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ERS: A simple scoring system to predict early recurrence after surgical resection for hepatocellular carcinoma

Charlotte Costentin[1] | Etienne Audureau[2] | Young Nyun Park[3] | Serena Langella[4] | Eric Vibert[5] | Alexis Laurent[6] | François Cauchy[7] | Olivier Scatton[8] | Mircea Chirica[9] | Rami Rhaiem[10] | Emmanuel Boleslawski[11] | Luca di Tommaso[12,13] | Alessandro Ferrero[4] | Hirohisa Yano[14] | Jun Akiba[15] | Matteo Donadon[13,16] | Martina Nebbia[17] | Olivier Detry[18] | Pierre Honoré[18] | Marcello Di Martino[19] | Lilian Schwarz[20] | Louise Barbier[21] | Jean-Charles Nault[22,23] | Hyungjin Rhee[24] | Chetana Lim[8] | Raffaele Brustia[6] | Valérie Paradis[25] | Catherine Guettier[26] | Brigitte Le Bail[27] | Shinya Okumura[28] | Jean-Frédéric Blanc[29] | Julien Calderaro[30]

Correspondence
Charlotte Costentin, Service d'Hépato-gastroentérologie et oncologie digestive, Avenue Maquis du Grésivaudan, 38700 La Tronche, France.
Email: ccostentin@chu-grenoble.fr

Abstract

Background: Surgical resection (SR) is a potentially curative treatment of hepatocellular carcinoma (HCC) hampered by high rates of recurrence. New drugs are tested in the adjuvant setting, but standardised risk stratification tools of HCC recurrence are lacking.

Objectives: To develop and validate a simple scoring system to predict 2-year recurrence after SR for HCC.

Methods: 2359 treatment-naïve patients who underwent SR for HCC in 17 centres in Europe and Asia between 2004 and 2017 were divided into a development (DS; $n = 1558$) and validation set (VS; $n = 801$) by random sampling of participating centres. The Early Recurrence Score (ERS) was generated using variables associated with 2-year recurrence in the DS and validated in the VS.

Results: Variables associated with 2-year recurrence in the DS were (with associated points) alpha-fetoprotein (<10 ng/mL:0; 10–100: 2; >100: 3), size of largest nodule (≥40 mm: 1), multifocality (yes: 2), satellite nodules (yes: 2), vascular invasion (yes: 1) and surgical margin (positive R1: 2). The sum of points provided a score ranging from 0 to 11, allowing stratification into four levels of 2-year recurrence risk (Wolbers' C-indices 66.8% DS and 68.4% VS), with excellent calibration according to risk categories. Wolber's and Harrell's C-indices apparent values were systematically higher for ERS when compared to Early Recurrence After Surgery

Abbreviations: BCLC, Barcelona clinic liver classification; HCC, Hepatocellular carcinoma; SR, Surgical resection.

for Liver tumour post-operative model to predict time to early recurrence or recurrence-free survival.

Conclusions: ERS is a user-friendly staging system identifying four levels of early recurrence risk after SR and a robust tool to design personalised surveillance strategies and adjuvant therapy trials.

KEYWORDS
hepatocellular carcinoma, prediction, recurrence, resection

1 | INTRODUCTION

Liver cancer is the fourth most frequent cause of cancer-related death worldwide and represents a major public health issue.[1,2] Hepatocellular carcinoma (HCC) accounts for over 90% of all primary liver cancers, and, unfortunately, only 30% of patients are eligible for potentially curative therapeutic approaches.[3] Liver transplantation is widely considered as the optimal treatment as it allows the removal of both the tumour and the underlying diseased liver parenchyma. Access to LT is, however, limited by organ shortage, and both surgical resection (SR) and percutaneous ablation are considered effective as first-line options. Indeed, a recent meta-analysis suggests that salvage transplantation may be a better treatment strategy for recurrent HCC patients with comparable post-operative complications compared to primary liver transplantation.[3,4] These conservative strategies are, however, hampered by high rates of recurrence.[5,6] Recurrence after SR for HCC occurs in up to 70% of patients within 5 years after hepatic resection and is a major cause of post-resection death.[1] Importantly, early (<2 years) recurrence seems to bear worse prognosis compared to late recurrence.[7,8]

To date, no adjuvant therapy has been validated and prevention of tumour recurrence is a major unmet need. The STORM trial, assessing sorafenib as an adjuvant therapy following curative treatment of patients with an intermediate or high risk of HCC recurrence, failed at improving recurrence free survival (RFS) and its primary endpoint.[9] Promising new drugs, such as checkpoint inhibitors,[10] are currently being evaluated in the adjuvant setting (NCT04227808; NCT04053972; NCT03867084 and NCT04102098) without validated and standardised scoring systems to predict HCC recurrence. Predictive tools are, therefore, urgently needed to standardise patients' stratification systems and outcomes comparison. In addition, timely diagnosis of HCC recurrence is critical to provide adequate care, and surveillance programmes should be best tailored to the individual risk of recurrence.

