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# Response-survival Association Differs by Hepatic Reserve in Unresectable HCC Receiving Atezolizumab Plus Bevacizumab

AKIFUMI KUWANO[1], MASAYOSHI YADA[1,2], KOSUKE TANAKA[1], TAIKAN HAMAMOTO[1], KAZUKI KUROSAKA[1], HIDEO SUZUKI[1] and KENTA MOTOMURA[1]

[1]Department of Hepatology, Aso Iizuka Hospital, Fukuoka, Japan;
[2]Department of Gastroenterology, Ichinomiyanishi Hospital, Ichinomiya, Japan

## Abstract

*Background/Aim:* Evidence supporting atezolizumab plus bevacizumab (Atez/Bev) for unresectable hepatocellular carcinoma (uHCC) in patients with Child–Pugh B (CP-B) liver function is limited. We investigated whether the prognostic significance of radiologic response differs according to hepatic reserve and evaluated the impact of baseline neutrophil-to-lymphocyte ratio (NLR).

*Patients and Methods:* We retrospectively analyzed 105 consecutive patients with uHCC treated with Atez/Bev (CP-A, n=82; CP-B, n=23). Tumor response was assessed by modified RECIST, and overall survival (OS) was estimated using Kaplan–Meier methods. Baseline NLR was evaluated using a prespecified cut-off of 2.56.

*Results:* Response was not evaluable more often in CP-B than in CP-A (21.7% *vs*. 4.8%). In CP-A, objective response and disease control were each associated with longer OS ($p$=0.002 and $p$=0.003, respectively). In CP-B, neither objective response nor disease control was significantly associated with OS; OS was similar for stable disease and objective response (10.6 *vs*. 10.7 months). Across the cohort, NLR <2.56 was associated with longer OS and remained prognostic in both CP-A and CP-B.

*Conclusion:* The prognostic meaning of radiologic response differed according to hepatic reserve. While objective response is strongly associated with survival in CP-A, disease stabilization may represent clinically meaningful benefit in CP-B. Baseline NLR may aid risk stratification in CP-B uHCC treated with Atez/Bev.

**Keywords:** Hepatocellular carcinoma, atezolizumab plus bevacizumab, Child–Pugh B, NLR, disease control.

## Introduction

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality, and systemic therapy is the mainstay of treatment for patients who are not eligible for curative or locoregional therapies (1-5). Atezolizumab plus bevacizumab (Atez/Bev) has demonstrated improved survival and tumor control compared with sorafenib in

Akifumi Kuwano, MD, PhD, Department of Hepatology, Aso Iizuka Hospital, 3-83 Yoshio-machi, Iizuka, Fukuoka 820-8505, Japan. Tel: +81 948223800, Fax: +81 948295744, e-mail: akuwanoh1@aih-net.com

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patients with unresectable HCC (uHCC), and is now widely used as a standard first-line regimen (2-5).

However, most pivotal clinical trials of Atez/Bev predominantly enrolled patients with preserved hepatic function, mainly those with Child–Pugh class A (CP-A) disease. Evidence regarding patients classified as Child–Pugh class B (CP-B) remains limited (5, 6). In real-world practice, patients with CP-B represent a clinically important population with limited treatment options, difficulty in maintaining therapy, and a higher risk of hepatic decompensation owing to lower hepatic reserve. Although real-world studies and recent meta-analyses have reported the safety and effectiveness of Atez/Bev in patients with CP-B, the most clinically informative efficacy endpoints in this population remain uncertain (7-12).

Radiologic tumor response is widely used to assess the efficacy of systemic therapy and has been reported to correlate with survival (13). However, the clinical relevance of the objective response rate (ORR), which reflects tumor shrinkage, may not be uniform across strata of liver function. In patients with impaired hepatic reserve, dose intensity and treatment continuation are often constrained, and prognosis may be influenced not only by tumor shrinkage but also by disease stabilization and hepatic dysfunction. From this perspective, maintaining stable disease (SD) may capture clinically meaningful benefit better than objective response in patients with CP-B.

