UNIVERSIDADE FEDERAL DE MINAS GERAIS

Faculdade de Medicina

Programa de Pós-graduação em Ciências Aplicadas à Cirurgia e à Oftalmologia

Henrique Araújo Lima

ESTRATIFICAÇÃO DE RISCO PRÉ-OPERATÓRIO E MODELAGEM PROGNÓSTICA PARA RECORRÊNCIA E SOBREVIDA EM CARCINOMA HEPATOCELULAR APÓS RESSECÇÃO HEPÁTICA

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Tese apresentada ao Programa de Pós-graduação em Ciências Aplicadas à Cirurgia e à Oftalmologia da Faculdade de Medicina da Universidade Federal de Minas Gerais, como requisito parcial para a obtenção do grau de Doutor.

Linha de Pesquisa: Bases moleculares de Neoplasias

Orientadora: Profa. Vivian Resende

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ATA DE DEFESA DE TESE

Às oito horas e trinta minutos do dia treze de fevereiro de dois mil e vinte e cinco, na Faculdade de Medicina, na sala 526, realizou-se a sessão pública para a defesa da Tese de **HENRIQUE ARAÚJO LIMA**. A presidência da sessão coube a Profa. Vivian Resende (Orientadora) – UFMG. Inicialmente, a presidente fez a apresentação da Comissão Examinadora assim constituída: Vivian Resende (Orientadora) – UFMG, Cristiano Xavier Lima – UFMG, Eduardo José Brommelstroet Ramos – UFPR, Marcelo Moura Linhares – UNIFESP e Paula Vieira Teixeira Vidigal – UFMG. Em seguida, o candidato fez a apresentação do trabalho que constitui sua Tese de Doutorado, intitulada: ESTRATIFICAÇÃO DE RISCO PRÉ-OPERATÓRIO E MODELAGEM PROGNÓSTICA PARA RECORRÊNCIA E SOBREVIDA EM CARCINOMA HEPATOCELULAR APÓS RESSECÇÃO HEPÁTICA. Seguiu-se a arguição pelos examinadores e logo após, a Comissão reuniu-se, sem a presença do candidato e do público e decidiu considerar aprovado a Tese de Doutorado. O resultado final foi comunicado publicamente ao candidato pela presidente da Comissão. Nada mais havendo a tratar, o presidente encerrou a sessão e lavrou a presente ata que, depois de lida, se aprovada, será assinada pela Comissão Examinadora.

Belo Horizonte, 13 de fevereiro de 2025.

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DEDICATÓRIA

Dedico esta tese de Doutorado aos meus pais, Roberto e Sueli,

à minha irmã Jacqueline, à minha esposa, Anna Cecília

e ao meu filho.

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Aos pacientes,

que este estudo possa contribuir para um cuidado melhor.

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EPÍGRAFE

Sine fide ratio in falsam suae omnipotentiae speciem est casura. Fides sine ratione periculum adit ne a certa personarum vita abstrahatur
BENEDICTUS PP. XVI, *CARITAS IN VERITATE*

"*A razão sem a fé está destinada a perder-se na ilusão da própria omnipotência, enquanto a fé sem a razão corre o risco do alheamento da vida concreta*"

RESUMO

O carcinoma hepatocelular comumente surge no contexto de doença hepática crônica e parênquima hepático subjacente comprometido. Embora a escolha das estratégias terapêuticas seja influenciada pela complexa interação entre esses fatores clínicos, a cirurgia ainda é a melhor opção de tratamento com intenção curativa. No entanto, a recorrência após ressecção ainda é um grande desafio devido às suas altas taxas e frequente progressão para recidiva não transplantável (RNT). Identificar os padrões de recorrência, incluindo taxas de risco máximo e intervalo de recorrência, bem como fatores de risco pré-operatórios para RNT, é fundamental para melhorar os desfechos. Além disso, a heterogeneidade no carcinoma hepatocelular (CHC) persiste mesmo dentro de categorias de sistemas de classificação consagrados, como o BCLC (Barcelona Clinic Liver Cancer). Especificamente, a não recomendação de ressecção para CHC em estágio intermediário do BCLC permanece controversa.

Este trabalho busca caracterizar e analisar os padrões de recorrência do CHC, bem como aumentar a granularidade na classificação de pacientes no pré-operatório. Nosso intuito é contribuir para o melhor entendimento dos padrões de recorrência do CHC, e consequentemente, refinar as estratégias de vigilância pós-operatória. Além disso, os resultados a serem apresentados podem auxiliar na melhor estratificação de risco pré-operatório, otimizando a seleção das melhores estratégias de tratamento para cada subgrupo de pacientes. Com base em dados internacionais de grandes bases de dados multi-institucionais, nossas modelagens prognósticas para recorrência e sobrevivência também visam melhorar o prognóstico e desfecho desses pacientes.

Palavras-chave: Carcinoma hepatocelular; Ressecção hepática; Padrões de recorrência; Modelo prognóstico.

ABSTRACT

Hepatocellular carcinoma (HCC) commonly arises in the context of chronic liver disease and an impaired underlying liver parenchyma. While the choice of therapeutic strategies is influenced by the complex interplay of these clinical factors, surgery remains the best curative-intent treatment option. However, recurrence after resection remains a significant challenge due to its high rates and frequent progression to non-transplantable recurrence (NTR). Identifying recurrence patterns, including peak risk rates and recurrence intervals, as well as preoperative risk factors for NTR, is essential to improve outcomes. Moreover, heterogeneity in HCC persists even within established classification systems such as the Barcelona Clinic Liver Cancer (BCLC) staging system. Specifically, the non-recommendation of liver resection for intermediate-stage HCC in the BCLC system remains controversial.

This study aims to characterize and analyze the recurrence patterns of HCC while enhancing the granularity of preoperative patient classification. Our goal is to contribute to a better understanding of HCC recurrence patterns and, consequently, refine postoperative surveillance strategies. Furthermore, the findings to be presented may aid in improving the prognosis and outcomes for these patients. Based on international data from large multi-institutional databases, our prognostic models for recurrence and survival also aim to improve preoperative risk stratification, optimizing patient selection for curative-intent liver resection.

Keywords: Hepatocellular Carcinoma; Hepatic resection; Recurrence Patterns; Prognostic Model.

LISTA DE ABREVIATURAS E SIGLAS

AFP	Alfafetoproteína / Alpha-fetoprotein
AJCC	Comitê Conjunto Americano de Estadiamento de Câncer / American Joint Committee on Cancer
AUC	Área Abaixo da Curva / Area Under the Curve
BCLC	Barcelona Clinic Liver Cancer
CHC	Carcinoma Hepatocelular / HCC Hepatocellular carcinoma
CLIP	Programa Italiano de Câncer de Fígado / Cancer of the Liver Italian Program
cm	Centímetros / Centimeters
CP	Child-Pugh
IC	Intervalo de Confiança / Confidence Interval
JIS	Sistema de Estadiamento Integrado do Japão / Japan Integrated Staging
p-value	Valor de Probabilidade / Probability Value
RH	Ressecção Hepática / HR Hepatic resection
RNT	Recidiva Não-Transplantável / NTR Non-transplantable Recurrence
SG	Sobrevida global / OS Overall Survival
SLD	Sobrevida Livre de Doença / RFS Recurrence-free Survival
T	Tamanho do Tumor / Tumor Size
TBS	Escore de Carga Tumoral / Tumor Burden Score
TH	Transplante Hepático / HT Hepatic Transplant
THS	Transplante Hepático Secundário / SLT Salvage Livre Transplant
vs.	Versus
%	Porcentagem / Percentage
<	Menor que / Less then
x2	Teste do Qui-quadrado / Chi-square Test

SUMÁRIO

1. INTRODUÇÃO

O carcinoma hepatocelular (CHC) é um dos cânceres mais comuns e uma das principais causas de morte relacionada ao câncer em todo o mundo, com incidência crescente.[1] A cirurgia é a única opção curativa, mas suas indicações são limitadas e as taxas de recorrência permanecem altas, sendo a recorrência precoce (≤2 anos) geralmente associada à metástases e a recorrência tardia (>2 anos) frequentemente decorrente de novos tumores em parênquimas hepáticos comprometidos.[2] Apesar dos avanços, não existem terapias sistêmicas adjuvantes eficazes, tornando essencial a seleção adequada dos pacientes e a vigilância pós-operatória. A vigilância atual, que inclui exames de imagem e dosagem de alfa-fetoproteína (AFP), segue diretrizes vagas e controversas.[3] O risco de recorrência varia conforme fatores clínicos, exigindo estratégias de acompanhamento individualizadas. As análises tradicionais de sobrevida (Kaplan–Meier) não capturam adequadamente a dinâmica do risco de recorrência, enquanto a análise da função de risco pode fornecer informações valiosas sobre os riscos específicos ao longo do tempo para os pacientes remanescentes.[4]

Os tratamentos curativos incluem a ressecção hepática (RH) e o transplante hepático (TH), sendo o TH preferido por tratar tanto o tumor quanto a doença hepática subjacente.[5] No entanto, a escassez de órgãos pode tornar a RH necessária, mesmo diante das altas taxas de recorrência. Embora o transplante hepático de resgate seja uma opção para alguns casos de recorrência, uma parte considerável dessas recorrências não é passível de transplante.[6] A previsão do risco de recidiva não transplantável (RNT) no pré-operatório poderia melhorar a seleção de pacientes para tratamento cirúrgico. O Tumor Burden Score (TBS), uma métrica que combina o tamanho e o número de tumores, já foi validado para estratificação prognóstica de tumor hepático por meio de exames de imagem.[7] A alfa-fetoproteína (AFP) também está associada à agressividade do CHC e também pode ajudar a prever a RNT.[8] No entanto, apesar desses marcadores, ainda não existe uma ferramenta pré-operatória simples para estimar o risco de RNT, o que poderia auxiliar na seleção de pacientes e na otimização dos desfechos.

O sistema de estadiamento Barcelona Clinic Liver Cancer (BCLC), continua sendo uma ferramenta amplamente utilizada e fundamental para prever o prognóstico e orientar o manejo do CHC. O BCLC integra carga tumoral, função hepática [refinado por Child-Pugh e model for end-stage liver disease (MELD)] e *performance status* do paciente para orientar o prognóstico e o tratamento.[9] Ele classifica o HCC em cinco estágios; BCLC 0 (Muito inicial): Tumor único ≤2 cm, tratado com opções curativas (ressecção, transplante ou ablação); BCLC A (Inicial): Até três nódulos ≤3 cm, também tratado com terapias curativas; BCLC B (Intermediário): Tumores grandes/multifocais sem invasão vascular, tratados com quimioembolização

transarterial (TACE) ou terapia sistêmica, quando não atingem critérios expandidos de transplante; BCLC C (Avançado): Presença de invasão vascular ou metástase, tratados com terapias sistêmicas; BCLC D (Terminal): Qualquer carga tumoral associada a disfunção hepática grave, tratados com cuidados paliativos. Atualizações recentes incorporaram novos marcadores, como o escore albumina-bilirrubina (ALBI) e a AFP, mas aumentaram sua complexidade. A doença intermediária (BCLC B) constitui uma população altamente heterogênea, gerando debate contínuo sobre sua utilidade clínica. Vários critérios de subclassificação incorporando fatores como níveis de AFP, tamanho e número de tumores foram propostos, mas com eficácia controversa. Notavelmente, alguns pacientes com BCLC B e TBS médio apresentam melhores desfechos de sobrevida do que pacientes BCLC A com TBS elevado.[10] Portanto, uma análise mais detalhada do papel de fatores-chave, como o TBS e a AFP pré-operatórios, pode auxiliar na subclassificação de pacientes com CHC intermediário submetidos à ressecção cirúrgica e identificar aqueles que podem se beneficiar mais da cirurgia, melhorando os desfechos de sobrevida a longo prazo.

O estadiamento adequado é essencial para o tratamento e prognóstico do CHC. Apesar de sua ampla utilização, o sistema BCLC tem sido criticado por ser excessivamente restritivo, especialmente em relação à ressecção hepática para CHC intermediário. Mesmo após atualizações, o BCLC ainda não recomenda a ressecção além da doença em estágio inicial, apesar das evidências que demonstram sua viabilidade em pacientes selecionados. Além disso, o BCLC categoriza os pacientes com base em critérios rígidos que podem não refletir completamente a complexidade da doença. Existem várias classificações alternativas, mas nenhuma foi amplamente aceita. As atualizações recentes do BCLC incorporam marcadores de descompensação hepática e AFP, mas à custa de simplicidade. Dada a heterogeneidade nas características do tumor, biologia tumoral e função hepática, seria interessante refinar a estratificação dos pacientes utilizando um escore simples que integre indicadores de morfologia tumoral, biologia tumoral e função hepática. O valor prognóstico desse proposto escore precisaria ser comparado aos sistemas já existentes, como BCLC, Japan Integrated Staging (JIS)[11] e Cancer of the Liver Italian Program (CLIP),[12] a fim de aprimorar a estratificação do tratamento do CHC.

Neste contexto, apresentamos, a seguir, alguns estudos para aprofundar o entendimento dos padrões de recorrência do CHC após ressecção hepática, melhorar a estratificação de risco pré-operatório e abordar a heterogeneidade existente dentro de sistemas clássicos de classificação e prognóstico.

2. JUSTIFICATIVA

A recorrência do CHC após RH é um desafio significativo devido às altas taxas e frequente progressão para RNT (além dos critérios de Milão). Identificar os padrões de recorrência, incluindo taxas de risco máximo e tempo de recorrência, bem como fatores de risco pré-operatórios para RNT, é fundamental para melhorar os desfechos.

Além disso, a heterogeneidade no CHC ainda persiste dentro das subcategorias do sistema BCLC. Especificamente, a não recomendação de ressecção para CHC em estágio intermediário do BCLC permanece controversa. No entanto, alguns pacientes podem obter benefícios de sobrevida a longo prazo se submetidos a hepatectomia. Reconhecendo a heterogeneidade neste sistema, desenvolvemos modelos para melhor discriminar e prever o prognóstico após a ressecção com intuito curativo.

Este trabalho busca, em primeiro lugar, caracterizar e analisar os padrões de recorrência após a RH inicial para CHC, bem como identificar variáveis pré-operatórias para subclassificar pacientes com CHC em estágio intermediário do BCLC. Além disso, propomos um novo sistema de pontuação simples, para estratificar o prognóstico dos pacientes com CHC, composto por variáveis representativas da morfologia tumoral, biologia tumoral e função hepática. Nosso intuito é que estes resultados possam ajudar a refinar estratégias de vigilância, otimizar a seleção de pacientes e melhorar os resultados do tratamento.

3. HIPÓTESE

Um maior conhecimento sobre os padrões de recorrência do CHC, a predição de RNT, assim como um maior detalhamento no sistema de classificação BCLC poderiam ser úteis para refinar estratégias de vigilância, otimizar a seleção de pacientes e melhorar os desfechos pós tratamento cirúrgico.

4. OBJETIVOS

4.1 Geral

Caracterizar melhor os padrões de recorrência do CHC, otimizar a predição de RNT e promover maior detalhamento e poder discriminatório no sistema de classificação BCLC.

4.2 Específicos

- Caracterizar a taxa condicional instantânea de recorrência utilizando a função de risco (Hazard Function).
    - Determinar a influência de fatores clínicos-chave, como BCLC, TBS e AFP, no tempo e na taxa de pico de recorrência após a ressecção do CHC.
- Caracterizar e analisar os padrões de recorrência após a ressecção inicial do CHC.
    - Identificar preditores pré-operatórios de RNT, para construir e validar um modelo de risco pré-operatório, visando otimizar estratégias iniciais de tratamento para o CHC.
    - Desenvolver uma calculadora online de fácil uso para o escore de RNT.
- Examinar o impacto de variáveis pré-operatórias na subclassificação de pacientes com CHC em estágio intermediário do BCLC submetidos à ressecção cirúrgica.
    - Analisar o prognóstico de pacientes com CHC intermediário do BCLC após a ressecção em relação aos níveis séricos pré-operatórios de AFP e ao TBS.
- Estratificar o prognóstico de pacientes com CHC após ressecção com intuito curativo utilizando um sistema de pontuação simples (escore “TAC”).
    - Desenvolver e avaliar o escore “TAC” em relação ao prognóstico a longo prazo após a ressecção de CHC.
    - Caracterizar o desempenho do escore TAC na estratificação de pacientes com CHC em relação ao BCLC, aos sistemas JIS e CLIP.

5. MÉTODO

Durante este Doutorado foram geradas as seguintes publicações, mas esta Tese terá como tema apenas as 4 primeiras. Os artigos que compõem esta Tese de Doutoramento estão, também, anexados.

1. LIMA, HENRIQUE A.; Alaimo, Laura ; Brown, Zachary J. ; Endo, Yutaka ; Moazzam, Zorays ; Tsilimigras, Diamantis I. ; Shaikh, Chanza ; Resende, Vivian ; Guglielmi, Alfredo ; Ratti, Francesca ; Aldrighetti, Luca ; Marques, Hugo P. ; Soubrane, Olivier ; Lam, Vincent ; Poultsides, George A. ; Popescu, Irinel ; Alexandrescu, Sorin ; Martel, Guillaume ; Hugh, Tom ; Endo, Itaru . **Application of Hazard Functions to Investigate Recurrence After Curative-Intent Resection for Hepatocellular Carcinoma**. HPB , v. 25, p. 260-268, 2022.

2. LIMA, HENRIQUE A.; Moazzam, Zorays ; Endo, Yutaka ; Alaimo, Laura ; Shaikh, Chanza ; Munir, Muhammad Musaab ; Resende, Vivian ; Guglielmi, Alfredo ; Marques, Hugo P. ; Cauchy, François ; Lam, Vincent ; Poultsides, George A. ; Popescu, Irinel ; Alexandrescu, Sorin ; Martel, Guillaume ; Hugh, Tom ; Endo, Itaru ; Kitago, Minoru ; Shen, Feng ; Pawlik, Timothy M. **TBS-Based Preoperative Score to Predict Non-transplantable Recurrence and Identify Candidates for Upfront Resection Versus Transplantation for Hepatocellular Carcinoma.** ANNALS OF SURGICAL ONCOLOGY , v. 30, p. 3363-3373, 2023.

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A metodologia específica de cada estudo está devidamente descrita na sessão de métodos dos respectivos artigos a seguir. No entanto, alguns pontos importantes são comuns a todos os estudos e devem ser mencionados.

O TBS é uma medida quantitativa utilizada para avaliar a extensão da presença de um tumor, frequentemente, aplicado nos tumores hepáticos para avaliar o prognóstico e orientar estratégias de tratamento.[7] O TBS incorpora duas dimensões principais da carga tumoral e é calculado segundo o teorema de Pitágoras:

1. Tamanho do Tumor: Refere-se ao maior diâmetro do tumor primário ou das lesões metastáticas.
2. Número de Tumores: Considera o número total de tumores detectáveis.
3. $TBS = \sqrt{(\alpha^2 + \beta^2)}$

   Sendo:

   α o diâmetro máximo do maior tumor.

   β o número de tumores.

A população dos estudos foi extraída de um banco de dados internacional e multi-institucional de pacientes submetidos à ressecção hepática para CHC entre 2000 e 2020. Os centros hepatobiliares de alto volume participantes incluíam: The Ohio State University Wexner Medical Center, Columbus, OH, EUA; Yokohama City University School of Medicine, Yokohama, Japão; Keio University, Tokyo, Japão; University of Colorado, Denver, Colorado, EUA; Eastern Hepatobiliary Surgery Hospital Second Military Medical University, Xangai, China; University of Verona, Verona, Itália; Ospedale San Raffaele, Milão, Itália; Curry Cabral Hospital, Lisboa, Portugal; APHP, Beaujon Hospital, Clichy, França; Westmead Hospital, Sydney, Austrália; Stanford University, Stanford, CA, EUA; Fundeni Clinical Institute, Bucareste, Romênia; University of Ottawa, Ottawa, Canadá; The University of Sydney, School of Medicine, Sydney, Austrália; HC-UFMG, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil. Todos os estudos foram aprovados pelos Comitês de Ética em Pesquisa (Institutional Review Board) das instituições participantes.

Os critérios de exclusão variaram dependendo do estudo, mas de maneira geral, pacientes que foram submetidos a ressecção sem intenção curativa, faleceram dentro de 90 dias após a cirurgia, realizaram cirurgia paliativa, apresentaram margens macroscopicamente positivas, ou não tinham dados para as variáveis de interesse foram excluídos do estudo.

6. RESULTADOS

6.1. Artigo 1

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ORIGINAL ARTICLE

Application of hazard functions to investigate recurrence after curative-intent resection for hepatocellular carcinoma

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Abstract

Background: Defining patterns and risk of recurrence can help inform surveillance strategies and patient counselling. We sought to characterize peak hazard rates (pHR) and peak time of recurrence among patients who underwent resection of hepatocellular carcinoma (HCC).

Methods: 1434 patients who underwent curative-intent resection of HCC were identified from a multi-institutional database. Hazard, patterns, and peak rates of recurrence were characterized.

Results: The overall hazard of recurrence peaked at 2.4 months (pHR: 0.0384), yet varied markedly. The incidence of recurrence increased with Barcelona Clinic Liver Cancer (BCLC) stage 0 (29%), A (54%), and B (64%). While the hazard function curve for BCLC 0 patients was relatively flat (pHR: <0.0177), BCLC A patients recurred with a peak at 2.4 months (pHR: 0.0365). Patients with BCLC B had a bimodal recurrence with a peak rate at 4.2 months (pHR: 0.0565) and another at 22.8 months. The incidence of recurrence also varied according to AFP level (≤400 ng/mL: 52.6% vs. >400 ng/mL: 36.3%) and Tumor Burden Score (low: 73.7% vs. medium: 50.6% vs. high: 24.2%) (both $p < 0.001$).

Conclusion: Recurrence hazard rates for HCC varied substantially relative to both time and intensity/peak rates. TBS and AFP markedly impacted patterns of hazard risk of recurrence.

