Original Article

Real-world experience of lenvatinib-based therapy in patients with advanced hepatocellular carcinoma

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Background: Given the significant advancements in the management of hepatocellular carcinoma (HCC) and the emergence of novel treatment approaches, establishing reliable predictors has become crucial for optimizing patient selection and therapeutic sequencing in HCC. In this study, we aimed to investigate the prognostic factors and treatment efficacy associated with lenvatinib-based therapy.

Methods: We retrospectively enrolled 53 patients receiving lenvatinib monotherapy, and 19 patients receiving lenvatinib plus immune checkpoint inhibitor combination therapy as their first-line systemic treatment for unresectable HCC at a single medical center. We employed univariate and multivariate Cox regression analyses to ascertain the factors influencing survival in these cohorts.

Results: For lenvatinib monotherapy and the combination therapy, the objective response rates were 30.2% and 63.2%, respectively (P=0.03); the median progression-free survival (PFS) durations were 7 months [95% confidence interval (CI): 4.5–9.5] and 12 months (95% CI: 6.4–17.6), respectively (P=0.74); and the median overall survival (OS) was not reached in either group (P=0.93). Although patients receiving the combination therapy had a greater treatment response, no significant survival differences were observed between the lenvatinib monotherapy and combination therapy subgroups, even after inverse probability of treatment weighting (IPTW). Patients who received lenvatinib monotherapy could be stratified based on a combination of albumin-bilirubin (ALBI) grade (either grade 1 or 2a) and a neutrophil-lymphocyte ratio (NLR) of ≤5.8. Compared to the other subgroups combined, those who met both of these criteria exhibited PFS with a hazard ratio (HR) of 0.382 (95% CI: 0.168–0.871; P=0.02), corresponding to 11 and 5 months, respectively; and an OS (HR: 0.198, 95% CI: 0.043–0.920; P=0.04) of not reached versus 12 months, respectively, according to multivariate Cox regression analysis.

Conclusions: In our study cohort, there were no statistically significant differences observed in the survival rates between patients treated with lenvatinib monotherapy and those treated with a combination of lenvatinib and immunotherapy. The incorporation of ALBI grade and NLR facilitates the stratification of survival outcomes in patients with unresectable HCC undergoing lenvatinib monotherapy.

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Introduction

Hepatocellular carcinoma (HCC) ranks prominently among the primary causes of cancer-associated mortality (1,2). Lenvatinib is a multikinase inhibitor that has received approval for use as a first-line treatment for advanced HCC. The efficacy of lenvatinib has been demonstrated in the phase 3 REFLECT trial (3). The mechanism of action of the drug involves blocking the activity of enzymes and growth factor receptors involved in cancer growth and progression (4). Recent guidelines suggest using lenvatinib as alternative first-line treatment of advanced HCC (5,6). Certain patients, such as those who cannot receive combination therapy with atezolizumab and bevacizumab, may benefit from first-line treatment with lenvatinib. However, the effectiveness of lenvatinib has not been directly compared with that of combination of atezolizumab and bevacizumab.

Reliable prognostic markers are essential for effectively administering novel therapeutic agents. Biomarkers are crucial for enhancing patient categorization and optimizing the sequence of therapeutic interventions. One of the most important prognostic markers in HCC is the albumin-bilirubin (ALBI) grade (7,8). The ALBI grade is used to assess liver function in patients with HCC. The ALBI grade is determined on the basis of serum albumin and bilirubin concentrations. The relationship between the ALBI grade and survival outcomes in patients with HCC who have been treated with tyrosine kinase inhibitors (TKIs) has been extensively examined in multiple studies (9-13). The ALBI grade demonstrated a significant inverse correlation with both overall survival (OS) and progression-free survival (PFS). The neutrophil-lymphocyte ratio (NLR) serves as an indicator of systemic inflammation. Studies have demonstrated its efficacy in predicting outcomes among HCC patients undergoing treatment with TKIs (14-17). Numerous studies have explored the correlation between NLR and survival outcomes in patients with HCC who underwent treatment with lenvatinib. A retrospective analysis involving 237 HCC patients treated with lenvatinib demonstrated a significant association between elevated pretreatment NLR levels and decreased OS and PFS outcomes (15). The results of a retrospective analysis involving 1,325 patients with HCC who were treated with lenvatinib indicated a correlation between a reduction in the NLR during the course of treatment and an extended OS (17). The results indicate that NLR serves as a potential prognostic indicator for patients with HCC undergoing lenvatinib treatment. Whether the ALBI grade and NLR can be combined to effectively predict the outcomes of lenvatinib therapy is unclear (18). Lenvatinib may be an effective therapeutic agent in HCC. Prognostic markers are essential for effectively administering lenvatinib and for optimizing patient selection and risk stratification. Therefore, our primary aim was to investigate these prognostic factors associated with lenvatinib monotherapy.

Highlight box

Key findings

- The combination of albumin-bilirubin (ALBI) grade and neutrophil-lymphocyte ratio (NLR) predicts outcomes of first-line lenvatinib monotherapy in patients with unresectable hepatocellular carcinoma (HCC).

What is known and what is new?

- The correlation between ALBI grade and survival outcomes in patients with HCC treated with tyrosine kinase inhibitors (TKIs) has been well-studied, demonstrating a significant inverse relationship. Similarly, multiple studies have explored the connection between NLR and survival outcomes in patients with HCC treated with lenvatinib.
- This study represents the initial application of empirical data to evaluate the prognostic efficacy of combining the ALBI grade and NLR in the primary systemic treatment of unresectable HCC using lenvatinib monotherapy.

What are the implications, and what should change now?

- The research highlights the significant potential of lenvatinib in clinical settings, based on the identified prognostic factors of combining the ALBI grade and NLR. Further studies are needed to fully understand the relationship between lenvatinib and these factors, thereby enhancing its use in patient care.

In the phase 3 LEAP-002 trial, patients with unresectable HCC received lenvatinib combined with immune checkpoint inhibitor (ICI) as first-line treatment; however, the co-primary endpoints were not met (19-22). The present retrospective study also compared the efficacy of lenvatinib monotherapy with that of lenvatinib plus ICI combination therapy in patients with unresectable HCC in a real-world setting. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-351/rc).

