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Original Article

Prognostic Nutritional Index Predicts Outcomes in Hepatocellular Carcinoma Treated with Atezolizumab and Bevacizumab: A Propensity Score-matched Analysis

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Abstract

Background and Aims: The prognostic nutritional index (PNI), calculated from serum albumin and lymphocyte count, reflects a patient's immune-nutritional status and has been proposed as a prognostic marker in hepatocellular carcinoma (HCC). However, its role in advanced HCC patients treated with atezolizumab plus bevacizumab (Ate/Bev) remains unclear. In this study, we aimed to evaluate the prognostic value of PNI in patients receiving first-line Ate/Bev therapy. ***Methods:*** We retrospectively analyzed 362 patients with unresectable HCC who received Ate/Bev between November 2020 and June 2023 across two centers. Based on prior literature, a cutoff of 45 was used to classify patients into low-PNI (<45) and high-PNI (≥45) groups. Propensity score matching was performed to balance baseline characteristics. ***Results:*** After propensity score matching, 130 patients (65 per group) were included in the analysis. The high-PNI group showed a significantly lower incidence of grade ≥ 3 treatment-related adverse events (10.8% vs. 24.6%, $p = 0.039$), a higher objective response rate (38.4% vs. 20.0%, $p = 0.037$), and significantly longer overall survival (16.7 vs. 7.9 months, $p = 0.009$). Although progression-free survival was longer in the high-PNI group (4.8 vs. 3.0 months), the difference was not statistically significant ($p = 0.597$). Multivariate analysis confirmed that PNI was an independent predictor of overall survival (hazard ratio: 0.574, 95% confidence interval: 0.353–0.933, $p = 0.025$), after adjusting for vascular invasion, alpha-fetoprotein levels, concurrent therapy, and post-treatment interventions. ***Conclusions:*** PNI is an independent prognostic factor for overall survival in advanced HCC patients treated with Ate/Bev in real-world clinical practice. Incorporating PNI into routine assessments may enhance risk stratification and guide therapeutic decision-making.

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Introduction

Hepatocellular carcinoma (HCC) ranks as the third leading cause of cancer-related deaths globally, with approximately 800,000 fatalities each year.[1] While early-stage HCC can be treated with curative locoregional therapies, many patients are diagnosed at an advanced stage, where effective treatment options remain limited, leading to poor prognosis. However, recent advancements in systemic therapies, including targeted treatments and immunotherapies, have expanded treatment possibilities and improved survival outcomes for advanced HCC patients.[2] Atezolizumab, an immune checkpoint inhibitor (ICI) targeting programmed death-ligand 1, has shown promising efficacy and safety when combined with bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, in clinical trials.[3] The IMbrave150 study demonstrated that atezolizumab plus bevacizumab (Ate/Bev) significantly improved the objective response rate (ORR) (27.3% vs. 11.9%, $p < 0.001$) and lowered the haz-

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ard ratio (HR) for death to 0.58 in patients with unresectable HCC, compared to sorafenib, the former standard first-line treatment.[3]

Further follow-up data confirmed the survival benefits of Ate/Bev, reporting a median overall survival (OS) of 19.2 months, significantly surpassing the 13.4 months observed with sorafenib ($p < 0.001$).[4] Based on these findings, international guidelines now recognize Ate/Bev as the preferred first-line treatment option for advanced HCC.[5–7]

Recent studies underscore the significant impact of nutritional status on inflammation, immune function, and treatment response in cancer patients. Malnutrition is a prevalent issue, and prior research has established a strong association between poor preoperative nutritional status and unfavorable prognosis.[8,9] The prognostic nutritional index (PNI), derived from serum albumin and lymphocyte levels, is a well-established biomarker used to assess immuno-nutritional status and survival outcomes across various cancers, including HCC.[10–12] Previous research has demonstrated that PNI serves as a reliable prognostic indicator for early-stage HCC patients undergoing different therapeutic approaches, such as liver transplantation, hepatic resection, and microwave ablation.[13–15] Despite its recognized prognostic value in early-stage HCC, few studies have comprehensively investigated the role of PNI in predicting outcomes for patients with advanced HCC receiving first-line treatment with Ate/Bev. Therefore, this study aimed to assess the prognostic significance of PNI in advanced HCC patients treated with first-line Ate/Bev in real-world clinical practice.

Methods

Patients

This study evaluated patients with unresectable HCC who received Ate/Bev between November 2020 and June 2023 at two centers of the Chang Gung Memorial Hospital system: the Linkou and Kaohsiung branches. HCC diagnosis was confirmed using dynamic imaging techniques, including computed tomography or magnetic resonance imaging. In cases where imaging results were inconclusive, histological confirmation was obtained through ultrasound-guided tumor biopsy. To be eligible, patients had to have unresectable HCC classified as either intermediate or advanced stage according to the Barcelona Clinic Liver Cancer (BCLC) system. They were also required to be receiving Ate/Bev as a first-line systemic treatment and to have a Child-Pugh classification of A or B. Exclusion criteria included prior systemic therapy, concurrent malignancies, insufficient clinical data for prognostic assessment, or a Child-Pugh class C classification.

