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ORIGINAL RESEARCH

Predictive Modeling and Mendelian Randomization for Identifying HCC Patients with High Response to TACE with Atezolizumab and Bevacizumab

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Purpose: Hepatocellular carcinoma (HCC) is a major cause of cancer deaths. This study developed a clinical prediction model to identify patients likely to respond to transcatheter arterial chemoembolization (TACE) combined with atezolizumab and bevacizumab (Atez/Bev), using Mendelian randomization (MR) to validate the therapeutic effect on HCC via *PDCD1, CD274*, and *VEGFA*.

Patients and Methods: A retrospective analysis of 258 unresectable HCC patients administered TACE, with or without Atez/Bev therapy, was conducted. Propensity score matching (PSM) was employed to compare objective response rates (ORRs). A predictive model for response to TACE+Atez/Bev was developed using logistic regression and validated. MR was used to analyze the causal relationships between the *PDCD1, CD274, VEGFA* genes and Atez/Bev efficacy.

Results: After PSM, the TACE+Atez/Bev group demonstrated significantly higher ORR compared with the TACE group (73.8% vs 56.3%, p=0.031). Multivariate logistic regression identified hepatic vein invasion, albumin (ALB), and platelets (PLT) as key outcome factors, which were used to develop a nomogram with AUCs of 0.81 and 0.89 in the training and validation cohorts, respectively. Calibration curve analysis showed good agreement with actual outcomes, and decision curve analysis highlighted the nomogram's potential for patient selection. MR analyses provided genetic support for the therapeutic target, revealing a significant protective association between *PDCD1* inhibition and HCC risk (inverse-variance weighted, DrugOR=0.713, 95% CI: 0.599–0.848, p<0.001). This finding substantiates the biological rationale for the *PDCD1* inhibitor atezolizumab. No significant associations were found for *CD274* or *VEGFA*.

Conclusion: We developed a predictive model for TACE+Atez/Bev therapy, enabling effective patient screening. MR validated *PDCD1*'s role in HCC immunotherapy at the genetic level.

Keywords: atezolizumab, bevacizumab, TACE, nomogram, Mendelian randomization

Introduction

Hepatocellular carcinoma (HCC) is one of the most aggressive malignancies, presenting a significant challenge to public health globally. It ranks sixth among cancers in terms of incidence and represents the third leading cause of cancer-related mortality worldwide. In 2020 alone, an estimated 900,000 new cases of HCC were diagnosed, with approximately 830,000 deaths attributed to the disease.[1] This highlights the critical need for effective treatment strategies, particularly as HCC incidence continues to rise, especially in regions with high rates of chronic hepatitis B and C infections, as well as cirrhosis, the most significant risk factor for HCC.

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For patients diagnosed with early-stage HCC, surgical resection or liver transplantation remains the treatment of choice, offering the potential for curative outcomes. However, these treatments are only viable for a small proportion of patients, as many cases are diagnosed at more advanced stages. Studies have shown that around 70% of HCC patients present with advanced disease, which renders them ineligible for curative surgical interventions.[2] Furthermore, even patients diagnosed at earlier stages may not be eligible for surgery due to various factors such as large tumor size, unfavorable tumor location, and advanced age, all of which can complicate surgical resection.[3] This underscores the need for alternative therapies that can confer clinical benefits to patients not eligible for surgery or transplantation.

For patients with intermediate to advanced HCC, transcatheter arterial chemoembolization (TACE) has become an increasingly applied treatment option. TACE involves delivering chemotherapeutics directly into the hepatic artery and embolizing tumor-feeding vessels, which results in ischemic tumor necrosis.[4] While TACE is effective for many patients, its efficacy is limited by several factors. Firstly, not all patients respond well to TACE, with studies reporting that only 20–60% of patients experience significant benefits from this treatment when used alone.[5] Furthermore, as a localized treatment, TACE cannot address extrahepatic metastases, which limits its effectiveness in patients with disseminated disease or liver metastases.

In recent years, immunotherapy combined with targeted therapy has emerged as a promising treatment strategy for advanced HCC. A landmark study conducted in 2020, the IMbrave 150 trial, proposed the combination of atezolizumab and bevacizumab (Atez/Bev) as the new standard for first-line treatment of advanced HCC.[6] The combination therapy showed an objective response rate (ORR) of 30% in patients with intermediate to advanced HCC, which increased to 44% in patients with BCLC stage B, surpassing other available systemic treatment regimens.[7]

Recent findings[8] indicated that combining interventional therapy, such as TACE, with immunotherapy and targeted therapies like Atez/Bev can provide better clinical outcomes in patients with advanced HCC. However, a significant challenge remains: there are currently no established criteria or predictive tools to identify which patients may benefit the most from the combination of TACE and Atez/Bev therapy.[9] Without such a tool, clinicians face a huge challenge in selecting the right candidates for this combined treatment, potentially leading to either suboptimal treatment outcomes or unnecessary side effects in cases unlikely to respond.

To address this gap, we developed a predictive model based on pre-treatment clinical data, aimed at identifying HCC cases who are more likely to respond positively to TACE combined with Atez/Bev therapy (TACE+Atez/Bev). This model incorporates a variety of clinical factors, including tumor characteristics, liver function indexes, and patient demographics, to predict treatment responses more accurately. By improving the ability to select patients who are most likely to benefit from this combination therapy, we hope to enhance treatment outcomes while also reducing the economic burden on patients who may have limited response and otherwise undergo unnecessary or ineffective treatments.

Ultimately, the goal of this approach is twofold: to improve the therapeutic efficacy of TACE+Atez/Bev treatment and to help clinicians make more informed decisions regarding treatment options. Accurately identifying patients who are likely to benefit from the treatment can provide more personalized and effective care, reduce unnecessary healthcare expenses, and ultimately improve the survival and quality of life of HCC patients.

Methods

Patients

This retrospective study included 258 patients with unresectable HCC who underwent TACE or TACE+Atez/Bev in The Third Affiliated Hospital, Sun Yat-sen University between January 1, 2020 and December 31, 2023. Of these, 141 patients were included in the TACE group and 117 in the TACE+Atez/Bev group. Inclusion criteria were: (1) unresectable HCC; (2) completion of enhanced MRI/CT scans of the upper abdomen within two weeks prior to treatment at the study site; (3) a minimum follow-up period of 3–6 months after the first TACE or TACE+Atez/Bev treatment at the institution. Exclusion criteria were: (1) previous antitumor treatments; (2) primary malignant tumors in other organs or dysfunction of vital organs such as the heart, brain, or kidneys; (3) incomplete imaging or laboratory data or loss to follow-up. The workflow of this study is shown in Supplementary Figure S1.

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of The Third Affiliated Hospital, Sun Yat-sen University (No. II2025-498-01). The requirement for informed consent was waived due to the retrospective nature of the study.

Unresectable HCC

Unresectable HCC was defined based on the 2023 guidelines from the American Association for the Study of Liver Diseases (AASLD) and the 2023 clinical practice guidelines from the National Comprehensive Cancer Network (NCCN):[10] intermediate HCC, Child-Pugh class A or B liver function, large or multiple nodular HCC, and no major vascular invasion or extrahepatic metastasis; advanced HCC, Child-Pugh class A or B liver function, macroscopic vascular invasion, extrahepatic spread, or cancer-related symptoms (performance status 1–2).

Assessment Before Treatment

All patients underwent routine laboratory testing before treatment, including the following: complete blood count (lymphocytes, neutrophils and platelets [PLT]), liver function indexes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], total bilirubin [TBIL], albumin [ALB]), coagulation function indexes (prothrombin time [PT]), hepatitis virus infection tests (Hepatitis B surface antigen [HBsAg], hepatitis B virus DNA load [HBV DNA load]), and tumor marker (alpha-fetoprotein [AFP]). Additionally, tumor burden was assessed by ultrasound, enhanced CT, and enhanced MRI prior to treatment.

Follow-Up

All patients were followed up either in outpatient clinics or during hospitalization every 21 to 30 days for a minimum of 3 months to monitor tumor changes. Follow-up assessments included physical exams, liver function tests, tumor marker tests, and enhanced CT or MRI scans of the liver, gallbladder, pancreas, and spleen. According to mRECIST criteria[11] the following definitions were adopted: complete response (CR), disappearance of all arterial-phase enhancements of lesions; partial response (PR), reduction of $\geq 30\%$ in the sum of the diameters of all arterial-phase enhancements; stable disease (SD), tumors not meeting criteria for PR or progression; progressive disease (PD), increase of $\geq 20\%$ in the sum of the diameters of all arterial-phase enhancements or appearance of new lesions. The ORR included patients achieving CR or PR.

