Current status, trends, and predictions in the burden of gallbladder and biliary tract cancer in China from 1990 to 2019

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Abstract

Background: Gallbladder and biliary tract cancer (GBTC) has greatly damaged the health of patients and is accompanied by a dismal prognosis. The worldwide distribution of GBTC shows extensive variance and the updated data in China is lacking. This study was to determine the current status, trends, and predictions in the burden of GBTC over the past 30 years in China.

Methods: This was a descriptive, epidemiological, secondary analysis of the Global Burden of Disease, Injuries, and Risk Factor Study 2019 data. Data including incidence, prevalence, mortality, and disability-adjusted life years (DALYs) of GBTC in China by year, age, and sex were assessed. Joinpoint regression analysis was conducted to evaluate trends of disease burden due to GBTC from 1990 to 2019. Nordpred age-period-cohort analysis was applied for the projection of mortality and incidence due to GBTC from 2019 to 2044.

Results: Nationally, there were 38,634 (95% uncertainty interval [UI]: 27,350–46,512) new cases and 47,278 (95% UI: 32,889–57,229) patients due to GBTC, causing 34,462 (95% UI: 25,220–41,231) deaths, and 763,584 (95% UI: 566,755–920,493) DALYs in 2019. Both cases and rates of burden owing to GBTC were heavier among males and at old age. From 1990 to 2019, the age-standardized rates of incidence, prevalence, mortality, and DALYs of GBTC generally increased from 1990 to 2019, with average annual percentage change at 0.8% (95% confidential interval [CI]: 0.6–1.0%), 1.3% (95% CI: 1.1–1.5%), 0.4% (95% CI: 0.2–0.6%), and 0.2% (95% CI: 0.1–0.4%), respectively. Even though the age-standardized incidence rate and age-standardized mortality rate in both sexes were predicted to decline gradually from 2019 to 2044, the number of new cases and deaths were expected to grow steadily.

Conclusions: GBTC is becoming a major health burden in China, particularly among males and older individuals. Given the aging population and increasing burden, effective strategies and measurements are urged to prevent or reduce the number of new cases and deaths of GBTC.

Keywords: Gallbladder cancer; Biliary tract cancer; Global burden of disease; China; Prediction; Aging

Introduction

Gallbladder and biliary tract cancer (GBTC) has greatly damaged the survival and health of patients and brought a serious burden of disease. GBTC is the leading component of biliary tract carcinoma (BTC), accounting for about 3% of all digestive system tumors.[1] Gallbladder cancer (GBC) comprises approximately 80% to 95% of BTC,[2] and its global incidence ranks sixth among gastrointestinal tumors.[3] The vast majority of GBTC is adenocarcinoma, characterized by high-grade malignancy and low surgical resection rate. Most patients are diagnosed in the advanced stage due to its insidious onset and thus have a poor prognosis. Although surgery and curative liver transplantation are options for selected patients, GBTC has a poor prognosis with a 5-year survival rate <5%.[4]

The evaluation of disease burden can systematically, scientifically, and comprehensively quantify the comparable health damage caused by diseases, injuries, and risk factors in different regions, years, ages, and genders. The

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worldwide distribution of GBC has been recorded with extensive variance.[5] The latest epidemiological studies have shown that the morbidity and mortality of GTBC in China are at the most serious level[6] and the incident cases have increased by a huge number in the past few decades.[7] From 1972 to 1994, BTC was the fastest rising malignant tumor in Shanghai.[8] However, updated data and estimates regarding GTBC burden at the national level in China are still lacking in reports.

To provide information and guidance for public health policies and preventive and curative programs, our study was to determine the current status and trends of disease burden for GBTC over the past 30 years and to predict that of the near future in China based on the Global Burden of Disease (GBD) Study 2019.[9]

Methods

Data source and study design

The GBD 2019 is a publicly available dataset coordinated by the Institute for Health Metrics and Evaluation (IHME). GBD 2019 provides a comprehensive assessment of the descriptive epidemiology of a mutually exclusive and collectively exhaustive list of diseases and injuries for 204 countries and regions from 1990 to 2019.[9] Details of the methodology used in the GBD 2019 study are available on the IHME website (http://ghdx.healthdata.org/gbd-2019). The source of input data is derived from systematic reviews, survey data, hospital administrative data, disease registries, inpatient and outpatient data, claims, and case notifications. For raw data that were inaccessible in certain countries or regions, DisMod-MR 2.0 produces an imputed estimate for each epidemiological parameter based on available data from surrounding countries. GBD 2019 measures included: deaths, years of life lost (YLLs), years lived with disability (YLDs), disability-adjusted life years (DALYs), prevalence, incidence, life expectancy, healthy life expectancy, maternal mortality ratio, and summary exposure value. The retrieval of the database generated by GBD 2019 can be found on the website (http://ghdx.healthdata.org/gbd-results-tool).

We conducted a secondary analysis of the GBD 2019 dataset for the mainland of China to describe the disease burden of GBTC. The outcomes of interests were extracted including incidence, prevalence, mortality, and DALYs during 1990 to 2019. Informed consent was not required for the exclusion of individual level primary data.

Disease burden

The information on the estimation of GBD 2019 has been introduced elsewhere (https://www.thelancet.com/gbd). In summary, all the estimates of the quantity of interest were generated by standardized tools based on the process. Firstly, the Cause of Death Ensemble model was conducted to estimate the mortality due to specific causes from various data sources. In a linear-step mixed-effects model, a sociodemographic index was applied to generate crude mortality-to-incidence ratios. And then spatiotemporal Gaussian process regression was performed to obtain the final mortality-to-incidence ratio. The quantity of interest was estimated by the mathematical relationship between them.

Incidence is computed by new cases as a numerator divided by the total population while prevalence is calculated as the total cases divided by the total population. The mortality rate is calculated as the estimated number of deaths divided by the total population. DALYs are calculated by summing the YLLs (multiplied by the estimated number of deaths by the age of participants and the standard life expectancy of the corresponding age) and YLDs (multiplied by the prevalence and a distinct disability weight in the Bayesian regression model). All the quantities of interest were presented as per 100,000.

$$\text{Age-standardized rate} = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_i} \times 100,000$$

Age-standardized rate (ASR) was calculated as above. Considering the GBD world population, the sum of products of age-specific rates (a_i) and the standard number of reference population in the same age subgroup (w_i), and then divided by the total standard population weights (A denotes the counts of age subgroups).[9]

Analysis

The burden of GBTC was represented by incidence, prevalence, mortality, and DALYs across the year, age, and sex, including numbers and ASRs. The burdens of disease are expressed as ASR unless otherwise specified, which is better for understading the evaluation of the shifting pattern of disease burden. For age-related quantity of interests, we selected the age groups with 5-year intervals to draw a thorough description of differences and trends with aging. The statistical analysis was performed using R studio (version 4.0.3). Each quantity was calculated with a 95% uncertainty interval (UI) and significance hypothesis tests were two-sided.

