Am J Transl Res 2025;17(8):6180-6190
www.ajtr.org /ISSN:1943-8141/AJTR0163064

Original Article

Clinical efficacy and predictive indicators of cindilizumab combined with XELIRI protocol in advanced colorectal carcinoma patients

Weigeng Liu[1], Huhu Xue[1], Qian Lei[2], Ziyuan Jia[1], Shuang He[3], Guorui Ma[4]

[1]Department of Proctology II, Xi'an Daxing Hospital, Xi'an 710082, Shaanxi, China; [2]Department of Anorectal Surgery in Central Digestive Disease Ward, Baoji High-Tech Hospital, Baoji 721000, Shaanxi, China; [3]Tumor Diagnosis and Treatment Center, The First Hospital of Yulin, Yulin 719000, Shaanxi, China; [4]Department of General Surgery I, Dingxi People's Hospital, No. 22 Anding Road, Anding District, Dingxi 743000, Gansu, China

Received January 3, 2025; Accepted July 1, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: Objective: To evaluate the therapeutic efficacy of adding cindilizumab to the Xeloda-Irinotecan (XELIRI) regimen in patients with advanced colorectal cancer and to identify clinical and molecular biomarkers predictive of treatment response. Methods: A retrospective analysis was conducted on 197 patients with advanced colorectal carcinoma treated between January 2019 and June 2023. Patients were divided into two cohorts: the standard treatment group receiving XELIRI alone (n=103) and the combined treatment group receiving XELIRI with cindilizumab (n=94). Treatment response was assessed according to RECIST criteria and classified as responsive (complete response [CR] or partial response [PR]) or non-responsive (stable disease [SD] or progressive disease [PD]). Logistic regression analysis was performed to identify independent predictors of treatment response. Adverse events were recorded throughout the treatment course. Results: The experimental cohort demonstrated statistically higher objective response rate (ORR) and disease control rate (DCR) compared to the standard treatment cohort (ORR: 38.30% versus 22.33%, P=0.015; DCR: 80.85% versus 66.02%, P=0.019). The incidence of hypothyroidism and renal impairment was significantly higher in the combination group (P=0.002). Logistic regression identified carcinoembryonic antigen (CEA) (OR=1.336, P<0.001), tumor diameter (OR=2.818, P=0.001), KRAS/NRAS gene status (OR=6.229, P=0.001), and treatment regimen (OR=0.079, P<0.001) as independent predictors of treatment response. Receiver operating characteristic (ROC) curve analysis showed that their combined prediction significantly improved predictive efficacy (AUC=0.881), with high sensitivity and specificity. Conclusion: Cindilizumab combined with XELIRI regimen improves ORR and DCR in patients with advanced colorectal cancer but may increase the risk of hypothyroidism and renal impairment. CEA, tumor diameter, KRAS/NRAS gene, and treatment regimen are independent predictors of treatment response. The combined predictive model demonstrates robust diagnostic performance.

Keywords: Cindilizumab, XELIRI, advanced colorectal cancer, lymphatic metastasis, KRAS/NRAS gene

Introduction

Colorectal cancer (CRC) is a malignant tumor originating from the mucosa and glandular epithelium of the large intestine, with high global morbidity and mortality rates [1]. According to global cancer statistics, CRC ranks as the fourth most common malignancy and the second leading cause of cancer-related deaths [2]. In China, the incidence of CRC has been increasing annually by approximately 3%-4%, with a rising trend in younger populations, placing a substantial burden on individuals, families, and the healthcare system [3, 4]. In metastatic CRC (mCRC), distant spread of tumor cells is the primary cause of mortality [5]. The most common sites of metastasis include the lymph nodes, liver, lungs, and peritoneum [6-8]. Approximately 50% of patients develop distant metastasis during disease progression, and about 20% present with metastasis at initial diagnosis [9]. Consequently, managing mCRC remains a major clinical challenge, highlighting the need for effective treatment strategies to enhance patients' quality of life and clinical outcomes.

https://doi.org/10.62347/KZDR9031

Current therapeutic approaches for mCRC include surgical resection, radiotherapy, chemotherapy, and targeted treatments [10]. Chemotherapy remains a cornerstone of treatment, with capecitabine and irinotecan widely used for their anti-tumor effects via inhibition of DNA synthesis [11, 12]. However, there is uncertainty in the efficacy of the Xeloda and Irinotecan (XELIRI) regimen (capecitabine and irinotecan) as it has shown variability in CRC, particularly in patients experiencing significant adverse reactions to irinotecan [11, 13]. As a result, combined strategies involving XELIRI with other therapeutics, such as targeted therapy and immunotherapy, are gaining attention to enhance treatment efficacy and improve patient quality of life [12, 14].

Cindilizumab, a PD-1 inhibitor, has demonstrated potent anti-tumor activity by blocking the PD-1/PD-L1 signaling pathway, thereby overcoming tumor immune evasion and re-activating cytotoxic lymphocytes [15, 16]. Notably, cindilizumab has demonstrated a 50-fold higher affinity for PD-1 compared to nivolumab and a 10-fold higher affinity compared to pembrolizumab, along with superior in vitro stability [15]. While cindilizumab has been incorporated into several mCRC treatment protocols, the optimal chemotherapeutic combination remains inadequately defined.

Previous investigations have predominantly focused on PD-1 inhibitors combined with diverse cytotoxic protocols, whereas this study investigates the therapeutic efficacy of cindilizumab integrated with XELIRI regimen. Furthermore, prognostic biomarkers were identified to guide individualized treatment strategies for patients with mCRC. Such personalized treatment paradigms demonstrate potential for enhanced clinical efficacy while optimizing safety profiles, ultimately improving patient outcomes and quality of life for patients with advanced colorectal cancer.

