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Cost-effectiveness analysis of FOLFOXIRI/FOLFOXIRI and mFOLFOX6/FOLFIRI treatment in first-line and second-line chemotherapy for metastatic colorectal cancer

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ABSTRACT

Objectives The aim of this study was to evaluate the cost-effectiveness of FOLFOXIRI/FOLFOXIRI compared with mFOLFOX6/FOLFIRI in first-line and second-line chemotherapy for metastatic colorectal cancer (mCRC) from the perspectives of the USA and China, respectively, and provide a decision-making basis for clinical selection of these two regimens.

Design The study used a decision-analytic Markov model to simulate the process of mCRC, including three distinct health states: progression-free survival, progressive disease and death. Clinical data were derived from the TRIBE2 trial.

Costs and utilities were obtained from local public databases and literature. One-way sensitivity analyses and probabilistic sensitivity analysis were also performed to explore the parameters' uncertainty in this study.

Participants The main included patients were histologically confirmed colorectal adenocarcinoma.

Interventions First-line and second-line treatment with either FOLFOXIRI/FOLFOXIRI or mFOLFOX6/FOLFIRI.

Main outcome measures Costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were calculated over a lifetime horizon as primary outcomes.

Results Patients treated with the FOLFOXIRI/FOLFOXIRI regimen produced 0.08 QALYs in the USA while 0.04 QALYs in China compared with the mFOLFOX6/FOLFIRI regimen. The final ICERs for FOLFOXIRI/FOLFOXIRI were US$5127.70 per QALY and US$30 478.33 per QALY in the USA and China, which are below the willingness-to-pay (WTP) thresholds. In the USA, when the WTP was US$100 000 for each QALY gained, the probability was nearly 99.6% that the FOLFOXIRI/FOLFOXIRI treatment was cost-effective. In China, when the WTP was US$36 053.01 (3 × GDP) for each QALY gained, the probability was nearly 54.7% that FOLFOXIRI/FOLFOXIRI treatment was cost-effective.

Conclusion Patients with mCRC treated with FOLFOXIRI/FOLFOXIRI as first-line and second-line chemotherapy may improve health outcomes and expend financial resources more efficiently than mFOLFOX6/FOLFIRI whether in China or the USA, which benefits not only individual survival but also the health care system from a value perspective.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This work aimed to evaluate the cost-effectiveness of FOLFOXIRI/FOLFOXIRI compared with mFOLFOX6/FOLFIRI in first-line and second-line chemotherapy for metastatic colorectal cancer from the perspectives of the USA and China.
⇒ One limitation of this study is that an inevitable limitation was the use of a Weibull distribution to infer consequences beyond the lifetime horizon of the TRIBE2 trial.
⇒ Different therapies were estimated according to the information published for the TRIBE2 trial with patients recruited from 58 Italian oncology units, which were not designed clinical trials specifically targeting the Chinese and US populations.

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer death. Approximately 140 people die each day from CRC in the USA in 2023.[1] CRC was one of the top 10 cancer types for estimated cases and deaths worldwide for men and women; incidence and mortality were 10.0% and 9.4% in 2020 in both sexes.[2] The incidence of CRC in China ranks the second among malignant tumours and the death rate ranks the fourth, and the incidence and death rate of colorectal cancer have shown an upward trend from 2000 to 2016.[3] Among people diagnosed with CRC, 20% have metastatic CRC (mCRC), and 40% present with recurrence after previously treated localised disease.[4] The prognosis of mCRC is poor, with a 5-year survival rate of less than 20%.[5] While approximately 25% of patients present with metastases at initial diagnosis, the clinical outcome for patients with mCRC has improved over the last decade, with better response, progression-free survival (PFS) and overall survival (OS).[6]

According to National Comprehensive Cancer Network guidelines, FOLFOX (fluorouracil, leucovorin and oxaliplatin) and FOLFIRI (fluorouracil, leucovorin and irinotecan) systemic therapy are the first-line and second-line chemotherapy for mCRC.[7–9] Recently, targeted therapy is often involved in a combination of chemotherapy for mCRC treatment, which is effective in prolonging patient survival. Vascular endothelial growth factor inhibitor bevacizumab and epidermal growth factor receptor antibody cetuximab are widely used in combination for the treatment.[10–13] FOLFIRI and FOLFOX are widely used in clinical practice, and their efficacy and safety have been confirmed.[14] Comparisons of FOLFOX and FOLFIRI for first-line treatment of mCRC demonstrated similar overall survival.[15] A systematic review and meta-analysis of seven randomised controlled trials found that combination therapy (bevacizumab plus FOLFOX or FOLFIRI) was associated with improved progression-free survival but not overall survival.[16] Most patients eventually receive both regimens by transitioning from one to the other when mCRC grows progressively despite treatment or when dose-limiting toxicity requires switching therapies.[5]

