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Prognostic nutritional index predicts survival in intermediate and advanced hepatocellular carcinoma treated with hepatic arterial infusion chemotherapy combined with PD-(L)1 inhibitors and molecular targeted therapies

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Abstract

Background This study aimed to evaluate the predictive efficacy of the prognostic nutritional index (PNI) in patients with intermediate and advanced hepatocellular carcinoma (HCC) treated with a regimen consisting of hepatic arterial infusion chemotherapy (HAIC), PD-(L)1 inhibitors, and molecular targeted therapies (MTTs).

Methods A retrospective analysis was performed on the data of 88 HCC patients received triple therapy between January 2020 and August 2022 at three medical centers. Univariate and multivariable analyses were conducted to assess the relationship between PNI and survival outcomes.

Results The median follow-up was 11.0 months (IQR: 8.0–17.0). The PNI cut-off value of 38.6 was determined using receiver operating characteristics (ROC) analysis. The median overall survival (OS) durations were 29.0 and 8.0 months in the high-PNI (≥ 38.6) and low-PNI (≤ 38.6) groups, respectively (HR = 0.306, 95% CI, 0.170–0.552, $P < 0.001$), and the median progression-free survival (PFS) durations were16.0 and 6.0 months, respectively (HR = 0.521, 95% CI, 0.303–0.896, $P = 0.014$). A higher complete response rate was observed in the high-PNI group (17.5% vs. 3.2%, $P = 0.033$). The univariate and multivariable analyses revealed that a PNI of ≥ 38.6 had an independent influence on both median OS (HR = 0.296; 95% CI, 0.159–0.551, $P < 0.001$) and median PFS (HR = 0.560; 95% CI, 0.318–0.987, $P = 0.045$).

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Conclusion The PNI is an objective and convenient tool that can potentially predict the prognosis of patients treated with HAIC-based triple therapy.

Keywords Hepatocellular carcinoma, Prognostic nutritional index, Hepatic arterial infusion chemotherapy, Molecular targeted therapies, Immunotherapy

Introduction

The high morbidity and mortality of hepatocellular carcinoma (HCC) impose a heavy economic health burden worldwide. Despite potential changes in the etiological composition of HCC, patients in China are still predominantly infected with hepatitis B virus (HBV) [1]. Unfortunately, the majority of cases are detected in the intermediate or advanced stages, and only about one third are eligible for early radical treatment (surgical resection, transplantation, or ablation) at an early stage [1, 2]. Optimizing treatment and improving survival rates for those experiencing intermediate and advanced HCC is a pressing issue.

The diversification of systemic anti-tumor agents has changed the therapeutic landscape for advanced HCC [3, 4]. However, although therapeutic modalities such as PD-(L)1 inhibitors plus molecular targeted therapies (MTTs) [5, 6] or dual immunotherapy [7] have improved the median overall survival (OS) duration of patients compared to those taking sorafenib, the low response rate is still a challenge that has to be overcome. Combining interventional therapy with systemic drugs may be an important option in solving this dilemma. Transarterial chemoembolization (TACE) is the standard of care for intermediate-stage HCC, and the triplet regimen of TACE combined with targeted immunotherapy [8] has demonstrated good progression-free survival (PFS), OS, and tumor control rates in intermediate- and advanced-stage patients, predominantly with HBV infections. However, TACE was not appropriate for all individuals. For patients with intermediate and advanced HCC, liver function, performance status, and tumor characteristics should always be taken into account when determining the optimal treatment regimen.

Hepatic arterial infusion chemotherapy (HAIC) is a complementary, non-antagonistic, local treatment used in addition to TACE, mainly in East Asian countries [9]. Compared to TACE, HAIC can increase local drug concentrations with a low incidences of liver injury [10] and serious adverse events (AEs) [11]. It is therefore more suitable for tumors that are diffuse, infiltrative, high-burden and associated with features such as main portal vein tumor thrombosis (PVTT), or portal vein fistulae [11–15]. It may be difficult for these patients to benefit from TACE, in this case, they are known as TACE-unsuitable [16]. The HAIC triple regimen combining PD-(L)1 inhibitors and MTTs has initially demonstrated a good safety profile, high anti-tumor activity, high clinical efficacy [17, 18], and a high translational success rate [19, 20].

