

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a gallbladder cancer registry study in China: the Chinese Research Group of Gallbladder Cancer (CRGGC) study
AUTHORS	Ren, Tai; Li, Yongsheng; Zhang, Xi; Geng, Yajun; Shao, Ziyu; Li, Maolan; Wu, Xiangsong; Wang, Xu-An; Liu, Fatao; Wu, Wenguang; Shu, Yijun; Bao, Runfa; Gong, Wei; Dong, Ping; Dang, Xueyi; Liu, Chang; Liu, Changjun; Sun, Bei; Liu, Jun; Wang, Lin; Hong, Defei; Qin, Renyi; Jiang, Xiaoqing; Zhang, Xuewen; Xu, Junmin; Jia, Jianguang; Yang, Bo; Li, Bing; Dai, Chaoliu; Cao, Jingyu; Cao, Hong; Tao, Feng; Zhang, Zaiyang; Wang, Yi; Jin, Huihan; Cai, Hongyu; Fei, Zhewei; Gu, Jianfeng; Han, Wei; Feng, Xuedong; Fang, Lu; Zheng, Linhui; Zhu, Chunfu; Wang, Kunhua; Zhang, Xueli; Li, Xiaoyong; Jin, Chong; Qian, Yeben; Cui, Yunfu; Xu, Yuzhen; Wang, Xiang; Liu, Houbao; Hua, Yawei; Liu, Chao; Hao, Jihui; Wang, Chuanlei; Li, Qiyun; Li, Xun; Liu, Jiansheng; Li, Mingzhang; Qiu, Yudong; Wu, Buqiang; Zheng, Jinfang; Chen, Xiaoliang; Zhu, Haihong; Hua, Kejun; Yan, Maolin; Wang, Peng; Zang, Hong; Ma, Xiaoming; Hong, Jian; Liu, Yingbin

VERSION 1 – REVIEW

REVIEWER	Linda Lundgren Department of Surgery, County Council of Östergötland and Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, Linköping, Sweden
REVIEW RETURNED	24-Apr-2020

GENERAL COMMENTS	<p>Thank you for this interesting and dedicated protocol. The implementation of this study is important and the protocol seems to be well designed.</p> <p>The weaknesses of the study seem to be thoroughly addressed. Unfortunately it seems that a large proportion of the incidental gallbladder cancer patients will be lost due to patients being turned to other hospital for re-resection. Hopefully it will be possible to retrieve some outcome data regarding incidental gallbladder cancer patients as well, since these patients constitutes a relatively large proportion of GBC patients.</p>
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REVIEWER	Nina Afshar Cancer Council Victoria University of Melbourne Australia
REVIEW RETURNED	23-May-2020

GENERAL COMMENTS	In this study, Ren and colleagues wrote a protocol for a national gallbladder cancer registry study in China. I think the manuscript
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	<p>needs more clarity in terms of recruitment and methods. There are sections of the manuscript that are really confusing.</p> <p>ABSTRACT Introduction, line 9: 'and' should be replaced by comma. Methods, line 23: The authors mentioned that patients are identified from 1 January 2008. I think they should also mention the end of the recruitment in the abstract.</p> <p>INTRODUCTION Line 8: Five-year survival rate of 5% is incorrect unless the authors mean that the cancer has spread to a distant part of the body (Stage 4). Lines 26-28: I don't agree with this statement 'On the other hand, the data of several national cancer registries are limited by flawed coding systems for GBC.'</p> <p>METHODS AND ANALYSIS Lines 37-49: It's not very clear what the first and second phases are. If the end of the recruitment for the first phase is 31 December 2019, with the target of 6000 patients, What is the second phase?</p> <p>Clinical outcome and follow-up I am not familiar with protocols format but I was thinking that this section should be more clear about potential analytical methods that researchers are going to use. Lines 53-58 Estimating five-year overall survival for early stages of the disease is not recommended. I would suggest using net survival or cancer-specific survival. Date of last contact doesn't make sense. It doesn't mean that the patient died. So, It's necessary that the investigators get vital status from Chinese death registries.</p> <p>Page 15, lines 3-6 Definition of disease free survival is not correct. It should be from the first treatment to the date of recurrence. Did the author mean progression free survival rather than disease-free survival? Page 15, line 8: 'preoperative' should be postoperative as patients had surgery. Page 15, line 11: 'patient survival'...As I mentioned before, survival status should be defined using linkage to Chinese death registries. Page 15, line 17: 'date of death'...the authors should mention how and from where they get the date of death.</p> <p>I wonder whether the investigators could compare number of cases, and sex/age distribution with a national cancer registry (Surely each state/province in China has a cancer registry).</p>
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REVIEWER	Cheng-Maw Ho National Taiwan University Hospital, Taipei, Taiwan
REVIEW RETURNED	23-Sep-2020

GENERAL COMMENTS	As a statistical reviewer, I cannot find any methodology described in this protocol paper. All information described in the paper is about how quality data are collected retrospectively.
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REVIEWER	Mohammad Ali Mansournia TUMS, Iran
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REVIEW RETURNED	26-Sep-2020
GENERAL COMMENTS	I do not see the plan of statistical analysis including definition and handling of censoring in this cohort protocol.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to the Authors:

Reviewer 1

1. Thank you for this interesting and dedicated protocol. The implementation of this study is important and the protocol seems to be well designed. The weaknesses of the study seem to be thoroughly addressed.

Author response: Thank you!

2. Unfortunately it seems that a large proportion of the incidental gallbladder cancer patients will be lost due to patients being turned to other hospital for re-resection. Hopefully it will be possible to retrieve some outcome data regarding incidental gallbladder cancer patients as well, since these patients constitutes a relatively large proportion of GBC patients.

