Potential indications for liver transplant in Child-Pugh A and Model for End-stage Liver Disease exception for hepatocellular carcinoma in Japan

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Abstract

Aim. Expanded criteria for HCC known as 5-5-500 (size ≤5 cm, number ≤5, alpha-fetoprotein ≤500 ng/ml) as well as model for end-stage liver disease (MELD) exception were implemented in Japan in 2019. In the present study, we evaluated LT indications and the Japanese allocation policy for HCC. **Methods.** Adults with HCC were evaluated between January 2013 and December 2017 in a multicenter study in Japan. The patients were ≤65 years-old, in line with the limits of Japanese transplant center limits. **Results.** HCC patients (n=289) were classified as Child-Pugh A (74%), B (18%), or C (8%). Of these, 178 (62%) and 185 (64%) met the Milan and 5-5-500 criteria, respectively. The respective 1- and 5-year overall survival rates of patients who met the criteria were 100% and 88.1% in Child-Pugh A, 91.7% and 30.6% in B, and 72.9% and 0% in C without access to LT. For Child-Pugh A patients, we developed a risk score using the Child-Pugh score, des-gamma-carboxy prothrombin, TNM grade, as well as albumin-bilirubin (ALBI) and TNM (ALBI-T) which predicted worse prognosis. Additionally, we showed the characteristics of patients who achieved MELD exception point high enough to receive an organ: survival at least 2 years after waitlist registration, relatively good liver functional reserve, and sufficient tumor control with multiple treatments. **Conclusions.** High-risk patients, identified by our scoring system and ALBI-T ≥2 in Child-Pugh A, should be considered for LT eligibility. The allocation policy for HCC should be revised based on precise evaluations on a regular basis.

Key words: Child-Pugh, 5-5-500, AFP, ALBI, ALBI-T

A list of abbreviations: AFP, alpha-fetoprotein; AIC, Akaike's Information Criterion; ALBI, albumin-bilirubin; ALBI-T, Scoring system determined by albumin-bilirubin grade and tumor-node-metastasis stage of Liver Cancer Study Group of Japan 6th edition; BCLC, Barcelona Clinical Liver Cancer stage; BSC, Best supportive care; DAA, direct-acting antiviral; DCP, des-gamma-carboxy prothrombin; DDLT, deceased donor liver transplantation; FIB-4, fibrosis-4; HBV, hepatitis B virus; c-index, Harrell's C-statistic; HCC, hepatocellular carcinoma; HR, hazard ratio; mALBI, modified ALBI; MASH, metabolic dysfunction-associated steatohepatitis; MELD, model for end-stage liver disease; TNM-LCSGJ 6th, tumor-node-metastasis stage of Liver Cancer Study Group of Japan 6th edition.

INTRODUCTION

Although a trend toward an increased number of deceased donors was finally achieved with more than 100 cases in Japan in 2023, the number of deceased donors per million still remains poor in Japan.[1] Under these circumstances, liver transplantation (LT) depends on living donors, which places a burden on the family. The severe shortage of deceased donors has resulted in unmet needs concerning organ donation.[2]

An allocation policy based on the model for end-stage liver disease (MELD) has been implemented since May 2019 in Japan. Exception points are given when the calculated MELD does not reflect the disease severity e.g. autosomal dominant polycystic kidney disease, repeated cholangitis or portal hypertension after Kasai portoenterostomy for biliary atresia, hepatopulmonary syndrome, and hepatocellular carcinoma (HCC). Furthermore, the inclusion criteria for waitlist registration have been expanded to include Child-Pugh B and C since January 2024 in Japan.

HCC is one of the diseases for which LT is a treatment. The incidence of HCC has increased over time on a global scale.[3] LT is an ideal treatment strategy for HCC because it not only eliminates the tumor but also replaces the damaged liver.[4] Clinical practice guidelines, such as the Barcelona Clinic Liver Cancer (BCLC) staging system, stratify HCC patients to receive LT according to their tumor burden, cancer-related symptoms, and liver function.[5] LT may be considered for early-stage HCC (BCLC-A; e.g. cases with a high risk of recurrence) and intermediate stage HCC (BCLC-B) if the extended liver transplant criteria are met according to local regulations. Asia-Pacific clinical practice guidelines recommend that patients with HCC with the liver classification Child-Pugh B be considered for LT.[6] However, the algorithm of HCC in

Japan has suggested that LT for HCC be recommended only for patients categorized as Child-Pugh C.[7]

In terms of tumor factors, the Milan criteria have been the international gold standard and benchmark for LT criteria. Extended criteria using the total tumor volume,[8] total tumor diameter,[9] sum of the largest tumor size and the number of tumors,[10] and tumor markers[11-13] have been reported. Based on data from a Japanese nationwide survey (n=965), a new criterion known as the 5-5-500 rule (HCC size ≤5 cm, number ≤5, alpha-fetoprotein AFP ≤500 ng/ml) has been established[14] and implemented as a national allocation policy in Japan since August 2019;[4] however, there are no basic data on HCC based on the current Japanese allocation policy.

In the present study, we demonstrated the survival of patients with primary HCC who met the criteria, showing the potential indication for LT even in Child-Pugh A cases as well as the high waitlist mortality rate with the current MELD exception.

METHODS

Patients

This retrospective cohort study followed the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Hokkaido University Hospital (#023-0183). Due to a severe shortage of organ donors in Japan, eligibility for deceased donor LT (DDLT) has strict limitations. We collected data (n=294) from patients 18–65 years old, according to the age limits of Japanese transplant centers. Five patients were excluded due to insufficient data, and we retrospectively evaluated the remaining patients (n=289) with HCC primarily detected who had been diagnosed and visited the Department of Gastroenterological Surgery I and Gastroenterology in Hokkaido University Hospital (n=81), Department of Hepatology, Sapporo Kosei General Hospital (n=137), Center for Gastroenterology, Teine Keijinkai Hospital (n=54), and Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine (n=22) between January 1, 2013, and December 31, 2017. To validate the clinical risk scores for Child-Pugh A patients with HCC within Japan criteria, we evaluated a validation cohort (n=75) from an HCC database (n=179) of patients indicated for surgical resection at Hokkaido University Hospital. The cohort met the following criteria: age 18-65 yeas, with primary HCC diagnosed between 2010 and 2020.

MELD exception point

To evaluate the current national policy, under which HCC patients with Child-Pugh B and C (but not A) can be registered on the wait-list, and where 2 MELD exception points are added every 3 months to the calculated MELD at wait-list registration, we collected data from patients with HCC who met the Japan criteria and had Child-Pugh

B or C, according to the current allocation rules in Japan for patients eligible with Child-Pugh B or C.

Classification of the hepatic function

The albumin-bilirubin (ALBI) score was calculated using the following formula: (Log_{10} bilirubin (mmol/L) × 0.66) + (albumin (g/L) × -0.085). The ALBI grade was defined as follows: Grade 1, ALBI score ≤-2.60, Grade 2; -2.60< to ≤-1.39, Grade 3; -1.39<.[15] ALBI grade 2 was further divided into 2 subgrades with a cutoff value of -2.270 as the modified ALBI grade (mALBI): Grade 2a: >-2.60 to <-2.27 and Grade 2b: -2.27 to -1.39.[16] The fibrosis-4 (FIB-4) index was calculated as follows: (age [years] × AST [U/L])/(Plt [10^9/L] × ALT [U/L]$^{1/2}$).

