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ORIGINAL ARTICLE

A preoperative risk score based on early recurrence for estimating outcomes after resection of hepatocellular carcinoma in the non-cirrhotic liver

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Abstract

Background: Liver resection is the mainstay treatment option for patients with hepatocellular carcinoma in the non-cirrhotic liver (NCL-HCC), but almost half of these patients will experience a recurrence within five years of surgery. Therefore, we aimed to develop a rationale-based risk evaluation tool to assist surgeons in recurrence-related treatment planning for NCL-HCC.

Methods: We analyzed single-center data from 263 patients who underwent liver resection for NCL-HCC. Using machine learning modeling, we first determined an optimal cut-off point to discriminate early versus late relapses based on time to recurrence. We then constructed a risk score based on preoperative variables to forecast outcomes according to recurrence-free survival.

Results: We computed an optimal cut-off point for early recurrence at 12 months post-surgery. We identified macroscopic vascular invasion, multifocal tumor, and spontaneous tumor rupture as predictor variables of outcomes associated with early recurrence and integrated them into a scoring system. We thus stratified, with high concordance, three groups of patients on a graduated scale of recurrence-related survival.

Conclusion: We constructed a preoperative risk score to estimate outcomes after liver resection in NCL-HCC patients. Hence, this score makes it possible to rationally stratify patients based on recurrence risk assessment for better treatment planning.

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Introduction

Hepatocellular carcinoma (HCC), the most prevalent type of liver tumor, is one of the leading causes of cancer-related deaths globally.[1,2] Although most cases of HCC arise in cirrhotic livers, approximately 20% of all cases of HCC documented in the literature are in people without cirrhosis.[3,4] This figure is likely at the low end of clinical reality, especially in regions where hepatitis B transmission is highly endemic.[5] Indeed, hepatitis B is a major etiology of HCC in many underserved areas,[6,7] and it is

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known to promote hepatic carcinogenesis independent of liver fibrosis progression.[8] HCC patients with non-cirrhotic liver present some demographic differences from cirrhotic patients, including a lower male preponderance and a bimodal age distribution with a higher proportion of younger individuals.[3] Outside of any scheduled surveillance program,[9,10] HCC in the non-cirrhotic liver (NCL-HCC) is often detected at advanced stages with a sizable tumor mass because of the stealth nature of the disease during its early stages and a larger liver function reserve.[11]

According to clinical practice guidelines for HCC,[9,12] liver resection (LR) is the treatment of choice in patients with no cirrhosis, for whom even major hepatectomies can be considered. However, despite LR being performed with curative intent, approximately 45% of NCL-HCC patients experience recurrence within five years of intervention.[13] Two phases of HCC recurrence have been described hitherto: early relapses, which occur within the first year after LR, and late relapses that take place between the fourth and fifth years post-surgery.[14] On the one hand, it has been suggested that early relapses of HCC are prone to being monoclonal (or monocentric), primarily caused by micrometastases, though it is possible that a second primary tumor may develop suddenly after surgery. On the other hand, late HCC relapses are considered rather multiclonal (or multicentric), mostly due to newly developed malignant lesions brought on by increased hepatitis activity. Genomic research has nuanced this paradigm, pointing out that a significant fraction of early relapses are, in fact, multicentric.[15,16]

Notwithstanding, there is a consensus in the literature to consider both early and late relapses as postoperative recurrences.[17] The evidence invariably indicates that the patient's post-recurrence survival is worse the earlier the relapse occurs.[18,19] Additionally, there has been mention that the type of surgical procedure performed may also play a role in early recurrence.[14] Therefore, it is paramount to clinically stratify NCL-HCC patients based on their risk of recurrence following LR. However, effective tools to inform prognosis and aid decision-making regarding HCC management in the absence of cirrhosis remain lacking. In this single-center study, we examined the variables associated with relapse in a series of patients who underwent curative-intent LR for NCL-HCC and constructed a preoperative risk score for assessing outcomes in these patients. Using this score, NCL-HCC patients can be rationally stratified into recurrence-risk categories for treatment planning.

Materials and methods

Declaration of ethical principles

The Institutional Review Board of the National Cancer Institute of Peru (INEN) approved the research, project number INEN 10-05. Patients or their legal guardians provided informed consent for their information to be stored and used for research. The study was conducted in strict accordance with the precepts contained in the Declaration of Helsinki on ethical principles for medical research involving human subjects and the Singapore Statement on research integrity.

Patients and study design

All NCL-HCC patients who underwent surgery in the INEN Department of Abdominal Surgery between January 1996 and December 2017 were included in a database. From this initial database, we applied the inclusion and exclusion criteria listed below and eventually enrolled 263 patients as part of our study population (Fig. 1). Inclusion criteria were patients with intrahepatic tumors who received a curative-intent LR without chemotherapy, radiation, or transarterial chemoembolization (TACE) before surgery. Exclusion criteria included subjects under 10 years of age,[20] liver tumors smaller than 5 cm in diameter,[21] fibrolamellar HCC,[22] tumor thrombus (TT) in the suprahepatic vena cava (SHVC),[23] and portal vein tumor thrombosis (PVTT) with grade Vp4.[24]

The HCC diagnosis was established based on both magnetic resonance imaging (MRI) and computed tomography (CT) scans according to the Liver Imaging Reporting and Data System (LI-RADS) version 2018.[25] Radiologists with expertise in hepatobiliary imaging reviewed MRI and CT scans to assess LR-5 definite HCC category, evaluate the portal venous system (LR-TIV), and determine the absence of full-fledged cirrhosis. All blood tests were performed in the clinical laboratory of INEN according to standard procedures. Alpha-fetoprotein (AFP) levels were measured from blood samples using an immunoassay. Hepatitis B and C serologies were tested using HBsAg and anti-HCV immunoassays, respectively.

