BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

Valuing health-related quality of life of patients with colorectal cancer in China using EQ-5D-5L

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022711
Article Type:	Research
Date Submitted by the Author:	08-Mar-2018
Complete List of Authors:	Huang, Weidong; Harbin Medical University, School of Health Management Yang, Jinjin; Harbin Medical University, School of Health Management Liu, Yang; Harbin Medical University, School of Health Management Liu, Chaojie; La Trobe University, School of Psychology and Public Health zhang, xin; harbin medical university, school of Health Management Fu, Wenqi; Harbin Medical University, School of Health Management Shi, Limei; Harbin Medical University, School of Health Management Liu, Guoxiang; Harbin Medical University, School of Health Management
Keywords:	Health-Related Quality of Life, Colorectal Cancer, EQ-5D-5L

SCHOLARONE™
Manuscripts

For peer review only

Valuing health-related quality of life of patients with colorectal cancer in China using EQ-5D-5L

Weidong Huang[1§], Jinjin Yang [1§], Yang Liu[1], Chaojie Liu[2], Xin Zhang[1], Wenqi Fu[1], Linmei Shi[1], Guoxiang Liu[1*]

[1]School of Health Management, Harbin Medical University, 157 Baojian Road, Nangang District, Harbin150086, China.

[2]School of Psychology and Public Health, La Trobe University, Melbourne VIC 3086, Australia.

Huang, Weidong; weidong218@126.com ;Harbin Medical University, School of Health Management

Yang, Jinjin; hrbmuyjj@126.com; Harbin Medical University, School of Health Management

Liu, Yang ; liuyangly1989@163.com; Harbin Medical University, School of Health Management

Liu, Chaojie; c.liu@latrobe.edu.au ; La Trobe University, School of Psychology and Public Health

Zhang,Xin; zhangxinzhx0801@126.com; Harbin Medical University, School of Health Management

Fu ,Wenqi; fuwenqi6688@163.com; Harbin Medical University, School of Health Management

Shi, Linmei; slm_jl@163.com; Harbin Medical University, School of Health Management

Liu, Guoxiang; lgx6301@163.com; Harbin Medical University, School of Health Management

[§]These authors made equal contributions.

[*]Authors to whom correspondence should be addressed –Guoxiang Liu, E-mail: lgx6301@163.com, Tel: 86-451-87502863.

The work was carried out in School of Health Management, Harbin Medical University, 157 Baojian Road, Nangang District, Harbin150086, China.

For peer review only

Abstract

Aim This study aimed to assess the Health-Related Quality of Life (HRQoL) of patients with Colorectal Cancer (CRC) and its determinants.

Method A cross-sectional questionnaire survey was conducted on 300 CRC patients in China's Heilongjiang province, measuring HRQoL using the EQ-5D-5L. Kruskal-Wallis analyses were performed to identify independent variables associated with the EQ-5D-5L utility scores. Predictors of the utility scores were confirmed using a Tobit regression model.

Results The respondents had a mean EQ-5D-5L utility score of 0.617 (SD =0.371) and a median of 0.740 (range: -0.348 to 1.000). Pain/discomfort and anxiety/depression were major complaints of the respondents, with a prevalence of over 60%. The Kruskal-Wallis analyses found lower utility scores in those who were not married, worked as a farmer, enrolled with the new rural cooperative medical scheme, and had lower household income (p<0.05). Those who were at a later stage of CRC, underwent surgical only therapy, and had a fistula also had lower EQ-5D-5L scores than others (p<0.05). The Tobit regression model confirmed these predictors, except for occupation and marital status.

Conclusion CRC patients have poor HRQoL. Efforts should be made to improve the management of pain/discomfort and anxiety/depression. Socio-economic status is a predictor of HRQoL.

Keywords: Health-Related Quality of Life；Colorectal Cancer； EQ-5D-5L

For peer review only

Strengths and limitations of this study

I This study assessed the health-related quality of life of patients with Colorectal Cancer(CRC) and its determinants in China with EQ-5D-5L which have scarcely been studied.

II The utility scores for CRC patients measured by the EQ-5D-5L can be used for health economic evaluations on clinical and public health interventions on CRC.

III The study was conducted in three large hospitals in one province, which may limit the generalisability of this study's findings.

For peer review only

Introduction

Colorectal cancer (CRC) is one of the most life-threatening cancers in the world: the third in prevalence (after lung and breast cancer) and the forth in mortality (after lung, liver and gastric cancer). It was estimated that 746,298 new cases of CRC were diagnosed in 2012 and 693,881 patients died from CRC worldwide [1]. Most CRC patients live in China. Around 376,300 new cases of CRC were diagnosed in China alone in 2015. CRC has become the fifth leading cause of cancer death in China (around 191,000 CRC patients died in 2015) [2].

Cancer is a devastating event for patients and their families. Living with cancer is a stressful experience. The therapeutic treatment for cancer often involves highly invasive surgical procedures, exposure to radiations and poisonous chemical medications despite uncertain prospects in many cases. The combined effect of cancer itself and adverse events associated with cancer treatment can lead to serious decline in health-related quality of life (HRQoL) of cancer patients [3].

HRQoL is a kind of patient reported outcome, which has been increasingly used for supporting clinical and public health decisions [3]. Assessing patient reported outcome is particularly important for caner because of the complexities of cancer events and cancer treatment. Cancer treatment is often very expensive with limited prospects of remission. Patient reported outcome presents an alternative option of evidence for decision making [4, 5].

However, the application of patient reported outcome has been compounded by its subjective nature. People's preference needs to be considered in quantifying and interpreting the results of patient reported outcome. Some researchers argue that people with different experiences (such as those with and without cancer) may give different preferences to the same health state[6]. Nevertheless, the use of public preference for assessing patient reported outcome has prevailed in health economic studies. This approach simplifies the preference scoring algorithm and justifies decisions from the perspective of a more representative population.

Several HRQoL instruments are available with a scoring system based on public

For peer review only

preference, such as the EuroQol five-dimension (EQ-5D) [7], the Health Utilities Index (HUI)[8], and the Short Form six-dimension (SF-6D) survey [9]. Their scoring algorithms are all anchored on 1.0 (full health) and 0 (death), with a negative score representing a health state worse than death.

The EQ-5D is perhaps the most widely used instrument for assessing HRQoL based on public preference. It has been recommended by many researchers and governmental agencies [10]. Extensive studies have been undertaken using the EQ-5D-3L for assessing HRQoL [11-15], because a scoring algorithm based on the preference of general public is available in many countries such as Finland [11], Turkey [12], the United Kingdom [13], and the Netherlands [15]. These include some studies on CRC patients [11-17]. Although a few studies have been conducted in China, investigating into the HRQoL of CRC patients [18], most have failed to generate a preference based score simply because of the absence of a scoring algorithm.

The EQ-5D-5L was developed based on its predecessor EQ-5D-3L. It expanded the number of combined health states and is therefore believed to be more sensitivity for detecting clinically important differences in HRQoL [19]. Recently, a scoring algorithm for the EQ-5D-5L was developed from a representative sample of adult general population in China [20]. This study used the EQ-5D-5L to assess HRQoL of CRC patients and its determinants.

For peer review only

Methods

Study subjects

A cross-sectional questionnaire survey was conducted in Heilongjiang province, northeastern of China, a province with about 38 million population. Heilongjiang ranks in the middle range in China in terms of its socioeconomic development, with $6,386 per capita GDP in 2015 [21].

Three major centers for cancer treatment participated in the study, each being located in a tertiary hospital in Harbin, the capital city of Heilongjiang province. They provide specialist care to cancer patients across the entire province.

Data were collected between December 2016 and April 2017. The CRC patients who received treatment in the three centers over the period were invited to enroll in this study. They had to 1) be clinically diagnosed with primary CRC; 2) be able to read, write, and speak in Chinese; and 3) be able to give informed consent. Those who were deemed incapable of completing the questionnaire due to physical and psychological difficulties were excluded from the study. The eligibility of participants was assessed by 8 trained interviewers with assistance from the medical doctors. These interviewers were recruited from research students in a medical university and had no servicing relationship with the patients. Training was offered to the interviewers prior to the survey.

A total of 346 eligible participants were identified by the interviewers. Of these identified participants, 26 declined to participate; ten were excluded because they were not made aware of their diagnoses; ten were excluded for other reasons. This resulted in a final sample size of 300.

Patient and Public Involvement

Patients included were selected by means of convenience sampling. All participants in this study understood the purpose of the study, agreed with it and signed the Informed Consent Term. The survey was administered through face-to-face interviews in a private office in the participating centers. But the respondents were encouraged to self complete the questionnaire. Assistance from the interviewers would be offered if requested. The interviewers collected and reviewed the questionnaires immediately once they were returned. The results will be fed back to the patient if needed.

The study protocol was reviewed and approved by the Research Ethics Committee, Public Health College of Harbin Medical University (Code: HMUIRB2014012).

