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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 cancer[1-3] 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 cases[8-10], 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 omitted[13]. 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 found[14]. 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 definition[15]. The coding problems in both patient identification and site-specific variables might lead to less stringent interpretation of the conclusions.

China is a high-GBC risk country, but little evidence has been based on the Chinese population[11]. 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 worldwide[12]. 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 2009-2013 [17] reported that 55.1% of GBC patients had advanced-stage tumours. Other reports were mainly single-centre studies with limited sample sizes[18] [19]. 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 cancer[6]. 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-

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

Data collection

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

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

After data entry and quality control in each centre, the data are anonymized and transferred to the servers in the data centre. The data centre is located at Shanghai Key Laboratory of Biliary Tract Disease Research, which is equipped with data servers and essential firewall and backup systems. The data centre is responsible for quality assessment, storage, sharing, and analysis of the data. A group of researchers in the

data centre manage the database.

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

Demographic data and medical history

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

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 nodes[7]. 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,

intraoperative blood loss, and American Society of Anesthesiologists (ASA) score.

Pathological data

Pathological data are recorded, including size of the tumour (in 3 dimensions), resection margin, tumour positioned on the hepatic or peritoneal side, tumour positioned on the fundus, body, neck, or cystic duct, depth of invasion (carcinoma in situ or lamina propria, muscularis, perimuscular connective tissue, full layer, serosa, adjacent organ, or major vascular invasion[7]), liver invasion, number of nodes examined, positive lymph nodes, number of hilar nodes examined, positive hilar lymph nodes, region of positive nodes, region of nodes examined (with codes the same as those used for the region of lymphadenectomy in surgery), grade, histology type (using ICD-O-3 codes[22]), microvascular invasion, and perineural invasion. Tumours will be staged according to the AJCC 8th staging manual according to pathological reports derived from the aforementioned variables. Notably, the description of "invasion of full layer" for depth of invasion is not suggested in the AJCC 8th manual but is commonly used in China.

Laboratory examination

Laboratory examination results for patients are collected with the date of examination. Indicators of interest include the following: (1) routine blood tests: white blood cell count, haemoglobin, and platelet count; (2) liver function tests: total bilirubin, direct bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase; (3) renal function tests: blood urea nitrogen and creatine; (4) lipid indicators: triglycerides and total cholesterol; (5) inflammation indicators: C-reactive protein and lactic dehydrogenase; (6) coagulation indicators: international normalized ratio, prothrombin time, activated partial thromboplastin time, and fibrinogen; (7) tumour markers: carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 125, and alpha fetoprotein; and (8) other tests: blood type and hepatitis B test. The test method and normal range of each indicator may vary across hospitals. Thus, we first

uniform the units of each indicator according to the first enrolled hospital; then, based on the first enrolled hospital, we normalize each result of laboratory examination by its normal range across different hospitals.

Radiology reports

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

Patient and public involvement

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

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.

DISCUSSION

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

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

GBC is a relatively rare but lethal malignancy, making it important to address the

standardization of its primary care, treatment, and post-treatment follow-up. Researchers have shown unsatisfactory adherence to clinical guidelines. Radical cholecystectomy was recommended for T1b GBC by the NCCN guidelines nearly 10 years ago; however, only 50% of T1b GBC patients in the U.S. received radical cholecystectomy[13]. Bergquist et al.[23] reported that from 2004 to 2012, only 28.2% of GBC patients with positive nodal disease received adjuvant chemotherapy in the National Cancer Database of the U.S. even though this was the recommended treatment in the NCCN guidelines. Knowing the current situation is essential for future improvement; however, no data have been reported on GBC treatment in China. Well-designed observational studies in China will help to point out weak points in clinical practice and, at the same time, summarize valuable clinical experience in the treatment of GBC and pave the way for further standardized treatment.

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

There are several limitations and potential biases in our study design. (1) The retrospective nature is inevitably related to information bias and heterogeneity in the data recording. This will cause difficulty in the standardization of data and a relatively large proportion of missing data. To overcome such bias, we composed and continue to update a codebook for standardization of each variable. Researchers responsible for data entry are trained and qualified at the data centre. The missing data are analysed to determine potential bias. (2) This is a retrospective study using convenience sampling. Thus, the cohort may not be completely representative of GBC patients in China.