Clinical data were collected and analyzed, including demographic variables such as age, gender, body mass index (BMI), and neutrophil-to-lymphocyte ratio (NLR), as well as the PNI. Baseline laboratory assessments, including liver function tests, alpha-fetoprotein (AFP) levels, serum albumin, and lymphocyte counts for calculating the PNI, were obtained within two weeks prior to the initiation of Ate/Bev therapy. Follow-up laboratory evaluations were performed every three to four weeks in alignment with treatment cycles and clinical assessments. The optimal cutoff value of NLR was defined as 3 based on our previous study.[16] Tumor-related characteristics were also assessed, covering Child-Pugh classification, viral etiology, BCLC stage, extrahepatic metastasis, microvascular invasion, and tumor size.

Data on treatment details, such as therapy duration, dose adjustments, early discontinuation rates, concurrent treatments, and post-treatment outcomes, were retrieved from electronic medical records. All patients received intravenous atezolizumab (1,200 mg) and bevacizumab (5–15 mg/kg) every three weeks. Discontinuation of Ate/Bev therapy occurred in cases of tumor progression, worsening liver function or performance status, severe treatment-related adverse events (TRAEs), or if the patient opted to stop treatment. The study was conducted following ethical guidelines and was approved by the Research Ethics Committee of Chang Gung Memorial Hospital (IRB No. 202301015B0).

Definition of PNI

PNI was calculated using the formula: PNI = [10 × serum albumin (g/dL)] + [0.005 × total lymphocyte count (/mm^3)]. A PNI of <45 was classified as low, while a PNI of ≥45 was considered high based on previous studies.[12]

Assessment of treatment response

Radiologic imaging was used to evaluate treatment response based on the modified Response Evaluation Criteria in Solid Tumors.[17] The ORR was defined as the proportion of patients who achieved either a complete response (CR) or a partial response (PR). The disease control rate included patients who experienced CR, PR, or stable disease. In contrast, progressive disease was identified when tumors showed clear signs of progression during assessment. Patients underwent follow-up imaging approximately every two to three months while receiving Ate/Bev therapy, or sooner if clinical deterioration was observed.

Assessment of adverse events

Adverse events were closely monitored, with clinicians and specialized nurses recording them at each follow-up visit. Patients attended monthly follow-up visits, with additional appointments scheduled as necessary based on the severity of TRAEs. As per treatment guidelines, dose adjustments or temporary interruptions of Ate/Bev were required for patients experiencing TRAEs of grade 3 or higher, or unacceptable grade 2 TRAEs. In instances where severe TRAEs (grade 3 or above) occurred, treatment was either paused or the dosage was reduced until the adverse effects improved to grade 1 or 2, following the manufacturer's recommendations.

Statistical analysis

Patients were followed until death, their last clinical visit, or December 2024—whichever occurred first. Mortality data were comprehensively collected from follow-up visits and medical records to ensure completeness and accuracy. Continuous variables were reported as either mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. Group comparisons were conducted using appropriate statistical tests, including Student's *t*-test, Mann–Whitney *U* test, chi-square test, or Fisher's exact test, as applicable. To reduce selection bias and adjust for potential confounders, propensity score matching (PSM) was performed using NCSS 12 Statistical Software (2018) (NCSS, LLC, Kaysville, Utah, USA). Logistic regression was used to calculate propensity scores based on age, sex, Child–Pugh class, viral etiology, BCLC stage, NLR, and BMI. Patients were matched at a 1:1 ratio between the high-PNI and low-PNI groups to achieve balanced baseline characteristics. OS and progression-free survival (PFS) were estimated using the Kaplan–Meier method. Survival differences between groups were compared using the log-rank test. Cox proportional hazards models were employed for both univariate and multivariate analyses to identify independent prognostic factors.

