Trends in hepatic functional reserve of patients with hepatocellular carcinoma treated with tyrosine kinase inhibitors

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Short title: Hepatic reserve change in HCC patients treated with TKIs

Abbreviations

HCC: hepatocellular carcinoma

TKI: tyrosine kinase inhibitor

AFP: α-fetoprotein

OS: overall survival

PFS: progression-free survival

TTP: time to progression

MVI: macroscopic vascular invasion

TNM: tumor node metastasis

BCLC: Barcelona Clinic Liver Cancer

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Abstract

Objective: Functional hepatic reserve is important when considering tyrosine kinase inhibitor (TKI) sequential therapy in patients with advanced hepatocellular carcinoma. We assessed ALBI score and Child-Pugh grade as an index of liver function during sorafenib and lenvatinib treatment.

Methods: A total of 212 patients with advanced HCC and Child-Pugh grade A status who initiated TKIs in our hospital were enrolled in this retrospective cohort study. A total of 74 of 212 patients underwent blood testing before starting sorafenib treatment and every 2 months after treatment initiation.

Results: In 74 patients, the median ALBI score before TKI treatment was -2.53 and after 2, 4, and 6 months was -2.45, -2.44, and -2.36, respectively. ALBI scores tended to increase during TKI therapy. In patients who experienced a time to progression (TTP) ≤3.8 months, ALBI scores increased at 2 months after treatment initiation, and at 4 and 6 months significant differences were observed ($p<0.01$). In all 212 patients, during first-line TKI treatment, the Child-Pugh score deteriorated to grade B or C in 72.2% of patients, and the median time to deterioration was 3.9 months. And the factor for hepatic reserve deterioration were serum albumin ≤ 3.8 g/dl and presence of macroscopic

vascular invasion (MVI). The hepatic reserve of 68.0% patients among the patients with deterioration of liver function recovered to Child-Pugh A following dose reduction, drug withdrawal, or treatment intended for recovery of liver function.

Conclusion: ALBI scores deteriorate in patients treated with TKIs, suggesting that tumor progression induces these changes.

Key words:

Hepatocellular carcinoma, sorafenib, lenvatinib, hepatic reserve

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide [1]. HCC commonly occurs in patients with chronic hepatitis or liver cirrhosis due to viral infection, alcohol use, non-alcoholic steatohepatitis, or diabetes [2].

Data from the SHARP trial [3] and Asia-Pacific study [4] indicated that sorafenib is an appropriate treatment option for patients with unresectable HCC. In the REFLECT study [5], lenvatinib was effective with respect to overall survival (OS) by statistical confirmation of non-inferiority when compared with sorafenib, and it was also associated with a significantly higher overall response rate (ORR) and longer progression-free survival (PFS) than sorafenib. Recently, these tyrosine kinase inhibitors (TKIs) have become the standard of care for systemic treatment of patients with advanced HCC who are not candidates for potential curative options, such as surgical resection, transplantation, and locoregional therapy. In recent years, the TKIs regorafenib and ramucirumab have been approved for clinical use as second-line treatment for patients with HCC that progressed on sorafenib based on the results of the RESORCE [6] and REACH-2 [7] trials. However, candidates for second-line therapy must have good hepatic reserve at first-line treatment failure to receive these agents.

Herein we assessed changes in functional hepatic reserve patients who had Child-Pugh A liver function at initiation of TKI therapy.

Material and Methods

Background of patients treated with TKI

A total of 212 patients with advanced HCC and Child-Pugh grade A status who initiated sorafenib or lenvatinib as first-line TKI therapy in our hospital between August 2009 and October 2019 were enrolled in this retrospective cohort study. A total of 74 patients were able to undergo evaluation of serum albumin and serum total bilirubin prior to initiating sorafenib or lenvatinib therapy and 2, 4, and 6 months after treatment initiation. Dose intensity (DI) was defined as the total amount of drug given in a fixed unit of time. Relative dose intensity (RDI) was the ratio of delivered to the planned dose intensity and can be expressed as a percentage.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Hiroshima University. Written informed consent was obtained from each patient after a detailed explanation of the study procedures was provided.

