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ORIGINAL SCIENTIFIC REPORT

# Impact of Tumor Burden Score on Conditional Survival after Curative-Intent Resection for Hepatocellular Carcinoma: A Multi-Institutional Analysis

**Ahmed N. Elfadaly[1] · Diamantis I. Tsilimigras[1] · J. Madison Hyer[1] · Alessandro Paro[1] · Fabio Bagante[1,2] · Francesca Ratti[3] · Hugo P. Marques[4] · Olivier Soubrane[5] · Vincent Lam[6] · George A. Poultsides[7] · Irinel Popescu[8] · Sorin Alexandrescu[8] · Guillaume Martel[9] · Aklile Workneh[9] · Alfredo Guglielmi[2] · Tom Hugh[10] · Luca Aldrighetti[3] · Itaru Endo[11] · Timothy M. Pawlik[1]**

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## Abstract

*Background* The impact of tumor burden score (TBS) on conditional survival (CS) among patients undergoing curative-intent resection of hepatocellular carcinoma (HCC) has not been examined to date.

*Methods* Patients who underwent liver resection of HCC between 2000 and 2017 were identified from a multi-institutional database. The impact of TBS and other clinicopathologic factors on 3-year conditional survival ($CS_3$) was examined.

*Results* Among 1,040 patients, 263 (25.3%) patients had low TBS, 668 (64.2%) had medium TBS and 109 (10.5%) had high TBS. TBS was strongly associated with OS; 5-year OS was 39.0% among patients with high TBS compared with 61.1% and 79.4% among patients with medium and low TBS, respectively ($p < 0.001$). While actuarial survival decreased as time elapsed from resection, CS increased over time irrespective of TBS. The largest differences between 3-year actuarial survival and $CS_3$ were noted among patients with high TBS (5-years postoperatively; $CS_3$: 78.7% vs. 3-year actuarial survival: 30.7%). The effect of adverse clinicopathologic factors including high TBS, poor/undifferentiated tumor grade, microvascular invasion, liver capsule involvement, and positive margins on prognosis decreased over time.

*Conclusions* CS rates among patients who underwent resection for HCC increased as patients survived additional years, irrespective of TBS. CS estimates can be used to provide important dynamic information relative to the changing survival probability after resection of HCC.

Ahmed N. Elfadaly and Diamantis I. Tsilimigras have contributed equally to this manuscript.

✉ Timothy M. Pawlik
tim.pawlik@osumc.edu

[1] Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

[2] Department of Surgery, University of Verona, Verona, Italy

[3] Department of Surgery, Ospedale San Raffaele, Milano, Italy

[4] Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal

[5] Department of Hepatobiliopancreatic Surgery, APHP, Beaujon Hospital, Clichy, France

[6] Department of Surgery, Westmead Hospital, Sydney, Australia

[7] Department of Surgery, Stanford University, Stanford, CA, USA

[8] Department of Surgery, Fundeni Clinical Institute, Bucharest, Romania

[9] Department of Surgery, University of Ottawa, Ottawa, Canada

[10] Department of Surgery, School of Medicine, The University of Sydney, Sydney, Australia

[11] Yokohama City University School of Medicine, Yokohama, Japan

## Introduction

Hepatocellular carcinoma is the sixth most common cancer worldwide and represents one of the main causes of cancer-related deaths in the United States [1–3]. While only 20–30% of patients present with resectable disease at the time of diagnosis, surgery remains the only potentially curative treatment option for patients with HCC [4, 5]. Over the years, several staging systems have been developed to define the extent of disease and help guide treatment recommendations [6, 7]. The American Joint Committee on Cancer (AJCC) and the Barcelona Clinic Liver Cancer (BCLC) staging systems represent the most common schemas used in clinical practice [6, 7]. More recently, the tumor burden score (TBS) has been demonstrated to stratify the prognosis of patients with resectable HCC accurately and has been proposed as a more accurate staging schema compared with the traditional BCLC staging system [8]. While these staging systems aim to predict prognosis among patients with HCC, survival estimates have traditionally been based solely on factors obtained at the time of diagnosis/surgery leading to a static rather than a dynamic measure of long-term survival. In turn, current staging systems are unable to provide a dynamic assessment of survival and fail to account for changes in survival probabilities relative to the time elapsed from diagnosis [9].

Conditional survival (CS) has been identified as possibly a superior and more clinically relevant method to evaluate outcomes compared with traditional survival estimates [10, 11]. Indeed, proponents of CS note that the probability of survival changes as patients survive past a certain time point [10, 11]. In turn, CS can more accurately track the dynamic changes in prognosis as patients survive for longer periods of time [12]. Little is known, however, about changes in CS over time among patients undergoing resection for HCC [9, 13, 14]. In particular, the association of HCC TBS with CS has not been examined to date. As such, the objective of the current study was to define the CS probabilities among patients undergoing curative-intent resection for HCC using a large international multi-institutional database. In particular, we sought to define the prognostic impact of HCC TBS, as well as other patient- and tumor-level factors, on CS relative to the time elapsed from surgery.