Measurement

Dependent variable: EQ-5D-5L score

The HRQoL of respondents was assessed by the EQ-5D-5L, which had been validated in cancer patients [22]. It measured problems in five dimensions: mobility, self-care,

For peer review only

usual activities, pain/discomfort, and anxiety/depression. Each dimension was rated along a five level scale: no problem, slight problem, moderate problem, severe problem, and extreme problem [23]. Responses to the five dimensions generated 3125 (5^5) combinations of HRQoL states, with “11111” indicating “no problems at all” and “55555” indicating “extreme problems” in all five dimensions. Each combination was then be given a single score using a scoring algorithm based on public preference. In health economics, this is usually called “utility score”. In this study, we used the Chinese EQ-5D-5L value set [20] to estimate the utility score for each respondent, which ranged from -0.391 to 1.000.

Independent variables

Candidate variables that potential associated with HRQoL of CRC patients included those variables that met one of the following three criteria: (1) socio-economic status; (2) clinical association with the outcome of interest; and (3) previously shown to be associated with the health-related quality of life among Chinese population[24]. This hypothesis was developed in line with several systematic reviews [24-26]. Thus, we identified a set of candidate variables, including: data about the clinical characteristics of respondents were collected through a review of medical records, which included the stage of CRC (I, II, III, IV), therapeutic regimen (surgery, radiotherapy/chemotherapy, surgery followed by postoperative chemotherapy, Chemotherapy followed by surgery), and presence of Fistula (yes or no). The socio-demographic characteristics of respondents were collected through the questionnaire survey, which included sex, age, religion, ethnicity, education, marital status, occupation, medical insurance, and household income.

Statistical analysis

The final statistical analyses included 300 questionnaires, excluding five that contained some missing data.

The EQ-5D-5L utility scores of respondents followed a non-normal distribution (Kolmogorov-Smirnov test, $p < 0.05$). We presented both mean (standard deviation, SD) and median (range) scores and applied Kruskal-Wallis analyses to determine

For peer review

differences in the utility scores of the respondents with different characteristics.

We then established a Tobit regression model on the EQ-5D-5L utility scores, including all of the independent variables that showed statistical significance ($p<0.05$) in the Kruskal-Wallis analyses. The ceiling effect is common in HRQoL studies, in which a significant number of respondents report the highest score [27-29]. This is particularly evident with the EQ-5D instruments[29, 30] leading to some utility scores censored at 1.0. In this study, 16.7% respondents scored the highest possible score 1.0, which argue that a general linear regression model is inappropriate for censored data because the values do not necessarily represent the exact values once they reached the censored threshold. For censored data, Tobit regression model is advised [27-29, 31, 32].

All statistical analyses were conducted using the SPSS version 18 and the STATA version 12.0. A p value of less than 0.05 was considered an indication of statistical significance.

Results

The respondents had a mean age of 59 years (ranging from 28 years to 84 years). The majorities were men (65%), married (90%), ethnic Han (96%), and had no religious belief (94%). About 17% of the respondents obtained a university degree. All of the respondents were covered by social health insurance, albeit across three different schemes. Their household income was higher compared with the average level (¥27,830) in Heilongjiang. About half of the respondents were still in paid workforce at the time of the survey. More than half (54%) of respondents received surgical treatment, but only 16.33% had a fistula. Most patients were at stage II (37.0%) and stage III (38.0%) of CRC (Table 1).

Problems in pain/discomfort were most frequently reported (60%), followed by anxiety/depression (59%), usual activities (53%), self-care (49%), and mobility (46%). About 16.7% of respondents report no problems at all in all five dimensions (Table 2).

The respondents had an average utility score of 0.617 and a median of 0.740

For peer review only

(Table 3). No significant differences in the utility scores were found in those with different age, sex, ethnicity, religious belief, and level of education ($p>0.10$). Lower EQ-5D-5L utility scores were found in those who were not married, worked as a farmer, enrolled with the new rural cooperative medical scheme, and had lower income ($p<0.05$). The EQ-5D-5L utility scores also varied with clinical characteristics. Those who were at a later stage of CRC, underwent surgical treatment only, and had a fistula had lower utility scores compared with others ($p<0.05$).

The Tobit regression model confirmed that low household income, membership with the new rural cooperative medical scheme, a later stage of DRC, surgical only therapy, and presence of fistula were significant predictors of low EQ-5D-5L utility scores. However, occupation and marital status became statistically insignificant in predicting utility scores after controlling for other factors (Table 4).

For peer review only

Discussion

Understanding CRC patients' HRQoL and factors associated with it is essential in evaluating future health technologies. To the best of our knowledge, this is the first study to present utility scores for CRC patients measured by the EQ-5D-5L. The results can be used for health economic evaluations on clinical and public health interventions on CRC. Previous attempts on cost-utility analyses on CRC interventions have been deterred by the lack of such utility scores [4]. The baseline health utility values, defined in the present study by using the EQ-5D-5L questionnaire, could be used by researchers in the calculation of quality adjusted life-years, which are central to economic evaluations including cost-utility analysis.

This study found that CRC patients live with significantly lower HRQoL than the local general public as measured by the EQ-5D utility scores [29]. This finding is consistent with previous studies [11, 13, 17]. The CRC participants of our study also appear to have lower utility scores than those from Finland [11] Japan[33] and the UK [14]. In a Finnish health survey, the mean score for cancer patients was 0.813

measured by the EQ-5D, compared with our 0.614[11]. In a Japanese study investigating the HRQoL score of long-term survivors, the EQ-5D was 0.865 in nonstoma patients and 0.842 in patients with a stoma [33]. The mean score of EQ-5D was 0.79 in a single-center and prospective study in United Kingdom[14]. However, interpretation of such differences needs to be cautious because the Finland, Japan and UK studies used the EQ-5D-3L and the same EQ-5D-3L valuation algorithm (UK TTO). Empirical evidence shows that the EQ-5D-5L has lower ceiling effect and higher discriminatory power than the EQ-5D-3L [11, 14, 22]; and the Chinese general public prefers lower values on most conditions than their Western counterparts[29]. In addition, the characteristics of our CRC patients may also differ from those of other studies. Especially in our study, the patients from tertiary hospitals usually have a heavier condition in China[34].

We found that pain/discomfort is the most frequently reported problem (60%) of respondents, similar to that reported by CRC patients in the Netherlands and the UK [15]. This study also revealed that 59% of CRC patients experienced anxiety/depression. Indeed, anxiety/depression is perhaps the most common psychological problem among all cancer patients [35, 36]. Further efforts should be made to improve the management of pain/discomfort and anxiety/depression.

There is some debate about the association between HRQoL and the stage of CRC. We found a decreasing trend in HRQoL with the progress of CRC, consistent with those reported in Australia and some European countries [26, 37-39]. However Hornbrook and colleagues reported worse HRQoL in patients with stage II CRC compared with those in stage III and IV [17].

CRC patients undergoing surgical procedures often have lower HRQoL [26, 40]. Our study provides additional evidence to this conclusion. It is widely accepted that surgical procedures are usually associated with increased pain/discomfort, complications, and inconvenience to daily activities. However, it is not clear why surgery in combination with other treatment measures can produce a higher utility score than surgery alone. The presence of fistula is a clear indication of poor HRQoL. A HRQoL instrument (mCOH-QOL-Ostomy) has been developed specifically for

For peer review only

CRC patients with fistula [41].

Low socio-economic status is a significant predictor of low HRQoL in CRC patients. In this study, household income and social health insurance entitlements were found to be associated with HRQoL of CRC patients, consistent with findings of previous studies conducted in China [18] and some other countries [37, 38]. Medical treatment for CRC is very expensive. A survey of 37 tertiary hospitals in 13 provinces in China revealed a high level of catastrophic expenditure for CRC patients [42]. This is a particular concern for those living with low income and those with limited insurance entitlements. Although China has achieved universal health insurance coverage, considerable disparities exist in terms of the entitlements across the three government subsidized basic health insurance programs [43]. Rural patients in China are not only more likely to have lower household income, but also are least protected by their health insurance coverage, the new rural cooperative medical scheme. They usually bear a higher proportion of out-of-pocket expenses than their urban counterparts do.

This study has several limitations. As a cross-sectional survey, no causal relationships can be assumed. The study was conducted in three large hospitals in one province, which is not a representative sample of China: generalization of the results needs to be cautious. It is also important to note that the sample was drawn from hospital settings and was biased toward more advanced cancers [44].

In conclusion, this study presents utility scores for CRC patients measured by the EQ-5D-5L. CRC patients have poor HRQoL, with pain/discomfort and depression/anxiety as the most frequently reported problems. The HRQoL of CRC patients is associated with the stage of CRC and treatment regimen. But low socio-economic status such as low levels of income and insurance entitlements is also a predictor of low HRQoL.

For peer review only

Ethical Statements and consent to participate

This study was approved by the Ethics Committee of Harbin Medical University (Project Identification Code: HMUIRB2014012). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Acknowledgements

The authors are most grateful to the study participants.

Funding

This study was funded by the National Natural Scientific Foundation of China (Grant No.71503062, 71673071), the Heilongjiang Postdoctoral Fund (Grant No. LBH-Z16137, LBH-Z16240), the China Postdoctoral Fund (Grant No. 2017M611402), the Key Lab of Health Technology Assessment, National Health and Family Planning Commission of China (Fudan University)(Grant No. FHTA2017-08).

Authors' Contributions

JY participated in the design of the study and the writing of the manuscript. WH designed the study, performed the statistical analyses and drafted the manuscript. GL supervised and interpreted the statistical findings and wrote the manuscript. YL and CL helped draft the manuscript. WF, LS and XZ conceived the study and participated in the design. All authors read and approved the final manuscript.