Assessment of hepatic functional reserve

We evaluated Child-Pugh grade and albumin-bilirubin (ALBI) score calculated using the following formula [8] and Child-Pugh grade as measures of functional hepatic reserve:

ALBI = (log10 serum total bilirubin (μmol/L) × 0.66) + (serum albumin (g/L) × −0.085)

ALBI scores were divided into three levels: grade 1 (< −2.60), grade 2 (−2.60 ≤ ALBI ≤ −1.39), and grade 3 (> −1.39). For more detailed evaluations of patients with ALBI grade2, we used modified ALBI (mALBI) grade [9] consisting of 4 levels: grade 1 (<-2.60), grade 2a (-2.60 ≤ALBI <-2.27), grade 2b (-2.27 ≤ALBI ≤-1.39), grade 3 (>-1.39)

TKI treatment

Patients received 400 mg sorafenib twice daily or 8 mg/12 mg lenvatinib once daily based on body weight. Treatment interruptions and dose reductions were permitted for adverse drug reactions. Patients continued therapy until death or until they met one of the following criteria: (i) adverse events that required termination of treatment; (ii) deterioration of Eastern Cooperative Oncology Group (ECOG) performance status (PS); (iii) worsening liver function; or (iv) withdrawal of consent. In our hospital, patients continued sorafenib or lenvatinib after onset of radiological progressive disease (PD) as defined by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) when no definitive treatment was available as second-line therapy. Criteria for treatment discontinuation after PD were severe adverse effects leading to discontinuation,

symptomatic progression, deterioration of hepatic reserve, deterioration of ECOG PS, and death.

Evaluation of response to sorafenib and lenvatinib

Radiological response was evaluated by computed tomography (CT) after sorafenib and lenvatinib initiation using mRECIST.

Statistical analysis

Univariate analysis was performed by log-rank test. Multivariate analysis was performed by Cox proportional hazard regression. The Wilcoxon rank sum test was performed to compare differences in ALBI scores before and after treatment. Variables were identified as being significant if they had p-values <0.05 by univariate analysis. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Changes in ALBI score during TKI treatment were assessed.

Results

Patient background characteristics

The backgrounds of all 212 patients are summarized in Table 1. The median age was 69.5 (range, 20-88) years, and 176 patients (83.1%) were male. Overall, 167 patients (78.8%) were treated with sorafenib. Of all 212 patients, 83 (39.2%) had ALBI grade 1, 64 (30.2%) had ALBI grade 2a and 65 (30.7%) had ALBI grade 2b hepatic reserve. The hepatic functional reserve of 139 patients (65.6%) was poor, reflected by a Child-Pugh score of 5.

Characteristics and clinical data of 74 patient whose ALBI score changes were evaluated prior to initiating TKI treatment and 2, 4, and 6 months after treatment initiation are summarized in Table 2. The median patient age was 68 (range, 46-87) years, and 64 of the 74 patients (86.5%) were male. Thirty patients (40.5%) had ALBI grade 1 hepatic function. Twenty patients (27.0%) had ALBI 2a grade and 24 (32.4%) had ALBI 2b grade. The median ALBI score was -2.53 (range, -3.61 to -1.68).

Response to TKI treatment

During the monitoring period, 195 patients progressed radiologically. The median time to progression (TTP) among all 212 patients was 3.8 months, and was 3.5 months in the sorafenib group and 7.3 months in the lenvatinib group.

ALBI score changes

Figure 1 shows the changes in ALBI score during treatment. In all 74 patients, the median ALBI score before TKI treatment was -2.53 and after 2, 4, and 6 months was -2.45, -2.44, and -2.36, respectively. ALBI scores tended to increase during TKI therapy.

ALBI score changes by subgroup

No differences in ALBI score change was observed between patients in the sorafenib and lenvatinib groups at each time point, although the ALBI score significantly increased ($p<0.01$) from baseline to 6-month evaluation in the sorafenib group (Figure 2). The ALBI score increased from baseline to 2 months after TKI initiation to a greater degree in the TTP ≤3.8 months group compared with the TTP >3.8 months group, and at 4 and 6 months, a significant difference ($p<0.01$) was observed between the two groups (Figure 3). The ALBI score in the ALBI 1 group increased and ALBI 2b group decreased from baseline to 2 months after initiation of TKIs. But the median ALBI score in the ALBI 1 group was lower than that in the ALBI 2a and 2b group at each time point (Figure 4).