The triplet regimen FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin and irinotecan) was investigated for treatment of patients with poor prognosis mCRC (right-sided tumours, *BRAF V600E* variants, large tumour volume).[15] The FOLFOXIRI regimen could improve response rate, progression-free survival and OS compared with FOLFIRI, with increased, but manageable, toxicity in patients with mCRC with favourable prognostic characteristics.[17] Another study showed FOLFOXIRI plus bevacizumab, as compared with FOLFIRI plus bevacizumab, improved the outcome in patients with mCRC and increased the incidence of some adverse events, which may be associated with the intensification of the treatment, but no significant differences in the rate of serious adverse events or deaths were observed.[18] However, the application of the three-drug regimen FOLFOXIRI may be relatively limited,[19] and this combination may worsen the patient's quality of life and increase overall medical costs because the targeted agents are expensive.[20]

Recently, from the perspective of healthcare decision-makers, it is important to analyse the relative effectiveness and cost-effectiveness of a treatment regimen. Cost-effectiveness analysis based on randomised controlled phase III clinical trials is widely used and recommended by the Chinese Pharmacoeconomics Guidelines.[21] Although some international studies have evaluated the cost-effectiveness of bevacizumab or cetuximab in mCRC,[22–24] there was not any study focused on the cost-effectiveness of FOLFOXIRI/FOLFOXIRI compared with mFOLFOX6/FOLFIRI treatments in first-line and second-line chemotherapy. In the TRIBE2 study, compared with mFOLFOX6/FOLFIRI treatment, FOLFOXIRI/FOLFOXIRI improved progression-free survival and overall survival in mCRC patients. The aim of this study was to evaluate the comparative cost-effectiveness of FOLFOXIRI/FOLFOXIRI and mFOLFOX6/FOLFIRI plus bevacizumab in first-line and second-line chemotherapy for mCRC from the perspectives of the USA and China, and to provide a decision-making basis for clinical selection of these two regimens.

PATIENTS AND METHODS

Patients and treatments

The TRIBE2 study was a phase 3, open-label, randomised study that enrolled patients with an Eastern Cooperative Oncology Group performance status of 2, previously untreated mCRC. The main inclusion criteria were histologically confirmed colorectal adenocarcinoma, age between 18 and 75 years, recruited from 58 Italian oncology units. Eligible patients were randomly assigned (1:1) to receive either FOLFOXIRI/FOLFOXIRI and mFOLFOX6/FOLFIRI plus bevacizumab chemotherapy. In the control group, patients were given the first-line treatment: mFOLFOX6 along with bevacizumab, followed by FOLFIRI plus bevacizumab after disease progression. In the experimental group, patients received the FOLFOXIRI regimen along with bevacizumab followed by the reintroduction of the same regimen after disease progression.[25] Combination treatments were repeated every 14 days for up to eight cycles followed by fluorouracil and leucovorin (at the same dose administered at the last induction cycle) plus bevacizumab maintenance until disease progression, unacceptable adverse events or consent withdrawal. Median progression-free survival 2 was 19.2 months in the experimental group and 16.4 months in the control group (HR 0.74; 95% CI 0.63 to 0.88; p=0.0005). Median overall survival was 27.4 months in the experimental group and 22.5 months in the control group (HR 0.82; 95%CI 0.68 to 0.98; p=0.032). During the first-line treatment, the most frequent of all-cause grade 3–4 events were diarrhoea (57 (17%) vs 18 (5%)), neutropenia (168 (50%) vs 71 (21%)) and arterial hypertension (25 (7%) vs 35 (10%)) in the experimental group compared with the control group. Overall, the study suggested that upfront FOLFOXIRI plus bevacizumab followed by the reintroduction of the same regimen after disease progression may be a better treatment strategy to sequential administration of chemotherapy doublets, in combination with bevacizumab, for selected mCRC patients. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Model structure

A Markov model was established to evaluate the costs and health outcomes of treating mCRC with FOLFOXIRI/FOLFOXIRI regimen compared with mFOLFOX6/FOLFIRI therapy both in combination with bevacizumab. According to the nature of disease progression, the model was defined by three mutually exclusive health states (figure 1): PFS, progressive disease (PD) and death, reflecting different characteristics of the disease. All patients started from the PFS state with a probability

