



# Health-related quality of life in advanced colorectal cancer patients in China: a nationwide hospital-based survey

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**Background:** Colorectal cancer (CRC) is one of the most common cancers in China, and most CRC patients have already reached an advanced stage by the time of initial diagnosis. Due to the loss of health as a result of cancer, it has consequence on the treatment which may affect the psychophysical and social impairment of CRC patients. These indicators (psychophysical, function and social impairment) affect the health-related quality of life (HRQOL). There are limited studies that focus on advanced CRC patients in

China. This study aimed to assess the HRQOL and its associated factors of advanced CRC patients in China.

**Methods:** This was a cross-sectional, nationwide, hospital-based, and multi-center survey. According to the traditional administrative district definition, we selected 19 hospitals in 7 regions by multi-stage stratified sampling in China. For each eligible CRC patient with stage III or IV in the selected hospitals, socio-demographics, clinical information, and HRQOL were collected based on patients' self-reporting and/or medical records between March 2020 and March 2021. Patients completed the Functional Assessment of Cancer Therapy Colorectal (FACT-C) plus-traditional Chinese version of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-9.

**Results:** A total of 4,589 CRC patients (mean age 60.1 years, including 2,730 males and 1,859 females) were included. The total score of HRQOL in population was  $128.2 \pm 24.70$ . There were significant differences in the overall score of HRQOL in gender, education level, occupation, region, disease type, and disease stage ( $P < 0.05$ ). The score of HRQOL was better in males, undergraduates and above, unemployed/laid-off, and southwestern and central China. Multivariate analysis showed that education level, occupation, location, number of hospitals visited and treatment methods, and gender were associated with utilities of CRC patients.

**Conclusions:** The HRQOL is an important outcome measure for CRC patients. The HRQOL scores differed according to socio-demographic and clinical characteristics, and findings of these factors were associated with education level, occupation, region, number of visited and treatment methods, and gender.

**Keywords:** Health-related quality of life (HRQOL); colorectal cancer (CRC); China

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## Introduction

Colorectal cancer (CRC) is a crucial public health issue, ranking third and second in new cases and deaths worldwide in 2020 (1). In 2020, there were an estimated 1.9 million new cases and about 935,000 deaths, accounting for 10% and 9.4% in CRC incidence and death, respectively (1). The incidence rate of CRC in China has displayed an annually increasing trend (2). The latest data from the national cancer registry showed that in 2019, about 110,546 new cases and 53,810 deaths occurred in China, ranking the fourth in incidence and fifth in mortality among all cancers (3). Although the 5-year overall survival (OS) rate has been increasing, the rate for patients with III–IV stage CRC is only about 20% or lower. The majority of patients have developed to an advanced stage at their initial diagnosis, in China, patients have commonly reached stage III or IV by their first diagnosis. Therefore, it is very important to pay attention to the diagnosis, treatment, and quality of life (QOL) of CRC patients in China. QOL is essential in the management of CRC patients as it contributes to the well-being of cancer patients, influences survival and response therapy (4). Factors such as smoking, diet, physical activities

and alcohol are linked with QOL. Finding showed that moderate and/or intense physical activities are associated with high physical QOL as a result of decrease level of fatigue and distress (5). Based on above reasons, we carried out this study, which focused on the national multicenter health-related quality of life (HRQOL) of advanced CRC and its influencing factors. As we know, the HRQOL is affected by physical and psychological factors. Patients who have physical symptoms such as abdominal pain, fatigue, diarrhea, flatulence, and altered stool and urinary frequency can be susceptible to deterioration of HRQOL and psychological status, for example, anxiety and depression (6). Although CRC patients frequently experience psychological distress, it can be alleviated or diminished when those patients come to accept their diagnosis and subsequent treatment. Many articles have reported that HRQOL could predict chemotherapy response and toxicity, survival, intervention, diagnosis, and so on (7). But there are limited studies that centered on patients with advanced CRC in China. In order to choose a preferable treatment modality, associated variable factors such as cancer type, social character, and disease stage are important in the assessment of HRQOL (8). However, nation-wide representative data

of advanced CRC patients in China has yet to be reported. In this study, we selected the Functional Assessment of Cancer Therapy Colorectal plus-Quality of Life Questionnaire-C9 (FACT-C plus-QLQ-C9) questionnaire (including 46 items), which consisted of all FACT-C items plus 9 items from QLQ-core (C) 30 by using experts' opinion to establish a HRQOL scale.

