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Protocol for a national gallbladder cancer registry study in China: the Chinese Research Group of Gallbladder Cancer (CRGGC) study

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Abstract

Introduction

Gallbladder cancer (GBC), the sixth most common gastrointestinal tract cancer and poses a significant disease burden in China. However, no national representative data are available on the clinical characteristics, treatment and prognosis of GBC in the Chinese population.

Methods and analysis

The Chinese Research Group of Gallbladder Cancer (CRGGC) study is a multicentre retrospective registry cohort study. Clinically diagnosed GBC patients are identified from January 1, 2008, by reviewing the electronic medical records (EMRs) from 76 tertiary and secondary hospitals across 28 provinces in China. Patients with pathological and radiological diagnoses of malignancy, including cancer in situ, from the gallbladder and cystic duct are eligible, according to the National Comprehensive Cancer Network (NCCN) 2019 guidelines. Patients are excluded if GBC is the secondary diagnosis in the discharge summary. The demographic characteristics, medical history, physical examination results, surgery information, pathological data, laboratory examination results, and radiology reports are collected in a standardized case report form. By May 2021, approximately 6,000 GBC patients will be included. The clinical follow-up data will be updated until 5 years after the last admission for GBC of each patient.

The study aimed (1) to depict the clinical characteristics, including demographics, pathology, treatment, and prognosis of GBC patients in China; (2) to evaluate the adherence to clinical guidelines of GBC; and (3) to improve clinical practice for diagnosing and treating GBC and provide references for policy makers.

Ethics and dissemination

The protocol of the CRGGC has been approved by the Committee for Ethics of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (SHEC-C-2019-

085) and registered in ClinicalTrials.gov (NCT04140552). All results of this study will be published in peer-reviewed journals and presented at relevant conferences.

Study registration number: NCT04140552

Strengths and limitations of this study

1. The Chinese Research Group of Gallbladder Cancer (CRGGC) study is the first large-scale registry cohort study of gallbladder cancer (GBC) in China, covering 76 tertiary and secondary hospitals across 28 provinces.
2. A standardized quality control and data management plan was designed to ensure the accuracy and reliability of the data.
3. The EMR systems are not consistent across hospitals, which may introduce variance in data recording and result in difficulty in systematic data formatting and integration.
4. This is a retrospective study using convenience sampling. The study population may not be completely representative of GBC patients in China.
5. There is a lack of biospecimens from involved patients.

INTRODUCTION

Gallbladder cancer (GBC) is the most common type of biliary tract cancer¹⁻³ and one of the most lethal malignancies, with a 5-year survival rate of 5%¹. Much effort has been made to optimize the treatment of GBC; however, the prognosis remains dismal^{4,5}, and the quality of current evidence for GBC is still far from perfect. Due to its relatively low incidence, clinical trials on GBC are difficult to conduct. Most recommendations and guidelines for GBC from the National Comprehensive Cancer Network (NCCN; 2019 version 4) and American Joint Committee on Cancer (AJCC; 8th version) were derived from evidence of moderate quality^{6,7}. Most of these studies were single-centre studies with limited sample sizes and generally no more than 300 cases⁸⁻¹⁰, which might introduce systematic bias into the conclusion.

On the other hand, the data of several national cancer registries are limited by flawed coding systems for GBC. The nomenclature of GBC in the literature is inconsistent. GBC defined by the AJCC 8th staging manual is a primary cancer in the gallbladder and cystic duct (C23.9 and part of C24.0; ICD-O-3 codes)⁷. However, many epidemiological studies refer to “GBC” as “GBC and extrahepatic cholangiocarcinoma (ECC; C23.9 and C24.0)”, leading to confusion in its incidence, mortality, and other epidemiological features^{11,12}. In addition, cystic duct cancer is undistinguishable from ECC in most cancer registry studies, which means that this specific subset of patients is likely to be omitted¹³. Moreover, a commonly used coding system for surgery, the Facility Oncology Registry Data System, classifies GBC as “all other sites”, making it unlikely to define the extent of surgery and distinguish patients who undergo re-resection after GBC is incidentally found¹⁴. Regarding regional lymph nodes, the Collaborative Stage (version 0204) system defines celiac, superior mesenteric, and para-aortic lymph nodes as regional nodes, which is not consistent with either the AJCC 7th or AJCC 8th definition¹⁵. The coding problems in both patient identification and site-specific variables might lead to less stringent interpretation of the conclusions.

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China is a high-GBC risk country, but little evidence has been based on the Chinese population¹¹. Data from GLOBOCAN show that, taking GBC and ECC together, the number of annual new cases in China accounts for 24.7% of new cases worldwide¹². Currently, the largest retrospective study of GBC in China was conducted by Zou *et al.*¹⁶, including 3,922 patients from 116 hospitals in 28 provinces of China during 1986-1998. This study described the demographic characteristics of GBC in China, without further data on detailed staging, treatment, and prognosis information. Another study of 2,379 GBC patients from 5 northwestern provinces during 2009-2013¹⁷ reported that 55.1% of GBC patients had advanced-stage tumours. Other reports were mainly single-centre studies with limited sample sizes¹⁸¹⁹. The critical characteristics in the diagnosis, treatment, and prognosis of GBC in China are unknown.

Therefore, this study aimed to design a national GBC cohort, the Chinese Research Group of Gallbladder Cancer (CRGGC) study, (1) to comprehensively evaluate the clinical characteristics, including demographics, pathology, treatment, and prognosis of GBC patients in China; (2) to evaluate adherence to clinical guidelines of GBC; and (3) to improve clinical practice and guidelines for GBC and provide references for policy makers.

METHODS AND ANALYSIS

Registry design

The CRGGC study is a multicentre retrospective registry cohort study. The project was launched by the Shanghai Key Laboratory of Biliary Tract Disease Research, with collaborators from 76 tertiary and secondary hospitals across 28 provinces in China (until March 8, 2020; see online supplementary file 1). We review the electronic medical records (EMRs) of all diagnosed GBC patients from January 1, 2008, and extract the related clinical and treatment information. The clinical follow-up data will be updated until 5 years after the last admission for GBC of each patient.

Patient enrolment

Patients are identified with various search strategies: (1) ICD-10 code equals C23.9, or C24.0 with “cystic duct”; (2) discharge diagnosis includes “gallbladder cancer” (search strategy in Chinese: (“胆囊”) AND (“癌” OR “恶性肿瘤” OR “占位”)), which means “gallbladder”/“cystic duct” AND (“cancer” OR “malignancy” OR “space-occupying lesion”)); and (3) pathological reports include “gallbladder cancer”. All 3 search strategies are applied in each centre. The results are merged for subsequent exclusion. These search strategies were designed to be redundant because some search strategies may not be applicable in specific EMR systems and in specific periods.

All identified admissions to the hospital are manually filtered according to the diagnostic criteria of the NCCN 2019 version 4 guidelines for hepatobiliary cancer⁶. Patients with a pathological or radiological diagnosis of malignancy, including cancer in situ, from the gallbladder and cystic duct are eligible. Patients are excluded if GBC is the secondary diagnosis in the discharge summary because patients admitted for other diseases are likely to have obscure cancer traits.

The first phase of this study includes patients diagnosed before December, 31, 2019. According to our preliminary estimation, more than 6,000 cases will meet our inclusion criteria. We expect to finish phase one data collection by May 2021. After finishing enrolment of a short-term target of 2,000 cases, a primary analysis will be performed. The follow-up will be updated until 5 years after the admission of each patient. More centres are expected to participate in the CRGGC study; thus, the collaborator list may be expanded.

Clinical outcomes and follow-up

The main outcome is the 5-year overall survival (OS) rate. OS is defined as the duration between the date of first diagnosis and the date of death or the date of last contact, whichever comes first. We will also include the following outcomes: disease-

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4 free survival (DFS), defined as the duration between the date of first diagnosis and the
5 date of recurrence; 3-year OS rate; and 90-day mortality (for patients who undergo
6 surgery), which will be used to indicate perioperative mortality. Clinical follow-up is
7 defined as the routine practice of hospitals of collecting patient data on treatment,
8 tumour recurrence and patient survival, either by outpatient/inpatient records or
9 telephone. We require hospitals to equip such a system and at least one follow-up per
10 year to join our collaboration. Based on these data, we update patients' follow-up
11 statuses every 12 months. The data being collected include date of recurrence, date of
12 death, date of last contact, whether re-resection was performed if the malignancy was
13 found incidentally, and whether the patient received adjuvant therapy.
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23 **Data collection**

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26 The workflow of data collection and quality control is shown in Fig. 1. Before
27 data collection, a group of hepatobiliary specialists designed a structured case report
28 form, aiming to delineate features of GBC patients and answer corresponding clinical
29 questions. The case report form includes the following information: demographic
30 characteristics, medical history, physical examination results, surgery information,
31 pathological data, laboratory examination results, and radiology reports. We compiled
32 a codebook to standardize the definition of each variable. The data centre is
33 responsible for training doctors to collect data. Data collection is carried out by using
34 EpiData (v4.6.0.2, EpiData Association, Denmark).
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44 Automated logic checks are applied to prevent out-of-range values. Duplicated
45 entry is required. If any discrepancies are found, a third specialist will be brought in
46 for discussion and make a final decision.
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50 After data entry and quality control in each centre, the data are anonymized and
51 transferred to the servers in the data centre. The data centre is located at Shanghai Key
52 Laboratory of Biliary Tract Disease Research, which is equipped with data servers
53 and essential firewall and backup systems. The data centre is responsible for quality
54 assessment, storage, sharing, and analysis of the data. A group of researchers in the
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4 data centre manage the database.
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6 The data manager assesses the quality of the data after transfer to the data centre.
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8 The assessment is based on the structure of missing data and a comparison to baseline
9 data. First, we apply a grading system, where variables are classified into essential,
10 important, and normal importance. Based on the proportion of missing values in each
11 category, the entries are graded as level A, B, C, or D in quality. Entries of category D
12 quality are normally excluded from analysis. Second, outliers and inconsistent data
13 are identified. Third, we compare baseline characteristics of the new data to previous
14 data, with indicators including sex ratio, mean age, proportion of TNM stage, and 5-
15 year OS. We apply the chi-square test, t-test, and log-rank test between the two
16 datasets. When a significant difference is found, the data manager analyses and
17 records suspicious data. The data manager inquires about the data in question with the
18 data source and asks for confirmation. The desensitized data are accessible to
19 collaborators after the completion of the database. A research proposal to the CRGGC
20 Scientific Committee is essential for analysis of the data.
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33 **Demographic data and medical history**