In addition, there is growing interest in simple pretreatment biomarkers that reflect systemic inflammation. The neutrophil-to-lymphocyte ratio (NLR) has been associated with prognosis across multiple malignancies and has also been reported as a useful prognostic marker in HCC (14-16).

In this study, we retrospectively analyzed real-world patients with uHCC treated with Atez/Bev to investigate whether the prognostic implications of radiologic antitumor effect differ according to baseline liver function (CP-A *vs*. CP-B). We also examined the association between baseline NLR and clinical outcomes.

## Patients and Methods

*Patients.* This single-center, retrospective study evaluated 105 patients with uHCC treated with Atez/Bev at Aso Iizuka Hospital from December 2018 to October 2025. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Aso Iizuka Hospital (approval no. 22008). Informed consent was obtained using the opt-out method.

*Treatment protocol.* Intravenous atezolizumab (1,200 mg) and bevacizumab (15 mg/kg) was administered intravenously every three weeks, according to the protocol established in the IMbrave150 study (5). Treatment was continued until the disease progressed or unacceptable side effects occurred.

*Adverse events.* Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (17).

*Evaluation of efficacy.* Treatment response was assessed by the treating physician with computed tomography or magnetic resonance imaging every 6 to 12 weeks after therapy initiation using the Modified Response Evaluation Criteria in Solid Tumors (18). Disease control was defined as complete response (CR), partial response (PR), or SD. Objective response was defined as either PR or CR. Patients were seen every three weeks in follow-up, and treatment was continued until the disease progressed or intolerable side effects occurred. Not evaluated (NE) was defined as lack of post-baseline imaging due to early discontinuation, clinical deterioration, or death before the first scheduled assessment. In the intention-to-treat analysis, patients with NE were treated as non-responders.

*NLR.* Baseline NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count at the start of Atez/Bev treatment. Based on a

Table I. *Patient characteristics in the Child–Pugh A and B groups.*

| Characteristic | CP-B | CP-A | *p*-Value |
|---|---|---|---|
| Number | 23 | 82 | |
| Age, years | 74.0 (67.0-80.0) | 74.0 (66.0-82.5) | 0.996 |
| Sex, n (men/women) | 17/6 | 64/18 | 0.680 |
| MVI positive, n | 8 (34.8%) | 24 (29.3%) | 0.614 |
| EHS positive, n | 4 (17.4%) | 23 (28.0%) | 0.273 |
| Maximum tumor size, cm | 4.2 (2.0-6.0) | 4.2 (2.5-7.0) | 0.162 |
| More than five tumors | 15 (65.2%) | 47 (57.3%) | 0.667 |
| Etiology | 13/10 | 48/34 | 0.863 |
| Viral/non-viral | | | |
| Diabetes, n | 13 | 29 | 0.069 |
| Alb, g/dl | 2.7 (2.5-3.0) | 3.8 (3.4-4.1) | <0.001 |
| T.Bil, mg/dl | 1.1 (0.9-1.8) | 0.9 (0.7-1.2) | 0.017 |
| ALBI score | −1.31 (−1.71 to −1.26) | −2.41 (−2.70 to −2.17) | <0.001 |
| mALBI grade 1/2a/2b/3 | 0/0/10/13 | 28/26/28/0 | <0.001 |
| NLR | 3.38 (1.95-4.99) | 2.37 (1.74-3.40) | 0.080 |
| CP score 5/6/7/8/9, n | 0/0/8/9/6 | 52/30/0/0/0 | <0.001 |
| BCLC stage, n | | | 0.572 |
| A | 0 | 2 | |
| B | 10 | 38 | |
| C | 13 | 42 | |
| Treatment line (n, first/second) | 18/5 | 61/21 | 0.701 |
| TACE during treatment, n (%) | 1 (4.4%) | 18 (21.9%) | 0.029 |
| Tumor marker | | | |
| AFP, ng/ml | 232.0 (45.7-1,218.7) | 37.0 (6.8-1,137.4) | 0.511 |
| PIVKA-II, mAU/ml | 1276.0 (133.5-11,445.5) | 419.5 (80.3-2,978.5) | 0.221 |
| Dose reduction or de-escalation of BEV | 7 (30.4%) | 20 (24.4%) | 0.563 |

