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A simplified prediction model for early intrahepatic recurrence after hepatectomy for patients with unilobar hepatocellular carcinoma without macroscopic vascular invasion: An implication for adjuvant therapy and postoperative surveillance

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ABSTRACT

Background: An accurate prediction model of early recurrence of hepatocellular carcinoma (HCC) after hepatectomy is important to ascertain the postoperative adjuvant treatment and surveillance.
Methods: This is a retrospective cohort study including 1125 patients with HCC underwent curative hepatic resection. They were randomly divided into training (n = 562) and validation (n = 563) sets. Early intrahepatic recurrence within 18 months from surgery is the primary outcome. In the training set, a prediction scoring model (Recurrent Liver Cancer Score RLCS) was developed, which was legitimised in the validation set.
Results: RLCS was developed based on four clinicopathologic risk factors (serum alpha fetoprotein, tumor size, multiple tumors or satellite nodules, and microvascular invasion). Low-risk and high-risk groups had statistically significant differences in early recurrence rates (18% vs. 43.8%). The 5-year recurrence-free survival rates of low risk and high risk groups were 52.9% and 27.8%, respectively. This model showed good calibration and discriminatory ability in the validation set (*c*-index of 0.647).
Conclusion: RLCS is a user-friendly prediction scoring model which can accurately predict the occurrence of early intrahepatic recurrence of HCC. It establishes the basis of postoperative adjuvant treatment and surveillance in future studies.

1. Introduction

Hepatocellular carcinoma (HCC) is the commonest primary liver malignancy and it has a global incidence of more than 850,000 new cases annually [1]. Current guideline recommends hepatectomy, radiofrequency ablation and liver transplantation as curative treatment options for early hepatocellular carcinoma [2]. Over the years, hepatectomy is the most commonly adopted treatment for patients with HCC and compensated liver function in many centers. Nonetheless, high intrahepatic recurrence rate (up to 60%) limits its efficacy, resulting in unsatisfactory patients' long-term survival [3].

Intrahepatic tumor recurrence following hepatectomy can be classified into early and late recurrence. It has been suggested that early recurrence is linked to clinically undetectable intrahepatic metastasis from original tumor, whereas late recurrence originates from tumorigenesis within the underlying cirrhotic liver [4]. While it is difficult to alter the underlying cirrhotic liver except by liver transplantation, there are potential strategies to counteract the intrahepatic tumor spread to control or even prevent early recurrence, and thus improve the prognosis. Up till now, the role of adjuvant therapy for HCC remains controversial [5–7]. One possible explanation could be related to the heterogeneous patient grouping, in which high-risk patients for early recurrence was seldom chosen to be the studied group. This might dilute the effect of the adjuvant treatment. Therefore, an accurate and user-friendly prediction model for early recurrence in patients with HCC undergone hepatectomy is mandatory to identify high-risk patients who are most likely to benefit from adjuvant treatment. Furthermore, the postoperative surveillance scheme is another focusing area to be linked to the recurrence risk assessment of patients with HCC. Theoretically, more vigorous surveillance imaging should be

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offered to high-risk patients, enabling detection of early recurrent tumor for subsequent effective treatment or even salvage liver transplant.

This retrospective study aims to develop and validate a prediction risk-scoring model for early recurrence after curative hepatectomy for patients with HCC.

2. Methods

2.1. Study design and patient selection

This was a retrospective study using a prospectively collected database at the Department of Surgery of The University of Hong Kong. From January 1989 to December 2014, 1125 patients with HCC, who underwent curative hepatectomy as the first treatment, were reviewed. The following exclusion criteria were adopted: (1) patients received palliative hepatectomy (2) patients received combined hepatectomy and local ablative therapy (3) patients received local ablative treatment or trans-arterial chemoembolization or systemic treatment before hepatectomy (4) patients with hospital mortality after hepatectomy. (5) patients with tumor invasion to major branches of portal vein and hepatic vein. (6) patients with tumor invasion to adjacent organs. (7) patients with bilobar HCC. A simplified prediction risk-scoring model (known as Recurrent Liver Cancer Score RLCS) was developed and validated in the cohort of patients using a split-sample approach [8]. The whole cohort was randomly divided into a training set (n = 562) and a validation set (n = 563). The model was first developed in the training set and the findings were corroborated independently in the validation set. This study was reviewed and approved by the Institutional Review Broad of The University of Hong Kong/Hospital Authority Hong Kong West Cluster. (IRB reference no. UW 19–119)