## Methods

### Study population and inclusion criteria

Patients who underwent curative-intent resection for HCC between January 2000 and January 2017 were included in the analytic cohort. Data were retrieved from a multi-institutional database from 11 major international hepatobiliary centers: The Ohio State University Wexner Medical Center, Columbus, OH, USA; Yokohama City University School of Medicine, Yokohama, Japan; 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, USA; Fundeni Clinical Institute, Bucharest, Romania; University of Ottawa, Ottawa, Canada; and The University of Sydney, School of Medicine, Sydney, Australia. Patients with advanced HCC (i.e., BCLC-C), individuals who did not undergo curative-intent resection, had missing data on tumor size and number, or had missing follow-up data were excluded. The Institutional Review Board of each participating institution approved the study protocol.

### Variables, definitions and outcomes

Data on patient demographic and tumor characteristics were collected from electronic medical records. Variables analyzed included age, sex, American Society of Anesthesiologists (ASA) physical status classification, pre-operative cirrhosis, infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), serum α-fetoprotein levels (AFP), type of surgery (i.e., minimally invasive surgery [MIS] vs. open), extent of resection (i.e., major vs. minor), largest tumor size, number of lesions, BCLC stage, pathologic tumor grade, microvascular invasion, liver capsule involvement, resection margin status on final pathology (i.e., R0, R1), and TBS.

A subset of patients who underwent concomitant ablation in addition to resection at the time of surgery ($n = 60$). While tissue biopsy was not obtained on all lesions that were ablated, these lesions were classified as LI-RADS 5 (definitely HCC) on imaging by experienced hepato-radiologists at each center. These lesions were included in the TBS score. TBS was defined as the distance from the origin of a Cartesian plane where maximum tumor size is on the x-axis and the number of tumors is on the y-axis, so that $TBS^2 = (\text{maximum tumor diameter})^2 + (\text{number of tumors})^2$, as previously described [8, 15]. Based on previously reported cut-offs of TBS [8], patients were categorized as having low (TBS $\leq$ 3.36), medium (TBS 3.36–13.74) or high TBS (TBS $\geq$ 13.74) [8]. The TBS cut-offs were validated using the multi-institutional database as well as an external validation cohort [8]. Resection of three or more Couinaud segments was considered as a major hepatectomy [16].

### Statistical analysis

Descriptive statistics were presented as median (interquartile range [IQR]) for continuous variables and frequency (%) for categorical variables. OS estimates were calculated using the Kaplan-Meier method. CS was measured using the conditional Kaplan-Meier method and reflected survival either with or without recurrence (i.e., conditional overall survival). Overall survival (OS) was defined as the time interval between liver resection and death or last follow-up. CS was defined as the probability of surviving an additional number of y years, provided that a patient has already survived for x years (with or without recurrence), so that $CS(x|y) = S(x + y)/S(x)$, with S(x) representing the OS at x years, estimated using the Kaplan-Meier method [17]. Differences in CS among different patient subgroups were evaluated using standardized differences (*d*); *d* is a measure of the effect size used when outcomes such as conditional survival are presented as proportions. $d < 0.1$ indicates a very small difference, $d = 0.1$–$0.3$ represents a small difference, while $d = 0.3$–$0.5$ constitutes a moderate difference and $d > 0.5$ is regarded as a large difference [17]. All statistical analyses were performed with the SPSS, v26 (IBM Corp. Armonk, NY, USA) and JMP, v14 (SAS Institute Inc., Cary, NC, USA) statistical packages.

## Results

### Baseline characteristics of study cohort

A total of 1,040 patients who underwent curative-intent resection for HCC and met inclusion criteria were included in the final analytic cohort. Median age was 67 years (IQR: 59–74), the majority of patients were male ($n = 780$, 75.1%) and had an ASA score of $\leq 2$ ($n = 574$, 62.9%) (Table 1). History of HBV and HCV infection was present in 26.2% ($n = 269$) and 30.5% ($n = 314$) of patients, respectively; 396 (38.2%) patients had cirrhosis at the time of HCC resection. Approximately, one-third of patients underwent a major liver resection ($n = 353$, 35.0%). Median tumor size was 5 cm (3.0–8.5) and median TBS was 5.1 (3.4–9.0). Overall, 25.3% ($n = 263$) of patients had low TBS, 64.2% ($n = 668$) had medium TBS and 10.5% ($n = 109$) had high TBS. On pathology, 37.8% ($n = 337$) of patients had microvascular invasion, while 32.1% ($n = 240$) had liver capsule involvement. The vast majority of patients had a negative margin resection (R0 resection, $n = 895$, 88.5%) (Table 1).

