

Real-world investigation for camrelizumab combined with apatinib in patients with advanced hepatocellular carcinoma

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Received April 21, 2025; Accepted August 14, 2025

DOI: 10.3892/ol.2025.15299

Abstract. Apatinib, an oral tyrosine kinase inhibitor, combined with camrelizumab, a programmed cell death protein 1 inhibitor, has shown promising treatment efficacy for patients with advanced hepatocellular carcinoma (HCC). However, real-world evidence supporting this combination regimen is limited, and prognostic factors for these patients have not been thoroughly investigated. Therefore, the present real-world study aimed to assess the efficacy and safety of camrelizumab plus apatinib in patients with advanced HCC, and identify prognostic factors associated with response to treatment. A total of 39 patients with advanced HCC who received camrelizumab combined with apatinib were included in the present retrospective study. All patient data, such as treatment response, follow-up outcomes and incidence of adverse events were collected for analysis. The results revealed complete response, partial response, stable disease and progressive disease rates of 25.6, 10.3, 46.2 and 17.9%, respectively. In addition, the objective response and disease control rates were 35.9 and 82.1%, respectively. The median progression-free survival (PFS) was 24.0 months (95% confidence interval, 5.0-43.0). Furthermore, the cumulative PFS rates at 12, 24 and 36 months were 52.8, 44.0 and 39.1%, respectively. However, median overall survival (OS) was not reached during the follow-up period. The OS rates at 12, 24 and 36 months were 72.4, 72.4 and 66.3%, respectively. Multivariate Cox regression analysis also revealed that extrahepatic metastasis was independently associated with

higher mortality risk (hazard ratio, 9.217; $P=0.049$). The most common adverse events were anemia (79.5%), thrombocytopenia (69.2%), leukopenia (64.1%), pain (56.4%), neutropenia (41.0%), fever (33.3%) and hypertension (28.2%). In conclusion, camrelizumab combined with apatinib shows promising treatment efficacy and a manageable toxicity in patients with advanced HCC. Additionally, extrahepatic metastasis could be associated with worse OS in these patients. Nevertheless, due to the small sample size, retrospective and single-arm study design in the current study, further study with a larger sample size, prospective, controlled design is required.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-associated mortality, with an incidence of ~0.8 million cases in 2022, worldwide (1,2). Although, surgical resection, transplantation and local ablation are the standard treatment approaches for patients with early-stage HCC, nearly half of patients are diagnosed with advanced-stage disease at initial presentation (3). Systemic therapy is recommended for patients with advanced HCC, among which sorafenib is the standard first-line treatment for over a decade (3,4). However, recent advances in tyrosine kinase inhibitors (TKIs) have reshaped the therapeutic landscape of advanced HCC, and its combination with immunotherapy may improve the prognosis of these patients (4,5).

Apatinib is an oral TKI that inhibits tumor angiogenesis, and has shown promising efficacy when combined with programmed cell death protein 1 (PD-1) inhibitors in patients with advanced HCC (6-8). For example, a previous study reported an objective response rate (ORR) of 50.0% and a disease control rate (DCR) of 91.3% in patients with advanced HCC treated with apatinib combined with a PD-1 inhibitor (7). Additionally, in another study, patients with advanced HCC who received apatinib plus PD-1 inhibitor showed a median progression-free survival (PFS) of 6.7 months and a median overall survival (OS) of 22.5 months (8). Therefore, apatinib plus PD-1 inhibitor has become a promising treatment strategy for advanced HCC.

Camrelizumab, a high-affinity immunoglobulin G4k monoclonal antibody of PD-1, has demonstrated promising efficacy in treating patients with advanced HCC (9,10).