However, we attempt to include centres in every province in China. Moreover, most cancer patients in China are treated in tertiary hospitals. (3) Biospecimens of the involved patients are not collected. Future collaboration on this issue will be considered.

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Authors' Contributions

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

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

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Competing interests statement

All authors declare no competing interests.

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Figure legends

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

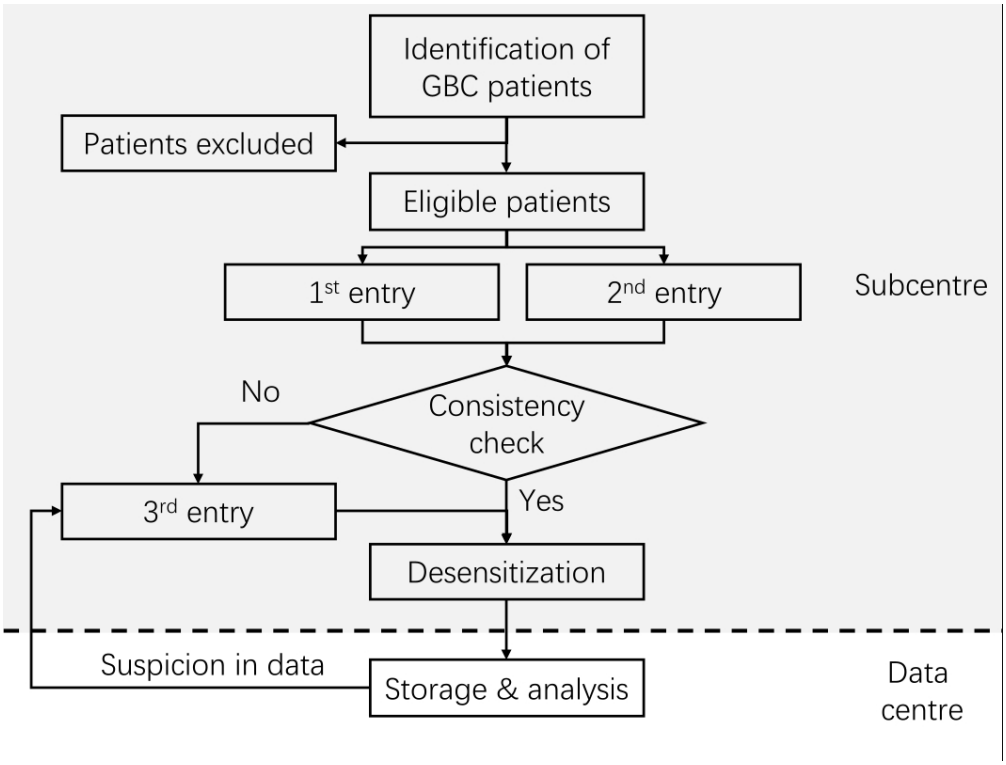

Fig. 1 Workflow of data collection and quality control in CRGGC.

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 • 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

		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

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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Protocol for a 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, to December 31, 2019, 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 cancer[1-3] and one of the most lethal malignancies, with a 5-year survival rate of 5-15%[1 4 5]. Much effort has been made to optimize the treatment of GBC; however, the prognosis remains dismal[4 6], 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[7 8]. Most of these studies were single-centre studies with limited sample sizes and generally no more than 300 cases[9-11], which might introduce systematic bias into the conclusion.

On the other hand, common-used coding systems addressed little on 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)[8]. 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[12 13]. 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 omitted[14]. 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 found[15]. 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 definition[16]. The coding problems in both patient identification and site-specific variables might lead to less stringent interpretation of the conclusions.

China is a high-GBC risk country, but little evidence has been based on the Chinese population[12]. 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 worldwide[13]. Currently, the largest retrospective study of GBC in China was conducted by Zou *et al.*[17], 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 2009-2013 [18] reported that 55.1% of GBC patients had advanced-stage tumours. Other reports were mainly single-centre studies with limited sample sizes[19] [20]. The critical characteristics in the diagnosis, treatment, and prognosis of GBC in China are unknown.