Disclosure Statement

None

Data sharing statement

Data are available from the corresponding author on request.

For peer review only

Reference

1. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2014
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA: a cancer journal for clinicians* 2016; **66:** 115-32.
3. Ravens-Sieberer U. Measuring and monitoring quality-of-life in population surveys: Still a challenge for public health research. *Sozial- und Präventivmedizin* 2002; **47:** 203-4.
4. Huang W, Liu G, Zhang X, Fu W, Zheng S, Wu Q, et al. Cost-effectiveness of colorectal cancer screening protocols in urban Chinese populations. *PloS one* 2014; **9:** e109150.
5. Drummond MF SM, Torrance GW, O'Brien B, Stoddart GL. (2005 3rd ed edition) *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press, New York.
6. Greenberg D, Earle C, Fang CH, Eldar-Lissai A, Neumann PJ. When is cancer care cost-effective? A systematic overview of cost-utility analyses in oncology. *Value in Health* 2010; **102:** 82.
7. Brooks R. EuroQol: the current state of play. *Health Policy* 1996; **37:** 53.
8. Feeny DD, Furlong W, Boyle M, Torrance GW. Multi-Attribute Health Status Classification Systems. *PharmacoEconomics* 1995; **7:** 490-502.
9. Kharroubi SA, Brazier JE, Roberts J, O'Hagan A. Modelling SF-6D health state preference data using a nonparametric Bayesian method. *Journal of Health Economics* 2007; **26:** 597-612.
10. Räsänen P, Roine E, Sintonen H, Semberg-Konttinen V, Ryynänen OP, Roine R. Use of quality-adjusted life years for the estimation of effectiveness of health care: A systematic literature review. *International Journal of Technology Assessment in Health Care* 2006; **22:** 235.
11. Farkkila N, Sintonen H, Saarto T, Jarvinen H, Hanninen J, Taari K, et al. Health-related quality of life in colorectal cancer. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2013; **15:** e215-22.
12. Polat U, Arpaci A, Demir S, Erdal S, Yalcin S. Evaluation of quality of life and anxiety and depression levels in patients receiving chemotherapy for colorectal cancer: impact of patient education before treatment initiation. *Journal of gastrointestinal oncology* 2014; **5:** 270-5.
13. Downing A, Morris EJ, Richards M, Corner J, Wright P, Sebag-Montefiore D, et al. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33:** 616-24.
14. Wilson TR, Alexander DJ, Kind P. Measurement of health-related quality of life in the early follow-up of colon and rectal cancer. *Diseases of the colon and rectum* 2006; **49:** 1692-702.
15. Stein D, Joulain F, Naoshy S, Iqbal U, Muszbek N, Payne KA, et al. Assessing health-state utility values in patients with metastatic colorectal cancer: a utility study in the United Kingdom and the Netherlands. *International journal of colorectal disease* 2014; **29:** 1203-10.
16. Hornbrook MC, Wendel CS, Coons SJ, Grant M, Herrinton LJ, Mohler MJ, et al. Complications Among Colorectal Cancer Survivors. *Medical Care* 2011; **49:** 321-6.
17. Wong CK, Lam CL, Poon JT, Kwong DL. Clinical correlates of health preference and generic health-related quality of life in patients with colorectal neoplasms. *PloS one* 2013; **8:** e58341.
18. Wang JW, Sun L, Ding N, Li J, Gong XH, Chen XF, et al. The association between comorbidities and the quality of life among colorectal cancer survivors in the People's Republic of China.

Patient preference and adherence 2016; **10:** 1071-7.

19. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research An International Journal of Quality of Life Aspects of Treatment Care & Rehabilitation* 2011; **20:** 1727.
20. Luo N, Liu G, Li M, Guan H, Jin X, Randhendriksen K. Estimating an EQ-5D-5L Value Set for China. *Value in Health* 2017; **20:** 662-9.
21. Statistics HPBo. (2015) *Heilongjiang Statistical Yearbook*. China Statistics Press, Peking.
22. Kim SH, Kim HJ, Lee SI, Jo MW. Comparing the psychometric properties of the EQ-5D-3L and EQ-5D-5L in cancer patients in Korea. *Quality of Life Research An International Journal of Quality of Life Aspects of Treatment Care & Rehabilitation* 2012; **21:** 1065-73.
23. Group EQC. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16:** 199-208.
24. Hu X, Gong Y, Wang C, Zhang Y, Feng X. The quality of life for patient with colorectal neoplasm and its influential factors. *Tumor* 2003**:** 343-5.
25. Bours MJ, Bw VDL, Winkels RM, van Duijnhoven FJ, Mols F, van Roekel EH, et al. Candidate Predictors of Health-Related Quality of Life of Colorectal Cancer Survivors: A Systematic Review. *Oncologist* 2016; **21**
26. Der BWAL, Van. Predictors of health-related quality of life of colorectal cancer survivors: a systematic literature review. 2016
27. Sullivan PW, Ghushchyan VH. EQ-5D Scores for Diabetes-Related Comorbidities. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2016; **19:** 1002-8.
28. Sullivan PW, Ghushchyan VH, Globe G, Sucher B. Health-related quality of life associated with systemic corticosteroids. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2017; **26:** 1037-58.
29. Huang W, Yu H, Liu C, Liu G, Wu Q, Zhou J, et al. Assessing Health-Related Quality of Life of Chinese Adults in Heilongjiang Using EQ-5D-3L. *International Journal of Environmental Research & Public Health* 2017; **14**
30. Bharmal M, Rd TJ. Comparing the EQ-5D and the SF-6D descriptive systems to assess their ceiling effects in the US general population. *Value in Health the Journal of the International Society for Pharmacoeconomics & Outcomes Research* 2006; **9:** 262.
31. Twisk J, Rijmen F. Longitudinal tobit regression: a new approach to analyze outcome variables with floor or ceiling effects. *Journal of Clinical Epidemiology* 2009; **62:** 953-8.
32. Tran BX, Ohinmaa A, Long TN. Quality of life profile and psychometric properties of the EQ-5D-5L in HIV/AIDS patients. *Health & Quality of Life Outcomes* 2012; **10:** 132.
33. HAMASHIMA, CHISATO. Long-term quality of life of postoperative rectal cancer patients. *Journal of Gastroenterology & Hepatology* 2002; **17:** 571-6.
34. Gao K, Gan X. Medical Units Distribution and Influence Factors on the Selection of Patients. *Chinese Health Service Management* 2014; **31:** 516-7.
35. Strong V, Waters R, Hibberd C, Rush R, Cargill A, Storey D, et al. Emotional distress in cancer patients: the Edinburgh Cancer Centre symptom study. *British journal of cancer* 2007; **96:** 868.
36. Soa WKW, Ling WM, Leung FY, Lo JCK, Yeung M, Li GKH. Anxiety, depression and quality of life

For peer review only

among Chinese breast cancer patients during adjuvant therapy. *European Journal of Oncology Nursing* 2010; **14:** 17-22.

37. Paika V, Creed F, Kampletsas EO, Siafaka V, Gkika S, Mavreas V, et al. Personality variables are associated with colorectal cancer patients' quality of life independent of psychological distress and disease severity. *Psychooncology* 2010; **19:** 273-82.
38. Sharma A, Sharp DM, Walker LG, Monson JRT. Predictors of Early Postoperative Quality of Life after Elective Resection for Colorectal Cancer. *Annals of Surgical Oncology* 2007; **14:** 3435-42.
39. Rinaldis M, Pakenham KI, Lynch BM. Relationships between quality of life and finding benefits in a diagnosis of colorectal cancer. *British Journal of Psychology* 2010; **101:** 259.
40. Chambers SK, Meng X, Youl P, Aitken J, Dunn J, Baade P. A five-year prospective study of quality of life after colorectal cancer. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2012; **21:** 1551-64.
41. Liu L, Herrinton LJ, Hornbrook MC, Wendel CS, Grant M, Krouse RS. Early and late complications among long-term colorectal cancer survivors with ostomy or anastomosis. *Diseases of the colon and rectum* 2010; **53:** 200-12.
42. Huang HY, Shi JF, Guo LW, Zhu XY, Wang L, Liao XZ, et al. Expenditure and financial burden for common cancers in China: a hospital-based multicentre cross-sectional study. *Lancet* 2016; **388:** S10-S.
43. Dong K. Medical insurance system evolution in China ☆. *China Economic Review* 2009; **20:** 591-7.
44. Yang SM, Li JY, Gale RP, Huang XJ. The mystery of chronic lymphocytic leukemia (CLL): Why is it absent in Asians and what does this tell us about etiology, pathogenesis and biology? *Blood Reviews* 2015; **29:** 205-13.

