Simple Scoring System for Predicting TACE Unsuitable among Intermediate-Stage Hepatocellular Carcinoma Patients in the Multiple Systemic Treatment Era

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Keywords
Barcelona Clinic Liver Cancer-B hepatocellular carcinoma · Transcatheter arterial chemoembolization unsuitable · Transcatheter arterial chemoembolization refractoriness · Concept of Indication of TACE Reframing Un-Suitable condition to Manage Intermediate stage liver CANcer score · Tumor marker score

Abstract
Background/Aim: With the development of systemic treatment methods for unresectable hepatocellular carcinoma (uHCC), the concept of unsuitable for transcatheter arterial chemoembolization (TACE) has become important. This study aimed to establish a simple predictive scoring system for determining TACE unsuitable status.

Materials/Methods: From 1998 to 2015, 196 patients with intermediate-stage uHCC with Child-Pugh A (score 5:6 = 108:88) and given TACE as the initial treatment were enrolled. At the baseline, tumor burden (Milan criteria-out, up-to-7 in/out, and up-to-11 in/out: 0–2 points) and modified albumin-bilirubin grade 1/2a or 2b (0–1 point) were added to determine the score for TACE unsuitable (CITRUS-MICAN score; low <2 and high ≥2). In addition, a previously reported tumor marker (TM) score, in which alpha-fetoprotein (AFP) was ≥100 ng/mL, fucosylated AFP ≥10%, and des-gamma-carboxy prothrombin ≥100 mAU/mL (each 1 point) (total 0, 1, or ≥2 points), was used for additionally evaluating tumor malignancy potential. Prognosis was retrospectively evaluated based on those scores.

Results: Median survival time (MST) was better for low compared to high CITRUS-MICAN score (42.0 vs. 26.4 months) (p = 0.002). A 2-step evaluation using...
the combination of CITRUS-MICAN and TM scores showed an MST of 43.2 months for low CITRUS-MICAN/TM score 0/1 (rank-A) and 39.6 months for low CITRUS-MICAN/TM score ≥2 (rank-B2), while it was 46.8 months for high CITRUS-MICAN/TM score 0 (rank-B1), 28.8 months for high CITRUS-MICAN/TM score 1 (rank-B2), and 22.8 months for high CITRUS-MICAN/TM score ≥2 (rank-C). For rank-A cases (n = 51), MST was 43.2 months, while it was 46.8 months for rank-B1 (n = 12), 31.2 months for rank-B2 (n = 82), and 22.8 months for rank-C (n = 51, p = 0.001). Conclusion: The results showed that rank-C indicates absolute TACE unsuitable status. For rank-A patients, good prognosis with TACE can be expected, while TACE refractoriness status during the clinical course should be carefully evaluated so as to anticipate the appropriate timing for switching to systemic treatment in rank-B1 and -B2 patients.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the fifth most common malignancy worldwide [1], while intrahepatic recurrence is well known to commonly occur after curative treatment. During the clinical course of repeated HCC recurrence, some cases become classified as beyond the Milan criteria (MC) [2], many of which are not indicated for curative treatment such as surgical resection or radiofrequency ablation. As the standard treatment for intermediate-stage HCC cases (Barcelona Clinic Liver Cancer stage [BCLC]-B), transcatheter arterial chemoembolization (TACE) is generally recommended [3, 4].

Systemic treatments have been developed, and 6 different regimens are presently (September 2021) available in Japan for unresectable HCC (uHCC) patients with good hepatic function (Child-Pugh class A), that is, sorafenib [5], regorafenib [6], lenvatinib [7], ramucirumab [8], atezolizumab plus bevacizumab [9], and cabozantinib [10]. However, it has been reported that the objective response rate after second TACE was worse than that after the first procedure (24–33 vs. 40–52%) [11]. Additionally, the procedure itself has been shown to have a bad influence on hepatic function, with a decline in albumin level observed in 26% during the chronic phase after TACE [11] and deviation from albumin-bilirubin (ALBI) grade 1 ranging from 18.4% to 21.4% following a single TACE procedure [12]. It has also been noted that not a small percentage of patients show Child-Pugh class B at the time of TACE refractoriness status (20–26%) [11, 13, 14], which could have a large negative impact on survival, and thus the concept of TACE refractoriness has been proposed [15].

