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Editorial Board Member of *World Journal of Clinical Oncology*, Zhen-Yu Pan, MD, PhD, Professor, Department of Radiation Oncology, Huizhou Hospital Affiliated to Guangzhou Medical University, Huizhou 516002, Guangdong Province, China. 2023621056@gzhmu.edu.cn

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WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Cohort study on the treatment of *BRAF V600E* mutant metastatic colorectal cancer with integrated Chinese and western medicine

Jiang-Yu Bian, Yu-Fang Feng, Wen-Ting He, Tong Zhang

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Jiang-Yu Bian, Tong Zhang, Department of Oncology, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing 100091, China

Yu-Fang Feng, Department of Oncology, The Fourth Clinical Medical College of Xinjiang Medical University, Urumqi 830001, China

Wen-Ting He, Department of Oncology, Traditional Chinese Medicine Hospital Affiliated to Xinjiang Medical University, Urumqi 830001, China

Co-corresponding authors: Wen-Ting He and Tong Zhang.

Corresponding author: Tong Zhang, MD, Associate Chief Physician, Department of Oncology, Xiyuan Hospital of China Academy of Chinese Medical Sciences, No. 1 Xiyuan Playground, Haidian District, Beijing 100091, China. ashtray7654@126.com

Abstract

BACKGROUND

Patients with *BRAF V600E* mutant metastatic colorectal cancer (mCRC) have a low incidence rate, poor biological activity, suboptimal response to conventional treatments, and a poor prognosis. In the previous cohort study on mCRC conducted by our team, it was observed that integrated Chinese and Western medicine treatment could significantly prolong the overall survival (OS) of patients with colorectal cancer. Therefore, we further explored the survival benefits in the population with *BRAF V600E* mutant mCRC.

AIM

To evaluate the efficacy of integrated Chinese and Western medicine in the treatment of *BRAF V600E* mutant metastatic colorectal cancer.

METHODS

A cohort study was conducted on patients with *BRAF V600E* mutant metastatic colorectal cancer admitted to Xiyuan Hospital of China Academy of Chinese Medical Sciences and Traditional Chinese Medicine Hospital of Xinjiang Uygur Autonomous Region from January 2016 to December 2022. The patients were divided into two cohorts.

RESULTS

A total of 34 cases were included, with 23 in Chinese-Western medicine cohort

(cohort A) and 11 in Western medicine cohort (cohort B). The median overall survival was 19.9 months in cohort A and 14.2 months in cohort B, with a statistically significant difference (P = 0.038, hazard ratio = 0.46). The 1-3-year survival rates were 95.65% (22/23), 39.13% (9/23), and 26.09% (6/23) in cohort A, and 63.64% (7/11), 18.18% (2/11), and 9.09% (1/11) in cohort B, respectively. Subgroup analysis showed statistically significant differences in median OS between the two cohorts in the right colon, liver metastasis, chemotherapy, and first-line treatment subgroups (P < 0.05).

CONCLUSION

Integrated Chinese and Western medicine can prolong the survival and reduce the risk of death in patients with *BRAF V600E* mutant metastatic colorectal cancer, with more pronounced benefits observed in patients with right colon involvement, liver metastasis, combined chemotherapy, and first-line treatment.

Key Words: Metastatic colorectal cancer; *BRAF V600E* mutation; Integrated Chinese and Western medicine; Cohort study

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Core Tip: Patients with *BRAF V600E* mutant metastatic colorectal cancer (mCRC) have a much lower median overall survival than patients without *BRAF V600E* mutations. This study employed a retrospective cohort design and confirmed that in the real world, compared to chemotherapy and/or targeted therapy, combined treatment with integrated Chinese and Western medicine significantly extended overall survival and reduced the risk of death in *BRAF V600E* mutated mCRC patients, while being more effective in patients involving right colon, liver metastases, combined chemotherapy, and first-line therapy.

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INTRODUCTION

In patients with metastatic colorectal cancer (mCRC), BRAF mutation are found in approximately 5%-12% of cases, with the majority (about 80%) being *BRAF V600E* mutation. Research has demonstrated that *BRAF V600E* mutant mCRC exhibits unique biological activity and clinical characteristics when compared to *non-BRAF V600E* mutant mCRC[1].