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36 The EMR data for each patient are collected for every hospital visit from January
37 1, 2008. The baseline data are retrieved, including the following aspects: (1)
38 demographics: age at diagnosis, sex, race, and date of diagnosis; (2) medical history:
39 emergency operation, chief complaint, endoscopic retrograde cannulation of the
40 pancreas (ERCP) performed within 30 days before surgery, percutaneous transhepatic
41 cholangial drainage (PTCD) performed within 30 days before surgery, neoadjuvant
42 therapy, and method of diagnosis (pathology, radiology, or other); (3) past medical
43 history: history of gallstone, history of gallbladder polyps, history of other
44 malignancies, hypertension, diabetes mellitus, and other comorbidities; (4) social and
45 personal history: marital status, smoking history, and use of alcohol; and (5) other
46 aspects: weight, height, family history, and total expenditure.
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Surgery information

1. The preoperative and intraoperative diagnoses are recorded. A diagnosis of “gallbladder cancer”, “gallbladder tumour”, or “space-occupying lesion in gallbladder” is regarded as the detection of malignancy.
2. Regional lymphadenectomy requires the resection of hilar nodes⁷. Further clearance of lymph nodes is classified as extended lymphadenectomy.
3. The extent of lymphadenectomy includes the cystic duct, common bile duct, portal vein, hepatic artery, common hepatic artery, post-superior pancreatic, celiac, superior mesenteric, suprapyloric, left gastric artery, and paraaortic lymph nodes^{7 20 21}.
4. Combined hepatectomy is classified as no hepatectomy, liver wedge resection/partial hepatectomy, IVb+V segmentectomy, hemihepatectomy, extent more than hemihepatectomy, radiofrequency ablation, and hepatectomy for other reasons.
5. If the malignancy is diagnosed after surgery, further treatment information may not be available (the patient may turn to a second hospital for re-resection). Patients in this case are categorized as “simple cholecystectomy performed; further treatment not available”. If re-resection is available, its operative reports will be reviewed as previously mentioned.
6. ERCP, PTCD, and transarterial chemoembolization (TACE) are not defined as surgery but as supportive treatment.
7. Palliative surgery is defined as resection of the primary tumour, reconstruction of the digestive tract, or both when there is evidence of distant metastasis or unresectable tumour.

Other surgery-related variables include date of surgery, laparoscopic surgery, combined bile duct resection, tumour positioned on the hepatic or peritoneal side, perivascular invasion, perforation, porcelain gallbladder, duration of surgery,

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4 intraoperative blood loss, and American Society of Anesthesiologists (ASA) score.
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6 **Pathological data**

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8 Pathological data are recorded, including size of the tumour (in 3 dimensions),
9 resection margin, tumour positioned on the hepatic or peritoneal side, tumour
10 positioned on the fundus, body, neck, or cystic duct, depth of invasion (carcinoma in
11 situ or lamina propria, muscularis, perimuscular connective tissue, full layer, serosa,
12 adjacent organ, or major vascular invasion⁷), liver invasion, number of nodes
13 examined, positive lymph nodes, number of hilar nodes examined, positive hilar
14 lymph nodes, region of positive nodes, region of nodes examined (with codes the
15 same as those used for the region of lymphadenectomy in surgery), grade, histology
16 type (using ICD-O-3 codes²²), microvascular invasion, and perineural invasion.
17 Tumours will be staged according to the AJCC 8th staging manual according to
18 pathological reports derived from the aforementioned variables. Notably, the
19 description of “invasion of full layer” for depth of invasion is not suggested in the
20 AJCC 8th manual but is commonly used in China.
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34 **Laboratory examination**

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36 Laboratory examination results for patients are collected with the date of
37 examination. Indicators of interest include the following: (1) routine blood tests: white
38 blood cell count, haemoglobin, and platelet count; (2) liver function tests: total
39 bilirubin, direct bilirubin, albumin, alanine aminotransferase, aspartate
40 aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase; (3) renal
41 function tests: blood urea nitrogen and creatine; (4) lipid indicators: triglycerides and
42 total cholesterol; (5) inflammation indicators: C-reactive protein and lactic
43 dehydrogenase; (6) coagulation indicators: international normalized ratio,
44 prothrombin time, activated partial thromboplastin time, and fibrinogen; (7) tumour
45 markers: carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen
46 125, and alpha fetoprotein; and (8) other tests: blood type and hepatitis B test. The test
47 method and normal range of each indicator may vary across hospitals. Thus, we first
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4 uniform the units of each indicator according to the first enrolled hospital; then, based
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6 on the first enrolled hospital, we normalize each result of laboratory examination by
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8 its normal range across different hospitals.
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10 **Radiology reports**

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12 Radiological reports are collected with the date of examination. The following
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14 indicators will be collected: the type of examination (ultrasound, computed tomography,
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16 magnetic resonance imaging, and/or other types) and the conclusion of the examination
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18 (inflammation, polyp, tumour, gallstone, and/or others).
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20 **Patient and public involvement**

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23 Patients or the public involvement were not applied in the plans of this research.
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25 **ETHICS AND DISSEMINATION**

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28 The protocol of the CRGGC has been approved by the Committee for Ethics of
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30 Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (SHEC-C-2019-
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32 085) and registered in ClinicalTrials.gov (NCT04140552). All results of this study will
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34 be published in peer-reviewed journals and presented at relevant conferences.
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36 **DISCUSSION**

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39 The CRGGC study is a large multicentre registry cohort study to evaluate the
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41 clinical presentation, treatment, and prognosis of GBC patients in China. The focus of
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43 CRGGC is to 1) describe the status quo of treatment and survival of GBC patients in
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45 China and 2) improve the standardized treatment of GBC.
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48 Upon reviewing the published studies on GBC, we found a lack of large
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50 observational studies on GBC in China focusing on its clinical features and prognosis.
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52 Moreover, international studies on GBC were limited by small sample sizes and flawed
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54 coding systems for GBC. Our data will establish a collaborative platform for GBC
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56 research, providing valuable data from China.

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58 GBC is a relatively rare but lethal malignancy, making it important to address the
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4 standardization of its primary care, treatment, and post-treatment follow-up.
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6 Researchers have shown unsatisfactory adherence to clinical guidelines. Radical
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8 cholecystectomy was recommended for T1b GBC by the NCCN guidelines nearly 10
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10 years ago; however, only 50% of T1b GBC patients in the U.S. received radical
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12 cholecystectomy¹³. Bergquist et al.²³ reported that from 2004 to 2012, only 28.2% of
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14 GBC patients with positive nodal disease received adjuvant chemotherapy in the
15
16 National Cancer Database of the U.S. even though this was the recommended
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18 treatment in the NCCN guidelines. Knowing the current situation is essential for
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20 future improvement; however, no data have been reported on GBC treatment in
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22 China. Well-designed observational studies in China will help to point out weak
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24 points in clinical practice and, at the same time, summarize valuable clinical
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26 experience in the treatment of GBC and pave the way for further standardized
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28 treatment.

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30 GBC cases in China account for nearly 1/4 of cases worldwide; thus, GBC poses
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32 a significant disease burden in China. However, few clinical studies of the diagnosis
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34 and treatment of GBC have been performed in China, making this significant
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36 population underrepresented. By launching the CRGGC study, we also expect to
37
38 boost collaborations among Chinese researchers. We hope this collaboration could
39
40 induce further translational research and clinical trials in China, providing essential
41
42 evidence on GBC treatment.

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44 There are several limitations and potential biases in our study design. (1) The
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46 retrospective nature is inevitably related to information bias and heterogeneity in the
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48 data recording. This will cause difficulty in the standardization of data and a relatively
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50 large proportion of missing data. To overcome such bias, we composed and continue
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52 to update a codebook for standardization of each variable. Researchers responsible for
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54 data entry are trained and qualified at the data centre. The missing data are analysed to
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56 determine potential bias. (2) This is a retrospective study using convenience sampling.
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58 Thus, the cohort may not be completely representative of GBC patients in China.
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4 However, we attempt to include centres in every province in China. Moreover, most
5 cancer patients in China are treated in tertiary hospitals. (3) Biospecimens of the
6 involved patients are not collected. Future collaboration on this issue will be
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8 considered.
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Authors' Contributions

LYB is the principal investigator steering the CRGGC and collaboration with other

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4 centres. Tai Ren, Yongsheng Li, Xi Zhang wrote and revised the manuscript. Tai Ren,
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6 Yongsheng Li, Yajun Geng, Ziyu Shao, Maolan Li, Xiangsong Wu, Xu-An Wang,
7
8 Wenguang Wu, Yijun Shu, Runfa Bao, Wei Gong, and Ping Dong discussed and
9
10 drafted the CRF, standard operation procedure in data collection and management,
11
12 and standard of quality control. Tai Ren and Yongsheng Li are responsible for study
13
14 management and coordination. All authors are responsible for data collection and
15
16 quality control in their hospitals. All authors reviewed the manuscript for intellectual
17
18 content and approved the final version of the report.

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37
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41 42 **Competing interests statement**

43
44 All authors declare no competing interests.