Since the prognosis of HCC patients is defined by tumor progression and hepatic reserve function [16–18], it is important for attending physicians to keep in mind avoidance of hepatic function deterioration during the clinical course of TACE treatment. To avoid harmful TACE without adequate therapeutic efficacy, BCLC-B subgrading systems [19–22], an algorithm [23], and scoring [24, 25] for TACE refractoriness have been proposed. Furthermore, with the increasing number of effective systemic treatments, the concept of TACE unsuitable [26, 27] has also been proposed and become an important concept for avoiding worsening hepatic function caused by the TACE procedure in uHCC patients, who are not expected to show a good therapeutic response following TACE. The aim of the present study was to establish a simple predictive scoring system for determining TACE unsuitable cases.

Materials and Methods

From 1998 to 2020, 5,985 naïve HCC Japanese patients were diagnosed and treated at 6 different institutions up to August 2021. Those diagnosed after 2016, when multiple MTA drugs became available, were excluded, and thus the present study included 196 BCLC-B patients with multiple tumors and classified as Child-Pugh class A who were diagnosed before 2015 and received TACE as the first treatment (Fig. 1). Overall survival after initial TACE was retrospectively evaluated.

Underlying Liver Disease

Positive anti-hepatitis C virus findings were considered to indicate that HCC was due to hepatitis C virus, whereas HCC due to hepatitis B virus was determined when the hepatitis B virus surface antigen was positive. For patients with a history of alcohol abuse (≥60 g/day) [28, 29], underlying liver disease was judged as related to alcohol.

Liver Function Assessment

Child-Pugh classification, ALBI grade [17, 30], and modified ALBI (mALBI) grade [31, 32], for which ALBI grade 2 was divided into 2 subgrades (mALBI 2a and 2b) using an ALBI score of −2.27 as the cutoff value, were used for hepatic reserve function assessment.

Predictive Scores for TACE Unsuitable and Refractoriness

Beyond the up-to-7 criteria (UT7) and mALBI grade 2b have been reported as items for judging TACE unsuitable status [26, 27]. For the present study, in addition to the MC, the UT7 and up-to-11 criteria (UT11), the latter of which is used as one of the items for tumor burden in BCLC-B subgrading [22], were adopted as criteria for defining tumor burden status. Cases beyond MC/within UT7 were defined as “low tumor burden,” beyond UT7/within UT11 as...
“middle tumor burden,” and beyond UT11 as “high tumor burden.” A TACE unsuitable score system using those 3 tumor burden classes and mALBI 2b was then constructed to mimic the Japan Integrated Staging (JIS) score [33] for easy use and termed the Concept of Indication of TACE Reframing Un-Suitable condition to Manage Intermediate stage liver CANcer (CITRUS-MICAN) score (Table 1). Moreover, the TACE unsuitable concept includes tumor malignant potential (e.g., gross pattern or pathological features) [26, 27], and therefore a previously reported tumor marker (TM) score was used for ancillary evaluation of the malignant potential of HCC in relation to TACE refractoriness. For calculating TM scores, positivity for alpha-fetoprotein (AFP) was defined as ≥100 ng/mL, while that for fucosylated AFP (AFP-L3) was ≥10% and for des-gamma-carboxy prothrombin (DCP) was ≥100 mAU/mL, with the number of positive tumor markers added up for a score of 0, 1, or ≥2 [25]. In the present study, a 2-step evaluation, including CITRUS-MICAN score as the first step and TM score as an ancillary second step, was used for evaluation of prognosis.

**HCC Diagnosis and Treatment**

HCC diagnosis was based on an increasing course of AFP, as well as dynamic CT [3], MRI [34, 35], and/or pathological findings obtained during the clinical course. BCLC staging [36] and tumor node metastasis (TNM) staging, determined based on criteria for TNM staging for HCC presented by the Liver Cancer Study Group of Japan (LCSGJ), 6th edition (TNM-LCSGJ) [37], were used for evaluation of tumor progression.

**Statistical Analysis**

For statistical analyses, the Kaplan-Meier method and a log-rank test were used. Prognostic predictive and discriminatory abilities of the scoring models were assessed using a c-index metric and Akaike’s information criterion [38]. p values <0.05 were considered to indicate statistical significance. Easy-R (EZR), ver. 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [39], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used to perform all of the statistical analyses.

**Results**

Characteristics of the 196 enrolled patients are shown in Table 2. Median age was 72 years and 85.2% were male. The Child-Pugh class of all enrolled was A (Child-Pugh score 5:6 = 108:88), the average ALBI score was −2.44 (mALBI grade 1:2a:2b = 73:52:71), and TNM-LCSGJ stage II was noted in 13 and stage III in 183.