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Key words: camrelizumab, apatinib, advanced hepatocellular carcinoma, efficacy, safety

Previously, several clinical trials have suggested that these patients can benefit from camrelizumab combined with apatinib (11,12). For example, the RESCUE trial reported an ORR of 34.3%, and a 12-month OS rate of 74.7% in patients with advanced HCC who were treated with camrelizumab plus apatinib as first-line therapy. Additionally, an ORR of 22.5% and a 12-month OS rate of 68.2% was reported in patients who received this regimen as a second-line treatment (11). Additionally, the CARES-310 trial revealed that camrelizumab combined with apatinib as first-line therapy for patients with advanced HCC could result in an ORR of 25.4%, a DCR of 78.3%, a median PFS of 5.6 months and a median OS of 23.8 months (12). However, real-world evidence on camrelizumab plus apatinib in patients with advanced HCC is limited, and therefore further validation is needed. Furthermore, prognostic factors affecting treatment outcomes have not been fully elucidated.

Therefore, the present real-world study aimed to evaluate the efficacy and safety of camrelizumab plus apatinib in patients with advanced HCC, as well as to identify potential prognostic factors associated with treatment outcome in these patients.

Materials and methods

Patients. The present retrospective, single-arm study aimed to evaluate the efficacy and tolerability of camrelizumab combined with apatinib in patients with advanced HCC. The inclusion criteria were as follows: i) Patients diagnosed with advanced HCC, which was defined as Barcelona Clinic Liver Cancer stage C (13); ii) age >18 years; iii) treated with camrelizumab plus apatinib; iv) available complete treatment response data based on imaging examinations; v) complete follow-up data, including disease status and survival data; vi) no history of organ transplantation; and vii) no history of autoimmune disease requiring systemic therapy. The exclusion criteria were the following: i) Patients suffering from liver malignancies other than HCC, such as intrahepatic cholangiocarcinoma or metastatic liver cancer; ii) patients diagnosed with hematological malignancies or other primary cancers; iii) Eastern Cooperative Oncology Group performance status (ECOG PS) of >2; and iv) uncontrolled or severe comorbidities, such as heart failure and chronic renal failure. Patients were enrolled from the Handan Central Hospital between March 2020 and January 2024. The study protocol was approved by the Institutional Review Board of the Handan Central Hospital (approval no. 2024029). Written informed consent was obtained from all patients or their family members.

Data collection. All data were extracted from electronic medical records and included demographic characteristics, treatment history, such as surgery or transarterial chemoembolization (TACE), ECOG PS, disease-related information, treatment details, treatment response data and follow-up outcomes. Treatment lines were counted based on systematic therapy only, while prior locoregional therapies (such as TACE) did not affect the line-counting of systematic treatments. Treatment response was assessed every 3 months using computed tomography scan or magnetic resonance imaging.

Table I. Clinical characteristics of patients with advanced HCC.

Characteristic	Patients with advanced HCC (n=39)
Age (mean ± SD), years	59.4±11.4
Sex	
Female	8 (20.5)
Male	31 (79.5)
HBV history	27 (69.2)
Liver cirrhosis history	23 (59.0)
A history of surgery or TACE	18 (46.2)
ECOG PS	
1	38 (97.4)
2	1 (2.6)
Maximum tumor diameter (median IQR), cm	5.0 (4.0-9.3)
Maximum tumor diameter ≥10 cm	8 (20.5)
Portal vein invasion	13 (33.3)
Extrahepatic metastasis	17 (43.6)
ALB (median IQR), g/l	68.6 (57.1-72.2)
Abnormal ALB	28 (71.8)
TBIL (median IQR), μmol/l	16.4 (13.8-38.3)
Abnormal TBIL	23 (59.0)
ALT (median IQR), U/l	36.0 (26.0-51.0)
Abnormal ALT	26 (66.7)
AST (median IQR), U/l	63.0 (34.0-114.0)
Abnormal AST	12 (30.8)
AFP (median IQR), ng/ml	24.2 (3.9-1210.0)
AFP ≥200 ng/ml	14 (35.9)
Number of TACEs	
0	29 (74.4)
1	8 (20.5)
2	2 (5.1)
Treatment line of systematic therapy	
First-line	29 (74.4)
Second or later	10 (25.6)

Data presented as n (%). HCC, hepatocellular carcinoma; HBV, hepatitis B virus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, α-fetoprotein; TACE, transarterial chemoembolization.