45 46 **Word Count:**

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49 3209 (from abstract to discussion)
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4 **Figure legends**
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6 Fig. 1 Workflow of data collection and quality control in CRGGC.
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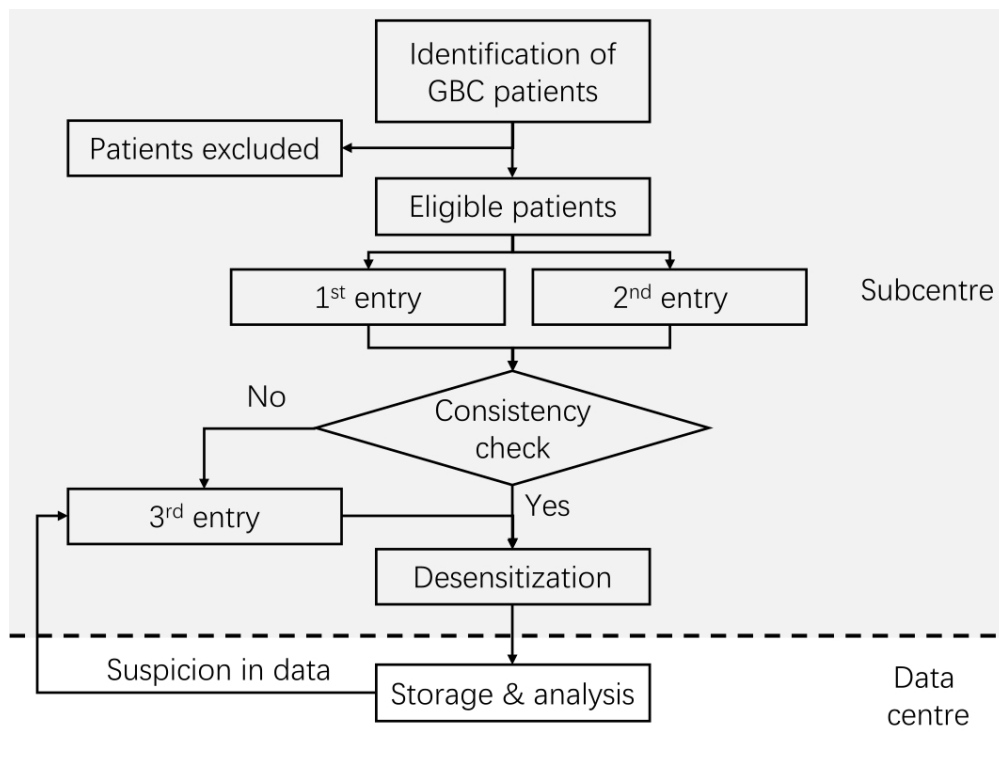


Fig. 1 Workflow of data collection and quality control in CRGGC.

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Protocol for a national gallbladder cancer registry study in China: the Chinese Research Group of Gallbladder Cancer (CRGGC) study

Tai Ren; Yongsheng Li, Xi Zhang, ... , Ying-Bin Liu, MD, FACS, on behalf of the CRGGC

ONLINE SUPPLEMENTARY FILE 1

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STROBE checklist of cohort studies

	Item No	Recommendation	Page Number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	6
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <ul style="list-style-type: none"> • Setting: hospitals in different regions in China • Locations: eTable 1; • Period of recruitment: from 1st January 2009, to 31st August 2018 • Follow-up: the last follow-up date was 10th Oct 2019 • Data collection: from September 2018 to June 2019 	10-11
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-15
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	10-15
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA

Statistical methods	12	(a) Describe all statistical methods , including those used to control for confounding	NA
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA
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	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
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	NA
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
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	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	NA

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		analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
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	18

For peer review only

BMJ Open

Protocol for a gallbladder cancer registry study in China: the Chinese Research Group of Gallbladder Cancer (CRGGC) study

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4 **Protocol for a gallbladder cancer registry study in China: the Chinese Research**
5 **Group of Gallbladder Cancer (CRGGC) study**
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40 **Keywords:** gallbladder cancer, cohort study, China, clinical epidemiology, tumour
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1 **Abstract**

2 **Introduction**

3 Gallbladder cancer (GBC), the sixth most common gastrointestinal tract cancer and
4 poses a significant disease burden in China. However, no national representative data
5 are available on the clinical characteristics, treatment, and prognosis of GBC in the
6 Chinese population.

7 **Methods and analysis**

8 The Chinese Research Group of Gallbladder Cancer (CRGGC) study is a multicentre
9 retrospective registry cohort study. Clinically diagnosed GBC patients are identified
10 from January 1, 2008, to December 31, 2019, by reviewing the electronic medical
11 records (EMRs) from 76 tertiary and secondary hospitals across 28 provinces in
12 China. Patients with pathological and radiological diagnoses of malignancy, including
13 cancer in situ, from the gallbladder and cystic duct are eligible, according to the
14 National Comprehensive Cancer Network (NCCN) 2019 guidelines. Patients are
15 excluded if GBC is the secondary diagnosis in the discharge summary. The
16 demographic characteristics, medical history, physical examination results, surgery
17 information, pathological data, laboratory examination results, and radiology reports
18 are collected in a standardized case report form. By May 2021, approximately 6,000
19 GBC patients will be included. The clinical follow-up data will be updated until 5
20 years after the last admission for GBC of each patient.

21 The study aimed (1) to depict the clinical characteristics, including demographics,
22 pathology, treatment, and prognosis of GBC patients in China; (2) to evaluate the
23 adherence to clinical guidelines of GBC; and (3) to improve clinical practice for
24 diagnosing and treating GBC and provide references for policy makers.

25 **Ethics and dissemination**

26 The protocol of the CRGGC has been approved by the Committee for Ethics of
27 Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (SHEC-C-2019-

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4 28 085) and registered in ClinicalTrials.gov (NCT04140552). All results of this study
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6 29 will be published in peer-reviewed journals and presented at relevant conferences.
7

8 30 **Study registration number:** NCT04140552
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10 31 **Strengths and limitations of this study**
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- 12
13 32 1. The Chinese Research Group of Gallbladder Cancer (CRGGC) study is the first
14
15 33 large-scale registry cohort study of gallbladder cancer (GBC) in China, covering
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17 34 76 tertiary and secondary hospitals across 28 provinces.
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19 35 2. A standardized quality control and data management plan was designed to ensure
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21 36 the accuracy and reliability of the data.
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23 37 3. The EMR systems are not consistent across hospitals, which may introduce
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25 38 variance in data recording and result in difficulty in systematic data formatting
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27 39 and integration.
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29 40 4. This is a retrospective study using convenience sampling. The study population
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31 41 may not be completely representative of GBC patients in China.
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33 42 5. There is a lack of biospecimens from involved patients.
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44 INTRODUCTION

45 Gallbladder cancer (GBC) is the most common type of biliary tract cancer¹⁻³ and
46 one of the most lethal malignancies, with a 5-year survival rate of 5-15%^{1 4 5}. Much
47 effort has been made to optimize the treatment of GBC; however, the prognosis
48 remains dismal^{4 6}, and the quality of current evidence for GBC is still far from perfect.
49 Due to its relatively low incidence, clinical trials on GBC are difficult to conduct.
50 Most recommendations and guidelines for GBC from the National Comprehensive
51 Cancer Network (NCCN; 2019 version 4) and American Joint Committee on Cancer
52 (AJCC; 8th version) were derived from evidence of moderate quality^{7 8}. Most of these
53 studies were single-centre studies with limited sample sizes and generally no more
54 than 300 cases⁹⁻¹¹, which might introduce systematic bias into the conclusion.

55 On the other hand, common-used coding systems addressed little on GBC. The
56 nomenclature of GBC in the literature is inconsistent. GBC defined by the AJCC 8th
57 staging manual is a primary cancer in the gallbladder and cystic duct (C23.9 and part
58 of C24.0; ICD-O-3 codes)⁸. However, many epidemiological studies refer to “GBC”
59 as “GBC and extrahepatic cholangiocarcinoma (ECC; C23.9 and C24.0)”, leading to
60 confusion in its incidence, mortality, and other epidemiological features^{12 13}. In
61 addition, cystic duct cancer is undistinguishable from ECC in most cancer registry
62 studies, which means that this specific subset of patients is likely to be omitted¹⁴.
63 Moreover, a commonly used coding system for surgery, the Facility Oncology
64 Registry Data System, classifies GBC as “all other sites”, making it unlikely to define
65 the extent of surgery and distinguish patients who undergo re-resection after GBC is
66 incidentally found¹⁵. Regarding regional lymph nodes, the Collaborative Stage
67 (version 0204) system defines celiac, superior mesenteric, and para-aortic lymph
68 nodes as regional nodes, which is not consistent with either the AJCC 7th or AJCC 8th
69 definition¹⁶. The coding problems in both patient identification and site-specific
70 variables might lead to less stringent interpretation of the conclusions.

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4 71 China is a high-GBC risk country, but little evidence has been based on the
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6 72 Chinese population¹². Data from GLOBOCAN show that, taking GBC and ECC
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8 73 together, the number of annual new cases in China accounts for 24.7% of new cases
9
10 74 worldwide¹³. Currently, the largest retrospective study of GBC in China was
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12 75 conducted by Zou *et al.*¹⁷, including 3,922 patients from 116 hospitals in 28 provinces
13
14 76 of China during 1986-1998. This study described the demographic characteristics of
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16 77 GBC in China, without further data on detailed staging, treatment, and prognosis
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18 78 information. Another study of 2,379 GBC patients from 5 northwestern provinces
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20 79 during 2009-2013¹⁸ reported that 55.1% of GBC patients had advanced-stage
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22 80 tumours. Other reports were mainly single-centre studies with limited sample sizes¹⁹
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24 81 ²⁰. The critical characteristics in the diagnosis, treatment, and prognosis of GBC in
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26 82 China are unknown.

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29 83 Therefore, this study aimed to design a GBC cohort, the Chinese Research Group
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31 84 of Gallbladder Cancer (CRGGC) study, (1) to comprehensively evaluate the clinical
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33 85 characteristics, including demographics, pathology, treatment, and prognosis of GBC
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35 86 patients in China; (2) to evaluate adherence to clinical guidelines of GBC; and (3) to
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37 87 improve clinical practice and guidelines for GBC and provide references for policy
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39 88 makers.

