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Camrelizumab combined with apatinib in the treatment of patients with hepatocellular carcinoma: a real-world assessment

Dongbo CHEN#, Xiangxun CHEN#, Lei XU, Yichun WANG, Liyang ZHU*, Mei KANG

Department of Radiation Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

**Correspondence: 773080192@qq.com*

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Although a phase II clinical trial confirmed that camrelizumab combined with apatinib is effective in patients with hepatocellular carcinoma (HCC), we generally lack data on the results of this regimen in real-world clinical practice. In this study, the efficacy and safety of camrelizumab combined with apatinib in the treatment of patients with HCC were re-evaluated. Data from 86 patients with HCC were collected and combinatorically treated with camrelizumab and apatinib at the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China. The objective remission rate and disease control rate were 25.6% and 72.1%, respectively. The median progression-free survival was 5 months (95% CI 3.7–6.3 months), and the median overall survival time was 19.0 months (95% CI 16.9–21.1 months). The 12- and 18-month survival rates were 70.9% and 54.2%, respectively. The most common grade 3-4 adverse events were hypertension (24.4%), thrombocytopenia (16.3%), and hyperbilirubinemia (9.3%). Multivariate regression analysis showed that operation history was an independent risk factor for overall survival.

Key words: hepatocellular carcinoma; safety; efficacy; camrelizumab; apatinib

Hepatocellular carcinoma (HCC) is a global health problem, as its incidence has increased sharply in recent years. It is the fourth most common form of malignant tumor reported by the World Health Organization and one of the main leading causes of cancer-related death [1–3]. Most patients with HCC cannot undergo surgical treatment after initial diagnosis and eventually receive systematic treatment [4, 5]. Some drugs provide definite survival benefits similar to monotherapy. The median overall survival time (OS) of first-line treatment using sorafenib and lenvatinib (as well as donafenib in China) has been reported to be 11–14 months [5–7]. Regorafenib, cabozantinib, and ramucirumab exhibited an OS period of 8–11 months as second-line treatments [8–10].

Programmed death 1 (PD-1) inhibitors have also demonstrated good clinical activity as second-line therapies for patients with HCC in phase I/II studies. However, their response rates were only 15–20% in the phase III study of a single-drug treatment in the first and second line, which did not significantly improve the OS rate of patients with HCC [11, 12]. The IMbrave150 study reported the effectiveness of the first-line application of atezolizumab combined with bevacizumab in the treatment of patients with unresectable HCC. The median progression-free survival (PFS) of the patients was 6.8 months, and the OS rate at 12 months was 67.2% [13]. The results of the KEYNOTE-524 research study indicated that the objective remission rate (ORR) of locally advanced patients with unresectable HCC after treatment using pembrolizumab combined with lenvatinib was 46.0% [14].

The curative effect of single-drug targeted therapy or immunotherapy on patients with HCC is limited. The first-line combination therapy approved by the Food and Drug Administration (FDA) has been shown to be effective only in a few regions of the world. Therefore, it is an urgent medical requisite to find drugs with significantly enhanced curative effects for patients with HCC [15, 16]. Camrelizumab is a PD-1 inhibitor that can bind to the human PD-1 receptor and block the PD-1 or programmed cell death 1 ligand 1 (PD-L1) pathway, thereby restoring the antitumor immunity of the body and forming the basis of cancer immunotherapy [17]. Apatinib is a tyrosine inhibitor that selectively acts on vascular endothelial growth factor receptor 2 (VEGFR-2). It can specifically inhibit the tyrosine kinase activity of VEGFR-2 and reduce tumor angiogenesis [17]. Phase I and II clinical trials indicated that camrelizumab combined

with apatinib exhibited tolerable side effects and prominent antitumor activity in patients with HCC [18–20].

Therefore, in this study, a single-center retrospective analysis was conducted to evaluate the efficacy and safety of drug treatment using camrelizumab combined with apatinib for patients with HCC in China.

Patients and methods

Study design and patients. In this study, data were retrospectively collected from 86 patients with HCC at the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China, from September 2019 to October 2021. The data collection deadline was November 9, 2022. The Ethics Committee of the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China approved this study according to the Helsinki Declaration (approval number: Quick-PJ 2022-08-30). As this study was retrospective, written consent provided by the patients was not needed.