Materials and methods

Study design and participants

This retrospective analysis included 197 individuals diagnosed with advanced-stage CRC who received treatment at Xi'an Daxing Hospital between January 2019 and June 2023. Patients were stratified into two cohorts based on the treatment regimen: the standard treatment group (n=103) received the XELIRI regimen exclusively, while the combined treatment group (n=94) received a combination of cindilizumab and the XELIRI regimen. This study was approved by the Medical Ethics Committee of Xi'an Daxing Hospital (approval number: 2019 Aan-SQ).

Inclusion and exclusion criteria

Inclusion criteria: (1) Histopathologically confirmed advanced CRC with radiologically measurable target lesions; (2) Completion of at least four treatment cycles with either XELIRI monotherapy or cindilizumab plus XELIRI combination therapy; (3) Eastern Cooperative Oncology Group (ECOG) score of 0-2 [17]; (4) Presence of at least one objectively measurable lesion on imaging; (5) Availability of complete clinical and follow-up data.

Exclusion criteria: (1) Known hypersensitivity to any component of cindilizumab or the XELIRI regimen; (2) Prior exposure to systemic chemotherapy or immunotherapy for advanced colorectal cancer; (3) Presence of severe cardiac, hepatic, or renal insufficiency, or other serious complications; (4) History of cognitive impairments, psychiatric disorders, or neurological conditions; (5) Pregnant or lactating women.

Treatment regimen

In the standard treatment group, patients received the XELIRI regimen, which included irinotecan (Jiangsu Hengrui Pharmaceutical Co., Ltd., H20061276) at 150 mg/m^2 administered intravenously on days 1 and 8, and capecitabine (Shanghai Roche Pharmaceutical, YBH-08582008) at 1,000 mg/m^2 orally twice daily for 14 consecutive days. Each treatment cycle lasted 21 days, and patients received a total of 4 cycles. The combined treatment group was treated with additional cindilizumab (Cinda Biopharmaceutical (Suzhou) Co., Ltd., S20180016) at a dose of 200 mg intravenously on day 1 of each cycle, alongside the XELIRI regimen, for a total of 4 cycles.

Primary outcomes

Efficacy was evaluated after completion of 4 treatment cycles according to the Response

Evaluation Criteria in Solid Tumors (RECIST). Treatment responses were categorized as progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). The objective response rate (ORR) was calculated as (CR + PR)/total number of patients ×100%, and the disease control rate (DCR) was calculated as (CR + PR + SD)/total number of patients ×100% [18]. Patient were further stratified into two groups based on treatment response: the responsive cohort (CR + PR) and the non-responsive cohort (SD + PD). Logistic regression analysis was performed to identify independent factors correlated with therapeutic effectiveness.

Prognostic analysis

Logistic regression modeling was used to identify independent predictors of treatment efficacy. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the predictive accuracy of specific clinical and molecular markers.

Secondary outcomes

Multivariate logistic regression analysis was conducted to identify independent predictors of treatment response. Next, a ROC curve analysis was performed to evaluate the predictive accuracy of selected clinical biomarkers. For safety analysis, all adverse events exceeding mild severity were recorded and managed according to established protocols.

Statistical methods

Data were analyzed using SPSS 25.0 and R Studio software. Kolmogorov-Smirnov test was used to assess the normality of continuous variables, and the Bartlett test was used to evaluate homogeneity of variance. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$) and analyzed using the independent samples t-test. Count data were described in terms of frequency (n) and percentage (%) and analyzed using the chi-square test (χ^2). Logistic regression models were employed to analyze the relationship between various factors and treatment efficacy. ROC curve analysis was performed to evaluate the predictive value of the selected clinical indicators. Differences were considered statistically significant at $P<0.05$.

Results

Comparison of baseline data between the two groups

No significant differences were observed between the two groups in terms of age, body mass index (BMI), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), primary tumor site, tumor diameter, pathological type, histological grade, KRAS/NRAS gene status, Eastern Cooperative Oncology Group (ECOG) score, lymph node metastasis, prior surgical history, smoking status, alcohol consumption, hypertension, or diabetes (all $P>0.05$) (**Table 1**).

Comparison of treatment response between the two groups

The combination group demonstrated a significantly higher ORR of 38.30%, compared to 22.33% in the standard treatment group (XELIRI alone) ($P=0.015$). The DCR was also significantly improved in the combination group (80.85% vs. 66.02%, $P=0.019$) (**Table 2**).

Comparison of adverse reactions between the two groups

No significant differences were observed between the two groups in the incidence of common chemotherapy-related adverse reactions, including nausea, vomiting, anemia, diarrhea, neutropenia, and thrombocytopenia (all $P>0.05$). However, the combination group exhibited a significantly higher incidence of hypothyroidism and renal impairment. Specifically, 15 patients in the combination group developed hypothyroidism compared to 3 in the standard treatment group ($P=0.002$), and 18 patients in the combination group experienced renal impairment, compared to 5 in the standard treatment group ($P=0.002$) (**Table 3**).

