

# Study Protocol

A Multicenter prospective cohort study on  
the risk factors for gallbladder cancer

Researcher : Wang Jianming

Research institute : Huazhong University of Science

Tongji Hospital, Tongji Medical College

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# Study Protocol Summary

|                                 |  |
|---------------------------------|--|
| Title                           | A Multicenter prospective cohort study on the risk factors for gallbladder cancer  |
| Research Institute              | Huazhong University of Science Tongji Hospital, Tongji Medical College   |
| Number of research Institute    | 220  |
| Research Purposes               | <ol style="list-style-type: none"><li>1. To study the correlation between benign gallbladder disease and gallbladder cancer;</li><li>2. Explain the timing of intervention for benign gallbladder disease, the mode of intervention, and the benefits of early prevention of gallbladder cancer, and further calculate the difference in socioeconomic benefits (the cost of medical care caused by the disease).</li></ol>  |
| Research Design                 | Prospective, multi-centred research  |
| Sample size determination basis | <p>This trial is a prospective study, the main purpose of the study is to investigate the association between benign gallbladder disease and gallbladder carcinoma; to explain the timing of intervention, intervention and early prevention of benign gallbladder disease; according to the national epidemiology of gallbladder cancer Center Clinical Research (unpublished), 2000 National Cholecystoma Clinical Epidemiology Report, and 2005 Clinical Analysis of 2379 Cases of Gallbladder Carcinoma in 17 Hospitals in Five Northwest Provinces, Pre-experimental data, using samples The volume estimation formula, <math>\alpha = 0.05</math>, <math>\beta = 0.1</math>, plans to enroll 100,000 people.</p> |

|                      |  |
|----------------------|--|
| Standard constrain   | <p>Subjects who met the following four criteria entered the study.</p> <p>(1) A benign gallbladder disease (according to any imaging test result) during a physical examination or visit;</p> <p>(2) healthy people without gallbladder disease;</p> <p>(3) Age greater than 18 years and less than 80 years old;</p> <p>(4) Sign the informed consent form.</p> |
| Exclusion criteria   | <p>Subjects can not enter the study by combining any of the following</p> <p>(1) Concomitant diseases such as severe mental illness, severe heart, lung and kidney;</p> <p>(2) Refusal of follow-up requirements.</p>  |
| Observation index    | <p>( 1 ) Incidence of gallbladder cancer;</p> <p>( 2 ) Gallbladder-related disease mortality;</p> <p>( 3 ) Gallbladder-related disease surgery rate;</p> <p>( 4 ) Gallbladder related diseases surgery;</p> <p>( 5 ) Medical expenses for gallbladder related diseases;</p>  |
| Research period      | 3 years  |
| Statistical analysis | The Linklab information collection system is used for data entry and verification. All data was counted using SPSS 21.0.   |

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## 一、Background

Gallbladder cancer is the most common malignant biliary tract neoplasm. The incidence of gallbladder cancer is increasing year by year, ranking sixth in the incidence of digestive tract cancer. [1] There are significant differences in the incidence of gallbladder cancer globally. It has been reported that the incidence of gallbladder cancer varies 25 times in different regions. The reasons for this difference may be related to environmental exposure differences and inherent genetic susceptibility. The highest incidence was found in the Andes Mountains of South America, Eastern and Central Europe (such as Hungary, Germany and Poland), Israel, while the incidence was lower in the United States and most Western and Mediterranean countries (such as Britain, France and Norway). In Asia, the incidence of gallbladder cancer is also at a high level, especially among women and men in northern India and Pakistan, while Korea has the highest incidence in Asia. The incidence of primary gallbladder cancer in China accounted for 0.4%–3.8% of biliary tract diseases in the same period, and there were regional differences. [2].

The main risk factors of gallbladder cancer include gallstone, gallbladder polyp, gallbladder adenoma, chronic inflammation of gallbladder, etc. [3][4]. However, in recent years, there is still lack of relevant risk factors evaluation data, so on the basis of large-scale epidemiological investigation, large-scale prospective research is needed to further clarify the level of risk factors related to gallbladder cancer.