Data are expressed as numbers with or without percentage and medians (interquartile range). CP: Child–Pugh; MVI: macrovascular invasion; EHS: extrahepatic spread; Alb: albumin; T.Bil: total bilirubin; ALBI: albumin-bilirubin; mALBI: modified albumin-bilirubin; NLR: neutrophil-to-lymphocyte ratio; BCLC: Barcelona Clinic Liver Cancer stage; TACE: transarterial chemoembolization; AFP: alpha-fetoprotein; PIVKA-II: vitamin K absence or antagonist-II; BEV: bevacizumab.

previous report, patients were dichotomized using an NLR cut-off value of 2.56 (14).

*Statistical analysis.* Statistical analyses were conducted using JMP 18 software (SAS Institute Inc., Cary, NC, USA). Data are presented as medians with interquartile range (IQR). Categorical data were compared using the $\chi^2$ test. Survival was analyzed using the Kaplan–Meier method and compared using the log-rank test. $p<0.05$ was considered significant.

## Results

*Patient characteristics.* Characteristics of the 105 patients according to group are shown in Table I. The CP-A and CP-B groups comprised 82 and 23 patients, respectively. Median age was 74 years (IQR=67-82), and 81 (77.1%) were men. A viral etiology was present in 61 patients (58.1%). At treatment initiation, 55 patients (52.4%) had Barcelona Clinic Liver Cancer stage C disease, 48 (45.7%) stage B, and two (1.9%) stage A. Atez/Bev was used as first-line systemic therapy in 79 patients (75.2%). Macrovascular invasion was observed in 32 patients (30.5%), and extrahepatic metastasis in 27 (25.7%).

Measures of baseline liver function were worse in the CP-B group. Median albumin was significantly lower in the CP-B group [2.7 g/dl (IQR=2.5-3.0) *vs*. 3.8 g/dl ([IQR=3.4-4.1); $p<0.001$], while median total bilirubin was significantly higher [1.1 mg/dl (IQR=0.9-1.8) *vs*. 0.90 mg/dl (IQR=0.70-1.2); $p=0.017$]. The median ALBI score was significantly worse in the CP-B group [−1.31 (IQR=−1.71 to −1.26) *vs*. −2.41 (IQR=−2.70 to −2.17); $p<0.001$]. There

Table II. *Comparison of best responses in the Child–Pugh A and B groups (intention-to-treat).*

| | CP-B | CP-A | *p*-Value |
|---|---|---|---|
| Overall response | 23 | 82 | 0.023 |
| CR | 0 (0.0%) | 3 (3.7%) | |
| PR | 4 (17.4%) | 34 (41.4%) | |
| SD | 8 (34.8%) | 18 (22.0%) | |
| PD | 6 (26.1%) | 23 (28.0%) | |
| NE | 5 (21.7%) | 4 (4.8%) | |
| ORR (CR+PR) | 4 (17.4%) | 37 (45.1%) | 0.015 |
| DCR (CR+PR+SD) | 12 (52.2%) | 55 (67.1%) | 0.223 |

CP: Child–Pugh; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluated; ORR: objective response rate; DCR: disease control rate.