40 41 89 **METHODS AND ANALYSIS**

42 43 44 90 **Registry design**

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46 91 The CRGGC study is a multicentre retrospective registry cohort study. The
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48 92 project was launched by the Shanghai Key Laboratory of Biliary Tract Disease
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50 93 Research, with collaborators from 76 tertiary and secondary hospitals across 28
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52 94 provinces in China (until March 8, 2020; see online supplementary file 1). We review
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54 95 the electronic medical records (EMRs) of all diagnosed GBC patients from January 1,
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56 96 2008, to December 31, 2019, and extract the related clinical and treatment
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58 97 information. The clinical follow-up data will be updated until 5 years after the last
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4 98 admission for GBC of each patient.
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6 99 **Patient enrolment** 7

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9 100 Patients are identified with various search strategies: (1) ICD-10 code equals
10 101 C23.9, or C24.0 with “cystic duct”; (2) discharge diagnosis includes “gallbladder
11 102 cancer” (search strategy in Chinese: (“胆囊”) AND (“癌” OR “恶性肿瘤” OR “占
12 103 位”), which means “gallbladder”/“cystic duct” AND (“cancer” OR “malignancy” OR
13 104 “space-occupying lesion”)); and (3) pathological reports include “gallbladder cancer”.
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19 105 All 3 search strategies are applied in each centre. The results are merged for
20 106 subsequent exclusion. These search strategies were designed to be redundant because
21 107 some search strategies may not be applicable in specific EMR systems and in specific
22 108 periods.
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28 109 All identified admissions to the hospital are manually filtered according to the
29 110 diagnostic criteria of the NCCN 2019 version 4 guidelines for hepatobiliary cancer⁷.
30 111 Patients with a pathological or radiological diagnosis of malignancy, including cancer
31 112 in situ, from the gallbladder and cystic duct are eligible. Patients are excluded if GBC
32 113 is the secondary diagnosis in the discharge summary because patients admitted for
33 114 other diseases are likely to have obscure cancer traits.
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41 115 The study includes patients diagnosed before December, 31, 2019. According to
42 116 our preliminary estimation, more than 6,000 cases will meet our inclusion criteria. We
43 117 expect to finish data collection by May 2021. After finishing enrolment of a short-
44 118 term target of 2,000 cases, a primary analysis will be performed. The follow-up will
45 119 be updated until 5 years after the admission of each patient. More centres are expected
46 120 to participate in the CRGGC study; thus, the collaborator list may be expanded.
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54 121 **Clinical outcomes and follow-up** 55

56 122 The main outcome is the 5-year overall survival (OS) rate. OS is defined as the
57 123 duration between the date of first diagnosis and the date of death or date of last
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4 124 follow-up, where event other than death was defined as censor. We will also include
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6 125 the following outcomes: progression-free survival (PFS), defined as the duration
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8 126 between the date of first diagnosis and the date of recurrence; cancer-specific survival
9
10 127 (CSS), defined as the duration between the date of first diagnosis and the date of
11
12 128 cancer-caused death or date of last follow-up, where other events was defined as
13
14 129 censor; 3-year OS rate; and 90-day mortality (for patients who undergo surgery),
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16 130 which will be used to indicate perioperative mortality. Clinical follow-up is defined as
17
18 131 the routine practice of hospitals of collecting patient data on treatment, tumour
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20 132 recurrence and patient survival, either by outpatient/inpatient records or telephone.
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22 133 We require hospitals to equip such a system and at least one follow-up per year to join
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24 134 our collaboration. Based on these data, we update patients' follow-up statuses every
25
26 135 12 months. The data being collected from clinical follow-up include date of
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28 136 recurrence, date of death, date of last contact, whether re-resection was performed if
29
30 137 the malignancy was found incidentally, and whether the patient received adjuvant
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32 138 therapy.

33 34 35 139 **Data collection**

36
37 140 The workflow of data collection and quality control is shown in Fig. 1. Before
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39 141 data collection, a group of hepatobiliary specialists designed a structured case report
40
41 142 form, aiming to delineate features of GBC patients and answer corresponding clinical
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43 143 questions. The case report form includes the following information: demographic
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45 144 characteristics, medical history, physical examination results, surgery information,
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47 145 pathological data, laboratory examination results, and radiology reports. We compiled
48
49 146 a codebook to standardize the definition of each variable. The data centre is
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51 147 responsible for training doctors to collect data. Data collection is carried out by using
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53 148 EpiData (v4.6.0.2, EpiData Association, Denmark).

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56 149 Automated logic checks are applied to prevent out-of-range values. Duplicated
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58 150 entry is required. If any discrepancies are found, a third specialist will be brought in
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4 151 for discussion and make a final decision.

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6 152 After data entry and quality control in each centre, the data are anonymized and
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8 153 transferred to the servers in the data centre. The data centre is located at Shanghai Key
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10 154 Laboratory of Biliary Tract Disease Research, which is equipped with data servers
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12 155 and essential firewall and backup systems. The data centre is responsible for quality
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14 156 assessment, storage, sharing, and analysis of the data. A group of researchers in the
15
16 157 data centre manage the database.

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19 158 The data manager assesses the quality of the data after transfer to the data centre.
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21 159 The assessment is based on the structure of missing data and a comparison to baseline
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23 160 data. First, we apply a grading system, where variables are classified into essential,
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25 161 important, and normal importance. Based on the proportion of missing values in each
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27 162 category, the entries are graded as level A, B, C, or D in quality. Entries of category D
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29 163 quality are normally excluded from analysis. Second, outliers and inconsistent data
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31 164 are identified. Third, we compare baseline characteristics of the new data to previous
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33 165 data, with indicators including sex ratio, mean age, proportion of TNM stage, and 5-
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35 166 year OS. We apply the chi-square test, t-test, and log-rank test between the two
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37 167 datasets. When a significant difference is found, the data manager analyses and
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39 168 records suspicious data. The data manager inquires about the data in question with the
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41 169 data source and asks for confirmation. The desensitized data are accessible to
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43 170 collaborators after the completion of the database. A research proposal to the CRGGC
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45 171 Scientific Committee is essential for analysis of the data.

46 47 48 172 **Demographic data and medical history**

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50 173 The EMR data for each patient are collected for every hospital visit from January
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52 174 1, 2008. The baseline data are retrieved, including the following aspects: (1)
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54 175 demographics: age at diagnosis, sex, race, and date of diagnosis; (2) medical history:
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56 176 emergency operation, chief complaint, endoscopic retrograde cannulation of the
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58 177 pancreas (ERCP) performed within 30 days before surgery, percutaneous transhepatic
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4 178 cholangial drainage (PTCD) performed within 30 days before surgery, neoadjuvant
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6 179 therapy, and method of diagnosis (pathology, radiology, or other); (3) past medical
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8 180 history: history of gallstone, history of gallbladder polyps, history of other
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10 181 malignancies, hypertension, diabetes mellitus, and other comorbidities; (4) social and
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12 182 personal history: marital status, smoking history, and use of alcohol; and (5) other
13
14 183 aspects: weight, height, family history, and total expenditure.

16 184 **Surgery information**

- 19 185 1. The preoperative and intraoperative diagnoses are recorded. A diagnosis of
20
21 186 “gallbladder cancer”, “gallbladder tumour”, or “space-occupying lesion in
22
23 187 gallbladder” is regarded as the detection of malignancy.
- 25 188 2. Regional lymphadenectomy requires the resection of hilar nodes⁸. Further
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27 189 clearance of lymph nodes is classified as extended lymphadenectomy.
- 30 190 3. The extent of lymphadenectomy includes the cystic duct, common bile duct,
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32 191 portal vein, hepatic artery, common hepatic artery, post-superior pancreatic,
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34 192 celiac, superior mesenteric, suprapyloric, left gastric artery, and paraaortic lymph
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36 193 nodes^{8 21 22}.
- 38 194 4. Combined hepatectomy is classified as no hepatectomy, liver wedge
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40 195 resection/partial hepatectomy, IVb+V segmentectomy, hemihepatectomy, extent
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42 196 more than hemihepatectomy, radiofrequency ablation, and hepatectomy for other
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44 197 reasons.
- 46 198 5. If the malignancy is diagnosed after surgery, further treatment information may
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48 199 not be available (the patient may turn to a second hospital for re-resection).
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50 200 Patients in this case are categorized as “simple cholecystectomy performed;
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52 201 further treatment not available”. If re-resection is available, its operative reports
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54 202 will be reviewed as previously mentioned.
- 56 203 6. ERCP, PTCD, and transarterial chemoembolization (TACE) are not defined as

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4 204 surgery but as supportive treatment.

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6 205 7. Palliative surgery is defined as resection of the primary tumour, reconstruction of
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8 206 the digestive tract, or both when there is evidence of distant metastasis or
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10 207 unresectable tumour.

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13 208 Other surgery-related variables include date of surgery, laparoscopic surgery,
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15 209 combined bile duct resection, tumour positioned on the hepatic or peritoneal side,
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17 210 perivascular invasion, perforation, porcelain gallbladder, duration of surgery,
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19 211 intraoperative blood loss, and American Society of Anesthesiologists (ASA) score.

20 21 22 **Pathological data**

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24 213 Pathological data are recorded, including size of the tumour (in 3 dimensions),
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26 214 resection margin, tumour positioned on the hepatic or peritoneal side, tumour
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28 215 positioned on the fundus, body, neck, or cystic duct, depth of invasion (carcinoma in
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30 216 situ or lamina propria, muscularis, perimuscular connective tissue, full layer, serosa,
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32 217 adjacent organ, or major vascular invasion⁸), liver invasion, number of nodes
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34 218 examined, positive lymph nodes, number of hilar nodes examined, positive hilar
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36 219 lymph nodes, region of positive nodes, region of nodes examined (with codes the
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38 220 same as those used for the region of lymphadenectomy in surgery), grade, histology
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40 221 type (using ICD-O-3 codes²³), microvascular invasion, and perineural invasion.
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42 222 Tumours will be staged according to the AJCC 8th staging manual according to
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44 223 pathological reports derived from the aforementioned variables. Notably, the
45
46 224 description of “invasion of full layer” for depth of invasion is not suggested in the
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48 225 AJCC 8th manual but is commonly used in China.

49 50 51 **Laboratory examination**

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53 227 Laboratory examination results for patients are collected with the date of
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55 228 examination. Indicators of interest include the following: (1) routine blood tests: white
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57 229 blood cell count, haemoglobin, and platelet count; (2) liver function tests: total

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4 230 bilirubin, direct bilirubin, albumin, alanine aminotransferase, aspartate
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6 231 aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase; (3) renal
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8 232 function tests: blood urea nitrogen and creatine; (4) lipid indicators: triglycerides and
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10 233 total cholesterol; (5) inflammation indicators: C-reactive protein and lactic
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12 234 dehydrogenase; (6) coagulation indicators: international normalized ratio,
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14 235 prothrombin time, activated partial thromboplastin time, and fibrinogen; (7) tumour
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16 236 markers: carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen
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18 237 125, and alpha fetoprotein; and (8) other tests: blood type and hepatitis B test. The test
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20 238 method and normal range of each indicator may vary across hospitals. Thus, we first
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22 239 uniform the units of each indicator according to the first enrolled hospital; then, based
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24 240 on the first enrolled hospital, we normalize each result of laboratory examination by
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26 241 its normal range across different hospitals.

