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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

Tumour chemotherapy sensitivity test may predict clinical outcomes in colorectal cancer patients receiving oxaliplatin and fluoropyrimidine-based regimens

Si-Jia Li, Yi-Xuan Lu, Fang-Yue Zheng, Yi-Cong Bian, Li-Yan Miao, Chen-Rong Huang

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Abstract

BACKGROUND

Chemotherapy is an essential treatment for colorectal cancer (CRC) patients after surgery, but many patients do not benefit from chemotherapy because tumour heterogeneity results in varied responses.

AIM

To study the effectiveness of *in vitro* chemosensitivity tests adenosine triphosphate-based tumour chemotherapy sensitivity test (ATP-TCA) for tailoring postoperative chemotherapy regimens for patients with CRC.

METHODS

Between January 2015 to December 2021, a total of 1549 CRC patients underwent surgery and *in vitro* chemosensitivity testing using ATP-TCA. A subset of 405 patients who met the survival assessment criteria were followed to collect data on overall survival (OS) and disease-free survival (DFS). Cox regression analysis revealed independent prognostic factors that affect OS and DFS for those receiving oxaliplatin (L-OPH) and fluoropyrimidine-based regimens, aiding in the development of clinical predictive models. The relationships between the ATP-TCA results and clinical outcomes were analysed using the Kaplan-Meier method.

RESULTS

Tumour heterogeneity and resistance to multiple drugs were observed in 1549 patients. The sensitivity to 5-fluorouracil (5-FU) combined with L-OPH was tested among 1474 of these patients, yielding a sensitivity rate of 11.9%. ATP-TCA results were identified as an independent prognostic factor for DFS [P = 0.002, hazard ratio (95% confidence interval): 4.98 (1.81-13.72)] in patients with resectable CRC. Compared with drug-resistant patients, sensitive CRC patients treated with 5-FU and L-OPH had significantly prolonged DFS (P = 0.027). Further Kaplan-Meier analysis indicated that ATP-TCA sensitivity was significantly associated with improved OS (P = 0.048) and DFS (P = 0.003) in patients with stage III CRC.

CONCLUSION

The response of CRC patients to the combination regimen of 5-FU and L-OPH is heterogeneous. This study confirmed that the ATP-TCA is a valuable tool for predicting clinical outcomes, such as DFS, in patients with resectable CRC receiving chemotherapy. Although further validation with multicentre data is still necessary, these findings support that the ATP-TCA may function as a guiding tool for personalized chemotherapy administration, thereby optimizing treatment opportunities for patients.

Key Words: Colorectal cancer; Precision oncology; Adenosine triphosphate-based tumour chemotherapy sensitivity test; Clinical prediction model; Chemosensitivity; 5-fluorouracil; Oxaliplatin

Core Tip: In this study, retrospectively evaluated the clinical application of adenosine triphosphate-based tumour chemotherapy sensitivity test (ATP-TCA) and revealed that it is an independent prognostic factor for disease-free survival in patients with resectable colorectal cancer. Additionally, an ATP-TCA-sensitive chemotherapy regimen was shown to significantly improve overall survival and disease-free survival in colorectal patients in stage III. Although the necessity for further validation, this study provides evidence supporting the extension of ATP-TCA assays to combination chemotherapy regimens for colorectal cancer while providing a theoretical basis and perspective for future advancements in personalized medicine.

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INTRODUCTION

Colorectal cancer (CRC) is a prevalent and highly lethal malignancy worldwide that results in an estimated 903859 deaths reported in 2022 according to the International Agency for Research on Cancer, making it the second leading cause of cancer-related mortality globally[1]. Among them, China has significantly higher CRC morbidity than other countries, accounting for approximately 26.7% of the global incidence[2]. Currently, the primary therapeutic modalities for treating CRC include surgical intervention, postoperative adjuvant chemotherapy, radiotherapy, targeted therapy, immuno-therapy and other approaches[3-6]. Patients with pathological tumour-node-metastasis stage II or III disease typically need postoperative adjuvant chemotherapy[3,7]. Postoperative adjuvant chemotherapy has the potential to effectively control residual tumour cells, thereby reducing the risk of recurrence and metastasis, prolonging survival, and enhancing quality of life. However, owing to tumour heterogeneity and the development of drug resistance, not all CRC patients can benefit from first-line drug regimens based on oxaliplatin (L-OPH) and fluoropyrimidine agents [such as 5-fluorouracil (5-FU), capecitabine, and deoxy-fluorouridine] for postoperative adjuvant chemotherapy in CRC patients[8-10]. Relying solely on clinical experience without accounting for individual differences may result in a lack of insight, underscoring the utmost importance of tailoring chemotherapy regimens to suit each patient's unique needs[11]. Although techniques such as genetic testing and programmed death ligand-1 assessment enable more accurate drug response prediction, their clinical utility is limited by a subsequent lack of specific treatment options. Additionally, a high percentage of tumour patients have no detectable mutations and thus cannot benefit from corresponding targeted therapies. The adenosine triphosphate-based tumour chemotherapy sensitivity test (ATP-TCA) is a viable method for assessing individual chemosensitivity by quantifying the *in vitro* drug inhibition rate of tumour cell growth. The clinical application value of *in vitro* tumour cell chemosensitivity assays in guiding individualized treatment for patients with lung cancer[12], gastric cancer[13], and leukaemia[14] has been well established by our research group. However, the heterogeneity of the response of CRC patients to combination drug regimens based on L-OPH and fluoropyrimidine, as well as the correlation between *in vitro* chemosensitivity and clinical outcomes, remains unclear. The aim of the present study was to examine the associations between ATP-TCA outcomes and clinical outcomes in patients diagnosed with CRC.

