Male gender and obesity are risk factors of gallbladder polyps in a large northwest Chinese population

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Abstract

Objectives

The aim of this study was to determine the prevalence and related risk factors of gallbladder polyps in a northwest Chinese population.

Methods

A retrospective investigation was conducted on the prevalence and risk factors of gallbladder polyps among subjects who underwent physical examination in Shanxi Harmony Healthy Examination Center, from January 2016 to December 2020. Demographic, serum biochemistry, and ultrasonography data were collected from all patients. The correlations between the prevalence of gallbladder polyps and sex, age, body mass index (BMI), serum biochemistry, liver viral markers were calculated for all patients.

Results

A total of 67438 people aged from 18 to 75 years were enrolled in the study. Overall prevalence of gallbladder polyps in northwest China was approximately 7.8% and with the highest prevalence among middle-aged men. Analysis risk factors for increased odds ratios (ORs) of gallbladder polyps development were female (OR = 0.746; 95%CI, 0.624–0.891, P = 0.001) and BMI(25-27.5kg/m^2) (OR = 1.243; 95%CI, 1.035–1.494, P = 0.020), BMI(≥ 27.5 kg/m^2) (OR = 1.274; 95%CI, 1.038–1.562, P = 0.020). Other demographic characteristic and serum biochemistry parameters, including blood pressure, blood lipids, liver and renal function, liver viral markers did not correlate with the prevalence of gallbladder polyps.

Conclusions

Prevalence of gallbladder polyps among northwest Chinese people are a little higher to those reported for other populations. Male gender and BMI were strong risk factors for gallbladder polyps formation.

Introduction

Gallbladder polys (GBP) is the most common biliary diseases and are defined as lesions protruding from the mucosa of gallbladder[1]. The estimated prevalence of GBP is approximately 5% in the global population[2]. In population studies, gallbladder polyps can be easily diagnosed by abdominal ultrasonography with high sensitivity (90.1%) and specificity (93.9%)[3, 4]. Most GBP are classified as “pseudo”-polyps with no malignancy potential and do not need any follow-up or intervention. Only 5% of GBP are considered “true” GBP, which include adenocarcinomas or adenomas that need to be surgically removed[2]. Although the malignancy rate of GBP is as low as 3%-8%[5], the overall 5-year survival rate for gallbladder cancer has been less than 5%. Early treatment can significantly improve patient survival rate and late or missed diagnoses may be fatal[6]. Therefore, GBP should be detected as early as possible.

It is important to investigate the risk factors of GBP formation, which will be help to make clinical strategy for treatment and prevention. Obesity may be a major risk factor for the development of many diseases, including gallbladder disease. The prevalence of overweight and obesity is not only high but increasing substantially worldwide, especially in the developing country like China[7], of which the adult overweight is reported from 11.7% in 1991 to 29.2% in 2009[8]. GBP can be comprised of cholesterol of associated with inflammation [9], and it is plausible that serum lipids, particularly hyperlipidemia, as well as other metabolic index may be associated with GBP. In previous studies of the Chinese population, the risk factors for GBP were male and glucose intolerance individuals [10], as well as hepatitis B virus [11]. Sex and BMI were not reported to be related with GBP in Danish and Japanese populations[1, 12]. Prevalence of gallbladder polyps is rarely reported in China, and the risk factors for these diseases are not fully understood [3] [13]. A better understanding of the prevalence and risk factors of gallbladder polyps may improve the prevention and treatment strategies of this disease. Therefore, the purpose of this study was to determine the prevalence and risk factors of gallbladder polyps in a northwest Chinese population.

Materials And Methods

Study population and design

This study was conducted at Shanxi Harmony Healthy Examination Center, from January 2016 to December 2020. All subjects underwent a general medical examination, which included anthropometric data, serum laboratory test and abdomen ultrasonography. All subjects filled in the unified information form. Age, gender, weight, height and blood pressure data were abstracted. Body mass index（BMI）(kg/m^2) was used to measure obesity.

Ultrasonography examination was carried out after an overnight fast and performed by specific abdomen experts using a high resolution ultrasonic probe (Logiq E9 GE Medical systems, USA). Subjects were supine, left leaning, and scanned along the long or horizontal axis between ribs to clearly show the outline and echo of gallbladder. The ultrasound diagnostic criteria of gallbladder polyps is “hyperechonic immobile echoes protruding from the gallbladder wall into the lumen without an acoustic shadow”. All images were evaluated by experienced ultrasound physicians. Intraobserver and interobserver reliability were evaluated in 30 US using intraclass correlation coefficients (ICCs). Intraobserver reliability for the two observers was calculated by repeated US. Interobserver reliability was calculated between the two times separate measurements of two observers respectively.