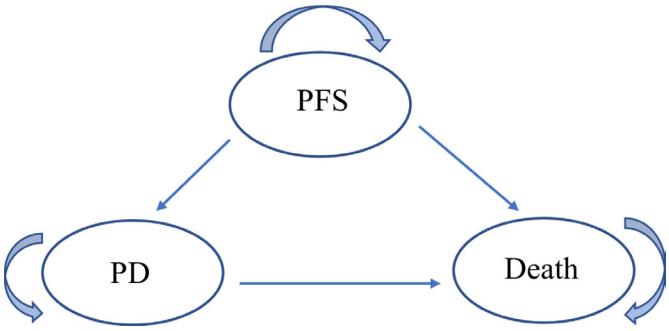

Figure 1 The Markov state transition model: The Markov model considers the transition states of metastatic colorectal cancer. All patients start in the progression-free survival (PFS) state and receive treatment according to three treatment plans. Patients can enter the state of progressive disease (PD) and subsequently move to the state of death.

of 1, then they could stay in the same state or transfer to other states based on transition probabilities. The Markov model was used to simulate a hypothetical cohort of patients with mCRC based on the TRIBE2 trial. Combination treatments were repeated every 14 days for up to eight cycles.

The analysis was conducted from the perspective of the healthcare systems in China and the USA. Each model cycle represents 14 days; evaluation was conducted in 10-year horizons. Based on the Markov model, we have discovered that 99.99% of patients with colorectal cancer are in a state of mortality after a 10-year research period. A 5% discount rate per year was applied to both costs and outcomes, in line with China's Guidelines for Pharmacoeconomic Evaluations 2020.[21 26] While all outcomes and costs were discounted by 3% annually in the USA.[27] The Markov model was developed and run in Tree Age Pro 2020. Life-time healthcare costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were the main outputs of this model. The current analysis was conducted from the US third-party payer and Chinese healthcare perspectives, which means that the two scenarios shared the same clinical and utility inputs except the local cost estimates and life table data.

Effectiveness parameters

The survival functions were used to calculate the transfer probabilities among the states based on the parametric survival curves of PFS and OS from the TRIBE2 trial clinical trial. Data points from the curve were extracted by Get Data Graph Digitizer software package and then were fit into the parametric survival models by R (V. 3.5.1) software. The Weibull distribution was used to fit the survival curve because it can have an increasing hazard rate and is suitable for modelling the events occurring early during follow-up periods. We found model verification indicated highly anastomosis and good reproduction (online supplemental figure S1). The transfer probabilities of mCRC for the three health states were estimated based on the formulation: p=1 exp (scale*[t]^shape-scale*[t+1]^shape),[23] the shape parameters and scale parameters were extracted from new survival curves (online supplemental table S1).

Utility estimates

Each health state was assigned a health utility preference on a scale of 0 (death) to 1 (perfect health). To compute the total QALYs in the Markov model, survival time was adjusted by the utility. We assumed that the health utility preference was only associated with the disease status. Mean utility values of 0.85 (95% CI 0.68 to 1.00) and 0.68 (95%CI 0.54 to 0.82) for patients in PFS and PD states presented in online supplemental table S2 were obtained from the previously published literature.[1 22 28] Regardless of the country assessed, the utility value was the same. Moreover, regardless of the therapy applied, the utility values of the PFS and PS states were the same.[22 29]

Cost estimates

Analysis was carried out from US third-party payer and Chinese healthcare perspectives. Direct medical expenses considered in this study included the cost of drugs, treatment of major adverse effects (AEs), hospitalisation or administration and follow-up tests for patients. The price of oxaliplatin, leucovorin, fluorouracil, bevacizumab and irinotecan in China was estimated using local prices (Jiangsu Province, 2023), while the retail price in the USA was obtained from the Centers for Medicare & Medicaid Services: https://www.cms.gov/medicare/payment. The dosage of the anticancer drugs was estimated by a typical body surface area of 1.71 m^2 and weight of 64.3 kg based on the mean values in China,[8] while a body surface area of 1.86 m^2 and weight of 82 kg based on mean US values.[30]

The incidence rates of grade 3/4 AEs in this model were obtained from the TRIBE2 trial data. Mainly adverse effects in this study were neutropenia, arterial hypertension, venous thromboembolism, asthenia, diarrhoea, nausea and stomatitis (online supplemental table S3). After disease progression, no substantial differences in the incidence of grade 3 or 4 adverse events were reported between the control and experimental groups, except neurotoxicity. Asthenia was assumed to have no specific medical management. The costs of AEs were based on the treatment in local hospitals and published literature.[27 31–33] The methods used for these cost calculations were previously described by Tumeh *et al*.[34] Hospitalisation in China and administration in the USA were also considered. The costs of follow-up tests included CT, biochemical test, blood routine examination, oncology assessment and outpatient visit; in China, the actual charging standards of local medical institutions are obtained, while in the USA, these costs are obtained from published studies.[31 35] Costs in this study were converted into US dollars (1 US$=7.1310 CNY, 30/11/2023). The values, range and distribution of each parameter which are based on the related literature and from the local charge are presented in table 1, respectively.