With the development of modern imaging technology and in-depth understanding of gallbladder diseases, the detection rate of benign lesions of gallbladder (gallbladder polyps,

gallbladder adenomyosis, gallbladder adenoma, gallbladder stones, etc.) is increasing year by year, while some benign lesions of gallbladder can gradually evolve into gallbladder cancer through a series of pathophysiological processes. Radical resection is the only possible method to cure or improve the long-term survival rate of gallbladder cancer. However, due to the difficulty in early diagnosis of gallbladder cancer, the unknown etiology and lack of specific clinical manifestations, most patients were found to be advanced, with low resection rate and insensitive to radiotherapy and chemotherapy. [7] Most patients have lost the chance of operation at the time of consultation, and the overall 5-year survival rate is less than 5%. [5][6]. In the early stage of gallbladder cancer, because the biliary surgeon is not clear about the standard of standardized operation, the recurrence and metastasis of gallbladder cancer occur soon after operation, which seriously affects the prognosis [8]. Therefore, the correct understanding of benign gallbladder diseases, intervention time and intervention measures have always been a serious challenge for surgeons.

Correct understanding of the relationship between benign lesions of gallbladder and gallbladder cancer and rational grasp of the timing of surgical treatment are the urgent needs of many clinicians.

The purpose of this study was to establish a prospective cohort of benign gallbladder diseases and to explore the correlation between benign gallbladder diseases and gallbladder cancer, the timing of intervention and socio-economic benefits. In order to further understand the epidemiological trend, diagnosis and treatment of benign gallbladder diseases in China, the Biliary Surgery Group of the Surgical Society of the Chinese Medical Association plans

to launch a nationwide epidemiological survey of gallbladder cancer (2018). This study will provide a more detailed basis for the diagnosis and treatment of benign gallbladder diseases in China.

## **二、Purpose**

1. To study the correlation between benign diseases of gallbladder (such as gallstone, gallbladder polyp, gallbladder adenoma, cholecystitis, etc.) and gallbladder cancer;

2. To clarify the intervention timing, intervention methods and benefits of early prevention of gallbladder cancer for benign gallbladder diseases, and to further calculate the difference of socioeconomic benefits (medical costs caused by diseases).

## **三、Content**

### **3.1 Type**

Prospective, multi-centred research

### **3.2 Population**

- (1) Patients with benign gallbladder diseases
- (2) Healthy people without gallbladder disease

#### **3.2.1 Inclusion Criteria**

The subjects entered the study if they met the following four criteria.

(1) Benign diseases of gallbladder were found during physical examination or consultation (according to the results of any imaging examination);

(2) Healthy people without gallbladder disease;

(3) older than 18 years old and younger than 80 years old;

(4) Sign the informed consent.

### **3.2.2 Exclusion criteria**

If any of the following items are combined, participants will not be able to enter the study.

(1) Complicated with severe mental illness, severe heart, lung and kidney diseases;

(2) Refusal of follow-up requests.

### **3.2.3 Exit case**

#### **(1) Judgment**

No matter when and why they quit, as long as they have not completed the whole follow-up observation, they are considered as cases of Midway withdrawal.

#### **(2) Standard**

- 1) Withdrawal from the study due to adverse events;
- 2) Serious breach of the plan;
- 3) Patients withdraw their informed consent.
- 4) Researchers believe that subjects need to quit.
- 5) others;

### **3.2.4 Management**

Detailed records of withdrawal cases have been followed up, and statistical analysis of its observation indicators, the source documents should be kept for reference. Withdrawal rate should not exceed 20% during follow-up.

### **3.2.5 Group**

Non exposed group: Healthy people without gallbladder disease

Exposed group: Imaging examination confirmed gallbladder disease (non-gallbladder cancer).



### 3.3 Number of cases and grouping method

This study is an observational study. There is two groups of subjects and 100,000 cases are planned to be enrolled.

### 3.4 Research procedures and related examinations

#### 3.4.1 Research period

Case entry period:

All clinical research centers completed case collection within 20 years after the start of the study.

#### 3.4.2 Formulate CRF table and recruitment

- 1) Collect the information of patients: general demographic data; current medical history, past medical history, occupational history, residence history, personal habits, diet history, etc; imaging examination, blood routine, biochemistry, liver and kidney function, coagulation function, tumor markers and urine routine tests, routine preoperative examination (abdominal color Doppler ultrasound, CT, MR). Medical expenses related to diseases (including medical treatment, treatment, transportation, missed work, etc.).
- 2) Recruited subjects can be enrolled into the group after they have informed the patient about the research and signed the informed consent form of the clinical study; the relevant information of patients is recorded in the data collection form.