Table III. *Adverse events in the Child–Pugh (CP) A and B groups.*

| | CP-B | CP-A | *p*-Value |
|---|---|---|---|
| Number | 23 | 82 | |
| Proteinuria | 5 (21.7%) | 23 (28.0%) | 0.606 |
| Ascites | 3 (13.0%) | 3 (3.7%) | 0.118 |
| Bleeding-related events | 2 (8.7%) | 3 (3.7%) | 0.301 |
| Adrenocortical insufficiency | 1 (4.3%) | 5 (6.1%) | 1.000 |
| Rash | 1 (4.3%) | 2 (2.4%) | 0.528 |
| Elevated liver enzymes | 0 (0.0%) | 3 (3.7%) | 1.000 |
| Interstitial pneumonia | 0 (0.0%) | 2 (2.4%) | 1.000 |
| Diarrhea | 0 (0.0%) | 1 (1.2%) | 1.000 |
| Thrombocytopenia | 0 (0.0%) | 1 (1.2%) | 1.000 |

was no significant difference in baseline NLR between the CP-B and CP-A groups [3.38 (IQR=1.95-4.99) *vs*. 2.37 (IQR=1.74-3.40), *p*=0.080]. The proportion of patients with NLR <2.56 did not significantly differ between the CP-B and CP-A groups (39.1% *vs*. 59.8%; *p*=0.131). Maximum tumor diameter was comparable in the CP-B and CP-A groups [4.2 cm (IQR=2.0-6.0) *vs*. 4.2 cm (IQR=2.5-7.0), *p*=0.162]. More than five tumors were observed in 57.3% of CP-A patients and 65.2% of CP-B patients (*p*=0.667). Baseline alpha-fetoprotein levels were not significantly different between the CP-B and CP-A groups [232.0 ng/ml (IQR=45.7-1218.7) *vs*. 37.0 ng/ml (IQR=6.8-1137.4); *p*=0.511].

*Effect of Atez/Bev in the CP-A and CP-B groups.* The best overall treatment response in the CP-A and CP-B groups (intention-to-treat) is summarized in Table II. Response was not evaluated in a significantly higher proportion of patients in the CP-B group (21.7% *vs*. 4.8%; *p*<0.001). The ORR was significantly lower in the CP-B group (17.4% *vs*., 45.1%; *p*=0.015). The disease control rate (DCR) did not significantly differ between the CP-B and CP-A groups (52.2% and 67.1%, respectively; *p*=0.223).

*Safety.* Adverse events are summarized in Table III. The incidence rates of proteinuria in the CP-B and CP-A groups were 21.7% and 28.0%, respectively (*p*=0.606). The rates for ascites were 13.0% and 3.7%, respectively (*p*=0.118), and those for bleeding-related events were 8.7% and 3.7%, respectively (*p*=0.301). Other adverse events were infrequent and did not significantly differ between the groups.

*Overall survival (OS).* The median follow-up was 13.7 months. Median OS was 17.4 months in the entire cohort,

