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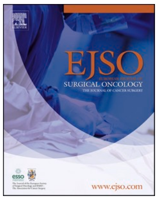

Pre and postoperative machine learning models and point-based scores to predict risk of early recurrence in upfront resected large Hepatocellular carcinoma

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ABSTRACT

Background: Large Hepatocellular Carcinoma (LHCC) are aggressive tumours characterized by a high risk of early recurrence (ER). Although several models predicting this risk exist for HCC, no one is specific for tumours $\geq$5 cm. The aim of this study is to develop classic and machine learning (ML) models able to identify patients with this pattern of recurrence.

Method: A retrospective, multicentric analysis of 12 hepato-biliary centres. Only upfront resected LHCC were included. ER was defined as recurrence within 8 months after resection. Logistic Regression (LR), Elastic Net, Decision Tree, k-nearest neighbors, Random Forest (RF) and Extreme Gradient Boosting were trained and compared though the resulting c-statistic.

Results: Between 2016 and 2022, 724 patients met the inclusion criteria. ER was reported in in 225 (31.1 %) patients. Among the five ML models, RF showed the best performance to predict ER (pre- and postoperative c-statistic: 0.685–0.719). LR showed similar accuracy compared to RF, both preoperatively (c-statistic: 0.678) and

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postoperatively (c-statistic: 0.720). This model was therefore used for two point-based scores, which were split into three groups according to the risk of ER: low, intermediate and high risk (ER for preoperative score: 15 %, 31 % and 45 %; postoperative score 17 %, 40 % and 63 %, respectively). Both scores correctly stratify patients' overall survival and risk of death ($p < 0.001$).

Conclusion: Two easy-to-use point-based scores were created, able to predict the risk of ER. These can be easily implemented in clinical practice and define best candidates for perioperative therapies (https://thibaut-goetsch.shinyapps.io/lhcc_score_preop and https://thibaut-goetsch.shinyapps.io/lhcc_score_postop).

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumour, with an incidence of more than 700000 cases per year worldwide [1–3]. Beyond its well-known poor prognosis, the significance of this pathology lies in its social determinants, with alcohol consumption and metabolic syndrome being the leading cause of its development [4,5]. Different curative options are available, including liver transplantation, surgical resection and percutaneous ablation, whose choice depends on patient performance status, age, tumour extent and underlying liver conditions [6,7]. In this context, tumour size plays a crucial role in the therapeutic decision-making. Large HCC (LHCC), defined as tumour with a maximum diameter ≥5 cm, are in fact generally beyond the eligibility criteria for liver transplantation and are also contraindicated for thermal ablation. Moreover, these tumours are characterized by greater aggressiveness and a higher risk of recurrence, particularly within the first months after resection [8–10]. This specific pattern of early recurrence, which is associated with poorer survival, was recently reviewed by some authors leading to a modification of its definition. New cut-offs have been proposed at 8–9 months, which can better stratify outcomes compared the old threshold of 2 years [11,12]. A key statistical tool in the clinician's armamentarium for the management of these tumours is predictive model, which has been extensively reported in the literature. Both traditional logistic regression-based models and newer machine learning approaches belong to this category. Although used on a large scale, none has demonstrated clear superiority over the others in different fields [13,14]. These models help identify specific subgroup of patients who, after surgical resection for instance, may be at high risk for adverse oncologic scenario, including poorer survival, higher rate of recurrence or even of early recurrence. In HCC several models exist in literature, but none is specifically designed for the LHCC subgroup [15–18]. Furthermore, most of these models rely on postoperative variables and on the outdated definition of early recurrence.

The aim of this study was to apply predictive models in the field of LHCC by developing and internally validating different scoring systems based on preoperative and postoperative available data to stratify the likelihood of early recurrence after surgical resection.