MR Analysis

The summary data for HCC were derived from GWAS summary data, which included 197,611 East Asian cases. According to the DrugBank database (https://go.drugbank.com/), the targets of atezolizumab are *PDCD1* and *CD274*, while the target of bevacizumab is *VEGFA*. Using the eQTLGen database (https://www.eqtlgen.org/cis-eqtls.html), instrumental variables for targeting *CD274, PDCD1*, and *VEGFA* in HCC treatment were identified. These variables were single nucleotide polymorphisms (SNPs) located within ±100 kb of the *PDCD1, CD274*, or *VEGFA* locus and associated with gene expression ($p < 5$ e-08). To minimize the impact of strong linkage disequilibrium (LD), an LD threshold of $r^2 = 0.3$ was applied. A total of 7 significant SNPs for *PDCD1*, 7 for *CD274*, and 14 for *VEGFA* were retained for analysis.

Instrumental variables for various drug target genes were matched to outcomes, and analyses were conducted using inverse variance weighting (IVW), MR-Egger, weighted median, simple mode, and weighted mode methods, with IVW being the primary method. Heterogeneity was assessed by the MR-Egger and IVW methods, and Cochrane's Q test was employed to evaluate the heterogeneity of genetic instruments ($p > 0.05$ indicated no heterogeneity). Horizontal pleiotropy was tested by MR-Egger regression ($p > 0.05$ indicated no horizontal pleiotropy).

The leave-one-out method was used to ensure no single SNP significantly influenced the results, sequentially excluding each SNP and comparing IVW results to those obtained using all variants. Data analysis was performed with single-sample MR and the MR-PRESSO package in R version 4.3.0.

Statistical Analysis

Missing data were handled by complete-case analysis with listwise deletion. The proportion of missing values across all study variables was less than 5%, which is generally considered an acceptable threshold for this method. Propensity score matching (PSM) was performed using a 1:1 matching ratio to compare the TACE and TACE+Atez/Bev groups. The HCC patients treated with TACE+Atez/Bev were randomly partitioned into a training cohort (70%) for model construction and an internal validation cohort (30%). This ratio is a widely adopted standard in prediction model studies,[12,13] aiming to balance the need for ample data to reliably estimate model parameters with the necessity of reserving a sufficiently large, independent set for unbiased evaluation. The independent two-sample *t*-test, chi-square (χ^2) test, or Fisher's exact test was used to assess differences in clinical characteristics between the TACE and TACE+Atez/Bev groups, as well as between the training and validation cohorts. Variables with $p < 0.1$ in univariate binary logistic regression analysis were included in multivariate binary logistic regression to identify independent predictors. The final nomogram model was constructed using the "rms" package in R. Model performance was assessed using ROC curves, calibration curves, and decision curve analysis (DCA). To further evaluate the model's predictive value, patients administered TACE+Atez/Bev were stratified into the high- and low-response groups based on the cutoff value, and their outcomes were compared.

A *p*-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using R (version 4.3.0) with the "stats", "rms", "rmda", "MatchIt", and "pROC" packages.

Results

Baseline Characteristics of the TACE and TACE+Atez/Bev Groups

This study included 141 patients with unresectable HCC treated with TACE and 117 treated with TACE+Atez/Bev. Before PSM, compared with the TACE group, patients in the TACE+Atez/Bev group were younger (53.94 ± 11.39 vs 57.68 ± 12.30, $p = 0.013$), had larger tumor diameters (94.23 ± 41.72 mm vs 75.69 ± 44.75 mm, $p = 0.001$), and had more tumors located in the left liver (81.20% vs 19.15%, $p < 0.001$). Additionally, the TACE+Atez/Bev group showed less portal vein invasion (21.37% vs 41.84%, $p = 0.001$), less hepatic vein invasion (25.64% vs 46.10%, $p = 0.001$), fewer distant metastases (85.47% vs 95.74%, $p = 0.008$), and more cases classified as BCLC stage C or D (87.18% vs 75.80%, $p = 0.048$). This group also included fewer patients with ascites (64.10% vs 45.39%, $p = 0.004$), fewer with portal hypertension (41.88% vs 60.28%, $p = 0.005$), and more with AFP levels ≥ 200 ng/mL (57.26% vs 41.13%, $p = 0.014$). Biochemically, the TACE+Atez/Bev group exhibited lower bilirubin levels (15.61 ± 9.72 μmol/L vs 24.40 ± 32.77 μmol/L, $p = 0.005$), lower ALBI scores (−2.40 ± 0.60 vs −1.95 ± 0.67, $p < 0.001$), shorter prothrombin times (13.79 ± 0.96 s vs 14.72 ± 2.03 s, $p < 0.001$), higher proportions of Child-Pugh class A cases (85.47% vs 60.99%, $p < 0.001$), higher lymphocyte counts (1.59 ± 0.83 vs 1.40 ± 0.56, $p = 0.025$), and higher platelet levels (205.44 ± 98.84 vs 172.25 ± 99.95, $p = 0.008$) compared with the TACE group (Table 1).

Table 1 Baseline Characteristics of the Patients in the TACE and TACE+Atez/Bev Groups Before and After PSM

Variables	Before PSM			After PSM		
	TACE (n = 141)	TACE+Atez/Bev (n = 117)	*p*-value	TACE (n = 80)	TACE+Atez/Bev (n = 80)	*p*-value
Gender n (%)			0.148			0.608
Male	121 (85.82)	108 (92.31)		70 (87.50)	73 (91.25)	
Female	20 (14.18)	9 (7.29)		10 (12.50)	7 (8.75)	
Age (years) (mean±SD)	57.68 ± 12.30	53.94 ± 11.39	0.013	58.09±12.90	54.98±10.70	0.099
Tumor size (cm) n (%)	75.69 ± 44.75	94.23 ± 41.72	0.001	84.76±39.12	87.80±39.84	0.627
Tumor position n (%)			< 0.001			< 0.001
Left liver	27 (19.15)	95 (81.20)		12 (15.00)	68 (85.00)	
Right liver	114 (80.85)	22 (18.80)		68 (85.00)	12 (15.00)	

(*Continued*)

Table 1 (Continued).

Variables	Before PSM			After PSM		
	TACE (n = 141)	TACE+Atez/Bev (n = 117)	*p*-value	TACE (n = 80)	TACE+Atez/Bev (n = 80)	*p*-value
Tumor number n (%)			0.509			0.739
One	45 (31.91)	32 (27.35)		26 (32.50)	29 (36.25)	
Two or more	96 (68.09)	85 (72.65)		54 (67.50)	51 (63.75)	
Portal vein invasion n (%)			0.001			1.00
No	59 (41.84)	25 (21.37)		21 (26.25)	20 (25.00)	
Yes	82 (58.16)	92 (78.63)		59 (73.75)	60 (75.00)	
Hepatic vein invasion n (%)			0.001			0.502
No	65 (46.10)	30 (25.64)		29 (36.25)	24 (30.00)	
Yes	76 (53.90)	87 (74.56)		51 (63.75)	56 (70.00)	
Bile duct invasion n (%)			0.367			0.764
No	133 (94.33)	106 (90.60)		75 (93.75)	73 (91.25)	
Yes	8 (5.67)	11 (9.40)		5 (6.25)	7 (8.75)	
Lymphatic metastasis n (%)			0.992			0.764
No	129 (91.49)	108 (92.31)		73 (91.25)	75 (93.75)	
Yes	12 (8.51)	9 (7.69)		7 (8.75)	5 (6.25)	
Distant metastasis n (%)			0.008			0.764
No	135 (95.74)	100 (85.47)		75 (93.75)	73 (91.25)	
Yes	6 (4.26)	17 (14.53)		5 (6.25)	7 (8.75)	
BCLC stage n (%)			0.048			0.552
0 or A	9 (6.38)	6 (5.13)		5 (6.25)	4 (5.00)	
B	25 (17.73)	9 (7.69)		11 (13.75)	7 (8.75)	
C or D	107 (75.89)	102 (87.18)		64 (80.00)	69 (86.25)	
Cirrhosis n (%)			0.233			1.00
No	42 (29.79)	44 (37.61)		33 (41.25)	34 (42.50)	
Yes	99 (70.21)	73 (62.39)		47 (58.75)	46 (57.50)	
Ascites n (%)			0.004			1.00
No	64 (45.39)	75 (64.10)		50 (62.50)	50 (62.50)	
Yes	77 (54.61)	42 (35.90)		30 (37.50)	30 (37.50)	
Portal hypertension, n (%)			0.005			0.261
No	56 (39.72)	68 (58.12)		43 (53.75)	51 (63.75)	
Yes	85 (60.28)	49 (41.88)		37 (46.25)	29 (36.25)	
Hepatitis, n (%)			0.437			1
No	16 (11.35)	9 (7.69)		7 (8.75)	7 (8.75)	
Yes	125 (88.65)	108 (92.31)		73 (91.25)	73 (91.25)	
HBV DNA load, n (%)			0.635			0.417
<100 UL/mL	57 (40.43)	43 (36.75)		28 (35.00)	34 (42.50)	
≥ 100 UL/mL	84 (59.57)	74 (63.25)		52 (65.00)	46 (57.50)	
AFP, n (%)			0.014			0.874
<200 ng/mL	83 (58.87)	50 (42.74)		40 (50.00)	42 (52.50)	
≥ 200 ng/mL	58 (41.13)	67 (57.26)		40 (50.00)	38 (47.50)	
ALT (U/L) (mean±SD)	48.65 ± 47.50	55.80 ± 67.15	0.319	47.56±41.76	47.85±32.82	0.961
AST n (%)			0.546			1.00
≤ 80 U/L	107 (75.89)	84 (71.79)		61 (76.25)	60 (75.00)	
>80 U/L	34 (24.11)	33 (28.21)		19 (23.75)	20 (25.00)	

(*Continued*)

Table 1 (Continued).