2.2. Management protocol

The diagnosis of HCC was based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver [9]. HCC was diagnosed when the radiologic imaging techniques (spiral contrasted CT scan or contrasted MRI) showed typical features of HCC (contrast enhancement in the arterial phase and rapid wash-out of contrast in the venous or delayed phase) and/or the serum alpha fetoprotein (AFP) level was elevated (> 400 ηg/mL). The data on the preoperative images relied on hospital records and the images were not reviewed by independent radiologist specifically for this study.

Hepatectomy was the preferred curative treatment modality in patients with HCC and preserved liver function in the authors' center. The selection criteria and surgical techniques of hepatectomy have been described previously [10]. In short, the extent of resection depended on the anatomical location of the tumor. The aim of surgery was to obtain a macroscopically tumor-free margin after resection. Major hepatectomy (defined as ≥ 3 Couinaud's segments [11]) was restricted to patients with Child-Pugh class A [12] liver function and an indocyanine green clearance rate at 15 min (ICG-15) [13] of ≤15%. For patients with Child-Pugh class B or poor ICG-15 of > 15%, minor hepatectomy (defined as resection of < 3 Couinaud's segments) was considered whenever feasible. Patients with the evidence of tumor invasion into the major blood vessels (portal vein or hepatic vein), those with tumor invasion to adjacent organ and those with bilobar HCC were selectively considered for surgery in the authors' center, but these patients were excluded from the analysis for the sake of better generalization of the scoring model.

All patients underwent CT scan of abdomen and thorax and measurement of serum AFP level at 3-month intervals after operation for the surveillance of recurrence. The same diagnostic criteria as primary tumor was adopted to define intrahepatic recurrence. Dual tracer PET scan using FDG and C^{11}-acetate was performed in selected patients with suspicious extrahepatic metastasis. Various treatment options, including hepatic re-resection, radiofrequency ablation, salvage transplant and trans-arterial chemoembolization (TACE), were offered to patients with intrahepatic recurrence, depending on tumor status (i.e. the location, size and number) and patients' liver function.

2.3. Outcomes of interest

The primary outcome measure was the early intrahepatic tumor recurrence, which was defined as tumor recurrence in liver remnant within 18 months after hepatectomy. The secondary outcome measures were the long-term overall and recurrence-free survival rates.

2.4. Prognostic factors

Nineteen clinico-pathologic factors of potential influence on early recurrence were included in the analysis. Patients' demographic factors were age, sex, hepatitis B and C status, liver function in terms of Child-Pugh classification, ICG – 15, model for end-stage liver disease (MELD) [14] and presence of cirrhosis as indicated by both preoperative imaging studies and histology. Tumor factors were serum alpha fetoprotein level (AFP), tumor size, multiple tumors or satellite nodules, tumor differentiation and microvascular tumor invasion. Operative factors were type of hepatectomy, resection margin, intraoperative blood loss, requirement of blood transfusion and severe postoperative complication.