Risk factors for HCC

Tumor-node-metastasis (TNM) staging for HCC was based on the TNM of the Liver Cancer Study Group of Japan (TNM-LCSGJ), 6th edition.[17] T factors were defined as solitary tumor, size <2 cm, with no vascular invasion; T1 cases fulfilled 3 factors, T2 cases fulfilled 2 factors, T3 cases fulfilled 1 factor, and T4 cases did not fulfill any factors. The stages of LCSGJ were as follows: stage I, T1N0M0; stage II, T2N0M0; stage III, T3N0M0; stage IVa, T4N0M0, or any TN1M0; and stage IVb, any T any N M1. ALBI-T and mALBI-T scores were also calculated by summing the TNM-LCSGJ score (stages I, II, III, and IV are allocated to scores of 0, 1, 2, and 3, respectively) and ALBI grade (1, 2, 3 are allocated to scores 0, 1, 2)[16] or mALBI grade (1, 2a, 2b, and 3 are allocated to scores 0, 1, 2, 3)[18] respectively. The tumor burden score was calculated by combining the tumor size and number of tumor.[19] The HALT-HCC score was calculated using the following formula: (1.27 × tumor burden score) + (1.85 ×

lnAFP) + (0.26 × MELD-Na).[4]

Statistical analyses

Patient characteristics are reported as median values and interquartile ranges (IQRs). The Mann Whitney U-test and Fisher's exact test were used for comparisons between groups. The Cox proportional hazards model was used for multivariate analyses. Overall survival curves were compared using the log-rank test. Statistical analyses were performed using the JMP Pro software program version 16 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism software version 5 (GraphPad Software Inc, San Diego, CA, USA). A *p*-value <0.05 was considered to indicate statistical significance in all cases.

RESULTS

Patient characteristics

A total of 289 adult patients between 18 and 65 (median: 59.7) years old (Table 1) who were generally eligible for DDLT in Japanese transplant centers and had been diagnosed with primary HCC between January 2013 and December 2017 were enrolled from a multicenter study in Hokkaido, Japan. Liver diseases associated with hepatitis B virus infection, hepatitis C virus infection, alcohol intake, and metabolic dysfunction-associated steatohepatitis (MASH)/cryptogenic, accounted for 35.3%, 31.1%, 19.4%, and 11.8%, respectively (Table 1), and the liver function was classified as Child-Pugh A, B, and C in 74.0%, 18.0%, and 8.0% respectively. Solitary HCC was observed in 63.7% of patients. Approximately 61.6% and 64.0% of HCCs were categorized as meeting the Milan and 5-5-500 criteria, respectively (Table 1).

Overall survival rates of HCC patients who met the Japan criteria in each Child-Pugh classification

A total of 147 (68.7%) of 214 patients with Child-Pugh A, 28 (53.8%) of 52 patients with Child-Pugh B, and 14 (60.9%) of 23 in Child-Pugh C met the Milan or 5-5-500 criteria (Japan criteria) (Figure 1). We also observed that revised criteria, 5-5-500 rules, increased the number of eligible patients for each Child-Pugh classification by 5%. Furthermore, the respective 1- and 5-year overall survival rates for patients in Japan criteria were 100% and 88.1% for Child-Pugh A (n=147), 91.7% and 30.6% for Child-Pugh B (n=28), and 72.9% and 0% for Child-Pugh C (n=14) without access to LT (Figure 2). The demographics of patients with HCC who met the Japan criteria in each Child-Pugh classification were presented in Supplemental (Suppl) table 1. Additionally, treatments for HCC within each Child-Pugh classification were shown in Suppl. Figure

1. As expected, patients with HCC controlled by monotherapy, such as surgical resection and ablation, exhibited a better prognosis in Child-Pugh A (Suppl. Figure 1A). Although the treatment strategy for HCC influenced prognosis, it might depend on the level of control over the HCC.

Prognoses of Child-Pugh A patients who met the Japan criteria

We evaluated prognostic factors in patients with Child-Pugh A who met the Japanese criteria. A univariate analysis (Table 2) revealed that the TNM-LCSGJ grade (hazard ratio [HR]=3.929), number of HCCs (HR=3.010), Child-Pugh score (HR=2.970), HCC size + number (HR=2.946), ALBI score (HR=2.827), ALBI grade (HR=2.860), mALBI grade (HR=2.451), tumor burden score (HR=2.377), DCP (HR=1.821), HCC size (HR=1.688), and FIB-4 index (HR=1.656) were significant prognostic risk factors. To evaluate the multivariate analysis by Cox proportional hazards model, we selected risk factors with the greatest prognostic significance and avoided including factors composed of the same elements, such as Child-Pugh score and ALBI. A multivariate analysis showed that the TNM-LCSGJ grade (HR=3.050), DCP (HR=1.885), and Child-Pugh score (HR=1.347) were significant prognostic factors (Table 2). The risk score was calculated using the following formula: Risk score (Z) = 0.9063*IF (X_1 = 6, 1, IF (X_1 = 5, 0)) + 0.0001102*X_2 + 0.8562*X_3. Here, X_1 represents the Child-Pugh score for Child-Pugh A. X_2 is the value of DCP (mAU/ml), and X_3 indicates the stage number in the TNM scoring system. Additionally, the total HR at 5 years after HCC detection was calculated using the following formula: HR = 0.017*exp(Z). ROC curve based on the 5-year survival data showed that AUC of newly created scoring system was 0.78046. Appropriate cut-off value provided 1.72. Furthermore, markedly reduced 5-year overall survival rates (Figure 3) were observed in patients with Child-Pugh

score 6 (n=21, 63.5%, Figure 3A), FIB-4 index ≥2.67 (n=78, 83.4%, Figure 3B), ALBI grade 2 (n=52, 82.9%, Figure 3C), mALBI grade 2b (n=25, 68.2%, Figure 3D), DCP ≥300 (n=17, 80.0%, Figure 3E), HCC >2 cm (n=63, 82.7%, Figure 3F), ≥2 HCCs (n=22, 62.9%, Figure 3G), size + number between 3 and 5 (n=52, 88.0%) and ≥5 (n=28, 71.0%, Figure 3H), tumor burden score ≥5 (n=9, 55.6%, Figure 3I), TNM-LCSGJ stage II (n=61, 84.3%) and stage III (n=12, 58.3%, Figure 3J). To evaluate clinical risk scores combined with liver functional reserve and HCC factors, we applied ALBI-T[16] (Figure 4A and Table 2) and mALBI-T[18] (Figure 4B and Table 2), which have previously demonstrated effective stratification models for HCC, as well as the newly created scoring system described above (Figure 4C). These models provided good stratification of HCC patients who met the Japan criteria in Child-Pugh A. Additionally, Akaike's Information Criterion (AIC) and Harrell's C-statistic (c-index) for these scoring systems showed similar AIC values across models, but the c-index for the newly created scoring system in this study (0.6918) was slightly higher than that of ALBI-T (0.6701) and mALBI-T (0.5865). To further validate these results, we tested them on a validation dataset (n=75, Suppl. Table 2), collected between 2010 and 2020 from liver surgery unit at Hokkaido University Hospital. This cohort met the following criteria: age (18-65), Child-Pugh A, and primary HCC within Japan criteria. Duplicated cases from the primary dataset were excluded, and patients who underwent LT were not included. The newly created risk score (cutoff 1.72) and ALBI-T both provided strong stratification of survival data (Suppl. Figure 2), with the c-index for the created risk score slightly higher than that of ALBI-T (0.6621 vs, 0.6559). However, because the validation cohort was biased toward HCC patients treated with surgical resection, further studies are warranted. Taken together, given that the 5-year overall survival rates following living donor LT and DDLT for HCC patients were 70.7% and 78.6%,

respectively, in Japan,[20] and considering the comparison with the prognosis of Child-Pugh B and C patients, the patients with high risk by created risk score, ALBI-T ≥2 were deemed feasible for consideration for LT as a treatment option.

The evaluation of current exception points for HCC in Japanese allocation policy

The Japanese regulations for enlistment on the DDLT waitlist state that patients with HCC need to meet both the Japan criteria and have a Child-Pugh classification of B or C. In the current organ allocation system in Japan, patients who meet the inclusion criteria can earn an additional 2 points every 3 months on top of the MELD score calculated at the time of waitlist registration, i.e. patients with HCC can acquire 8 points per year. According to data from the Japan Organ Transplant Network, patients with a MELD score of ≥28 are eligible to undergo DDLT in Japan. Then, we calculated the MELD exception score for HCC patients who met the Japan criteria and were classified as Child-Pugh B or C, assuming they were registered on the waiting list for DDLT according to the current allocation policy in Japan. Indeed, four patients received LT, including two from a living donor.