The inclusion criteria were as follows: 1) patients with HCC diagnosed clinically (evaluated by radiology using enhanced computed tomography or magnetic resonance imaging combined with detection of serum tumor markers) or pathologically; 2) over 18 years old; 3) Eastern Cooperative Oncology Group (ECOG) ≤3, Barcelona Clinic Liver Cancer (BCLC) stage A–D stage, Child-Pugh class A–C (The guidelines do not recommend immunotherapy combined with antiangiogenic drugs for patients with ECOG scores of 3 and BCLC D. However, some patients and their families strongly demand active treatment in the clinic, so they used the drug after signing the informed consent form); 4) at least one measurable lesion; 5) complete follow-up until death or study stop (November 09, 2022). The exclusion criteria included the following: 1) ECOG >3; 2) severe esophageal varices detected by gastroscopy; 3) a history of autoimmune diseases; 4) class III–IV cardiopulmonary insufficiency and hypertension, which are not controlled; and 5) hemorrhagic symptoms or definite bleeding tendency and abnormal coagulation function occurring within 3 months of receiving the treatment.

The patient received an intravenous injection of camrelizumab (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China) 200 mg (for body weight ≥50 kg) or 3 mg/kg (for body weight <50 kg) followed by oral apatinib (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China) at a dosage of 250 mg/day every 3 weeks. Patients were treated until they exhibited intolerable side effects or tumor progression. According to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), 4 weeks after the start of treatment, computerized X-ray tomography or nuclear magnetic resonance imaging technology was used to evaluate the treatment response [21]. This response was reassessed every 8–12 weeks until the patient died or until the study was discontinued. Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0) [22].

Statistical analysis. All data were analyzed using SPSS 27 and R 4.2.2. All data were represented by the mean ± standard deviation and n (%). Student's t-test (or the Mann-Whitney test) was used for continuous variable comparisons, and the chi-square or Fisher exact test was used to compare categorical variables. The Kaplan-Meier method was used to estimate OS and PFS. Multivariate Cox regression analysis was used to determine the independent prognostic factors.

Results

Patient characteristics. From September 2019 to October 2021, 86 eligible patients were registered and received combined treatment with camrelizumab and apatinib. Most patients were males (n=77, 89.5%), including 65 patients in the first-line treatment succession and 21 patients in the second-line or above treatment succession (Table 1). The mean age of the patients was 57.2 years (ranging from 28 to 79 years). 48.8% (n=42) of the study patients had cirrhosis, most patients were BCLC phase C (n=32, 76.2%). The most common underlying liver disease was hepatitis B (n=54, 62.8%). Macrovascular invasion was observed in 28 (32.6%) patients, 27 (31.4%) patients exhibited serum alpha-fetoprotein (AFP) levels above 400 ng/ml. According to the albumin-bilirubin grade (ALBI) score, more than half of the patients exhibited advanced liver dysfunction (ALBI grade ≥2) (n=51, 59.3%). Three patients classified as BCLC D received combined treatment based on the strong demands of the patient and their families, as well as the comprehensive evaluation of the doctor.

Efficacy. As of November 9, 2022, which was the data collection deadline, the median follow-up time of the patients was 13.5 months, and 52 patients died. Two (2.3%) and 20 (23.3%) patients exhibited complete remission (CR) and partial remission (PR), respectively, with ORRs of 25.6%, and 40 (46.5%), and 22 (25.6%) patients with stable disease (SD) and progressive disease (PD), respectively, reported a disease control rate (DCR) of 72.1% (Table 2).