#### 3.4.3 Follow-up

##### (1) Follow-up period

Subjects were followed up once a year after they entered the queue. Outpatient, home or telephone follow-up was

conducted. Understand the general situation of the subjects, laboratory examination results, radiological examination results, treatment and so on.

## **(2) Follow-up Protocol**

- 1) Follow-up staff: Attending and special follow-up staff
- 2) Follow up mode: Outpatient, door-to-door or telephone follow-up.
- 3) Follow-up period: 20 years
- 4) Follow-up content: Collect information according to the main content of CRF table.
- 5) Follow-up End: ①Gallbladder tumor;  
②Dead;  
③Acceptance of cholecystectomy.

### **3.4.4 Observation index**

- (1) Incidence of gallbladder cancer;
- (2) Mortality of gallbladder-related diseases;
- (3) Surgical rate of gallbladder-related diseases;
- (4) Surgical methods for gallbladder-related diseases;
- (5) Medical expenses for gallbladder-related diseases.

## **四、Statistical Analysis**

### **4.1 Sample size estimation**

(1) Patients who meet the discharge criteria should be admitted to the group continuously without selectivity.

(2) This experiment is an observational study. The main purpose of this study is to study the correlation between benign diseases of gallbladder (such as gallstone, gallbladder polyp, gallbladder adenoma, cholecystitis, etc.)

and the occurrence of gallbladder cancer, to clarify the timing, mode of intervention for benign diseases of gallbladder and the benefits of early prevention of gallbladder cancer, and to further calculate its socioeconomic Benefit difference (medical cost caused by disease). The incidence of gallbladder cancer was calculated according to the data of the previous "National Multicenter Clinical Study of Gallbladder Cancer Epidemiology" (unpublished), 2000 "National Clinical Epidemiological Investigation Report of Gallbladder Cancer" and 2015 "Clinical Analysis of 2379 Cases of Gallbladder Cancer in 17 Hospitals of Northwest Five Provinces". Calculate, use the sample size estimation formula,  $\alpha = 0.05$ ,  $\beta = 0.1$ , estimate the sample size of 100,000 people.

## 4.2 Data statistics and analysis

### (1) Statistical grouping

- The patients were grouped according to their basic information and tabulated, such as:
  - Age: Old ( $>60$  years) , Middle-aged (45–59 years) , Youth ( $\leq 45$ )
  - Sex: Male, Female
  - Location: According to the province where the patient is located
  - History of present illness: Time of consultation, time of onset, symptoms of consultation, signs of admission, etc.
  - Anamnesis: According to the past medical history, it can be divided into: biliary tract diseases (gallstones, gallbladder polyps), tumors, cardiovascular diseases, surgical history, etc.
  - .....

## (2) Statistics and Analysis of Research Data

Linklab information acquisition system is used to input and verify data. All data were collected by SPSS 21.0. The data were analyzed by conventional single factor statistical analysis and advanced statistical methods (using CMH chi-square on demand, multifactor generalized linear regression, tendency score, etc.).

(3) For the missing values of the main evaluation indicators, Multi-Filling method is used to correct and sensitivity analysis.

## (5) Summary statistics

– Metrological data give mean, standard deviation, minimum, maximum, P25, median and P75; Counting data give frequency distribution and corresponding percentage.

# 五、 Research on Related Ethics

## 5.1 Audit by Ethics Committee

This clinical study must follow the ethical principles of the Helsinki Declaration, the ethical regulations of China and the management norms and regulations of clinical research. The information related to this program and written informed consent must be submitted to the Ethics Committee, which can formally carry out the research only after obtaining written approval from the Ethics Committee. Researchers must submit annual reports to the Ethics Committee at least annually, if applicable. When the study is suspended and/or completed, the researcher must notify the Ethics Committee in writing; the researcher must report to the Ethics Committee in a timely manner the changes that have taken place in all the research work (such as the revision of the programme and/or informed consent).

