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ORIGINAL ARTICLE

# A preoperative nomogram for predicting long-term survival after resection of large hepatocellular carcinoma (>10 cm)

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## Abstract

**Background:** It has previously been demonstrated that a fraction of patients with hepatocellular carcinoma (HCC) > 10 cm can benefit from liver resection. However, there is still a lack of effective decision-making tools to inform intervention in these patients.

**Methods:** We analysed a comprehensive set of clinical data from 234 patients who underwent liver resection for HCC >10 cm at the National Cancer Institute of Peru between 1990 and 2015, monitored their survival, and constructed a nomogram to predict the surgical outcome based on preoperative variables.

**Results:** We identified cirrhosis, multifocality, macroscopic vascular invasion, and spontaneous tumour rupture as independent predictors of survival and integrated them into a nomogram model. The nomogram's ability to forecast survival at 1, 3, and 5 years was subsequently confirmed with high concordance using an internal validation. Through applying this nomogram, we stratified three groups of patients with different survival probabilities.

**Conclusion:** We constructed a preoperative nomogram to predict long-term survival in patients with HCC >10 cm. This nomogram is useful in determining whether a patient with large HCC might truly benefit from liver resection, which is paramount in low- and middle-income countries where HCC is often diagnosed at advanced stages.

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## Introduction

Hepatocellular carcinoma (HCC), the main form of primary liver cancer, is one of the leading causes of tumour-related deaths worldwide.[1,2] While it can only be performed for a minority of patients, surgery remains the mainstay of HCC treatment to date. The type of surgical procedure to be performed depends on

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tumour burden, liver function, and performance status, as defined in staging systems for clinical decision-making. According to these staging systems, liver resection (LR) is limited to very early and early tumours where cirrhosis is prevalent at diagnosis.[3,4] However, LR is the treatment of choice for HCC in non-cirrhotic patients, for whom even major hepatectomies can be considered.[3] HCC in non-cirrhotic patients represents about 20% of all the cases reported in the literature.[5] Clinically, non-cirrhotic HCC is often diagnosed at more advanced stages with a sizeable tumour mass, because of the stealth nature of the disease during its onset due to a higher liver function reserve and the absence of prodromes.[6]

In the context of treatment expansion beyond the Milan criteria,[7] the decision to perform surgical intervention is based on isolated tumours, absence of portal hypertension, and preserved liver function; but there is no relevant tool for the prediction of HCC patients' outcomes.[8] As a consequence, there is still some uncertainty as to whether LR should be performed when the tumour size is larger than 10 cm in diameter, because of the high incidence of perioperative mortality and the perceived absence of survival benefit.[4] While different trained centres have demonstrated the practicability of LR for large HCC with acceptable outcomes, it still appears that for a fraction of patients, LR has no benefit with higher postoperative and early recurrence-related mortality rates.[9,10] Several variables have been associated with poor prognosis in patients with large HCC, including cirrhosis, multiple tumour lesions, macroscopic vascular invasion (MVI), spontaneous rupture of the tumour, low platelet count, as well as high alpha-fetoprotein (AFP) and bilirubin levels.[11–18] However, the value of these variables has not precisely been measured to predict outcomes among patients with HCC larger than 10 cm in diameter. Therefore, it is imperative to develop tools and guidelines for assessing whether or not a patient would benefit from LR in a context of large HCC.[19]

In the present monocentric study, we examined the variables affecting the survival of patients with HCC larger than 10 cm in diameter to construct and validate a nomogram for predicting overall survival (OS) in these patients. This nomogram aims to stratify surgical benefit and determine which patients with large HCC should undergo LR.

## Methods

### Ethics statement

The Institutional Review Board of the National Cancer Institute of Peru (INEN), Lima, Peru, approved this study (Protocol N° INEN 10-05). Written informed consent was provided by patients or legal guardians for their information to be stored and used for clinical research. The present study was conducted in strict accordance with the ethical principles contained in the Declaration of Helsinki and the Singapore Statement, as well as the legislation of Peru and the Ethics Evaluation Committee of INEN.

### Patients and study design

We compiled a database of all HCC patients treated by surgery between January 1990 and December 2015 in the INEN Department of Abdominal Surgery. From this initial database, we selected every patient with an intrahepatic tumour >10 cm who underwent curative-intent LR ($n$ = 234). Data extracted for the construction of the nomogram were exclusively based on preoperative factors including patient demographics, serologies for hepatitis B and C, haematological and biochemical parameters, AFP levels, tumour characteristics, and liver function. Computed tomography (CT) scan and magnetic resonance imaging (MRI) were reviewed by radiologists with dedicated hepatobiliary imaging expertise to determine localization, size, and focality of the tumour, spontaneous tumour rupture, gross vascular invasion (i.e., MVI), bile duct tumour thrombus (BDTT), and cirrhosis. All blood tests were performed in the clinical laboratory of INEN, according to standard protocols. AFP levels were measured from blood samples using immunoassay. Hepatitis B and C serologies were tested using both HBsAg and anti-HCV immunoassays. None of the patients in the present study was treated with chemotherapy or radiation before LR.