Demographic, clinical and risk factor information was collected by reviewing participants' health examination reports through a computer system. Venous blood serum samples were drawn in the morning after fasted for at least 8 hours. Levels of fasting plasma glucose (FPG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin(Tbil),direct bilirubin (Dbil) , γ-glutamyl transferase (γ-GTP), triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), uric acid (UA), and creatinine(Cr), blood urea nitrogen (BUN) were measured using an ROCHE 701 automatic chemistry analyzer (ROCHE Group, Switzerland).

Statistical analysis

The Age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), fasting plasma glucose (FPG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin(Tbil),direct bilirubin (Dbil) , γ-glutamyl transferase (γ-GTP), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol(LDL-C), Uric acid (UA), and creatinine(Cr), blood urea nitrogen (BUN) on the risk of gallbladder polyps were analyzed with the use of multilevel mixed-effects logistic regression analysis. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and P values were calculated. All analyses were conducted with the statistical package STATA 13.1 (StataCorp LP, College Station, TX, USA), and GraphPad Prism 8 (GraphPad Software, USA). P values <0.05 were considered statistically significant.

Ethics statement

The study protocol was approved by the ethics committees of Harmony Healthy Examination Center. All participants obtained informed consent.

Results

The informatic database at Harmony Healthy Examination Center was used to compile a list of all participants to the institution from January 2016 to December 2020. During that time, 73671 participants with physical examination and related blood tests were recorded. Excluded data missing of age, sex, BMI, blood pressure and related blood tests, 67438 participants were included. Their median age was 46 years and 35674 (52.9%) were male and 31764 (47.1%) were female. The overall prevalence of GBP in this series was 7.8%, lower than the previous Chinese study, which was 9.5% (*3*). The prevalence was further stratified with the age of GBP (**Fig 1**). GBP was more common in middle-aged subjects, peaking at 41-50 years of age (10.1%). The difference between males and females was stratified by age (**Fig 2**). The prevalence of GBP in males was significantly higher than that compared to females in all age groups (except in participants aged >70 years). The total prevalence in males was 8.8% (3139/35674) *vs.* 6.6% (2096/31764) in females. The prevalence of GBP was stratified according to BMI (**Fig.3**). The prevalence of GBP was increased with BMI. There was a higher prevalence of GBP in people of overweight and obesity group (9.0%) compared with normal weight group (7%). Lean people had a significant low prevalence of GBP (3.6% in all), while the prevalence was not significant different between overweight and obesity group. The difference between males and females was stratified by BMI (**Fig 4**). Prevalence of GBP was higher in male than in female in BMI over 18.5, and lower in BMI below 18.5. Male overweight and obesity have the highest prevalence of GBP compared with female (overweight group: 9.5% vs. 7.8%; obesity group: 9.5% vs. 7.2%).

The relationship between demographic variables and blood laboratory tests, including sex, age, BMI, SBP, DBP, FBG, TC, TG, LDL, HDL, UA,γ-GT, AST, ALT, Tbil, Dbil, Cr, BUN with GBP were also examined (**Table 1**). There was no significant difference between GBP group and non GBP group. However, elevated BMI (25.48±3.20 *vs* 24.94±3.48 kg/m2; $P < 0.001$), older male sex (46.30±10.83 *vs* 45.10±13.12; $P = 0.013$; and higher DBP (79.95±11.83 vs. 78.74±11.97, p=006), higher UA (324.29±84.47 vs. 316.77±86.93, p=0.019), higher Cr (63.90±13.25 vs. 61.87±14.26, p<0.001), higher BUN (4.82±1.20 vs. 4.72±1.20, p=0.026) characterized patients with GBP. A multilevel mixed-effects logistic regression analysis was applied to assess particular risk factors. No significance between the GBP and no GBP groups was found for Age，SBP, DBP, TG, TC, HDL, LDL, UA, FBG, ALT, AST, Tbil, Dbil, Cr, BUN. Male sex (OR 0.746; 95%CI: 0.624-0.891; $P = 0.001$)，BMI（25-27.5）(OR 1.243; 95%CI:1.035-1.494; $P = 0.020$) and BMI（≥27.5）(OR 1.274; 95%CI: 1.038-1.562; $P = 0.020$) remained the primary risk factors for GBP（**Table 2**）.