## 5.2 informed consent

Informed consent may not be used until it has been approved

by the ethics committee. Before participating in this study, each subject or his legal representative should read the informed consent form and give him or her sufficient time to understand the details of this study after the detailed answers of the research doctor, so that the subjects or their legal representatives can be fully informed, and the subjects have the right to voluntarily choose whether to participate or follow up. The study was withdrawn at that time. Any modification of the informed consent must be approved by the ethics committee of the research hospital, and the patients without leaving the hospital must sign the new version of the informed consent. The informed consent shall be signed voluntarily by the subject himself or his legal representative. The informed consent signed by the researcher and the subjects themselves or their legal representatives is in duplicate and each party keeps one copy. Informed consent is kept for reference as an important document of clinical trials.

## **六、Cryptosecurity**

1. The collection and processing of personal data of subjects selected for this study is limited to the data necessary for the purpose of this study. The information contained in the Research Institute (including data) is only provided to the project collaboration group for review. Without the approval of the project leader and the project collaboration group, it is strictly prohibited to provide any information to third parties unrelated to the study.

2. The project manager has the right to publish or publish information or data related to this test. If other individuals or units concerned with this test wish to publish or publish the test results or related data, they need to obtain the prior consent of the project leader. Project leaders should obtain the consent of researchers if they need to present the names of researchers in publications,

publications or advertisements.

## 七. Project participants

### 7.1 Research Institutes

- Research center: Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology
- Collaboration unit:

| Number | Collaboration unit   | Researcher    |
|--------|--|---------------|
| 1      | Anhui provincial hospital  | Jia Weidong   |
| 2      | China Meitan General Hospital  | Li Tao        |
| 3      | Beijing Tsinghua Changgeng Hospital                                      | Zeng Jianping |
| 4      | Beijing Tiantan Hospital Affiliated to Capital Medical University        | Cheng Shi     |
| 5      | Xuanwu Hospital, Capital Medical University                              | Zheng Yamin   |
| 6      | Beijing Youan Hospital Affiliated to Capital Medical University          | Zeng Daobing  |
| 7      | General Hospital of the Chinese People's Liberation Army                 | Wang Jing     |
| 8      | Peking Union Medical College Hospital                                    | He Xiao Dong  |
| 9      | Beijing Century Temple Hospital Affiliated to Capital Medical University | Peng Jirun    |
| 10     | Zhongshan Hospital Affiliated to Xiamen University                       | Su Yongjie    |
| 11     | Zhangzhou Zheng Xing hospital  | Li Jianguo    |
| 12     | Union Medical College Hospital Affiliated to Fujian Medical University   | Chen Yanling  |
| 13     | First Affiliated Hospital of Fujian Medical University                   | Zhang Zhibo   |
| 14     | Meng Chao Liver and Gallbladder Hospital of Fujian Medical University    | Zeng Yongyi   |
| 15     | Second Hospital of Lanzhou University                                    | Cheng Zhibin  |

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| 16 | Foshan Chancheng District Central Hospital                                    | Peng Liang     |
| 17 | Guangzhou First People's Hospital   | Gu Weili       |
| 18 | First Affiliated Hospital of Shantou University                               | Yan Jiang      |
| 19 | First Affiliated Hospital of Shenzhen University                              | Zhan Yongqiang |
| 20 | Peking university shenzhen hospital   | Liu Jikui      |
| 21 | Sun Yat-sen University Cancer Center  | Li Shengping   |
| 22 | Sun Yixian Memorial Hospital of Sun Yat-sen University                        | Chen Yajin     |
| 23 | Zhongshan People's Hospital   | Chang Xiaojian |
| 24 | Affiliated Hospital of Guangdong Medical College                              | Chen Nianping  |
| 25 | Guigang People's Hospital   | Luo Hanchuan   |
| 26 | Guiping People's Hospital   | Wei Xiaoyuan   |
| 27 | Liuzhou People's Hospital   | Liu Qiang      |
| 28 | First Affiliated Hospital of Guangxi Medical University                       | Peng Tao       |
| 29 | Cancer Hospital Affiliated to Guangxi Medical University                      | Wu Feixiang    |
| 30 | Guangxi Zhuang Autonomous Region People's Hospital                            | Liu Tianqi     |
| 31 | Sow District Hospital of traditional Chinese Medicine                         | Zhou Qiang     |
| 32 | Danzhai County People's Hospital  | Wang Huigang   |
| 33 | Jinsha People's Hospital  | Wang Changkuan |
| 34 | Liupanshui People's Hospital  | Cheng Yongpeng |
| 35 | Tongren First People's Hospital   | Zhu Yingqian   |
| 36 | Xingyi People's Hospital  | Peng Yanchun   |
| 37 | People's Hospital of Xingyi City, Guizhou Province                            | Luo Yunbo      |
| 38 | Affiliated Hospital of Zunyi Medical College, Guizhou Province                | Liu Yao        |
| 39 | Second Affiliated Hospital of Guizhou Medical University (Kaili 418 Hospital) | Shu Xiao       |
| 40 | Affiliated Hospital of Guizhou Medical University                             | Sun Chengyi    |