Data extracted from primary cancers included patient demographics (age and gender), serological diagnoses of hepatitis B and C, hematological parameters, biochemistry of liver function, AFP level, and primary tumor morphology and characteristics. During data compilation, operative and pathology reports were reviewed by hepatobiliary cancer pathologists to ensure inclusion criteria were met (i.e., HCC diagnosis, exclusion of fibrolamellar HCC, and gross negativity of the resection margins). This control feedback information was not used in the construction of the risk score, which was only based on preoperative variables. Recurrences, including local, regional, and distant cancers, were detected during the follow-up of the patients, who were monitored for the period of time elapsing between the hepatectomy and the diagnosis of recurrence. Treatment associated with recurrent HCC was documented as well.

Surgical procedure

Surgery was the mainstay of treatment for NCL-HCC patients at INEN, in accordance with the recommendations of both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD).[9,12] LR was carried out as previously described.[26,27]

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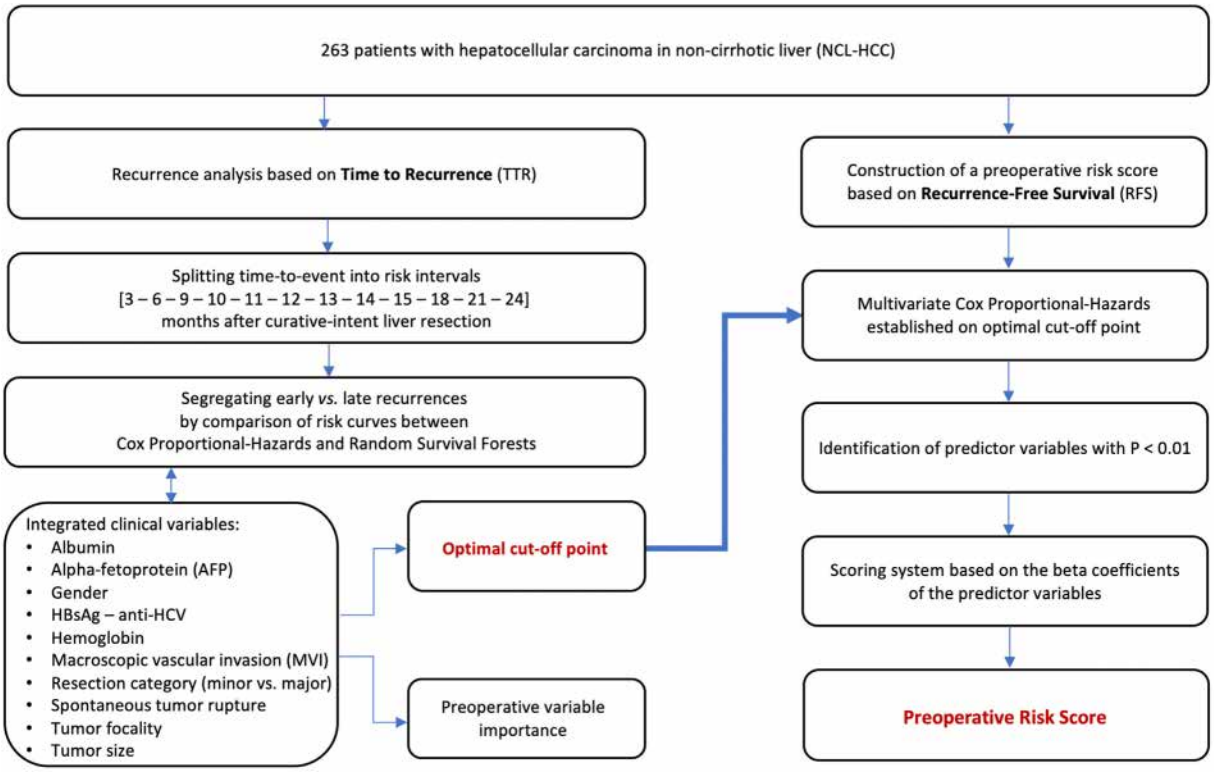

Figure 1 Flow chart describing the construction of the preoperative risk score aimed at estimating outcomes after resection of NCL-HCC