**Table 1** Clinicopathologic characteristics of the entire cohort

| Variables | Total ($n = 1040$) |
|---|---|
| Age† | 67 (59–74) |
| *Sex* | |
| Male | 780 (75.1%) |
| Female | 258 (24.9%) |
| *ASA-PS* | |
| $\leq 2$ | 574 (62.9%) |
| $> 2$ | 339 (37.1%) |
| Cirrhosis | 396 (38.2%) |
| *HBV infection* | |
| No | 759 (73.8%) |
| Yes | 269 (26.2%) |
| *HCV infection* | |
| No | 715 (69.5%) |
| Yes | 314 (30.5%) |
| *AFP, ng/mL* | |
| $\leq 400$ | 715 (80.7%) |
| $> 400$ | 171 (19.3%) |
| Minimally invasive surgery | 254 (24.5%) |
| *Type of resection* | |
| Minor | 656 (65.0%) |
| Major | 353 (35.0%) |
| Concomitant ablation | 60 (5.8%) |
| Tumor size of largest nodule, cm† | 5.0 (3.0–8.5) |
| Tumor number† | 1 (1–1) |
| *Tumor* burden score† | 5.1 (3.4–9.0) |
| Low | 263 (25.3%) |
| Medium | 668 (64.2%) |
| High | 109 (10.5%) |
| *BCLC stage* | |
| BCLC-0 | 62 (6.0%) |
| BCLC-A | 820 (78.8%) |
| BCLC-B | 158 (15.2%) |
| *Grade* | |
| Well to moderate | 800 (80.6%) |
| Poor to undifferentiated | 192 (19.4%) |
| *Microvascular invasion* | |
| No | 554 (62.2%) |
| Yes | 337 (37.8%) |
| *Liver capsule involvement* | |
| No | 507 (67.9%) |
| Yes | 240 (32.1%) |
| *Margin Status* | |
| R0 | 895 (88.5%) |
| R1 | 116 (11.5%) |

†Median (IQR) IQR = interquartile range; ASA-PS = American Society of Anesthesiologists-Performance score; HBV = hepatitis B virus; HCV = hepatitis C virus; AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer

### Assessment of OS based on different clinicopathologic factors

In the entire cohort, 1-, 3- and 5-year OS was 89.3%, 74.7% and 63.3%, respectively. Several factors were associated with 5-year OS including patient age ($\leq$ 65 years: 66.6% vs. $>$ 65 years: 60.0%, $p = 0.006$), pre-operative serum AFP (AFP $\leq$ 400 ng/mL: 66.8% vs. AFP $>$ 400 ng/mL: 47.6%, $p < 0.001$), extent of resection (major: 56.3% vs. minor: 67.8%, $p < 0.001$), tumor grade

**Table 2** Clinicopathologic factors relative to actuarial OS

| Variables | Patient survival (%) | | | *p*-value |
|---|---|---|---|---|
| | 1-year OS | 3-year OS | 5-year OS | |
| All patients | 89.3% | 74.7% | 63.3% | |
| *Age* | | | | 0.006 |
| $\leq$ 65 | 91.9% | 78.0% | 66.6% | |
| $>$ 65 | 86.5% | 71.2% | 60.0% | |
| *Sex* | | | | 0.90 |
| Male | 89.7% | 74.8% | 63.2% | |
| Female | 88.0% | 74.4% | 63.2% | |
| *ASA-PS* | | | | 0.22 |
| $\leq$ 2 | 91.4% | 76.2% | 68.1% | |
| $>$ 2 | 87.9% | 74.7% | 60.7% | |
| Cirrhosis | | | | 0.19 |
| No | 90.8% | 74.6% | 65.0% | |
| Yes | 86.8% | 74.7% | 60.1% | |
| *AFP, ng/mL* | | | | $<$ 0.001 |
| $\leq$ 400 | 91.4% | 78.0% | 66.8% | |
| $>$ 400 | 83.4% | 63.7% | 47.6% | |
| *Type of resection* | | | | $<$ 0.001 |
| Minor | 91.7% | 79.4% | 67.8% | |
| Major | 85.6% | 66.9% | 56.3% | |
| *Tumor burden score* | | | | $<$ 0.001 |
| Low | 93.4% | 87.4% | 79.4% | |
| Medium | 90.8% | 73.3% | 61.1% | |
| High | 70.2% | 53.0% | 39.0% | |
| *BCLC stage* | | | | 0.005 |
| BCLC-0 | 95.0% | 89.8% | 80.1% | |
| BCLC-A | 89.1% | 74.7% | 64.1% | |
| BCLC-B | 88.4% | 67.1% | 52.6% | |
| *Grade* | | | | $<$ 0.001 |
| Well to moderate | 91.7% | 78.4% | 67.2% | |
| Poor to undifferentiated | 83.6% | 62.5% | 50.4% | |
| *Microvascular invasion* | | | | $<$ 0.001 |
| No | 93.2% | 82.5% | 69.2% | |
| Yes | 84.5% | 61.2% | 52.7% | |
| *Liver capsule involvement* | | | | 0.01 |
| No | 89.5% | 75.5% | 64.6% | |
| Yes | 86.0% | 63.8% | 51.0% | |
| *Margin status* | | | | 0.02 |
| R0 | 90.1% | 76.2% | 65.2% | |
| R1 | 85.2% | 62.7% | 52.2% | |

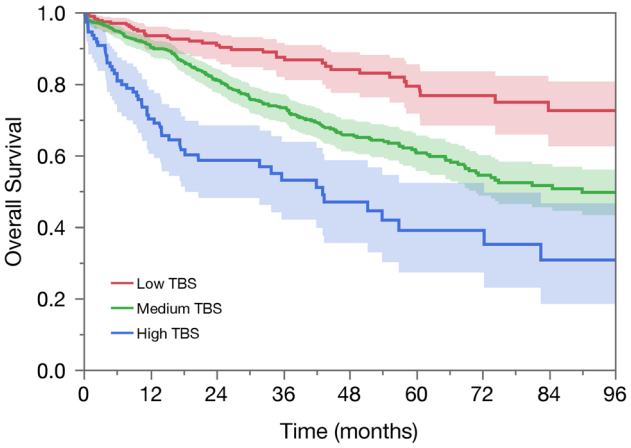


**Fig. 1** Kaplan-Meier curves demonstrating differences in OS among patients undergoing resection for HCC with low, medium and high TBS