Child-Pugh liver function deterioration

During first-line TKI treatment, the Child-Pugh score deteriorated to grade B or C in 72.2% of patients (Figure 5), and the median time to Child-Pugh B or C score was 3.9 months. Causes of deterioration of liver function were albumin decrease (88.9% of patients), prothrombin time prolongation (41.2%), bilirubin increase (27.5%), development of ascites (10.5%), and encephalopathy (2.0%). Factors implicated in

deterioration of hepatic functional reserve in univariate analysis included serum albumin ≤3.8 g/dL, prothrombin activity ≤ 87 %, serum alpha fetoprotein > 137.6 ng/ml, serum *des-*γ-carboxy prothrombin > 802.5 mAU/ml, number of intrahepatic tumors ≥ 4, tumor size relative to the liver ≥ 50 %, intrahepatic tumor size >27 mm and presence of macroscopic vascular invasion (MVI), while multivariate analysis only revealed serum albumin ≤3.8 g/dL and presence of MVI to be associated with liver function deterioration (Table 3). Time from Child A to B/C grade in the serum albumin ≤3.8 g/dL group and presence of MVI group were significantly ($p<0.01$) shorter (Figure 5).

Factors involved in recovery to Child-Pugh grade A score

The hepatic reserve of 104 (68.0%) patients among 153 patients with deterioration of liver function recovered to Child-Pugh A following dose reduction, drug withdrawal, or treatment intended for recovery of liver function. The median time to recovery to Child-Pugh A was 1.2 months.

Discussion

Sorafenib, regorafenib, lenvatinib, and ramucirumab can be used for patients with unresectable HCC. The RESORCE and REACH-2 trials demonstrated that sequential therapy such as sorafenib followed by regorafenib or sorafenib followed by ramucirumab improved the survival of patients after sorafenib failure [6][7]. However,

candidates for second-line TKI treatment need to have good hepatic functional reserve at detection of PD after first-line TKI treatment. Previous studies have reported that liver function deteriorates during TKI therapy [10][11][12]. In the present study, the ALBI scores of 74 patients worsened at 2, 4, and 6 months after initiation of first-line TKI therapy. We divided patients into two group depending on whether their median TTP was shorter or longer than 3.8 months. Patients in the TTP $\leq$3.8 months group experienced ALBI score increases earlier than those in the TTP >3.8 group (Figure 3), suggesting that tumor progression is associated with worsening of liver function. At 6 months, patients in the sorafenib group had higher ALBI scores compared to baseline, while no changes were observed in the lenvatinib group (Figure 2). In the REFLECT study, patients in the lenvatinib group experienced longer TTP compared with those in the sorafenib group, similar to the results of the present study. We believe that the difference in the ability of these two drugs to control tumor progression is responsible for the difference in ALBI scores at 6 months. While the ALBI scores of patients in the ALBI 1 group increased and ALBI 2b group decreased initially, the median ALBI score in the ALBI 1 group was lower than that in the ALBI 2a and 2b group at the 2-, 4-, and 6-month timepoints (Figure 4).

In the assessment of all 212 patients, we identified serum albumin ≤3.8 g/dL and presence of MVI as being associated with deterioration of Child-Pugh A to B/C liver function during TKI therapy (Table 3). The most frequent cause of Child-Pugh score increase was decreased serum albumin. Thus, it appears that high serum albumin level at TKI initiation is required to maintain good liver function. Previous reports have stated that serum albumin, Child-Pugh score, and ALBI grade are important for selection of candidates for second-line therapy (Child-Pugh A and ECOG performance status 0 or 1 at PD) [10][13][15]. Repeated TACE has been reported to cause hepatic functional reserve deterioration [14], so it is necessary to initiate TKI before liver function deterioration for sequential therapy. Branched-chain amino acids (BCAA) have been reported to be effective in maintaining serum albumin levels [16], suggesting that nutrition therapy is important for patients receiving TKI therapy. In our hospital, the Metabolic Care Unit (MCU), which consists of doctors, dietitians, and physical therapists, treats patients who are receiving molecularly targeted agents. The MCU provides nutrition therapy and exercise therapy, and administers BCAA. In the present study, after dose reduction, dose interruption, and/or treatment intended to improve hepatic reserve (e.g., albumin replacement, BCAA), overall, 104 patients whose hepatic functional reserve deteriorated from Child-Pugh A to B/C experienced liver function

improvement to Child-Pugh A. Even when hepatic functional reserve deteriorates, the function may improve with appropriate management. Therefore, hepatic reserve should be assessed when planning sequential therapy.