Author response: Thanks for pointing out this important issue. We have added this part into discussion. (Page 186, line 441-443)

Patients underwent either primary surgery or resection will be involved in this cohort, as indicated by pathologically diagnosed GBC. However, patients turn to other hospital may yield incomplete following information (surgery, adjuvant therapy, etc.). These patients were identified and classified uniquely (defined on Page 13, line 316) to aid future sensitivity analysis. Fortunately, follow-up data (surgery, adjuvant therapy, survival, etc.) in some hospitals were maintained even if patients turned to other hospitals.

Reviewer 2

1. In this study, Ren and colleagues wrote a protocol for a national gallbladder cancer registry study in China. I think the manuscript needs more clarity in terms of recruitment and methods. There are sections of the manuscript that are really confusing.

ABSTRACT

Introduction, line 9: 'and' should be replaced by comma.

Author response: Thanks for your thorough review. This error was corrected. (Page 6, line 123)

2. Methods, line 23: The authors mentioned that patients are identified from 1 January 2008. I think they should also mention the end of the recruitment in the abstract.

Author response: The end of the recruitment has been addressed both in this part and methods. (Page 6, line 128; page 9, line 214)

3. INTRODUCTION

Line 8: Five-year survival rate of 5% is incorrect unless the authors mean that the cancer has spread to a distant part of the body (Stage 4).

Author response: The 5-year overall survival of 5% in overall GBC patients was reported in Hundal2014 and common-cited, but several large cohorts did suggested a better prognosis (Lindner2018, SEER database). Hereby we revised the number to include all these results. (Page 8, line 164)

4. Lines 26-28: I don't agree with this statement 'On the other hand, the data of several national cancer registries are limited by flawed coding systems for GBC.'

Author response: We agree that the expression was inaccurate. We have revised the expression to address problems caused by coding systems in GBC research. (Page 8, line 173)

5. METHODS AND ANALYSIS

Lines 37-49: It's not very clear what the first and second phases are. If the end of the recruitment for the first phase is 31 December 2019, with the target of 6000 patients, What is the second phase?

Author response: This description was removed. Originally we intended to write a little of future plan, but it's really confusing without further description. (Page 9, line 214; page 10, line 233 and 235)

6. Clinical outcome and follow-up

I am not familiar with protocols format but I was thinking that this section should be more clear about potential analytical methods that researchers are going to use.

I wonder whether the investigators could compare number of cases, and sex/age distribution with a national cancer registry (Surely each state/province in China has a cancer registry).

Author response: Thank you for the advice. We have added a section of statistical analysis to address our primary plan to analyze the data. (Page 15, line 365-391)

7. Lines 53-58

Estimating five-year overall survival for early stages of the disease is not recommended. I would suggest using net survival or cancer-specific survival.

Author response: Cancer-specific survival was added as a secondary outcome. The overall survival for early stage GBC varies across regions. For T1b GBC, the National Cancer Data Base data from the US reported a 5-year overall survival rate of around 50% (Vo2019), but several groups reported much higher numbers from 70%-90% (Kim2018, Yoon2014, Ogura1991). Regarding the high malignancy of GBC, 5-year overall survival was still chosen as the primary outcome even for early stage GBC. (Page 11, line 244-247)

8. Date of last contact doesn't make sense. It doesn't mean that the patient died. So, It's necessary that the investigators get vital status from Chinese death registries.

Page 15, line 11: 'patient survival'...As I mentioned before, survival status should be defined using linkage to Chinese death registries.

Page 15, line 17: 'date of death'...the authors should mention how and from where they get the date of death.

Author response: We revised the expression and defined censor in the follow-up, which had been expressed wrongly in the former version. (Page 10, line 241-243)

We plan to retrieve survival information from clinical follow-up data from each hospital, which are reliable and desensitized. This part was addressed on Page 11, line 253.

We would like to confirm the follow-up data by linking to the death registries. Unfortunately there is no official way to apply for such data in China.

9. Page 15, lines 3-6 Definition of disease free survival is not correct. It should be from the first treatment to the date of recurrence. Did the author mean progression free survival rather than disease-free survival?

Author response: It should be progression free survival. Thank you for the correction. (Page 11, line 243)

10. Page 15, line 8: 'preoperative' should be postoperative as patients had surgery.

Author response: Sorry, we only found 'preoperative' in the 'surgery information' part. In this part, we would like to investigate whether the patient had the malignancy diagnosis before surgery, which

is recorded on the operation notes. This information was valuable because failure to detect a malignancy before surgery may lead to risk of incident GBC. (Page 13, line 303)

Reviewer 3

As a statistical reviewer, I cannot find any methodology described in this protocol paper. All information described in the paper is about how quality data are collected retrospectively.

Author response: Thanks for your time. We have added a section of statistical analysis to address our primary plan to analyze the data. (Page 15, line 365-391)

Reviewer 4

I do not see the plan of statistical analysis including definition and handling of censoring in this cohort protocol.

Author response: Thanks for your time. We have added a section of statistical analysis to address our primary plan to analyze the data. (Page 15, line 365-391)

VERSION 2 – REVIEW

REVIEWER	Cheng-Maw Ho National Taiwan University Hospital, Taiwan
REVIEW RETURNED	30-Oct-2020

GENERAL COMMENTS	I have no statistical concerns.
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REVIEWER	Mohammad Ali Mansournia TUMS, Iran
REVIEW RETURNED	02-Nov-2020

GENERAL COMMENTS	It is now acceptable for publication.
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VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments to the Authors:

Reviewer 3

1. I have no statistical concerns.

Author response: Thank you!

Reviewer 4

1. It is now acceptable for publication.

Author response: Thank you!