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ORIGINAL ARTICLE

Retrospective Study

Impact of baseline body mass index on the long-term prognosis of advanced hepatocellular carcinoma treated with immunotherapy

Yu-Qin Wang, Di Pan, Zhi-Yuan Yao, Yu-Qi Li, Peng-Fei Qu, Run-Bang Wang, Qing-Hao Gu, Jie Jiang, Zheng-Xiang Han, Hao-Nan Liu

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Abstract

BACKGROUND

Primary liver cancer is the sixth most common cancer worldwide, with hepatocellular carcinoma (HCC) being the most prevalent form. Despite the current availability of multiple immune or immune combination treatment options, the prognosis is still poor, so how to identify a more suitable population is extremely important.

AIM

To evaluate the clinical effectiveness of combining lenvatinib with camrelizumab for patients with hepatitis B virus (HBV)-related HCC in Barcelona Clinic Liver Cancer (BCLC) stages B/C, considering various body mass index (BMI) in different categories.

METHODS
Retrospective data were collected from 126 HCC patients treated with lenvatinib plus camrelizumab. Patients were divided into two groups based on BMI: The non-overweight group (BMI < 25 kg/m^2, n = 51) and the overweight/obese group (BMI ≥ 25 kg/m^2, n = 75). Short-term prognosis was evaluated using mRECIST criteria, with subgroup analyses for non-overweight (BMI: 18.5-24.9 kg/m^2), overweight (BMI: 25-30 kg/m^2), and obese (BMI ≥ 30 kg/m^2) patients. A Cox proportional hazards regression analysis identified independent prognostic factors for overall survival (OS), leading to the development of a column-line graph model.

RESULTS
Median progression-free survival was significantly longer in the obese/overweight group compared to the non-overweight group. Similarly, the median OS was significantly prolonged in the obese/overweight group than in the non-overweight group. The objective remission rate and disease control rate for the two groups of patients were, respectively, objective remission rate (5.88% *vs* 28.00%) and disease control rate (39.22% *vs* 62.67%). Fatigue was more prevalent in the obese/overweight group, while other adverse effects showed no statistically significant differences (P > 0.05). Subgroup analysis based on BMI showed that obese and overweight patients had better progression-free survival and OS than non-overweight patients, with obese patients showing the best outcomes. Multifactorial regression analysis identified BCLC grade, alpha-fetoprotein level, portal vein tumor thrombosis, and BMI as independent prognostic factors for OS. The column-line graph model highlighted the importance of BMI as a major predictor of patient prognosis, followed by alpha-fetoprotein level, BCLC classification, and portal vein tumor thrombosis.

CONCLUSION
BMI is a long-term predictor of the efficacy of lenvatinib plus camrelizumab, and obese/overweight patients have a better prognosis.

Key Words: Hepatocellular carcinoma; Camrelizumab; Lenvatinib; Efficacy; Safety

Core Tip: Primary liver cancer is the sixth most common cancer and the third leading cause of cancer-related death worldwide, with hepatocellular carcinoma (HCC) being the most prevalent form. Numerous combination therapies involving programmed cell death protein 1/programmed cell death ligand 1 inhibitors and antiangiogenic targeted therapies have been investigated and approved as first-line systemic therapy for patients with advanced HCC. In the era of immune checkpoint inhibitors, nutritional assessment, including body mass index (BMI), can be considered a new prognostic predictor. However, the impact of BMI on the prognosis of patients with hepatitis B virus-related HCC remains controversial. We initiated a retrospective clinical study to explore the impact of BMI level on the prognosis of hepatitis B virus-related HCC patients treated with lenvatinib plus carelizumab.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the primary type of liver cancer, which ranks as the sixth most prevalent cancer and serves as the third major contributor to cancer-related fatalities across the globe[1,2]. In China, hepatitis B virus (HBV) infection accounts for the majority of HCC cases[3,4]. Although there have been improvements in HCC therapies, numerous patients continue to face restricted treatment choices and unfavorable outcomes[5]. This situation arises because HCC is often detected at a late stage, preventing many patients from accessing potentially curative treatments[6]. Therefore, nonsurgical treatments, such as immunotherapy and targeted therapy, are critical for managing HCC[7]. Large clinical trials and meta-analyses indicate that immunotherapy, especially when combined with targeted therapy, is more effective in patients with hepatitis B-associated HCC than in those with nonviral-associated HCC[8,9].

Lenvatinib, a multitarget oral tyrosine kinase inhibitor, exhibiting antitumor and antiangiogenic effects[10]. The REFLECT study[11] resulted in the approval of lenvatinib in 2018 as a primary therapy for advanced HCC by the Food and Drug Administration, and the National Medical Products Administration, to be used alongside sorafenib[12]. A worldwide, open-label study led by Finn *et al*[13] demonstrated that the combination of programmed cell death protein 1 (PD-1) inhibitors and anti-vascular endothelial growth factor improved the with unresectable HCC outcome.

Subsequently, combination therapies integrating PD-1/programmed cell death ligand 1 (PD-L1) inhibitors with antiangiogenic targeted treatments have been investigated and approved as first-line systemic options for advanced HCC patients[14,15].

Camrelizumab, a PD-1/PD-L1 inhibitor, was approved by the United States Food and Drug Administration for HCC [16]. The PD-1 and PD-L1 interaction within tumor tissues impairs effector T-cell activity, weakens antitumor immune responses, and promotes tumor growth[17]. Camrelizumab combined with lenvatinib has proven effective as both first- and second-line treatments for HCC patients. The RESCUE study reported that advanced HCC patients treated with lenvatinib and camrelizumab had an objective remission rate (ORR) of 34.3%[18].

In the era of immunotherapy, nutritional assessment, including body mass index (BMI), serves as a novel prognostic predictor[19]. A study demonstrated that immunotherapy was significantly more effective in overweight melanoma patients (BMI ≥ 25 kg/m^2) compared to non-overweight patients (P = 0.024), with a trend toward prolonged overall survival (OS) (P = 0.056)[20]. In addition, Wang *et al*[21] found that obese patients (BMI ≥ 30 kg/m^2) receiving immune-checkpoint inhibitors (ICIs) exhibited improved progression-free survival (PFS) (P = 0.003) and OS (P = 0.049). The influence of BMI on the prognosis of patients with HBV-related HCC is still debated. Although lenvatinib combined with camrelizumab is a standard treatment for HBV-associated HCC at Barcelona Clinic Liver Cancer (BCLC) stages B and C, real-world evidence on the impact of BMI on its clinical effectiveness is lacking. As a result, thorough investigation is essential. We carried out a retrospective clinical analysis to assess how different BMI levels influence the outcomes of patients with HBV-related HCC who received treatment with lenvatinib and camrelizumab.

MATERIALS AND METHODS

Study design and patients

Retrospective clinical data were collected from HBV-related HCC patients treated with lenvatinib and camrelizumab between January 2019 and December 2023. Inclusion criteria were: (1) HCC diagnosis per 2018 American Association for the Study of Liver Diseases guidelines[22]; (2) Patients aged 18 or older; (3) Available BMI data; (4) At least one measurable tumor lesion; (5) Received a minimum of two treatment cycles; (6) Child-Pugh class A or B; (7) BCLC stage B or C; (8) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2 or lower; and (9) Positive serum hepatitis B surface antigen or HBV-DNA.