BRAF V600E mutant mCRC have been associated with older age, right-sided colon involvement, and female gender. These mutations are also correlated with reduced chemotherapy response and poor prognosis, making them a poor prognostic biomarker. The median overall survival (mOS) for patients with *BRAF V600E* mutant mCRC is typically only 9-14 months[2,3], which is significantly lower than the mOS of approximately 40 months for *non-BRAF V600E* mutant mCRC patients[4]. To address this challenge in clinical treatment, previous studies have explored the use of integrated Chinese and Western medicine in prolonging the overall survival (OS) of mCRC patients[5-7]. However, there is currently a lack of clinical research specifically focusing on the use of integrated Chinese and Western medicine in treating *BRAF V600E* mutant mCRC. In this study, our team aims to compare the survival outcomes of patients with *BRAF V600E* mutant mCRC who were treated with integrated Chinese and Western medicine *vs* those treated with Western medicine alone. We will conduct a retrospective cohort study in a real-world setting to gather data and analyze the effectiveness of this treatment approach. By doing so, we hope to contribute valuable insights into the potential benefits of integrated Chinese and Western medicine for patients with *BRAF V600E* mutant mCRC.

MATERIALS AND METHODS

Source of cases

This study collected data from patients with *BRAF V600E* mutant mCRC who were treated at Xiyuan Hospital of China Academy of Chinese Medical Sciences and Xinjiang Uyghur Autonomous Region Traditional Chinese Medicine Hospital from January 1, 2016 to December 31, 2022.

Inclusion criteria

The study included patients who met the following: (1) Confirmed diagnosis of colorectal cancer through pathology; (2) Detection of *BRAF V600E* mutation using second-generation gene sequencing technology; (3) Presence of distant metastasis or local recurrence, clinical stage IV; (4) Age ≥ 18 years; and (5) Karnofsky Performance Score ≥ 70.

Exclusion criteria

The study excludes patients who meet any of the following criteria: (1) Severe organ dysfunction in the heart, liver, lungs, kidneys, *etc.*; (2) Patients with complete intestinal obstruction or unable to take oral medications for various reasons; (3) History of previous or concurrent malignant tumors, excluding cured basal cell carcinoma of the skin and cervical carcinoma in situ; (4) Unable to be followed up in an outpatient or telephone setting; and (5) Severe information deficiency that affects treatment evaluation.

Exit or dropout criteria and handling

If a patient cannot be followed up in an outpatient setting and three consecutive telephone follow-ups cannot be connected (due to reasons such as no answer, phone off, or refusal to answer), or if the contact number is invalid, it is considered as a lost to follow-up (dropout) case. The outcome indicator is calculated until the last follow-up time available for that patient.

Exposure factors and grouping

A retrospective cohort study was conducted, with "whether receiving ≥ 3 months of traditional Chinese medicine 'staged treatment'" as the exposure factor. Participants who meet this exposure factor are assigned to the Chinese-Western medicine cohort (cohort A) and receive integrated Chinese and Western medicine. Participants who do not meet this exposure factor are assigned to the Western medicine cohort (cohort B) and receive standard Western medicine treatment.

Western medicine treatment

According to the "Clinical Practice Guidelines for Colorectal Cancer" (2021 edition) recommended by the National Comprehensive Cancer Network[8], the treatment regimen for colorectal cancer encompasses chemotherapy drugs, including fluorouracil. Additionally, targeted drugs like cetuximab, bevacizumab, regorafenib, and vemurafenib are also recommended. The specific implementation of these treatment drugs and dosages is determined by the clinical doctor based on the guidelines. It is important for the doctor to assess the individual patient's condition and make personalized treatment decisions accordingly.

Chinese medicine treatment

The Chinese medicine treatment for colorectal cancer can be divided into three stages as follows.

Stage 1: From the day before chemotherapy to the 6th day. During this stage, it is recommended to take Liu Jun An Wei Fang orally. This herbal formula consists of ingredients such as Taizishen, fried Baizhu, Fuling, and Jiang Banxia. Take one dose daily, decocted in water, and consume it warm twice in the morning and evening.