Briefly, anatomical resection was carried out through a midline or J-shaped abdominal incision, depending on the morphology and physical characteristics of the tumor. The incision was followed by extensive abdominal exploration to rule out distant tumor lesions and assess the remnant liver. When necessary, this examination was accompanied by ultrasound exploration. After detaching the hilar plate, afferent vascular control was achieved at the hilum by the intrahepatic glissonean approach. A Pringle maneuver or hemi-hepatic inflow occlusion was performed based on the circumstances. For tumors involving the inferior vena cava or hepatic veins, total hepatic vascular exclusion was performed. The conventional approach was used until 2005; from then on, the anterior approach with or without a hanging maneuver was applied.[28] Liver parenchymal transection was achieved with a resection margin of at least 1 cm using the clamp-crush technique. Medium-sized blood vessels and bile ducts were ligated, while smaller ones were cauterized. Hepatic veins were controlled in an extrahepatic manner unless they were in the transection plane. After the surgical specimen was removed, hemostasis was achieved by cauterizing the bleeding from the liver bed using an argon plasma coagulator and topical hemostat agents. The transection surface was evaluated by direct visualization and a white gauze compress to detect open bile ducts, which were ligated. To further rule out any possibility of biliary fistula, a catheter was placed into the cystic duct and air was injected.[29] For trisectionectomy, pneumobilia combined with ultrasound was used to check the integrity of the remnant liver's biliary tract. Closed drainage was only installed when there was a risk of biliary leakage. Multi-transfused patients were transferred to the intensive care unit. Patients were monitored throughout their hospital stay, and the drain was taken out only once the risk of biliary fistula was discarded.

Patients' surveillance

Follow-up monitoring included 30- and 90-day postoperative mortality, as well as HCC recurrence and survival until March 2022. Patients had thorough examinations twice in the first two months after leaving the hospital. Liver regeneration and function were assessed by abdominal CT scans and liver function tests that included AFP monitoring. Adjuvant chemotherapy was not administered routinely. If the AFP level returned to normal (<10 ng/mL) two months after hepatectomy, patients were checked every two months for the first year, then every four months after that. In cases with continual elevation or rising AFP levels (>10 ng/mL) from two months onward, patients were scanned for recurrence using a full-body CT, complemented by MRI or positron emission tomography/CT (PET/CT), if required. The diagnosis of recurrent HCC was established according to consensus criteria.[17]

In the case of intrahepatic recurrence, tumor re-resection was performed as soon as practicable. When the recurrent cancer was unresectable, palliative treatments such as TACE, percutaneous

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ethanol injection, radiofrequency ablation, targeted therapy, or, as an alternative, best supportive care, were prescribed. Radiation therapy was administered for bone metastases, while surgical pulmonary resection was performed to treat solitary lung metastases. The National Registry of Identification and Civil Status of Peru (RENIEC) was consulted to determine the fate of patients with no follow-up.

Nomenclature

Curative-intent LR was interpreted as an anatomic hepatectomy performed with a resection margin of at least 1-cm width and in the absence of distant metastases. The LR categories were classified according to the Brisbane 2000 Terminology of Liver Anatomy and Resections.[30,31] Minor and major hepatectomy procedures were interpreted as the resection of <4 or ≥4 segments, respectively. Postoperative mortality was defined as a fatality occurring within 90 days after hepatectomy in or out of the hospital, categorized according to the Dindo–Clavien Classification.[32] Thereon, any death, regardless of the cause, was considered an event in the survival analysis. Any relapse of a malignant hepatocellular neoplasm, whether it occurred locally, regionally, or distantly, was referred to as a recurrence — regardless of the time after surgery. The time to recurrence (TTR) was defined as the time from the date of curative-intent LR to the time of the first relapse of HCC.[33] Recurrence-free survival (RFS) was interpreted as the time from the date of curative-intent LR to the time of the first relapse of HCC or death from any cause.[33]

Statistics

Data was inputted into Excel software version 16.16.27 (Microsoft) before being transferred to PostgreSQL relational database management system version 14.4 (PostgreSQL Global Development Group). Statistical analyses were computed in the R software environment version 4.2.1 (R Core Team) and Stata software for statistics and data science version 14.0 (StataCorp LLC), with a significance alpha level set to 0.05 or 0.01 depending on the model analysis task. Missing data was addressed by the method of multiple imputation with the R package mice version 3.14.0.[34] Variables with more than 10% missing data were not considered in the model analysis. Survival data analyses were performed using the R packages survival version 3.4-0 and survminer version 0.4.9. Estimates of survival probability from the date of hepatectomy were calculated using the Kaplan–Meier method,[35] while the log-rank test was used for comparing survival distributions.[36] Machine learning to model prediction was achieved by random survival forests using the R packages randomForestSRC version 3.2.0 and survex version 0.2.2. A minimum P-value approach, combined with random survival forest model performance, was used to determine the optimal cut-off point between early and late recurrences based on TTR.[33] Figures were charted using Prism software version 9 (GraphPad Software Inc.).

Results

Clinical presentation and characteristics

Table 1 shows an overview of the preoperative characteristics of the 263 NCL-HCC patients included in the study who underwent curative-intent LR at the INEN Department of Abdominal Surgery between January 1996 and December 2017. An examination of the structure of the study population over this period, performed by analysis of variance (ANOVA), did not reveal any significant evolution in terms of tumor presentation, clinical pathology, or blood chemistry ($P > 0.05$). The mean age of the patients was relatively young, with half under 40 years old. The tumors resected had an average diameter of more than 15 cm, with the largest HCC specimen measuring 33 cm. There was no significant association between preoperative variables and the risk of HCC relapse when patients were not categorized into early and late recurrence groups (all $P > 0.05$; Table 1).