The primary purpose of this study is to investigate HRQOL and associated factors of advanced CRC patients in multiple nationwide centers in China. Therefore, we hypothesized that the overall impact has an influence on the QOL of CRC patients in China. We present the following article in accordance with the SURGE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-991/rc>).

## Methods

### Setting

This was a nationwide, multicenter, hospital-based, and cross-sectional survey conducted in China. According to the traditional Administrative District definition, mainland China was divided into seven different geographic regions (northern, northeastern, northwestern, central, eastern, southern, and southwestern) (9), which involved different levels of CRC burden (10). Multi-stage stratified sampling was adopted to determine the participating hospitals. In stage I, 2 cities of each region were selected by simple random sampling. In stage II, a tertiary cancer hospital and/or a general hospital was selected from each city. A total of 19 hospitals (10 tertiary cancer hospitals and 9 general hospitals) were selected. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Henan Cancer Hospital (No. 2019273), and the study was approved by all institutional review boards of the participating hospitals. Informed consent was taken from all the patients.

### Population

According to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system (11), we chose CRC patients pathologically diagnosed with stage III or IV from the selected hospitals. The CRC patients were coming from the inpatients, who were recruited by the trained interviewers

of the cancer centers (including the department of oncology medicine, oncology surgery, radiotherapy and chemotherapy and anorectal surgery) from the selected hospitals.

All eligible patients provided their informed consent before enrolment. The inclusion criteria were as follows: clinically confirmed stage III or IV CRC patients; aged  $\geq 18$  years; without any dementia, language communication disorder and able to understand the investigation procedure. The exclusion criteria were as follows: severe physical, cognitive, and/or verbal impairments that would interfere with a patient's ability to complete the questionnaire.

### Sample size

It was estimated that there were about 400,000 advanced CRC patients in China (12,13). To ensure that the national survey is geographically representative, it was designed that about 1% patients would be enrolled. Considering the non-response rate of 10%, more than 4,445 patients would be enrolled into this survey.

### Instruments

Based on the traditional Chinese FACT-C and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (14,15), 45 items were selected using experts' opinion to establish a scale named FACT-C plus QLQ-C9, consisting of 4 function subscales (physical, social or family, emotional, functional). Each positive item is valued on a 5-point Likert scale (not at all =0, a little bit =1, somewhat =2, quite a bit =3, very much =4), while the negative items are valued reversely (not at all =4, a little bit =3, somewhat =2, quite a bit =1, very much =0). The reliability of FACT-C plus QLQ-C9 and 4 scale was high in our study. The Cronbach's  $\alpha$  coefficient of HRQOL, physiological status, emotional status, social or family status, and functional status were 0.80, 0.74, 0.93, 0.86, and 0.85 in our questionnaire. The validity of the questionnaire was tested by calculating the correlation between the score of each item and the score of its field. A large correlation coefficient indicated good content validity. The validity of physiological status, emotional status, and social or family status was good in our study, in which the correlation coefficient was above 0.5. In addition, a pilot survey was conducted in September and October 2019 in 2 hospitals (Henan Cancer Hospital and The First Affiliated Hospital of Baotou Medical College) in order to validate standard operating procedures and the questionnaires.

### **Procedure**

The survey was initiated in March 2020, after all participating centers had obtained ethics committee approval. All patients with III or IV stage provided informed consent before investigation, and the whole investigation process took about 20 min to complete. The survey was conducted face-to-face by trained interviewers. If the patients who have difficulties in reading and completing the scales, trained interviewers help reading and explain, or family members help answer questions. We collected demographic information (birthdate, gender, location, occupational situation, marital status and family members, education, annual household income, and medical insurance type), types of cancer (colon cancer, rectal cancer, and both), disease stage, treatment mode, and other factors (metastasis at the first diagnosis, colonoscopy screening, and number of hospitals visited). During the entire investigation process, we adhered to a strict quality control scheme including data collection, filing, entry, checking, revision, and data locking. Upon completion of the questionnaires, the trained interviewers checked them immediately to avoid missing items and logical errors. If the questionnaires had missing items or obvious logical mistakes (such as missing items and errors), the trained interviewers called the patient to amend and check the information.