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|----|---|---------------|
| 41 | Hainan Provincial People's Hospital   | ZHENG Jinfang |
| 42 | Affiliated Hospital of Hainan Medical College                               | Yang Yan      |
| 43 | Cangzhou Central Hospital   | Li Xuefeng    |
| 44 | The Fourth Hospital of Hebei Medical University                             | Peng Li       |
| 45 | Hebi City People's Hospital, Henan Province                                 | Chang Yunfeng |
| 46 | People's Liberation Army 150 Central Hospital                               | Sun Gaobin    |
| 47 | Jingshan County People's Hospital, Hubei Province                           | Yang Yong     |
| 48 | Fuyang City People's Hospital, Henan Province                               | Gao Deshan    |
| 49 | Tangyin County People's Hospital, Henan Province                            | Su Shi        |
| 50 | The First Affiliated Hospital of Zhengzhou University                       | Tang Zhe      |
| 51 | Henan Cancer Hospital   | Zhou Jinxue   |
| 52 | Luohe Central Hospital  | Han Yanhua    |
| 53 | The Second Affiliated Hospital of Harbin Medical University                 | Cui Yunyu     |
| 54 | The Third Affiliated Hospital of Harbin Medical University (Tumor Hospital) | Zhang Yubao   |
| 55 | The Fourth Affiliated Hospital of Harbin Medical University                 | Xu Lishan     |
| 56 | The First Affiliated Hospital of Harbin Medical University                  | Yin Dalong    |
| 57 | Heilongjiang Provincial People's Hospital                                   | Jin Zhengxi   |
| 58 | Jianghai Oilfield General Hospital  | Zhang Yusheng |
| 59 | Anlu Pu'ai Hospital   | Deng Youfa    |
| 60 | Chongyang County People's Hospital  | Wang Qingxian |
| 61 | Dawu County People's Hospital   | Deng Haibo    |
| 62 | Daye People's Hospital  | Liu Baokuo    |
| 63 | Daye City Hospital  | Xiong Chunbo  |
| 64 | Daye Nonferrous Pharmaceuticals Affiliated Hospital                         | Xu Ping       |
| 65 | Dangyang People's Hospital  | Xu Yuandeng   |

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| 66 | Ezhou Central Hospital  | Chen Yifa      |
| 67 | Enshi State Central Hospital  | Li Jinmei      |
| 68 | Gezhouba Central Hospital   | Luo Jing       |
| 69 | Public Security County People's Hospital  | Chen Houbin    |
| 70 | Public Security County Hospital   | Zou Xianxiong  |
| 71 | Hanchuan People's Hospital  | Yong Yongjun   |
| 72 | Hong'an County People's Hospital  | Gan Shenghong  |
| 73 | Honghu People's Hospital  | Li Ping        |
| 74 | Honghu City Schistosomiasis Specialist Hospital   | Cao Yu         |
| 75 | Union Hospital of Tongji Medical College, Huazhong University of Science and Technology | Feng Xiansong  |
| 76 | Huangpi District People's Hospital  | Hu Yanjun      |
| 77 | Huanggang Central Hospital  | He Qianjin     |
| 78 | Huanggang Chinese Medicine General Surgery  | Wang Xiao      |
| 79 | Huangmei County People's Hospital   | Wang Dahai     |
| 80 | Huangmei County Chinese Medicine Hospital   | Yang Yuning    |
| 81 | Huangshi Pu'ai Hospital   | Shi Huxi       |
| 82 | First Hospital of Huangshi City   | Liu Xisong     |
| 83 | Yellowstone Central Hospital  | Xia Guobing    |
| 84 | Huangzhou District People's Hospital  | Wang Jianguo   |
| 85 | Jiayu County People's Hospital  | Chen Yong      |
| 86 | Jianli County People's Hospital   | Yan Denggao    |
| 87 | Jianshi County People's Hospital  | Tang Liangqing |
| 88 | Jiangling County People's Hospital  | Wang Qingshan  |
| 89 | The 161st Hospital of the Chinese People's Liberation Army                              | Xu Ke          |
| 90 | Jingzhou First People's Hospital  | Li Wei         |
| 91 | Jingzhou Central Hospital   | Yang Zhiqi     |
| 92 | Lichuan People's Hospital   | Xiang Xianhui  |
| 93 | Luotian County People's Hospital  | Yu Shengfeng   |
| 94 | Macheng Central Hospital  | Yu Yiming      |
| 95 | Nanxun County People's Hospital   | Huang Ying     |
| 96 | Hunchun County People's Hospital  | Wang Zhirong   |
| 97 | Qianjiang Central Hospital  | Yin Tongzhi    |