Table 1 Mean level of different characteristics for gallbladder polyps

Characteristic	GB Positive (n=5235)	GB Negative (n=62203)	p-value[#]
Age (years)	46.30±10.83	45.10±13.12	0.013
BMI (kg/m^2)	25.48±3.20	24.94±3.48	<0.001
SBP (mmHg)	125.65±17.42	124.95±18.15	0.298
DBP (mmHg)	79.95±11.83	78.74±11.97	0.006
TG (mmol/L)	1.66±1.02	1.67±1.15	0.764
TC (mmol/L)	4.67±0.86	4.62±0.90	0.126
HDL (mmol/L)	1.31±0.36	1.32±0.35	0.303
LDL (mmol/L)	2.67±0.75	2.61±0.75	0.056
UA (umol/L)	324.29±84.47	316.77±86.93	0.019
FBG (mmol/L)	5.54±1.21	5.54±1.25	0.918
ALT (U/L)	23.12±15.17	23.25±16.97	0.836
AST (U/L)	20.67±7.80	21.29±9.22	0.070
γ-GT (U/L)	31.53±26.57	32.03±36.98	0.711
Tbil (umol/L)	12.88±5.31	12.78±5.60	0.638
Dbil (umol/L)	4.50±1.60	4.50±1.81	0.960
Cr (umol/L)	63.90±13.25	61.87±14.26	<0.001
BUN (mmol/L)	4.82±1.20	4.72±1.20	0.026

Data are presented as mean valve ± standerd deviation; [#] 2-sample t-test; BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; AST, aspartate aminotransferase, ALT, alanine aminotransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL, low density lipoprotein; UA, Uric acid; γ-GTP, γ-glutamyl transferase; Tbil, total bilirubin; Dbil, direct bilirubin; Cr, Blood creatinine; BUN, Blood urea nitrogen.

Table 2 Risk factors for gallbladder polyps							
Characteristic		Univariate analysis			Multivariate analysis		
		Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
Age (years)	-	1.007	1.001-1.013	**0.013**	1.006	0.100-1.012	0.086
Gender	Male	1	-	-	1	-	-
	Female	0.731	0.628-0.852	**<0.001**	0.746	0.624-0.891	**0.001**
BMI (kg/m^2)	<18.5	0.497	0.232-1.65	0.072	0.539	0.250-1.159	0.114
	18.5-25	1	-	-	1	-	-
	25-27.5	1.306	1.099-1.552	**0.002**	1.243	1.035-1.494	**0.020**
	≥27.5	1.302	1.086-1.561	**0.004**	1.274	1.038-1.562	**0.020**
SBP (mmHg)	≤139	1	-	-	1	-	-
	140-159	1.023	0.843-1.242	0.815	0.847	0.673-1.066	0.157
	160-179	1.102	0.775-1.566	0.588	0.859	0.570-1.294	0.468
	≥180	0.821	0.297-20269	0.703	0.586	0.201-1.710	0.328
DBP (mmHg)	≤89	1	-	-	1	-	-
	90-99	1.198	0.978-1.467	0.081	1.163	0.924-1.463	0.199
	100-109	1.174	0.861-1.602	0.310	1.165	0.813-1.670	0.406
	≥110	1.328	0.708-2.488	0.377	1.441	0.725-2.863	0.297
TG (mmol/L)	<1.7	1	-	-	1	-	-
	1.7-5.7	1.094	0.941-1.272	0.244	0.972	0.817-1.157	0.752
	≥5.7	0.768	0.356-1.658	0.502	0.731	0.328-1.626	0.442
TC	<3.1	1	-	-	1	-	-

(mmol/L)	3.1-7.2	1.434	0.861-2.388	0.166	1.281	0.762-2.152	0.350
	≥7.2	1.338	0.506-3.540	0.558	1.015	0.257-4.006	0.983
HDL (mmol/L)	≥1.0	1	-	-	1	-	-
	<1.0	1.017	0.842-1.228	0.863	0.902	0.730-1.114	0.338
LDL (mmol/L)	<2.6	1	-	-	1	-	-
	2.6-4.9	1.123	0.971-1.299	0.118	1.033	0.885-1.206	0.677
	≥4.9	1.253	0.497-3.162	0.633	1.446	0.356-5.882	0.606
UA (umol/L)	≤360	1	-	-	1	-	-
	360-420	1.159	0.960-1.398	0.124	1.011	0.825-1.239	0.914
	≥420	1.526	0.925-1.437	0.207	1.016	0.795-1.298	0.900
FBG (mmol/L)	<6.1	1	-	-	1	-	-
	6.1-7.0	1.155	0.909-1.467	0.238	1.040	0.812-1.332	0.754
	≥7.0	1.030	0.766-1.387	0.843	0.926	0.677-1.265	0.627
ALT (U/L)	≤40	1	-	-	1	-	-
	40-80	0.909	0.696-1.188	0.485	0.820	0.604-1.112	0.202
	>80	0.809	0.424-1.543	0.520	0.733	0.328-1.639	0.450
AST (U/L)	≤40	1	-	-	1	-	-
	40-80	0.970	0.611-1.540	0.897	1.195	0.677-2.109	0.539
	>80	0.552	0.074-4.109	0.562	0.880	0.104-7.482	0.907
γ-GT (U/L)	≤40	1	-	-	1	-	-
	40-80	1.120	0.919-1.363	0.261	0.990	0.796-1.232	0.929
	>80	0.812	0.576-1.144	0.233	0.731	0.502-1.066	0.103