The imaging findings were reviewed centrally and categorized according to the response evaluation criteria in solid tumors criteria (14). The follow-up data included the timing and occurrence of disease progression and death. PFS and OS rates were estimated based on follow-up data. PFS was defined as the time from treatment initiation to the first disease progression or all-cause mortality. OS was defined as the time from treatment

Table II. Treatment response of patients with advanced HCC.

Outcome	Patients with advanced HCC (n=39)
Response	
CR	10 (25.6)
PR	4 (10.3)
SD	18 (46.2)
PD	7 (17.9)
ORR	14 (35.9)
DCR	32 (82.1)

Data presented as n (%). HCC, hepatocellular carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

initiation to mortality from any cause. The median follow-up duration was 10.0 months (range, 1.0–54.0 months). Finally, the adverse events were recorded by clinicians and screened by investigators based on the Common Terminology Criteria for Adverse Events version 5.0 (available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf).

Treatment information. Patients received camrelizumab at a dose of 200 mg intravenously for 3 weeks, combined with apatinib at a dose of 250 mg taken orally once daily. In addition, several patients underwent TACE according to their own willingness, disease status and physician recommendation.

Statistical analysis. All statistical analyses were performed using SPSS software (version 26.0; IBM Corp.). Post hoc statistical power analysis using PASS software (version 15.0.5; NCSS LLC) was performed. Descriptive statistics were applied to summarize the results. PFS and OS in patients with advanced HCC were calculated using Kaplan-Meier curves. The Log-rank test was used to compare Kaplan-Meier curves between subgroups. Univariate and multivariate Cox regression analyses were carried out to identify prognostic factors associated with PFS and OS. All variables in the univariate analysis were incorporated into the multivariate model using the enter method. A Fisher's exact test was used to compare ORR and DCR between subgroups. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features. The mean age of the 39 patients included in the present study was 59.4 ± 11.4 years. A total of 8 women (20.5%) and 31 men (79.5%) were enrolled. Among all patients, 13 (33.3%) presented with portal vein invasion and 17 (43.6%) with extrahepatic metastasis. A total of 29 patients (74.4%) received camrelizumab + apatinib as first-line therapy, while 10 patients (25.6%) were treated with this regimen as

