Serum Lipid, Total Bile Acid and Total Bilirubin Levels are the Risk Factors of Gallstones

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Research

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Abstract

Background: The risk factors for gallstones among the population in the Meizhou area remains unclear.

Methods: A total of 816 gallstone disease patients and 818 control participants was included in the study. Serum lipid levels of all participants were measured. Information recorded included age, sex, and gallstone disease risk factors.

Results: Of the 1,634 enrolled individuals, with ages between 13 and 101 years, 727 were males and 907 females. The differences in serum TG ($P<0.001$), LDL-C ($P=0.043$), TBA ($P<0.001$), and T-BIL ($P<0.001$) levels between patients and controls were statistically significant. There were no statistically significant differences in age, percentage of ever drinker, the percentage of ever smokers, the prevalence of hypertension, prevalence of diabetes mellitus, serum levels of TC, HDL-C, Apo-A1, Apo-B, and Apo-A1/Apo-B between the patients and controls. There were statistically significant differences in the frequencies of gallstones in common bile duct ($\chi^2=13.909$, $P<0.001$), and intrahepatic bile ducts ($\chi^2=8.289$, $P=0.004$) between male and female patients. There were no statistically significant differences in the prevalence of the different gallstones sizes between male and female patients. Serum TBA ($P<0.001$) and T-BIL ($P<0.001$) levels in patients with gallstones in common bile duct higher than gallstones in gall bladder and intrahepatic bile ducts patients. Logistic regression analysis indicated that participants with high TG, LDL-C, TBA, and T-BIL had a significantly higher risk of gallstone disease.

Conclusions: In general, high serum levels of TG, LDL-C, TBA, and T-BIL are the main risk factors for gallstone formation in the Meizhou area.

Introduction

Gallstone disease is a disease with the occurrence of symptoms or complications caused by the formation of masses in the gallbladder or biliary tract caused by abnormally high cholesterol or bilirubin levels in the bile[1]. Mass/masses in the gallbladder or biliary tract is called gallstone/gallstones. Gallstones can cause such as abdominal pain, jaundice, and fever symptoms, and can lead to clinical diseases including cholecystitis, cholangitis, and acute pancreatitis[2]. In addition, studies have shown that more than 90% of gallbladder cancer patients have a history of gallstone, gallstone as one of high risk factors in the occurrence and development of gallbladder cancer[3, 4]. The prevalence of gallstones in adults worldwide is about 10–15%[1, 5]. Studies reported the prevalence of gallstone in China between 4.2% and 23%[6–8].

The risk of gallstone disease may vary according to the presence of various genetic and environmental factors[1, 9]. Epidemiological studies have shown some risk factors for gallstones, including metabolic abnormalities[5], obesity[10], hyperinsulinaemia[11], and type 2 diabetes[12, 13]. Besides, the genetic factors are also correlated to the form of gallstones. Studies have found associations between some genes and gallstone disease, including ATP-binding cassette, subfamily G, member 8 (ABCG8), UDP glucuronosyltransferase family member A1 (UGT1A1), ATP-binding cassette, subfamily B, member 4 (ABCB4), ATP-binding cassette, subfamily B, member 11 (ABCB11), cystic fibrosis transmembrane conductance regulator (CFTR), and cytochrome P450, subfamily 2A, polypeptide 1 (CYP7A1) genes[14–16]. In general, it is essential for both risk prediction and prevention of gallstone disease by identifying risks.

Previous epidemiological investigation showed that the incidence of gallstones in Guangdong province was about 8.0%[17]. Meizhou is located in the northeast of Guangdong Province, at the junction of Fujian, Guangdong, and Jiangxi. Meizhou is one of the places where Hakka people are concentrated[18]. Hakka is a branch of the Han ethnic group whose ancestral home is northern China. There was no related research on the risk factors for gallstones among the population in this area. The objective of this study was to investigate the risk factors for gallstone disease among the population in this area, thus providing a scientific basis for the prevention and treatment of gallstones in this region.