(well/moderate: 67.2% vs. poor/undifferentiated: 50.4%, $p < 0.001$), microvascular invasion (yes: 52.7% vs. no: 69.2%, $p < 0.001$), liver capsule involvement (yes: 51.0% vs. no: 64.6%, $p = 0.01$), resection margin status (R0: 65.2% vs. R1: 52.2%, $p = 0.02$) and BCLC stage (BCLC-0: 80.1% vs. BCLC-A: 64.1% vs. BCLC-B: 52.6%, $p = 0.005$) (Table 2). In addition, TBS was strongly associated with OS; 5-year OS was 39.0% among patients with high TBS compared with 61.1% and 79.4% among patients with medium and low TBS, respectively ($p < 0.001$, Fig. 1).

### Assessment of actuarial versus conditional survival in the entire cohort

While actuarial survival decreased from the time of surgery, CS was noted to increase over time. For example, while 3-year actuarial survival decreased from 58.2% at 3-years to 53.0% at 5 years post-resection, $CS_3$ was noted to increase from 77.9% at 3 years to 83.7% at 5-years following resection in the entire cohort (Fig. 2a). In turn, the $CS_3$ estimates were 76.4%, 77.9%, and 83.7% in the entire cohort, given that patients had survived 1-, 3-, and 5-years, respectively. CS estimates for a certain number of years relative to the number of years elapsed after resection are presented in Table 3.

Changes in actuarial and CS estimates showed a similar pattern after stratifying by TBS. In particular, while 3-year actuarial survival decreased progressively after HCC resection, $CS_3$ increased incrementally over time among all TBS groups (Fig. 2b-d). Of note, the largest differences between 3-year actuarial survival and $CS_3$ were noted in the high TBS group, reaching a $CS_3$ of 78.7% at 5-years compared with the 30.7% actuarial survival at 8-years (i.e., a 3-year actuarial survival at 5-years) postoperatively. Importantly, the $CS_3$ estimates at 5-years in the high TBS group approached that of the medium TBS group at the same time point ($CS_3$ at 5-years; high TBS: 78.7%; medium TBS: 81.2%; low TBS: 91.3%) (Fig. 2b-d).

### Comparison of CS estimates among different subgroups over time

The impact of patient-, tumor- and surgery-related characteristics on $CS_3$ at different time points after resection was assessed using standardized differences (*d*) as a measure of effect size (Table 4). In general, $CS_3$ in each subgroup increased as years elapsed; yet, the impact of each clinicopathologic factor on $CS_3$ changed over time (Fig. 3a-c). For example, age had a small effect on $CS_3$ immediately following surgery (78.0% vs. 71.2%, $d = 0.16$) until 5 years postoperatively, when the impact on $CS_3$ became moderate (88.4% vs. 76.5%, $d = 0.33$). In addition, while there was no effect of preoperative cirrhosis on $CS_3$ immediately after surgery (74.6% vs. 74.7%, $d = 0$), the effect of cirrhosis on CS increased only slightly at 3 years postoperatively (73.0% vs. 80.7%, $d = 0.19$). In contrast, preoperative AFP levels > 400 ng/ml had a relatively constant, moderate effect on $CS_3$ from the time of resection (78.0% vs. 63.7%, $d = 0.33$) to 3-years following hepatectomy (80.3% vs. 66.6%, $d = 0.33$) (Fig. 3a). Interestingly, the effect of certain pathologic characteristics including tumor grade, microvascular involvement, liver capsule invasion and resection margin status on CS followed by a similar pattern (Fig. 3b). In particular, the effect of margin status on $CS_3$ was largest immediately following surgery (76.2% vs. 62.7%, $d = 0.31$) and progressively decreased until 3-years postoperatively, when patients with R0 margin only had a slightly better $CS_3$ than patients with R1 margins (79.3% vs. 74.0%, $d = 0.13$). Similarly, microvascular invasion had a strong effect on $CS_3$ at the time of hepatectomy (61.2% vs. 82.5%, $d = 0.50$), which progressively decreased until 3-years postoperatively (74.6% vs. 78.0%, $d = 0.13$) (Fig. 3b).

Of note, the difference in $CS_3$ between BCLC-B and BCLC-0/A patients remained small throughout the study period from the time of resection (67.1% vs. 75.9%, $d = 0.20$) to 3-years postoperatively (73.8% vs. 78.7%, $d = 0.11$), except for 1-year following surgery when the impact of BCLC stage on $CS_3$ was moderate (61.7% vs. 78.8%, $d = 0.40$). In contrast, the impact of TBS on $CS_3$ was largest at the time of liver resection (high TBS: 53.0% vs. low/medium TBS: 77.2%, $d = 0.56$) and decreased up to 3-years postoperatively (73.6% vs. 78.2%, $d = 0.11$) (Fig. 3c).