Methods

Patient recruitment and definitions

Patients were retrospectively recruited from a tertiary medical care center in Taiwan. Between June 2019 and September 2022, a total of 72 patients with unresectable HCC received lenvatinib-based therapy as their first-line systemic treatment and were subsequently included in this study. Lenvatinib-based therapy was lenvatinib monotherapy (n=53) or lenvatinib plus ICI combination therapy (n=19). Patients weighing 60 kg or more were administered 12 mg/day, while those weighing less than 60 kg were given 8 mg/day, in accordance with the recommendations of the REFLECT trial. Most of the patients in this cohort were eligible for Taiwan National Health Insurance, which covered lenvatinib, but not ICIs, which were nivolumab (standard dose: 1–3 mg/kg Q2W) and pembrolizumab (standard dose: 200 mg Q3W). Patients who opted to receive ICIs had to pay out of pocket. Therefore, the prescribed dosages of ICIs varied based on each patient's financial ability. Both baseline and during-treatment clinical characteristics were evaluated and recorded. These characteristics included age, sex, Child-Pugh classification, the Barcelona Clinic Liver Cancer (BCLC) staging and Eastern Cooperative Oncology Group (ECOG) performance status. Additionally, pertinent laboratory data were collected, which encompassed aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin and alpha-fetoprotein. The platelet count and international normalized ratio (INR) were also assessed. To evaluate the response to treatment, patients were subjected to contrast-enhanced dynamic computed tomography (CT) scans or magnetic resonance imaging (MRI) at intervals of every 2 to 3 months. The response of the tumor to therapy based on lenvatinib was assessed utilizing the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (23). Fibrosis-4, ALBI scores, and NLR were calculated according to the following formulas: fibrosis-4 = [age (years) × AST concentration (U/L)]/[platelet count (10^9/L) × √ALT concentration (U/L)] (24) and ALBI score = [Log_{10} bilirubin concentration (μmol/L) × 0.66] + [albumin concentration (g/L) × −0.085] (7). The ALBI grades can be delineated as follows: Grade 1 corresponds to an ALBI score of ≤−2.60; Grade 2 falls within the range of >−2.60 to ≤−1.39; and Grade 3 is characterized by scores >−1.39 (7). NLR = neutrophil count (/μL)/lymphocyte count (/μL) (25). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). In this study, the need for patient informed consent was exempted due to the encryption of patient identification numbers, ensuring the safeguarding of their privacy. The Research Ethics Committee of China Medical University Hospital granted approval for this investigation (Reference: CMUH110-REC3-027).

Statistical analysis

In the analysis, categorical data were examined using Fisher's exact test where appropriate. Continuous data, presented as medians with interquartile ranges, underwent a normality assessment using the Kolmogorov-Smirnov test. The Mann-Whitney *U* test was employed for those datasets that deviated from normality. To ascertain the optimal cutoff values for continuous variables, receiver operating characteristic curves were analyzed, focusing on both the area under the curve and the Youden index. OS and PFS were gauged using Kaplan-Meier curves. The log-rank test facilitated the comparison of groups in univariate analysis. For the identification of survival predictors, hazard ratios (HRs) were derived from both univariate and multivariate Cox regression models. Similarly, odds ratios (ORs) were determined for treatment response predictors using both univariate and multivariate logistic regression analyses. A multivariate analysis was conducted stepwise, incorporating variables that demonstrated P values of 0.20 or less in the univariate analysis (26). Treatment response and survival outcomes (PFS and OS) in the two patient cohorts (lenvatinib monotherapy and lenvatinib plus ICI combination therapy) were analyzed before and after inverse probability of treatment weighting (IPTW). The statistical analyses for this study were conducted utilizing SPSS version 26.0 (IBM, Armonk, NY, USA) and R software version 4.2.2, sourced from the Comprehensive R Archive Network (http://cran.us.r-project.org). Additionally, the

EZR graphical user interface, developed by Y. Kanda at Saitama Medical Center, Jichi Medical University, Saitama, Japan, was employed. A P value of less than 0.05 was deemed statistically significant. Furthermore, 95% confidence intervals (CIs) were derived for the results.

Results

Baseline characteristics

A total of 72 patients with unresectable HCC received lenvatinib monotherapy (n=53) or lenvatinib plus ICI combination therapy (n=19) as their first-line regimen of systemic therapy. In the studied cohort, the median age was 64 years with an interquartile range of 16 years. Out of the total, 57 participants (79.2%) were male. A significant majority, 69 participants (95.8%), were classified under the Child-Pugh class A. Additionally, 47 of the participants (65.3%) fell under the BCLC stage C classification, and 56 participants (77.8%) met the REFLECT criteria (*Table 1*). The ICIs were pembrolizumab (n=18) or nivolumab (n=1). In total, 17 patients (23.6%) died during follow-up. The median follow-up period was 15 months. Patients receiving lenvatinib monotherapy were less likely to have extrahepatic metastasis and had lower alpha-fetoprotein and higher NLRs than those receiving lenvatinib plus ICI combination therapy (*Table 1*).

PFS and overall survival after lenvatinib-based therapy

In the study, the median PFS was observed to be 8 months with a 95% CI ranging from 5.4 to 10.6 months. The median OS was not reached as depicted in *Figure 1*. A comparison of treatment modalities revealed that patients undergoing the combination therapy demonstrated an extended PFS with a median of 12 months (95% CI: 6.4–17.6 months). This is in contrast to the patients who were administered lenvatinib as a monotherapy, where the median PFS was 7 months (95% CI: 4.5–9.5 months) as shown in *Figure 2A*. The log-rank test, however, indicated no statistical significance (P=0.74). Furthermore, the median OS was not reached in both treatment groups, and there was no notable variance in OS between the cohorts as illustrated in *Figure 2B* (log-rank test, P=0.93).

Best of treatment response to lenvatinib-based therapy

The response to the treatment was assessed based on the mRECIST guidelines (Table S1). In a comparative analysis of patients treated with lenvatinib as a monotherapy versus those treated with a combination of lenvatinib and ICI, notable differences were observed in objective response rates (ORRs) and disease control rates. Specifically, the ORR was 30.2% for the lenvatinib monotherapy group and 63.2% for the combination therapy group. Similarly, disease control rates stood at 90.6% for lenvatinib monotherapy and 94.8% for the combination therapy. Statistically, the ORR for the lenvatinib plus ICI combination therapy was significantly elevated compared to the lenvatinib monotherapy (P=0.03). The treatment efficacy assessed by RECIST criteria is shown in Table S1. It indicates an ORR of 24.5% for lenvatinib monotherapy and 31.6% for lenvatinib plus ICI. The treatment response rate by RECIST criteria shows numerically lower values than those assessed by mRECIST criteria.