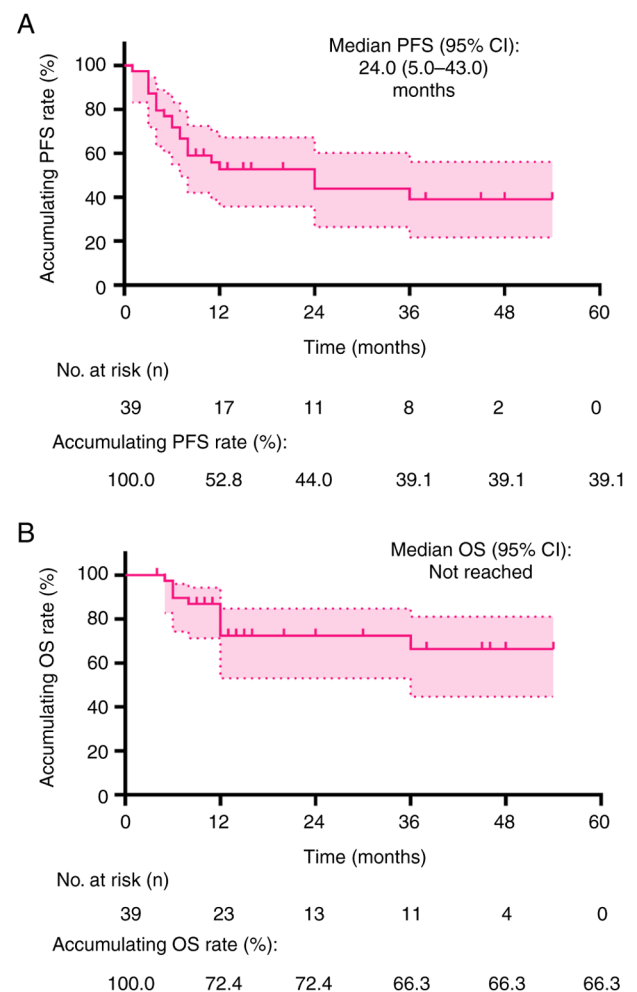


Figure 1. Kaplan-Meier curves of PFS and OS in patients with advanced hepatocellular carcinoma who received camrelizumab plus apatinib. (A) Median (95% CI) PFS and accumulating PFS rates at 12, 24, 36, 48 and 60 months in patients. (B) The median (95% CI) OS and accumulating OS rates at 12, 24, 36, 48 and 60 months in patients. PFS, progression-free survival; OS, overall survival; CI, confidence interval.

second- or later-line therapy. The detailed patient characteristics are listed in Table I.

Treatment response. Among all patients, 10 (25.6%) achieved a complete response, 4 (10.3%) reached partial response, 18 (46.2%) had stable disease and 7 (17.9%) exhibited progressive disease. The ORR and DCR were 35.9 and 82.1%, respectively (Table II).

PFS and OS. The median PFS was 24.0 months [95% confidence interval (CI): 5.0–43.0 months]. The accumulated PFS rates at 12, 24 and 36 months were 52.8, 44.0 and 39.1%, respectively (Fig. 1A). Furthermore, the median OS was not reached during the follow-up period. The cumulative OS rates at 12, 24 and 36 months were 72.4, 72.4 and 66.3%, respectively (Fig. 1B).

Subgroup analysis. The subgroup analysis was performed based on use of TACE or not and demonstrated that the ORR, DCR, PFS and OS were similar between patients with and without TACE (all $P > 0.05$; Table SI).

Table III. Cox regression analyses on PFS in patients with advanced hepatocellular carcinoma.

Factors	Univariate analysis			Multivariate analysis		
	P-value	HR	95% CI		P-value	HR
			Lower	Upper		
Age (>60 years vs. ≤60 years)	0.074	0.398	0.145	1.093	0.170	0.415
Sex (male vs. female)	0.650	1.290	0.429	3.878	0.579	0.667
HBV history (yes vs. no)	0.629	1.264	0.489	3.270	0.475	2.294
Liver cirrhosis history (yes vs. no)	0.518	1.339	0.552	3.249	0.877	1.179
A history of surgery or TACE (yes vs. no)	0.453	1.390	0.589	3.282	0.942	0.953
Maximum tumor diameter (≥10 cm vs. <10 cm)	0.841	0.894	0.300	2.670	0.700	1.364
Portal vein invasion (yes vs. no)	0.549	1.310	0.541	3.170	0.098	0.329
Extrahepatic metastasis (yes vs. no)	0.430	1.414	0.599	3.338	0.157	2.646
Abnormal ALB (yes vs. no)	0.658	1.240	0.478	3.218	0.533	0.613
Abnormal TBIL (yes vs. no)	0.333	1.570	0.631	3.908	0.842	0.876
Abnormal ALT (yes vs. no)	0.342	1.585	0.613	4.096	0.388	1.856
Abnormal AST (yes vs. no)	0.044	2.461	1.024	5.913	0.111	3.762
AFP (≥200 ng/ml vs. <200 ng/ml)	0.391	0.660	0.256	1.704	0.113	0.315
Treatment line of systematic therapy (second or later vs. first)	0.547	1.338	0.518	3.460	0.237	2.043

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, α -fetoprotein; TACE, transarterial chemoembolization.