Hepatic resection categories

Table 2 details the descriptive categorical statistics for the 263 LRs according to the Brisbane 2000 Terminology of Liver Anatomy and Resections.[30,31] Major hepatectomy procedures with four or more segments resected made up the majority of LRs, accounting for 82.1% of all interventions. Propensity score matching (PSM) was applied to 88 patients who had a right hepatectomy, 44 of whom underwent the anterior approach and 44 the conventional approach, to rule out any bias due to the diversity of surgical procedures practiced before and after 2005. On our hands, neither overall survival (OS) nor RFS were significantly different ($P = 0.635$ and 0.995, respectively).

Timing of relapse and optimal cut-off point to define early recurrence

The overall median follow-up for 263 NCL-HCC patients was 35 months (IQR = 82), extending up to 310 months after curative-intent LR. In the follow-up period, 155 patients (58.9%) experienced HCC relapse after surgery with a median TTR of nine months (IQR = 13). Indicatively, recurring patients were followed up for a median time of 23 months (IQR = 38). The cumulative rate of recurrence at 1, 3, and 5 years post-intervention was 38%, 52.1%, and 56.6%, respectively.

Early and late HCC recurrences were identified using a single cut-off point in time to define relapse patterns based on TTR.[33] To determine the optimal cut-off point, we initially fitted a multivariate Cox proportional-hazard model as a baseline for time thresholds progressing in three-month steps (with a one-month fine scale enfolded around the critical time point), starting at three months until 24 months after surgery (Fig. 1). The model with the highest predictive performance was used as a reference. Each time threshold was then subjected to a random survival forest analysis (500 trees), with 70% of the patients randomly assigned by permutation testing to a training set ($n = 185$) and 30% to a validation set ($n = 78$). Of note, the

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Table 1 Preoperative clinical and tumor characteristics of the 263 patients having developed HCC without cirrhosis

Feature	Parameter	Overall	Recurrence		P-value
			Absent	Present	
Total number		263	108	155	
Preoperative clinical characteristics					
Age (years)	Mean ± SD	44 ± 20.6	46.8 ± 20.1	42.1 ± 20.6	0.07*
	Median	40	43	38.5	
	Range	[10–94]	[12–94]	[10–89]	
	IQR	36.8	36.4	36.5	
Gender	Female	104 (39.5%)	39 (36.1%)	65 (41.9%)	0.34**
	Male	159 (60.5%)	69 (63.9%)	90 (58.1%)	
AFP (ng/mL)	Normal	57 (21.7%)	27 (25%)	30 (19.4%)	0.27**
	Elevated	206 (78.3%)	81 (75%)	125 (80.1%)	
	Mean ± SD	99,390 ± 237,170	75,560 ± 225,715	115,995 ± 244,179	0.17*
	Median	6,317	3,284	10,099	
	Range	[0–1,690,900]	[0–1,647,000]	[0–1,690,900]	
	IQR	72,921	50,044	87,511	
Albumin (g/L)	Homeostatic	215 (81.7%)	88 (81.5%)	127 (81.9%)	0.93**
	Hypoalbuminemia	48 (18.3%)	20 (18.5%)	28 (18.1%)	
	Mean ± SD	38.7 ± 6.5	39.1 ± 6.3	38.5 ± 6.6	0.49*
	Median	39	40	38	
	Range	[22–53]	[22–53]	[22–52]	
	IQR	9	9	9	
Total bilirubin (μmol/L)	Homeostatic	201 (76.4%)	86 (79.6%)	115 (74.2%)	0.31**
	Hyperbilirubinemia	62 (23.6%)	22 (20.4%)	40 (25.8%)	
	Mean ± SD	26.6 ± 60.6	22.1 ± 56.8	29.4 ± 62.9	0.42*
	Median	15	15	15	
	Range	[0.7–487]	[0.7–487]	[1–478]	
	IQR	8.4	7.5	9.2	
Hemoglobin (g/dL)	Homeostatic	106 (40.3%)	43 (39.8%)	63 (40.6%)	0.89**
	Anemia	157 (59.7%)	65 (60.2%)	92 (59.4%)	
	Mean ± SD	12.6 ± 2.2	12.6 ± 2.1	12.5 ± 2.3	0.22*
	Median	12.6	12.9	12.5	
	Range	[3.6–20]	[7.1–19.3]	[3.6–20]	
	IQR	2.5	2.4	2.6	
HBV (HBsAg)	Positive	126 (47.9%)	48 (44.4%)	78 (50.3%)	0.35**
	Negative	137 (52.1%)	60 (55.6%)	77 (49.7%)	
HCV (anti-HCV)	Positive	4 (1.5%)	2 (1.9%)	2 (1.3%)	0.71**
	Negative	259 (98.5%)	106 (98.1%)	153 (98.7%)	
Preoperative tumor features					
Size (cm)	Mean ± SD	15.2 ± 5.6	14.4 ± 4.9	15.7 ± 6	0.58*
	Median	15	14.5	15	
	Range	[5.3–33]	[5.5–27]	[5.3–33]	
	IQR	7.2	7.2	9	
Tumor focality	Solitary	173 (65.8%)	75 (69.4%)	98 (63.2%)	0.29**
	Multiple	90 (34.2%)	33 (30.6%)	57 (36.8%)	

(*continued on next page*)

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Table 1 (*continued*)