We divided the patients into two groups at a cutoff value of 28 for the MELD exception score. As expected, the overall survival data demonstrated that the patients with higher MELD exception (hi ex-MELD group) showed better survival rates than those in the lower MELD exception group (lo ex-MELD; Figure 5). The hi ex-MELD group achieved a survival rate exceeding two years after registration on the waitlist although long-term survival was not achievable without LT (5-year survival was 25%). In this simulation, the waitlist mortality rate is 42.9%. Furthermore, the comparison between these two groups showed a significantly higher proportion of Child-Pugh B and higher frequencies of treatment, including transarterial chemoembolization,

ablation, and surgery, in the hi ex-MELD group than in the lo ex-MELD group (Table 3).

DISCUSSION

In the present study, we collected a dataset based on patients with HCC, limited to those ≤65 years old. To mitigate the scarcity of deceased donors, Japanese transplant centers have implemented strict age limits for waitlist registration, typically <60 or <65 years old. A previous multicenter study of patients diagnosed with primary HCC in Japan (n=20,547) found that more than 50% of patients were over 70 years old (mean age, 68.6 years old).[21] The exact prevalence of patients meeting the HCC criteria for LT among the population eligible for DDLT based on age was unknown. In addition, the underlying disease profile of HCC has undergone significant changes since the approval of direct-acting antivirals (DAAs). Our data included the post-DAA era, as DAAs received insurance approval in July 2014 in Japan. Thus, we predict that this study will provide valuable evidence for real-world clinical practice.

Because of the Japanese national rules for allocation policy and waitlist registration for DDLT based on Child-Pugh classification, the HCC data in each Child-Pugh classification are important. We demonstrated that HCC patients categorized as Child-Pugh A accounted for around 70% of the evaluated population. Consistently, a previous large-scale report from a single institute in Japan showed that approximately 80% of HCC patients were categorized as Child-Pugh A during the period from 2010 to 2019 (n=655).[22] The report also demonstrated that the percentages of HCC in Child-Pugh A significantly increased over time.[22] Recently, the Japanese clinical guidelines instated a limitation of Child-Pugh classification due to confounding factors (albumin and ascites).[23] The ALBI score has been reported to be a superior clinical scoring system for representing the liver functional reserve compared to the Child-Pugh score, particularly Child-Pugh A and B.[18] Indeed, the clinical prognostic factors of HCC patients are mainly associated with tumor burden and liver functional preservation.

The prognosis of Child-Pugh A patients with HCC was stratified by Child-Pugh score as well as ALBI grade.[22] Recent study has demonstrated that ALBI score is superior to the Child-Pugh score, which includes subjective measures such as the grade of ascites and encephalopathy[15]. Moreover, the mALBI-T score has been reported a better prognostic stratification ability and predictive model than other scoring systems.[18] Consistently, we found that the prognosis of Child-Pugh A HCC patients was well-stratified by the ALBI-T grade (Fig. 4A): for those with a grade of ≥2. Additionally, the newly created risk scores, which incorporate the Child-Pugh score, DCP, and TNM stage, also effectively stratified the prognosis of Child-Pugh A patients, including those in the validation cohort. The newly created risk score includes DCP, a strong prognostic factor[11, 24] that may influence our findings. This score demonstrated the best predictive ability, as evaluated by c-index. Thus, LT may be the best treatment option and appropriately indicated for high-risk Child-Pugh A patients, as assessed by the newly created risk score and ALBI-T. Although at present Japanese national insurance does not guarantee LT for HCC in Child-Pugh A cases, our data suggest that HCC, even in Child-Pugh A cases, may be suitable for LT. However, the precise suitability likely depends on factors such as donor organ availability and the evaluation for recurrence risk posttransplantation.

We also noted that 50%-60% of Child-Pugh B and C HCC patients met the Japan criteria. This means that approximately 15% of patients diagnosed with primary HCC were eligible for LT in Japan. However, the waitlist mortality rate was calculated to be approximately 40%. Donor shortage is a critical issue that needs to be addressed. LT in Japan remains dependent on living donors, although the number of deceased donors has increased, exceeding 100 cases in 2023. Recently, an increased occurrence of HCC has been observed in cases of liver disease despite sustained

viral responses of HCV being achieved with DAAs, both in Japan as well as around the world.[25, 26] In particular, MASH-related HCC cases are rapidly increasing in frequency, such that MASH is now the fastest-growing cause of HCC worldwide.[27] Reportedly, familial predisposition to obesity made it unlikely to find a living donor among family members.[28] Thus, HCC is expected to account for a substantial portion of the waitlist for DDLT.

An appropriate MELD exception point should be determined in a fair and equitable manner. Generally, equivalence of waitlist mortality as well as transplantation rates between HCC and non-HCC patients is an indicator of the utility and effectiveness of HCC exception.[29] MELD exception may result in an overcorrection and thus imbalance in the waitlist.[30] Previously, the HCC exception in the United States has provided faster access to DDLT for patients with HCC compared to non-HCC patients.[31] Updates to the allocation policy based on the correct evaluation have been proposed.[32] In the present study, we first showed the characteristics of patients who had acquired enough MELD exception points to receive DDLT under the Japanese national rule. We found that patients who were eligible for sufficient MELD exception points to undergo DDLT were required to survive at least two years after waitlist registration. To achieve this, a better liver functional reserve at the waitlist registration, i.e. Child-Pugh B, and tumor control with appropriate locoregional therapies are important. Furthermore, if our proposal to extend eligibility to HCC patients with an ALBI-T score ≥ 2 in Child-Pugh A is adopted for the DDLT waitlist, 84.3 % of these patients would qualify for a MELD exception score ≥ 28 under the current MELD exception rule. In this case, well-controlled HCC by surgery and ablation therapy demonstrated a better prognosis in Suppl. Figure 1A suggesting that HCC in Child-Pugh A may be recommended a locoregional therapy during waiting for

DDLT. Although it is necessary to avoid any imbalance in organ allocation among different diseases, a waitlist mortality rate exceeding 40% as shown in our data is considered to be significantly high. This effectively conveys the necessity for regular evaluations and revisions to establish appropriate exception points, highlighting the importance of publishing data on waitlist mortality and DDLT rates, which are currently lacking in Japan.

Several limitations associated with the present study warrant mention. First, we collected data from major hospitals that treat HCC in Sapporo, Japan. However, the number of patients was limited. Additionally, the validation cohort may have potential bias due to treatment with surgical resection. To more accurately validate our study, a nationwide survey would be necessary. Second, patients were diagnosed with primary HCC between January 2013 and December 2017 in the post-DAA era to evaluate the 5-year survival rate. However, recent developments in the treatment of HCC, such as atezolizumab with bevacizumab and multi-kinase inhibitors, confer a superior survival.[33, 34] Further studies on this point will be required, including new treatment strategies.

In conclusion, we presented data focusing on treatment strategies for LT in Japan. The study design targeting eligible ages for LT and the data within the HCC criteria for LT would be informative. While addressing the issue of donor shortage is crucial, revising the allocation rules for DDLT with thorough considerations and evaluations is also necessary.

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CONFLICT OF INTEREST

Author Dr. Ryosuke Minami owns stock of Eli Lilly.

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Figure legends

Figure 1. The HCC status categorized by the 5-5-500 and Milan criteria in each Child-Pugh classification. The Japan criteria include both the 5-5-500 and Milan criteria, which were represented by thick lines on the pie chart.

Figure 2. The overall survival rate of patients who met the Japan criteria in each Child-Pugh classification.

Figure 3. Overall survival rates of Child-Pugh A patients who met the Japan criteria for each prognostic factor, as follows: Child-Pugh score (A), Fibrosis-4 (FIB-4) index (B), albumin-bilirubin (ALBI) score (C), modified (m) ALBI score (D), des-gamma-carboxy prothrombin (DCP) (E), size (F) and number (G) of HCCs, size (cm) + number of HCCs (H), tumor burden score (TBS) (I), and tumor-node-metastasis (TNM) stage of liver cancer study group of Japan 6th edition (J). Overall survival curves of Child-Pugh B (gray open triangles and line) and Child-Pugh C (gray open circles and line) were shown for comparison of each survival rate. Log-rank test, *P<0.05, **P<0.01, ***P<0.001.