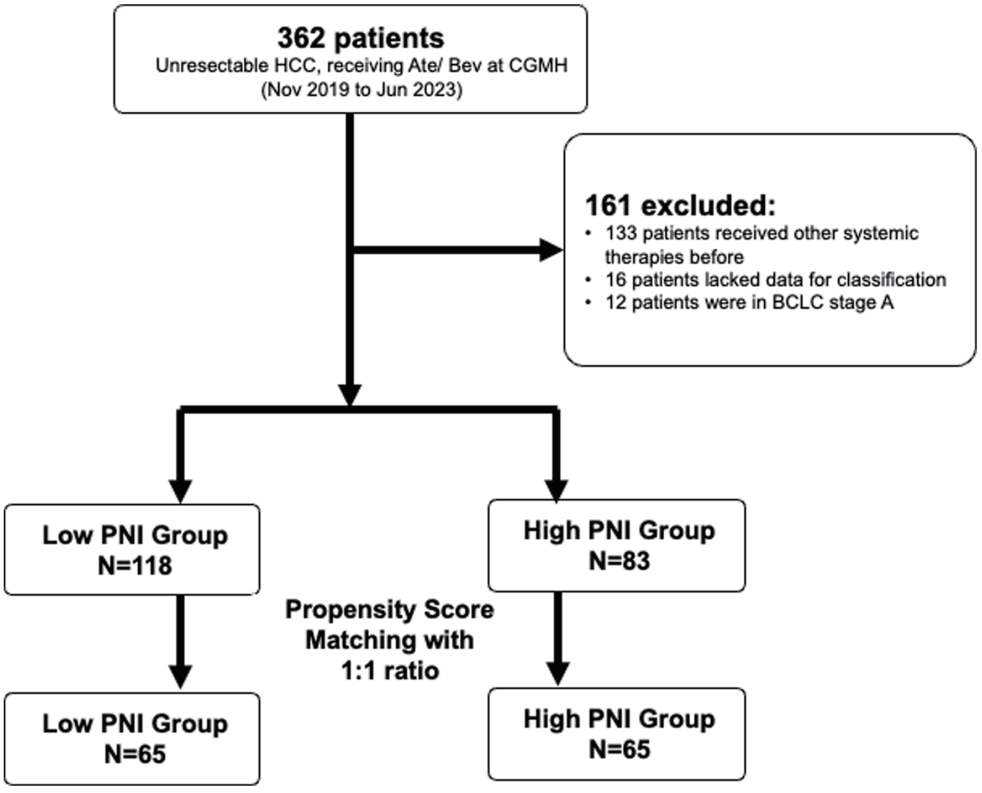

Fig. 1. Flow chart of the study population. Ate/Bev, atezolizumab plus bevacizumab; BCLC stage, Barcelona Clinic Liver Cancer stage; CGMH, Chang Gung memorial hospital; PNI, prognostic nutritional index.

A two-tailed *p*-value < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

The study enrollment flowchart is presented in Figure 1.

A total of 362 patients with unresectable HCC received Ate/Bev between November 2020 and June 2023. Of these, 161 patients were excluded for the following reasons: 133 had previously received systemic therapies, 16 had insufficient clinical classification data, and 12 were categorized as BCLC stage A. Ultimately, 201 patients met the eligibility criteria for analysis. Following 1:1 PSM, 130 patients were included in the final analysis—65 in the low-PNI group and 65 in the high-PNI group. Before PSM, the high-PNI group included a significantly younger population (60.3 vs. 64.1 years, p = 0.022) and a higher proportion of patients with Child-Pugh class A liver function (97.6% vs. 85.6%, p = 0.004) compared to the low-PNI group (Table 1). The high-PNI group also had a significantly higher BMI (27.6 vs. 24.5, p < 0.001) and a more favorable NLR (3.3 vs. 5.8, p < 0.001). More patients in the high-PNI group received combination treatments alongside Ate/Bev, although the difference was not statistically significant. The most frequently combined locoregional therapy was proton beam radiotherapy, followed by conventional radiotherapy and transarterial chemoembolization (TACE). The Ate/Bev treatment duration was longer in the high-PNI group than in the low-PNI group, but the difference was not statistically significant.

After Ate/Bev failure, a significantly greater proportion of patients in the high-PNI group received subsequent therapy compared to those in the low-PNI group (59.2% vs. 39.6%, p = 0.008). In both groups, the most commonly used second-line treatments were lenvatinib monotherapy or lenvatinib-based combinations with pembrolizumab, nivolumab, or chemotherapy. Some patients also received other ICIs, including nivolumab plus ipilimumab or ICI monotherapies (nivolumab or pembrolizumab). After PSM, demographic characteristics, liver function status, and tumor features were balanced between the two groups.

Treatment response before and after PSM

Treatment response was assessed using radiological imaging (computed tomography or magnetic resonance imaging) (Table 2).

Before PSM, the ORR was significantly higher in the high-PNI group compared to the low-PNI group (35.1% vs. 18.6%; p = 0.017). The mortality rate was also significantly lower in the high-PNI group (45.8% vs. 66.1%, p = 0.004). After PSM, the high-PNI group maintained a superior ORR (38.4% vs. 20%; p = 0.037). However, the disease control rate and mortality rate showed no significant differences between the groups.

TRAEs before and after PSM

Before PSM, the overall incidence of any-grade TRAEs did not differ significantly between the high- and low-PNI groups (57.8% vs. 70.3%, p = 0.067). However, the rate of severe TRAEs (grade ≥ 3) was significantly lower in the high-PNI group (13.2% vs. 25.4%, p = 0.035) (Table 3). After PSM,

Table 1. Baseline characteristics of patients receiving Ate/Bev based on the PNI before and after PSM