During data compilation, pathology reports made by pathologists specialized in hepatobiliary cancers were reviewed to ensure inclusion criteria were met (i.e., HCC diagnosis and gross negativity of the resection margins). This control feedback information was not used in the construction of the nomogram, which was only based on preoperative variables.

### Surgical procedure

Anatomical resection was the surgical procedure of choice for tumours >10 cm.[20] Briefly, surgical interventions were performed through midline, J-shaped, or bilateral subcostal abdominal incision, according to the tumour topography and the physical characteristics of the patient. After incision, the abdominal cavity was extensively explored to rule out any possibility of distant tumour lesions, and the status of the future remnant liver was evaluated. When necessary, this examination was complemented by ultrasound exploration. After detaching the hilar plate, we started the afferent vascular control with the ligation and the division of the arterial and portal pedicles at the hilum. Pringle manoeuvre or hemi-hepatic inflow occlusion was performed according to the circumstances. The total hepatic vascular exclusion was performed for tumours involving inferior vena cava or hepatic veins. We used the conventional approach until 2005; from this year onwards, the anterior approach with or without a hanging manoeuvre was applied.[21] Liver parenchymal transection was performed by crush-clamping, ensuring a resection margin of at least 1-cm width. Medium-sized blood vessels and bile ducts were ligated, whereas the smallest ones were cauterized. Hepatic veins were controlled in an extrahepatic manner, except when they were in the transection plane. After the removal of the surgical piece, haemostasis was achieved by cauterizing liver bed bleeding using an argon plasma coagulator

and topical haemostat agents. The transection surface was evaluated by direct visualization and with a white gauze compress to detect any open bile ducts, which were then sutured using polypropylene. To rule out suspicion of biliary fistula, a catheter was inserted into the cystic duct and air was injected. In the case of trisectionectomy, pneumobilia combined with ultrasound was used to check the integrity of the biliary tract in the remnant liver. Closed drainage was only installed if there was a risk of biliary leakage. After surgical intervention, cirrhotic patients were always admitted to the intensive care unit. Non-cirrhotic patients, however, were transferred to the intensive care unit at the discretion of the surgical team, according to their postoperative health status. Patients were monitored throughout their hospital stay, and the drain was removed when the biliary fistula was discarded.

### Follow-up of the patients

Follow-up monitoring included surgical report, 30- and 90-day postoperative mortality, as well as HCC recurrence and OS until December 2019. Patients underwent an extensive check-up twice during the first month after leaving the hospital, then every two months during the first year, and finally, every four months from the third year onwards. Liver regeneration and function were assessed by abdominal CT scan and liver function tests, including monitoring of the AFP serum level. Adjuvant chemotherapy was not routinely administered. While AFP concentration was above 10 ng/mL, the eventuality of recurrent or metastatic HCC was explored using chest and abdominal CT and bone scintigraphy. When necessary, the exam was completed by PET/CT and MRI. In cases of intrahepatic recurrence, the feasibility of surgical intervention was promptly evaluated, and when possible, tumour re-resection was performed *quam primum*. When recurrent HCC was unresectable, palliative treatments such as transarterial chemoembolization (TACE), percutaneous ethanol injection, radiofrequency ablation, or targeted therapy were applied. Surgical pulmonary resection was carried out in cases of single lung metastasis. Bone metastases were treated with radiation therapy. In cases without any follow-up, the National Registry of Identification and Civil Status of Peru (RENIEC) was solicited to determine the fate of the patient.

### Nomenclature

Curative-intent hepatectomy was interpreted as LR performed in absence of distant metastasis and remnant liver free of gross invasion. Hepatic resection categories were defined according to the Brisbane 2000 Terminology of Liver Anatomy and Resections.[22] Postoperative mortality was categorized according to the Dindo–Clavien Classification.[23] Diagnosis of post-hepatectomy liver failure (PHLF) was made when either or both the International Study Group for Liver Surgery (ISGLS) criteria and the 50-50 criteria were fulfilled.[24,25] Postoperative mortality was defined as any death occurring within 90 days after hepatectomy in or out of the hospital. Any reappearance of HCC was considered as a recurrence.[26]