Comparison of baseline data between patients with different efficacy outcomes

Patients were categorized into effective (CR + PR) and ineffective (SD + PD) groups based on treatment efficacy. The effective group had significantly lower levels of CEA (24.65±2.73 ng/mL vs. 27.09±3.33 ng/mL), AFP (33.36±4.32 ng/mL vs. 37.28±4.49 ng/mL), and tumor diameter (6.25±0.74 cm vs. 6.87±0.78 cm)

Table 1. Comparison of baseline data between the two groups

Item	Standard treatment group (n=103)	Combined treatment group (n=94)	t/χ^2	P
Age ($\bar{x}$±s, years)	51.02±6.89	52.82±7.41	1.760	0.080
Gender [case (%)]			1.093	0.296
Male	30	59		
Female	29	79		
BMI ($\bar{x}$±s, kg/m^2)	22.50±3.45	23.08±2.97	1.271	0.205
CEA ($\bar{x}$±s, ng/mL)	26.79±2.91	25.96±3.68	-1.772	0.078
AFP ($\bar{x}$±s, ng/mL)	36.46±4.45	35.78±5.06	-0.997	0.320
Primary focal site [case (%)]			0.275	0.872
Right hemicolon	59	51		
Left hemicolon	31	29		
Rectum	13	14		
Tumor Diameter ($\bar{x}$±s, cm)	6.75±0.82	6.63±0.81	-1.079	0.282
Pathological type [case (%)]			0.155	0.925
Poorly differentiated	15	12		
Moderately differentiated	61	56		
Well-differentiated	27	26		
Histological classification [case (%)]			0.437	0.804
Adenocarcinoma	86	79		
Adenosquamous carcinoma	11	8		
Undifferentiated carcinoma	6	7		
KRAS/NRAS genes [case (%)]			0.035	0.851
mutation	43	38		
No-mutation	60	56		
ECOG [case (%)]			1.028	0.311
0-1	87	84		
2	16	10		
Lymph node metastasis [case (%)]			0.014	0.905
Yes	37	33		
No	66	61		
Previous surgical history [case (%)]			0.163	0.687
Yes	61	53		
No	42	41		
Smoking history [case (%)]			0.379	0.538
Yes	45	37		
No	58	57		
History of alcohol abuse [case (%)]			0.587	0.444
Yes	33	35		
No	70	59		
Hypertension [case (%)]			0.058	0.810
Yes	62	55		
No	41	39		
Diabetes mellitus [case (%)]			0.068	0.794
Yes	38	33		
No	65	61		

Note: BMI: Body Mass Index, CEA: Carcinoembryonic Antigen, AFP: Alpha-fetoprotein, KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, NRAS: Neuroblastoma Ras Viral Oncogene Homolog, ECOG: Eastern Cooperative Oncology Group.

Table 2. Comparison of treatment response between the two groups

Group	CR	PR	SD	PD	ORR	DCR
Control group (n=103)	7 (6.80)	16 (15.53)	45 (43.69)	35 (33.98)	23 (22.33)	68 (66.02)
Observation group (n=94)	11 (11.70)	25 (26.60)	40 (42.55)	18 (19.15)	36 (38.30)	76 (80.85)
χ^2					5.973	5.498
P					0.015	0.019

Note: CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, ORR: Overall Response Rate, DCR: Disease Control Rate.

Table 3. Comparison of the incidence of adverse reactions between the two groups

Group	Nausea and vomiting	Anemia	Diarrhea	Neutropenia	Thrombocytopenia	Hypothyroidism	Renal function impairment
Control group (n=103)	13	5	10	66	43	3	5
Observation group (n=94)	11	6	9	59	45	15	18
χ^2	0.039	0.218	0.001	0.036	0.746	10.074	9.739
P	0.844	0.641	0.975	0.849	0.388	0.002	0.002

compared to the ineffective group (P<0.001 for all). Furthermore, a higher proportion of patients with KRAS/NRAS mutations was higher in the effective group (66% vs. 50%, P< 0.001), and a greater proportion of patients in the effective group received the combination treatment (40% vs. 19%, P<0.001) (**Table 4**).

Logistic regression analysis of independent factors affecting treatment efficacy

A logistic regression analysis was performed using treatment efficacy as the dependent variable (0= ineffective, 1= effective) and baseline clinical characteristics as independent variables. The analysis identified significant associations between treatment efficacy and the following factors: CEA (OR=1.336, P< 0.001), tumor diameter (OR=2.818, P=0.001), KRAS/NRAS mutation status (OR=6.061, P< 0.001), lymph node metastasis (OR=6.240, P<0.001), and treatment regimen (OR=0.305, P<0.001) (**Figure 1**). Among these factors, multivariate regression analysis identified CEA (OR=1.336, P<0.001), tumor diameter (OR= 2.818, P=0.001), KRAS/NRAS gene status (OR=6.229, P=0.001), and treatment regimen (OR=0.079, P<0.001) as independent factors influencing treatment efficacy (**Figure 2**).

ROC curve analysis for predicting treatment efficacy

As shown by ROC curve analysis, individual factors, such as CEA, tumor diameter, KRAS/NRAS mutation status, lymph node metastasis, and treatment regimen, provided moderate predictive value, with AUC values ranging from 0.640 to 0.733. However, the combination of these factors significantly improved predictive accuracy, with an AUC of 0.881, sensitivity of 76.09%, and specificity of 86.44%, demonstrating high reliability and accuracy in predicting treatment efficacy (**Table 5**; **Figure 3**).

Discussion

CRC originates from the malignant transformation of epithelial cells in the colon or rectum and is often asymptomatic in its early stages [19]. As the disease progresses, patients may present with altered bowel habits, diarrhea, and abdominal pain. In advanced stages, systemic symptoms such as anorexia, weight loss, and anemia become more prominent, reflecting disease progression [20, 21]. Advanced CRC is frequently associated with a significant risk of recurrence and chemoresistance, constraining therapeutic options and leading to unfavorable prognosis [22]. At this stage, surgical resection is generally not feasible, and management typically shifts to second-line chemotherapy or palliative care aimed at controlling disease progression, alleviating symptoms, and prolonging survival [23]. The goal of this study was to measure the therapeutic benefits of combining cindilizumab with the XELIRI regimen in advanced CRC and to identify key predictive factors of treatment response.