	Before PSM			After PSM		
	PNI < 45 (n = 118)	**PNI ≥ 45 (n = 83)**	***p*-value**	**PNI < 45 (n = 65)**	**PNI ≥ 45 (n = 65)**	***p*-value**
Male sex, n (%)	90 (76.3)	66 (79.5)	0.587	50 (76.9)	53 (81.5)	0.517
Age (years)	64.1 ± 10.3	60.3 ± 12.6	0.022	62.9 ± 10.8	61.9 ± 12.4	0.625
Child-Pugh class, A, n (%)	101 (85.6)	81 (97.6)	0.004	62 (95.4)	63 (96.9)	0.648
B, n (%)	17 (14.4)	2 (2.4)		3 (4.6)	2 (3.1)	
Viral etiology, n (%)	89 (75.4)	69 (83.1)	0.189	50 (76.9)	52 (80)	0.67
HBV infection, n(%)	69 (58.5)	57 (68.7)	0.141	38 (58.5)	42 (64.6)	0.471
HCV infection, n(%)	22 (18.6)	17 (20.5)	0.746	13 (20)	14 (21.5)	0.829
BCLC stage, B, n (%)	23 (19.5)	9 (10.8)	0.099	8 (12.3)	8 (12.3)	1.000
C, n (%)	95 (80.5)	74 (89.2)		57 (87.7)	57 (87.7)	
EHM, n(%)	51 (43.2)	38 (45.8)	0.719	33 (50.8)	29 (44.6)	0.482
MVI, n(%)	69 (58.5)	49 (59)	0.937	39 (67)	37 (56.9)	0.722
Tumor size > 5cm, n(%)	95 (81.9)	63 (75.9)	0.303	50 (79.4)	48 (73.8)	0.461
Tumor number ≥ 3, n (%)	78 (66.1)	52 (62.7)	0.586			
BMI, kg/m^2	24.5 ± 12.8	27.6 ± 13.8	<0.001	24.7 ± 3.5	24.8 ± 3.5	0.844
BMI ≥ 24, n (%)	61 (51.7)	41 (50.6)	0.881	36 (55.4)	37 (56.9)	0.86
AST, IU/L	92.6 ± 76.1	68.8 ± 53.9	0.011	78.4 ± 47.6	63.8 ± 61.6	0.063
ALT, IU/L	66.2 ± 30.7	61.3 ± 46.7	0.560	63.5 ± 37.3	54.9 ± 81	0.379
AFP, ng/mL	22,494 ± 5,977	21,365 ± 1,854	0.902	26,574 ± 21,568	24,328 ± 18,006	0.421
AFP ≥ 400, n(%)	58 (50.4)	40 (48.8)	0.819	32 (51.6)	29 (44.6)	0.43
NLR	5.8 ± 3.9	3.3 ± 1.7	<0.001	3.7 ± 1.6	3.6 ± 1.7	0.682
NLR > 3, n(%)	91 (77.1)	39 (47)	<0.001	41 (63.2)	42 (64.9)	0.691
Concurrent treatment, n(%)	37 (31.4)	34 (41)	0.161	21 (32.3)	28 (43.1)	0.205
PBT	20	20		9	18	
RTO	10	4		6	3	
TACE	6	7		5	4	
Treatment cycle	5.4 ± 6.3	6.8 ± 6.3	0.179	5.9 ± 6.7	6.8 ± 8	0.506
Treatment period, months	4.4 ± 7.4	5.8 ± 8.6	0.231	4.4 ± 6.9	5.8 ± 8.8	0.231
Treatment stop, n (%)	112 (94.9)	78 (94)	0.773	61 (93.8)	62 (95.4)	0.698
Post treatment, n (%)	44 (39.6)	45 (59.2)	0.008	24 (40)	31 (51.7)	0.2
Len	14	8		10	7	
Len-combination	7	10		4	6	
Other ICI	7	6		4	5	

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate transaminase; Ate/Bev, atezolizumab plus bevacizumab; BCLC stage, Barcelona Clinic Liver Cancer stage; BMI, body mass index; EHM, extra-hepatic metastasis; ICI, immune checkpoint inhibitor; Len, lenvatinib; NLR, neutrophil-to-lymphocyte ratio; PBT, proton beam radiotherapy; PNI, prognostic nutritional index; PSM, propensity score matching; RTO, radiotherapy; TACE, transarterial chemoembolization.

the high-PNI group continued to show a significantly lower incidence of severe TRAEs (10.8% vs. 24.6%, $p = 0.039$). The most common TRAEs in the high-PNI group included elevated aspartate transaminase (26.5%), increased alanine aminotransferase (22.2%), elevated bilirubin (19.5%), and proteinuria (14.9%). In the low-PNI group, more than 20% of patients experienced increased alanine aminotransferase (30.7%), AST (23.1%), and bilirubin (23.1%) levels.

Severe TRAEs leading to temporary or permanent discontinuation of Ate/Bev were primarily due to liver function deterioration or hyperbilirubinemia in both groups. Additionally, upper gastrointestinal bleeding was a notable concern, particularly in the low-PNI group. Before PSM, the incidence of severe upper gastrointestinal bleeding was 5.1% in the low-PNI group and 1.2% in the high-PNI group. After PSM, these rates were 4.6% and 1.5%, respectively.

PFS and its associated factors

Kaplan-Meier analysis showed a median PFS of 4.8 months in the high-PNI group and 3.0 months in the low-PNI group

Table 2. Treatment response of patients receiving Ate/Bev based on the PNI before and after PSM

Variables	Before PSM			After PSM		
	PNI < 45 (n = 118)	PNI ≥ 45 (n = 83)	p-value	PNI < 45 (n = 65)	PNI ≥ 45 (n = 65)	p-value
Treatment response evaluation, n (%) †	86 (72.9)	77 (92.8)		50 (76.9)	60 (92.3)	
Complete response, n (%)	2 (2.3)	1 (1.3)	0.078	2 (4)	1 (1.7)	0.163
Partial response, n (%)	14 (16.3)	26 (33.8)		8 (16)	22 (36.7)	
Stable disease, n(%)	32 (37.2)	22 (28.6)		18 (36)	15 (25)	
Progression disease, n (%)	38 (44.2)	28 (36.4)		22 (44)	22 (36.7)	
Objective response rate	18.6%	35.1%	0.017	20%	38.4%	0.037
Disease control rate	55.8%	63.6%	0.310	56%	63.3%	0.434
Death, n (%)	78 (66.1)	38 (45.8)	0.004	41 (63.1)	31 (47.7)	0.078

(Fig. 2A). Although the high-PNI group showed a trend toward better PFS, the difference was not statistically significant.