Therefore, this study aimed to design a 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, to December 31, 2019, 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 cancer[7]. 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 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 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 date of last

follow-up, where event other than death was defined as censor. We will also include the following outcomes: progression-free survival (PFS), defined as the duration between the date of first diagnosis and the date of recurrence; cancer-specific survival (CSS), defined as the duration between the date of first diagnosis and the date of cancer-caused death or date of last follow-up, where other events was defined as censor; 3-year OS rate; and 90-day mortality (for patients who undergo surgery), which will be used to indicate perioperative mortality. Clinical follow-up is defined as the routine practice of hospitals of collecting patient data on treatment, tumour recurrence and patient survival, either by outpatient/inpatient records or telephone. We require hospitals to equip such a system and at least one follow-up per year to join our collaboration. Based on these data, we update patients' follow-up statuses every 12 months. The data being collected from clinical follow-up include date of recurrence, date of death, date of last contact, whether re-resection was performed if the malignancy was found incidentally, and whether the patient received adjuvant therapy.

Data collection

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

Automated logic checks are applied to prevent out-of-range values. Duplicated entry is required. If any discrepancies are found, a third specialist will be brought in

for discussion and make a final decision.

After data entry and quality control in each centre, the data are anonymized and transferred to the servers in the data centre. The data centre is located at Shanghai Key Laboratory of Biliary Tract Disease Research, which is equipped with data servers and essential firewall and backup systems. The data centre is responsible for quality assessment, storage, sharing, and analysis of the data. A group of researchers in the data centre manage the database.

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

Demographic data and medical history

The EMR data for each patient are collected for every hospital visit from January 1, 2008. The baseline data are retrieved, including the following aspects: (1) demographics: age at diagnosis, sex, race, and date of diagnosis; (2) medical history: emergency operation, chief complaint, endoscopic retrograde cannulation of the pancreas (ERCP) performed within 30 days before surgery, percutaneous transhepatic

cholangial drainage (PTCD) performed within 30 days before surgery, neoadjuvant therapy, and method of diagnosis (pathology, radiology, or other); (3) past medical history: history of gallstone, history of gallbladder polyps, history of other malignancies, hypertension, diabetes mellitus, and other comorbidities; (4) social and personal history: marital status, smoking history, and use of alcohol; and (5) other aspects: weight, height, family history, and total expenditure.

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 nodes[8]. 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[8 21 22].
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, intraoperative blood loss, and American Society of Anesthesiologists (ASA) score.

Pathological data

Pathological data are recorded, including size of the tumour (in 3 dimensions), resection margin, tumour positioned on the hepatic or peritoneal side, tumour positioned on the fundus, body, neck, or cystic duct, depth of invasion (carcinoma in situ or lamina propria, muscularis, perimuscular connective tissue, full layer, serosa, adjacent organ, or major vascular invasion[8]), liver invasion, number of nodes examined, positive lymph nodes, number of hilar nodes examined, positive hilar lymph nodes, region of positive nodes, region of nodes examined (with codes the same as those used for the region of lymphadenectomy in surgery), grade, histology type (using ICD-O-3 codes[23]), microvascular invasion, and perineural invasion. Tumours will be staged according to the AJCC 8th staging manual according to pathological reports derived from the aforementioned variables. Notably, the description of "invasion of full layer" for depth of invasion is not suggested in the AJCC 8th manual but is commonly used in China.

Laboratory examination

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

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

Radiology reports

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

Statistical analysis

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

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

treatment modalities, and prognosis[24]. The distribution of hospitals' average GBC patients per year will be described in bar plot; 1 to 2 cut-off points will be determined by inspecting the pattern to classify hospitals into low- and high-volume. Correlation between hospital volume and patients' characteristics will be shown by either Pearson's R, Spearman's ρ, or χ^2, whichever appropriate. Potential correlated variables includes (but not limited to) sex, age at diagnosis, TNM stage, gallstone, surgery type, and adjuvant therapy.