Table 1 Cost parameters in China and the USA

	China		USA	
	Cost (range) (US$)	Source	Cost (range) (US$)	Source
Drug costs				
mFOLFOX6 plus bevacizumab	1891.7 (1513.4–2270.1)	Local	2862.6 (2290.1–3435.1)	CMS.gov
FOLFIRI plus bevacizumab	1893.8 (1515.1–2272.6)	Local	2880.9 (2304.7–3457.1)	CMS.gov
FOLFOXIRI plus bevacizumab	2683.6 (2146.9–3220.3)	Local	2906.0 (2324.8–3487.1)	CMS.gov
AEs costs (grade 3 or 4)				
Neutropenia	27.7 (22.1–33.3)	Local	868.0 (694.4–1041.6)	Li *et al* 2021
Arterial hypertension	51.6 (41.3–61.9)	Local	51.9 (41.5–62.3)	Goldstein *et al* 2015
Venous thromboembolism	2456.9 (1965.5–2848.3)	Local	5567.0 (4453.6–6680.4)	Goldstein *et al* 2015
Diarrhoea	6.2 (4.9–7.5)	Local	81.6 (65.3–97.9)	Goldstein *et al* 2015
Nausea	8.3 (6.6–10.0)	Local	678.2 (542.6–813.9)	Guy *et al* 2018
Stomatitis	1090.1 (872.1–1308.1)	Local	10 073.7 (8058.9–12 088.4)	Wan *et al* 2017
Follow-up test costs				
Biochemical test/cycle	27.2 (21.8–32.7)	Local	15.2 (12.2–18.3)	Li *et al* 2021
Blood routine examination/cycle	7.6 (6.1–9.2)	Local		
CT/cycle	31.4 (25.1–37.7)	Local	541.7 (433.3–650.0)	Li *et al* 2021
Oncology assessment/outpatient visit	4.9 (3.9–5.9)	Local	78.1 (62.5–93.7)	Guy *et al* 2018
Hospital cost/administration cost				
mFOLFOX6/FOLFIRI	48.8 (39.0–58.6)	Local	428.7 (343.0–514.5)	CMS.gov
FOLFOXIRI/ FOLFOXIRI			317.3 (253.8–380.8)	CMS.gov

'Local' was the actual charging standards of local medical institutions in Jiangsu Province (2023).
AEs, adverse events; CT, computerised tomography; FOLFIRI, fluorouracil, leucovorin and irinotecan; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin and irinotecan; mFOLFOX6, fluorouracil, leucovorin and oxaliplatin.

Sensitivity analysis

To verify the impact of basic variables on the results of the analysis, both one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed. The utility of PFS and OS included in the sensitivity analysis was assigned lower and upper limits obtained from credible intervals, while other parameters are a range of ±20% of the base case value. In one-way sensitivity analysis, only one model parameter changed within a set range, and a Tornado diagram was created to determine the impacts of changes in each variable based on the ICER. In addition, when performing PSA, uncertain parameters in this study were assessed based on 1000 Monte Carlo repetitions. All parameters were randomly changed simultaneously during every repetition, and the results were presented as cost-efficiency probabilistic curves and scatter plot diagrams.

RESULTS

Base case results

The base case results are presented in table 2, costs for mFOLFOX6/FOLFIRI regimen in the USA and China were US$7500.25 and US$4314.16, and increased the effectiveness by 0.48 QALYs and 0.37 QALYs. Costs for the FOLFOXIRI/FOLFOXIRI regimen in the USA and China were US$7931.80 and US$5549.08, and increased the effectiveness by 0.56 QALYs and 0.41 QALYs, respectively, per 2-week cycle. In the primary analysis, compared with mFOLFOX6/FOLFIRI therapy, patients treated with the FOLFOXIRI/FOLFOXIRI regimen increased the effectiveness by 0.08 QALYs in the USA while 0.04 QALYs in China. The final ICERs for FOLFOXIRI/FOLFOXIRI were US$5127.70 per QALY and US$30 478.33 per QALY in the USA and China. These ICERs are below the specified thresholds (US$100 000 in the USA and US$36 053.01 in China).