Numerous scoring systems predicting survival or recurrence after SR of HCC have been published,[11–13] but several drawbacks (including low predictive performance, need for complicated nomograms and lack of validation) have so far limited their application in clinical practice. More recently, Chan et al published the Early Recurrence After Surgery for Liver tumour (ERASL) post-resection model, based on usual variables (gender, ALBI grade, microvascular invasion, alphafetoprotein (AFP), tumour size and tumour number). It was developed in a large cohort of Asian patients and subsequently validated in external Eastern and Western smaller cohorts.[14] ERASL post-resection allows stratification into three levels of recurrence risk at 2 years and requires an online open-access calculator (https://jscalc.io/calc/Fu3bREKIInObXCtj). Robust molecular subclasses of HCC have also been reported by gene sequencing and/or gene expression profiling over the last decade. However, although molecular biology remains a promising field for the development of personalised treatments in patients with HCC, the implementation of these tumour subgroups in clinical practice remains challenging, as these experiments are costly and require a molecular biology and bioinformatics expertise that is not widely available.[15,16]

We thus aimed, in the present study, to develop and validate a novel and user-friendly scoring system to stratify the risk of early tumour recurrence after SR for HCC.

Key points

- Surgical resection (SR) is a potentially curative treatment of hepatocellular carcinoma (HCC) hampered by high rates of recurrence.
- The Early Recurrence Score (ERS) is a user-friendly staging system identifying four levels of risk of 2-year recurrence after resection.
- ERS is a robust recurrence tool for risk stratification to design personalised surveillance and adjuvant therapy trials.

2 | MATERIALS AND METHODS

2.1 | Study population

We retrospectively analysed data from a multicentre cohort study of 2359 patients undergoing SR for Barcelona Clinic of Liver Cancer (BCLC) 0/A HCC between 2004 and 2017 in 17 institutions from 4 European (France: 1299 patients, 10 centres; Italy, Spain and Belgium: 425 patients, 4 centres) and 2 Asian countries

(Japan and South Korea: 635 patients, 3 centres). Common exclusion criteria to all centres were pre-operative anti-tumoural treatment, R2 resection according to the residual tumour classification,[17] extrahepatic metastasis or portal/hepatic vein tumour thrombosis at the time of surgery and equivocal histological features suggestive of hepato-cholangiocarcinoma. Procedures were followed in accordance with CHARMS and TRIPOD guidelines.[18,19] The study complied with ethical standards and with the Helsinki Declaration of 1975, as revised in 2008, and was performed according to the legislations of each participating centre. For the present analysis, random sampling of participating centres was used to divide study population into a development set (2/3; $N = 1558$ from 12 centres) used for building the scoring system and a validation set (1/3; $N = 801$ from 5 centres) to validate its discrimination and calibration properties.

2.2 | Data collection

Patients' follow-up was standardised across centres and performed using magnetic resonance imaging and/or computed tomography scan every 3 months for 2 years and every 6 months afterwards. Imaging analysis was performed according to sites procedures (blinded or not for patient data). The following features were collected from medical charts: age at the time of SR, gender, risk factors of liver disease as reported by the investigators (alcohol intake, hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, metabolic syndrome, hemochromatosis and undetermined), pre-operative bilirubin, albumin and AFP serum level. All tumour features collected were retrieved from pathological reports only: tumour size (size of the largest nodule in case of multifocal disease), number of nodules, microvascular invasion, satellite nodules (tumour nodules located less than 2 cm from the main tumour),[20,21] surgical margin and degree of differentiation according to the World Health Organization.[22]

2.3 | Endpoints

The primary clinical endpoint considered for predictive modelling was time to early tumour recurrence, as defined by the time between surgery and initial recurrence within 2 years following SR, with death prior to recurrence considered as a competing risk. It is indeed considered to reflect metastasis from the primary tumour rather than a result of de novo carcinogenesis[23] and therefore an appropriate endpoint to identify patients who would benefit from future adjuvant therapies. Overall survival was analysed as a secondary descriptive endpoint, as defined as time from initial surgery to death or 4-year follow-up time point. Sensitivity analyses to assess model discrimination were performed considering time to early recurrence with death prior to recurrence as a censored event, and RFS with recurrence and death both considered as the events of interest.

2.4 | Statistical analysis

Recurrence risk analysis was performed using the Fine & Gray approach to survival analysis to account for the competing risk of death prior to recurrence on HCC recurrence.[24] BCLC stage was not included in the analysis because of its correlation with several pathological variables. Precisely defining liver disease risk factors may in some cases be challenging. For simplicity, risk factors were omitted from the scoring system analysis.

A two-step strategy was followed for multivariate analysis, first entering all predictors associated with recurrence at the $p < .2$ level in univariate analysis, then applying a stepwise backwards approach by removing not significant factors at the $p < .05$ level until the final model was reached. To limit overfitting, predictors not reaching strict statistical significance at the .05 level but identified as clinically important were considered in the final model. All continuous predictors were systematically categorised into binary variables, determining optimal thresholds through recursive partitioning analysis (RPA) using the conditional inference tree methodology.[25] In a nutshell, RPA algorithm recursively examines all dichotomous splits across all values of the observed variables to identify the optimal value to partition study population into groups with differentiated recurrence risk. Subhazard ratios (SHRs) were reported along with their 95% confidence intervals, while regression coefficients (log(SHR)) were considered for use as weights to compute the final score.[26] We rescaled (multiplied) and rounded them to the closest integer, using a recursive algorithm to determine the optimal solution that both improved simplicity of use in the clinical setting and preserved initial model performance.[27] A total score was then computed by adding the corresponding rounded weights for each patient.