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| 98  | National Pharmacy Dongfeng General Hospital          | Zhou Wenbo      |
| 99  | Luxi County People's Hospital                        | Liu Fengshun    |
| 100 | Songzi City People's Hospital                        | He Qianzhang    |
| 101 | Sui County People's Hospital                         | Shen Tao        |
| 102 | Suizhou Central Hospital                             | Peng Gang       |
| 103 | Tongshan County People's Hospital                    | Cheng Shouren   |
| 104 | Tuanfeng County People's Hospital                    | Xu Shiyong      |
| 105 | Wuchang Railway Hospital                             | Gao Xuzhong     |
| 106 | Wuhan University People's Hospital                   | Ding Youming    |
| 107 | Zhongnan Hospital of Wuhan University                | He Yueming      |
| 108 | Wuhan Dongxihu Hospital                              | Cai Lie         |
| 109 | Wuhan Puai Hospital                                  | You Jian        |
| 110 | Hubei Rongjun Hospital                               | Yang Guochao    |
| 111 | Wuhan Sixth Hospital                                 | Liu Wen         |
| 112 | Wuhan Xinzhou District People's Hospital             | Lu Jinxi        |
| 113 | Wuhan Central Hospital                               | Cai Changchun   |
| 114 | Wuxue People's Hospital                              | Ju Yiqing       |
| 115 | Lishui County People's Hospital                      | Chen Xiaoming   |
| 116 | Xiantao City People's Hospital                       | Zeng Changjiang |
| 117 | Xianning First People's Hospital                     | Hu Guoxing      |
| 118 | Xianning Central Hospital                            | Wang Daihong    |
| 119 | Xiangyang Central Hospital                           | Liao Xiaofeng   |
| 120 | Fuyang City Hospital of Traditional Chinese Medicine | Hu Bichuan      |
| 121 | Xiaochang County People's Hospital                   | Deng Xiaobin    |
| 122 | Xiaogan Central Hospital                             | Hu Yongjun      |
| 123 | Hubei Xinhua Hospital                                | Zhu Yixiang     |
| 124 | Yangxin County People's Hospital                     | Ma Xianshi      |
| 125 | Yangxin County Third People's Hospital               | Song Jinwen     |
| 126 | Yichang Second People Hospital                       | Huo Lei         |
| 127 | Yiling District People's Hospital, Yichang City      | Li Jianwen      |
| 128 | Yichang Central Hospital                             | Zheng Jun       |
| 129 | Yichang People's Hospital                            | Ge Liang        |
| 130 | Yidu People's Hospital                               | Hu Wen          |
| 131 | Yidu Chinese Medicine Hospital                       | Yin Qinghua     |

