.058	<0.001	0.594±0.050	<0.001
Iwate risk	0.679±0.073	0.315	0.629±0.062	0.019
Complexity Score risk	0.628±0.064	0.033	0.583±0.052	<0.001
Paris risk	0.664±0.069	0.207	0.566±0.060	<0.001
10-level index risk	0.640±0.070	0.060	0.590±0.061	0.001

Data are presented as mean ± standard deviation. Differences are compared between other different models and our models.

BMI is an unfavorable variable for feasibility and safety of LLR in western countries (14,25). But in our study, no association between a high BMI was indicated. Perhaps, the discrepancy between overweight and normal patients were quite small, which resulted in no significant difference in multiple logistic regression analysis. Additionally, the elevated ALT in serum, a classical injury marker, is demonstrated to be a positive correlation with severity of the damage in liver. Increased ALT always reflects a poor tolerance of stress and a damaged compensatory ability pathologically and physiologically, which could be an efficient predictive factor for both conversion and complication. Moreover, liver cirrhosis was another negatively prognostic element for complication. This might be responsible from two reasons. Initially, secondary portal hypertension and disordered coagulation function increase the possibility of bleeding, which is the ongoing hinder for widespread application of LLR. On the basis of fundamental research, the capacity of liver regeneration derived from hepatocyte deficiency is attenuated in diseased liver (e.g., fibrosis, cholestasis, steatosis, post-chemotherapy, etc.) (26-28). The delayed proliferation volumetrically and functionally aggravates the probability of complication.

In accordance with the present results, tumor location is another crucial variable to conversion (10,13,14). For instance, right posterior lobectomy is much harder than left lateral lobectomy, although both are minor hepatectomy. Compared with tumor belonging to anterolateral segments, the removal of tumor in posterosuperior segment presents a relatively higher morbidity because of poor visualization. Limited operating space and inadequate exposure give rise to increasing risk of conversion. For tumor in the junction area of anterolateral and posterosuperior segments, complicated hepatectomies such as hemihepatectomy or mesohepatectomy are always forced to perform, which presents a positive relationship with conversion. Theoretically, major resection contributes to higher surgical difficulty level and risk of conversion and complication. Insufficient future liver remnant (FLR) often raises the rate of complication, even the postoperative hepatic failure. In malignant tumor, liver resection is requisite to achieve a tumor-free margin. In fact, it is often difficult to achieve ideal tumor margins adjacent to the great vessels or hilum using laparoscopic techniques. Therefore, expanding the resection improves the likelihood of negative margins, which in turn contributes to a higher risk of postoperative liver failure or small-for-size syndrome because of an insufficient FLR.

Overall, compared with other models in regard to patient selection, some highlights of our models should be mentioned. First of all, both tumor factor and patients characteristics could have an effect on surgical outcomes. Some models were only focused on tumor factor but