The mPFS (median progression-free survival) of all patients was reported as 5.0 months (95% CI 3.7–6.3 months), with the mPFS of the first-line patients as 6.0 months (95% CI 4.2–7.8 months) and the second-line and above patients as 5.0 months (95% CI 2.8–7.2 months) (Figure 1). The mOS (median overall survival) of the patients was 19.0 months (95% CI 16.9–21.1). The mOS of the first-line patients was 19.0 months (95% CI 16.1–21.9 months) and that of the second-line and above patients was 16.0 months (95% CI 13.9–18.1 months). There was no significant difference in overall survival between the two groups (Figure 2). Kaplan-Meier estimated the 6-month survival rate as 83.7%, the 9-month survival rate as 77.9%, the 12-month survival rate as 70.9%, and the 18-month survival rate as 54.2%. Subgroup analysis showed that out of 86 patients, 22 did not meet the

Table 1. Baseline characteristics of 86 patients.

Characteristics	All patients (n=86)	Characteristics	All patients (n=86)
Age (years, mean±SD)	57.2±9.6	HBV infection	54 (62.8%)
<60	53 (61.6%)	Tumor distribution	
≥60	33 (38.4%)	Single	27 (31.4%)
Weight (kg, mean±SD)	64.2±10.3	Multiple	59 (68.6%)
≤60	33 (38.4%)	Extrahepatic metastasis	44 (51.2%)
>60	53 (61.6%)	Prior treatment	
Sex, male	77 (89.5%)	Targeted therapy	17 (19.8%)
ECOG		Chemotherapy	11 (12.8%)
0	39 (45.3%)	Surgery	31 (36.0%)
1	39 (45.3%)	TACE/TAE/RFA	29 (33.7%)
2	7 (8.1%)	Macrovascular invasion	13 (15.1%)
3	1 (1.2%)	Laboratory parameters	
ALBI grade		Hb (g/l, mean±SD)	128.5±19.3
1	35 (40.7%)	Platelet (10^9/l, mean±SD)	146.8±66.8
2	46 (53.5%)	WBC (10^{12}/l, mean±SD)	5.8±2.6
3	5 (5.8%)	Neutrophils (10^9/l, mean±SD)	4.0±2.2
AFP ≥400 ng/ml	27 (31.4%)	Lymphocyte (10^9/l)	8.1±10.3
Macrovascular invasion	28 (32.6%)	LMR (mean±SD)	4.1±4.3
Cirrhosis	42 (48.8%)	ALT (U/l, mean±SD)	49.9±64.4
Child-Pugh score A	32(76.2%)	AST (U/l, mean±SD)	66.9±61.5
Child-Pugh score B	9 (21.4%)	TBIL (mmol/l, mean±SD)	21.5±15.7
Child-Pugh score C	1 (2.4%)	ALP (U/l, mean±SD)	190.5±164.8
BCLC stage A	1 (2.4%)	TBA (mmol/l, mean±SD)	15.6±15.4
BCLC stage B	6 (14.3%)	ALB (g/l, mean±SD)	37.0±6.30
BCLC stage C	32 (76.2%)	GGT (U/l, mean±SD)	220.9±251.5
BCLC stage D	3 (7.1%)	ALBI (mean±SD)	−2.3±0.6

Abbreviations: ALB-albumin; ALBI grade-albumin-bilirubin grade; ALT-alanine aminotransferase; ALP-alkaline phosphatase; AFP-alpha-fetoprotein; AST-aspartate aminotransferase; BCLC-Barcelona Clinic Liver Cancer; ECOG-Eastern Cooperative Oncology Group; GGT-γ-glutamyl transferase; Hb-hemoglobin; HBV-hepatitis B virus; LMR-lymphocytosis; SD-standard deviation; TACE-transcatheter arterial chemoembolization; TAE-transhepatic arterial embolization; TBA-total bile acid; TBIL-total bilirubin; RFA-radiofrequency ablation; WBC-white blood cell

criteria for phase II clinical enrolment (including 21 patients with a Child-Pugh grade of B–C, 8 patients with an ECOG score of 2–3, and 3 patients with BCLC D). The OS of eligible patients was 22.0 months (95% CI 17.0–27.0), while the OS of non-enrolled patients was 16.0 months (95% CI 12.8–19.2) (Figure 3), with statistically significant differences between the two groups (p=0.048). Three patients with BCLC D had a survival period of less than 6 months. Cox multivariate regression analysis revealed that the independent risk factor for OS was whether the patients had previously undergone surgery (Figure 4).

