Radiographic tumor burden score is useful for stratifying prognosis of hepatocellular carcinoma patients undergoing resection at different Barcelona Clinic Liver Cancer stages.

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Abstract

Purpose

The Barcelona Clinic Liver Cancer (BCLC) staging system has been recommended for prognostic prediction. However, prognosis is variable at different BCLC stages. We aimed to evaluate whether the radiographic tumor burden score (TBS) could be used to stratify prognosis in different BCLC stages.

Methods

Hepatocellular carcinoma (HCC) patients undergoing liver resection (LR) at BCLC-0, -A, or -B stage in our institution in 2007–2018 were divided into derivation and validation cohorts. Overall survival (OS) was analyzed according to the TBS and BCLC stage. TBS cutoff values for OS were determined with X-tile.

Results

Of the 749 patients in the derivation cohort, 138 (18.4%) had BCLC-0, 542 (72.3%) BCLC-A, and 69 (9.2%) BCLC-B HCC; 81 (10.8%) had a high TBS (> 7.9), 474 (63.3%) a medium TBS (2.6–7.9), and 194 (25.9%) a low TBS (< 2.6). OS worsened progressively with increasing TBS in the cohort ($p < 0.001$) and in BCLC-A ($p = 0.04$) and BCLC-B ($p = 0.002$) stages. Multivariate analysis showed that the TBS was associated with OS of patients with BCLC-A (medium vs. low TBS: hazard ratio [HR] = 2.390, 95% CI = 1.024–5.581, $p = 0.04$; high vs. low TBS: HR = 3.885, 95% CI = 1.443–10.456, $p = 0.007$) and BCLC-B (high vs. medium TBS: HR = 2.542, 95% CI = 1.077–6.002, $p = 0.033$) HCC. The TBS could also be used to stratify the OS of patients in the validation cohort ($p < 0.001$).

Conclusion

The TBS could be used to stratify the OS of the entire cohort and BCLC stages A and B of HCC patients undergoing LR.

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide [1]. Liver resection (LR) is reserved for patients with preserved liver function in the absence of extrahepatic metastasis and macrovascular invasion [2, 3]. LR improves overall survival (OS) across the Barcelona Clinic Liver Cancer (BCLC) stages [4]. However, LR also carries a higher risk compared to non-surgical treatments. Therefore, preoperative prediction of the outcome for HCC patients undergoing LR is important and helpful for clinical decision-making.

The BCLC staging system has been repeatedly validated and is recommended for prognostic prediction [3]. In the recent version of the BCLC staging system, single large HCC > 5cm is designated as BCLC-A rather than BCLC-B [3]. However, as tumor size increases, the risk of microvascular invasion and micrometastasis increases and the outcome worsens [5]. A previous study showed that the prognosis of patients with a single large HCC > 5 cm undergoing LR was similar to that of patients at BCLC stage B [6]. Therefore, prognosis is variable for patients undergoing LR at BCLC stage A. BCLC stage B is also well known for its heterogeneous prognosis [7].

The tumor burden score (TBS) was originally proposed by Sasaki et al. [8]. They found that the TBS was an accurate tool to predict the OS of patients with colorectal liver metastasis undergoing resection. The TBS is simple to use, and previous studies have demonstrated its impact in resected and non-resected HCC cases [9–15]. Tsilimigras et al. studied patients with BCLC-0, -A, and -B HCC who underwent LR, and showed that pathological TBS could stratify the OS of the entire cohort and at BCLC stages A and B [9]. However, pathological TBS could not preoperatively predict the prognosis of HCC patients who underwent LR.

Therefore, the objective of this study was to evaluate whether radiographic TBS could be used to stratify the OS of an entire cohort and at BCLC stages A and B of HCC patients undergoing LR.

Materials And Methods

The Institutional Review Board of Chang Gung Memorial Hospital-Kaohsiung Branch approved this study (reference number: 202000398B0) and waived the need for informed consent due to the retrospective and observational nature of the study design. Data were extracted from the Kaohsiung Chang Gung Memorial Hospital HCC registry. The vital status of every patient in the registry is updated annually by linking to the website of the Ministry of Health and Welfare of Taiwan (Cancer Screening and Tracing Information Integrated System for Taiwan [https://hosplab.hpa.gov.tw/CSTIIS/index.aspx]).

Patients with newly diagnosed HCC who underwent LR at Kaohsiung Chang Gung Memorial Hospital from 2007 to 2018 were enrolled in this study. The inclusion criterion was HCC at BCLC stage 0, A, or B. The exclusion criteria were unknown preoperative alpha-fetoprotein (AFP) level (only in the derivation cohort), age < 18 years, unknown pathological stage, pathology N1 or M1, and non-curative LR. Curative LR was defined as complete resection of macroscopic tumors with microscopically negative surgical margins. Finally, 749 patients who underwent LR in 2011–2018 served as a derivation cohort, and 275 patients who underwent LR in 2007–2010 served as a validation cohort. The cancer registry data collection in Taiwan started in 2006. The references used for the cancer registry data include the Facility Oncology Registry Data Standards (https://www.facs.org/-/media/files/quality-programs/cancer/ncdb/fords-2016.ashx) and Surveillance, Epidemiology, and End Results (SEER) (https://seer.cancer.gov/). Laboratory and pathology data, including AFP, liver fibrosis, Child–Pugh class, hepatitis B surface antigen (HBsAg), and anti-hepatitis C virus (HCV) antibody, have been recorded since 2011 for HCC in Taiwan. Therefore, we used patients who underwent LR in 2011–2018 as a derivation

cohort due to the completeness of the available data in the HCC registry starting from 2011. The raw data for the derivation cohort are available via the following digital object identifier: https://www.dropbox.com/scl/fi/vluatxipqj7totcjppxrb/TBS-derivation-cohort.xlsx?dl=0&rlkey=3neo09dz0m3hsrsuir7eri19a

The raw data for the validation cohort are available via the following digital object identifier: https://www.dropbox.com/scl/fi/p9ay89ms05r3s8m4uxbof/TBS-validation-cohort.xlsx?dl=0&rlkey=55uosqj2rw4k85s9cipbc0161

Tumor size and number were assessed by preoperative contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). A multidisciplinary team (MDT) discussed each patient's case before LR. Liver nodules with a maximum diameter of ≥ 1 cm were counted as HCC nodules if typical HCC imaging features were present (i.e., arterial phase hyperenhancement with washout in the portal venous or delayed phases) in cirrhotic patients [3]. Whether or not to count liver nodules that did not meet the image criteria for HCC as HCC nodules was based on the MDT discussion.