**Prognostic Predictive Value of CITRUS-MICAN Score**

Median survival time (MST) was 40.8 months (95% CI: 19.2–80.4) for CITRUS-MICAN score 0, 43.2 months (95% CI: 32.4–51.6) for score 1, 27.6 months (95% CI: 21.6–37.2) for score 2, and 23.4 months for score 3 (95% CI: 12.0–44.4) (p = 0.016) (Fig. 2a). Thus, MST for patients in the low CITRUS-MICAN score group (score 0/1) was significantly better than that for those in the high score group (score 2/3) (42.0 months [95% CI: 33.6–50.4] vs. 26.4 months [95% CI: 21.6–33.6]) (p = 0.002) (Fig. 2b).

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**Table 1. CITRUS-MICAN score**

| Tumor burden | mALBI grade 1/2a | mALBI grade 2b |
|--------------|------------------|----------------|
| Low tumor burden | 0 | 1 |
| Middle tumor burden | 1 | 2 |
| High tumor burden | 2 | 3 |

**Table 2. Characteristics of enrolled patients (n = 196)**

| Characteristic | Value |
|---------------|-------|
| Gender, male:female | 167:29 |
| Diabetes mellitus, n (%) | 87 (44.4) |
| AST, U/L* | 55 (39–84) |
| ALT, U/L* | 49 (28–74) |
| Platelets, ≥10^4/µL* | 13.6 (9.3–18.7) |
| T-bilirubin, mg/dL* | 0.8 (0.6–1.0) |
| Albumin, g/dL* | 3.7 (3.5–4.1) |
| Prothrombin time, %* | 91.6 (80.2–99.2) |
| ALBI score* | −2.44 (−2.19 to −2.70) |
| mALBI 1:2a:2b | 73:52:71 |
| Child-Pugh score 5:6 | 108.88 |
| Maximum tumor size, cm | 4.7 (3.4–7.0) |
| TNM-LCSGJ 6th, I/II | 33:35:23:29:76 |
| Tumor number (2:3:4:5:6 or more) | 33:35:23:29:76 |
| AFP (100 ng/mL or more, n (%)) | 75 (38.3) |
| AFP-L3 (10% or more, n (%)) | 83 (42.3) |
| DCP (100 mAU/mL or more, n (%)) | 140 (71.4) |
| Died, n (%) | 154 (78.6) |
| Cause of death, HCC: liver failure: gastrointestinal bleeding: others: unknown | 88:11:2:17:36 |
| Observation period, months | 27.6 (11.7–46.8) |

HCV, hepatitis C virus; HBV, hepatitis B virus; AST, aspartate transaminase; ALT, alanine aminotransferase; ALBI score, albumin-bilirubin score; mALBI grade, modified ALBI grade; low tumor burden, beyond Milan criteria and within up-to-7 criteria (UT7); middle tumor burden, beyond UT7 and within up-to-11 criteria (UT11); high tumor burden, beyond UT11.
Prognostic Predictive Value of TM Score

MST was 51.6 months (95% CI: 33.6–80.4) for TM score 0, 38.4 months (95% CI: 28.8–44.4) for TM score 1, and 24.0 months (95% CI: 16.8–30.0) for TM score ≥2 ($p = 0.018$) (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520292).

Two-Step Evaluation Using a Combination of CITRUS-MICAN and TM Scores

MST was 43.2 months in both the low CITRUS-MICAN/TM score 0 ($n = 20$) (95% CI: 22.8–115.2) and score 1 ($n = 31$) (95% CI: 34.8–49.2) groups (rank-A), while it was 39.6 months (95% CI: 14.4–60.0) in patients...
**Fig. 3.** Kaplan-Meier curves according to tumor marker score. 