However, there is a lack of effective means for screening potential HAIC recipients. Several clinical studies have found that mutated genes [14], the low expression of the chemokine CCL28, and betacellulin [18] can help predict response and efficacy in HAIC. Immuno-nutritional biomarkers, such as the prognostic nutritional index (PNI), which are known for their objectivity and simplicity, are gradually being explored with regard to their predictive role in the treatment of HCC with PD-(L)1 inhibitors [21] or MTTs [22]. However, this predictive efficacy is unknown in patients undergoing treatment with the HAIC triad. Therefore, this retrospective study aimed to identify potential prognostic factors in HCC patients treated with triple therapy, including PNI.

Materials and methods

Patients

A retrospective analysis was conducted on HCC patients who consecutively received the triple therapy (HAIC + PD-(L) 1 inhibitors + MTTs) from January 2020 to August 2022 in three affiliated hospitals of universities (tertiary medical institutions) (Fig. 1). The inclusion criteria were as follows: a clear pathological diagnosis of HCC or typical imaging manifestations using enhanced computed tomography (CT) or magnetic resonance (MRI) imaging; age > 18 years; classified as Child-Pugh grade A or B; an Eastern cooperative oncology group (ECOG) performance score ≤ 1; use of modified Response Evaluation Criteria in Solid Tumors (mRECIST) assessment with at least one measurable lesion; and Barcelona Liver Clinic Cancer (BCLC) stage C or B patients for whom TACE is not suitable (confluent multinodular type, massive or infiltrative type, simple nodular type with extra - nodular growth, poorly differentiated type, or intrahepatic multiple disseminated nodules) [16]. The exclusion criteria included the following: other systemic or local treatments prior to triple therapy; undertaking fewer than 2 cycles of triple therapy; HAIC with raltitrexed plus cisplatin; combination with other tumors; patients with definite active infections, autoimmune diseases, or long-term glucocorticoid use; and patients with incomplete follow-up data or who were lost to follow-up.

HAIC procedure, PD-(L)1 inhibitors, and MTTs

The specific operation of the HAIC was consistent with our previous report [17], and the regimens were all

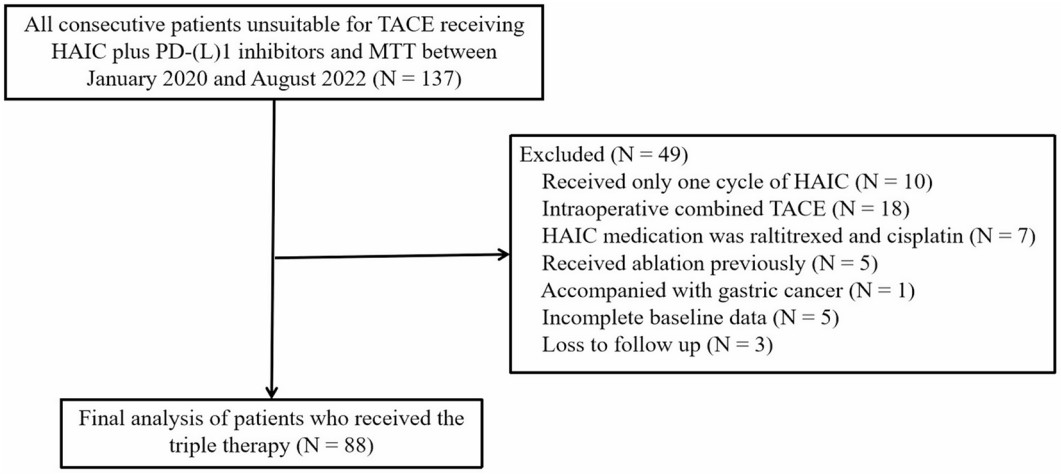

Fig. 1 The study's flow diagram

FOLFOX. The dosing sequence was oxaliplatin (85 mg/m^2 or 130 mg/m^2, titrated over 2 hours), calcium folinate (400 mg/m^2, titrated over 2 hours), and fluorouracil regimen injection (400 mg/m^2), followed by continuous titration for 46 h (2400 mg/m^2). This was repeated every 3–4 weeks for up to 6 cycles. PD-(L)1 inhibitors and MTTs are started 3–7 days after the end of HAIC, laboratory tests permitting. PD-(L)1 inhibitors do not allow dose reductions, but do permit dose interruptions due to AEs and dose interval adjustments.