After PSM, the median PFS remained 4.8 months in the high-PNI group versus 3.0 months in the low-PNI group (p = 0.597) (Fig. 2B). In the PSM cohort, multivariate analysis identified MVI, AFP ≥ 400 ng/mL, and lack of concurrent treatments as significant predictors of shorter PFS. However, PNI was not independently associated with PFS in either univariate or multivariate analyses (Table 4).

OS and its associated factors

Before PSM, the high-PNI group had a significantly better median OS compared to the low-PNI group (19.7 vs. 6.8 months, p < 0.001) (Fig. 2C). After PSM, the high-PNI group maintained a significantly longer OS (16.7 vs. 7.9 months, p = 0.009) (Fig. 2D).

In the matched cohort, multivariate analysis revealed that PNI ≥ 45 was independently associated with improved OS (HR = 0.574; 95% CI: 0.353–0.933; p = 0.025), after adjusting for MVI, AFP ≥ 400 ng/mL, concurrent treatments, and post-treatment therapies (Table 5).

Discussion

This study is the first to highlight the prognostic role of the PNI in patients with unresectable HCC treated with Ate/Bev, using a rigorous and comprehensive PSM approach. The strong prognostic value of PNI demonstrated here underscores the critical influence of nutritional and inflammatory status on cancer treatment outcomes. PNI, which combines serum albumin levels and lymphocyte counts, reflects both nutritional health and systemic immune status. Serum albumin functions not only as a marker of nutritional status but also as an indicator of systemic catabolism and inflammation. Hypoalbuminemia is associated with increased catabolic activity, diminished hepatic protein synthesis, and poor physiologic reserve, all of which may negatively impact treatment response and drug metabolism.[18] Lymphocyte count, another key element of PNI, reflects the host's adaptive immune com-

Table 3. Treatment-related adverse events of patients receiving Ate/Bev based on the PNI before and after PSM

Variables	Before PSM				After PSM			
	PNI < 45 (n = 118)		PNI ≥ 45 (n = 83)		PNI < 45 (n = 65)		PNI ≥ 45 (n = 65)	
	Any, n (%)	Grade ≥ 3, n (%)	Any, n (%)	Grade ≥ 3, n (%)	Any, n (%)	Grade ≥ 3, n (%)	Any, n (%)	Grade ≥ 3, n (%)
Total TRAE	83 (70.3)	30 (25.4)	48 (57.8)	11 (13.2)	46 (70.8)	16 (24.6)	37 (56.9)	7 (10.8)
AST increase, n (%)	38 (32.2)	5 (4.2)	20 (23.8)	2 (2.4)	20 (30.7)	3 (4.5)	17 (26.5)	1 (1.5)
ALT increase, n (%)	34 (28.8)	6 (5.1)	16 (19.3)	2 (2.4)	17 (23.1)	3 (4.5)	14 (22.2)	1 (1.5)
T-bil increase, n (%)	32 (27.1)	7 (5.9)	16 (19.3)	2 (2.4)	17 (23.1)	3 (4.5)	13 (19.5)	2 (2.9)
Proteinuria, n (%)	20 (16.9)	2 (1.7)	12 (14.5)	0	11 (16.9)	1 (1.5)	10 (14.9)	0
Fatigue, n (%)	19 (16.1)	1 (0.8)	6 (7.2)	0	10 (15.4)	1 (1.5)	4 (5.9)	0
Thrombocytopenia, n (%)	17 (14.4)	0	10 (12)	1 (1.2)	10 (15.4)	0	8 (12.4)	1 (1.5)
Hypertension, n (%)	12 (10.2)	3 (2.5)	7 (8.4)	3 (3.6)	9 (13.8)	2 (3.1)	5 (7.7)	1 (1.5)
UGI bleeding, n (%)	12 (10.2)	6 (5.1)	3 (3.6)	1 (1.2)	7 (10.8)	3 (4.6)	2 (3.1)	1 (1.5)
Poor appetite, n (%)	7 (5.9)	0	6 (7.2)	0	4 (6.2)	0	2 (3.1)	0
Skin rash, n(%)	6 (5.1)	0	4 (4.8)	0	4 (6.2)	0	2 (3.1)	0
Diarrhea, n (%)	2 (1.7)	0	2 (2.4)	0	2 (3.1)	0	0	0

*The p-values for any TRAE between the two groups were 0.067 before PSM and 0.1 after PSM; for severe TRAE, they were 0.035 before PSM and 0.039 after PSM. Ate/Bev, atezolizumab plus bevacizumab; HFSR, hand-foot skin reaction; Len, lenvatinib; PNI, prognostic nutritional index; PSM, propensity score matching; TRAE, treatment-related adverse event; UGI bleeding, upper gastrointestinal bleeding.