Variables	Before PSM			After PSM		
	TACE (n = 141)	**TACE+Atez/Bev (n = 117)**	***p*-value**	**TACE (n = 80)**	**TACE+Atez/Bev (n = 80)**	***p*-value**
GGT (U/L) (mean±SD)	175.02 ± 203.57	204.58 ± 194.71	0.237	188.13±232.71	211.12±217.61	0.52
TBIL (μmol/L) (mean±SD)	24.40 ± 32.77	15.61 ± 9.72	0.005	15.72±10.52	16.57±11.16	0.622
ALB n (%)			0.193			0.867
<35 g/L	63 (44.68)	42 (35.90)		26 (32.50)	28 (35.00)	
≥ 35 g/L	78 (55.32)	75 (64.10)		54 (67.50)	52 (65.00)	
ALBI (mean±SD)	−1.95 ± 0.67	−2.40 ± 0.60	< 0.001	−2.19±0.55	−2.41±0.67	0.024
PT (s) (mean±SD)	14.72 ± 2.03	13.79 ± 0.96	< 0.001	13.97±1.14	13.93±1.02	0.792
Child Pugh grade n (%)			< 0.001			1.00
A	86 (60.99)	100 (85.47)		66 (82.50)	65 (81.25)	
B	55 (39.01)	17 (14.53)		14 (17.50)	15 (18.75)	
Lymphocyte ($\times 10^9$) (mean±SD)	1.40 ± 0.56	1.59 ± 0.83	0.025	1.46±0.56	1.57±0.93	0.357
Neutrophil ($\times 10^9$) (mean±SD)	3.94 ± 2.24	4.13 ± 2.03	0.478	4.36±2.12	4.15±2.07	0.538
PLT ($\times 10^9$) (mean±SD)	172.25 ± 99.95	205.44 ± 98.84	0.008	201.00±103.84	209.19±98.88	0.610
PLR (mean±SD)	131.13 ± 72.62	143.82 ± 80.13	0.184	149.12±78.47	150.93±81.15	0.886
NLR (mean±SD)	3.24 ± 2.60	3.09 ± 2.90	0.646	3.28±1.74	3.28±3.38	0.986
ALRI (mean±SD)	65.18 ± 87.47	59.05 ± 68.11	0.537	56.02±63.69	56.85±70.36	0.938
ANRI (mean±SD)	21.98 ± 21.53	22.32 ± 26.00	0.908	18.42±18.64	19.07±18.46	0.826
Remission n (%)			0.02			0.020
No	66 (46.81)	33 (28.21)		35 (43.75)	21 (26.25)	
Yes	75 (53.19)	84 (71.79)		45 (56.25)	59 (73.75)	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ALB, albumin; ALBI, albumin-bilirubin; ALRI, albumin-to-lymphocyte ratio index; ANRI, albumin-to-neutrophil ratio index; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; PSM, propensity score matching; PT, prothrombin time; PLT, platelet; PLR, platelet to lymphocyte ratio; TACE, transcatheter arterial chemoembolization; Atez/Bev, atezolizumab and bevacizumab; TBIL, total bilirubin.

After PSM based on clinical variables such as tumor size, tumor number, portal vein invasion, hepatic vein invasion, bile duct invasion, lymphatic metastasis, distant metastasis, BCLC stage, AFP levels, cirrhosis, ascites, hepatitis, TBIL, ALB, PT, Child-Pugh grade, and PLT, 80 matched patients were obtained in both the TACE and TACE+Atez/Bev groups. Following PSM, aside from tumor position ($p < 0.001$) and ALBI score ($p = 0.024$), there were no significant differences in the remaining clinical variables between the two groups (Table 1).

After PSM, the ORR was significantly higher in the TACE+Atez/Bev group compared with the TACE group (73.8% vs 56.3%, $p = 0.031$) (Figure 1). Representative imaging changes before and after treatment for the TACE and TACE +Atez/Bev groups are presented in Figure 2.

Construction of the Nomogram Model

In this study, some patients with unresectable HCC did not achieve tumor burden reduction after TACE+Atez/Bev therapy and even experienced disease progression. To address this problem, we explored clinical factors associated with the efficacy of TACE+Atez/Bev and developed a prediction model to identify HCC patients with a high likelihood of responding to this treatment.

Patients in the TACE+Atez/Bev group were randomly divided into the training (n = 82) and validation (n = 35) cohorts at a 7:3 ratio. Compared with the training cohort, the validation cohort had fewer patients with more than one tumor (85.71% vs 65.07%, $p = 0.038$), fewer BCLC stage 0 or A cases (7.32% vs 0, $p < 0.001$), and fewer patients with an HBV DNA load ≥ 100 UL/mL (92.68% vs 65.71%, $p < 0.001$). Additionally, the validation cohort exhibited lower levels of ALT (153.42 ± 218.31 U/L vs 97.83 ± 70.61 U/L, $p < 0.001$), GGT (406.12 ± 343.49 U/L vs 342.68 ± 267.85 U/L, $p < 0.001$), and TBIL (23.21 ± 19.38 μmol/L vs 17.57 ± 6.75 μmol/L, $p < 0.001$) (Table 2).

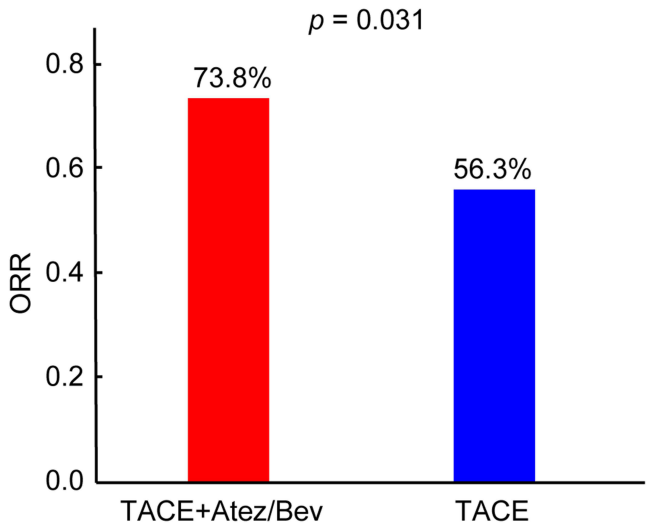

Figure 1 ORRs in the TACE and TACE+Atez/Bev groups after PSM.
Abbreviations: ORR, objective response rate; TACE, transcatheter arterial chemoembolization; Atez/Bev, atezolizumab and bevacizumab.

In the training cohort, univariate and multivariate logistic regression analyses were performed to identify clinical factors associated with response to TACE+Atez/Bev treatment in unresectable HCC. Univariate logistic regression analysis revealed that hepatic vein invasion, ascites, AST, lymphocyte count, and PLT were significantly associated with treatment response ($p < 0.05$).

Multivariate logistic regression analysis identified hepatic vein invasion (OR = 5.530; 95% CI, 1.126–32.177; $p = 0.041$), ALB (OR = 7.761; 95% CI, 1.246–59.544; $p = 0.034$), and PLT (OR = 1.013; 95% CI, 1.004–1.026; $p = 0.017$) as independent factors promoting response to TACE+Atez/Bev treatment in unresectable HCC (Table 3).