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|-----|--|---------------|
| 132 | Yingshan County People's Hospital                                  | Shifeng       |
| 133 | Yingcheng County People's Hospital                                 | Wang Wuxing   |
| 134 | Changyang County People's Hospital                                 | Zhou Jigang   |
| 135 | Changyang County Hospital of Traditional Chinese Medicine          | Yan Wandong   |
| 136 | People's Liberation Army Wuhan General Hospital                    | Lu Yuping     |
| 137 | Zhongxiang People's Hospital                                       | Su Jinsong    |
| 138 | Hubei Cancer Hospital  | Wu Dongde     |
| 139 | Zigui County People's Hospital                                     | Li Xuechun    |
| 140 | Hunan Provincial People's Hospital                                 | Mao Xianhai   |
| 141 | Xiangxi People's Hospital  | Wang Wener    |
| 142 | Zhangpu County Chinese Medicine Hospital                           | Xiang Jianwen |
| 143 | Huarong County People's Hospital                                   | Wang Xuexiang |
| 144 | Central South University Xiangya Hospital                          | Tang Huihuan  |
| 145 | Zhuzhou Central Hospital   | Tang Caixi    |
| 146 | Baishen First Hospital of Jilin University                         | Wang Guangyi  |
| 147 | Jilin University Sino-Japanese Friendship Hospital                 | Li Wei        |
| 148 | Changzhou Third People's Hospital                                  | Xu Locke      |
| 149 | Nantong Cancer Hospital  | Shao Bingfeng |
| 150 | Jiujiang City Duchang County People's Hospital                     | Wang Longgang |
| 151 | Second Affiliated Hospital of Nanchang University                  | Zou Shubing   |
| 152 | The First Affiliated Hospital of Nanchang University               | Li Yong       |
| 153 | The First Affiliated Hospital of Dalian Medical University         | Wang Zhongyu  |
| 154 | The First Affiliated Hospital of Jinzhou Medical University        | Bai Guang     |
| 155 | Shenyang Military Region General Hospital                          | Han Lei       |
| 156 | Shengjing Hospital affiliated to China Medical University          | Wu Shuodong   |
| 157 | Liaoning Cancer Hospital   | Hua Xiangdong |
| 158 | The First Affiliated Hospital of Inner Mongolia Medical University | Wang Zhenxia  |

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| 159 | Baotou Cancer Hospital  | Zhao Qijun     |
| 160 | Ordos City Center Hospital  | Bai Hua Tian   |
| 161 | Ningxia Medical University General Hospital                       | Yu Songning    |
| 162 | Ningxia Hui Autonomous Region People's Hospital                   | Li Mingwei     |
| 163 | Affiliated Hospital of Qinghai University                         | Fan Haining    |
| 164 | Qinghai Provincial People's Hospital                              | Guo Yamin      |
| 165 | Qilu Hospital of Shandong University                              | Zhixu Pavilion |
| 166 | Binzhou People's Hospital   | Xia Xiuliang   |
| 167 | Shan County Dongda Hospital                                       | Li Hongsheng   |
| 168 | Jining First People's Hospital                                    | Jonson         |
| 169 | Laiwu City People's Hospital                                      | Zhao Zhiqiang  |
| 170 | Shandong Provincial Hospital                                      | Lu Jun         |
| 171 | Liaocheng People's Hospital                                       | Zhang Jinliang |
| 172 | Linyi Cancer Hospital   | Li Enshan      |
| 173 | Qingdao University Affiliated Hospital                            | Wu Liquan      |
| 174 | Qingdao Municipal Hospital  | Shi Guangjun   |
| 175 | Rizhao City Hospital  | Xu Guixing     |
| 176 | Yankuang Group General Hospital                                   | Jiang Sifeng   |
| 177 | Shanxi Grand Hospital   | Zhao Haoliang  |
| 178 | People's Liberation Army 323 Hospital                             | Yan Qimin      |
| 179 | First Affiliated Hospital of Xi'an Jiaotong University            | Qi Zhimin      |
| 180 | Renji Hospital, Shanghai Jiaotong University School of Medicine   | Wang Jian      |
| 181 | Ruijin Hospital, Shanghai Jiao Tong University School of Medicine | Han Tianquan   |
| 182 | Xinhua Hospital, Shanghai Jiao Tong University School of Medicine | Tang Zhaohui   |
| 183 | Shanghai Tenth People's Hospital                                  | Yin Lu         |
| 184 | Zhongshan Hospital affiliated to Fudan University                 | Liu Houbao     |
| 185 | West China Hospital of Sichuan University                         | Li Fuyu        |