Model discrimination for time to recurrence was assessed by computing the Wolber's concordance index (C-index) for prognostic models with competing risks[28] at 6-, 12-, 18- and 24-month follow-up. Model discrimination for sensitivity analyses based on time to recurrence with death as a censoring event and RFS was assessed by computing Harrell's C-indices. Calibration of the model was assessed graphically by comparing the predicted probability of HCC recurrence within 24 months to the observed probability across all possible risk classes yielded by the scoring system. Model validation was conducted using the validation set. We selected ERASL post-resection,[14] to compare with ERS. ERASL post-resection allows the assessment of early recurrence risk after SR using clinical, biological and pathological parameters. Of note, ERASL post-resection was developed and validated for predicting time to recurrence considering death as a censoring event, though it was initially stated to predict RFS.[29,30]

Most variables were complete or had less than 10% of missing data, to the exception of positive surgical margin (17%) and albumin level (29%). To reduce potential selection bias arising from complete-case analysis, all predictive analyses (including ERS development and evaluation of ERS and post-resection ERASL predictive performances) were performed after missing data imputation using missForest, a non-parametric imputation method based on random

forest that accommodates non-linearities and interactions.[31] Data were assumed to be missing at random, conditional on the outcome and other predictors. Descriptive statistics after missing data imputation are given in Table S1.

All analyses were performed at the two-tailed $p < .05$ level, using Stata v16.1 (StataCorp) for descriptive analyses and R 4.0.0+ (R Foundation) using the packages pec, cmprsk and party for competing risks analyses and validation. This observational study is reported according to the STARD checklist for diagnostic accuracy studies.

3 | RESULTS

3.1 | Characteristics of patients and tumours

An overall strong male predominance was observed (81%, 1907/2359), and mean age at surgery was 62.5 years. The main risk factors of liver disease were HCV (32%, 711/2238) and HBV (24%, 539/2238) infections. As expected in a series of patients treated by SR, a relatively low rate of cirrhotic livers was observed (48%, 1040/2154). A minority of patients had multifocal disease (9%, 199/2250). Adverse prognostic factors such as satellite nodules and microvascular invasion were identified in 20% (481/2359) and 43% (1023/2357) of the cases, respectively. Surgical margins were positive in 8% (153/1964) of the patients. A total of 1558 and 801 patients were included into the development and the validation sets, respectively. Patients' and tumours' main characteristics at the time of surgery are shown in Table 1. Clinical, biological and pathological significant differences were observed between the development and the validation set, both before (Table 1) and after missing data imputation (Table S1).

Median follow-up time was 34 months (interquartile range, 15–67 months). Recurrence was identified in 1067 patients (45%), and 762 patients (32%) had early recurrence (within 2 years after surgery).

3.2 | Prognostic model for early recurrence in the development set

We investigated the development set to identify the features associated with 2-year recurrence (Table 2). Univariate analysis showed significant association between early recurrence and age ($p = .009$), viral aetiology (HCV $p = .017$; HBV $p = .048$), "other aetiology" ($p = .018$), alpha-fetoprotein ($p < .0001$), albumin ($p = .03$) and bilirubin serum levels ($p = .026$), largest nodule diameter ($p < .0001$), multifocal tumours ($p = .001$), satellite nodules ($p < .0001$), microvascular invasion ($p < .0001$) and positive surgical margins ($p < .0001$). Also, the following thresholds were identified as clinically meaningful and optimal after RPA analysis for categorising continuous predictors: <12/≥12 μmol/L (bilirubin), <38/≥38 g/L (albumin), <10/10–100/>100 ng/mL (AFP) and <40/≥40 mm (largest nodule diameter). After multivariate analysis, six predictors were retained in the final model, including AFP (10–100 ng/mL: $p < .0001$; >100 ng/mL: $p < .0001$), size of largest nodule (≥40 mm: $p = .037$), multifocality (yes: $p = .008$), satellite nodules (present: $p < .0001$), surgical margin (positive R1: $p = .003$) and vascular invasion (present: $p = .118$), with the latter factor being forced into the model considering its clinical relevance despite $p > .05$ (Table 3).

3.3 | The ERS scoring system

Regression coefficients of the six predictors were then rescaled and rounded to the closest integers (i.e. multiplied by 4, identified as the optimal rescaling factor to preserve model discrimination) to provide weights suitable for use in clinical practice (Table 3): AFP (10–100 ng/mL: 2 points; >100 ng/mL: 3 points), size of largest nodule (≥40 mm: 1 point), multifocality (yes: 2 points), satellite nodules (present: 2 points), vascular invasion (present: 1 point) and surgical margin (positive: 2 points).