Stage 2: From the 7th day to the 20th day of chemotherapy. During this stage, it is advised to take Qi Tu Er Zhi Fang orally with modifications. This formula includes ingredients like raw Huangqi, Tusizi, Nüzhenzi, and Mò Hànlián. Take one dose daily, decocted in water, and consume it warm twice in the morning and evening.

Stage 3: Maintenance treatment stage of first-line or second-line Western medicine treatment. In this stage, which involves single-drug chemotherapy ± targeted therapy, the overall treatment principle is to "strengthen the spleen, nourish the kidneys, and detoxify". The prescription is primarily based on Si Jun Zi Tang, with flexible modifications using Chinese herbs that have functions such as clearing heat and detoxification, resolving phlegm and dispersing nodules, and promoting blood circulation and resolving stasis. Some examples of these herbs include Baihua Shechetoucao, Banzhilian, Shijianchuan, Shemei, and Longkui.

Follow-up

In addition to regular follow-up visits during hospitalization and outpatient visits, a telephone follow-up is also required every 3 months. The key points of the follow-up include the patient's survival status, whether they have received Chinese medicine treatment for more than 3 months, and any major adverse reactions during the treatment period.

Outcome

Overall survival: To calculate the OS for mCRC patients, we need to consider the time from diagnosis to death. For patients who are still alive at the last follow-up, their OS is calculated based on the time from diagnosis to the last follow-up, considering them as censored. For patients lost to follow-up, their OS is calculated based on the time from diagnosis to the last follow-up before the loss, also considering them as censored.

Cumulative survival rates at 1, 2, and 3 years for two cohorts: The number of surviving patients at 1, 2, and 3 years is divided by the total number of cases in each group.

Statistical analysis

Using SAS JMP (Pro 14.0) software for data processing. Baseline analysis: *t*-test was used for continuous variables, rank sum test was used for non-conforming variables, and χ^2 test was used for categorical variables. If the sample size does not meet the requirements for the χ^2 test, Fisher's exact test will be used. OS analysis will be conducted using the Kaplan-Meier method to plot survival curves, and group comparisons will be performed using the log-rank test. Cumulative survival rates at 1, 2, and 3 years will be calculated. The significance level is set at $\alpha = 0.05$. A *P* value less than 0.05 in-

dicates a statistically significant difference. Subgroup analysis will be conducted based on primary site (left colon/right colon), chemotherapy (yes/no), targeted therapy (yes/no), and liver metastasis (yes/no).

RESULTS

Patients

This study included a total of 586 participants, with 34 participants meeting the inclusion criteria. Among them, 23 participants were in the Chinese-Western medicine treatment group (cohort A), and 11 participants were in the Western medicine treatment group (cohort B; Figure 1). The last follow-up was conducted on June 20, 2023. 31 participants died by the last follow-up, and there were no cases lost to follow-up. The median follow-up time was 32.5 months. Baseline information is shown in Table 1.

OS

The mOS for the cohort A was 19.9 months, while the mOS for the cohort B was 14.2 months. The difference was statistically significant [P = 0.038, hazard ratio (HR) = 0.46], as shown in Figure 2.

The cumulative survival rates for the first, second, and third years in cohort A were 95.65% (22/23), 39.13% (9/23), and 26.09% (6/23) respectively. In cohort B, the survival rates for the first, second, and third years were 63.64% (7/11), 18.18% (2/11), and 9.09% (1/11) respectively.

Subgroup analysis

In the subgroup analysis of right-sided colon, liver metastasis, chemotherapy, and first-line treatment, there was a statistically significant difference in mOS in both cohorts. In the targeted therapy subgroup, the cohort A showed an extension of 12.8 months in mOS compared to the cohort B. However, due to the small sample size, the difference in mOS did not reach statistical significance (Table 2 and Figure 3).

Safety

No liver and kidney function damage, abnormal electrocardiogram, and allergic reaction related to Chinese medicine treatment were found. The incidence of adverse events related to Chinese medicine treatment: diarrhea and oral mucositis (both grade 1) in the Chinese-Western medicine cohort, and the condition improved after symptomatic treatment.