To evaluate each metric trend in disease, annual percentage change (APC) and corresponding 95% confidential intervals (CIs) were computed based on the Joinpoint Regression Program (Version 4.9.0.0 Statistical Research and Application Branch, the United States National Cancer Institute; surveillance.cancer.gov/joinpoint). The simplest model possible for the data was fitted by connecting different line segments on a logarithmic scale. Model selection was performed by the Monte Carlo permutation test, which determines the P value from the permutation distributions derived from F-statistic as a goodness-of-fit measure.[10] In this process, the ASRs were applied and transformed into logarithmic form for each quantity of interest.[11] Besides, the average annual percentage change (AAPC) was also estimated referring to the secular trend for the full range of the study periods. The Z test was applied to evaluate whether an APC was statistically significant from zero at $\alpha = 0.05$ (P value <0.05 indicates a significant increase or decrease).

The ASRs of mortality and incidence due to GBTC by sex were predicted by Nordpred age-period-cohort analysis from 2019 to 2044. It was applied based on power5 age-period-cohort models to calculate prediction. The changing population structure of China during 1990 to 2044 was estimated by age, sex, and extracted from World Population Prospects 2019, Online Edition (https://population.un.org/wpp/Download/Standard/CSV/). As for world standard population weight, setting reference for prediction was computed by WHO population proportions for each age group (https://seer.cancer.gov/stdpopulations/world.who.html). The method of projection has been fully proved reliable and robust previously.[12,13] Besides the Bayesian age-period-cohort (BAPC) model,[14] integrated nested Laplace approximation approach[15] was performed to generate age-standardized projected rates for sensitivity analysis.

Results

Current status

The numbers and ASRs of burden due to GBTC in 1990 and 2019 at national level are presented in Table 1. In 2019, there were 38,634 (95% UI: 27,350–46,512) new cases of GBTC, with an age-standardized incidence rate (ASIR) of 2.01 (95% UI: 1.41–2.41) per 100,000. From 1990 to 2019, the number of incident cases of GBTC increased by 211% (95% UI: 47–322%), and the ASIR increased by 27% (95% UI: −40% to 70%). GBTC accounted for 34,462 (95% UI: 25,220–41,231) deaths, and the age-standardized mortality rate (ASMR) was 1.82 (95% UI: 1.32–2.17) per 100,000. The number of deaths from GBTC increased by 185% (95% UI: 36–287%) and the ASMR increased by 13% (95% UI: −45% to 51%). There were 47,278 (95% UI: 32,889–57,229) patients and 763,584 (95% UI: 566,755–920,493) DALYs owing to GBTC nationally in 2019. The age-standardized prevalence rate (ASPR) was 2.40 (95% UI: 1.66–2.91) per 100,000 and the age-standardized DALYs rate of GBTC was 37.71 (95% UI: 27.91–45.35) per 100,000 in China in 2019. Both cases and ASRs of GBTC burden were higher among males than those among females in 2019 at the national level.

Figure 1 presents the cases and rates for the burden of GBTC by age and sex in 2019. The incident rates of males were higher than those of females across all age groups, while the incident cases of males were lower than that of females in 65 to 69 years age group (2930.53 *vs*. 2991.45). The incident rate reached its peak at 90 to 94 years group with 44.83 (95% UI: 29.01–54.30) per 100,000 among males. Once females reach their age of 85 to 89 years, the incident rate decreased rapidly (26.27, 95% UI: 15.07–34.73) per 100,000 [Figure 1A]. Since GBTC is a deadly disease, the pattern of the burden of metrics shared similar characteristics. The prevalent rate of males was 1.6 times higher than that of females at 85 to 89 years of age group, which reached their peaking value (40.69 *vs*. 25.20) per 100,000 [Figure 1B]. The rate of mortality in females increased with age increasing: from 0.02 (95% UI: 0.02–0.03) per 100,000 at 20 to 24 years to 32.74 (95% UI: 19.44–42.05) per 100,000 [Figure 1C]. The DALYs rate surged to 409.68/100,000 and 244.57/100,000 among males at 85 to 89 years old and females at 75 to 79 years old, respectively [Figure 1D]. The incidence, prevalence, and mortality due to GBTC did not rise drastically until people reached the age of 65 to 69 years old, with rates under 10/100, 1000.

Trends

As shown in Figure 2, Joinpoint regression analysis identified trends of burden due to GBTC in China from 1990 to 2019. The four metrics of burden had similar temporary variation during the study period (Joinpoints were 1998, 2001, 2004, 2010, and 2015, respectively). ASIR, ASPR, ASMR, and ASR of DALYs due to GBTC increased with statistical significance in China over the past 30 years, AAPCs were 0.8% (95% CI: 0.6–1.0%), 1.3% (95% CI: 1.1–1.5%), 0.4% (95% CI: 0.2–0.6%), and 0.2% (95% CI: 0.1–0.4%), respectively. The details of APCs of each metric of burden from 1990 to 2019 are

Table 1: Numbers and ASRs of GBTC burden and changes from 1990 to 2019 in China by sex.