Tbil (umol/L)	3.4-17.1	1	-	-	1	-	-
	17.1-34.2	1.016	0.838-1.232	0.872	1.047	0.843-1.301	0.677
	≥34.2	0.868	0.349-2.161	0.761	1.204	0.438-3.306	0.719
Dbil (umol/L)	0-6.8	1	-	-	1	-	-
	>6.8	0.764	0.536-1.090	0.137	0.680	0.444-1.041	0.076
Cr (umol/L)	Male<116; Female<90	1	-	-	1	-	-
	Male≥116; Female≥90	0.749	0.179-3.133	0.692	0.783	0.184-3..323	0.740
BUN (mmol/L)	1.8-7.1	1	-	-	1	-	-
	>7.1	1.22	0.779-1.616	0.536	1.008	0.696-1.461	0.964

Univariate analysis showed that female gender, age and BMI were significantly related to the occurrence of gallbladder polyps. Estimated ORs were adjusted for all these risk factors. Multilevel mixed-effects logistic regression analysis further demonstrated that gender and BMI were risk factors for gallbladder polyps. OR, odds ratio; 95% CI, 95% confidence interval; BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; AST, aspartate aminotransferase, ALT, alanine aminotransferase; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL, low density lipoprotein; UA, Uric acid; γ-GTP, γ-glutamyl transferase; Tbil, total bilirubin; Dbil, direct bilirubin; Cr, Blood creatinine; BUN, Blood urea nitrogen.

Discussion

This is a large retrospective study to evaluate the prevalence and risk factors of GBP in northwest Chinese population. The prevalence in the current study of GBP (7.8%) is higher than a Beijing Center study (6.9%)[11], but lower than previously reported in Taiwan (9.5%) [3], similar to a Zhejiang area study (7.4%)[14]. Results from Korea study has a prevalence of 5.4%[15], while Japanese study shows a prevalence of 5.6% [1]. The estimated prevalence is about 5% of the global population[3]. Compared with the prevalence of GBP in western society (1.0-6.9%) [16–18], Asian, especially Chinese, had a higher tendency to develop GB polyps. The reason for the vary prevalence rates of GBP may be related with the difference among countries and regions. For example, Japanese study reported regional and temporal differences in the prevalence of GBP ,and it was 3.9% in a rural area in 1988 and 12.3% in an urban area in 1933[19]. On the other hand, the increase of life expectancy, health awareness and ultrasound resolution may be the reasons. In this study the multilevel mixed-effects logistic regression analysis showed that gender and BMI were independent risk of GBP, and the risk of GBP in men was significantly higher than that of women. The risk of GBP in men was 1.43 times higher than in women, and in obesity was 1.29 times higher than in normal weight people. Males and those with higher BMI were at a high risk of developing GBP.

Rates in healthy adults according to gender indicated a higher prevalence of GBP in men[3, 20], which consistent with our study. The formation of GBP is still unclear, the majority of GBP are benign, and are most commonly cholesterol polyps with a prevalence of about 46–70% [5, 21]. Acyl-CoA: cholesterol acyltransferase 2 (ACAT2) is an estrogen-sensitive enzyme facilitating the cholesteryl ester incorporation into apoprotein B and papillary hyperplasia in the gallbladder mucosa. Estrogen, a sex steroid hormone, can impair the esterification of cholesterol by reducing the activity of both hepatic and intestinal ACAT2[22]. Cholesterol polyp is characterized by excessive accumulation of cholesteryl esters in gallbladder mucosa, which is a local manifestation of cholesterol metabolic disorder[23]. In this study, we saw the narrow gap of prevalence between male and female in 51–60 years compared with participants in 41–50 years, in accordance with the decreasing of estrogen in postmenopausal. And the prevalence of GBP for female and male were almost the same over 61 years. These results indicate that estrogen may be a protective factor from the development of GBP.

