Acupuncture and Herbal Medicine

Retrospective cohort study on the postoperative survival rate enhancement of patients with colorectal cancer using three traditional Chinese medicine formulations: evidence from 1,361 cases

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Abstract

Background: Prior studies have affirmed the safety and effectiveness of traditional Chinese medicine in treating colorectal cancer patients. However, definitive evidence regarding whether traditional Chinese medicine can significantly enhance the survival of colorectal cancer patients remains elusive. This study seeks to provide conclusive insights by examining the postoperative administration of Xihuang capsules, Pingxiao capsules, and Zilongjin tablets and its impact on the 5-year overall survival (OS) and disease-free survival (DFS) rates among colorectal cancer patients.

Methods: A retrospective study was conducted, involving 1,361 patients selected from the medical center. This retrospective study was carried out at a medical center in Tianjin, China. We assessed differences in postoperative OS and DFS between the control group and the medication group using Kaplan–Meier survival analysis and Cox proportional hazards modeling. Additionally, propensity score matching was used to mitigate imbalances in baseline characteristics among patients.

Results: Before propensity score matching, Xihuang capsules could prolong the 5-year OS (79.9% *vs*. 81.4%, $P = 0.0480$) and 5-year DFS (74.9% *vs*. 79.5%, $P = 0.0046$) of patients after surgery. Similar conclusions were obtained after propensity score matching: OS (74.8% *vs*. 78.3%, $P = 0.0084$), DFS (72.7% *vs*. 78.9%, $P = 0.008$). Patients taking Pingxiao capsules showed improved 5-year OS (77.2% *vs*. 84.0%, $P = 0.0383$) and 5-year DFS (69.9% *vs*. 80.0%, $P = 0.0157$) after propensity score matching. Patients taking Zilongjin tablets showed improvement in the 2-year OS (84.2% *vs*. 93.1%, $P = 0.0390$) and 1-year DFS (88.2% *vs*. 92.0%, $P = 0.0320$) after propensity score matching.

Conclusion: Xihuang capsules and Pingxiao capsules significantly improved the 5-year OS and DFS of patients with colorectal cancer after surgery. Zilongjin tablets showed improvement in the 2-year OS and 1-year DFS after surgery for patients.

Keywords: Colorectal cancer, Disease-free survival, Traditional Chinese medicine, Overall survival

Introduction

The incidence of colorectal cancer is rising globally, particularly in high-income countries. Currently, it ranks third in terms of global cancer cases and has the fourth-highest mortality rate[1]. Notably, in China, the incidence of colorectal cancer, including early-onset cases, has been increasing despite the implementation of screening programs. Common treatments for colorectal cancer include surgical resection, radiation, chemotherapy, and targeted therapy, with surgery often being the initial choice, followed by adjuvant therapy[2]. As new drugs for treatment continually emerge, traditional Chinese medicine (TCM) has gained widespread application, particularly in Asia,

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and has shown efficacy in middle-to-late-stage cancer treatment[3,4]. The therapeutic potential of TCM has been investigated in various cancers, including breast[5], lung, colorectal[6], and liver cancer[7]; however, the specific underlying mechanisms and effects on patient survival remain to be elucidated.

Date source

In this study, we examined the therapeutic effects of three TCM formulations—Xihuang capsules, Pingxiao capsules, and Zilongjin tablets—approved by the China National Medical Products Administration for cancer treatment. We aimed to assess the impact of each type of TCM, administered individually to patients with colorectal cancer, on the 5-year overall and disease-free survival (DFS) rates.

Patients with colorectal cancer who underwent radical resection at the Tianjin Union Medical Center between 2012 and 2019 were enrolled in this study. The observation group received standard postoperative treatment supplemented with TCM intervention, whereas the control group received conventional treatment alone. Adjuvant TCM included Xihuang capsules (Hebei Wanbang Folon Pharmaceutical Co., Ltd., Hebei, China), Pingxiao capsules (Xian C.P. Pharmaceutical Co., Ltd., Xian, China), and Zilongjin tablets (Tianjin Pharmaceutical Da Ren Tang Group Co., Ltd., Tianjin, China), which are approved by the China Food and Drug Administration for adjunctive cancer therapy. The inclusion criteria included an initial diagnosis of colorectal cancer suitable for radical resection; age between 18 and 80 years; preoperative chest, abdominal, and pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scans conducted; confirmation of tumor absence at the first follow-up; cancer-free resection margins; absence of abnormal bleeding tendencies; no neoadjuvant chemotherapy or other treatment administered prior to surgery; no known HIV infection; absence of severe acute or chronic illnesses in the preceding 3 months; no history of drug abuse or psychiatric disorders; and no pregnancy or lactation. Patient data were sourced from medical center records, and the inclusion criteria were referenced from prior large-scale retrospective studies. The study was conducted in accordance with the ethical guidelines outlined in the *Declaration of Helsinki* and was approved by the research ethics committee.