Based on the 3 clinical features with $p < 0.05$ identified in multivariate logistic regression analysis, a nomogram model was developed (Figure 3A) to predict the likelihood of tumor response to TACE+Atez/Bev treatment in patients with unresectable HCC. Each subtype of the selected clinical features was assigned a score in the nomogram. By summing the scores of all variables and referencing the total points scale, the predicted probability of tumor response could be easily determined.

Calibration and Verification of the Nomogram

Calibration curve analysis demonstrated that the predicted probabilities of tumor response closely aligned with the actual outcomes (Figure 3B and C). ROC curve analysis showed that the nomogram exhibited strong predictive performance, with AUCs of 0.81 (95% CI, 0.70–0.92) and 0.89 (95% CI, 0.79–0.99) in the training and validation cohorts, respectively (Figure 3D and E). The optimal operating point on the ROC curve for the training cohort was determined as the "cut-off value", which was 0.957. The selected cut-off (0.957) balances sensitivity (0.746) and specificity (0.870) in the training cohort, prioritizing the reliable identification of high-response patients for close monitoring while minimizing false-positive calls to prevent unnecessary treatment in low-risk patients, thereby meeting clinical needs for precise stratification. DCA further indicated that the nomogram was a valuable predictive tool for identifying patients likely to respond to TACE+Atez/Bev treatment (Figure 3F).

Using the cut-off value, patients undergoing TACE+Atez/Bev treatment were divided into the high-response (n = 63) and low-response (n = 54) groups. The high-response group achieved an ORR of 80.95%, significantly higher than the value of 61.11% observed in the low-response group ($p = 0.017$).

Mendelian Randomization

The predictive model constructed using clinical data from TACE+Atez/Bev could serve as a powerful tool for identifying HCC patients with high response rate. Building on this finding, the mechanisms of action of atezolizumab and bevacizumab were explored, aiming to validate their efficacy at the genetic level and provide a more precise basis for personalized treatment.

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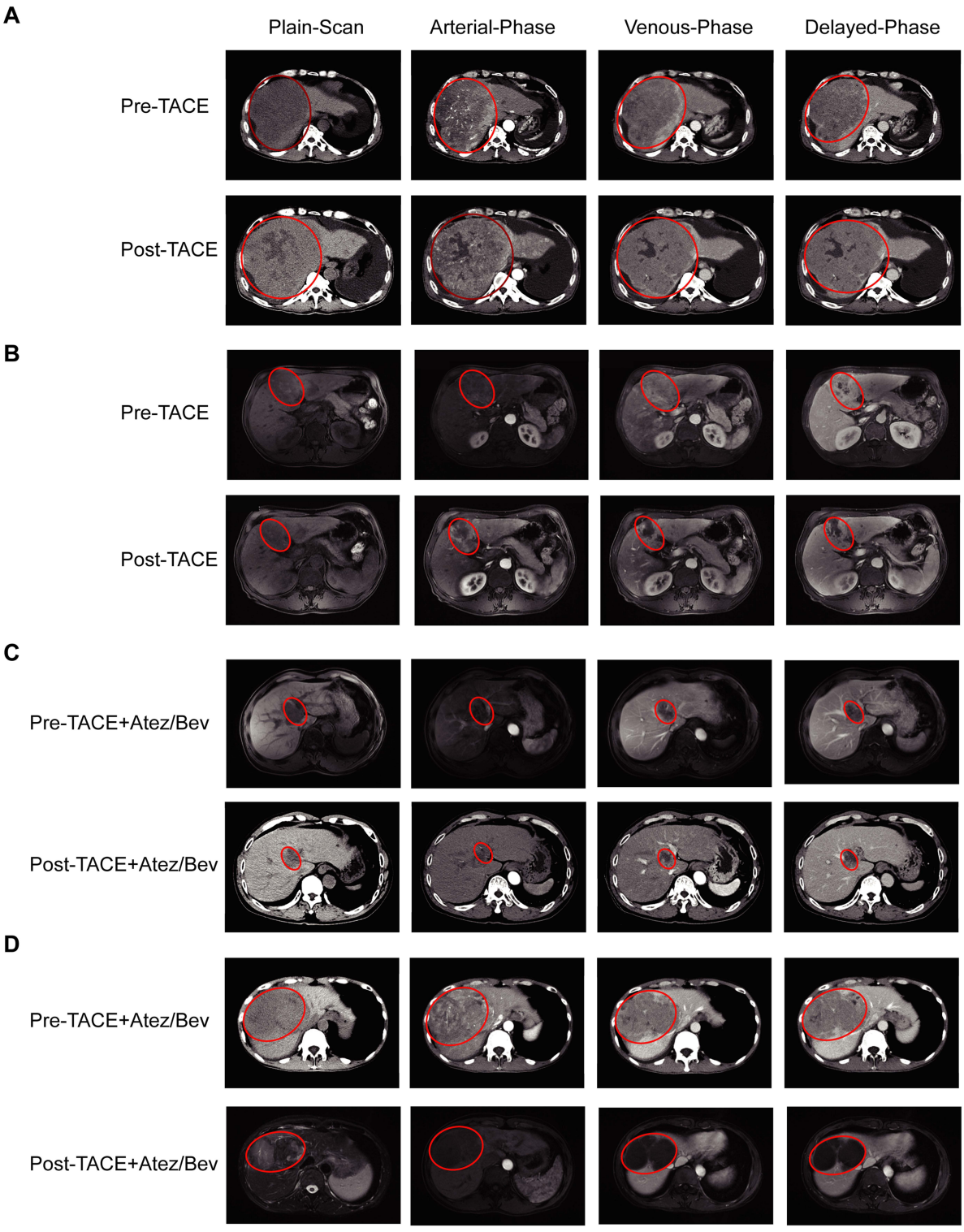

Figure 2 Representative MR or CT images for TACE and TACE+Atez/Bev treatment in HCC patients according to the mRECIST criteria. The areas marked by the red circles in the images indicate the locations of HCC. (**A**) A 58-year-old male HCC patient with a lesion diameter of 161 mm underwent CT 4 days before TACE, followed by CT 50 days after TACE. Plain-scan, arterial-phase, venous-phase, and delay-phase images showed the tumor exhibited PD, with the lesion diameter increasing to 194 mm. (**B**) A 52-year-old male HCC patient with a lesion diameter of 66 mm underwent MRI 3 days before TACE, followed by MRI 60 days after TACE. The lesion showed PR, with the diameter decreasing to 59 mm and 63.64% necrosis. (**C**) A 56-year-old male HCC patient with a lesion diameter of 51 mm underwent MRI 7 days before TACE+Atez/Bev, followed by CT 50 days after TACE+Atez/Bev. The tumor exhibited SD, with the diameter decreasing to 47 mm. (**D**) A 48-year-old male HCC patient with a lesion diameter of 125 mm underwent CT 3 days before TACE+Atez/Bev, followed by MRI 63 days after TACE. The lesion showed CR, with the diameter decreasing to 100 mm and 100% necrosis. The area marked by the red circle indicates the location of the tumor.

Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; TACE, transcatheter arterial chemoembolization; Atez/Bev, atezolizumab plus bevacizumab; PD, progressive disease; PR, partial response; SD, stable disease; CR, complete response; HCC, hepatocellular carcinoma; mRECIST, modified response evaluation criteria in solid tumors.

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Table 2 Baseline Characteristics of Patients in the Training and Validation Cohorts

Variable	TACE+Atez/Bev		
	Training Set (n = 82)	Validation Set (n = 35)	*P*-value
Gender, n (%)			0.322
Male	77 (93.90)	31 (88.57)	
Female	5 (6.10)	4 (11.43)	
Age (years), (mean±SD)	54.90 ± 10.62	51.69 ± 12.91	0.163
Tumor size (cm), n (%)	93.78 ± 42.00	95.29 ± 41.66	0.859
Tumor position, n (%)			0.414
Left liver	17 (20.73)	5 (14.29)	
Right liver	65 (79.27)	30 (85.71)	
Tumor number, n (%)			0.038
One	27 (32.93)	5 (14.29)	
Two or more	55 (67.07)	30 (85.71)	
Portal vein invasion, n (%)			0.087
No	21 (25.61)	4 (11.43)	
Yes	61 (74.37)	31 (88.57)	
Hepatic vein invasion, n (%)			0.063
No	17 (20.73)	13 (37.14)	
Yes	65 (79.27)	22 (62.86)	
Bile duct invasion, n (%)			0.237
No	76 (92.68)	30 (85.71)	
Yes	6 (7.32)	5 (14.29)	
Lymphatic metastasis, n (%)			0.816
No	76 (92.68)	32 (91.43)	
Yes	6 (7.32)	3 (8.57)	
Distant metastasis, n (%)			0.961
No	70 (85.37)	30 (85.71)	
Yes	12 (14.63)	5 (14.29)	
BCLC stage, n (%)			<0.001
0 or A	6 (7.32)	0 (0)	
B	5 (6.10)	4 (11.43)	
C or D	71 (86.58)	31 (88.57)	
Cirrhosis, n (%)			0.628
No	32 (39.02)	12 (34.29)	
Yes	50 (60.98)	23 (65.71)	
Ascites, n (%)			0.51
No	51 (62.20)	24 (68.57)	
Yes	31 (37.80)	11 (31.43)	
Portal hypertension, n (%)			0.745
No	51 (62.20)	19 (54.29)	
Yes	31 (37.80)	16 (45.71)	
Hepatitis, n (%)			0.816
No	6 (7.32)	3 (8.57)	
Yes	76 (92.68)	32 (91.43)	
HBV DNA load, n (%)			<0.001
<100 UL/mL	6 (7.32)	12 (34.29)	
≥ 100 UL/mL	76 (92.68)	23 (65.71)	
AFP, n (%)			0.696
<200 ng/mL	36 (43.90)	14 (40.00)	
≥ 200 ng/mL	46 (56.10)	21 (60.00)	

(*Continued*)

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Table 2 (Continued).