Figure 4. Overall survival rates of Child-Pugh A patients who met the Japan criteria were well-stratified by the prognostic risk factors of the albumin-bilirubin (ALBI) score and tumor-node-metastasis stage of the Liver Cancer Study Group of Japan 6th edition (TNM-LCSGJ 6th) and newly created risk score. The ALBI score and TNM-LCSGJ 6th were used to determine the ALBI-T score[35] (A). The modified ALBI (mALBI) and TNM-LCSGJ 6th were used to determine the mALBI-T score[18] (B). The created risk score was derived from significant risk factors outlined in Table 2, including the Child-Pugh score (5 or 6), des-gamma-carboxy prothrombin (DCP), and TNM-LCSGJ 6^{ths} stage. The formula for risk score is as follows: Risk score = 0.9063*IF (X_1 = 6, 1, IF (X_1 = 5, 0)) + 0.0001102*X_2 + 0.8562*X_3. X_1 represents the Child-Pugh score. X_2 is the DCP

value (mAU/ml), and X_3 indicates the stage number according to the TNM system. The area under the curve (AUC) was 0.78046, based on the ROC curve analysis of the 5-year survival data. A cutoff value of 1.72 for the risk score was used to divide the patients into low-risk (n=100) and high-risk (n=47) groups (C). Overall survival curves of Child-Pugh B (gray open triangles and line) and Child-Pugh C (gray open circles and line) were shown for comparison of each survival rate. Log-rank test, ***P<0.001.

Figure 5. Overall survival rates of the Child-Pugh B or C patients who met the Japan criteria are shown. The patients who had a ≥28 MELD exception achieved a significant long-term survival compared to those with a <28 MELD exception. The patients (n=4) who underwent LT were censored on the date of LT. Log-rank test. ***P<0.0001.

FIGURE 1

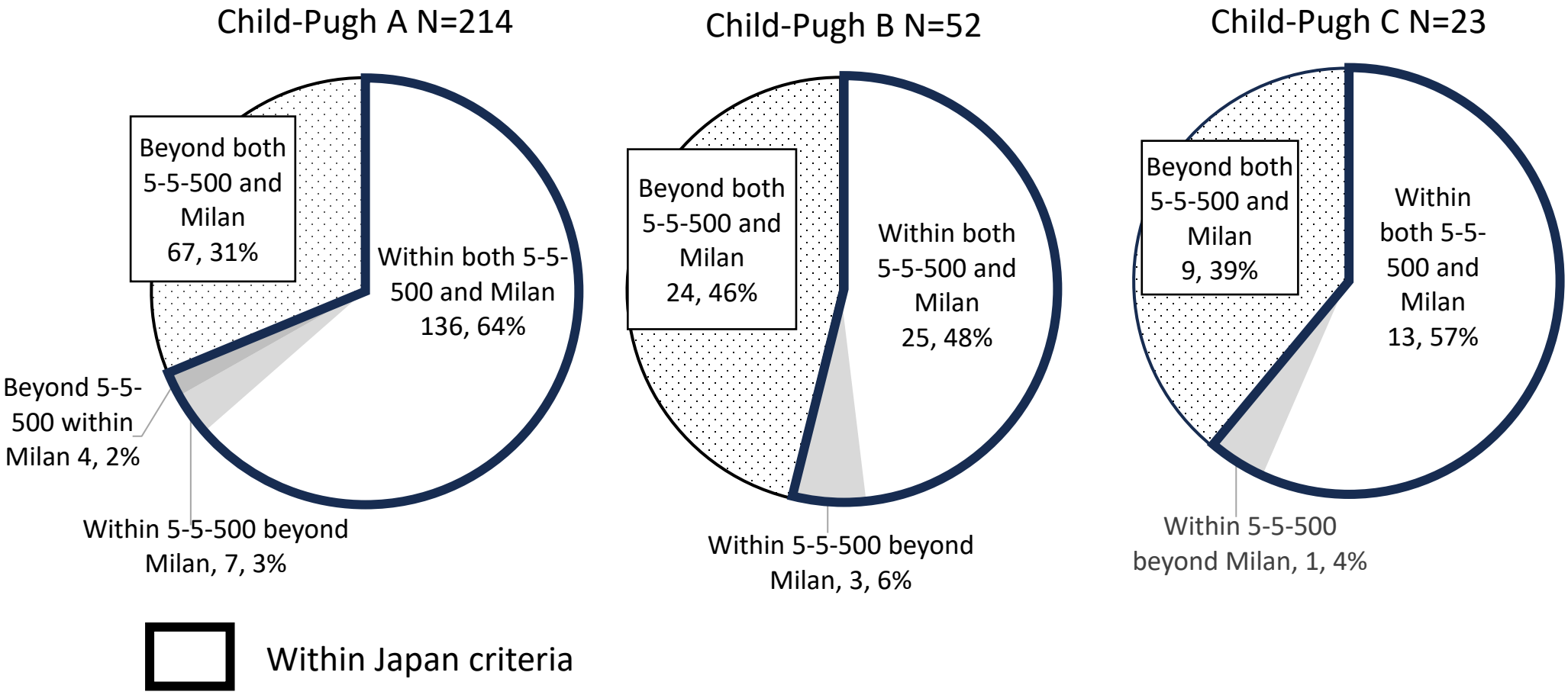

Child-Pugh A N=214
Beyond both 5-5-500 and Milan 67, 31%
Within both 5-5-500 and Milan 136, 64%
Beyond 5-5-500 within Milan 4, 2%
Within 5-5-500 beyond Milan, 7, 3%
Child-Pugh B N=52
Beyond both 5-5-500 and Milan 24, 46%
Within both 5-5-500 and Milan 25, 48%
Within 5-5-500 beyond Milan, 3, 6%
Child-Pugh C N=23
Beyond both 5-5-500 and Milan 9, 39%
Within both 5-5-500 and Milan 13, 57%
Within 5-5-500 beyond Milan, 1, 4%
Within Japan criteria