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

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

As proposed in both NCCN and Chinese Medical Association guidelines[7 25], GBC more advance than T1b requires resection of liver bed and regional lymphadenectomy. Moreover, patients with nodal metastasis are recommended to take chemotherapy. These three indicators will be described to evaluate the adherence to clinical guidelines of GBC. Also, their significance in prognosis will be tested by survival analysis.

Patient and public involvement

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

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.

DISCUSSION

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

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

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

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

There are several limitations and potential biases in our study design. (1) The retrospective nature is inevitably related to information bias and heterogeneity in the data recording. This will cause difficulty in the standardization of data and a relatively large proportion of missing data. To overcome such bias, we composed and continue to update a codebook for standardization of each variable. Researchers responsible for data entry are trained and qualified at the data centre. The missing data are analysed to determine potential bias. (2) This is a retrospective study using convenience sampling. Thus, the cohort may not be completely representative of GBC patients in China. However, we attempt to include centres in every province in China. Moreover, most cancer patients in China are treated in tertiary hospitals. (3) Biospecimens of the involved patients are not collected. Future collaboration on this issue will be considered. (4) As patients with incidental GBC may turn to other hospitals for re-resection, resulting in incomplete treatment information. We addressed this problem by defining these patients separately to aid further sensitivity analysis.

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Authors' Contributions

LYB is the principal investigator steering the CRGGC and collaboration with other centres. Tai Ren, Yongsheng Li, Xi Zhang wrote and revised the manuscript. Tai Ren, Yongsheng Li, Yajun Geng, Ziyu Shao, Maolan Li, Xiangsong Wu, Xu-An Wang, Wenguang Wu, Yijun Shu, Runfa Bao, Wei Gong, and Ping Dong discussed and drafted the CRF, standard operation procedure in data collection and management, and standard of quality control. Tai Ren and Yongsheng Li are responsible for study management and coordination. All authors are responsible for data collection and quality control in their hospitals. All authors reviewed the manuscript for intellectual content and approved the final version of the report.

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Competing interests statement

All authors declare no competing interests.

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Figure legends

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

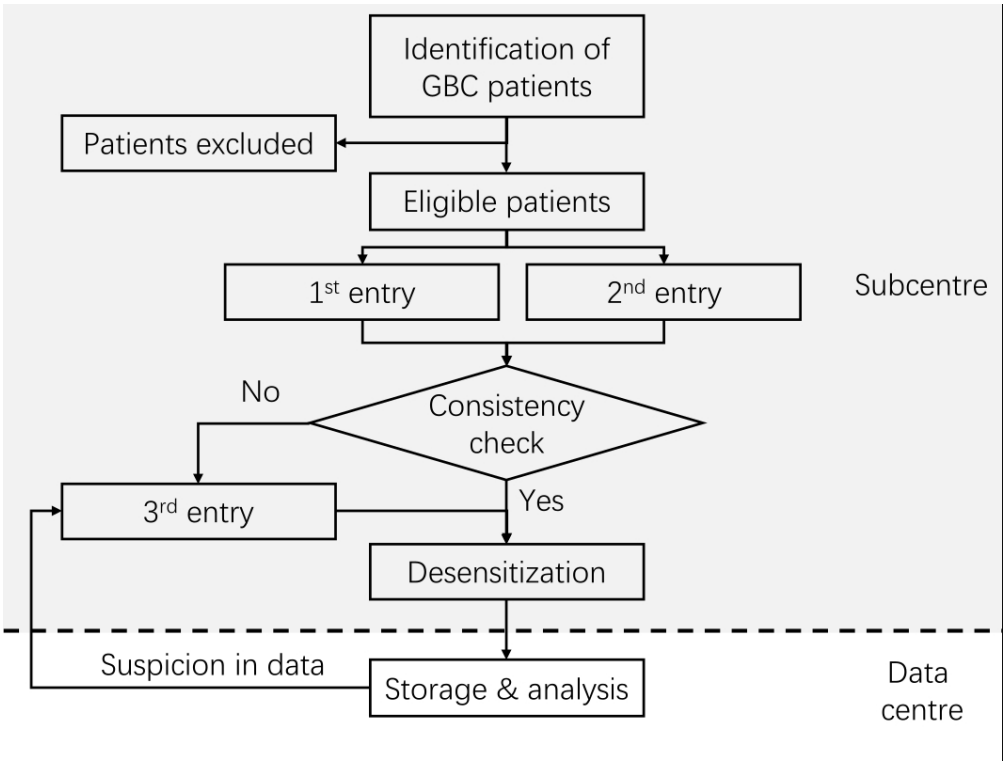

Fig. 1 Workflow of data collection and quality control in CRGGC.