2.5. Statistical analysis

Statistical comparisons of patient demographics and tumor characteristics were performed by Chi-square test with Yates' correction or the Fisher's exact test to compare categorical variables and Mann-Whitney *U* test to compare continuous variables. In the development phase of RLCS, a logistic regression model was adopted to identify the independent risk factors for early tumor recurrence in the training set. Simplified scoring method [15] was adopted to convert the odds ratio of individual independent risk factor to a risk scoring point. The optimal cut-off value of RLCS was determined by the maximal *Youden* index of receiver-operating characteristics (ROC) curve [16]. Two risk categories (low and high) were then constructed according the total score of each individual patient. The model performance was assessed by calibration and discrimination methods. To assess accuracy of the model's predictive ability, a calibration plot was generated comparing the predicted with the observed probabilities of early recurrence. Hosmer-Lemeshow goodness-of-fit test was used to assess the quality of this calibration [17]. A p-value > 0.05 indicates good calibration of the model. To assess the model's ability to discriminate between those with or without occurrence of early recurrence, the concordance statistic (c-index) was calculated using ROC curve [18]. A value of 0.5 indicated that the model had no discriminatory ability, and a value of 1.0 indicated that the model had perfect discrimination. In the validation phase, the model was fitted with the patients' clinico-pathologic characteristics of the validation set to predict the early recurrence. The predictions were then compared with the actual outcome values. Calibration plot and concordance statistics were adopted to assess the performance of this prediction model in this validation set. Finally, the performance of RLCS was compared with the other well-known staging models (Hong Kong Liver Cancer [HKLC] staging [19], 7th Union Internationale Contre le Cancer [UICC] staging [20], Barcelona Clinic of Liver Cancer [BCLC] staging [21], prognostic normogram by Shim [22], and REACH score by Tokumitsu [23]) with respect to their discriminatory power on the basis of ROC curve analysis.

All statistical tests were two-sided and a significant difference was considered when $p < 0.05$. SPSS version 24.0 statistical software (SPSS, Chicago, Illinois, US) was used for statistical analyses.

Table 1
Patient demographics and tumor characteristics of whole cohort, derivation set and validation set.

Characteristics	Whole cohort (n = 1125)	Training set (n = 562)	Validation set (n = 563)	*p value*¶
Age	57 (5 – 84)	57 (5 – 84)	58 (7 – 84)	0.445
Male: Female	887 : 238	430 : 132	457 : 106	0.560
Hepatitis B viral infection	944 (83.9)	475 (84.5)	469 (83.3)	0.801
Hepatitis C viral infection	43 (3.8)	20 (3.6)	23 (4.1)	0.793
Comorbidity	462 (41.1)	234 (41.6)	228 (40.5)	0.698
Child-Pugh classification Class A: Class B	749 : 39	379 : 18	370 : 21	0.625
ICG – 15 (%)	10.7 (1.2–64.2)	10.5 (1.2–64.2)	10.9 (1.6–57.1)	0.472
MELD	8 (7 – 20)	9 (7 – 15)	8 (7 – 20)	0.311
Presence of cirrhosis	688 (61.2)	349 (62.1)	339 (60.2)	0.516
Serum AFP level (ηg/ml)	4 (1 – 1043700)	4 (1 – 1043700)	7.5 (1–388800	0.167
Serum AFP level (ηg/ml) ≤ 200: > 200	718 : 400	346 : 212	372 : 188	0.123
Type of hepatectomy Major: Minor	550 : 575	272 : 290	278 : 285	0.742
Resection margin ≤ 1 cm: > 1 cm	646: 450	321: 227	325: 223	0.806
Intraoperative blood loss (L)	0.5 (0.1–15)	0.66 (0.2–14)	0.68 (0.1–15)	0.563
Blood transfusion required	182 (16.2)	92 (16.4)	90 (16)	0.861
Severe postoperative complication[a]	80 (7.1)	41 (7.3)	39 (6.9)	0.810
Size of largest tumor (cm)	3 (0.7–28)	4.5 (0.8–28)	4.5 (7 – 22)	0.939
No. of tumor nodules Single: Multiple	947 : 178	471 : 91	476 : 87	0.734
Tumor differentiation[b] Grade I/II: Grade III/IV	882 : 223	441 : 109	441 : 114	0.765
Microvascular invasion	471 (41.9)	244 (43.3)	227 (40.3)	0.292
Presence of satellite nodules	75 (6.7)	40 (7.1)	35 (6.2)	0.545
Cirrhosis on histology	788 (70)	397 (70.6)	391 (69.4)	0.696

Continuous variables are expressed as median with range.
Categorical variables are expressed as number of patients (percentage).
ICG – 15, Indocyanine green retention at 15 min; MELD, model for end-stage liver disease; AFP, alpha fetoprotein.
Child-Pugh classification and MELD are only applied to patients with cirrhosis on histology.
Statistical comparison was performed between training and validation set.
[a] Severe postoperative complication according to Clavian-Dindo grade III or above.
[b] Tumor grading according to Edmondson and Steiner system.