242 **Radiology reports**

243 Radiological reports are collected with the date of examination. The following
244 indicators will be collected: the type of examination (ultrasound, computed tomography,
245 magnetic resonance imaging, and/or other types) and the conclusion of the examination
246 (inflammation, polyp, tumour, gallstone, and/or others).

247 **Statistical analysis**

248 The continuous variables will be described visually by histogram and summarized
249 as mean±standard deviation or median (interquartile range), for normal- and skewed-
250 distributed values. The discrete variables will be summarized as frequency (percentage).
251 The proportion of missing data will be described, and an indicator of missing will be
252 deployed for analysis. Differences with a two-sided $P<0.05$ were considered as
253 statistically significant.

254 We will calculate the average number of GBC diagnosed per year in each hospital,
255 because the volume for cancer patients showed impact on patients' characteristics,

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4 256 treatment modalities, and prognosis²⁴. The distribution of hospitals' average GBC
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6 257 patients per year will be described in bar plot; 1 to 2 cut-off points will be determined
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8 258 by inspecting the pattern to classify hospitals into low- and high-volume. Correlation
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10 259 between hospital volume and patients' characteristics will be shown by either Pearson's
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12 260 R, Spearman's ρ , or χ^2 , whichever appropriate. Potential correlated variables includes
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14 261 (but not limited to) sex, age at diagnosis, TNM stage, gallstone, surgery type, and
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16 262 adjuvant therapy.

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19 263 Time trends for age, sex, TNM stage, surgery type, adjuvant therapy, and diagnosis
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21 264 time will be shown by scatter plot fitted by linear or locally estimated scatterplot
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23 265 smoothing, whichever appropriate.

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26 266 The median survival time and loss to follow-up rate will be described. The Kaplan-
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28 267 Meier method will be applied to assess the survival of patients, stratified by TNM stage
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30 268 and by whether surgery performed. Cox proportional hazards regression will be applied
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32 269 to evaluate predictors of prognosis, including (but not limited to) age, sex, T stage, N
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34 270 stage, M stage, adjuvant therapy, extent of resection, gallstone, resection margin,
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36 271 histological grade, perineural invasion, and microvascular invasion.

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39 272 As proposed in both NCCN and Chinese Medical Association guidelines^{7 25}, GBC
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41 273 more advance than T1b requires resection of liver bed and regional lymphadenectomy.
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43 274 Moreover, patients with nodal metastasis are recommended to take chemotherapy.
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45 275 These three indicators will be described to evaluate the adherence to clinical guidelines
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47 276 of GBC. Also, their significance in prognosis will be tested by survival analysis.

48 49 277 **Patient and public involvement**

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51 278 Patients or the public involvement were not applied in the plans of this research.

52 53 279 **ETHICS AND DISSEMINATION**

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56 280 The protocol of the CRGGC has been approved by the Committee for Ethics of
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58 281 Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (SHEC-C-2019-
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4 282 085) and registered in ClinicalTrials.gov (NCT04140552). All results of this study will
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6 283 be published in peer-reviewed journals and presented at relevant conferences.
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8 284 **DISCUSSION**

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10 285 The CRGGC study is a large multicentre registry cohort study to evaluate the
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12 286 clinical presentation, treatment, and prognosis of GBC patients in China. The focus of
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14 287 CRGGC is to 1) describe the status quo of treatment and survival of GBC patients in
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16 288 China and 2) improve the standardized treatment of GBC.
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19 289 Upon reviewing the published studies on GBC, we found a lack of large
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21 290 observational studies on GBC in China focusing on its clinical features and prognosis.
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23 291 Moreover, international studies on GBC were limited by small sample sizes and flawed
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25 292 coding systems for GBC. Our data will establish a collaborative platform for GBC
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27 293 research, providing valuable data from China.
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30 294 GBC is a relatively rare but lethal malignancy, making it important to address the
31
32 295 standardization of its primary care, treatment, and post-treatment follow-up.
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34 296 Researchers have shown unsatisfactory adherence to clinical guidelines. Radical
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36 297 cholecystectomy was recommended for T1b GBC by the NCCN guidelines nearly 10
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38 298 years ago; however, only 50% of T1b GBC patients in the U.S. received radical
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40 299 cholecystectomy¹⁴. Bergquist et al.²⁶ reported that from 2004 to 2012, only 28.2% of
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42 300 GBC patients with positive nodal disease received adjuvant chemotherapy in the
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44 301 National Cancer Database of the U.S. even though this was the recommended
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46 302 treatment in the NCCN guidelines. Knowing the current situation is essential for
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48 303 future improvement; however, no data have been reported on GBC treatment in
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50 304 China. Well-designed observational studies in China will help to point out weak
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52 305 points in clinical practice and, at the same time, summarize valuable clinical
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54 306 experience in the treatment of GBC and pave the way for further standardized
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56 307 treatment.
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4 308 GBC cases in China account for nearly 1/4 of cases worldwide; thus, GBC poses
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6 309 a significant disease burden in China. However, few clinical studies of the diagnosis
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8 310 and treatment of GBC have been performed in China, making this significant
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10 311 population underrepresented. By launching the CRGGC study, we also expect to
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12 312 boost collaborations among Chinese researchers. We hope this collaboration could
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14 313 induce further translational research and clinical trials in China, providing essential
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16 314 evidence on GBC treatment.

17
18 315 There are several limitations and potential biases in our study design. (1) The
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20 316 retrospective nature is inevitably related to information bias and heterogeneity in the
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22 317 data recording. This will cause difficulty in the standardization of data and a relatively
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24 318 large proportion of missing data. To overcome such bias, we composed and continue
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26 319 to update a codebook for standardization of each variable. Researchers responsible for
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28 320 data entry are trained and qualified at the data centre. The missing data are analysed to
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30 321 determine potential bias. (2) This is a retrospective study using convenience sampling.
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32 322 Thus, the cohort may not be completely representative of GBC patients in China.
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34 323 However, we attempt to include centres in every province in China. Moreover, most
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36 324 cancer patients in China are treated in tertiary hospitals. (3) Biospecimens of the
37
38 325 involved patients are not collected. Future collaboration on this issue will be
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40 326 considered. (4) As patients with incidental GBC may turn to other hospitals for re-
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42 327 resection, resulting in incomplete treatment information. We addressed this problem
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44 328 by defining these patients separately to aid further sensitivity analysis.

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356 **Authors' Contributions**

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4 357 LYB is the principal investigator steering the CRGGC and collaboration with other
5
6 358 centres. Tai Ren, Yongsheng Li, Xi Zhang wrote and revised the manuscript. Tai Ren,
7
8 359 Yongsheng Li, Yajun Geng, Ziyu Shao, Maolan Li, Xiangsong Wu, Xu-An Wang,
9
10 360 Wenguang Wu, Yijun Shu, Runfa Bao, Wei Gong, and Ping Dong discussed and
11
12 361 drafted the CRF, standard operation procedure in data collection and management,
13
14 362 and standard of quality control. Tai Ren and Yongsheng Li are responsible for study
15
16 363 management and coordination. All authors are responsible for data collection and
17
18 364 quality control in their hospitals. All authors reviewed the manuscript for intellectual
19
20 365 content and approved the final version of the report.

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44 45 46 377 **Competing interests statement**

47
48 378 All authors declare no competing interests.

49 50 51 379 **Word Count:**

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53 380 3514 (from abstract to discussion)

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4 457 **Figure legends**

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6 458 Fig. 1 Workflow of data collection and quality control in CRGGC.
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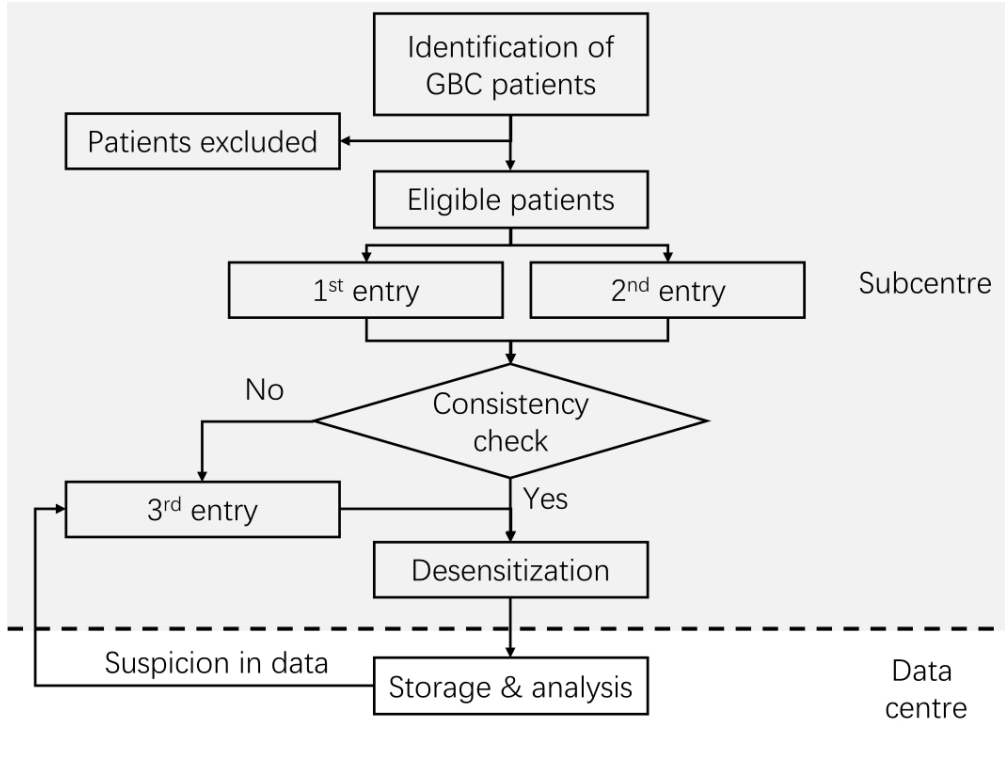


Fig. 1 Workflow of data collection and quality control in CRGGC.