### **Statistical analysis**

The original data were entered by two trained research assistants using EpiData software version 3.1 (EpiData, Inc., Redwood City, CA, USA). All the data cleaning and analyses were performed with Statistical Analysis System 9.3 (SAS Institute, Cary, NC, USA). It was considered standard to complete more than 95% in the questionnaires. In the case of missing data, missing value was input. Data were presented as mean  $\pm$  standard deviation (SD) for continuous variables and percentages (%) for categorical variables. The *t*-test or variance analysis was performed to compare the dimensions of HRQOL in populations disaggregated by demographic information (gender, age, clinical stage), types of cancer, disease stage, treatment mode, and other factors. We adopted multiple linear regression although its use has been criticized for potentially satisfactory fitting to skewed data, as multiple linear regression was most commonly used in HRQOL studies. Dummy variables were created for multicategory variables, and the dummies for the missing values were entered for each category. Variables

with  $P < 0.10$  in univariate regression model were entered into the multivariable regression model. Using stepwise regression method, variables with  $P < 0.05$  were determined as statistically significant in the final multifactor model. All statistical analyses were conducted with a two-tailed test at a significance level of 0.05.

## **Results**

### ***The sociodemographic information***

A total of 4,589 CRC cases were included from 19 hospitals, including 3,036 patients (66.15%) and 1,553 family members of patients (33.85%). The mean age of the participants was  $60.1 \pm 11.62$  years, including 2,730 males and 1,859 females with the ratio of male to female was 1.47:1. The married patients were 94.1%, 29.0% of patients had completed primary school and below, 39.3% were government civil servants & public institution personnel, 98.8% had medical insurance, 53.8% were rectal cancer (*Table 1*).

### ***The score of HRQOL in advanced CRC patients***

The total score of HRQOL in the study population was  $128.2 \pm 24.70$ , including the scores of physical, emotional, social or family, and functional factors ( $53.2 \pm 9.57$ ,  $33.9 \pm 9.05$ ,  $23.0 \pm 5.68$ , and  $18.1 \pm 7.20$ , respectively). The overall score of HRQOL was statistically significantly different according to gender, education level, occupation, and region ( $P < 0.05$ ), which was better in males, Master's degree and above, other occupation. There was no statistically significant difference in marriage status, age, and medical insurance types. The score of physical capacity was statistically significant in gender, occupation, and region ( $P < 0.05$ ), which was better in males, unemployed or laid-off, and central. The region and marriage status were statistically significant in score of social or family, and on the contrary in other factors. There were statistically significant differences in emotional and functional factors according to age, gender, education, and region, yet there was no statistically significant difference in marriage, age, medical insurance types, and region, to the exception of education (*Table 2*).

### ***Comparison of total scores of HRQOL in clinical characters***

Regarding the specific clinical characters for CRC, we observed significant differences in metastasis at the first

**Table 1** The characteristics of advanced CRC patients

Characteristics	Number of patients	Proportion (%)
Gender		
Male	2,730	59.5
Female	1,859	40.5
Marital status		
Married	4,318	94.1
Not married/divorced/widowed	271	5.9
Level of education		
Primary school and below	1,333	29.0
Junior high school	1,478	32.2
High school or Secondary technical school	1,044	22.8
Master degree and above	734	16.0
Occupation		
Government civil servants & Public institution personnel	1,804	39.3
Service industry and self-employed	817	17.8
Other occupations	1,968	42.9
Medical insurance type		
Public health insurance	4,107	98.5
Commercial medical insurance	13	0.3
Self-pay	51	1.2
Disease type		
Colon cancer	2,063	45.0
Rectal cancer	2,470	53.8
Both	55	1.2
Region		
Eastern	1,319	28.7
Northern	565	12.3
Southern	672	14.6
Central	690	15.0
Northeastern	364	7.9
Southwestern	652	14.2
Northwestern	327	7.1
Disease stage		
Stage I/II	887	20.1
Stage III	1,970	44.7
Stage IV	1,550	35.2
Unknown	182	3.9
Number of hospitals visited*		
1	1,267	29.2
2	2,248	51.8
≥3	829	19.1