Variable	TACE+Atez/Bev		
	Training Set (n = 82)	Validation Set (n = 35)	*P*-value
ALT (U/L), (mean±SD)	153.42 ± 218.31	97.83 ± 70.61	<0.001
AST, n (%)			0.265
≤ 80 U/L	60 (73.17)	20 (60.61)	
>80 U/L	22 (26.83)	13 (39.39)	
GGT (U/L), (mean±SD)	406.12 ± 343.49	342.68 ± 267.85	<0.001
TBIL (μmol/L), (mean±SD)	23.21 ± 19.38	17.57 ± 6.75	<0.001
ALB, n (%)			0.854
<35 g/L	29 (35.37)	13 (37.14)	
≥ 35 g/L	53 (64.63)	22 (62.86)	
ALBI, (mean±SD)	−2.40 ± 0.66	−2.40 ± 0.41	0.951
PT (s), (mean±SD)	13.84 ± 0.90	13.67 ± 1.11	0.392
Child Pugh grade, n (%)			0.961
A	70 (85.37)	30 (85.71)	
B	12 (14.63)	5 (14.29)	
Lymphocyte ($\times10^9$), (mean±SD)	1.66 ± 0.93	1.44 ± 0.49	0.181
Neutrophil ($\times10^9$), (mean±SD)	3.98 ± 1.82	4.48 ± 2.44	0.222
PLT ($\times10^9$), (mean±SD)	205.29 ± 94.02	205.80 ± 110.79	0.980
PLR, (mean±SD)	142.78 ± 83.71	142.26 ± 73.12	0.831
NLR, (mean±SD)	3.01 ± 3.24	3.26 ± 1.91	0.668
ALRI, (mean±SD)	58.39 ± 74.95	60.58 ± 49.39	0.874
ANRI, (mean±SD)	22.45 ± 28.33	22.01 ± 19.85	0.933

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ALB, albumin; ALBI, albumin-bilirubin; ALRI, albumin-to-lymphocyte ratio index; ANRI, albumin-to-neutrophil ratio index; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; PSM, propensity score matching; PT, prothrombin time; PLT, platelet; PLR, platelet to lymphocyte ratio; TACE, transcatheter arterial chemoembolization; Atez/Bev, atezolizumab and bevacizumab; TBIL, total bilirubin.

Table 3 Univariate and Multivariate Logistic Regression Analyses in the Training Cohort

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Gender n (%)				
Male	ref			
Female	1. 00 (0.221–32.235)	0.681		
Age (years), (mean±SD)	0.99 (0.943–1.0371)	0.705		
Tumor size (cm), n (%)	1.001 (0.990–1.014)	0.804		
Tumor position, n (%)				
Left liver	ref			
Right liver	0.338 (0.109–1.040)	**0.055**	0.441 (0.100–1.925)	0.269
Tumor number, n (%)				
One	ref			
Two or more	0.639 (0.205–1.801)	0.412		
Portal vein invasion, n (%)				
No	ref			
Yes	1.406 (0.463–4.049)	0.532		
Hepatic vein invasion, n (%)				
No	ref			
Yes	4.098 (1.340–12.926)	**0.013**	5.530 (1.126–32.177)	**0.041**

(*Continued*)

Table 3 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Bile duct invasion, n (%)				
No	ref			
Yes	0.764 (0.138–5.801)	0.765		
Lymphatic metastasis, n (%)				
No	ref			
Yes	0.357 (0.062–2.065)	0.229		
Distant metastasis, n (%)				
No	ref			
Yes	0.321 (0.089–1.148)	**0.076**	0.452 (0.064–3.030)	0.410
BCLC stage, n (%)				
0 or A	ref			
B	0.750 (0.064–8.834)	0.819		
C or D	1.368 (0.231–8.089)	0.729		
Cirrhosis, n (%)				
No	ref			
Yes	0.595 (0.203–1.619)	0.321		
Ascites, n (%)				
No	ref			
Yes	0.338 (0.122–0.904)	**0.032**	0.416 (0.091–1.821)	0.242
Portal hypertension, n (%)				
No	ref			
Yes	0.507 (0.188–1.345)	0.172		
Hepatitis, n (%)				
No	ref			
Yes	1.204 (0.338–4.774)	0.777		
HBV DNA load, n (%)				
<100 UL/mL	ref			
≥ 100 UL/mL	0.835 (0.295–2.245)	0.724		
AFP, n (%)				
<200 ng/mL	ref			
≥ 200 ng/mL	0.453 (0.154–1.226)	0.129		
ALT (U/L), (mean±SD)	0.995 (0.981–1.002)	0.265		
AST n (%)				
≤ 80 U/L	ref			
>80 U/L	0.332 (0.116–0.942)	**0.038**	0.371 (0.043–3.067)	0.348
GGT (U/L), (mean±SD)	0.998 (0.996–1.001)	0.192		
TBIL (μmol/L), (mean±SD)	0.956 (0.898–1.001)	0.101		
ALB, n (%)				
<35 g/L	ref			
≥ 35 g/L	2.695 (1.001–7.408)	**0.050**	7.761 (1.246–59.544)	**0.034**
ALBI, (mean±SD)	0.423 (0.150–1.042)	**0.086**	1.359 (0.288–4.620)	0.629
PT (s), (mean±SD)	0.605 (0.337–1.041)	**0.076**	1.040 (0.449–2.462)	0.927
Child Pugh grade, n (%)				
A	ref			
B	0.321 (0.089–1.148)	**0.076**	8.542 (0.906–114.435)	0.079
Lymphocyte ($\times 10^9$), (mean±SD)	3.113 (1.199–9.551)	**0.032**	0.874 (0.430–3.095)	0.744
Neutrophil ($\times 10^9$), (mean±SD)	0.929 (0.717–1.218)	0.577		
PLT ($\times 10^9$), (mean±SD)	1.007 (1.001–1.014)	**0.041**	1.013 (1.004–1.026)	**0.017**
PLR, (mean±SD)	0.999 (0.994–1.005)	0.785		

(*Continued*)

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Table 3 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
NLR, (mean±SD)	0.764 (0.544–0.975)	**0.099**	0.619 (0.351–1.005)	0.082
ALRI, (mean±SD)	0.993 (0.985–1.000)	**0.063**	1.000 (0.989–1.013)	0.952
ANRI, (mean±SD)	0.990 (0.971–1.007)	0.244		

Notes: In the univariate analysis, bold font indicates *P*-value < 0.1, denoting variables selected for the multivariate analysis; in the multivariate analysis, bold font indicates statistical significance at *P*-value < 0.05.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ALB, albumin; ALBI, albumin-bilirubin; ALRI, albumin-to-lymphocyte ratio index; ANRI, albumin-to-neutrophil ratio index; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; OR, odds ratio; PT, prothrombin time; PLT, platelet; PLR, platelet to lymphocyte ratio; TBIL, total bilirubin.

As anticipated, IVW analysis showed that inhibiting *PDCD1* significantly reduced the risk of HCC progression (DrugOR = 0.713, 95% CI, 0.599–0.848; $p < 0.001$). The β values derived from the MR Egger, weighted median, simple mode, and weighted mode methods were all > 0, consistent with IVW data, further confirming the reliability of IVW findings (Figure 4A). However, *CD274* suppression and *VEGFA* inhibition were not significantly correlated with HCC development (Supplementary Figure S2).