For peer review only

Table 1 Socio-demographic and clinical characteristics of respondents

Characteristic	N	%
Sex		
Male	195	65.00
Female	105	35.00
Age (years)		
⩽ 40	50	16.67
50-59	92	30.67
60-69	105	35.00
⩾ 70	53	17.66
Religious belief		
Yes	18	6. 00
No	282	94. 00
Ethnicity		
Han	288	96.00
Other	12	4.00
Level of education		
Primary school or below	64	21.33

Junior high school	103	34.34
Senior high school	82	27.33
University	51	17. 00
Marital status		
Married	270	90.00
Other	30	10.00
Occupation		
Public sector employee	38	12.67
Private sector employee	36	12.00
Self-employed or unemployed	55	18.33
Farmer	63	21.00
Retired	108	36.00
Health insurance		
Basic medical insurance for urban employees	154	51.33
Basic medical insurance for urban residents	62	20.67
New rural cooperative medical scheme	84	28.00
Annual household income (Yuan)		
<20000	56	18.67
20000–39999	84	28. 00
40000-59999	72	24.00
60000-79999	39	13.00
>80000	49	16.33
Therapeutic regimen		
Surgery	163	54.33
Radiotherapy/Chemotherapy	44	14.67
Surgery followed by postoperative Chemotherapy	51	17.00
Chemotherapy followed by surgery	18	6.00
Other	24	8.00
Stage of DRC		
I	40	13.33
II	111	37.00
III	114	38.00
IV	35	11.67
Fistula		
Yes	49	16.33
No	251	83.67
Total	300	100

Table 2 Problems reported by respondents in the five dimensions of EQ-5D-5L

Problems	Mobility	Self-care	Usual Activity	Pain/Discomfort	Anxiety/Depression
No	53.7%	51.0%	46.7%	39.7%	40.7%
Slight	14.3%	15.4%	18.3%	25.0%	23.3%
Moderate	11.3%	12.0%	13.3%	25.3%	24.3%

For peer review only

Severe	10.0%	11.3%	12.0%	7.0%	9.3%
Extreme	10.7%	10.3%	11.7%	3.0%	2.4%

Table 3 EQ-5D-5L index scores in respondents with different characteristics

	N	Mean±SD	Median (range)	P
Sex				0.942
Male	195	0.614±0.378	0.731 (-0.348-1.00)	
Female	105	0.621±0.361	0.751 (-0.348-1.00)	
Age				0.330
⩽49	50	0.561±0.398	0.670 (-0.348-1.00)	
50-59	92	0.686±0.327	0.819 (-0.348-1.00)	
60-69	105	0.592±0.373	0.687(-0.251-1.00)	
⩾70	53	0.598±0.407	0.782 (-0.265-1.00)	
Religious belief				0.537
Yes	18	0.612±0.375	0.740 (-0.348-1.00)	
No	282	0.683±0.302	0.772 (0.139-1.00)	
Ethnicity				0.166
Han	288	0.620±0.374	0.749 (-0.348-1.00)	
Other	12	0.541±0.307	0.618 (-0.044-0.89)	
Level of education				0.180
Primary school or below	64	0.581±0.363	0.646 (-0.298-1.00)	
Junior high school	103	0.583±0.376	0.661 (-0.348-1.00)	
Senior high school	82	0.638±0.373	0.744 (-0.348-1.00)	
University	51	0.696±0.365	0.833 (-0.201-1.00)	
Marital status				*0.026*
Married	270	0.635±0.359	0.746 (-0.348-1.00)	
Other	30	0.452±0.445	0.455 (-0.348-0.95)	
Occupation				*0.007*
Public sector employee	38	0.734±0.341	0.895 (-0.201-1.00)	
Private sector employee	36	0.706±0.328	0.833 (-0.184-1.00)	
Self-employed or unemployed	55	0.603±0.359	0.659 (-0.348-1.00)	
Farmer	63	0.500±0.411	0.600 (-0.348-1.00)	
Retired	108	0.621±0.326	0.756 (-0.201-1.00)	
Health insurance				*0.001*
Basic medical insurance for urban employees	154	0.674±0.352	0.825 (-0.251-1.00)	
Basic medical insurance for urban residents	62	0.645±0.354	0.720 (-0.348-1.00)	
New rural cooperative medical scheme	84	0.490±0.392	0.586 (-0.348-1.00)	
Annual household income (Yuan)				*0.002*
<20000	56	0.505±0.419	0.586 (-0.348-1.00)	
20000–39999	84	0.566±0.369	0.685 (-0.348-1.00)	
40000-59999	72	0.625±0.375	0.763 (-0.251-1.00)	
60000-79999	39	0.691±0.300	0.824 (-0.044-1.00)	

For peer review only

>80000	49	0.759±0.315	0.882 (-0.201-1.00)	
Therapeutic regimen				*0.000*
Surgery	163	0.517±0.389	0.600 (-0.348-1.00)	
Radiotherapy/Chemotherapy	44	0.757±0.271	0.830 (-0.071-1.00)	
Surgery followed by postoperative chemotherapy	51	0.712±0.359	0.848 (-0.298-1.00)	
Chemotherapy followed by surgery	18	0.734±0.320	0.847 (-0.005-1.00)	
Other	24	0.748±0.274	0.854 (0.120-1.00)	
Stage of disease				*0.001*
I	40	0.768±0.296	0.893 (0.025-1.00)	
II	111	0.656±0.344	0.821 (-0.348-1.00)	
III	114	0.562±0.394	0.698 (-0.265-1.00)	
IV	35	0.495±0.395	0.637(-0.348-1.00)	
Fistula				*0.000*
Yes	49	0.408±0.397	0.409 (-0.348-1.00)	
No	251	0.657±0.353	0.808 (-0.348-1.00)	
Total	300	0.617±0.371	0.740 (-0.348-1.00)	

Table 4. Results of Tobit regression model on EQ-5D-5L index scores of respondents

Variables	Coefficient	95% Confidence interval		*P* value
Marital status (Ref=other)				
Married	0.128	-0.010	0.267	0.070
Occupation (Ref=Retired)				
Public sector employee	0.069	-0.073	0.210	0.340
Private sector employee	0.073	-0.069	0.215	0.313
Self-employed or unemployed	0.011	-0.139	0.163	0.879
Farmer	0.104	-0.080	0.288	0.265
Health insurance (Ref=New rural cooperative medical scheme)				
Urban employees basic medical insurance	0.126	-0.047	0.299	*0.152*
Urban residents basic medical insurance	0.157	0.001	0.313	*0.049*
Stage of disease (Ref=IV)				
I	0.626	0.444	0.809	*0.000*
II	0.423	0.273	0.574	*0.000*
III	0.297	0.151	0.442	*0.000*
Annual household income(Ref=>80000)				
<20000	-0.261	-0.422	-0.100	*0.002*
20000–39999	-0.220	-0.358	-0.081	*0.002*
40000-59999	-0.155	-0.294	-0.016	0.029
60000-79999	-0.145	-0.306	0.015	*0.076*
Therapeutic regimen(Ref=other)				
Surgery	-0.261	-0.423	-0.098	*0.002*

For peer review only

Radiotherapy/Chemotherapy	0.135	-0.057	0.326	0.167
Surgery followed by postoperative chemotherapy	0.177	-0.166	0.202	0.849
Chemotherapy followed by surgery	0.053	-0.178	0.284	0.653
Fistula（Ref=no）				
yes	-0.224	-0.337	-0.111	*0.000*

For peer review only

BMJ Open

Assessing health-related quality of life of patients with colorectal cancer using EQ-5D-5L: a cross-sectional study in Heilongjiang of China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022711.R1
Article Type:	Research
Date Submitted by the Author:	13-Jun-2018
Complete List of Authors:	Huang, Weidong; Harbin Medical University, School of Health Management Yang, Jinjin; Harbin Medical University, School of Health Management Liu, Yang; Harbin Medical University, School of Health Management Liu, Chaojie; La Trobe University, School of Psychology and Public Health zhang, xin; harbin medical university, school of Health Management Fu, Wenqi; Harbin Medical University, School of Health Management Shi, Limei; Harbin Medical University, School of Health Management Liu, Guoxiang; Harbin Medical University, School of Health Management
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Health economics
Keywords:	Health-Related Quality of Life, Colorectal Cancer, EQ-5D-5L

SCHOLARONE™
Manuscripts

For peer review only

Assessing health-related quality of life of patients with colorectal cancer using EQ-5D-5L: a cross-sectional study in Heilongjiang of China

Weidong Huang[1§], Jinjin Yang [1§],Yang Liu[1], Chaojie Liu[2], Xin Zhang[1], Wenqi Fu[1], Linmei Shi[1], Guoxiang Liu[1*]

[1]School of Health Management, Harbin Medical University, 157 Baojian Road, Nangang District, Harbin150086, China.

[2]School of Psychology and Public Health, La Trobe University, Melbourne VIC 3086, Australia.

Huang, Weidong; weidong218@126.com; Harbin Medical University, School of Health Management

Yang, Jinjin; hrbmuyjj@126.com; Harbin Medical University, School of Health Management

Liu, Yang; liuyangly1989@163.com; Harbin Medical University, School of Health Management

Liu, Chaojie; c.liu@latrobe.edu.au; La Trobe University, School of Psychology and Public Health

Zhang, Xin; zhangxinzhx0801@126.com; Harbin Medical University, School of Health Management

Fu, Wenqi; fuwenqi6688@163.com; Harbin Medical University, School of Health Management

Shi, Linmei; slm_jl@163.com; Harbin Medical University, School of Health Management

Liu, Guoxiang; lgx6301@163.com; Harbin Medical University, School of Health Management

[§]These authors made equal contributions.

[*]Authors to whom correspondence should be addressed – Guoxiang Liu, E-mail: lgx6301@163.com, Tel: 86-451-87502863.

The work was carried out in the School of Health Management, Harbin Medical University, 157 Baojian Road, Nangang District, Harbin 150086, China.