\*, the data was missing. Other occupations including freelance, entrepreneurs, retirees, and unemployed or laid-off. CRC, colorectal cancer; SD, standard derivation.



diagnosis, number of hospital visited, treatment, and targeted drugs were being used. The CRC patients with no metastasis at the first diagnosis, receiving surgery plus chemotherapy, not using targeted drugs, and who visited one hospital had higher scores of HRQOL, and those without such features had worse scores of HRQOL. There were no significant differences in disease type and disease stage. Comparing patients with colon cancer and those with rectal cancer, both patient groups had higher scores of functional and physical factors. Significant differences were observed with respect to functional and physical among CRC patients with stage I/II, stage III, and stage IV. The CRC patients with stage III and IV had higher scores of physical and functional, respectively. Except colonoscopy screening, the score of physical assessments had significant differences in whether or not metastasis was present at the first diagnosis, methods of treatment, whether or not targeted drugs were being used, the number of hospitals visited, which was higher in those with no metastasis at the first diagnosis, receiving surgery + chemotherapy, if they had visited one hospital, and were not using targeted drugs. In addition, we observed significant differences between CRC patients with social/family and emotional factors with respect to the number of hospitals visited and whether or not they were using targeted drugs (Table 3).

Participants who had visited at least 3 hospitals or were using targeted drugs had higher scores of social or familial factors, but it was different from that of emotional factors in those who had visited 1 hospital and were not using targeted drugs. Significant differences were found in function score

in methods of treatment among those who were receiving surgery plus chemotherapy higher (Table 3).

### *The multiple linear regression of HRQOL in advanced CRC patients*

There were 9 candidate predictors which showed associations with HRQOL scores in the univariate analyses for advanced CRC patients, with the exception of marriage, age, medical insurance, and disease stage. The HRQOL scores were significantly higher for the CRC patients in the southwestern ( $\beta=18.08$ ,  $P<0.001$ ), women ( $\beta=3.66$ ,  $P<0.001$ ), primary school and below ( $\beta=4.28$ ,  $P<0.001$ ), service industry/migrant workers ( $\beta=4.22$ ,  $P<0.001$ ), visited 1 hospital ( $\beta=3.89$ ,  $P<0.001$ ), and surgery + chemotherapy ( $\beta=5.38$ ,  $P<0.001$ ). Multivariate analysis confirmed 6 of the 9 variables as correlated. Those who had gender, education level, occupation, region, number of hospitals visited, and treatment methods were more likely to have correlated with HRQOL (Table 4).

## Discussion

The main purpose of this study was to evaluate the QOL of China's mainland advanced CRC patients and to assess the influence of gender, age, disease type, disease stage, treatment mode, and other factors on the dimensions of the FACT-C plus QLQ-C9 instruments. To our knowledge, this was the first attempt at a nationwide, multicenter level study in mainland China to elaborate on the related

**Table 2** The score of HRQOL in advanced CRC patients ( $\bar{x}\pm s$ , points)

Variables	Physiological status	Social/family status	Emotional status	Functional status	HRQOL
<b>Gender</b>					
Male	54.0±9.31	23.0±5.61	34.5±8.87	18.6±7.18	130.0±24.36
Female	52.2±9.83	22.9±5.79	32.9±9.23	17.5±7.18	125.4±24.95
t	6.04	0.80	5.70	5.06	6.16
P value	<0.001	0.426	<0.001	<0.001	<0.001
<b>Marital status</b>					
Married	54.0±9.31	23.0±5.62	33.8±9.02	18.1±7.21	128.2±24.72
Not married/divorced/widowed	52.2±9.83	22.3±6.62	34.3±9.48	18.4±7.01	128.2±24.45
t	-0.24	2.13	-0.79	-0.69	0.00
P value	0.811	0.033	0.430	0.488	1.000

**Table 2** (continued)

Table 2 (continued)