This study had several limitations, including being a retrospective, non-randomized controlled study and the short observation period of lenvatinib-treated patients.

Identified causes of deterioration of hepatic functional reserve were not only chronic factors such as liver failure and tumor progression, but also temporary factors such as adverse effects associated with TKIs, tumor lysis, and combination therapy (e.g., TACE). Therefore, since liver function improves in some patients after dose adjustment and administration of treatments intended to improve hepatic reserve, it is necessary to determine the appropriate timing for switching from first- to second-line therapy with consideration of improving hepatic functional reserve.

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Statement of Ethics: This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Hiroshima University (IRB number 695). Written informed consent was obtained from each patient after a detailed explanation of the study procedures.

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Author Contributions: S. Uchikawa and T. Kawaoka designed the study, analyzed the data, and wrote the paper; S. Uchikawa acquired the data; S. Uchikawa performed the statistical analysis; T. Kawaoka and H. Aikata reviewed the results; H. Akikata revised the manuscript for important intellectual content.

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Figure Legends

Figure 1. ALBI score changes

Figure 2. Comparison of ALBI score changes between patients treated with sorafenib vs lenvatinib

Figure 3. Comparison of ALBI score changes between patients in the TTP ≤3.8 months and TTP >3.8 months groups

Figure 4. Comparison of ALBI score changes between the ALBI 1, 2a and 2b groups

Figure 5. Transition rate from Child-Pugh A to B/C

Table 1: Pretreatment patient characteristics of all 212 patients

Variable	n=212
Age (range), y*	69.5 (20-88)
Regimen, sorafenib/lenvatinib, n	167/45
Gender, M/F, n	176/36
Etiology, viral/NBNC, n	152/60
Serum albumin (range), g/dL*	3.8 (2.9-4.9)
Serum total bilirubin (range), mg/dL*	0.8 (0.3-1.9)
Prothrombin activity (range), %*	87 (45-131)
mALBI grade, 1/2a/2b, n	83/64/65
Child-Pugh score, 5/6, n	139/73
Size of intrahepatic tumor (range), mm*	27.0 (0-194)
Extrahepatic metastasis, absent/present, n	81/131
No. of intrahepatic tumors, ≤3/>4, n	84/128
Tumor size relative to the liver, <50%/≥50%, n	174/38
Macroscopic vascular invasion, absent/present, n	157/55
BCLC stage, A/B/C, n	10/58/144
TNM stage, 2/3/4a/4b, n	25/47/32/108
Serum α-fetoprotein (range), ng/mL*	137.6 (0.5-2650000)
Serum *des*-γ-carboxy prothrombin (range), mAU/mL*	802.5 (10-1083990)
Relative dose intensity for a month (range), %*	100 (17.9-100)

M, male; F, female; NBNC, non-hepatitis B virus and non-hepatitis C virus; ALBI, albumin-bilirubin; mALBI, modified albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; TNM, tumor node metastasis

Table 2: Pretreatment patient characteristics of the 74 patients whose ALBI scores were evaluated every 2 months

Variable	n=74
Age (range), y*	68 (46-87)
Regimen, sorafenib/lenvatinib, n	55/19
Gender, M/F, n	64/10
Etiology, viral/NBNC, n	51/23
Serum albumin (range), g/dL*	3.8 (2.9-4.9)
Serum total bilirubin (range), mg/dL*	0.8 (0.3-1.8)
Prothrombin activity (range), %*	88 (54-131)
mALBI grade, 1/2a/2b, n	30/20/24
Child-Pugh score, 5/6, n	49/25
Size of intrahepatic tumor (range), mm*	25.4 (0-150)
Extrahepatic metastasis, absent/present, n	26/48
No. of intrahepatic tumors, ≤3/>4, n	37/37
Tumor size relative to the liver, <50%/≥50%, n	67/7
Macroscopic vascular invasion, absent/present, n	58/16
BCLC stage, A/B/C, n	6/15/53
TNM stage, 2/3/4a/4b, n	7/16/8/43
Serum α-fetoprotein (range), ng/mL*	74.9 (0.5-403000)
Serum *des*-γ-carboxy prothrombin (range), mAU/mL*	475.5 (10-1083990)
Relative dose intensity for a month (range), %*	100 (17.9-100)