Toxicity. Among the 86 patients treated with camrelizumab combined with apatinib, 80 (93.0%) patients had at least one treatment-related adverse events (TRAE) (Table 3). Safety was similar between the patients in the first- and second-line cohorts. The most common TRAEs at any level were hypertension (n=56, 65.1%), anemia (n=48, 55.8%), and hyperbilirubinemia (n=45, 52.3%). Sixty patients (69.8%) reported TRAEs of grade 3 or above. The most common adverse events were hypertension (n=21, 24.4%), thrombocytopenia (n=14, 16.3%), and hyperbilirubinemia (n=8, 9.3%). Eight patients (9.3%) terminated the combined treatment of camrelizumab and apatinib due to TRAEs.

Table 2. Evaluation of tumor efficacy.

Best response	All patients	First-line	Second-line and above
	(n=86)	(n=65)	(n=21)
Complete remission	2 (2.3%)	2 (3.1%)	0
Partial remission	20 (23.3%)	17 (26.2%)	3 (14.3%)
Stable disease	40 (46.5%)	29 (44.6%)	11 (52.4%)
Disease progression	22 (25.6%)	15 (23.1%)	6 (28.6%)
Not evaluable	2 (2.3%)	2 (3.1%)	0
ORR, n (%)	22 (25.6%)	19 (29.2%)	3 (14.3%)
DCR, n (%)	62 (72.1%)	48 (73.8%)	14 (66.7%)

Three patients developed upper gastrointestinal bleeding, two patients terminated treatment without any specific reason, and one (1.2%) experienced drug-related death due to upper gastrointestinal bleeding and rupture of liver lesions entering the pleural cavity.

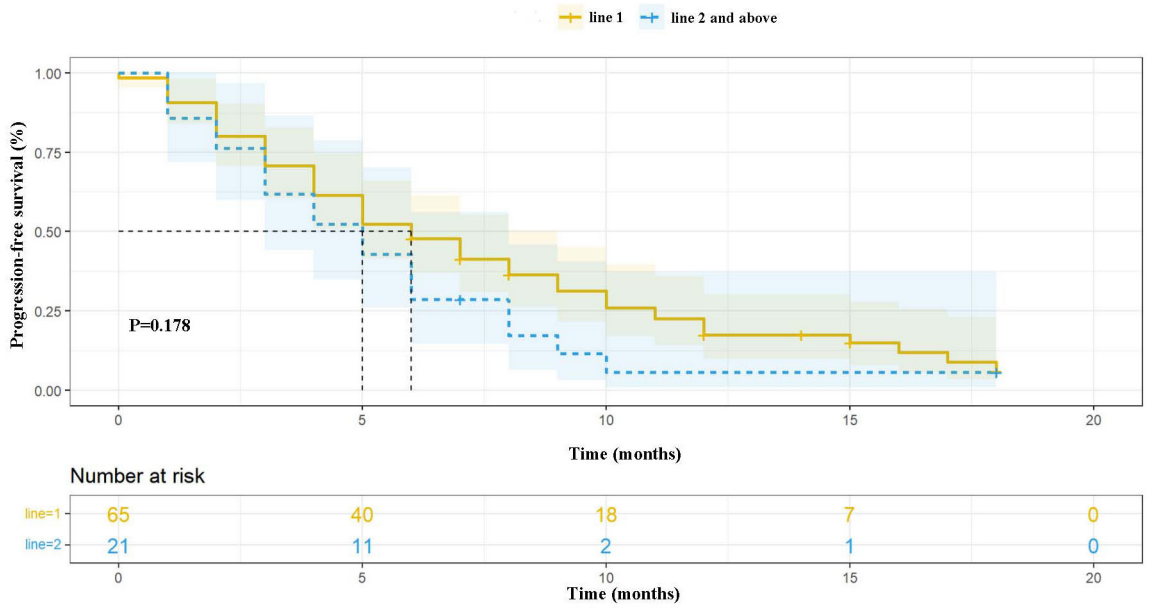

Figure 1. Kaplan-Meier curves of PFS for first-line and second-line and above treatments