Materials And Methods

Population Samples

A total of 1,634 individuals were recruited from the inpatients of Meizhou People's Hospital (Huangtang Hospital), Guangdong province, China, between January 2016 and June 2020; the sample consisted of 816 gallstone disease patients and 818 individuals with non-gallstone disease (controls). Gallstone disease patients' diagnoses were determined by gastroenterologist according to clinical symptoms and ultrasound, cholecystography, computed tomography (CT)/magnetic resonance imaging (MRI). The information recorded included age, sex, and gallstone disease risk factors (smoking history, drinking history, hypertension, diabetes, etc). All control subjects were randomly selected from the Meizhou People's Hospital during the same period.

Serum Index Measurements

On day 2 of admission, about 5 ml of blood was extracted from each subject, and the serum was immediately isolated and analyzed. Total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A1 (Apo-A1), and apolipoprotein B (Apo-B), total bile acid (TBA), and total bilirubin (T-BIL) analysis was carried out using cholesterol esterase/peroxidase (CHOD/PAP) enzymatic method, glycerophosphate oxidase/peroxidase (GPO-PAP) enzymatic method, direct surfactant removal method, direct immunoinhibition method, and immunoturbidimetry method, circulating enzymatic method (3 α -hydroxysteroid dehydrogenase), and chemical oxidation method (sodium nitrite), respectively. Samples were evaluated using the Olympus AU5800 system (Olympus Corporation, Tokyo, Japan).

Statistical analysis

SPSS statistical software version 21.0 (IBM Inc., State of New York, USA) was performed for data analysis. Continuous variable data were expressed as mean $\pm$ standard deviation (SD), while categorical variables were described as percentages. T test or Mann-Whitney U test was used for continuous variable data analysis. Chi-square test was used for categorical variable data analysis. Logistic regression analysis was applied to assess the interactions between plasma lipid level and various factors (smoking history, drinking history, hypertension, diabetes, etc.) in gallstone disease. $P < 0.05$ was considered statistically significant.

Results

Population characteristics

Characteristics of the 816 cases with gallstones and the 818 controls are shown in Table 1. Of the 1,634 enrolled individuals, with ages between 13 and 101 years, 727 were males (44.5%) (mean age $\pm$ SD: 56.4 $\pm$ 17.1 years, range 14–93) and 907 females (55.5%) (mean age $\pm$ SD: 55.6 $\pm$ 16.4 years, range 13–101). The differences in TG ($P < 0.001$), LDL-C ($P = 0.043$), TBA ($P < 0.001$), and T-BIL ($P < 0.001$) levels between patients and controls were statistically significant. There were no statistically significant differences in age, percentage of ever drinker, percentage of ever smokers, prevalence of hypertension and diabetes mellitus, serum levels of TC, HDL-C, Apo-A1, Apo-B, and Apo-A1/Apo-B between the patients and controls. The differences in TG ($P < 0.001$), Apo-A1/Apo-B ($P < 0.001$), TBA ($P < 0.001$), and T-BIL ($P < 0.001$) levels between male patients and male controls were statistically significant, and TG ($P < 0.001$), TC ($P = 0.001$), LDL-C ($P = 0.013$), TBA ($P < 0.001$), and T-BIL ($P < 0.001$) levels were significant among females.

Table 1
Clinical features of patients with gallstones and healthy controls.