Efficacy of lenvatinib therapy with or without immunotherapy

To evaluate the effectiveness of the lenvatinib-based treatments, the characteristics of the two subgroups were analyzed pre- and post-IPTW, as presented in Table S2. Patients receiving lenvatinib plus ICI combination therapy exhibited significantly higher ORRs than those receiving lenvatinib monotherapy before IPTW (OR: 3.857, P=0.02; *Table 2*). Nevertheless, after IPTW, there were no statistically significant differences in ORR between the subgroups (P=0.13). The assessment of survival outcomes revealed no statistically significant disparities in PFS and OS between the two subgroups, both before and after implementing IPTW (refer to *Table 2*).

Prognostic factors for PFS after lenvatinib monotherapy

The study aimed to identify factors predictive of PFS prior to the commencement of lenvatinib monotherapy. Univariate Cox regression analysis indicated that NLR (>5.8 *vs.* ≤5.8), and the combination of ALBI grade 1 or 2a with NLR ≤5.8 (present *vs.* absent) were significantly correlated with PFS, as outlined in *Table 3*. Subsequent multivariate Cox regression analysis determined that the combination of ALBI grade 1 or 2a and NLR ≤5.8 was a standalone predictor of PFS, specifically when both the ALBI grade and NLR were included in the model (refer to *Table 3*; HR: 0.382, 95% CI: 0.168–0.871, P=0.02). Incorporating both the ALBI grade and NLR allowed for effective patient

Table 1 Baseline characteristics of patients with HCC receiving first-line lenvatinib therapy

Variables	Entire cohort (n=72)	Lenvatinib monotherapy (n=53)	Lenvatinib plus immunotherapy (n=19)	P value
Age, years	64 [16]	64 [14.5]	63 [22]	0.11
Male	57 (79.2)	41 (77.4)	16 (84.2)	0.74
Etiologies				0.76
HBV	42 (58.3)	30 (56.6)	12 (63.2)	
HCV	17 (23.6)	14 (26.4)	3 (15.8)	
Others	13 (18.1)	9 (17.0)	4 (21.1)	
Child-Pugh class				>0.99
A	69 (95.8)	51 (96.2)	18 (94.7)	
B	3 (4.2)	2 (3.8)	1 (5.3)	
ECOG				0.47
0-1	61 (84.7)	46 (86.8)	15 (78.9)	
2-3	11 (15.3)	7 (13.2)	4 (21.1)	
FIB-4	2.44 [2.92]	2.74 [3.39]	1.60 [1.60]	0.29
FIB-4 >3.25	22 (30.6)	19 (35.8)	3 (15.8)	0.15
ALBI	–2.63 [0.71]	–2.63 [0.66]	–2.58 [1.07]	0.01
ALBI				0.17
Grade 1	38 (52.8)	29 (54.7)	9 (47.4)	
Grade 2a	16 (22.2)	13 (24.5)	3 (15.8)	
Grade 2b	16 (22.2)	11 (20.8)	5 (26.3)	
Grade 3	2 (2.8)	0 (0)	2 (10.5)	
BCLC stage				0.17
B	25 (34.7)	21 (39.6)	4 (21.1)	
C	47 (65.3)	32 (60.4)	15 (78.9)	
Previous LRT	54 (75.0)	41 (77.4)	13 (68.4)	0.54
PVT	16 (22.2)	14 (26.4)	2 (10.5)	0.21
Vp4	5 (6.9)	3 (5.7)	2 (10.5)	0.60
EHM	38 (52.8)	22 (41.5)	16 (84.2)	0.01
Bile duct invasion	2 (2.8)	0 (0)	2 (10.5)	0.07
Tumor volume ≥50% of liver volume	0 (0)	0 (0)	0 (0)	–

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Entire cohort (n=72)	Lenvatinib monotherapy (n=53)	Lenvatinib plus immunotherapy (n=19)	P value
REFLECT criteria				0.34
Without	16 (22.2)	10 (18.9)	6 (31.6)	
Within	56 (77.8)	43 (81.1)	13 (68.4)	
Adverse event	53 (73.6)	39 (73.6)	14 (73.7)	>0.99
AFP, ng/mL	19.3 [380.1]	16.8 [491.0]	27.6 [98.2]	0.03
NLR	2.99 [3.19]	3.19 [4.04]	2.62 [1.70]	0.03
AST, U/L	31.5 [29.8]	32 [29.5]	28 [36]	0.20
ALT, U/L	32 [33.3]	31 [31.5]	36 [35]	0.80
INR	1.03 [0.13]	1.03 [0.13]	1.02 [0.16]	0.99
Platelet count, 10^9/L	157 [124]	147 [119]	171 [161]	0.10
LRT[†]	30 (41.7)	25 (47.2)	5 (26.3)	0.11

Data are presented as n (%) or median [IQR]. [†], locoregional therapy was radiofrequency ablation, transarterial chemoembolization, or radiotherapy. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group performance status; FIB-4, fibrosis index based on four factors; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; LRT, locoregional therapy; PVT, portal vein thrombosis; EHM, extrahepatic metastasis; AFP, alpha-fetoprotein; NLR, neutrophil-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range.

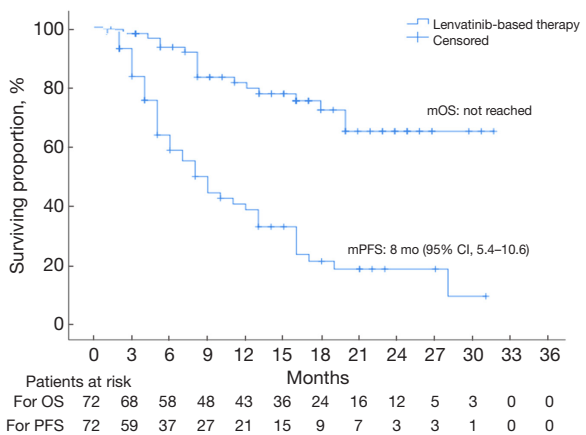

Figure 1 Progression-free survival and overall survival after initiation of lenvatinib therapy. mo, month; mOS, median overall survival; mPFS, median progression-free survival.

stratification by PFS, as depicted in *Figure 3A* (log-rank test, P=0.006). At the 6-month mark, PFS rates for patients categorized within ALBI grade 1 or 2a and NLR ≤5.8 stood at 71.0%, compared to 32.5% for the other subgroups combined. Additionally, the median PFS durations were 11 months (95% CI: 6.0–16.0) for the former group, and 5 months (95% CI: 4.2–5.8) for the latter composite group.