For peer review only

Abstract

Aim This study aimed to assess the health-related quality of life (HRQoL) of patients with colorectal cancer (CRC) and its determinants.

Methods A cross-sectional questionnaire survey was conducted on 300 newly diagnosed CRC patients in China's Heilongjiang province, measuring HRQoL using the EQ-5D-5L. Kruskal-Wallis analyses were performed to identify the independent variables associated with the EQ-5D-5L utility scores. Predictors of the utility scores were confirmed using a Tobit regression model.

Results The respondents had a mean EQ-5D-5L utility score of 0.617 (SD=0.371) and a median of 0.740 (range: -0.348 to 1.000). Pain/discomfort and anxiety/depression were major complaints of the respondents, with a prevalence of over 60% (all levels inclusive). The Kruskal-Wallis analyses found lower utility scores in those who were not married, worked as a farmer, enrolled with the new rural cooperative medical scheme, and had lower household income (p<0.05). Those who were at a later stage of CRC, underwent surgical only therapy, and had a stoma also had lower EQ-5D-5L scores than others (p<0.05). The Tobit regression model confirmed these predictors, except for occupation and marital status.

Conclusion CRC patients have poor HRQoL, with pain/discomfort and depression/anxiety as the most frequently reported problems. The poor HRQoL is associated with the seriousness of the disease condition, as well as the low socio-economic status of the patients.

Keywords: Health-Related Quality of Life; Colorectal Cancer; EQ-5D-5L

For peer review only

Strengths and limitations of this study

I This study estimated EQ-5D-5L utility scores for patients with colorectal cancer (CRC), which can be used for health economic evaluations.

II Tobit regression model was established to determine the predictors of the utility scores derived from the censored data.

III The cross-sectional design prevented us from drawing causal conclusions.

☐ The study was conducted in three tertiary hospitals in one province, which may limit the generalisability of its findings.

☐ The sample was likely to bias toward more advanced cancer patients.

For peer review only

Introduction

Colorectal cancer (CRC) is one of the most common cancers in the world: the third in prevalence (after lung and breast cancer) and the fourth in mortality (after lung, liver and gastric cancer). It was estimated that 746,298 new cases of CRC were diagnosed in 2012 and 693,881 patients died from CRC worldwide [1]. A higher incidence of CRC was found in developed nations (29.2 per 100,000 inhabitants in Europe, Northern America, Australia, New Zealand and Japan) compared with their less developed counterparts (11.7 per 100,000 inhabitants in Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia and Polynesia) [2]. However, China has a level of CRC incidence almost on par with the developed nations, with 376,300 new cases being diagnosed alone in 2015 (27.4 per 100,000 inhabitants). Most CRC patients live in China [3]. CRC has become the fifth leading cause of cancer death in China (around 191,000 CRC patients died in 2015: 13.9 per 100,000 inhabitants) [3].

HRQoL is a patient-reported outcome, which has been increasingly used to support clinical and public health decisions [4]. Assessing patient-reported outcomes is particularly important for cancer research because of the complexities of cancer events and cancer treatment. Cancer treatment is often very expensive with limited prospects of remission. Patient-reported outcomes present an alternative option of evidence for decision making [5, 6].

However, the application of patient-reported outcomes has been compounded by its subjective nature. People’s preferences need to be considered in quantifying and interpreting the results of patient-reported outcomes. Some researchers argue that people with different experiences (such as those with and without cancer) may have different preferences in relation to the same health state [7]. Nevertheless, the use of public preference to assess patient-reported outcomes has prevailed in health economic studies. This approach simplifies the preference scoring algorithm and justifies decisions from the perspective of a more representative population.

For peer review only

Several HRQoL instruments are available with a scoring system based on public preference, such as the EuroQol five-dimension (EQ-5D) [8], the Health Utilities Index (HUI)[9], and the Short-Form Six-Dimension (SF-6D) survey [10]. Their scoring algorithms are all anchored on 1.0 (full health) and 0 (death), with a negative score representing a health state worse than death.

The EQ-5D is perhaps the most widely used instrument for assessing HRQoL based on public preference. It has been recommended by many researchers and governmental agencies [11]. Extensive studies have been undertaken using the EQ-5D-3L for assessing HRQoL [12-16] because a scoring algorithm based on the preference of the general public is available in many countries, such as Finland [12], Turkey [13], the UK [14], and the Netherlands [16]. These include some studies on CRC patients [12-18]. Although a few studies have been conducted in China investigating the HRQoL of CRC patients [19], most have failed to generate a preference-based score simply because of the absence of a scoring algorithm.

The EQ-5D-5L was developed based on its predecessor EQ-5D-3L. It expanded the number of combined health states and is therefore believed to be more sensitive for detecting clinically important differences in HRQoL [20]. Recently, a scoring algorithm for the EQ-5D-5L was developed from a representative sample of the adult general population in China [21]. This study used the EQ-5D-5L to assess the HRQoL of CRC patients.

Methods

Study subjects and data collection

A cross-sectional questionnaire survey was conducted in Heilongjiang province, northeastern China, a province with a population of about 38 million. Heilongjiang ranks in the middle range in China in terms of its socioeconomic development, with $6,386 per capita GDP in 2015 [22].

Three major centers for cancer treatment, located in the capital city of Heilongjiang province, participated in the study. They were affiliated to a medical

For peer review only

university and provided specialist care to cancer patients across the entire province.

Data were collected between December 2016 and April 2017. The newly diagnosed CRC patients who received treatment in the three centers over the period were invited to enroll in this study. The participants had to have a confirmed diagnosis of primary CRC; have not received any treatment from other hospitals; be able to read, write, and speak in Chinese; and be able to give informed consent. Those who were deemed incapable of completing the questionnaire due to physical or psychological difficulties were excluded from the study.

The survey was conducted while the participants stayed in the hospitals. A list of eligible participants was provided by the hospitals. But the survey was administered by trained interviewers, who had no servicing relationship with the patients. The interviewers were recruited from research students in a medical university.

Eight trained interviewers approached the eligible participants and explained the purpose of this study. Written informed consent was obtained prior to the survey. The questionnaires were completed through face-to-face interviews in a private office, unless the participants requested an interview in the ward. Respondents were encouraged to complete the questionnaire independently, with assistance from the interviewers being made available if requested. The interviewers collected and reviewed the questionnaires immediately once they were returned. The results will be fed back to the patient and asked him/her to complete missing items if needed.

A total of 346 eligible participants were confirmed by the interviewers. Of these eligible participants, 26 declined to participate (including 15 who were deemed incapable of completing the questionnaire due to physical and psychological difficulties); 10 were excluded because they were not made aware of their diagnoses; 10 were excluded due to missing critical information in relation to the EQ-5D-5L data and socio-demographic and clinical characteristics of the respondents. This resulted in a final sample size of 300. On average, the respondents completed the survey 26 days after diagnosis (SD=15 days; range: 2 to 61 days).

Patient and public involvement

This study used an existing survey instrument. Patients were not involved in the recruitment to and conduct of the study. The utility scores were estimated based on

For peer review only

public preference and were not disseminated to the study participants. Publications of the results will be made open to the public. However, we are not able to disseminate the publications to the patient participants individually simply because we did not record the contact details of the patients.

The study protocol was reviewed and approved by the Research Ethics Committee, Public Health College of Harbin Medical University (Code: HMUIRB2014012).

For Peer review only

Measurement

The survey consisted of the validated Chinese version of EQ-5D-5L, and the clinical features and socio-economic characteristics of the respondents.

Dependent variable: EQ-5D-5L score

The HRQoL of the respondents was assessed by the EQ-5D-5L, which has been validated in cancer patients [23]. It measures problems in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension was rated along a five-level scale: no problem, slight problem, moderate problem, severe problem, and extreme problem [24]. Responses to the five dimensions generated 3125 (5^5) combinations of HRQoL states, with "11111" indicating "no problems at all" and "55555" indicating "extreme problems" in all five dimensions. Each combination was then be given a single score using a scoring algorithm based on public preference. In health economics, this is usually called the "utility score". In this study, we used the Chinese EQ-5D-5L value set [21] to estimate the utility score for each respondent, which ranged from -0.391 to 1.000.

Independent variables

Independent variables that might be associated with the HRQoL of CRC patients were determined with reference to several systematic reviews [25-27], including the clinical features and socio-economic characteristics of the respondents. Data on the clinical features of the respondents were collected through a review of medical records, which included the stage of CRC (I, II, III, IV), therapeutic regimen (surgery, radiotherapy/chemotherapy, surgery followed by postoperative chemotherapy,

chemotherapy followed by surgery), and the presence of a stoma (yes or no). The socio-demographic characteristics of the respondents were collected through the questionnaire survey, which included gender, age, religion, ethnicity, education, marital status, occupation, medical insurance, and household income.

Statistical analysis

The EQ-5D-5L utility scores of respondents followed a non-normal distribution (Kolmogorov-Smirnov test, $p<0.05$). We presented both mean (standard deviation, SD) and median (range) scores and applied Kruskal-Wallis analyses to determine the differences in the utility scores of the respondents with different characteristics.