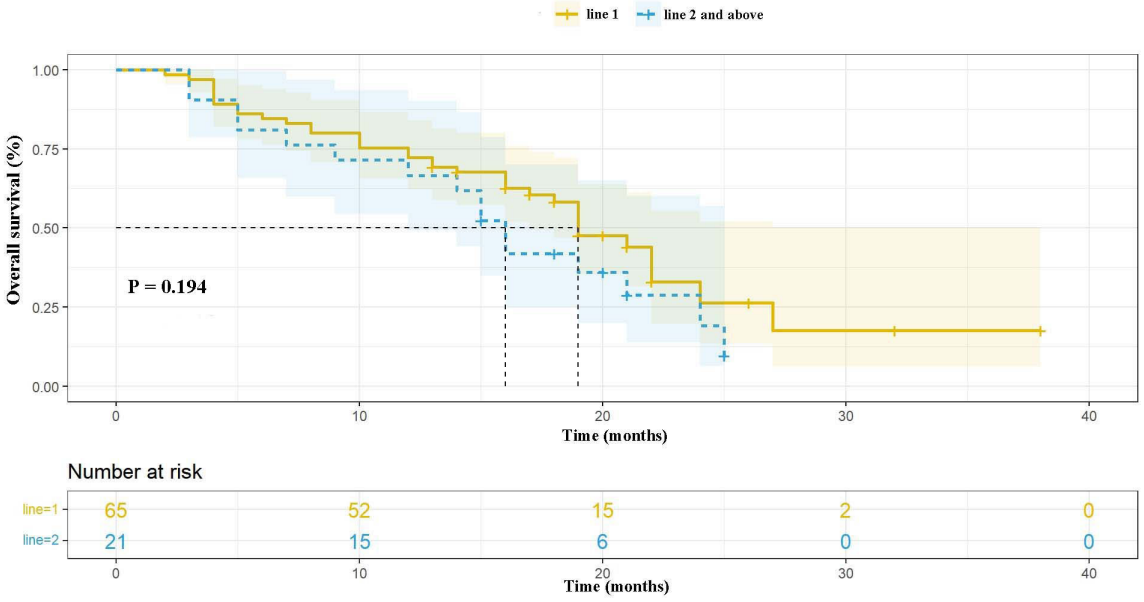

Figure 2. Kaplan-Meier curves of OS for the first-line and second-line and above treatments.

Discussion

HCC is a refractory tumor, and combined immunotherapy, including a combination of antiangiogenic targeted drugs and systemic chemotherapy, has been utilized as the main strategy to improve the curative effect of immune checkpoint inhibitor (ICI) monotherapy in patients with HCC [14, 23–25]. The IMbrave150 study compared the therapeutic effect and safety of atezolizumab combined with bevacizumab versus sorafenib in patients with unresectable HCC who had not previously received systemic therapy. The subgroup from China exhibited an mPFS of 5.7 months upon combination treatment with atezolizumab and bevacizumab. The 6- and 12-month survival rates were 86.6% and 76.7%, respectively, and mOS was not attained [26]. These results suggest that combination drug treatment is advanta-