3. Results

3.1. Clinico-pathologic characteristics of patients

The patient demographics, tumor characteristics and operative details of the whole cohort, both training and validation sets were shown in Table 1. In the whole cohort (n = 1125), most of patients were male, hepatitis B carrier, and had preserved liver function. 61.2% of patients had liver cirrhosis on preoperative imaging studies. Regarding operative details, 48.9% of patients had major hepatectomy and all patients had margin negative resection, of which 41.1% had resection margin more than 1 cm. The median intraoperative blood loss was 500 mL with 16.2% of patients requiring blood transfusion. There were 7.1% of patients who developed severe postoperative complications (Clavien-Dindo grade III or above [24]). Concerning tumor status, the maximal tumor size was up to 28 cm. Solitary tumor was found in 84.2% of patients, whereas 15.8% of patients had multiple tumors. Poor pathological tumor characteristics occurred in 41.9% of patients with microvascular invasion, 6.7% of patients with satellite nodules and 20.2% of patients with grade III/IV tumor differentiation. There were 70% of patients who had cirrhosis on histology. One hundred patients (8.8%) had normal liver on preoperative imaging studies, but cirrhosis on histology. Preoperative imaging had sensitivity of 87.3% and specificity of 100% in predicting cirrhosis.

There were no significant differences between the training and validation sets in terms of patients' demographic factors, tumor factors and operative factors.

3.2. Primary outcome

The early tumor recurrence rate of whole cohort, derivation set and validation set was 30.2% (340 of 1125 patients), 29.5% (166 of 562 patients) and 30.9% (174 of 563 patients), respectively.

3.3. Development of RLCS model

In training set, the multivariable logistic regression analysis of 19 clinico-pathologic factors for early tumor recurrence identified 4 poor independent prognostic factors. They were AFP > 200 ηg/mL, tumor size > 5 cm, multiple tumors or satellite nodules and microvascular invasion (Table 2). The allocation of number of points in the prediction model referred to the odds ratio of each predictive risk factor in the final model of multivariable analysis (Table 3). The proportion of patients developing early recurrence in each risk scoring group was shown in Table 4. The calibration plot demonstrated a good correlation between predicted probabilities of early recurrence of individual risk groups and the observed primary outcome, with Hosmer-Lemeshow statistic of 5.429 with 8 *df* ($p = 0.711$). The ROC curve showed the discriminatory power of HKRLCS with *c*-statistics index of 0.705 (95% confidence interval [CI], 0.658–0.753). ($p = < 0.001$) The optimal cut-off point of RLCS by the maximal *Youden* index was 3.5, with sensitivity and specificity of 0.747 and 0.559, respectively. Two risk categories were created according to the cut-off value of RLCS: low-risk group (< 4 points) and high-risk group (≥4 points). The early tumor recurrence rates of low and high risk groups were 18% (56 of 311 patients) and 43.8% (110 of 251 patients), respectively. The difference observed between 1, 3, and 5-year overall survival rates of low-risk (98.4%, 86.4% and 77.6%) and high-risk groups (87.3%, 61.5% and 47.3%)