MATERIALS AND METHODS

Patients' selection

Patients with histologically confirmed CRC who underwent surgical treatment and ATP-TCAs at our hospital between January 1, 2015 to December 31, 2021 were enrolled in this study. The inclusion criteria for survival assessment were as follows: (1) Patients who underwent radical colorectal resection; (2) Patients with histologically confirmed high-risk stage II or III CRC according to the American Joint Committee on Cancer/Union for International Cancer Control staging guidelines for CRC (8^{th} edition); (3) Patients who received at least one cycle of chemotherapy with L-OPH and fluoropyrimidines (5-FU/capecitabine/desofloxuridine); and (4) Patients who underwent ATP-TCA to detect the drug sensitivity of the combined 5-FU and L-OHP chemotherapy regimen. Additionally, patients who received neoadjuvant therapy before surgery, radiotherapy, targeted therapy or immunotherapy before disease progression, as well as those with other concurrent tumours, were excluded from the survival assessment.

Ethical approval for this study was obtained from the Research Ethics Board of the First Affiliated Hospital of Soochow University (No. 2023178). All procedures involving human participants were conducted in accordance with the ethical standards set by institutional and national research committees as well as the principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments.

Study design

The correlation between the ATP-TCA results of the combination drug regimen consisting of 5-FU + L-OHP was retrospectively analysed in patients who met the survival assessment criteria, with a focus on clinical prognosis in these patients. The study design is illustrated in Figure 1.

ATP-TCA-based chemosensitivity assay

The chemosensitivity of surgically resected CRC specimens to three single chemotherapy regimens [L-OHP, 5-FU, and irinotecan (SN-38)] or two combined chemotherapy regimens (5-FU + L-OHP and 5-FU + SN-38) was assessed *in vitro* using the ATP-TCA method. The tumour samples were collected from each patient and placed in sterile containers containing tissue preservation solution. Within 24 hours, adipose and necrotic tissues were aseptically removed from the sample, and 1 cm^3 of tumour tissue was extracted for chemosensitivity detection using the ATP-TCA. In brief, the tumour samples were dissected into small fragments, dissociated into cell suspensions using trypsin, and subsequently filtered through a 100 μm mesh sieve. After cell counting and viability assessment, the cells were evenly distributed into 96-well plates (1×10^4 per well to 3×10^4 cells per well) and subjected to the selected chemotherapy regimen. In accordance with the instructions provided with the kit, each chemical drug was diluted to five different concentrations (12.5%, 25%, 50%, 100%, and 200% of the peak plasma concentrations corresponding to conventional clinical doses). Each individual test drug concentration (TDC) was assessed in duplicate wells (X), while untreated cells (M0) and blank complete assay medium without cells (MI) served as controls. The cells were incubated at 37 °C under a CO_2 atmosphere of 5% and a humidity exceeding 95% for 5-7 days. The cells were subsequently lysed, and adenosine triphosphate levels were quantified using a microplate luminometer (Berthold Detection Systems, Germany) through a luciferin-luciferase luminescence reaction. The inhibition rate was calculated as follows: Inhibition rate (%) = [1 - (X - MI)/(M0 - MI)] × 100%. M0 served as the control for 100% tumour cell viability. X and MI represent the fluorescence intensities of the different wells as described above. Dose inhibition rate curves were generated, and the IC_{90} and IC_{50} values, which represent the concentrations at which 90% and 50% inhibition occurred, respectively, were determined using SPSS software.

Survival assessment

The recurrence rate and mortality rate of patients eligible for survival assessment were obtained *via* medical records inquiry and regular follow-up until March 2023. Overall survival (OS) and disease-free survival (DFS) were measured from the date of surgery to the date of death or disease progression, with the last follow-up time serving as the endpoint for survival assessment in cases where such events did not transpire (censored data).

Statistical analysis

The *in vitro* chemosensitivity results were classified in accordance with the reagent instructions and established studies [12-15] as follows: (1) Strong sensitivity, with an $IC_{90} \leq 100\%$ TDC and an $IC_{50} \leq 25\%$ TDC; (2) Partial sensitivity, with an $IC_{90} > 100\%$ TDC and an $IC_{50} \leq 25\%$ TDC; (3) Weak sensitivity, with an $IC_{90} \leq 100\%$ TDC and an $IC_{50} > 25\%$ TDC; and (4) Resistance, with an $IC_{90} > 100\%$ TDC and an $IC_{50} > 25\%$ TDC. Patients eligible for survival assessment exhibiting strong *in vitro* chemosensitivity or partial sensitivity were assigned to the sensitive group, whereas those demonstrating weak sensitivity or resistance to chemotherapy were allocated to the resistant group.