Prognostic factors for OS after lenvatinib monotherapy

In our study, we sought to identify factors that could predict OS prior to the initiation of lenvatinib monotherapy. Univariate Cox regression analysis demonstrated that the ECOG performance status (2 or 3 *vs.* 0,1), ALBI grade (2b or 3 *vs.* 1 or 2a), REFLECT criteria (without *vs.* within), NLR (>5.8 *vs.* ≤5.8), and the combination of ALBI grade 1 or 2a with NLR ≤5.8 were all significantly associated with OS (refer to *Table 4*). Upon further analysis using multivariate Cox regression, only the combination of ALBI grade 1 or 2a and NLR ≤5.8 emerged as an independent predictor of OS. This was evident in the model that specifically considered the interaction between ALBI grade and NLR (as illustrated in *Table 4*; HR: 0.198, 95% CI: 0.043–0.920, P=0.04). The integrated measure of ALBI grade and NLR could potentially serve as a tool to stratify OS outcomes in patients, as depicted in *Figure 3B* (log-rank

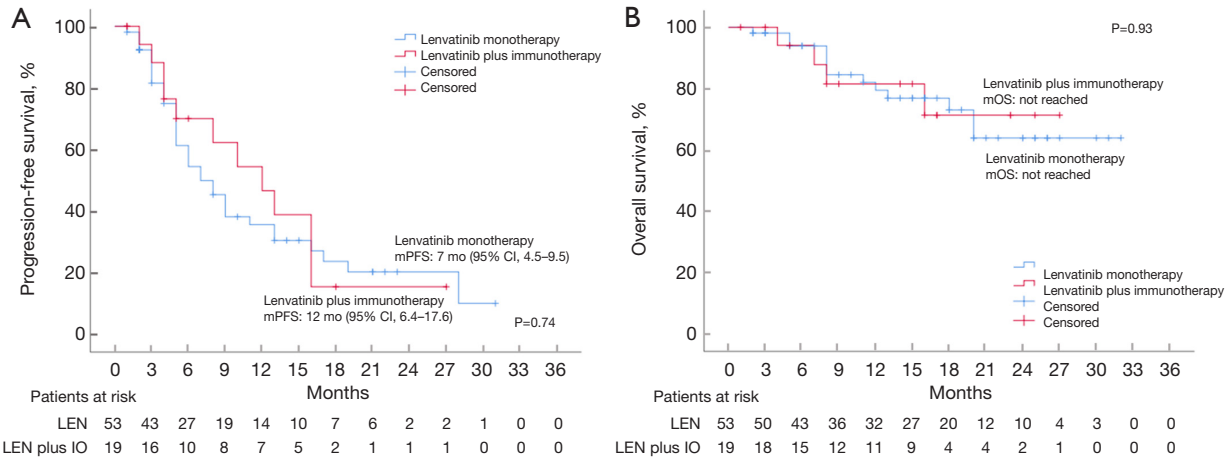

Figure 2 Progression-free survival (A) and overall survival (B) after initiation of lenvatinib monotherapy and lenvatinib plus immune checkpoint inhibitor combination therapy. CI, confidence interval; IO, immune-oncologic therapy (immunotherapy); LEN, lenvatinib; mo, month; mOS, median overall survival; mPFS, median progression-free survival.

Table 2 Treatment responses and survival outcomes in lenvatinib monotherapy and lenvatinib plus immune checkpoint inhibitor combination therapy treatment groups

Treatment outcomes	Lenvatinib monotherapy	Lenvatinib plus immunotherapy	P value
Treatment responses (mRECIST), OR (95% CI)			
Entire cohort, unadjusted			
Objective response rate	1	3.857 (1.281–11.62)	0.02
Disease control rate	1	1.500 (0.157–14.34)	0.73
Cohort, inverse probability of treatment weighting			
Objective response rate	1	2.809 (0.748–10.55)	0.13
Disease control rate	1	2.021 (0.205–19.97)	0.55
Survival outcomes, HR (95% CI)			
Entire cohort, unadjusted			
Progression-free survival	1	0.900 (0.465–1.741)	0.76
Overall survival	1	0.949 (0.309–2.916)	0.93
Cohort, inverse probability of treatment weighting			
Progression-free survival	1	0.799 (0.609–1.047)	0.10
Overall survival	1	1.241 (0.416–3.703)	0.70

mRECIST, modified Response Evaluation Criteria in Solid Tumours; OR, odds ratio; CI, confidence interval; HR, hazard ratio.

test, P<0.001). Specifically, at the 6-month mark, OS rates for patients with ALBI grade 1 or 2a and NLR ≤5.8 were 96.9%, in contrast to 86.2% for other subgroups combined. Remarkably, the median OS for patients in the ALBI grade 1 or 2a and NLR ≤5.8 subgroup had not yet been reached, as showcased in *Figure 3B*.

Prognostic factors for best of treatment response to lenvatinib monotherapy

The results of the linear regression analysis indicated that none of the factors significantly predicted objective response or disease control (refer to Tables S3,S4). The median OS

Table 3 Univariate and multivariate Cox regression analyses of predictors of progression-free survival for patients with HCC receiving first-line lenvatinib monotherapy (n=53)

Variables	Univariate		Multivariate			
	Hazard ratio (95% CI)	P value	Model 1		Model 2	
			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (≥65 *vs.* <65 years)	0.773 (0.394–1.516)	0.45				
Gender (male *vs.* female)	1.213 (0.548–2.682)	0.63				
Etiologies (viral *vs.* non-viral hepatitis)	0.634 (0.277–1.451)	0.28				
ECOG (2,3 *vs.* 0,1)	1.656 (0.684–4.008)	0.26				
FIB-4 (>3.25 *vs.* ≤3.25)	0.980 (0.492–1.952)	0.96				
ALBI grade (2b,3 *vs.* 1,2a)	2.131 (0.959–4.739)	0.06	1.135 (0.269–4.796)	0.86	*	*
BCLC stage (C *vs.* B)	0.686 (0.353–1.335)	0.27				
Previous LRT (yes *vs.* no)	0.651 (0.282–1.503)	0.31				
Portal vein thrombosis (yes *vs.* no)	0.646 (0.301–1.387)	0.26				
Extrahepatic metastasis (yes *vs.* no)	0.988 (0.487–2.004)	0.97				
REFLECT criteria (without *vs.* within)	0.641 (0.289–1.423)	0.27				
Adverse event (yes *vs.* no)	1.464 (0.562–3.815)	0.44				
AFP (>9 *vs.* ≤9 ng/mL)	1.580 (0.784–3.186)	0.20	1.127 (0.518–2.455)	0.76	1.097 (0.514–2.341)	0.81
NLR (>5.8 *vs.* ≤5.8)	2.272 (1.031–5.007)	0.042	1.948 (0.473–8.013)	0.36	*	*
ALBI grade 1,2a and NLR ≤5.8 *vs.* others	0.369 (0.170–0.800)	0.01	*	*	0.382 (0.168–0.871)	0.02