The resulting six-item scoring system (thereafter named *Early Recurrence Score [ERS]*) ranged from 0 to 11. To further improve the applicability of the scoring system, four classes of risk of early recurrence were defined from quartiles of the numerical ERS score: low ERS (sum = 0 or 1, $n = 507$, 2-year recurrence rate: 22.7%), intermediate ERS (sum 2 or 3, $n = 500$, 2-year recurrence rate: 31.5%), high ERS (sum 4 or 5, $n = 362$, 2-year recurrence rate: 43.2%) and very high ERS (sum >5, $n = 189$, 2-year recurrence rate: 62.0%) ($p < .0001$) (Figure 1A). Detailed patients' numbers by ERS score and corresponding predicted/observed recurrence rates in ERS risk classes are given in Figure S1 and Table S2.

3.4 | Discriminative performance and validation of the ERS

We investigated the performance of the ERS scoring system. We computed the discrimination indices of each individual predictors included in the score and observed that AFP serum level, satellite nodules and microvascular invasion showed the highest c statistics of 60.5%, 56.6% and 55.0% for the prediction of recurrence at 24 months, respectively. The feature with the least performance was multifocal tumour (52.1% at 24 months). Discrimination indices of the final model in its different forms (raw coefficients, rounded weights [ERS] and risk classes [risk class ERS: low/intermediate/high/very high risk]) and according to the different sets are shown in Table 4. Wolbers' C-indexes ranged from 74.2% (at 6 months) to 65.1% (at 24 months) for rounded ERS (the transition from raw to rounded coefficients did not result in a significant decrease in discriminative performance) and from 73.0% (at 6 months) to 64.0% (at 24 months) for the four risk classes ERS in the development set. Calibration between predicted and observed recurrence rates was excellent, as shown by classes of recurrence risks (Figure 1A). Predicted and observed cumulative incidence rates were as follows: 21.5% and 22.7% (low risk); 30.7% and 31.5% (intermediate risk); 44.5% and 43.2% (high risk); and 65.9% and 62% (very high risk) (Table S2).

TABLE 1 Clinical, biological and pathological features of the training and validation sets.

	Development set (DS)		Validation set (VS)		
	N = 1558		*N* = 801		
	Available data (*N*)	Estimate	Available data (*N*)	Estimate	*p*-value
Age, years					
Mean (±SD)	1558	63.9 (±12.2)	801	59.9 (±12.1)	<.0001
≥50		1338 (85.9%)		636 (79.4%)	<.0001
≥60		1096 (70.3%)		456 (56.9%)	<.0001
Gender, women	1558	313 (20.1%)	801	139 (17.4%)	.122
Liver disease aetiology					
Alcohol intake	1461	353 (24.2%)	777	126 (16.2%)	<.0001
HCV infection	1461	537 (36.8%)	777	174 (22.4%)	<.0001
HBV infection	1461	211 (14.4%)	777	328 (42.2%)	<.0001
NASH	1461	254 (17.4%)	777	105 (13.5%)	.018
Undetermined aetiology	1461	276 (18.9%)	777	124 (16.0%)	.093
Other aetiologies	1461	34 (2.3%)	777	2 (0.3%)	<.0001
Cirrhosis	1356	608 (44.8%)	798	432 (54.1%)	<.0001
ALBI grade					
1	1077	526 (48.8%)	583	387 (66.4%)	<.0001
2		535 (49.7%)		193 (33.1%)	
3		16 (1.5%)		3 (0.5%)	
Alphafetoprotein, ng/mL					
Median (IQR)	1549	9.0 (4.0;65.0)	801	17.6 (4.4;148.0)	.0002
<10		795 (51.3%)		328 (40.9%)	<.0001
10–100		413 (26.7%)		249 (31.1%)	
>100		341 (22.0%)		224 (28.0%)	
Albumine					
Median (IQR)	1079	39.0 (36.0;42.0)	590	42.0 (37.0;45.0)	<.0001
<38		421 (39.0%)		158 (26.8%)	<.0001
Bilirubin					
Median (IQR)	1436	12.0 (8.0;17.0)	783	11.9 (8.5;16.0)	.664
≥12		687 (47.8%)		368 (47.0%)	.722
Largest nodule diameter, cm					
Median (IQR)	1455	40.0 (25.0;65.0)	789	35.0 (25.0;60.0)	.147
≥40		735 (50.5%)		376 (47.7%)	.2
Multifocal tumour	1460	118 (8.1%)	790	81 (10.3%)	.087
Satellite nodules	1558	320 (20.5%)	801	161 (20.1%)	.829
Vascular invasion	1558	662 (42.5%)	799	361 (45.2%)	.219
Poor differenciation	1340	242 (18.1%)	773	108 (14.0%)	.015
Positive surgical margin (R1)	1452	91 (6.3%)	512	62 (12.1%)	<.0001

We next investigated our validation set which included 801 patients from 5 other clinical centres. As observed in the development set, the individual predictors showing the highest discrimination indices were also AFP serum level, satellite nodules and microvascular invasion of 58.6%, 60.7% and 59.4% for the prediction of recurrence at 24 months, respectively.