	N (95% UI)			ASR, per 100,000 (95% UI)		
Burden	1990	2019	Change	1990	2019	Change
Overall						
Incidence	12,436 (10,310, 20,007)	38,634 (27,350, 46,512)	2.11 (0.47, 3.22)	1.58 (1.32, 2.51)	2.01 (1.41, 2.41)	0.27 (−0.40, 0.70)
Prevalence	13,708 (11,345, 21,652)	47,278 (32,889, 57,229)	2.45 (0.61, 3.70)	1.64 (1.37, 2.59)	2.40 (1.66, 2.91)	0.47 (−0.40, 0.70)
Mortality	12,083 (9983, 19,476)	34,462 (25,220, 41,231)	1.85 (0.36, 2.87)	1.61 (1.35, 2.54)	1.82 (1.32, 2.17)	0.13 (−0.45, 0.51)
DALYs	309,016 (254,137, 486,145)	763,584 (566,755, 920,493)	1.47 (0.20, 2.36)	35.18 (29.16, 56.02)	37.71 (27.91, 45.35)	0.07 (−0.48, 0.45)
Male						
Incidence	5662 (4404, 9482)	19,761 (13,243, 24,912)	2.49 (0.7, 4.29)	1.56 (1.25, 2.51)	2.25 (1.52, 2.79)	0.44 (−0.28, 1.09)
Prevalence	6347 (4928, 10,559)	24,133 (15,812, 30,655)	2.80 (0.83, 4.80)	1.60 (1.27, 2.60)	2.63 (1.74, 3.30)	0.64 (−0.28, 1.09)
Mortality	5439 (4309, 9162)	17,764 (12,880, 22,424)	2.27 (0.65, 3.76)	1.62 (1.33, 2.59)	2.09 (1.53, 2.60)	0.29 (−0.32, 0.82)
DALYs	146,740 (115,524, 241,026)	410,611 (293,207, 522,303)	1.80 (0.44, 3.11)	34.26 (27.38, 56.37)	42.60 (30.64, 53.79)	0.24 (−0.36, 0.80)
Female						
Incidence	6774 (5289, 11,594)	18,872 (11,321, 24,679)	1.79 (0.14, 3.13)	1.64 (1.27, 2.82)	1.84 (1.10, 2.41)	0.12 (−0.54, 0.65)
Prevalence	7361 (5656, 12,338)	23,145 (13,575, 30,377)	2.14 (0.26, 3.69)	1.70 (0.99, 2.15)	2.23 (1.31, 2.93)	0.31 (−0.54, 0.65)
Mortality	6643 (5142, 11,478)	16,697 (10,295, 21,303)	1.51 (0.07, 2.71)	1.66 (1.29, 2.84)	1.64 (1.01, 2.09)	−0.01 (−0.57, 0.45)
DALYs	162,275 (123,279, 279,484)	352,972 (220,461, 453,953)	1.18 (−0.07, 2.24)	36.45 (27.95, 62.67)	33.57 (20.96, 43.23)	−0.08 (−0.60, 0.37)

ASR: Age-standardized rate; DALYs: Disability-adjusted life years; GBTC: Gallbladder and biliary tract cancer; UI: Uncertainty interval.

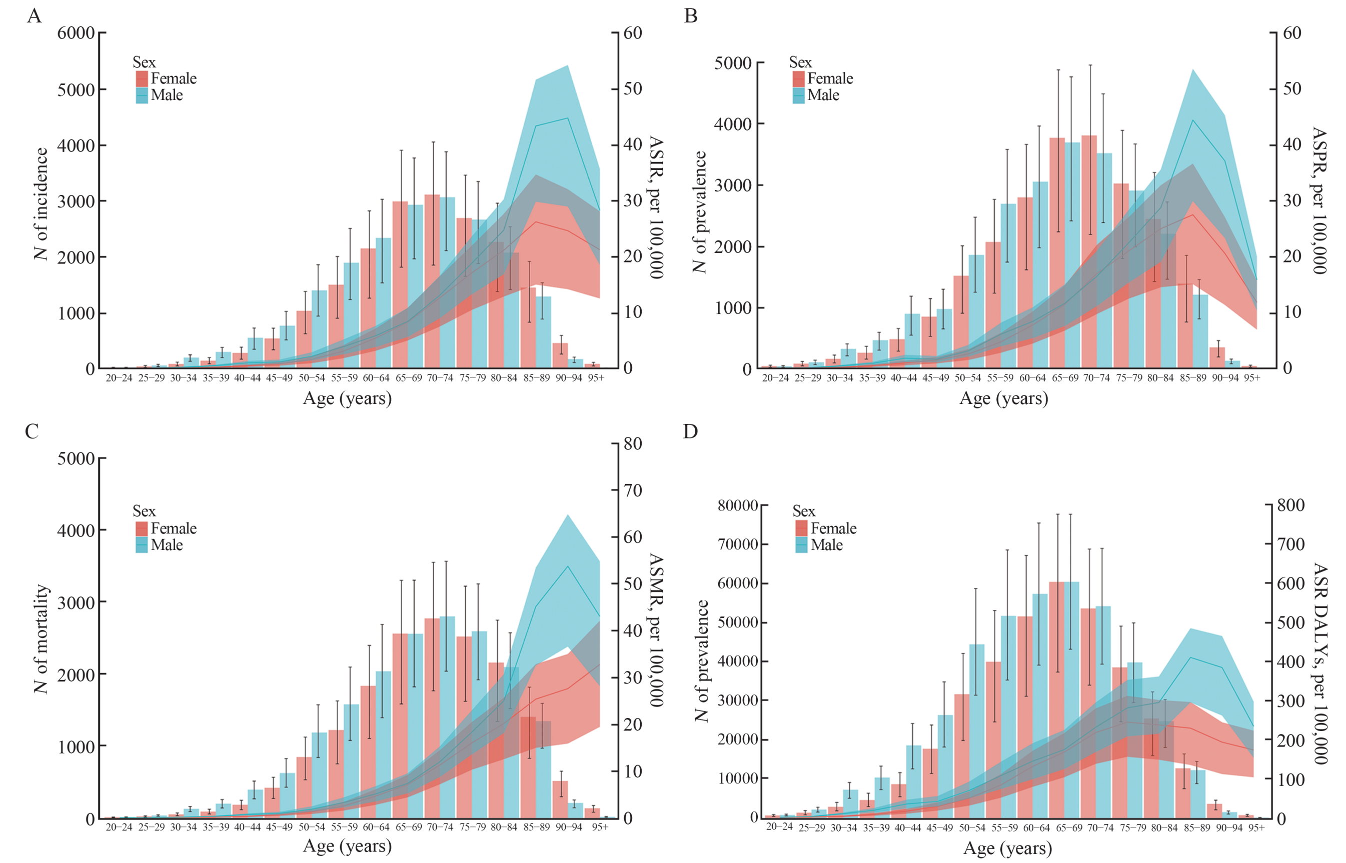

Figure 1: The cases and rates of incidence (A), prevalence (B), mortality (C), and DALYs (D) due to GBTC by age and sex. Error bar and shading indicate the 95% UIs. Bars indicate numbers and lines indicate rates. ASIR: Age-standardized incidence rate; ASMR: Age-standardized mortality rate; ASPR: Age-standardized prevalence rate; ASR: Age-specific rate; DALYs: Disability-adjusted life-years; GBTC: Gallbladder and biliary tract cancer; N: Number; UIs: Uncertainty intervals.

presented in Table 2. For ASIR, ASPR, ASMR, and ASR of DALYs due to GBTC, a rapid decrease was detected from the inception to 1998 with APCs at −1.3% (95% CI: −1.4%, −1.1%), −0.9% (95% CI: −1.0%, −0.8%), −1.5% (95% CI: −1.6%, −1.4%), and −1.7% (95% CI: −1.8%, −1.7%), respectively, and followed by two dramatic increases during 1998–2004 with APCs at ≥5%. The ASIR and ASPR did not stop rising up until 2010 (APCs: 0.8%, 95% CI: 0.5%, 1.0%; APCs: 1.4%, 95% CI: 1.1%, 1.7%), when all the metrics began gradually declining.