The data were randomly separated into training and validation sets at a 7:3 ratio. Univariate and multivariate Cox regression analyses were performed on the training set to identify independent prognostic factors, with the validation set used for internal validation. Factors with $P < 0.1$ according to the univariate analysis were included in the multivariate

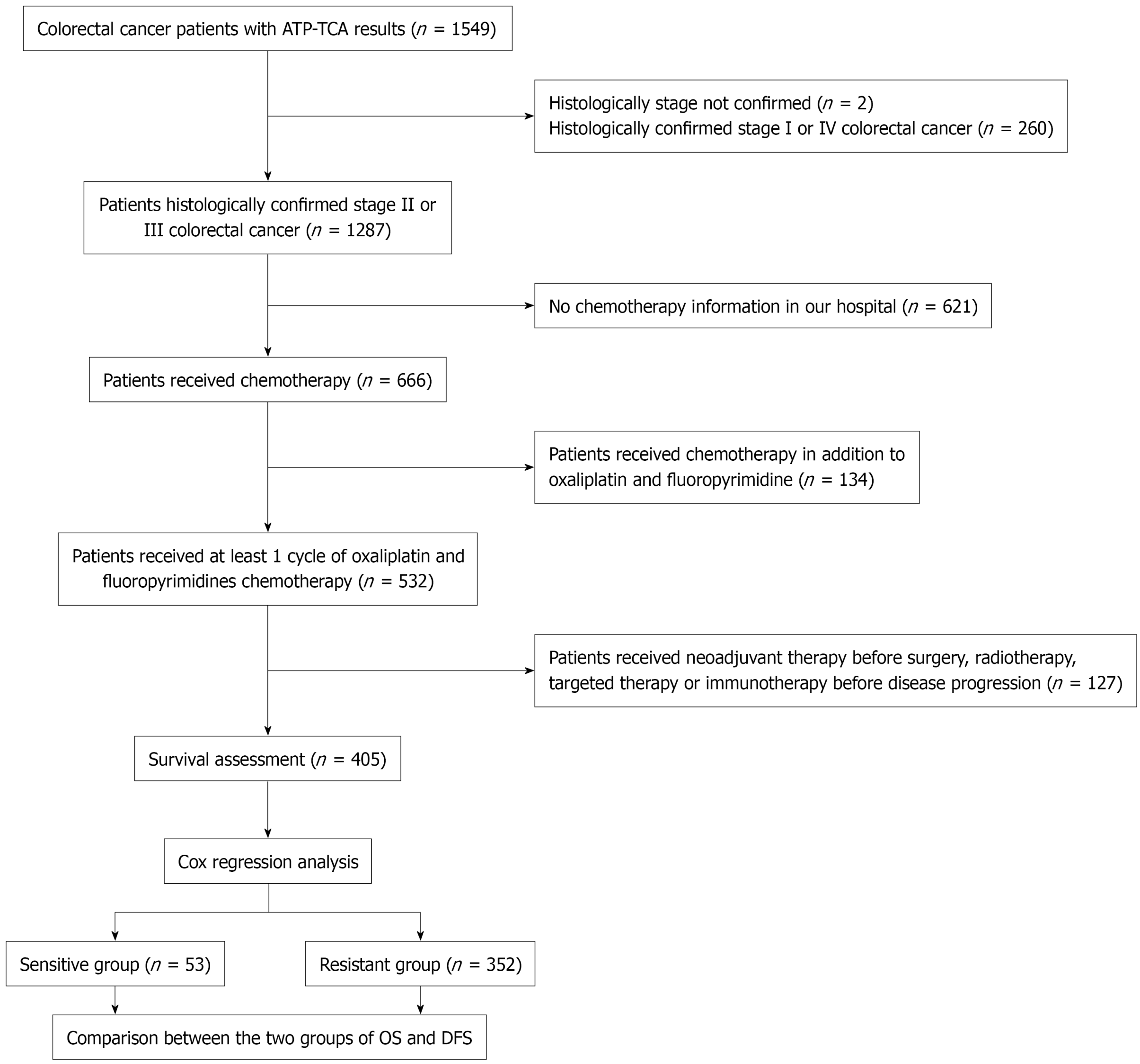


Figure 1 Flow chart of the study design. ATP-TCA: Adenosine triphosphate-based tumour chemotherapy sensitivity test; OS: Overall survival; DFS: Disease-free survival.

model. The clinical predictive model was validated *via* calibration curves, receiver operating characteristic curves based on the area under the curve (AUC), and decision curve analysis, this analysis is visually presented as a nomogram. Survival curves were generated using the Kaplan-Meier method, and the log-rank test was used to compare OS and DFS between the drug-resistant group and the drug-sensitive group. Statistical significance was defined as $P < 0.05$. The data were analysed using GraphPad Prism 9 software and R version 4.3.3. Descriptive statistics were employed to characterize the patients, whereas nonparametric tests and Fisher's exact test were used for group comparisons.

RESULTS

Patients and study scheme

The study included a total of 1549 patients diagnosed with CRC, and the characteristics of these patients are presented in Table 1.

Chemosensitivity and tumour heterogeneity in CRC

The ATP-TCA results of the 1549 tumour samples demonstrated the heterogeneity of chemosensitivity in CRC (Table 2). A total of 1474 patients were screened for combined chemotherapy regimens consisting of 5-FU + L-OHP and 5-FU + SN-38, whereas 75 patients underwent testing for single-drug regimens involving 5-FU, L-OHP, and SN-38 *in vitro*. The combination chemotherapy regimens exhibited sensitivities of 11.9% and 18.0% for 5-FU + L-OHP and 5-FU + SN-38, respectively. The sensitivities of the single-drug chemotherapy regimens were 5.3%, 5.3%, and 16.0% for the drugs 5-FU, L-OHP, and SN-38, respectively. These findings suggest that combination therapy results in greater sensitivity than

Table 1 Characteristics of the patients included in the chemosensitivity assay (*n* = 1549), *n* (%)