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** - Current analysis focused mainly on descriptive statistics. When specific questions are addressed in future analysis, sensitivity analyses will be designed.	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	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 for the present study and, if applicable, for the original study on which the present article is based	18

BMJ Open

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

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Secondary Subject Heading:	Oncology, Epidemiology, Surgery
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Protocol for a 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 will be identified from January 1, 2008, to December , 2019, 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 will be 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 will be 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. The survival data are not validated through Chinese death registry.

INTRODUCTION

Gallbladder cancer (GBC) is the most common type of biliary tract cancer[1-3] and one of the most lethal malignancies, with a 5-year survival rate of 5-15%[1 4 5]. Much effort has been made to optimize the treatment of GBC; however, the prognosis remains dismal[4 6], 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[7 8]. Most of these studies were single-centre studies with limited sample sizes and generally no more than 300 cases[9-11], which might introduce systematic bias into the conclusion.

On the other hand, common-used coding systems addressed little on 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)[8]. 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[12 13]. 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 omitted[14]. 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 found[15]. 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 definition[16]. The coding problems in both patient identification and site-specific variables might lead to less stringent interpretation of the conclusions.

China is a high-GBC risk country, but little evidence has been based on the Chinese population[12]. 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 worldwide[13]. Currently, the largest retrospective study of GBC in China was conducted by Zou *et al.*[17], 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 2009-2013 [18] reported that 55.1% of GBC patients had advanced-stage tumours. Other reports were mainly single-centre studies with limited sample sizes[19] [20]. The critical characteristics in the diagnosis, treatment, and prognosis of GBC in China are unknown.

Therefore, this study aimed to design a 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 will review the electronic medical records (EMRs) of all diagnosed GBC patients from January 1, 2008, to December, 2019, and extract the related clinical and treatment information. The clinical follow-up data will be updated until 5 years after the last

admission of each GBC patient.

Patient enrolment

Patients will be 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 will be applied in each centre. The results will be merged for subsequent exclusion. These search strategies are 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 will be manually filtered according to the diagnostic criteria of the NCCN 2019 version 4 guidelines for hepatobiliary cancer[7]. Patients with a pathological or radiological diagnosis of malignancy, including cancer in situ, from the gallbladder and cystic duct are eligible. Patients will be 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 study will include patients diagnosed before December, 2019. According to our preliminary estimation, more than 6,000 cases will meet our inclusion criteria. We expect to finish 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). OS is defined as the duration from the date of first diagnosis to the date of death, and it is censored at the

date of the last follow-up when the patients are alive. We will also include the following outcomes: progression-free survival (PFS), defined as the duration between the date of first diagnosis and the date of recurrence, and censored at the date of the last follow-up when the patients have no evidence of recurrence.; cancer-specific survival (CSS), defined as the duration between the date of first diagnosis and the date of cancer-caused death, and censored at the date of the last follow-up when the patients are alive or died from other causes; 3-year OS; and 90-day mortality (for patients who undergo surgery), which will be used to indicate perioperative mortality. Clinical follow-up is defined as the routine practice of hospitals of collecting patient data on treatment, tumour recurrence and patient survival, either by outpatient/inpatient records or telephone. We require hospitals to equip such a system and at least one follow-up per year to join our collaboration. Based on these data, we will update patients' follow-up statuses every 12 months. The data being collected from clinical follow-up will include date of recurrence, date of death, date of last contact, whether re-resection is performed if the malignancy is found incidentally, and whether the patient receives adjuvant therapy.