Figure 3 delineated the difference in trends in burden due to GBTC from 1990 to 2019 between males and females. The ASIR, ASMR, and ASR of DALYs among males did not exceed that among females until 1997 (1.47 *vs*. 1.45 per 100,000), 1995 (1.52 *vs*. 1.50 per 100,000), and 1998 (31.28 *vs*. 30.91 per 100,000), respectively. During 1998 to 2004, the ASPRs almost overlapped between males and females [Figure 3B]. All the metrics began to show a disparity by sex in around 2005. Table 2 indicated that all the burdens of males increased faster than that of females during 2005 to 2010 and then decreased slower during 2011 to 2019. The ASIRs, ASPRs, ASMR, and ASR DALYs in males have been through a steady increase from 1990 to 2019, with AAPC at 1.2% (95% CI: 1.0–1.5%), 1.7% (95% CI: 1.4–2.0%), 0.9% (95% CI: 0.6–1.1%), and 0.7% (95% CI: 0.5–1.0%), respectively. For females, ASIR and ASPR generally showed a slight increase with AAPC at 0.4% (95% CI: 0.1–0.7%) and 0.9% (95% CI: 0.6–1.2%), respectively. While relatively stable trends were observed in ASMR and ASR of DALYs among females.

Predictions

Age-period-cohort analysis was conducted to predict the ASIRs and ASMRs of GBTC by sex, and the trends and projections are presented in Figure 4. The ASRs in both males and females were predicted to decrease from 2020 to 2044. The variation of temporary trends between sex was similar, but the velocity of decreasing was more pronounced in females. And the ASIRs and ASMRs in 2040 to 2044 are expected to be lower than those in 1990 among females. Consistent results are found in Figure 5, which was performed by BAPC to assess the robustness of the projection. The sensitivity analysis applied ASRs in each observed year to predict the ASRs and their 95% highest density interval from 2020 to 2044. The tendencies were predicted to remain relatively stable compared with the results of the age-period-cohort model since the latter computed the average of rates in 5 years.

As is revealed in Figure 6, the number of new cases and deaths due to GBTC were expected to continue to rise in China in the following 24 years. In the first decade, the

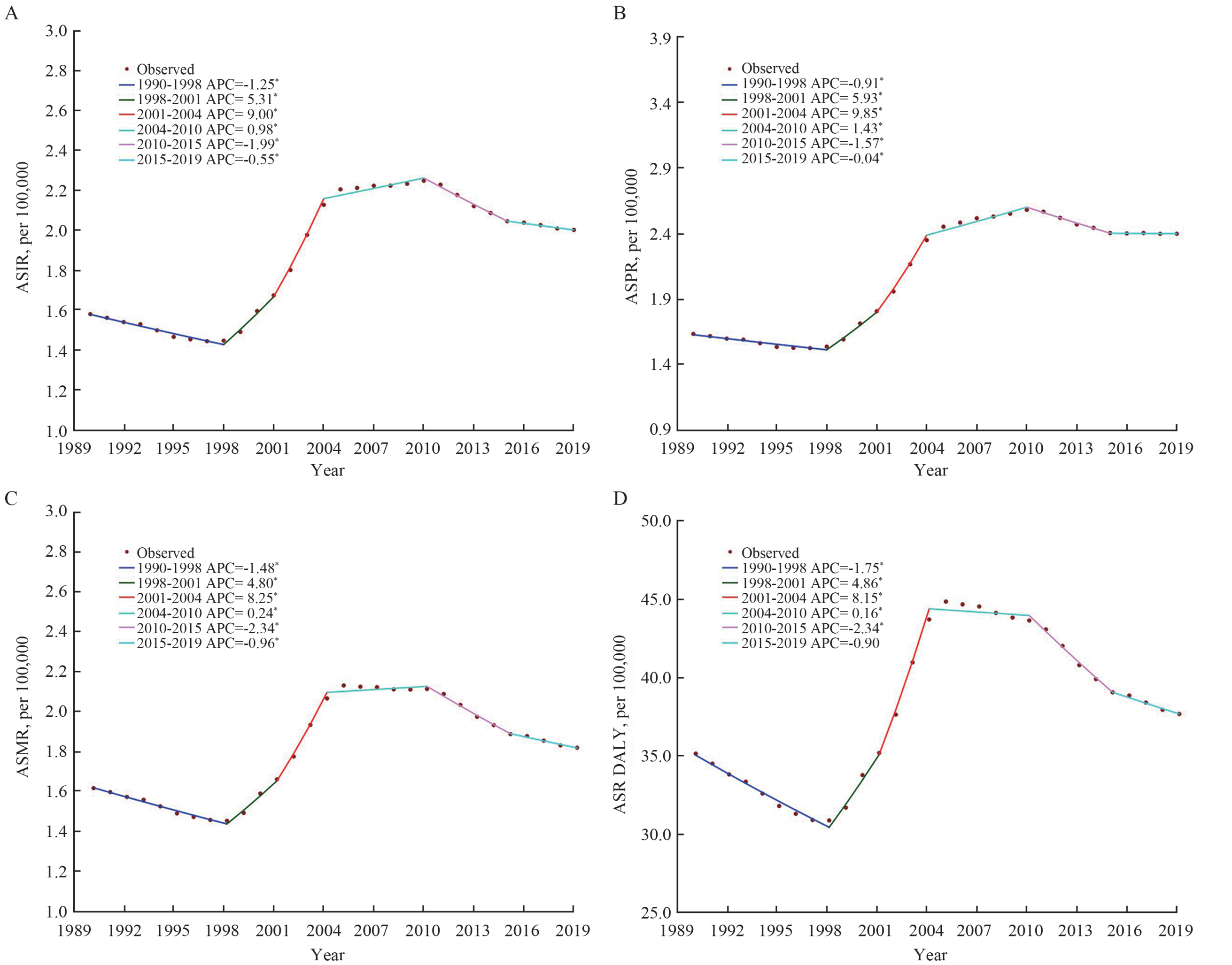

Figure 2: The trends in ASRs of incidence (A), prevalence (B), mortality (C), and DALYs (D) due to GBTC from 1990 to 2019 by Joinpoint regression. APC: Annual percentage change; ASIR: Age-standardized incidence rate; ASMR: Age-standardized mortality rate; ASPR: Age-standardized prevalence rate; ASRs: Age-standardized rates; DALYs: Disability-adjusted life-years; GBTC: Gallbladder and biliary tract cancer.