Materials and measurement

Patients in the medication group received only one of the three types of TCM, administered as follows: Xihuang pill and Pingxiao capsule at 1 to 2 g per dose (equivalent to 4–8 pills) three times daily and Zilongjin tablets at 2.6 g per dose (equivalent to four tablets) three times daily. Patients in the control group did not receive adjuvant therapy, whereas those in the experimental group received TCM as adjuvant therapy. Patients meeting the treatment and inclusion criteria were identified, and comprehensive information on age, sex, surgery time, postoperative pathology, and prescribed adjuvant therapy was collected. Treatment efficacy in patients with colorectal cancer was assessed through initial and subsequent follow-ups every 3 months over a 5-year period. Each follow-up involved a thorough evaluation, including physical examination; carcinoembryonic antigen serum marker analysis; and enhanced CT/MRI scans of the chest, abdomen, and pelvis, with detailed records maintained to document any recurrence patterns and subsequent treatments.

To account for potential confounding factors, propensity score matching was performed based on clinical variables, such as age, sex, tumor stage, histological grade, chemotherapy regimen, vascular invasion, and neural invasion. The matched groups comprising patients receiving TCM and those in the control group were compared using chi-square tests, Kruskal–Wallis tests, Kaplan–Meier methods, and log-rank tests for survival analysis, with an additional milestone analysis conducted for Zilongjin. Multivariate Cox analysis was used to assess treatment efficacy and identify prognostic factors influencing survival, with statistical significance set at $P < 0.05$ for all tests.

Data analysis

After robust data collection and screening, 1,361 patients with colorectal cancer were included in our study. Among them, 943 patients underwent traditional chemotherapy and radiotherapy following curative surgery, whereas 418 patients were orally administered one of the three TCMs as adjuvants for approximately 6 months. The average duration of medication for patients taking Xihuang capsules, Pingxiao capsules, and Zilongjin pills was 7.2 months (interquartile range [IQR] = 0.8 months), 5.7 months (IQR = 0.7 months), and 6.1 months (IQR = 0.5 months), respectively. In the TCM group, 104 patients were administered Zijinlong tablets, 80 were administered Pingxiao capsules, and 234 were administered Xihuang capsules [Supplementary Figure S1, http://links.lww.com/AHM/A130]. Supplementary Table S1 (http://links.lww.com/AHM/A130) summarizes the clinical characteristics of patients, revealing significant differences in age, sex, tumor stage, location, histology, and chemotherapy regimens between patients in the two groups (all $P < 0.001$). Propensity score matching was used to address these discrepancies, yielding no significant differences in baseline characteristics between the control and experimental groups, thereby ensuring comparability [Supplementary Table S1, http://links.lww.com/AHM/A130]. In the Xihuang capsule group, male patients were predominant, whereas females comprised a larger proportion of patients in the Pingxiao capsule and Zilongjin tablet groups. Most patients in all three groups had stage II or III disease, with multidrug combination chemotherapy being the predominant postoperative chemotherapy regimen. Additionally, the Xihuang capsule group comprised more patients with rectal cancer than those with colon cancer, whereas the Pingxiao capsule and Zilongjin tablet groups predominantly comprised patients with colon cancer.

Results of patients

In the control group, 244 individuals (25.9%) died, whereas in the TCM group, 93 (22.2%) died ($P = 0.1733$).