Data collection

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

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

Duplicated entry will be required. If any discrepancies are found, a third specialist will be brought in for discussion and make a final decision.

After data entry and quality control in each centre, the data will be anonymized and transferred to the servers in the data centre. The data centre is located at Shanghai Key Laboratory of Biliary Tract Disease Research, which is equipped with data servers and essential firewall and backup systems. The data centre will be responsible for quality assessment, storage, sharing, and analysis of the data. A group of researchers in the data centre will manage the database.

The data manager will assess the quality of the data after transfer to the data centre. The assessment is based on the structure of missing data and a comparison to baseline data. First, we will apply a grading system, where variables are classified into essential, important, and normal importance. Based on the proportion of missing values in each category, the entries will be graded as level A, B, C, or D in quality. Entries of category D quality will be normally excluded from analysis. Second, outliers and inconsistent data will be identified. Third, we will compare baseline characteristics of the new data to previous data, with indicators including sex ratio, mean age, proportion of TNM stage, and 5-year OS. We will apply chi-square test, t-test, and log-rank test between the two datasets. When a significant difference is found, the data manager will analyse and record suspicious data. The data manager will inquire about the data in question with the data source and ask for confirmation. The desensitized data will be accessible to collaborators after the completion of the database. A research proposal to the CRGGC Scientific Committee will be essential for analysis of the data.

Demographic data and medical history

The EMR data for each patient will be collected for every hospital visit from January 1, 2008. The baseline data will be retrieved, including the following aspects: (1) demographics: age at diagnosis, sex, race, and date of diagnosis; (2) medical

history: emergency operation, chief complaint, endoscopic retrograde cannulation of the pancreas (ERCP) performed within 30 days before surgery, percutaneous transhepatic cholangial drainage (PTCD) performed within 30 days before surgery, neoadjuvant therapy, and method of diagnosis (pathology, radiology, or other); (3) past medical history: history of gallstone, history of gallbladder polyps, history of other malignancies, hypertension, diabetes mellitus, and other comorbidities; (4) social and personal history: marital status, smoking history, and use of alcohol; and (5) other aspects: weight, height, family history, and total expenditure.

Surgery information

1. The preoperative and intraoperative diagnoses will be 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 nodes[8]. 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[8 21 22].
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 will be 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, intraoperative blood loss, and American Society of Anesthesiologists (ASA) score.

Pathological data

Pathological data will be recorded, including size of the tumour (in 3 dimensions), resection margin, tumour positioned on the hepatic or peritoneal side, tumour positioned on the fundus, body, neck, or cystic duct, depth of invasion (carcinoma in situ or lamina propria, muscularis, perimuscular connective tissue, full layer, serosa, adjacent organ, or major vascular invasion[8]), liver invasion, number of nodes examined, positive lymph nodes, number of hilar nodes examined, positive hilar lymph nodes, region of positive nodes, region of nodes examined (with codes the same as those used for the region of lymphadenectomy in surgery), grade, histology type (using ICD-O-3 codes[23]), microvascular invasion, and perineural invasion. Tumours will be staged according to the AJCC 8th staging manual according to pathological reports derived from the aforementioned variables. Notably, the description of "invasion of full layer" for depth of invasion is not suggested in the AJCC 8th manual but is commonly used in China.

Laboratory examination

Laboratory examination results for patients will be collected with the date of

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

Radiology reports

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

Statistical analysis

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

We will calculate the average number of GBC diagnosed per year in each hospital, because the volume for cancer patients showed impact on patients' characteristics, treatment modalities, and prognosis[24]. The distribution of hospitals' average GBC patients per year will be described in bar plot; 1 to 2 cut-off points will be determined by inspecting the pattern to classify hospitals into low- and high-volume. Correlation between hospital volume and patients' characteristics will be shown by either Pearson's R, Spearman's ρ, or χ^2, whichever appropriate. Potential correlated variables includes (but not limited to) sex, age at diagnosis, TNM stage, gallstone, surgery type, and adjuvant therapy.