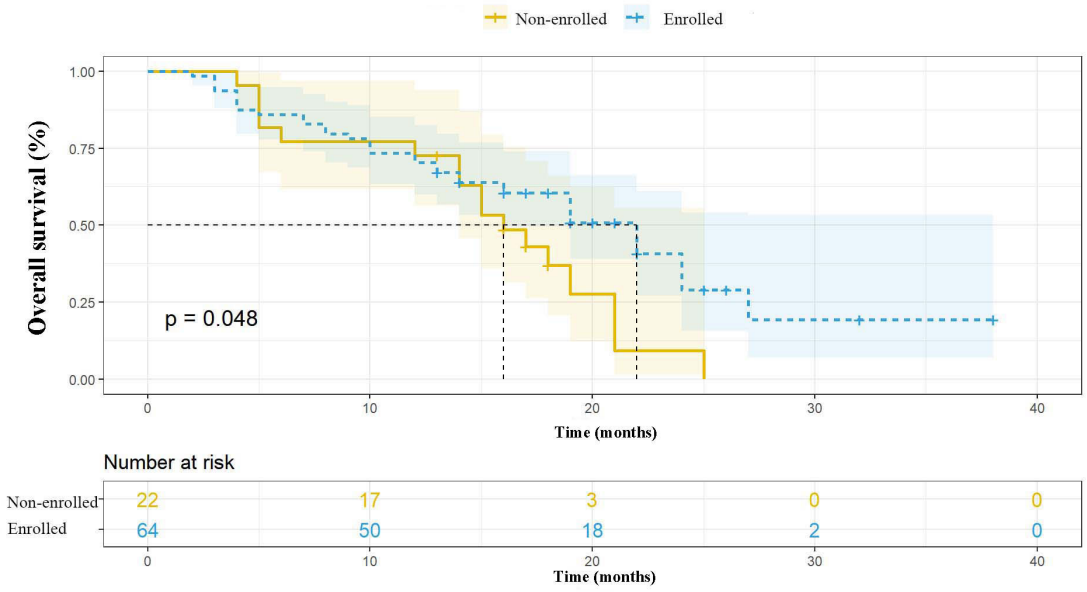

Figure 3. Kaplan-Meier curves of OS for the non-enrolled group and the enrolled group.

Table 3. Treatment-related adverse events and the number of occurrences.

	All patients (n=86)		First-line (n=65)		Second-line (n=21)	
Any	80 (93.0%)		63 (96.9%)		17 (91.0%)	
Grade 3/4	60 (69.8%)		47 (72.3%)		13 (61.9%)	
Led to treatment discontinuation	14 (16.3%)		12 (18.5%)		2 (9.5%)	
Led to death	1 (1.2%)		1 (1.5%)		0	
	Grade Any	**Grade** 3/4	**Grade** Any	**Grade** 3/4	**Grade** Any	**Grade** 3/4
Hypertension	56 (65.1%)	21(24.4%)	44 (67.7%)	17 (26.2%)	12 (57.1%)	7 (33.3%)
Proteinuria	43 (50.0%)	4 (4.7%)	33 (50.8%)	3 (4.6%)	10 (47.6%)	1 (4.8%)
Hand-foot syndrome	42 (48.8%)	6 (7.0%)	33 (50.8%)	5 (7.7%)	9 (42.9%)	1 (4.8%)
Reactive cutaneous capillary endothelial proliferation	20 (23.3%)	0	13 (20.0%)	0	8 (38.1%)	0
Hematuria	21 (24.4%)	0	14 (21.5%)	0	7 (33.3%)	0
Abdominal pain	25 (29.1%)	1 (1.2%)	20 (30.8%)	1 (1.5%)	5 (23.8%)	0
Abdominal distention	21 (24.4%)	0	16 (24.6%)	0	5 (23.8%)	0
Leukopenia	38 (44.2%)	3 (3.5%)	30 (46.2%)	3 (4.6%)	8 (38.1%)	0
Anemia	48 (55.8%)	1 (1.2%)	36 (55.4%)	1 (1.5%)	12 (57.1%)	0
Neutropenia	35 (40.7%)	7 (8.1%)	28 (43.1%)	6 (9.2%)	7 (33.3%)	1 (4.8%)
Thrombocytopenia	42 (48.8%)	14 (16.3%)	33 (50.8%)	11 (16.9%)	9 (42.9%)	3 (14.3%)
Aspartate aminotransferase increased	40 (46.5%)	5 (5.8%)	32 (49.2%)	4 (6.2%)	8 (38.1%)	1(4.8%)
Alanine aminotransferase increased	42 (48.8%)	7 (8.1%)	30 (46.2%)	5 (7.7%)	12 (57.1%)	2 (9.5%)
Hyperbilirubinemia	45 (52.3%)	8 (9.3%)	33 (50.8%)	6 (9.2%)	12 (57.1%)	2 (9.5%)
Hypoalbuminemia	41 (47.7%)	0	30 (46.2%)	0	11 (52.4%)	0
Hypokalemia	8 (9.3%)	2 (2.3%)	7 (10.8%)	2 (3.1%)	1 (4.8%)	0
Hypothyroidism	15 (17.4%)	0	12 (18.5%)	0	3 (14.3%)	0