Exclusion criteria included: (1) Absence of tumor visualization within 6 weeks prior to anti-PD-1 therapy; (2) Presence of other malignancies or non-primary HCC; (3) Concurrent hepatitis C or other viral infections; (4) Incomplete clinical data; (5) Prior PD-1 inhibitor or targeted drug treatment; and (6) HBV reactivation during combination therapy. Finally, we included 126 patients for analysis. The study process is illustrated in Figure 1. This retrospective study received approval from the Ethics Review Committee of the Affiliated Hospital of Xuzhou Medical University (Ethics Approval No. XYFY2022-KL207-01) and adhered to the principles outlined in the Declaration of Helsinki. The requirement for written informed consent was waived due to the study's retrospective nature.

Definition

A trained nurse recorded height and weight measurements before the initial administration of lenvatinib with camrelizumab. BMI was computed from the patient's height and weight data. The World Health Organization classifies normal weight as a BMI of 18.5-24.9 kg/m^2, overweight as a BMI of ≥ 25 kg/m^2, and obesity as a BMI of ≥ 30 kg/m^2. The Japanese Obesity Association has reported a significant increase in obesity-related chronic diseases, including type 2 diabetes mellitus, among individuals with a BMI of ≥ 25 kg/m^2. As a result, this study established 25 kg/m^2 as the cutoff for BMI [23,24]. The 2018 hepatitis B guidelines set forth by the American Association for the Study of Liver Diseases categorize HBV reactivation using three specific criteria. Hepatic impairment, according to the Common Terminology Criteria for Adverse Events version 5.0, is identified when alanine aminotransferase or aspartate aminotransferase levels exceed 5 times the upper normal limit.

Grouping and treatment protocol

Patients were categorized based on BMI into two groups: Those with a BMI below 25 kg/m^2 and those with a BMI of 25 kg/m^2 or higher. Camrelizumab, at a dosage of 200 mg per cartridge, was given intravenously, utilizing one cartridge at a time, every three weeks. Patients under 60 kg received an oral dose of 8 mg lenvatinib (two 4 mg capsules) daily, while those weighing 60 kg or more received 12 mg (three 4 mg capsules) daily.

Evaluation

Patients underwent either a computed tomography chest scan or an enhanced abdominal scan using computed tomography or magnetic resonance imaging at the study's onset and every 6 to 8 weeks thereafter. Long-term effectiveness was assessed using OS and PFS. Short-term effectiveness was evaluated using mRECIST criteria. All adverse events (AEs) were documented and analyzed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

Analyses of the data were conducted utilizing R software version 4.4.0. Categorical variables were represented as counts along with their corresponding percentages. The median OS and PFS were calculated employing the Kaplan-Meier

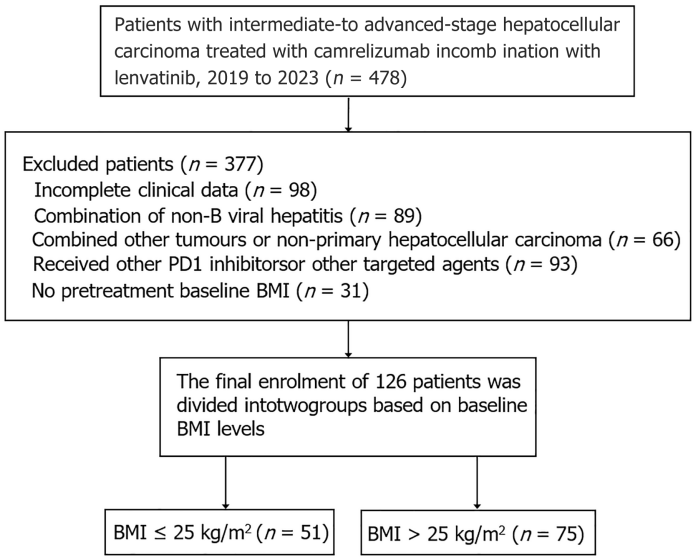

Figure 1 Flow diagram depicting the patients with infiltrative hepatocellular camrelizumab enrolled in the study. PD1: Programmed cell death protein 1; BMI: Body mass index.

method. For both univariate and multivariate analyses, Cox proportional hazards regression was utilized. The focus of the multivariate analysis was specifically on variables exhibiting *P* values below 0.05 from the univariate analysis to identify independent prognostic elements for OS and PFS. A nomogram prediction model was created based on the independent prognostic factors identified in the multivariate OS analysis, aimed at forecasting outcomes at 9, 12, and 18 months. The predictions generated by the model were subsequently compared with actual patient outcomes. All statistical tests conducted were two-sided, with *P* values lower than 0.05 deemed to indicate statistical significance.

RESULTS

Patient characteristics

This retrospective study analyzed 126 patients with BCLC stage B or C HCC treated with lenvatinib and camrelizumab from January 2019 to December 2023 (see Figure 1). Among these participants, 51 were categorized as non-overweight (BMI < 25 kg/m²), while 75 fell into the obese/overweight category (BMI ≥ 25 kg/m²). A total of 377 patients were excluded due to incomplete clinical records (*n* = 98), coexisting non-B viral hepatitis (*n* = 89), other tumors or non-primary HCC (*n* = 66), use of alternative PD-1 inhibitors or targeted therapies (*n* = 93), and lack of baseline BMI data (*n* = 31). Table 1 provides a comprehensive overview of the patient characteristics, including variables such as age, gender, BMI classification, smoking status, alcohol consumption, presence of hypertension, diabetes, cirrhosis, vascular invasion, extrahepatic metastasis, ECOG performance status, Child-Pugh classification, BCLC stage, application of interventional therapy, and various laboratory parameters. Importantly, there were no statistically significant differences in these baseline characteristics between the two groups, with all *P* values exceeding 0.05, indicating a well-balanced distribution of factors across the study cohorts.

Tumor response

Tumor responses are shown in Table 2. Among all the included patients, 1 patient achieved complete response (CR), 22 achieved partial response (PR), 43 developed stable disease (SD), and 59 developed progression disease (PD) according to the mRECIST criteria. The non-super-reconstituted and obese/super-reconstituted ORR accounted for 5.88% and 28.00% (*P* = 0.002) and disease control rate (DCR) accounted for 39.22% and 62.67% (*P* = 0.010), respectively.