Sensitivity Analysis

Heterogeneity testing using MR Egger and IVW for the 7 SNPs of *PDCD1* revealed Cochrane's Q > 0.05, indicating no significant heterogeneity among the assessed SNPs (Supplementary Table S1). MR Egger regression analysis showed $p = 0.666$, suggesting no horizontal pleiotropy among the SNPs (Supplementary Table S2). The leave-one-out method demonstrated that removing any individual SNP associated with HCC did not result in significant differences, indicating that no single SNP drove the causal association between *PDCD1* and HCC (Figure 4B). Scatter plots showed a concentrated distribution of SNP effects, suggesting that the impact of *PDCD1* inhibition on HCC was consistent across different MR methods (Figure 4C). Funnel plot analysis indicated symmetrical distribution of points derived from the IVW and MR Egger methods around the center, suggesting no significant small-sample bias (Figure 4D). The forest plot confirmed that the 7 SNPs had significant impacts on HCC (Figure 4E). These results and effect estimates across various methods support *PDCD1* as a potentially effective therapeutic target for HCC.

Discussion

In the rapidly evolving field of cancer treatment, HCC remains a significant global public health challenge. With 70% of patients diagnosed at advanced stages, effective treatment remains challenging, requiring ongoing exploration and innovation. In this study, the ORR in patients administered TACE alone was 53.19%, compared to 71.79% in the TACE+Atez/Bev group. However, some HCC patients still do not respond to TACE+Atez/Bev treatment. To address this issue, we developed an efficient predictive model to help clinicians identify patients likely to benefit from TACE+Atez/Bev. Furthermore, we validated the efficacy of Atez/Bev in HCC management through MR analysis. TACE remains the most frequently used intervention for HCC, encompassing conventional TACE and drug-eluting bead TACE.[14] Clinically, HCC exhibits significantly more pronounced arterial vascular formation compared with surrounding liver parenchyma. TACE works by embolizing the tumor's blood supply and locally delivering chemotherapeutic agents, combining cytotoxic effects with tumor tissue ischemia to induce necrosis.[14] However, evidence suggests that TACE can lead to tumor ischemia and hypoxia, potentially stimulating angiogenesis and promoting tumor growth. A study of early- to mid-stage HCC found that even in BCLC stage A or B, the 3-year overall survival (OS) rate with TACE alone was less than 50%.[3] Another study of BCLC stage B HCC patients reported an ORR of only 41.3% for TACE combined with placebo.[15] A meta-analysis revealed that for HCC patients with portal vein tumor thrombus, the ORR with TACE alone ranged from 0% to 32%, with a 1-year OS of 0–36.8%.[16] These findings highlight the limitations of TACE as a standalone treatment option for unresectable HCC, underscoring the need for more effective therapeutic strategies.

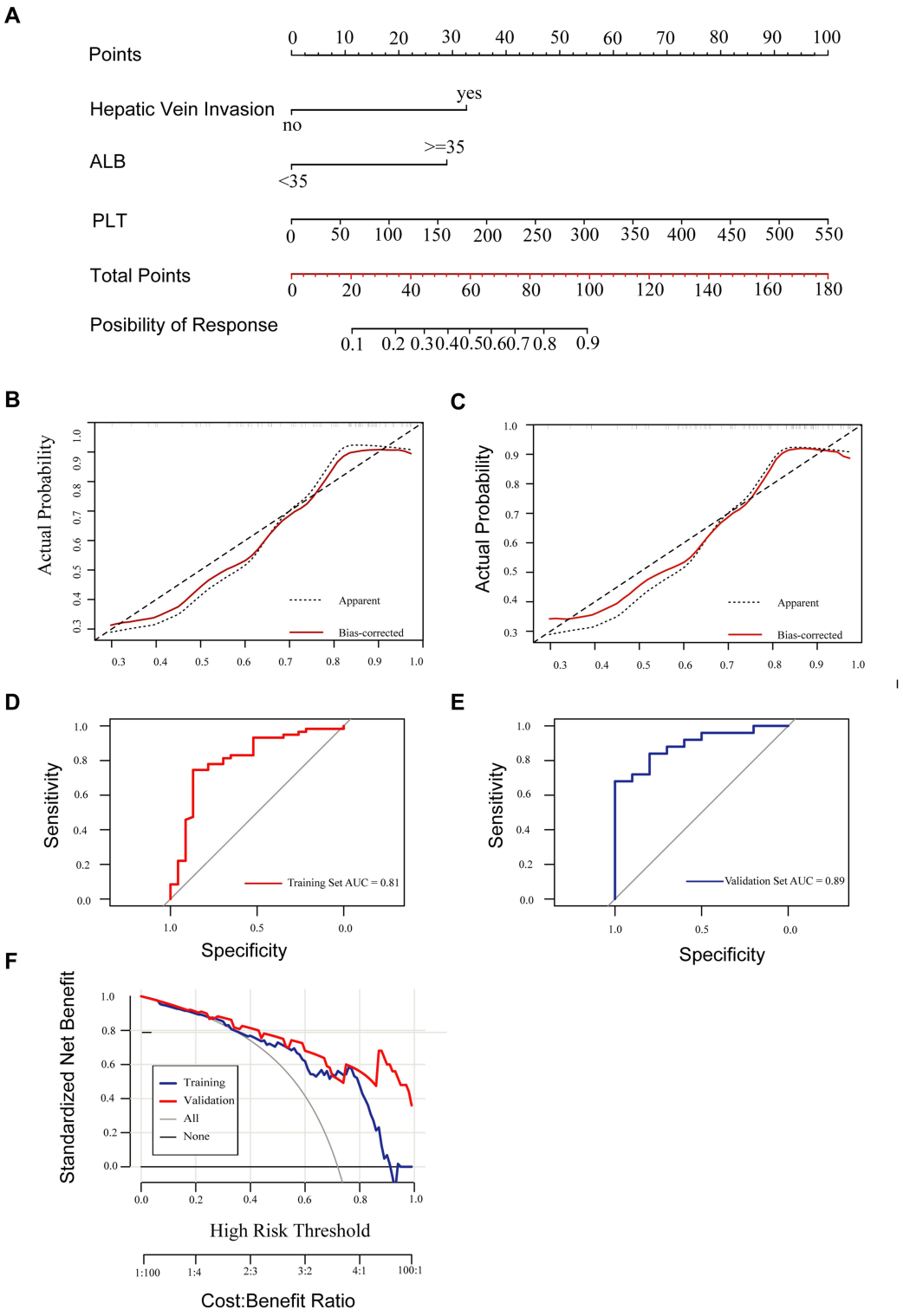

Figure 3 Nomogram for predicting response to TACE+Atez/Bev treatment based on pre-treatment clinical factors and its predictive performance. (**A**) Nomogram for estimating response to TACE+Atez/Bev treatment before initiation. Usage instructions: locate the scores corresponding to the patient's hepatic vein invasion status, ALB level, and PLT count in sequence, sum these scores to get the total score, then map the total score to the "Probability of treatment response" axis, which will allow you to estimate the patient's likelihood of responding to TACE+Atez/Bev therapy. (**B**) Validation of the nomogram's predictive performance in estimating response to TACE+Atez/Bev in the training cohort (n = 82). (**C**) Validation of the nomogram's predictive performance in estimating response to TACE+Atez/Bev in the validation cohort (n = 35). (**D**) ROC curves for the selected clinical features in the training cohort. (**E**) ROC curves for the selected clinical features in the validation cohort. (**F**) DCA of the nomogram in the training and validation cohorts.

Abbreviations: ALB, albumin; PLT, platelet; ROC, receiver operating characteristic. DCA, Decision curve analysis.