2. Materials and methods

2.1. Study design and data collection

Data of patients undergoing hepatic resection for a HCC ≥5 cm with a curative intent, between January 2015 and December 2021, prospectively collected by twelve hepato-biliary high-volume centres [19] across Italy, France and Korea were gathered in a common database. Exclusion criteria were cases: i) resected for a recurrent HCC, ii) defined not resectable at diagnosis, iii) undergoing preoperative loco-regional or systemic therapies or adjuvant treatments, iv) history of extrahepatic disease or macroscopic invasion of first or second portal branches, v) mixed histology of cholangiocellular carcinoma and HCC and vi) incomplete clinical data or follow-up inferior to 6 months. The study was aligned to the ethical standards of the Helsinki declaration, and no specific informed consent was obtained given the retrospective and observational nature of the analysis. Data were reported in adherence with the STROBE and the TRIPOD + AI statements [20,21].

2.2. Patient management

Blood laboratory tests were always performed to detect liver function through the Child-Pugh and the model for end-stage liver disease (MELD), alpha-fetoprotein (AFP) level and platelets count as an indirect sign of portal hypertension. Patient medical history and comorbidities assessed through the American society of anaesthesiology (ASA) score and the Charlson comorbidity index (CCI) score were collected. Preoperative imaging always consisted in a triphasic contrast enhanced (CE) thoraco-abdominal CT scan and, if indicated by the surgeon – as in case of suspicion of underlying cirrhosis – an CE-MRI, both performed within 40 days by the day of surgery. Size of the lesion was measured as its maximum diameter during portal venous acquisition [22,23]. In patients with no history or radiologic signs of chronic liver disease biopsy of the lesion was performed histologic confirmation of HCC [24]. Cases were discussed at local HPB multidisciplinary meeting and surgical resection validated by the members. Surgical strategy and type of approach were chosen by the senior surgeon. Major hepatectomy was defined according to the Brisbane terminology and its recent updates (major ≥3 segments) [25]. The Clavien-Dindo classification was used to score post-operative complications [26,27]. Post hepatectomy liver failure was classified according to the ISGLS score [28]. Pathologic data included tumour size, satellite nodules (defined as tumours <2 cm in size located <2 cm from the main tumour) [29], microvascular infiltration, capsular invasion, surgical margin (R1 considered as ≤1 mm) and tumour grading (according to the WHO classification) [30]. Patient follow-up was planned ad suggested by the EASL recommendations [31]. Any doubtful lesion detected at imaging during surveillance or AFP serum increase was discussed at the local HPB multidisciplinary meeting to verify HCC recurrence. If confirmed, patient's performance status and disease extent guided treatment allocation strategy. Data on site and time of recurrence during follow-up were recorded.

2.3. Outcome measure

The primary outcome measure was the identification of those cases experiencing an early recurrence after surgical resection. The reason for setting this outcome is related to the oncologic aggressiveness and the adverse survival rates reported for this specific pattern of recurrence [9,32,33]. Cut-off for early recurrence was set at 8 months, as this threshold was recently reported as the most accurate for identifying patients with worse outcomes and eligible to significantly less curative-intent treatments [11,34].

2.4. Statistical analysis

Qualitative outcomes were described with frequencies and percentages and compared using Chi-square or Fisher's exact test. Quantitative outcomes were described with medians and quartiles (i.q.r.) and compared using Wilcoxon's test. All variables were first reviewed for missing data and outlier values. Quantitative outcomes were segmented and inspected graphically for linearity of effect, to find the most relevant thresholds for categorization. A threshold of $p < 0.20$ was used for selection of variables for multivariate analysis through logistic regression.