DISCUSSION

The survival of mCRC patients with *BRAF V600E* mutant is significantly worse than that of patients without this mutation, which poses a challenge in the clinical treatment of mCRC[9]. Due to the small proportion of this population, it is difficult to conduct large-scale clinical studies. The combination of three drugs (oxaliplatin, irinotecan, fluoropyrimidine) with vemurafenib is the standard first-line treatment for *BRAF V600E* mutant mCRC[10], survival period is no more than 14 months. This study results confirm that compared with traditional chemotherapy and/or targeted therapy, the combination of Chinese medicine treatment can significantly prolong the OS of patients, reduce the risk of death, and demonstrate good safety. A comparison of baseline data between the two cohorts revealed no statistically significant differences, indicating that the groups were balanced and comparable. Survival analysis showed that the mOS in the Chinese-Western medicine cohort and the Western medicine cohort was 19.9 months and 14.2 months, respectively, with a statistically significant difference (P = 0.038, HR = 0.46), suggesting that the integration of Chinese and Western medicine can significantly improve the survival time of patients and reduce the risk of death by 54%. The survival rates in the 1, 2, and 3 years in the Chinese-Western medicine cohort were all higher than those in the Western medicine cohort. Moreover, the benefits of combining Chinese medicine treatment were more pronounced in the first-line treatment, with an mOS of 21 months (P = 0.003, HR = 0.25), suggesting that clinicians should integrate Chinese medicine treatment early on while providing patients with standard first-line treatment, as earlier integration of Chinese medicine treatment leads to more significant improvements in patient survival benefits[7], rather than starting Chinese medicine treatment after conventional Western medicine treatment fails. In the prespecified subgroups, except for the first-line treatment subgroup, the survival periods in the Chinese-Western medicine cohort exceeded 2 years for the right-sided and combined targeted therapy subgroups. For the liver metastasis and combined chemotherapy subgroups, the survival periods reached 21 months, which were significantly longer than those in the Western medicine cohort, with statistically significant differences. For the left-sided and non-liver metastasis subgroups, the mOS were 19.9 *vs* 16.3 months and 19.2 *vs* 16.25 months, respectively, indicating a trend of longer survival compared to the Western medicine cohort. All patients in the Western medicine cohort received chemotherapy, while 7 patients in the Chinese-Western medicine cohort only received pure Chinese medicine treatment due to intolerance to chemotherapy, and their mOS still reached 18 months. This suggests that regardless of how modern medicine categorizes the characteristics of mCRC populations, the combination of Chinese medicine treatment can be beneficial.

Why can the combination of Chinese medicine treatment achieve benefits across "all populations" without being limited by population characteristics? The essence of Chinese medicine treatment lies in its holistic approach and syndrome differentiation and treatment. It adjusts the relationship between the body's “pathogenic factors” and “vital energy” through the method of "reducing excess and supplementing deficiency", aiming to achieve or approach a

Table 1 Baseline characteristics of patients, *n* (%)

Project	Cohort A (*n* = 23)	Cohort B (*n* = 11)	Rank sum /χ^2 /Fisher's test	*P* value
Age (year)	54 (51.64)	53 (44.70)	-0.387	0.698
Gender				
Male	12 (52.17)	4 (36.36)	-	0.477
Female	11 (47.83)	7 (63.63)		
Primary site				
Right-side colon	12 (52.17)	6 (54.55)	0.017	0.896
Left-side colon	11 (47.83)	5 (45.45)		
Liver metastasis				
Yes	11 (47.83)	5 (45.45)	0.017	0.896
No	12 (52.17)	6 (54.55)		
Peritoneal metastasis				
Yes	5 (21.74)	3 (27.27)	-	1.000
No	18 (78.26)	8 (72.73)		
Chemotherapy				
Yes	16 (69.57)	11 (100.00)	-	0.069
No	7 (30.43)	0 (0.00)		
Targeted therapy				
Yes	14 (60.87)	6 (54.55)	0.122	0.726
No	9 (39.13)	5 (45.45)		

Table 2 Subgroup analysis

Subgroup	mOS (month)		χ^2	*P* value	HR (95%CI)
	Cohort A	Cohort B			
Right-side colon	25.5	10.15	6.335	0.012	0.25 (0.07, 0.83)
Liver metastasis	21	8.1	7.192	0.007	0.22 (0.06, 1.80)
Targeted therapy	26	13.2	3.918	0.073	0.40 (0.14, 1.20)
Chemotherapy	21	14.2	5.475	0.019	0.38 (0.17, 0.90)
First-line treatment	21	13.2	8.597	0.003	0.25 (0.09, 0.67)

mOS: Median overall survival.

balanced state of "Yin and Yang in harmony". However, in addition to the disease itself, treatment factors can also cause the body's functions to deviate from their normal state. Chinese medicine treatment can promptly and dynamically correct this "deviation".