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

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

As proposed in both NCCN and Chinese Medical Association guidelines[7 25], GBC more advance than T1b requires resection of liver bed and regional lymphadenectomy. Moreover, patients with nodal metastasis are recommended to take chemotherapy. These three indicators will be described to evaluate the adherence to clinical guidelines of GBC. Also, their significance in prognosis will be tested by survival analysis.

Patient and public involvement

Patients or the public involvement are not in the plans of this research.

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.

DISCUSSION

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

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

GBC is a relatively rare but lethal malignancy, making it important to address the standardization of its primary care, treatment, and post-treatment follow-up. Researchers have shown unsatisfactory adherence to clinical guidelines. Radical cholecystectomy was recommended for T1b GBC by the NCCN guidelines nearly 10 years ago; however, only 50% of T1b GBC patients in the U.S. received radical cholecystectomy[14]. Bergquist et al.[26] reported that from 2004 to 2012, only 28.2% of GBC patients with positive nodal disease received adjuvant chemotherapy in the National Cancer Database of the U.S. even though this was the recommended treatment in the NCCN guidelines. Knowing the current situation is essential for future improvement; however, no data have been reported on GBC treatment in China. Well-designed observational studies in China will help to point out weakness

in clinical practice and, at the same time, summarize valuable clinical experience in the treatment of GBC and pave the way for further standardized treatment.

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

There are several limitations and potential biases in our study design. (1) The retrospective nature is inevitably related to information bias and heterogeneity in the data recording. This will cause difficulty in the standardization of data and a relatively large proportion of missing data. To overcome such bias, we composed and continue to update a codebook for standardization of each variable. Researchers responsible for data entry are trained and qualified at the data centre. The missing data are analysed to determine potential bias. (2) This is a retrospective study using convenience sampling. Thus, the cohort may not be completely representative of GBC patients in China. However, we attempt to include centres in every province in China. Moreover, most cancer patients in China are treated in tertiary hospitals. (3) Biospecimens of the involved patients are not collected. Future collaboration on this issue will be considered. (4) As patients with incidental GBC may turn to other hospitals for re-resection, resulting in incomplete treatment information. We addressed this problem by defining these patients separately to aid further sensitivity analysis. (5) Currently we haven't made collaboration with Chinese death registry, thus part of the death information may be lost and the follow-up data might be biased due to lack of validation. On the one hand, the CRGGC study actively seek cooperation with relevant registries; on the other hand, we require collaborated hospitals to equip

clinical follow-up system, compare prognosis data in each hospital to identify systematic bias, and update follow-up data yearly.

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Authors' Contributions

Dr. Yingbin Liu is the principal investigator steering the CRGGC, and responsible for conceptualization, funding acquisition, and supervision of the study. Dr. Tai Ren, Dr. Yongsheng Li, Dr. Xi Zhang, and Dr. Yingbin Liu wrote and revised the manuscript. Dr. Tai Ren, Dr. Yongsheng Li, Dr. Yajun Geng, Dr. Ziyu Shao, Dr. Maolan Li, Dr. Xiangsong Wu, Dr. Xu-An Wang, Dr. Wenguang Wu, Dr. Yijun Shu, Dr. Runfa Bao, Dr. Wei Gong, and Dr. Ping Dong discussed and drafted the case report form, standard operation procedure in data collection and management, and standard of quality control. Dr. Tai Ren and Dr. Yongsheng Li are responsible for data curation and coordination. Dr. Xi Zhang is responsible for the methodology. Dr. Tai Ren, Dr. Yongsheng Li, and Dr. Xi Zhang will be responsible for data analysis and reporting of the work. Dr. Xueyi Dang, Dr. Chang Liu, Dr. Changjun Liu, Dr. Bei Sun, Dr. Jun Liu, Dr. Lin Wang, Dr. Defei Hong, Dr. Renyi Qin, Dr. Xiaoqing Jiang, Dr. Xuewen Zhang, Dr. Junmin Xu, Dr. Jianguang Jia, Dr. Bo Yang, Dr. Bing Li, Dr. Chaoliu Dai, Dr. Jingyu Cao, Dr. Hong Cao, Dr. Feng Tao, Dr. Zaiyang Zhang, Dr. Yi Wang, Dr. Huihan Jin, Dr. Hongyu Cai, Dr. Zhewei Fei, Dr. Jianfeng Gu, Dr. Wei Han, Dr. Xuedong Feng, Dr. Lu Fang, Dr. Linhui Zheng, Dr. Chunfu Zhu, Dr. Kunhua Wang, Dr. Xueli Zhang, Dr. Xiaoyong Li, Dr. Chong Jin, Dr. Yeben Qian, Dr. Yunfu Cui, Dr. Yuzhen Xu, Dr. Xiang Wang, Dr. Houbao Liu, Dr. Yawei Hua, Dr. Chao Liu, Dr. Jihui Hao, Dr. Chuanlei Wang, Dr. Qiyun Li, Dr. Xun Li, Dr. Jiansheng Liu, Dr. Mingzhang Li, Dr. Yudong Qiu, Dr. Buqiang Wu, Dr. Jinfang Zheng, Dr. Xiaoliang Chen, Dr. Haihong Zhu, Dr. Kejun Hua, Dr. Maolin Yan, Dr. Peng Wang, Dr. Hong Zang, Dr. Xiaoming Ma, Dr. Jian Hong, Dr. Wei Gong, and Dr. Yingbin Liu are responsible for resources, data collection, and quality control in collaborated hospitals. All authors reviewed the manuscript for intellectual content and approved the final version of the report.