geous over single-drug targeting or immunization alone. A nonrandomized, open-label phase II clinical trial studied the curative effect of camrelizumab combined with apatinib in the treatment of HCC. For the first- and second-line successions, the ORRs were 34.3% and 22.5%, respectively. The mPFS of the two groups was 5.7 and 5.5 months, respectively. The 12-month survival rates of the two groups were 74.7% and 68.2%, respectively. The mOS was not attained, which was not inferior to the efficacy of the IMbrave150 study [20]. Our study exhibited the mPFS of all patients who received

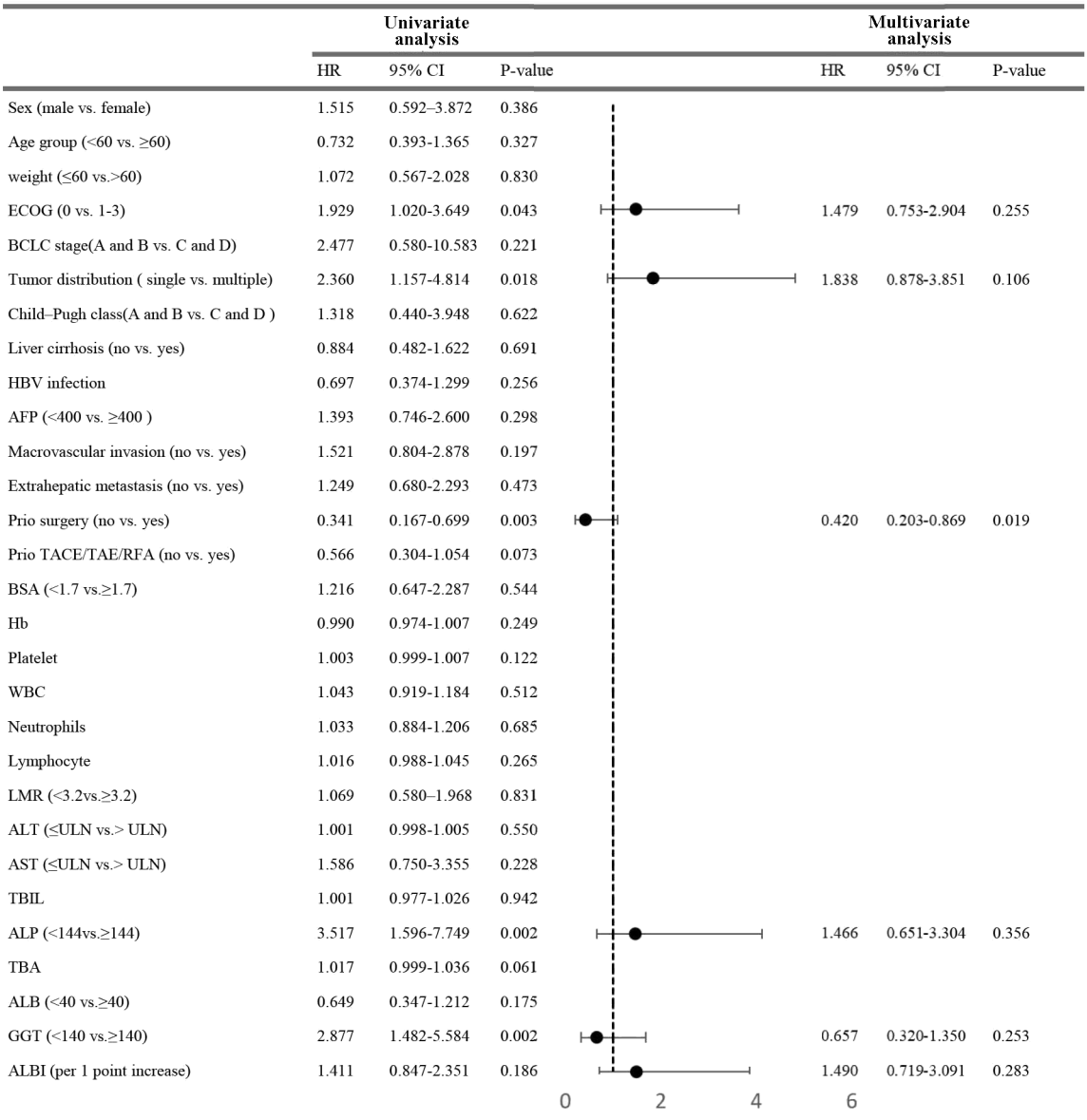

Figure 4. Univariate Cox proportional hazards regression model analysis for OS. Abbreviations: ALB-albumin; ALBI-albumin-bilirubin; ALT-alanine aminotransferase; ALP-alkaline phosphatase; AFP-alpha-fetoprotein; AST-aspartate aminotransferase; BCLC-Barcelona Clinic Liver Cancer; BSA-body surface area; CI-confidence interval; ECOG PS-Eastern Cooperative Oncology Group Performance Status; GGT-γ-glutamyl transpeptidase; Hb-hemoglobin; HBV-hepatitis B virus; HR-hazard ratio; OS-overall survival; LMR-lymphocyte/monocyte ratio; RFA-radiofrequency ablation; TACE-transcatheter arterial chemoembolization; TAE-transcatheter arterial embolization; TBA-total bile acid; WBC-white blood cell; TBIL-total bilirubin

camrelizumab combined with apatinib as 5.0 months, with mPFS of first-line patients as 6.0 months and second-line patients, and above as 5.0 months. The mOS of all patients was 19.0 months. Kaplan-Meier estimated the 6-month survival rate as 83.7%, the 9-month survival rate as 77.9%, the 12-month survival rate as 70.9%, and the 18-month survival rate as 54.2%. The patient population in our study was more diverse than that in the phase II study, and some patients exhibited poorer constitution, so the survival period was shortened as in the phase II clinical trial. In this study, mPFS and OS were superior to the second-line monotherapy of apatinib (mPFS 4.5 months, mOS 8.7 months) or second-line monotherapy of camrelizumab (mPFS 2.0 months, mOS 14.0 months) [27, 28]. This further proved that camrelizumab combined with apatinib exhibited a promising antitumor effect in patients with HCC. Compared with the historical data of PD-1 and targeted monotherapy, PFS and OS had significant advantages. Subgroup analysis showed that the OS of patients eligible for phase II enrolment was 22.0 months, while the OS of patients not eligible for enrolment was 16.0