Gallbladder mucosa esterifies sterols, absorbs lipids, and synthesizes triglycerides and cholesterol to form cholesterol crystals[24, 25]. On the other hand, it may be due to cholesterol deposition in the blood, similar to the formation of atherosclerotic plaque[26]. GBP has been confirmed to be associated with increased risk of coronary heart disease[24]. In the present study, however, we found no association between lipid level, FBG, blood pressure and the risk of GBP by multilevel mixed-effects logistic regression analysis.

Obesity and its complications (including metabolic syndrome, type 2 diabetes, cardiovascular disease, and cancer, etc.) are a global pandemic, and was found to be most strongly associated with the risk of GBP in the present study. We found the prevalence of GBP was increased with BMI. The lean group (BMI < 18.5) has the lowest prevalence of 3.6%, and the normal weight group (BMI 18.5–25) has a higher of 7%, while the overweight (BMI25-27.5) and obesity group(BMI ≥ 27.5) have the same prevalence of 9%. But the results are always contradictory. Lin[3] and Jorgensen [27] reported the prevalence of GBP was not associated with BMI, weight factors, glucose or lipid profile. However, Segawa K suggested that obesity contributed to the development of cholesterol polyps, which showed the prevalence of GB polyps rose in accordance with the rise in obesity index, which was highest among the middle-aged (40–51 years), similar to the curve of the obesity index[1]. Obesity, as well as dysfunction of lipid profile, high blood glucose and high FBG were the diagnose criteria of Metabolic syndrome (MS). In Lim's study, multivariate logistic regression analysis revealed MS was the risk factor for GBP, but not other components of FBS, serum lipid and blood pressure[20]. Another study shows a higher non-HDL-c/HDL-c ratio is independently related to a higher risk of GBP formation in Chinese men[28]. These metabolic components may be combined to have an effect of the GBP developing. As the increasing prevalence of obesity and MS, keeping BMI and metabolic index under normal range is important to decrease the rising of GBP. Compared with non GBP group, the levels of age, DBP and UA, Cr, BUN in GBP group were statistically significant; however, these variables had no significant correlation in multivariate logistic regression analysis. These results showed that no blood biochemistry index could measure the risk of GBP.

This study has several limitations. First, patients come from one health screening center and therefore can only represent the limited areas. Second, regardless of size and type, cholesterol polyps, adenomatous polyps, and inflammatory polyps were included in the GBP group, may have an impact on the results. However, it is difficult to make a clear histological diagnosis of GBP by means of noninvasive ultrasound alone. Future studies should attempt to classify GBP by histological findings after surgery.

In conclusion, GBP found incidentally during abdominal ultrasound appear to be strongly associated with gender and metabolic index. Our study imply that male gender and BMI were independent risk factors for prevalence of GBP, and obesity contributes to the formation of GBP. In the future, it is necessary to clarify the relationship between obesity and GBP according to the histological classification and the mechanism of obesity on the formation of GBP.

Declarations

Ethics approval and consent to participate

The clinical study was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Ethics Committee of Harmony Healthy Examination Center. All participants have signed the written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y.L. , JJ.Y.and S.Q designed the study.Y.L. and JJ.Y. wrote the main manuscript text and prepared figures and tables. All authors revised the manuscript and approved the final version.