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Introduction

Hepatocellular carcinoma (HCC) is among the top five most common malignancies and a leading cause of cancer-related mortality worldwide.[1,2] Surgical resection offers the only potential opportunity for cure but is reserved for patients with well-preserved liver function and anatomically resectable tumors.[3] Long-term prognosis after resection remains variable with 5-year overall survival ranging from 40 to 70%, primarily due to a high incidence of recurrence (60–70%) after curative-intent surgery.[4–6] Early recurrence, occurring within two years of resection, is thought to be related to metastasis and tumor dissemination of the primary HCC. Late recurrence, which

occurs after two years, is more often related to a *de novo* tumor arising in the diseased liver.[7] Although there have been advances in systemic therapies, none have proven to be effective in the adjuvant setting. Therefore, appropriate selection of patients to undergo surgery and proper postoperative surveillance after curative-intent resection is important to improve overall outcomes.

Surveillance with cross-sectional imaging and the serum tumor marker alpha-fetoprotein (AFP) is widely adopted.[8,9] However, post-resection follow-up guidelines remain vague and controversial without taking into account the various risk of postoperative recurrence.[6,10–12] For example, imaging, and blood tests are recommended every 3–6 months in the first two years and every 6–12 months thereafter, according to the National Comprehensive Cancer Network (NCCN) guidelines[13]; but these intervals are not fully endorsed by other organizations.[14,15] As the timing of HCC recurrence varies based on several clinical factors, different Barcelona Clinic Liver Cancer (BCLC) stages of HCC may be associated with different hazard rates and therefore may require distinct follow-up periods. In turn, it is imperative to better understand time-specific risk and peak recurrence in order to optimize surveillance and facilitate the timely treatment of recurrent disease.

To date, recurrence and survival outcomes of patients have been widely conveyed using plots of the survival function (Kaplan–Meier methodology), which show cumulative probabilities at a given time for the entire cohort. In contrast, the hazard function provides information about the risk of an event at a time only for patients remaining at risk, which is not readily evident in the survival function. In particular, the hazard function tracks an instantaneous conditional failure rate over time among the surviving patients.[16] Patients with colorectal and breast cancer have been previously studied in this context; however, hazard function analysis has not been applied to patients with HCC.[17,18] As such, the objective of the current study was to characterize the instantaneous conditional recurrence rate, as well as peak rates of recurrence among patients with HCC using the hazard function. In addition, we sought to determine the influence of key clinical factors, such as BCLC, tumor burden score (TBS), and AFP on peak recurrence time and rate following HCC resection.

Method

Study population and data

Patients who underwent curative-intent resection for HCC between 2000 and 2020 were identified from an international multi-institutional database. The participating high volume hepatobiliary centers included: The Ohio State University Wexner Medical Center, Columbus, OH; Yokohama City University School of Medicine, Yokohama, Japan; Eastern Hepatobiliary Surgery Hospital Second Military Medical University, Shanghai, China; University of Verona, Verona, Italy; Ospedale San Raffaele, Milano, Italy; Curry Cabral Hospital, Lisbon, Portugal; APHP, Beaujon Hospital, Clichy, France; Westmead Hospital, Sydney, Australia; Stanford University, Stanford, CA; Fundeni Clinical Institute, Bucharest, Romania; University of Ottawa, Ottawa, Canada; and The University of Sydney, School of Medicine, Sydney, Australia. The study was approved by the Institutional Review Board of the participating institutions. Patients who underwent non-curative intent resection, had positive macro- or microscopic margins, and individuals with missing follow-up data were excluded from the study.

Variables, definitions, and outcomes

Demographic and clinicopathologic parameters were collected: age, sex, American Society of Anesthesiologists (ASA) classification, presence of cirrhosis, hepatitis B liver infection (HBV) and hepatitis C liver infection (HCV), ascites within 30 days prior to surgery, preoperative laboratory parameters [platelet count (PLT), albumin, total bilirubin, prothrombin time (PT), AFP], Child–Pugh class, BCLC stage, TBS score, surgical approach (open or minimally invasive), extent of resection (major or minor) and type of resection (anatomic or nonanatomic). Pathologic tumor characteristics included maximum diameter of the largest tumor, histological grade, presence of lymphovascular invasion, liver capsule involvement, number of lesions (solitary or multiple), presence of tumor necrosis, and perineural invasion. As previously reported, TBS incorporated size and number of lesions in the following formula: TBS^2 = $(\text{maximum tumor diameter})^2 + (\text{number of tumors})^2$. Tumor diameter and number of lesions were confirmed by postoperative pathology.[19,20] High AFP was considered >400 ng/mL, and TBS cut-off values were lowest 25% of TBS (low TBS), between the 25th and 90th percentiles (medium TBS), and the highest 10% of TBS (high TBS), as previously described.[7,18] Liver resection was categorized as a major hepatectomy if three or more contiguous Couinaud liver segments were resected.[21] The primary outcome was recurrence-free survival (RFS). RFS was expressed as the time interval measured from the date of primary surgery to the date of first recurrence or the date of the last follow-up if recurrence did not occur. Tumor recurrence was defined as the appearance of a new lesion on imaging, with or without histological confirmation.

Statistical analysis

Continuous variables were reported as medians with interquartile range (IQR) and categorical variables as numbers and percentages. The Kaplan–Meier method and log-rank test were used to perform the disease-free survival analysis. All p-value <0.05 was considered statistically significant. The survival analyses were performed both for the entire cohort and after stratifying patients by BCLC criteria, AFP levels, and TBS. For the variables of interest, the RFS hazard function was applied to plot the hazard rates and the peak of recurrence over time. The kernel smoothing method provided estimates of hazard function from

Table 1 Demographics and clinicopathologic characteristics of patients

Variables	Total (n = 1434)
Age, years, median *(IQR)*	63 (53–71)
Sex, n *(%)*	
Male	1122 (78.2)
Female	312 (21.8)
ASA Score > II, n (%)	395 (42.5)
Cirrhosis, n (%)	697 (48.6)
Hepatitis B Liver Infection, n (%)	411 (30.4)
Hepatitis C Liver Infection, n (%)	325 (22.8)
Ascites, n (%)	41 (3.0)
Platelet count > 150 x 10^3/μL, n (%)	752 (56.0)
Albumin > 3.5 g/dL, n (%)	935 (81.6)
PT-INR > 1.1, n (%)	174 (13.2)
Alpha-fetoprotein > 400 ng/mL, n (%)	323 (25.3)
Child-Pugh Classification, n (%)	
A	1072 (97.4)
B	29 (2.6)
BCLC Classification, n (%)	
0	74 (6.7)
A	890 (80.8)
B	137 (12.4)
TBS Score, n (%)	
Low (<3.35)	353 (24.8)
Medium (3.35–13.24)	927 (65.2)
High (>13.24)	141 (9.9)
Minimally Invasive Surgery, n (%)	170 (16.6)
Extent of Resection, n (%)	
Major	370 (36.0)
Minor	657 (64.0)
Type of Resection, n (%)	
Anatomic	820 (79.8)
Nonanatomic	207 (20.2)
Tumor size, cm, median (IQR)	5 (3.0–8.5)
Multiple Tumours, n (%)	205 (14.4)
Grade, n (%)	
Well to moderate differentiated	849 (60.7)
Poor to undifferentiated	549 (39.3)
Lymphovascular Invasion, n (%)	326 (37.2)
Perineural Invasion, n (%)	15 (3.2)
Liver Capsule Involvement, n (%)	360 (33.5)

Categorical variables presented as frequency (%); continuous variables presented as median (M, IQR); *IQR* interquartile range; *ASA* American Society of Anaesthesiology; *PT* prothrombin time; *INR* international normalized ratio; *BCLC* Barcelona Clinic Liver Cancer; *TBS* Tumor Burden Score

right-censored data. Recurrence was defined as an event and the units of measure for hazard rates were events per month. Statistical analyses were performed using SPSS version 28 (IBM Corporation, Armonk, NY, USA) and R software, version 4.1.3 (R Foundation for Statistical Computing, R Core Team, Vienna, Austria) with additional packages "muhaz", "survival", "ggplot 2", "survminer".

Results

Patient characteristics

Among 1434 patients who underwent curative-intent liver resection for HCC, median age was 63 years (IQR, 53–71) and 1122 (78.2%) patients were male; 395 (42.5%) patients had a preoperative ASA > II and 25.3% of patients had an AFP >400 ng/mL (n = 323) (Table 1). Overall, 697 (48.6%) patients had liver cirrhosis with 1072 (97.4%) classified as Child-Pugh A and only 29 (2.6%) classified as Child-Pugh B. Additionally, most patients were classified as BCLC A (n = 890, 80.8%), with BCLC 0 and BCLC B accounting for 74 (6.7%) and 137 (12.4%) patients, respectively. Most patients had unifocal disease (n = 1,217, 85.6%), while 205 (14.4%) patients had multifocal tumors. Most patients underwent a minor hepatectomy (n = 657, 64.0%), while a smaller proportion of patients underwent a major hepatectomy (n = 370, 36.0%). Furthermore, most patients had an anatomic hepatic resection (n = 820, 79.8%), while fewer individuals underwent a non-anatomic hepatectomy (n = 207, 20.2%).

Overall, the majority of patients had a medium TBS (n = 927, 65.2%), while a smaller subset of individuals had either a low (n = 353, 24.8%) or high (n = 141, 9.9%) TBS. The median tumor size was 5 cm (IQR, 3.0–8.5). On final pathological assessment, most patients had well to moderately differentiated tumors (n = 849, 60.7%), while fewer had poor to undifferentiated tumors (n = 549, 39.3%). Lymphovascular invasion was present in 326 (39.3%) patients, perineural invasion in 15 (3.2%) patients, and liver capsule invasion in 360 (33.5%) patients.

Survival function: hazard of disease recurrence

With a median follow-up of 37 months (IQR, 15–67), 700 (49.8%) patients had experienced a recurrence. Among patients classified as BCLC 0, A, and B, recurrence occurred in 28.8% (21/73), 49.2% (433/880), and 64.2% (86/134) of patients, respectively. The median RFS was 57 months (IQR, 51–63), and overall, the 3-year RFS was 62.4% (95% CI: 59–66) (Fig. 1a). Additionally, there were differences in RFS among patients categorized as BCLC 0, A, B with a 3-year RFS of 73.7% (95% CI: 63–86), 50.6% (95% CI: 47–54), and 24.2% (95% CI: 17–35), respectively ($p < 0.001$) (Fig. 1b). The most frequent site of recurrence was intrahepatic (75.0%, n = 343), a smaller subset of patients experienced extrahepatic recurrence (n = 87, 19.0%),

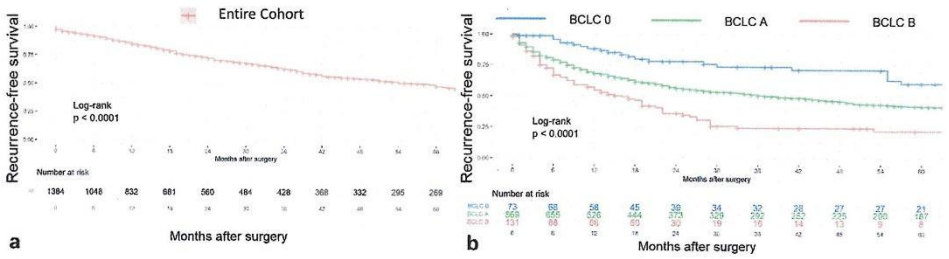

Figure 1 Recurrence-free survival for the entire cohort and relative to BCLC criteria. (a) RFS analysis for the entire cohort by the Kaplan–Meier method. (b) RFS analysis of Barcelona Clinic Liver Cancer (BCLC) 0, A, and B criteria by the Kaplan–Meier method

and both intrahepatic and extrahepatic recurrence (n = 32, 7.0%).

Hazard functions for recurrence were then examined. Among the entire cohort of patients, the hazard function for recurrence peaked at 2.4 months (peak rate: 0.0384) followed by a gradual decrease and long hem to the right (Fig. 2a). The hazard rates were then stratified by different clinical factors and demonstrated different dynamics of recurrence. When RFS curves based on BCLC staging were analyzed, BCLC 0 patients demonstrated a recurrence peak at 7.2 months (peak rate: 0.0170), while BCLC A patients had the earliest peak at 2.4 months (peak rate: 0.0365), which gradually decreased with a long hem to the right. Patients within BCLC B criteria had 2 peaks; the first at 4.2 months (peak rate: 0.0565) and the second at 22.8 months (peak rate: 0.0417) (Fig. 2b).

RFS curves of TBS subgroups were then evaluated. Three-year RFS among patients with TBS low, medium, and high was 73.7% (95% CI: 63–86), 50.6% (95% CI: 47–54), and 24.2% (95% CI: 17–35), respectively ($p < 0.001$) (Fig. 3a). Patients with higher TBS had consistently higher hazard rates of recurrence throughout the surveillance period. In fact, patients with high TBS had a hazard curve with the highest peak rate (0.0628) at 4.2 months, while patients with medium TBS had an earlier recurrence peak at 3.6 months, but a slightly lower peak rate (0.0368). Patients with low TBS had a relatively flat hazard curve with a peak at 7.8 months (peak rate: 0.0176) (Fig. 2c).

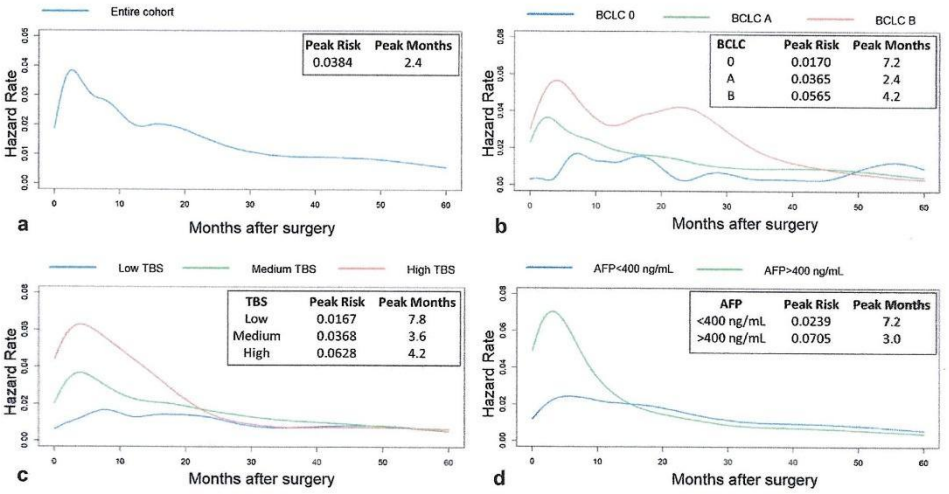

Figure 2 Smoothed Hazard Functions for the entire cohort and stratified by BCLC, TBS, and AFP. (a) Smoothed hazard functions for recurrence for the entire cohort. (b) Smoothed hazard functions for recurrence stratified by Barcelona Clinic Liver Cancer (BCLC) criteria. (c) Smoothed hazard functions for recurrence stratified by Tumor Burden Score (TBS). (d) Smoothed hazard functions for recurrence stratified by Alpha-fetoprotein (AFP), tracking instantaneous conditional recurrence at time t. Units of measure were events per month

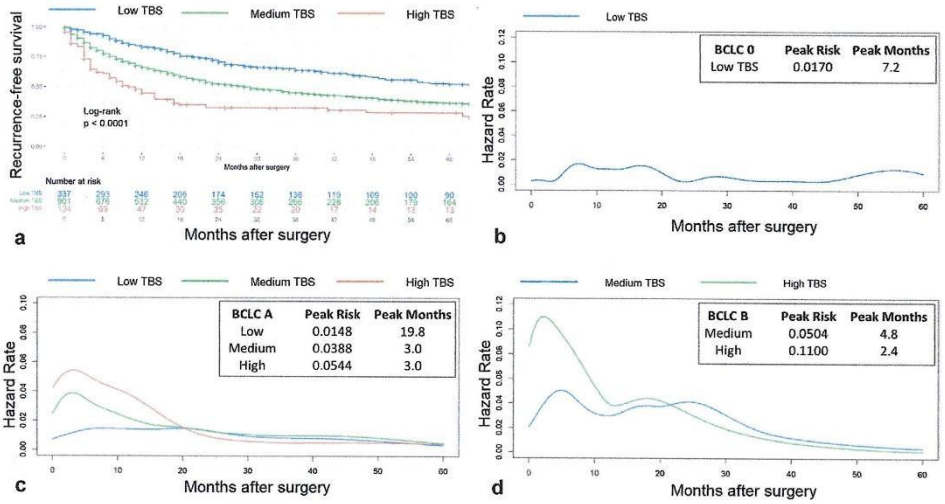

Figure 3 Recurrence-free survival relative to TBS and smoothed hazard functions for BCLC stratified by TBS. (a) RFS curves of Low, Medium, and High Tumor Burden Score (TBS) by the Kaplan–Meier method. (b) Low TBS smoothed hazard functions for recurrence among patients with Barcelona Clinic Liver Cancer (BCLC) 0 criteria. (c) Smoothed hazard functions for recurrence stratified by TBS among patients with BCLC A criteria. (d) Low and Medium TBS hazard functions for recurrence among patients with BCLC B criteria, tracking instantaneous conditional recurrence at time t. Units of measure were events per month

TBS was further stratified by BCLC staging. BCLC 0 patients were only categorized as low TBS and demonstrated a peak at 7.2 months (peak rate: 0.0170) (Fig. 3b). BCLC A patients with medium and high TBS had hazard curves that peaked earlier (both at 3 months) with a more pronounced peak rate among patients with high TBS (peak rate: 0.0544) versus medium TBS (peak rate: 0.0388). Meanwhile, patients with low TBS had a delayed modest peak at 19.8 months (peak rate: 0.0148) (Fig. 3c). No patients classified as BCLC B had a low TBS. Patients classified as BCLC B with high TBS had a hazard curve with an earlier peak month and higher peak rate versus patients with medium TBS (peak month: 2.4 vs 4.8, peak rate: 0.1100 vs 0.0504, respectively) (Fig. 3d).

RFS curves were then evaluated after stratifying by AFP levels. Three-year RFS among patients with low AFP and high AFP was 52.6% and 36.3% (95% CI: 49–56, 31–42), respectively ($p < 0.001$) (Fig. 4a). Fig. 2d demonstrates the hazard functions for patients undergoing resection of HCC relative to AFP. The hazard curve for patients with low AFP peaked at 7.2 months with a peak rate of 0.0239 and a relatively smooth flat shape throughout the surveillance period. In contrast, patients with high AFP had a hazard curve that peaked sharply at 3.0 months (peak rate: 0.0705), after which the curve had a long hem to the right.

AFP levels were further stratified according to BCLC staging. BCLC stage 0 patients with low AFP demonstrated an oscillating hazard curve (peak rate: 0.0177 at 16.2 months), while high AFP demonstrated a curve with two peaks at 7.8 and 16.2 months with peak rates of 0.0230 and 0.0177 (Fig. 4b). Conversely, BCLC A patients with high AFP demonstrated a recurrence curve with a sharp hazard rate peak of 0.0722 at 3.0 months with a rapid decrease, while the hazard rate curve for patients with low AFP remained relatively stable during the surveillance time (peak rate: 0.0216 at 9.0 months) (Fig. 4c). As for BCLC B patients, patients with high AFP showed a recurrence curve with a peak at 3.0 months (peak rate: 0.0761) followed by a plateau and a decrease throughout the surveillance period. In contrast, patients with low AFP had a peak hazard rate at 5.4 months (peak rate: 0.0490) followed by a smoothed increase to a more modest second peak (peak rate: 0.0373) at 22.8 months and a long hem to the right (Fig. 4d).

Fig. 5 shows the hazard function for BCLC B patients stratified by both TBS and AFP levels, comparing patients with high TBS and high AFP versus medium TBS and low AFP. Patients with medium TBS and low AFP demonstrated a hazard curve with a peak at 5.4 months and a peak rate of 0.0459; patients with high TBS and high AFP demonstrated a sharper peak at 1.8 months with a peak rate of 0.1585.