The combination of Chinese medicine treatment with Western medicine treatment in this study follows the treatment concept of "staged treatment" in Chinese medicine. This approach involves adjusting the balance between "supporting the righteous" and "dispelling the evil" in Chinese medicine treatment based on the principles of traditional Chinese medicine syndrome differentiation, as well as considering the impact of Western medicine conventional treatment methods (such as surgery, chemotherapy, targeted therapy, and immunotherapy) and the disease itself on the body's yin and yang balance. By incorporating the concept of "preventing and treating diseases" in Chinese medicine, staged treatment aims to correct the imbalance of Yin and Yang and help the body achieve or restore a state of "harmonious yin and yang". This approach enhances the effectiveness of Chinese medicine treatment and contributes to achieving better therapeutic outcomes. During the induction chemotherapy phase, Professor Yang Yufei proposed the Jianpi Bushen Sequential Formula, which primarily focuses on supporting the "vital energy", specific usage is as follows: "Staged treatment" in Chinese medicine consists of three stages. Stage 1: This stage begins one day before chemotherapy and lasts until day 6. The treatment principle is to invigorate the spleen and stomach and stop vomiting, with the aim of alleviating

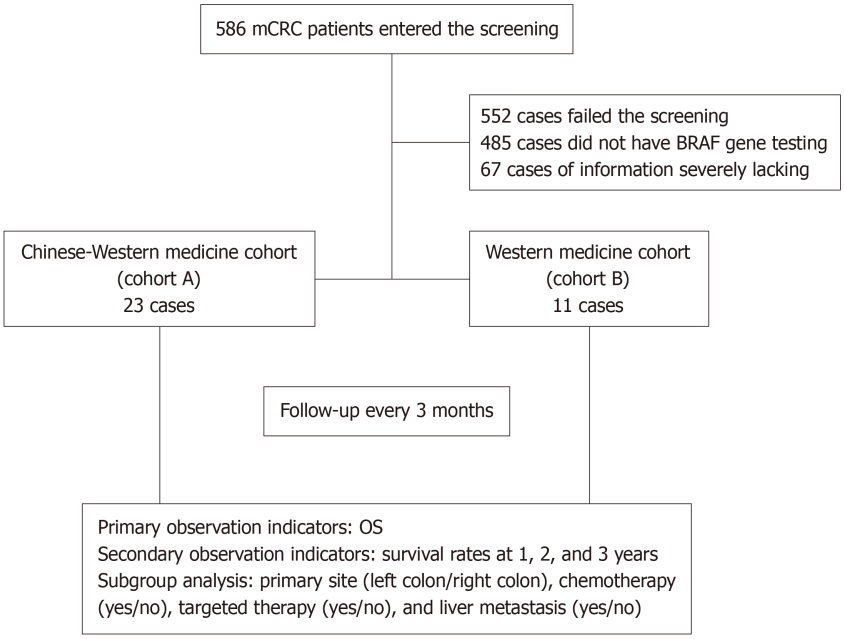

Figure 1 Screening flowchart. mCRC: Metastatic colorectal cancer; OS: Overall survival.

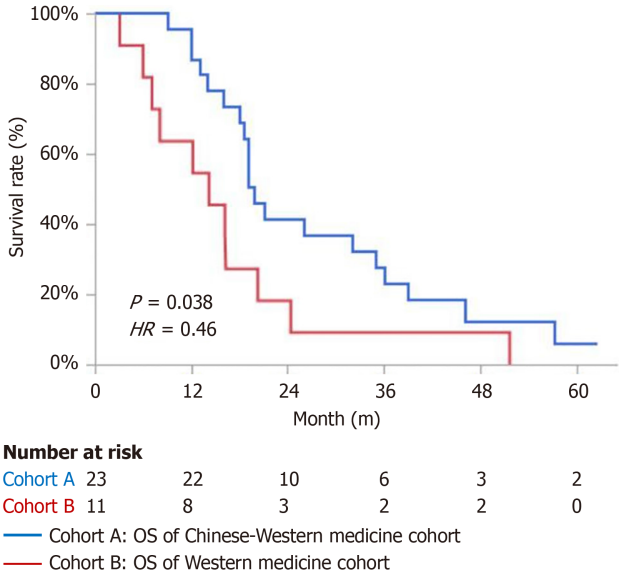

Figure 2 Comparison of overall survival between two cohorts. HR: Hazard ratio; OS: Overall survival.