We then established a Tobit regression model on the EQ-5D-5L utility scores, including all of the independent variables that showed statistical significance ($p<0.05$) in the Kruskal-Wallis analyses. The ceiling effect is common in HRQoL studies, in which a significant number of respondents report the highest score [28-30]. This is particularly evident with the EQ-5D instruments [30, 31], leading to some utility scores censored at 1.0. In this study, 16.7% of respondents scored the highest possible score 1.0. A general linear regression model is inappropriate for censored data because the values do not necessarily represent the exact values once they reach the censored threshold. For censored data, the Tobit regression model is advised [28-30, 32, 33].

All statistical analyses were conducted using the SPSS version 18 and the STATA version 12.0. A *p* value of less than 0.05 was considered an indication of statistical significance.

Results

The respondents had a mean age of 59 years (ranging from 28 years to 84 years). The majority was men (65%), married (90%), ethnic Han (96%), and had no religious belief (94%). About 17% of the respondents had obtained a university degree. All of the respondents were covered by social health insurance, albeit across three different schemes. Their household income was higher compared with the average level

For peer review only

(¥27,830) in Heilongjiang. About half of the respondents were still in the paid workforce at the time of the survey. More than half (54%) of respondents had received surgical treatment, but only 16.33% had a stoma. Most patients were at stage II (37.0%) and stage III (38.0%) of CRC (Table 1).

Problems in pain/discomfort were most frequently reported (60%, all levels inclusive), followed by anxiety/depression (59%, all levels inclusive), usual activities (53%, all levels inclusive), self-care (49%, all levels inclusive), and mobility (46%, all levels inclusive). About 16.7% of respondents reported no problems at all in all five dimensions (Table 2).

The respondents had an average utility score of 0.617 and a median of 0.740 (Table 3). The distribution of the EQ-5D-5L utility scores skewed toward the right higher values (Figure 1). No significant differences in the utility scores were found in those of a different age, gender, ethnicity, religious belief, and level of education (p>0.10). The Kruskal-Wallis analyses found lower EQ-5D-5L utility scores in those who were not married, worked as a farmer, enrolled with the new rural cooperative medical scheme, and had lower income (p<0.05). The EQ-5D-5L utility scores also varied with clinical characteristics. Those who were at a later stage of CRC, had undergone surgical treatment only, and had a stoma had lower utility scores compared with the others (p<0.05).

The Tobit regression model confirmed that low household income, membership of the new rural cooperative medical scheme, a later stage of CRC, surgical only therapy, and the presence of a stoma were significant predictors of low EQ-5D-5L utility scores. However, occupation and marital status became statistically insignificant in predicting utility scores after controlling for other factors (Table 4).

Discussion

This study presents the utility scores for newly diagnosed CRC patients measured by the EQ-5D-5L. To the best of our knowledge, this is the first study of its kind in China.

For peer review only

The results can be used for health economic evaluations of clinical and public health interventions on CRC. Previous attempts on cost-utility analyses of CRC interventions have been deterred by the lack of such utility scores [5]. The findings of this study provide baseline health utility values for CRC patients, which can be used by researchers in calculating quality-adjusted life years, an indicator essential for health economic evaluations, including cost-utility analyses. The study also revealed clinical and socio-economic factors associated with the utility scores of CRC patients, which can help clinical and policy decision makers to better allocate resources.

This study found that CRC patients live with significantly lower HRQoL than the local general public as measured by the EQ-5D utility scores (0.617 vs. 0.959) [30]. This finding is consistent with previous studies [12, 14, 18]. The CRC respondents of our study also appear to have lower utility scores than those from Finland (0.813) [12] Japan (0.842-0.865) [34, 35] and the UK (0.79) [15]. However, the interpretation of such differences needs to be cautious because the utility scores of the local general population in China and those in Finland, Japan and the UK were derived from the EQ-5D-3L. Empirical evidence shows that the EQ-5D-5L has a lower ceiling effect and higher discriminatory power than the EQ-5D-3L [12, 15, 23, 30]. In addition, the clinical and socio-economic characteristics of our CRC patients may also differ from those of other studies. Our sample was drawn from three tertiary hospitals and these patients tend to have more advanced diseases [36]. This study captured the utility scores of CRC patients soon after their diagnoses (26 days on average), much earlier than those of the studies in Finland (6-8 months) [12], Turkey (6 months after chemotherapy) [13], and England (12-36 months) [14].

We found that pain/discomfort is the most frequently reported problem (60%, all levels inclusive) of respondents, similar to that reported by CRC patients in the Netherlands and the UK [16]. This study also revealed that 59% of CRC patients experienced anxiety/depression. Indeed, anxiety/depression is perhaps the most common psychological problem among all cancer patients [37, 38]. Further efforts should be made to improve the management of pain/discomfort and

For peer review only

anxiety/depression.

There is some debate about the association between HRQoL and the stage of CRC. We found a decreasing trend in HRQoL with the progress of CRC, consistent with those reported in Australia and some European countries [26, 39-41]. However Hornbrook and colleagues reported worse HRQoL in patients with stage II CRC compared with those in stage III and IV [18].

CRC patients undergoing surgical procedures often have lower HRQoL [26, 42]. Our study provides additional evidence for this conclusion. It is widely accepted that surgical procedures are usually associated with increased pain/discomfort, complications, and inconvenience in daily activities. However, it is not clear why surgery in combination with other treatment measures can produce a higher utility score than surgery alone. The presence of a stoma is a clear indication of poor HRQoL. A HRQoL instrument (mCOH-QOL-Ostomy) has been developed specifically for CRC patients with a stoma [43].

Low socio-economic status is a significant predictor of low HRQoL in CRC patients. In this study, household income and social health insurance entitlements were found to be associated with the HRQoL of CRC patients, consistent with findings of previous studies conducted in China [19] and some other countries [39, 40]. Medical treatment for CRC is very expensive. A survey of 37 tertiary hospitals in 13 provinces in China revealed a high level of catastrophic expenditure for CRC patients [44]. This is a particular concern for those living with low income and those with limited insurance entitlements. Although China has achieved universal health insurance coverage, considerable disparities exist in terms of entitlements across the three government subsidized basic health insurance programs covering rural residents, urban residents and urban employees, respectively [45]. Rural patients in China are not only more likely to have lower household income, but also are least protected by their health insurance coverage. The new rural cooperative medical scheme (NRCMS), launched in 2003, is characterized by voluntary enrollment, low premium contribution

For peer review only

(about US$20 per person in 2016), and fixed governmental subsidies (about US$60 per person in 2016). These led to high population coverage of insurance at the cost of limited benefits. The rural insured usually bear a higher proportion of out-of-pocket expenses than their urban counterparts.

This study has several limitations. As a cross-sectional survey, no causal relationships can be assumed. The study was conducted in three tertiary hospitals in one province, which is not a representative sample of China; hence, generalization of the results needs to be cautious. It is also important to note that the sample was drawn from hospital settings and was biased toward more advanced cancer patients [46].

In conclusion, this study presents utility scores for CRC patients measured by the EQ-5D-5L. CRC patients have poor HRQoL, with pain/discomfort and depression/anxiety as the most frequently reported problems. The low HRQoL of CRC patients is associated with more advanced stages of CRC, the presence of a stoma and surgery only treatment. But low socio-economic status, such as low levels of income and insurance entitlements, is also a predictor of low HRQoL.

Ethical Statements and consent to participate

This study was approved by the Ethics Committee of Harbin Medical University (Project Identification Code: HMUIRB2014012). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants in the study.

Acknowledgements

The authors are most grateful to the study participants.

Funding

This study was funded by the National Natural Scientific Foundation of China (Grant No.71503062, 71673071), the Heilongjiang Postdoctoral Fund (Grant No. LBH-Z16137, LBH-Z16240), the China Postdoctoral Fund (Grant No.

For peer review only

2017M611402), the Key Lab of Health Technology Assessment, National Health and Family Planning Commission of China (Fudan University) (Grant No. FHTA2017-08).

Authors' Contributions

JY participated in the design of the study and the writing of the manuscript. WH designed the study, performed the statistical analyses and drafted the manuscript. GL and CL supervised and interpreted the statistical findings and wrote the manuscript. YL helped draft the manuscript. WF, LS and XZ conceived the study and participated in the design. All authors read and approved the final manuscript.

Competing interests

None declared

Data sharing statement

Data are available from the corresponding author on request.

Reference

1. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2014
2. Kuipers EJ. Colorectal cancer. *Nature Reviews Disease Primers* 2015; **1:** 15065.
3. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA: a cancer journal for clinicians* 2016; **66:** 115-32.
4. Ravens-Sieberer U. Measuring and monitoring quality-of-life in population surveys: Still a challenge for public health research. *Sozial- und Präventivmedizin* 2002; **47:** 203-4.
5. Huang W, Liu G, Zhang X, Fu W, Zheng S, Wu Q, et al. Cost-effectiveness of colorectal cancer screening protocols in urban Chinese populations. *PloS one* 2014; **9:** e109150.
6. Drummond MF SM, Torrance GW, O'Brien B, Stoddart GL. (2005 3rd ed edition) *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press, New York.
7. Greenberg D, Earle C, Fang CH, Eldar-Lissai A, Neumann PJ. When is cancer care cost-effective? A systematic overview of cost-utility analyses in oncology. *Value in Health* 2010; **102:** 82.
8. Brooks R. EuroQol: the current state of play. *Health Policy* 1996; **37:** 53.
9. Feeny DD, Furlong W, Boyle M, Torrance GW. Multi-Attribute Health Status Classification Systems. *PharmacoEconomics* 1995; **7:** 490-502.
10. Kharroubi SA, Brazier JE, Roberts J, O'Hagan A. Modelling SF-6D health state preference data using a nonparametric Bayesian method. *Journal of Health Economics* 2007; **26:** 597-612.
11. Räsänen P, Roine E, Sintonen H, Semberg-Konttinen V, Ryynänen OP, Roine R. Use of quality-adjusted life years for the estimation of effectiveness of health care: A systematic

For peer review only

literature review. *International Journal of Technology Assessment in Health Care* 2006; **22:** 235.