Table 4. Comparison of baseline data of patients in the valid and invalid groups

Item	Effective group (n=59)	Invalid group (n=138)	t/χ^2	P
Age ($\bar{x}$±s, years)	51.66±7.27	52.09±7.2	1.288	0.198
Gender [case (%)]			1.093	0.296
Male	30	59		
Female	29	79		
BMI ($\bar{x}$±s, kg/m^2)	22.78±3.20	22.82±3.23	0.078	0.938
CEA ($\bar{x}$±s, ng/mL)	24.65±2.73	27.09±3.33	5.378	<0.001
AFP ($\bar{x}$±s, ng/mL)	33.36±4.32	37.28±4.49	4.974	<0.001
Primary focal site [case (%)]			1.106	0.575
Right hemicolon	30	80		
Left hemicolon	19	41		
Rectum	10	17		
Tumor Diameter ($\bar{x}$±s, cm)	6.25±0.74	6.87±0.78	5.316	<0.001
Pathological type [case (%)]			0.703	0.704
Poorly differentiated	9	18		
Moderately differentiated	32	85		
Well-differentiated	17	35		
Histological classification [case (%)]			2.395	0.302
Adenocarcinoma	46	119		
Adenosquamous carcinoma	7	12		
Undifferentiated carcinoma	6	7		
KRAS/NRAS genes [case (%)]			23.271	<0.001
mutation	9	72		
No-mutation	50	66		
ECOG [case (%)]			0.010	0.922
0-1	51	120		
2	8	18		
Lymph node metastasis [case (%)]			20.601	<0.001
Yes	7	63		
No	52	75		
Previous surgical history [case (%)]			0.129	0.719
Yes	33	81		
No	26	57		
Smoking history [case (%)]			0.207	0.649
Yes	26	56		
No	33	82		
History of alcohol abuse [case (%)]			2.040	0.153
Yes	16	52		
No	43	86		
Hypertension [case (%)]			0.385	0.535
Yes	37	80		
No	22	58		
Diabetes mellitus [case (%)]			0.538	0.463
Yes	19	52		
No	40	86		
Treatment			11.191	<0.001
XELIRI	19	76		
XELIRI with Cindilizumab	40	54		

Note: BMI: Body Mass Index, CEA: Carcinoembryonic Antigen, AFP: Alpha-fetoprotein, KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, NRAS: Neuroblastoma Ras Viral Oncogene Homolog, ECOG: Eastern Cooperative Oncology Group, XELIRI: Xeloda-Epirubicin-Capecitabine Irinotecan.

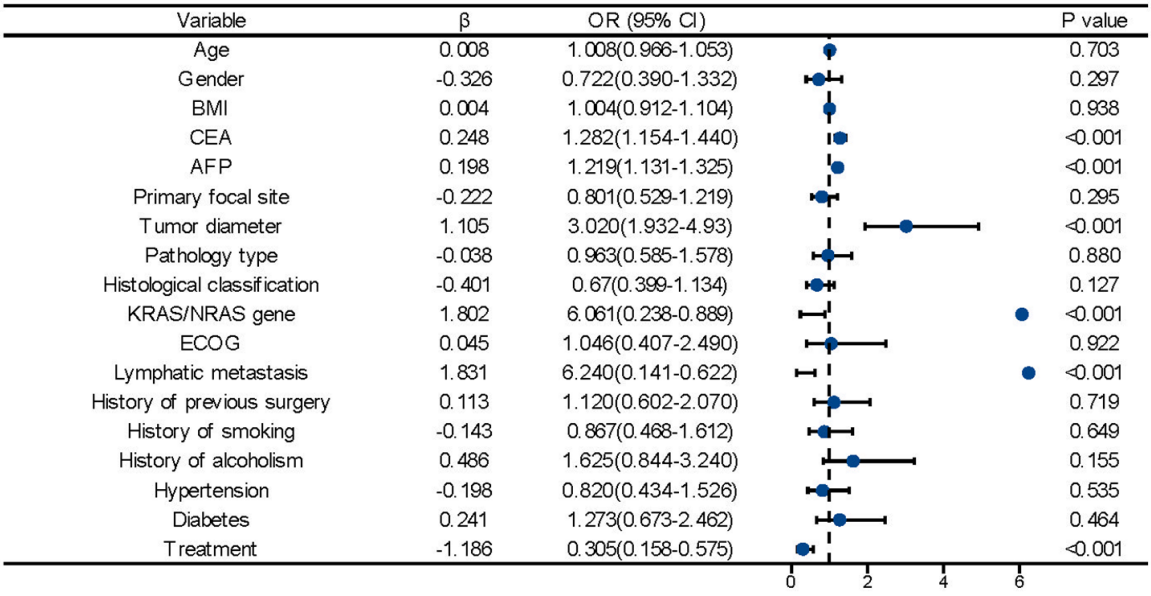

Figure 1. Univariate logistic regression analysis of factors associated with treatment efficacy. Note: BMI: Body Mass Index, CEA: Carcinoembryonic Antigen, AFP: Alpha-fetoprotein, KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, NRAS: Neuroblastoma Ras Viral Oncogene Homolog, ECOG: Eastern Cooperative Oncology Group.