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|-----|--|----------------|
| 186 | Chengdu Military Region General Hospital of Sichuan Province         | Tang Lijun     |
| 187 | Deyang People's Hospital, Sichuan Province                           | Zeng Hui       |
| 188 | Suining Central Hospital, Sichuan Province                           | Dai Yi         |
| 189 | Zizhong County People's Hospital, Sichuan Province                   | Zhuo Shijie    |
| 190 | Tianjin Third Central Hospital                                       | Devotion       |
| 191 | Tianjin Fourth Central Hospital                                      | Wang Fengqi    |
| 192 | Tianjin Nankai Hospital  | Li Zhonglian   |
| 193 | Tianjin Medical University Cancer Hospital                           | Li Qiang       |
| 194 | The First Affiliated Hospital of Shihezi University Medical College  | Peng Xinyu     |
| 195 | Xinjiang Uygur Autonomous Region Chinese Medicine Hospital           | Duan Shaobin   |
| 196 | Affiliated Tumor Hospital of Xinjiang Medical University             | Ding Wei       |
| 197 | Xinjiang Uygur Autonomous Region People's Hospital                   | Meng Hao 孟壕    |
| 198 | First Affiliated Hospital of Kunming Medical University              | Wang Kunhua    |
| 199 | Second Affiliated Hospital of Kunming Medical University             | Li Weiming     |
| 200 | Second Affiliated Hospital of Zhejiang University School of Medicine | Li Jiangtao    |
| 201 | Hangzhou Normal University Affiliated Hospital                       | Pan Zhijian    |
| 202 | Lishui Central Hospital, Zhejiang Province                           | Tu Chaoyong    |
| 203 | Zhejiang Yongjia Chinese Medicine Hospital                           | Xie Dongmei    |
| 204 | Daping Hospital of the Third Military Medical University             | Chen Ping      |
| 205 | Third Military Medical University Xinqiao Hospital                   | Ding Shengcai  |
| 206 | Southwest Military Hospital, Third Military Medical University       | Chen Zhiyu     |
| 207 | Chongqing Fuling Central Hospital                                    | Zeng Jiangchao |

|     |   |               |
|-----|---|---------------|
| 208 | Hepatobiliary Surgery, Chongqing<br>Emergency Medical Center                    | Liu Yongguo   |
| 209 | Second Military Medical University<br>Eastern Hepatobiliary Surgery<br>Hospital | Zhang Yongjie |

## 7.2 List of researchers in the center

| Name          | job title | division of work                                  |
|---------------|-----------|---|
| Wang Jianming | professor | overall plan                                      |
| Tian Li       | Doctor    | Information collection,<br>personnel coordination |
| Lu Yun        | master    | Information collection,<br>personnel coordination |

## 八. Reference

- [1] Hundal R, Shaffer E A. Gallbladder cancer: epidemiology and outcome[J]. Clin Epidemiol, 2014, 6(1):99-109.
- [2] Zou Shengquan, Zhang Lin. National Epidemiological Investigation Report on Gallbladder Cancer [J]. Chinese Journal of Practical Surgery, 2000, 20(1):43-46.
- [3] Cariati A, Andorno E. Cholesterol Gallstones Larger Than 3 cm Appear to be Associated With Gallbladder Cancer: Identification of an High Risk Group of Patients That Could Benefit From Preventive Cholecystectomy. [J]. Annals of Surgery, 2016, 263(3):e56.
- [4] Department of Biliary Surgery, Chinese Medical Association Surgery Branch. Guideline for the diagnosis and treatment of gallbladder cancer (2015)[J]. Chinese Journal of Digestive Surgery, 2015, 14(11):881-890.

- [5] Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer[J]. Nature Genetics, 2015, 47(9):1003.
- [6] Kanthan R, Senger JL, Ahmed S, Kanthan SC. Gallbladder Cancer in the 21st Century. J Oncol 2015;2015:967472.
- [7] Rakic M, Patrlj L, Kopljar M, Klicek R, Kolovrat M, Loncar B, Basic Z. Gallbladder cancer. Hepatobiliary Surg Nutr 2014;3:221-226.
- [8] Lee D G, Lee S H, Kim J S, et al. Loss of NDRG2 promotes epithelial-mesenchymal transition of gallbladder carcinoma cells through MMP-19-mediated Slug expression. [J]. Journal of Hepatology, 2015, 63(6):1429-1439.