Characteristics	Value
Sex	
Male	909 (58.68)
Female	640 (41.32)
Age, years, mean ± SD	64.01 ± 11.62
Histology	
Adenocarcinoma	1539 (99.35)
Neuroendocrine carcinoma	5 (0.32)
Melanoma	2 (0.13)
Small cell carcinoma	1 (0.06)
Squamous carcinoma	1 (0.06)
Adenosquamous carcinoma	1 (0.06)
Sampling position	
Colon	884 (57.07)
Rectum	571 (36.86)
Colon + rectum	94 (6.07)
Stage	
I	198 (12.78)
II	594 (38.35)
III	693 (44.74)
IV	62 (4.00)
Not confirmed	2 (0.13)

Table 2 Summary of the chemosensitivity to chemotherapy regimens (*n* = 1549)

Drugs	*n*	Level of chemosensitivity				Sensitivity rate (%)
		Strong	Partial	Weak	Resistant	
5-FU + L-OHP	1474	22	153	1	1298	11.9
5-FU + SN-38	1474	48	217	1	1208	18.0
5-FU	75	1	3	0	71	5.3
L-OHP	75	1	3	0	71	5.3
SN-38	75	2	10	0	63	16.0

Strong sensitivity, IC_{90} ≤ 100% test drug concentration (TDC) and IC_{50} ≤ 25% TDC; partial sensitivity, IC_{90} > 100% TDC and IC_{50} ≤ 25% TDC; weak sensitivity, IC_{90} ≤ 100% TDC and IC_{50} > 25% TDC; resistant, IC_{90} > 100% TDC and IC_{50} > 25% TDC. 5-FU: 5-fluorouracil; L-OHP: Oxaliplatin; SN-38: Irinotecan.

monotherapy with either drug does.

Analysis of ATP-TCA results for patients eligible for survival assessment

Among the 1549 patients who underwent the ATP-TCA, survival data were available for 405 patients according to the eligibility criteria. Among these patients, 53 presented *in vitro* sensitivity to 5-FU + L-OHP, whereas the remaining 352 presented resistance. The median follow-up period from the time of surgery was 2.78 years (1.70-4.42 years) as of March 2023, on the basis of the available follow-up data. Disease progression was observed in 135 patients (33.33%), among whom 54 patients (13.33%) died from the disease. A total of 405 patients were randomly allocated into the training and validation sets, with no significant differences between them (Supplementary Table 1). Table 3 presents the clinical data of CRC patients who in the training set, categorized into a sensitive group and a drug-resistant group. No significant

Table 3 Patient characteristics in the training set (*n* = 283), *n* (%)

Characteristics	Sensitive group (*n* = 36)	Resistant group (*n* = 247)	*P* value
Sex			
Male	20 (55.56)	141 (57.09)	0.863
Female	16 (44.44)	106 (42.91)	
Age, years			
mean ± SD	63.44 ± 8.71	59.33 ± 10.96	0.032[a]
Histology			
Adenocarcinoma	53 (100.00)	352 (100.00)	-
Sampling location			
Colon	20 (55.56)	169 (68.42)	0.126
Rectum	16 (44.44)	78 (31.58)	
Stage			
II	13 (36.11)	85 (34.41)	0.841
III	23 (63.89)	162 (65.59)	

[a]$P < 0.05$.

Table 4 Univariate and multivariate Cox proportional hazards regression analyses of the overall survival of patients in the training set

Variables	Univariate analysis		Multivariate analysis	
	P value	HR (95%CI)	*P* value	HR (95%CI)
Age, years	< 0.001[c]	1.08 (1.04-1.13)	< 0.001[c]	1.10 (1.05-1.14)
Sex				
Male	0.365	1.00 (reference)	-	-
Female		0.72 (0.36-1.46)		-
Sampling position				
Colon	0.671	1.00 (reference)	-	-
Rectum		0.85 (0.42-1.76)		-
Stage				
II	0.017[a]	1.00 (reference)	0.019[a]	1.00 (reference)
III		3.17 (1.23-8.19)		3.13 (1.21-8.10)
ATP-TCA				
Sensitive	0.100	1.00 (reference)	0.048[a]	1.00 (reference)
Resistant		5.31 (0.73-38.85)		7.48 (1.02-55.16)

[a]$P < 0.05$.
[c]$P < 0.001$.
HR: Hazard ratio; CI: Confidence interval; ATP-TCA: Adenosine triphosphate-based tumour chemotherapy sensitivity test.

differences were observed between the two groups in terms of demographic characteristics such as sex, histology, sampling location or stage. However, the patients in the sensitive group were significantly older than those in the resistant group were ($P = 0.032$).

Independent prognostic factors and clinical prediction models in patients eligible for survival assessment

Through both univariate and multivariate regression analyses in the training set, three and four covariates were respectively identified as potential independent prognostic factors for OS (Table 4) and DFS (Table 5), respectively. Further internal validation was performed. Kaplan-Meier analysis of the validation set revealed that DFS was sig-

Table 5 Univariate and multivariate Cox proportional hazards regression analyses of the disease-free survival of patients in the training set

Variables	Univariate analysis		Multivariate analysis	
	P value	HR (95%CI)	*P* value	HR (95%CI)
Age, years	0.012[a]	1.03 (1.01-1.05)	0.003[b]	1.04 (1.01-1.06)
Sex				
Male	0.700	1.00 (reference)	-	-
Female		0.92 (0.61-1.40)		-
Sampling position				
Colon	0.071	1.00 (reference)	0.030[a]	1.00 (reference)
Rectum		1.47 (0.97-2.22)		1.59 (1.05-2.41)
Stage				
II	< 0.001[c]	1.00 (reference)	< 0.001[c]	1.00 (reference)
III		2.77 (1.64-4.69)		2.76 (1.63-4.68)
ATP-TCA				
Sensitive	0.008[b]	1.00 (reference)	0.002[b]	1.00 (reference)
Resistant		3.92 (1.44-10.68)		4.98 (1.81-13.72)

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
HR: Hazard ratio; CI: Confidence interval; ATP-TCA: Adenosine triphosphate-based tumour chemotherapy sensitivity test.