**a** MST for both the low CITRUS-MICAN/TM score 0 \((n = 20)\) and 1 \((n = 31)\) groups was 43.2 months (95% CI: 34.8–49.2 and 34.8–49.2, respectively) (rank-A) and 39.6 months (95% CI: 14.4–60.0) for the low CITRUS-MICAN/TM score ≥2 group \((n = 40)\) (rank-B2) \((p = 0.603)\). **b** MST was 46.8 months (95% CI: 22.8–72.0) for the high CITRUS-MICAN/TM score 0 \((n = 12)\) (rank-B1), 28.8 months (95% CI: 18.0–45.6) for the high CITRUS-MICAN/TM score 1 \((n = 42)\) (rank-B2), and 22.8 months (95% CI: 14.4–28.2) for the high CITRUS-MICAN/TM score ≥2 \((n = 51)\) (rank-C) groups \((p = 0.044)\). **c** Kaplan-Meier curves according to 2-step evaluations. MST was 43.2 months (95% CI: 34.8–51.6) for the rank-A \((n = 51)\), 46.8 months (95% CI: 22.8–72.0) for the rank-B1 \((n = 12)\), 31.2 months (95% CI: 24.0–45.6) for the rank-B2 \((n = 82)\), and 22.8 months (95% CI: 14.4–28.8) for the rank-C \((n = 51)\) groups \((p = 0.001)\). MST, median survival time.
with a low CITRUS-MICAN/TM score ≥2 (n = 40) (rank-B2) (Fig. 3a). In the high CITRUS-MICAN/TM score 0 group (n = 12), MST was 46.8 months (95% CI: 22.8–72.0) (rank-B1), while that in the high CITRUS-MICAN/ TM score 1 group (n = 42) was 28.8 months (95% CI: 18.0–45.6) (rank-B2) and in the high CITRUS-MICAN/ TM score ≥2 group (n = 51) was 22.8 months (95% CI: 14.4–28.2) (rank-C) (Fig. 3b). As for prognosis based on this 2-step evaluation method, MST for the rank-A group (n = 51) was 43.2 months (95% CI: 34.8–51.6), for the rank-B1 group (n = 12) was 46.8 months (95% CI: 22.8–72.0), for the rank-B2 group (n = 82) was 31.2 months (95% CI: 24.0–45.6), and for the rank-C group (n = 51) was 22.8 months (95% CI: 14.4–28.8) (p = 0.001) (Fig. 3c).

Although there were no significant differences for MST among TM scores in low CITRUS-MICAN score patients, the Kaplan-Meier curves for the low TM scores (0, 1) were superior to that of the highest TM score (≥2) during the early period (≤2 years) after introducing TACE. Therefore, overall survival rate (OSR) until 2 years was analyzed, and the results are shown in Table 3. OSR at 0.5, 1.0, 1.5, and 2.0 years was similar in the rank-A and rank-B2 groups, respectively, while OSR for the rank-C group was worse.

MST was 51.6 months (95% CI: 22.8–115.2) for BCLC-B1 stage (Bolondi’s and Kindai criteria) and 31.2 months (95% CI: 26.4–39.6) for BCLC-B2 stage cases (p = 0.005) (online suppl. Fig. 2). The C-index and Akaike’s information criterion values with Bolondi’s and Kindai criteria were 0.532 and 1,315.6, respectively, while those were 0.559 and 1,314.6, respectively, with CITRUS-MICAN score, and 0.599 and 1,312.1, respectively, with the 2-step evaluation using CITRUS-MICAN and TM scores.

**Discussion**

In the present study, a good predictive value was obtained using a 2-step evaluation method based on CITRUS-MICAN and TM scores in BCLC-B HCC patients with Child-Pugh A given TACE as the initial treatment. As a first-step evaluation using the CITRUS-MICAN score, the MST of patients with a low CITRUS-MICAN score was 42.0 months, while that of those with a high score was 26.4 months. Recently, multiple systemic treatments have been developed, and their efficacy for improving prognosis by use of a treatment sequence in uHCC cases has been reported. In addition to the concept of TACE refractoriness [15], TACE unsuitable was recently proposed [26]. When the CITRUS-MICAN score...
is high (2 or 3) in the first-step evaluation, systemic treatment with atezolizumab plus bevacizumab or first-line MTA drugs might be adopted instead of TACE as the initial treatment.

Recently, the “5-5-500” rule (tumor size, number, and DCP) for liver transplantation has been proposed as an indication criterion for liver transplantation [40]. Based on this report, also around 10 (summing up tumor size and number) might be an additional border for evaluation of tumor burden. Therefore, we used previously reported UT11 criteria [22] in addition to Milan and UT7 criteria, as one of the items for tumor burden. In the OPTIMIS study, objective response to initial TACE in Japan and globally was 52 and 40%, respectively, while that after 2 or more times was 26–33 and 24–26%, respectively [11]. High tumor burden is often an important factor related to worsening hepatic function associated with TACE [41, 42], while mALBI grade 1 or 2a has been reported as a favorable prognostic factor for obtaining good prognosis with sequential MTA drug treatment [43–46]. In some cases, TACE can have not only a less therapeutic effect but also a harmful influence on hepatic function. Therefore, we established a scoring system using only 2 factors thought to have a relationship with hepatic function affected by TACE.