Factors	Univariate analysis			Multivariate analysis				
	P-value	HR	95% CI		P-value	HR	95% CI	
			Lower	Upper			Lower	Upper
Age (>60 years vs. ≤60 years)	0.364	0.533	0.137	2.076	0.816	0.774	0.090	6.696
Sex (male vs. female)	0.407	2.404	0.302	19.109	0.986	1.024	0.078	13.524
HBV history (yes vs. no)	0.740	0.805	0.225	2.885	0.427	3.856	0.138	107.513
Liver cirrhosis history (yes vs. no)	0.855	0.890	0.254	3.120	0.491	0.347	0.017	7.053
A history of surgery or TACE (yes vs. no)	0.464	1.598	0.455	5.611	0.914	0.882	0.091	8.525
Maximum tumor diameter (≥10 cm vs. <10 cm)	0.485	1.619	0.418	6.270	0.087	12.040	0.699	207.526
Portal vein invasion (yes vs. no)	0.766	0.813	0.208	3.174	0.067	0.084	0.006	1.192
Extrahepatic metastasis (yes vs. no)	0.361	1.788	0.514	6.224	0.049	9.217	1.007	84.329
Abnormal ALB (yes vs. no)	0.657	1.362	0.348	5.340	0.410	2.512	0.280	22.509
Abnormal TBIL (yes vs. no)	0.833	1.147	0.321	4.107	0.286	0.271	0.025	2.988
Abnormal ALT (yes vs. no)	0.589	1.452	0.374	5.632	0.835	1.292	0.115	14.483
Abnormal AST (yes vs. no)	0.310	1.942	0.540	6.990	0.194	5.234	0.430	63.667
AFP (≥200 ng/ml vs. <200 ng/ml)	0.434	0.538	0.114	2.539	0.080	0.077	0.004	1.355
Treatment line of systematic therapy (second or later vs. first)	0.255	2.090	0.588	7.434	0.054	10.809	0.957	122.073

Table V. Adverse events in patients with advanced hepatocellular carcinoma.

Adverse event	Total (n=39)	Camrelizumab treatment-related (n=39)
Anemia	31 (79.5)	2 (5.1)
Thrombocytopenia	27 (69.2)	1 (2.6)
Leukopenia	25 (64.1)	0 (0.0)
Pain	22 (56.4)	0 (0.0)
Neutropenia	16 (41.0)	2 (5.1)
Fever	13 (33.3)	7 (17.9)
Hypertension	11 (28.2)	0 (0.0)
Decreased appetite	9 (23.1)	0 (0.0)
Nausea and vomiting	9 (23.1)	0 (0.0)
Diarrhea	3 (7.7)	2 (5.1)
Fatigue	3 (7.7)	1 (2.6)
RCCEP	3 (7.7)	3 (7.7)

Data presented as n (%). RCCEP, reactive cutaneous capillary endothelial proliferation.

Factors affecting PFS and OS. Univariate Cox regression analysis revealed that abnormal aspartate aminotransferase levels (yes vs. no) were associated with higher risk of disease progression or mortality [hazard ratio (HR), 2.461; $P=0.044$]. However, in multivariate Cox regression analysis, none of the evaluated clinical characteristics were associated with PFS (all $P>0.05$; Table III). Furthermore, regarding OS, univariate Cox regression analysis revealed no associations between OS and clinical features (all $P>0.05$). By contrast, multivariate Cox regression analysis identified that extrahepatic metastasis (yes vs. no) was independently associated with higher mortality risk (HR, 9.217; $P=0.049$; Table IV).