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Competing interests statement

All authors declare no competing interests.

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Figure legends

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

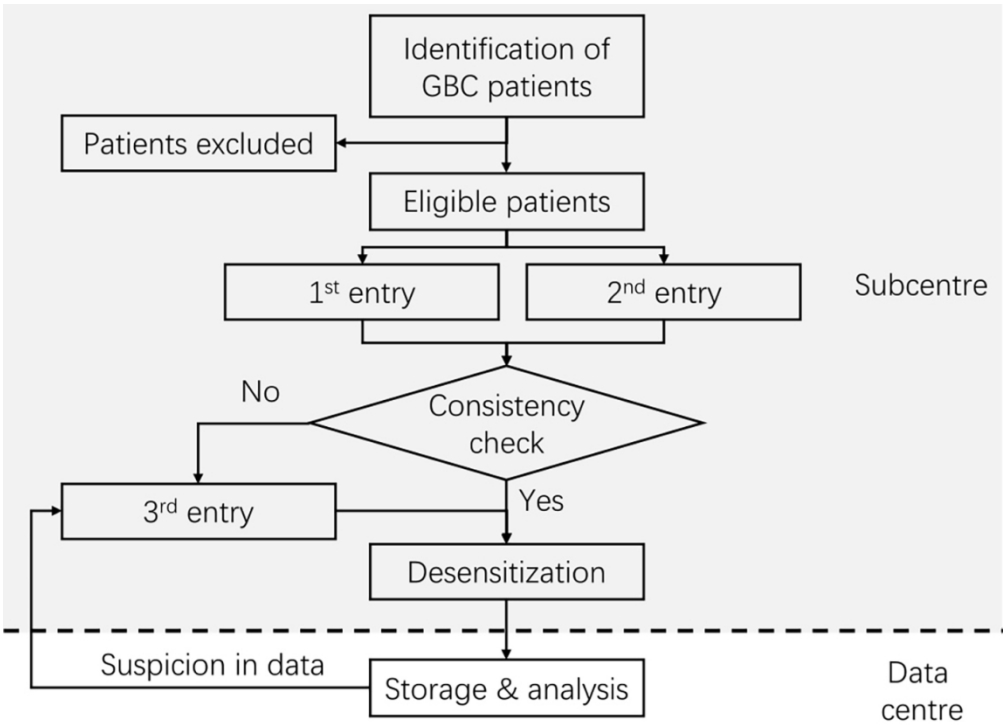

Fig. 1 Workflow of data collection and quality control in CRGGC.

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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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** - Current analysis focused mainly on descriptive statistics. When specific questions are addressed in future analysis, sensitivity analyses will be designed.	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	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 for the present study and, if applicable, for the original study on which the present article is based	18