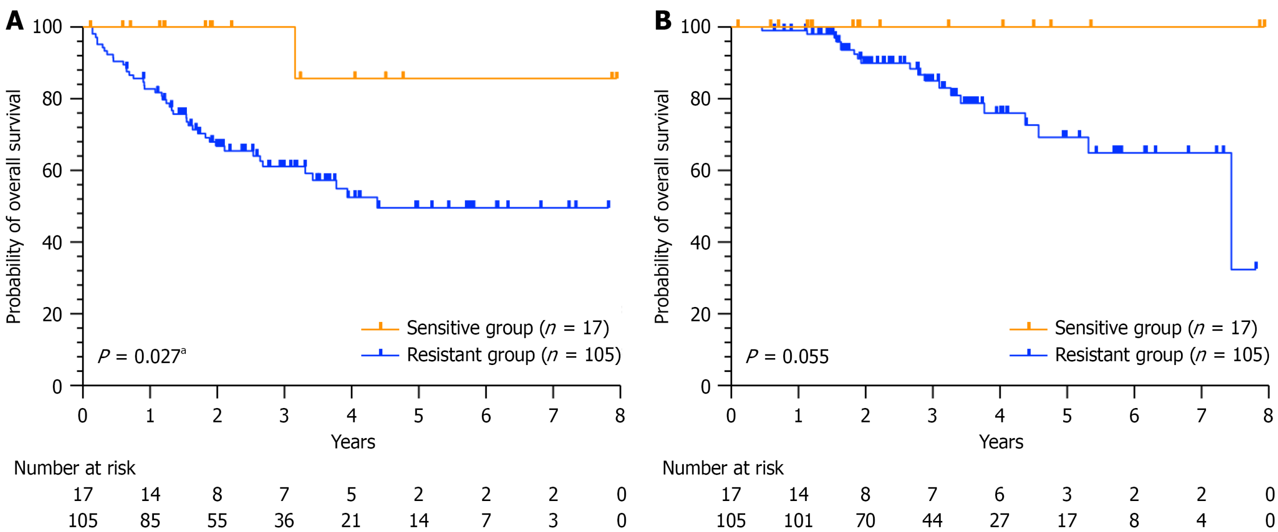
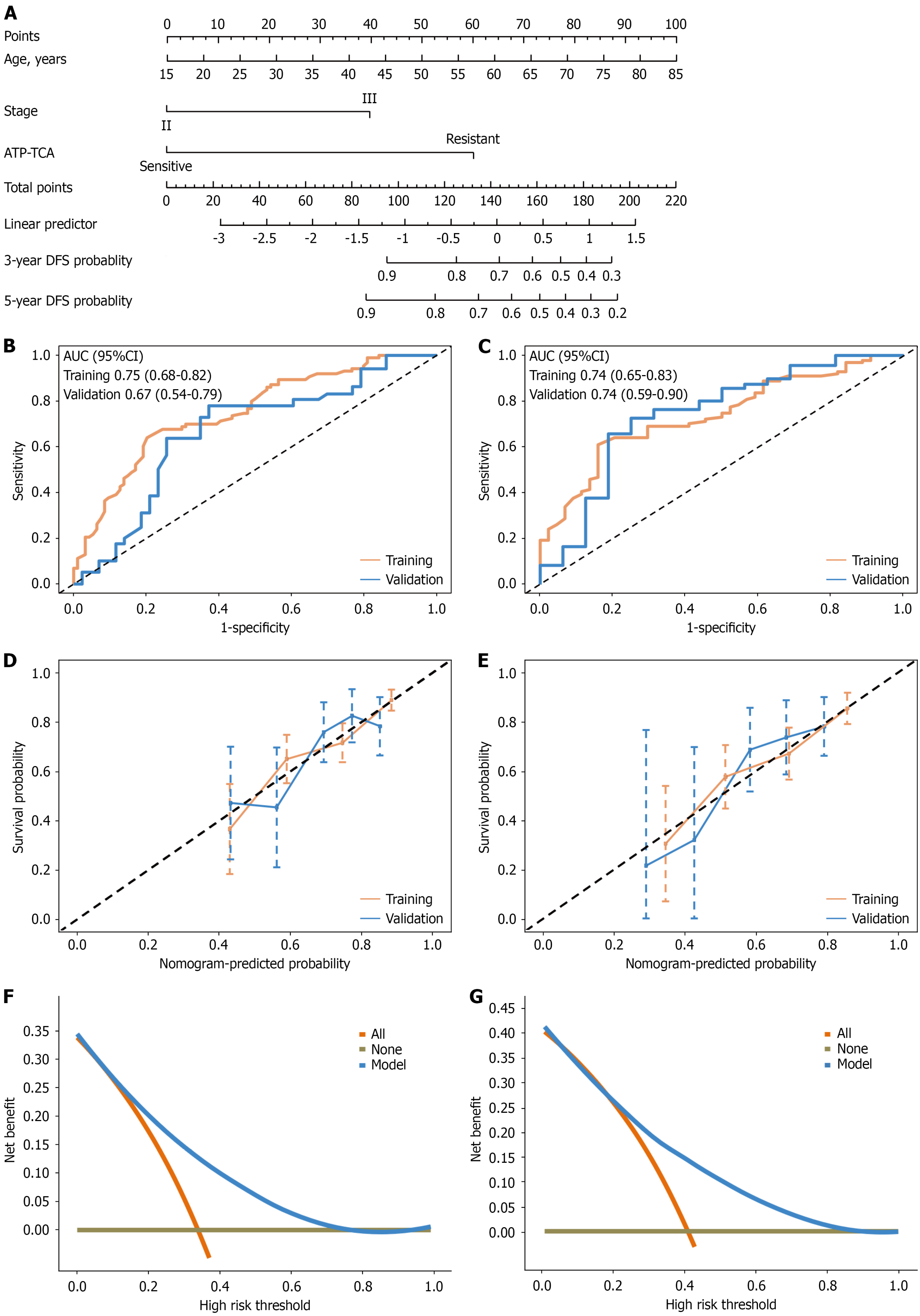