Moreover, 424 individuals (45%) in the control group and 157 individuals (37.6%) in the TCM group experienced tumor recurrence ($P = 0.0128$). Although no statistically significant differences were observed in the overall survival (OS) between the control and medication groups after curative surgery for colorectal cancer, separate observations were conducted within the TCM group. The 1-, 2-, 3-, and 5-year OS rates for the control and Xihuang capsule groups were 97.6%, 91.2%, 86.2%, and 79.9% and 97.8%, 95.9%, 91.4%, and 81.4%, respectively ($P = 0.048$). Moreover, patients in the Xihuang capsule group demonstrated improved DFS rates compared with those in the control group ($P = 0.0046$) (Figure 1). The 1-, 2-, 3-, and 5-year OS rates for the control and Pingxiao capsule groups were 95.9%, 89.4%, 84.1%, and 75.3% and 97.4%, 96.1%, 90.0%, and 83.0%, respectively ($P = 0.1047$) (Figure 2). The DFS rates were also higher in the Pingxiao capsule group compared with those in the control group ($P = 0.0241$). The 1-, 2-, 3-, and 5-year OS rates for the control and Zijinlong groups were 95.9%, 89.5%, 84.1%, and 75.3% and 97.8%, 93.6%, 82.3%, and 66.4%, respectively ($P = 0.4727$). The 1-, 2-, 3-, and 5-year DFS rates in the control group were 93.3%, 85.7%, 80.6%, and 74.8%, respectively, whereas those in the medication group were 92.0%, 80.2%, 73.0%, and 67.0%, respectively ($P = 0.53$) (Figure 3). In the Cox regression analysis, the use of Xihuang, Pingxiao, and Zilongjin capsules was associated with extended OS and DFS rates in patients with colorectal cancer. The independent adverse prognostic factors for OS and DFS in the TCM group were age, histological stage, tumor location, chemotherapy regimen, vascular invasion, and neural invasion [Supplementary Tables S2–S4, http://links.lww.com/AHM/A130].

After propensity score matching, patients treated with Xihuang capsules showed improved long-term OS, with 1-, 2-, 3-, and 5-year OS rates of 97.1%, 94.5%, 88.7%, and 78.3% compared with those of 96.3%, 89.6%, 83.9%, and 74.8%, respectively, in the control group ($P = 0.0084$) (Figure 1). Similarly, patients receiving Pingxiao capsules exhibited significantly higher OS rates at 1, 2, 3, and 5 years compared with those in the control group ($P = 0.0383$) (Figure 2). However, no significant difference was observed in the OS rates between patients in the control and Zilongjin groups ($P = 0.5470$) (Figure 3). Regarding DFS, patients treated with Xihuang capsules exhibited higher rates at 1, 2, 3, and 5 years compared with those in the control group ($P = 0.008$) (Figure 1).

Similarly, patients receiving Pingxiao capsules showed significantly improved DFS rates compared with those in the control group ($P = 0.0157$) (Figure 2).

However, no statistically significant differences were observed in the DFS rates between patients treated with Zilongjin tablets and those in the control group ($P = 0.49$) (Figure 3).