12. Farkkila N, Sintonen H, Saarto T, Jarvinen H, Hanninen J, Taari K, et al. Health-related quality of life in colorectal cancer. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2013; **15:** e215-22.
13. Polat U, Arpaci A, Demir S, Erdal S, Yalcin S. Evaluation of quality of life and anxiety and depression levels in patients receiving chemotherapy for colorectal cancer: impact of patient education before treatment initiation. *Journal of gastrointestinal oncology* 2014; **5:** 270-5.
14. Downing A, Morris EJ, Richards M, Corner J, Wright P, Sebag-Montefiore D, et al. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33:** 616-24.
15. Wilson TR, Alexander DJ, Kind P. Measurement of health-related quality of life in the early follow-up of colon and rectal cancer. *Diseases of the colon and rectum* 2006; **49:** 1692-702.
16. Stein D, Joulain F, Naoshy S, Iqbal U, Muszbek N, Payne KA, et al. Assessing health-state utility values in patients with metastatic colorectal cancer: a utility study in the United Kingdom and the Netherlands. *International journal of colorectal disease* 2014; **29:** 1203-10.
17. Hornbrook MC, Wendel CS, Coons SJ, Grant M, Herrinton LJ, Mohler MJ, et al. Complications Among Colorectal Cancer Survivors. *Medical Care* 2011; **49:** 321-6.
18. Wong CK, Lam CL, Poon JT, Kwong DL. Clinical correlates of health preference and generic health-related quality of life in patients with colorectal neoplasms. *PloS one* 2013; **8:** e58341.
19. Wang JW, Sun L, Ding N, Li J, Gong XH, Chen XF, et al. The association between comorbidities and the quality of life among colorectal cancer survivors in the People's Republic of China. *Patient preference and adherence* 2016; **10:** 1071-7.
20. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research An International Journal of Quality of Life Aspects of Treatment Care & Rehabilitation* 2011; **20:** 1727.
21. Luo N, Liu G, Li M, Guan H, Jin X, Randhendriksen K. Estimating an EQ-5D-5L Value Set for China. *Value in Health* 2017; **20:** 662-9.
22. Statistics HPBo. (2015) *Heilongjiang Statistical Yearbook*. China Statistics Press, Peking.
23. Kim SH, Kim HJ, Lee SI, Jo MW. Comparing the psychometric properties of the EQ-5D-3L and EQ-5D-5L in cancer patients in Korea. *Quality of Life Research An International Journal of Quality of Life Aspects of Treatment Care & Rehabilitation* 2012; **21:** 1065-73.
24. Group EQC. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16:** 199-208.
25. Bours MJ, Bw VDL, Winkels RM, van Duijnhoven FJ, Mols F, van Roekel EH, et al. Candidate Predictors of Health-Related Quality of Life of Colorectal Cancer Survivors: A Systematic Review. *Oncologist* 2016; **21**
26. Der BWAL, Van. Predictors of health-related quality of life of colorectal cancer survivors: a systematic literature review. 2016
27. Hu X, Gong Y, Wang C, Zhang Y, Feng X. The quality of life for patient with colorectal neoplasm and its influential factors. *Tumor* 2003**:** 343-5.
28. Sullivan PW, Ghushchyan VH. EQ-5D Scores for Diabetes-Related Comorbidities. *Value in*

For peer review only

health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2016; **19:** 1002-8.

29. Sullivan PW, Ghushchyan VH, Globe G, Sucher B. Health-related quality of life associated with systemic corticosteroids. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2017; **26:** 1037-58.

30. Huang W, Yu H, Liu C, Liu G, Wu Q, Zhou J, et al. Assessing Health-Related Quality of Life of Chinese Adults in Heilongjiang Using EQ-5D-3L. *International Journal of Environmental Research & Public Health* 2017; **14**

31. Bharmal M, Rd TJ. Comparing the EQ-5D and the SF-6D descriptive systems to assess their ceiling effects in the US general population. *Value in Health the Journal of the International Society for Pharmacoeconomics & Outcomes Research* 2006; **9:** 262.

32. Twisk J, Rijmen F. Longitudinal tobit regression: a new approach to analyze outcome variables with floor or ceiling effects. *Journal of Clinical Epidemiology* 2009; **62:** 953-8.

33. Tran BX, Ohinmaa A, Long TN. Quality of life profile and psychometric properties of the EQ-5D-5L in HIV/AIDS patients. *Health & Quality of Life Outcomes* 2012; **10:** 132.

34. HAMASHIMA, CHISATO. Long-term quality of life of postoperative rectal cancer patients. *Journal of Gastroenterology & Hepatology* 2002; **17:** 571-6.

35. Kameyama H, Shimada Y, Yagi R, Yamada S, Hotta S, Tajima Y, et al. Quality of Life of Patients after Colorectal Cancer Surgery as Assessed Using EQ-5D-5L Scores. *Gan to Kagaku Ryoho Cancer & Chemotherapy* 2017; **44:** 1083-5.

36. Gao K, Gan X. Medical Units Distribution and Influence Factors on the Selection of Patients. *Chinese Health Service Management* 2014; **31:** 516-7.

37. Strong V, Waters R, Hibberd C, Rush R, Cargill A, Storey D, et al. Emotional distress in cancer patients: the Edinburgh Cancer Centre symptom study. *British journal of cancer* 2007; **96:** 868.

38. Soa WKW, Ling WM, Leung FY, Lo JCK, Yeung M, Li GKH. Anxiety, depression and quality of life among Chinese breast cancer patients during adjuvant therapy. *European Journal of Oncology Nursing* 2010; **14:** 17-22.

39. Paika V, Creed F, Kampletsas EO, Siafaka V, Gkika S, Mavreas V, et al. Personality variables are associated with colorectal cancer patients' quality of life independent of psychological distress and disease severity. *Psychooncology* 2010; **19:** 273-82.

40. Sharma A, Sharp DM, Walker LG, Monson JRT. Predictors of Early Postoperative Quality of Life after Elective Resection for Colorectal Cancer. *Annals of Surgical Oncology* 2007; **14:** 3435-42.

41. Rinaldis M, Pakenham KI, Lynch BM. Relationships between quality of life and finding benefits in a diagnosis of colorectal cancer. *British Journal of Psychology* 2010; **101:** 259.

42. Chambers SK, Meng X, Youl P, Aitken J, Dunn J, Baade P. A five-year prospective study of quality of life after colorectal cancer. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2012; **21:** 1551-64.

43. Liu L, Herrinton LJ, Hornbrook MC, Wendel CS, Grant M, Krouse RS. Early and late complications among long-term colorectal cancer survivors with ostomy or anastomosis. *Diseases of the colon and rectum* 2010; **53:** 200-12.

44. Huang HY, Shi JF, Guo LW, Zhu XY, Wang L, Liao XZ, et al. Expenditure and financial burden for common cancers in China: a hospital-based multicentre cross-sectional study. *Lancet* 2016; **388:** S10-S.

For peer review only

45. Dong K. Medical insurance system evolution in China ☆. *China Economic Review* 2009; **20:** 591-7.

46. Yang SM, Li JY, Gale RP, Huang XJ. The mystery of chronic lymphocytic leukemia (CLL): Why is it absent in Asians and what does this tell us about etiology, pathogenesis and biology? *Blood Reviews* 2015; **29:** 205-13.