Sensitivity analyses

For the US population in this study, US$100 000 was set as an acceptable threshold.[36] In accordance with China's Guidelines for Pharmacoeconomic Evaluations,[21] our study takes three gross national product (GDP) per capita in 2022 as the willingness-to-pay (WTP) threshold. According to the website of the National Bureau of Statistics, China's GDP per capita in 2022 was 85 698 yuan (US$12 019.35).[37] The results of univariable sensitivity analyses are illustrated as tornado diagrams to describe the

Table 2 Base case results

Result	FOLFOXIRI/ FOLFOXIRI	mFOLFOX6/FOLFIRI	Incremental difference
China			
Cost, US$	5549.08	4314.16	1234.92
LY	0.60	0.54	0.06
QALY	0.41	0.37	0.04
ICER US$/QALY	30 478.33		
The USA			
Cost, US$	7931.80	7500.25	431.55
LY	0.82	0.70	0.12
QALY	0.56	0.48	0.08
ICER US$/QALY	5127.70		

FOLFIRI, fluorouracil, leucovorin and irinotecan; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin and irinotecan; ICER, incremental cost-effectiveness ratio; LY, life year; mFOLFOX6, fluorouracil, leucovorin and oxaliplatin; QALY, quality-adjusted life year.

impact of the studied parameters on the model. In China, the cost of drugs in the FOLFOXIRI/FOLFOXIRI group had the greatest impact on the ICER results. The cost of drugs in the mFOLFOX6/FOLFIRI group, discount rate and the utility value of patients in the PD state were also factors affecting the outcomes of the ICERs, as shown in figure 2a. In the USA, among the factors analysed, the cost of drugs in the FOLFOXIRI/FOLFOXIRI group also had the greatest impact on ICERs. The cost of drugs in the mFOLFOX6/FOLFIRI group also revealed great influences on the ICER results, as shown in figure 2b. The effects of other parameters were negligible. Taken together, varying the key parameters in a sensible range had limited impact on the results.

The range of values determined from the two countries and their respective distributions was simulated 1000 times by using the Monte Carlo model; the scatter points represent the incremental cost and effectiveness values (figure 3). In the USA, most points of the FOLFOXIRI/FOLFOXIRI regimen in the first quadrant indicated higher QALYs, and all scatter is distributed below WTP, indicating that the FOLFOXIRI/FOLFOXIRI regimen is more cost-effective compared with the mFOLFOX6/FOLFIRI group.

The PSA results are illustrated as a cost-effectiveness acceptability curve (online supplemental figure S2), which shows the relative cost-effectiveness changed with numerical changes in the WTP threshold. In China, when the WTP was US$36 053.01 for each QALY gained, the probability was nearly 54.7% that the FOLFOXIRI/FOLFOXIRI treatment was cost-effective. In the USA, when the WTP was US$100 000 for each QALY gained, the probability was nearly 99.6% that the FOLFOXIRI/FOLFOXIRI treatment was cost-effective. Thus, once the WTP is higher than US$36 053.01 in China and US$100 000 in the USA, FOLFOXIRI/FOLFOXIRI treatment was better cost-effective compared with mFOLFOX6/FOLFIRI regimen.

DISCUSSION

In recent years, a series of novel regimens have been used in the treatment of mCRC, and the survivals of patients with mCRC have been improved significantly. Safety, effectiveness and economy are the aims of the rational administration of drugs. In this study, we explored the cost-effectiveness of FOLFOXIRI/FOLFOXIRI compared with mFOLFOX6/FOLFIRI treatments in first-line and second-line chemotherapy based on efficacy and safety in the TRIBE2 study. Our research indicated that compared with mFOLFOX6/FOLFIRI therapy, patients treated with FOLFOXIRI/FOLFOXIRI regimen produced 0.08 QALYs in the USA while 0.04 QALYs in China. The final ICERs for FOLFOXIRI/FOLFOXIRI were US$5127.70 per QALY and US$30 478.33 per QALY in the USA and China. These ICERs are far below the specified thresholds. Our analysis demonstrated that FOLFOXIRI/FOLFOXIRI treatment was more cost-effective compared with mFOLFOX6/FOLFIRI regimen for mCRC when WTP thresholds are higher than US$36 053.01 in China and US$100 000 in the USA per QALY.