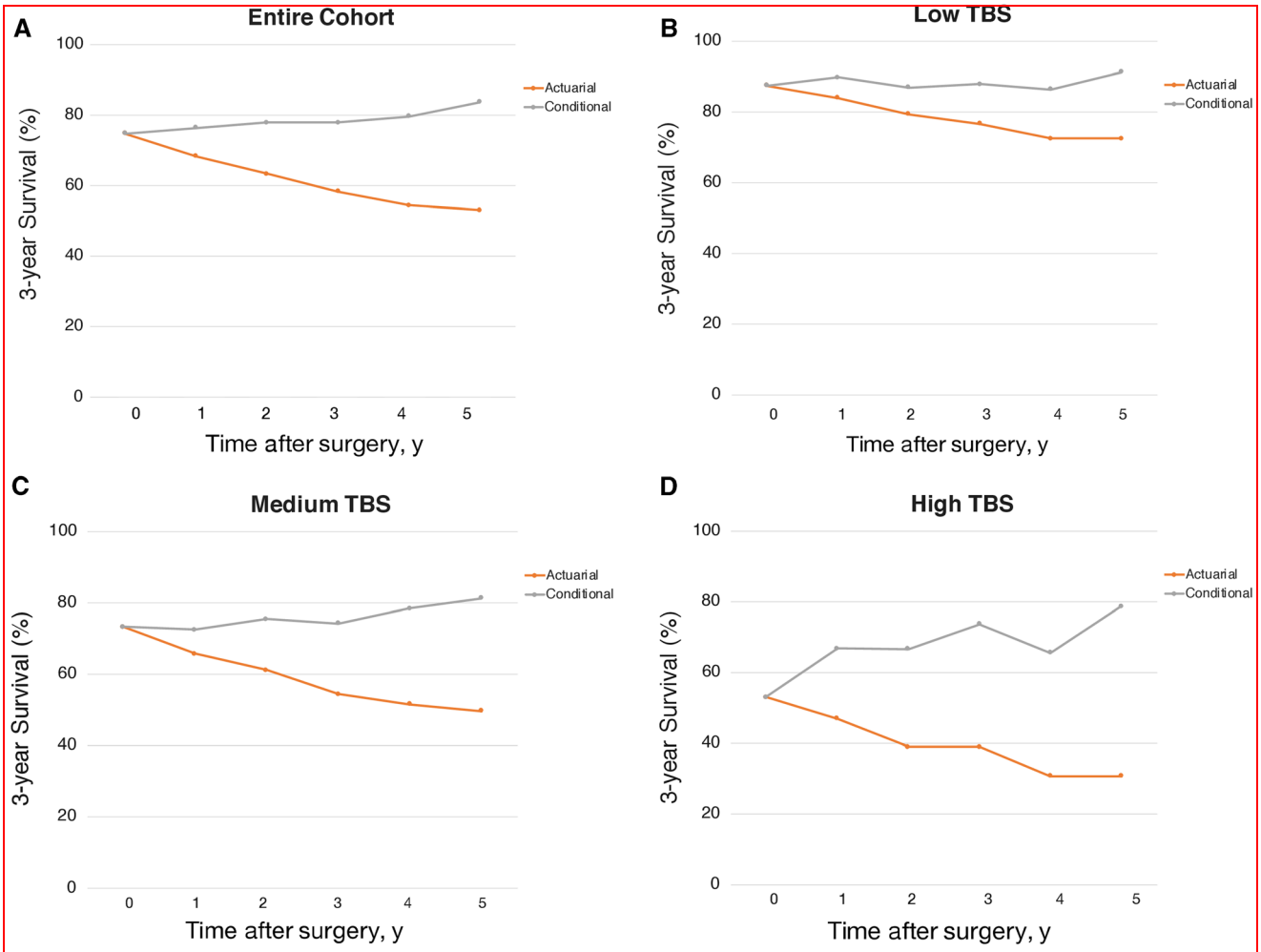


**Fig. 2** Three-year conditional and actuarial survival in the (**a**) entire cohort and among patients with low (**b**), medium (**c**) and high TBS (**d**)

**Table 3** Conditional survival in the entire cohort

| Total Survival Time (year) | If the patient has survived (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1y | 2y | 3y | 4y | 5y | 6y | 7y |
| 1 | | | | | | | |
| 2 | 91.0 | | | | | | |
| 3 | 83.7 | 91.9 | | | | | |
| 4 | 76.4 | 83.9 | 91.3 | | | | |
| 5 | 70.9 | 77.9 | 84.7 | 92.8 | | | |
| 6 | 65.2 | 71.6 | 77.9 | 85.3 | 91.9 | | |
| 7 | 60.8 | 66.8 | 72.7 | 79.6 | 85.8 | 93.3 | |
| 8 | 59.4 | 65.2 | 71.0 | 77.7 | 83.7 | 91.1 | 97.6 |

For example, if a patient has survived to 2 years, the survival probability of reaching 5 years of total survival is 77.9%