The score validated well with Wolbers' C-indexes ranging from 73.3% (at 6 months) to 68.4% (at 24 months) for the model with rounded coefficients (Table 4). Calibration between predicted and observed recurrence rates by risk classes was excellent (Figure 1B). Predicted and observed cumulative incidence rates were as follows: 21.5% and 19.1% (low risk); 30.7% and 32.5% (intermediate risk); 44.5% and 45.9% (high risk) and 65.9% and 75.8% (very high risk) (Table S2).

3.5 | ERS risk classes and overall survival

We next investigated the performance of the ERS score to predict overall survival, our secondary descriptive endpoint. Results in the development and validation series of 1558 and 801 patients are

TABLE 2 Predictors of time to early tumour recurrence in the development set, $N = 1558$: univariate analysis.

	SHR (95% CI)	*p*-value
Age, years		
Continuous	0.990 (0.983; 0.998)	.009
≥50	0.78 (0.62; 0.98)	.036
≥60	0.84 (0.69; 1.01)	.062
Gender, women	0.83 (0.66; 1.05)	.123
Liver disease aetiology		
Alcohol intake	1.07 (0.87; 1.32)	.522
HCV infection	0.79 (0.65; 0.96)	.017
HBV infection	1.28 (1.00; 1.64)	.048
NASH	0.84 (0.65; 1.08)	.174
Undetermined aetiology	1.22 (1.00; 1.48)	.052
Other aetiologies	0.31 (0.12; 0.82)	.018
Cirrhosis	1.21 (1.01; 1.44)	.034
ALBI grade		
1	1 (ref)	.001
2	1.38 (1.16; 1.65)	.0003
3	1.59 (0.65; 3.88)	.308
Alphafetoprotein, ng/mL		
Continuous	1.000005 (1.000003; 1.000008)	<.0001
<10	1 (ref)	<.0001
10–100	1.85 (1.50; 2.28)	<.0001
>100	2.43 (1.95; 3.02)	<.0001
Albumine		
Continuous	0.977 (0.956; 0.998)	.03
<38	1.37 (1.15; 1.64)	.0005
Bilirubin		
Continuous	1.008 (1.001; 1.016)	.026
≥12	1.28 (1.07; 1.53)	.006
Largest nodule diameter, cm		
Continuous	1.005 (1.002; 1.007)	<.0001
≥40	1.38 (1.16; 1.65)	.0004
Multifocal tumour	1.64 (1.22; 2.19)	.001
Satellite nodules	2.04 (1.68; 2.48)	<.0001
Vascular invasion	1.46 (1.22; 1.74)	<.0001
Poor differenciation	1.20 (0.95; 1.51)	.129
Positive surgical margin (R1)	2.04 (1.50; 2.78)	<.0001

Abbreviations: 95% CI, 95% confidence interval; SHR, subhazard ratio from Fine-Gray competing risks survival modelling; based on the above results, 17 predictors associated with early tumour recurrence at a *p*-value < .2 were considered for multivariate analysis (EPV: events per variable = 762/17 = 44.8).

presented in Figure S2. The ERS score retained its prognostic value and allowed the identification of four risk classes linked to different overall 4-year survival. The 4-year survival rates of patients with low, intermediate, high and very high ERS risk classes were 84.6% and 84.3%, 77.3% and 85.6%, 61.4% and 72.7%, and 47.7% and 45.6% in the development and validation sets, respectively. Overall survival rates at 2- and 4-year follow-up in the four ERS risk classes are given in Table S3.

3.6 | Comparison with the ERASL post-resection score

We finally aimed to determine how our system performed compared the previously published ERASL post-resection score to determine the risk of recurrence at 2 years. The Wolber's C-indices for recurrence at 2 years for the ERASL post-resection total score and the ERASL post-resection simplified classes were 59.1% and 57.4% (development set) and 66.0% and 63.2% (validation set), respectively. They appeared systematically lower for ERASL post-resection compared to ERS, regardless of the time frame considered (6, 12, 18 or 24 months) (Table 4). Results from sensitivity analyses considering either time to recurrence with death as a censored event (Table S4A) or RFS (Table S4B) yielded similar findings, with systematically higher apparent Harrell's C-indices values for ERS when compared to ERASL (validation set: ERS vs. ERASL classes: $p = .015$ [time to recurrence], $p = .020$ [RFS]; ERS vs. ERASL continuous scores: $p = .137$ [time to recurrence], $p = .194$ [RFS]).

4 | DISCUSSION

By investigating a large multicentre international series of Western and Eastern patients with HCC treated by SR, we developed and validated a simple score for the prediction of early HCC recurrence. The ERS relies on six easily available variables in routine practice and allows for the identification of four levels of risk of early recurrence. All constituting components of ERS had previously been reported to be independent predictors of shorter disease-free survival, and our results confirm previous findings supporting the hypothesis that early recurrence is predicted by intrinsic HCC characteristics and the radicality of the SR.[11,12,14]

It is now admitted that early recurrence is most often the result of metastasis from the removed primary cancer rather than de novo carcinogenesis.[7,32] It is associated with poorer clinical outcome. Tools to identify patients with a high risk of early recurrence are therefore critically needed. No adjuvant therapy is currently recommended following surgery, but a recent study suggested that transarterial chemoembolisation could improve survival in patients with intermediate or high risk of recurrence.[33] Our data highlight that all individual predictors of recurrence are not equally important: AFP serum level performed the best and multifocality the least. Moreover, the combination of individual predictors in a multi-variable score (ERS) performed better than any of the individual component, underlying the need for standardised tools taking into account multiple variables and their relative weight.