PFS and OS

The obese/overweight group had a significantly longer median PFS of 8.53 (8.10-9.39) months compared to the non-overweight group, which had a median PFS of 6.30 (6.11-7.23) months (*P* < 0.001, Figure 2A). The obese/hyper combined group had a significantly longer median OS of 15.30 (10.58-19.90) months, compared to 11.90 (7.28-NA) months in the non-hyper combined group (*P* = 0.001) (Figure 2B). Analysis by BMI classification-normal weight (BMI: 18.5-24.9 kg/m²), overweight (BMI: 25-30 kg/m²), and obese (BMI ≥ 30 kg/m²) - showed significant differences in median PFS and OS (*P* ≤ 0.001). Obese patients exhibited the best median PFS (10.00 months, 7.80-10.43) compared to normal weight (6.30 months, 6.11-7.23) and overweight patients (8.47 months, 8.00-9.30), with hazard ratios (HRs) of 0.13 [95% confidence interval (CI): 0.06-0.31] and 0.36 (95%CI: 0.19-0.69), respectively. Median OS was significantly longer in obese (HR = 0.28; 95%CI 0.14-0.57) and overweight patients (HR = 0.48; 95%CI 0.25-0.90) compared to normal-weight patients (Table 3). Median PFS was 6.30 months (6.11-7.23) for normal weight, 8.47 months (8.00-9.30) for overweight, and 10.00 months (7.80-10.43) for

Table 1 Baseline characteristics of the body mass index < 25 kg/m² and body mass index ≥ 25 kg/m² groups, *n* (%)

Variables	BMI < 25 kg/m² (*n* = 51)	BMI ≥ 25 kg/m² (*n* = 75)	χ^2	*P* value
HBV DNA (IU/mL)			0.31	0.579
HBV > 2000	25 (49.02)	33 (44.00)		
HBV ≤ 2000	26 (50.98)	42 (56.00)		
HBe			2.05	0.152
Negative	32 (62.75)	56 (74.67)		
Positive	19 (37.25)	19 (25.33)		
Child-Pugh class			0.52	0.472
A	28 (54.90)	46 (61.33)		
B	23 (45.10)	29 (38.67)		
PVTT			3.12	0.077
No	26 (50.98)	50 (66.67)		
Yes	25 (49.02)	25 (33.33)		
BCLC stage			0.30	0.586
B	24 (47.06)	39 (52.00)		
C	27 (52.94)	36 (48.00)		
Metastasis			0.00	0.979
No	28 (54.90)	41 (54.67)		
Yes	23 (45.10)	34 (45.33)		
AFP (ng/mL)			3.01	0.083
> 1210	27 (52.94)	28 (37.33)		
≤ 1210	24 (47.06)	47 (62.67)		
Sex			0.97	0.323
Female	16 (31.37)	30 (40.00)		
Male	35 (68.63)	45 (60.00)		
Age (years)			1.00	0.316
< 60	26 (50.98)	45 (60.00)		
≥ 60	25 (49.02)	30 (40.00)		
ECOG			3.49	0.062
0-1	27 (52.94)	52 (69.33)		
2	24 (47.06)	23 (30.67)		
ALT (U/L)			1.14	0.286
> 40	26 (50.98)	31 (41.33)		
≤ 40	25 (49.02)	44 (58.67)		
Total bilirubin (μmol/L)			1.29	0.256
> 34	35 (68.63)	44 (58.67)		
≤ 34	16 (31.37)	31 (41.33)		
Diabetes			0.83	0.361
No	41 (80.39)	55 (73.33)		
Yes	10 (19.61)	20 (26.67)		
Hypertensive			0.11	0.736
No	15 (29.41)	20 (26.67)		

Yes	36 (70.59)	55 (73.33)		
Cirrhosis			0.18	0.675
No	28 (54.90)	44 (58.67)		
Yes	23 (45.10)	31 (41.33)		
Smoking			1.33	0.248
No	31 (60.78)	53 (70.67)		
Yes	20 (39.22)	22 (29.33)		
Alcohol			0.47	0.491
No	35 (68.63)	47 (62.67)		
Yes	16 (31.37)	28 (37.33)		
Interventional			0.84	0.358
No	25 (49.02)	43 (57.33)		
Yes	26 (50.98)	32 (42.67)		

BMI: Body mass index; HBV: Hepatitis B virus; PVTT: Portal vein tumor thrombosis; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-fetoprotein; ECOG: Eastern Cooperative Oncology Group; ALT: Alanine aminotransferase.

Table 2 Tumor response between body mass index < 25 kg/m² and body mass index ≥ 25 kg/m² groups, *n* (%)

Variables	BMI < 25 kg/m² (*n* = 51)	BMI ≥ 25 kg/m² (*n* = 75)	χ^2	*P* value
CR				
0	51 (100.00)	73 (97.33)		
1	0 (0.00)	1 (1.33)		
PR				
0	48 (94.12)	56 (74.67)		
1	3 (5.88)	19 (25.33)		
SD				
0	34 (66.67)	49 (65.33)		
1	17 (33.33)	26 (36.00)		
PD				
0	20 (39.22)	47 (62.67)		
1	31 (60.78)	28 (37.33)		
ORR			9.63	0.002
0	48 (94.12)	54 (72.00)		
1	3 (5.88)	21 (28.00)		
DCR			6.70	0.010
0	31 (60.78)	28 (37.33)		
1	20 (39.22)	47 (64.00)		

BMI: Body mass index. CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progression disease; ORR: Objective responds rates; DCR: Disease control rates.

obese patients, $P < 0.001$. Median OS for these groups was 11.90 months (7.28-NA), 14.40 months (9.47-19.50), and 16.60 months (10.80-21.30), $P = 0.001$ (Figure 2C and D).

Univariate and multifactorial analyses of PFS and OS

Table 4 presents the outcomes of both unifactorial and multifactorial Cox proportional hazards regression analyses for

Table 3 Cox subgroup analyses of the prognostic factors for progression-free survival and overall survival based on body mass index

BMI group	HR (95%CI)
Overall survival	
18.5-24.9	1 (Reference)
25.0-29.9	0.48 (0.25-0.90)
≥ 30.0	0.28 (0.14-0.57)
P value	0.002
Progression-free survival	
18.5-24.9	1 (Reference)
25.0-29.9	0.36 (0.19-0.69)
≥ 30.0	0.13 (0.06-0.31)
P value	< 0.001

BMI: Body mass index; HR: Hazard ratio; CI: Confidence interval.

Table 4 Univariate and multivariate analyses of the prognostic factors for progression-free survival

Factors	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
AFP (≤ 1210 *vs* > 1210), ng/mL	1.11 (0.71-1.74)	0.642	-	-
Age (≥ 60 *vs* < 60), years	1.68 (1.09-2.60)	0.019	1.13 (0.70-1.83)	0.624
Alcohol (yes *vs* no)	0.94 (0.60-1.46)	0.784	-	-
ALT (> 40 *vs* ≤ 40), U/L	0.86 (0.56-1.30)	0.468	-	-
BCLC stage (C *vs* B)	1.85 (1.17-2.93)	0.008	2.60 (1.56-4.33)	< 0.001
BMI (normal *vs* overweight/obesity)	0.28 (0.15-0.52)	< 0.001	0.32 (0.17-0.59)	< 0.001
Child-Pugh score (B *vs* C)	2.71 (1.73-4.23)	< 0.001	2.30 (1.44-3.67)	< 0.001
Diabetes (yes *vs* no)	0.88 (0.53-1.49)	0.644	-	-
Cirrhosis (yes *vs* no)	0.98 (0.64-1.49)	0.922	-	-
ECOG (2 *vs* 0-1)	2.37 (1.50-3.72)	< 0.001	2.22 (1.37-3.61)	0.001
HBe (positive *vs* negative)	1.29 (0.82-2.03)	0.273	-	-
HBV-DNA (HBV ≤ 2000 *vs* HBV > 2000), IU/mL	1.27 (0.83-1.95)	0.276	-	-
Hypertensive (yes *vs* no)	1.10 (0.68-1.78)	0.709	-	-
PVTT (yes *vs* no)	1.06 (0.66-1.67)	0.820	-	-
Metastasis (yes *vs* no)	0.81 (0.53-1.23)	0.321	-	-
Sex (male *vs* female)	0.89 (0.58-1.35)	0.576	-	-
Smoking (yes *vs* no)	1.02 (0.65-1.61)	0.919	-	-
Total bilirubin (≤ 34 *vs* > 34), μmol/L	0.30 (0.18-0.50)	< 0.001	0.38 (0.21-0.67)	0.001
Interventional (yes *vs* no)	0.77 (0.48-1.22)	0.263	-	-

HR: Hazard ratio; CI: Confidence interval; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; BMI: Body mass index; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; PVTT: Portal vein tumor thrombosis.