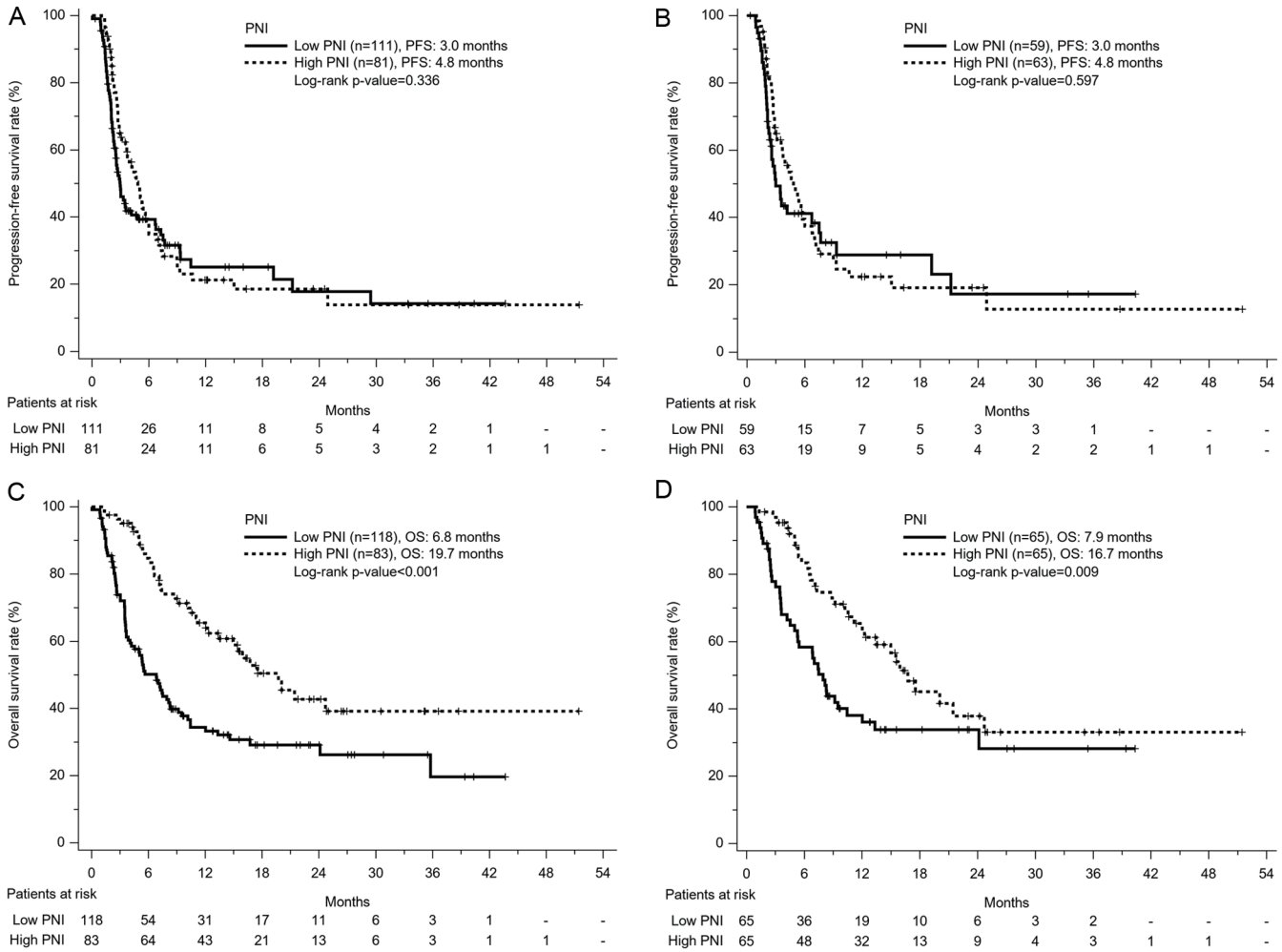

Fig. 2. Kaplan-Meier survival curves of patients received Ate/Bev for (A) PFS of the high- PNI and low-PNI groups; (B) PFS of the high-PNI and low-PNI groups after PSM; (C) OS of the high-PNI and low-PNI groups; (D) OS of the high-PNI and low-PNI groups after PSM. Ate/Bev, atezolizumab plus bevacizumab; OS, overall survival; PFS, progression-free survival; PNI, prognostic nutritional index.

Table 4. Factors associated with progression-free survival in patients receiving Ate/Bev in the PSM cohort

Variable	Comparison	Univariate analysis			Multivariate analysis		
		H.R.	95% CI	*p*-value	H.R.	95% CI	*p*-value
Age, years	Increase per year	0.983	0.965–1.001	0.057			
Sex	Male vs. Female	1.036	0.606–1.771	0.897			
Child-Pugh class	B vs. A	1.106	0.403–3.035	0.845			
Etiology	Viral vs. non-viral	1.297	0.716–2.349	0.391			
EHM	Yes vs. No	0.966	0.626–1.492	0.877			
MVI	Yes vs. No	1.315	0.843–2.952	0.228	1.849	1.155–2.96	0.01
BMI	Increase per unit	0.957	0.901–1.015	0.143			
AFP, ng/mL	≥400 vs. < 400	1.926	1.241–2.989	0.003	2.138	1.369–3.341	<0.001
Concurrent treatment	Yes vs. No	0.383	0.24–0.611	<0.001	0.305	0.186–0.5	<0.001
PNI	≥45 vs. <45	0.89	0.576–1.374	0.598			
NLR	≥3 vs. <3	1.329	0.845–2.091	0.218			

AFP, alpha-fetoprotein; Ate/Bev, atezolizumab plus bevacizumab; BCLC stage, Barcelona Clinic Liver Cancer stage; BMI, body mass index; EHM, extra-hepatic metastasis; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index.