FIGURE 2

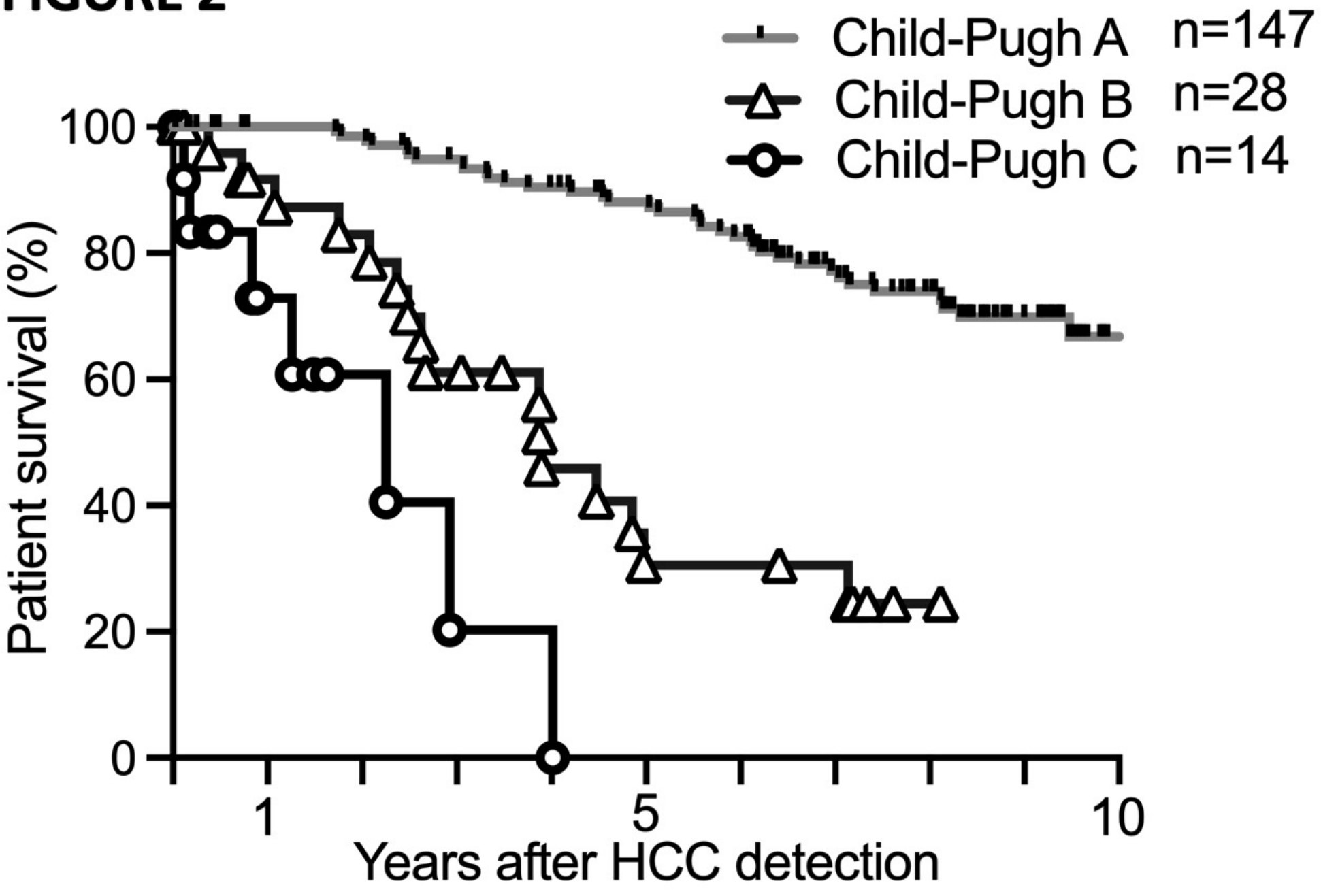

Child-Pugh A n=147
Child-Pugh B n=28
Child-Pugh C n=14
100
80
60
40
20
0
Patient survival (%)
1
5
10
Years after HCC detection