Health expenditures have become a severe issue worldwide, especially for countries with limited health resources. The estimated global spending on health will increase from US$9.21 trillion in 2014 to US$24.24 trillion in 2040.[38] Cost-effectiveness analyses provide a standard methodology for examining the cost of a drug in the context of the survival benefit, quality of life, costs of administration and AEs, and duration of therapy. FOLFOX and FOLFIRI were confirmed to be similar in terms of costs and benefits for the initial treatment of metastatic colorectal cancer.[39 40] Recently, several studies in other countries have evaluated the cost-effectiveness of CRC treatments which mainly concentrated in FOLFIRI/FOLFOXIRI combined with cetuximab/bevacizumab/panitumumab and other regimens.[23 24 41 42] TRIBE and TRIBE2 were phase III randomised trials that demonstrated the superiority in terms of OS, progression-free

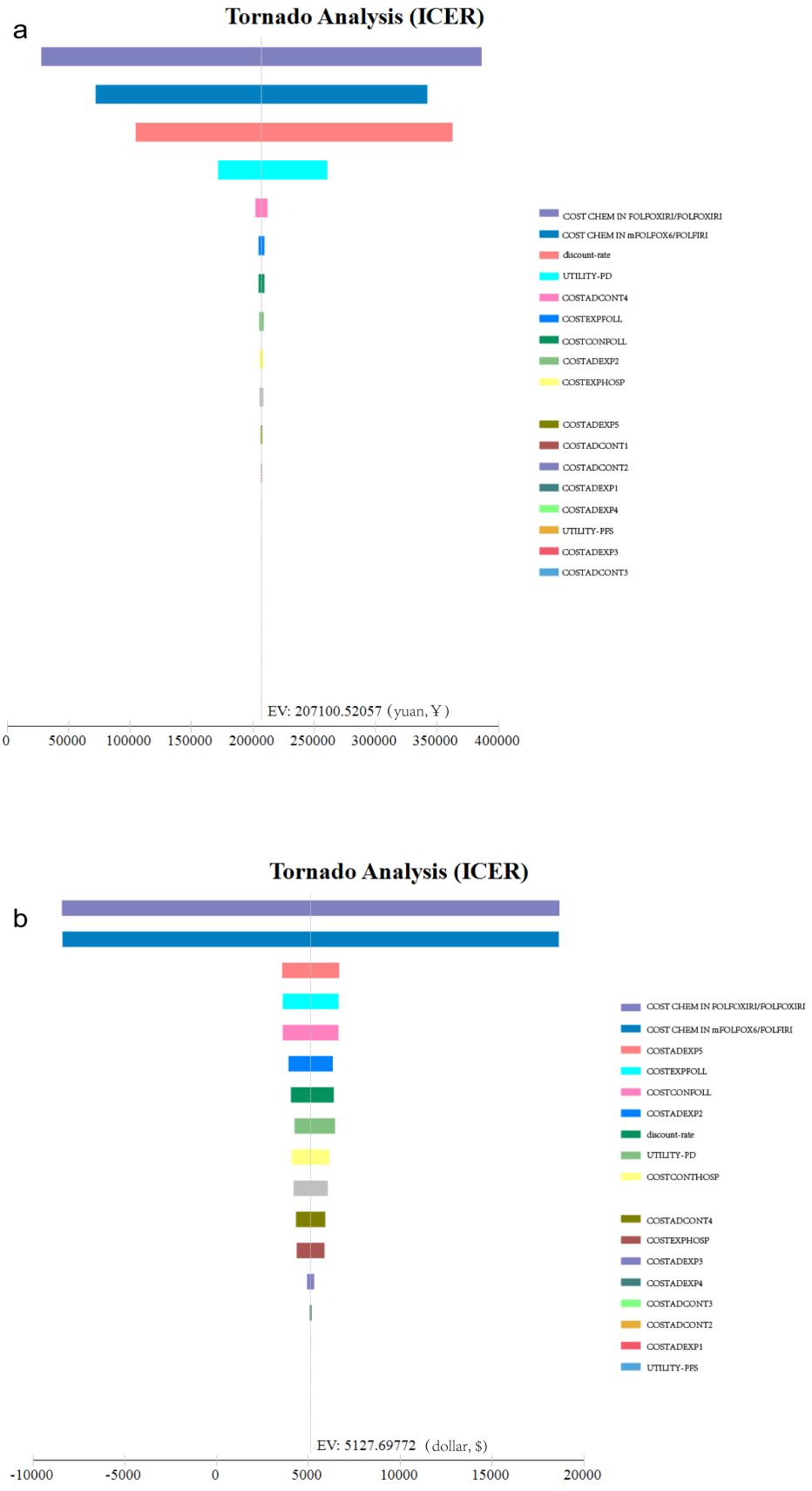

Figure 2 One-way sensitivity analysis: (**a**) from the perspectives of China and (**b**) from the perspectives of the USA. The horizontal axis of the tornado graph indicates the range of influence of each factor on the result, and the vertical axis indicates the name of each uncertainty factor. The factors are listed in descending order of their influence on incremental cost-effectiveness ratios (ICERs).