Protocol for a national gallbladder cancer registry study in China: the Chinese Research Group of Gallbladder Cancer (CRGGC) study

Tai Ren; Yongsheng Li, Xi Zhang, ... , Ying-Bin Liu, MD, FACS, on behalf of the CRGGC

ONLINE SUPPLEMENTARY FILE 1

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STROBE checklist of cohort studies

	Item No	Recommendation	Page Number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	6
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-11
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-15
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	10-15
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-16
Statistical methods	12	(a) Describe all statistical methods , including those used to control for confounding	15-16
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	15
		(d) If applicable, explain how loss to follow-up was addressed	10-11; 16

(e) Describe any **sensitivity analyses** NA
 - Current analysis focused mainly on descriptive statistics. When specific questions are addressed in future analysis, sensitivity analyses will be designed.

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	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
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	NA
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
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	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA

Other information

Funding	22	Give the source of funding and the role of the funders	18
		for the present study and, if applicable, for the original	
		study on which the present article is based	

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BMJ Open

Protocol for a gallbladder cancer registry study in China: the Chinese Research Group of Gallbladder Cancer (CRGGC) study

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Oncology, Epidemiology, Surgery
Keywords:	ONCOLOGY, Hepatobiliary disease < GASTROENTEROLOGY, SURGERY

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1 **Abstract**

2 **Introduction**

3 Gallbladder cancer (GBC), the sixth most common gastrointestinal tract cancer and
4 poses a significant disease burden in China. However, no national representative data
5 are available on the clinical characteristics, treatment, and prognosis of GBC in the
6 Chinese population.

7 **Methods and analysis**

8 The Chinese Research Group of Gallbladder Cancer (CRGGC) study is a multicentre
9 retrospective registry cohort study. Clinically diagnosed GBC patients will be
10 identified from January 1, 2008, to December , 2019, by reviewing the electronic
11 medical records (EMRs) from 76 tertiary and secondary hospitals across 28 provinces
12 in China. Patients with pathological and radiological diagnoses of malignancy,
13 including cancer in situ, from the gallbladder and cystic duct are eligible, according to
14 the National Comprehensive Cancer Network (NCCN) 2019 guidelines. Patients will
15 be excluded if GBC is the secondary diagnosis in the discharge summary. The
16 demographic characteristics, medical history, physical examination results, surgery
17 information, pathological data, laboratory examination results, and radiology reports
18 will be collected in a standardized case report form. By May 2021, approximately
19 6,000 GBC patients will be included. The clinical follow-up data will be updated until
20 5 years after the last admission for GBC of each patient.

21 The study aimed (1) to depict the clinical characteristics, including demographics,
22 pathology, treatment, and prognosis of GBC patients in China; (2) to evaluate the
23 adherence to clinical guidelines of GBC; and (3) to improve clinical practice for
24 diagnosing and treating GBC and provide references for policy makers.

25 **Ethics and dissemination**

26 The protocol of the CRGGC has been approved by the Committee for Ethics of
27 Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (SHEC-C-2019-

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4 28 085) and registered in ClinicalTrials.gov (NCT04140552). All results of this study
5
6 29 will be published in peer-reviewed journals and presented at relevant conferences.
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8 30 **Study registration number:** NCT04140552
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10 31 **Strengths and limitations of this study**
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- 12
13 32 1. The Chinese Research Group of Gallbladder Cancer (CRGGC) study is the first
14
15 33 large-scale registry cohort study of gallbladder cancer (GBC) in China, covering
16
17 34 76 tertiary and secondary hospitals across 28 provinces.
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19 35 2. A standardized quality control and data management plan was designed to ensure
20
21 36 the accuracy and reliability of the data.
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23 37 3. The EMR systems are not consistent across hospitals, which may introduce
24
25 38 variance in data recording and result in difficulty in systematic data formatting
26
27 39 and integration.
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29 40 4. This is a retrospective study using convenience sampling. The study population
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31 41 may not be completely representative of GBC patients in China.
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33 42 5. There is a lack of biospecimens from involved patients. The survival data are not
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35 43 validated through Chinese death registry.
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45 INTRODUCTION

46 Gallbladder cancer (GBC) is the most common type of biliary tract cancer¹⁻³ and
47 one of the most lethal malignancies, with a 5-year survival rate of 5-15%^{1 4 5}. Much
48 effort has been made to optimize the treatment of GBC; however, the prognosis
49 remains dismal^{4 6}, and the quality of current evidence for GBC is still far from perfect.
50 Due to its relatively low incidence, clinical trials on GBC are difficult to conduct.
51 Most recommendations and guidelines for GBC from the National Comprehensive
52 Cancer Network (NCCN; 2019 version 4) and American Joint Committee on Cancer
53 (AJCC; 8th version) were derived from evidence of moderate quality^{7 8}. Most of these
54 studies were single-centre studies with limited sample sizes and generally no more
55 than 300 cases⁹⁻¹¹, which might introduce systematic bias into the conclusion.

56 On the other hand, common-used coding systems addressed little on GBC. The
57 nomenclature of GBC in the literature is inconsistent. GBC defined by the AJCC 8th
58 staging manual is a primary cancer in the gallbladder and cystic duct (C23.9 and part
59 of C24.0; ICD-O-3 codes)⁸. However, many epidemiological studies refer to “GBC”
60 as “GBC and extrahepatic cholangiocarcinoma (ECC; C23.9 and C24.0)”, leading to
61 confusion in its incidence, mortality, and other epidemiological features^{12 13}. In
62 addition, cystic duct cancer is undistinguishable from ECC in most cancer registry
63 studies, which means that this specific subset of patients is likely to be omitted¹⁴.
64 Moreover, a commonly used coding system for surgery, the Facility Oncology
65 Registry Data System, classifies GBC as “all other sites”, making it unlikely to define
66 the extent of surgery and distinguish patients who undergo re-resection after GBC is
67 incidentally found¹⁵. Regarding regional lymph nodes, the Collaborative Stage
68 (version 0204) system defines celiac, superior mesenteric, and para-aortic lymph
69 nodes as regional nodes, which is not consistent with either the AJCC 7th or AJCC 8th
70 definition¹⁶. The coding problems in both patient identification and site-specific
71 variables might lead to less stringent interpretation of the conclusions.

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4 72 China is a high-GBC risk country, but little evidence has been based on the
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6 73 Chinese population¹². Data from GLOBOCAN show that, taking GBC and ECC
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8 74 together, the number of annual new cases in China accounts for 24.7% of new cases
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10 75 worldwide¹³. Currently, the largest retrospective study of GBC in China was
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12 76 conducted by Zou *et al.*¹⁷, including 3,922 patients from 116 hospitals in 28 provinces
13
14 77 of China during 1986-1998. This study described the demographic characteristics of
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16 78 GBC in China, without further data on detailed staging, treatment, and prognosis
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18 79 information. Another study of 2,379 GBC patients from 5 northwestern provinces
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20 80 during 2009-2013¹⁸ reported that 55.1% of GBC patients had advanced-stage
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22 81 tumours. Other reports were mainly single-centre studies with limited sample sizes¹⁹
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24 82 ²⁰. The critical characteristics in the diagnosis, treatment, and prognosis of GBC in
25
26 83 China are unknown.

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29 84 Therefore, this study aimed to design a GBC cohort, the Chinese Research Group
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31 85 of Gallbladder Cancer (CRGGC) study, (1) to comprehensively evaluate the clinical
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33 86 characteristics, including demographics, pathology, treatment, and prognosis of GBC
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35 87 patients in China; (2) to evaluate adherence to clinical guidelines of GBC; and (3) to
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37 88 improve clinical practice and guidelines for GBC and provide references for policy
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39 89 makers.

40 41 90 **METHODS AND ANALYSIS**

42 43 44 91 **Registry design**

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46 92 The CRGGC study is a multicentre retrospective registry cohort study. The
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48 93 project was launched by the Shanghai Key Laboratory of Biliary Tract Disease
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50 94 Research, with collaborators from 76 tertiary and secondary hospitals across 28
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52 95 provinces in China (until March 8, 2020; see online supplementary file 1). We will
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54 96 review the electronic medical records (EMRs) of all diagnosed GBC patients from
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56 97 January 1, 2008, to December, 2019, and extract the related clinical and treatment
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58 98 information. The clinical follow-up data will be updated until 5 years after the last
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4 99 admission of each GBC patient.
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6 100 **Patient enrolment**

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9 101 Patients will be identified with various search strategies: (1) ICD-10 code equals
10 102 C23.9, or C24.0 with “cystic duct”; (2) discharge diagnosis includes “gallbladder
11 103 cancer” (search strategy in Chinese: (“胆囊”) AND (“癌” OR “恶性肿瘤” OR “占
12 104 位”), which means “gallbladder”/“cystic duct” AND (“cancer” OR “malignancy” OR
13 105 “space-occupying lesion”)); and (3) pathological reports include “gallbladder cancer”.
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19 106 All 3 search strategies will be applied in each centre. The results will be merged for
20 107 subsequent exclusion. These search strategies are designed to be redundant because
21 108 some search strategies may not be applicable in specific EMR systems and in specific
22 109 periods.
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28 110 All identified admissions to the hospital will be manually filtered according to
29 111 the diagnostic criteria of the NCCN 2019 version 4 guidelines for hepatobiliary
30 112 cancer⁷. Patients with a pathological or radiological diagnosis of malignancy,
31 113 including cancer in situ, from the gallbladder and cystic duct are eligible. Patients will
32 114 be excluded if GBC is the secondary diagnosis in the discharge summary because
33 115 patients admitted for other diseases are likely to have obscure cancer traits.
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41 116 The study will include patients diagnosed before December, 2019. According to
42 117 our preliminary estimation, more than 6,000 cases will meet our inclusion criteria. We
43 118 expect to finish data collection by May 2021. After finishing enrolment of a short-
44 119 term target of 2,000 cases, a primary analysis will be performed. The follow-up will
45 120 be updated until 5 years after the admission of each patient. More centres are expected
46 121 to participate in the CRGGC study; thus, the collaborator list may be expanded.
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54 122 **Clinical outcomes and follow-up**

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56 123 The main outcome is the 5-year overall survival (OS). OS is defined as the
57 124 duration from the date of first diagnosis to the date of death, and it is censored at the
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4 125 date of the last follow-up when the patients are alive. We will also include the
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6 126 following outcomes: progression-free survival (PFS), defined as the duration between
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8 127 the date of first diagnosis and the date of recurrence, and censored at the date of the
9
10 128 last follow-up when the patients have no evidence of recurrence.; cancer-specific
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12 129 survival (CSS), defined as the duration between the date of first diagnosis and the date
13
14 130 of cancer-caused death, and censored at the date of the last follow-up when the
15
16 131 patients are alive or died from other causes; 3-year OS; and 90-day mortality (for
17
18 132 patients who undergo surgery), which will be used to indicate perioperative mortality.
19
20 133 Clinical follow-up is defined as the routine practice of hospitals of collecting patient
21
22 134 data on treatment, tumour recurrence and patient survival, either by
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24 135 outpatient/inpatient records or telephone. We require hospitals to equip such a system
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26 136 and at least one follow-up per year to join our collaboration. Based on these data, we
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28 137 will update patients' follow-up statuses every 12 months. The data being collected
29
30 138 from clinical follow-up will include date of recurrence, date of death, date of last
31
32 139 contact, whether re-resection is performed if the malignancy is found incidentally, and
33
34 140 whether the patient receives adjuvant therapy.