Correlation between radiographic and pathological tumor size and number

We randomly selected 180 patients and evaluated the correlation between radiographic and pathological tumor size and number. The raw data for this subgroup of patients are available via the following digital object identifier: https://www.dropbox.com/scl/fi/vc3mhzuv6sszcrv5fmd0n/image-pathology-correlation-all-patients-raw-data-for-submission.xlsx?dl=0&rlkey=8glr30hn6imluqayvrlczpw7w

Tumor differentiation was assessed with Edmondson and Steiner's classification [16]. Fibrosis was assessed with the Ishak score [17]. Cirrhosis was defined as fibrosis with an Ishak score of 5 or 6. Major resection was defined as resection of ≥ 3 Couinaud segments.

The 6th version of the American Joint Committee on Cancer (AJCC)/tumor–node–metastasis (TNM) staging [18] was applied to our HCC registry data from 2007 to 2010, 7th version of the AJCC/TNM staging [19] was applied to the data from 2010 to 2017, and the 8th version [20] was applied to the data since 2018. Therefore, we presented pathology T stage in the current study as stage 1 or 2 versus 3 or 4. T stage 1 or 2 was a single tumor with or without vascular invasion or multiple tumors with none > 5 cm. T stage 3 or 4 was multiple tumors with any > 5 cm, or tumors with major vascular invasion, perforation of visceral peritoneum, or direct invasion of adjacent organs other than the gallbladder.

Outcome measurement

The outcome measurement was OS, defined as the interval between the date of LR and the date of the last follow-up or death.

Definitions of BCLC stages and TBS

A single tumor of ≤ 2 cm was defined as BCLC stage 0; a single tumor of > 2 cm, or two to three tumors of ≤ 3 cm, as BCLC stage A; and two to three tumors of ≥ 3 cm, or ≥ four tumors, as BCLC stage B [3]. Tumor size was defined by the size of the largest tumor if there were multiple tumors. TBS^2 = (maximum tumor diameter (cm))^2 + (number of tumors)^2 [8]. The cutoff values of TBS for OS were determined with X-tile [21], a bioinformatics tool created by Camp et al.

Statistical analysis

The characteristics of the patients are presented as number (%) and were compared using the chi-square test. Kaplan–Meier survival curves and the log-rank test were used to compare OS between groups. Covariates in the multivariable model were chosen a priori for clinical relevance. The potential confounders included age, cirrhosis, TBS, AFP (≤ 400 ng/mL vs. > 400 ng/mL) [22], and tumor differentiation. These variables were fully adjusted in the multivariate model. Results are presented as hazard ratio (HR) with 95% confidence interval (CI). The kappa value was calculated to indicate the radiographic–pathological tumor number agreement (0.41–0.60 indicated moderate agreement; 0.61–0.80 indicated good agreement; and > 0.81 indicated excellent agreement). The relationship between radiographic tumor size and pathological measurements was analyzed using Pearson correlation coefficients. Relationships were considered to be nonexistent when the correlation coefficient (r) was < 0.20, weak when r = 0.21–0.40, moderate when r = 0.41–0.60, strong when r = 0.61–0.80, and almost perfect when r > 0.80. Statistical analyses were performed using SPSS version 22.0. Two-tailed significance values were applied, and p < 0.05 was defined as statistically significant.

Results

Characteristics of the derivation cohort

A total of 749 HCC patients who underwent LR met the inclusion criteria and were enrolled in the derivation cohort. Overall, 138 patients (18.4%) had a BCLC score of 0, 542 (72.4%) had a BCLC score of A, and 69 (9.2%) had a BCLC score of B (Table 1). Of the 749 patients, 394 (52.6%) were HBsAg positive, 252 (33.6%) were anti-HCV antibody positive, 352 (47.0%) had a major resection, 254 (33.9%) were > 65 years of age, 576 (76.9%) were male, 120 (16.0%) had an AFP level of > 400 ng/ml, and 737 (98.4%) were Child–Pugh class A. Pathological examination showed 290 patients (38.7%) with cirrhosis, 29 (3.9%) with poorly differentiated tumors, and 63 (8.4%) with pathology T stage 3 or 4. The highest proportion of BCLC stage A patients were in the > 65-year age group. The highest proportion of BCLC stage 0 patients had cirrhosis, while the BCLC stage B group included the highest number of patients with AFP ≥ 400 ng/ml, major resection, and pathology T stage 3 or 4.

Cutoff values of tumor burden score

Patients were divided into three groups according to the TBS: high TBS (> 7.9; n = 81 [10.8%]); medium TBS (2.6–7.9; n = 474 [63.3%]); and low TBS (< 2.6; n = 194 [25·9%]) (Fig. 1). All 138 patients with BCLC stage 0 HCC had a low TBS. Patients with BCLC stage A tumors had a low (n = 82 [15.1%]), medium (406

[74.9%]), or high (54 [10.0%]) TBS, whereas those with BCLC stage B HCC had a medium (42 [60.9%]) or high (27 [39.1%]) TBS.

TBS could be used to stratify the OS of the derivation cohort

After a median follow-up of 19.9 (inter quantile range (IQR) = 10.9–85.9) months, the 5-year OS following LR of the derivation cohort was 70.6% (95% CI = 66.3–75.3%). The five-year OS varied based on BCLC stage (85, 73, and 48% for BCLC stages 0, A, and B, respectively; $p < 0.001$). The TBS could be used to stratify OS (5-year OS: 87.5, 72, and 48% for low, medium, and high TBS, respectively; $p < 0{\cdot}001$) (Fig. 2).

