

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study
<b>AUTHORS</b>	Lee, Ko-Chao; Chung, Kuan-Chih; Chen, Hong-Hwa; Cheng, Kung-Chuan; Wu, Kuen-Lin; Lu, Chien-Chang

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Seung-Bum Ryoo Department of Surgery, Seoul National University Hospital, Seoul, Korea
<b>REVIEW RETURNED</b>	04-Dec-2017

<b>GENERAL COMMENTS</b>	<p>I have reviewed the manuscript of ‘Short-term postoperative outcomes of colorectal cancer among patients with chronic liver diseases: a national population-based study’. It was an interesting paper with including the important issues for outcomes of surgery for colorectal cancer in chronic liver disease. The study was a large cohort study and deduced the useful results. However, there are numerous points to have to be considered carefully.</p> <ol style="list-style-type: none"><li>1. The primary endpoint is vague. We already know the prevalence of postoperative complications is higher in liver cirrhosis patients from numerous previous studies. However, in your results, there was no significant differences between cirrhotic and non-cirrhotic patients. You have to explain more about the result of the primary outcome and definitely describe in the abstract. And you also have to explain the postoperative complications was not different but in-hospital mortality is higher in cirrhotic patients. It can even be considered that in-hospital mortality had developed not by the postoperative complications but by other accidental causes</li></ol>
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	<p>2. The study could be better if analyzed according to the severity of liver cirrhosis. We can use the Child-Pugh Classifications or MELD score for determine the risk of cirrhosis. In general, the patients with mild liver cirrhosis can undergo the surgery without severe complications.</p> <p>3. In Table 2 and 3, univariate and multivariate analysis to identify factors associated with postoperative complications and in-hospital mortality. Length of hospital stay is the most relevant factors and the only significant factor related to postoperative complications with OR, 1.13 and 95% CI, 1.12-1.15. However, there was no reference.</p> <p>4. Introduction needs to be shortened with important points of this issues. For example, molecular pathway with the colorectal cancer might be not important in this study.</p>
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<b>REVIEWER</b>	Iosief Abraha Regional Health Authority of Umbria, Italy
<b>REVIEW RETURNED</b>	11-Dec-2017

<b>GENERAL COMMENTS</b>	<p>The study assessed the factors associated with postoperative complications and in-hospital mortality in colorectal cancer patients with chronic liver disease who received colorectal surgery using a large national database. The study was retrospective, observational in design.</p> <p>The authors concluded that there is a correlation between post-operative mortality in patients with colorectal cancer.</p> <p>As acknowledged by the authors the unit of analysis was not the individual patients but the medical records within the database and it represents an important limitation of their work.</p> <p>The authors will need to underline another limitation of their study.</p> <p>The study used several ICD-9 codes to characterize the disease, comorbidities as well as the interventions received. However, it is unclear whether the accuracy of the ICD-9 codes related – at least – to the diagnosis of the colorectal cancer (153, 154) has been determined elsewhere (Med Care. 1999 May;37(5):436-44; DOI: 10.1155/2012/298369). Authors will need to clarify this and discuss that validating ICD-9 codes is a relevant issue in performing epidemiological studies (DOI: 10.1136/bmjopen-2015-010409).</p> <p>Minor issue: the time frame 2005 – 2014 should also be reported in the abstract</p>
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<b>REVIEWER</b>	Hannes Neeff
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	Clinic for General and Digestive Surgery, Dept of Surgery, Medical Faculty of the University of Freiburg, Germany
<b>REVIEW RETURNED</b>	13-Dec-2017