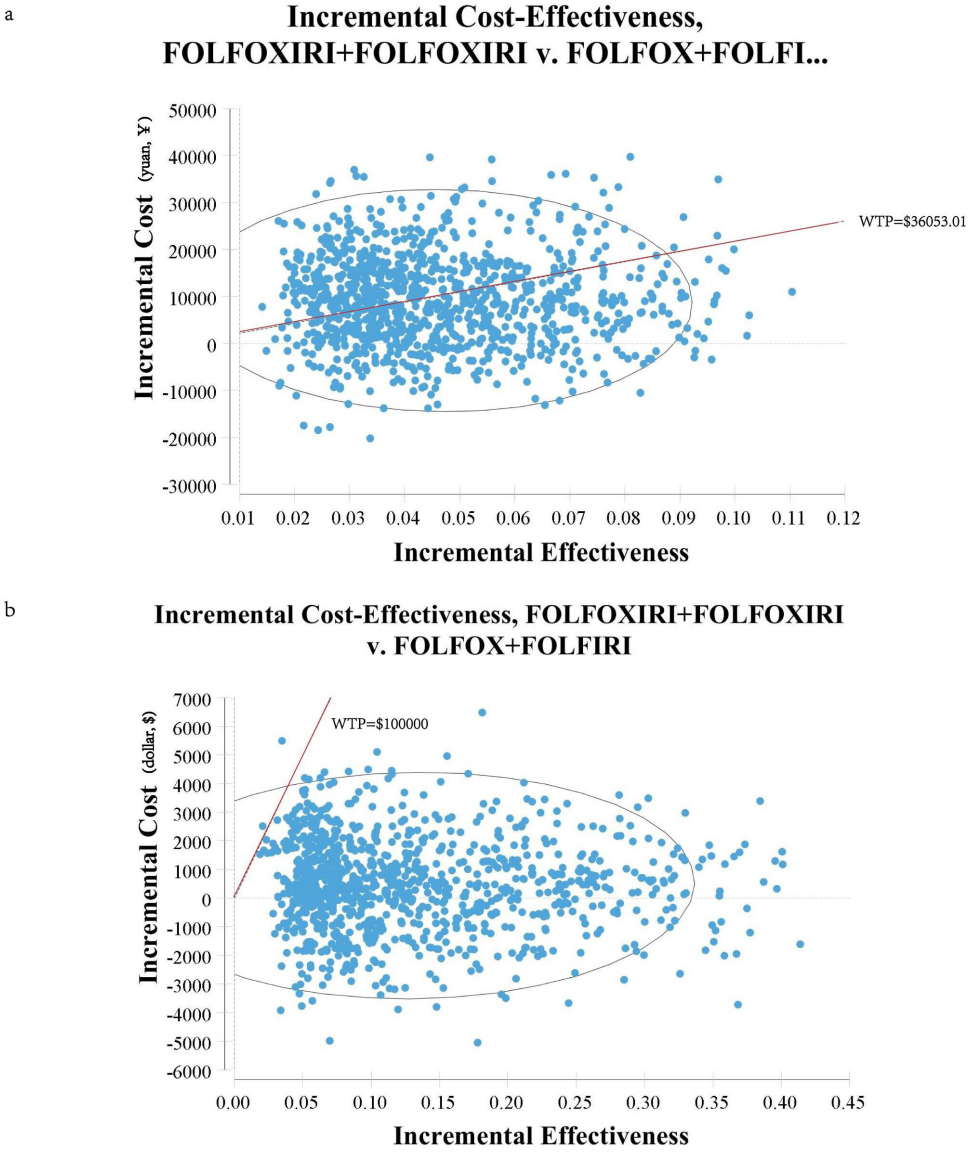

Figure 3 Probabilistic sensitivity analyses: (a) from the perspectives of China and (b) from the perspectives of the USA. The dot represents the results of the Monte Carlo simulation, and the ellipse represents the 95% CI. The red dotted line represents the willingness to pay. A dot falling below the red line indicates that the test group has a cost effect compared with the corresponding control group.

survival (PFS), and objective response rate (ORR) of the triplet (FOLFOXIRI) over the combination of doublet (FOLFIRI/FOLFOX).[18 25] Nevertheless, little or no previous research has explored the cost-effectiveness of FOLFOXIRI/FOLFOXIRI therapy compared with FOLFOX/FOLFIRI for mCRC. Our analysis based on the TRIBE2 trial is the first Markov model-based study to explore the efficacy and cost of the combined regimen FOLFOXIRI/FOLFOXIRI versus mFOLFOX6/FOLFIRI from the perspective of Chinese and US society, which are used as the first-line and second-line chemotherapy for mCRC. In line with the TRIBE2 trial data, the results suggest that the FOLFOXIRI/FOLFOXIRI regimen may be a better choice than mFOLFOX6/FOLFIRI, given that the former can increase both LYs and QALYs. According to our analysis, FOLFOXIRI/FOLFOXIRI treatment provided an incremental 0.04 QALYs at an increase of US$1234.92 compared with the mFOLFOX6/FOLFIRI group in China, while FOLFOXIRI/FOLFOXIRI treatment provided an incremental 0.08 QALYs at an increase of US$431.55 compared with the mFOLFOX6/FOLFIRI group in the USA, both resulting in an ICER below the WTP threshold. There are valuable clinical benefits from FOLFOXIRI/FOLFOXIRI treatment despite the increased costs.