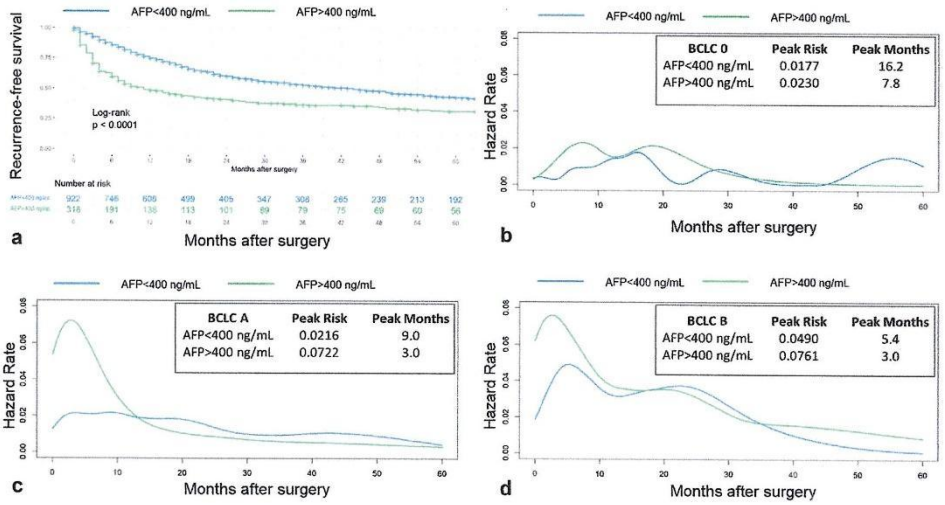

Figure 4 Recurrence-free survival relative to AFP and smoothed hazard functions for BCLC stratified by AFP. (a) RFS curves stratified by Alpha-fetoprotein (AFP) levels by the Kaplan–Meier method. Smoothed hazard functions for recurrence stratified by AFP levels among patients within (b) Barcelona Clinic Liver Cancer (BCLC) 0, (c) BCLC A, and (d) BCLC B criteria, tracking instantaneous conditional recurrence at time t. Units of measure were events per month

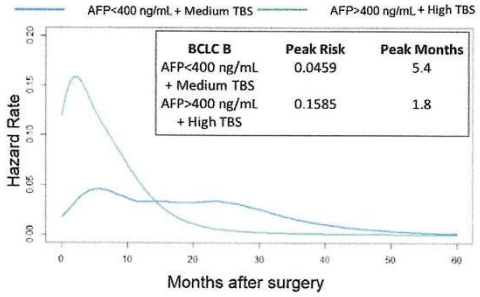

Figure 5 Smoothed hazard functions for BCLC B stratified by TBS and AFP. Smoothed hazard functions for recurrence stratified by Medium Tumor Burden Score (TBS) and Alpha-fetoprotein (AFP) < 400 ng/mL, and High TBS and AFP >400 ng/mL among patients within Barcelona Clinic Liver Cancer (BCLC) B criteria, tracking instantaneous conditional recurrence at time t. Units of measure were events per month

Discussion

Surgery remains the optimal potentially curative-intent treatment option for HCC.[11,15,22] However, recurrence is a major obstacle to long-term survival for many patients with HCC. Recurrence can vary significantly, presenting in a bimodal distribution, and there is often a lack of widespread adoption of optimal cut-off values to define early and late recurrence.[6,23,24] The current study was important because we used a large international database to demonstrate that the risk of recurrence following curative-intent resection of HCC was dynamic and influenced by multiple clinical factors. Specifically, using the hazard function, various recurrence hazard rates were characterized relative to BCLC staging, as well as TBS and AFP. In turn, the overall pattern of recurrence – including both the peak rate, as well as the peak timing – was defined among various cohorts of patients who had undergone curative-intent resection of HCC. These data may contribute to a better understanding of the dynamics associated with recurrence of HCC, thereby helping to predict recurrence, counsel patients, as well as guide future management decisions related to surveillance and future adjuvant therapy.[25]

Currently, there is no global consensus on optimal post-operative surveillance for patients with HCC. In fact, over the last two decades, more than 20 comprehensive guidelines for HCC have been published.[10–12] Despite the plethora of guidelines, empiric data on the peak rate and timing of recurrence following curative-intent resection of HCC have been lacking, leading to ongoing controversy regarding post-operative surveillance strategies.[10–12] For example, imaging studies and AFP are recommended every 3–6 months in the first two years, followed by every 6–12 months according to the NCCN guidelines.[13] In contrast, the Japanese Society of Hepatology recommends a surveillance interval of 3–4 months in the first year and suggests

CT/MRI every 6–12 months.[14] Meanwhile, the European Association for the Study of the Liver recommends a standard surveillance interval of 3–4 months in the first year.[15] None of these guidelines have been informed by empiric data regarding the relative risk of recurrence at different times in the post-operative setting. In addition, tailored surveillance strategies based on *a priori* risk of recurrence related to differences in BCLC staging, TBS, or AFP levels have not been proposed.

Data from the current study indicated that recurrence predominantly occurred within the first year following surgery, yet differed markedly according to BCLC stages. Specifically, patients who had BCLC 0 HCC were noted to have a recurrence hazard curve that remained relatively low with a stable hazard rate over the entire 5-year surveillance period. In contrast, patients with BCLC A disease had a recurrence hazard curve with the earliest peak rate that then gradually decreased with a long hem to the right; interestingly, patients within the BCLC B criteria demonstrated a curve with two distinct peaks (Fig. 2). Previous studies have noted varying hazard recurrence functions among patients with colon and breast cancer.[17,18] In particular, patients with non-metastatic colorectal cancer patients tended to recur within two years and recurrence rates differed according to the stage. Stage III patients had an earlier peak (11.6 months) and a peak rate of 0.0105, while patients with stage II disease had a delayed peak (13.7 months) with a peak rate of 0.0046; patients with stage I colon cancer had a relatively flat and consistently low hazard curve.[17] In a separate study, patients with non-metastatic breast cancer were noted to have the highest hazard for recurrence during the first five years with a peak in the first two years.[18] Collectively, the data strongly suggest that recurrence is heterogeneous phenomenon that varies among patients based on clinical factors. As such, a more nuanced understanding of the hazard, peak rates, and timing of recurrence needs to be considered by providers in the post-operative setting to inform care.

Patients with BCLC B HCC have traditionally not been recommended to undergo surgical resection according to the algorithm.[26] BCLC B stage disease can represent heterogeneous disease biology and some investigators have advocated for resection of select patients. For example, in a propensity score-matched analysis of BCLC B patients, Hsu et al. reported a 5-year survival of 43% among patients who underwent resection versus only 15% for those individuals treated with TACE.[27] Additionally, a recent meta-analysis demonstrated a survival benefit of resection versus TACE for patients with BCLC B/C HCC.[28] Our group has advocated for the use of TBS and AFP to better define which cohort of patients with intermediate/advanced HCC may most benefit from resection.[29] In fact, patients with BCLC B HCC with medium TBS had better survival than patients with BCLC A HCC with a high TBS.[20] Interestingly, in the current study, BCLC B patients with medium TBS had delayed recurrence (peak rate: 0.0505 at 4.8 months) compared with BCLC A patients who had high TBS (peak rate: 0.0544 at 3.0 months). The "Kinki criteria" have also been proposed to subdivide BCLC B patients further into B1, B2, and B3 based upon liver function and tumor status; B1 tumors should undergo resection given the well-preserved liver function, while B2/B3 tumors should be managed with ablation, TACE or systemic therapy.[30] Interestingly, BCLC A patients demonstrated an earlier recurrence peak time compared with BCLC B patients. The reasons for this finding were likely multifactorial and possibly related to differences in patient selection, underlying tumor-specific factors, as well as treatment strategies. For example, despite being designated as a "lower" stage, BCLC A had a higher incidence of poor/undifferentiated grade tumors (n = 403, 46.1% vs n = 53, 39.0%, p = 0.122), hepatitis B infection (n = 315, 37.5% vs n = 28, 21.9%, p < 0.001), and tumor necrosis (n = 203, 22.8% vs n = 29, 21.2%, p < 0.001) compared with BCLC B patients – all surrogates for tumor aggressiveness.[31–33] Moreover, BCLC A patients less often received adjuvant systemic chemotherapy (BCLC A n = 54, 6.1% vs. BCLC B n = 16, 11.7%; p < 0.01).[34] In addition, the long study period (2000–2020) may have contributed to these findings. In particular, the quality of imaging to diagnose and stage HCC has improved over time.[35] As such, it was possible that patients classified as BCLC A in the early years may have been under-staged, due to the presence of multiple clustered lesions interpreted as a single tumor by lower resolution imaging methods.

In the current study, the bimodal distribution of HCC recurrence among patients with BCLC-B HCC is perhaps not surprising, given the heterogeneity of this patient population, as well as the traditional early and late bimodal distribution of HCC recurrence. While the early recurrence peak may represent "true" recurrence, the second peak may represent "de novo" HCC development in the liver. Similar to TBS, we observed high hazard rates for recurrence clustered into the first year of post-operative follow-up among patients with high AFP levels. In fact, patients with high AFP presented with the highest hazard peak rate, which was almost 3-fold higher than patients with low AFP. Subgroup analyses stratified by BCLC stage confirmed that TBS and AFP were independent predictors for RFS and had a synergistic impact on risk of recurrence.[29,36–38]

Data from hazard function analyses can offer useful guidance for individual surgical decision-making, as well as planning surveillance imaging. While patients at the highest risk of recurrence should undergo more intensive surveillance in the immediate post-operative period, individuals who are more likely to have delayed recurrence may undergo less rigorous surveillance.[39,40] The goal of surveillance is to detect recurrent disease at the earliest possible stage. To this point, Xu et al. used six months interval surveillance, consisting of abdominal imaging and/or AFP measurement, and reported that compliance with surveillance was an independent predictor of OS.[41] These data suggest that postoperative surveillance does impact long-

term outcomes. As such, the present findings can better inform providers about the timing, rate, as well as overall odds of recurrence – especially relative to tumor-specific factors such as BCLC, TBS, and AFP. Not only may these data lead to more tailored surveillance strategies, but this information may help direct which patients are at the highest risk of recurrence and therefore may benefit from adjuvant treatment.

Several limitations should be considered in this study. Given the retrospective design, selection bias may have impacted which patients were offered surgery. Furthermore, while the multi-institutional nature of the cohort was a strength, surgical technique, patient selection, and treatment strategies may vary between individual centers. Moreover, surveillance protocols may vary among these international centers. Information about which guidelines were used to direct surveillance was not available and compliance with specific surveillance protocols over the entire study period was not known due to the retrospective nature of the study. Future studies will need to investigate hazards of recurrence among groups of patients with different clinicopathologic, geographic, and molecular HCC characteristics, as well as assess the performance of prediction tools to inform surveillance using various methodological approaches including decision curve analyses.

In conclusion, recurrence hazard rates for HCC varied substantially relative to both time and intensity/peak rates. TBS and AFP markedly impacted the hazard risk of recurrence, as well as the timing and peak rates of recurrence, among patients with different BCLC stage diseases. While patients with BCLC 0/A disease were generally at low risk of recurrence – and therefore may need less surveillance – patients with high TBS and/or AFP require enhanced surveillance even if the patients have early BCLC disease. For BCLC B patients, short-interval surveillance should be recommended during the first three years, as this time interval represented the highest chance for recurrence.

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Disclaimer

None.

Conflicts of Interest

None to declare.

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6.2. Artigo 2

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

TBS-Based Preoperative Score to Predict Non-transplantable Recurrence and Identify Candidates for Upfront Resection Versus Transplantation for Hepatocellular Carcinoma

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ABSTRACT

Background. Recurrence following liver resection (LR) for hepatocellular carcinoma (HCC) can be as high as 50–70%. While salvage liver transplantation may be feasible, patients may develop a non-transplantable recurrence (NTR) (recurrence beyond Milan criteria). We sought to identify preoperative risk factors to predict NTR after resection.

Patients and Methods. Patients who underwent curative-intent LR for HCC were identified from a multi-institutional database. Preoperative factors associated with NTR were identified and a risk score model (NTR score) was developed and validated.

Results. Among 1620 patients, 842 (52.0%) developed recurrence; among patients with recurrence, NTR occurred in 341 (40.5%) with a median recurrence-free survival (RFS) of 30 months (24.7–35.3 months). On multivariable analysis, factors associated with NTR included alpha fetoprotein (AFP) > 400 ng/mL [hazard ratio (HR) 1.71, 95% confidence interval (CI) 1.33–2.19], albumin–bilirubin grade (ALBI) (referent low, medium ALBI: HR 1.41, 95% CI 1.10–1.81, high ALBI: HR 2.47, 95% CI 0.91–6.68), and tumor burden score (TBS) (referent low, high TBS: HR 2.55, 95% CI, 1.99–3.28). A simplified TBS-based NTR score was developed using the β-coefficients of each factor (C-index 0.68, 95% CI 0.65–0.71). Higher NTR score was associated with incrementally worse 5-year RFS (low 44.8%, medium 37.5%, high 24.5%) [area under the curve (AUC) 0.59] and increased incidence of NTR (low 13.7%, medium 25.4%, high 38.2%) (AUC 0.65) (both $p < 0.001$). Moreover, higher NTR score was associated with higher risk of extrahepatic recurrence (low 11.3%, medium 28.8%, high 37.5%) ($p < 0.001$).

Conclusion. NTR following curative-intent resection of HCC occurred in one in five patients. A simple TBS-based

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NTR score accurately predicted the risk of NTR and may help identify candidates for upfront resection versus transplantation.

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death, with its incidence projected to increase even further over the next decade.[1,2] Curative-intent treatment options typically include liver resection (LR) and liver transplantation (LT).[3] Given that chronic liver disease often accompanies HCC, LT has been advocated as the preferred treatment option, as both the tumor and underlying impaired liver are addressed.[4,5] Due to the scarcity of donor organs, remaining on the waitlist for LT may result in disease progression and dropout.[6] As such, LR may be a more timely and acceptable treatment, especially for individuals with well-preserved liver function.[6] However, recurrence following resection of even early-stage HCC may be as high as 70% at 5 years.[7,8] For patients with recurrence, treatment options may involve re-resection or ablation, while a subset of individuals may be candidates for salvage liver transplantation (SLT).[9,10] However, as many as 40% of patients who recur present with a non-transplantable recurrence (NTR).[11] In turn, the prediction of NTR risk at the time of initial presentation may be important in deciding between index LR or LT for the primary management of early-stage HCC. Although several authors have attempted to predict NTR on the basis of pathological factors, these postoperative risk scores miss the opportunity to help inform primary treatment selection.[12,13] As such, the prediction of NTR prior to index LR may allow for better patient selection at the time of initial presentation, thereby facilitating improved long-term outcomes.

Tumor Burden Score (TBS) is a new concept that combines diameter and number of lesions based on the Pythagorean theorem [TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2]. This metric characterizes tumor burden as a continuous variable facilitating improved prognostic stratification of patients.[14–16] Although initially developed and validated on the basis of postoperative pathologic parameters, TBS has since been demonstrated to be equally accurate in stratifying patients on the basis of preoperative cross-sectional imaging (radiological TBS).[17] In addition to morphology (e.g., tumor size and number), tumor biology is also important to estimating prognosis among patients with HCC. To that end, alpha-fetoprotein (AFP) has long been used as a serum biomarker of HCC disease aggressiveness.[18,19] In fact, some investigators have reported that AFP may be helpful to predict NTR following initial LR.[11,20] Other data have suggested that tumor size, multifocality, and fibrosis may also be associated with NTR.[21]

To date, however, there is no comprehensive tool to estimate NTR in the preoperative setting. As such, the purpose of the current study was to characterize and analyze patterns of recurrence after initial LR for HCC. In particular, using a large, international multi-institutional database, we sought to identify preoperative predictors of NTR including TBS and AFP to construct and validate a simple preoperative NTR risk model to optimize upfront treatment strategies for HCC. To facilitate clinical applicability, an easy-to-use online calculator of the NTR score was also developed.

PATIENTS AND METHODS

Study Population and Exclusion Criteria

Patients who underwent curative-intent resection for HCC between 2000 and 2020 were identified from an international multi-institutional database that included the following institutions (% of patients): The Ohio State University Wexner Medical Center, Columbus, OH, USA (6.9%), Keio University, Tokyo, Japan (3.5%), Eastern Hepatobiliary Surgery Hospital, Shanghai, China (24.6%), HC-UFMG, Federal University of Minas Gerais, Belo Horizonte, Brazil (1.8%), University of Verona, Verona, Italy (5.4%), Curry Cabral Hospital, Lisbon, Portugal (10.7%), APHP, Beaujon Hospital, Clichy, France (6.1%), Westhead Hospital, Sydney, Australia (5.5%), Stanford University, Stanford, CA, USA (5.7%), Fundeni Clinical Institute, Bucharest, Romania (4.8%), University of Ottawa, Ottawa, Canada (3.5%), The University of Sydney, School of Medicine, Sydney, Australia (2.0%), University of Colorado, Denver, Colorado, USA (3.0%), and Yokohama City University, Yokohama, Japan (16.5%). Patients who died within 90 days of surgery ($n = 52$), with missing data for the variables of interest ($n = 543$), macroscopic residual disease after resection (R2) ($n = 25$), and who underwent non-curative-intent surgery ($n = 64$) were excluded. Only patients older than 18 years were included, irrespective of multifocal disease or not. The study was approved by the institutional review board of the participating institutions.

Variables of Interest, Definition, and Outcomes

Variables of interest included patient demographic information [i.e., age, sex, Charlson comorbidity score (CCI), Scheuer Classification Stage and Grade, diabetes mellitus, chronic alcohol intake, baseline liver disease (i.e., fibrosis; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosis cholangitis), chronic viral hepatitis (hepatitis B virus and/or hepatitis C virus), and body mass index

(BMI)], laboratory data [serum AFP, ALBI (albumin–bilirubin), prothrombin time-international normalized ratio (PT-INR), and platelets (PLT)], and clinicopathological characteristics [Child–Pugh Classification, minimally invasive surgery, anatomical resection, major resection, diameter of the largest lesion (cm), number of lesions, liver capsule, perineural and lymphovascular invasion, tumor grade, recurrence site, time and number, and resection margin status]. TBS incorporated maximum preoperative tumor size and lesion number into the Pythagorean formula [TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2].[17] Patients were categorized as having a low or high TBS, based on a cutoff value (5.80) defined using AUC-receiver operating characteristic (ROC) in intracohort analysis that reflected the median TBS of this cohort (5.10) and that of previous studies;[16,22–24] AFP was classified as high when > 400 ng/mL, and ALBI as low, medium, and high (≤ -2.60, > -2.60 to ≤ -1.39, > -1.39, respectively) as previously described.[25,26] Liver resection was categorized as a major hepatectomy if ≥ 3 contiguous Couinaud liver segments were resected.[27] Liver inflammation was defined as Scheuer's inflammation grade (G2–4), and fibrosis as Scheuer's chronic stage (F4).[28]

The primary outcome was NTR, which was defined as recurrence beyond Milan criteria, characterized by one or more of the following tumor characteristics at the time of recurrence: single tumor > 5 cm, tumor number > 3, tumor number 2–3 but size > 3 cm, macroscopic vascular invasion, or extrahepatic recurrence.[29] The secondary outcome was recurrence-free survival (RFS), defined as the time elapsed between the date of LR and recurrence confirmed by biopsy or evidence of a suspicious lesion on imaging, or death from any cause.[15] After LR, patients were monitored every 3–4 months for the first 2 years, and every 6 months thereafter. During follow-up, patients were monitored by serum tumor markers and imaging examinations (ultrasound, computed tomography, and magnetic resonance imaging).

Statistical Analysis

Continuous variables were presented as medians [interquartile ranges (IQRs)] and compared with the Mann–Whitney U test, while categorical variables were reported as frequencies (%) and compared with the chi-squared or Fisher's exact test. The Kaplan–Meier method and log-rank test were used for recurrence and NTR analyses. Clinically relevant preoperative variables associated with recurrence and non-transplantable recurrence were selected based on previous literature.[11,21] Cox regression analysis was performed and variables with $p < 0.10$ in univariable model (Supplementary Table 1) were included in the multivariable model, with backward exclusion to identify predictors of RFS and NTR. A NTR risk score was developed based on the β-coefficients of variables independently associated with NTR (β low AFP: referent, β high AFP: 0.537; β low TBS: referent, β high TBS: 0.937; β low ALBI: referent, β medium ALBI: 0.344, β high ALBI: 0.903). Simplified points were assigned to each category as follows: low AFP = 0, high AFP = 1, low TBS = 0, high TBS = 1, low ALBI = 0, medium ALBI = 0.5, and high ALBI = 1. Summing up the points, the derived score was on a scale of 0.0 to 3.0, which was then divided, using cutoffs of 0.5 and 2.0 (low NTR score ≤ 0.5, medium NTR score > 0.5 and < 2.0, high NTR score ≥ 2.0) corresponding to the median value and 90th percentile.[15,17] The performance of the model was evaluated using Harrell's concordance index (C-index) and calibrated with a bootstrap sample of 5000 to decrease the overfit bias. The recurrence hazard function was utilized to plot hazard rates over time, and the kernel smoothing method was used to smooth estimates of hazard function from right-censored data.[30] The level of significance was set at $\alpha = 0.05$ for all statistical analyses. All statistical analyses were performed using SPSS software version 28.0 (IBM Corporation, Armonk, NY) and R version 4.2.0 (R Project for Statistical Computing, Vienna, Austria) packages.

RESULTS

Demographic Characteristics

A flowchart demonstrating how the cohort was derived is depicted in Fig. 1. Among 1620 patients who underwent curative-intent LR for HCC, median age was 64 years (IQR 64–65 years) and 1266 (78.2%) patients were male. Nearly one-third of patients had cirrhosis (Scheuer Classification Stage F4, $n = 209$, 28.7%); chronic liver disease (Scheuer Classification G2–4) was present in 161 (21.5%) individuals, and 902 (56.0%) had viral hepatitis. The vast majority had a well-compensated liver and were classified as Child–Pugh A ($n = 1467$, 97.0%). Overall, based on preoperative cross-sectional imaging, most patients had low TBS ($n = 916$, 56.5%). Median AFP was 20.0 ng/mL (IQR 4.0–401.3 ng/mL) and 424 (29.5%) patients had high AFP (> 400 ng/mL) (Table 1). Median ALBI was -2.73 (IQR -2.99 to -2.43). At time of surgery, 431 (35.5%) patients underwent a major hepatic resection; an R0 resection margin was achieved in 1427 (89.7%) patients. On final pathology, perineural invasion ($n = 24$, 4.3%), lymphovascular invasion ($n = 439$, 41.7%), and liver capsule involvement ($n = 426$, 35.4%) were present in a subset of patients. The median length of stay in the hospital was 10.0 days (IQR 6.0–14.0 days) and 448 (46.3%) patients experienced at least one postoperative complication (Clavien–

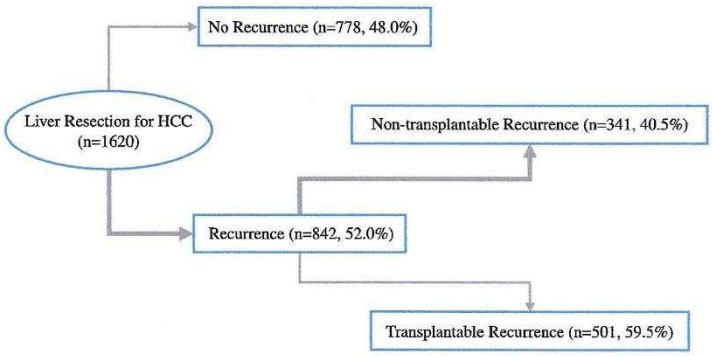

FIG. 1 Flowchart from the entire cohort of patients who underwent resection for hepatocellular carcinoma (HCC) to the target population of patients who experienced non-transplantable recurrence

Dindo I 17.9%, IIa 60.7%, IIb12.9%, IIIa 4.5%, IIIb 3.1%, IV 0.7%, and V 0.2%).