*, indicate that the variable had a confounding effect on other factors and was therefore not included in the multivariate analysis. Model 1: no combination of ALBI and NLR model; Model 2: combination of ALBI and NLR model. HCC, hepatocellular carcinoma; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIB-4, fibrosis index based on four factors; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer staging; LRT, locoregional therapy; AFP, alpha-fetoprotein; NLR, neutrophil-lymphocyte ratio.

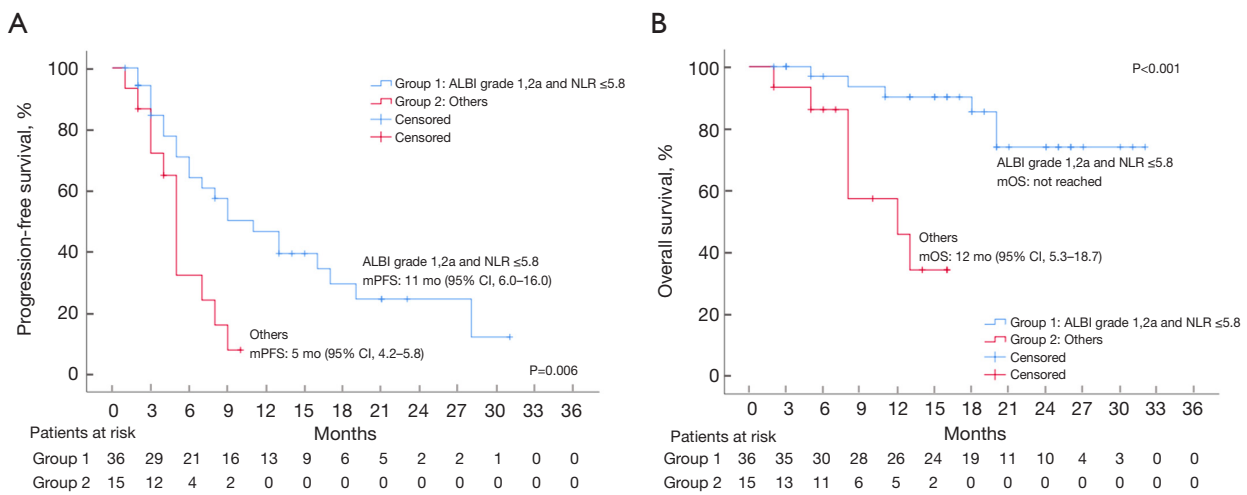

Figure 3 Progression-free survival (A) and overall survival (B) after initiation of lenvatinib monotherapy, stratified by combination of ALBI grade and NLR. ALBI, albumin-bilirubin; mo, month; mOS, median overall survival; mPFS, median progression-free survival; CI, confidence interval; NLR, neutrophil-lymphocyte ratio.

Table 4 Univariate and multivariate Cox regression analyses of predictors of overall survival for HCC patients receiving first-line monotherapy with lenvatinib (n=53)

Variables	Univariate		Multivariate			
			Model 1		Model 2	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (≥65 *vs.* <65 years)	1.094 (0.363–3.298)	0.87				
Gender (male *vs.* female)	0.726 (0.223–2.362)	0.60				
Etiologies (viral *vs.* non-viral hepatitis)	0.494 (0.150–1.623)	0.25				
ECOG (2,3 *vs.* 0,1)	3.899 (1.021–14.89)	0.047	1.682 (0.168–16.85)	0.66	1.391 (0.134–14.43)	0.78
FIB-4 (>3.25 *vs.* ≤3.25)	1.160 (0.379–3.551)	0.80				
ALBI grade (2b,3 *vs.* 1,2a)	11.38 (2.997–43.21)	<0.001	8.437 (0.709–100.4)	0.09	*	*
BCLC stage (C *vs.* B)	1.897 (0.581–6.202)	0.29				
Previous LRT (yes *vs.* no)	0.423 (0.109–1.635)	0.21				
Portal vein thrombosis (yes *vs.* no)	2.447 (0.817–7.328)	0.11	1.656 (0.496–5.531)	0.41	1.621 (0.494–5.320)	0.43
Extrahepatic metastasis (yes *vs.* no)	0.817 (0.250–2.672)	0.74				
REFLECT criteria (without *vs.* within)	0.251 (0.072–0.873)	0.03	0.779 (0.071–8.512)	0.84	0.585 (0.057–5.997)	0.65
AFP (>9 *vs.* ≤9 ng/mL)	2.966 (0.808–10.89)	0.10	0.548 (0.119–2.514)	0.44	2.189 (0.493–9.724)	0.30
Adverse event (yes *vs.* no)	2.175 (0.278–17.01)	0.46				
NLR (>5.8 *vs.* ≤5.8)	5.681 (1.583–20.39)	0.008	0.759 (0.068–8.458)	0.82	*	*
ALBI grade 1,2a and NLR ≤5.8 *vs.* others	0.119 (0.030–0.468)	0.002	*	*	0.198 (0.043–0.920)	0.04

*, indicated that the variable has a confounding effect on other factors, and thus was not included in the multivariate analysis. Model 1: no combination of ALBI and NLR model; Model 2: combination of ALBI and NLR model. HCC, hepatocellular carcinoma; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIB-4, fibrosis index based on four factors; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; LRT, locoregional therapy; AFP, alpha-fetoprotein; NLR, neutrophil-lymphocyte ratio.

of the subgroup with objective responses was significantly higher than that of the subgroup that achieved stable and progressive disease (median OS: not reached *vs.* 20 months, log-rank test, P=0.03).