TBS could be used to stratify OS at the BCLC stages A and B

To evaluate whether TBS could be used to stratify the OS at BCLC stages A and B, subgroup analyses were performed for BCLC stage A and B patients. In the BCLC stage A group, OS worsened progressively with increasing TBS (5-year OS: 87.5, 70, and 63% for low, medium, and high TBS, respectively; $p = 0.04$) (Fig. 3a). Of the patients with BCLC stage B HCC, those with a high TBS had a worse 5-year OS than those with a medium TBS (23% vs. 65%; $p = 0.002$) (Fig. 3b).

Multivariate analysis of prognostic factors associated with overall survival in BCLC stages A and B

Multivariate analysis showed that an age of > 65 years (HR = 2.195, 95% CI = 1.461–3.298, $p < 0.001$), the presence of cirrhosis (HR = 1.978, 95% CI = 1.309–2.988, $p = 0.001$), medium TBS vs. low TBS (HR = 2.390, 95% CI = 1.024–5.581, $p = 0.04$), and high vs. low TBS (HR = 3.885, 95% CI = 1.443–10.456, $p = 0.007$) were associated with OS in BCLC stage A (Table 2). Multivariate analysis showed that an age of > 65 years (HR = 3.269, 95% CI = 1.297–8.237, $p = 0.012$), AFP > 400 ng/ml (HR = 2.938, 95% CI = 1.138–7.589, $p = 0.026$), and high vs. medium TBS (HR = 2.542, 95% CI = 1.077–6.002, $p = 0.033$) were associated with OS in BCLC stage B (Table 2).

Validation of TBS

Fifty-six patients (20.4%) had BCLC stage 0, 196 (71.3%) had BCLC stage A, and 23 (8.4%) had BCLC stage B HCC in the validation cohort. In this cohort, 72 patients (26.2%) had a high TBS, 163 (59.3%) had a medium TBS, and 40 (14.5%) had a high TBS (Table 3). In addition, TBS could be used to stratify the OS of the validation cohort. Patients with a low, medium, and high TBS had a 5-year OS of 88, 78, and 50% respectively ($p < 0.001$) (Fig. 4a). The TBS could also be used to stratify OS in BCLC stage A (5-year OS = 83, 82, and 60% for low, medium, and high TBS, respectively; $p = 0.03$) (Fig. 4b).

Correlation between radiographic and pathological tumor size and number

The characteristics of this subgroup of 180 patients are shown in Table 4. Thirty-nine patients (21.7%) were BCLC stage 0, 129 (71.7%) BCLC stage A, and 12 (6.7%) BCLC stage B. In addition, 161 (89.4%) patients had a radiographic solitary tumor and 19 (10.6%) had radiographic multiple tumors; 160 (88.9%) patients had a pathological solitary tumor and 20 (11.1%) had pathological multiple tumors. The median

(IQR) radiographic tumor size was 29 (22–50) mm. The median (IQR) pathological tumor size was 28.5 (21–50) mm. Kappa was 0.665, indicating good agreement between radiographic and pathological tumor number. The discrepancy between radiographic and pathological tumor numbers was mainly in nodules < 1 cm, found either by radiographic or pathological examination. Of the 180 patients, 12 (6.7%) showed a discrepancy between radiographic and pathological tumor numbers. Of these patients, seven had satellite nodules < 1 cm that were identified on pathological examination but were not detected in imaging studies; five patients had radiographic tumors < 1cm which were not found on pathological examination. The correlation between radiographic and pathological tumor size was almost perfect (r = 0.973; p < 0.001).

Discussion

Our data showed that radiographic TBS could be used to stratify the OS, both for the entire cohort and for BCLC stages A and B, of HCC patients undergoing LR. This information is useful for preoperative prognostic prediction. This study used the X-tile bioinformatics tool [21] to determine the optimal TBS cutoff values for OS (low TBS was defined as < 2.6, medium TBS as 2.6–7.9, and high TBS as > 7.9), which were different from those of Tsilimigras et al. (low TBS was defined as < 3.36, medium as 3.36–13.74, and high as > 13.74) [9]. The discrepancies between the two studies may be due to different patient characteristics and, most importantly, the use of pathologically defined TBS by Tsilimigras et al. [9] in contrast to our use of radiographically defined TBS.

We enrolled patients with BCLC stage B HCC in this study. The BCLC guidelines recommend transarterial chemo-embolization for BCLC stage B patients [3]. However, the selected patients with BCLC B (e.g., patients with multiple tumors located in one lobe of the liver or patients with the main tumor(s) located in one lobe of the liver and a small tumor located on the surface of the contralateral lobe of the liver) were eligible for LR [23].

Some previous studies aimed to stratify prognosis of HCC patients undergoing LR at different BCLC stages. Tsilimigras et al. proposed a TBS-based preoperative score to predict the OS of BCLC stage B HCC patients undergoing LR. The parameters used in this model included radiographic TBS, cirrhosis, AFP, and the American Society of Anesthesiologists (ASA) classification. This model could categorize patients into distinct prognostic groups in relation to OS [10].

In the case of BCLC stage A, the cutoff value of tumor size to define single large HCC for prognostic stratification is controversial. A study based on patients from Western countries used 5 cm [6] while a study from China used 7 cm [24] as the cutoff value to define single large HCC for prognostic stratification of HCC patients undergoing LR.

The discrepancy between radiographic and pathological tumor numbers was mainly in nodules determined to be < 1 cm either by radiographic or by pathological examination. Diagnosis of sub-centimeter HCC may be challenging [25]. Diagnostic performance in sub-centimeter HCC detection can be improved with gadoxetic acid-enhanced MRI [26]. However, MRI is not feasible for patients with

inadequate breath-holding ability, claustrophobia, MRI contraindications, etc. Therefore, the American guidelines do not recommend MRI in preference to CT for diagnostic evaluation of patients with HCC [2].

The strength of this study is the use of the radiographic TBS rather than the pathological TBS. The radiographic TBS is useful for preoperative prognostic prediction. This study used valid data for vital status because the vital status of every single patient was confirmed by linking to the authoritative website of the Ministry of Health and Welfare of Taiwan. The study has several limitations: (1) it is a single institutional study, which may not be generalizable to other institutions; (2) there was no external validation; (3) the number of BCLC stage B cases in the validation cohort was small (n = 23), and, therefore, we did not analyze whether the TBS could be used to stratify the prognosis of the cohort in this stage; (4) the HCC registry data did not include pathological data, e.g., for vascular invasion and satellite tumors, which are well-known factors of poor prognosis of HCC patients [27, 28], as well as information on comorbidities (e.g., ASA classification), performance status, and details of liver function, which are associated with the prognosis of HCC patients [2, 3].