Figure 2 Kaplan-Meier survival curves to evaluate the survival outcomes of patients in the validation set. A: Disease-free survival outcomes of patients in the validation set; B: Overall survival outcomes of patients in the validation set. [a]$P < 0.05$.

nificantly longer among patients in the sensitive group than among those in the resistant group (Figure 2A, $P = 0.027$). In contrast, only a nonsignificant trend towards prolonged OS was observed (Figure 2B, $P = 0.055$). Clinical prediction models for 3-year and 5-year DFS were subsequently developed specifically for CRC patients treated with L-OPH and fluoropyrimidine-based regimens.

The clinical prediction model for DFS is visually represented as a nomogram in Figure 3A. The C-indexes for the training and validation sets were 0.68 [95% confidence interval (CI): 0.62-0.74] and 0.67 (95%CI: 0.59-0.75), respectively. The receiver operating characteristic curve analysis demonstrated that the AUC values for predicting 3-year DFS were 0.75 (95%CI: 0.68-0.82) in the training set and 0.67 (95%CI: 0.54-0.79) in the validation set in Figure 3B. Similarly, the AUC values for 5-year DFS were 0.74 (95%CI: 0.65-0.83) and 0.74 (95%CI: 0.59-0.90) in the training and validation sets, respectively (Figure 3C). The calibration curves for both the 3-year and the 5-year DFS rates indicated a high degree of


A
Points
Age, years
Stage
III
II
ATP-TCA
Resistant
Sensitive
Total points
Linear predictor
3-year DFS probablity
5-year DFS probablity
B
AUC (95%CI)
Training 0.75 (0.68-0.82)
Validation 0.67 (0.54-0.79)
Sensitivity
1-specificity
Training
Validation
C
AUC (95%CI)
Training 0.74 (0.65-0.83)
Validation 0.74 (0.59-0.90)
Sensitivity
1-specificity
Training
Validation
D
Survival probability
Nomogram-predicted probability
Training
Validation
E
Survival probability
Nomogram-predicted probability
Training
Validation
F
Net benefit
High risk threshold
All
None
Model
G
Net benefit
High risk threshold
All
None
Model

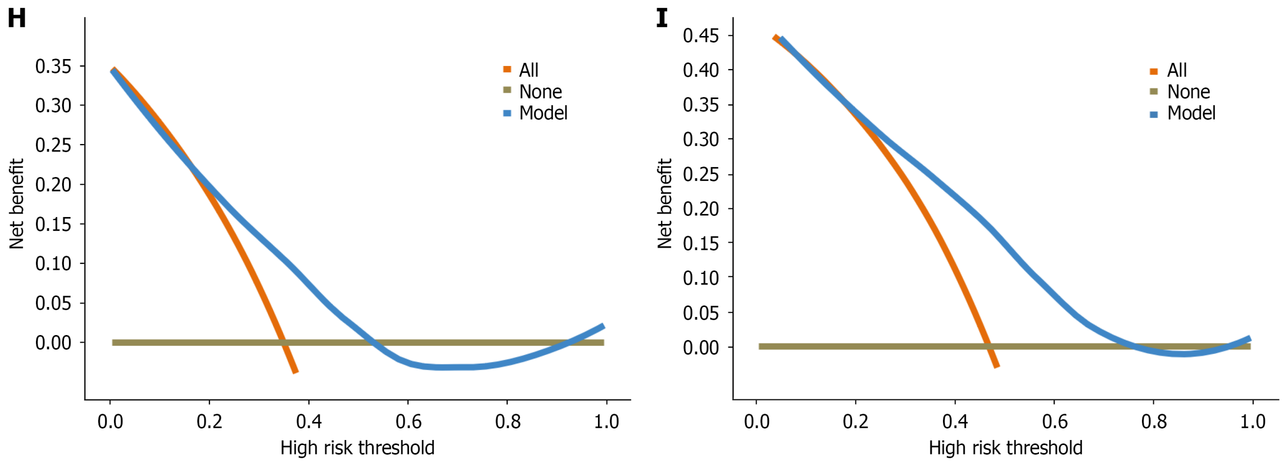


Figure 3 Clinical prediction model for disease-free survival in patients with colorectal cancer. A: Nomogram of disease-free survival (DFS) outcomes; B: Receiver operating characteristic of the clinical prediction model for 3-year DFS; C: Receiver operating characteristic curve of the clinical prediction model for 5-year DFS; D: Calibration curve for the clinical prediction model for 3-year DFS outcomes; E: Calibration curve for the clinical prediction model for 5-year DFS outcomes; F: Decision curve analysis (DCA) of the clinical prediction model for 3-year DFS in the training set; G: DCA of the clinical prediction model for 5-year DFS in the training set; H: DCA of the clinical prediction model for 3-year DFS in the validation set; I: DCA of the clinical prediction model for 5-year DFS in the training set. ATP-TCA: Adenosine triphosphate-based tumour chemotherapy sensitivity test; DFS: Disease-free survival; AUC: Area under the curve; CI: Confidence interval.

consistency between the predicted outcomes and the actual observed results (Figure 3D and E). Furthermore, decision curve analysis demonstrated that this model provides significant net benefits across a wide range of threshold probabilities (Figure 3F-I).