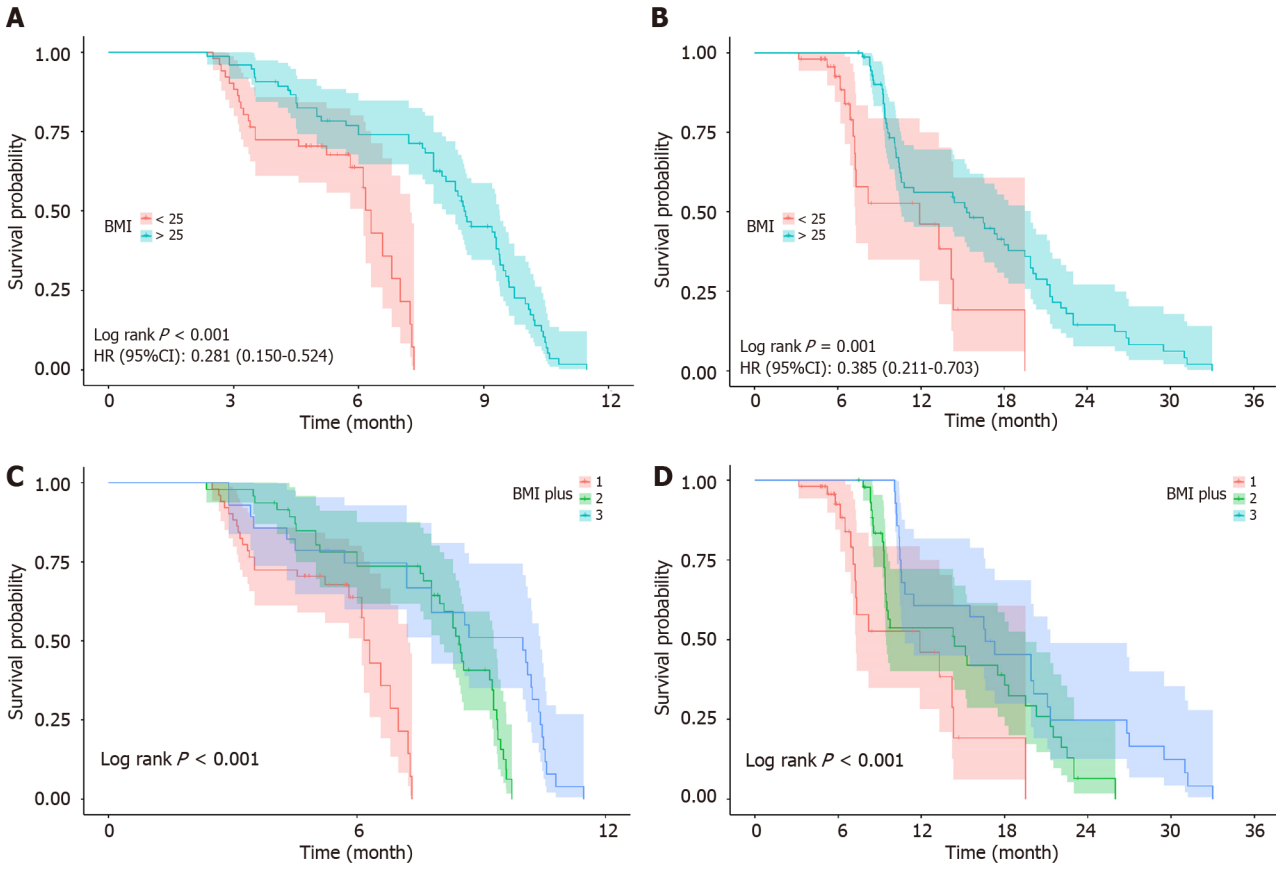

Figure 2 Graph depicting the effect of different body mass index values on long-term survival of patients and further subgroup analysis.
A: Kaplan-Meier plot of in the body mass index (BMI) ≤ 25 kg/m^2 and BMI > 25 kg/m^2 groups; B: Kaplan-Meier plot of overall survival in the BMI ≤ 25 kg/m^2 and BMI > 25 kg/m^2 groups; C: Kaplan-Meier plot of analysis of progression-free survival subgroup by BMI; D: Kaplan-Meier plot of analysis of the overall survival subgroup by BMI. BMI: Body mass index; HR: Hazard ratio; CI: Confidence interval.

PFS. The multivariate analysis identified several independent prognostic factors for PFS in patients with HCC, including Child-Pugh grading (HR = 2.30, 95%CI: 1.44-3.67), BCLC classification (HR = 2.60, 95%CI: 1.56-4.33), ECOG score (HR = 2.22, 95%CI: 1.37-3.61), BMI (HR = 0.32, 95%CI: 0.17-0.59), and total bilirubin (HR = 0.38, 95%CI: 0.21-0.67). Similarly, Table 5 outlines the results of univariate and multivariate Cox proportional hazards regression analyses for OS. The multivariate analysis revealed BCLC classification (HR = 0.43, 95%CI: 0.26-0.70), alpha-fetoprotein (AFP) levels (HR = 0.42, 95%CI: 0.25-0.72), presence of portal vein tumor thrombus (PVTT) (HR = 2.23, 95%CI: 1.26-3.93), and BMI (HR = 0.22, 95%CI: 0.11-0.45) as independent prognostic factors for OS in HCC patients. Based on these identified independent prognostic factors, nomogram prediction models for 9, 12, and 18 months were constructed (Figure 3). The concordance indexes (c-indexes) for the prediction models in the training and validation datasets were 0.731 and 0.722, respectively, indicating good predictive accuracy.

Validation of prognostic models

Patients were assigned randomly into two groups, with 88 individuals designated for the training dataset and 38 individuals for the internal validation dataset, adhering to a ratio of 7:3. The baseline characteristics for both the training and validation datasets are outlined in Table 6. The area under the receiver operating characteristic curve (AUC) for 9-month OS was 0.838 for the training set and 0.816 for the internal validation set, as shown in Figure 4A and B. At the 12-month mark, the AUC for OS were recorded as 0.762 and 0.674 (Figure 4C and D), while at 18 months, they were 0.830 and 0.714 (Figure 4E and F). Calibration curves depicting OS at 9, 12, and 18 months for both the training and validation sets were generated (Figure 5). These calibration curves demonstrated that the predicted risk from the model aligned with the actual risk occurrences.