Conclusion

The radiographic TBS could be used to stratify the OS of the entire cohort of and BCLC stage A and B HCC patients who underwent LR. This information may be useful in preoperative prognostic prediction.

Declarations

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Authors' Contributions

1. Conception or design of the work: YHY, CCW
2. The acquisition, analysis, or interpretation of data: WFL, YWL, CCW, CCY, CCL, YFC
3. Drafted the work: YHY, WFL
4. Revised it critically for important intellectual content: CCW

5. Approved the version to be published: all authors
6. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors

References

1. Global Burden of Disease Cancer Collaboration (2019), Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol; 5:1749–1768. doi: 10.1001/jamaoncol.2019.2996.
2. Marrero JA, Kulik LM, Sirlin CB, et al (2018). Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology; 68:723–750. doi: 10.1002/hep.29913
3. EASL Clinical Practice Guidelines (2018). Management of hepatocellular carcinoma. J Hepatol; 69:182–236. doi: 10.1016/j.jhep.2018.03.019
4. Vitale A, Burra P, Frigo AC, et al (2015). Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol; 62:617–624. doi: 10.1016/j.jhep.2014.10.037.
5. Pawlik TM, Delman KA, Vauthey J-N, et al (2005). Tumor size predicts vascular invasion and histologic grade: implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl; 11:1086–1092. doi: 10.1002/lt.20472.
6. Tsilimigras DI, Bagante F, Sahara K, et al (2019). Prognosis After Resection of Barcelona Clinic Liver Cancer (BCLC) Stage 0, A, and B Hepatocellular Carcinoma: A Comprehensive Assessment of the Current BCLC Classification. Ann Surg Oncol; 26:3693–3700. doi: 10.1245/s10434-019-07580-9.
7. Kudo M (2016). Heterogeneity and Subclassification of Barcelona Clinic Liver Cancer Stage B. Liver Cancer; 5:91 – 6. doi: 10.1159/000367768.
8. Sasaki K, Morioka D, Conci S, et al (2018). The tumor burden score: a new‘metro-ticket’ prognostic tool for colorectal liver metastases based on tumor size and number of tumors. Ann Surg; 267: 132–141. doi: 10.1097/SLA.0000000000002064
9. Tsilimigras DI, Moris D, Hyer JM, et al (2020). Hepatocellular carcinoma tumour burden score to stratify prognosis after resection. Br J Surg; 107:854–864. doi: 10.1002/bjs.11464.
10. Tsilimigras DI, Mehta R, Paredes AZ, et al (2020). Overall Tumor Burden Dictates Outcomes for Patients Undergoing Resection of Multinodular Hepatocellular Carcinoma Beyond the Milan Criteria. Ann Surg;272: 574–581. doi: 10.1097/SLA.0000000000004346.
11. Moris D, Shaw BI, McElroy L, et al (2020). Using Hepatocellular Carcinoma Tumor Burden Score to Stratify Prognosis after Liver Transplantation. Cancers (Basel); 12:3372. doi: 10.3390/cancers12113372.

12. Elfadaly AN, Tsilimigras DI, Hyer JM, et al (2021). Impact of Tumor Burden Score on Conditional Survival after Curative-Intent Resection for Hepatocellular Carcinoma: A Multi-Institutional Analysis. World J Surg;45:3438–3448. doi: 10.1007/s00268-021-06265-3.
13. Tsilimigras DI, Hyer JM, Diaz A, et al (2021). Synergistic Impact of Alpha-Fetoprotein and Tumor Burden on Long-Term Outcomes Following Curative-Intent Resection of Hepatocellular Carcinoma. Cancers (Basel)11; 13:747.
14. Vitale A, Lai Q, Farinati F, et al (2018); Italian Liver Cancer (ITA.LI.CA) group. Utility of Tumor Burden Score to Stratify Prognosis of Patients with Hepatocellular Cancer: Results of 4759 Cases from ITA.LI.CA Study Group. J Gastrointest Surg; 22:859–871. doi: 10.1007/s11605-018-3688-y.
15. Firl DJ, Sasaki K, Agopian VG, et al (2020). Charting the Path Forward for Risk Prediction in Liver Transplant for Hepatocellular Carcinoma: International Validation of HALTHCC Among 4,089 Patients. Hepatology; 71:569–582. doi: 10.1002/hep.30838.
16. Edmonson H, Steiner P (1954). Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer;7: 462–503. doi: 10.1002/1097-0142(195405)7:3<462::aid-cncr2820070308>3.0.co;2-e.
17. Everhart JE, Wright EC, Goodman ZD, et al (2010). Prognostic value of Ishak fibrosis stage: findings from the hepatitis C antiviral long-term treatment against cirrhosis trial. Hepatology 2010;51: 585–594. doi: 10.1002/hep.23315.
18. Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M, eds. AJCC cancer staging manual, 6th edn. Chicago: Springer, 2002. 435p.
19. American Joint Committee on Cancer. American Joint Committee on Cancer Staging Manual, 7th ed, Edge SB, Byrd DR, Compton CC, et al (Eds), Springer, New York 2010. p.175
20. Abou-Alfa GK, Pawlik TM, Shindoh J, et al. Liver. In: AJCC Cancer Staging Manual, 8th ed, Amin MB (Ed), AJCC, Chicago 2017. p.287
21. Camp RL, Dolled-Filhart M, Rimm DL (2004). X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res; 10: 7252–7259. doi: 10.1158/1078-0432.CCR-04-0713.
22. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998; 28:751–5. doi: 10.1002/hep.510280322.
23. Wada H, Eguchi H, Noda T, et al (2016). Selection criteria for hepatic resection in intermediate-stage (BCLC stage B) multiple hepatocellular carcinoma. Surgery; 160:1227–1235. doi: 10.1016/j.surg.2016.05.023.
24. Wang YY, Zhong JH, Xu HF, et al (2019). A modified staging of early and intermediate hepatocellular carcinoma based on single tumour > 7 cm and multiple tumours beyond up-to-seven criteria. Aliment Pharmacol Ther; 49:202–210. doi: 10.1111/apt.15074.
25. Lee YJ, Lee JM, Lee JS, et al (2015). Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. Radiology; 275: 97–109

[PMID: 25559230 DOI: 10.1148/ radiol.14140690

26. Yu MH, Kim JH, Yoon JH, et al (2014). Small (≤ 1-cm) hepatocellular carcinoma: diagnostic performance and imaging features at gadoxetic acid-enhanced MR imaging. Radiology; 271: 748–760 [PMID: 24588677 DOI: 10.1148/ radiol.14131996
27. Poon RT, Fan ST, Lo CM, et al (2002). Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function. Ann Surg; 235:373–382. doi: 10.1097/00000658-200203000-00009.
28. Tabrizian P, Jibara G, Schrager B, et al (2015). Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg; 261:947–955. doi: 10.1097/SLA.0000000000000710.