A bootstrap procedure was implemented with stepwise procedure base on the Akaike information criterion (AIC) for variable selection. Final model used variables selected in the majority of resamples. A bootstrap procedure was used to estimate an optimism adjusted c-statistic and its 95 % confidence interval through Wald's interval [35]. Calibration was inspected graphically and evaluated with the calibration slope and intercept using weighted linear regression of observed frequencies on deciles of expected probability. Coefficients were multiplied and rounded, minimizing average linear predictor's error, to produce a practical score. Risk groups were finally established based on observed risks differences and sufficient size. Elastic Net, Decision Tree, k-nearest neighbors (KNN), Random Forest and Extreme Gradient Boosting (XGBoost) were trained on the same data. Preoperative model included gender, body mass index (BMI), ASA score, Charlson's Comorbidity Index (CCI), age, preoperative cirrhosis, CHILD score, MELD score, platelets count, hepatitis B virus (HBV) status, hepatitis C virus (HCV) status, history of viral infection, last serum alpha fetoprotein (AFP) available, HCC size, single or multiple nodules, need for portal vein embolization and western/eastern patient. Postoperative model added to the previous features type of operation, type of hepatectomy, post-hepatectomy liver failure, CD ≥ 3 complications, tumour size at pathology, microvascular infiltration, surgical margins, satellite nodules and WHO differentiation grade. A ten-fold cross-validation was used for tuning of hyperparameters and for internal validation, with a stratification on the combination of continent and outcome. Selection of hyperparameters was based on the c-statistic. The best thresholds of probability for machine learning models were selected to optimize Youden's index and to present confusion matrices. Statistical analysis used R v.4.3.3 and the package *tidymodels*.

3. Results

3.1. *General features*

Among the 724 patients included, 566 (78.2 %) were male and the median age was 68 years (i.q.r.: 59–73 years). Early recurrence was

Table 1

Comparison of clinical, radiological and pathological features according to the presence of an early recurrence.

Variables	Overall *n* = 724 (%)	No early recurrence *n* = 499 (%)	Early recurrence *n* = 225 (%)	p-value
Gender				0.6
Male	566 (78.2)	393 (78.8)	173 (76.9)	
Female	158 (21.8)	106 (21.2)	52 (23.1)	
BMI (kg/m2), median (i.q.r.)	25.0 (22.6–27.7)	25.0 (22.8–28.0)	24.2 (22.2–27.1)	***0.007***
ASA				0.3
1	66 (9.1)	43 (8.6)	23 (10.2)	
2	375 (51.8)	269 (53.9)	106 (47.1)	
3	269 (37.2)	179 (35.9)	90 (40.0)	
4	14 (1.9)	8 (1.6)	6 (2.7)	
CCI, median (i.q.r.)	5 (3–6)	5 (3–6)	5 (3–6)	0.9
Age (years), median (i.q.r.)	68 (59–73)	69 (60–74)	64 (56–73)	***<0.001***
Child-Pugh score				***0.049***
No cirrhosis	392 (54.1)	269 (53.9)	123 (54.7)	
A	317 (43.8)	224 (44.9)	93 (41.3)	
B	15 (2.1)	6 (1.2)	9 (4.0)	
Platelets count, median (i.q.r.)	206 (160–272)	200 (160–270)	216 (161–275)	0.2
HBV status				***0.007***
Negative	516 (71.3)	371 (74.3)	145 (64.4)	
Positive	198 (27.3)	124 (24.8)	74 (32.9)	
Former infection	10 (1.4)	4 (0.8)	6 (2.7)	
HCV status				0.4
Negative	580 (80.1)	394 (79.0)	186 (82.7)	
Positive	133 (18.4)	98 (19.6)	35 (15.6)	
Former infection	11 (1.5)	7 (1.4)	4 (1.8)	
AFP (ng/mL), median (i.q.r.)	29 (5–132)	27 (5–88)	37 (6–300)	***0.006***
Tumour size (mm), median (i.q.r.)	70 (60–97)	70 (58–90)	80 (60–120)	***<0.001***
Number of nodules				***0.005***
Single	553 (76.4)	396 (79.4)	157 (69.8)	
Multiple	171 (23.6)	103 (20.6)	68 (30.2)	
PVE performed	66 (9.1)	46 (9.2)	20 (8.9)	0.9
Type of hepatectomy				***0.004***
Minor	389 (53.7)	286 (57.3)	103 (45.8)	
Major	335 (46.3)	213 (42.7)	122 (54.2)	
Type of approach				***<0.001***
Open	443 (61.2)	281 (56.3)	162 (72.0)	
Minimally- Invasive	281 (38.8)	218 (43.7)	63 (28.0)	
Severe CD	72 (9.9)	43 (8.6)	29 (12.9)	0.075
PHLF	43 (6.0)	21 (4.3)	22 (9.8)	***0.004***
Satellites nodules	170 (23.5)	94 (18.8)	76 (33.8)	***<0.001***
Microvascular invasion	421 (58.1)	264 (52.9)	157 (69.8)	***<0.001***
R status				***<0.001***
R0	668 (92.3)	473 (94.8)	195 (86.7)	
R1	56 (7.7)	26 (5.2)	30 (13.3)	
WHO grade				***0.049***
Well	189 (26.1)	139 (27.9)	50 (22.2)	
Moderately	428 (59.1)	296 (59.3)	132 (58.7)	
Poorly	107 (14.8)	64 (12.8)	43 (19.1)	
Continent				***<0.001***
Asia	177 (24.4)	104 (20.8)	73 (32.4)	
Europe	547 (75.6)	395 (79.2)	152 (67.6)	