Comparison of OS and DFS between stage II or III CRC patients in the sensitive group and the resistant group

To further investigate this topic, we performed a stratified analysis based on tumour stage. However, owing to the limited sample size, a stratified clinical prediction model was not developed, instead, only Kaplan-Meier survival curve analysis was conducted. Among the 148 patients diagnosed with high-risk stage II disease, OS and DFS were longer among those in the sensitive group than among those in the drug-resistant group (P = 0.167, P = 0.032). Notably, a statistically significant difference was observed in the DFS (P < 0.05, Figure 4A and B). In a cohort of 257 patients diagnosed with stage III disease, the OS and DFS rates in the sensitive group were significantly greater than those in the resistant group (P = 0.048 and P = 0.003, respectively, Figure 4C and D).

DISCUSSION

Approximately one-third of all global CRC cases occur in China, and this proportion is increasing[2,16]. In clinical practice, the ATP-TCA assay is frequently utilized for individualized chemotherapy regimens in cancer patients. Previous studies have demonstrated that the ATP-TCA can effectively identify the heterogeneity of responses to specific chemotherapy agents, whether used alone or in combination, in patients with CRC[17,18]. Our findings corroborate these results. Although the ATP-TCA results demonstrated that cells were more sensitive to the SN-38-based regimen than other regimens *in vitro*, SN-38 may have severe side effects, such as diarrhoea. Therefore, it is not recommended as an adjuvant chemotherapy in version 2019 of the Chinese Society of Clinical Oncology guidelines for CRC[19]. Our study focused primarily on analysing the correlation between ATP-TCA results of the adjuvant chemotherapy regimen consisting of 5-FU + L-OHP and their associated clinical outcomes.

The sensitivity of patients to the 5-FU + L-OHP regimen was 11.9%, which differs from that in previous reports. This difference may be due to factors such as patient population diversity, variations in inclusion and exclusion criteria, and different thresholds for defining sensitivity *vs* resistance. Cox regression analysis confirmed that the ATP-TCA ratio serves as an independent prognostic factor for DFS [P = 0.002, hazard ratio (95%CI): 4.98 (1.81-13.72)] in patients with CRC. Furthermore, clinical prediction models for predicting DFS were successfully developed and validated, thereby increasing enhancing the precision of clinical treatment. In patients whose tumours were predicted to be sensitive to 5-FU + L-OHP, chemotherapy significantly increased DFS (P = 0.027). Although Cox regression analysis in the training set suggested that ATP-TCA results could serve as an independent prognostic factor of OS in CRC patients, Kaplan-Meier analysis in the validation set indicated only a trend towards improved OS in the sensitive group compared with the resistant group (P = 0.055), which did not reach statistical significance. The observed effect may be explained by periodic follow-up examinations, allowing for early intervention upon the detection of recurrence. This prompt initiation of treatment likely contributed to the extension of OS. Additionally, Kaplan-Meier analysis was performed separately for patients in stages II and III. The results indicated that in stage II, the DFS of the sensitive group was significantly longer than that of the resistant group (P = 0.032). Although OS tended to increase, this increase did not reach statistical