**Table 4** Three-year conditional overall survival ($CS_3$) stratified by risk factors

| Variables | Time elapsed since resection (%) | | | | | |
|---|---|---|---|---|---|---|
| | 0y | 1y | 2y | 3y | 4y | 5y |
| All patients | 74.7 | 76.4 | 77.9 | 77.9 | 79.6 | 83.7 |
| *Age* | | | | | | |
| ≤ 65 | 78.0 | 80.0 | 78.4 | 80.0 | 81.3 | 88.4 |
| > 65 | 71.2 | 72.7 | 77.4 | 75.8 | 76.3 | 76.5 |
| *d* | 0.16 | 0.17 | 0.02 | 0.10 | 0.12 | 0.33 |
| *Cirrhosis* | | | | | | |
| No | 74.6 | 76.4 | 78.9 | 80.7 | 80.7 | 85.1 |
| Yes | 74.7 | 76.0 | 75.8 | 73.0 | 76.2 | 81.0 |
| *d* | 0 | 0.01 | 0.07 | 0.19 | 0.11 | 0.11 |
| *AFP, ng/mL* | | | | | | |
| ≤ 400 | 78.0 | 79.1 | 78.8 | 80.3 | 79.1 | 82.5 |
| > 400 | 63.7 | 61.4 | 67.7 | 66.6 | – | – |
| *d* | 0.33 | 0.42 | 0.26 | 0.33 | – | – |
| *Tumor burden score* | | | | | | |
| Low/Medium | 77.2 | 77.2 | 78.7 | 78.2 | 80.9 | 84.4 |
| High | 53.0 | 66.8 | 66.6 | 73.6 | 65.5 | 78.7 |
| *d* | 0.56 | 0.24 | 0.29 | 0.11 | 0.39 | 0.16 |
| *BCLC stage* | | | | | | |
| BCLC-0/A | 75.9 | 78.8 | 79.1 | 78.7 | 80.1 | 84.5 |
| BCLC-B | 67.1 | 61.7 | 69.9 | 73.8 | 75.8 | – |
| *d* | 0.20 | 0.40 | 0.22 | 0.12 | 0.11 | – |
| *Grade* | | | | | | |
| Well to moderate | 78.4 | 78.5 | 78.7 | 77.7 | 78.3 | 82.7 |
| Poor to undifferentiated | 62.5 | 65.0 | 74.0 | 77.3 | 83.1 | – |
| *d* | 0.37 | 0.32 | 0.11 | 0.01 | − 0.12 | – |
| *Microvascular invasion* | | | | | | |
| No | 82.5 | 80.0 | 78.0 | 80.0 | 80.8 | 85.5 |
| Yes | 61.2 | 66.2 | 74.6 | 80.7 | 84.4 | 81.4 |
| *d* | 0.50 | 0.33 | 0.08 | − 0.02 | − 0.09 | 0.12 |
| *Liver capsule involvement* | | | | | | |
| No | 75.5 | 76.9 | 77.8 | 79.9 | 79.9 | 81.3 |
| Yes | 63.8 | 64.8 | 69.2 | 79.9 | 87.4 | – |
| *d* | 0.26 | 0.28 | 0.20 | 0 | − 0.19 | – |
| *Margin status* | | | | | | |
| R0 | 76.2 | 77.5 | 78.9 | 79.3 | 80.4 | 83.9 |
| R1 | 62.7 | 65.6 | 71.0 | 74.0 | – | – |
| *d* | 0.31 | 0.28 | 0.19 | 0.13 | – | – |

## Discussion

Traditional assessment of survival for HCC patients is typically calculated from the time of diagnosis or treatment with the use of widely accepted staging schemas or prognostic scores [6, 7, 18–22]. Nevertheless, traditional prognostic scores tend to underestimate prognosis, since this is heavily influenced by patients who die shortly after surgery. In contrast, CS—i.e., the probability of survival based on the number of years a patient has survived—may be better suited to describe the dynamic changes in patient prognosis over time and better predict real-time survival probabilities in both the immediate and late postoperative periods [23–25]. The current study was important because