Tables

Table 1
Characteristics of the derivation cohort.

	Total, n = 749	BCLC 0, n = 138	BCLC A, n = 542	BCLC B, n = 69	p
Age (yr)					0.004
≦ 65	495 (66.1%)	103 (74.6%)	309 (62.5%)	53 (76.8%)	
> 65	254 (33.9%)	35 (25.4%)	203 (37.5%)	16 (23.2%)	
Sex					0.187
Male	576 (76.9%)	103 (74.6%)	414 (76.4%)	59 (85.5%)	
Female	173 (23.1%)	35 (25.4%)	128 (23.6%)	10 (14.5%)	
Cirrhosis					< 0.001
Yes	290 (38.7%)	72 (52.2%)	201 (37.1%)	17 (24.6%)	
No	422 (56.3%)	65 (47.1%)	307 (56.6%)	50 (72.5%)	
Unknown	37 (4.9%)	1 (0.7%)	34 (6.3%)	2 (2.9%)	
HBs Ag					0.093
Positive	394 (52.6%)	80 (58.0%)	272 (50.2%)	42 (60.9%)	
Negative	355 (47.4%)	58 (42.0%)	270 (49.8%)	27 (39.1%)	
Anti-HCV					0.120
Positive	252 (33.6%)	55 (39.9%)	179 (33.0%)	18 (26.1%)	
Negative	497 (66.4%)	83 (60.1%)	363 (67.0%)	51 (73.9%)	
AFP (ng/ml)					< 0.001
≦ 400	629 (84.0%)	123 (89.1%)	142 (85.2%)	44 (63.8%)	
> 400	120 (16.0%)	15 (10.9%)	80 (14.8%)	25 (36.2%)	
Child Pugh class					0.323
A	737 (98.4%)	138 (100%)	532 (98.2%)	67 (97.1%)	
B	11 (1.5%)	0	9 (1.7%)	2 (2.9%)	
Unknown	0	0	1 (0.2%)	0	
Type of resection					< 0.001
Major	352 (47.0%)	38 (27.5%)	260 (48.0%)	54 (78.3%)	

BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein;

	Total, n = 749	BCLC 0, n = 138	BCLC A, n = 542	BCLC B, n = 69	p
Minor	309 (53.0%)	100 (72.5%)	282 (52.0%)	15 (21.7%)	
Tumor differentiation					0.847
Poor	29 (3.9%)	4 (2.9%)	22 (4.1%)	3 (4.3%)	
Moderate	658 (87.9%)	119 (86.2%)	478 (88.2%)	61 (88.4%)	
Well	56 (7.5%)	13 (9.4%)	22 (4.1%)	5 (7.2%)	
Necrosis	5 (0.7%)	2 (1.4%)	3 (0.6%)	0	
Pathology T stage					< 0.001
1–2	686 (91.6%)	135 (97.8%)	516 (95.2%)	35 (50.7%)	
3–4	63 (8.4%)	3 (2.2%)	26 (4.8%)	34 (49.3%)	
Tumor burden score					< 0.001
Low < 2.6	196 (26.2%)	138 (100%)	58 (10.7%)	0	
Medium:2.6–7.9	477 (63.7%)	0	434 (80.1%)	43(62.3%)	
High > 7.9	76 (10.1%)	0	50 (9.2%)	26 (37.7%)	

BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein;

Table 2
Multivariate Cox regression analysis of overall survival in Barcelona Clinic Liver Cancer (BCLC) stages A and B.

	BCLC stage A		**BCLC stage B**	
	HR (95%CI)	p	HR (95%CI)	p
Age (yr)				
≦ 65	1.00 (reference)		1.00 (reference)	
> 65	2.195 (1.461–3.298)	< 0.001	3.269 (1.297–8.237)	0.012
Cirrhosis				
No	1.00 (reference)		1.00 (reference)	
Yes	1.978 (1.309–2.988)	0.001	1.258(0.496–3.190)	0.629
AFP (ng/ml)				
≦ 400	1.00 (reference)		1.00 (reference)	
> 400	1.364 (0.833–2.233)	0.217	2.938(1.138–7.589)	0.026
Tumor burden score				
Low	1.00 (reference)			
Medium	2.390 (1.024–5.581)	0.04	1.00 (reference)	
High	3.885(1.443–10.456)	0.007	2.542 (1.077–6.002)	0.033
Tumor differentiation				
Well or moderate	1.00 (reference)		1.00 (reference)	
Poor	2.196(0.936–5.152)	0.07	2.062 (0.512–8.309)	0.309
BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein;				

Table 3
Characteristics of the validation cohort.