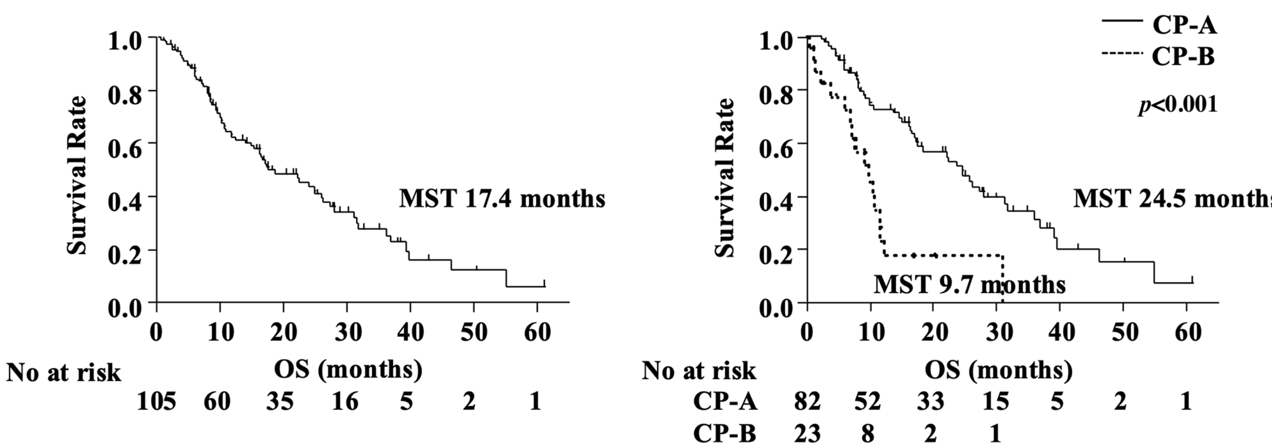


Figure 1. *Kaplan–Meier estimates of overall survival (OS) in all patients and in patients grouped according to Child–Pugh class. MST: Median survival time; CP-A: Child–Pugh class A; CP-B: Child–Pugh class B.*

24.5 months in the CP-A group, and 9.7 months in the CP-B group ($p$<0.001) (Figure 1). Within the CP-B group, median OS was 12.0 months for Child–Pugh score 7, 9.7 months for score 8, and 5.4 months for score 9 ($p$<0.001).

In the CP-A group, OS was significantly longer in patients with an objective response (CR or PR) than in those without (32.9 *vs*. 17.1 months, $p$=0.002) (Figure 2). In addition, OS was significantly longer in those in whom disease control was achieved than in those it was not (30.2 *vs*. 15.6 months, $p$=0.003) (Figure 2). OS was also longer in CP-A patients with an objective response than in those with SD (36.0 *vs*. 17.1 months), although the difference was not significant ($p$=0.074).

In the CP-B group, an objective response was infrequent, and OS did not significantly differ between patients with and without an objective response (10.7 and 9.7 months, respectively; $p$=0.476) (Figure 2). Although OS was better in patients in whom disease control was achieved (10.6 *vs*. 6.9 months), the difference was favorable but non-significant ($p$=0.073) (Figure 2). OS was similar in patients with SD and those with CR/PR (10.6 and 10.7 months, respectively; $p$=0.759).

*NLR.* In the entire cohort, OS was significantly longer in patients with NLR <2.56 than NLR ≥2.56 (27.9 *vs*. 14.7 months; $p$=0.003). This was also true in the CP-A group (31.5 *vs*. 23.6 months; $p$=0.037) and the CP-B group (18.0 *vs*. 6.4 months; $p$=0.003) (Figure 3). These data indicate that baseline NLR may provide prognostic information even in patients with impaired hepatic reserve.

*Transition to subsequent therapy.* After excluding patients who continued Atez/Bev treatment or discontinued it after achieving an objective response, the rate of transition to subsequent therapy was 64.2% in the CP-A group and 13.6% in the CP-B group ($p$<0.001).

## Discussion

This study demonstrated that the prognostic implications of radiologic response to Atez/Bev differ according to the patient's hepatic reserve and that maintaining disease stabilization may represent a key therapeutic goal for patients with CP-B. In those with CP-A disease, OS was significantly better in patients with an objective response; this was not the case in patients with CP-B disease. Among patients with CP-B, OS was somewhat longer in patients in whom disease control was achieved, but not significantly so, and comparable between patients with SD and those with an objective response. These findings suggest that the clinical meaning of radiologic endpoints differs between patients with differing degrees of liver function, and that