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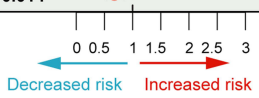
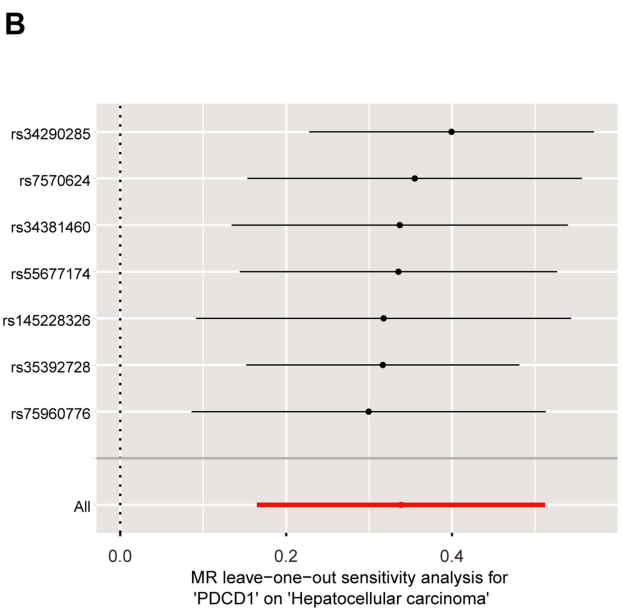
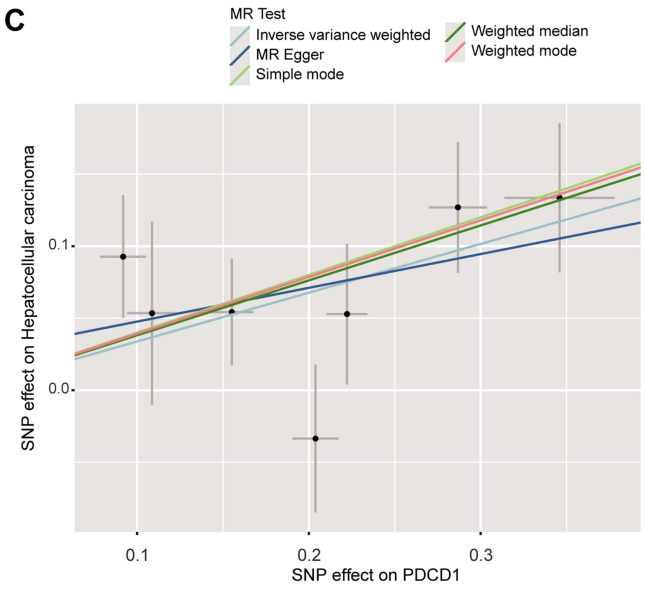
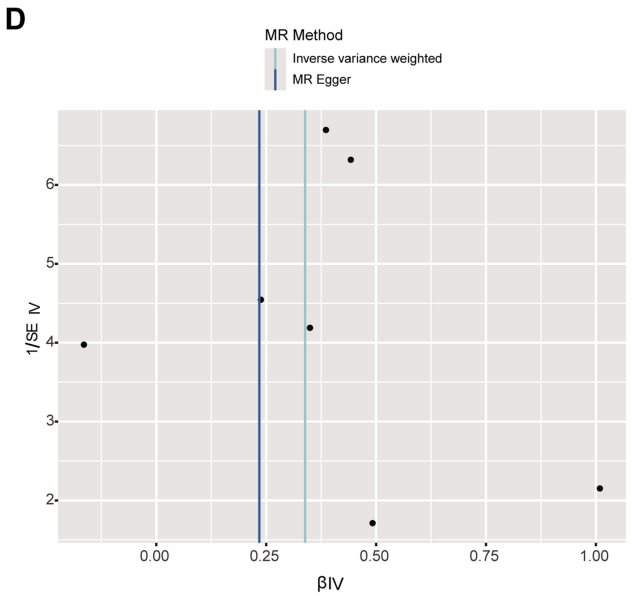
A

Disease	Gene	nSNP	Method	p-value	DrugOR (95% CI)
HCC	PDCD1 inhibition	7	Inverse variance weighted	**<0.001**	0.713 (0.599 to 0.848)
		7	MR Egger	0.385	0.791 (0.488 to 1.282)
		7	Weighted median	**<0.001**	0.683 (0.554 to 0.842)
		7	Simple mode	**0.031**	0.670 (0.507 to 0.887)
		7	Weighted mode	**0.014**	0.675 (0.538 to 0.846)









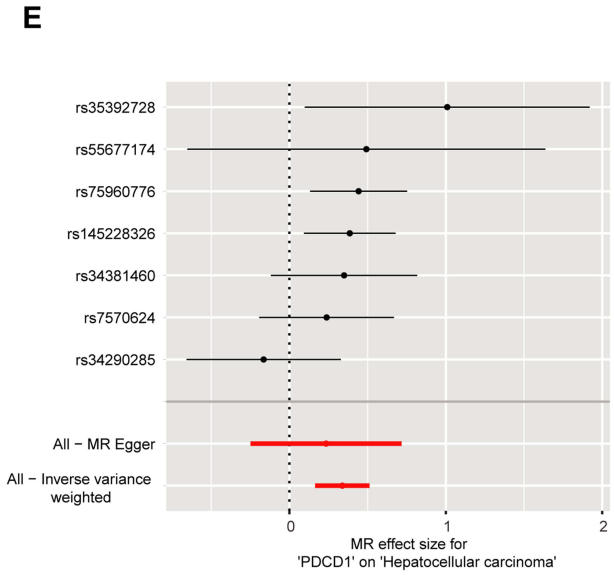


Figure 4 Causality and sensitivity analysis of *PDCD1* in HCC. (**A**) Causality analysis of *PDCD1* in HCC. (**B**) MR leave-one-out sensitivity analysis of *PDCD1* in HCC. (**C**) Scatter plot of SNP effects on *PDCD1* and HCC. (**D**) Funnel plot of SNP MR effect sizes for *PDCD1* in HCC. (**E**) MR effect sizes of SNPs for *PDCD1* in HCC.
Abbreviations: PDCD1, programmed cell death protein 1; HCC, hepatocellular carcinoma; MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

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Currently, targeted combination immunotherapy is a prominent area of systemic treatment in HCC, with the combination of atezolizumab and bevacizumab established as a first-line systemic treatment option in clinical guidelines.[17,18] Atezolizumab, a humanized monoclonal IgG1 antibody, binds to PD-L1, blocking its interaction with PD-1 and B7.1 receptors, both inhibitory receptors expressed on T cells. It has been approved for the treatment of bladder, lung, and breast cancers. Bevacizumab, also a humanized monoclonal IgG1 antibody, binds to VEGF ligands, inhibiting angiogenesis, and is approved for the treatment of colorectal, lung, kidney, cervical, and ovarian cancers, as well as glioblastoma. Both drugs are metabolized primarily through proteolytic enzymes, requiring minimal hepatic or renal metabolism, which reduces their impacts on liver and kidney functions.[19] A real-world study[20] indicated that in HCC patients with vascular invasion and/or extrahepatic metastasis, Atez/Bev alone achieved an ORR of 30.8%, consistent with the IMbrave 150 study. *Casadei-Gardini* et al suggested that Atez/Bev treatment is more suitable for HCC patients with coexisting viral hepatitis compared with lenvatinib,[21] suggesting that Atez/Bev may represent a promising treatment direction for HBV-related HCC, particularly in regions where HBV is prevalent. Although many studies have demonstrated that Atez/Bev is an effective systemic treatment for unresectable HCC, the therapeutic outcomes with Atez/Bev alone remain suboptimal.

In a study by *Wang* et al assessing intermediate-stage HCC exceeding the "up-to-seven" criteria,[22] TACE combined with Atez/Bev showed encouraging efficacy and acceptable safety, with ORR and disease control rate (DCR) of 61.9% and 100%, respectively. In this study, patients administered TACE combined with Atez/Bev achieved an ORR of 71.79%. After applying PSM to minimize bias between the experimental and control groups, the ORR further increased to 73.75%, significantly higher than in patients administered TACE alone. Similarly, a study by *Cao* et al[23] confirmed that the ORR is significantly higher in patients treated with TACE combined with Atez/Bev versus those administered Atez/Bev alone. Evidence suggests that Atez/Bev may exert anti-VEGF effects before TACE, enhancing the overall efficacy of TACE. However, a significant number of patients still fail to achieve satisfactory therapeutic outcomes with TACE+Atez/Bev treatment.

To further identify cases more likely to respond to TACE combined with Atez/Bev treatment, a clinical predictive model was developed. In this study, univariate and multivariate logistic regression analyses revealed that hepatic vein invasion, ALB $\geq$ 35 g/L, and high PLT were significantly associated with the response of HCC patients to TACE combined with Atez/Bev treatment. Multivariate analysis revealed that hepatic vein invasion was significantly associated with an increased risk of treatment response (OR = 5.530, $p = 0.041$), suggesting that patients with vascular invasion are more likely to respond to TACE+Atez/Bev therapy and that this factor can serve as a potential positive predictive indicator for treatment response in clinical practice. HCC patients with ALB $\geq$ 35 g/L had a 7.761-fold higher probability of treatment response than those with ALB < 35 g/L, which implies better liver function in these patients, enabling them to better tolerate the side effects of TACE+Atez/Bev therapy and achieve a favorable response and aligns with the clinical principle that "the better the patient's baseline status, the better the treatment outcome". In addition, for every 1×10/L increase in PLT, the probability of treatment response rose by 1.3%, indicating that patients with higher PLT levels are more sensitive to TACE+Atez/Bev intervention.