Of note, TBS was associated with several clinicopathologic characteristics. In particular, patients with high TBS were more likely to have a higher median ALBI (low TBS −2.75 versus high TBS – 2.68, $p < 0.002$). Moreover, perineural invasion (low TBS $n = 8$, 2.5% versus high TBS $n = 16$, 6.6%), lymphovascular invasion (low TBS $n = 196$, 32.7% versus high TBS $n = 243$, 53.6%), liver capsule involvement (low TBS: $n = 219$, 31.3% vs. high TBS: $n = 207$, 41.0%), and R1 margin status (low TBS $n = 74$, 8.3% versus high TBS $n = 90$, 12.9%) also increased with higher TBS. In addition, patients with a high TBS were more likely to present with a high preoperative AFP > 400 ng/mL (low TBS $n = 178$, 21.6% versus high TBS $n = 246$, 40.1%; $p < 0.001$).

Postoperative Outcomes

At a median follow-up of 37.0 months (IQR 15–67 months), the median RFS was 30 months (24.7–35.3 months) for the entire cohort, and 842 (52.0%) patients experienced a recurrence with a median time-to-recurrence of 15.0 months (IQR 5.0–41.0 months). Among the 842 patients who recurred, 341 (40.5%) had an NTR, while the other 501 (59.5%) patients recurred within the Milan criteria. Of note, patients with high TBS on initial HCC presentation were more likely to experience a recurrence (low TBS $n = 413$, 45.1% versus high TBS $n = 429$, 60.9%), as well as recur earlier (median time to recurrence, low TBS 19.0 months versus high TBS 9.0 months) with an extrahepatic component of disease (low TBS $n = 52$, 14.2% versus high TBS $n = 119$, 31.4%) (all $p < 0.001$) (Supplementary Table 2). The extent of intrahepatic recurrence relative to tumor size [median, low TBS 1.8 cm (IQR 1.1–2.8 cm) versus High TBS 2.0 cm (IQR 1.5–3.3 cm), $p = 0.002$] was also higher in patients with a high TBS HCC; in contrast, tumor number [median, low TBS 1.0 (IQR 1.0–2.0) versus high TBS 1.0 (IQR 1.0–3.0), $p = 0.045$] was comparable.

On multivariable analysis, several factors were independently associated with RFS. Specifically, after controlling for other clinicopathologic factors, Scheuer Classification Stage F4 (HR 1.97, 95% CI 1.36–2.87), AFP > 400 ng/mL (HR 1.58, 95% CI 1.06–2.34), and TBS (high TBS, HR 2.25, 95% CI 1.55–3.27) remained independent adverse predictors of overall RFS. When assessing NTR specifically, AFP > 400 ng/mL (HR 1.71, 95% CI 1.33–2.19) and TBS (low referent; high TBS HR 2.55, 95% CI 1.99–3.28) were both independent predictors of NTR (Table 2). However, rather than F4 disease, ALBI was associated with NTR (low referent; medium ALBI HR 1.41, 95% CI 1.10–1.81, high ALBI HR 2.47, 95% CI 0.91–6.68). The NTR risk score was developed based on the β-coefficients of variables independently associated with NTR. Harrell's C-index for the NTR score was 0.679 (95% CI 0.65–0.71), even after correction for optimism (0.679 in bootstrapping with 5000 iterations). The online model to predict NTR in patients undergoing resection for HCC is available at https://limaosu.shinyapps.io/henrique_NTR/.

NTR Score Influence on Survival and Clinicopathological Features

The NTR score was able to stratify patients relative to RFS, as well as NTR. Specifically, patients with incrementally higher NTR scores had worse median RFS [low NTR 46.0 months (37.4–54.6), medium NTR 23.0 months (16.1–19.9 months), high NTR 8.0 months (5.4–10.5 months)], as well as worse 3-year (low NTR 56.8% versus medium NTR 43.8% versus high NTR 28.4%) and 5-year (low NTR 44.8% versus medium NTR 37.5% versus high NTR 24.5%; AUC 0.59) RFS (all $p < 0.001$) (Fig. 2). In addition, NTR score was associated with a higher median size of the recurrent tumor [low NTR 1.7 cm (IQR 1.5–1.9

TABLE 1 Clinicopathologic characteristics of patients

Variables	Total ($n = 1620$)	Low TBS ($n = 916$)	High TBS ($n = 704$)	p value
Age (years)	64 (64–65)	64 (56–71)	64 (53–72)	0.340
Gender, male	1266 (78.2%)	761 (78.3%)	550 (78.2%)	0.994
BMI (kg/m^2)	25.0 (24.0–25.0)	24.8 (22.2–27.4)	24.2 (21.9–27.1)	0.104
Diabetes mellitus	422 (26.7%)	263 (29.4%)	159 (23.1%)	**0.005**
Chronic alcohol intake	371 (22.9%)	219 (23.9%)	152 (21.6%)	0.395
Charlson Comorbidity Index ≤ 9	1122 (98.8%)	619 (98.9%)	503 (98.6%)	0.699
Scheuer Classification Stage F4	209 (28.7%)	161 (40.8%)	48 (14.4%)	**< 0.001**
Baseline liver disease				**< 0.001**
Fibrosis	551 (34.0%)	352 (38.4%)	199 (28.3%)	
NASH	75 (4.6%)	51 (5.6%)	24 (3.4%)	
PSC	4 (0.2%)	4 (0.4%)	0 (0.0%)	
None	411 (25.4%)	168 (18.3%)	243 (34.5%)	
Viral liver disease	902 (56.0%)	577 (63.3%)	325 (46.4%)	**< 0.001**
Scheuer Classification Grade 2–4	161 (21.5%)	112 (27.5%)	49 (14.4%)	**< 0.001**
PLT $> 150 \times 10^3$ µL	842 (55.8%)	392 (45.5%)	450 (69.4%)	**< 0.001**
ALBI				0.051
Low	824 (63.0%)	499 (65.7%)	325 (59.4%)	
Medium	469 (35.9%)	252 (32.2%)	217 (39.7%)	
High	14 (1.1%)	9 (1.2%)	5 (0.9%)	
PT-INR > 1.1	161 (12.0%)	90 (11.8%)	71 (12.3%)	0.815
AFP > 400 ng/mL	424 (29.5%)	178 (21.6%)	246 (40.1%)	**< 0.001**
Child-Pugh Score A	1467 (97.0%)	835 (97.0%)	632 (97.1%)	0.909
Minimally invasive surgery	250 (15.5%)	209 (22.8%)	41 (5.8%)	**< 0.001**
Major resection	431 (35.5%)	136 (20.0%)	295 (55.3%)	**< 0.001**
Anatomical resection	956 (78.8%)	472 (69.4%)	484 (90.8%)	**< 0.001**
Liver capsule involvement	426 (35.4%)	219 (31.3%)	207 (41.0%)	**< 0.001**
Lymphovascular invasion	439 (41.7%)	196 (32.7%)	243 (53.6%)	**< 0.001**
Perineural invasion	24 (4.3%)	8 (2.5%)	16 (6.6%)	**0.019**
Margin status				**0.002**
R1	164 (10.3%)	74 (8.3%)	90 (12.9%)	
R0	1427 (89.7%)	822 (91.7%)	605 (87.1%)	
Grade				**< 0.001**
Well to moderate	1000 (63.5%)	604 (67.8%)	396 (57.9%)	
Poor to undifferentiated	575 (36.5 %)	287 (32.2 %)	288 (42.1%)	

Data presented as median (IQR) for continuous measures, and n (%) for categorical measures

BMI body mass index, *NASH* non-alcoholic steatohepatitis, *PSC* primary sclerosis cholangitis, *PLT* platelets, *ALBI* albumin-bilirubin, *INR* international normalized ratio, *AFP* alpha-fetoprotein, *TBS* Tumor Burden Score, *IQR* interquartile range

Bold font indicates statistical significance ($p < 0.05$)

cm) versus medium NTR: 2.1 cm (IQR 2.0–2.5 cm) versus high NTR 2.3 cm (IQR 2.0–3.0 cm)], as well as the likelihood to recur with multiple lesions (low NTR 38.0% versus medium NTR 52.3% versus high NTR 55.4%) (both $p < 0.001$). Furthermore, patients with a high NTR score more often experienced an extrahepatic site of recurrence following primary resection of the index HCC (low NTR 38.0% versus medium NTR 52.3% versus high NTR 55.4%; $p < 0.001$). Patients with a high NTR score also more often had a very-early recurrence (i.e., < 6.0 months of primary LR) (high NTR 64.5% versus medium NTR 31.4% versus low NTR 21.9%; $p \leq 0.001$) (Table 3). In turn, NTR score strongly correlated with the risk of NTR with the proportion of NTR incrementally increasing (low NTR 13.71% versus medium NTR 25.39% versus high NTR 38.18%; $p < 0.001$) (AUC 0.65) (Fig. 3). On

TABLE 2 Multivariable Cox regression analysis for preoperative factors associated with recurrence free survival (RFS) and non-transplantable recurrence (NTR)

Variables	RFS entire cohort			NTR		
	HR	95% CI	*p* value	HR	95% CI	*p*-Value
Age > 60 years	–	–	–	–	–	–
Scheuer Classification Grade 2–4	–	–	–	–	–	–
Scheuer Classification Stage F4	**1.97**	**1.36–2.87**	**< 0.001**	–	–	–
Viral liver disease	–	–	–	–	–	–
AFP > 400 ng/mL	**1.58**	**1.06–2.34**	**< 0.023**	**1.71**	**1.33–2.19**	**< 0.001**
PLT > 150 × 10^{y} μL	–	–	–	–	–	–
ALBI						
Low	Ref			Ref		
Medium	–	–	–	**1.41**	**1.10–1.81**	**0.006**
High	–	–	–	2.47	0.91–6.68	0.076
TBS class						
Low	Ref			Ref		
High	**2.25**	**1.55–3.27**	**< 0.001**	**2.55**	**1.99–3.28**	**< 0.001**

AFP alpha-fetoprotein, *PLT* platelets, *ALBI* albumin-bilirubin, *TBS* Tumor Burden Score, *RFS* recurrence-free survival

Bold font indicates statistical significance ($p < 0.05$)

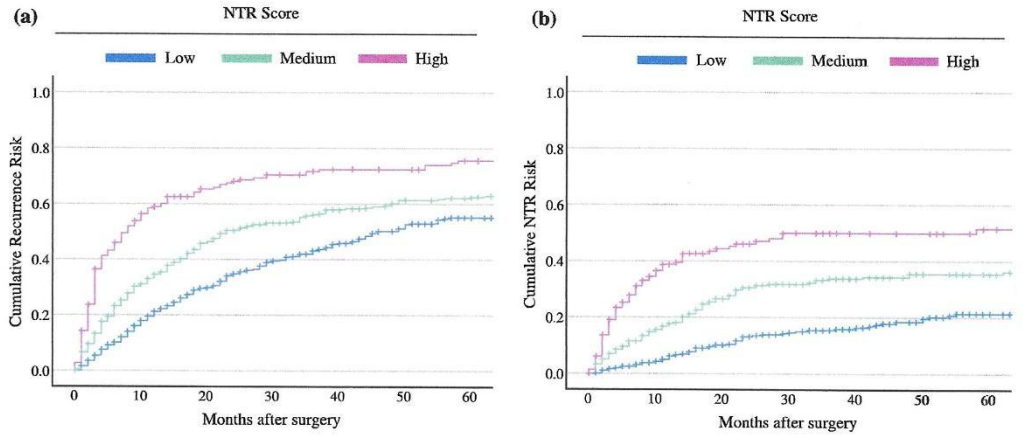

FIG. 2 Kaplan–Meier hazard curves demonstrate the cumulative risk of recurrence (**A**) and non-transplantable recurrence (NTR) (**B**) based on the non-transplantable recurrence score (NTR score)

multivariable analysis, the risk of NTR was associated with the NTR score (referent, low: medium NTR: HR 1.88, 95% CI 1.17–3.09 versus high NTR: 4.65, 95% CI 2.83–7.64) (both $p < 0.001$). On sensitivity analysis, each unit increase in the NTR score was independently associated with a 117% higher possibility of NTR (HR 2.17, 95% CI 1.68–2.80).

Hazard functions for NTR rate were then examined relative to NTR score. Overall, patients with a higher NTR score maintained a consistently higher hazard of NTR throughout the surveillance period. In contrast, patients with low NTR score had a relatively flat hazard curve (peak rate 0.0069 at 13.8 months). Interestingly, patients with medium NTR score had two peaks; the first NTR peak was at 3.0 months (peak rate 0.0177) and the second peak at 16.2 months (peak rate 0.0156). In comparison, patients with high NTR score had a single peak which was substantially greater when compared with low or medium NTR score (0.0514), and occurred very early at 3.0 months, with a long hem to the right (Fig. 4).

TABLE 3 Patterns of recurrence according to preoperative non-transplantable recurrence score (NTR score)

Variables	NTR score			*p* value
	Low	Medium	High	
Median RFS (months)	46 (37.4–54.6)	23 (16.1–29.9)	8 (5.4–10.5)	**< 0.001**
3-Year RFS	56.8%	43.8%	28.4%	**< 0.001**
5-Year RFS	44.8%	37.5%	24.5%	**< 0.001**
Recurrence				**< 0.001**
Yes	247 (45.2%)	243 (54.1%)	155 (70.5%)	
No	300 (54.8%)	206 (45.9%)	65 (29.5%)	
Recurrence category				**< 0.001**
Transplantable	172 (69.6%)	129 (53.1%)	71 (45.8%)	
Non-transplantable	75 (30.4%)	114 (46.9%)	84 (54.3%)	
Recurrence site				**< 0.001**
Intrahepatic	197 (88.7%)	141 (71.2%)	85 (62.5%)	
Extrahepatic	25 (11.3%)	57 (28.8%)	51 (37.5%)	
Recurrence number				**0.004**
Single	119 (62.0%)	72 (47.7%)	41 (44.6%)	
Multiple	73 (38.0%)	79 (52.3%)	51 (55.4%)	
Recurrence time				**< 0.001**
Very early (< 6 months)	53 (21.9%)	99 (31.4%)	98 (64.5%)	
Early (6–24 months)	113 (46.7%)	100 (41.8%)	43 (28.3%)	
Late (> 24 months)	76 (31.4%)	40 (16.7%)	11 (7.2%)	
Recurrence size, cm, median (IQR)	1.7 (1.5–1.9)	2.1 (2.0–2.5)	2.3 (2.0–3.0)	**< 0.001**

NTR non-transplantable recurrence, *IQR* interquartile range, *RFS* recurrence-free survival
Bold font indicates statistical significance ($p < 0.05$)

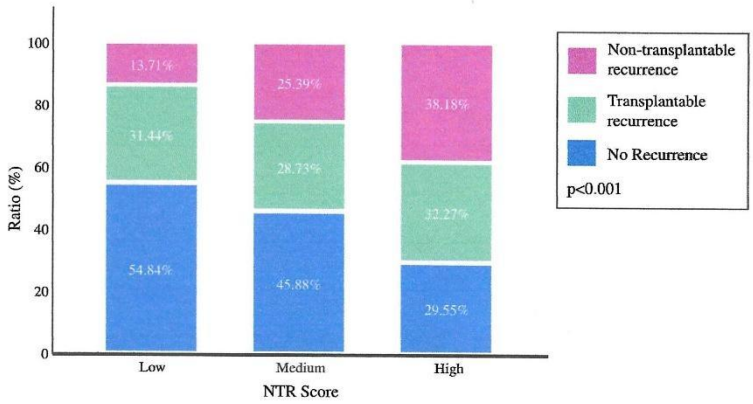

FIG. 3 Recurrence patterns stratified by the non-transplantable recurrence (NTR) score after curative-intent surgical resection for hepatocellular carcinoma

DISCUSSION

HCC is a complex disease with carcinogenesis frequently compounded by impaired underlying liver parenchyma.[3,31] Surgery remains the mainstay of treatment with several previous studies and meta-analyses that compared primary LT versus LR.[2,6,12,32–34] Overall, data from the literature have favored upfront LT as this therapeutic approach treats both the tumor and the underlying carcinogenic environment, thereby resulting in better RFS.[2,6,12,33,34] The shortage of organs is a major challenge, however, to utilize LT due to demand and limited donors, which can result in dropouts from the waiting list with possible disease progression.[2,3,6,12] In this context, LR is often employed as a curative-intent option, despite its being associated with a markedly higher risk of recurrence

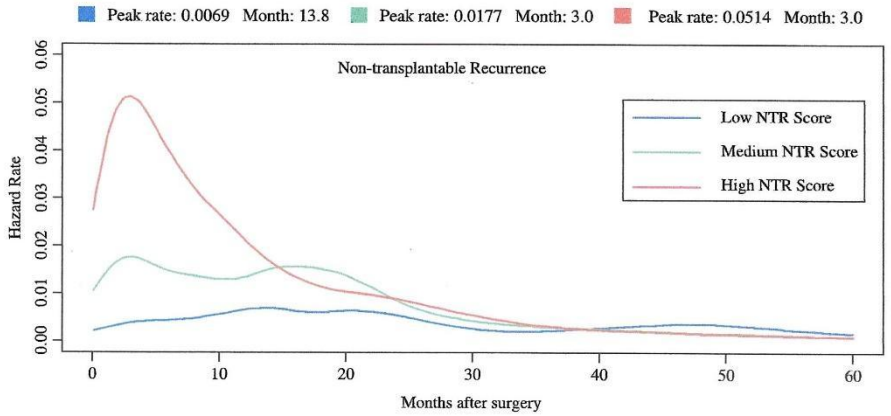

FIG. 4 Smoothed hazard functions for non-transplantable recurrence (NTR) stratified by non-transplantable recurrence score (NTR score), tracking instantaneous conditional NTR at time *t*. Units of measurement were events per month

(up to 70%) versus LT (10–20%).[7,35] In turn, primary resection with subsequent SLT has been advocated as a possible therapeutic strategy.[36] To ensure SLT, patients who undergo index LR require strict surveillance to detect recurrence at an early stage to prevent progression to NTR.[13] The current study was important because we developed a preoperative risk model to predict the development of NTR; in turn, these data may be used to guide the choice of treatment strategy, as well as postoperative surveillance regimens. In particular, by utilizing a large international multi-institutional database, we developed and validated a simple preoperative risk score for NTR, which was made available as an online easy-to-use calculator, which successfully stratified patients relative to RFS and NTR. Of note, patients with a higher NTR score had an incrementally higher risk of NTR following index resection of HCC (low 13.71%, medium 25.39%, high 38.18%, $p < 0.001$) (AUC 0.65), with a 117% higher hazard of NTR for each unit increase. Of note, the NTR score was also associated with an incrementally higher incidence of recurrence (5-year RFS: low NTR 44.8% versus medium NTR 37.5% versus high NTR 24.5%, $p < 0.001$) (AUC 0.59), particularly larger, earlier, multiple, and systemic recurrences. Moreover, hazard functions for NTR rates demonstrated that patients with a high NTR score had the highest risk of recurrence marked by the greatest hazard rate peak (0.0514), as well as the earliest recurrence time (3.0 months).

High rates of NTR are a major concern regarding the success of upfront LR. Therefore, predicting the risk of NTR at the time of initial presentation may optimize decision-making regarding index LR versus LT for the primary management of early-stage HCC. In line with previous studies, the current study noted an overall 52% incidence of recurrence and, of particular note, the NTR rate was 40.5% among patients who experienced a recurrence.[11,21] The relatively high rate of NTR further highlights the need to preoperatively stratify the overall risk and nature of recurrence in patients with HCC. Although previous models aimed at predicting NTR relied on pathological features, risk models based on preoperative variables may offer greater clinical utility to guide treatment decisions on primary treatment selection and postoperative surveillance strategies.[12,13,37] Of note, the role of preoperative AFP levels to stratify patients relative to NTR risk has been a topic of interest.[11,20] Furthermore, tumor size, multifocality, and fibrosis has also been identified as independent adverse prognosticators for NTR.[21] The optimal initial management of patients with HCC to prevent NTR remains, however, a subject of debate. As such, the NTR score was developed using preoperative variables that are routinely assessed in a clinical setting and can be easily computed using the provided online calculator. The incorporation of radiological TBS, AFP, and ALBI enabled the development of a holistic and accurate prediction model. In particular, the NTR score accurately stratified the risk of NTR.

Size and number of tumors are known predictors of tumor recurrence and worst outcomes,[17,38] with TBS more recently being proposed as a comprehensive continuous metric of tumor morphology that effectively stratified patients with HCC relative to prognosis.[15] Data from the current study demonstrated that patients with high TBS on initial HCC presentation were more likely to recur, as well as recur earlier at an extrahepatic site. Moreover, higher grades of TBS were associated with a higher incidence of

NTR. These results are in line with the bimodal distribution of HCC recurrence, in which early recurrence is generally a result of a residual tumor, whereas late recurrence is largely due to multicentric carcinogenesis.[37] In addition, elevated preoperative AFP (> 400 ng/mL) is widely recognized as a biomarker of HCC tumor aggressiveness and unfavorable prognosis. Furthermore, AFP has been demonstrated to dictate worse outcomes synergistically relative to TBS.[18,19,39] In line with previous studies, both elevated AFP (HR 1.58, 95% CI 1.06–2.34), and high TBS (high TBS HR 2.25, 95% CI 1.55–3.27) were identified as independent adverse prognostic factors for RFS. In particular, both elevated AFP (HR 1.71, 95% CI 1.33–2.19) and high TBS (HR 2.55, 95% CI 1.99–3.28) also were associated with a higher risk of developing NTR. Notably, underlying liver dysfunction can contribute to a carcinogenic microenvironment and subsequent de novo tumor development. As such, metrics that accurately and objectively quantify the impairment of liver function have marked applicability in risk scores. The ALBI grading system has been proposed as an alternative to the widely adopted Child–Pugh classification. ALBI is a simpler and more objective metric to assess liver function, as it eliminates subjective variables such as degree of encephalopathy and ascites.[40] Of note, the use of ALBI to quantify liver dysfunction has been endorsed by the recently updated Barcelona Clinic Liver Cancer (BCLC) guidelines.[41] In the present study, a higher ALBI grade was associated with a higher risk of NTR (low referent, medium ALBI: HR 1.41, 95% CI 1.10–1.81, high ALBI: HR 2.47, 95% CI 0.91–6.68). As such, the results highlight the synergistic effect of poor tumor morphology, tumor biology, and underlying liver dysfunction to dictate poor HCC outcomes.