predicted numbers of incidence among males were close to the lower estimated numbers, whose corresponding rates decreased by 1% annually based on the rates in 2019. The projection of mortality lasted for another 5 years. And then, the numbers of incidence and mortality added up between lower and stable estimated numbers, whose corresponding rates remain as 2019 [Figure 6A, C]. As for females, the predicted numbers in both incidence and mortality remain lower than reference but kept a steady increase [Figure 6B, D]. The number of incident cases was expected to increase from 19,979 in 2019 to 34,227 in 2044 among males, and the number increased from 19,063 in 2019 to 31,603 in 2044 among females. The increasing numbers of mortality would reach 30,604 and 27,617 among males and females in 2044, respectively.

Discussion

This study provided a comprehensive evaluation of the current status in 2019, trends over the past 30 years, and predictions from 2020 to 2044 in the burden due to GBTC in China based on the GBD 2019. The main findings of this study are as follows: the numbers of new cases, patients, deaths, and DALYs due to GBTC at the national level in 2019 were high in both sexes. The ASRs of burden for GBTC were higher among males and the old had larger number of cases or higher rates of burden in both sexes in 2019. The general trends in the burden of GBTC increased from 1990 to 2019, with a turning point in 2010. And the disparity between sexes was amplified around 2005. The numbers of incidence and mortality owing to GBTC were likely to increase steadily from 2020 to 2044, albeit with the decrease in ASRs in both sexes.

The estimated ASRs and number of burdens due to GBTC in our study remained high in China. The latest investigation analyzed data from Chinese cancer registries in 2014, reporting the ASRs by world standard population of incidence and mortality were 2.37/100,000 and 1.71/100,000.[16] According to GBD 2019 data, the ASIR and ASMR in China in 2014 were 2.09 (95% UI: 1.52–2.33) per 100,000 and 1.93 (95% UI: 1.67–2.49) per 100,000, respectively. The results were consistent and the minor disparities mostly resulted from the model and data

Table 2: APC of GBTC ASR burden from 1990 to 2019 in China by sex.

	Incidence		Prevalence		Mortality		DALYs	
Trends	Year	APC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)
Overall								
Trend 1	1990–1998	−1.3 (−1.4, −1.1)	1990–1998	−0.9 (−1.0, −0.8)	1990–1998	−1.5 (−1.6, −1.4)	1990–1998	−1.7 (−1.8, −1.7)
Trend 2	1998–2001	5.3 (4.1, 6.5)	1998–2001	5.9 (4.6, 7.3)	1998–2001	4.8 (3.7, 5.9)	1998–2001	4.9 (4.0, 5.8)
Trend 3	2001–2004	9.0 (7.8, 10.2)	2001–2004	9.8 (8.5, 11.2)	2001–2004	8.3 (7.1, 9.4)	2001–2004	8.1 (7.2, 9.1)
Trend 4	2004–2010	0.8 (0.5, 1.0)	2004–2010	1.4 (1.1, 1.7)	2004–2010	0.2 (0, 0.5)	2004–2010	−0.2 (−0.4, 0)
Trend 5	2010–2015	−2.0 (−2.3, −1.6)	2010–2015	−1.6 (−2.0, −1.2)	2010–2015	−2.3 (−2.7, −2)	2010–2015	−2.3 (−2.6, −2.1)
Trend 6	2015–2019	−0.6 (−0.9, −0.2)	2015–2019	0 (−0.4, 0.4)	2015–2019	−1 (−1.3, −0.6)	2015–2019	−0.9 (−1.2, −0.6)
AAPC*	1990–2019	0.8 (0.6, 1.0)	1990–2019	1.3 (1.1, 1.5)	1990–2019	0.4 (0.2, 0.6)	1990–2019	0.2 (0.1, 0.4)
Male								
Trend 1	1990–1996	−1.2 (−1.5, −0.8)	1990–1996	−0.9 (−1.3, −0.6)	1990–1996	−1.3 (−1.6, −1)	1990–1996	−1.7 (−2, −1.3)
Trend 2	1996–1999	1.3 (−0.7, 3.3)	1996–1999	1.8 (−0.3, 3.9)	1996–1999	0.9 (−1, 2.7)	1996–1999	1.0 (−1.0, 3.1)
Trend 3	1999–2005	7.2 (6.7, 7.7)	1999–2005	7.9 (7.4, 8.4)	1999–2005	6.6 (6.2, 7.0)	1999–2005	6.8 (6.3, 7.3)
Trend 4	2005–2011	1.1 (0.6, 1.5)	2005–2011	1.5 (1.1, 2.0)	2005–2011	0.6 (0.2, 1.1)	2005–2011	0.1 (−0.4, 0.5)
Trend 5	2011–2019	−1.1 (−1.4, −0.9)	2011–2019	−0.7 (−0.9, −0.4)	2011–2019	−1.5 (−1.7, −1.3)	2011–2019	−1.4 (−1.7, −1.2)
AAPC*	1990–2019	1.2 (1.0, 1.5)	1990–2019	1.7 (1.4, 2.0)	1990–2019	0.9 (0.6, 1.1)	1990–2019	0.7 (0.5, 1.0)
Female								
Trend 1	1990–1998	−1.7 (−1.9, −1.5)	1990–1998	−1.3 (−1.5, −1.1)	1990–1998	−2 (−2.2, −1.8)	1990–1998	−2.2 (−2.3, −2)
Trend 2	1998–2001	5.0 (3.0, 7.1)	1998–2001	5.6 (3.6, 7.6)	1998–2001	4.5 (2.5, 6.6)	1998–2001	4.3 (2.7, 5.9)
Trend 3	2001–2004	9.1 (7, 11.3)	2001–2004	10.1 (8.0, 12.2)	2001–2004	8.3 (6.2, 10.5)	2001–2004	7.9 (6.3, 9.6)
Trend 4	2004–2010	−0.1 (−0.5, 0.4)	2004–2010	0.6 (0.2, 1.0)	2004–2010	−0.7 (−1.1, −0.2)	2004–2010	−1.2 (−1.5, −0.9)
Trend 5	2010–2015	−2.7 (−3.3, −2.1)	2010–2015	−2.3 (−2.9, −1.7)	2010–2015	−3.1 (−3.7, −2.5)	2010–2015	−3.1 (−3.5, −2.6)
Trend 6	2015–2019	−0.4 (−1.0, 0.2)	2015–2019	0.2 (−0.4, 0.8)	2015–2019	−0.8 (−1.4, −0.2)	2015–2019	−0.8 (−1.3, −0.3)
AAPC*	1990–2019	0.4 (0.1, 0.7)	1990–2019	0.9 (0.6, 1.2)	1990–2019	−0.1 (−0.4, 0.2)	1990–2019	−0.3 (−0.5, 0)