Table 2
Univariate and multivariate analyses of potential prognostic factors affecting early recurrence in training set.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	0.990 (0.976–1.004)	0.166		
Gender (male)	0.856 (0.554–1.322)	0.483		
Hepatitis B viral infection	1.164 (0.709–1.911)	0.547		
Hepatitis C viral infection	0.782 (0.280–2.187)	0.639		
Child-Pugh grade B	2.443 (0.952–6.269)	0.063		
ICG -15 (> 15%)	1.239 (0.800–1.920)	0.338		
MELD (> 10)	0.532 (0.229–1.237)	0.143		
Cirrhosis on preoperative imaging	1.170 (0.803–1.704)	0.414		
Cirrhosis on histology	1.344 (0.876–1.655)	0.823		
Serum AFP level (> 200ηg/ml)	2.039 (1.408–2.952)	< 0.001	1.670 (1.126–2.478)	0.011
Tumor size (> 5 cm)	2.205 (1.526–3.186)	< 0.001	1.627 (1.096–2.413)	0.016
Multiple tumors or satellite nodules	3.302 (2.082–5.236)	< 0.001	2.571 (1.572–4.205)	< 0.001
Tumor differentiation (Grade III/IV)	1.206 (0.770–1.889)	0.414		
Microvascular invasion	3.119 (2.142–4.542)	< 0.001	2.436 (1.643–3.610)	< 0.001
Major hepatectomy	0.961 (0.669–1.380)	0.828		
Resection margin (< 1 cm)	0.927 (0.638–1.346)	0.689		
Intraoperative blood loss (> 3L)	1.901 (0.922–3.919)	0.082		
Blood transfusion	1.248 (0.775–2.009)	0.362		
Severe postoperative complications	0.858 (0.419–1.755)	0.675		

OR, odds ratio; CI, confidence interval; ICG-15, indocyanine green retention at 15 min; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein.
The prognostic factors with *p*-value < 0.1 are selected for multivariate analysis.

Table 3
Allocation of points in the prediction scoring system.

Risk factor	Categories	Odds ratio	Points assigned
Serum AFP level (> 200ηg/ml)	0	0	0
	1	1.670	2
Tumor size (> 5 cm)	0	0	0
	1	1.627	2
Multiple tumors or satellite nodules	0	0	0
	1	2.571	4
Microvascular invasion	0	0	0
	1	2.436	3

Points allocation based on odds ratio of individual risk factor: Odds ratio OR > 1.0 and < 1.5, 1 point; OR ≥ 1.5 and < 2.0, 2 points; OR ≥ 2.0 and < 2.5, 3 points; OR ≥ 2.5 and < 3.0, 4 points.

Table 4
Percentage of patients developing early recurrence in each risk score group in the training set.

Risk score	No. of patients[a]	No. of patients developing early recurrence	Early tumor recurrence rate (%)
0	139	18	13
2	112	21	18.7
3	60	17	28
4	46	15	32.6
5	83	30	36
6	15	5	33
7	57	27	47
8	7	3	43
9	22	15	68
11	21	15	71

[a] Number of patients in each risk score group.

were statistically significant. ($p = < 0.001$) (Fig. 1a) Meanwhile, difference between the 1, 3, and 5-year recurrence-free survival rates of low-risk (85.6%, 62.4% and 52.9%) and high-risk groups (50.5%, 34.9% and 27.8%) were also statistically significant. ($p = < 0.001$) (Fig. 1b)

3.4. Validation of RLCS model

RLCS was validated in a separate cohort (validation set), in which the probability of early tumor recurrence rates was predicted. Three patient were excluded from ROC curve analysis because of missing data of variable required by the model. The low-risk group had early tumor recurrence rate of 22.7% (78 of 343 patients), whereas the high-risk group had the recurrence rate of 44.2% (96 of 217 patients). The calibration yielded good agreement between predicted and observed outcomes with Hosmer-Lemeshow statistic of 4.081 with 8 *df* ($p = 0.876$). The *c*-statistics index for predicting early recurrence was 0.647 (95% CI, 0.597–0.696). ($p = < 0.001$) The 1, 3, and 5-year overall survival rates of low-risk group (96.2%, 88.3% and 78.9%) was significantly better than those of high-risk group (85.2%, 60.1% and 45.2%). ($p = < 0.001$) Meanwhile, difference between the 1, 3, and 5-year recurrence-free survival rates of low-risk (81.5%, 64.8% and 53.6%) and high-risk groups (49.6%, 33% and 23.6%) were also statistically significant. ($p = < 0.001$)

