ORIGINAL ARTICLE

The association between gallstone disease and plaque in the abdominopelvic arteries

Halil İbrahim Serin, Yunus Keser Yilmaz[1], Yaşar Turan[2], Ergin Arslan[3], Mustafa Fatih Erkoç, Aytaç Doğan[4], Mehmet Celikbilek[5]

Departments of Radiology, [1]Cardiovascular Surgery, [2]Cardiology and [3]General Surgery, Faculty of Medicine, Bozok University, [5]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Faculty of Medicine, Bozok University, Yozgat, [4]Department of Radiology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

Background: The aim of this study was to assess the atheromatous plaque, in the abdominopelvic arteries as a marker of cardiac risk in patients with or without gallstone disease (GD). **Materials and Methods:** A total of 136 patients were enrolled in this cross-sectional study. Forty-eight patients had GD and the remaining 88 patients did not. The presence or absence of gallstones was noted during abdominal ultrasonography while vascular risk factors such as plaque formation, intima-media thickness, plaque calcification, mural thrombus, stenosis, aneurysm, and inflammation were recorded during an abdominopelvic computed tomography scan. In addition, percentage of the abdominopelvic aorta surface covered by atheromatous plaque was calculated. **Results:** The mean age of patients with GD and without GD was 50.81 ± 16.20 and 50.40 ± 12.43, respectively. Patients with GD were more likely to have diabetes mellitus, a higher body mass index (BMI) ($P < 0.001$), and higher cholesterol ($P < 0.01$), and low-density lipoprotein-cholesterol ($P < 0.02$) levels. No significant differences were found between the groups regarding other atherosclerotic risk factors. Patients with GD had significantly higher rates of the vascular risk factors as intima-media thickness, plaque formation, calcification, aneurysm, mural thrombosis, stenosis, and inflammation in all abdominal arterial segments other than aneurysm in the femoral arteries. In addition, patients with GD had severe atheromatous plaques in the abdominal aorta, common iliac, external iliac, and common femoral artery (CFA). In patients with GD, parameters of age, BMI, and systolic and diastolic blood pressure were all correlated with the severity of the atheromatous plaque in abdominal aorta, common iliac, external iliac, and CFA. **Conclusion:** We demonstrated a direct relationship between GD and abdominopelvic atheromatous plaque, which is a marker for increased cardiovascular risk, for the first time in the literature. Patients with GD exhibit greater abdominopelvic atherosclerosis and therefore, have a higher risk of cardiovascular disease.

Key words: Abdominopelvic arteries, atheromatous plaque, gallstone disease

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INTRODUCTION

Gallstone disease (GD; cholelithiasis) is a common disorder with a varying prevalence in different populations worldwide.[1] It is a multifactorial disease and has several risk factors including sex, age, genetic factors, race, obesity, rapid weight loss, diet, alcohol consumption, diabetes mellitus (DM), hyperlipidemia, drug use, and pregnancy.[2]

Atherosclerotic cardiovascular disorders lead to significant morbidity and mortality worldwide.[3] Thus, early diagnosis and preventive measures are important for individuals with a high cardiovascular risk.[4] Aortic atheromatous plaque is a marker of systemic atherosclerosis,[5] and calcified atheromatous plaques in the abdomen and thorax are significant predictors of increased cardiovascular risk. Hypertension, DM, dyslipidemia, smoking, physical inactivity, obesity and diet, age, sex, and family history are all known risk factors for atherosclerotic cardiovascular disease (CVD).[6]

GD and atherosclerosis share certain risk factors including gender, age, genetic background, race, obesity,

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Address for correspondence: Dr. Halil İbrahim Serin, Department of Radiology, Faculty of Medicine, Bozok University, 66000 Yozgat, Turkey. E-mail: raddrhiserin@gmail.com

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diet, alcohol consumption, diabetes, and hyperlipidemia. However, controversial results have been obtained in various studies regarding the association between GD and cardiovascular disorders.[7-12] To the best of our knowledge, no study has sought to evaluate the direct relationship between GD and aortic atheromatous plaque as a manifestation of atherosclerosis, to date. This study was designed to investigate whether there is an association between abdominopelvic atheromatous plaque and GD.