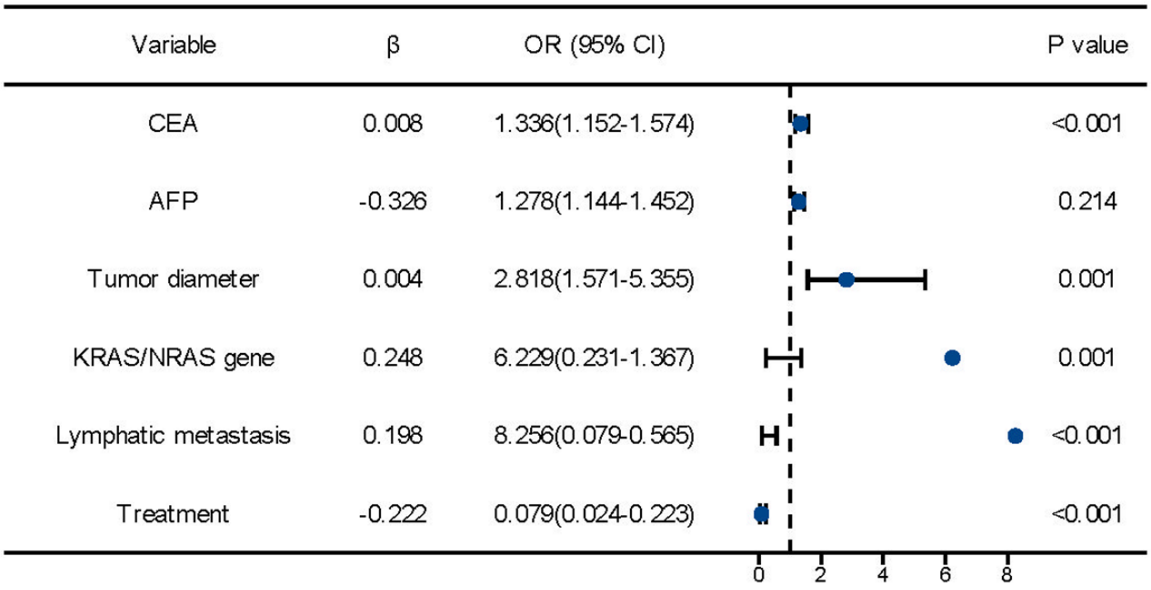

Figure 2. Multivariate logistic regression analysis of independent predictors of treatment Efficacy. Note: CEA: Carcinoembryonic Antigen, AFP: Alpha-fetoprotein, KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, NRAS: Neuroblastoma Ras Viral Oncogene Homolog.

Combining cindilizumab with the XELIRI regimen led to much better outcomes in treating advanced CRC. The combination group significantly improved both ORR and DCR, indicating that cindilizumab amplified the therapeutic impact of the XELIRI regimen. Immune evasion is a hallmark of malignancy and a major obstacle to effective treatment. This process involves mechanisms like the loss of specific antigen expression and suppression of immune T cell activity, which compromise the efficacy of chemotherapy [24, 25]. The emergence of immune checkpoint inhibitors has driven substantial progress in treating various solid and

Table 5. Predictive performance of each independent factor alone and their combination for treatment response

Marker	AUC	Cut off	95% CI	Specificity	Sensitivity
CEA	0.712	25.645	0.638-0.785	66.10%	68.84%
Tumor diameter	0.733	6.520	0.654-0.811	72.88%	72.46%
KRAS/NRAS gene	0.685	0.5	0.622-0.747	84.75%	52.17%
Lymphatic metastasis	0.669	0.5	0.610-0.728	88.14%	45.65%
Treatment	0.640	0.5	0.567-0.712	67.80%	60.14%
Combined	0.881	0.5	0.834-0.928	86.44%	76.09%

Note: CEA: Carcinoembryonic Antigen, KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, NRAS: Neuroblastoma Ras Viral Oncogene Homolog.

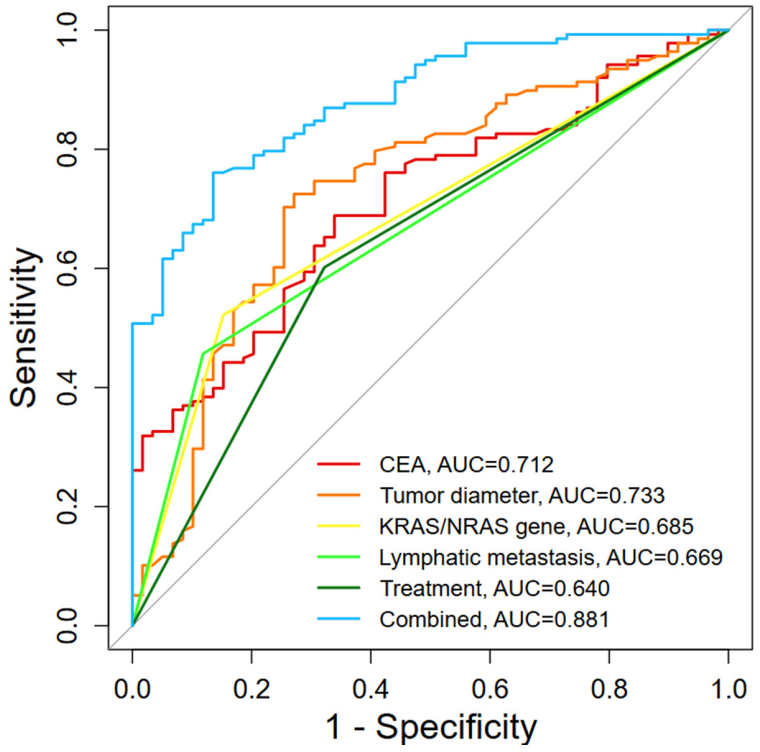

Figure 3. ROC curves for each independent influencing factor alone and their combination for predicting treatment efficacy. Note: CEA: Carcinoembryonic Antigen, KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, NRAS: Neuroblastoma Ras Viral Oncogene Homolog.