The combination of PD-(L)1 inhibitors and MTTs were mainly atezolizumab + bevacizumab (4/4.5%), sintilimab + bevacizumab (17/19.3%), sintilimab + lenvatinib (8/9.1%), tislelizumab + donafenib (15/17.0%), tislelizumab + lenvatinib (9/10.2%), camrelizumab + sorafenib (14/15.9%), camrelizumab + lenvatinib (13/14.8%), and camrelizumab + apatinib (8/9.1%).

Data collection

Laboratory tests and imaging data (from a chest plain scan CT, abdominal enhanced CT, or MRI) were collected from patients within 3 days prior to HAIC treatment. Immuno-nutrition, inflammation, and liver function scores, from measurements such as PNI, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and Child-Pugh grade were calculated. PNI [22] was derived from peripheral blood albumin (g/L) + 5* absolute peripheral blood lymphocyte count (10^9/L). NLR was obtained by dividing the peripheral blood neutrophil value (10^9/L) by the lymphocyte count (10^9/L). PLR was defined as the absolute peripheral blood platelet count (10^9/L) divided by the lymphocyte count, and SII was defined as platelet count × neutrophil/lymphocyte counts.

Follow-up

Imaging assessments were performed every 4–8 weeks after triple therapy, and tumor response rates were estimated by two independent radiologists with 5–10 years of experience in diagnostic abdominal imaging according to the mRECIST criteria. Routine laboratory tests were conducted prior to each treatment cycle. Standardized antiviral therapy with entecavir or tenofovir was administered before the triple therapy in patients with hepatitis B surface antigen positivity, regardless of HBV DNA levels.

The occurrence of AEs was recorded in detail. Triple therapy was continued until intolerable AEs or disease progression (PD) were observed. HAIC was stopped after a maximum of 6 cycles and then maintained using PD-(L)1 inhibitors and MTTs. Patients were followed-up with until death or the end of this study (August 31, 2023).

Outcomes

The primary outcome was OS, and the secondary outcomes included PFS, ORR, disease control rate (DCR), and the incidence of AEs. OS was defined as the time interval between the start of triple therapy and all-cause death or the study termination date. PFS was defined as the time interval between the start of triple therapy and the occurrence of PD, all-cause death, or study cut-off, whichever occurred first. ORR was defined as the sum of complete response (CR) and partial response (PR), while DCR was calculated as the sum of ORR and SD. All AEs were recorded and classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corporation, Somers, NY) and R 3.4.1 (http://www.R-project.org). All statistical tests were two-tailed,

and P values < 0.05 were considered statistically significant. Categorical variables were expressed as frequency (%) and continuous variables as median and interquartile range (IQR). Differences in clinical data were analyzed using the Mann-Whitney U test, chi-squared test, Kruskal-Wallis H test, or Wilcox test, depending on the type of the parameters. Cox proportional hazards regression was used in univariate and multivariable analyses to identify factors affecting median OS and PFS. Variables with $P < 0.1$ in univariate analyses were included in multivariable analyses and converted to categorical variables (PNI and NLR) based on receiver operating characteristics (ROC) curves and best cut-off values. Cumulative survival was described using Kaplan-Meier curves and compared using log-rank tests. The contribution of each parameter to the risk of outcome was presented as a hazard ratio (HR) with a 95% confidence interval (CI).

Table 1 Baseline characteristics of patients

Variables	Total ($n = 88$)
Age (years), M (Q_1, Q_3)	59.00 (51.00, 69.00)
Gender, n (%)	
male	72 (81.82)
female	16 (18.18)
Hepatitis B virus, n (%)	78 (88.64)
Cirrhosis, n (%)	66 (75.00)
Alpha-fetoprotein ≥ 100 ng/ml, n (%)	62 (70.45)
CRP ≥ 1 mg/dl, n (%)	43 (48.86)
Infiltrative type	22 (25.00)
Main portal vein invasion	55 (62.50)
Extrahepatic metastasis	15 (17.05)
PNI	41.45 (36.94, 46.95)
NLR	3.10 (2.10, 5.20)
PLR	136.04 (94.06, 196.72)
SII	423.75 (251.50, 981.04)
Child-Pugh score (points)	6.00 (5.00, 6.00)
Child-Pugh grade, n (%)	
A	68 (77.27)
B	20 (22.73)
ECOG, n (%)	
0	46 (52.27)
1	42 (47.73)
BCLC stage	
B	27 (30.68)
C	61 (69.32)
Size of largest nodule (cm)	
< 10	48 (54.55)
≥ 10	40 (45.45)
Tumor distribution	
Uni-lobar	33 (37.50)
Bi-lobar	55 (62.50)