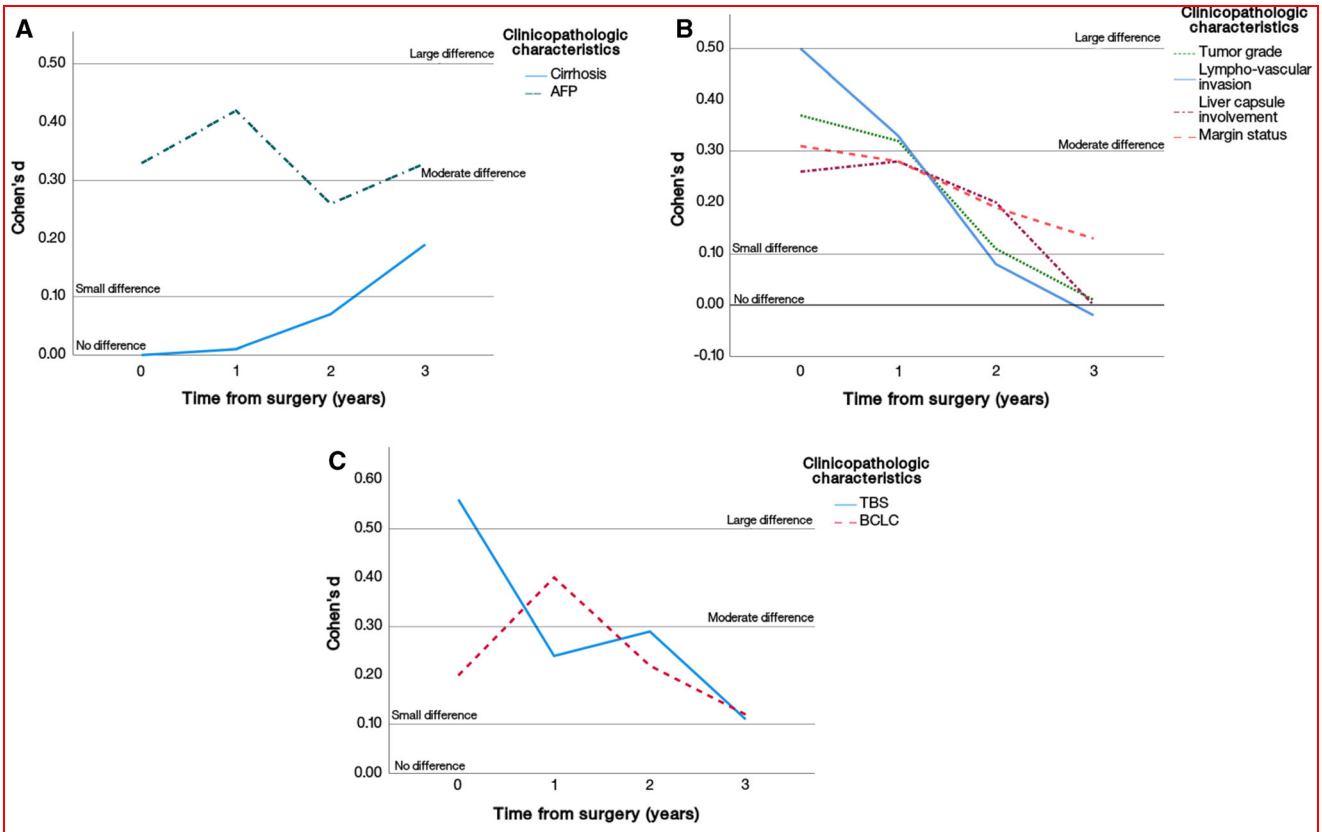


**Fig. 3** Line graphs demonstrating the variability of the standardized *d* values pertaining to certain clinicopathologic risk factors over time

we defined the CS rates in a large cohort of patients undergoing curative-intent resection for HCC. The current study noted that CS increased with every additional year a patient survived following curative-intent resection of HCC, in contrast to the actuarial survival that decreased over time. While the impact of unfavorable clinicopathologic factors (i.e. poor/undifferentiated tumor grade, microvascular invasion, margin status) on prognosis was most prominent shortly after surgery, their effect on outcomes decreased over time. In addition, CS increased over time irrespective of the TBS, with the largest differences between actuarial and CS noted among patients with high TBS. While TBS had the strongest impact on CS at the time of surgery, the impact of TBS in prognosis significantly decreased 3-years postoperatively. To the best of our knowledge, this is the first study to examine the impact of HCC TBS on CS after curative-intent resection for HCC.

Traditional assessment of prognosis has been performed using the Kaplan Meier method and prognostic factors have been almost universally assessed at the time of surgery [8, 26]. In fact, all available staging schemas and prognostic scores have assessed survival as a static rather than a dynamic measure [22, 27]. The odds, a patient survives for an additional amount of time changes, however, as patients accrue survival time. In turn, survival estimates based on available staging systems or prognostic scores become less accurate as time elapses from resection [9]. CS estimates the probability of surviving an additional number of years given that a patient has already survived for a certain length of time [14, 17, 23, 28]. As such, CS has been proposed as a more clinically relevant method to estimate survival probabilities during the follow-up period and thus evaluate prognosis in real life [14, 17, 23, 28]. Although a number of investigators have reported the CS estimates for a number of malignancies, including colon cancer, gastric cancer, pancreatic cancer, and cholangiocarcinoma [17, 23, 28, 29], there are only limited data specific to HCC [9, 13]. More specifically, the association of HCC TBS—a strong predictor of outcomes among patients with resectable HCC[8, 26]—and CS had not been previously investigated.

The current study reported on the actuarial versus CS among patients who underwent curative-intent resection for HCC with varied TBS. While the prognostic role of certain clinicopathological variables can be assessed at a given time using actuarial survival, CS provides a dynamic assessment of prognostic factors and their effect on outcomes over time. In particular, the current study aimed to

assess the impact of different factors on actuarial survival first and went one step further to evaluate the differential impact of the same factors on outcomes at different time points postoperatively. This information can be useful to patients in the postoperative setting and might help inform prognosis in real-life scenarios. While actuarial survival decreased over time, CS was noted to increase as time elapsed from resection among patients in the entire cohort (Fig. 2a). In particular, while 3-year actuarial survival decreased from 58.2% at 3-years to 53.0% at 5-years post-resection, $CS_3$ was noted to increase from 77.9% at 3-year to 83.7% at 5-years following resection in the entire cohort. In line with our findings, Shah et al. similarly reported that the probability of survival at 5-years post-resection was 79.3% and increased to 87.0% among patients who had already survived for 2- and 3-years, respectively [9]. Interestingly, in the current study, CS increased over time irrespective of the TBS with the largest differences between actuarial and CS noted in the high TBS group (Fig. 2b-d). Indeed, among patients with high TBS, $CS_3$ increased up to 78.7% at 5-years postoperatively, as opposed to the 30.7% estimated actuarial survival at 8-years (i.e., a 3-year actuarial survival at 5-years) following resection. Of note, the $CS_3$ of patients with high TBS around the 5th postoperative year approached that of patients with medium TBS at the same time point. One explanation for the large differences in actuarial versus CS among patients with high TBS may have been due to actuarial survival being heavily influenced by high-risk patients who died shortly after surgery. Another explanation for these findings could be the receipt of adjunct therapies for high-risk high TBS patients [30]. While the role of adjuvant chemotherapy in patients with resected HCC remains controversial, evidence has suggested that it might be beneficial for patients at high risk for recurrence [30–32]. In addition, the advent of immunotherapy and the use of checkpoint inhibitors has shown promise in the adjuvant setting [33]. Finally, although transarterial embolization (TACE) has been primarily used in the neoadjuvant setting, data from meta-analyses of randomized trials have suggested that TACE might reduce recurrence rates and thus may be of benefit in high-risk patients following resection [34, 35]. The data from the current study demonstrated that high-risk, high TBS patients who survived past the first few years following surgery have a survival probability that approached that of lower-risk, lower TBS individuals [9, 13].