Table 5. Factors associated with overall survival in patients receiving Ate/Bev in the PSM cohort

Variable	Comparison	Univariate analysis			Multivariate analysis		
		H.R.	95% CI	*p*-value	H.R.	95% CI	*p*-value
Age, years	Increase per year	1.002	0.982–1.023	0.821			
Sex	Male vs. Female	0.688	0.403–1.175	0.171			
Child-Pugh class	B vs. A	1.93	0.777–4.798	0.157			
Etiology	Viral vs. non-viral	0.819	0.475–1.412	0.472			
EHM	Yes vs. No	1.092	0.687–1.736	0.709			
MVI	Yes vs. No	2.693	1.597–4.539	<0.001	4.909	2.68–8.989	<0.001
BMI	Increase per unit	0.947	0.885–1.015	0.123			
AFP, ng/mL	≥400 vs. <400	1.708	1.063–2.744	0.027	1.662	1.001–2.627	0.005
Concurrent treatment	Yes vs. No	0.487	0.293–0.81	0.006	0.273	0.152–0.492	<0.001
Post treatment	Yes vs. No	0.433	0.269–0.698	<0.001	0.335	0.196–0.572	<0.001
PNI	≥45 vs. <45	0.541	0.339–0.864	0.01	0.574	0.353–0.933	0.025
NLR	≥3 vs. <3	1.901	1.132–3.19	0.015			

AFP, alpha-fetoprotein; Ate/Bev, atezolizumab plus bevacizumab; BCLC stage, Barcelona Clinic Liver Cancer stage; BMI, body mass index; EHM, extra-hepatic metastasis; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; PSM, propensity score matching.

petence, particularly the activity of cytotoxic T cells, which are central to the efficacy of ICIs targeting programmed cell death-1/programmed death-ligand 1 pathways.[19] A reduced lymphocyte population may therefore signify an immunosuppressed tumor microenvironment and attenuated anti-tumor immune responses, potentially explaining the poorer ORRs observed in low-PNI patients.[20] These observations suggest that low PNI reflects not only malnutrition but also an immunologically compromised and pro-inflammatory state that is less conducive to successful immunotherapy.

Previous studies have established its value in early-stage HCC. For instance, Ho *et al*. identified PNI as the most reliable predictor of OS in early-stage HCC patients,[21] while Chan *et al*. confirmed its significance for both OS and disease-free survival in patients undergoing curative surgery.[14] In the context of advanced HCC, our study further supports these findings: even after PSM, the high-PNI group exhibited a significantly better ORR than the low-PNI group (38.4% vs. 20%, $p = 0.037$). Higher rates of CR and PR in the high-PNI group suggest that optimal nutritional status enhances the efficacy of immuno-oncology therapies. This is consistent with existing literature showing that poor nutrition and systemic inflammation impair immune function and reduce treatment responsiveness.[22] Therefore, nutritional optimization may be a promising strategy to improve the effectiveness of immunotherapies. Moreover, the high-PNI group achieved a significantly longer OS than the low-PNI group (16.7 vs. 7.9 months, $p = 0.009$). This substantial survival difference suggests that PNI may serve as a valuable biomarker for risk stratification and personalized treatment planning. Good nutritional status is often associated with better tolerance to immunotherapy and a greater likelihood of receiving additional systemic treatments, which are crucial for managing advanced HCC and achieving disease control.

All patients included in the current study were classified as Child–Pugh A or B7 at treatment initiation, and none required albumin supplementation before or during Ate/Bev therapy. Following treatment discontinuation, albumin transfusion was administered only to patients who developed hepatic decompensation after disease progression. Notably, eight patients (7%) in the PNI < 45 group progressed to Child–Pugh class C and required albumin replacement, whereas no such cases were observed in the PNI ≥ 45 group. These findings suggest that patients with preserved baseline nutritional status are less likely to develop hepatic failure or require albumin support after treatment, further supporting the prognostic relevance of PNI.

Before PSM, patients in the high-PNI group tended to be younger and had a higher proportion of Child–Pugh class A liver function, higher BMI, and more favorable NLR. These baseline differences highlight the close relationship between nutritional reserve and treatment tolerance. BMI can reflect a patient's nutritional status, and a lower BMI is often linked to malnutrition and reduced PNI scores.[23,24] In our cohort, the low-PNI group had a significantly lower BMI than the high-PNI group (24.5 vs. 27.6, $p < 0.001$). Likewise, an elevated NLR is indicative of systemic inflammation and has been associated with poorer outcomes in HCC.[25] To account for these potential confounders, our PSM analysis adjusted for age, sex, Child–Pugh class, viral etiology, BCLC stage, BMI, and NLR. After matching, the differences in baseline characteristics were minimized, yet high-PNI patients still exhibited better treatment tolerance and survival outcomes. Interestingly, while NLR was associated with mortality in univariate analysis, this effect diminished in the multivariate model. BMI, on the other hand, was not significantly associated with mortality in either analysis, suggesting that overall nutritional status (as captured by PNI) may be a more robust prognostic indicator than body weight alone in this population.