	Total, n = 275	BCLC 0, n = 56	BCLC A, n = 196	BCLC B, n = 23	p
Age (yr)					0.544
≦ 65	190 (69.1%)	42 (75%)	133 (67.9%)	15 (65.2%)	
> 65	85 (30.9%)	14 (25%)	63 (32.1%)	8 (34.8%)	
Sex					0.201
Male	207 (75.3%)	37 (66.1%)	152 (77.6%)	18 (78.3%)	
Female	68 (24.7%)	19 (33.9%)	44 (22.4%)	5 (21.7%)	
Type of resection					< 0.001
Major	155 (56.4%)	19 (33.9%)	115 (58.7%)	21 (91.3%)	
Minor	120 (43.6%)	37 (66.1%)	81 (41.3%)	2 (8.7%)	
Tumor differentiation					0.039
Poor	14 (5.1%)	0	13 (6.6%)	1 (4.3%)	
Moderate	210 (73.4%)	39 (69.6%)	151 (77.0%)	20 (87.0%)	
Well	40 (14.5%)	15 (26.8%)	24 (12.2%)	1 (4.3%)	
Necrosis	11 (4%)	2	8 (4.1%)	1 (4.3%)	
Pathology T stage					< 0.001
1–2	245 (89.1%)	53 (94.6%)	177 (90.3%)	15 (65.2%)	
3–4	30 (10.9%)	3 (5.4%)	19 (9.7%)	8 (34.8%)	
Tumor burden score					< 0.001
Low (< 2.6)	72 (26.2%)	56 (100%)	16 (8.2%)		
Medium (2.6–7.9)	163 (59.3%)	0	150 (76.5%)	13 (56.5%)	
High (> 7.9)	40 (14.5%)	0	30 (15.3%)	10 (43.5%)	
BCLC, Barcelona Clinic Liver Cancer;					

Table 4
Characteristics of 180 randomly selected patients for determining the correlation between radiographic and pathological tumor numbers and sizes.

Variables	
Age (yr)	64(56–70)
Male sex	135 (75%)
Cirrhosis	
Yes	55(30.6%)
No	110(61.1%)
Unknown	15(8.3%)
HBs Ag	
Positive	96(53.3%)
Negative	84(46.7%)
Anti-HCV	
Positive	52(28.9%)
Negative	128(71.1%)
AFP (ng/ml)	
≦ 400	161(89.4%)
> 400	19(10.6%)
BCLC stage	
0	39(21.7%)
A	129(71.7%)
B	12(6.7%)
Type of resection	
Major	77(42.8%)
Minor	103(57.2%)
Tumor differentiation	
Poor	15(8.3%)

Data were presented as number (%) or median (IQR); BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein;

Variables	
Moderate	157(87.2%)
Well	7(3.9%)
Necrosis	1(0.6%)
Pathology T stage	
1–2	169(93.9%)
3–4	11(6.1%)
Radiographic tumor number	
1	161(89.4%)
≧ 2	19(10.6%)
Pathology tumor number	
1	160(88.9%)
≧ 2	20(11.1%)
Radiographic tumor size (mm)	29(22–50)
pPathology tumor size (mm)	28.5(21–50)
Data were presented as number (%) or median (IQR); BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein;	

Figures

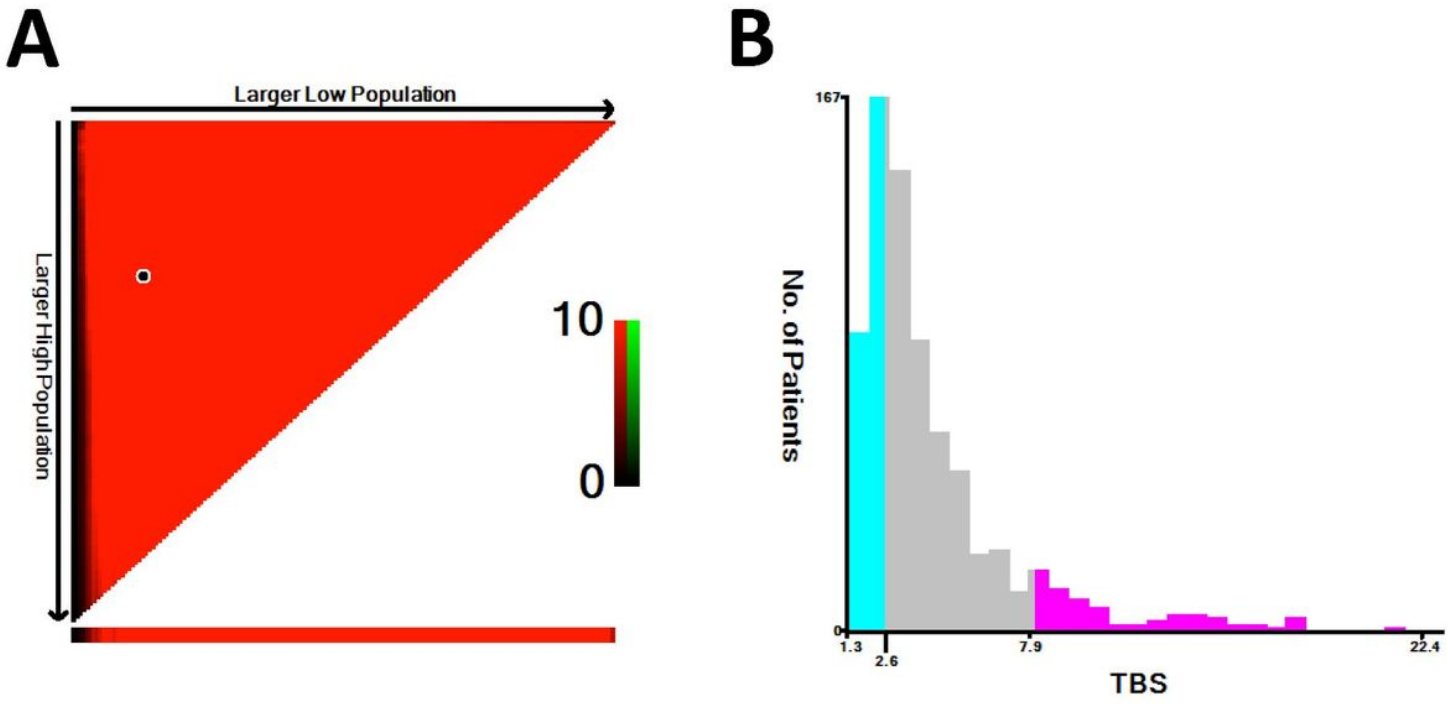

Figure 1

Cutoff values of the tumor burden score (TBS) for overall survival were determined with X-tile, a bioinformatics tool created by Camp et al. (A) Data represented graphically in a right-triangular grid in which each pixel represents the data from a given set of divisions. The vertical axis represents all possible “high” populations with their size increasing from top to bottom. Similarly, the horizontal axis represents all possible “low” populations with their size increasing from left to right. (B) The number of patients in each group for a given set of divisions.