*median

M, male; F, female; NBNC, non-hepatitis B virus and non-hepatitis C virus; ALBI, modified albumin-bilirubin; BCLC, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; TNM, tumor node metastasis

Table 3: Predictive factors for hepatic functional reserve deterioration in patients treated with TKIs

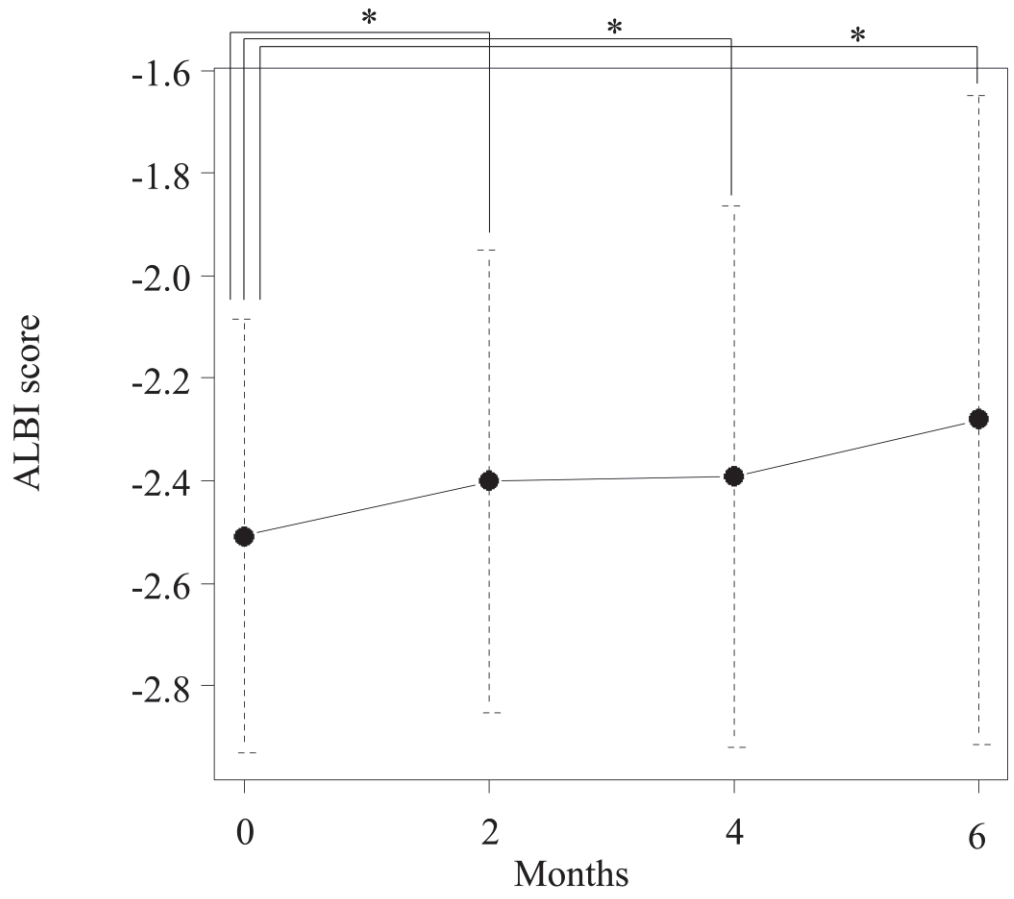
	Univariate analysis* p-value	Multivariate analysis***		
		HR	95% CI	p-value
Age, ≤69.5/>69.5	0.706			
Regimen, sorafenib/lenvatinib	0.213			
Gender, M/F	0.480			
Etiology, viral/NBNC	0.774			
Serum albumin, ≤3.8/>3.8 g/dL	<0.01	0.438	0.31-0.62	<0.01
Serum total bilirubin, ≤0.8/>0.8 md/dL	0.064			
Prothrombin activity, ≤87/>87%	<0.01			
Size of intrahepatic tumor, ≤27/>27 mm	<0.01			
Extrahepatic metastasis, absent/present	0.164			
No. of intrahepatic tumors, ≤3/≥4	<0.01			
Tumor size relative to the liver, <50/≥50%	<0.01			
Macroscopic vascular invasion, absent/present	<0.01	1.85	1.26-2.73	<0.01
BCLC stage, A/B/C	0.731			
Serum alpha fetoprotein, ≤137.6/>137.6 ng/mL	0.027			
Serum *des*-γ-carboxy prothrombin, ≤802.5/>802.5 mAU/mL	<0.01			
Relative dose intensity for a month, <100/100 %	0.76			