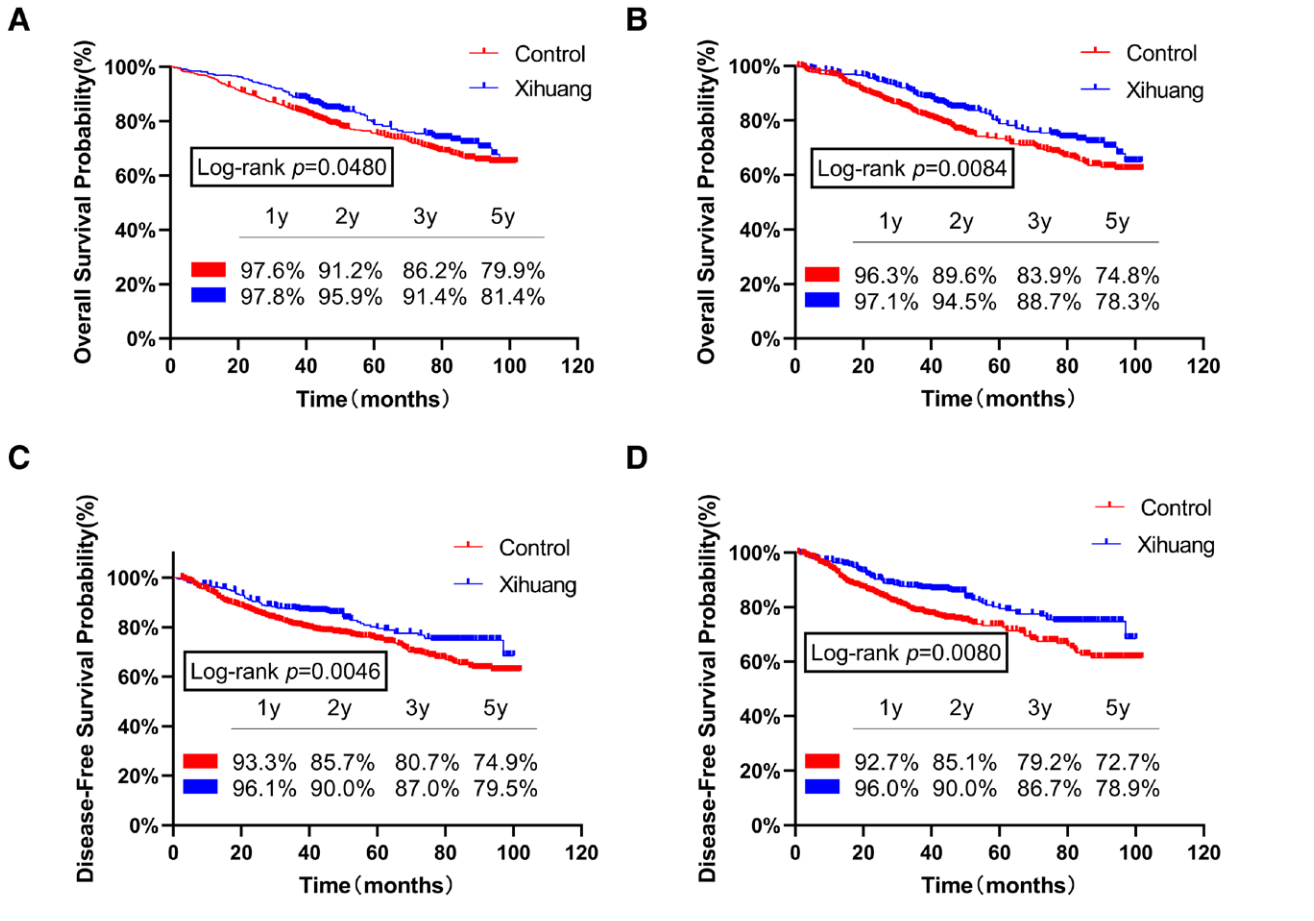

Figure 1. The overall survival and disease-free survival curves of patients with colorectal cancer after radical resection were compared between the control and Xihuang capsule groups. Before (A, C) and after (B, D) propensity score matching.