<b>GENERAL COMMENTS</b>	<p>The reviewed paper "Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study" analyses the effects of chronic liver disease and outcome after colorectal surgery. It has been done using the NIS database. From a primary sample of 153000 patients 1555 patients with chronic liver disease and CRC surgery were matched 1:4 with controls. Primary endpoint were postoperative complications, secondary end point was in hospital mortality.</p> <p>The results of the paper are unfortunately very conflicting mainly due to the conclusions drawn from the statistical results. In particular major concerns are:</p> <ol style="list-style-type: none"> <li>1. Patients were only included with chronic liver disease but WITHOUT cirrhosis. While this explains the small number of only 1% of the original population (155000) it should be stated more early in the paper that cirrhosis was excluded (this is only explained in the Results section).</li> <li>2. While complications were assessed for 14 different complication ICD codes, only overall complications are given. The only correlation was hospital length of stay. It is well known that complications prolong hospital length of stay. The conclusion "postoperative complications among RCR patients with underlying CLD was positively associated with length of stay, but was not associated with the presence of CLD" does not make sense to me.</li> <li>2. The final conclusion " The associating factors identified in our population-based study make it possible to correlate peri- or postoperative complications and mortality in CRC patients with with underlying CLD, and can help to improve clinical management and outcomes in this group of CRC patients" is simply not accurate: How can clinical management be changed?</li> </ol> <p>In summary the authors should try to analyze specific complications from the 14 ICD separately in order to try and find any useful correlation which might change clinical practice. As of now there is little value for the clinician in these findings.</p> <p>Minor concerns: The number of 51000 deaths per year from CRC should be more clearly stating that this ist only for the US while deaths from cirrhosis are given worldwide (1.000.000).T his is confusing.</p> <p>In the discussion segment it is stated that approximately 20% of the study population had CLD. If matching was correctly done 1:4 it should be exactly 20%.</p> <p>The phrasing "duration of hospital stay was significantly associated with the prevalence of postoperative complications" is unfortunate because it alludes to "staying in the hospital makes complications". Also it reads: A long hospital stay makes for "higher mortality". These are only mathematical correlations (as the authors state with no causality) but this is still confusing.</p> <p>The paper - from a clinical standpoint - unfortunately does not help to give better care to patients with CLD and CRC. The analysis of the specific complications might help in this respect.</p>
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## VERSION 1 – AUTHOR RESPONSE

Point-by-point response to reviewers' comments:

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Seung-Bum Ryoo

Institution and Country: Department of Surgery, Seoul National University Hospital, Seoul, Korea

Competing Interests: None declared

I have reviewed the manuscript of 'Short-term postoperative outcomes of colorectal cancer among patients with chronic liver diseases: a national population-based study'. It was an interesting paper with including the important issues for outcomes of surgery for colorectal cancer in chronic liver disease. The study was a large cohort study and deduced the useful results. However, there are numerous points to have to be considered carefully.

1. The primary endpoint is vague. We already know the prevalence of postoperative complications is higher in liver cirrhosis patients from numerous previous studies. However, in your results, there was no significant differences between cirrhotic and non-cirrhotic patients. You have to explain more about the result of the primary outcome and definitely describe in the abstract. And you also have to explain the postoperative complications was not different but in-hospital mortality is higher in cirrhotic patients. It can even be considered that in-hospital mortality had developed not by the postoperative complications but by other accidental causes.

Response: We have now clarified that our study excluded patients with liver cirrhosis, and the current study did not compare post-operative complications and in-hospital mortality between cirrhotic and non-cirrhotic patients. We have also revised our Results section, and included a more detailed analysis of specific postoperative complications (including postoperative infection, postoperative bleeding, cardiac arrest/heart failure, respiratory complications, and digestive complications). Our data showed that the presence of CLD was significantly associated with a higher risk of postoperative bleeding, and a higher risk of in-hospital mortality. These data have now been described in the Abstract.

2. The study could be better if analyzed according to the severity of liver cirrhosis. We can use the Child-Pugh Classifications or MELD score for determine the risk of cirrhosis. In general, the patients with mild liver cirrhosis can undergo the surgery without severe complications.

Response: The current study did not recruit patients with liver cirrhosis.

3. In Table 2 and 3, univariate and multivariate analysis to identify factors associated with postoperative complications and in-hospital mortality. Length of hospital stay is the most relevant factors and the only significant factor related to postoperative complications with OR, 1.13 and 95% CI, 1.12-1.15. However, there was no reference.

Response: Since length of stay (LOS) is a continuous variable, we did not need to add a reference group. Interpretation of the odds ratio here tells us that the odds of post-operative complications increased 1.13 times when the length of stay increased by 1 day from LOS of zero.

4. Introduction needs to be shortened with important points of this issues. For example, molecular pathway with the colorectal cancer might be not important in this study.

Response: The Introduction section has been shortened to make it more succinct.

Reviewer: 2

Reviewer Name: Iosief Abraha

Institution and Country: Regional Health Authority of Umbria, Italy Competing Interests: None declared

The study assessed the factors associated with postoperative complications and in-hospital mortality in colorectal cancer patients with chronic liver disease who received colorectal surgery using a large national database. The study was retrospective, observational in design.