Variables	Physiological status	Social/family status	Emotional status	Functional status	HRQOL
Age (years)					
<40	53.6±9.63	23.0±5.62	33.9±9.76	18.7±6.99	129.1±25.42
40–59	53.2±9.48	23.2±5.63	33.5±9.23	18.4±7.02	128.3±24.08
≥60	53.2±9.60	22.8±5.72	34.2±8.81	17.9±7.36	128.0±25.07
t	0.18	2.57	3.41	3.99	0.23
P value	0.835	0.076	0.033	0.019	0.798
Level of education					
Primary school and below	53.4±9.66	22.9±5.51	33.6±9.21	17.4±7.01	127.2±24.82
Junior high school	53.1±9.76	23.0±5.71	34.0±8.88	17.8±7.32	127.8±25.15
High school or Secondary technical school	52.9±9.43	22.9±5.87	33.9±8.93	18.4±7.20	128.1±24.40
Master's degree and above	53.7±9.17	23.1±5.67	34.1±9.26	19.7±7.03	130.7±23.88
F	1.13	0.30	0.85	18.38	3.17
P value	0.337	0.828	0.467	<0.001	0.023
Occupation					
Government servants & public institution	53.0±9.44	23.1±5.77	34.2±8.99	18.5±7.26	
Service industry and self-employed	52.4±9.47	22.6±5.56	32.4±9.25	17.1±6.82	124.2±24.29
Other occupation	53.8±9.69	23.1±5.65	34.2±8.97	18.2±7.26	129.2±24.97
F	7.44	2.79	13.42	10.74	12.38
P value	<0.001	0.062	<0.001	<0.001	<0.001
Medical insurance type					
Public health insurance	53.3±9.55	23.0±5.64	34.0±9.00	18.1±7.20	128.2±24.77
Commercial medical insurance	55.5±8.27	21.3±5.75	35.2±8.60	18.1±6.78	130.1±24.41
Self-pay	51.6±8.94	22.1±5.78	32.3±9.70	17.1±6.59	123.7±22.28
F	1.12	1.23	0.96	0.44	0.85
P value	0.326	0.292	0.383	0.642	0.426
Region					
Eastern	52.7±9.95	23.2±5.92	33.7±9.08	17.3±7.45	126.9±26.15
Northern	52.2±9.18	22.6±6.29	33.5±8.30	17.8±6.73	126.1±23.40
Southern	52.7±9.52	22.7±5.35	30.1±9.69	19.0±6.48	124.6±23.29
Central	56.2±8.37	22.9±4.84	36.2±7.16	18.0±6.81	132.9±22.08
Northeastern	51.4±10.50	23.0±5.60	33.4±10.36	18.4±8.02	126.6±28.69
Southwestern	55.3±9.05	24.3±4.52	37.1±8.62	20.0±7.51	136.7±23.25
Northwestern	50.3±8.68	20.8±7.21	32.1±8.14	16.2±6.51	119.4±20.33
F	25.57	14.81	45.68	16.28	28.36
P value	<0.001	<0.001	<0.001	<0.001	<0.001

HRQOL, health-related quality of life.