### Statistical analyses

Survival probability estimates were calculated by the Kaplan–Meier method from the date of surgery.[27] Log-rank test was used for survival distribution comparison.[28] 30- and 90-day postoperative mortality was assessed, and subsequently, any death, regardless of cause, was considered an event in the survival analysis. The performance of the independent predictors of survival was assessed in a Cox proportional-hazards regression model.[29] The validity of the fitted Cox model was tested using the residuals method: the proportional-hazards assumption was checked using the scaled Schoenfeld residuals and influential observations were examined using the dfbeta residuals.[30–32] Prognostic discrimination of the nomogram model was examined by the concordance index (*C*-index) with 95% confidence interval (95% CI). The holdout cross-validation method was used to assess the internal validity of the nomogram. Seventy percent of patients were then randomly assigned by permutation into a derivation set to construct the nomogram ($n$ = 164), whereas 30% of the patients were assigned into a validation set to test the nomogram ($n$ = 70). Statistical analyses were performed with an alpha significance level of 0.05 in R environment version 3.6.3, using survival and survminer exploratory survival data analysis packages. Nomogram was constructed using R package rms.

## Results

### Perioperative clinical characteristics

Table 1 presents an overview of the perioperative characteristics of the 234 patients with an intrahepatic tumour >10 cm who underwent curative-intent LR in the INEN Department of Abdominal Surgery between January 1990 and December 2015. Over these 25 years, an examination of the patient population structure did not reveal any significant evolution in terms of tumour presentation, clinical pathology, and blood chemistry. The mean age of the patient cohort was relatively young with half of the patients less than 33 years old. The average size of the tumours resected was more than 16 cm in diameter, with the largest specimen reaching 33 cm. Around 9% of the LRs were performed in patients with cirrhosis ($n$ = 22).

### Hepatic resection categories

Table 2 presents the descriptive categorical results for the 234 LRs performed, according to the Brisbane 2000 Terminology of Liver Anatomy and Resections.[22] The vast majority of LRs were major hepatectomies with four or more segments resected, which represented 86% of the interventions.

**Table 1** Perioperative clinical characteristics of the 234 patients with HCC >10 cm

| Feature | Parameter | Number | Percentage |
|---|---|---|---|
| **Preoperative characteristics** | | | |
| Age (years) | Mean ± sd. | 40.4 ± 20.6 | |
| | Median | 32.5 | |
| | Range | [5–89] | |
| | IQR | 36.2 | |
| Gender | Female | 139 | 59.4% |
| | Male | 95 | 40.6% |
| Cirrhosis | Present | 22 | 9.4% |
| | Absent | 212 | 90.6% |
| Albumin (g/dL) | Mean ± sd. | 3.8 ± 0.6 | |
| | Median | 3.8 | |
| | Range | [2.2–5.3] | |
| | IQR | 0.9 | |
| AFP (ng/mL) | Mean ± sd. | 97,648 ± 253,304 | |
| | Median | 6416.5 | |
| | Range | [1–1690,900] | |
| | IQR | 74094.6 | |
| Bilirubin (μmol/L) | Mean ± sd. | 27.4 ± 53.3 | |
| | Median | 16.7 | |
| | Range | [1–478] | |
| | IQR | 10 | |
| Haemoglobin (g/dL) | Mean ± sd. | 12.4 ± 2 | |
| | Median | 12.1 | |
| | Range | [6.6–20] | |
| | IQR | 2.2 | |
| Platelet count (mcL) | Mean ± sd. | 243,000 ± 66,592 | |
| | Median | 250,000 | |
| | Range | [99,000-553000] | |
| | IQR | 86,750 | |
| HBV (HBsAg) | Present | 107 | 45.7% |
| | Absent | 127 | 54.3% |
| HCV (anti-HCV) | Present | 4 | 1.7% |
| | Absent | 230 | 98.3% |
| BDTT | Present | 10 | 4.3% |
| | Absent | 224 | 95.7% |
| MVI | Present | 34 | 14.5% |
| | Absent | 200 | 85.5% |
| Tumour features | | | |
| Tumour size (cm) | Mean ± sd. | 16.4 ± 4.5 | |
| | Median | 15.5 | |
| | Range | [10.1–33] | |
| | IQR | 5.7 | |
| Tumour focality | Solitary | 147 | 62.8% |
| | Multiple | 87 | 37.2% |
| Tumour extension | Unilobar | 145 | 62% |
| | Bilobar | 89 | 38% |
| Spontaneous tumour rupture | Present | 19 | 8.1% |
| | Absent | 215 | 91.9% |
| Intraoperative characteristics and follow-up | | | |
| Estimated blood loss (mL) | Mean ± sd. | 809 ± 653.2 | |
| | Median | 600 | |
| | Range | [100–4000] | |
| | IQR | 600 | |
| Surgical approach | Anterior | 100 | 42.7% |
| | Conventional | 134 | 57.3% |
| Postoperative mortality | 30 days | 7 | 3% |
| | 90 days | 9 | 3.9% |
| Recurrence | Absent | 76 | 32.5% |
| | Present | 158 | 67.5% |
| Follow-up | Events | 179 | 76.5% |
| | Censored | 55 | 23.5% |

Footnote: Mean values are presented ± standard deviation (sd.). AFP, alpha-fetoprotein; BDTT, Bile duct tumour thrombus; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, Interquartile range; MVI, Macroscopic vascular invasion.