3.5. Comparison between RLCS and other staging models

The discriminatory power of RLCS and other well-known staging models, including recently published normogram by Shim and REACH score by Tokumitsu, were compared by ROC curve analysis. HKRLCS has high discriminatory power in predicting early recurrence after hepatectomy among those prediction models: its *c*-index was 0.647 (Standard error SE: 0.025), which was higher than that of HKLC staging (0.566 [SE, 0.027]), UICC staging (0.635 [SE, 0.026]), BCLC staging (0.558 [SE, 0.026]), REACH score (0.646 [SE, 0.026]). However, the *c*-index of RLCS is less than the normogram by Shim (0.648 [SE, 0.025]). Three patients in the validation group were excluded from ROC curve analysis of the normogram by Shim because of the missing data required by the model.

4. Discussion

This retrospective cohort study established an accurate and user-friendly prediction risk-scoring model (RLCS) for early tumor recurrence after curative hepatectomy for HCC. It provided good calibration and discriminatory power in both training and validation sets, and it has high predictive power among those known competing staging models.

High rates of intrahepatic tumor recurrence after curative hepatectomy remain a great challenge to clinicians. Previous studies have

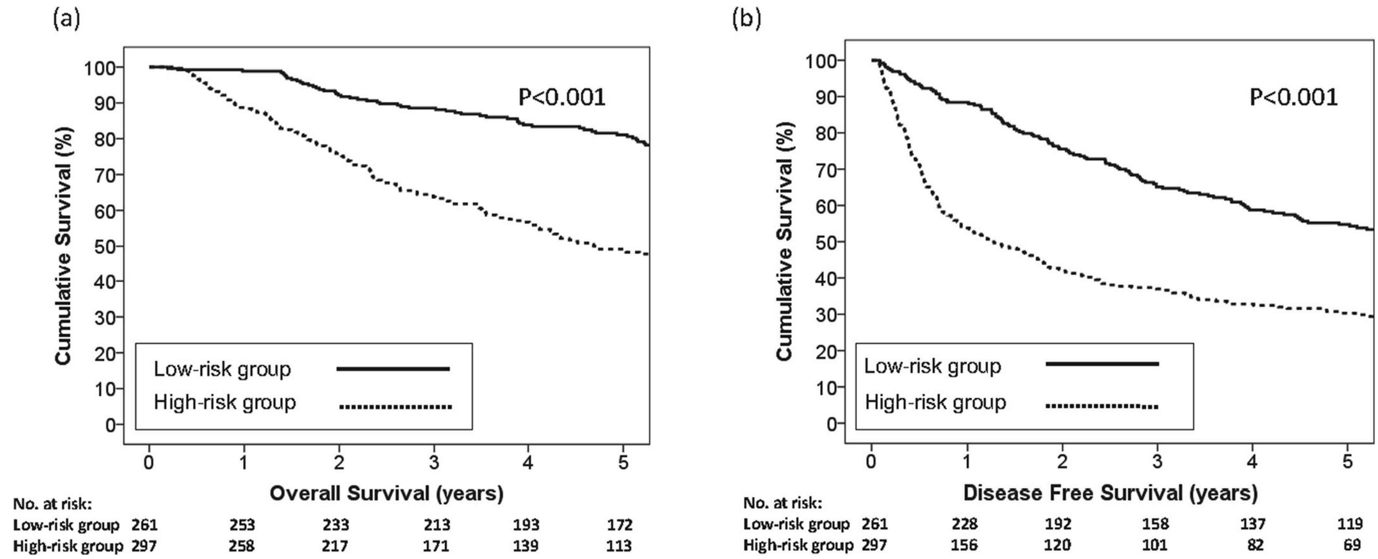

Fig. 1. (a) Overall survival rates of low-risk and high-risk patients according to RLCS in training set **(b)** Recurrence-free survival rates of low-risk and high-risk patients according to RLCS in training set.