Feature	Parameter	Overall	Recurrence		P-value
			Absent	Present	
Spontaneous rupture	Absent	237 (90.1%)	97 (89.8%)	140 (90.3%)	0.89**
	Present	26 (9.9%)	11 (10.2%)	15 (9.7%)	
BDTT	Absent	253 (96.2%)	106 (98.1%)	147 (94.8%)	0.17**
	Present	10 (3.8%)	2 (1.9%)	8 (5.2%)	
MVI	Absent	142 (54%)	62 (57.4%)	80 (51.6%)	0.56**
	Macro	35 (13.3%)	12 (11.1%)	23 (14.8%)	
	Micro	86 (32.7%)	34 (31.5%)	52 (33.6%)	

Mean values are presented ± standard deviation (SD). Percentages are expressed as the ratio of the total number of patients for the considered criterion. AFP, alpha-fetoprotein; BDTT, bile duct tumor thrombus; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MVI, macroscopic vascular invasion. Elevated AFP >10 ng/mL; Hypoalbuminemia <3.4 g/L; Hyperbilirubinemia >20.5 µmol/L; Anemia <13.8 g/dL in male and <12.1 g/dL in female. *two-sided *t*-student; **Pearson's Chi-squared test.

Table 2 Hepatic resection categories of the 263 NCL-HCC patients

Resection category	Couinaud segments (Sg) referred to	Number	Percentage
Right hepatectomy	Sg5,6,7,8 ± Sg1	89	33.8%
Left hepatectomy	Sg2,3,4 ± Sg1	67	25.5%
Extended right hepatectomy	Sg4,5,6,7,8 ± Sg1	59	22.4%
Bisegmentectomy	Sg2,3	7	5.4%
	Sg5,6	4	
	Sg4,5	2	
	Sg7,8	1	
Extended left hepatectomy	Sg2,3,4,5,8 ± Sg1	13	4.9%
Right anterior + left medial sectionectomy	Sg4,5,8	9	3.4%
Segmentectomy	Sg4	4	2.3%
	Sg6	2	
Left hepatectomy extended to segment 5	Sg2,3,4,5 ± Sg1	2	0.8%
Right anterior sectionectomy	Sg5,8	2	0.8%
Left medial sectionectomy + bisegmentectomy	Sg4,5,6	1	0.4%
Right posterior sectionectomy extended to segment 5	Sg5,6,7	1	0.4%

random survival forest's performance stabilized before 500 trees (Supplementary Fig. 1). The log-rank P-values and the random survival forest model performance were compared to that of the reference Cox proportional-hazard model for each time threshold. Thereby, a threshold of 12 months was defined as the optimal cut-off time point to differentiate early versus late HCC recurrence (log-rank P = 2E-09 and random survival forest AUC = 0.78, Brier score = 0.23, and C-index = 0.69) (Fig. 2a). Patients with recurrence within 12 months after curative-intent LR had significantly worse OS than those who relapsed beyond 12 months following the intervention (Fig. 2b). According to the random survival forest model, the five preoperative variables contributing to early HCC recurrence with the maximum propensity weighting at 12 months post-surgery were, in order of importance, MVI, tumor focality, spontaneous tumor rupture, serum albumin, and tumor size (Fig. 2c).

Preoperative risk stratification tool for estimating outcomes after hepatectomy

To construct a preoperative risk score based on RFS, we selected the three preoperative variables with a P-value <0.01 in the Cox proportional-hazard model at the 12-month TTR optimal cut-off point, i.e., MVI (HR = 2.81; 95% CI 1.88–4.21; P = 5.4E-07), spontaneous rupture (HR = 2.01; 95% CI 1.31–3.01; P = 0.001), and tumor focality (HR = 1.56; 95% CI 1.15–2.01; P = 0.004) (Supplementary Table 1). While applying this stringent statistical significance, tumor size and serum albumin were not retained as predictor variables for the construction of the risk score (P = 0.044 and 0.589, respectively). The beta coefficients of the three independent predictors selected were rounded to the nearest integer and multiplied by a constant to obtain a scoring system that assigns 28 points to MVI, 20 points to spontaneous rupture, and 16 points to multifocal tumors — a value of