BMI: Body-mass index, i.q.r.: Interquartile range, ASA: American Society of Anesthesiologists, CCI: Charlson Comorbidity Index, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, AFP: Alpha-fetoprotein, PVE: Portal vein embolization, CD: Clavien-Dindo, PHLF: Post hepatectomy liver failure, WHO: World health organization.

diagnosed in 225 (31.1 %) patients, with a significant heterogeneity between Asia and Europe (41.2 vs 27.8 %, respectively, $p = 0.001$). Among the clinical variables, these cases had a significative lower BMI ($p = 0.007$), were younger ($p < 0.001$) and with a higher rate of positive of former HBV infection ($p = 0.007$). Patients experiencing recurrence within 8 months had also a higher preoperative AFP serum level ($p = 0.006$) with a more often larger ($p < 0.001$) and multiple ($p = 0.005$) tumour. Most of these patients underwent a major hepatectomy ($p = 0.004$), performed by an open approach ($p = 0.001$) and with a higher rate of PHLF ($P = 0.004$), but without any difference in terms of severe CD. The rate of MVI ($p < 0.001$), positive margin status ($p < 0.001$), satellite nodules ($p < 0.001$) and poorly differentiation ($p = 0.049$) was significantly higher in patients with early recurrence. Comparison of all variables between the two cohorts are shown in Table 1.

3.2. Machine learning models

Among the five machine learning models, random forest showed the best performance to discriminate and predict early recurrence. Results are detailed in Supplementary Table 1.

Preoperative random forest model reached a c-statistic of 0.685 (95 % CI: 0.658–0.711). Most important variables were AFP serum level, HCC size, BMI, age, platelets count and Charlson comorbidity index (Supplementary Fig. 1). Confusion matrix showed a sensitivity of 52.9 %, a specificity of 75.4 %, a positive predictive value of 49.2 % and a negative predictive value of 78.0 %. Calibration slope was 1.16 (95 % CI: 0.76–1.56) and intercept was −0.05 (95 % CI: −0.19-0.08).

Postoperative random forest model reached a c-statistic of 0.719 (95 % CI: 0.689–0.749). Most influential variables were AFP, tumour size at pathology, BMI, HCC size, age, platelets count and Charlson comorbidity index (Supplementary Fig. 2). Confusion matrix showed a sensitivity of 57.8 %, a specificity of 79.2 %, a positive predictive value of 55.6 % and a negative predictive value of 80.6 %. Calibration slope was 1.27 (95 % CI: 0.86–1.68) and intercept was −0.08 (95 % CI: −0.23-0.05). Fig. 1 shows the risk matrix of the frequency of early recurrence in the cohort as a function of the most important variables.