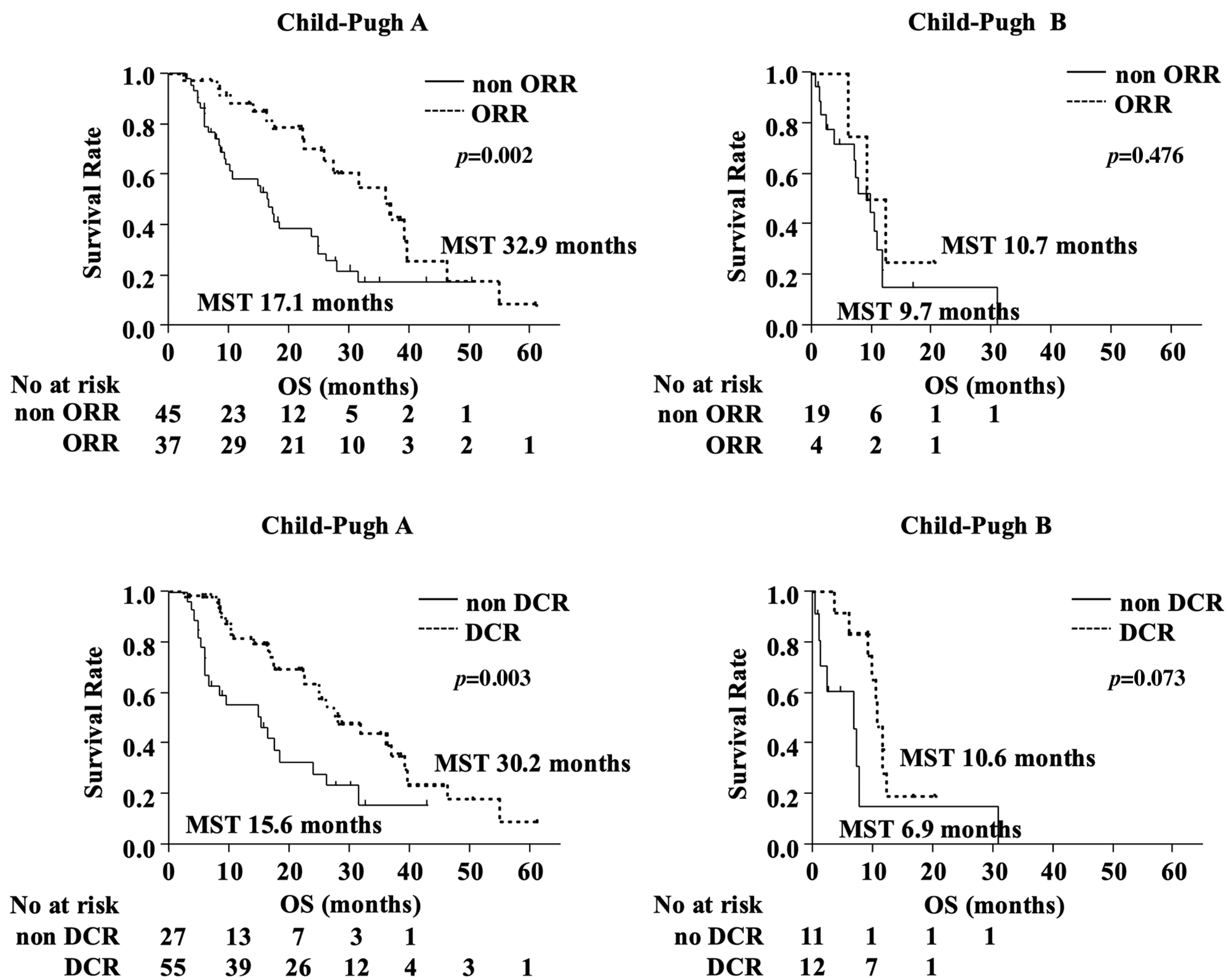


Figure 2. *Kaplan–Meier estimates of overall survival in patients stratified according to radiologic response and Child–Pugh class. Objective response was defined as complete response or partial response. Disease control was defined as complete or partial response, or stable disease. Patients whose treatment response was not evaluated were included in the non-response group in the intention-to-treat analysis. ORR: Objective response rate; OS: overall survival; MST: median survival time; DCR: disease control rate.*

response-based metrics should be contextualized based on baseline hepatic reserve. A practical explanation is that patients with CP-B often discontinue treatment early because of hepatic decompensation and/or deterioration in performance status, and therefore may not reach the appropriate timing for radiologic assessment. As a result, the apparent association between objective response and OS may be attenuated. Moreover, because clinical trajectories in patients with CP-B are strongly influenced not only by tumor progression but also by worsening liver function, maintaining disease stability may represent clinically meaningful benefit even without marked radiographic tumor shrinkage. Our observation that OS was similar between CP-B patients with SD and those with an objective response further supports the concept that tumor shrinkage may not be the dominant determinant of survival in patients with impaired hepatic reserve. In real-world practice for advanced uHCC with portal vein