* The ASR was deemed to be in an increasing trend if AAPC and its lower boundary were both >0, or a decreasing trend if AAPC and its upper boundary were both >0; otherwise, the CI contains 0 then the trend of ASR was uncertain over time. AAPC: Average annual percentage change; APC: Annual percentage changes; ASR: Age-standardized rate; CI: Confidential interval; DALYs: Disability-adjusted life years; GBTC: Gallbladder and biliary tract cancer.

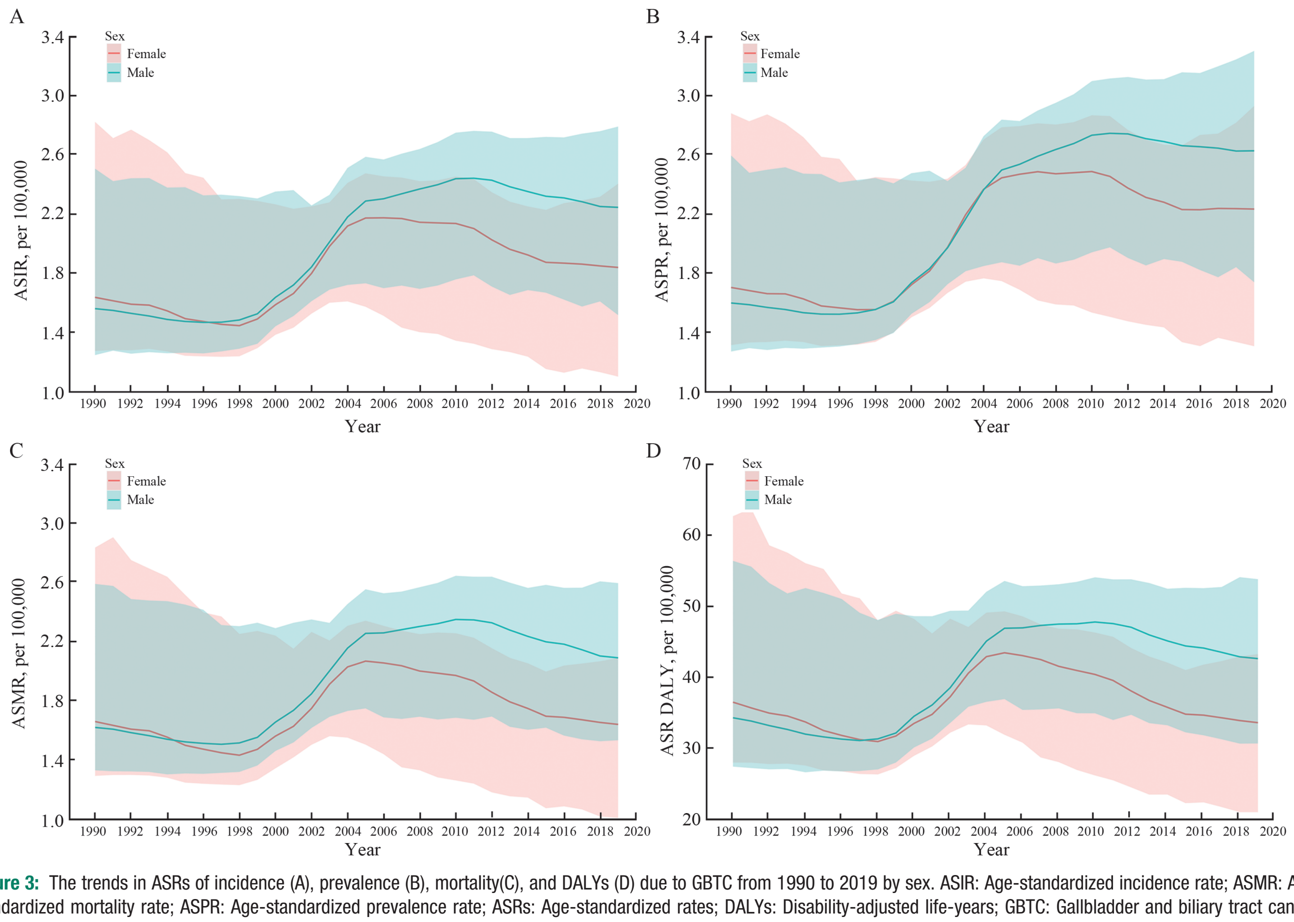

Figure 3: The trends in ASRs of incidence (A), prevalence (B), mortality(C), and DALYs (D) due to GBTC from 1990 to 2019 by sex. ASIR: Age-standardized incidence rate; ASMR: Age-standardized mortality rate; ASPR: Age-standardized prevalence rate; ASRs: Age-standardized rates; DALYs: Disability-adjusted life-years; GBTC: Gallbladder and biliary tract cancer.