*log-rank test

**Cox proportional hazard regression

M, male; F, female; NBNC, non-hepatitis B virus and non-hepatitis C virus; OR, odds ratio; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer

Figure 1: ALBI score changes



*p<0.01
Wilcoxon rank sum test

Figure 2: Comparison of ALBI score changes between patients treated with sorafenib vs lenvatinib

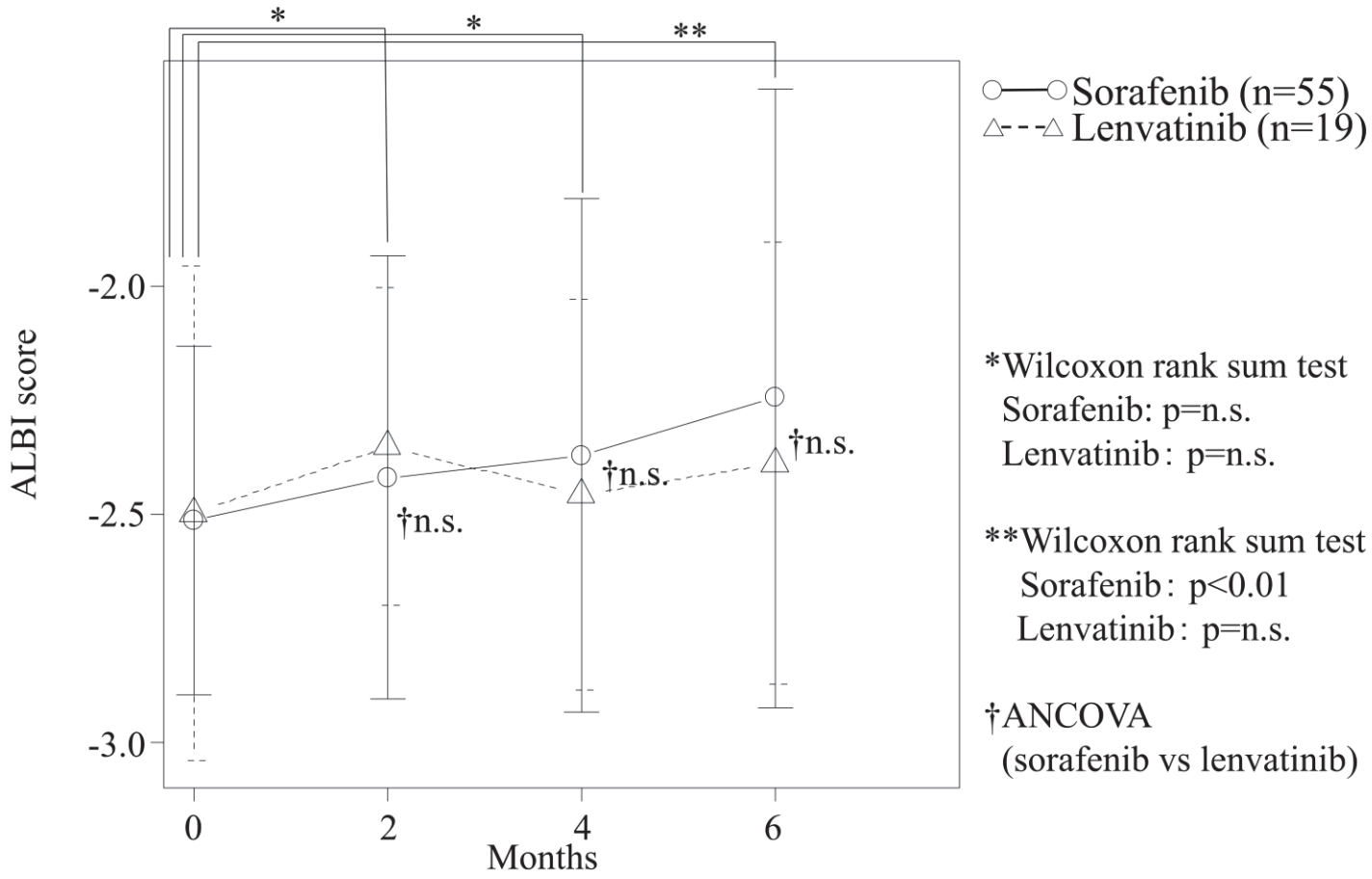


Figure 3: Comparison of ALBI score changes between patients in the TTP ≤3.8 months and TTP >3.8 months groups