New drugs are currently tested in the adjuvant setting.[10,34] The identification of subgroups of patients with a very low risk of

TABLE 3 Predictors of time to early tumour recurrence in the development set, $N = 1558$: final multivariate model and weights for score calculation.

	SHR (95% CI)	*p*-value	Regression coefficient (95% CI)	Final weight
Alphafetoprotein, ng/mL				
<10	1 (ref)	<.0001	—	0
10–100	1.76 (1.42; 2.17)	<.0001	0.56 (0.35; 0.78)	2
>100	2.09 (1.67; 2.62)	<.0001	0.74 (0.51; 0.96)	3
Largest nodule diameter, cm				
≥40	1.22 (1.01; 1.48)	.037	0.20 (0.01; 0.39)	1
Multifocal tumour	1.52 (1.12; 2.07)	.008	0.42 (0.11; 0.73)	2
Satellite nodules	1.70 (1.37; 2.11)	<.0001	0.53 (0.32; 0.74)	2
Vascular invasion	1.16 (0.96; 1.41)	.118	0.15 (−0.04; 0.34)	1
Positive surgical margin (R1)	1.66 (1.19; 2.31)	.003	0.50 (0.17; 0.84)	2

Abbreviations: 95% CI, 95% confidence interval; SHR, subhazard ratio from Fine-Gray competing risks survival modelling.

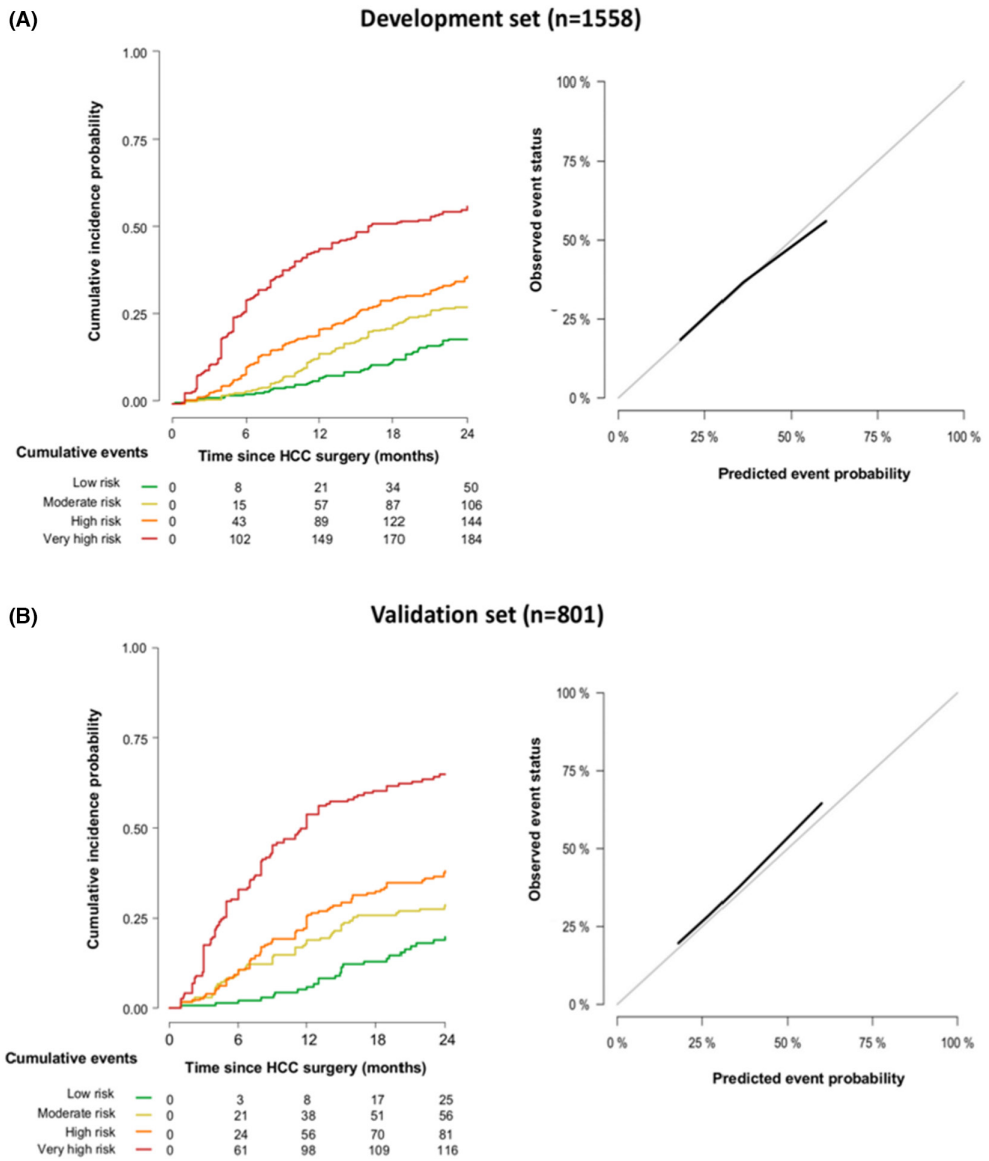

FIGURE 1 Two-year cumulative incidence of HCC recurrence by risk class and corresponding calibrations plots of predicted vs. observed recurrence rates (in classes) in the development set (A) and the validation set (B).