Data are expressed as n (%) or quartile. Abbreviations: CRP, C-reactive protein; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. SII, systemic immune-inflammation index. ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer

Results

Baseline characteristics

A total of 88 patients with intermediate and advanced HCC unfit for TACE were included in the study, and the clinical characteristics of the patients are summarized in Table 1. The median age of all patients was 59.0 years (IQR: 51.0–69.0), with 72 (81.8%) being male. HBV accounted for 88.6% of the etiological components of liver disease. There were 46 (52.3%) and 42 (47.7%) individuals with ECOG 0 and 1, respectively. Child-Pugh classifications A and B comprised 68 (72.3%) and 20 (22.7%) of the patients, respectively. Out of the patients with BCLC stage C, 61 patients (69.3%) had main PVTT and 15 patients (17.1%) had extrahepatic metastases.

The median follow-up was 11.0 months (IQR: 8.0–17.0), and the median numbers of interventions were 3.0 (IQR: 2.0–4.0) and 6.0 (IQR: 4.0-9.8) for HAIC and PD-(L)1 inhibitors, respectively. At the end of the study, 45 (51.1%) patients had died, with a median OS duration of 16.0 months (HR = 3.009, 95% CI, 10.102–21.898) and a PFS duration of 10.0 months (HR = 1.962, 95% CI, 6.155–13.845).

Optimal cut-off values for immuno-nutritional and inflammatory markers

The ROC curves and cut-off value calculations for PNI and NLR are displayed in Fig. 2A-B and Supplementary Fig. 1A-B. The most effective threshold values for predicting the median OS for PNI and NLR were determined to be 38.6 and 3.8, respectively. The area under the curve (AUC) for PNI was 0.704 (95% CI, 0.592–0.815), while the AUC for NLR was 0.580 (95% CI, 0.459–0.702). Supplementary Fig. 2 shows the ROC curves of PNI compared with PLR, SII, and CRP. The analysis demonstrated that the AUC of PNI was optimal. According to the study objective, 57 (64.8%) patients were assigned to the high-PNI group and 31 (35.2%) patients to the low-PNI group.

Efficacy and survival analysis

Pursuant to the mRECIST criteria, the best tumor response consisted of 11 (12.5%) CR, 26 (29.6%) PR, 23 (26.1%) SD, and 32 (36.4%) PD. The ORR and DCR were 44.3% (39/88) and 67.1% (59/88), respectively. Patients with high PNI scores had a greater CR rate (17.5% vs. 3.2%, $P = 0.033$) than those with low PNI scores, while there were no statistically significant differences in ORR (50.9% vs. 32.3%, $P = 0.090$) or DCR (68.4% vs. 64.5%, $P = 0.710$).

As depicted in Figs. 3A-B, the median OS durations in the high PNI and low PNI groups were 29.0 and 8.0 months (HR = 0.306, 95% CI, 0.170–0.552, $P < 0.001$) and the median PFS durations were 16.0 and 6.0 months (HR = 0.521, 95% CI, 0.303–0.896, $P = 0.014$), respectively. In addition, we constructed Kaplan-Meier survival