provided evidence that early and late intrahepatic recurrences were associated with intrahepatic metastasis and multicentric oncogenesis, respectively [4,25]. Despite similar treatments, the prognosis for patients with early recurrence was worse than those with late recurrence (median survival: 15.8 months vs. 29.6 months) [4]. To prevent early intrahepatic recurrence and prolong patients' survival, studies have investigated the efficacy of different adjuvant treatment modalities, including interferon, TACE, ^{131}Iodine-labeled lipiodol administration and adoptive immunotherapy [26–28]. Ueno et al. [27] reported that adjuvant TACE could reduce the risk of early recurrence, but not late recurrence, after curative hepatectomy in a case-control study involving 127 patients. However, more recently, Jiang et al. [29] showed in a propensity sore analysis of 229 patients with HCC that adjuvant TACE does not improve overall and recurrence-free survival. In fact, systemic review and meta-analysis failed to show a strong evidence to support the use of these adjuvant therapies [5–7]. One possible explanation might be related to the heterogeneous patient grouping and the resulting dilution effect on adjuvant treatment in various non-randomized and randomized controlled studies. In other words, if studies focused on the effects of adjuvant therapy only on high risk patients, the results might be different. It would therefore be clinically relevant to identify those patients who are of high risk of developing early intrahepatic recurrence after curative hepatectomy. They can then be the focus of future clinical trials on adjuvant treatment. A prediction model, based on readily available risk factors, which can accurately identify high risk patients for early recurrence, is the solution for this clinical question. Another important clinical implication of the mentioned prediction model relates to surveillance for recurrence in the postoperative period. Theoretically, the high-risk patient group should have more aggressive surveillance program using accurate radiographic studies to detect early recurrent tumor to be eradicated in due time. In some centers, preemptive salvage transplant is offered to high-risk patients after hepatectomy to prolong patient survival [30].

Although numerous clinico-pathologic risk factors have been reported to account for recurrence after curative hepatectomy for HCC, studies focusing on the development and testing of accurate prediction model for tumor recurrence are few. Up till now, most of the reported prediction scoring models did not specifically focus on early recurrence following hepatectomy. These included a recurrence-free survival nomogram for AFP-negative patients by Gan et al. [31], a recurrence clinical risk score by Zheng et al. [32], prognostic prediction model for large HCC by Hwang et al. [33] and Shanghai score by Sun et al. [34] There are three recently published studies proposing prediction risk models for early recurrence of HCC [22,23,35]. Although accurate, those models involved sophisticated statistical equations to evaluate the risk stratification. The present study is unique in developing a simplified user-friendly prediction scoring model (RLCS) for early recurrence of HCC from a large cohort of patients with validation. This score carries high discriminatory power in predicting the risk of early recurrence (low-risk vs. high-risk groups = 18% vs. 43.8%). Its accuracy in predicting long-term prognosis is also demonstrated in the patients' overall and recurrence-free survival.

One major advantage of RLCS is the utilization of four readily available clinico-pathologic risk factors for recurrence in curative hepatectomy for HCC. The AFP level is available preoperatively as part of diagnostic process for patients with HCC. Its biological predictive value of HCC has been emphasized in the field of liver transplantation [36]. It is well accepted that high AFP level denotes highly aggressive tumor and the chance of intrahepatic metastasis might be higher than tumor with low AFP level. Tumor size, tumor number, microvascular invasion and satellite tumor nodules can be easily assessed by routine pathological examination of specimens. These parameters are readily available, making this model user friendly, when compared with some other studies which used sophisticated radiologic and genetic parameters in their prediction models [37,38].

It is worth mentioned that microvascular invasion is an important prognostic risk factor for early recurrence in RLCS model. The clinical significance of microvascular invasion has been repeatedly emphasized in the literature [39], and its preoperative prediction model has also been advocated. Zheng et al. [40] proposed a multivariable model combining AFP, tumor size, hepatitis status and quantitative radiographic feature to predict microvascular invasion of HCC, with high positive and negative predictive values.