**Table 3** The comparison total scores of HRQOL in clinical characters

Variables	Physiological status	Social/family status	Emotional status	Functional status	HRQOL
Disease type					
Colon cancer	53.6±9.53	23.0±5.89	34.1±9.06	18.4±7.18	129.1±24.53
Rectal cancer	52.9±9.62	23.0±5.51	33.7±9.06	17.8±7.21	127.3±24.89
Both	53.9±7.43	24.0±5.65	33.1±8.52	20.0±6.64	130.0±21.36
F	3.67	0.92	1.00	5.53	2.88
P value	0.025	0.400	0.368	0.004	0.056
Disease stage					
Stage I/II	53.7±9.47	22.9±5.87	34.0±9.06	18.5±7.19	129.1±24.48
Stage III	52.9±9.64	23.0±5.55	33.7±9.04	17.8±7.23	127.3±24.96
Stage IV	54.3±7.42	23.9±5.88	32.8±8.42	20.0±6.65	129.7±21.48
F	3.80	0.62	0.84	6.23	2.94
P value	0.022	0.539	0.432	0.002	0.053
Colonoscopy screening					
Yes	52.2±9.77	22.3±7.53	34.7±9.40	19.0±8.16	128.2±27.17
No	53.3±9.56	23.0±5.62	33.9±9.03	18.1±7.17	128.2±24.63
t	-1.16	-1.34	1.05	1.40	0.00
P value	0.247	0.179	0.294	0.161	0.996
Whether metastasis was present at the first diagnosis					
No	53.8±9.36	22.9±5.55	34.0±8.73	18.2±7.11	128.9±24.17
Yes	52.3±9.82	23.1±5.89	33.6±9.56	18.1±7.34	126.9±25.52
t	5.34	-0.64	1.54	0.29	2.66
P value	<0.001	0.524	0.125	0.768	0.008
Number of hospitals visited					
1	53.8±9.84	22.8±5.40	34.5±8.67	18.3±7.32	129.3±25.38
2	53.6±9.26	23.1±5.72	33.9±9.06	18.2±7.04	128.8±23.96
≥3	51.6±9.79	23.3±5.93	32.7±9.52	17.6±7.25	125.1±25.06
F	16.38	2.32	9.57	2.45	8.64
P value	<0.001	0.099	<0.001	0.086	<0.001
Treatment					
Surgery	54.0±9.60	23.4±5.12	34.3±9.07	17.6±7.83	129.3±25.93
Chemotherapy	52.6±9.17	22.5±5.98	33.8±8.81	17.0±6.66	126.1±22.67
Radiotherapy	52.9±9.97	22.2±6.81	29.2±11.15	15.0±6.80	119.3±28.44
Surgery + chemotherapy	55.0±9.26	22.9±5.65	34.6±9.00	19.2±7.00	131.7±24.20
Surgery + radiotherapy	53.3±8.12	24.7±4.92	32.6±9.20	18.5±6.39	129.0±21.81

**Table 3** (continued)



Table 3 (continued)

Variables	Physiological status	Social/family status	Emotional status	Functional status	HRQOL
Surgery + chemotherapy + radiotherapy	52.4±9.71	23.1±5.26	34.0±8.83	17.8±7.17	127.2±24.48
F	5.66	1.31	1.72	7.58	4.00
P value	<0.001	0.256	0.127	<0.001	0.001
Using targeted drugs					
Yes	51.8±9.77	23.2±5.96	33.3±9.43	18.1±6.90	126.3±24.40
No	53.9±9.41	22.9±5.54	34.1±8.86	18.1±7.33	129.0±24.81
t	-6.61	2.05	-2.89	0.02	-3.37
P value	<0.001	0.040	0.004	0.985	<0.001

HRQOL, health-related quality of life.

HRQOL scores of advanced CRC patients, which are essential for visualizing the overall situation of China, in order to facilitate further updates of the prevention strategy and policy development. Meanwhile, this study further explained the relationships between the demographic and clinical characteristics with HRQOL scores among patients with advanced CRC in China. In our study, using the FACT-C plus QLQ-C9 had good reliability and validity. Cronbach's  $\alpha$  coefficient always assessed the reliability of the questionnaire as suitable, using an acceptable cut-off value of 0.70 (16). Validity of the questionnaire was tested by calculating the correlation between the score of each item and the score of its field.

A large correlation coefficient indicates good content validity. A model may be deemed good if its correlation coefficient value was 0.50 or above (16). In this study, the Cronbach's  $\alpha$  coefficient and correlation coefficient were above 0.8 and 0.5, respectively, so the FACT-C plus QLQ-C9 instrument have high scores of reliability and validity.

Our study directly revealed that HRQOL of advanced CRC patients in China was markedly lower than that of the general population (17), but was higher in advanced CRC patients who were male, received less education, unemployed or laid-off, and from southwestern. Comparing males and feminine HRQOL scores, the HRQOL score was higher in males than in females, similar to the findings of the literature reports (18,19). This was shown to be related to their family responsibilities and psychological aspects wherein CRC disease may affect females more than males. The male-to-female-ratio was 1.5, which was aligned with the gender ratio of CRC patients in China. This has been supported in the

subscale analysis of functional factors in HRQOL, which was related to good quality of physical status in males. It is noteworthy that emotional status and physical status may affect males more than females, which is distinct from the report by Baider reported (20). Males were always deemed as "strong", with little communication, sense of embarrassment, and so on, if the males with advanced CRC had more a serious status such as high psychological pressure, leading to reduced tolerance in comparison to females.