chemotherapy-related gastrointestinal reactions such as nausea and vomiting. A commonly used prescription during this stage is modified Liu Jun An Wei Fang [11,12]. Stage 2: This stage starts from day 7 and continues until day 20 of chemotherapy. The treatment principle is to warm and tonify the spleen and kidney, nourish essence, and enrich the marrow. The goal is to improve chemotherapy-related bone marrow suppression. Qi Tu Er Zhi Fang, Shi Quan Da Bu Tang, and other prescriptions are commonly used during this stage[11,12]. Stage 3: This stage is the maintenance treatment stage of Western medicine first-line or second-line treatment, which includes single-agent chemotherapy ± targeted therapy. During this relatively mild maintenance treatment phase, the treatment principle is to "strengthen the spleen, nourish the kidney, and detoxify", embodying a simultaneous reinforcement of "supporting the righteous" and "dispelling the evil". The main prescription used during this stage is Si Jun Zi Tang, with the flexibility to add or subtract Chinese herbs with functions such as clearing heat and detoxification, resolving phlegm and dispersing nodules, promoting blood circulation, and removing blood stasis. Some examples of these herbs include *Hedyotis diffusa*, *Semen Nelumbinis*, *Colla Corii Asini*, *Rhizoma Gastrodiae*, and *Herba Lysimachiae*[13]. Clinical practice and evidence-based medicine data have shown that the treatment concept of "seeking balance" significantly improves the survival benefits of patients.

The selected evaluation indicators in this study are objective and quantifiable, which helps minimize the risk of bias. However, as a retrospective study, there are significant difficulties in collecting comprehensive information on outpatient patients. This could potentially lead to data omissions and other limitations. Additionally, the study only investigated