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Figures

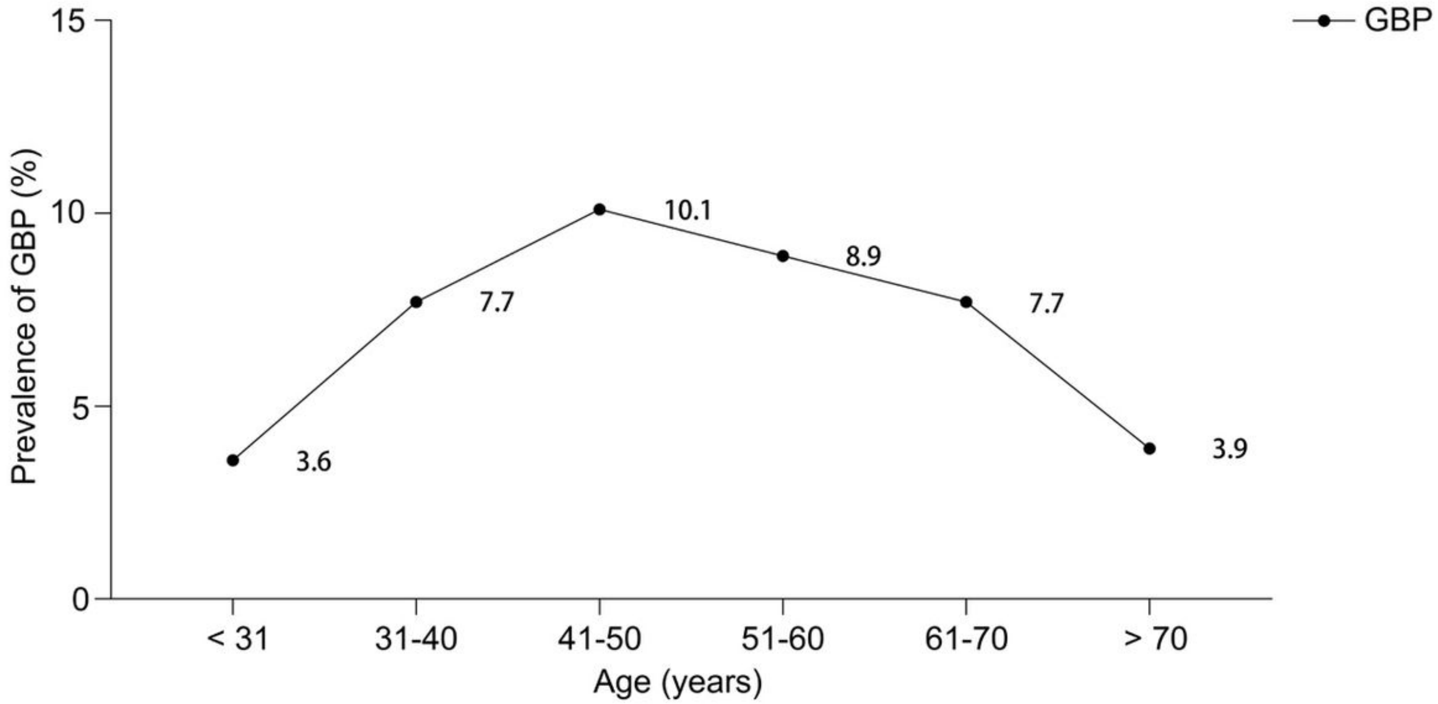

Figure 1

Prevalence of gallbladder polyps in different age groups in Chinese subjects. Prevalence of gallbladder polyps was more common in middle age, peaking in subjects aged 41-50 years. GP, gallbladder polyps.