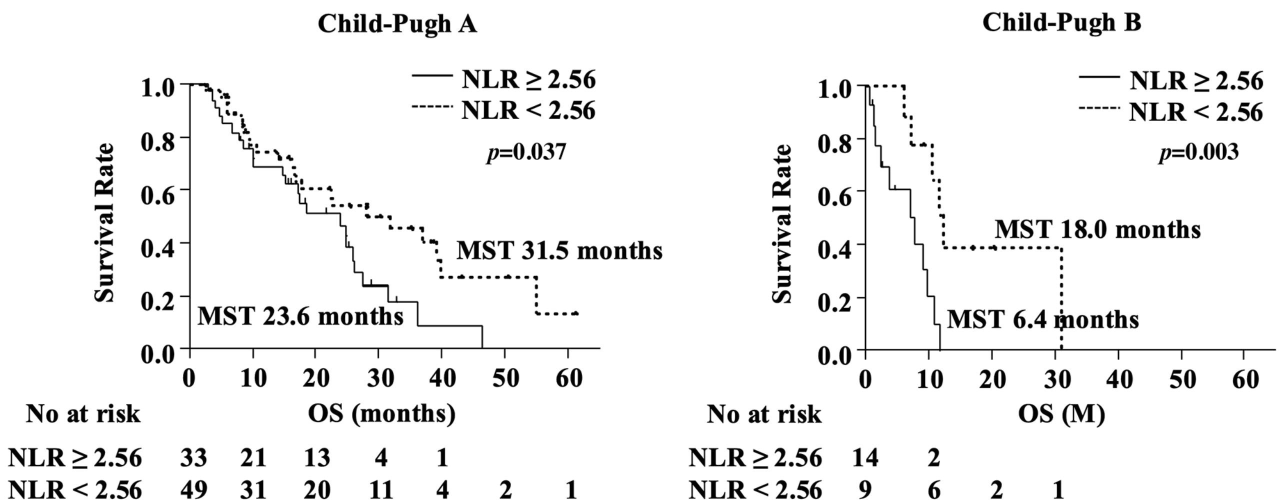


Figure 3. *Kaplan–Meier estimates of overall survival in patients stratified by Child–Pugh class and neutrophil-to-lymphocyte ratio using a ratio cutoff of 2.56. NLR: Neutrophil-to-lymphocyte ratio; MST: median survival time; OS: overall survival.*

tumor thrombus, Atez/Bev and hepatic arterial infusion chemotherapy may achieve comparable outcomes, suggesting that in high-risk patients, maintaining disease control while preserving liver function may provide clinically meaningful benefit, potentially outweighing the importance of radiographic tumor shrinkage (19). The treatment response and OS in this study were comparable to those reported in several previous studies of Atez/Bev in patients with CP-B (8, 9, 20, 21).

Another key finding is the prognostic value of systemic inflammation reflected by baseline NLR. NLR is an inexpensive and widely available biomarker, and in our cohort, NLR <2.56 was associated with more favorable OS not only in patients with CP-B, but also in the overall cohort and the CP-A subgroup (14-16, 22). In particular, because patients with CP-B are less likely to receive subsequent systemic therapy, NLR obtained at treatment initiation may be helpful for estimating prognosis and potential treatment benefit. Notably, among patients with CP-B, those with baseline NLR <2.56 had longer survival, suggesting that systemic therapy with Atez/Bev may be more justifiable when systemic inflammation is low. Thus, baseline NLR could help identify patients with CP-B who are more likely to derive clinically meaningful benefit from Atez/Bev despite impaired hepatic reserve. Notably, in the overall cohort, lower NLR was also associated with achieving both objective response and disease control (data not shown). Soluble CD163, a macrophage activation marker, has been reported to predict response to Atez/Bev in advanced HCC (23). Together with our findings, this suggests that a macrophage-associated inflammatory/immunosuppressive milieu may negatively influence treatment efficacy and prognosis.