Overall, the NTR score is a simple composite of assessable preoperative markers of tumor morphology, tumor biology, and liver function—the main determinants of outcomes relative to HCC. In fact, our model revealed strong discrimination to identify patterns of recurrence, as well as an incrementally increased risk of NTR. Specifically, the high rates of recurrence emphasize the need for stricter surveillance with the goal of reducing progression to NTR. However, the results suggested that aggressiveness of tumor biology might dictate a need for stricter surveillance strategies and proportionally more aggressive treatment. This was evidenced by the fact that patients with a higher NTR score were at a higher risk of developing larger, earlier, systemic, and multiple recurrences. The decision-making process for index LR versus LT is complex and involves a myriad of variables that extend beyond organ availability only. For example, geographic region, as well as institution capabilities and policies may also play important roles in the decision-making process.[42,43] Moreover, the patient's underlying clinicopathological characteristics and the surgeon's expertise are also important factors. Therefore, results from the current study serve to help inform the complex surgeon- and patient-specific decision-making related to resection versus transplantation for HCC. By helping identify a subset of patients at a disproportionate risk of worse recurrence, NTR score may help inform a more tailored treatment strategy. In particular, the results suggest that upfront transplantation among patients with high NTR is preferred, as well as enhanced surveillance for those individuals treated with LR. In addition, patients with high NTR treated initially with LR may benefit in the future from other adjuvant treatment modalities (i.e., immunotherapy, systemic chemotherapy) to optimize outcomes.[44] As such, the NTR score can help predict NTR, inform treatment strategies at diagnosis to improve patient selection and counseling, as well as guide optimal surveillance following resection of LR to reduce NTR.

Some limitations should be considered when interpreting the results of the current study. Owing to its retrospective nature, residual confounding due to selection bias was a possibility. Furthermore, although the international multi-institutional nature of the database was a strength, it contributed to possible variations in patient selection, operative techniques, and postoperative surveillance due to possible differences in guidelines followed by the various institutions. In addition, the database relied solely on patients who underwent curative-intent LR for HCC; as such, direct comparisons between LR and LT treatment strategies could not be made. Future studies to analyze early-stage recurrence patterns and compare outcomes of clinically similar patients undergoing LR versus LT, as well as external validation, are warranted.

In conclusion, NTR following curative-intent resection of HCC occurred in 1 in 5 patients. A higher NTR score was associated with adverse clinicopathological features, as well as an incrementally increasing incidence of recurrence and NTR. An easy-to-use online TBS-based NTR calculator predicted the risk of NTR and may be helpful to identify which patients should be considered for upfront resection versus transplantation.

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6.3. Artigo 3

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ORIGINAL ARTICLE

Tumor Burden Score and Serum Alpha-fetoprotein Subclassify Intermediate-Stage Hepatocellular Carcinoma

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Abstract

Background Resection of Barcelona Clinic Liver Cancer (BCLC) intermediate-stage hepatocellular carcinoma (HCC) remains controversial. While not recommended by the BCLC algorithm, some patients may indeed benefit from hepatectomy. We sought to identify that subset of patients who might derive long-term survival benefit from resection.

Methods Intermediate-stage HCC patients who underwent curative-intent resection were identified from an international multi-institutional database. Factors associated with long-term prognosis were identified using multivariate analysis and a risk score was developed and assessed.

Results Among 194 patients, most individuals had two tumors ($n = 123$, 63.4%) with a median size of 6.0 cm (IQR, 4.0–8.4) for a median tumor burden score (TBS) of 6.5 (IQR, 5.0–9.1); median alpha-fetoprotein (AFP) was 23.9 ng/mL (IQR, 5.0–503.2), and median overall survival (OS) was 69 months (IAR, 60.7–77.3). Factors associated with OS included AFP (referent ≤ 20 ng/mL, > 20 ng/mL: HR 1.78 95%CI, 1.09–2.89) and TBS (referent TBS ≤ 8.0, TBS > 8.0: HR 1.72 95%CI, 1.07–2.75). While 71 (36.6%) patients had neither risk factor, 79 (40.7%) and 44 (22.7%) had 1 or 2, respectively. A simplified score stratified patients relative to recurrence-free survival (RFS) (0: 33.6% vs. 1: 18.0% vs. 2: 14.7%) (AUC 0.60) and recurrence time (i.e., < 6 months after surgery) (0: 21.3% vs. 1: 43.1% vs. 2: 68.6%) (AUC 0.69) (both $p < 0.001$). Of note, a higher score was also associated with incrementally worse 5-year OS (0: 68.1% vs. 1: 61.0% vs. 2: 29.9%) (AUC 0.62) ($p < 0.001$).

Conclusion Long-term OS and RFS outcomes varied considerably. Using a simple risk score, patients with low AFP and low TBS were identified as the subset of individuals most likely to benefit from resection.

Keywords Intermediate-stage hepatocellular carcinoma · BCLC B · Tumor burden score · Alpha-fetoprotein · Multi-institutional database

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Introduction

First proposed in 1999, the Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma (HCC) remains one of the most widely utilized guidelines to predict prognosis and guide management strategies.[1,2] BCLC B disease accounts for 20–30% of all patients with HCC, yet includes a heterogeneous population of individuals ranging from those with preserved liver status and early-stage tumors to patients with extensive multifocal disease in the setting of cirrhotic parenchyma.[2,3] The heterogeneity among patients has led to persistent controversy on the use of the BCLC algorithm as it can deviate from actual clinical practice.[4] For example, over the past several decades, several groups have proposed different subclassification criteria for patients with HCC,[5–7] noting the feasibility of surgical resection for select patients with advanced disease.[8–10] Of note, many of these proposed systems include AFP levels, tumor size, and/or tumor number.[11] In particular, the most recent updated version of the BCLC staging stratified patients with intermediate-stage disease according to tumor burden and liver function.[12] However, the usefulness of these subclassifications has remained controversial.[13]

Alpha-fetoprotein (AFP) has been a long-standing surrogate of HCC tumor biology and elevated serum levels have been correlated with poor prognosis.[14] More recently, our research group has popularized the use of tumor burden score (TBS) to stratify patients with HCC and has demonstrated acceptable long-term outcomes after resection of lower TBS HCC "beyond" BCLC criteria.[9] In fact, patients with BCLC B and medium TBS had better survival than BCLC A patients with high TBS.[15] Moreover, serum AFP and TBS may have a synergistic impact to predict worse outcomes among patients with low/medium TBS HCC.[16] Building on these previous findings, the objective of the current study was to examine the impact of these preoperative variables to subclassify patients with intermediate-stage HCC following surgical resection. In particular, using a large international multi-institutional database, the purpose of the present study was to analyze the prognosis of intermediate HCC patients after resection relative to preoperative serum AFP and TBS. We hypothesized that preoperative AFP and radiologic TBS may help identify that subset of patients with intermediate-stage HCC who might derive the most long-term survival benefit from surgical resection.

Materials and Methods

Study Population

Patients diagnosed with HCC who underwent liver resection between 2000 and 2020 were identified from a large international multi-institutional database (The Ohio State University Wexner Medical Center, Columbus, OH, USA; Keio University, Tokyo, Japan; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; University of Verona, Verona, Italy; Curry Cabral Hospital, Lisbon, Portugal; HC-UFMG, Federal University of Minas Gerais, Belo Horizonte, Brazil; APHP, Beaujon Hospital, Clichy, France; Westhead Hospital, Sydney, Australia; Stanford University, Stanford, CA, USA; Fundeni Clinical Institute, Bucharest, Romania; University of Ottawa, Ottawa, Canada; The University of Sydney, School of Medicine, Sydney, Australia; University of Colorado, Denver, CO, USA; Yokohama City University, Yokohama, Japan). Exclusion criteria included non-BCLC B patients, death within 90 days of surgery ($n = 14$), non-curative intent surgery, and missing data for the variables of interest. Of note, no patients who underwent curative-intent surgery had grossly positive (R2) surgical resection margins. The Institutional Review Boards of all institutions approved this study.

Variables and Definitions

Collected demographic variables were age, sex, ASA (American Society of Anesthesiology) score, cirrhosis, and chronic viral hepatitis (hepatitis B virus and/or hepatitis C virus). Laboratory data included serum AFP, ALBI (albumin–bilirubin), NLR (neutrophil to lymphocyte ratio), prothrombin time-international normalized ratio (PT-INR), and platelets (PLT). Relevant clinicopathological characteristics were Child–Pugh Classification, minimally invasive surgery, portal vein embolization, anatomical resection, major resection, AJCC (American Joint Committee on Cancer) T category, diameter of the largest lesion (cm), number of lesions, liver capsule involvement, perineural invasion, microvascular invasion, lymphovascular invasion, tumor grade, recurrence site, time and number, and resection margin status (i.e., R0, R1). Tumor burden score (TBS) was calculated applying the Pythagorean formula [TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2] on preoperative imaging data.[17] For dichotomization between low and high

TBS, and low and high AFP, the AU-ROC intra-cohort analysis provided the cutoff values. If three or more contiguous Couinaud liver segments were resected, it was considered a major hepatectomy.[18] Intermediate stage or BCLC B patients were defined as 2–3 nodules of at least 3 cm or 4 or more nodules, as previously described.[2] The primary outcome was overall survival (OS), defined as the time interval between the date of hepatectomy and the date of death, or last follow-up. The secondary outcome was recurrence-free survival (RFS), defined as the time elapsed between the date of liver resection and recurrence (positive biopsy or suspicious lesion on follow-up imaging). Surveillance after surgery utilized serum tumor markers and imaging studies, including ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). Generally, follow-up was carried out every 3–4 months in the first 3 years, then every 6 months until the fifth year, and then annually.

Statistical Analysis

Continuous variables were reported as median and interquartile range (IQR) and compared with the Mann–Whitney *U* test. Categorical variables were reported as frequency and percentage (%) and compared with the chi-square test or Fisher exact test, as appropriate. Survival and hazard functions for recurrence and death were depicted by the Kaplan–Meier method and comparison between groups was performed by the log-rank test. Significant variables on bivariate analysis ($p < 0.05$) were included in multivariate Cox proportional hazard regression analysis with backward exclusion. Various combinations of TBS and serum AFP (i.e., low and low, high and low, low and high, high and high) were analyzed and simplified into three categories considering the presence of a "high value" as a risk factor (i.e., 0, 1, or 2 risk factors). The level of statistical significance was set at $\alpha = 0.05$ for all statistical analyses. All analyses were performed using SPSS software version 28.0 (IBM Corporation, Armonk, NY) and R version 4.2.0 (R Project for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics of Entire Cohort and Subgroups

Among 194 intermediate-stage HCC patients who met inclusion criteria, median age was 66 years (IQR 57–72) and most individuals were male ($n = 164$, 84.5%) (Table 1). The vast majority of patients ($n = 177$, 98.3%) were classified as Child–Pugh A, while only 3 (1.7%) patients were Child–Pugh B. A minority of patients had an ASA score > II ($n = 54$, 36.0%). Overall, the presence of cirrhosis and viral hepatitis represented about one-half of the cohort ($n = 83$, 42.8%, and $n = 103$, 53.4%, respectively). Most patients had two tumors ($n = 123$, 63.4%) with a median size of 6.0 cm (IQR, 4.0–8.4) for a median tumor burden score (TBS) of 6.5 (IQR, 5.0–9.1); median AFP was 23.9 ng/mL (IQR, 5.0–503.2). When subdividing the cohort using the AU-ROC cutoff value for TBS (8.0), 128 (66.0%) patients were classified as low TBS and 66 (34.0%) patients as high TBS. In addition, using the serum AFP AU-ROC cutoff value (20 ng/mL), 93 (47.9%) patients had low AFP, while 101 (52.1%) patients had high AFP. Considering "high values" as risk factors, 71 (36.6%) patients had neither risk factor, while 79 (40.7%) and 44 (22.7%) had 1 and 2 risk factors, respectively. Perhaps not surprisingly, major hepatic resection was most common among patients with 2 risk factors; the relative proportion of individuals who underwent a major hepatectomy incrementally increased with the number of risk factors (0: $n = 19$, 31.7%; 1: $n = 27$, 45.3%; 2: $n = 26$, 72.2%) ($p < 0.001$). Similarly, several histopathological variables were noted to have an increased incidence concomitant with the number of risk factors (i.e., microvascular invasion, 0: $n = 24$, 41.4%; 1: $n = 31$, 55.4%; 2: $n = 24$, 77.4%, $p = 0.005$). In contrast, the proportion of patients who underwent an R0 resection incrementally decreased with a higher number of risk factors (0: $n = 65$, 91.5%; 1: $n = 68$, 86.1%; 2: $n = 32$, 74.4%), while the incidence of R1 increased (0: $n = 6$, 8.5%; 1: $n = 11$, 13.9%; 2: $n = 11$, 25.6%) ($p = 0.041$). On final pathological assessment, most tumors were well-to-moderately differentiated; of note, the proportion of HCC tumors that were poor-to-undifferentiated increased with higher number of risk factors (well/moderate vs. poor/undifferentiated: 0 = 57, 81.4% vs. 13, 18.6%; 1 = 49, 62.0% vs. 30, 38.0%; 2 = 27, 61.4% vs. 17, 38.6%, respectively; $p = 0.018$).

Association of AFP and TBS with Clinicopathological Features, OS, and Patterns of Recurrence

On multivariate analysis, preoperative factors that remained independently associated with OS included serum AFP (low AFP: referent; high AFP: HR 1.78, 95% CI, 1.09–2.89; $p = 0.021$) and TBS (low TBS: referent; high TBS: HR 1.72, 95% CI, 1.07–2.75; $p = 0.025$) (Table 2). A simple sum of these risk factors was then analyzed relative to different postoperative clinicopathological variables on multivariate cox regression. Of note, an increased number of risk factors (0 Factors: Referent; 1 Factor: HR 1.29, 95% CI, 0.73–2.29, $p = 0.337$; 2 Factors: HR 2.48, 95% CI, 1.36–4.54, $p = 0.003$), as well as margin status (R0: Referent; R1: HR 2.40, 95% CI, 1.26–4.56; p = 0.007), remained as independent predictors of OS. In particular, there was a markedly incremental increase in the hazard of death

Table 1 Clinicopathologic characteristics of patients according to the number of risk factors (high TBS and/or high AFP)

Variables	0 Factors ($n=71$, 36.6%)	1 Factor ($n=79$, 40.7%)	2 Factors ($n=44$, 22.7%)	p-value
Age, years	69 (67–72)	63 (61–69)	64 (62–68)	**0.033**
Gender, male	59 (83.1%)	66 (83.5%)	39 (88.6%)	0.692
ASA > II	18 (31.0%)	27 (43.5%)	9 (30.0%)	0.269
Cirrhosis	32 (45.1%)	38 (48.1%)	13 (29.5%)	0.122
Viral liver disease	39 (54.9%)	44 (56.4%)	20 (45.5%)	0.480
PLT > 150×10^3 μL	27 (40.3%)	34 (44.2%)	15 (41.7%)	0.896
ALBI	−2.76 (−2.85 to −2.66)	−2.67 (−2.73 to −2.59)	−2.61 (−2.84 to −2.35)	0.161
NLR	2.13 (1.87–2.44)	2.34 (2.00–2.56)	2.97 (2.46–4.49)	0.095
PT-INR > 1.1	5 (8.5%)	10 (15.2%)	6 (20.7%)	0.261
Child–Pugh Score				0.598
A	66 (98.5%)	75 (97.4%)	36 (100.0%)	
B	1 (1.5%)	2 (2.6%)	0 (0.0%)	
Portal vein embolization	4 (5.6%)	8 (10.1%)	5 (11.6%)	0.475
Minimally invasive surgery	6 (8.5%)	6 (7.5%)	1 (2.3%)	0.416
Major resection	19 (31.7%)	27 (45.3%)	26 (72.2%)	**<0.001**
Anatomical resection	47 (78.3%)	45 (72.6%)	33 (91.7%)	0.080
AJCC T stage				0.565
T1a/1b	22 (31.0%)	31 (39.2%)	15 (34.1%)	
T2/3/4	49 (69.0%)	48 (60.8%)	29 (65.9%)	
Liver capsule involvement	28 (48.3%)	33 (47.8%)	21 (61.8%)	0.363
Microvascular invasion	24 (41.4%)	31 (55.4%)	24 (77.4%)	**0.005**
Lymphovascular invasion	24 (41.4%)	30 (54.5%)	24 (77.4%)	**0.005**
Perineural invasion	1 (9.1%)	2 (9.5%)	2 (33.3%)	0.281
Margin status				**0.041**
R1	6 (8.5%)	11 (13.9%)	11 (25.6%)	
R0	65 (91.5%)	68 (86.1%)	32 (74.4%)	
Grade				**0.018**
Well to moderate	57 (81.4%)	49 (62.0%)	27 (61.4%)	
Poor to undifferentiated	13 (18.6%)	30 (38.0%)	17 (38.6%)	

P-values in bold font face signify statistical significance ($p < 0.05$). Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures

ASA, American Society of Anesthesiologists; *PLT*, platelets; *ALBI*, albumin-bilirubin; *NLR*, neutrophil to lymphocyte ratio; *PT-INR*, prothrombin international normalized ratio; *AJCC*, American Joint Committee on Cancer; *AFP*, alpha-fetoprotein; *TBS*, Tumor Burden Score; *IQR*, interquartile range

concomitant with the number of risk factors, particularly for high TBS/high AFP patients (Table 3). With a median follow-up of 32.5 (IQR 15.0–63.0) months, median OS was 69 (IQR 60.7–77.3) months for the entire cohort. Of note, 3-year (0: 77.6%; 1: 77.5%; 2: 47.8%) and 5-year (0: 68.1%; 1: 61.0%; 2: 29.9%) OS incrementally decreased in the presence of 0, 1, or 2 factors (AUC 0.62) ($p \leq 0.001$) (Fig. 1).

The number of prognostic risk factors was also associated with a higher hazard of recurrence. While median RFS was 14 (IQR 10.7–17.3) months for the entire cohort, 3-year (0: 38.8%; 1: 27.4%; 2: 14.7%) and 5-year (0: 33.6%; 1: 18.0%; 2: 14.7%) RFS incrementally decreased among patients with 0, 1, or 2 factors (AUC 0.60) ($p \leq 0.001$) (Fig. 2). Moreover, TBS and AFP were strongly associated with the timing and patterns of recurrence. In particular, most individuals ($n=24$, 68%) with 2 risk factors presented with very early recurrence versus patients with 0 risk factors who recurred presented with later recurrence ($n=37$, 78.8%). Furthermore, the proportion of very early recurrence incrementally increased in the presence of 0, 1, or 2 factors (21.3%, 43.1%, 68.6%, respectively; $p<0.001$) (AUC 0.69) (Fig. 3 and Supplementary Table 1).

Discussion

The BCLC staging system for HCC, which includes information on liver function, tumor size, and tumor number, has been widely adopted as a means to provide therapeutic guidance and estimate prognosis.[19] Patients with intermediate stage (BCLC B) HCC encompass a highly heterogeneous population, not

Table 2 Cox regression analysis for preoperative factors associated with overall survival

Variable	Bivariate			Multivariate		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Age	0.99	0.98–1.02	0.917	-	-	-
Cirrhosis	1.13	0.71–1.78	0.610	-	-	-
Viral liver disease	1.01	0.63–1.61	0.970	-	-	-
AFP						
Low	Ref			Ref		
High	**1.95**	**1.21–3.15**	**0.006**	**1.78**	**1.09–2.89**	**0.021**
PLT > 150×10^3 µL	0.95	0.58–1.54	0.824	-	-	-
PT-INR > 1.1	1.59	0.74–3.41	0.237	-	-	-
ALBI	1.83	0.99–3.38	0.053	-	-	-
NLR	1.08	0.95–1.22	0.234	-	-	-
TBS class						
Low	Ref			Ref		
High	**1.91**	**1.21–3.04**	**0.006**	**1.72**	**1.07–2.75**	**0.025**

P-values in bold font face signify statistical significance ($p < 0.05$)

AFP, alpha-fetoprotein; *PLT*, platelets; *PT-INR*, prothrombin-international normalized ratio; *ALBI*, albumin-bilirubin; *NLR*, neutrophil to lymphocyte ratio; *TBS*, Tumor Burden Score

Table 3 Cox regression analysis for factors associated with overall survival

Variable	Bivariate			Multivariate		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Microvascular invasion	1.77	0.96–3.24	0.066	-	-	-
Lymphovascular invasion	0.58	0.32–1.08	0.084	-	-	-
Perineural invasion	2.16	0.26–18.30	0.479	-	-	-
Liver capsule involvement	0.73	0.45–1.20	0.213	-	-	-
AJCC T stage						
T1a/1b	Ref					
T2/3/4	1.23	0.75–2.02	0.403	-	-	-
Margin						
R0	Ref			Ref		
R1	**3.14**	**1.69–5.82**	**< 0.001**	**2.40**	**1.26–4.56**	**0.007**
Grade						
Well to moderate	Ref					
Poor to undifferentiated	1.45	0.93–2.37	0.097	-	-	-
TBS and AFP						
0 risk factors	Ref			Ref		
1 risk factor	1.29	0.73–2.27	0.390	1.29	0.73–2.29	0.377
2 risk factors	**2.98**	**1.67–5.31**	**< 0.001**	**2.48**	**1.36–4.54**	**0.003**

P-values in bold font face signify statistical significance ($p < 0.05$)

AJCC, American Joint Committee on Cancer; *TBS*, Tumor Burden Score; *AFP*, alpha-fetoprotein

only regarding tumor burden but also hepatic functional reserve. For example, patients with BCLC B HCC may present with Child–Pugh scores of 5–9, tumors as few as two (if one > 3 cm) confined to one hemi-liver, or up to multiple tumors in both hemi-livers in the absence of vascular invasion and metastases. The estimated prognosis for patients in these very distinct subgroups may differ substantially, and consequently, so should their management. Given that patients with intermediate-stage HCC may benefit from surgical resection, it is important to identify means to select patients who would benefit the most from this therapeutic option.[13,20] The current study was important because, using a large international multi-institutional database, we sought to stratify BCLC B patient prognosis after liver resection relative to preoperative serum AFP and TBS. Specifically, we sought to identify that subset of patients with intermediate-stage HCC who might derive a long-term survival benefit from surgical resection, thus aiding surgeons to select patients for this treatment strategy. Of note, a