141 **Data collection**

142 The workflow of data collection and quality control is shown in Fig. 1. Before
143 data collection, a group of hepatobiliary specialists designed a structured case report
144 form, aiming to delineate features of GBC patients and answer corresponding clinical
145 questions. The case report form includes the following information: demographic
146 characteristics, medical history, physical examination results, surgery information,
147 pathological data, laboratory examination results, and radiology reports. We have
148 compiled a codebook to standardize the definition of each variable. The data centre
149 will be responsible for training doctors to collect data. Data collection will be carried
150 out by using EpiData (v4.6.0.2, EpiData Association, Denmark).

151 Automated logic checks will be applied to prevent out-of-range values.

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4 152 Duplicated entry will be required. If any discrepancies are found, a third specialist
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6 153 will be brought in for discussion and make a final decision.
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8 154 After data entry and quality control in each centre, the data will be anonymized
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10 155 and transferred to the servers in the data centre. The data centre is located at Shanghai
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12 156 Key Laboratory of Biliary Tract Disease Research, which is equipped with data
13
14 157 servers and essential firewall and backup systems. The data centre will be responsible
15
16 158 for quality assessment, storage, sharing, and analysis of the data. A group of
17
18 159 researchers in the data centre will manage the database.
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21 160 The data manager will assess the quality of the data after transfer to the data
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23 161 centre. The assessment is based on the structure of missing data and a comparison to
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25 162 baseline data. First, we will apply a grading system, where variables are classified into
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27 163 essential, important, and normal importance. Based on the proportion of missing
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29 164 values in each category, the entries will be graded as level A, B, C, or D in quality.
30
31 165 Entries of category D quality will be normally excluded from analysis. Second,
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33 166 outliers and inconsistent data will be identified. Third, we will compare baseline
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35 167 characteristics of the new data to previous data, with indicators including sex ratio,
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37 168 mean age, proportion of TNM stage, and 5-year OS. We will apply chi-square test, t-
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39 169 test, and log-rank test between the two datasets. When a significant difference is
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41 170 found, the data manager will analyse and record suspicious data. The data manager
42
43 171 will inquire about the data in question with the data source and ask for confirmation.
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45 172 The desensitized data will be accessible to collaborators after the completion of the
46
47 173 database. A research proposal to the CRGGC Scientific Committee will be essential
48
49 174 for analysis of the data.
50

51 175 **Demographic data and medical history**

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54 176 The EMR data for each patient will be collected for every hospital visit from
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56 177 January 1, 2008. The baseline data will be retrieved, including the following aspects:
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58 178 (1) demographics: age at diagnosis, sex, race, and date of diagnosis; (2) medical
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4 179 history: emergency operation, chief complaint, endoscopic retrograde cannulation of
5
6 180 the pancreas (ERCP) performed within 30 days before surgery, percutaneous
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8 181 transhepatic cholangial drainage (PTCD) performed within 30 days before surgery,
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10 182 neoadjuvant therapy, and method of diagnosis (pathology, radiology, or other); (3)
11
12 183 past medical history: history of gallstone, history of gallbladder polyps, history of
13
14 184 other malignancies, hypertension, diabetes mellitus, and other comorbidities; (4)
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16 185 social and personal history: marital status, smoking history, and use of alcohol; and
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18 186 (5) other aspects: weight, height, family history, and total expenditure.

187 **Surgery information**

- 188 1. The preoperative and intraoperative diagnoses will be recorded. A diagnosis of
189 “gallbladder cancer”, “gallbladder tumour”, or “space-occupying lesion in
190 gallbladder” is regarded as the detection of malignancy.
- 191 2. Regional lymphadenectomy requires the resection of hilar nodes⁸. Further
192 clearance of lymph nodes is classified as extended lymphadenectomy.
- 193 3. The extent of lymphadenectomy includes the cystic duct, common bile duct,
194 portal vein, hepatic artery, common hepatic artery, post-superior pancreatic,
195 celiac, superior mesenteric, suprapyloric, left gastric artery, and paraaortic lymph
196 nodes^{8 21 22}.
- 197 4. Combined hepatectomy is classified as no hepatectomy, liver wedge
198 resection/partial hepatectomy, IVb+V segmentectomy, hemihepatectomy, extent
199 more than hemihepatectomy, radiofrequency ablation, and hepatectomy for other
200 reasons.
- 201 5. If the malignancy is diagnosed after surgery, further treatment information may
202 not be available (the patient may turn to a second hospital for re-resection).
203 Patients in this case will be categorized as “simple cholecystectomy performed;
204 further treatment not available”. If re-resection is available, its operative reports

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4 205 will be reviewed as previously mentioned.
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6 206 6. ERCP, PTCD, and transarterial chemoembolization (TACE) are not defined as
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8 207 surgery but as supportive treatment.
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11 208 7. Palliative surgery is defined as resection of the primary tumour, reconstruction of
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13 209 the digestive tract, or both when there is evidence of distant metastasis or
14
15 210 unresectable tumour.
16

17 211 Other surgery-related variables include date of surgery, laparoscopic surgery,
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19 212 combined bile duct resection, tumour positioned on the hepatic or peritoneal side,
20
21 213 perivascular invasion, perforation, porcelain gallbladder, duration of surgery,
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23 214 intraoperative blood loss, and American Society of Anesthesiologists (ASA) score.
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26 215 **Pathological data**

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28 216 Pathological data will be recorded, including size of the tumour (in 3
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30 217 dimensions), resection margin, tumour positioned on the hepatic or peritoneal side,
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32 218 tumour positioned on the fundus, body, neck, or cystic duct, depth of invasion
33
34 219 (carcinoma in situ or lamina propria, muscularis, perimuscular connective tissue, full
35
36 220 layer, serosa, adjacent organ, or major vascular invasion⁸), liver invasion, number of
37
38 221 nodes examined, positive lymph nodes, number of hilar nodes examined, positive
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40 222 hilar lymph nodes, region of positive nodes, region of nodes examined (with codes the
41
42 223 same as those used for the region of lymphadenectomy in surgery), grade, histology
43
44 224 type (using ICD-O-3 codes²³), microvascular invasion, and perineural invasion.
45
46 225 Tumours will be staged according to the AJCC 8th staging manual according to
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48 226 pathological reports derived from the aforementioned variables. Notably, the
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50 227 description of “invasion of full layer” for depth of invasion is not suggested in the
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52 228 AJCC 8th manual but is commonly used in China.
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55 229 **Laboratory examination**

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58 230 Laboratory examination results for patients will be collected with the date of
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4 231 examination. Indicators of interest include the following: (1) routine blood tests: white
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6 232 blood cell count, haemoglobin, and platelet count; (2) liver function tests: total
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8 233 bilirubin, direct bilirubin, albumin, alanine aminotransferase, aspartate
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10 234 aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase; (3) renal
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12 235 function tests: blood urea nitrogen and creatine; (4) lipid indicators: triglycerides and
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14 236 total cholesterol; (5) inflammation indicators: C-reactive protein and lactic
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16 237 dehydrogenase; (6) coagulation indicators: international normalized ratio,
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18 238 prothrombin time, activated partial thromboplastin time, and fibrinogen; (7) tumour
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20 239 markers: carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen
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22 240 125, and alpha fetoprotein; and (8) other tests: blood type and hepatitis B test. The test
23
24 241 method and normal range of each indicator may vary across hospitals. Thus, we will
25
26 242 first uniform the units of each indicator according to the first enrolled hospital; then,
27
28 243 based on the first enrolled hospital, we will normalize each result of laboratory
29
30 244 examination by its normal range across different hospitals.

245 **Radiology reports**

246 Radiological reports will be collected with the date of examination. The following
247 indicators will be collected: the type of examination (ultrasound, computed tomography,
248 magnetic resonance imaging, and/or other types) and the conclusion of the examination
249 (inflammation, polyp, tumour, gallstone, and/or others).

250 **Statistical analysis**

251 The continuous variables will be described visually by histogram and summarized
252 as mean±standard deviation or median (interquartile range), for normal- and skewed-
253 distributed values. The discrete variables will be summarized as frequency (percentage).
254 The proportion of missing data will be described, and an indicator of missing will be
255 deployed for analysis. Differences with a two-sided $P<0.05$ are considered as
256 statistically significant.

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4 257 We will calculate the average number of GBC diagnosed per year in each hospital,
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6 258 because the volume for cancer patients showed impact on patients' characteristics,
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8 259 treatment modalities, and prognosis²⁴. The distribution of hospitals' average GBC
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10 260 patients per year will be described in bar plot; 1 to 2 cut-off points will be determined
11
12 261 by inspecting the pattern to classify hospitals into low- and high-volume. Correlation
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14 262 between hospital volume and patients' characteristics will be shown by either Pearson's
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16 263 R, Spearman's ρ , or χ^2 , whichever appropriate. Potential correlated variables includes
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18 264 (but not limited to) sex, age at diagnosis, TNM stage, gallstone, surgery type, and
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21 265 adjuvant therapy.