Although we initially hypothesized that PNI would correlate with longer PFS, our findings did not support a statistically significant relationship. While the high-PNI group did have longer median PFS than the low-PNI group (4.8 vs. 3.0 months), the difference was not significant. Multivariate analysis revealed that MVI, AFP levels ≥400 ng/mL, and absence of concurrent therapy were more strongly associated with shorter PFS. These findings emphasize the importance of tumor biology and treatment strategies in determining disease progression and suggest that PNI's impact may be more pronounced in influencing response rates and OS rather than PFS alone.

Despite the promise of Ate/Bev in treating advanced HCC, its ORR in clinical trials typically does not exceed 30%. This has led to growing interest in combining Ate/Bev with locoregional therapies to improve treatment efficacy. For example, Huang *et al*. reported that Ate/Bev combined with TACE and hepatic arterial infusion chemotherapy yielded a median PFS of 10.1 months, with OS not yet reached.[26] Similarly, Su *et al*. demonstrated that adding high-dose radiotherapy to Ate/Bev significantly improved ORR (50.0% vs. 11.8%, $p < 0.01$) and OS (not reached vs. 5.5 months, $p = 0.01$) compared to Ate/Bev alone.[27] In our study, more patients in the high-PNI group received combination treatments with Ate/Bev, although the difference was not statistically significant—possibly due to the limited sample size. Proton beam therapy was the most common locoregional modality used, followed by conventional radiotherapy and TACE. Notably, concurrent therapy was an independent predictor of both improved PFS and OS in multivariate analysis, suggesting that patients who received combined modalities experienced better outcomes than those treated with Ate/Bev alone.

Furthermore, a greater proportion of patients in the high-PNI group received post-treatment therapies compared to the low-PNI group (59.2% vs. 39.6%, $p = 0.008$ before PSM; 51.7% vs. 40%, $p = 0.2$ after PSM). Access to post-treatment options significantly affected survival: patients who received second-line therapies had much better post-Ate/Bev OS (11.7 vs. 2.9 months, $p < 0.001$). In multivariate analysis, post-treatment therapy remained a strong predictor of reduced mortality (HR = 0.335, 95% CI: 0.196–0.572, $p < 0.001$). The most commonly used second-line therapies were lenvatinib or lenvatinib-based combinations with pembrolizumab, nivolumab, or chemotherapy—consistent with current clinical practice for patients progressing on first-line immunotherapy.

An important finding relates to TRAEs, which can limit treatment adherence and negatively affect quality of life, especially in nutritionally compromised patients. In the PSM cohort, the overall incidence of TRAEs was 63.8%. The low-PNI group had a significantly higher incidence of severe TRAEs (24.6% vs. 10.8%, $p = 0.039$). These adverse effects likely contributed to shorter treatment duration in the low-PNI group (4.4 vs. 5.8 months), reinforcing the notion that better nutritional status may improve not only efficacy but also safety and tolerability of treatment. While both groups experienced common adverse effects like elevated liver enzymes, patients with high PNI generally tolerated treatment better. This supports the idea that addressing malnutrition could reduce the severity of TRAEs and improve treatment adherence and outcomes.

This study has several limitations. First, PNI can be influenced by factors beyond nutritional status, such as chronic inflammation, infection, or impaired liver synthetic function, which may confound its prognostic accuracy. Second, the retrospective design introduces potential selection bias, although PSM was employed to reduce confounding. Third, the study population consisted predominantly of Asian patients, which may limit the generalizability of the findings to other ethnic groups. Lastly, the study did not evaluate the impact of nutritional interventions before or during treatment—an area that warrants future investigation to determine whether improving PNI could lead to better clinical outcomes.

Conclusions

This study provides strong evidence that the PNI is a clinically meaningful prognostic biomarker in advanced HCC treated with Ate/Bev. Higher PNI was associated with better response, longer survival, fewer severe adverse events, and greater access to subsequent therapy after PSM. These findings support the use of PNI as a practical tool to guide risk stratification and patient counseling. Further prospective, multicenter studies are warranted to confirm its utility and to determine whether proactive nutritional or metabolic intervention in patients with low PNI can translate into improved outcomes in real-world practice.

†Treatment response based on those who received image evaluation, including computed tomography or magnetic resonance imaging. Ate/Bev, atezolizumab plus bevacizumab; PNI, prognostic nutritional index; PSM, propensity score matching.

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Conflict of interest

All authors declare that they have no conflict of interest.

Author contributions

Conceptualization and study design (JHW, CYL), analysis and interpretation of the data (YHK, WT), writing of the original draft (YHK), data acquisition (YHK, WT, YHC, PTL, THW, CWS, WTC, CCL, CHH, SNL, SML, JHW, CYL), and supervision (JHW, CYL). All authors read and approved the final manuscript.

Ethical statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Chang Gung Memorial Hospital, IRB No. 202301015B0) and with the Helsinki Declaration (as revised in 2024). Informed consent was obtained from all patients for inclusion in the study. The Institutional Review Board of Chang Gung Medical Foundation waived the requirement for written informed consent.

Data sharing statement

The datasets used and analyzed during the current study are not publicly available to protect patient privacy but are available from the corresponding author upon reasonable request.

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