3.3. Logistic regression model and risk score creation

Results of the multivariate model led to the creation of two risk scores, shown in Table 2. The preoperative logistic model included age, BMI, tumour size, AFP and number of nodules. The apparent c-statistic was 0.678 and the optimism-corrected c-statistic was 0.662 (95 % CI: 0.661–0.664). Calibration slope was 0.89 (95 % CI: 0.58–1.20) and intercept was 0.04 (95 % CI: −0.06-0.14, Supplementary Fig. 3A). The resulting score was split into three risk groups (Supplementary Fig. 4A): low risk (score ≤ -4: 15 % risk of early recurrence, n = 189), intermediate risk (score between −3 and 3: 31 % risk of early recurrence, n = 327) and high risk of early recurrence (score >3: 45 % risk of early recurrence, n = 208). After adding peri- and postoperative variables at univariate and multivariate analysis, the new logistic model included age, BMI, tumour size, AFP, number of nodules, HBV status, satellite nodules, surgical margins, microvascular infiltration, post-hepatectomy liver failure and type of approach (Table 2). The apparent c-statistic was 0.720 and the optimism-corrected c-statistic was 0.697 (95 % CI: 0.696–0.699). Calibration slope was 1.01 (95 % CI: 0.82–1.20) and intercept was 0.00 (95 % CI: −0.07-0.07, Supplementary Fig. 3B). The resulting postoperative score was split into three risk groups (Supplementary Fig. 4B): low risk (score ≤5: 17 % risk of early recurrence, n = 394), intermediate risk (score between 6 and 13: 40 % risk of early recurrence, n = 216) and high risk of early recurrence (score >13: 63 % risk of early recurrence, n = 114). Comparison of ROC curves between these risk scores and the random forest models, both with preoperative and postoperative variables, is shown in Fig. 2. To enhance clinical applicability of these models, two calculators were developed and made available online to predict the risk of early recurrence with preoperative (https://thibaut-goetsch.shinyapps.io/lhcc_score_preop) and perioperative variables (https://thibaut-goetsch.shinyapps.io/lhcc_score_postop).

3.4. Survival analysis

The median OS in patients with a low, intermediate and high risk of early recurrence according to the preoperative model were 35 months (95 % CI: 25–50), 29 months (95 % CI: 22–50) and 17 months (95 % CI: 11–24) respectively ($p < 0.001$, Fig. 3A). Postoperative risk score was able to better predict survival curves, with a median OS of 44 months (95 % CI: 31–62), 22 months (95 % CI: 18–29) and 5 months (95 % CI: 4–9) for low, intermediate and high risk respectively ($p < 0.001$, Fig. 3B).

4. Discussion

Predictive models have been extensively developed in the medical field, and, in particular, in surgical scenario they have been largely described to predict postoperative and oncologic outcomes with the aim of personalizing therapeutic algorithm in potentially resectable patients [36,37]. Similarly, liver surgeons use these statistical tools in patients

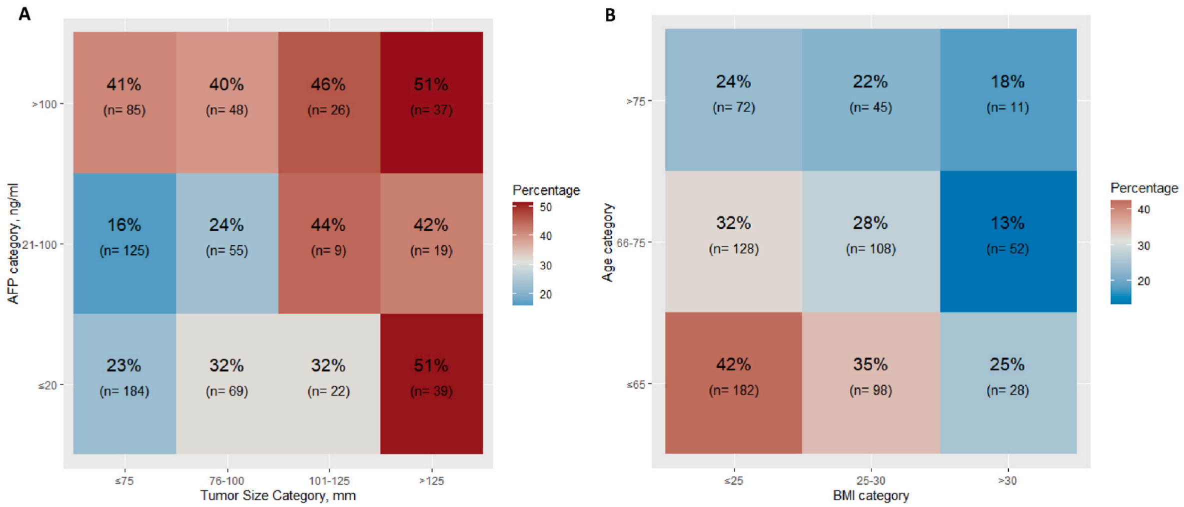

Fig. 1. Risk matrix of the frequency of early recurrence in the cohort as a function of **A)** alpha-fetoprotein (AFP) and tumour size and **B)** age and body mass index (BMI).