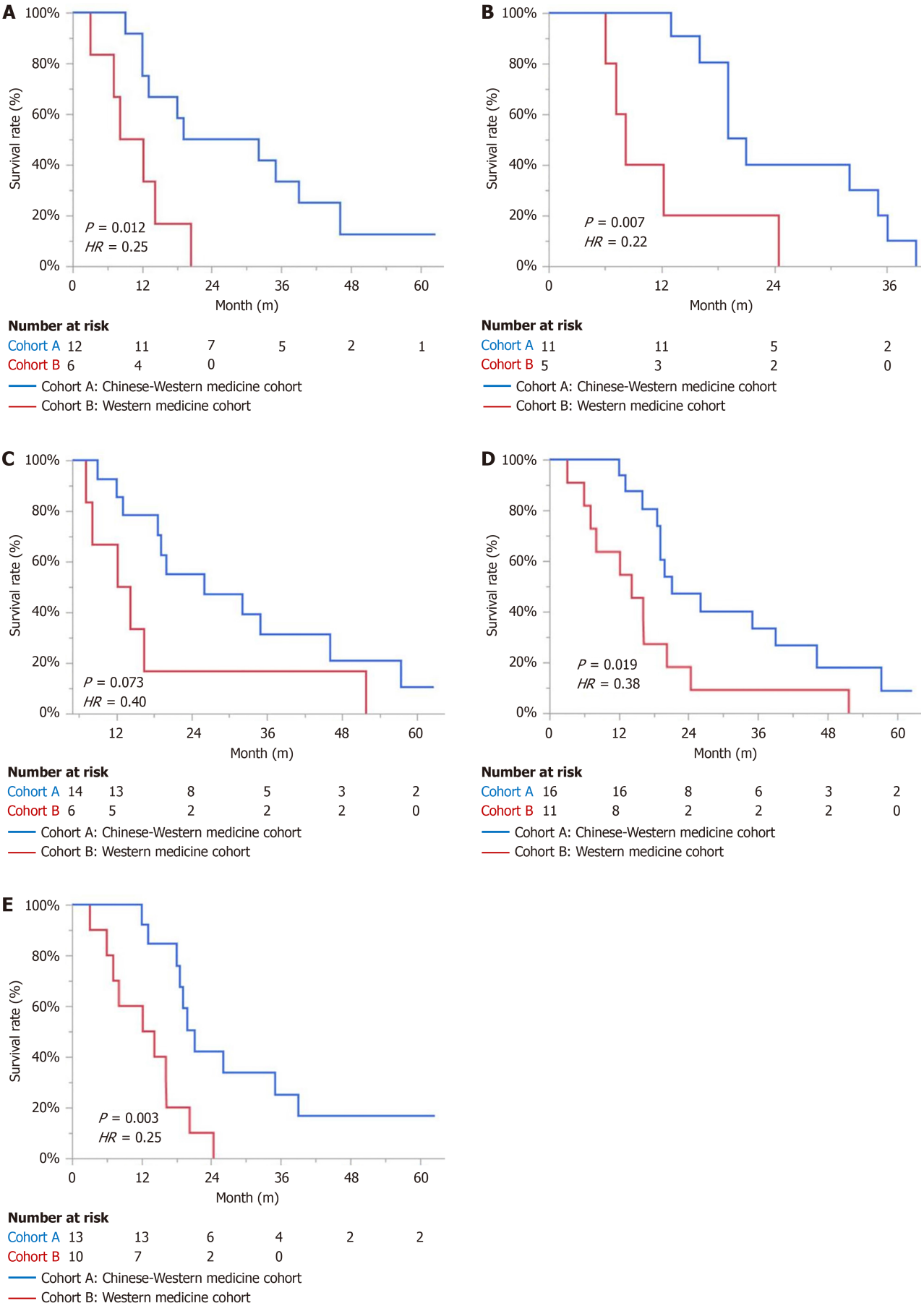

Figure 3 Comparison of overall survival in subgroup. A: Overall survival (OS) of right-side colon; B: OS of liver metastases; C: OS of targeted therapy; D: OS of chemotherapy; E: OS of 1st line therapy. HR: Hazard ratio; OS: Overall survival.

patients from two hospitals and the sample size of the study is relatively limited, which may limit the generalizability of the findings. Conducting surveys in multiple medical institutions would provide a more diverse and representative sample.

Chinese medicine and Western medicine have two distinct theoretical systems and development approaches, both dedicated to improving the survival of cancer patients. They can complement each other and achieve win-win cooperation. We hope that in both clinical practice and scientific research, there can be strengthened collaboration and mutual promotion between Chinese medicine and Western medicine. Let integrated of Chinese and Western medicine truly become a cancer treatment model with Chinese medical characteristics.

CONCLUSION

This study employed a retrospective cohort design to examine the survival benefits of integrated Chinese and Western medicine compared to solely Western medicine treatment in patients with *BRAF V600E* mutant mCRC in the real world. The findings of the study confirmed that the integrated Chinese and Western medicine significantly extended the OS of *BRAF V600E* mutant mCRC patients, in comparison to chemotherapy and/or targeted therapy. At the same time, integrated Chinese and Western medicine reduced the risk of death in these patients, with more pronounced benefits observed in patients with right colon involvement, liver metastasis, combined chemotherapy, and first-line treatment. In conclusion, this study provides more clinical treatment options for the patients with *BRAF V600E* mutant mCRC and provides evidence-based medical evidence for the clinical application of integrated Chinese and Western medicine in the treatment of these patients.

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FOOTNOTES

Author contributions: Guarantor of integrity of entire study, manuscript preparation, manuscript definition of intellectual content, and manuscript final version approval were conducted by Zhang T; Study concepts, study design, and clinical studies were conducted by Zhang T and He WT; Literature research, data acquisition, and manuscript editing were conducted by Bian JY and Feng YF; Data analysis/interpretation was conducted by Zhang T and Bian JY; Statistical analysis and manuscript revision/review were conducted by He WT; Since this study includes two research centers in Beijing and Xinjiang, and the research workload of the two centers is balanced, He WT and Zhang T are listed as co-corresponding authors.

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ORCID number: Wen-Ting He 0000-0003-2160-1529; Tong Zhang 0000-0002-4041-0499.

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