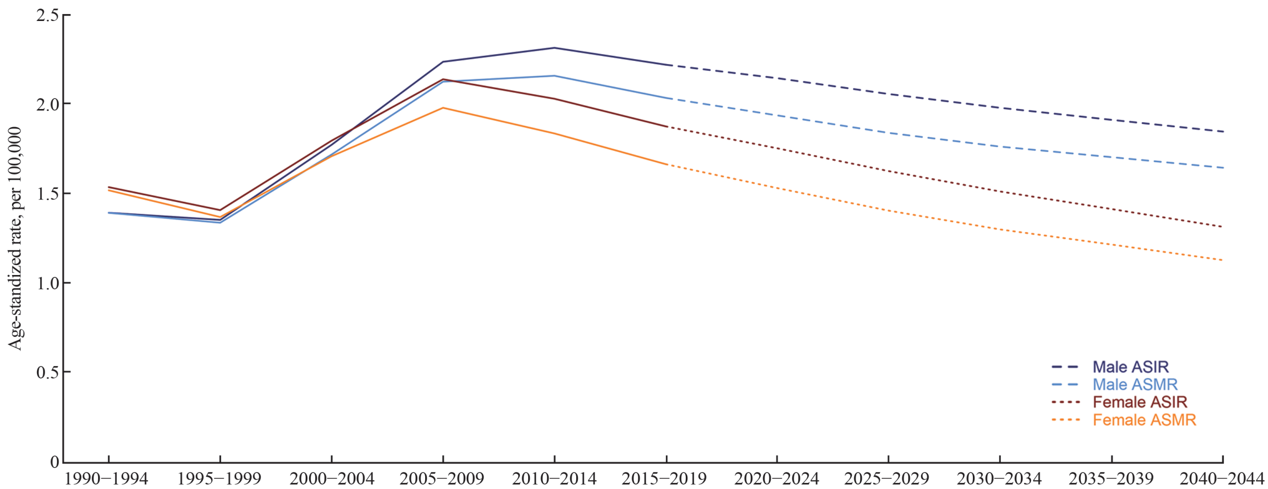

Figure 4: The trends and predictions in ASIRs and ASMRs of GBTC in China from 1990 to 2044 by sex. Solid lines denote observed values (ASRs were generated by the average of 5 years) and dashed lines denote predicted rates (predicted by age-period-cohort analysis). ASIR: Age-standardized incidence rate; ASMR: Age-standardized mortality rate; ASR: Age-standardized rate; GBTC: Gallbladder and biliary tract cancer.

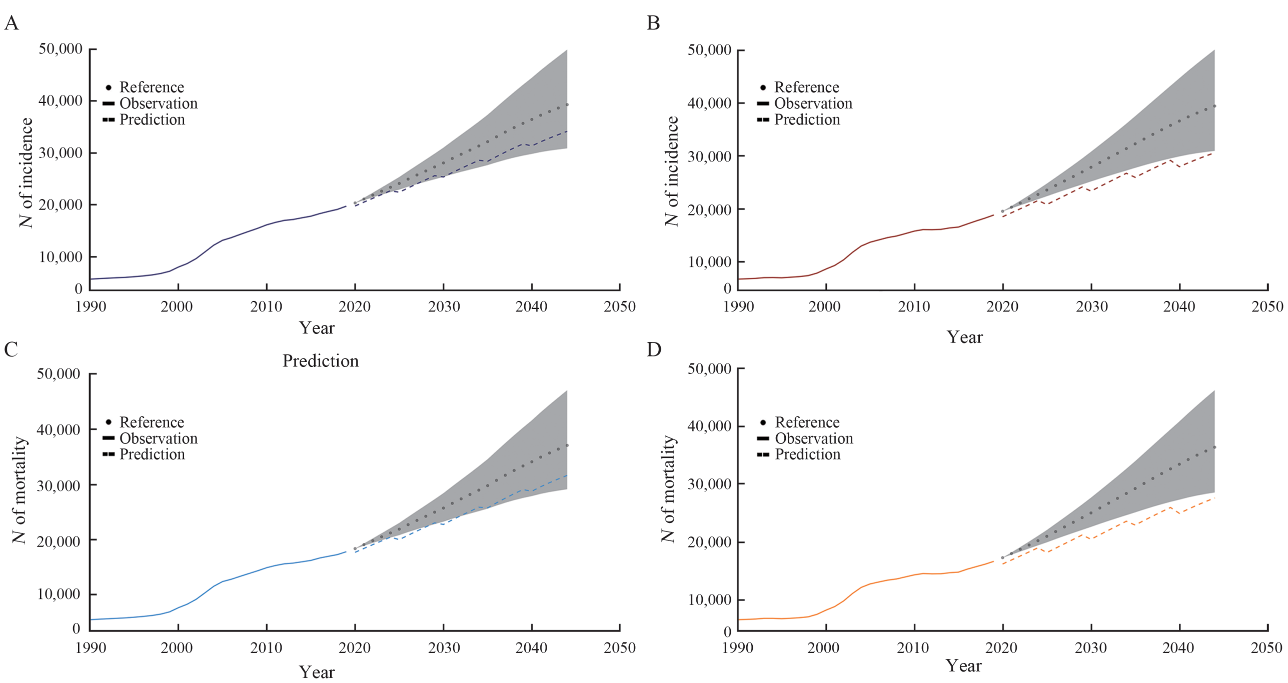

Figure 5: The trends and predictions in ASIRs for males (A) and females (B), ASMRs for males (C) and females (D) of GBTC from 1990 to 2044. Solid dots and lines denote observed values (ASRs were extracted from GBD 2019) and vertical dashed lines indicate where the prediction starts. The dashed lines denote predicted rates, the blue shadow represents 95% highest density interval of predicted values (predicted by BAPC analysis). ASIR: Age-standardized incidence rate; ASMR: Age-standardized mortality rate; ASRs: Age-standardized rates; BAPC: Bayesian age-period-cohort; GBD: Global Burden of Disease; GBTC: Gallbladder and biliary tract cancer; N: Number.

used in GBD estimation. China is a high-GBTC risk country and accounts for 1/4 of cases worldwide.[17-19] There were 199,211 new cases, 172,440 patients, 172,440 deaths, and 3621,472 DALYs due to GBTC globally in 2019, the burden in China took up over one-fifth. The number of new cases owing to GBTC in China accounts for 24.7% worldwide, based on the data from Global cancer statistics 2018.[3] The shared lifestyle and metabolic factors including high-fat, high caloric diet, obesity, and diabetes may account for the burden in China.[19] Regional variations in both GBC and BTC were documented in current studies.[5,20] These extensive variations were caused by the disparities in geography, ethnicity, and culture, which addressed the effect of environmental and genetic factors on the development and progression of GBTC.[2,21]

In 2019, we found that Chinese males had a higher burden of GBTC than females. Existing studies indicated that females were two times more likely to have GBTC than