## Survival analysis in Cox proportional-hazards regression model

The 30- and 90-day postoperative mortality rates were 3% and 3.9%, respectively. The OS and disease-free survival (DFS) rates five years after LR were 32.3% and 24.3%, respectively (Fig. 1 a). We then performed a univariate analysis, as well as correlation analysis, to identify independent preoperative variables that influenced patient survival. The variables monitored included age and gender of the patients, levels of AFP, albumin and bilirubin, platelet count, infection with HBV and/or HCV, cirrhosis (diagnosed on CT scan), BDTT, MVI, tumour size (above vs. below median), tumour focality (solitary vs. multiple), tumour extension (unilobar vs. bilobar), tumour spontaneous rupture, haemoglobin concentration, as well as perioperative variables, i.e., LR category (according to the Brisbane 2000 Terminology of Liver Anatomy and Resections), surgical approach (anterior vs. conventional), number of segments resected, blood loss (volume), postoperative mortality, recurrence, and DFS (Tables 1 and 2).

The independent preoperative variables significantly associated with OS were cirrhosis ($P$ = 4.55E-08), multifocality ($P$ = 1.77E-07), MVI ($P$ = 9.24E-11), and spontaneous tumour rupture ($P$ = 5.39E-05) (Fig. 1 b-f). These four predictors were introduced into a multivariate analysis using the Cox

Table 2 Hepatic resection categories of the 234 HCC >10 cm

| Resection category | Couinaud segments referred to | Number | Percentage |
|---|---|---|---|
| Right hepatectomy | Sg5,6,7,8 ± Sg1 | 85 | 36.3% |
| Left hepatectomy | Sg2,3,4 ± Sg1 | 54 | 23.1% |
| Right trisectionectomy | Sg4,5,6,7.8 ± Sg1 | 50 | 21.4% |
| Right anterior + medial sectionectomy | Sg4,5,8 | 19 | 8.2% |
| Left trisectionectomy | Sg2,3,4,5,8 ± Sg1 | 12 | 5.1% |
| Bisegmentectomy | Sg5,6 | 7 | 3% |
| Left lateral sectionectomy | Sg2,3 | 5 | 2.1% |
| Bisegmentectomy | Sg7,8 | 1 | 0.4% |
| Segmentectomy | Sg1 | 1 | 0.4% |

proportional-hazards regression model. Statistical tests showed a non-significant relationship between Schoenfeld residuals and time for each covariate included in the Cox model, validating the proportional-hazards assumption (Fig. 2 a). Dfbeta statistics confirmed that none of the observations was exceedingly influential individually, even though dfbeta values for tumour focality were some more scattered (Fig. 2 b).

### Construction of the nomogram

A holdout method was applied to the dataset to construct and validate a nomogram able to predict the survival of patients with HCC >10 cm.[33] First, a derivation set was built from randomization with 70% of the patients ($n$ = 164). With this derivation set, the ratio of calculated beta coefficients from the Cox regression model was used to determine the adjusted predictive effects of the four independent variables in the nomogram and the number of points to be allocated (Fig. 3 a). Using baselines of no cirrhosis, solitary tumour, no MVI, and no spontaneous tumour rupture, predictive effects were calculated for cirrhosis (beta coefficient = 1.22; $P$ = 3.72E-07), multifocal tumour (beta coefficient = 0.67; $P$ = 3.17E-05), spontaneous tumour rupture (beta coefficient = 0.93; $P$ = 2.41E-04), and MVI (beta coefficient = 0.98; $P$ = 3.23E-06). The nomogram model showed interesting prognostic discrimination with a $C$-index of 0.693 (95% CI: 0.650–0.726).

Second, a validation set made up of the remaining 30% of patients was used to test the nomogram model ($n$ = 70). In this validation set, the nomogram demonstrated consistency in predicting OS with a $C$-index of 0.684 (95% CI: 0.639–0.729). For the holdout evaluation, patients were stratified into three groups (G1-3) according to the total points assigned (G1: 0 points, G2: between 1 and 100 points, and G3: more than 100 points). The probability calibration curves confirmed the reliability in the survival prediction of the nomogram for G1-3 at 1, 3, and 5 years after LR (Fig. 3 b). The nomogram also demonstrated relatively good survival prediction at 10 years after surgery, but with less accuracy.