Table 2

Creation of the two point-based pre- and postoperative scores based on the results of the logistic regression model to predict risk of early recurrence after resection of large HCC and definition of 3 risk classes according to the total score (apply a score of 0 for the reference value in each variable).

Variables	**Category**	**Preoperative Risk Score**			**Postoperative Risk Score**		
		Regression coefficients (95% CI)	**p-value**	**Score**	**Regression coefficients (95% CI)**	**p-value**	**Score**
Intercept		–0.95 (–1.31-–0.61)			–1.48 (–2.01-–0.97)		
BMI	≤25						
	25-30	–0.19 (–0.55-0.16)	0.29	***–2***	–0.11 (–0.49-0.25)	0.55	***–1***
	>30	–0.85 (–1.47-–0.27)	0.005	***–7***	–0.83 (–1.48—0.23)	0.009	***–8***
Tumour size	≤75						
	75-125	0.36 (–0.01-0.72)	0.05	***3***	0.32 (–0.06-0.70)	0.1	***3***
	>125	0.77 (0.27-1.28)	0.003	*7*	0.75 (0.24-1.27)	0.004	*7*
Age	≤65						
	>65	–0.46 (–0.79-–0.13)	0.007	***–4***	–0.28 (–0.63-0.08)	0.13	***-3***
AFP	≤100						
	>100	0.68 (0.33-1.04)	<0.001	***6***	0.53 (0.16-0.90)	0.005	***5***
Number of nodules	Single						
	Multiple	0.58 (0.20-0.95)	0.002	***5***	0.46 (0.07-0.85)	0.02	***4***
HBV status	Never						
	Positive or Former				0.38 (–0.01-0.76)	0.05	***4***
Satellite nodules	No						
	Yes				0.51 (0.12-0.90)	0.01	***5***
Surgical margins	R0						
	R1				0.62 (0.03-1.22)	0.04	***6***
Microvascular infiltration	No						
	Yes				0.44 (0.08-0.81)	0.02	***4***
PHLF	No						
	Yes				0.74 (0.07-1.41)	0.03	*7*
Approach	Open						
	MI				–0.43 (–0.81—0.06)	0.03	***-4***
Early recurrence risk category		*Low*		***≤–4***			***≤5***
		Intermediate		***–3 - 3***			***6 - 13***
		High		***>3***			***>13***

CI: Confidence interval, BMI: Body-mass index, AFP: Alpha-fetoprotein, HBV: Hepatitis B Virus, PHLF: Post hepatectomy liver failure.

with HCC, either through general models applicable to all surgical candidates or through specific models tailored to well-defined subgroup of patients, as HBV related HCC, single HCC, tumours with low or high AFP serum level, etc … [17,18,38–40] Probably the most common outcome reported is the identification of more aggressive cases which translates in the ability of predicting patients with a higher risk of early recurrence [15,16,18,40]. As it happens in other tumours, this pattern is in fact associated with impaired survival rates and a lower chance of undergoing effective locoregional or systemic treatments [9,10,34]. A particular subset of patients with HCC is those who are diagnosed with a tumour with a diameter of 5 cm or more, generally defined as LHCC. These tumours are normally characterized by a higher aggressiveness and generally a higher rate of early recurrence, which can be observed in up to the 45–60 % of the resected series [10,32,33,41]. However, although the already developed models highlight how tumour size affects recurrence, specific tools available for LHCC are lacking. Furthermore, the best temporal cut-off for the definition of early recurrence was recently reviewed in HCC, and an interval of 8–9 months is probably more able to define adverse cases compared to the most used 2 years threshold [11,12]. The models developed in this study, therefore, cover the unmet clinical need of easily and correctly identifying LHCC cases with a more aggressive pattern and with a higher risk of early recurrence [42]. To our knowledge this is the first attempt of development, with an internal cross-validation, similar models in HCC ≥5 cm. These tools could be helpful in the standardization of a more targeted and personalized approach of these tumours, in line with the recently published recommendations [6]. Furthermore, as assessed by different trials in the last years, and the IMbrave 050 in particular [43,44], the identification of those diseases with a high risk of early recurrence is essential to define the best candidates to perioperative systemic therapies, or even locoregional treatments [45].