In our study, we found that advanced CRC patients with lower education had higher scoring HRQOL than those with higher education, which was similar with functional status in subscale analysis. These results were similar to those of Ratjen *et al.* (21), which showed that patients with higher education pay more attention to their health, actively cooperate with treatment, and correct erroneous lifestyle and habits, so as to achieve better prognosis and improve their HRQOL (22). Meanwhile, it is suggested that medical staff should provide targeted health education measures and methods according to the educational and cultural level of patients.

This study showed that the HRQOL score of advanced CRC patients with other occupational status was higher than those with government servants or public institution and service industry, and self-employed, which was different from Laghousi *et al.*'s results (23). The other occupational status population included freelance, entrepreneurs, retirees, self-employed, and unemployed or laid-off, and such people may have pensions, insurance, and more funds, so they beard less pressure than those working in organizations, enterprises, and institutions. This was

**Table 4** The Multiple linear regression of HRQOL in advanced CRC patients

Variables	Category	$\beta$	SD	P value
Gender	Female (reference group = male)	-3.66	0.76	<0.001
Level of education	Reference group = Master's degree and above			
	Primary school and below	-4.28	1.21	<0.001
	Junior high school	-3.89	1.13	0.001
	High school or Secondary technical school	-3.31	1.18	0.005
Occupation	Reference group = other occupation			
	Government agencies/enterprises/institutions	-0.63	0.85	0.461
	Service industry/self-employed	-4.22	1.05	<0.001
Region	Reference group = northwestern			
	Eastern	7.91	1.49	<0.001
	Northern	6.52	1.68	<0.001
	Southern	4.21	1.64	0.010
	Central	13.02	1.64	<0.001
	Northeastern	5.86	1.86	0.002
	Southwestern	18.08	1.63	<0.001
Disease type	Reference group = both			
	Colon cancer	-1.42	3.44	0.679
	Rectal cancer	-3.27	3.44	0.342
Whether or not metastasis was present at the time of first diagnosis	Yes (reference group = none)	-1.57	0.79	0.047
Number of hospitals visited	Reference group = $\geq 3$			
	1	3.89	1.08	<0.001
	2	3.55	0.95	<0.001
Treatment	Reference group = surgery + chemotherapy + radiotherapy			
	Surgery	3.20	1.28	0.012
	Chemotherapy	0.44	1.97	0.823
	Radiotherapy	-6.90	6.02	0.252
	Surgery + chemotherapy	5.38	0.85	<0.001
	Surgery + radiotherapy	2.27	4.56	0.619

HRQOL, health-related quality of life; CRC, colorectal cancer;  $\beta$ , beta parameter; SD, standard deviation.

shown in subscale analysis of social or family status and the majority of patients with public health insurance. There was no significant statistical difference in HRQOL score between medical insurance types. The study have reported that the impact of medicaid insurance on HRQOL is usually related to CRC outcomes such as late diagnosis, high tumor

recurrence rate, and low survival rate (24). However, in our study, the majority of patients almost had advanced CRC, with comparable clinical manifestation, treatment mode, and distress.

In order to reflect the HRQOL of advanced CRC patients in mainland China, we recruited more than 4,400

patients from the 7 geographic regions through multi-stage stratified sampling, not only to ensure geographic representativeness and generalization, but also to enable comparison of different regions. From our study, we discovered that southwestern had higher HRQOL than other areas. Notably, emotional status, functional status, and social or family were higher in southwestern, but central was higher in physical status. The possible reason is that there are great regional economic differences and uneven distribution of medical resources.

In a study that did not incorporate analyses of treatment and distress, it was reported that HRQOL was found to vary by disease type, wherein it was higher in patients with urological cancer than those of with CRC (25). Our findings showed that disease type (colon, rectal cancer, and both), disease stages (I/II, III, and IV) did not significantly impact HRQOL, which is inconsistent with Silva *et al.*'s (26) and Bours's report (27). The main reason is that patients cannot distinguish the relationship between colon cancer and rectal cancer in mainland China. Due to the distress and complexity of disease, patients with both disease type (colon and rectal) and stage IV had a propensity to worse physical status and better functional status. This is a meaningful research result reflecting that the population has a good implementation effect of three-level prevention. That depends on the difficulty of treatment, method of treatment, cost of treatment, and so on.