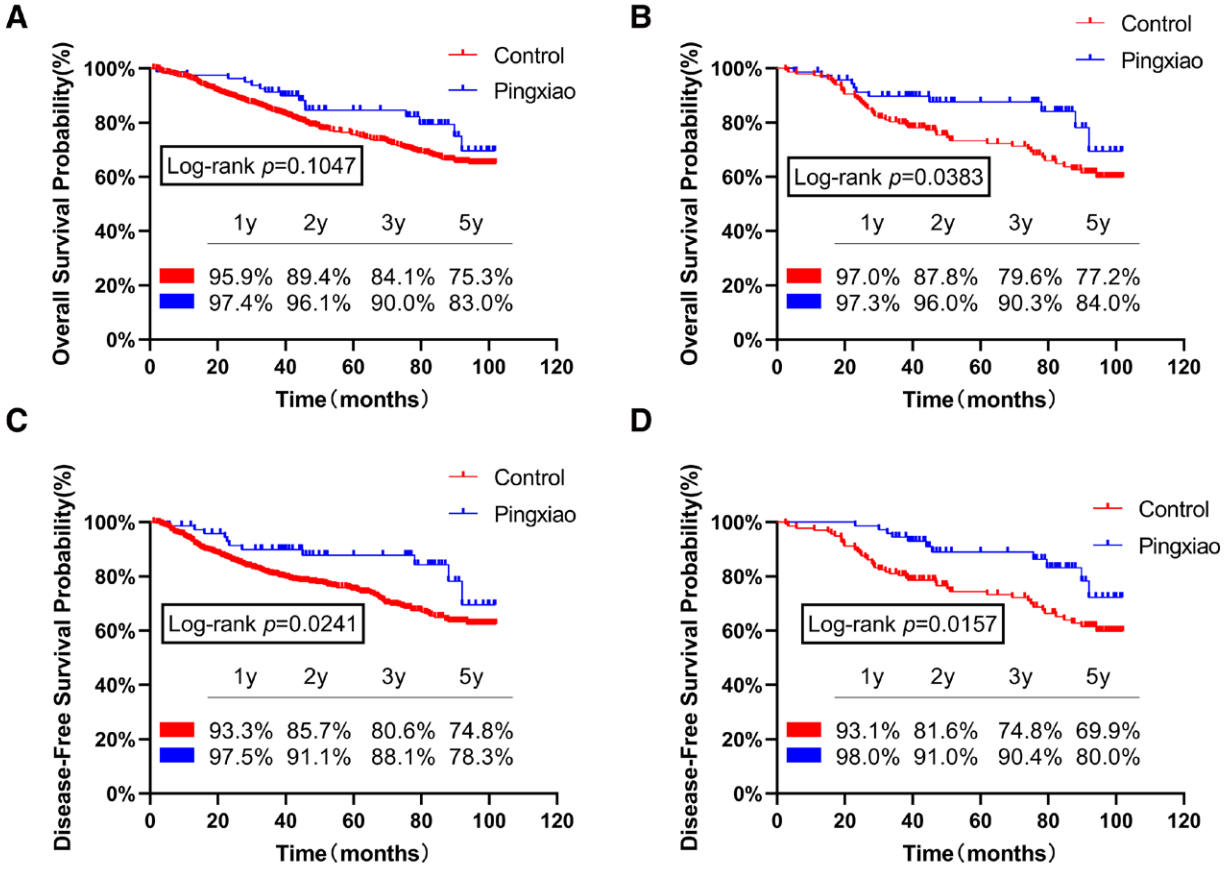

Figure 2. The overall survival and disease-free survival curves of patients with colorectal cancer after radical resection were compared between the control and Pingxiao capsule groups. Before (A, C) and after (B, D) propensity score matching.

After propensity score matching, patients using Zilongjin postoperatively showed significant differences in OS rates before 24 months ($P = 0.039$), which diminished thereafter ($P = 0.440$) [Supplementary Figure S2, http://links.lww.com/AHM/A130]. Similarly, regarding DFS, significant differences were observed between the groups before 12 months ($P = 0.032$), which diminished subsequently ($P = 0.352$) [Supplementary Figure S3, http://links.lww.com/AHM/A130].

Discussion

Previous studies have investigated the efficacy of these three herbs in the treatment of patients with cancer. Xihuang capsules are used as an adjuvant therapy for various middle- and late-stage cancers. The therapeutic benefits of Xihuang pills/capsules in patients with cancer encompass several aspects[8], including enhancement of complete or partial remission, mitigation of adverse reactions, improved quality of life, regulation of immune function, pain alleviation, extended patient survival, reduced incidence of metastasis and recurrence, decreased inflammation, and reduced tumor marker levels. Furthermore, in a randomized controlled study conducted by Ge et al.[9], the addition of Xihuang pills/capsules to conventional antitumor treatments for breast cancer resulted in a favorable adjuvant effect that effectively inhibited breast cancer progression and improved patient survival. A previous study by Zhang et al.[3] revealed that naringenin is the active component in Xihuang pill/capsule that effectively treats triple-negative breast cancer (TNBC) *via* inhibition of cancer stem cells, thereby implying the potential mechanism of action of this TCM. The therapeutic efficacy of Xihuang pill in advanced colorectal cancer was demonstrated in a study conducted by Yu and An[10], who reported that, compared with chemotherapy alone, the combination of Xihuang pill and chemotherapy improves the quality of life and enhances coagulation function in patients with advanced colorectal cancer. Furthermore, Xihuang pill has been shown to assist in the treatment of lung cancer[11], cervical cancer[12], and liver cancer[13].