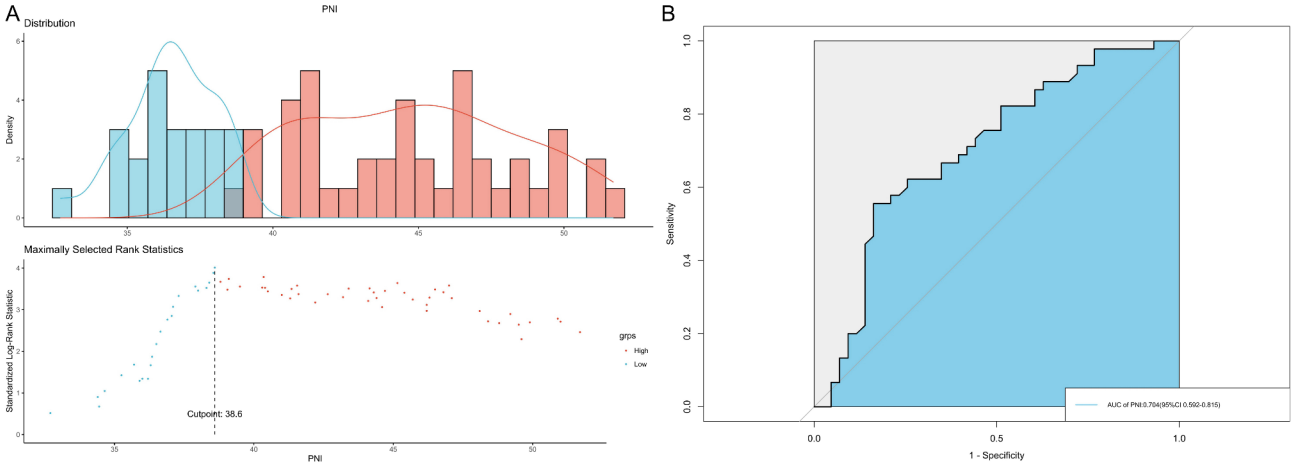

Fig. 2 The cutoff value (**A**) and the ROC curve (**B**) of PNI. Panel A displays the distribution of PNI values (upper graph) and the maximally selected rank statistics (lower graph) to determine the optimal cut-point of PNI, which was identified as 38.6. Different colors represent different groups. Panel B shows the ROC curve of PNI, with an area under the curve of 0.704 (95% CI: 0.592–0.815). ROC, receiver operating characteristic; PNI, prognostic nutritional index

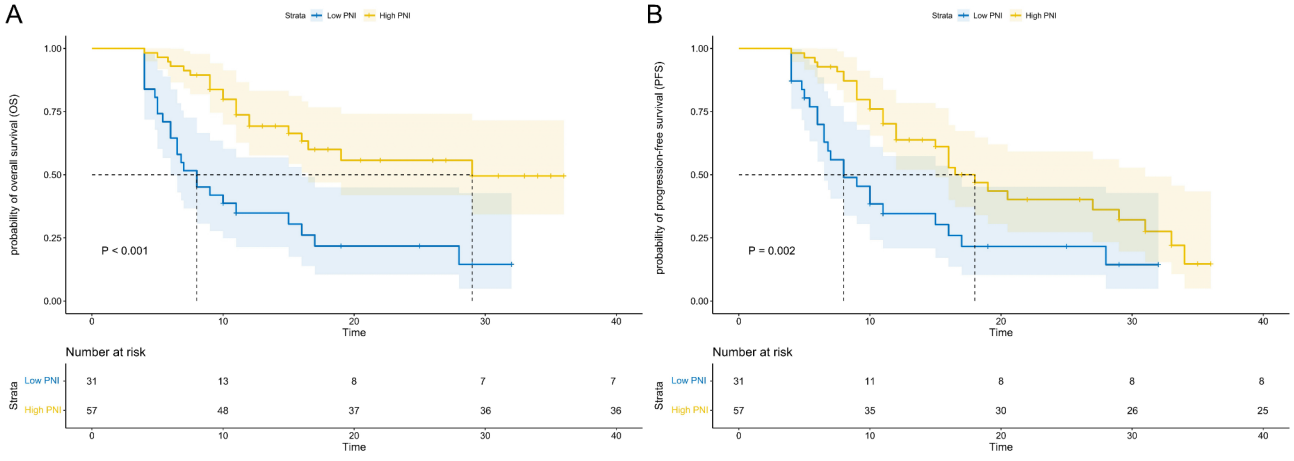

Fig. 3 Kaplan-Meier curves for OS (**A**) and PFS (**B**) in 88 patients treated with HAIC triple therapy. (**A**) OS according to PNI (high- vs. low-group). (**B**) PFS accord ing to PNI (high- vs. low-group). OS, overall survival; PFS, progression-free survival; HAIC, hepatic arterial infusion chemotherapy; PNI, prognostic nutritional index

curves using the PNI cutoff values previously reported in the literature (42, 45, 44.5, 44.9, and 46.9, respectively). The results indicated that all P-values were less than 0.05 (Supplementary Fig. 3).