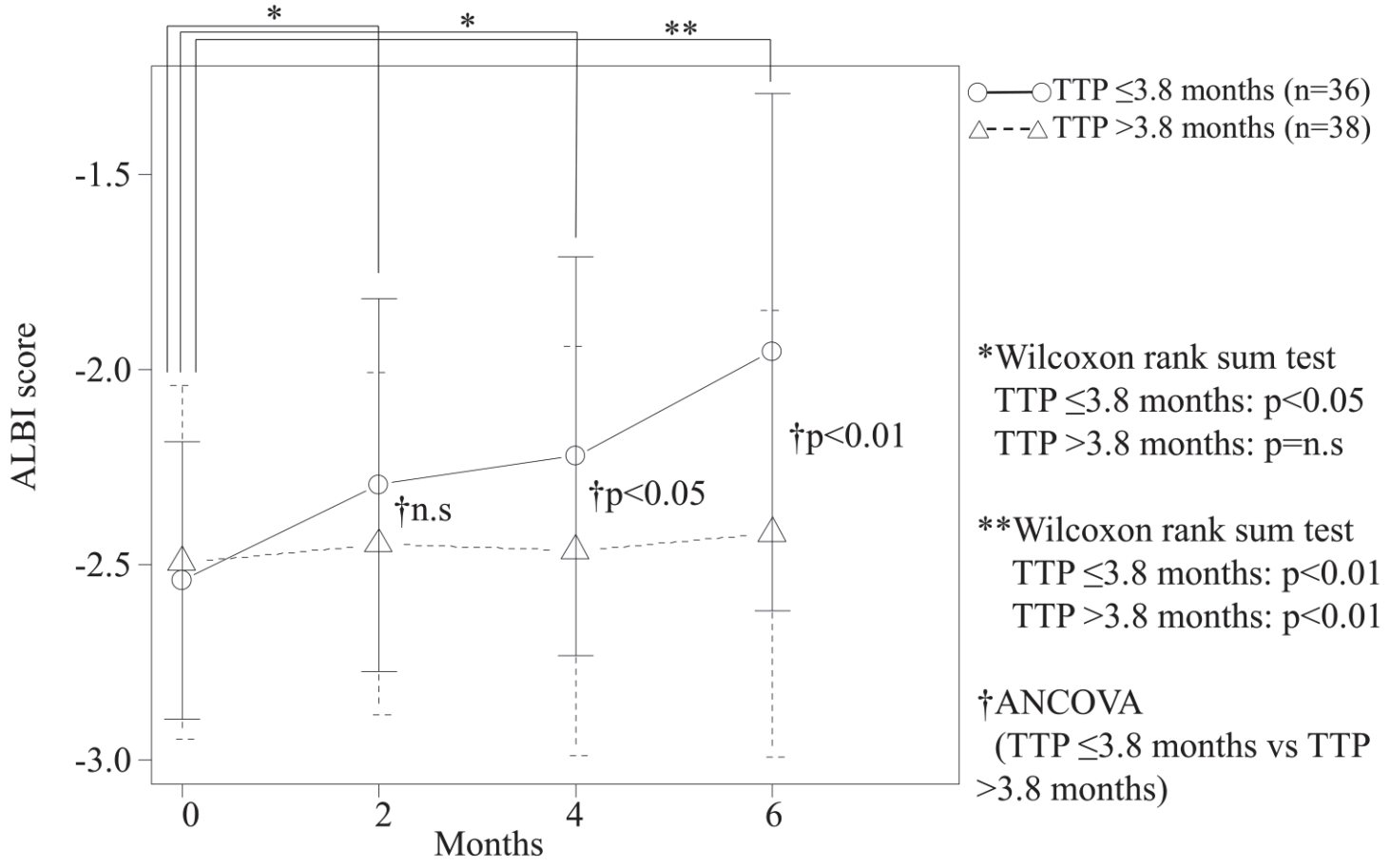


Figure 4: Comparison of ALBI score changes between the ALBI 1, 2a and 2b groups