When applied to the total patient cohort ($n$ = 234), the stratified patient groups displayed significant differences in terms of survival probability and incidence proportion of recurrence, notably G1 vs. G2 ($P$ = 1.44E-09 and 1.29E-08, respectively) and G2 vs. G3 ($P$ = 5.85E-05 and 2.11-E05, respectively) (Fig. 3 c,d).

## Discussion

Peru is among the Latin American countries with the highest incidence of HCC.[34] Being the main specialist cancer hospital of the country, INEN serves the majority of Peruvian patients diagnosed with liver cancer. The staff of the INEN Department of Abdominal Surgery treats annually more than 120 patients with HCC, performing about 20 LR for liver tumour larger than 10 cm in diameter. Surgeons have described the consistent presentation of massive or disseminated HCC at the time of the first examination, resulting in nearly 80% of the patients with unresectable disease.[35] For instance, the median tumour size in patients attending care at INEN is 12 cm in diameter, while 90% of HCC develops in a non-cirrhotic liver.[35] This clinical epidemiology is prototypical in low- and middle-income countries, where HCC is frequently detected at advanced stages.[36,37] This situation prompted the staff of the INEN Department of Abdominal Surgery to re-evaluate the therapeutic guidelines for HCC over 10 cm in diameter.[20,38]

Hepatectomy remains the best therapeutic option for very large HCC. A meta-analysis combining the outcomes of LR for 5223 HCC >10 cm reported that 5-year OS ranged from 25% to 45%, which was comparable to the outcomes of surgical resections performed for HCC <10 cm.[8] However, this meta-analysis revealed a high recurrence rate in a significant fraction of patients, resulting in only 15%–35% 5-year DFS.[8] The earlier recurrences appear to have the worst impact on patients' survival: authors have reported 0% 5-year survival in patients who developed recurrence within six months after LR, 27% in patients who developed recurrence between 6 and 12 months after LR, and 67% in patients who developed recurrence after the first year onwards.[39] Early recurrence has been associated with biomedical features that include cirrhosis, size and focality, higher tumour grades, lymph node metastases, MVI, BDTT, and high AFP levels.[26,40] Moreover, surgical parameters might also influence recurrences, such as the type of resection performed (anatomical vs. non-anatomical), the choice of the approach technique (anterior vs. conventional), or even blood transfusion.[41,42] It results that, in a context of large HCC, LR is associated with poor outcomes in a fraction of patients who display high postoperative mortality associated with early recurrence.[9,10] However, there was still a lack of tools and guidelines to inform whether or not such a patient would benefit from LR; hence, patients for whom surgery would be considered futile remained poorly characterised.

In the present study, we aimed to construct a nomogram based on predictive variables that determine the postsurgical