Pingxiao capsules have shown promise as adjuvant therapy for cancer. In a study conducted by Wenjuan et al.[14], Pingxiao capsules increased the sensitivity of patients with TNBC to radiotherapy. Yuqing et al.'s[15] study suggested the safety and effectiveness of Pingxiao capsules in the treatment of patients with breast cancer. Regarding the treatment of colorectal cancer, Yu et al.'s[16] research indicated that the antitumor mechanisms of Pingxiao capsules involve inducing anticancer immunity, establishing a healthy microbiota composition, and improving drug metabolism, among other mechanisms. The specific underlying mechanism of action of Zilongjin, a medication newly approved by the Chinese Food and Drug Administration for antitumor treatment, has not yet been elucidated, and there is limited research on this topic. Nevertheless, existing studies have demonstrated

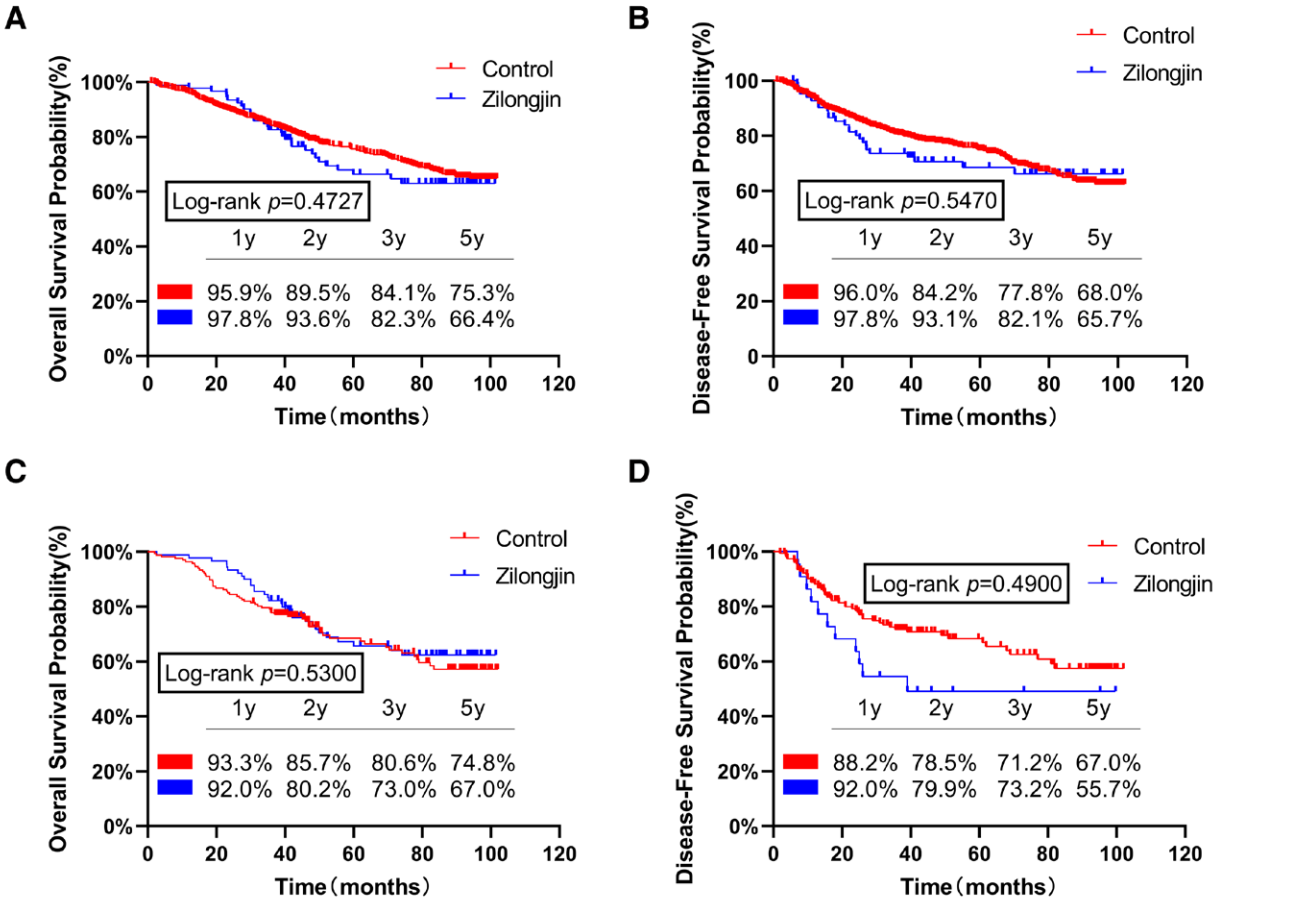

Figure 3. The overall survival and disease-free survival curves of patients with colorectal cancer after radical resection were compared between the control and Zilongjin tablet groups. Before (A, C) and after (B, D) propensity score matching.