	Total (n = 1634)			Male (n = 727)			Female (n = 907)		
	Patient Group (n = 816)	Control Group (n = 818)	P values	Patient Group (n = 345)	Control Group (n = 382)	P values	Patient Group (n = 471)	Control Group (n = 436)	P values
Age, y	57.0 ± 14.3	54.9 ± 18.7	0.011	58.6 ± 14.1	54.3 ± 19.2	0.001	55.8 ± 14.4	55.3 ± 18.3	0.700
Ever drinker (n, %)	21 (2.6%)	14 (1.7%)	0.237 ($\chi^2 = 1.448$)	21 (6.1%)	14 (3.7%)	0.165 ($\chi^2 = 2.321$)	0 (0)	0 (0)	-
Ever smoker (n, %)	49 (6.0%)	36 (4.4%)	0.149 ($\chi^2 = 2.131$)	49 (14.2%)	36 (9.4%)	0.050 ($\chi^2 = 4.010$)	0 (0)	0 (0)	-
Hypertension (n, %)	161 (19.7%)	141 (17.2%)	0.203 ($\chi^2 = 1.685$)	73 (21.2%)	67 (17.5%)	0.222 ($\chi^2 = 1.528$)	88 (18.7%)	74 (17.0%)	0.501 ($\chi^2 = 0.452$)
Diabetes Mellitus (n, %)	105 (12.9%)	90 (11.0%)	0.253 ($\chi^2 = 1.352$)	54 (15.7%)	46 (12.0%)	0.163 ($\chi^2 = 1.992$)	51 (10.8%)	44 (10.1%)	0.718 ($\chi^2 = 0.131$)
TG, mmol/L	1.430 ± 1.164	1.103 ± 1.280	< 0.001	1.409 ± 1.083	1.057 ± 1.208	< 0.001	1.445 ± 1.221	1.143 ± 1.340	< 0.001
TC, mmol/L	6.099 ± 28.336	4.256 ± 3.001	0.064	7.003 ± 43.374	3.863 ± 1.432	0.158	5.437 ± 3.782	4.600 ± 3.855	0.001
HDL-C, mmol/L	2.335 ± 24.617	1.574 ± 3.876	0.383	3.237 ± 37.623	1.373 ± 2.074	0.334	1.674 ± 3.709	1.749 ± 4.938	0.793
LDL-C, mmol/L	3.749 ± 20.866	2.259 ± 2.652	0.043	4.349 ± 31.311	2.005 ± 0.848	0.144	3.310 ± 6.080	2.482 ± 3.531	0.013
Apo-A1, g/L	1.723 ± 9.589	1.202 ± 1.524	0.126	1.668 ± 11.793	1.144 ± 1.576	0.390	1.763 ± 7.593	1.254 ± 1.477	0.169
Apo-B, g/L	1.944 ± 28.065	0.901 ± 3.600	0.292	3.182 ± 43.079	0.896 ± 4.599	0.303	1.038 ± 2.362	0.905 ± 2.412	0.401
Apo-A1/Apo-B	1.664 ± 5.520	1.801 ± 0.875	0.485	1.320 ± 0.622	1.821 ± 0.910	< 0.001	1.917 ± 7.239	1.783 ± 0.844	0.702
TBA, umol/L	23.667 ± 57.103	5.795 ± 9.157	< 0.001	32.181 ± 66.397	6.423 ± 9.887	< 0.001	17.430 ± 48.325	5.244 ± 8.440	< 0.001
T-BIL, umol/L	26.743 ± 37.567	15.440 ± 10.755	< 0.001	34.948 ± 46.030	16.637 ± 11.941	< 0.001	20.732 ± 28.474	14.391 ± 9.487	< 0.001

Total (n = 1634)	Male (n = 727)	Female (n = 907)
Values for age expressed as mean $\pm$ SD.		
TG, triglycerides;		
TC, total cholesterol;		
HDL-C, high-density lipoprotein-cholesterol;		
LDL-C, low-density lipoprotein-cholesterol;		
Apo-A1, apolipoprotein A1;		
Apo-B, apolipoprotein B;		
TBA, total bile acid;		
T-BIL, total bilirubin.		

Comparison Of Gallstones Between Males And Females

Among the gallstone disease patients, the frequencies of gallstones in the gall bladder, common bile duct, intrahepatic bile ducts, gall bladder and common bile duct, common bile duct and intrahepatic bile ducts, and gall bladder and intrahepatic bile ducts were 71.7%, 10.2%, 2.8%, 12.9%, 1.6%, and 0.9% according to stone locations, respectively. There were statistically significant differences in the frequencies of gallstones in the common bile duct ($\chi^2 = 13.909$, $P < 0.001$), and intrahepatic bile ducts ($\chi^2 = 8.289$, $P = 0.004$) between male and female patients (Table 2). The proportion of gallstones in common bile duct in men was higher than that in women, while the proportion of intrahepatic bile ducts was lower.

Table 2
Comparison of gallstones between males and females.