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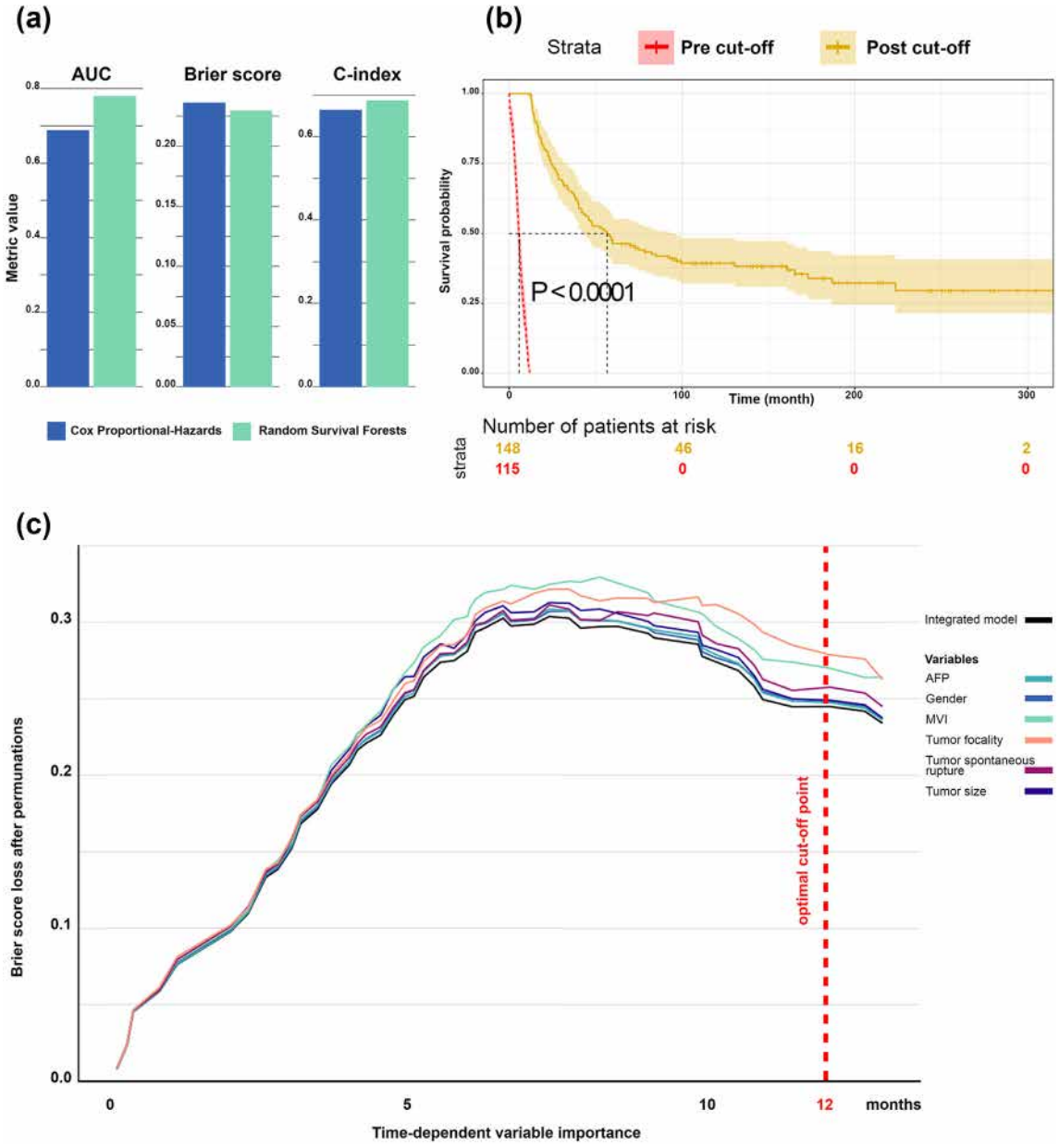

Figure 2 Determination of the optimal cut-off point based on TTR for early versus late recurrence of NCL-HCC following curative-intent LR. **(a)** Bar plots comparing the performance statistics of the Cox proportional-hazard model (blue) versus the random survival forest model (green) at 12 months post-surgery. AUC, area under the curve; C-index, concordance index. **(b)** OS probability curves in time (months) of NCL-HCC patients having relapsed before (red) or after (yellow) 12 months post-surgery. Colored bands indicate the 95% confidence interval. Significance alpha level <0.05. **(c)** Time-dependent variable importance curves of the random survival forest model represented by the Brier score loss after permutations (Y-axis) as a function of time post-surgery in months (X-axis). The red dashed line indicates the optimal cut-off point at 12 months. Displayed variables: Integrated model, black; AFP, light blue; Gender, dark blue; MVI, green; Tumor focality, orange; Spontaneous tumor rupture, maroon; Tumor size, dark blue

0 points was allotted to unobserved predictor variables (Fig. 3a). The preoperative risk score is calculated by adding up the points obtained from each predictor.

Under this scoring system, a risk score was determined for each of the 263 NCL-HCC patients. According to the score value obtained, the individuals were stratified into three risk categories: low-risk (0 points), moderate-risk (≤20 points), and high-risk (>20 points) (Fig. 3a). Patient groups thus stratified resulted in 144 low-risk individuals with 0 points, 79 moderate-risk individuals with less than or equal to 20 points, and 40 high-risk