the effectiveness of Zilongjin in cancer treatment. For instance, Zhang et al.[17] revealed that the mechanism of action of Zilongjin in the treatment of lung cancer is associated with alterations in key genes. Tian et al.[18] suggested that the mechanism of action of Zilongjin in combating breast cancer involves changes in the expression of certain proteins. However, there is limited research on whether Zilongjin can extend the survival of patients with cancer. The results of our research suggest that Zilongjin is associated with an improved 2-year OS rate and an increased 1-year DFS rate in patients with postoperative colorectal cancer. A potential reason for these findings is related to the duration of medication use by the patients. Therefore, we recommend that patients with cancer taking Zilongjin orally should consider its long-term use after surgery. This may help achieve sustained relief from postoperative cancer recurrence and progression, ultimately extending the OS of patients. Additionally, our findings provide clinical guidance for future research on the mechanism of action of Zilongjin and identification of its active compounds.

This study has certain limitations in its research design and data sources. First, there were differences in clinical characteristics between the control and medication groups, including age, sex, tumor stage, tumor histological grade, postoperative conventional chemotherapy regimens, tumor location, and mismatch repair (MMR) status, among others. Although propensity score matching analysis was used in this study to balance the impact of different clinical variables on the experimental results, it was impossible to completely eliminate selection bias in this retrospective study. Therefore, future research should include long-term, prospective, randomized controlled trials. Second, this study was a retrospective analysis of patients from a single cancer center. While many researchers have reported the efficacy and safety of treatments involving Chinese medicines such as the Xihuang pill, Pingxiao capsule, and Zilongjin in patients with late-stage cancer, it is important to include more patients from multicenter cohorts to observe their clinical outcomes and ensure result accuracy. Third, TCM as an adjunctive treatment is not recommended as a first-line treatment in the colorectal cancer guidelines. The use of TCM is associated with various patient-related factors, such as patient willingness for aggressive treatment and a positive mindset, which can also influence patient prognosis. However, our study did not collect and predict the impact of these factors on outcomes. Therefore, more specific research is required to evaluate the therapeutic effects of these drugs.

Conclusion

Despite its limitations, our study holds significant clinical relevance. The results indicate that adjuvant TCM, specifically Xihuang pill and Pingxiao capsule, can

effectively extend the 5-year OS of patients with postoperative colorectal cancer. In contrast, Zilongjin tablets effectively prolong the 2-year OS and 1-year DFS of patients. These three oral TCMs have significant clinical value as postoperative adjuvant treatments for patients with colorectal cancer.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Kailong Zhao, Yi Zhang, Hongzhou Li, Leixin Jin conceived the project. Leixin Jin, Kailong Zhao, Qiurong Han, Tianyi Chen, Zhiqiang Feng, Yao Yao collected the data and researched Paper. Kailong Zhao, Weizheng Liang, Jun Xue, and Chunze Zhang analyzed the data. Wenke Zheng, Xipeng Zhang, and Qinghuai Zhang reviewed the article. Kailong Zhao wrote the manuscript with help from all of the authors. All authors read and approved the final manuscript.

Ethical approval of studies and informed consent

The study obtained approval from the Tianjin Union Medical Ethics Committee and was conducted in accordance with the principles of the Helsinki Declaration. Prior to the commencement of the study, participants provided informed consent by signing a consent form.

Acknowledgments

None.

Data availability

Due to restrictions on ethical approval involving patient data and anonymity, the datasets analyzed during the current study are not publicly available but can be obtained from the appropriate authors upon reasonable request. If you would like to obtain data from the study, please contact corresponding author Professor Chunze Zhang.

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