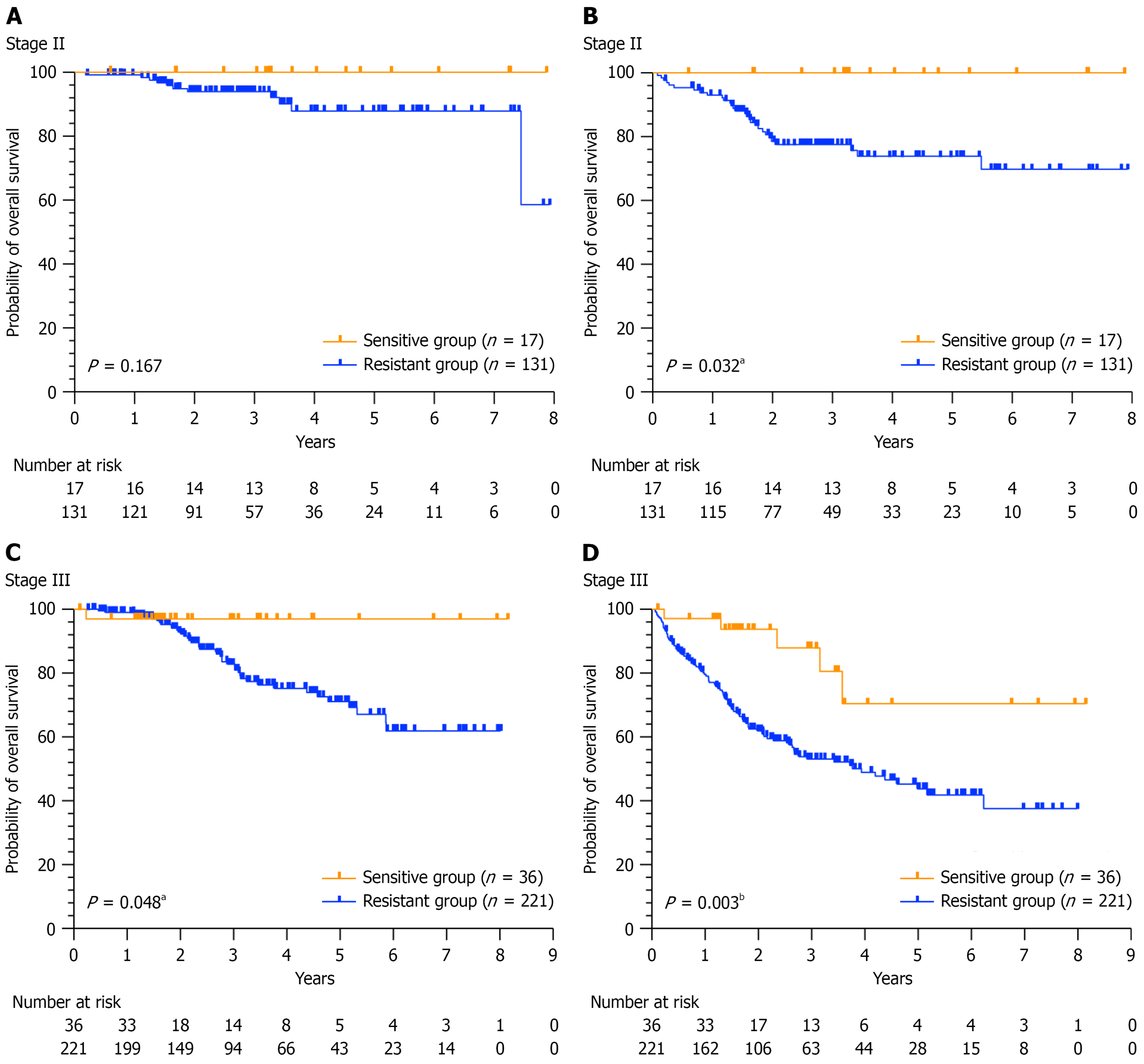


Figure 4 Kaplan-Meier survival curves for evaluating the survival outcomes of patients diagnosed with stage II or III colorectal cancer. A: Overall survival outcomes of patients with stage II colorectal cancer (CRC); B: Disease-free survival outcomes of patients with stage II CRC; C: Overall survival outcomes of patients with stage III CRC; D: Disease-free survival outcomes of patients with stage III CRC. $^aP < 0.05$, $^bP < 0.01$.

significance (P = 0.167). In stage III patients, both OS (P = 0.048) and DFS (P = 0.003) were significantly longer in the sensitive group than in the resistant group. The results of this study suggest that *in vitro* ATP-TCA results could predict the benefits of adjuvant chemotherapy in patients with CRC.

Research by Hur *et al*[20] revealed that for patients with unresectable colorectal liver metastasis, ATP-TCA yielded positive short-term treatment responses to L-OPH and a fluoropyrimidine-based regimen and improved resectability. Kim *et al*[21] reported that stage III CRC patients who were eligible for surgery and classified as L-OPH and a fluoropyrimidine-based regimen-sensitive had longer OS and DFS trends than those who were deemed resistant. Although these increases did not reach statistical significance because of the limited sample size (sensitive group, n = 65; resistant group, n = 10), the researchers maintain that these data indirectly support the potential application of ATP-TCA. On the basis of this research, the present study significantly increased the number of included patients and increased the patient population across various clinical stages. A total of 405 patients were included in the survival assessment, consisting of 148 patients in stage II (sensitive group, n = 17; resistant group, n = 131) and 257 patients in stage III (sensitive group, n = 36; resistant group, n = 221).

This study is subject to sample selection bias. To focus on the effects of chemotherapy, we excluded all patients who had received neoadjuvant (13), targeted (16), radiotherapy (33) or immunotherapy (87). Some patients received multiple treatments from the aforementioned options concurrently. Of the 532 patients screened, 127 were excluded based on this criterion, representing 23% of the screening population. Although this exclusion ensured internal consistency, it significantly limits the generalizability of our findings. Therefore, these conclusions are applicable only to patients receiving chemotherapy, which somewhat limits the clinical application of the ATP-TCA. Given the retrospective design and considerable loss to follow-up, the median follow-up period was 2.78 years. Consequently, the generalizability of our conclusions is restricted to the midterm prognosis of CRC patients. To address these limitations, we will continue to collect a larger cohort, extend the follow-up duration, and seek multicentre collaborations to validate our findings.

CONCLUSION

In conclusion, in this study, the clinical application of the ATP-TCA was retrospectively evaluated, revealing that this assay is an independent prognostic factor for DFS in patients with resectable CRC. Additionally, an ATP-TCA-sensitive chemotherapy regimen was shown to significantly improve OS and DFS in stage III CRC patients. Despite the need for further validation, this study provides evidence supporting the extension of the ATP-TCA to combination chemotherapy regimens for CRC while providing a theoretical basis and perspective for future advancements in personalized medicine.

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FOOTNOTES

Author contributions: Li SJ, Miao LY, and Huang CR designed the research study; Li SJ, Lu YX, Zheng FY, Bian YC, Miao LY, and Huang CR performed the research; Li SJ, Lu YX, and Zheng FY analyzed the data and wrote the manuscript. All authors have read and approve the final manuscript. Miao LY and Chen-Rong Huang contributed equally to this study and are co-corresponding authors.

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