Parameter	Total (n = 816)	Male (n = 345)	Female (n = 471)	P value (male vs. female)
Stone location				
Gall bladder	585 (71.7%)	236 (68.4%)	349 (74.1%)	0.084 ($\chi^2 = 3.179$)
Common bile duct	83 (10.2%)	51 (14.8%)	32 (6.8%)	< 0.001 ($\chi^2 = 13.909$)
Intrahepatic bile ducts	23 (2.8%)	3 (0.9%)	20 (4.2%)	0.004 ($\chi^2 = 8.289$)
Gall bladder + Common bile duct	105 (12.9%)	50 (14.5%)	55 (11.7%)	0.246 ($\chi^2 = 1.408$)
Common bile duct + Intrahepatic bile ducts	13 (1.6%)	4 (1.2%)	9 (1.9%)	0.573 ($\chi^2 = 0.717$)
Gall bladder + Intrahepatic bile ducts	7 (0.9%)	1 (0.3%)	6 (1.3%)	0.249 ($\chi^2 = 2.267$)
The diameter of the largest stone				
< 0.5 cm	66 (8.1%)	24 (7.0%)	42 (8.9%)	0.363 ($\chi^2 = 1.030$)
0.5–0.9 cm	177 (21.7%)	79 (22.9%)	98 (20.8%)	0.492 ($\chi^2 = 0.513$)
1.0-1.9 cm	313 (38.4%)	140 (40.6%)	173 (36.7%)	0.275 ($\chi^2 = 1.248$)
≥ 2.0 cm	260 (31.9%)	102 (29.6%)	158 (33.5%)	0.254 ($\chi^2 = 1.453$)

Among the gallstone disease patients, the diameter of the stones was less than 0.5 cm in 66 (8.1%) cases, 0.5–0.9 cm in 177 (21.7%) cases, 1.0-1.9 cm in 313 (38.4%), and more than or equal to 2.0 cm in 260 (31.9%) cases. There were no statistically significant differences in the prevalence of the different gallstones sizes between male and female patients (Table 2).

Comparison of lipid levels between patients with different gallstone locations and sizes

Relationships between different gallstone locations and sizes and serum lipid levels were analyzed. Subjects with the gallstones in the gall bladder and common bile duct (n = 105), common bile duct and intrahepatic bile ducts (n = 13), and gall bladder and intrahepatic bile ducts (n = 7) were excluded because of gallstones at multiple locations. In this study, the TBA ($P < 0.001$) and T-BIL ($P < 0.001$) levels in patients with gallstones in common bile duct higher than gallstones in gall bladder and intrahepatic bile ducts patients. There were no significant differences in serum lipid levels in patients with different gallstones sizes (Table 3).

Table 3
Comparison of lipid levels between patients with different gallstones.

	Stone location		Intrahepatic bile ducts (n = 23)	<i>P</i> values	Stone size				<i>P</i> values
	Gall bladder (n = 585)	Common bile duct (n = 83)			< 0.5 cm (n = 66)	0.5- 1 cm (n = 177)	1- 2 cm (n = 313)	≥ 2 cm (n = 260)	
TG, mmol/L	1.515 ± 1.286	1.237 ± 0.880	1.255 ± 0.774	0.109	1.460 ± 1.061	1.471 ± 1.418	1.375 ± 1.122	1.459 ± 1.044	0.771
TC, mmol/L	6.633 ± 33.451	4.682 ± 1.174	5.056 ± 0.940	0.847	4.947 ± 1.320	5.234 ± 5.511	7.617 ± 45.516	5.153 ± 2.303	0.692
HDL-C, mmol/L	2.747 ± 29.069	1.278 ± 0.418	1.420 ± 0.400	0.878	1.370 ± 0.477	1.318 ± 0.363	3.632 ± 39.489	1.710 ± 4.988	0.697
LDL-C, mmol/L	4.189 ± 24.629	2.624 ± 0.845	2.786 ± 0.830	0.815	2.731 ± 0.939	3.220 ± 6.783	4.671 ± 32.863	3.258 ± 5.986	0.796
Apo-A1, g/L	1.973 ± 11.316	1.075 ± 0.381	1.270 ± 0.487	0.737	1.190 ± 0.355	1.327 ± 2.281	2.365 ± 15.003	1.354 ± 3.714	0.514
Apo-B, g/L	2.384 ± 33.143	0.809 ± 0.253	0.883 ± 0.207	0.890	0.878 ± 0.274	0.865 ± 0.284	3.451 ± 45.225	1.136 ± 3.171	0.689
Apo- A1/ Apo-B	1.749 ± 6.502	1.426 ± 0.613	1.535 ± 0.717	0.892	1.478 ± 0.742	1.711 ± 3.296	1.929 ± 8.538	1.362 ± 0.595	0.663
TBA, umol/L	12.671 ± 37.322	55.354 ± 84.571	17.483 ± 38.810	< 0.001	27.717 ± 59.828	24.444 ± 53.439	21.229 ± 52.955	25.044 ± 63.481	0.781
T-BIL, umol/L	19.242 ± 22.656	52.131 ± 57.729	23.474 ± 25.426	< 0.001	26.702 ± 34.930	30.812 ± 51.073	24.404 ± 28.157	26.797 ± 37.271	0.349
TG, triglycerides;									
TC, total cholesterol;									
HDL-C, high-density lipoprotein-cholesterol;									
LDL-C, low-density lipoprotein-cholesterol;									
Apo-A1, apolipoprotein A1;									
Apo-B, apolipoprotein B;									
TBA, total bile acid;									
T-BIL, total bilirubin.									