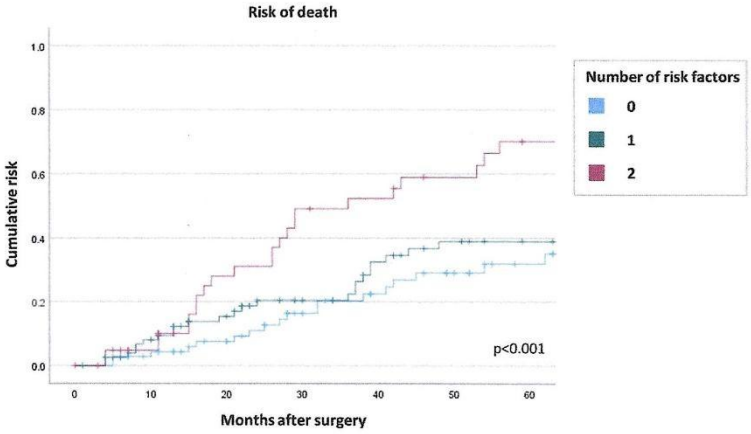

Fig. 1 Kaplan–Meier hazard curves demonstrate the cumulative risk of death based on the different number of risk factors (high tumor burden score, TBS; and/or high alpha-fetoprotein, AFP)

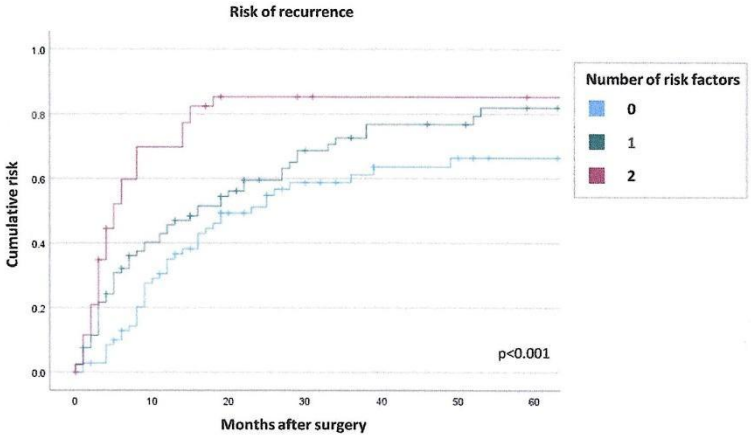

Fig. 2 Kaplan–Meier hazard curves demonstrate the cumulative risk of recurrence based on the different number of risk factors (high tumor burden score, TBS; and/or high alpha-fetoprotein, AFP)

simplified risk score was able to stratify patients relative to OS and RFS. In particular, a higher risk score was associated with incrementally worse 5-years OS (0 factors: 68.1% vs. 1 factor: 61.0% vs. 2 factors: 29.9%) (AUC 0.62) ($p<0.001$), as well as higher hazards of death (referent 0, 1 factor: 1.29 95%CI, 0.73–2.29 vs. 2 factors: 2.48 95%CI, 1.36–4.54; $p=0.003$). A higher risk score was also associated with worse RFS (0 factors: 33.6% vs. 1 factor: 18.0% vs. 2 factors: 14.7%) (AUC 0.60) and very early recurrence (i.e., <6 months after surgery) (0 factors: 21.3% vs. 1 factor: 43.1% vs. 2 factors: 68.6%) (AUC 0.69) (both $p<0.001$).

According to the BCLC guidelines, TACE and systemic therapy are the primary treatment strategies for BCLC B patients, yet many clinicians have questioned these recommendations.[10,13,21] In several large cohort studies, the OS of patients who received systemic therapy (i.e., SOFIA: 20.6; INSIGHT: 19.5; GIDEON: 15.6 months) was similar to individuals who underwent TACE.[22–24] Moreover, RFS was as low as 13.4 months, 9.1 months, and 7.4 months for individuals with 2, 3, and ≥4 nodules treated with TACE, respectively.[25] Several studies have demonstrated that TACE may not provide the most benefit for patients, although some authors report better outcomes for select patients treated with resection.[13,26,27] In fact, clinical practice often differs from the guidelines, and liver resection is used for HCC beyond BCLC criteria recommendations not infrequently.[28] To this point, several meta-analyses have noted superior outcomes among patients with BCLC B stage disease following resection compared with non-surgical therapy.[10,29] Furthermore, in a propensity score-matched analysis, Hsu et al. reported

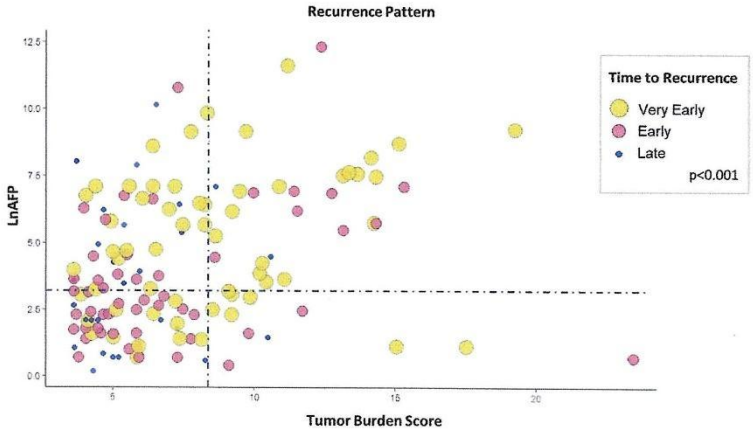

Fig. 3 Scatter plot of recurrence pattern according to recurrence time (very early, < 6 months; early, > 6 and < 12 months; and late, > 12 and < 24 months) stratified by tumor burden score (TBS) and serum logarithmic alpha-fetoprotein (LnAFP) after primary surgical resection for hepatocellular carcinoma (HCC). As the distribution of serum AFP was markedly skewed to the right, natural logarithm transformation was conducted to better portray distribution

a 5-year survival of 43% among resected individuals versus 15% among individuals treated with TACE.[30] In addition, one multicenter study that included 737 patients with BCLC B HCC who underwent liver resection had an overall 5-year survival of 57%. A similar 5-year OS of 52–55% has been reported using patient data from Asia, as well as large multi-institutional international cohorts of patients.[9,21] Similarly, the current study reported a 5-year OS of 56.3% and median RFS of 14.0 months for resected intermediate HCC. In light of these studies, liver resection for BCLC B HCC may be an appropriate—even preferred—treatment option in a select subset of patients with acceptable long-term outcomes.[31]

Better sub-stratification of patients within the BCLC B category has become a topic of great interest given the heterogeneity of this patient population and the BCLC exclusion of these individuals from surgical resection.[32] Only recently has the updated version of BCLC suggested stratifying intermediate-stage patients into three treatment groups, yet liver resection continues to be excluded as a therapeutic recommendation. These new BCLC sub-categories for intermediate-stage patients include individuals who meet the "Extended Liver Transplant Criteria,"[33] individuals with a preserved portal flow with tumors fit for TACE, and patients with diffuse, infiltrative, extensive HCC for whom systemic therapy is recommended.[12] Several research groups have proposed other sub-classifications of patients with BCLC B disease, such as the Bolondi system, as well as the KINKI and CHIP scores—although none have enjoyed widespread adoption due to being somewhat complicated and hard to apply.[5,6,34] In contrast, in the current study, we proposed a simply integer-based scoring system based on two factors—one related to tumor morphology (i.e., TBS) and the other biology (AFP). The score was able to successfully stratify patients relative to overall survival with a 3-year (0: 77.6%; 1: 77.5%; 2: 47.8%) and 5-year (0: 68.1%; 1: 61.0%; 2: 29.9%) OS that incrementally decreased in the presence of 0, 1, or 2 risk factors ($p < 0.001$) (Fig. 1).

Tumor morphology and biology are the important drivers of long-term outcomes. TBS has been proposed as a simple comprehensive metric that summarizes tumor morphology based on a continuous number that incorporates both tumor size and number using the Pythagorean theory.[17] Of note, tumor burden—as assessed by TBS—has been validated as a strong predictor of recurrence and worse survival outcomes.[15–17] In addition, AFP has long been considered a surrogate of tumor biology and has been associated with response to therapy, as well as long-term prognosis among patients with hepatobiliary tumors.[12,14,16,35–37] Recently, our group reported a synergistic impact of high TBS and high AFP among patients with HCC independent of tumor stage.[16] The current study builds on this previous work by focusing exclusively on patients with intermediate-stage BCLC B stage disease. By specifically investigating only BCLC B patients, we focused on the most controversial subset of patients relative to the indication for surgical resection; we were also able to tailor the analysis to identify optimal cut-off values for TBS and AFP in this specific population. Interestingly, both TBS and AFP were independent predictors of several adverse clinical-pathological factors (Table 3). Given that these pathological factors can only be ascertained after resection, preoperative radiologic TBS and serum AFP may act as powerful surrogates in the pre-operative setting to determine the likelihood of unfavorable pathologic characteristics.[38] In turn, perhaps not surprisingly, high TBS and high AFP were also each independent risk factors associated with adverse overall and recurrence-free survival (Table 2).

Recurrence remains a major challenge after resection of HCC. Data from the current study indicated that the risk of recurrence hazard dramatically increased in the presence

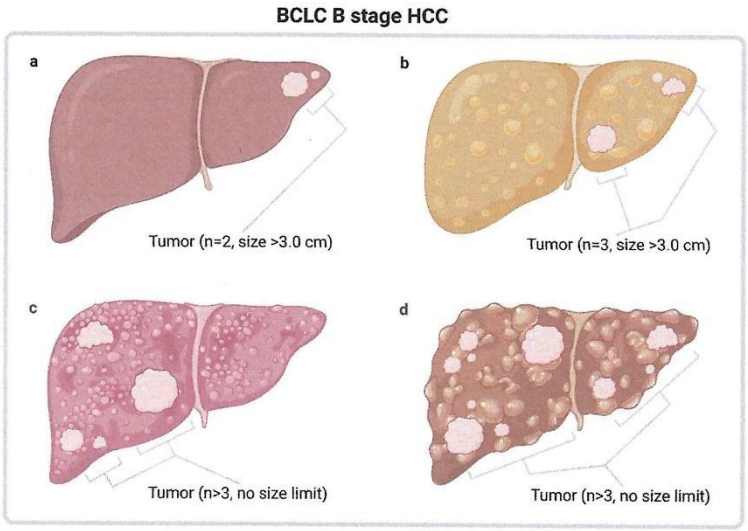

Fig. 4 Clinical scope of intermediate-stage hepatocellular carcinoma (HCC). BCLC B class encompass a heterogeneous group of patients with preserved liver function (Child–Pugh A or B), various possible HCC presentation, and potentially diverse underlying liver diseases, ranging from normal parenchyma (**a**) and steatosis (**b**) to fibrosis (**c**) and cirrhosis (**d**) (created with BioRender.com)

of 0, 1, or 2 risk factors (Fig. 2). While the reasons for this are likely multifaceted, a strong association between the number of risk factors and unfavorable clinicopathological features, such as microvascular and lymphovascular invasion and poor to undifferentiated grade, was noted (Table 1, Supplementary Table 1). In addition, a higher risk factor score was also associated with the timing of recurrence as patients with two risk factors were much more likely to experience a very early recurrence (0, 1, or 2 risk factors: 21.3%, 43.1%, 68.6%, respectively; $p < 0.001$) (Fig. 3). These data are consistent with the bimodal distribution of HCC recurrence in which early recurrence likely corresponds to "true recurrence" due to poor biology associated with the index HCC, while late recurrence represents de novo multicentric carcinogenesis.[39] As such, the use of this risk score may help identify patients with BCLC B disease that are at the greatest risk of recurrence, especially in the very early postoperative period.

Data from this study should be interpreted in light of several limitations. Due to the retrospective design, selection bias was possible. The international multi-institutional nature of the database was a strength; however, the utilization of data from multiple centers introduced the possibility of heterogeneity regarding patient selection, surgical procedures, and compliance with surveillance protocols. In addition, the current study included only patients who underwent curative-intent liver resection; thus, the findings may not be representative of all patients in the BCLC B population (Fig. 4).

Conclusion

In conclusion, patients with intermediate BCLC stage HCC had a highly heterogeneous prognosis with long-term overall and recurrence-free survival that varied considerably following curative-intent resection. Patients with low TBS and low AFP were identified as the subset of patients most likely to benefit from resection. In turn, the combination of TBS and AFP into a simple integer-based risk score performed well in stratifying patients with BCLC B HCC relative to overall and recurrence-free survival. In addition, the TBS-AFP tool categorized patients at the highest risk of recurrence, as well as identified individuals most likely to recur in the very early period following resection of BCLC B HCC. The use of this simple TBS-AFP risk score may help surgeons identify which patients with BCLC B HCC may benefit the most from surgical resection.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11605-022-05469-9.

Declarations

Conflict of Interest The authors declare no competing interests.

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6.4. Artigo 4

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RESEARCH ARTICLE

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TAC score better predicts survival than the BCLC following resection of hepatocellular carcinoma

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Abstract

Background: Heterogeneity in hepatocellular carcinoma (HCC) still exists within the Barcelona clinic liver cancer (BCLC) subcategories. We developed a simple model to better discriminate and predict prognosis following resection.

Methods: Patients who underwent curative-intent resection for HCC were identified from a multi-institutional database. Predictive factors of survival were identified to develop TAC (tumor burden score [TBS], alpha-fetoprotein [AFP], Child–Pugh CP]) score.

Results: Among 1435 patients, median TBS was 5.1 (interquartile range [IQR]: 3.2–8.1), median AFP was 18.3 ng/ml (IQR 4.0–362.5), and 1391 (96.9%) patients were classified as CP-A. Factors associated with overall survival (OS) included TBS (low: referent; medium: HR 2.26, 95% CI: 1.73–2.96; high: HR = 3.35,

95% CI: 2.22–5.07), AFP (<400 ng/ml: referent; >400 ng/ml: HR = 1.56, 95% CI: 1.27–1.92), and CP (A: referent; B: HR = 1.81, 95% CI: 1.12–2.92) (all $p < 0.05$). A simplified risk score demonstrated superior concordance index, Akaike information criteria, homogeneity, and area under the curve versus BCLC (0.620 vs. 0.541; 5484.655 vs. 5536.454; 60.099 vs. 16.194; 0.62 vs. 0.55, respectively), and further stratified patients within BCLC groups relative to OS (BCLC 0, very low: 86.8%, low: 47.8%) (BCLC A, very low: 79.7%, low: 68.1%, medium: 52.5%, high: 35.6%) (BCLC B, low: 59.8%, medium: 43.7%, high: N/A).

Conclusion: TAC is a simple, holistic score that consistently outperformed BCLC relative to discrimination power and prognostication following resection of HCC.

KEYWORDS

Barcelona clinic liver cancer, hepatocellular carcinoma, multi-institutional database, prognosis, resection, tumor burden score

1 | INTRODUCTION

Adequate staging is important to treat and stratify patients with hepatocellular carcinoma (HCC). To this end, the Barcelona Clinic Liver Cancer (BCLC) system has been widely adopted in the Western world as a means to risk stratify patients, as well as inform treatment strategies related to HCC.[1] Since the BCLC was first introduced in 1999, surgical practices have continually improved, therapeutic interventions have evolved, and selection of patients has become more sophisticated.[2] In turn, despite recent updates, the BCLC algorithm has been criticized for being too restrictive relative to curative-intent treatment recommendations. In particular, liver resection has long been argued to be a viable treatment option for individuals with intermediate-stage HCC, which is a deviation from BCLC recommendations.[3–5] In fact, the latest BCLC update still does not recommend liver resection beyond BCLC 0/A, despite increasing evidence of its feasibility and efficacy in selected patients.[6,7] Moreover, BCLC groups comprise a very heterogeneous population that may derive differential long-term benefits relative to varied treatment strategies. As such, better stratification of patients with intermediate stage HCC remains a topic of great interest to delineate who may most benefit from surgical resection.

Multiple alternative classifications have been proposed, which have either been independent or supplementary to the BCLC system.[8–12] None of these previous classifications have experienced worldwide adoption and an easy-to-use, clinically relevant stratification scheme for patients with intermediate stage HCC remains not defined. For example, BCLC score components are largely based on liver function and arbitrary values for tumor size and number, characterized in a dichotomous manner, that fails to provide a holistic assessment. The latest BCLC update attempted to address these shortcomings by incorporating assessment of liver decompensation (e.g., jaundice, ascites, encephalopathy) independent of the Child–Pugh (CP) with substratification based on the albumin–bilirubin (ALBI) score; in addition, the use of serum alpha-fetoprotein (AFP) was added regardless of tumor burden.[7] In an effort to improve prognostic prediction, the updated BCLC sacrificed simplicity by adding factors to reflect clinical complexity and nuances related to many patients who have HCC.

The heterogeneity in treatment benefit from resection, as well as treatment stratification of patients with HCC, is likely related to differences in tumor morphology, tumor biology, and liver function. As such, we sought to stratify the prognosis of patients with HCC using a simple scoring system composed of tumor burden score (TBS), serum AFP, and CP, which reflect each of these factors, respectively. In particular, TBS has been validated as a simple composite metric of overall tumor size and number[6]; moreover, AFP has been associated with HCC prognosis and CP is the traditional means to assess liver function.[13,14] Therefore, using a large international multi-institutional database, the purpose of the current study was to develop and assess the TAC score relative to long-term prognosis following resection of HCC, as well as characterize the performance of the TAC score to stratify patients with HCC relative to BCLC,[7] Japan Integrated Staging (JIS),[10] and Cancer of the Liver Italian Program (CLIP).[9]

2 | METHODS

2.1 | Study population

Patients who underwent liver resection for HCC between 2000 and 2020 were identified from an international multi-institutional database that included: The Ohio State University Wexner Medical Center, Columbus, OH, USA; Keio University, Tokyo, Japan; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; University of Verona, Verona, Italy; Curry Cabral Hospital, Lisbon, Portugal; HC-UFMG, Federal University of Minas Gerais, Belo Horizonte, Brazil;

APHP, Beaujon Hospital, Clichy, France; Westhead Hospital, Sydney, Australia; Stanford University, Stanford, CA, USA; Fundeni Clinical Institute, Bucharest, Romania; University of Ottawa, Ottawa, Canada; University of Colorado, Denver, Colorado, USA; Yokohama City University, Yokohama, Japan. Patients with missing data, who experienced death within 90-days from surgery, had palliative surgery, or macroscopic residual disease after resection (R2) were excluded. The Institutional Review Board of all institutions approved this study.

2.2 | Variables and definitions

Demographic and preoperative clinicopathologic data included age, sex, comorbidities (Charlson comorbidity index),[15] baseline liver disease, laboratory exams (i.e., platelets, prothrombin international normalized ratio), imaging tumor characteristics (i.e., size and the number), surgical characteristics of liver resection (major resection: ≥3 Couinaud segments),[16] and pathological examination of the specimen. Preoperative liver function was assessed according to the CP classification and tumor staging was defined according to the *AJCC Cancer Staging Manual, 8th edition*.[17] Patients were categorized according to the following staging systems: BCLC,[7] JIS,[10] and CLIP.[9] TBS incorporated maximum tumor size and number of tumors on preoperative imaging into the Pythagorean theorem (TBS^2 = [maximum tumor diameter]^2 + [number of tumors]^2).[18] Patients were categorized as low, medium, or high TBS (cutoff values: 3.36 and 13.74), and as low, or high AFP (cutoff value: 400 ng/ml), as previously defined.[19,20] Non-transplantable recurrence was defined as recurrence beyond the Milan criteria.[21] The primary outcome was 5-year overall survival (OS), defined as the time interval between the date of liver resection to the date of death from any cause, or last follow-up. The secondary outcome was recurrence-free survival (RFS), defined as the time between hepatectomy and recurrence (positive biopsy or suspicious lesion on follow-up imaging).[19] In the postoperative setting, serum tumor markers and imaging studies (ultrasound, computed tomography, and magnetic resonance imaging) were utilized for monitoring. In general, follow-up occurred every 3–4 months in the first 3 years, and every 6 months until the fifth year, then annually.

2.3 | Statistical analysis

Categorical variables were reported as frequencies (%) and compared with the χ^2 test or Fisher exact test. Continuous variables were expressed as median values (interquartile range [IQR]), and compared with Mann–Whitney *U* tests. Survival and recurrence probabilities were compared using a log-rank test and depicted using the Kaplan–Meier curve. Relevant preoperative characteristics were assessed relative to OS through Cox proportional hazard regression analysis with backward exclusion. Variables with $p < 0.05$ were included in the multivariate analysis. The performance of the TAC score was analyzed and compared with the other staging schemas using Harrell's concordance index (C-index), Akaike information criteria (AIC), and homogeneity, measured by the χ^2 test.[22] The impact of various subgroups with the TAC score relative to OS was analyzed using Cox regression; sensitivity analyses (using it as a continuous variable) were also performed. The level of statistical significance was set at $\alpha = 0.05$. All analyses were performed using SPSS software version 28.0 (IBM Corporation) and R version 4.2.0 (R Project for Statistical Computing) statistical packages.

3 | RESULTS

3.1 | Baseline characteristics

Among 1435 patients who met inclusion criteria, median age was 63 years (IQR 54–71) and most patients were male ($n = 1149$, 80.1%) (Table 1). The vast majority of individuals ($n = 1391$, 96.9%) were classified as CP A, while only 44 (3.1%) were CP B. Overall, roughly one-half of patients presented with cirrhosis ($n = 655$, 45.6%); the prevalence of hepatitis B and C was 39.7% ($n = 569$) and 23.5% ($n = 336$), respectively. Median AFP was 18.3 ng/ml (IQR 4.0–362.5); while 1087 (75.7%) patients had a low AFP on presentation, 348 (24.3%) patients had a high AFP. Median tumor size was 4.9 cm (IQR 3.0–8.0) with the majority of patients having a solitary tumor ($n = 1189$, 82.9%). In turn, median TBS was 5.1 (IQR, 3.2–8.1); the majority of patients were categorized as having a medium TBS ($n = 949$, 66.1%), while fewer patients were classified with either low ($n = 390$, 27.2%) or high ($n = 96$, 6.7%) TBS. At the time of surgery, most patients underwent a minor resection ($n = 667$, 64.4%), while a smaller subset underwent a major hepatectomy ($n = 369$, 35.6%). On postoperative pathology, margin status was R0 in the overwhelming majority of patients ($n = 1297$, 91.2%); 854 (60.6%) and 557 (55.0%) patients had a well-or-moderately differentiated tumor and no microvascular invasion, respectively.