AEs

Patients in both groups predominantly reported various grades of AEs, with the most common being reactive cutaneous capillary endothelial proliferation, proteinuria, nausea, leukopenia, hyperbilirubinemia, and thrombocytopenia (Table 7). No patients stopped treatment due to AEs. Patients with BMI > 25 kg/m^2 were more likely to experience fatigue (P < 0.05), while other AEs did not differ significantly (P > 0.05).

Table 5 Univariate and multivariate analyses of the prognostic factors for overall survival

Factors	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
AFP (≤ 1210 *vs* > 1210), ng/mL	0.59 (0.36-0.95)	0.031	0.42 (0.25-0.72)	0.002
Age (≥ 60 *vs* < 60), years	0.70 (0.43-1.12)	0.139	-	-
Alcohol (yes *vs* no)	1.02 (0.64-1.63)	0.932	-	-
ALT (≤ 40 *vs* > 40), U/L	1.21 (0.77-1.92)	0.409	-	-
BCLC stage (C *vs* B)	0.59 (0.37-0.94)	0.028	0.43 (0.26-0.70)	0.001
BMI (normal *vs* overweight/obesity)	0.39 (0.21-0.70)	0.002	0.22 (0.11-0.45)	< 0.001
Child-Pugh score (B *vs* C)	0.77 (0.48-1.22)	0.266	-	-
Diabetes (yes *vs* no)	0.92 (0.52-1.60)	0.755	-	-
Cirrhosis (yes *vs* no)	1.15 (0.72-1.84)	0.562	-	-
ECOG (2 *vs* 0-1)	0.66 (0.40-1.07)	0.090	-	-
HBe (positive *vs* negative)	1.09 (0.67-1.78)	0.717	-	-
HBV-DNA (HBV ≤ 2000 *vs* HBV > 2000), IU/mL	0.67 (0.42-1.07)	0.091	-	-
Hypertensive (yes *vs* no)	1.20 (0.71-2.05)	0.494	-	-
PVTT (yes *vs* no)	2.36 (1.35-4.12)	0.003	2.23 (1.26-3.93)	0.006
Metastasis (yes *vs* no)	0.79 (0.50-1.26)	0.328	-	-
Sex (male *vs* female)	1.11 (0.70-1.77)	0.658	-	-
Smoking (yes *vs* no)	1.33 (0.81-2.19)	0.266	-	-
Total bilirubin (≤ 34 *vs* > 34), μmol/L	1.26 (0.78-2.02)	0.348	-	-
Interventional (yes *vs* no)	0.75 (0.47-1.19)	0.224	-	-

HR: Hazard ratio; CI: Confidence interval; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; BMI: Body mass index; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; PVTT: Portal vein tumor thrombosis.

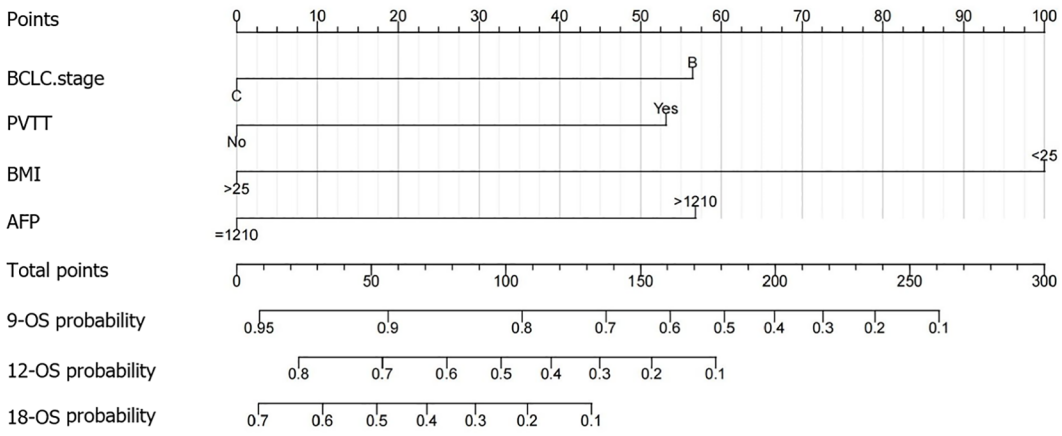

Figure 3 Graph depicting the prognostic model for predicting 9-, 12-, and 18-month overall survival. BCLC: Barcelona Clinic Liver Cancer; PVTT: Portal vein tumor thrombus; BMI: Body mass index; AFP: Alpha-fetoprotein; OS: Overall survival.

DISCUSSION

This study is the first to comprehensively examine the impact of BMI on the efficacy of camrelizumab plus lenvatinib treatment in patients with HBV-related HCC and to develop a predictive model for comparing their long-term prognosis. The results showed that median OS, median PFS, ORR, and DCR were significantly better in obese/overweight (BMI ≥ 25 kg/m²) patients than in non-overweight (BMI < 25 kg/m²) patients. Independent prognostic factors for PFS were Child-Pugh classification, BCLC classification, ECOG score, BMI, and total bilirubin levels. For OS, independent prognostic

Table 6 Comparison of training set and validation set features, *n* (%)

Characteristic	Test (*n* = 38)	Train (*n* = 88)	χ^2	*P* value
HBV DNA (IU/mL)			3.06	0.080
HBV > 2000	13 (34.21)	45 (51.14)		
HBV ≤ 2000	25 (65.79)	43 (48.86)		
HBe			0.38	0.537
Negative	28 (73.68)	60 (68.18)		
Positive	10 (26.32)	28 (31.82)		
Child-Pugh class			0.27	0.603
A	21 (55.26)	53 (60.23)		
B	17 (44.74)	35 (39.77)		
PVTT			2.62	0.106
No	27 (71.05)	49 (55.68)		
Yes	11 (28.95)	39 (44.32)		
BCLC stage			0.00	1.000
B	19 (50.00)	44 (50.00)		
C	19 (50.00)	44 (50.00)		
Metastasis			0.50	0.480
No	19 (50.00)	50 (56.82)		
Yes	19 (50.00)	38 (43.18)		
AFP (ng/mL)			0.03	0.872
> 1210	17 (44.74)	38 (43.18)		
≤ 1210	21 (55.26)	50 (56.82)		
Sex			1.34	0.247
Female	11 (28.95)	35 (39.77)		
Male	27 (71.05)	53 (60.23)		
BMI			0.02	0.880
≤ 25	15 (39.47)	36 (40.91)		
> 25	23 (60.53)	52 (59.09)		
Age (years)			1.78	0.182
< 60	18 (47.37)	53 (60.23)		
≥ 60	20 (52.63)	35 (39.77)		
ECOG			0.54	0.464
0-1	22 (57.89)	57 (64.77)		
2	16 (42.11)	31 (35.23)		
ALT (U/L)			0.22	0.642
> 40	16 (42.11)	41 (46.59)		
≤ 40	22 (57.89)	47 (53.41)		
Total bilirubin (μmol/L)			2.81	0.094
> 34	28 (73.68)	51 (57.95)		
≤ 34	10 (26.32)	37 (42.05)		
Diabetes			3.24	0.072
No	25 (65.79)	71 (80.68)		