Logistic regression analysis was performed to determine independent predictors for gallstone disease (Table 4). On univariate regression analysis, there were significantly higher risks of gallstone disease in the presence of high age, high TG, TC, LDL-C, TBA, T-BIL concentrations (all $P < 0.05$). Further multiple logistic regression analysis indicated that participants with high TG (adjusted OR 1.136, 95% CI 1.015–1.272, $P = 0.026$), and high LDL-C (adjusted OR 1.483, 95% CI 1.159–1.898, $P = 0.002$), high TBA (adjusted OR 1.019, 95% CI 1.010–1.027, $P < 0.001$), and high T-BIL (adjusted OR 1.026, 95% CI 1.016–1.036, $P < 0.001$) had a significantly higher risk of gallstone disease. ROC analysis showed that the positive cutoff value of TG was 1.095 mmol/L (AUROC = 0.692, $P < 0.001$, 95% CI 0.666–0.718), LDL-C was 2.485 mmol/L (AUROC = 0.697, $P < 0.001$, 95% CI 0.671–0.722), serum TBA was 11.250 μmol/L (AUROC = 0.593, $P < 0.001$, 95% CI 0.566–0.621), and serum T-BIL was 26.250 μmol/L (AUROC = 0.597, $P < 0.001$, 95% CI 0.570–0.625).

Table 4
Logistic regression analysis of risk factors associated with gallstone disease.

Variables	Unadjusted values			Adjusted values		
	<i>P</i> value	β	OR (95% CI)	<i>P</i> value	β	Adjusted OR (95% CI)
Age, y	0.011	0.008	1.008 (1.002–1.013)	0.243	0.004	1.004 (0.997–1.010)
TG	< 0.001	0.265	1.304 (1.176–1.445)	0.026	0.128	1.136 (1.015–1.272)
TC	< 0.001	0.349	1.418 (1.312–1.533)	0.109	0.147	1.158 (0.968–1.386)
LDL-C	< 0.001	0.512	1.668 (1.492–1.865)	0.002	0.394	1.483 (1.159–1.898)
TBA	< 0.001	0.024	1.024 (1.017–1.032)	< 0.001	0.019	1.019 (1.010–1.027)
T-BIL	< 0.001	0.031	1.032 (1.023–1.040)	< 0.001	0.025	1.026 (1.016–1.036)
TG, triglycerides;						
TC, total cholesterol;						
LDL-C, low-density lipoprotein-cholesterol;						
TBA, total bile acid;						
T-BIL, total bilirubin.						
OR, odds ratio;						
CI, confidence interval.						

Discussion

Gallstone disease is mainly due to liver metabolism disorder, biliary motor dysfunction, abnormal bile cholesterol output, and other effects, resulting in the dissolution of the solid components in the bile, stone formation. The causes of gallstones are complex, and more and more studies have proved that they are related to age, gender, obesity, high-fat diet, abnormal lipid metabolism, and other factors[1]. The potential risk factors for gallstones of population in Meizhou area were analyzed in this study. Major risk factors for gallstone formation are high serum levels of TG, LDL-C, TBA, and T-BIL.