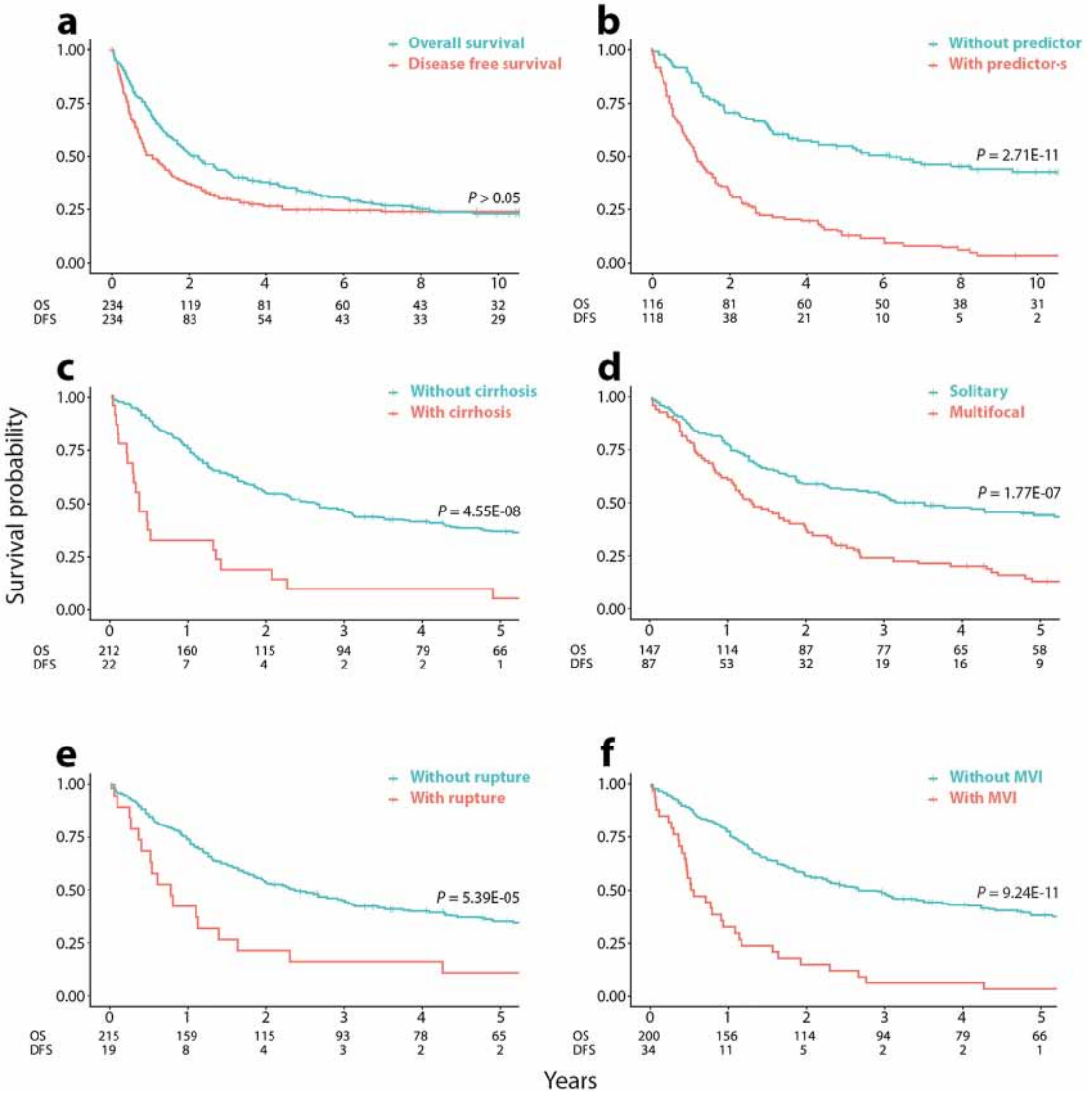


**Figure 1** Survival in time (years) of patients with HCC >10 cm undergoing LR. Kaplan–Meier curves illustrate survival **(a)** OS and DFS **(b)** with and without predictor·s (i.e., at least one of the four independent variables identified), over 10 years, **(c)** with and without cirrhosis, **(d)** with single and multifocal tumour, **(e)** with and without spontaneous tumour rupture, and **(f)** with and without MVI over 5 years. OS, Overall survival; DFS; Disease-free survival; MVI, macroscopic vascular invasion. *P*-values are calculated from the log-rank test

survival probability of patients who undergo LR for HCC larger than 10 cm in diameter. We analysed a cohort of 234 patients treated by the INEN Department of Abdominal Surgery between 1990 and 2015, which represents hitherto the largest patient cohort assembled in a single centre from the Western Hemisphere (Table 1).[12] The outcomes of LR in the patient cohort displayed low postoperative mortality and up to par OS and DFS at five years post-surgery, despite the number of major hepatectomies performed (Table 2). We then identified cirrhosis, multifocality, MVI, and spontaneous tumour rupture as independent predictors of survival and weighted them into a nomogram model for predictions of outcome in patients with large HCC (Figs 1–3). While the detrimental effect of these variables had been documented previously, their impact had not been included in a nomogram tailored for HCC larger than 10 cm in diameter.[11–18]

In our hands, this nomogram has demonstrated high predictive power in estimating the long-term survival of patients after LR for HCC >10 cm (Fig. 3 b). From our point of view, it represents a tool for selecting patients with large HCC who could benefit from LR, especially in the context of low- and middle-income countries. Application of the nomogram stratified the cohort into three groups of patients with different probabilities of survival (Fig. 3 c,d). The first group of patients (G1), scoring low in the