Our results should also be interpreted in the context of the expanding real-world evidence base for systemic therapy in patients with CP-B liver function. Comparative real-world studies in patients with CP-B have evaluated Atez/Bev *versus* lenvatinib, providing complementary data on the feasibility and outcomes of first-line options in those with impaired hepatic reserve (20, 21). In addition, outcomes of Atez/Bev in both patients with CP-A and CP-B have been reported, reinforcing the need to interpret efficacy endpoints with attention to hepatic reserve and real-world evaluability (8). Moreover, real-world data indicate that effective post–Atez/Bev therapy is not always feasible, particularly in CP-B patients with limited hepatic reserve (24). Collectively, these studies underscore that CP-B represents a clinically important yet heterogeneous group of patients, in whom treatment goals and appropriate endpoints may differ. In uHCC, survival is determined not only by radiologic tumor response but also by multiple factors, including liver function, comorbidities, and treatment tolerability (25). In particular, in patients with CP- B disease, limited hepatic reserve is a major constraint, and prognosis may differ even among patients within the same response category.

With respect to treatment selection for patients with poor hepatic reserve, best supportive care may be considered in some individuals. Fulgenzi *et al*. reported that best supportive care may be as effective as immune checkpoint inhibitor-based regimens in selected patients with CP-B HCC (26). In the prospective CheckMate 040 cohort 5 trial, nivolumab monotherapy in CP-B7-8 uHCC (n=49) achieved an investigator-assessed ORR of 12% and a DCR of 55%, with a median OS of 7.6 months and manageable toxicities (27). We previously compared treatments in patients with CP-B uHCC and found no significant difference (28). Further investigation is needed to clarify optimal treatment strategies and endpoints for patients with CP-B, including whether Atez/Bev offers a clinical advantage over other systemic options across the spectrum of hepatic reserve.

*Study limitations.* This study has several limitations in addition to its retrospective, single-center design. First, the limited number of patients with CP-B may have reduced its power to detect differences in response–survival associations and ability to conduct detailed subgroup analyses. Second, the radiologic assessment and imaging intervals were not strictly standardized, and the higher frequency of patients whose response was not evaluated in the CP-B group may have diluted the apparent association between OS and objective response. Third, although the NLR cut-off was prespecified based on a prior study, external validation in independent CP-B cohorts is warranted. Because radiologic response is determined after treatment initiation, the association between response categories and OS may have been affected by immortal time bias, whereby patients must survive and remain on treatment long enough to undergo response assessment. This concern is particularly relevant in patients with CP-B, in whom treatment response is not always evaluated and early discontinuation is more frequent. Therefore, our findings regarding treatment response and survival should be interpreted as associations rather than causal effects. Future studies using landmark analyses or time-dependent Cox models are warranted.

## Conclusion

In real-world uHCC treated with Atez/Bev, the prognostic implications of radiologic response differed according to liver function at the time of treatment initiation. In patients with CP-A, an objective response was strongly associated with longer OS, whereas in those with CP-B disease, objective response was infrequent and not prognostic. OS was comparable between CP-B patients with SD and those with an objective response, suggesting that achieving SD may represent clinically meaningful benefit. Baseline NLR <2.56 was associated with OS in patients with CP-B and may serve as a practical biomarker to support risk stratification and treatment decision-making in patients with impaired hepatic reserve.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

A.K., M.Y., and K.M. designed the study. A.K., H.S., T.H., K.K., K.T., and M.Y. assisted with data analyses. A.K. wrote the initial draft of the manuscript. M.Y. contributed to the analysis and interpretation of the data. M.Y. and K.M. assisted in the preparation and critical review of the manuscript. All Authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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## Artificial Intelligence (AI) Disclosure

No artificial intelligence tools were used in the preparation, analysis, or presentation of this manuscript.

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