

PEER REVIEW HISTORY

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This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing health-related quality of life of patients with colorectal cancer using EQ-5D-5L: a cross-sectional study in Heilongjiang of China
AUTHORS	Huang, Weidong; Yang, Jinjin; Liu, Yang; Liu, Chaojie; zhang, xin; Fu, Wenqi; Shi, Limei; Liu, Guoxiang

VERSION 1 – REVIEW

REVIEWER	Amy Downing University of Leeds, UK
REVIEW RETURNED	27-Apr-2018

GENERAL COMMENTS	<p>The authors have carried out a survey of CRC patients and evaluated HRQL using EQ-5D. Unfortunately there is some important information missing which makes it difficult to assess the results in context. The main one is that there is no information about where in the pathway of CRC the patients are - for example, are they newly diagnosed, are they several years out or is it a mixture? This is an important distinction as HRQL can change over time from diagnosis. Secondly, the details of how the patients were identified is not clear - did the interviewers identify eligible patients from a clinic list and approach them, was it done by the medical team first or a different way? Without this information it is hard to assess the results compared to previous studies and the generalisability.</p> <p>Specific comments:</p> <p>Title</p> <ol style="list-style-type: none">1. Evaluating may be a better word than Valuing <p>Abstract</p> <ol style="list-style-type: none">2. Methods - Needs to say how long since diagnosis.3. Results - Be clear that it is any level (slight or severe) pain, anxiety etc.4. Conclusion - Why pick out socioeconomic status when other variable significant too? <p>Introduction</p> <ol style="list-style-type: none">5. Perhaps use 'most common' rather than life-threatening.6. 'Most CRC patients live in China' - OK but need to account for population size. What is the incidence compared to other countries?7. 'HRQL is a kind of patient-reported outcome' - reads strangely.
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	<p>HRQL is a patient-reported outcome. 8. The intro is quite long, it would benefit from being shortened and the language improving.</p> <p>Methods 9. As mentioned above, needs more information about how the patients were identified and where they were in the cancer 'journey' - time since diagnosis. 10. Need some information about how the survey was developed. Did it simply include EQ-5D and some socio-demographic questions? Was any pilot testing carried out? 11. Page 7, line 23 - why was socio-economic status singled out here? Needs explanation. Wouldn't this come under 'patient factors' along with age, etc?</p> <p>Results 12. Fistula should be referred to as stoma - I think this is what you mean? 13. Explain that the figures quoted are referring to any level of problem (slight or severe)</p> <p>Discussion 14. Page 10, line 18-18 - 'the Chinese general population prefers lower values on most conditions....' I don't understand this point, please rephrase. 15. Page 10, line 23 - 'a heavier condition' - I think you mean more advanced disease? 16. Comparing results with those from Finland, UK etc seems a little odd given the differences in the populations. Are there other studies that it would be better to compare with? 17. I think there needs to be more discussion about how these results can be useful for health economic evaluation (if they can - I'm not an expert in this area). 18. Discussion needed about where these patients are in their cancer pathway.</p> <p>Tables 19. Table 1 - I find it a little hard to believe that there is no missing data. For example, stage was known for all patients. Was this a condition of eligibility? Occupation and income was complete too, so all patients gave this information in the survey? Was this because the interviewers filled the survey in with them? 20. Table 4- why was advanced stage chosen as the reference category? Seems a little odd. 21. I think some explanation is needed on how to interpret the co-coefficients in Table 4.</p> <p>Language - some editing needed to improve the readability.</p>
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REVIEWER	Risto Roine Helsinki and Uusimaa Hospital Group Finland
REVIEW RETURNED	03-May-2018

GENERAL COMMENTS	<p>The study provides utility scores for Chinese colorectal cancer (CRC) patients using the EQ-5D-5L. As the EQ.5D-5L has rarely been used in CRC patients before, the results can be considered important as they provide useful data for health economic analyses. The manuscript is mostly well written and concise, the statistical analysis appears adequate and the conclusions are reasonable. Below are listed some minor points that the authors could consider</p>
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	<p>to still improve the paper.</p> <ol style="list-style-type: none"> 1. How many patients were deemed incapable of completing the questionnaires? 2. What were the “other reasons” to exclude 10 patients? 3. How often did the respondents need assistance in completing the questionnaires? 4. In the statistics section the authors state: The final statistical analysis included 300 questionnaires, excluding five that contained some missing data”. Does this mean that only 295 patients were included in the final analysis? 5. As in most studies using the EQ-5D the distribution of the scores was, according to the authors, non-normal. I think it would be useful for the readers if the authors would provide a figure showing the distribution of the scores. It would also help to illustrate the prominent ceiling effect which has been commonly observed in EQ-5D studies even in patients with malignant diseases. 6. Contrary to what the authors claim in the discussion, there is at least one small previous Japanese study having used the EQ-5D-5L in colorectal cancer patients (Kameyama H et al.[Quality of Life of Patients after Colorectal Cancer Surgery as Assessed Using EQ-5D-5L Scores]. Gan To Kagaku Ryoho. 2017 Nov;44(12):1083-1085. Japanese.) This should be corrected. 7. It is postulated that the CRC patients of the study have a lower HRQoL than the local general population. However, the authors do not provide any numbers to substantiate this claim. I think such data would be needed. 8. As most of the readers are probably poorly informed of the new rural cooperative medical scheme in China, it would be useful if the authors would elaborate a bit more about the scheme and how it differs from the other health insurance schemes in China.
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Reviewer Name: Amy Downing