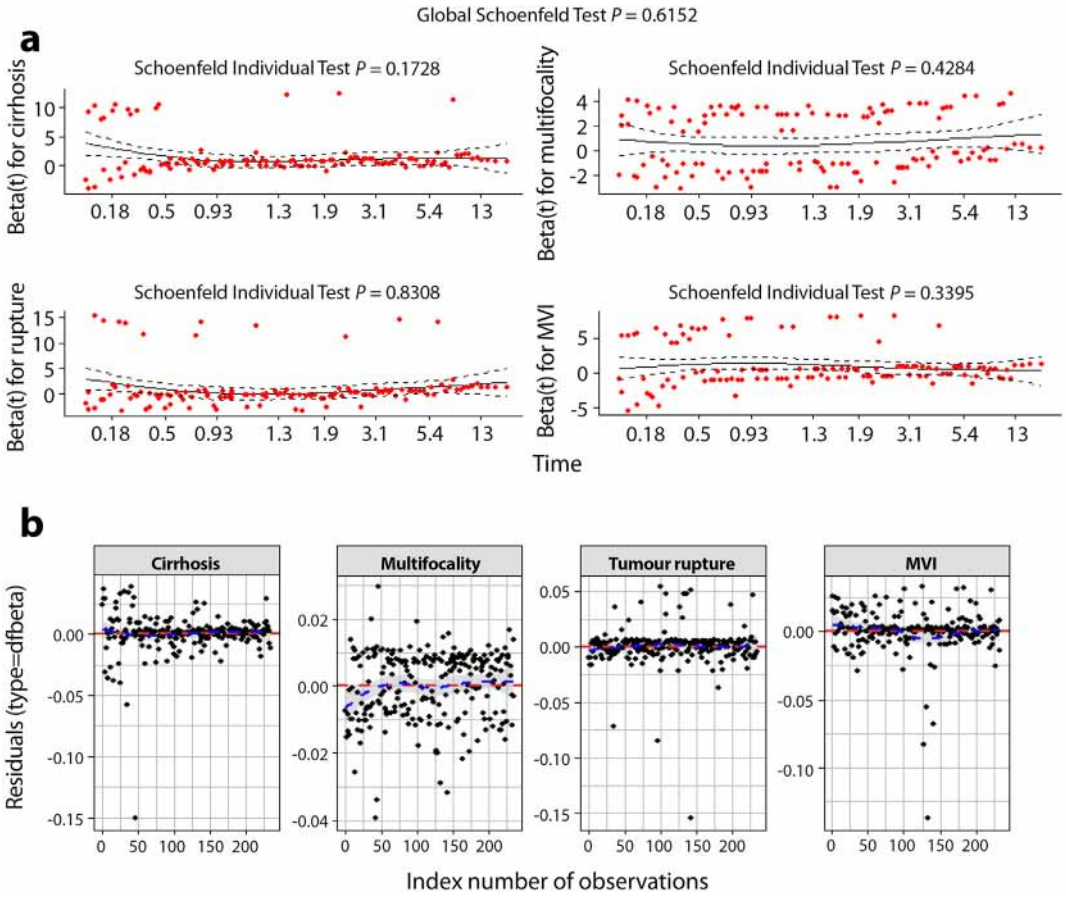


**Figure 2** Diagnostics of the Cox model assumptions. **(a)** Plots of Schoenfeld residuals against event times for each one of the four predictors in the model. Solid lines represent the locally weighted scatterplot smoothing (LOWESS) fit; dashed lines represent the ± 2-standard-error band around the fit. **(b)** Index plots of dfbeta residuals for the Cox regression of time to death on cirrhosis, multifocality, spontaneous tumour rupture, and MVI. The dashed red horizontal line represents a value of 0 for dfbeta; the dashed blue line represents the LOWESS fit

nomogram, presents a high long-term survival probability and corresponds to non-cirrhotic patients with solitary, non-invasive, and unruptured HCC.[8,14,43] This clinical presentation, which does not require adjuvant therapy, has previously been characterised as a nosological subtype of HCC with specific molecular characteristics.[44,45] The second group of patients (G2) displays a 60% probability of recurrence within 12 months and requires intensive monitoring after LR. Patients of this group should additionally receive adjuvant therapy, such as TACE associated with antiviral treatment or immunomodulation.[40] Finally, the third group of patients (G3) presents the highest postoperative mortality, with 15% at 90 days, and a probability of recurrence over 90% within 12 months. Therefore, the third group's patients who present with two or more features impacting survival appear not to benefit from surgery. To avoid futile surgery,[46] these patients should not be considered for LR and be managed with targeted therapy or the best supportive care.

There are some limitations to recognize in the present study. Of note, our analysis was performed in the context of a high prevalence of HBV, including a significant rate of occult infections.[47] Despite compiling a substantial cohort of HCC >10 cm, we retrospectively conducted our analysis with data from a single-centre collected over an extended 25-year period. We monitored, with the best efforts, the changes in patient population structure, perioperative variables, as well as surgical techniques, over the period to narrow this contingency. Finally, further investigations would be necessary to identify molecular biomarkers to improve patients' stratification, notably regarding the first group (G1). While these patients display a higher survival probability, there is still a 47% probability of mortality at 5 years in this group. The identification of molecular signatures should eventually help to better sub-stratify these patients with no preoperative predictor and optimize medical intervention.[48,49]

In conclusion, we believe that this new nomogram could represent a valuable tool to help decision-making of LR intervention or abstention in the management of HCC larger than 10 cm in diameter.