Prognostic factors for survival outcome to lenvatinib-based therapy

We also performed a prognostic analysis of PFS and OS for all 72 patients, including the prognostic factor of "lenvatinib monotherapy or combination therapy with an ICI". We found that there was no additional survival benefit from the ICI when used with lenvatinib therapy in our cohort. For both PFS and OS, the combination of ALBI grade 1/2a and NLR ≤5.8 was a significant prognostic factor (Tables S5,S6), which is similar to the finding for lenvatinib monotherapy.

Association of adverse event profile with lenvatinib-based therapy

The incidence and severity of adverse events in patients undergoing lenvatinib therapy were examined, as presented in *Table 5*. Among patients receiving lenvatinib monotherapy, the four most common adverse events of any grade were hypertension, diarrhea, palmar-plantar erythrodysesthesia, and proteinuria, with 37.7%, 28.3%, 26.4%, and 22.6%, respectively, of patients in this cohort experiencing these adverse events. By contrast, among patients receiving lenvatinib plus ICI combination therapy, hypertension, pruritus, diarrhea, and palmar-plantar erythrodysesthesia were the four most common adverse events of any grade, with 31.6%, 31.6%, 26.3%, and 26.3%, respectively, of the patients in this cohort experiencing these adverse events. None of the patients receiving lenvatinib

Table 5 Adverse events of lenvatinib therapy with or without immunotherapy

Adverse events	Lenvatinib monotherapy (n=53)		Lenvatinib plus immunotherapy (n=19)	
	Any grade, n (%)	Grade 3 or 4, n (%)	Any grade, n (%)	Grade 3 or 4, n (%)
Hypertension	20 (37.7)	0	6 (31.6)	0
Diarrhea	15 (28.3)	0	5 (26.3)	0
Fatigue	6 (11.3)	0	0	0
Palmar-plantar erythrodysesthesia	14 (26.4)	0	5 (26.3)	0
Proteinuria	12 (22.6)	1 (1.9)	3 (15.8)	0
Nausea	1 (1.9)	0	0	0
Vomiting	1 (1.9)	0	0	0
Blood bilirubin increased	0	0	0	0
AST, ALT elevation	0	0	1 (5.3)	0
Dysphonia	2 (3.8)	0	2 (10.5)	0
Hypothyroidism	2 (3.8)	0	2 (10.5)	0
Adrenal insufficiency	1 (1.9)	0	0	0
Abdominal pain	2 (3.8)	0	2 (10.5)	0
Pruritus	6 (11.3)	0	6 (31.6)	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

plus ICI combination therapy experienced grade 3 or 4 adverse events; however, one patient receiving lenvatinib monotherapy experienced grade 3 or 4 proteinuria, leading to renal impairment.

Discussion

The present research assessed the efficacy, safety, and prognostic determinants of lenvatinib when administered as an initial systemic therapy for advanced HCC in a sample of 72 patients. In recent years, researchers have focused on exploring the potential benefits of combining lenvatinib with ICIs to improve treatment outcomes. Lenvatinib has been found to activate the immune response in the tumor microenvironment by inhibiting the vascular endothelial growth factor and fibroblast growth factor receptors pathway, which makes it a promising candidate in combination with ICIs (27). The combination therapy of lenvatinib and ICIs has shown encouraging results in patients with advanced HCC in various empirical studies (20,22,28,29). The LEAP 002 study examined the efficacy of combining lenvatinib and pembrolizumab for first-line treatment in patients with unresectable HCC (22). While the combination therapy achieved one of the longest median OS (mOS) recorded in a phase III trial at 21.2 months, it did not meet the dual primary endpoints of OS and PFS. The lenvatinib-alone group had a mOS of 19.0 months. The ORR was higher in the combination therapy group (26.1%) compared to the lenvatinib-alone group (17.5%). Additionally, a phase II trial of nivolumab and lenvatinib in advanced HCC showed promising results with an ORR of 28%, a CR rate of 6%, and a PR rate of 22%. The median PFS was 9.0 months, and the median OS was 27.1 months (28). In a retrospective study involving 40 HCC patients, the combined regimen of lenvatinib and nivolumab demonstrated a superior ORR of 45.0% compared to 23.4% with lenvatinib monotherapy. Furthermore, PFS was prolonged at 7.5 months versus 4.8 months, and OS was extended to 22.9 months compared to 10.3 months in the monotherapy group (29). Another retrospective study of 71 patients with unresectable HCC found that lenvatinib plus pembrolizumab yielded disease control rates of 84.1% and 70.4% among systemic therapy-naïve and systemic therapy-experienced patients, respectively, without affecting ALBI scores (20). The present study found that the combination of lenvatinib and ICIs yielded higher ORR (63.2% *vs.* 30.2%) than lenvatinib monotherapy. However, both PFS and OS showed statistical

improvements with the combination therapy relative to lenvatinib alone (Table S1 and *Figure 2A,2B*). Furthermore, no significant differences were found in the treatment responses and survival outcomes between the lenvatinib and lenvatinib plus ICI groups, even after IPTW. These findings are consistent with those of the LEAP-002 study, which did not meet the predefined statistical significance threshold for OS and PFS (22). One possible explanation for the unfavorable outcomes observed is the strong performance of lenvatinib monotherapy as a control arm, which demonstrated a median OS of 19 months. This outcome was significantly longer than the 13.6 months observed in the REFLECT study (3). In terms of OS, patients with older age (≥65 years), extrahepatic spread, hepatitis B virus etiology, and higher alpha-fetoprotein level (>400 ng/mL) were found to be good candidates for the lenvatinib plus pembrolizumab regimen in subgroup analysis (22). We have also conducted subgroup analyses according to these four factors but failed to find any statistical differences across subgroups, possibly due to the sample size (Tables S7,S8). Further studies with larger patient cohorts are necessary to confirm and validate these findings.