Univariate and multivariable Cox regression analyses of patients who received triple therapy

In the univariate analysis, PNI ≥ 38.6, NLR ≥ 3.8, gender, cirrhosis, ECOG score, Child-Pugh grade, extrahepatic metastases, and tumor distribution were associated with the median OS (Table 2). After adjustment for confounders, the multifactorial analysis indicated that PNI ≥ 38.6 (HR = 0.296; 95% CI, 0.159–0.551, $P < 0.001$), gender (male vs. female, HR = 0.341; 95% CI, 0.165–0.705, $P = 0.004$), cirrhosis (HR = 2.676; 95% CI, 1.099–6.519, $P = 0.030$), and extrahepatic metastases (HR = 5.108; 95% CI, 2.421–10.777, $P < 0.001$) were independent influences on the median OS.

The multivariable analysis of PFS was similar to OS (Table 2), with PNI ≥ 38.6 (HR = 0.560; 95% CI, 0.318–0.987, $P = 0.045$), ECOG score (HR = 2.219; 95% CI, 1.269–3.880, $P = 0.005$), and extrahepatic metastases (HR = 2.647; 95% CI, 0.318–0.987, $P = 0.005$) being independent predictors of the median PFS.

Adverse events

Fifty-three (60.2%) patients experienced AEs of any grade (Table 3), with an incidence of 59.1% for grades 1–2 and 15.9% for grades 3–4, and no treatment-related deaths. The incidence of AEs was comparable in both the high- and low-PNI groups, for any grade (54.4% vs., 71.0%, $P = 0.125$), grades 1–2 (56.1% vs., 64.5%, $P = 0.443$), and grades 3–4 (12.3% vs., 22.6%, $P = 0.215$).

Table 2 Univariate and multivariate analysis of risk factors for OS and PFS

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
OS						
PNI ≥ 38.6	0.306	0.170–0.552	< 0.001	0.296	0.159–0.551	< 0.001
NLR ≥ 3.8	1.980	1.095–3.579	0.024			
Gender (male vs. female)	0.462	0.232–0.920	0.028	0.341	0.165–0.705	0.004
Cirrhosis	3.007	1.270–7.123	0.012	2.676	1.099–6.519	0.030
ECOG (1 vs. 0)	2.249	1.235–4.096	0.008			
Child-Pugh grade (B vs. A)	1.918	0.997–3.692	0.051			
Extrahepatic metastasis	3.682	1.846–7.345	< 0.001	5.108	2.421–10.777	< 0.001
Tumor distribution (bi-lobar vs. uni-lobar)	2.042	1.033–4.035	0.040			
PFS						
PNI ≥ 38.6	0.521	0.303–0.896	0.019	0.560	0.318–0.987	0.045
ECOG (1 vs. 0)	2.545	1.465–4.421	0.001	2.219	1.269–3.880	0.005
Child-Pugh grade (B vs. A)	1.757	0.960–3.216	0.068			
Extrahepatic metastasis	2.488	1.284–4.821	0.007	2.647	1.351–5.188	0.005
Tumor distribution (bi-lobar vs. uni-lobar)	1.717	0.958–3.075	0.069			

Abbreviations: OS, overall survival; PFS, progression-free survival; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; ECOG, Eastern Cooperative Oncology Group

Table 3 Treatment related adverse events

Adverse Events	Any grade (%)	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	2 (2.3%)	1 (1.1%)	0	1(1.1%)
Leukopenia	2 (2.3%)	1(1.1%)	1(1.1%)	0
Thrombocytopenia	12 (13.6%)	8 (9.1%)	0	4 (4.5%)
Elevated ALT	10 (11.4%)	9 (10.2%)	1(1.1%)	0
Elevated AST	20 (22.7%)	17 (19.3%)	3 (3.4%)	0
Hyperbilirubinemia	11 (12.5%)	8 (9.1%)	3 (3.4%)	0
Fatigue	14 (15.9%)	14 (15.9%)	0	0
Fever	10 (11.4%)	10 (11.4%)	0	0
Nausea/vomiting	18 (20.5%)	18 (20.5%)	0	0
Abdominal pain	6 (6.8%)	5 (5.7%)	1(1.1%)	0
Proteinuria	2 (2.3%)	2 (2.3%)	0	0
Hypertension	3 (3.4%)	3 (3.4%)	0	0
Hand-foot syndrome	5 (5.7%)	5 (5.7%)	0	0
Immune-related hypothyroidism	6 (6.8%)	6 (6.8%)	0	0
Immune-related myocarditis	1(1.1%)	0	0	1(1.1%)
RCCEP	7 (8.0%)	7 (8.0%)	0	0
Variceal bleeding	2 (2.3%)	0	2 (2.3%)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; RCCEP, reactive cutaneous capillary endothelial proliferation

Discussion

Our study preliminarily confirmed that baseline PNI was an independent predictor of the median OS in patients with intermediate and advanced HCC ineligible for TACE who received HAIC triplet therapy. Patients with high PNI scores (≥ 38.6) had superior OS, PFS, and CR rates.