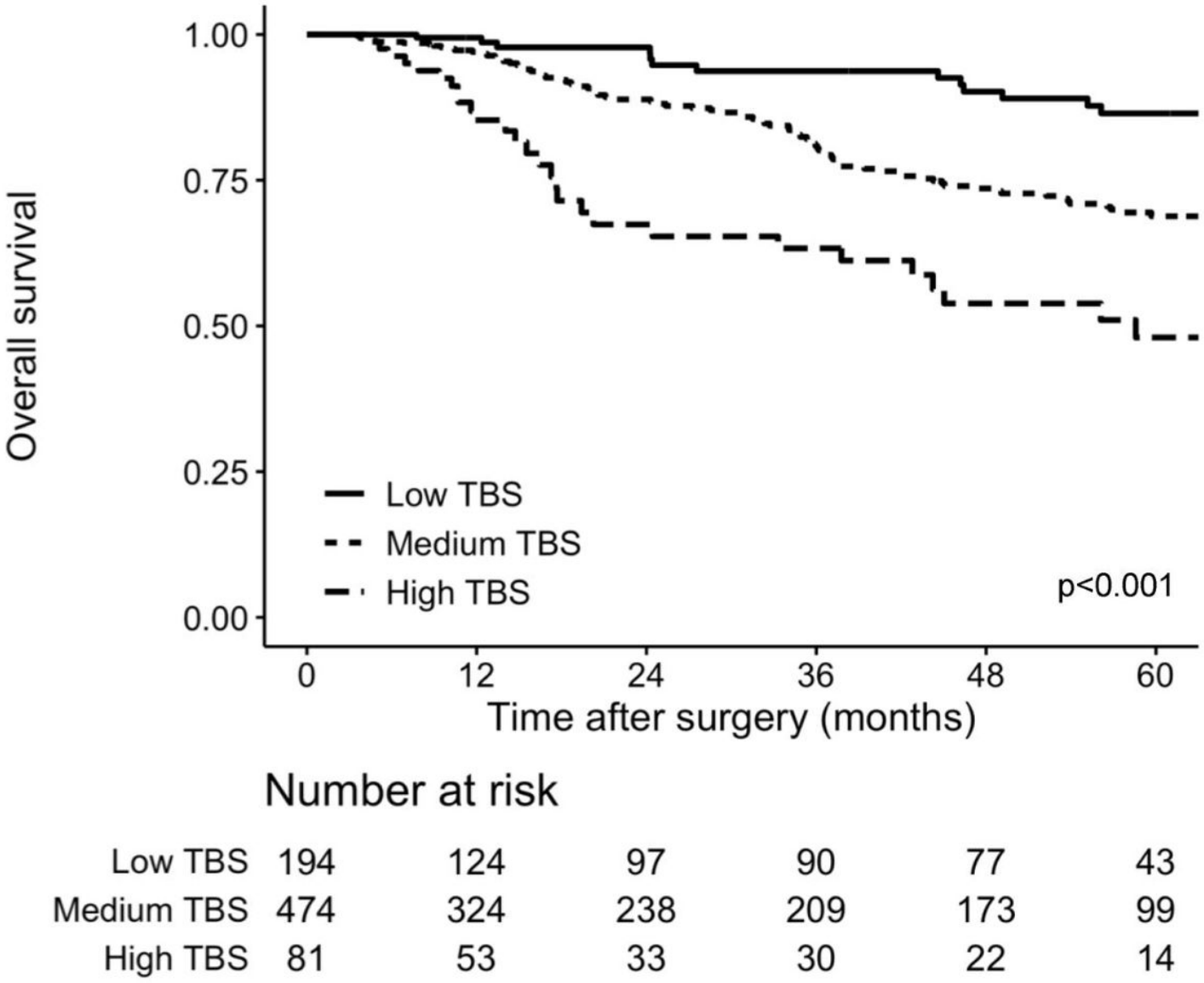

Figure 2

Kaplan–Meier survival curves for overall survival of the derivation cohort by tumor burden score (TBS).