months. This suggested that some patients who did not meet the clinical conditions can still benefit from it, although the curative effect was not as good as that of the enrolled patients. Three patients with BCLC D had a survival period of less than 6.0 months, suggesting that terminal patients are not suitable for combined therapy. Cox multivariate regression analysis revealed that the independent risk factor for OS was whether the patients had previously undergone surgery.

In this study, 93.0% of patients exhibited at least one TRAE, which was lower than that reported for the open-label phase II clinical trial [20]. Additionally, 69.8% of patients reported TRAEs of grade 3 or above. Three patients exhibited upper gastrointestinal bleeding, two patients terminated the treatment, and one experienced drug-related death due to upper gastrointestinal bleeding and rupture of liver lesions entering the pleural cavity. Hemorrhage is a common adverse reaction of apatinib, which still needs to be considered before implementing combination treatment. Compared with camrelizumab monotherapy, the incidence of reactive cutaneous capillary endothelial (RCCEP) in combination therapy is lower. Many studies have reported a similar situation, which may be attributed to the involvement of the VEGF signaling pathway in the pathogenesis of RCCEP [29–31].

This experiment presents several limitations. First, there was no control group with sorafenib, and second, this was a single-center retrospective study with a relatively small sample size, which may reduce the statistical effectiveness.

Conclusively, in this study, we demonstrated that camrelizumab combined with apatinib has a higher ORR, lasting response, long survival time, and manageable safety in the treatment of patients with HCC. Some patients who do not meet the clinical inclusion criteria can still benefit from the combined regimen (but not including BCLC stage D). Therefore, this combination therapy may be applied as a new treatment option for first- or multiline treatment of patients with HCC.

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