The authors have carried out a survey of CRC patients and evaluated HRQL using EQ-5D. Unfortunately there is some important information missing which makes it difficult to assess the results in context. The main one is that there is no information about where in the pathway of CRC the patients are - for example, are they newly diagnosed, are they several years out or is it a mixture? This is an important distinction as HRQL can change over time from diagnosis. Secondly, the details of how the patients were identified is not clear - did the interviewers identify eligible patients from a clinic list and approach them, was it done by the medical team first or a different way? Without this information it is hard to assess the results compared to previous studies and the generalisability.

A: Thanks. We totally agree with the suggestion and added details about how we identified the participants and their pathway of CRC: all participants had newly diagnosed CRC and they were recruited in the participating hospitals where they received treatment.

(Page 6 lines 2-18).

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.

Specific comments:

Title

Q1. Evaluating may be a better word than Valuing

A1: Thanks for the advice. We have revised the title in line with the advice.

(Page 1 lines 1-2):

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

Abstract

Q2. Methods - Needs to say how long since diagnosis.

A2 : Thanks. We have added some descriptions about diagnosis-to-survey time.

(Page 6 lines 27-28):

On average, the respondents completed the survey 26 days after diagnosis (SD=15 days; range 2 to 61 days).

Q3. Results - Be clear that it is any level (slight or severe) pain, anxiety etc.

A3: Thanks. We have made these clear in the revised texts.

(Page 2 lines 10 to 12):

Pain/discomfort and anxiety/depression were major complaints of the respondents, with a prevalence of over 60% (all levels inclusive).

Q4. Conclusion - Why pick out socioeconomic status when other variable significant too?

A4: Thanks. We have included all significant variables in the conclusion.

(Page 2 lines 18-21):

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.

Introduction

Q5. Perhaps use 'most common' rather than life-threatening.

A5: Thanks for the advice. We have changed the wording.

(Page 4 lines 2):

Colorectal cancer (CRC) is one of the most common cancers in the world:

Q6. 'Most CRC patients live in China' - OK but need to account for population size. What is the incidence compared to other countries?

A6: Thanks. We have added more descriptions about the prevalence of CRC in China in comparison with other countries.

(Page 4 lines 5-12):

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).

Q7. 'HRQL is a kind of patient-reported outcome' - reads strangely. HRQL is a patient-reported outcome.

A7: Thanks. We have changed the wording.

(Page 4 lines 15-16):

HRQoL is a patient-reported outcome, which has been increasingly used to support clinical and public health decisions [4].

Q8. The intro is quite long, it would benefit from being shortened and the language improving.

A8: Thanks. We have shortened the introduction.

Methods

Q9. As mentioned above, needs more information about how the patients were identified and where they were in the cancer 'journey' - time since diagnosis.

A9: Thanks. We have revised the method section in line with the advice.

(Page 6 lines 27-28):

On average, the respondents completed the survey 26 days after diagnosis (SD=15 days; range: 2 to 61 days).

Q10. Need some information about how the survey was developed. Did it simply include EQ-5D and some socio-demographic questions? Was any pilot testing carried out?

A10: Thanks. We have added some more detailed descriptions about the questionnaire.

(Page 7 lines 8-9):

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

Q11. Page 7, line 23 - why was socio-economic status singled out here? Needs explanation. Wouldn't this come under 'patient factors' along with age, etc?

A11: Thanks for your advice. We have made modification in line with your suggestion.

(Page 7 lines 23-25):

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.

Results

Q12. Fistula should be referred to as stoma - I think this is what you mean?

A12: Thanks for your advice. We have replace "fistula" with "stoma".

Q13. Explain that the figures quoted are referring to any level of problem (slight or severe)

A13: Thanks for the advice. We have made it clear in the revised version: (all levels inclusive).

(Page 9 lines 5-9):

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).

Discussion

Q14. Page 10, line 18-18 - 'the Chinese general population prefers lower values on most conditions....' I don't understand this point, please rephrase.

A14: Sorry for the ambiguous description. This sentence has been deleted.

Q15. Page 10, line 23 - 'a heavier condition' - I think you mean more advanced disease?

A15: Thanks. We have changed the wording, using the term "more advanced".

(Page 10 lines 17-20):

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 [35]

Q16. Comparing results with those from Finland, UK etc seems a little odd given the differences in the populations. Are there other studies that it would be better to compare with?

A16: Due to a shortage of studies in Asian countries, we compared our results with those from the EU countries. We have expressed cautious about the comparison.

(Page 10 lines 13-23):

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 [35]. 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].