FIGURE 3

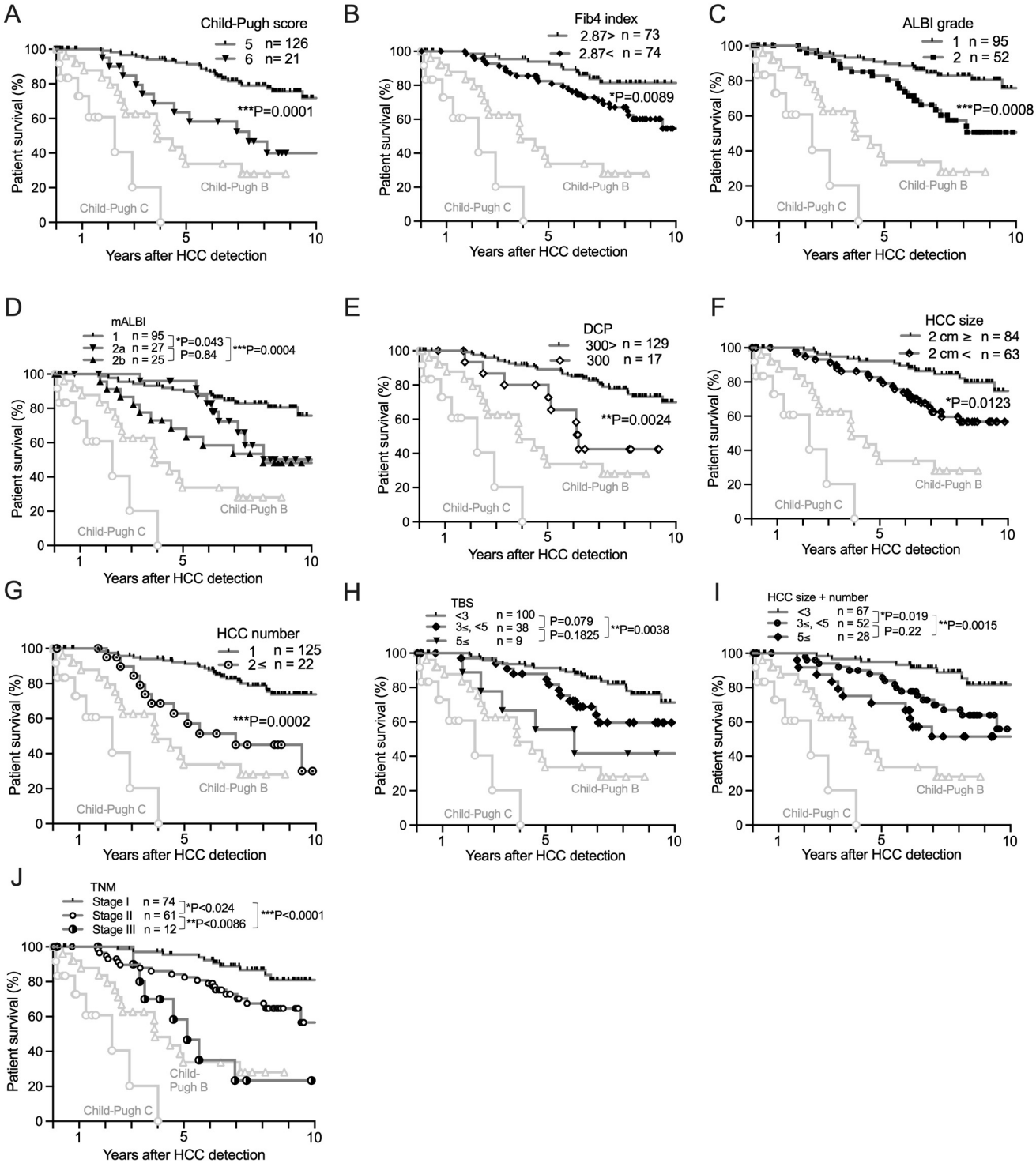
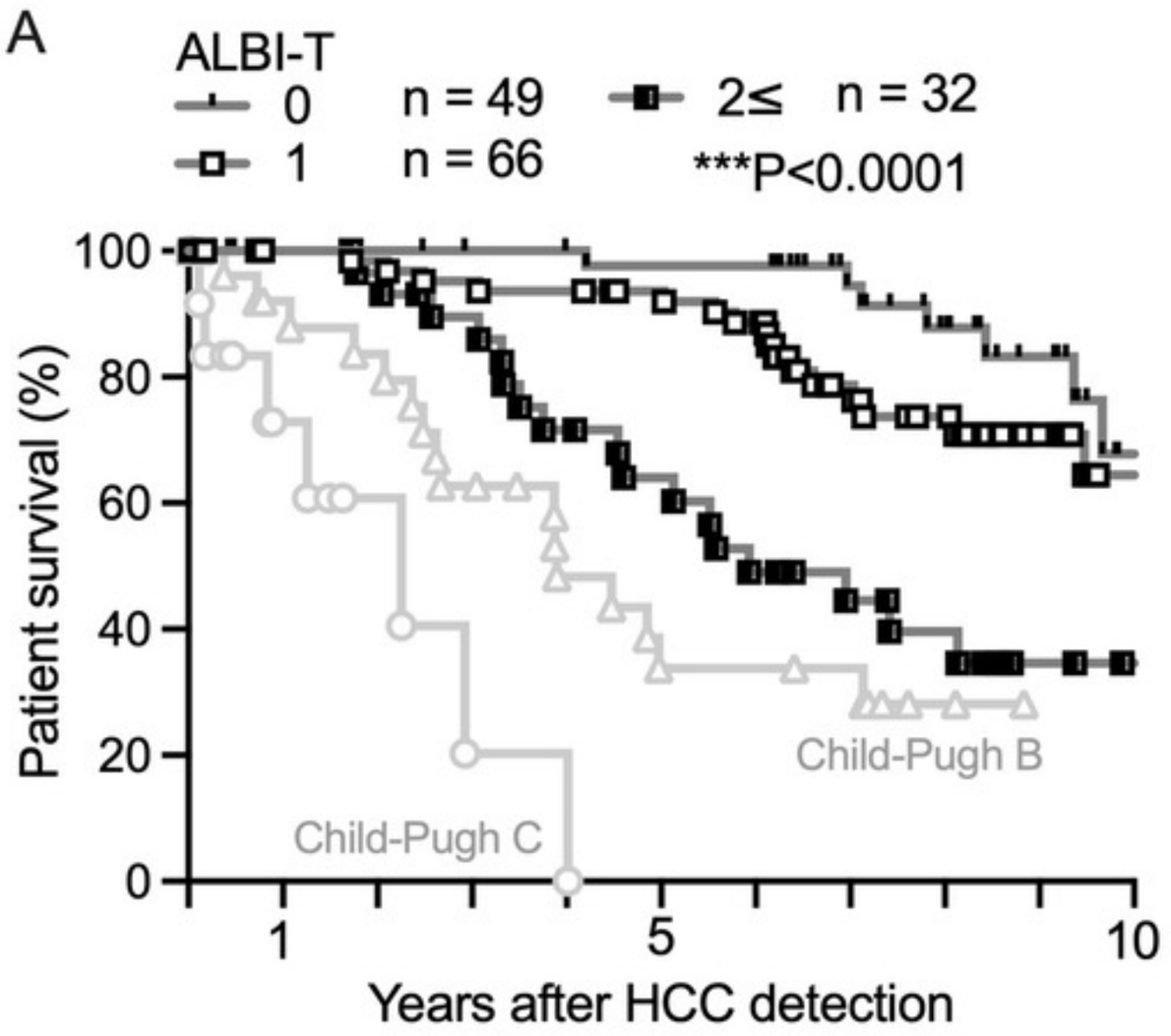
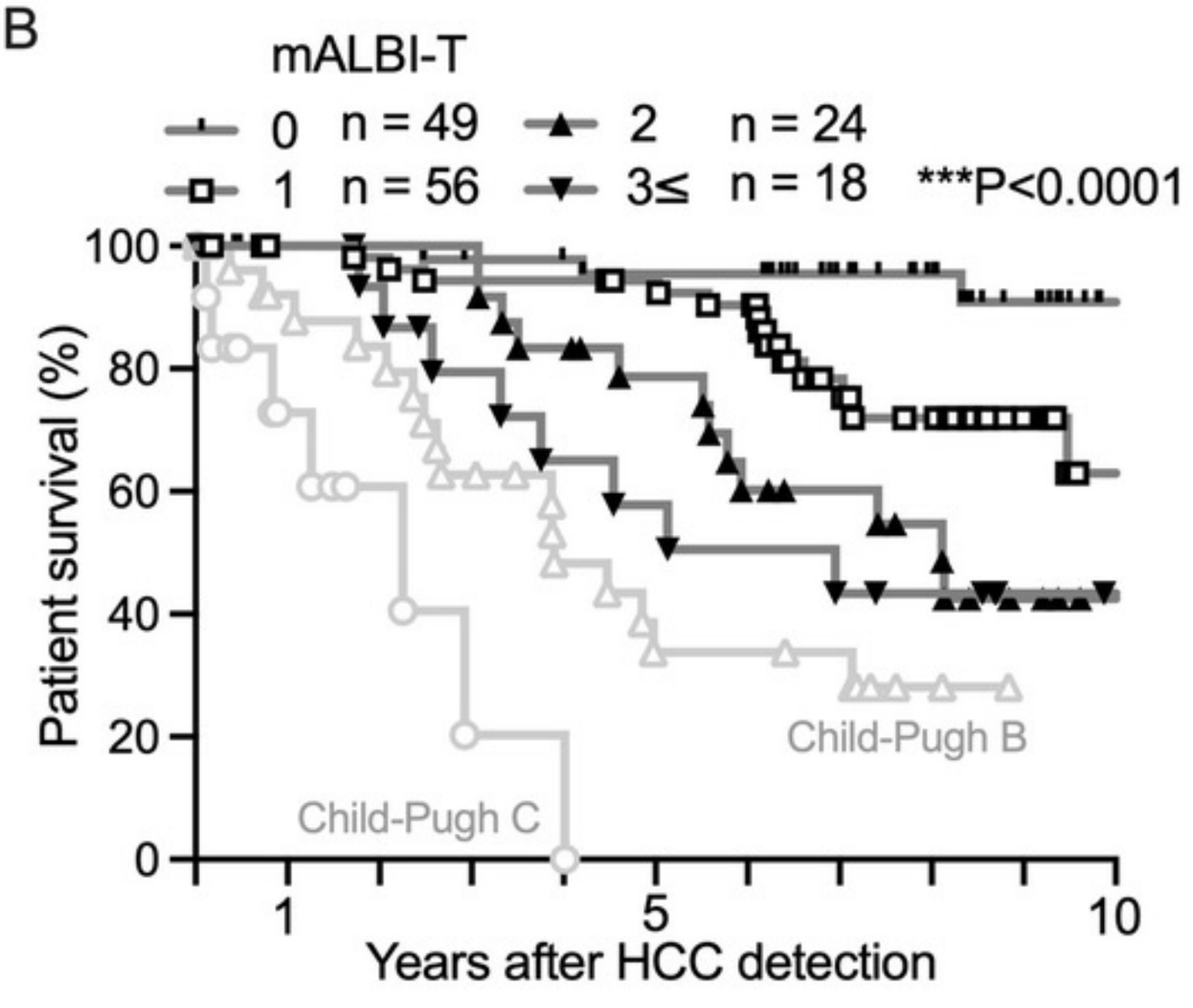

A
Child-Pugh score
5 n= 126
6 n= 21
***P=0.0001
Child-Pugh B
Child-Pugh C
Patient survival (%)
Years after HCC detection
B
Fib4 index
2.87> n = 73
2.87< n = 74
*P=0.0089
C
ALBI grade
1 n = 95
2 n = 52
***P=0.0008
D
mALBI
1 n = 95
2a n = 27
2b n = 25
*P=0.043
P=0.84
***P=0.0004
E
DCP
300> n = 129
300 n = 17
**P=0.0024
F
HCC size
2 cm ≥ n = 84
2 cm < n = 63
*P=0.0123
G
HCC number
1 n = 125
2≤ n = 22
***P=0.0002
H
TBS
<3 n = 100
3≤, <5 n = 38
5≤ n = 9
P=0.079
P=0.1825
**P=0.0038
I
HCC size + number
<3 n = 67
3≤, <5 n = 52
5≤ n = 28
*P=0.019
P=0.22
**P=0.0015
J
TNM
Stage I n = 74
Stage II n = 61
Stage III n = 12
*P<0.024
**P<0.0086
***P<0.0001
Child-Pugh B

FIGURE 4


A
ALBI-T
0 n = 49
1 n = 66
2≤ n = 32
***P<0.0001
Patient survival (%)
100
80
60
40
20
0
Child-Pugh B
Child-Pugh C
1
5
10
Years after HCC detection


B
mALBI-T
0 n = 49
1 n = 56
2 n = 24
3≤ n = 18
***P<0.0001
Patient survival (%)
100
80
60
40
20
0
Child-Pugh B
Child-Pugh C
1
5
10
Years after HCC detection