Adverse events. Adverse events are summarized in Table V. The most common adverse events were anemia (79.5%), thrombocytopenia (69.2%), leukopenia (64.1%) and pain (56.4%). Other adverse events included neutropenia (41.0%), fever (33.3%), hypertension (28.2%), decreased appetite (23.1%), nausea and vomiting (23.1%), diarrhea (7.7%), fatigue (7.7%) and reactive cutaneous capillary endothelial proliferation (RCCEP; 7.7%). All adverse events were of grade 1-2. In addition, camrelizumab treatment-related adverse events included fever (17.9%), RCCEP (7.7%), anemia (5.1%), neutropenia (5.1%), diarrhea (5.1%), thrombocytopenia (2.6%) and fatigue (2.6%). Treatment modifications, including dose reduction or delay, were required for 1 patient (2.6%) due to toxicity.

Discussion

Systemic therapy still remains the gold standard treatment approach for advanced HCC, with sorafenib serving as the standard first-line treatment for a number of years. However, in previous years, the combination of immune checkpoint inhibitors and TKIs has shown encouraging efficacy, thus emerging as a potential treatment option for this type of

cancer (4,12,15). Camrelizumab, as a PD-1 inhibitor, might also exert its antitumor effect by other mechanisms, such as regulating the immune infiltration, which is demonstrated by previous studies on tumor microenvironment-related biomarkers for predicting camrelizumab efficacy (16,17). Besides, camrelizumab combined with apatinib potentially exert synergistic effects. Previous studies demonstrated that apatinib could increase PD-1 expression in tumor-infiltrating CD4⁺ cells, thus improving the efficacy of camrelizumab (18,19). The present study reports the efficacy and safety of camrelizumab combined with apatinib in a single center; meanwhile, our study also reports the prognostic factors, which helps the early recognition of prognosis to facilitate early intervention and improve outcome in advanced HCC patients receiving camrelizumab combined with apatinib.

Clinically, previous studies have evaluated the efficacy of camrelizumab combined with apatinib in patients with advanced HCC, reporting ORR of 17.3-45.7%, DCR of 57.7-78.6%, median PFS of 5.5-5.7 months and 12-month OS rates of 68.2-76.5% in these patients (11,12,20). In the present study, an ORR of 35.9%, a DCR of 82.1%, a median PFS of 24.0 months and a 12-month OS rate of 72.4% was reported for patients with advanced HCC treated with the combination of camrelizumab plus apatinib. The results on ORR, DCR and 12-month OS rate were consistent with those of previous studies, while a prolonged median PFS was reported (11,12,20). This discrepancy could be due to differences in baseline patient characteristics. Notably, in the present study, the proportion of patients with extrahepatic metastasis was lower (43.6%) compared with that reported in previous studies (64.3-75.8%) (11,12). In addition, the proportion of patients with maximum tumor diameter of ≥ 10 cm was also lower (20.5%) compared with a previous study (40.4%) (20). Therefore, the aforementioned findings suggest that the patients included in the present study could suffer from a less aggressive disease compared with the previously published studies (11,12,20).

Notably, in the present study, the complete response rate was 25.6%, which was markedly higher compared with that reported in the CARES-310 phase III trial (1.1%). This difference could be attributed to the fact that in the present study, 25.6% of patients received TACE, which was not applied in the CARES-310 phase III trial (12). Therefore, it is hypothesized that TACE could improve the complete response of camrelizumab plus apatinib therapy in patients with advanced HCC. However, further studies are required to validate these findings.

The present study also aimed to identify factors affecting PFS and OS in patients with advanced HCC treated with camrelizumab plus apatinib. Multivariate Cox regression analyses demonstrated that extrahepatic metastasis was independently associated with higher mortality risk in these patients. This result was consistent with those reported in previous studies (21,22). However, this index was not associated with the mortality in the univariate Cox regression analysis, potentially due to small sample size. No other clinical factors were associated with PFS or OS in these patients. This finding could be due to the sample size, which could weaken statistical power. Furthermore, the subgroup analysis

indicated that the ORR, DCR and PFS were not different between patients with or without TACE. We hypothesize the potential reasons might be as follows: i) The small sample size would reduce the statistical power; and ii) patients who received TACE in addition to camrelizumab plus apatinib presented with heavier disease burden such as higher proportion of patients with maximum tumor diameter ≥ 10 cm (40.0 vs. 13.8%), with portal vein invasion (50.0 vs. 27.6%), and Child-Pugh stage B (50.0 vs. 6.3%) compared with those without TACE. Hence, the efficacy was not different between patients with or without TACE.