Previous research by *Ueno* et al attempted to develop nomogram models using CRP, AFP, and NLR to predict the efficacy of Atez/Bev treatment in HCC.[24] While the latter study utilized serological and tumor markers as predictive variables, it did not incorporate tumor imaging data or liver function indexes related to the patient's condition, resulting in relatively low predictive efficacy (AUC = 0.73, 95% CI, 0.60–0.80). Moreover, the obtained findings require further validation. Additionally, their study focused exclusively on Atez/Bev treatment, whereas most HCC cases in clinical practice undergo combined interventional treatments, particularly TACE. In this study, we innovatively combined TACE and Atez/Bev treatment to evaluate therapeutic efficacy, incorporating three easily obtainable pre-treatment clinical variables. This approach not only included imaging data but also accounted for tumor burden and liver function status, ensuring practical applicability in clinical settings. The predictive model demonstrated strong performance, with AUCs of 0.81 and 0.89 in the training and validation cohorts, respectively. Calibration curve analysis showed excellent consistency between the model's predictions and actual outcomes.

In clinical practice, imaging-visible invasion of the portal vein and/or hepatic vein system in HCC is often referred to as major vascular invasion. A previous study showed that major vascular invasion is closely associated with the efficacy

of Atez/Bev treatment.[25] *Awiwi* et al reported that hepatic venous tumor thrombus is an independent prognostic factor of poor progression-free survival (PFS) in advanced HCC; however, its impact on ORR remains unclear.[26] This study found that hepatic vein invasion is significantly associated with the efficacy of TACE combined with Atez/Bev treatment. Patients with hepatic vein invasion were more likely to achieve a tumor response compared with those without such invasion. However, studies assessing Atez/Bev treatment for hepatic vein tumor thrombus are scarce, and there is no consensus on the optimal treatment strategy for these patients. Existing research[20] predominantly focuses on HCC with portal vein tumor thrombus (PVTT), with fewer and smaller studies addressing hepatic vein tumor thrombus (HVTT). This lack of relevant research highlights an opportunity to explore the potential therapeutic effect of TACE combined with Atez/Bev in HCC. Further large-scale studies and clinical case data are required to assess the actual efficacy and potential applications of this treatment, providing robust evidence for developing precise treatment plans and improving prognostic management in patients with hepatic vein tumor thrombus.

ALB and PLT count are crucial indicators for evaluating liver function. It is well established that liver function status is an independent factor affecting OS in HCC patients.[27] Although Atez/Bev is not metabolized by the liver or kidneys and has minimal impact on liver or kidney function,[19] previous studies have shown that the efficacy of Atez/Bev is lower in patients with decompensated liver function compared with those with compensated liver function. Caution has been advised when considering Atez/Bev treatment for patients with poor liver function.[28] In this study of TACE+Atez/Bev treatment, patients with albumin levels ≥35 g/L and elevated PLT counts were more likely to achieve a tumor response, highlighting the importance of liver function status and systemic health in determining treatment efficacy.

To further validate the therapeutic efficacy of atezolizumab in HCC, MR analysis was conducted using drug targets, revealing that *PDCD1* inhibitors, eg, atezolizumab, significantly reduce the risk of HCC. *PDCD1* encodes the T cell receptor PD-1,[29] which prevents excessive immune activation by inhibiting T cell activity, maintaining immune tolerance. While *PDCD1* activation helps prevent autoimmune diseases, its overexpression in certain cancers allows tumor cells to evade immune surveillance, which makes *PDCD1* a critical target in cancer immunotherapy. A previous study[30] showed that *PDCD1* expression is significantly elevated in HCC compared with normal liver tissue. HCC cases with high *PDCD1* expression exhibit better RFS, OS, disease-specific survival (DSS), and PFS. *PDCD1* expression was positively correlated with many immune cells, including CD8+ T cells, B cells, macrophages, CD4+ T cells, dendritic cells, and neutrophils. These immune cells are essential components of the tumor immune microenvironment, playing pivotal roles in tumor immune infiltration and biological mechanisms. These findings suggest that atezolizumab has significant therapeutic potential in HCC.

VEGFA is a key regulator of angiogenesis, primarily secreted by hepatic stellate cells, Kupffer cells, and hepatocytes in the liver. It is involved in endothelial dysfunction and immune cell infiltration in chronic liver diseases.[31] Excess *VEGFA* was shown to promote liver tumor development, and anti-*VEGFA* therapies are widely considered for HCC treatment. *VEGFA* promotes angiogenesis in the early stage of tumors, but may exert negative effects in the late stage by inducing vascular abnormality and an immunosuppressive microenvironment.[32] Since this study did not distinguish tumor stages or vascular maturity, it might have masked the correlation between *VEGFA* and therapeutic efficacy in specific stages. Angiogenesis in HCC is regulated by multiple signaling pathways (eg, bFGF, Ang-2, etc). A single *VEGFA* indicator is insufficient to reflect the overall angiogenic status; even if *VEGFA* shows no significant correlation, its downstream pathways or combined indicators may still hold predictive value. Although this study failed to identify a direct association between *VEGFA* and the efficacy of HCC treatment, existing evidence underscores *VEGFA*'s regulatory role in the tumor immune microenvironment. Antiangiogenic agents, including bevacizumab, inhibit *VEGFA*, normalizing the altered tumor vasculature and reducing the number of immunosuppressive cells, including Tregs and MDSCs. These effects enhance the infiltration of immune cells, particularly CD8+ T cells, transforming the tumor microenvironment from an immunosuppressive state to one more favorable for immune responses.[33] This shift amplifies the effects of immunotherapy, including PD-1 and PD-L1 inhibitors, making the combination of atezolizumab and bevacizumab a compelling therapeutic approach for HCC.

CD274 is a key gene encoding PD-L1.[34] By binding to PD-1 on the surface of immune cells, PD-L1 inhibits T-cell activation and helps HCC cells evade immune surveillance, making it one of the core molecules in tumor immune escape.[35] Its expression is subject to complex regulation by multiple signaling pathways, including transcriptional

activation by ETV5, epigenetic suppression by EZH2, and MAPK, and is closely associated with the immune microenvironment of HCC. *CD274* yielded a negative result in MR analysis of HCC, primarily due to two core reasons: on the one hand, the expression regulatory network of *CD274* is highly complex, involving interactions across multiple levels such as genetics, epigenetics, and signaling pathways. A single genetic variant cannot adequately reflect its true expression level, which may lead to insufficient association between instrumental variables and exposure factors in MR analysis,[36] on the other hand, limitations in the design of MR studies may also contribute to the negative result. For example, the selected genetic variants may have issues of weak instrumental variables or insufficient sample size resulting in limited statistical power. These factors prevent the capture of potential causal associations between *CD274* and HCC, rather than indicating the absence of a true biological association.

Despite the innovations in this study, several limitations should be acknowledged. First, and most importantly, our predictive model was derived and validated within a single-center, retrospective cohort. The absence of an independent external validation cohort limits the generalizability of our findings to other institutions or patient populations. Second, the sample size available for model validation was constrained. This reflects a key real-world challenge, namely that combined atezolizumab and bevacizumab regimen is a high-cost therapy, which naturally limits the number of eligible and treated patients in a single-center setting, thereby affecting the potential size of the internal validation set. Third, despite the supportive evidence from MR analysis, the observational nature of the primary clinical data means that residual confounding cannot be fully ruled out, and causal inferences should be made with caution. To address these limitations, prospective validation in larger, multi-center cohorts is essential to confirm the robustness and clinical utility of our model. Furthermore, investigating the cost-effectiveness of this combination therapy could provide crucial evidence to improve patient access and facilitate the enrollment of larger cohorts in future studies.

Conclusion

This study demonstrates that TACE combined with atezolizumab plus bevacizumab is a promising strategy for unresectable HCC, significantly improving treatment response. We developed and validated a clinical prediction model with high predictive efficacy to identify patients most likely to benefit from this regimen. Furthermore, MR analysis provided genetic evidence supporting *PDCD1* as a therapeutic target, underpinning the biological rationale for this combination therapy. Nevertheless, this study has limitations, including its single-center, retrospective design and the constrained sample size, which necessitate future external validation in larger, multi-center cohorts. The integration of a clinical prediction model with genetic evidence offers an actionable framework for personalized treatment stratification, with the potential to improve clinical outcomes.

Data Sharing Statement

All data supporting the findings of this study are available within the paper and its Supplementary Information.

Ethics Approval and Consent to Participate

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of The Third Affiliated Hospital, Sun Yat-sen University (No. II2025-498-01). The requirement for informed consent was waived due to the retrospective nature of the study.

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Author Contributions

Wenhao Chen, Jiawei Liu and Shuxian Chen share first authorship.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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