The authors concluded that there is a correlation between post-operative mortality in patients with colorectal cancer.

As acknowledged by the authors the unit of analysis was not the individual patients but the medical records within the database and it represents an important limitation of their work.

The authors will need to underline another limitation of their study. The study used several ICD-9 codes to characterize the disease, co-morbidities as well as the interventions received. However, it is unclear whether the accuracy of the ICD-9 codes related – at least – to the diagnosis of the colorectal cancer (153, 154) has been determined elsewhere (Med Care. 1999 May;37(5):436-44; DOI: 10.1155/2012/298369). Authors will need to clarify this and discuss that validating ICD-9 codes is a relevant issue in performing epidemiological studies (DOI: 10.1136/bmjopen-2015-010409).

Response: We thank the reviewer for this suggestion. We have included these references in the Discussion section.

Minor issue: the time frame 2005 – 2014 should also be reported in the abstract

Response: The Abstract has been revised accordingly.

Reviewer: 3

Reviewer Name: Hannes Neeff

Institution and Country: Clinic for General and Digestive Surgery, Dept of Surgery, Medical Faculty of the University of Freiburg, Germany Competing Interests: None declared

The reviewed paper "Short-term postoperative outcomes of colorectal cancer among patients with chronic liver disease: a national population-based study" analyses the effects of chronic liver disease and outcome after colorectal surgery.

It has been done using the NIS database. From a primary sample of 153000 patients 1555 patients with chronic liver disease and CRC surgery were matched 1:4 with controls. Primary endpoint were postoperative complications, secondary end point was in hospital mortality.

The results of the paper are unfortunately very conflicting mainly due to the conclusions drawn from the statistical results.

In particular major concerns are:

1. Patients were only included with chronic liver disease but WITHOUT cirrhosis. While this explains the small number of only 1% of the original population (155000) it should be stated more early in the paper that cirrhosis was excluded (this is only explained in the Results section).

Response: We have now stated in the Abstract, as well as in the Methods section, that patients with cirrhosis were excluded.

2. While complications were assessed for 14 different complication ICD codes, only overall complications are given. The only correlation was hospital length of stay. It is well known that complications prolong hospital length of stay. The conclusion "postoperative complications among

CRC patients with underlying CLD was positively associated with length of stay, but was not associated with the presence of CLD" does not make sense to me.

Response: We have now revised our Results section to include a regression analysis of specific postoperative complications which were observed in > 5% of the study patients (postoperative infection, postoperative bleeding, cardiac arrest/heart failure, respiratory complications, and digestive complications). We have revised the Discussion and Conclusion sections to reflect these data.

2. The final conclusion " The associating factors identified in our population-based study make it possible to correlate peri- or postoperative complications and mortality in CRC patients with underlying CLD, and can help to improve clinical management and outcomes in this group of CRC patients" is simply not accurate: How can clinical management be changed?

In summary the authors should try to analyze specific complications from the 14 ICD separately in order to try and find any useful correlation which might change clinical practice. As of now there is little value for the clinician in these findings.

Response: We have now revised the Conclusion section based on our revised analysis of specific postoperative complications. Our results showed that the presence of CLD was significantly associated with a higher risk of postoperative bleeding, and a lower risk of respiratory complications. Our data suggested that postoperative bleeding should be closely monitored in CRC patients with CLD, since it may result in a higher risk of in-hospital mortality in these patients. We have also clarified that the respiratory complications evaluated were surgery-related. CLD-related pulmonary complications (hepatopulmonary syndrome, porto-pulmonary hypertension, and hepatic hydrothorax) were not evaluated separately. Further research is needed to extend and confirm our data.

Minor concerns: The number of 51000 deaths per year from CRC should be more clearly stating that this is only for the US while deaths from cirrhosis are given worldwide (1.000.000). This is confusing.

Response: These sentences have been revised accordingly.

In the discussion segment it is stated that approximately 20% of the study population had CLD. If matching was correctly done 1:4 it should be exactly 20%.

Response: We have corrected this accordingly.

The phrasing "duration of hospital stay was significantly associated with the prevalence of postoperative complications" is unfortunate because it alludes to "staying in the hospital makes complications". Also it reads: A long hospital stay makes for "higher mortality".