Previous studies also reported that the most common adverse events in patients with HCC treated with camrelizumab combined with apatinib were anemia (20.0-55.8%), thrombocytopenia (46.3-60.0%) and leukopenia (50.0-57.1%) (11,12,23-25). Consistently, in the present study, anemia (79.5%), thrombocytopenia (69.2%) and leukopenia (64.1%) were the most frequent adverse events in patients with advanced HCC treated with camrelizumab plus apatinib. By contrast, in the present study, the incidence of pain was 56.4%, which was higher than that reported in previous studies (26.8-49.2%) (11,23,25). This could be again explained by the fact that 25.6% of patients in the present study underwent TACE, which is commonly associated with the development of pain (20,26). The incidences of other adverse events, including decreased appetite, nausea and vomiting and diarrhea, were comparable with those observed in previous studies (10,27,28). These results indicate that camrelizumab combined with apatinib could be well-tolerated by patients with advanced HCC. However, further efforts are needed to optimize tolerability. Furthermore, in previous study, the most common adverse events following camrelizumab monotherapy includes the reactive cutaneous capillary endothelial proliferation (67%), proteinuria (23%), and increased alanine aminotransferase (22%) (10). The incidence of most adverse events were numerically far lower than the camrelizumab combined with apatinib therapy, which implied the clinicians to pay attention to balance the clinical efficacy benefit and the risk of adverse events when choosing the monotherapy regimen and the combination regimen.

The present study also has several limitations. Firstly, the inherent drawback of the retrospective and single-arm study design should be considered, which could induce several biases, such as selection bias and incomplete data availability. In addition, the lack of a control group made it difficult to draw a solid conclusion. Therefore, a further randomized and prospective study is needed to eliminate the selection bias in the baseline characteristics, and a control group should be included to explicitly evaluate the benefit of camrelizumab. Secondly, post hoc statistical power analysis using PASS software was performed based on the observed median PFS in the present study and a previous study (29), and a test efficacy of 89.6% was achieved when setting the α -value at 0.05. However, the sample size was still small which limited the statistical power. Furthermore, due to the short follow-up period, the incidence of endpoint events was low in the present study and the median OS was not reached. Consequently, the median OS of patients with advanced HCC

receiving camrelizumab plus apatinib needs more investigation. Thirdly, only patients with advanced HCC from China were enrolled, and therefore future studies involving patients across different geographical regions are warranted to further verify the results. Finally, previously, in patients with HCC, adjuvant therapy following the liver transplantation was reported to improve the prognosis of patients with HCC (30,31). However, this was not considered in the present study. Future studies are needed to evaluate whether the combination of liver transplantation with camrelizumab and apatinib would improve the survival of patients with advanced HCC.

In conclusion, camrelizumab combined with apatinib showed satisfactory treatment efficacy and acceptable tolerance in patients with advanced HCC. Furthermore, extrahepatic metastasis was independently associated with worse OS in the aforementioned patients. These findings could provide real-world evidence supporting the application of camrelizumab plus apatinib in treating patients advanced HCC. However, due to the small sample size in the present study, a further study with a larger sample size is required.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RQ and ZY conceived and designed the study. LY and YS collected the data. RA performed the data analysis. YH and HH contributed to the interpretation of the data. JX analyzed data and drafted the manuscript, while RQ and ZY provided critical revisions. RQ and ZY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the Handan Central Hospital (approval no. 2024029). All patients or their families provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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