non-solid cancers. The PD-1/PD-L1 pathway plays a central role in modulating anti-tumor immune responses, and its blockade can restore effective anti-tumor immune responses [26, 27]. A meta-analysis by Huang et al. demonstrated that PD-1/PD-L1 inhibitors significantly improved ORR and safety outcomes when used as first-line therapy for mCRC with mismatch repair deficiency [28]. Cindilizumab, a PD-1 inhibitor developed in China, exhibits high binding affinity and achieves receptor occupancy rate exceeding 95%, ensuring sustained immunologic activity [15, 16]. These pharmacologic properties promotes the infiltration of effector T cells into tumor tissues and potentiate a stronger and more robust anti-tumor immune response.

Our findings are consistent with previous research evaluating the efficacy of cindilizumab in combination with chemotherapy. For example, Fang et al. reported that a regimen including cindilizumab, bevacizumab, oxaliplatin, and capecitabine demonstrated favorable efficacy and safety in patients with unresectable mCRC. In their trial of 25 patients, the ORR reached 84%, with 21 patients achieving either CR or PR [29]. Similarly, our study suggests that cindilizumab exerts a synergistic effect when combined with the XELIRI, enhancing tumor sensitivity to treatment. This may be attributed to cindilizumab's role as a PD-1 inhibitor, which enhances antitumor immune responses, while chemotherapeutic agents such as capecitabine and irinotecan may further augment immune activation, contributing to the overall therapeutic efficacy.

Nevertheless, both therapeutic cohorts demonstrated considerable treatment-related adverse events, encompassing gastrointestinal disturbances (nausea and vomiting), hemato-

logical abnormalities (anemia, neutropenia, thrombocytopenia), diarrhea, endocrine dysfunction (hypothyroidism), and nephrotoxic manifestations. Notably, the combination group exhibited substantially higher incidences of hypothyroidism and renal impairment compared to the standard treatment cohort. These side effects are consistent with the known toxicity profiles of the XELIRI regimen, driven mainly by its two chemotherapy drugs. Irinotecan is associated with mucosal damage, often resulting in severe diarrhea, while capecitabine has been implicated in renal toxicity and may exacerbate renal dysfunction in susceptible patients [30]. Adding cindilizumab introduces a different set of immune-related adverse events. As a PD-1 inhibitor, cindilizumab activates the immune system to fight cancer. However, this activation can also lead to immune-mediated damage to normal tissues, especially the thyroid and kidneys. This explains the higher incidence of hypothyroidism and renal impairment observed in the combination group [31]. Therefore, it's essential to regularly monitor thyroid and renal function throughout the treatment course. Early detection and timely intervention, such as thyroid hormone therapy or nephroprotective measures, are essential to prevent serious complications. In clinical practice, patient education regarding these risks along with proactive surveillance protocols, plays a vital role in improving treatment safety and optimizing therapeutic outcomes.

Logistic regression analysis in this study identified several independent factors that significantly affect treatment outcomes, including CEA levels, tumor size, KRAS/NRAS mutations, lymph node metastasis, and the therapeutic approach. Elevated CEA levels are consistently linked to increased tumor aggressiveness and poorer prognosis. High CEA values typically reflect tumors with enhanced invasiveness, rapid growth kinetics, and reduced sensitivity to both chemotherapy and immunotherapy [32]. Tumor size is another critical factor, as larger tumors are usually associated with advanced cancer stages, higher metastatic potential, and reduced responsiveness to systemic treatment, making it a strong predictor of poor prognosis and treatment failure [33]. KRAS/NRAS mutations, frequently seen in CRC, are well-known contributors to resistance to therapies like EGFR inhibitors. Tumors with these mutations tend to be more aggressive and less responsive to conventional treatments, presenting substantial challenges in managing CRC [34]. Lymph node metastasis is also an important prognostic factor in CRC, as it signifies tumor dissemination beyond the primary site, complicating local disease control, which is associated with increased recurrence and reduced survival [35]. While each of these individual factors has prognostic value, their standalone predictive power for treatment response was limited. However, their combined prediction demonstrated considerably higher discriminative ability, reaching an AUC of 0.881, with a sensitivity of 76.09% and a specificity of 86.44%. This suggests that a multifactorial model that incorporates multiple clinical and molecular markers is more reliable in predicting treatment responses, offering the possibility of more personalized treatment strategies. The model's high sensitivity and specificity highlight its potential as an important clinical tool for predicting treatment response in mCRC patients and supporting customized treatment plans, ultimately enhancing patient survival rates.

Despite these promising findings, this study still has several limitations that warrants further attention. The relatively small sample size may restrict the broader applicability of our findings, and the lack of long-term follow-up precludes definitive conclusions regarding the durability of response and long-term safety profile. Two key areas merit further investigation. First, elucidating the mechanistic underpinnings of the observed toxicities is essential for developing evidence-based monitoring, which is a prerequisite for developing effective management protocols. Second, enhanced treatment personalization is imperative. Our results support the integration of biomarkers such as CEA, tumor size, and KRAS/NRAS mutational status into predictive models that can optimize patient selection and improve therapeutic outcomes. Therefore, future research should prioritize large-scale, multicenter randomized controlled trials with extended follow-up periods to comprehensively evaluate the long-term efficacy and safety of cindilizumab plus XELIRI. These studies should also evaluate the effectiveness of mitigation strategies for immune-related adverse events, ultimately enabling

more precise, safe, and effective care for patients with advanced colorectal cancer.