Although dyslipidemia is common in the population, the relationship between dyslipidemia and gallstone disease is still unclear. Premkumar M *et al.* reported that obesity, dyslipidemia, high fat, and caloric intake were found to increase the risk of gallstone disease[19]. A Korean study demonstrated that low HDL-cholesterol was an independent predictor, was significantly associated with gallbladder stone formation in premenopausal women[20]. Brasca AP *et al.* found that lower HDL-C and higher TG were associated with a higher probability of gallstone disease[21]. Chang CM *et al.* reported that hypercholesterolemia may have an additive effect in increasing gallstone disease risk in women in Taiwan[22]. Several studies have reported that high serum TG level is positively correlated with the occurrence of gallstones. High TG is most often a multifactorial disorder of VLDL metabolism. In most high TG patients, they were usually observed with supersaturated bile and diminished gallbladder motility, both contributing to gallstone formation[23]. It was seen that gallstone disease prevalence was associated with high TG in women[21].

When lipid levels increase, serum lipids can be secreted into bile through liver cell serous membrane transport, make the concentration of lipids in bile increases, lipid shows the supersaturated state in bile and crystallize inside the gallbladder, and form gallstone gradually. Bile are synthesized by the liver and secreted through the liver tubules. Their components include bile acids, cholesterol, phospholipids, and other components. Dyslipidemia leads to the accumulation of excess lipids in the liver, affecting the liver cells' function, reducing the secretion of bile acids, and also easy to form gallstones[23]. In patients with gallstones, increased bile acid synthesis and triglyceride concentrations in the liver may be due to increased microsomal triglyceride protein (MTP) activity[24].

The relationship between serum total bile acid, serum total bilirubin, and gallstones is still inconsistent. A study showed that delayed orocecal transit time (OCTT) leads to small intestinal bacterial overgrowth (SIBO) and thus enhance serum bile acid (SBA) levels lead to the formation of gallstones[25], while a study has reported no correlation between serum total bile acids and gallstones[26]. Serum total bilirubin[27] or serum total bilirubin trend[28] is a risk factor and predictor for common bile duct stone. A study reported that serum total bilirubin level is a risk factor for predicting gallstone disease in male Taiwanese vegetarians[29]. Some studies have shown no relationship between serum total bilirubin and gallstones[30, 31].

Whether gender is a risk factor for gallstone disease remains controversial. The results of this study suggest that gender is not associated with gallstone disease. This is consistent with previous research[32, 33]. However, some studies based on western populations suggest that females are more likely to develop gallstone disease than males[34, 35]. It is believed that sex hormones levels are associated with cholesterol metabolism, and gender may be related to cholesterol stones[36]. The relationship between gender and gallstone disease may be different between Asian and Western populations, which requires further study.

In this study, age is not associated with gallstone disease. Diehl *et al.* found that pigment stones patients were older than cholesterol stones patients[37]. Some studies have found that gallstone prevalence increased with age[38–40]. Old age was shown to represent a risk factor for gallstone disease[41]. Older people have underlying conditions such as hyperlipidemia, hypertension, and diabetes. Moreover, the function of a few organs, such as the gallbladder is abate, can lead to gallstone disease. In general, high serum levels of TG, LDL-C, TBA, and T-BIL are the main risk factors for gallstone formation in the Meizhou area.

Study Strengths And Limitations

This is the first study about the risk factors for gallstone disease among the population in the Meizhou area. The clinical characteristics, serum lipid, total bile acid, and total bilirubin levels indicators were included in the analysis to exclude the influence of related confounding factors on the results. There are some limitations to this study that should be noted. First, gallstone disease is a kind of multifactorial diseases caused by genetic and environmental factors. There were no assessment of potential gene-environment interactions. Second, this study's sample size is not very large, which may lead to some deviations in the results. Therefore, further study with a larger sample size is one of the next tasks.

Conclusions

In general, high serum levels of triglyceride, LDL-C, total bile acid, and total bilirubin are the main risk factors for gallstone formation in the Meizhou area.

Abbreviations

TG
triglycerides;
TC
total cholesterol;
HDL-C
high-density lipoprotein-cholesterol;
LDL-C
low-density lipoprotein-cholesterol;
Apo-A1
apolipoprotein A1;
Apo-B
apolipoprotein B;

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences, Meizhou Hospital Affiliated to Sun Yat-sen University.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Zhixiong Zhong and Dehui Zeng designed the study. Heming Wu, Dehui Zeng and Anxiang Zeng collected clinical data. Heming Wu, Qingyan Huang and Zhikang Yu analyzed the data. Heming Wu and Dehui Zeng prepared the manuscript. All authors were responsible for critical revisions, and all authors read and approved the final version of this work.

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