To increase the possibility of developing a reliable model, both traditional regression analysis and most recent ML systems have been explored. This type of approach is not new in literature [13,14]. In fact, although ML based models, as the XGBoost or the random forest, are able to analyse a large amount of data and assess complex non-linear relationships between variables, which translates in a potential optimal predictive performance, several authors did not find an over-performance of these tools over the more classic and older models. In line with these findings, this study reported similar outcomes among the different models assessed, or even a significant higher predictive power of the classic regression-based score compared to most of the five ML tools, in both preoperative and postoperative models (c-statistic: 0.678 and 0.720, respectively). For this reason, a point-based system derived

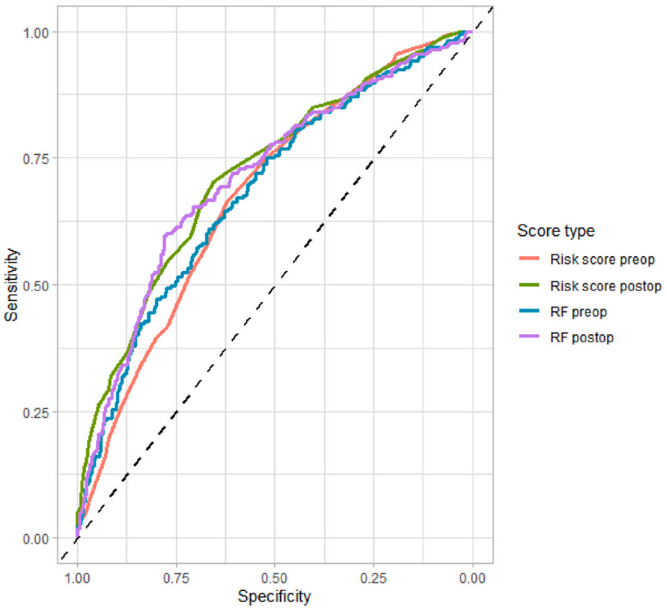

Fig. 2. ROC curves for the preoperative and postoperative point-based risk scores compared with the two random forest (RF) models, pre- and postoperative.

from the multivariable regression analysis was preferred, as it easily implementable in clinical practice and can be used by clinicians when evaluating a patient with a LHCC, before or after surgical resection (https://thibaut-goetsch.shinyapps.io/lhcc_score_preop and https://thibaut-goetsch.shinyapps.io/lhcc_score_postop). The resulting score was then split into three groups, characterized by an increasing risk of developing an early recurrence. To further strengthen the importance and the applicability of this score, the three risk groups were able to significantly differentiate the long-term survival of these patients, both pre and postoperatively.

The c-statistic obtained by the models, which reflect their statistic power, are in line with other previously reported for HCC [15,16,18], and inferior to those developed for other hepatobiliary tumours [37,46]. This emphasize how difficult is dealing with this complex disease, which probably carries a genetic background difficult to predict with classic data normally used in clinical practice. However, the creation of a simple model based on five preoperative variables, therefore before resection, and the inclusion of both eastern and western patients in our cohort represent a key strength of the developed models and of their applicability in a real scenario.

Among the variables included in the models, most of them are already described in other HCC predictive score. Preoperatively, the significance of the importance of BMI relies on the already known concept that metabolic-related HCC are generally associated with better oncologic outcomes [47–50]. MI approach, as a part of the postoperative score, is another variable extensively assessed in literature. While in fact part of the meta-analysis available in this context affirm the superiority of the MI approach only in the short-term outcomes, other large studies demonstrated that laparoscopy could achieve significantly higher R0 rate, wider margins and improved DFS rates [51–53].