Conclusion

Cindilizumab in combination with the XELIRI regimen significantly enhances treatment efficacy in patients with advanced colorectal cancer. Key predictors of therapeutic response include CEA levels, tumor size, KRAS/NRAS mutation status, lymph node involvement, and treatment modality. The high predictive accuracy of the combined model underscores its potential as a valuable tool for guiding personalized treatment strategies, ultimately improving patient outcomes and quality of life.

Disclosure of conflict of interest

None.

Address correspondence to: Guorui Ma, Department of General Surgery I, Dingxi People's Hospital, No. 22 Anding Road, Anding District, Dingxi 743000, Gansu, China. E-mail: 18293219986@163.com

References

[1] Gong RH, Chen SB and Chen GQ. Advances and challenges in targeted therapy for colorectal cancer: a focus on adenomatous polyposis coli and kirsten rat sarcoma virus mutations. J Transl Gastroenterol 2024; 2: 52-59.

[2] Rawla P, Sunkara T and Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol 2019; 14: 89-103.

[3] Siegel RL, Wagle NS, Cercek A, Smith RA and Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin 2023; 73: 233-254.

[4] Xu L, Zhao J, Li Z, Sun J, Lu Y, Zhang R, Zhu Y, Ding K, Rudan I, Theodoratou E, Song P and Li X; Global Health Epidemiology Research Group (GHERG). National and subnational incidence, mortality and associated factors of colorectal cancer in China: a systematic analysis and modelling study. J Glob Health 2023; 13: 04096.

[5] Cañellas-Socias A, Sancho E and Batlle E. Mechanisms of metastatic colorectal cancer. Nat Rev Gastroenterol Hepatol 2024; 21: 609-625.

[6] Bando H, Ohtsu A and Yoshino T. Therapeutic landscape and future direction of metastatic colorectal cancer. Nat Rev Gastroenterol Hepatol 2023; 20: 306-322.

[7] Liu Y, Zhang Q, Xing B, Luo N, Gao R, Yu K, Hu X, Bu Z, Peng J, Ren X and Zhang Z. Immune phenotypic linkage between colorectal cancer and liver metastasis. Cancer Cell 2022; 40: 424-437, e425.

[8] Bang K, Kim JE, Kim TW, Kim SY, Lim SB, Park IJ, Kim CW, Yoon YS and Hong YS. Clinical outcomes of curative surgical resection of peritoneal metastasis in patients with colorectal cancer: a long-term follow-up study. Cancer Med 2023; 12: 2861-2868.

[9] Ni Y, Liang Y, Li M, Lin Y, Zou X, Han F, Cao J and Li L. The updates on metastatic mechanism and treatment of colorectal cancer. Pathol Res Pract 2023; 251: 154837.

[10] Ohishi T, Kaneko MK, Yoshida Y, Takashima A, Kato Y and Kawada M. Current targeted therapy for metastatic colorectal cancer. Int J Mol Sci 2023; 24: 1702.

[11] Xu RH, Muro K, Morita S, Iwasa S, Han SW, Wang W, Kotaka M, Nakamura M, Ahn JB, Deng YH, Kato T, Cho SH, Ba Y, Matsuoka H, Lee KW, Zhang T, Yamada Y, Sakamoto J, Park YS and Kim TW. Modified XELIRI (capecitabine plus irinotecan) versus FOLFIRI (leucovorin, fluorouracil, and irinotecan), both either with or without bevacizumab, as second-line therapy for metastatic colorectal cancer (AXEPT): a multicentre, open-label, randomised, non-inferiority, phase 3 trial. Lancet Oncol 2018; 19: 660-671.

[12] Zekri J, Baghdadi MA, Ibrahim RB, Meliti A and Sobahy TM. Biweekly cetuximab in combination with capecitabine and oxaliplatin (XELOX) or irinotecan (XELIRI) in the first-line and second-line treatment of patients with RAS wild-type metastatic colorectal cancer. Ecancermedicalscience 2022; 16: 1490.

[13] Patt YZ, Lee FC, Liebmann JE, Diamandidis D, Eckhardt SG, Javle M, Justice GR, Keiser W, Salvatore JR, Bexon A and Lin E. Capecitabine plus 3-weekly irinotecan (XELIRI regimen) as first-line chemotherapy for metastatic colorectal cancer: phase II trial results. Am J Clin Oncol 2007; 30: 350-357.

[14] Ocvirk J, Rebersek M and Boc M. Bevacizumab in first-line therapy of metastatic colorectal cancer: a retrospective comparison of FOLFIRI and XELIRI. Anticancer Res 2011; 31: 1777-1782.

[15] Wang J, Fei K, Jing H, Wu Z, Wu W, Zhou S, Ni H, Chen B, Xiong Y, Liu Y, Peng B, Yu D, Jiang H and Liu J. Durable blockade of PD-1 signaling links preclinical efficacy of sintilimab to its clinical benefit. MAbs 2019; 11: 1443-1451.

[16] Liu X and Yi Y. Recent updates on Sintilimab in solid tumor immunotherapy. Biomark Res 2020; 8: 69.