3.2 | Development of TAC score

On multivariable analysis, after controlling for other competing risk factors, preoperative variables that were independently associated with OS following resection of HCC included presence of cirrhosis (HR 1.48, 95% CI: 1.22–1.81; $p < 0.001$), CP classification (A: referent; B: HR 1.81, 95% CI: 1.12–2.92; $p = 0.015$), AFP level (<400 ng/ml: referent; >400 ng/ml: HR 1.56, 95% CI: 1.27–1.92; $p < 0.001$), and TBS (low: referent; medium: HR 2.26, 95% CI: 1.73–2.96; high: HR 3.35, 95% CI: 2.22–5.07; $p < 0.001$) (Table 2). The β-coefficients of these variables (β low TBS: referent, β medium TBS: 0.815, β high TBS: 1.209; β low AFP: referent, β high AFP: 0.446; β CP-A: referent, β CP-B: 0.593) were used to compose the score based on a simplified point system (TBS low/medium/high = 0/1/2; AFP low/high = 0/1; CP A/B = 0/1, respectively). Subsequently, patients were categorized on a scale ranging from 0 to 4 and classified as "Very Low,"

TABLE 1 Clinicopathologic characteristics of patients

Variables	Overall	TAC score				p Value
		Very low (n = 321, 22.4%)	Low (n = 739, 51.5%)	Medium (n = 331, 23.1%)	High (n = 44, 3.1%)	
Age, years	63 (54–71)	62 (61–64)	64 (63–66)	60 (59–63)	62 (57–68)	0.033
Sex, male	1149 (80.1%)	265 (82.8%)	585 (79.2%)	261 (78.9%)	38 (86.4%)	0.348
ASA PS >2	331 (33.0%)	73 (31.7%)	179 (33.6%)	69 (32.7%)	10 (34.5%)	0.960
CCI ≤9	889 (62.0%)	204 (99.0%)	471 (98.9%)	189 (98.4%)	25 (100.0%)	0.876
Cirrhosis	655 (45.6%)	189 (58.9%)	323 (43.7%)	126 (38.1%)	17 (38.6%)	<0.001
HCV liver infection	336 (23.5%)	106 (33.0%)	178 (24.2%)	46 (14.0%)	6 (13.6%)	<0.001
HBV liver infection	569 (39.7%)	127 (39.6%)	273 (36.9%)	154 (46.5%)	15 (34.1%)	0.025
PLT × 10^3/ul	159 (91–221)	136 (86–181)	162 (89–221)	178 (109–261)	196 (91–282)	<0.001
PT-INR >1.1	166 (13.2%)	35 (12.5%)	80 (12.2%)	41 (14.1%)	10 (27.8%)	0.056
Minimally invasive surgery	217 (15.9%)	89 (29.1%)	104 (14.9%)	24 (7.5%)	0 (0.0%)	<0.001
Major resection	369 (35.6%)	25 (10.5%)	191 (34.7%)	127 (58.5%)	26 (86.7%)	<0.001
Anatomical resection	822 (79.3%)	145 (60.9%)	450 (81.7%)	197 (90.8%)	30 (100.0%)	<0.001
AJCC T stage						<0.001
T1a/1b	165 (11.5%)	108 (33.6%)	44 (6.0%)	12 (3.6%)	1 (2.3%)	
T2/3/4	1,270 (85.5%)	213 (66.4%)	695 (94.0%)	319 (96.4%)	43 (97.7%)	
Liver capsule involvement	390 (35.9%)	65 (26.9%)	206 (37.5%)	107 (40.8%)	12 (38.7%)	0.007
Microvascular invasion	456 (45.0%)	60 (26.3%)	224 (42.4%)	146 (64.6%)	26 (83.9%)	<0.001
Lymphovascular invasion	382 (42.4%)	55 (26.1%)	185 (39.4%)	119 (61.7%)	23 (85.2%)	<0.001
Perineural invasion	23 (5.0%)	3 (2.7%)	13 (5.5%)	3 (2.9%)	4 (33.3%)	<0.001
Margin status						0.188
R1	125 (8.8%)	26 (8.3%)	56 (7.6%)	38 (11.5%)	5 (11.4%)	
R0	1297 (91.2%)	286 (91.7%)	680 (92.4%)	292 (88.5%)	39 (88.6%)	
Grade						<0.001
Well to moderate	854 (60.6%)	216 (69.2%)	481 (66.4%)	140 (42.6%)	17 (38.6%)	
Poor to undifferentiated	555 (39.4%)	96 (30.8%)	243 (33.6%)	189 (57.4%)	27 (61.4%)	

Note: Data are presented as median (IQR) for continuous measures, and *n* (%) for categorical measures.

Abbreviations: AJCC, American Joint Committee on Cancer; ASA PS, American Society of Anesthesiologists Performance Status; CCI, Charlson comorbidity index; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; PLT, platelets; PT-INR, prothrombin international normalized ratio.

"Low," "Medium," "High," and "Very High" relative to risk of long-term mortality.

3.3 | Association of TAC score with clinicopathological features and OS

With a median follow-up of 38 months (IQR 16–67), median and 5-year OS was 96 months (IQR 75.5–116.5) and 65.4%, respectively. Individuals with very low ($n = 321$, 22.4%), low ($n = 739$, 51.5%), medium ($n = 331$, 23.1%), and high ($n = 44$, 3.1%) TAC scores had progressively worse 3-year (88.8%, 81.2%, 68.1%, 59.6%, respectively) and 5-year (81.4%, 66.5%, 51.1%, 32.3%, respectively) OS ($p \leq 0.001$) (Figure 1A,D). A higher TAC score was associated with adverse clinicopathological features, including advanced AJCC T disease, the presence of microvascular, and lymphovascular invasion, as well as poor-to-undifferentiated tumor differentiation (all $p < 0.001$) (Table 1). On multivariable analyses that controlled for pre- and postoperative variables, the TAC score remained independently associated with worse 5-year OS (very low: referent; low: HR 1.57, 95% CI: 1.08–2.28, $p = 0.019$; medium: HR 2.58, 95% CI: 1.71–3.88, $p < 0.001$; high: HR 4.21, 95% CI: 2.19–8.09, $p < 0.001$) (Table 3). In fact, on sensitivity analysis, each unit increase in the TAC score

TABLE 2 Cox regression analysis for preoperative factors associated with overall survival

	Bivariate			Multivariate		
Variable	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.00	1.00–1.01	0.264	-	-	-
Sex, male	0.84	0.65–1.09	0.187	-	-	-
ASA PS, >II	1.08	0.82–1.42	0.588	-	-	-
CCI ≤9	0.93	0.23–3.74	0.917	-	-	-
PLT × 10^3/ul	1.00	0.99–1.00	0.986	-	-	-
Cirrhosis	1.33	1.10–1.61	0.004	1.48	1.22–1.81	<0.001
HCV liver infection	1.09	0.86–1.40	0.475	-	-	-
HBV liver infection	0.84	0.69–1.02	0.076	-	-	-
Child–Pugh						
A	Ref			Ref		
B	1.93	2.00–3.09	0.007	1.81	1.12–2.92	0.015
AFP (ng/ml)						
<400	Ref			Ref		
>400	1.73	1.14–2.12	<0.001	1.56	1.27–1.92	<0.001
TBS class						
Low	Ref			Ref		
Medium	2.19	1.68–2.86	<0.001	2.26	1.73–2.96	<0.001
High	3.13	2.08–4.69	<0.001	3.35	2.22–5.07	<0.001

Abbreviations: AFP, alpha-fetoprotein; ASA PS, American Society of Anesthesiologists Performance Status; CCI, Charlson comorbidity index; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelets; TBS, tumor burden score.

was independently associated with a 62% higher likelihood of death (HR 1.62; 95% CI: 1.37–1.9, $p < 0.001$).

3.4 | Patterns of recurrence

Median and 5-year RFS were 31 months (IQR 26–36) and 38.3%, respectively. Higher TAC score was associated with a greater risk of recurrence, as 3-year (very low: 65.8%, low: 45.7%, medium: 35.1%, high: 26.1%) ($p \leq 0.001$) and 5-year (very low: 52.0%, low: 37.3%, medium: 29.5%, high: 26.1%) ($p \leq 0.001$). RFS incrementally worsened concomitantly as the TAC score increased (Figure 1C). Among the 761 (53%) patients who experienced recurrence, the incidence incrementally increased with higher TAC scores (very low: 38.1%, low: 52.9%, medium: 64.4%, high: 68.2%, $p < 0.001$). Moreover, TAC scores were associated with different patterns of recurrence. In particular, higher TAC values were associated with larger tumor recurrence, extrahepatic recurrent disease, as well as earlier and non-transplantable recurrence (all $p < 0.001$) (Figure 2 and Supporting Information: Table 1).

3.5 | Comparison of performance

The TAC score performed relatively well in both the training (C-index 0.62, 95% CI: 0.59–0.65) and internal bootstrap validation (0.62, 95% CI: 0.59–0.65). The prognostic performance of the TAC score was compared relative to other staging systems (i.e., CLIP, JIS, AJCC T stage, BCLC). Of note, the TAC score consistently outperformed other prognostic models (AUC: CLIP 0.59, JIS 0.57, AJCC T category 0.57, BCLC 0.55). The TAC score also had a lower AIC value (5484.655) compared with BCLC (5536.454) and the highest homogeneity index (60.099) (both $p < 0.001$). In addition, the predictive ability of the composite TAC score was superior to the performance of any of its individual components (i.e., TBS, AFP, CP) (Table 4).

3.6 | TAC and BCLC

Subsequent analyses were then performed to assess the performance of the TAC score in various subgroups of patients stratified by the BCLC staging system. Of note, the TAC score substratified patients classified as BCLC 0, A, and B relative to long-term outcomes. Specifically, higher TAC scores were associated with a higher risk of death with lower 3-year (BCLC 0, very low: 93.2%, low: 83.6%, $p = 0.007$) (BCLC A, very low: 87.4%, low: 82.8%, medium: 67.7%, high: 65.8%, $p \leq 0.001$) (BCLC B, low: 76.6%, medium: 69.9%, high: N/A, $p \leq 0.001$) and 5-year (BCLC 0, very low: 86.8%, low: 47.8%, $p = 0.007$) (BCLC A, very low: 79.7%, low: 68.1%, medium: 52.5%, high: 35.6%, $p \leq 0.001$) (BCLC B, low: 59.8%, medium: 43.7%, high: N/A, $p \leq 0.001$) incrementally decreasing as TAC score increased independent of BCLC classification (Figures 1B and 3).

4 | DISCUSSION

HCC is a primary liver tumor that commonly arises in the context of chronic liver disease and an impaired underlying liver parenchyma.[23] While choice of therapeutic strategies is influenced by the complex interaction between these clinical factors, liver resection, and transplant are often the best curative-intent treatment options.[24] Accurate prognostic stratification is important to assess which patients may benefit the most from a given treatment, as well as inform discussions around long-term outcomes. In this context, the BCLC staging system has been widely adopted in Western countries as a means to guide therapy, as well as determine prognosis based on liver function, tumor size, and tumor number.[1,7] However, despite advances in prognosis and treatment strategies, the recent updated BCLC algorithm still does not recommend hepatic resection as an option for intermediate-stage HCC. In turn, the stratification and prognosis of patients with HCC relative to different disease stages remain a topic of debate.[6,7] In fact, several alternative prognostication systems have been proposed, yet none have been widely adopted. The current study was important because we used a large

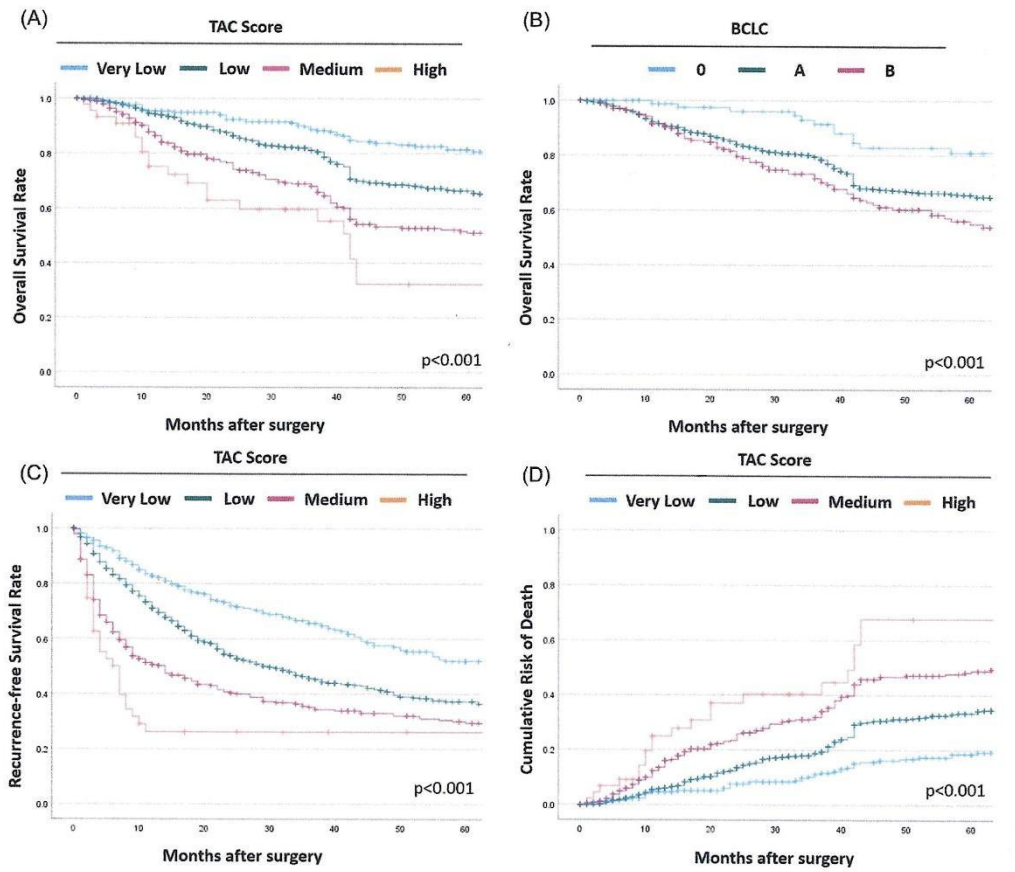

FIGURE 1 Estimated overall survival Kaplan–Meier curves stratified according to the TAC score (A) and the Barcelona clinic liver cancer (BCLC) system (B). Kaplan–Meier curves depict estimated recurrence-free survival (C) and cumulative risk of death (D) according to the TAC score.

multi-institutional database to develop and validate a simple preoperative prognostic model (TAC score) that successfully stratified long-term outcomes among patients with HCC, as well as outperformed the BCLC, AJCC T category, CLIP, and JIS. Of note, patients with higher TAC scores had an incrementally worse prognosis with a 62% higher hazard of death for each TAC unit increase. Moreover, the TAC score was associated with more aggressive patterns of recurrence (i.e., larger, earlier, systemic, and non-transplantable recurrences) and adverse clinicopathologic factors (higher AJCC T disease, presence of lymphovascular, and microvascular invasion, as well as poor-to-undifferentiated tumor grade). Furthermore, the TAC score was able to substratify patients within various BCLC categories, thereby highlighting the heterogeneity within BCLC groups 0/A/B.

The TAC score was developed based on variables that can be easily calculated and routinely assessed in the clinical setting. By incorporating TBS, AFP, and CP, TAC accounted for tumor morphology, biology, and liver function, respectively. TBS is a simple comprehensive continuous metric of tumor burden, which represents an improvement over traditional models that often treat size and number using dichotomous/subjective cut-off values.[18] TBS has been validated as an effective means to summarize overall tumor extent and, in turn, has been a powerful predictor of outcomes following resection of HCC.[6,19] Despite this, TBS has not been widely incorporated into prognostic models related to HCC. The TAC score also utilized serum AFP levels, which have long been recognized to correlate with tumor aggressiveness and, in turn, poor prognosis.[25–27] In fact, Tsilimigras et al.[14] demonstrated a synergistic effect of AFP with TBS to stratify patients with HCC relative to prognosis. In the current study we built off this previous work by combining TBS with AFP and CP classification, which is the most extensively used metric for liver function reserve, to develop a simple integer-based

TABLE 3 Cox regression analysis for factors associated with overall survival

	Bivariate			Multivariate		
Variable	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Cirrhosis	1.33	1.10–1.61	0.004	1.54	1.20–1.97	<0.001
Microvascular invasion	2.20	1.73–2.79	<0.001	1.68	1.30–2.16	<0.001
Perineural invasion	0.66	0.31–1.41	0.282	-	-	-
AJCC T stage						
T1a/1b	Ref					
T2/3/4	1.59	1.13–2.23	0.007	-	-	-
Margin						
R0	Ref					
R1	1.56	1.10–2.19	0.012	-	-	-
Grade						
Well to moderate	Ref					
Poor to undifferentiated	1.44	1.19–1.75	<0.001	1.50	1.15–1.94	0.003
TAC score						
Very low	Ref			Ref		
Low	1.89	1.39–2.56	<0.001	1.57	1.08–2.28	0.018
Medium	3.15	2.29–4.34	<0.001	2.58	1.71–3.88	<0.001
High	4.86	2.92–8.07	<0.001	4.21	2.19–8.09	<0.001

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval.

prognostic scoring system.[28] CP was used alone rather than including cirrhosis as a separate factor given that these two variables are colinear in nature. In addition, aside from overlapping CP in the assessment of liver status, the term "cirrhosis" can be vague and sometimes difficult to characterize in the preoperative setting with reliability.[29,30] Collectively, the TAC score combines elements of tumor morphology, biology, and liver function to act as a comprehensive scoring schema.

The TAC score performed well compared with other currently used schemas such as CLIP, JIS, AJCC staging, and the BCLC. In fact, TAC demonstrated overall superior prognostic performance following resection of HCC versus all of these aforementioned staging systems with the highest AUC, C-index, and homogeneity. While JIS and CLIP are also composed of simple, easy-to-calculate factors, these staging systems were not primarily designed or validated in cohorts of patients who underwent liver resection. With the expansion of hepatic resection for HCC, other staging systems such as the Model to Estimate Survival for HCC, Model to Estimate Survival in Ambulatory HCC patients, and Hong Kong Liver Cancer score have been developed and proposed in both Eastern or Western cohorts.[8,31,32] Of note, given that the etiology of HCC may differ in Western versus Eastern countries,[33] prognostic scoring systems need to include patients from both geographic locations. To that point, another strength of the current study was the broad, international representation of patients included in the cohort. As such, the TAC score has the advantage of not only being simple to use and having a demonstrably better prognostic performance relative to the CLIP, JIS, and BCLC, but it was also developed and validated in a diverse patient cohort that more likely reflects true clinical practice.

While likely multifactorial, the reason for the superior performance of the TAC score may be partially due to its role as a surrogate of adverse clinicopathological factors. Of note, patients with a higher TAC score were at a much higher likelihood to have more advanced T-disease, as well as the presence of lymphovascular and microvascular invasion, as well as poor-to-undifferentiated tumors (Table 1). Furthermore, the TAC score was also strongly associated with patterns of recurrence with RFS incrementally worsening with higher TAC scores (Figure 1). Recurrence is a major concern in resected HCC as a considerable number of patients will go on to develop non-transplantable recurrences, the main obstacle to the long-term success of primary liver resection.[34] Of note, the proportion of individuals who suffered a larger, earlier, systemic and non-transplantable recurrence incrementally increased with TAC scores (Figure 2, Supporting Information: Table 1). These results were consistent with a bimodal distribution of HCC recurrence, whereby early recurrence often correlates to residual tumor cells, while late recurrence originates from new multicentric carcinogenesis (i.e., de novo carcinogenesis).[25] The integration of tumor morphology, biology, and liver function in the TAC score may provide a better understanding of the anticipated disease course and natural history of HCC following initial resection. Therefore, the TAC prognostic model may provide insight to inform preoperative decision-making process relative to the anticipated benefit of HCC resection.

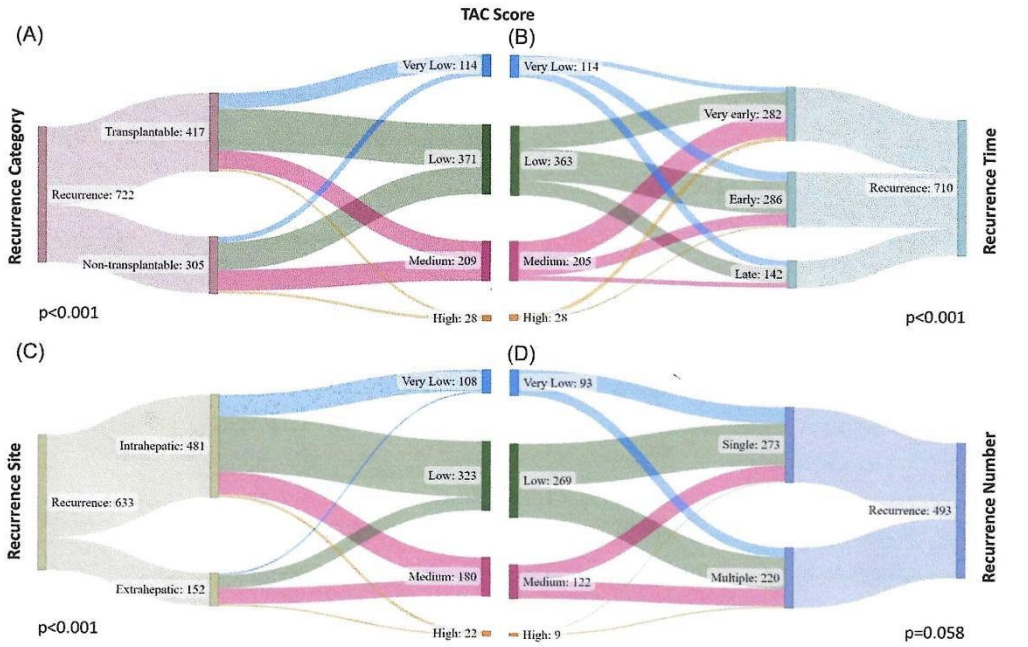

FIGURE 2 Sankey diagrams depicting patterns of recurrence according to the TAC score and recurrence category (A), time (B), site (C), and number (D)

TABLE 4 Comparison of predictive accuracy performance of the TAC Score, the Barcelona clinic liver cancer (BCLC) staging system, and others

System	Akaike information criterion	Homogeneity (χ^2)	C-index	95% CI
TAC score	5484.655	60.099	0.620	0.592–0.647
CLIP	5037.548	37.126	0.597	0.560–0.624
JIS	5061.988	26.493	0.578	0.553–0.603
AJCC T stage	5503.796	37.954	0.577	0.550–0.604
BCLC	5536.454	16.194	0.541	0.521–0.561
Components of the TAC score				
Imaging TBS class	5509.918	40.124	0.586	0.562–0.609
AFP >400 ng/ml	5528.074	27.614	0.568	0.544–0.592
Child–Pugh	5542.910	2.306	0.534	0.512–0.555

Abbreviations: AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer, 8th edition; BCLC, Barcelona clinic liver cancer; CI, confidence interval; CLIP, Cancer of the Liver Italian Program; JIS, Japan Integrated Score; TBS, tumor burden score.