Another salient point is that RLCS is among those known competing staging models with high predictive power of early recurrence. Traditionally, clinicians utilized staging systems (UICC [20] and BCLC [21] staging systems) to stratify HCC patients to receive different treatment modalities (curative or palliative). The predictive power of early recurrence in these staging systems is thus less well established and therefore, limited in clinical practice. The authors' center proposed HKLC [19] staging system in 2014. It was significantly better than BCLC system in its ability to predict prognosis and assign appropriate treatment. More importantly, HKLC system identified subset of BCLC intermediate and advanced-stage patients suitable for aggressive surgical treatment. Nonetheless, HKLC system involves all patients receiving different treatments (curative, palliative and conservative treatment) and its predictive accuracy for early recurrence in subset of patients undergone curative hepatectomy is less than RLCS. Two published prediction scoring models from Japan group and Korean group focus on prediction of early recurrence after hepatectomy [22,23]. Likewise, by ROC curve analyses in the validation group of the present study, RLCS has higher discriminatory power than the scoring model by Japan group but its discriminatory power is less than that of Korean group. Nevertheless, RLCS is a more user-friendly tool than that by Korean group, which utilizes normogram consisting of six factors.

The cut-off time interval for early recurrence in the present study was arbitrarily set at 18 months. This duration is in concordance with a study by Yamamoto et al. [41] which investigated the optimal duration of the early and later recurrence after hepatectomy using the "minimal *P*-value approach". It was found in that study that 17 months after hepatectomy was a useful cut-off value.

One major drawback of the present study is the retrospective nature. The studied period is across 25 years, in which there may be significant changes in surgical techniques, anesthetic management and perioperative care, which might influence the tumor recurrence rate and patient survival. The early tumor recurrence rates for Era (1989–1999), Era (2000–2010) and Era (2011–2014) were 39%, 32% and 26%, respectively. The 5-year overall survival rates for Era (1989–1999), Era (2000–2010) and Era (2011–2014) were 46%, 58% and 62%, respectively. (Data not presented in "Result" section) Secondly, it would be preferable that RLCS can be prospectively and externally validated in a separate cohort of patients of another center with different geographical region. For generalization, future study might test RLCS in the Western population, in which the predisposing risk factors for HCC are different from Eastern population. (HCV infection and fatty liver disease versus HBV infection) Thirdly, since there was no actual external validation, the comparison between RLCS and other scoring models might be biased. Fourthly, RLCS has not been applied separately to cirrhotic and non-cirrhotic patients. It would be interesting to test the calibration and discrimination of RLCS with respect to the presence of cirrhosis as cirrhosis might influence the aggressiveness of tumor, which in turn alter the chance of early recurrence. Finally, the applicability of RLCS in some Western centers in North America and Europe might be limited because of different treatment protocol from the authors' center. While curative hepatectomy is the preferred treatment option for all resectable HCC in authors' center, loco-regional ablation is mostly applied to solitary lesion of less than 3 cm in Western centers. Nonetheless, RLCS would has its role in most centers of Asia-Pacific region where the burden of HCC is high.

In conclusion, an accurate and user-friendly prediction scoring model (RLCS) is developed and validated to predict early recurrence rate after curative hepatectomy. It provides valuable information on the identification of high-risk patients to be targeted on in the future studies on adjuvant treatment and aggressive surveillance.

Declarations

Ethics approval

This retrospective study was reviewed and approved by the Institutional Review Broad of The University of Hong Kong/Hospital Authority Hong Kong West Cluster.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure of conflicts of interests

The authors declare that they have no competing interests.

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List of abbreviations

AFP	alpha fetoprotein
BCLC	Barcelona Clinic of Liver Cancer
CI	confidence interval
CT	computer tomography
HCC	hepatocellular carcinoma
HKLC	Hong Kong liver cancer
RLCS	Recurrence liver cancer score
ICG-15	Indocyanine green clearance rate at 15 min
OR	odds ratio
MELD	model for end-stage liver disease
MRI	magnetic resonance imaging
PET	positron emission tomography
ROC	receiver-operating characteristics
RFA	radiofrequency ablation
TACE	transarterial chemoembolization
UICC	Union Internationale Contre le Cancer

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.05.017.

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