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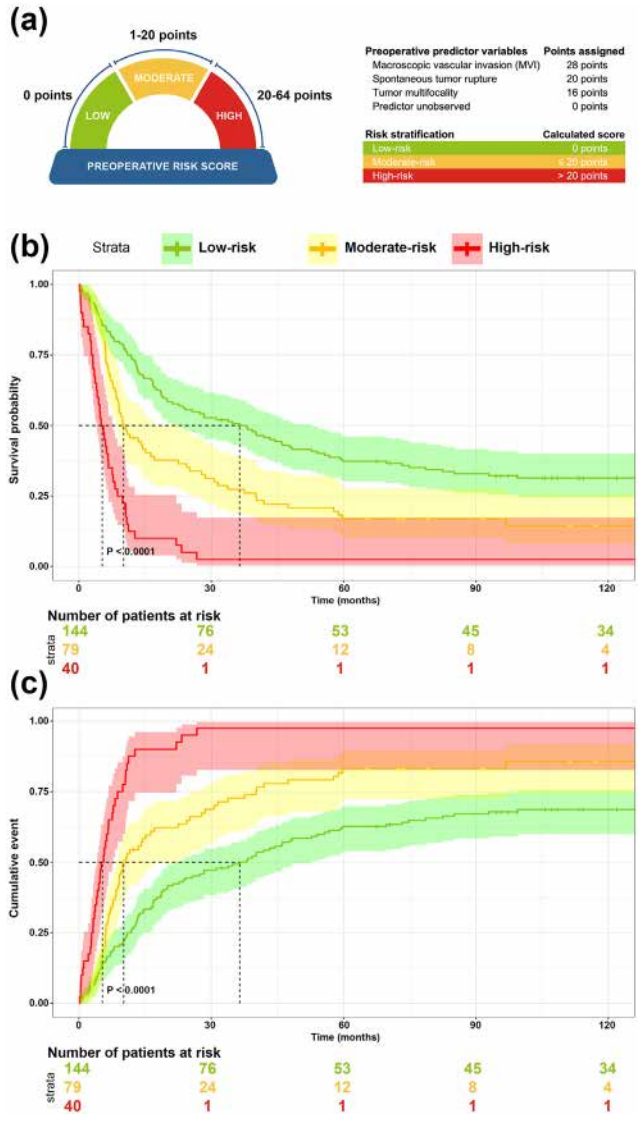

Figure 3 Construction of the preoperative risk score based on RFS for the stratification of NCL-HCC patients following curative-intent LR. **(a)** Graphical abstract explaining the scoring system to estimate the risk level stratified into low- (green), moderate- (yellow), and high-risk (red). **(b)** OS probability curves in time (months) for the 263 patients with NCL-HCC stratified into three risk groups according to the total points assigned in the preoperative risk scoring system. **(c)** Cumulative incidence of recurrence in time (months) for the 263 patients with NCL-HCC stratified into three risk groups according to the total point assigned in the preoperative risk scoring system. **(b,c)** High-risk group, red; Moderate-risk group, yellow; Low-risk group, green. Colored bands indicate 95% confidence interval. Significance alpha level <0.05

individuals with more than 20 points. Survival distributions for each risk category were then computed based on RFS using the Kaplan–Meier method and compared with log-rank tests (Fig. 3b). Depending on their category, the stratified patients displayed significant differences in terms of both RFS and recurrence incidence proportion (Fig. 3c).

Discussion

While several guidelines are related to HCC management in the cirrhotic liver, decision-support tools for the surgery of HCC in the non-cirrhotic liver are still lacking. However, this issue is paramount since NCL-HCC represents at least 20% of all HCC diagnosed globally, and it demonstrates biological features that make it much more amenable to surgery than cirrhotic HCC.[3,4] Indeed, the hepatic parenchyma is healthy or minimally diseased, making extensive liver resections possible.[37] On the other hand, HCC in the absence of cirrhosis is generally present in an advanced stage at the time of detection, with a massive tumor often invading the biliary tract and vascular structures.[38] As a consequence, almost half of the patients who undergo curative-intent hepatectomy for NCL-HCC will have experienced a recurrence within five years of surgery,[13] with a lower survival rate the earlier the relapse occurs.[39] Therefore, decision-support tools that integrate recurrence risk must be developed to assist surgeons in determining how a non-cirrhotic patient with HCC could benefit from a curative-intent hepatectomy. Yet such a tool is currently lacking.

The present study sought to fill this gap and construct a risk score based on preoperative variables to stratify patients according to survival assessment, incorporating the temporal pattern of early and late recurrences (Fig. 1). We analyzed data from 263 patients who underwent curative-intent LR for NCL-HCC between January 1996 and December 2017 at INEN, the main cancer specialist hospital in Peru (Tables 1 and 2). Actually, the surgical team at INEN have repeatedly reported that the majority of HCC patients attending the cancer center have no cirrhosis,[26,40] at odds with most surveys reported in the literature. To address this situation, our team aimed to develop a preoperative risk stratification tool specific to HCC in the non-cirrhotic liver.

Through machine learning, we first determined an optimal cut-off point in time to discriminate early versus late recurrence, preferentially based on TTR (Fig. 2a–c).[33] There is no consensus on this issue in the literature, which ranges from six to 24 months.[18,41] Such a cut-off point based on post-recurrence survival has been previously proposed at eight months post-surgery in a large multi-institutional survey,[13] but the data included HCC in both cirrhotic and non-cirrhotic livers. Based on our analysis, the optimal cut-off point specific to NCL-HCC was 12 months post-surgery (Fig. 2a), although 13 months could have been quite statistically relevant too. Among NCL-HCC patients, this 12-month cut-off point between early and late recurrences represented the optimal threshold associated with the greatest difference in survival outcomes (Fig. 2b). Beyond the differences in study endpoints and algorithmic approaches, this time lapse of four to five months between the multi-institutional

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survey and our study can be explained by the fact that cirrhosis is a significant factor in early relapse.[42] The discrepancy in risk-factor variables reinforces the view that HCCs in the cirrhotic and non-cirrhotic livers should be considered separately,[3] lowering the relevance of recurrence risk assessment models that treat both types of HCC with unified outcomes. Instead, it emphasizes the need to develop evaluation tools tailored to HCC in the absence of cirrhosis.