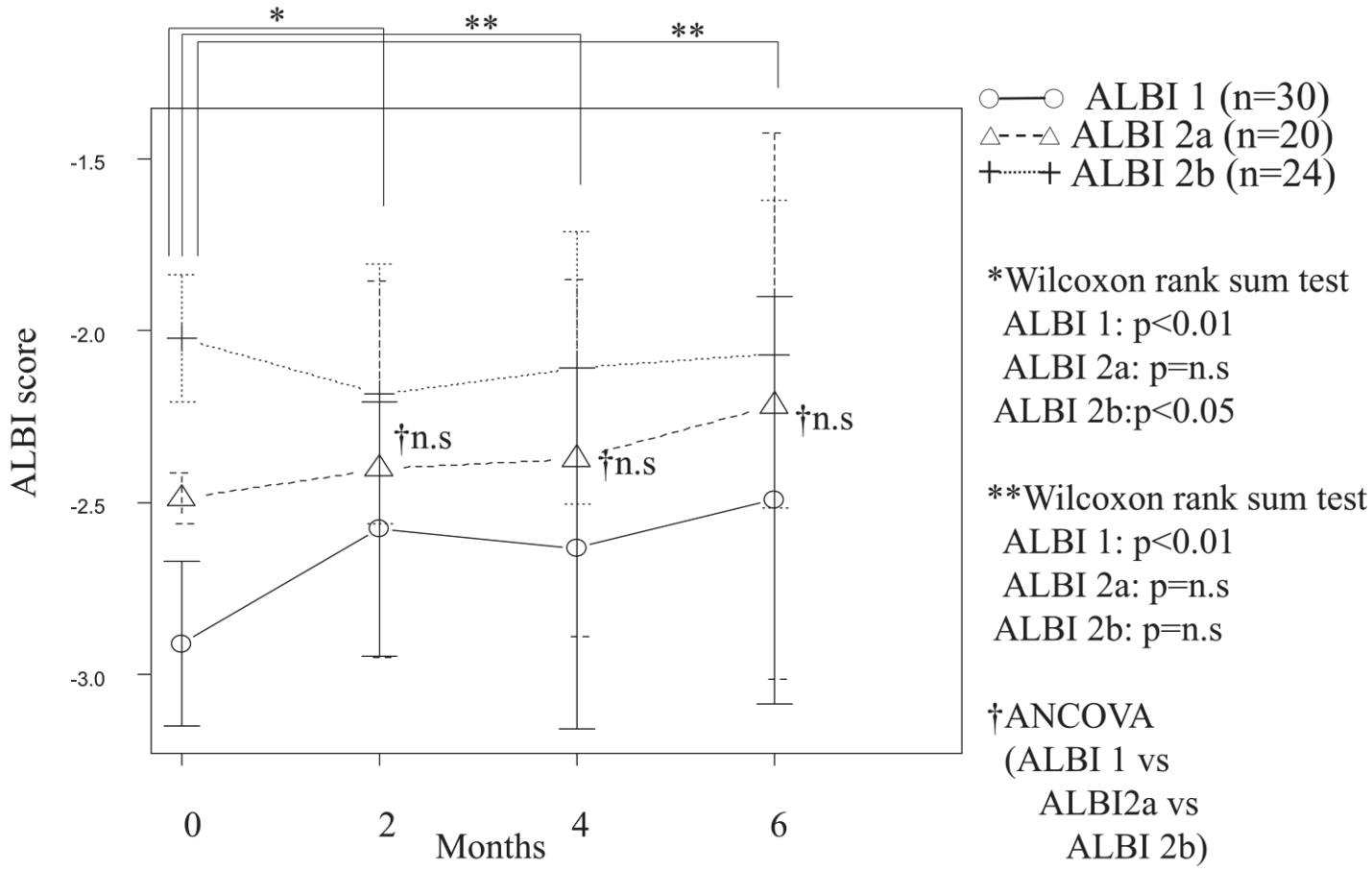


Figure 5: Transition rate from Child-Pugh A to B/C