Locally combined systemic therapy has become the mainstream treatment for patients with intermediate-to-advanced unresectable HCC. In previous studies, the ORR of a single-agent PD-(L)1 inhibitor or MTTs generally did not exceed 20%, and the combination of the two had a synergistic effect but only maintained an ORR of 20.5-34% and a PFS durations at 4.6–6.8 months [5, 6, 23]. Although the addition of TACE has improved tumor control and survival, it must be acknowledged that there are a large number of patients for whom TACE is inappropriate [8, 24], and there is still a huge unmet need in the clinical context. HAIC overcomes some of the limitations of TACE by rapidly shrinking the intrahepatic tumor and portal vein cancerous thrombus burden, which improves tumor control and conversion rate [25]. Our previous study [17] showed that the triple HAIC regimen was safe and effective in patients with intermediate and advanced HCC who were ineligible for TACE and also investigated some inflammatory markers such as NLR. Although NLR was found to be associated with prognosis in a small sample population, it did not have an independent effect on OS in this study. The possible reason is that NLR may not have the same prognostic relevance as PNI, as NLR only reflects the inflammatory state, whereas PNI represents both the body's nutritional and immune status.

Traditionally, albumin is regarded as a reflection of nutritional status, and malnutrition is a common problem in HCC patients with a background of cirrhosis, who usually experience hepatic insufficiency, inflammation, oxidative stress, inadequate intake, and even malignancy [26, 27], which manifest as decreased albumin levels and impaired immune function [28]. As we have described, patients with low PNI scores (< 38.6) have a high incidence of cirrhosis and ascites and are associated with worse liver function, ECOG scores, and

higher inflammatory markers, such as CRP. In addition, the depletion of lymphocytes, an important component of the immune system, especially CD4 + and CD8 + T cells, is a key factor in immunosuppression [29]. Reduced lymphocytes can lead to a weakened surveillance capacity of the immune system, thereby increasing the chance of immune escape of tumor cells and accelerating tumor progression [30, 31]. We found that almost half of the tumors in patients with low PNI scores were characteristically infiltrative, a morphological feature that is often associated with a more aggressive and poorer prognosis [12]. More intuitively, a low PNI score is associated with higher postoperative recurrence rates and worse OS and recurrence-free survival in HCC cohorts undergoing radical resection [28] or liver transplantation [32]. Additionally, there is a strong correlation between a low PNI score and adverse tissue characteristics such as tumor grade, microvascular invasion, lympho-vascular infiltration, and low tumor necrosis rate after intervention.

Searching for parameters that are readily available, quantifiable, and reproducible in clinical practice to forecast the outcome of HCC treatments is essential. The role of PNI in HCC is gradually being recognized, with an effective predictive range for the prognosis of liver transplantation or radical hepatic resection of 42 ~ 45 [28, 32] and an interval for predicting the prognosis of PD-(L)1 inhibitor, MTTs, or HAIC monotherapy of 44.5 ~ 46.9 [22, 33, 34]. Interestingly, we found that the previously reported PNI cutoff values were also applicable to our cohort (Supplementary Fig. 3). Specifically, the aforementioned studies on HAIC and targeted immunotherapy involved patient populations with characteristics similar to those in our study, primarily consisting of individuals with hepatitis B infection, liver cirrhosis, and BCLC stage C disease. Although cutoff values may vary across studies due to differences in patient and disease characteristics, this observation indirectly underscores the predictive performance of PNI for OS. Moreover, adopting a lower cutoff value could help identify more patients who may benefit from HAIC triple therapy.