Afterward, we identified MVI, spontaneous rupture, and tumor focality as independent preoperative predictors at 12 months post-surgery, and we weighted these factors into a scoring system, the sum of which provides an estimate of risk (Fig. 3a–c). Unexpectedly, AFP and tumor size were not retained as significant predictors, contrary to what has often been reported,[13] further underscoring HCC's biological idiosyncrasies in the non-cirrhotic liver. Likewise, our analysis did not reveal significant differences between surgical procedures performed at INEN, as previously suggested.[14] The achievement of the preoperative risk score resulted in stratifying NCL-HCC patients into three recurrence-related risk categories with different RFS rates (Fig. 3b, c). Low-risk patients with no points had a three-year RFS rate of 50%. This first group of patients, who do not require adjuvant therapy, presented preoperatively without any of the three predictors, corresponding to non-cirrhotic individuals with solitary, non-invasive, and unruptured HCC. Next, moderate-risk patients scoring less than 20 points were associated with a three-year RFS rate of 27%. This second group of patients clinically presented with a single predictor excluding MVI, i.e., spontaneous rupture or multifocal tumor. They require intensive surveillance after surgery and should receive adjuvant therapy,[17] such as TACE associated with antiviral treatment[43] or immunomodulation (e.g., atezolizumab and bevacizumab). Finally, high-risk patients with more than 20 points had the poorest RFS rate three years following surgery, at only 3%. This third group of patients was diagnosed before intervention with MVI and/or two or more predictors. The recruitment of these patients into clinical trials should be prioritized. On our hands, the implemented risk score has demonstrated high reliability in estimating the long-term outcomes of patients who underwent curative-intent LR for NCL-HCC, although the 95% confidence intervals slightly overlap beyond three years of surgery (Fig. 3b, c). From our point of view, this risk score represents an efficient, rational tool lacking until now for estimating prognosis and assisting decision-making in HCC management without cirrhosis.

Recurrences that adversely affect patients' outcomes may be linked not only to tumor characteristics at diagnosis but also to underlying liver disease in the non-tumor parenchyma. For instance, the literature reports that non-alcoholic fatty liver disease (NAFLD) is prevalent in approximately 25% of NCL-HCC patients.[44] There is also evidence that 30%–50% of HCCs occur without cirrhosis in patients with chronic HBV infection.[45] This observation is even more pronounced in cases of occult hepatitis B infection (OBI), in which almost 90% of related HCC is not associated with cirrhosis.[46] Previously, we reported 48% of overt HBV infections and 34% of OBI (detected only by ultra-sensitive molecular assays) among NCL-HCC patients in Peru,[47] a country where HBV is endemic. Initially, our risk score model did not retain overt HBV infection as a predictor variable; nevertheless, we wished to further include OBI as a latent variable to infer its impact in our model.[48] Multiple Cox regression models and random forest imputations fitting up to 1,000 trees failed to retain HBV infection as a risk factor; alpha levels not reaching significance. Without precluding further research on the role of HBV on HCC recurrence in the non-cirrhotic liver, this unvarying result demonstrates the robustness of predictors selected in our preoperative risk score to estimate outcomes after surgery in NCL-HCC patients.

The present study recognizes limitations. We did not analyze some features associated with liver conditions, such as fibrosis staging, NAFLD, and non-alcoholic steatohepatitis (NASH).[49] These variables are challenging to determine preoperatively with precision; therefore, they could perform unevenly in practice when applying the risk score. Moreover, there are mentions in the literature that liver fibrosis does not affect the outcomes after LR until cirrhosis is fully developed.[50] Also, based on our previous findings,[47] we strongly suspect that a significant fraction of patients in our series is, in fact, occultly infected with HBV, which is known to be a favorable terrain for HCC in the absence of cirrhosis but difficult to diagnose routinely. Using advanced computational tools, we simulated the influence of OBI on our modeling to ensure that it was not a latent variable detrimental to the scoring system. Finally, our study was conducted retrospectively with data from a single center collected over 21 years. To mitigate this limitation, we monitored changes in patient population structure, perioperative variables, and surgical procedures over the period.

In conclusion, we believe that the preoperative risk score developed herein represents a valuable tool to assist decision-making in HCC management without cirrhosis.

Authors contributions

Conceptualization, E.R.; Methodology, E.R., J.H. and S.B.; Validation, J.P.C, J.C.-M. and S.C.-Z.; Formal Analysis, E.R. and J.H.; Investigation, E.R., J.H. and R.F; Resources, K.C. and S.C.-Z.; Data Curation, E.R. and J.H.; Writing – Original Draft Preparation, E.R., J.H. and S.B.; Writing – Review & Editing, R.F., J.P.C., S.C.-Z. and P.P.; Visualization, J.H., J.P.C. and J.C.-M.; Supervision, P.P. and S.B.; Project Administration, E.R. and R.F.; Funding Acquisition, S.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board statement

The Institutional Review Board of the National Cancer Institute of Peru (INEN) has granted approval for research under project number INEN 10-05.

Data availability statement

The authors confirm that the data supporting the findings of this study are available in the article and its supplementary materials.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2024.02.010.

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