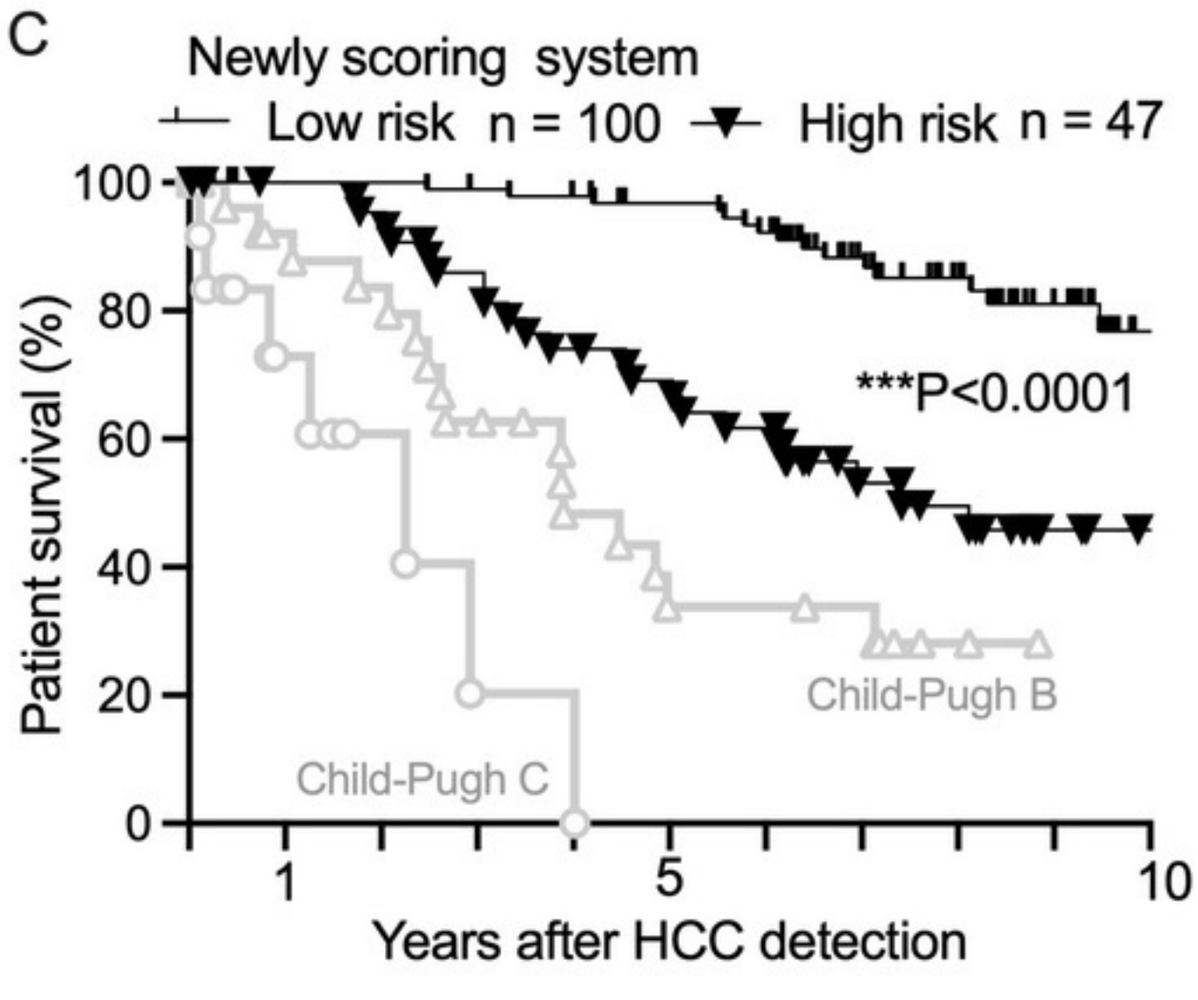

C
Newly scoring system
Low risk n = 100
High risk n = 47
***P<0.0001
Patient survival (%)
100
80
60
40
20
0
Child-Pugh B
Child-Pugh C
1
5
10
Years after HCC detection

FIGURE 5

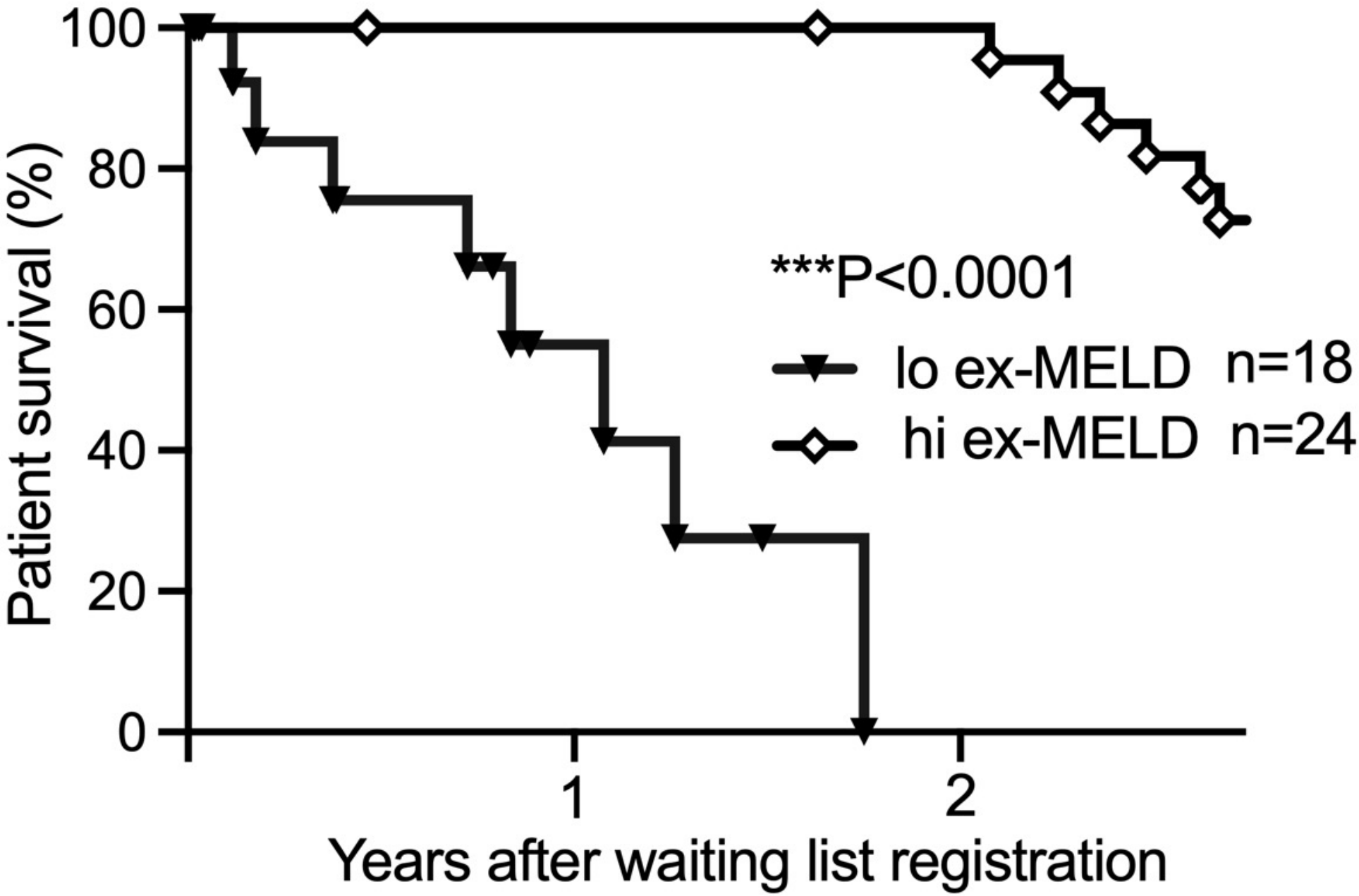

100
80
60
40
20
0
Patient survival (%)
***P<0.0001
lo ex-MELD n=18
hi ex-MELD n=24
1
2
Years after waiting list registration