Moreover, tumor malignant potential as well can often have a large influence on therapeutic response to TACE. Since assessment by TM score is considered to provide a good prediction of TACE refractoriness [25], we used TM score in this study as an ancillary second step after evaluation with CITRUS-MICAN score. The combination of a high CITRUS-MICAN score (2 or 3) and high TM score (≥2) (rank-C) is considered to definitively show TACE unsuitable status, while patients with a low TM score (0 or 1) and low CITRUS-MICAN score (0 or 1) (rank-A) who receive TACE as the initial treatment are expected to have the same prognosis as super-selective TACE cases. Unfortunately, the present database does not include initial therapeutic responses of TACE and information of introduction of tyrosine kinase inhibitor during clinical courses. In addition, the present cohort did not include recurrent cases. This scoring system is thought to be accepted for use in all BCLC-B patients because a previous study reported that there was no significant difference in therapeutic responses by TACE between naïve and recurrent patients with BCLC-B HCC [47]. For confirming utility of this scoring system, future additional study with more detailed clinical information and larger number of naïve and recurrent patients with BCLC-B will be needed. Whatever it is, as for patients ranked differently than those (rank-B1 or B2), TACE refractoriness status during the clinical course should be carefully evaluated following 1 or 2 sessions of TACE so as to not lose an appropriate chance of switching to systemic treatment for improving prognosis.

A vascular endothelial growth factor inhibitor has been reported to contribute to normalize the tumor vasculature [48], thus improving drug delivery by TACE and the therapeutic effect. As compared with TACE treatment alone, the efficacy of TACE plus sorafenib for progression-free survival [49] as well as LEN-TACE sequence therapy for improving overall survival [50] has been shown. Kudo et al. [50] reported that lenvatinib as well might be useful as an alternative to TACE treatment for BCLC-B beyond UT7 without a decline in ALBI score. Moreover, the newly developed atezolizumab plus bevacizumab therapy has been shown to have less negative influence on hepatic function [51]. When possible, conversion from palliative to curative treatment should be considered for achieving a cancer- and drug-free condition. Other recent studies, such as the TACTICS trial (TACE plus sorafenib vs. TACE) [49] and TACTICS-L [52], have also reported favorable responses. For development of effective therapy for TACE refractoriness or unsuitable conditions, additional investigations are needed to establish detailed therapeutic strategies for improving prognosis in such cases.

This study has some limitations, including its retrospective design and low number of enrolled patients, especially those with a high CITRUS-MICAN/TM score of 0 (rank-B1). Additional analysis with a larger-scale randomized controlled trial should be conducted in the future. Furthermore, evaluations of AFP-L3 and DCP are not commonly performed outside of Japan. However, the present results indicate that CITRUS-MICAN score alone might have good predictive value regarding prognosis in patients with BCLC-B HCC. Finally, the present cohort underwent treatments during a non-MTA drug or sorafenib only era and considered to be naïve cases. Re-analysis of recent patients who were eligible to receive multiple MTA/ICI agents and recurrent BCLC-B patients with a past history of treatment for HCC will be necessary.

In conclusion, the recently proposed concept of TACE unsuitable [26, 27] is thought to match with our results from clinical practice. We propose use of not only CITRUS-MICAN score but also a 2-step scoring system that includes CITRUS-MICAN and TM score to indicate early therapeutic response as a useful and simple method for revealing BCLC-B HCC patients best suited for sys-
temic treatment as the first-line therapy instead of TACE, or when those receiving TACE should be considered to switch to systemic treatment.

Statement of Ethics

The entire study protocol was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (No. 27–34). After receiving official approval, this study was conducted as a retrospective analysis of database records based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. All procedures were done in accordance with the Declaration of Helsinki. The data were made anonymous before analysis to protect patient privacy. Written informed consent was obtained from all patients before treatment, and this study received ethical approval for use of an opt-out methodology based on low risk to the participants.

Conflict of Interest Statement

Atsushi Hiraoka, MD, PhD, had received lecture fees from Bayer, Eisai, Eli Lilly, and Otsuka. Takashi Kumada, MD, PhD, had received lecture fees from Eisai. None of the other authors have potential conflicts of interest to declare.

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Author Contributions

A.H. and T.K. conceived the study and participated in its design and coordination. A.H., K.K., H.T., S.Y., K.T., T.H., S.K., A.N., and T.I. performed data curation. A.H. performed statistical analyses and interpretation. A.H., To.T., K.T., E.I., N.S., Ta.T., A.T., T.N., M.I., S.N., H.S., and K.N. drafted the text. All authors have read and approved the final version of the manuscript.

Data Availability Statement

Due to the nature of this research, participants in this study could not be contacted regarding whether the findings could be shared publicly, and thus supporting data are not available. The datasets generated and/or analyzed for the current study are not publicly available due to the nature of the research, as noted above.
TACE Unsuitability Score

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