The current study also examined the association of several clinicopathologic characteristics with CS and investigated whether the prognostic impact of these factors changed over time. Not surprisingly, age, serum AFP, tumor grade, microvascular invasion, liver capsule involvement resection margins, and TBS were each associated with OS (Table 2) [4, 8, 9, 26]. Perhaps of more interest, the impact of each prognostic factor relative to OS changed over time. For example, patients with cirrhosis had similar $CS_3$ as non-cirrhotic individuals immediately after surgery (74.6% vs. 74.7%, $d = 0$); in contrast, while $CS_3$ among cirrhotic patients did not increase over time, $CS_3$ did improve among non-cirrhotic patients (3-years postoperatively; $CS_3$: 73.0% vs. 80.7%, $d = 0.19$). It is well known that prognosis of cirrhotic patients with HCC relies not only on the tumor characteristics but also on the severity underlying liver disease. In turn, the presence of cirrhosis and poor underlying liver function along with a history of liver resection might together act as a double-hit for patients postoperatively, and compromise outcomes of cirrhotic individuals in the long-term. In addition, cirrhotic patients have higher risk of intrahepatic recurrence [36] and thus worse long-term outcomes, even after tumor resection when compared with non-cirrhotic individuals. This might explain the relative steady $CS_3$ in the cirrhotic group versus an increasing $CS_3$ in the non-cirrhotic group, which resulted in an increased $d$ value for cirrhosis over time. The prognostic impact of cirrhosis was, however, small over the study period. In contrast, preoperative AFP levels had a relatively constant, moderate effect on $CS_3$ from the time of resection (AFP $\leq$ 400 ng/ml vs. $>$ 400 ng/mL; 78.0% vs. 63.7%, $d = 0.33$) to 3-years following hepatectomy (80.3% vs. 66.6%, $d = 0.33$) (Fig. 3a). Of note, while patients with certain unfavorable clinicopathologic characteristics including poor/undifferentiated tumor grade, microvascular involvement, liver capsule invasion and positive resection margins had worse $CS_3$ at the time of resection, the impact of these factors on prognosis progressively decreased over time (Fig. 3b). In line with these findings, Cucchetti et al. reported that patients with adverse histologic features had comparable survival probabilities as patients with less advanced tumors or favorable histology after the 3rd postoperative year [14]. In the current study, we expanded on this work and noted that the impact of TBS on prognosis was most notable immediately after resection and gradually decreased as time elapsed from resection (Fig. 3c). This phenomenon has been described as the "natural selection effect" of individuals within a pool of individuals with widely different disease biology. Specifically, patients with the highest inherent risk die soon after surgery, whereas the survival of the remaining individuals with lower inherent risk will eventually reveal itself to be more favorable over time [28]. Collectively, the data suggested that risk stratification among patients should not overly rely on tools based solely on factors obtained at the time of diagnosis/resection. Rather, a dynamic assessment of survival may be a better, more accurate approach to assess prognosis as time elapses from diagnosis or resection [13].

Certain limitations need to be taken into consideration when interpreting the results of the present study. Due to the retrospective nature of the study, selection bias as to which patients were offered surgery was possible. In addition, given that this was a multi-institutional analysis, variations relative to indications for surgery, surgical techniques and perioperative care may have varied across the participating centers. The present study analyzed only patients who underwent resection for HCC, thus the results were not generalizable to patients undergoing other curative-intent treatment options for resectable HCC such as radiofrequency ablation or liver transplantation. CS may also have been impacted by underlying genetics/molecular profile of the HCC, as well as any intervening intervention used to treat a possible recurrence. These factors were included in the model. Furthermore, the database utilized did not contain data on adjuvant chemotherapy or other additional treatments, although probably very few patients -if any- received adjuvant therapies.

In conclusion, TBS was strongly associated with survival following HCC resection. CS rates among patients who underwent resection for HCC increased as patients survived additional years. In particular, the largest differences in actuarial versus CS were noted among patients with high TBS. While patients with a high HCC tumor burden generally have worse survival, a subset of patients will survive long-term. CS estimates can be used to provide important real-life information relative to the changing survival probability of patients with varied TBS after resection of HCC.

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**Declarations**

**Conflict of interest** None

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