Q17. I think there needs to be more discussion about how these results can be useful for health economic evaluation (if they can - I'm not an expert in this area).

A17: Thanks for your advice. We have added some discussions about the implications of this study on health economic evaluations on CRC interventions.

(Page 10 lines 1 -8):

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.

Q18. Discussion needed about where these patients are in their cancer pathway.

A18: Thanks for the advice. We have added some discussions in line with the advice.

(Page 10 lines 20-23):

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].

Tables

Q19. Table 1 - I find it a little hard to believe that there is no missing data. For example, stage was known for all patients. Was this a condition of eligibility? Occupation and income was complete too, so all patients gave this information in the survey? Was this because the interviewers filled the survey in with them?

A19: Thanks for the advice. We have added more detailed descriptions about how collected data. There were some returned questionnaires containing missing data, which were excluded from data analyses.

(Page 6 lines 9-20):

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.

Q20. Table 4- why was advanced stage chosen as the reference category? Seems a little odd.

A20: Thanks for the advice. We have changed stage I as the reference group (Table 4).

Q21. I think some explanation is needed on how to interpret the co-coefficients in Table 4.

A21: Thanks for the advice. We have made it clear that the coefficients in Table 4 are “regression coefficients”.

Q22. Language - some editing needed to improve the readability.

A22: Thanks for the advice. The revised manuscript was proofread by our colleague in La Trobe University.

Reviewer: 2

Reviewer Name: Risto Roine

The study provides utility scores for Chinese colorectal cancer (CRC) patients using the EQ-5D-5L. As the EQ-5D-5L has rarely been used in CRC patients before, the results can be considered important as they provide useful data for health economic analyses.

The manuscript is mostly well written and concise, the statistical analysis appears adequate and the conclusions are reasonable.

A: Thanks for the encouraging comments.

Below are listed some minor points that the authors could consider to still improve the paper.

Q1. How many patients were deemed incapable of completing the questionnaires?

A1: 15 CRC patients were deemed incapable of completing the questionnaire due to physical and psychological difficulties. We have added more detailed descriptions.

(Page 6 lines 21-26).

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.

Q2. What were the “other reasons” to exclude 10 patients?

A2: Thanks. We have provided a clearer description about the “other reasons” for exclusion.

(Page 6 lines 21-26).

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.

Q3. How often did the respondents need assistance in completing the questionnaires?

A3: Sorry, this information was not recorded in the survey.

Q4. In the statistics section the authors state: “The final statistical analysis included 300 questionnaires, excluding five that contained some missing data”. Does this mean that only 295 patients were included in the final analysis?

A4: Sorry for the language error. We have corrected the sentence: the final sample size was 300.

5. As in most studies using the EQ-5D the distribution of the scores was, according to the authors, non-normal. I think it would be useful for the readers if the authors would provide a figure showing the distribution of the scores. It would also help to illustrate the prominent ceiling effect which has been commonly observed in EQ-5D studies even in patients with malignant diseases.

A5: Thanks for the insightful advice. We have added a figure showing the distribution of the EQ-5D-5L scores (Figure 1).

Q6. Contrary to what the authors claim in the discussion, there is at least one small previous Japanese study having used the EQ-5D-5L in colorectal cancer patients (Kameyama H et al.[Quality

of Life of Patients after Colorectal Cancer Surgery as Assessed Using EQ-5D-5L Scores]. Gan To Kagaku Ryoho. 2017 Nov; 44(12):1083-1085. Japanese.) This should be corrected.

A6: Thanks. We have corrected the discussion.

(Page 9 lines 27):

To the best of our knowledge, this is the first study of its kind in China.

(Page 10 lines 11-12):

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].

Q7. It is postulated that the CRC patients of the study have a lower HRQoL than the local general population. However, the authors do not provide any numbers to substantiate this claim. I think such data would be needed.

A7: Thanks for the constructive advice. We have added relevant data in the discussion.

(Page 10 lines 9-10):

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].

8. As most of the readers are probably poorly informed of the new rural cooperative medical scheme in China, it would be useful if the authors would elaborate a bit more about the scheme and how it differs from the other health insurance schemes in China.

Q8: Thanks for the advice. We have added some brief descriptions about the new rural cooperative medical scheme.

(Page 11 lines 27-28 and Page 12 lines 1-4):

The new rural cooperative medical scheme (NRCMS), launched in 2003, is characterized by voluntary enrollment, low premium contribution (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.

VERSION 2 – REVIEW

REVIEWER	Amy Downing University of Leeds, UK
REVIEW RETURNED	29-Jun-2018

GENERAL COMMENTS	The authors have addressed my comments.
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REVIEWER	Risto Roine Helsinki and Uusimaa Hospital Group
REVIEW RETURNED	19-Jun-2018

GENERAL COMMENTS	The authors have provided adequate responses to the concerns of the reviewers and have revised the manuscript accordingly. The language of the manuscript could in some parts of the manuscript still be improved, for instance, in the methods section the sentence: Three major centers for cancer treatment participated in the study, each being located in the capital city of Heilongjiang province, participated in the study” should be revised.
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