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23 266 Time trends for age, sex, TNM stage, surgery type, adjuvant therapy, and diagnosis
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25 267 time will be shown by scatter plot fitted by linear or locally estimated scatterplot
26
27 268 smoothing, whichever appropriate.

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30 269 The median survival time and loss to follow-up rate will be described. The Kaplan-
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32 270 Meier method will be applied to assess the survival of patients, stratified by TNM stage
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34 271 and by whether surgery performed. Cox proportional hazards regression will be applied
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36 272 to evaluate predictors of prognosis, including (but not limited to) age, sex, T stage, N
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38 273 stage, M stage, adjuvant therapy, extent of resection, gallstone, resection margin,
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40 274 histological grade, perineural invasion, and microvascular invasion.

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42 275 As proposed in both NCCN and Chinese Medical Association guidelines^{7 25}, GBC
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44 276 more advance than T1b requires resection of liver bed and regional lymphadenectomy.
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46 277 Moreover, patients with nodal metastasis are recommended to take chemotherapy.
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48 278 These three indicators will be described to evaluate the adherence to clinical guidelines
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50 279 of GBC. Also, their significance in prognosis will be tested by survival analysis.

51 52 53 280 **Patient and public involvement**

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56 281 Patients or the public involvement are not in the plans of this research.
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282 **ETHICS AND DISSEMINATION**

283 The protocol of the CRGGC has been approved by the Committee for Ethics of
284 Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (SHEC-C-2019-
285 085) and registered in ClinicalTrials.gov (NCT04140552). All results of this study will
286 be published in peer-reviewed journals and presented at relevant conferences.

287 **DISCUSSION**

288 The CRGGC study is a large multicentre registry cohort study to evaluate the
289 clinical presentation, treatment, and prognosis of GBC patients in China. The focus of
290 CRGGC is to 1) describe the status quo of treatment and survival of GBC patients in
291 China and 2) improve the standardized treatment of GBC.

292 Upon reviewing the published studies on GBC, we found a lack of large
293 observational studies on GBC in China focusing on its clinical features and prognosis.
294 Moreover, international studies on GBC were limited by small sample sizes and
295 inconsistent coding systems for GBC. Our data will establish a collaborative platform
296 for GBC research, providing valuable data from China.

297 GBC is a relatively rare but lethal malignancy, making it important to address the
298 standardization of its primary care, treatment, and post-treatment follow-up.
299 Researchers have shown unsatisfactory adherence to clinical guidelines. Radical
300 cholecystectomy was recommended for T1b GBC by the NCCN guidelines nearly 10
301 years ago; however, only 50% of T1b GBC patients in the U.S. received radical
302 cholecystectomy¹⁴. Bergquist et al.²⁶ reported that from 2004 to 2012, only 28.2% of
303 GBC patients with positive nodal disease received adjuvant chemotherapy in the
304 National Cancer Database of the U.S. even though this was the recommended
305 treatment in the NCCN guidelines. Knowing the current situation is essential for
306 future improvement; however, no data have been reported on GBC treatment in
307 China. Well-designed observational studies in China will help to point out weakness

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4 308 in clinical practice and, at the same time, summarize valuable clinical experience in
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6 309 the treatment of GBC and pave the way for further standardized treatment.
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8 310 GBC cases in China account for nearly 1/4 of cases worldwide; thus, GBC poses
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10 311 a significant disease burden in China. However, few clinical studies of the diagnosis
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12 312 and treatment of GBC have been performed in China, making this significant
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14 313 population underrepresented. By launching the CRGGC study, we also expect to
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16 314 boost collaborations among Chinese researchers. We hope this collaboration could
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18 315 induce further translational research and clinical trials in China, providing essential
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20 316 evidence on GBC treatment.
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22
23 317 There are several limitations and potential biases in our study design. (1) The
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25 318 retrospective nature is inevitably related to information bias and heterogeneity in the
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27 319 data recording. This will cause difficulty in the standardization of data and a relatively
28
29 320 large proportion of missing data. To overcome such bias, we composed and continue
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31 321 to update a codebook for standardization of each variable. Researchers responsible for
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33 322 data entry are trained and qualified at the data centre. The missing data are analysed to
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35 323 determine potential bias. (2) This is a retrospective study using convenience sampling.
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37 324 Thus, the cohort may not be completely representative of GBC patients in China.
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39 325 However, we attempt to include centres in every province in China. Moreover, most
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41 326 cancer patients in China are treated in tertiary hospitals. (3) Biospecimens of the
42
43 327 involved patients are not collected. Future collaboration on this issue will be
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45 328 considered. (4) As patients with incidental GBC may turn to other hospitals for re-
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47 329 resection, resulting in incomplete treatment information. We addressed this problem
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49 330 by defining these patients separately to aid further sensitivity analysis. (5) Currently
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51 331 we haven't made collaboration with Chinese death registry, thus part of the death
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53 332 information may be lost and the follow-up data might be biased due to lack of
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55 333 validation. On the one hand, the CRGGC study actively seek cooperation with
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57 334 relevant registries; on the other hand, we require collaborated hospitals to equip
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335 clinical follow-up system, compare prognosis data in each hospital to identify
336 systematic bias, and update follow-up data yearly.
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5

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57 364 **Authors' Contributions**
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4 365 Dr. Yingbin Liu is the principal investigator steering the CRGGC, and responsible for
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6 366 conceptualization, funding acquisition, and supervision of the study. Dr. Tai Ren, Dr.
7
8 367 Yongsheng Li, Dr. Xi Zhang, and Dr. Yingbin Liu wrote and revised the manuscript.
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14 370 Dr. Wei Gong, and Dr. Ping Dong discussed and drafted the case report form,
15
16 371 standard operation procedure in data collection and management, and standard of
17
18 372 quality control. Dr. Tai Ren and Dr. Yongsheng Li are responsible for data curation
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20 373 and coordination. Dr. Xi Zhang is responsible for the methodology. Dr. Tai Ren, Dr.
21
22 374 Yongsheng Li, and Dr. Xi Zhang will be responsible for data analysis and reporting of
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42 384 Mingzhang Li, Dr. Yudong Qiu, Dr. Buqiang Wu, Dr. Jinfang Zheng, Dr. Xiaoliang
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45
46 386 Zang, Dr. Xiaoming Ma, Dr. Jian Hong, Dr. Wei Gong, and Dr. Yingbin Liu are
47
48 387 responsible for resources, data collection, and quality control in collaborated
49
50 388 hospitals. All authors reviewed the manuscript for intellectual content and approved
51
52 389 the final version of the report.

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22 401 **Competing interests statement**

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25 402 All authors declare no competing interests.

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4 481 **Figure legends**

5
6 482 Fig. 1 Workflow of data collection and quality control in CRGGC.

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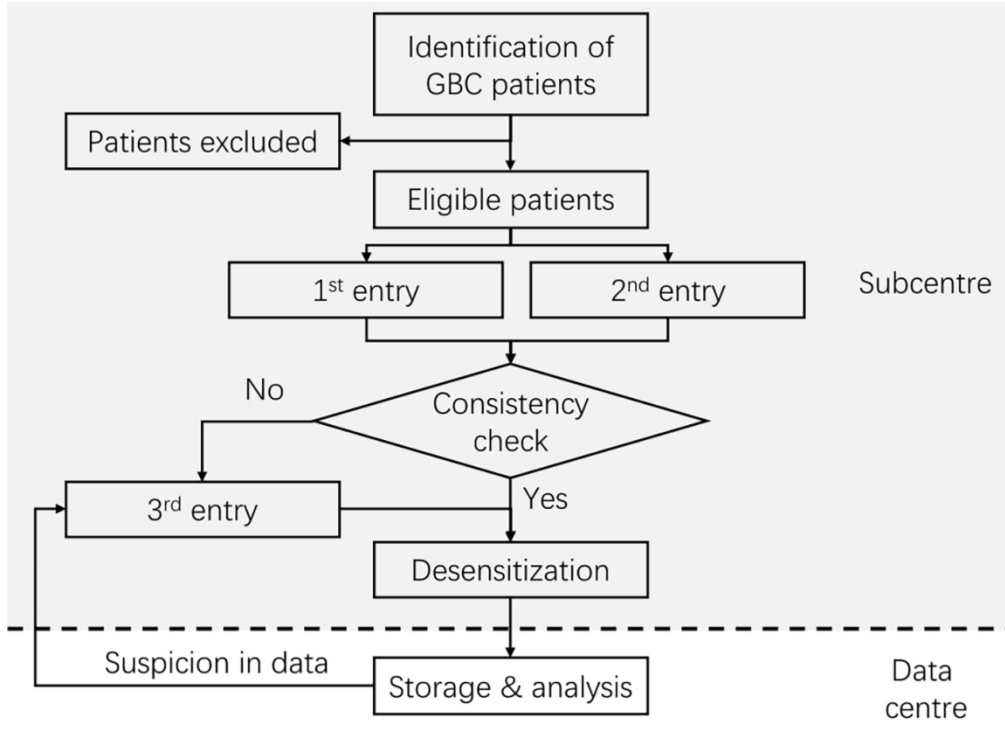


Fig. 1 Workflow of data collection and quality control in CRGGC.

118x90mm (300 x 300 DPI)

Protocol for a national gallbladder cancer registry study in China: the Chinese Research Group of Gallbladder Cancer (CRGGC) study

Tai Ren; Yongsheng Li, Xi Zhang, ... , Ying-Bin Liu, MD, FACS, on behalf of the CRGGC

ONLINE SUPPLEMENTARY FILE 1

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Hainan	Hainan Provincial People's Hospital	Prof. Jinfang Zheng

Review only

STROBE checklist of cohort studies

	Item No	Recommendation	Page Number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	6
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-11
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-15
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	10-15
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-16
Statistical methods	12	(a) Describe all statistical methods , including those used to control for confounding	15-16
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	15
		(d) If applicable, explain how loss to follow-up was addressed	10-11; 16

(e) Describe any **sensitivity analyses** NA
 - Current analysis focused mainly on descriptive statistics. When specific questions are addressed in future analysis, sensitivity analyses will be designed.

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	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
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	NA
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
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	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA

Other information

Funding	22	Give the source of funding and the role of the funders	18
		for the present study and, if applicable, for the original	
		study on which the present article is based	

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