TABLE 4 Model discrimination of the final score in training and validation sets: Wolber's C-indices.

	Development set				Validation set			
	6-months	12-months	18-months	24-months	6-months	12-months	18-months	24-months
Final multivariate model: raw coefficients	74.3%	69.6%	67.0%	65.3%	72.6%	70.9%	68.6%	68.1%
Final multivariate model: rounded coefficients	74.2%	69.5%	66.8%	65.1%	73.3%	71.5%	69.2%	68.4%
4-class simplified score	73.0%	68.6%	65.7%	64.0%	72.0%	69.7%	67.6%	67.0%
Individual predictors								
Alphafetoprotein, ng/mL, multicategorical	67.0%	63.8%	61.8%	60.5%	63.2%	60.8%	59,0%	58.6%
Satellite nodules	60.6%	57.8%	57.1%	56.6%	62.5%	62.4%	61.1%	60.7%
Vascular invasion	59.1%	57.8%	55.8%	55.0%	63,0%	60.6%	60.2%	59.4%
Largest nodule diameter ≥40 cm	58.4%	55.9%	54.6%	54.3%	58.6%	58.6%	58.5%	57.9%
Positive surgical margin (R1)	54.1%	53.1%	52.8%	52.5%	55.7%	53.9%	53.5%	52.9%
Multifocal tumour	54.3%	52.8%	52.4%	52.1%	55.4%	54.7%	53.7%	53.3%
ERASL								
Total score	66.1%	62.6%	59.9%	59.1%	69.6%	69.5%	67.2%	66.0%
Classes 1, 2, 3	63.7%	60.7%	58.1%	57.4%	66.5%	66.2%	64,0%	63.2%

recurrence may impact patients' surveillance protocols, and lighter protocols may be considered. Therefore, robust and reproducible scoring systems to standardise HCC recurrence risk prediction are of utmost importance to help stratification of patients to test adjuvant strategies and personalised surveillance protocols.

Our study has several strengths. ERS was designed and subsequently validated in a large database including Western and Eastern patients with any cause of underlying liver disease. The multicentre design supports the generalisability of our score. Our approach limits the risk of overfitting and may have produced a more robust system. Components of the ERS are routinely evaluated, allowing easy implementation in clinical practice. Indeed, most scoring systems published to date[11–13] bear serious limitations such as low predictive performance, need for complicated nomograms and lack of validation. However, ERASL post-resection seemed the most robust predictive tool available: based on variables easy to retrieve from patients charts, designed in a large cohort of patients and subsequently validated in smallest but multiple independent cohorts. Importantly, we show that ERS generally outperformed ERASL post-resection to predict time to early recurrence, either considering death prior to recurrence as a competing event or a censoring event and to predict RFS, with systematically higher apparent concordance indices found for the ERS, with statistically significant differences when comparing Harrell's C-indices for simplified 4- and 3-class ERS and ERASL scores.

Limitations are inherent to the retrospective and multicentric nature of our study. Some data could not be retrieved. No information pertaining to portal hypertension could be included in the predictive model. However, in a recent study addressing the issue of factors related to HCC recurrence after curative resection, portal hypertension markers such as oesophageal varices, spleen length or spleen stiffness measurements were only identified as predictors of HCC late recurrence.[35] They may indeed reflect the risk of de novo carcinogenesis, and it is therefore unlikely that they would have modified our model that aimed to predict early recurrence. Data regarding surgical approach were not available in most centres. There is conflicting data regarding the impact of surgical features on HCC recurrence. There is no consensus on whether perioperative blood transfusions is associated with recurrence after surgery.[36,37] The extent of resection, whether major or minor, and whether anatomical or non-anatomical, was mostly not reported to significantly influence on the risk of recurrence.[38] For these reasons, we do not expect the lack of data regarding the operative approach could undermine the relevance of our findings and accuracy of ERS to stratify patients according to their risk of HCC recurrence after surgery with curative intent. In addition, although we excluded patients with hepatic vein tumour thrombosis at the time of surgery, we did not collected discrepancies between pre- and per-operative tumour features such as portal vein invasion that would have been missed on the pre-operative tumour staging imaging. Also, several histological features, such as the macrotrabecular-massive subtype or the Vessels that Encapsulate Tumour Clusters (VETC) pattern, were shown to be strong and independent predictors of HCC recurrence.[39–41] Unfortunately, we could not implement this feature into our scoring system as information on these novel variants was not currently systematically reported. Moreover, several transcriptomic molecular features have been linked with the risk of HCC recurrence: stem cell signature, 5 gene score, proliferative subclass, etc.[42] Precision medicine with respect to minimising recurrence events after HCC resection is expected to be revolutionised by advances in pathology or circulating biomarkers detected such as DNA, tumour cells, microRNAs and exosomes. However, reliable biomarkers are still lacking, and implementation of tumour subgroups in clinical practice remains challenging due to technical challenges and cost. While research is ongoing, standardised and robust stratification