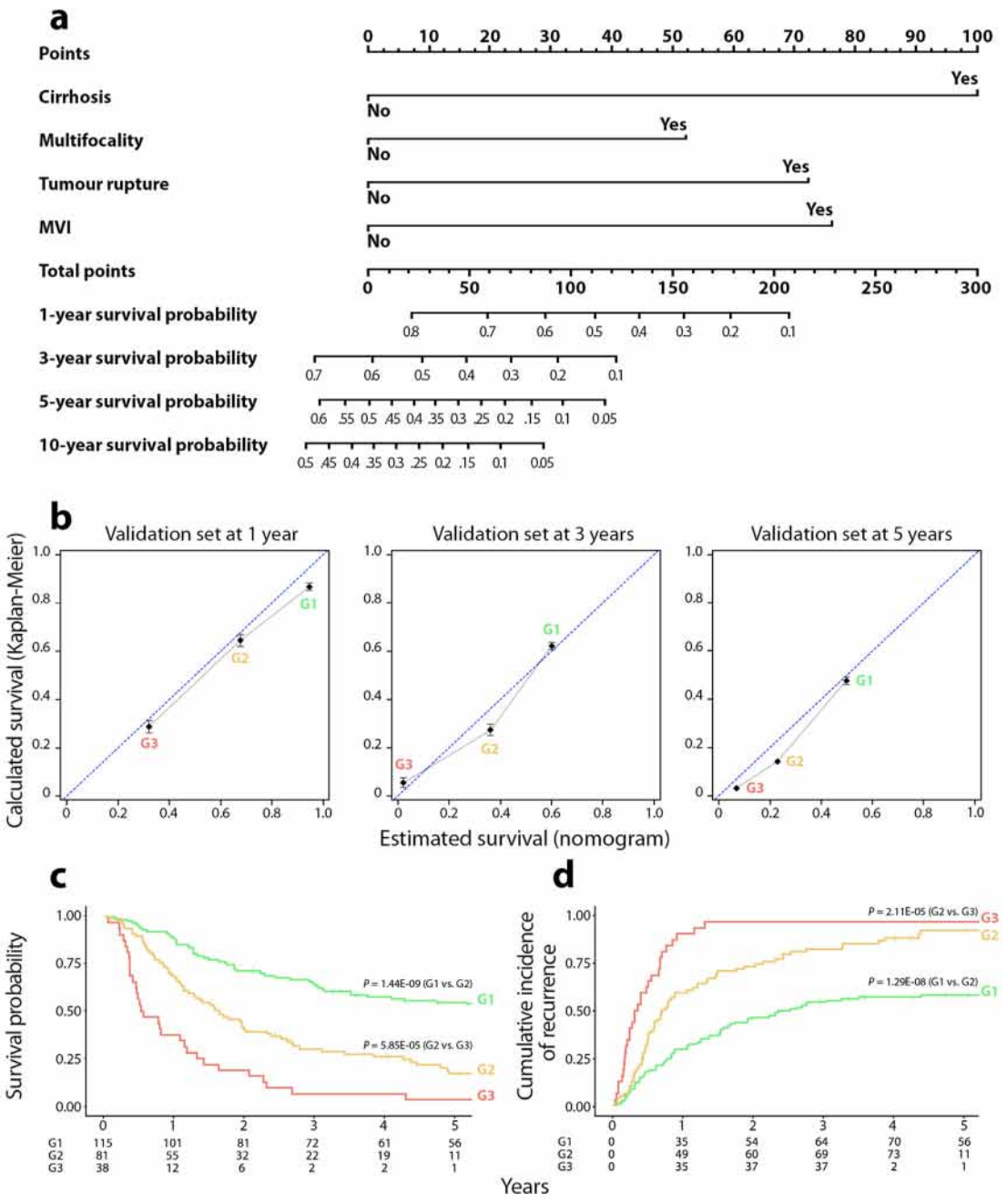


**Figure 3** Nomogram predicting survival of patients with HCC >10 cm undergoing LR. **(a)** Nomogram predicting 1-, 3-, 5-, and 10-year survival of HCC patients in the derivation set ($n$ = 164). The nomogram is used by adding the points identified on the scales of the four predictors (i.e., cirrhosis, multifocality, MVI, and spontaneous tumour rupture). **(b)** The calibration curves of the nomogram were plotted for 1-, 3-, and 5-year survival predictions. The X-axis represents the nomogram-predicted survival, and the Y-axis shows the mean survival and 95% confidence interval (error bars) calculated by the Kaplan–Meier method in the validation set ($n$ = 70). The blue dashed line represents the 45-degree ideal prediction. For the holdout evaluation, patients were categorized into G1 ($n$ = 35), G2 ($n$ = 24), and G3 ($n$ = 11) according to their total nomogram points. G1: 0 points (green); G2: $\leq$100 points (yellow); G3: >100 points (red). **(c)** Five-year survival probability of the total patient cohort ($n$ = 234) stratified into G1-3 according to their total points assigned in the nomogram prognostic model. **(d)** Five-year cumulative incidence of recurrence in the total patient cohort stratified into G1-3 according to their total points assigned in the nomogram prognostic model. $P$-values are calculated from the log-rank test

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**Conflict of interest**
None declared.

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