Although data comes from a large cohort and high-volume centres, some limitations must be reported. Firstly, the predictive scores derive from a retrospective analysis, with all the related bias. Another issue is the lack of some potential important variables, as the albumin-bilirubin grade, which was part of similar predictive models in other studies. Despite the widely diffuse attitude in literature of splitting the cohort for development and validation, cross-validation and bootstrap procedure for correction of optimism were chosen for internal validation over split-sample validation, since they produce more accurate estimations of model performances, as well as allow to use more data for model development [54]. Finally, some variations among the different centres could exist in terms of tumour management or in the radiological and pathological assessment.

5. Conclusions

In conclusion, two easy-to-use point-based scores were developed, which were able to overperform ML tools. These models stratify the risk of early recurrence after surgical resection for a LHCC and can be readily employed in clinical practice. Furthermore, both scores could accurately predict patients OS. The results of this study, therefore, paves the way for personalized medicine for these tumours by guiding the implementation of perioperative treatments in high-risk patients and optimizing surveillance strategies.

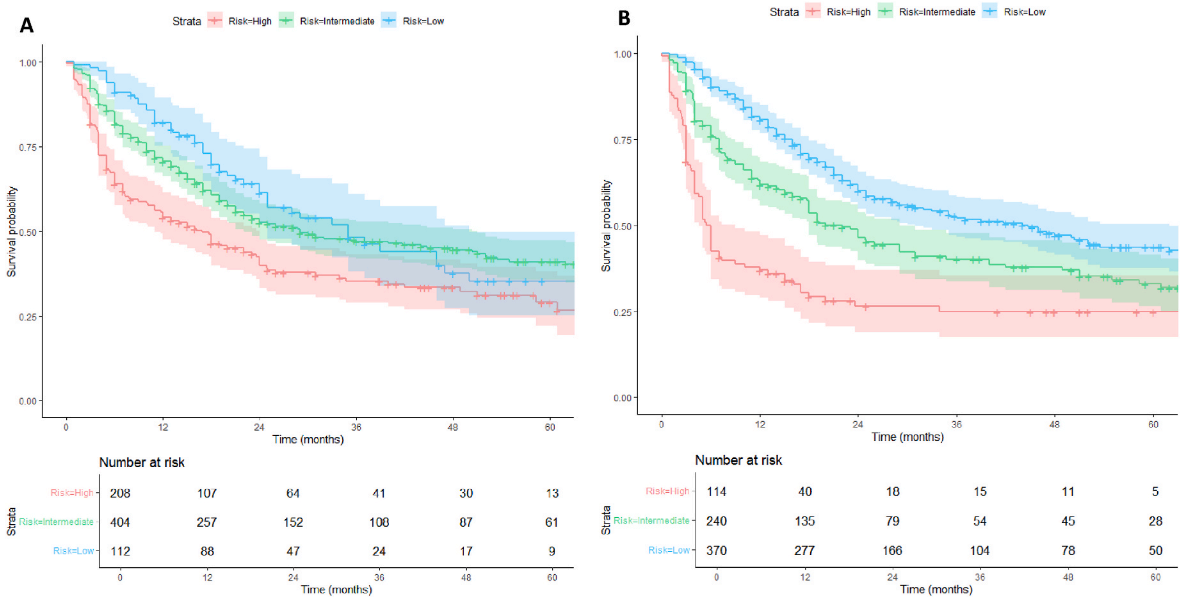

Fig. 3. Comparison of the Kaplan-Maier overall survival curves in the three risk groups according to the preoperative (A) and postoperative (B) risk scores.

CRediT author statement

Conceptualization:FG, TG, GC, FP, PP Methodology:FG, TG, FP, PP Validation:FG, TG, FP, PP Formal analysis:FG, TG; Investigation:FG, TG, GC Resources:FG, GC, AC, EF, FC, BB, RR, AT, EMM, AS, BA, RB Data curation:FG, GC, AC, EF, FC, BB, RR, AT, EMM, AS, BA, RB Writing – Original DraftFG, TG, FP, PP Writing – Review & Editing All authors Visualization:All authors Supervision:FP, PP Project administration:FG, PP All the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *EJSO*.

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Declaration of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.111319.

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