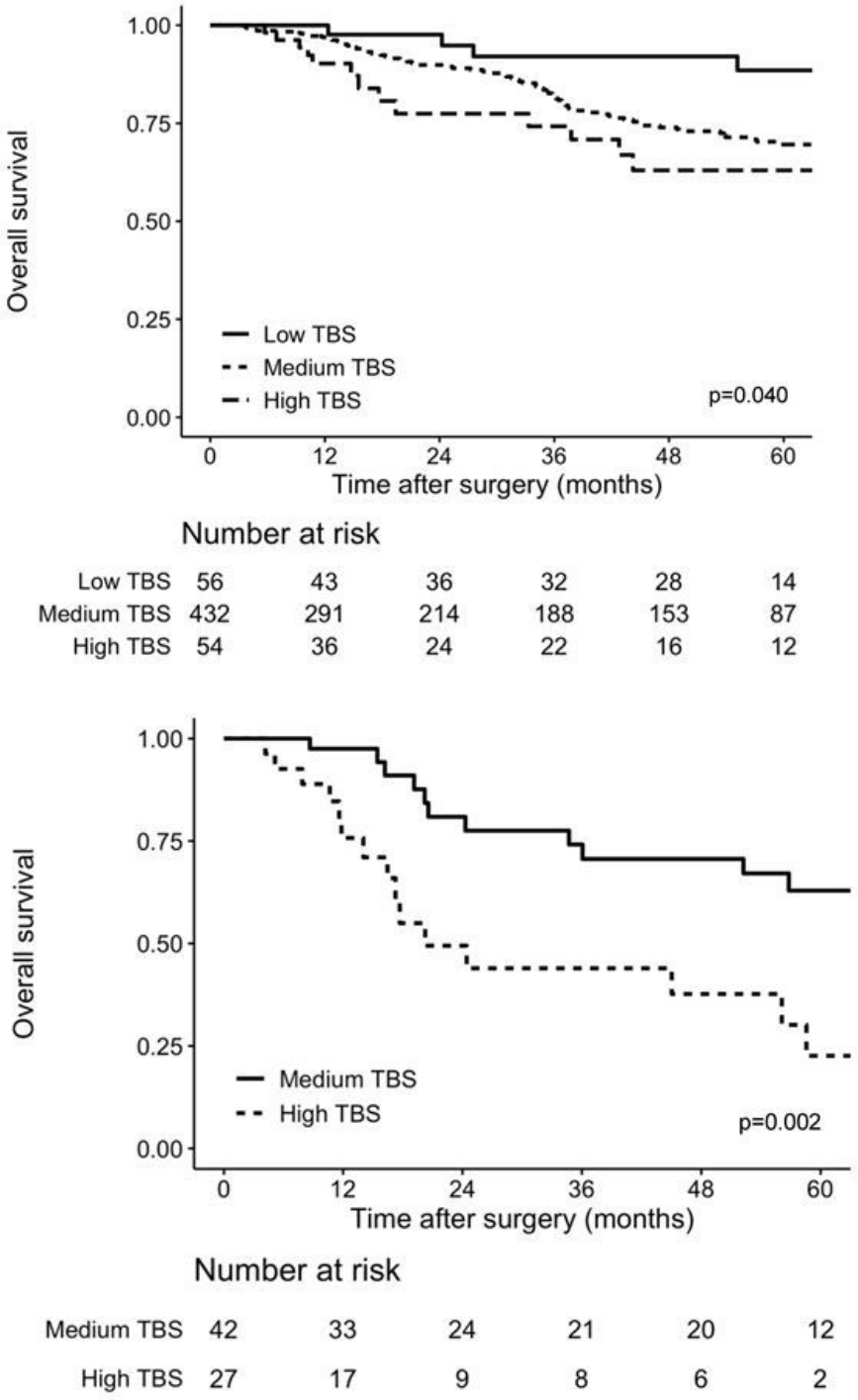

Figure 3

Kaplan–Meier survival curves by tumor burden score (TBS) for Barcelona Clinic Liver Cancer (BCLC) stages A and B. Overall survival of patients with (a) BCLC stage A hepatocellular carcinoma (HCC) and (b) BCLC stage B HCC.

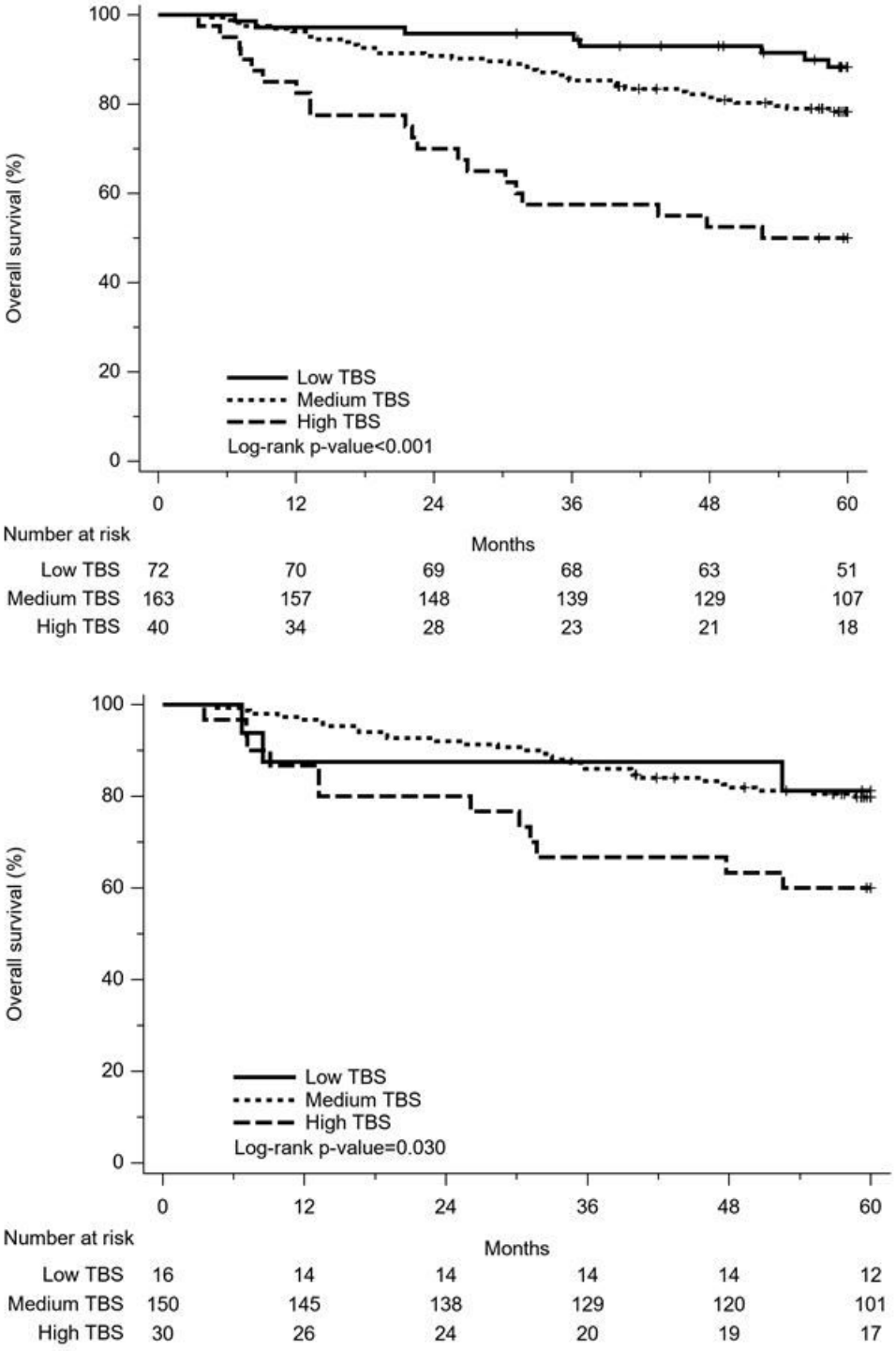

Figure 4

Kaplan–Meier survival curves by tumor burden score (TBS) for the validation cohort. Overall survival of (a) the entire cohort and (b) the Barcelona Clinic Liver Cancer (BCLC) stage A subgroup.