Our analysis of the HAIC triplet regimen further supports the importance of PNI in the prognostic assessment of HCC patients. In this population of likely poor responders to TACE, the difference in OS between patients with high and low PNI scores was more than three-fold. Additionally, while current research has focused more on improving patient survival outcomes, resulting in limited studies on PNI for predicting PFS, both our study and the work by Kang X [33] have yielded meaningful conclusions. These findings may be valuable for assessing tumor control and the efficacy of antitumor therapies. We know that immune imbalances and other indicators of nutritional status, such as sarcopenia [35], are difficult to improve in the short term, and it is more important to detect these adverse factors early through monitoring. However, whether simple albumin infusion can increase the PNI value or even improve treatment outcomes remains unknown.

Furthermore, we found that the presence of cirrhosis and extrahepatic metastases worsened the outcome of patients with HCC, which is broadly consistent with previous reports [36, 37]. As mentioned previously, patients with cirrhosis are a group with a high prevalence of hepatic and nutritional dysfunction [38], and appropriate monitoring of baseline liver function and nutrition in these patients is warranted. In this subset of extrahepatic metastases, it is difficult to achieve satisfactory efficacy with either single or combination therapy. In addition to traditional endovascular and systemic therapies, thermal ablation, cryoablation, and radioactive particle implantation have been used in combination in clinical practice, but whether they can improve patients' OS needs further clarification. In addition, it is generally believed that the risk of HCC and the risk of postoperative recurrence are higher in male patients than in female patients [39]. However, our study found that female patients had a worse prognosis, which may be related to our sample size, and the small number of female patients was not enough to support further statistical analyses.

There are several limitations to this study. Firstly, the sample size was small, and the retrospective nature of the study could not rule out selection bias. Second, there was a lack of in-depth molecular biology studies, which was one of the directions were trying to explore. Third, the wide variety of PD-(L)1 inhibitors and MTTs in real-world studies is difficult to avoid, and subgroup analyses need to be refined after enlarging the sample size. Fourth, the optimal cut-off for PNI is not fixed and not standardized, so the application of our findings to populations receiving other treatments should be cautious. Fifth, although PNI reflects a favorable tumor immune microenvironment and has potential predictive value for triple therapy, the predictive and prognostic significance of PNI requires further validation due to the single-arm cohort design of this study and the absence of a strictly defined control group.

Conclusion

Our study indicates that the pre-operative PNI is an objective, simple, and inexpensive immuno-nutritional marker that can assist in predicting the prognosis of patients who receive the triple therapy of HAIC. It may be an invaluable clinical tool in the decision-making process.

Abbreviations

PNI	Prognostic Nutritional Index
HCC	Hepatocellular Carcinoma
TACE	Transarterial Chemoembolization

HAIC	Hepatic Arterial Infusion Chemotherapy
MTTs	Molecular Targeted Therapies
ROC	Receiver Operating Characteristics
OS	Overall Survival
PFS	Progression-Free Survival
HBV	Hepatitis B Virus
AEs	Adverse Events
PVTT	Portal Vein Tumor Thrombosis
CT	Computed Tomography
MRI	Magnetic Resonance
ECOG	Eastern Cooperative Oncology Group
mRECIST	modified Response Evaluation Criteria in Solid Tumors
BCLC	Barcelona Liver Clinic Cancer
NLR	Neutrophil-to-Lymphocyte Ratio
PLR	Platelet-to-Lymphocyte Ratio
SII	Systemic Immune-Inflammation Index
PD	Disease Progression
DCR	Disease Control Rate
CR	Complete Response
PR	Partial Response
CTCAE	Common Terminology Criteria for Adverse Events
IQR	Interquartile Range
CI	Confidence Interval
AUC	Area Under the Curve

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions
All authors contributed to the conception and design of the study. Material preparation, data collection, and analyses were performed by Hao-Huan Tang, Ming-Qing Zhang, Zi-Chen Zhang, Chen Fan, and Shu-Shu Li. Hao-Huan Tang, Ming-Qing Zhang and Zi-Chen Zhang wrote the first draft of the manuscript. Wei Chen and Wei-Dong Wang led and managed the project comprehensively, and provided critical revisions to the intellectual content of the manuscript. Wei-Dong Wang undertakes project fund management. All authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Wuxi People's Hospital, affiliated with Nanjing Medical University, approved this study (No. KY23101) and conducted it in accordance with the tenets of the Declaration of Helsinki. Given the retrospective nature of the study, the Ethics Committee granted an exemption for written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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