based on available tools should be used in clinical trials testing new drugs in the adjuvant setting. In conclusion, we developed and validated a simple scoring system to assess the risk of early tumour recurrence for patients with HCC treated by SR. The ERS scoring system provides a framework for risk stratification which could be useful to design future post-resection surveillance strategies and serve as a standardised risk stratification system in upcoming adjuvant therapy trials.

AUTHOR CONTRIBUTIONS

Study concept and design: Costentin, Audureau and Calderaro. Acquisition of data: All authors. Analysis and interpretation of data: Costentin, Audureau and Calderaro. Drafting of the manuscript: Costentin, Audureau and Calderaro. Statistical analysis: Audureau. Study supervision: Costentin, Audureau and Calderaro. Critical revision and approval of the manuscript: All authors.

AFFILIATIONS

[1]Grenoble Alpes University, Institute for Advanced Biosciences, Research Center UGA/Inserm U 1209/CNRS 5309, Gastroenterology, Hepatology and GI Oncology Department, Digidune, Grenoble Alpes University Hospital, La Tronche, France
[2]Service de Santé Publique, Assistance Publique Hôpitaux de Paris, Hôpital Henri Mondor, and Université Paris-Est, A-TVB DHU, CEpiA (Clinical Epidemiology and Ageing) Unit EA7376, UPEC, Créteil, France
[3]Department of Pathology, Graduate School of Medical Science, Brain Korea 21 Project, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Department of General and Oncological Surgery, Ospedale Mauriziano "Umberto I", Turin, Italy
[5]Centre hépato-biliaire, Assistance Publique Hôpitaux de Paris, Hôpital Paul Brousse, Villejuif, France
[6]Service de Chirurgie Digestive, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Henri Mondor, Créteil, France
[7]Service de Chirurgie Hepato-Bilio-Pancréatique et Transplantation Hépatique, Hôpital Beaujon, AP-HP et Université de Paris, Clichy, France
[8]Service de Chirurgie Digestive, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Pitié Salpétrière, Paris, France
[9]Service de Chirurgie Digestive, CHU Grenoble-Alpes, Grenoble, France
[10]Service de Chirurgie Digestive, CHU de Reims, Reims, France
[11]Univ. Lille, INSERM U1189, CHU Lille, Service de Chirurgie Digestive et Transplantations, Lille, France
[12]Unit of Pathology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[13]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[14]Department of Pathology, Kurume University School of Medicine, Kurume, Japan
[15]Department of Diagnostic Pathology, Kurume University Hospital, Kurume, Japan
[16]Department of Hepatobiliary and General Surgery, Humanitas Clinical and Research Center – IRCCS, Rozzano, Italy
[17]Department of Surgery, Colon and Rectal Surgery Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[18]Department of Abdominal Surgery and Transplantation, Centre Hospitalier Universitaire de Liege, University of Liege, Liege, Belgium
[19]Department of Surgery, HPB Unit, University Hospital La Princesa, Madrid, Spain
[20]Service de Chirurgie Digestive, CHU de Rouen, Rouen, France
[21]Service de Chirurgie Digestive, CHU de Tours, Tours, France
[22]Liver Unit, Hôpital Avicenne, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Assistance-Publique Hôpitaux de Paris, Unité de Formation et de Recherche Santé Médecine et Biologie Humaine, Université Paris 13, Communauté d'Universités et Etablissements Sorbonne Paris Cité, Bobigny, France
[23]Centre de Recherche des Cordeliers, Sorbonne Université, Inserm, Université de Paris, team « Functional Genomics of Solid Tumors », Equipe labellisée Ligue Nationale Contre le Cancer, Labex OncoImmunology, Paris, France
[24]Department of Radiology, Research Institute of Radiological Science, Center for Clinical Imaging Data Science, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[25]Service d'Anatomie et de Cytologie Pathologique, Assistance Publique Hôpitaux de Paris, Hôpital Beaujon, Université de Paris, Clichy, France
[26]Service d'Anatomie et de Cytologie Pathologique, Assistance Publique Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin-Bicêtre, France
[27]Service de Pathologie, Hôpital Pellegrin, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France
[28]Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[29]Service Hépato-Gastroentérologie et Oncologie Digestive, Centre Médico-Chirurgical Magellan, Hôpital Haut-Lévêque, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France
[30]Département de Pathologie, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Henri Mondor, Créteil, France

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CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Charlotte Costentin https://orcid.org/0000-0001-6115-8512
Young Nyun Park https://orcid.org/0000-0003-0357-7967
Louise Barbier https://orcid.org/0000-0001-7759-5338
Jean-Charles Nault https://orcid.org/0000-0002-4875-9353
Valérie Paradis https://orcid.org/0000-0003-3142-3762

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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