At present, the treatment methods of CRC mainly include the following: surgical resection, radiotherapy, chemotherapy, palliative chemotherapy, targeted drug therapy, and immunotherapy (28). The study has confirmed that surgical resection is the main method of treatment for patients with stage II and III CRC (29). The study has also confirmed that surgical resection (laparoscopic resection and colectomy) can improve the HRQOL in patients at 1 month and 3–5 months after operation, and maintain a good HRQOL in patients at 6–8 months after operation (30). Therefore, in order to observe the standardized treatment and prevention of CRC patients in China, we suggest that researchers increase the follow-up duration of HRQOL in patients with advanced CRC. The method of chemotherapy, radiotherapy, and their combination can improve the local disease and survival rate of CRC, but side effects such as physical discomfort, dissatisfaction with life, and psychological pain generally led to diminished HRQOL (31).

In general, patients with CRC using treatment methods such as surgical resection, radiotherapy, systemic chemotherapy, and targeted therapy may experience

persistent pain and limited function, which may eventually reduce their QOL (32). The OS rate of patients with CRC who are treated with chemotherapy can significantly increase, for example 5-fluorouracil can improve the survival rate to 30%, but patients have subsequently lower scores in physical, social or family, emotional, and functional status compared to the general population. Previous research has confirmed that type of treatment might be closely related to HRQOL. Our findings showed that patients who underwent surgery plus chemotherapy had higher HRQOL, functional status, and physical status than those of other treatment methods. Our results suggested that patients with cancers requiring chemotherapy and radiotherapy are at greater risk of lower HRQOL scores than those with cancers that do not require other treatment methods. It was associated with treatment effect, treatment cost, patient income, and so on. It is unclear why surgery combined with other treatment measures can yield higher scores of HRQOL than treatment alone, which warrants further research in future (33). Consistent with other research results, the HRQOL of patients who had not used targeted drugs was better and the HRQOL of patients who received targeted drug adjuvant therapy was worse in our study (34). The reason may be the high price of targeted drugs, need for long-term medication, high cost of genetic testing, and the non-reimbursement of medical insurance.

The severity of metastasis at the first diagnosis and number of hospitals visited were also reflected by the HRQOL. In our study, there was a significant difference in HRQOL between patients who had visited one hospital and no metastasis at the first diagnosis. Patients with metastasis at the first diagnosis and had visit at least 3 hospitals needed more treatment methods, treatment cost, and more diagnostic interventions. So that led to lower HRQOL score with heavier disease burden. This result explains that emotional status and physical status impacted highly on HRQOL in patients with just one hospital visited.

The basic variables most often considered in building a CRC model include the following: gender, level of education, occupation, region, number of hospitals visited, and treatment methods. A recent multicenter study in mainland China showed it was higher in the HRQOL of patients with colorectal neoplasms, which was inconsistent with our study (35); however, the sample size of this study was much smaller than that of ours. Meanwhile, our survey was conducted nationwide, which was more representative of the HRQOL in patients with advanced CRC.

### Study strengths and limitations

This study had some strengths. First, our study helped to fill the gap in HRQOL scores of advanced CRC patients in mainland China, especially those with stage III or IV CRC at the first diagnosis. Second, our study was the first geographic representative study with a large sample of more than 4,400 patients in mainland China. Third, it provides a tool for the HRQOL score, which can be applied to the other cancer types.

This study also had some limitations. The study was cross-sectional; therefore, some biases were inevitable. Additionally, causal relationship between patients' clinical characteristics and HRQOL scores was not able to be established.

### Conclusions

The HRQOL is an important outcome indicator for advanced CRC patients. Females patients, primary school and below education level, from the Southwest region, who had visited 1 hospital, and undergone surgery + chemotherapy had higher HRQOL nationwide in China. The scores differed according to sociodemographic and clinical characteristics, and findings of these were associated with education level, occupation, region, number of hospitals visited and treatment methods, and gender. Therefore, the HRQOL should be developed as an assessment method for advanced CRC patients.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Henan Cancer Hospital (No. 2019273), and the study was approved by all institutional review boards of the participating hospitals. Informed consent was taken from all the patients.

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