Yes	13 (34.21)	17 (19.32)		
Hypertensive			1.12	0.289
No	13 (34.21)	22 (25.00)		
Yes	25 (65.79)	66 (75.00)		
Cirrhosis			0.01	0.911
No	22 (57.89)	50 (56.82)		
Yes	16 (42.11)	38 (43.18)		
Smoking			1.21	0.272
No	28 (73.68)	56 (63.64)		
Yes	10 (26.32)	32 (36.36)		
Alcohol			0.27	0.605
No	26 (68.42)	56 (63.64)		
Yes	12 (31.58)	32 (36.36)		
Interventional			0.94	0.332
No	23 (60.53)	45 (51.14)		
Yes	15 (39.47)	43 (48.86)		

HBV: Hepatitis B virus; PVTT: Portal vein tumor thrombosis; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-fetoprotein; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; ALT: Alanine aminotransferase.

factors were BCLC classification, AFP, PVTT, and BMI. Obese/overweight patients were more likely to experience fatigue ($P < 0.05$), while other AEs did not show significant differences ($P > 0.05$), and no deaths were associated with AEs.

Despite improvements in healthcare and living standards altering the etiology of HCC, the majority of HCC cases remain linked to HBV, particularly in Asia and Africa, including China[25-27]. The global prevalence of obesity is rising swiftly, wide[28,29], and several studies have a correlation between higher obesity levels and an elevated risk of developing HCC[30,31]. Chronic inflammatory responses to obesity, hyperglycemia, and insulin resistance significantly contribute to HCC development[32]. Obesity is widely considered to be linked with a higher risk and poorer prognosis of various malignancies. Paradoxically, retrospective studies of melanoma[19] and non-small cell lung cancer[33], have shown that higher BMI is linked to better prognosis in patients treated with ICIs, a phenomenon known as the 'obesity paradox', despite immunotherapy generally being associated with increased risk and poorer prognosis. The 'obesity paradox' refers to the phenomenon where immunotherapy, particularly ICI-based treatments, enhances survival rates in obese cancer patients.

The exact mechanism behind the "obesity paradox" remains unclear. Researchers suggest that obesity elevates leptin production, enhancing CD8+ tumor-infiltrating lymphocytes' function, metabolism, and activity, while also increasing PD-1 expression in immune cells and promoting PD-1/PD-L1 interactions. Thus, in obese patients with cancer, anti-PD-1/PD-L therapy can block enhanced PD-1/PD-L1 interactions and activate the immune response more effectively[21]. Although there are limited studies on the "obesity paradox" in HCC immunotherapy, our subgroup analysis suggests that obesity may positively impact the efficacy of immunotherapy. Adipokines such as leptin, lipocalin, and lecithin have been implicated in obesity-associated HCC[34], and these may influence the HCC microenvironment and immunotherapy response. Evidence indicates that antiangiogenic drugs are less effective in obese patients. Excessive obesity is linked to increased levels of vascular endothelial growth factor, a crucial regulator of tumor angiogenesis and a primary target for drug therapy. Thus, biologically, BMI may serve as a potential predictive biomarker[35,36].

This study presents new evidence suggesting that a high BMI may be linked to a better prognosis for patients with HBV-related HCC. While obesity/overweight elevates the risk of certain cancers, such as breast cancer, it may enhance the prognosis of HBV-associated HCC patients undergoing treatment with lenvatinib plus camrelizumab. However, according to the ECOG score, the general situation of overweight/obese patient is superior to that of non-overweight patient (ECOG: 47% *vs* 30%). Despite the lack of statistical significance, the overall conditions of the two groups remain important. The present findings have significant implications for nursing practice. By examining the relationship between baseline BMI and treatment outcomes, this study provides valuable insights that can assist nurses in designing more personalized and evidence-based care plans. In the process of managing a patient's BMI, it is crucial for nurses to perform a comprehensive assessment that encompasses not only the patient's medication regimen but also their overall health status and psychological well-being. Based on these thorough assessments, nurses can develop a tailored care plan that includes key components such as dietary adjustments, a balanced exercise routine, adherence to regular schedules, and psychological support. These interventions are aimed at fostering a healthy lifestyle and optimizing the patient's BMI, which can contribute to better treatment outcomes. In addition, nurses must remain vigilant in monitoring patients for nutritional risks, ensuring that they receive adequate nutritional support and timely interventions. This proactive approach is essential for maintaining the patient's overall health and supporting their recovery process. By closely

Table 7 Treatment-related adverse events in patients with hepatocellular camrelizumab, *n* (%)

Variables	BMI < 25 kg/m² (*n* = 51)	BMI ≥ 25 kg/m² (*n* = 75)	χ^2	*P* value
All grades: Rash	43 (84.31)	56 (74.67)	1.68	0.195
All grades: Nausea	26 (50.98)	30 (40.00)	1.48	0.223
All grades: Diarrhea	13 (25.49)	19 (25.33)	0.00	0.984
All grades: Fatigue	5 (9.80)	20 (26.67)	5.43	0.020
All grades: Myocarditis	3 (5.88)	9 (12.00)	0.70	0.401
All grades: Hyperbilirubinemia	9 (17.65)	10 (13.33)	0.44	0.507
All grades: Hypertension	4 (7.84)	10 (13.33)	0.93	0.336
All grades: Leukopenia	4 (7.84)	10 (13.33)	0.93	0.336
All grades: Thrombocytopenia	7 (13.73)	10 (13.33)	0.00	0.950
All grades: RCCEP	10 (19.61)	11 (14.67)	0.53	0.465
All grades: Neutropenia	4 (7.84)	10 (13.33)	0.93	0.336
All grades: Proteinuria	4 (7.84)	9 (12.00)	0.57	0.451
All grades: Hypothyroidism	5 (9.80)	8 (10.67)	0.02	0.876
All grades: Elevated ALT	6 (11.76)	10 (13.33)	0.07	0.795
All grades: Elevated AST	6 (11.76)	7 (9.33)	0.19	0.660
≥ 3 grades: Rash	5 (9.80)	10 (13.33)	0.36	0.548
≥ 3 grades: Nausea	2 (3.92)	6 (8.00)	0.30	0.583
≥ 3 grades: Diarrhea	0 (0.00)	4 (5.33)	1.34	0.247
≥ 3 grades: Fatigue	3 (5.88)	11 (14.67)	2.37	0.124
≥ 3 grades: Myocarditis	0 (0.00)	3 (4.00)	0.72	0.395
≥ 3 grades: Hyperbilirubinemia	0 (0.00)	3 (4.00)	0.72	0.395
≥ 3 grades: Hypertension	0 (0.00)	1 (1.33)	-	1.000
≥ 3 grades: Leukopenia	0 (0.00)	2 (2.67)	-	0.514
≥ 3 grades: Thrombocytopenia	0 (0.00)	2 (2.67)	-	0.514
≥ 3 grades: RCCEP	1 (1.96)	3 (4.00)	0.02	0.902
≥ 3 grades: Hypothyroidism	1 (1.96)	2 (2.67)	0.00	1.000
≥ 3 grades: Elevated ALT	1 (1.96)	3 (4.00)	0.02	0.902
≥ 3 grades: Elevated AST	3 (5.88)	4 (5.33)	0.00	1.000
≥ 3 grades: Neutropenia	0 (0.00)	0 (0.00)	-	-
≥ 3 grades: Proteinuria	0 (0.00)	0 (0.00)	-	-

BMI: Body mass index; RCCEP: Reactive cutaneous capillary endothelial proliferation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

observing and addressing these factors, nurses can play a critical role in improving patient outcomes and enhancing the quality of care provided.