The BCLC staging system classifies patients into different treatment/prognostic groups (i.e., 0/A/B/C/D), yet individuals within these groups can still have a very heterogeneous prognosis and derive vastly different benefits from the same therapeutic intervention.[1,24] For example, many surgeons believe that there is a role for hepatic resection among intermediate stage HCC.[4,35] However, the updated BCLC treatment algorithm still does not recommend liver resection beyond early-stage HCC, even in selected individuals.[6,7] Interestingly, stratification of patients using the TAC score highlighted the heterogeneity in prognosis among patients subclassified into the BCLC stages 0, A, and B stages. In particular, the TAC score noted a wide array of survival outcomes among patients in each of the different BCLC stage categories, suggesting that selected patients in each subgroup may benefit more from resection than other

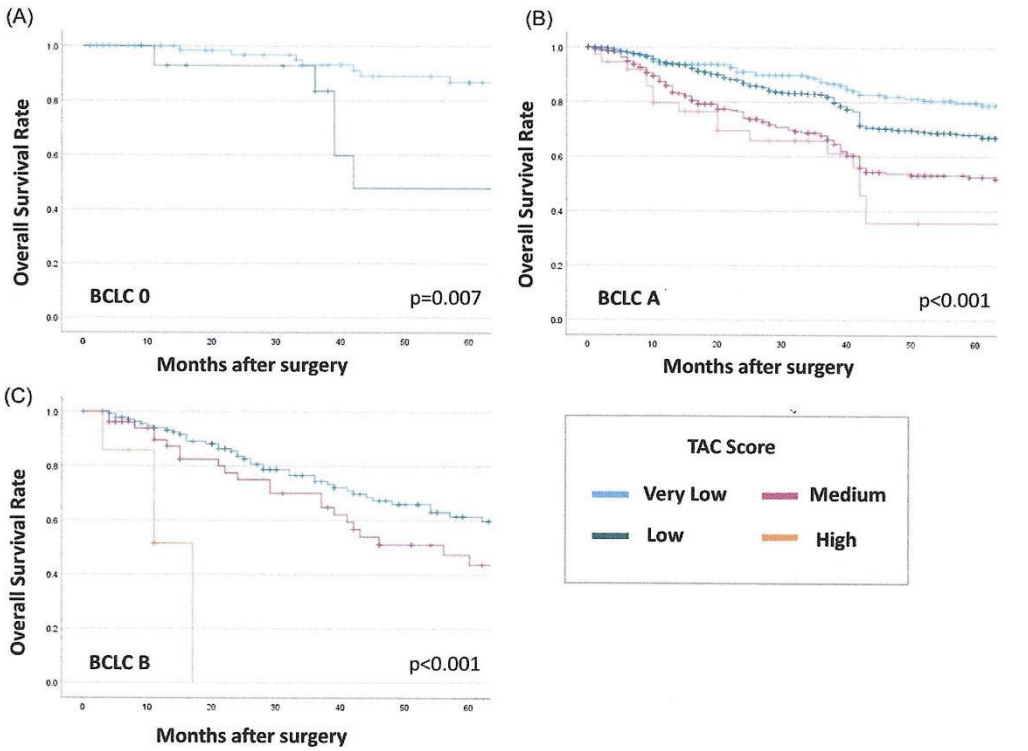

FIGURE 3 Estimated overall survival Kaplan–Meier curves stratified according to the TAC score among BCLC 0 (A), BCLC A (B), and BCLC B (C) patients. BCLC, Barcelona clinic liver cancer.

patients. While the BCLC algorithm restricted surgery to only patients with early-stage disease, the TAC score identified a subset of BCLC B patients with a 5-year OS of 59.8%. These results were in line with previous data from the literature that supported the feasibility and applicability of liver resection even among intermediate-stage patients.[6,36] Collectively, the data strongly suggested that the TAC score can provide an effective manner in which to better discriminate long-term survival of patients following resection of HCC, helping to determine which patients may benefit the most from hepatectomy.

Data from this study should be interpreted taking into account several limitations. Although the international multi-institutional cohort was a strength, differences in surgical techniques, patient selection, and compliance with surveillance protocols among institutions may have impacted the findings. In addition, the retrospective design of study may have resulted in selection bias, as well as residual bias within the analyses. The current study also included only patients who underwent curative-intent liver resection. Therefore, the prognostic ability of TAC cannot be generalized to nonsurgical candidates.

In conclusion, the TAC score was a simple, yet holistic composite prognostic tool that included readily available clinical parameters. Developed and validated using a large, multi-international cohort, the TAC score demonstrated very good prognostic performance that outperformed BCLC, as well as several other traditional prognostic scoring systems. Moreover, the TAC score was able to substratify patients within different BCLC categories (i.e., 0/A/B/C) to discriminate prognosis further, thereby highlighting the residual prognostic heterogeneity within each BCLC category. The TAC score may provide surgeons an accurate, easy-to-use prognostic tool to refine estimates related to long-term survival following resection of HCC to help inform which treatment strategies may survive patients best.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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

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7. DISCUSSÃO

A cirurgia continua sendo a opção ideal de tratamento potencialmente curativo para o CHC.[13-15] No entanto, a recidiva é um grande obstáculo para a sobrevivência a longo prazo. Essa pode variar significativamente, apresentando-se normalmente em uma distribuição bimodal, mas ainda sem uma padronização de valores de corte ideais para definição de recidiva "precoce" e "tardia".[16-18] O *artigo 1* foi importante porque utilizou um grande banco de dados internacional para demonstrar que o risco de recidiva após ressecção com intenção curativa do CHC é dinâmico e influenciado por múltiplos fatores clínicos. Especificamente, usando a função de risco, foram caracterizadas várias taxas de risco de recidiva em relação ao estágio BCLC, bem como ao TBS e AFP sérica. Por sua vez, o padrão geral de recidiva – incluindo tanto a taxa de pico quanto o momento do pico – foi definido entre várias coortes de pacientes. Enquanto pacientes com doença BCLC 0/A geralmente apresentaram baixo risco de recidiva –, portanto, podem necessitar de menos vigilância –, pacientes com TBS e/ou AFP elevados requerem vigilância intensificada, mesmo que estejam em estágios iniciais do BCLC. Para pacientes com BCLC B, é recomendada vigilância em intervalos curtos durante os primeiros três anos, já que esse intervalo de tempo representa o maior risco de recidiva. Esses dados podem contribuir para uma melhor compreensão das dinâmicas associadas à recidiva do CHC, ajudando assim a prever recidivas, orientar os pacientes e direcionar decisões futuras relacionadas à vigilância e terapia adjuvante.[19]

O CHC é uma doença complexa, com a carcinogênese frequentemente agravada pelo comprometido parênquima hepático subjacente.[2,14] Vários estudos prévios e meta-análises compararam a eficácia entre TH e RH como tratamento cirúrgico primário.[20-24] De forma geral, os dados da literatura favorecem o TH inicial, pois essa abordagem terapêutica trata tanto o tumor quanto o ambiente carcinogênico subjacente, resultando em melhor sobrevida livre de doença (SLD).[20-24] A escassez de órgãos, no entanto, é um grande desafio para o uso do TH, devido à alta demanda e ao número limitado de doadores.[2,20-22] Nesse contexto, a RH é frequentemente empregada como uma opção com intenção curativa, apesar de estar associada a um risco significativamente maior de recidiva (até 70%) em comparação com o TH (10–20%).[17,25] A ressecção primária seguida de TH secundário (THS) tem sido proposta como uma possível estratégia terapêutica.[26] Para garantir o THS, os pacientes submetidos à RH inicial exigem vigilância rigorosa para detectar recidivas precocemente e evitar a progressão para uma RNT.[27] O *artigo 2* foi importante porque desenvolvemos um modelo de risco pré-operatório para prever o desenvolvimento de RNT; esses dados podem ser usados para orientar a estratégia

de tratamento, bem como os regimes de vigilância pós-operatória. Em particular, utilizando um grande banco de dados internacional multi-institucional, desenvolvemos e validamos um escore de risco pré-operatório simples para RNT (*NTR score*), que foi disponibilizado como uma calculadora online (https://limaosu.shinyapps.io/henrique_NTR/) e estratificou com sucesso os pacientes em relação à SLD e RNT. No nosso estudo, a RNT após a ressecção com intenção curativa do CHC ocorreu em 1 em cada 5 pacientes. É importante destacar que pacientes com maior pontuação no *NTR score* apresentaram risco progressivamente maior de RNT após a ressecção inicial do CHC (Pontuação baixa 13,71%, média 25,39%, alta 38,18%, p<0,001) (AUC 0,65), com um aumento de 117% no risco de RNT para cada unidade adicional na pontuação. Além disso, o *NTR score* também foi associado a uma incidência progressivamente maior de recidiva (SLD em 5 anos: *NTR score* baixo 44,8% vs. *NTR score* médio 37,5% vs. *NTR score* alto 24,5%, p<0,001) (AUC 0,59), particularmente gerando recidivas maiores, mais precoces, múltiplas e sistêmicas. Ademais, as funções de risco para taxas de RNT demonstraram que pacientes com alto *NTR score* apresentaram o maior risco de recidiva, marcado pelo maior pico de taxa de risco (0,0514), bem como pelo tempo de recidiva mais precoce (3,0 meses).

O sistema de estadiamento BCLC para o CHC, que inclui informações sobre função hepática, tamanho do tumor e número de tumores, foi amplamente adotado como uma forma de orientar o tratamento e estimar o prognóstico.[28] Pacientes com CHC em estágio intermediário (BCLC B) englobam uma população altamente heterogênea, não apenas em relação à carga tumoral, mas também à reserva funcional hepática. Por exemplo, pacientes com CHC BCLC B podem apresentar escores de Child–Pugh de 5 a 9, desde apenas dois tumores (se um deles > 3 cm) confinados a um hemi-fígado, até múltiplos tumores em ambos os hemi-fígados na ausência de invasão vascular e metástases. O prognóstico estimado para pacientes nesses subgrupos heterogêneos pode variar substancialmente e, consequentemente, deveria, também, diferir o seu manejo. Uma vez que alguns pacientes com CHC em estágio intermediário podem se beneficiar da ressecção cirúrgica, é importante identificar meios para selecionar aqueles que mais se beneficiariam dessa opção terapêutica.[29,30] O *artigo 3* foi relevante porque, utilizando um grande banco de dados multi-institucional internacional, buscamos estratificar o prognóstico de pacientes BCLC B após ressecção hepática em relação aos níveis pré-operatórios AFP séricos e ao TBS. Especificamente, procuramos identificar o subgrupo de pacientes com CHC em estágio intermediário que mais poderia obter benefício em termos de sobrevida a longo prazo com a ressecção cirúrgica primária, auxiliando assim os cirurgiões na seleção de pacientes para essa estratégia de tratamento. Pacientes com TBS baixo e AFP baixo foram identificados como o subgrupo mais propenso a se beneficiar da ressecção. Notavelmente, um escore de risco

simplificado baseado nesses fatores foi capaz de estratificar os pacientes em relação à sobrevida global (SG) e à sobrevida livre de doença (SLD). Especificamente, um escore de risco mais elevado foi associado a uma pior SG em 5 anos (0 fatores: 68,1% vs. 1 fator: 61,0% vs. 2 fatores: 29,9%) (AUC 0,62) (p < 0,001), assim como a maiores riscos de morte [referência: 0; 1 fator: 1,29 (IC 95%, 0,73–2,29) vs. 2 fatores: 2,48 (IC 95%, 1,36–4,54); p = 0,003]. Um escore de risco mais elevado também foi associado a uma pior SLD (0 fatores: 33,6% vs. 1 fator: 18,0% vs. 2 fatores: 14,7%) (AUC 0,60) e a uma recidiva muito precoce (isto é, <6 meses após a cirurgia) (0 fatores: 21,3% vs. 1 fator: 43,1% vs. 2 fatores: 68,6%) (AUC 0,69) (ambos p < 0,001).

O CHC comumente surge no contexto de doença hepática crônica e parênquima hepático subjacente comprometido.[10] Embora a escolha das estratégias terapêuticas seja influenciada pela complexa interação entre esses fatores clínicos, a ressecção hepática e o transplante frequentemente são as melhores opções de tratamento com intenção curativa.[14] Uma estratificação prognóstica precisa é fundamental para avaliar quais pacientes podem se beneficiar mais de um determinado tratamento, além de informar discussões sobre os resultados a longo prazo. Nesse contexto, o sistema de estadiamento BCLC foi amplamente adotado em países ocidentais como uma ferramenta para orientar a terapia e determinar o prognóstico com base na função hepática, tamanho e número de tumores.[9,31] No entanto, apesar dos avanços no prognóstico e nas estratégias de tratamento, o algoritmo atualizado do BCLC ainda não recomenda a ressecção hepática como uma opção para paciente com CHC em estágio intermediário. Assim, a estratificação e o prognóstico de pacientes com CHC em diferentes estágios de classificação continua sendo tópico de debates.[9,32] De fato, vários sistemas prognósticos alternativos têm sido propostos, mas nenhum foi amplamente adotado. O *artigo 4* foi importante porque utilizamos um grande banco de dados multi-institucional para desenvolver e validar um modelo prognóstico pré-operatório simples (escore *TAC*) que estratificou com sucesso os desfechos a longo prazo de pacientes com CHC e superou os sistemas BCLC, categoria T do AJCC, CLIP e JIS.[11,33] O escore *TAC* é uma ferramenta prognóstica simples, porém abrangente, que incluiu parâmetros clínicos prontamente disponíveis. Notavelmente, pacientes com escores *TAC* mais altos apresentaram um prognóstico progressivamente pior, com um risco 62% maior de morte para cada acréscimo unitário no escore. Além disso, o escore *TAC* foi associado a padrões mais agressivos de recidiva (ou seja, recidivas maiores, mais precoces, sistêmicas e não transplantáveis) e a fatores clínico-patológicos adversos (doença T mais avançada no AJCC, presença de invasão linfovascular e microvascular, bem como grau tumoral pobremente diferenciado ou

indiferenciado). Além disso, o escore *TAC* foi capaz de sub-estratificar pacientes dentro de várias categorias do BCLC, destacando assim a heterogeneidade dentro dos grupos BCLC 0/A/B.

Algumas limitações devem ser consideradas ao interpretar os resultados destes estudos. Devido à natureza retrospectiva, viés de seleção pode ter influenciado quais pacientes foram submetidos à cirurgia, perpetuando fatores de confusão residuais. Embora a natureza internacional e multi-institucional do banco de dados seja um ponto forte das análises, a técnica cirúrgica, a seleção de pacientes e as estratégias de tratamento podem variar entre as diferentes instituições, assim como os protocolos de vigilância. Além disso, o banco de dados baseou-se exclusivamente em pacientes que foram submetidos à RH; portanto, não foi possível realizar comparações diretas entre estratégias de tratamento com RH e TH, e dados para utilizar o escore MELD não estavam disponíveis. Especificamente, os resultados podem não ser representativos de todos os pacientes da população BCLC B e impactar na generalizabilidade da capacidade prognóstica do *TAC* para pacientes não cirúrgicos.

Sob um olhar mais amplo, é importante reconhecer que modelos e classificações, por mais bem embasadas que sejam, não são absolutas, irretocáveis, e muito menos imutáveis. São, sim, ferramentas importantíssimas que auxiliam na quantificação de riscos e contribuem para a tomada de decisão da equipe médica. O amadurecimento clínico e científico leva inevitavelmente a um ceticismo produtivo, no qual a rigidez das definições dá lugar a uma interpretação mais contextualizada e multidisciplinar. No manejo de condições complexas, como o CHC, a decisão sobre o tratamento cirúrgico não deve prescindir, mas sim transcender algoritmos e escores pré-definidos, levando em consideração a variabilidade biológica, comorbidades, a resposta individual às terapias disponíveis e a expertise da equipe envolvida. Assim, a personalização do cuidado, embasada na melhor evidência disponível e na experiência clínica, deve ser o norteador último da tomada de decisão, reafirmando que a medicina, mais do que uma ciência exata, é uma arte aplicada à singularidade de cada paciente.

8. CONCLUSÃO

Os artigos apresentados nesta tese contribuem para o melhor entendimento dos padrões de recorrência do CHC após ressecção com intuito curativo, e consequentemente, nas estratégias de vigilância. Além disso, os resultados apresentados podem auxiliar na melhor estratificação de risco pré-operatório, auxiliando na definição das melhores estratégias de tratamento para cada subgrupo de pacientes. A partir de uma grande base de dados internacional multi-institucional, nossas modelagens prognósticas para recorrência e sobrevivência também trazem foco para a heterogeneidade dentro de sistemas clássicos de classificação e prognóstico, como o BCLC, e contribuem para refinar a avaliação de pacientes em contextos clínico-patológico-cirúrgicos complexos e desafiadores.

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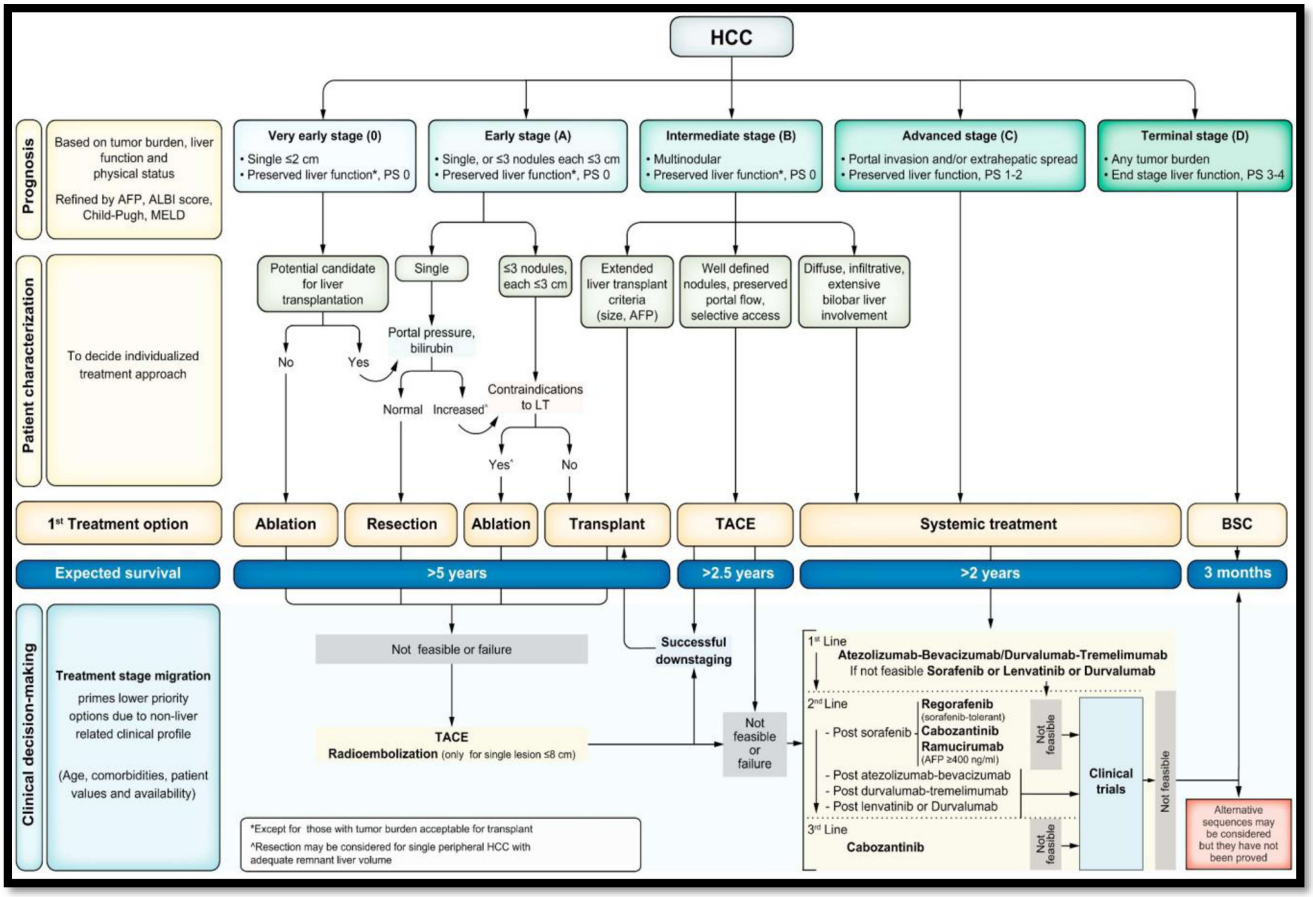
ANEXOS

Estadiamento e estratégia de tratamento BCLC em 2022.



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