In the present study, the combination of lenvatinib with ICIs did not result in significant improvements in PFS or OS and lenvatinib monotherapy was found to be effective as first-line treatment. The present study demonstrated that the combined use of ALBI and NLR can effectively stratify the PFS and OS of patients receiving lenvatinib monotherapy. The ALBI grade and NLR are simple and accessible biomarkers in patients with HCC (18). The ALBI grade has been shown to have higher discriminative performance than Child-Turcotte-Pugh class as an indicator for survival after HCC diagnosis, and it has been validated in large cohorts as a good prognostic factor for HCC (30,31). Furthermore, the modified ALBI grade (grade 1 or 2a *vs.* 2b or 3) has been demonstrated to be useful in stratifying the choice of therapeutic interventions in HCC (32,33), particularly in the context of lenvatinib therapy (11,34). Alpha-fetoprotein is considered an important indicator of the tumor burden and treatment response in HCC. However, the prognostic value of alpha-fetoprotein is limited. Approximately 50% of patients with HCC do not secrete alpha-fetoprotein (35). In a prospective study involving 113 patients who underwent curative resection for HCC, a higher NLR was observed in patients with larger tumors, multiple foci of HCC, a higher grade of HCC, and vascular invasion (36). A higher ratio between neutrophils and T lymphocytes in the peritumoral tissues is correlated with lower OS (37). A high NLR has been found to be correlated with CD163-positive tumor-associated macrophages, peritumoral CD163-positive and IL-17-expressing cells, and programmed death ligand 1 expression in the tumor center (38). The use of NLR as an indicative marker of inflammation and immunological status has been suggested in multiple studies, encompassing a range of diseases beyond just HCC (39-41). Furthermore, NLR has prognostic value in various cancer types (40). The NLR may potentially serve as a prognostic indicator for the effectiveness of sorafenib treatment in patients diagnosed with HCC (42). One meta-analysis, which included 18 studies encompassing a total of 2,745 cases, demonstrated that the prognostic impact on OS increased with higher NLR cutoff values. The authors concluded that patients with a lower baseline NLR exhibited a more favorable response to sorafenib (43). Additionally, another study involving 237 patients identified an NLR cutoff value of approximately 3.0–4.5 as being associated with PFS and OS in patients with unresectable HCC receiving lenvatinib (15). Based on these studies, a reasonable NLR cutoff value for targeted therapy appears to be approximately 3.0–5.0. Our study revealed that patients with a high NLR (optimal cut-off value of 5.8) had significantly worse PFS and OS. Moreover, we combined the ALBI and NLR as factors, which could predict survival outcomes. To the best of our knowledge, this is the first study to investigate the combined use of ALBI and NLR to stratify survival risks in patients receiving lenvatinib monotherapy. We found that this combination model accurately stratified PFS and OS in patients receiving lenvatinib therapy. For patient selection, utilizing ALBI and NLR improves precision in selecting candidates for systemic therapy and optimizes their treatment outcomes. High-risk patients with poor liver function or high inflammation may need customized treatment plans and alternative treatments. Integrating ALBI grade and NLR in HCC treatment strategies involving TKIs facilitates patient selection, optimizes treatment regimens, and improves clinical outcomes.

In this study, adverse events were predominantly those of grades 1 or 2 rather than grades 3 or 4. Hypertension, palmar-plantar erythrodysesthesia, and diarrhea were the adverse events most frequently reported with lenvatinib use, regardless of ICI use. The results of this research corroborate the findings of prior investigations (3,22). Interestingly, the incidence of hypothyroidism in our study was lower than that in clinical trials, at 3.8% for lenvatinib monotherapy and 10.5% for lenvatinib plus

ICI combination therapy. This finding suggests that thyroid function is not commonly monitored. Individuals with subclinical hypothyroidism are unlikely to report it because it does not cause noticeable discomfort (44). Only one severe adverse event (proteinuria, which led to renal impairment) was observed after lenvatinib therapy in the present study. Most of the observed adverse events were considered tolerable.

There are some limitations in the present study. Firstly, its design was retrospective and it was undertaken at a singular medical center. Moreover, the median duration of follow-up was 15 months. Therefore, patient selection bias may be present, and a longer follow-up duration may be necessary to accurately determine the median OS of our cohort. Secondly, despite employing IPTW to juxtapose the lenvatinib combined with ICI therapy against lenvatinib monotherapy, the sample size for the combination therapy was limited. Consequently, this restricted our ability to offer comprehensive data for subgroup analysis. Thirdly, in our study, we observed a relatively higher NLR value for stratifying survival outcomes compared to prior studies. This discrepancy may be attributed to a small sample size or potential cohort bias. Fourthly, the accurate assessment of the relative dose intensity of lenvatinib was challenged due to potential discrepancies in documenting dose adjustments made by patients during the course of their treatment in the medical records. Finally, the rates of adverse events were relatively low, especially for grades 3 and 4 adverse events. This might be partially attributed to the retrospective collection of data.

Conclusions

The present study represents the initial application of empirical data to evaluate the prognostic efficacy of combining the ALBI grade and NLR in the primary systemic treatment of unresectable HCC using lenvatinib monotherapy. The findings of this research provide significant insights into the clinical use of lenvatinib and its potential benefits for patients, as suggested by the identified prognostic factors. The relationship between lenvatinib and its prognostic factors warrants further investigation to facilitate a comprehensive understanding.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was secured from the Research Ethics Committee of China Medical University Hospital (CMUH110-REC3-027). The requirement for patient informed consent was exempted due to the anonymization of all identifiable data.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer

statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Cronin KA, Lake AJ, Scott S, et al. Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. Cancer 2018;124:2785-800.
3. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
4. Zhao Y, Zhang YN, Wang KT, et al. Lenvatinib for hepatocellular carcinoma: From preclinical mechanisms to anti-cancer therapy. Biochim Biophys Acta Rev Cancer 2020;1874:188391.
5. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76:681-93.
6. Benson AB, D'Angelica MI, Abrams T, et al. NCCN Guidelines® Insights: Biliary Tract Cancers, Version 2.2023. J Natl Compr Canc Netw 2023;21:694-704.
7. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550-8.
8. Demirtas CO, D'Alessio A, Rimassa L, et al. ALBI grade: Evidence for an improved model for liver functional estimation in patients with hepatocellular carcinoma. JHEP Rep 2021;3:100347.
9. Kuo YH, Wang JH, Hung CH, et al. Albumin-Bilirubin grade predicts prognosis of HCC patients with sorafenib use. J Gastroenterol Hepatol 2017;32:1975-81.
10. Wang HW, Chuang PH, Su WP, et al. On-Treatment Albumin-Bilirubin Grade: Predictor of Response and Outcome of Sorafenib-Regorafenib Sequential Therapy in Patients with Unresectable Hepatocellular Carcinoma. Cancers (Basel) 2021;13:3758.
11. Tada T, Kumada T, Hiraoka A, et al. Impact of modified albumin-bilirubin grade on survival in patients with HCC who received lenvatinib. Sci Rep 2021;11:14474.
12. Kelley RK, Miksad R, Cicin I, et al. Efficacy and safety of cabozantinib for patients with advanced hepatocellular carcinoma based on albumin-bilirubin grade. Br J Cancer 2022;126:569-75.
13. Hsu WF, Hsu SC, Chen TH, et al. Modified Albumin-Bilirubin Model for Stratifying Survival in Patients with Hepatocellular Carcinoma Receiving Anticancer Therapy. Cancers (Basel) 2022;14:5083.
14. Qi X, Li J, Deng H, et al. Neutrophil-to-lymphocyte ratio for the prognostic assessment of hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. Oncotarget 2016;7:45283-301.
15. Tada T, Kumada T, Hiraoka A, et al. Neutrophil-to-lymphocyte ratio is associated with survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib. Liver Int 2020;40:968-76.
16. Rimini M, Shimose S, Lonardi S, et al. Lenvatinib versus Sorafenib as first-line treatment in hepatocellular carcinoma: A multi-institutional matched case-control study. Hepatol Res 2021;51:1229-41.
17. Casadei-Gardini A, Rimini M, Kudo M, et al. Real Life Study of Lenvatinib Therapy for Hepatocellular Carcinoma: RELEVANT Study. Liver Cancer 2022;11:527-39.
18. Bannaga A, Arasaradnam RP. Neutrophil to lymphocyte ratio and albumin bilirubin grade in hepatocellular carcinoma: A systematic review. World J Gastroenterol 2020;26:5022-49.
19. Chen K, Wei W, Liu L, et al. Lenvatinib with or without immune checkpoint inhibitors for patients with unresectable hepatocellular carcinoma in real-world clinical practice. Cancer Immunol Immunother 2022;71:1063-74.
20. Wu CJ, Lee PC, Hung YW, et al. Lenvatinib plus pembrolizumab for systemic therapy-naïve and -experienced unresectable hepatocellular carcinoma. Cancer Immunol Immunother 2022;71:2631-43.
21. Yang X, Chen B, Wang Y, et al. Real-world efficacy and prognostic factors of lenvatinib plus PD-1 inhibitors in 378 unresectable hepatocellular carcinoma patients. Hepatol Int 2023;17:709-19.
22. Finn RS, Kudo M, Merle P, et al. LBA34 Primary results from the phase III LEAP-002 study: Lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). Ann Oncol 2022;33:S808-69.
23. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698-711.
24. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-25.
25. Peng W, Li C, Wen TF, et al. Neutrophil to lymphocyte ratio changes predict small hepatocellular carcinoma survival. J Surg Res 2014;192:402-8.
26. Maldonado G, Greenland S. Simulation study of

confounder-selection strategies. Am J Epidemiol 1993;138:923-36.
27. Kimura T, Kato Y, Ozawa Y, et al. Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. Cancer Sci 2018;109:3993-4002.
28. Vogel A, Siegler GM, Siebler J, et al. IMMUNIB trial (AIO-HEP-0218/ass): a single-arm, phase II study evaluating safety and efficacy of immunotherapy nivolumab in combination with lenvatinib in advanced-stage hepatocellular carcinoma (HCC). J Clin Oncol 2022;40:4107.
29. Wu WC, Lin TY, Chen MH, et al. Lenvatinib combined with nivolumab in advanced hepatocellular carcinoma-real-world experience. Invest New Drugs 2022;40:789-97.
30. Hiraoka A, Kumada T, Tsuji K, et al. Validation of Modified ALBI Grade for More Detailed Assessment of Hepatic Function in Hepatocellular Carcinoma Patients: A Multicenter Analysis. Liver Cancer 2019;8:121-9.
31. Kumada T, Toyoda H, Tada T, et al. Changes in Background Liver Function in Patients with Hepatocellular Carcinoma over 30 Years: Comparison of Child-Pugh Classification and Albumin Bilirubin Grade. Liver Cancer 2020;9:518-28.
32. Kudo M. Newly Developed Modified ALBI Grade Shows Better Prognostic and Predictive Value for Hepatocellular Carcinoma. Liver Cancer 2021;11:1-8.
33. Tokunaga T, Tanaka M, Tanaka K, et al. Modified albumin-bilirubin grade to predict eligibility for second-line therapies at progression on sorafenib therapy in hepatocellular carcinoma patients. Int J Clin Oncol 2021;26:922-32.
34. Tsuchiya K, Kurosaki M, Sakamoto A, et al. The Real-World Data in Japanese Patients with Unresectable Hepatocellular Carcinoma Treated with Lenvatinib from a Nationwide Multicenter Study. Cancers (Basel) 2021;13:2608.
35. Bai DS, Zhang C, Chen P, et al. The prognostic correlation of AFP level at diagnosis with pathological grade, progression, and survival of patients with hepatocellular carcinoma. Sci Rep 2017;7:12870.
36. Yamamura K, Sugimoto H, Kanda M, et al. Comparison of inflammation-based prognostic scores as predictors of tumor recurrence in patients with hepatocellular carcinoma after curative resection. J Hepatobiliary Pancreat Sci 2014;21:682-8.
37. He G, Zhang H, Zhou J, et al. Peritumoural neutrophils negatively regulate adaptive immunity via the PD-L1/PD-1 signalling pathway in hepatocellular carcinoma. J Exp Clin Cancer Res 2015;34:141.
38. Motomura T, Shirabe K, Mano Y, et al. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. J Hepatol 2013;58:58-64.
39. Huang Z, Fu Z, Huang W, et al. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. Am J Emerg Med 2020;38:641-7.
40. Cupp MA, Cariolou M, Tzoulaki I, et al. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med 2020;18:360.
41. Mouchli M, Reddy S, Gerrard M, et al. Usefulness of neutrophil-to-lymphocyte ratio (NLR) as a prognostic predictor after treatment of hepatocellular carcinoma. Ann Hepatol 2021;22:100249.
42. Bruix J, Cheng AL, Meinhardt G, et al. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. J Hepatol 2017;67:999-1008.
43. Liu L, Gong Y, Zhang Q, et al. Prognostic Roles of Blood Inflammatory Markers in Hepatocellular Carcinoma Patients Taking Sorafenib. A Systematic Review and Meta-Analysis. Front Oncol 2020;9:1557.
44. Shao YY, Cheng AL, Hsu CH. An Underdiagnosed Hypothyroidism and Its Clinical Significance in Patients with Advanced Hepatocellular Carcinoma. Oncologist 2021;26:422-6.

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