Table 1. The patient's demographics at HCC detection

	Patient n=289
Age, median, range	59.7 (23.8-65.9)
Male, n, %	248 (85.8%)
Primary liver disease, n, %	
HBV related	102 (35.3%)
HCV related	90 (31.1%)
EtOH	56 (19.4%)
MASH	19 (6.6%)
Cryptogenic	15 (5.2%)
PBC	4 (1.4%)
AIH	3 (1.0%)
Child-Pugh classification, n, %	
A	214 (74.0%)
B	52 (18.0%)
C	23 (8.0%)
MELD, mean ± SD	8.0 ± 3.5
NLR, mean ± SD	2.7 ± 2.5
Platelet ($x10^4/\mu l$), mean ± SD	14.0 ± 6.9
Albumin (mg/dl), mean ± SD	3.7 ± 0.7
Total bilirubin (mg/dl), mean ± SD	1.3 ± 1.8
AST (IU/L), median, range	47 (9-323)
ALT (IU/L), median, range	37 (9-275)
PT %, mean ± SD	82.3 ± 18.0
Serum creatinine (mg/dl), mean ± SD	0.82 ± 0.71
FIB-4 index, median, range	3.44 (0.65-33.54)
ALBI, median, range	-2.50 (-3.78 – -0.039)
ALBI grade, n, %	
1	125 (43.3%)
2	129 (44.6%)
3	35 (12.1%)
mALBI grade, n, %	
2a	50 (17.3%)
2b	79 (27.3%)
HCC max. diameter (mm), median, range	26.5 (5-210)
The number of HCC, n, %	

1	184 (63.7%)
2-3	51 (17.3%)
4-5	14 (4.8%)
6-10	4 (1.4%)
>11	37 (12.8%)
AFP (ng/ml)	13.2 (0.5-1,479,260)
DCP (mAU/ml)	59.0 (3.2-515,000)
With vascular invasion, n, %	57 (19.7%)
With distant metastasis, n, %	21 (7.3%)
TNM-LCSGJ 6th stage, n, %	
I	90 (31.1%)
II	96 (33.2%)
III	58 (20.1%)
IVa	25 (8.7%)
IVb	20 (6.9%)
Milan criteria, n, %	
Within	178 (61.6%)
Beyond	111 (38.4%)
5-5-500 rule, n, %	
Within	185 (64.0%)
Beyond	104 (36.0%)
ALBI-T, n, %	
0	49 (17.0%)
1	85 (29.4%)
2	54 (18.7%)
3	61 (21.1%)
4	32 (11.1%)
5	8 (2.8%)
mALBI-T, n, %	
0	49 (17.0%)
1	63 (21.8%)
2	49 (17.0%)
3	58 (20.1%)
4	34 (11.8%)
5	28 (9.7%)
6	8 (2.8%)

AFP, alfa-fetoprotein; AIH, authoimmune hepatitis; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCP, des-gamma-carboxy prothrombin; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; mALBI, modified ALBI; MELD, Model for end-stage liver disease; MASH, metabolic dysfunction-associated steatohepatitis; NLR, neutrophil to lymphocyte ratio; PBC, primary biliary cholangitis; PT, prothrombin time; TNM-LCSGJ 6^{th}, tumor-node-metastasis stage of Liver Cancer Study Group of Japan 6^{th} edition.

Table 2. Univariate and multivariate analyses of overall survival in Patients in Child-Pugh A with HCC within JC (N = 147)

Variable	Univariate HR	P	Multivariate HR	P
Age	0.320	0.4787		
Sex	0.298	0.5033		
Primary disease	0.247	0.5665		
Child-Pugh score	2.970	*0.0011	1.347	*0.04500
MELD score	0.528	0.2965		
NLR	0.189	0.6468		
FIB-4 index	1.656	*0.02207	0.463	0.34421
ALBI score	2.827	*0.0015		
ALBI grade	2.860	*0.0014		
mALBI grade	2.451	*0.0035		
AFP	0.301	0.5006		
DCP	1.821	*0.0151	1.885	*0.01304
HCC size	1.688	*0.0205		
Number of HCC	3.010	*0.0010		
HCC size + number	2.946	*0.0011		
Tumor burden score	2.377	*0.0042		
TNM-LCSGJ 6th grade	3.929	*0.0001	3.050	*0.00089
ALBI-T	5.216	*<0.0001		
mALBI-T	4.726	*<0.0001		

ALBI, albumin-bilirubin; DCP, des-gamma-carboxy prothrombin; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; mALBI, modified ALBI; MELD, Model for end-stage liver disease; NLR, neutrophil to lymphocyte ratio; TNM-LCSGJ 6th, tumor-node-metastasis stage of Liver Cancer Study Group of Japan 6th edition.

Table 3. Comparison between the low and high MELD exception groups

	Lo ex-MELD N=18	Hi ex-MELD N=24	P
Male, n, %	16 (88.9%)	19 (79.2%)	0.4028
Age, median, range	56.0 (34.8-65.5)	58.1 (41.4-65.5)	0.8989
Primary liver disease, n, %			0.3983
HBV / HCV / EtOH	3 (17%) / 8 (44%) / 3 (17%)	7 (29%) / 5 (21%) / 8 (33%)	
MASH or Cryptogenic / PBC	4 (22%) / 0	3 (13%) / 1 (4%)	
Child-Pugh score, mean ± SD	9.44 ± 2.25	8.38 ± 1.76	0.1482
Child-Pugh classification B / C, n, (%)	9 (50%) / 9 (50%)	19 (79.2%) / 5 (20%)	*0.0472
calculated MELD, mean ± SD	12.33 ± 3.62	11.83 ± 3.28	0.7010
Platelet (x10^4/ml), mean ± SD	8.24 ± 4.07	8.86 ± 4.90	0.7797
Total bilirubin (mg/dl), mean ± SD	1.98 ± 1.12	2.35 ± 2.68	0.9290
Albumin (mg/dl), mean ± SD	2.81 ± 0.58	3.00 ± 0.52	0.3104
Serum creatinine (mg/dl), mean ± SD	0.88 ± 0.30	0.75 ± 0.26	0.1403
PT (%), mean ± SD	58.8 ± 13.2	64.1 ± 18.8	0.4033
FIB-4 index, mean ± SD	8.53 ± 7.22	6.48 ± 3.34	0.3964
ALBI score, mean ± SD,	-1.39 ±0.56	-1.52 ±0.52	0.3470
mALBI grade, n (%)			0.2050
2a	1 (5.6%)	0	
2b	7 (38.9%)	15 (62.5%)	
3	10 (55.7%)	9 (37.5%)	
HCC number, mean ± SD	1.78 ± 1.00	1.38 ± 0.58	0.1995
HCC size (mm), mean ± SD	22.1 ± 11.6	19.3 ± 8.3	0.5075
HCC size + number, mean ± SD	3.98 ± 1.64	3.30 ± 1.10	0.1366
TNM-LCSGJ 6^{th} staging, n (%)			0.4329
I	5 (27.8%)	11 (45.8%)	
II	10 (55.6%)	11 (45.8%)	
III	3 (16.7%)	2 (8.3%)	
Tumor burden score, mean ± SD	2.95 ± 1.27	2.43 ± 0.85	0.1334
HALT-HCC, mean ± SD	11.4 ± 3.3	10.6 ± 2.5	0.4688
AFP (ng/ml), median, range	6.8 (1.2-176)	8.3 (2.5-335)	0.8488
DCP (mAU/ml), median, range	71 (6-2391)	55 (12-32785)	0.8588
NLR, median, range	2.37 (0.83-26.33)	1.93 (0.69-8.41)	0.4384
Frequencies of treatment, mean ± SD	0.71 ± 0.92	2.58 ± 1.77	*0.0002

AFP, alfa-fetoprotein; ALBI, albumin-bilirubin; DCP, des-gamma-carboxy prothrombin; FIB-4, fibrosis 4; HALT-HCC, Hazard associated with liver transplantation for hepatocellular carcinoma; HBV, hepatitis B virus; HCC,

hepatocellular carcinoma; HCV, hepatitis C virus; mALBI, modified ALBI; MELD, Model for end-stage liver disease; MASH, metabolic dysfunction-associated steatohepatitis; NLR, neutrophil to lymphocyte ratio; PBC, primary biliary cholangitis; PT, prothrombin time; TNM-LCSGJ 6^{th}, tumor-node-metastasis stage of Liver Cancer Study Group of Japan 6^{th} edition.