In this study, the findings from a multivariate Cox proportional hazards regression analysis demonstrated that BCLC classification, AFP levels, PVTT, and BMI function as independent prognostic factors for OS. Following this, we created a nomogram prediction model that integrated these independent risk factors. The analysis indicated that BMI had the most considerable impact on OS, with AFP levels and BCLC classification following in significance, while PVTT was observed to have the least influence. To assess the validity of the nomogram prediction model, we calculated the concordance index (c-index) and produced a calibration curve. The c-index for the validation set of the nomogram model in our study was 0.722. The calibration curves illustrated that our model was in close agreement with the actual data, thereby affirming its reliability and precision. However, the limited sample size hindered external validation. Subgroup analysis based on BMI categories [normal weight (18.5-24.9 kg/m²), overweight (25-30 kg/m²), and obese (≥ 30 kg/m²)] showed that overweight individuals had the best PFS and OS, followed by those who were obese, while normal weight patients exhibited the least favorable long-term prognosis. This finding contrasts with the study by Vithayathil *et al*[37] reported comparable efficacy

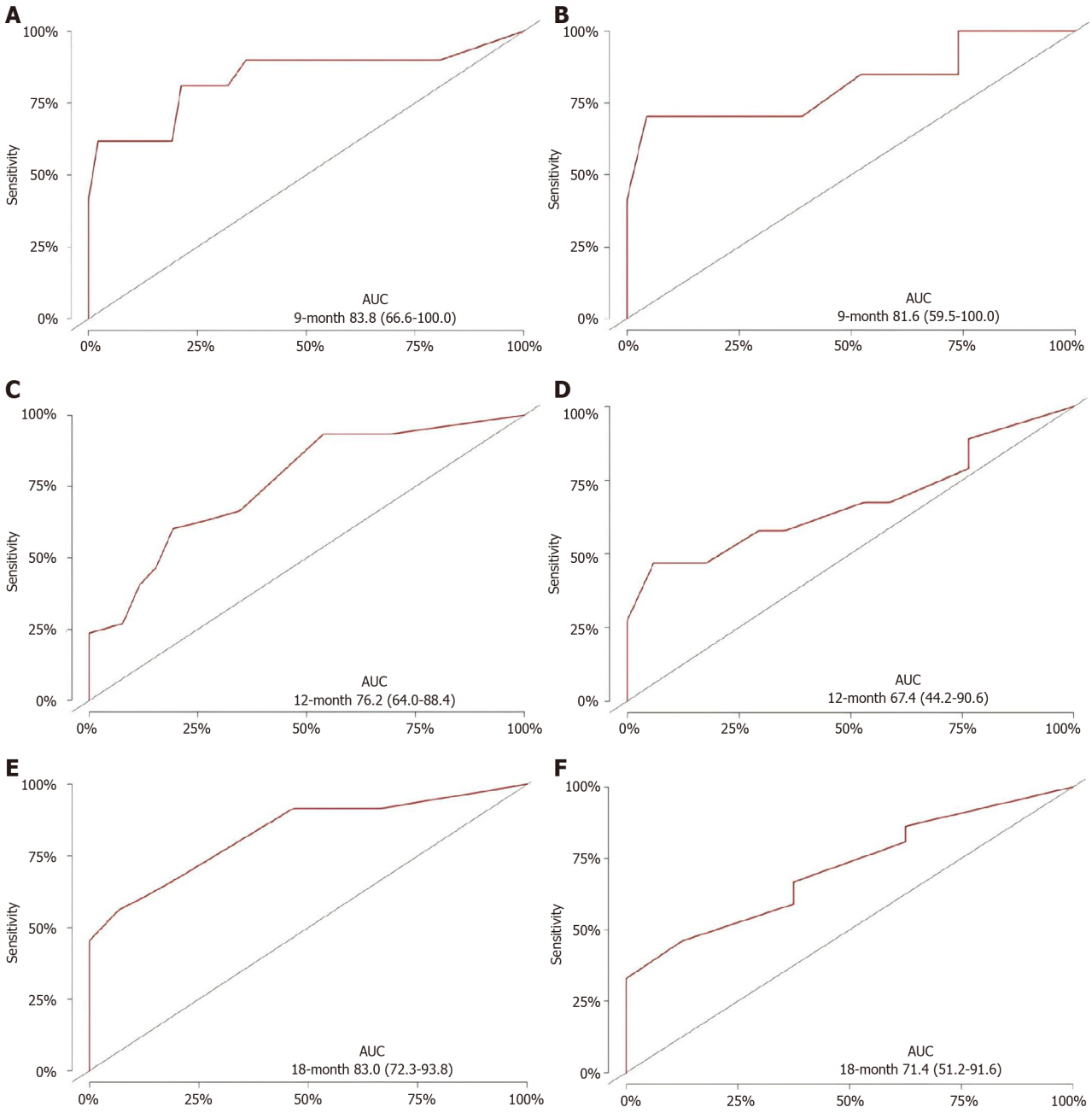

Figure 4 Graph depicting the operating characteristic evaluation plot for a prognostic model. A: Graph showing the training set receiver operating characteristic (ROC) evaluation plot for 9-month prognostic prediction model; B: Graph showing the validation set ROC evaluation plot for 9-month prognostic prediction model; C: Graph showing the training set ROC evaluation plot for 12-month prognostic prediction model; D: Graph showing the validation set ROC evaluation plot for 12-month prognostic prediction model; E: Graph showing the training set ROC evaluation plot for the 18-month prognostic prediction model; F: Graph showing the validation set ROC evaluation plot for the 18-month prognostic prediction model. AUC: Area under the receiver operating characteristic curve.

for both overweight/obese and non-overweight/obese patients treated with atirizumab plus bevacizumab. This may be due to the following reasons. First, the study by Vithayathil *et al*[37] included patients from Western countries, where nonalcoholic fatty liver disease was the predominant etiology of HCC. In contrast, the patients included in the present study were all from China and had hepatitis B-associated HCC. Previous studies have shown differences in the efficacy of targeted immunotherapy between nonviral and hepatitis B-associated HCC. Second, the different treatment regimens between our study and that of Vithayathil *et al*[37] may also have influenced the observed efficacy.