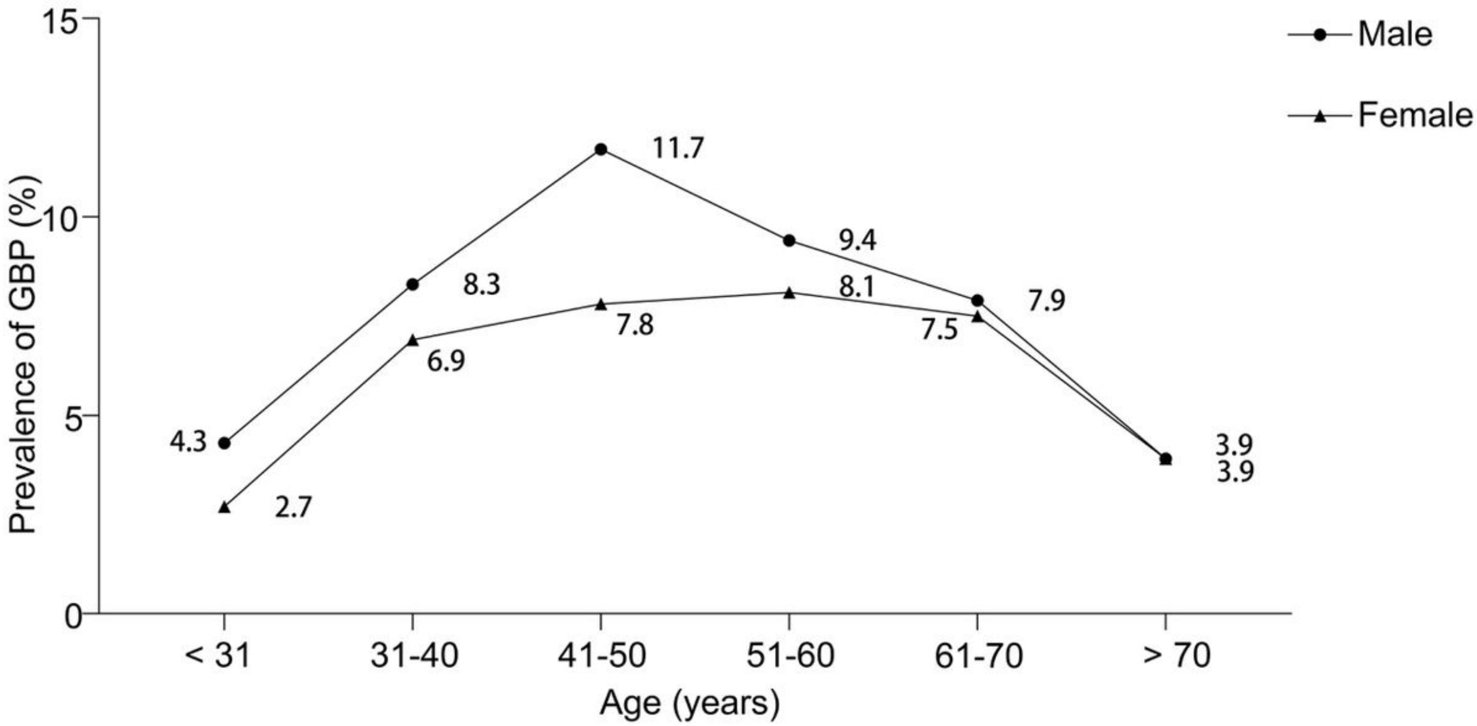

Figure 2

Prevalence of gallbladder polyps stratified by gender in different age groups in Chinese subjects. Prevalence of gallbladder polyps was higher in male than in female subjects in all age groups.