These are only mathematical correlations (as the authors state with no causality) but this is still confusing.

Response: This section has been revised accordingly. Our multivariate analysis showed that length of hospital stay was associated with a higher risk of specific postoperative complications such as postoperative infection, postoperative bleeding, respiratory complications, and digestive complications.

The paper - from a clinical standpoint - unfortunately does not help to give better care to patients with CLD and CRC. The analysis of the specific complications might help in this respect.

Response: We have now included a detailed analysis of specific postoperative complications that occurred in > 5% of our study population. We believe that identification of factors associated with

specific complications, and with in-hospital mortality may help in the clinical management of CRC patients with underlying CLD.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Seung-Bum Ryoo Department of Surgery, Seoul National University College of Medicine, Seoul, Korea
<b>REVIEW RETURNED</b>	16-Feb-2018

<b>GENERAL COMMENTS</b>	This study has to be reviewed statistically. and still vague in analysis results of data and conclusions
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<b>REVIEWER</b>	Iosief Abraha Regional Health Authority of Umbria
<b>REVIEW RETURNED</b>	17-Feb-2018

<b>GENERAL COMMENTS</b>	The the manuscript has been revised appropriately.
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<b>REVIEWER</b>	Hannes Neeff Faculty of Medicine, University of Freiburg, University Hospital Freiburg, Dept. for General and Digestive Surgery, Hugstetterstrasse 55, 79106 Freiburg, Germany
<b>REVIEW RETURNED</b>	13-Feb-2018

<b>GENERAL COMMENTS</b>	<p>Dear authors,</p> <p>I am still not convinced that the length of the hospital stay can be correlated with complications. For example: If a patients stays in the hospital for longer, his risk of postoperative bleeding increases? The only way of correlating theses outcomes would be the other way around: Postoperative complications do (or do not) increase: Hospital stay, early mortality, long term mortality and so on. A longer hospital stay may be correlated with UTI infections, Pneumonia etc. but not surgical complications: If so, the message would be: Discharge all patients early and they will have fewer complications . The other changes that have been made are satisfactory. However this statement (how do postoperative complications and hospital stay correlate with each other) is pivotal to the message of this paper I do not recommend its publication also in the present form.</p>
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### VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Seung-Bum Ryoo

Institution and Country: Department of Surgery, Seoul National University College of Medicine, Seoul, Korea  
Competing Interests: None

This study has to be reviewed statistically.  
and still vague in analysis results of data and conclusions

Response: We have now analyzed our data to evaluate the impact of postoperative complications on the length of hospital stay. Our data are presented in Table 6. We have revised the Results, Discussion, and Abstract sections accordingly. We have also revised the Conclusions section of the Abstract.

Reviewer: 2

Reviewer Name: IosiefAbraha

Institution and Country: Regional Health Authority of Umbria Competing Interests: None declared

The the manuscript has been revised appropriately.

Reviewer: 3

Reviewer Name: Hannes Neeff

Institution and Country: Faculty of Medicine, University of Freiburg, University Hospital Freiburg, Dept. for General and Digestive Surgery, Hugstetterstrasse 55 79106 Freiburg, Germany Competing Interests: None declared

Dear authors,

I am still not convinced that the length of the hospital stay can be correlated with complications. For example: If a patients stays in the hospital for longer, his risk of postoperative bleeding increases? The only way of correlating these outcomes would be the other way around: Postoperative complications do (or do not) increase: Hospital stay, early mortality, long term mortality and so on. A longer hospital stay may be correlated with UTI infections, Pneumonia etc. but not surgical complications: If so, the message would be: Discharge all patients early and they will have fewer complications.

The other changes that have been made are satisfactory.

However this statement (how do postoperative complications and hospital stay correlate with each other) is pivotal to the message of this paper I do not recommend its publication also in the present form.

Response: We thank the reviewer for this comment. We have now analyzed the correlation between the length of hospital stay and incidence of postoperative complications. The data are presented in Table 6. Our data indicated that patients with postoperative complications (including postoperative



infection, postoperative bleeding, cardiac arrest/heart failure, respiratory complications and digestive complications) had a significantly longer duration of hospital stay compared to patients who did not have postoperative complications. These data have now been included in the Results, Discussion, and the Abstract sections.