With well policy and economic support of the USA, when the WTP was US$100 000 for each QALY gained, the probability was nearly 99.6% that the FOLFOXIRI/FOLFOXIRI treatment was cost-effective. Based on the results of the sensitivity analysis, the price of drugs is the main factor influencing the economic efficiency of the drug administration. Different from the economic superiority of the USA, in order to enhance the quality of life of patients, China has been continuously promoting

new policies in recent years. For example, China started adopting the group purchasing organisation (GPO) model in 2015 to further reduce drug expenditures and reduce distribution costs.[43] National Medical Insurance negotiations are a major innovation in the admission of the medical insurance drug directory in recent years, designed to reduce people's medication burdens to ensure the need for medication for patients with major diseases, chronic diseases and serious illnesses. A total of 68 anticancer drugs have been included in the Chinese national medical insurance negotiation drug list over the years, covering breast cancer, lung cancer, colorectal cancer, stomach cancer, liver cancer and so on.[44] The best treatment decisions are driven by multiple factors, including drug costs, anticipated toxicities and practice patterns, in addition to therapeutic effects. The univariate sensitivity analyses revealed that the costs of drugs associated with each regimen highly influence the ICER. A change in the cost of the drug could cause significant effects on the ICERs obtained. With the decrease in the price of drugs against the background of such national policies, we can still come to the conclusion safely that for patients with mCRC, first-line and second-line treatment with FOLFOXIRI/FOLFOXIRI plus bevacizumab is a better option. In China, probabilistic sensitivity analysis results demonstrated a 54.7% probability that FOLFOXIRI/FOLFOXIRI is cost-effective at WTP values of US$36 053.01/QALY. However, the economic conditions of various provinces in our country are different. FOLFOXIRI/FOLFOXIRI may not be the most economic choice in some places like Henan (GDP US$8705.61, 2022) or Guangxi (GDP US$7323.28, 2022) where the economic level is relatively backward.

This work was the first research in the economic evaluation of mCRC drugs focused on FOLFOXIRI/FOLFOXIRI treatment, provides a reference for future analyses on the cost-effectiveness of drugs for the treatment of this type of cancer, and also for the economic evaluation of the treatment of upfront FOLFOXIRI combined with other drugs.[45] It also provides a reference for effective and economical clinical treatment therapies for patients in China and the USA, which is more practical and innovative.

Our analysis also has several limitations. First, an inevitable limitation was the use of a Weibull distribution to infer consequences beyond the lifetime horizon of the TRIBE2 trial. However, we validated the predicted and observed survival data, which indicated high anastomosis and good reproduction. Second, regional differences in economy and healthcare policy could lead to different final costs of treatments in China and the USA. Different therapies were estimated according to the information published for the TRIBE2 trial with patients recruited from 58 Italian oncology units, which were not designed as clinical trials specifically targeting the Chinese and US populations. However, there was no clear data suggesting that the efficacy of FOLFOXIRI, mFOLFOX6 and FOLFIRI treatment was related to race for patients with mCRC. Finally, the costs of managing grade 1/2 AEs were not included in this study, which might overestimate the economic results of FOLFOXIRI/FOLFOXIRI. This weakness may not be a major one, as implied by the findings in the one-way sensitivity analysis, which indicated that the costs related to AEs only have a tiny impact.

CONCLUSION

FOLFOXIRI/FOLFOXIRI therapy was estimated to be highly cost-effective for patients with metastatic colorectal cancer from the perspective of the USA and China healthcare systems at thresholds of US$100 000 and US$36 053.01 per QALY, respectively. The results of the study could also help with the decision-making of the patients, the physicians and the healthcare financial organisations.

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Patient consent for publication Not applicable.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of medical ethics committee, and the approval was obtained from our local ethics committee of Suzhou Dushu Lake Hospital (251004).

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Data availability statement Data are available in a public, open access repository. We are happy to distribute copies of our economic model to nonprofits everywhere, such as some universities or government agencies. Please, contact Xianglian Li at xianglian7116@126.com.

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