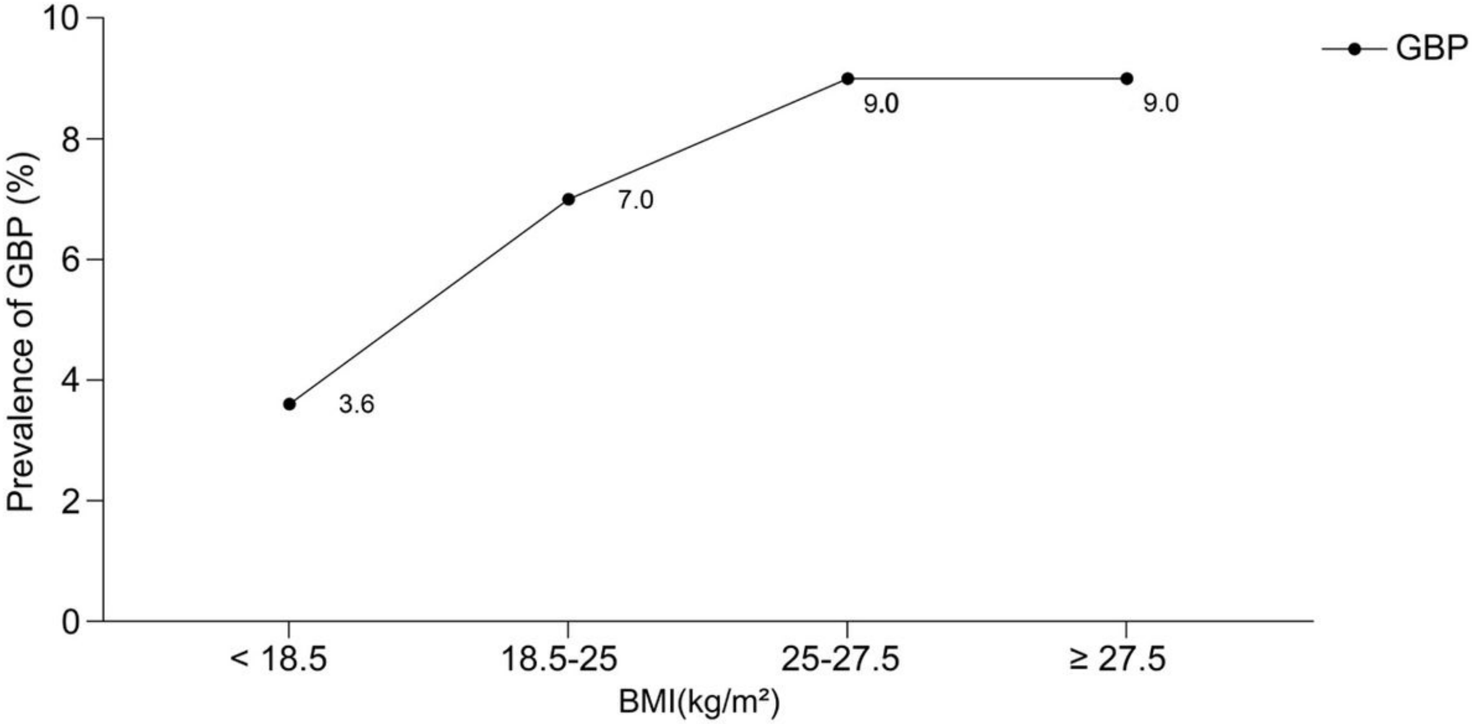

Figure 3

Prevalence of gallbladder polyps stratified by BMI in different age groups in Chinese subjects. Prevalence of gallbladder polyps was increased with BMI. BMI, Body mass index.

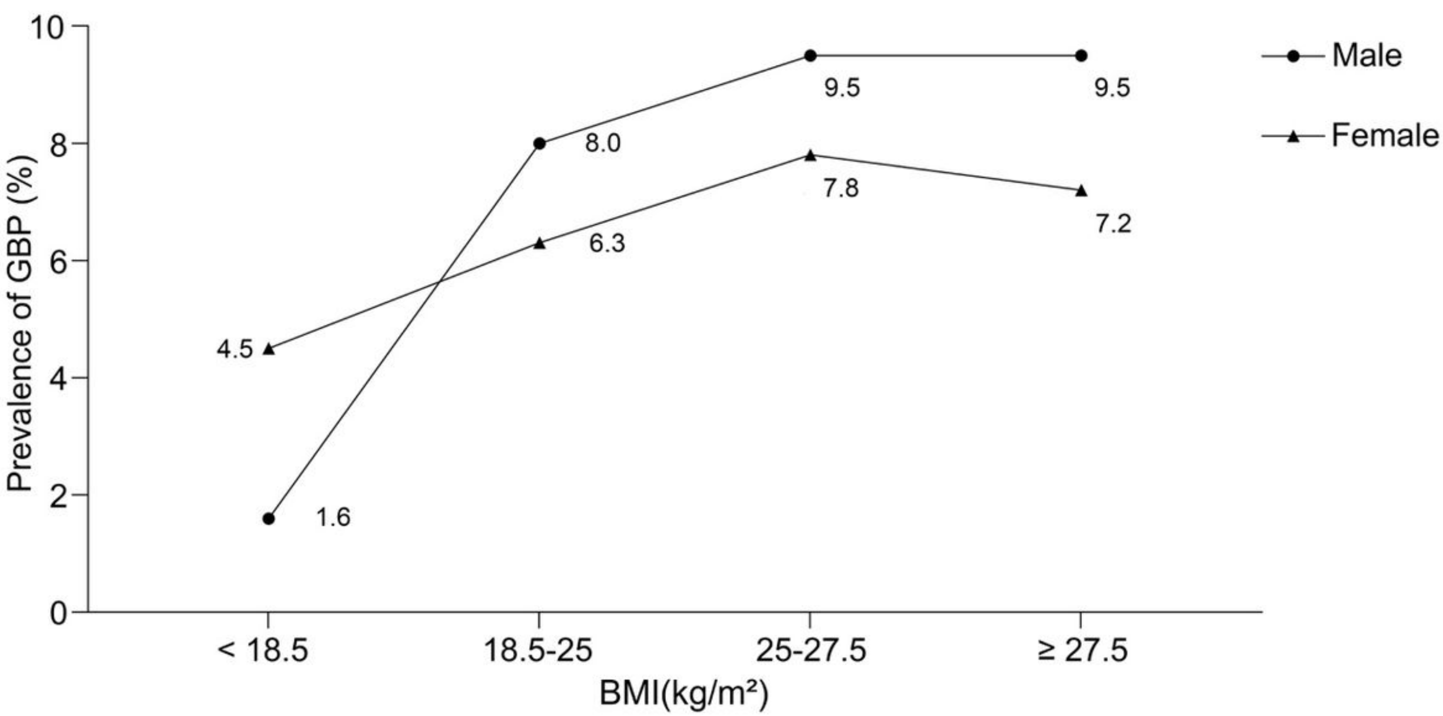

Figure 4

Prevalence of gallbladder polyps stratified by BMI in different age groups in Chinese subjects. Prevalence of gallbladder polyps was higher in male than in female in BMI over normal weight (BMI≥18.5), and lower in BMI (<18.5)