Our study also has some limitations. First, this is a retrospective analysis, which may limit the generalizability of our findings. Second, we exclusively examined the lenvatinib and camrelizumab regimen to minimize treatment bias. While this focused approach strengthens our analysis, it also means that our conclusions regarding other PD-1/PD-L1 inhibitors and targeted agents require further validation in future studies. Third, the exclusion of certain patients, while necessary to refine our analysis, may have reduced the statistical power of the study, potentially affecting the robustness of our results. Fourth, the retrospective nature of the study inherently introduces the possibility of selection and information biases, which could influence the reliability of the findings. Additionally, despite extensive searches of external datasets, we found no reports on the impact of BMI on the efficacy of lenvatinib combined with camrelizumab therapy in HCC

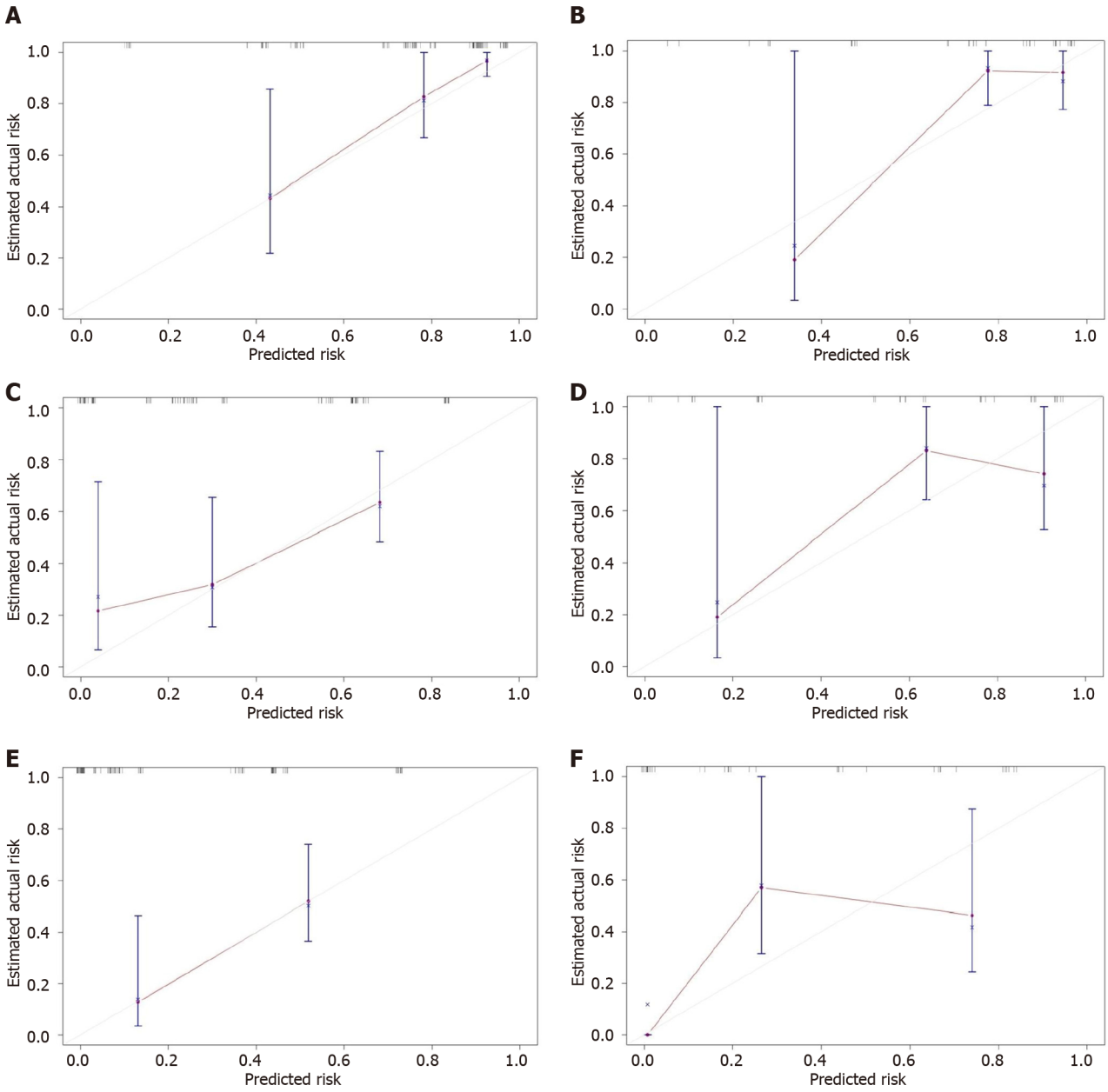

Figure 5 Graph illustrating the calibration plots for a prognostic model. A: Calibration plots for the training set 9-month overall survival (OS); B: Calibration plots for the validation set 9-month OS; C: Calibration plots for the training set 12-month OS; D: Calibration plots for the validation set 12-month OS; E: Calibration plots for the training set 18-month OS; F: Calibration plots for validation set 18-month OS.

patients. This lack of external data meant that we could not perform a validation against an independent dataset. To address these concerns, we plan to conduct a multicenter prospective study in the future to validate our model more comprehensively. Lastly, numerous phase III randomized controlled trials and high-quality meta-analyses have demonstrated that patients with hepatitis B-associated HCC experience improved outcomes with targeted combination immunotherapy compared to those with non-viral HCC. To eliminate the confounding effects of etiology (HBV *vs* non-viral) on the efficacy of lenvatinib combined with camrelizumab therapy, we included only patients with hepatitis B-associated HCC in our study. However, this decision, coupled with the limited sample size, may have introduced additional bias. Future studies should aim to include a broader patient population to further validate our findings.

CONCLUSION

Our study indicates that overweight or obese patients with HBV-associated HCC treated with lenvatinib and camrelizumab exhibit improved prognosis. In addition, subgroup analysis showed that obese patients had the best long-term prognosis.

FOOTNOTES

Author contributions: Wang YQ, Pan D, Han ZX, and Liu HN contributed to the conceptualization, writing-review and editing of this manuscript; Wang YQ and Liu HN were responsible for the methodology of this study; Wang YQ contributed to the formal analysis of this manuscript; Wang YQ, Pan D, and Yao ZY took part in the writing-original draft; Wang YQ, Han ZX, and Liu HN contributed to the project administration; Pan D, Yao ZY, and Li YQ were involved in the investigation of this manuscript; Pan D, Qu PF, and Wang RB took part in the data curation of this study; Pan D, Han ZX, and Liu HN contributed to the supervision of this manuscript; Li YQ, Qu PF, Gu QH, and Jiang J were responsible for the validation of this manuscript; Yao ZY contributed to the visualization of this article; Li YQ took part in the resources; Han ZX and Liu HN were involved in the supervision of this study. Wang YQ and Pan D contributed equally to the manuscript, they are co-first authors of this manuscript. Han ZX and Liu HN contributed to this manuscript equally, they are co-corresponding authors of this study.

Institutional review board statement: This research was carried out following the Declaration of Helsinki and received approval from the Ethics Committee at the Affiliated Hospital of Xuzhou Medical University (approval No. XYFY2022-KL207-01).

Informed consent statement: Given the retrospective design of this investigation, the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University granted us an exemption from obtaining written informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data included in this study can be obtained from the corresponding author.

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