[17] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP. Toxicity and response criteria of the Eastern coop-

erative oncology group. Am J Clin Oncol 1982; 5: 649-655.
[18] Iannessi A, Beaumont H, Liu Y and Bertrand AS. RECIST 1.1 and lesion selection: how to deal with ambiguity at baseline? Insights Imaging 2021; 12: 36.
[19] Brown KG, Ansari N and Solomon MJ. Contemporary management of advanced colorectal cancer: the Australian experience. Med J Aust 2024; 220: 222-224.
[20] Bener A, Öztürk AE, Dasdelen MF, Barisik CC, Dasdelen ZB, Agan AF, De La Rosette J and Day AS. Colorectal cancer and associated genetic, lifestyle, cigarette, nargileh-hookah use and alcohol consumption risk factors: a comprehensive case-control study. Oncol Rev 2024; 18: 1449709.
[21] Kim RD, Azad NS, Morse MA, Poplin E, Mahipal A, Tan B Jr, Mavroukakis SA, Fantini M, Tsang KY, Zaki A, Torrealba J, Arlen PM and Beg MS. Phase II study of ensituximab, a novel chimeric monoclonal antibody, in adults with unresectable, metastatic colorectal cancer. Clin Cancer Res 2020; 26: 3557-3564.
[22] Yang D, Li Y, Liu J, Jiang W and Ma D. Efficacy and tolerance of maintenance therapy in patients with incurable advanced colorectal cancer. Nan Fang Yi Ke Da Xue Xue Bao 2013; 33: 1815-1818.
[23] Tarpgaard LS, Winther SB and Pfeiffer P. Treatment options in late-line colorectal cancer: lessons learned from recent randomized studies. Cancers (Basel) 2023; 16: 126.
[24] Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, Li Q, Lu Y, Chen Y, Guo Y, Chen Z, Liu B, Jia W, Wu J, Wang J, Shao G, Zhang B, Shan Y, Meng Z, Wu J, Gu S, Yang W, Liu C, Shi X, Gao Z, Yin T, Cui J, Huang M, Xing B, Mao Y, Teng G, Qin Y, Wang J, Xia F, Yin G, Yang Y, Chen M, Wang Y, Zhou H and Fan J; ORIENT-32 study group. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. Lancet Oncol 2021; 22: 977-990.
[25] He R, Huang S, Lu J, Su L, Gao X and Chi H. Unveiling the immune symphony: decoding colorectal cancer metastasis through immune interactions. Front Immunol 2024; 15: 1362709.
[26] Yan S, Wang W, Feng Z, Xue J, Liang W, Wu X, Tan Z, Zhang X, Zhang S, Li X and Zhang C. Immune checkpoint inhibitors in colorectal cancer: limitation and challenges. Front Immunol 2024; 15: 1403533.
[27] Jin C, Zhu X, Huang X, Gong T, Wei Z and You J. Efficacy and safety of PD-1/PD-L1 and CTLA-4 immune checkpoint inhibitors in colorectal cancer: a meta-analysis. J Comp Eff Res 2022; 11: 203-212.
[28] Huang Z, Li C, Huang Y, Liang W and Tao H. Efficacy and safety of PD-1/L1 inhibitors as first-line therapy for metastatic colorectal cancer: a meta-analysis. Front Immunol 2024; 15: 1425596.
[29] Fang X, Zhu N, Zhong C, Wang L, Li J, Weng S, Hu H, Dong C, Li D, Song Y, Xu D, Wang J, Sun L, Wang J, Wang Z, Cao H, Liao X, Yu N, Xiao Q, Mi M, Zhang S, Ding K and Yuan Y. Sintilimab plus bevacizumab, oxaliplatin and capecitabine as first-line therapy in RAS-mutant, microsatellite stable, unresectable metastatic colorectal cancer: an open-label, single-arm, phase II trial. EClinicalMedicine 2023; 62: 102123.
[30] Garcia-Alfonso P, Muñoz-Martin A, Mendez-Ureña M, Quiben-Pereira R, Gonzalez-Flores E and Perez-Manga G. Capecitabine in combination with irinotecan (XELIRI), administered as a 2-weekly schedule, as first-line chemotherapy for patients with metastatic colorectal cancer: a phase II study of the Spanish GOTI group. Br J Cancer 2009; 101: 1039-1043.
[31] Wang Z, Liu Y, Wang K and Ma L. Efficacy and safety of PD-1 and PD-L1 inhibitors in advanced colorectal cancer: a meta-analysis of randomized controlled trials. BMC gastroenterol 2024; 24: 461.
[32] Dilek ON, Arslan Kahraman Dİ and Kahraman G. Carcinoembryonic antigen in the diagnosis, treatment, and follow-up of focal liver lesions. World J Gastrointest Surg 2024; 16: 999-1007.
[33] Yirgin H, Sibiç O, Tatlidil YE, Bozdağ E, Bozkurt MA, Devecioğlu EG, Aziret M and Ercan M. Effect of tumor size on prognosis in colorectal cancer. Ann Ital Chir 2023; 94: 63-72.
[34] Sanchez-Ibarra HE, Jiang X, Gallegos-Gonzalez EY, Cavazos-González AC, Chen Y, Morcos F and Barrera-Saldaña HA. KRAS, NRAS, and BRAF mutation prevalence, clinicopathological association, and their application in a predictive model in Mexican patients with metastatic colorectal cancer: a retrospective cohort study. PLoS One 2020; 15: e0235490.
[35] Sasaki T, Shigeta K, Matsui S, Seishima R, Okabayashi K and Kitagawa Y. Mesenteric location of lymph node metastasis for colorectal cancer. ANZ J Surg 2023; 93: 1257-1261.