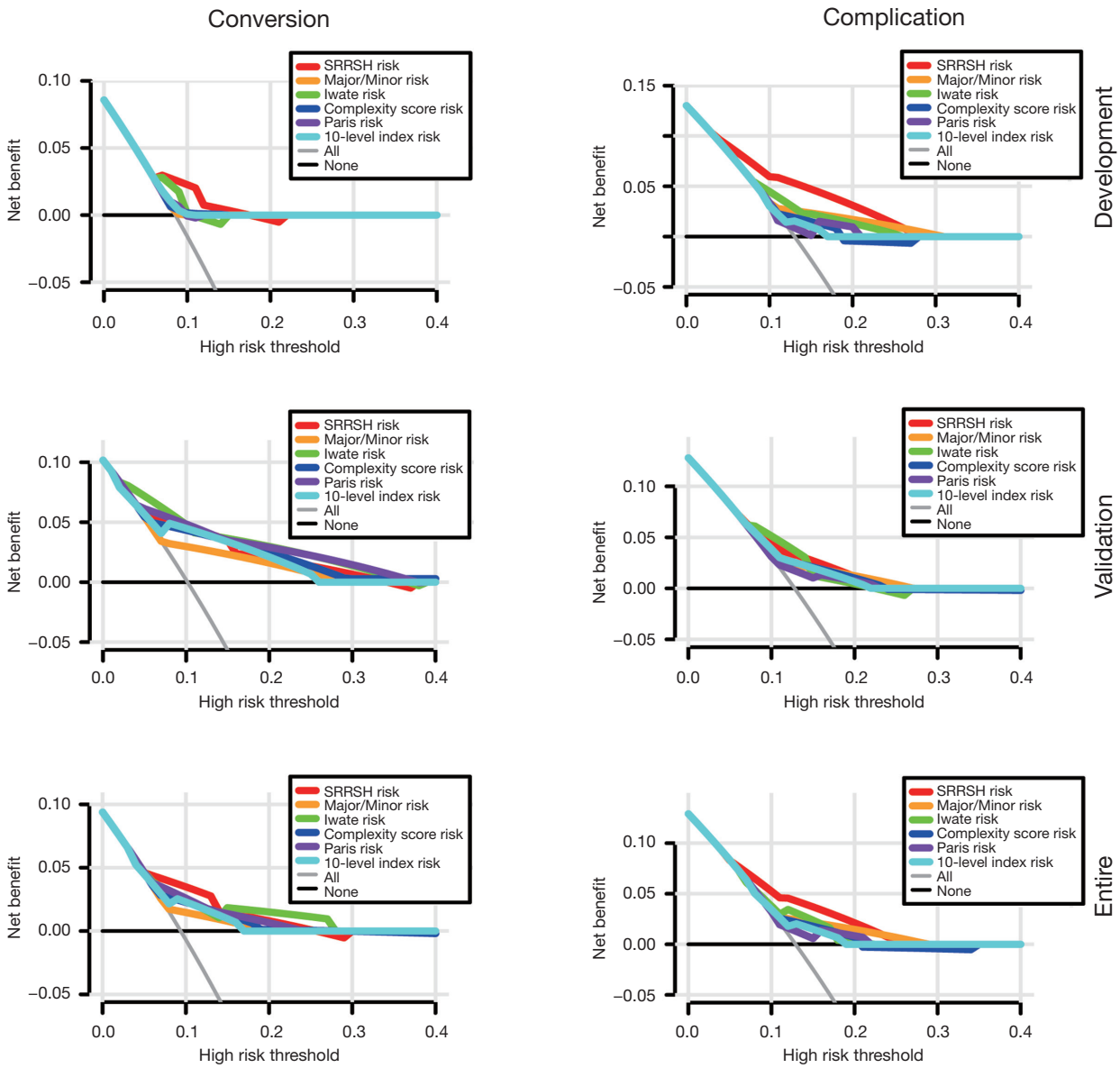

Figure 2 Decision curve analysis. Decision curve analysis are compared between different models, including SRRSH risk, major/minor risk, Iwate risk, Complexity Score risk, Paris risk, and 10-level index risk models. Black lines in the bottom indicate the net benefit of risk model in each of the curves across a range of threshold probabilities. The horizontal black line represents the assumption that no patients will experience the event, and the solid gray line represents the assumption that all patients will experience the event. The area under the curve represents efficiency of prediction.

ignoring the patients' general condition and liver function. In the present study, multiple analysis including tumor features and clinical characteristics was performed to establish the predictive models. The C-index and DCA represented a favorable discrimination, which was validated by extra internal cohort. Methodologically, the sophisticated method was quite novel and improved the credibility. The present study, to the best of our knowledge, was the first research establishing predicting models for feasibility and safety of LLR in terms of complication and conversion. Subsequent subgroup analysis indicated the SRRSH risk models were of great value in patient selection of LLR and could make patients and their families better understand the risk of LLR during the informed consent process.

However, the present study has some limitations that should be acknowledged. As the SRRSH risk models were derived from a single institution, an external validation trial was warranted definitely. Then, a majority of cases in our model were minor hepatectomy in normal liver; the generalization would be restrictive to some extent. Hence, more evidence on the benefits of laparoscopic approach for major resections or in diseased liver such cirrhosis are still needed to study whether the results would be justified in this setting. By accumulating LLR cases gradually, above-mentioned issues will be addressed as well as subgroup analysis with regard to major complication will be performed in our future work. Despite these limitations, we support that the SRRSH models present the remarkable capacities of predicting conversion, complication in LLR. And thereby, they could be a useful instrument to facilitate the patient selection for clinicians and communication with patients and their relatives during the informed consent process.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This is a retrospective study approved by the Ethical Committees for Human Subjects at Sir Run Run Shaw Hospital (SRRSH), School of Medicine, Zhejiang University, China.

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