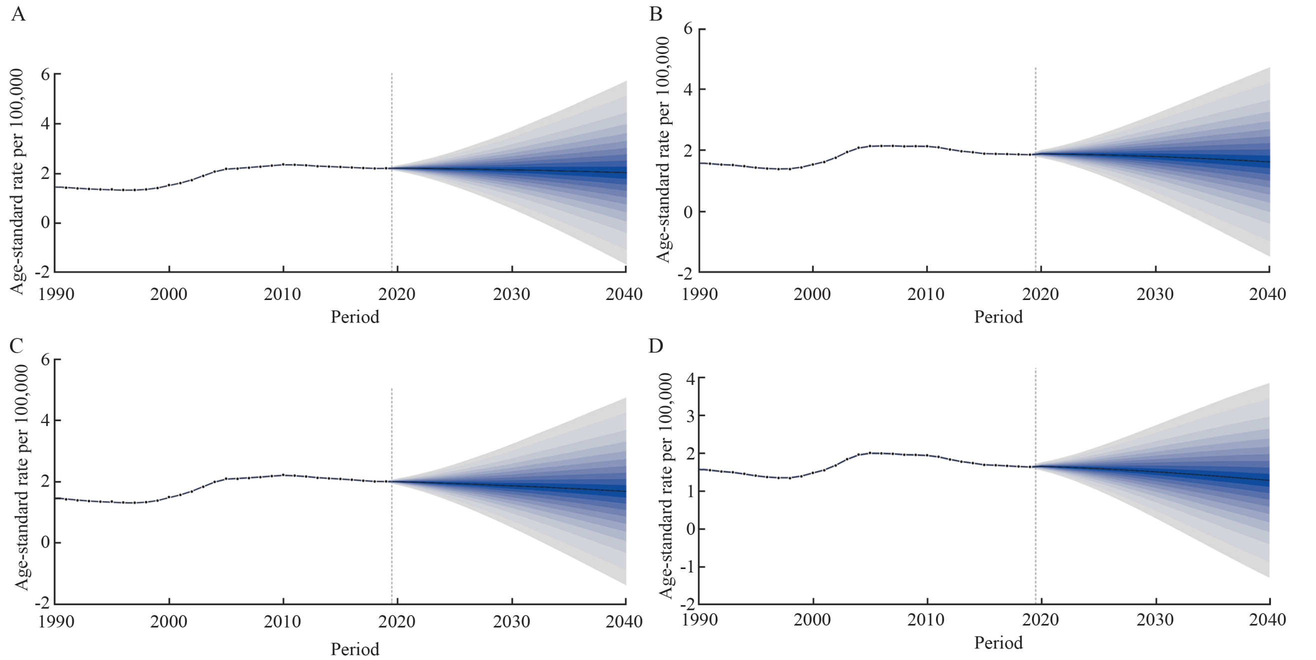

Figure 6: The trends and predictions in numbers of incident cases for males (A) and females (B), numbers of mortality for males (C) and females (D) of GBTC in China from 1990 to 2044. Solid lines denote observed values (numbers were extracted from GBD 2019) and dashed lines denote predicted rates (predicted by age-period-cohort analysis). Dots represent estimated numbers with baseline rate (based on rates of 2019) and shading areas indicate increase or decrease by 1% per year. ASIR: Age-standardized incidence rate; ASMR: Age-standardized mortality rate; GBD: Global Burden of Disease; GBTC: Gallbladder and biliary tract cancer.

males in Latin American countries, while in Japan and Korea there were >30% in men.[22] The association between the incidence of GBC and gender may be influenced by sex hormones, cholesterol cycling, and infection.[23,24] The gender disparity remains perplexing and the etiology mechanism needs to be identified. Besides, an increasing burden was observed among older adults in our results. Zou and Zhang[25] carried out a national study of GBC covering 116 hospitals from 28 Chinese provinces from 1986 to 1998. Another study recruited 2379 patients with gallbladder carcinoma from 17 hospitals in China.[26] Their results indicated that the older population was more common and mostly diagnosed at an advanced stage. The increasing incidence of GBTC with increasing age at a median age of 67 years, and the peak age of death aged >75 years.[2,27] The primary risk factor of GBTC was the occurrence of gallbladder disease,[28] and it was strongly associated with older age as well as other factors including obesity, physical activity, and hormonal factors.[7,29,30] Considering the characteristics of GBTC, corresponding primary prevention, medical treatment, and diagnosis care should be adapted to the gender and aging issue.

The burden of GBTC is increasing and poses a significant threat to the medical system in China. Our result revealed the announced rises observed in the numbers of the burden of GBTC, as well as the slight increase in ASRs during the past 30 years in China. The estimated trends were observed globally in a previous study based on GBD 2017, the numbers of new cases, deaths, and DALYs increased significantly while the ASIR, ASMR, and DALYs decreased globally from 1990 to 2017.[7] The disparity of trends mostly derived from the elongated lifespan, increasing population of aging, and promotion of medical detections. Following the findings above, Bao *et al*[31] reported an increase in the overall BTC incidence rate from 1977 to 2010 in Shanghai. Our results revealed the turning point of 2010 when the burden of GBTC started declining to various extents. From 1990 to 2008, the burden of GBTC increased substantially with the rapid growth of the economy in China. After the financial crisis, the pace of development slowed down[32] and there may come the lag effect of a decline in the burden of GBTC. As current studies pointed out, the burden of GBTC increased with increasing Socio-demographic Index globally.[7,22,33] The interaction may be caused by several explanations as follows: higher awareness and utilization of detection and cholecystectomy, an unhealthy lifestyle, increasing chronic disease, and aging population.[34]

Even though ASIRs and ASMRs were likely to decrease in both sexes, the number of new cases and deaths were expected to increase steadily in the coming 24 years. Considering the adverse outcomes in patients with GBTC, it is essential to develop and implement strategies for the prevention. Current research has emphasized the importance of controlling gallstones to substantially reduce the burden worldwide, which is associated with the incidence and mortality from GBTC.[35] Health policies and management are urged to implement to reduce modifiable risk factors of gallstones as well as GBTC, including smoking, unhealthy daily diet, obesity, lack of physical activity, and diabetes.[7,36] Owing to the huge variance between countries and regions in the burden of GBTC,[37] the investigations of preventable factors in the Chinese population are favorable for further health strategies and clinical guidelines.

This is a study based on the GBD 2019 study to describe the lasted status and chronological trends of GBTC in China and provide the projection for the coming 24 years. While limitations should be noted. On one hand, only GBD study 2019 data were included in this study, causing some uncertainties in the estimates. The GBD data were aggregated and adjusted via a back-estimation from the mortality data source. To supply a gap, all the data were presented with UIs for metrics, as well as CIs for measures in this study. On the other hand, this study did not include specific data in provinces to describe more detailed information about GBTC, and further study is favorable to include.

In conclusion, our study identified the national burden of GBTC with sex and age difference in 2019, described the increasing chronological trends of the burden by sex during the past 30 years, and predicted the decrease of ASRs but an increase in number in new cases and deaths from 2020 to 2044. The results not only provided updated information on the burden of GBTC in the Chinese population for further research but also indicated the corresponding strategies and measurements for the prevention and management of risk factors for GBTC.

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Conflicts of interest

None.

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