For peer review only

Figure legends

Figure 1. Distribution of the EQ-5D-5L utility scores of CRC patients

For peer review only

Table 1 Socio-demographic and clinical characteristics of respondents

Characteristic	N	%
Sex		
Male	195	65.00
Female	105	35.00
Age (years)		
⩽ 40	50	16.67
50-59	92	30.67
60-69	105	35.00
⩾ 70	53	17.66
Religious belief		
Yes	18	6.00
No	282	94.00
Ethnicity		
Han	288	96.00
Other	12	4.00
Level of education		
Primary school or below	64	21.33
Junior high school	103	34.34
Senior high school	82	27.33
University	51	17.00
Marital status		
Married	270	90.00
Other	30	10.00
Occupation		
Public sector employee	38	12.67
Private sector employee	36	12.00
Self-employed or unemployed	55	18.33
Farmer	63	21.00
Retired	108	36.00
Health insurance		
Basic medical insurance for urban employees	154	51.33
Basic medical insurance for urban residents	62	20.67
New rural cooperative medical scheme	84	28.00
Annual household income (Yuan)		
<20000	56	18.67
20000–39999	84	28.00
40000-59999	72	24.00
60000-79999	39	13.00
>80000	49	16.33
Therapeutic regimen		
Surgery	163	54.33
Radiotherapy/chemotherapy	44	14.67
Surgery followed by postoperative chemotherapy	51	17.00
Chemotherapy followed by surgery	18	6.00
Other	24	8.00
Stage of CRC		
I	40	13.33
II	111	37.00
III	114	38.00
IV	35	11.67
Stoma		
Yes	49	16.33
No	251	83.67
Total	300	100

For peer review only

Table 2 Problems reported by respondents in the five dimensions of EQ-5D-5L

Problems	Mobility	Self-care	Usual Activity	Pain/Discomfort	Anxiety/Depression
No	53.7%	51.0%	46.7%	39.7%	40.7%
Slight	14.3%	15.4%	18.3%	25.0%	23.3%
Moderate	11.3%	12.0%	13.3%	25.3%	24.3%
Severe	10.0%	11.3%	12.0%	7.0%	9.3%
Extreme	10.7%	10.3%	11.7%	3.0%	2.4%

For peer review only

Table 3 EQ-5D-5L index scores in respondents with different characteristics

	N	Mean±SD	Median (range)	P
Sex				0.942
Male	195	0.614±0.378	0.731 (-0.348-1.00)	
Female	105	0.621±0.361	0.751 (-0.348-1.00)	
Age				0.330
≤49	50	0.561±0.398	0.670 (-0.348-1.00)	
50-59	92	0.686±0.327	0.819 (-0.348-1.00)	
60-69	105	0.592±0.373	0.687(-0.251-1.00)	
≥70	53	0.598±0.407	0.782 (-0.265-1.00)	
Religious belief				0.537
Yes	18	0.612±0.375	0.740 (-0.348-1.00)	
No	282	0.683±0.302	0.772 (0.139-1.00)	
Ethnicity				0.166
Han	288	0.620±0.374	0.749 (-0.348-1.00)	
Other	12	0.541±0.307	0.618 (-0.044-0.89)	
Level of education				0.180
Primary school or below	64	0.581±0.363	0.646 (-0.298-1.00)	
Junior high school	103	0.583±0.376	0.661 (-0.348-1.00)	
Senior high school	82	0.638±0.373	0.744 (-0.348-1.00)	
University	51	0.696±0.365	0.833 (-0.201-1.00)	
Marital status				*0.026*
Married	270	0.635±0.359	0.746 (-0.348-1.00)	
Other	30	0.452±0.445	0.455 (-0.348-0.95)	
Occupation				*0.007*
Public sector employee	38	0.734±0.341	0.895 (-0.201-1.00)	
Private sector employee	36	0.706±0.328	0.833 (-0.184-1.00)	
Self-employed or unemployed	55	0.603±0.359	0.659 (-0.348-1.00)	
Farmer	63	0.500±0.411	0.600 (-0.348-1.00)	
Retired	108	0.621±0.326	0.756 (-0.201-1.00)	
Health insurance				*0.001*
Basic medical insurance for urban employees	154	0.674±0.352	0.825 (-0.251-1.00)	
Basic medical insurance for urban residents	62	0.645±0.354	0.720 (-0.348-1.00)	
New rural cooperative medical scheme	84	0.490±0.392	0.586 (-0.348-1.00)	
Annual household income (Yuan)				*0.002*
<20000	56	0.505±0.419	0.586 (-0.348-1.00)	
20000–39999	84	0.566±0.369	0.685 (-0.348-1.00)	
40000-59999	72	0.625±0.375	0.763 (-0.251-1.00)	
60000-79999	39	0.691±0.300	0.824 (-0.044-1.00)	
>80000	49	0.759±0.315	0.882 (-0.201-1.00)	
Therapeutic regimen				*0.000*
Surgery	163	0.517±0.389	0.600 (-0.348-1.00)	
Radiotherapy/chemotherapy	44	0.757±0.271	0.830 (-0.071-1.00)	
Surgery followed by postoperative chemotherapy	51	0.712±0.359	0.848 (-0.298-1.00)	
Chemotherapy followed by surgery	18	0.734±0.320	0.847 (-0.005-1.00)	
Other	24	0.748±0.274	0.854 (0.120-1.00)	
Stage of disease				*0.001*
I	40	0.768±0.296	0.893 (0.025-1.00)	
II	111	0.656±0.344	0.821 (-0.348-1.00)	
III	114	0.562±0.394	0.698 (-0.265-1.00)	
IV	35	0.495±0.395	0.637(-0.348-1.00)	
Stoma				*0.000*
Yes	49	0.408±0.397	0.409 (-0.348-1.00)	
No	251	0.657±0.353	0.808 (-0.348-1.00)	
Total	300	0.617±0.371	0.740 (-0.348-1.00)	

For peer review only

Table 4. Results of Tobit regression model on EQ-5D-5L index scores of respondents

Variables	Regression Coefficient	95% Confidence interval		*P* value
Marital status (Ref=other)				
Married	0.128	-0.010	0.267	0.070
Occupation (Ref=Retired)				
Public sector employee	0.069	-0.073	0.210	0.340
Private sector employee	0.073	-0.069	0.215	0.313
Self-employed or unemployed	0.011	-0.139	0.163	0.879
Farmer	0.104	-0.080	0.288	0.265
Health insurance (Ref=New rural cooperative medical scheme)				
Urban employees basic medical insurance	0.126	-0.047	0.299	0.152
Urban residents basic medical insurance	0.157	0.001	0.313	0.049*
Stage of disease (Ref=I)				
II	-0.203	-0.342	-0.065	0.004**
III	-0.329	-0.468	-0.192	0.000***
IV	-0.626	-0.809	-0.444	0.000***
Annual household income(Ref=>80000)				
<20000	-0.261	-0.422	-0.100	0.002**
20000–39999	-0.220	-0.358	-0.081	0.002**
40000-59999	-0.155	-0.294	-0.016	0.029*
60000-79999	-0.145	-0.306	0.015	0.076
Therapeutic regimen(Ref=other)				
Surgery	-0.261	-0.423	-0.098	0.002**
Radiotherapy/Chemotherapy	0.135	-0.057	0.326	0.167
Surgery followed by postoperative chemotherapy	0.177	-0.166	0.202	0.849
Chemotherapy followed by surgery	0.053	-0.178	0.284	0.653
Stoma（Ref=no）				
Yes	-0.224	-0.337	-0.111	0.000***

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

For peer review only

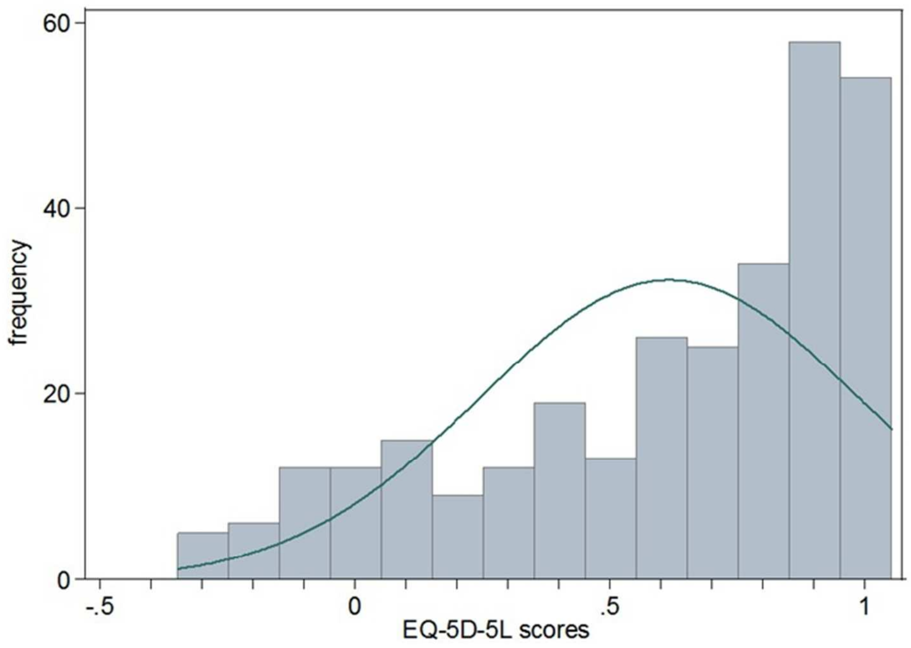

Figure 1 Distribution of the EQ-5D-5L values of CRC patients

Figure 1. Distribution of the EQ-5D-5L utility scores of CRC patients

216x166mm (96 x 96 DPI)

w only

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	**Recommendation**	**detail**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	P 5
Methods			
Study design	4	Present key elements of study design early in the paper	P 5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P 5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P 6
Bias	9	Describe any efforts to address potential sources of bias	P 6
Study size	10	Explain how the study size was arrived at	P 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P 8
		(*b*) Describe any methods used to examine subgroups and interactions	P 8
		(*c*) Explain how missing data were addressed	P 6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	P 6
		(*e*) Describe any sensitivity analyses	None.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P 8
		(b) Give reasons for non-participation at each stage	P 8

For peer review only

		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P 8
		(b) Indicate number of participants with missing data for each variable of interest	P 6/P 8
Outcome data	15*	Report numbers of outcome events or summary measures	P 8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P 8-9
		(*b*) Report category boundaries when continuous variables were categorized	P 18-20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	None.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	None.
Discussion			
Key results	18	Summarise key results with reference to study objectives	P 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P 12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P 9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	P 12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P 12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only