MATERIALS AND METHODS

Study population

The study population consisted of 136 consecutive patients (48 patients with GD and 88 patients without) who presented to the Gastroenterology Department of Bozok University, Medicine School between January and March 2015. This cross-sectional study included 67 men and 69 women aged 13–84 years. Anthropometric and biochemical evaluations were performed for all patients after ≥8 h of fasting. The patients' height and body weight were measured, and their body mass index (BMI) was calculated as follows: Weight in kilograms divided by the square of the height in meters (kg/m^2). In addition, the blood glucose and lipid profiles including the total cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and triglycerides were studied in a biochemistry laboratory. The exclusion criteria for this study were as follows: (1) coronary artery disease, (2) hypo/hyperthyroidism, (3) significant renal insufficiency (creatinine level >1.5 mg/dL) and any malignancy. The study was approved by the Human Subjects Committee at Bozok University and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

Procedures and variables assessment

The diagnosis of arterial hypertension was based on the following criteria: Systolic blood pressure (SBP) ≥135 mmHg and/or diastolic blood pressure (DBP) ≥85 mmHg (measured three times within the space of 30 min in the sitting position with a brachial sphygmomanometer), or the use of blood pressure-lowering agents. The diagnosis of type 2 diabetes was based on the revised criteria of the American Diabetes Association, with a fasting blood glucose >126 mg/dL on at least two occasions,[13] a previous diagnosis of type 2 diabetes, or current therapy with insulin or oral hypoglycemic agents.

All patients underwent an ultrasonography (US) examination. Noncontrasted and contrasted abdominopelvic computed tomography (CT) scans were performed for both groups of patients and were assessed by a single radiologist to eliminate subjective interpretations and variations in the measurements. The radiologist was blinded to the patients' data. The presence of stones in the gallbladder was noted on abdominopelvic US. Plaque formation, intima-media thickness, plaque calcification, mural thrombus, stenosis, aneurysm, and inflammation were noted on the abdominopelvic CT scan. Atherosclerotic plaque was defined as a structure > 1 mm^2 within and/or adjacent to the lumen of the artery that could clearly be distinguished from the lumen and surrounding tissue.[14] A thickness of >0.8 mm was defined as increased intima-media thickness (IMT).[15] Plaques with a small crater on their surface were defined as inflamed plaques.[16] A thrombus adherent to the wall of the vessel lumen was considered to be a mural thrombus. Occlusion of more than 50% of the lumen diameter was defined as stenosis.[17] An aneurysm was defined as a sudden doubling of the arterial cross-section at its largest diameter compared to the arterial diameter in a proximally adjacent section.[18]

US was performed with LOGIQ S7 Ultrasound System (GE Healthcare, South Korea). Abdominopelvic CT scans were performed using a Brilliance CT 64 Scanner (Philips Medical Systems Inc., Cleveland, Ohio, USA). The abdominal CT scan protocol included a section thickness of 3 mm and an overlapping interval of 1.5 mm. Scanning encompassed the abdominopelvic area between the diaphragm at the cranial aspect and the inferior part of the symphysis pubis at the caudal aspect.

Based on the US and CT results, patients were classified into two groups according to the presence of GD. In each group, the patients were stratified according to the IMT in the abdominal aorta, iliac and femoral arteries, plaque formation, plaque calcification, mural thrombus, stenosis, aneurysm, and inflammation. Atheromatous plaque ratios were estimated in two distinct segments of the aorta including the suprarenal and infrarenal aorta, the common iliac artery segment, and the external iliac-common femoral artery (CFA) segment. In each segment, the atheromatous plaque ratio was calculated as the area of atheromatous plaque involvement divided by the area of the total vascular surface.

Arterial surfaces were estimated as follows: the length of the vascular structures was separately measured for each segment on coronal sections of abdominopelvic CT scans. To obtain accurate measurements of the vascular surface, the arterial perimeter was measured on the axial section, which divides the vascular structure into two equal parts, assuming each segment tapers distally. The arterial surface area was estimated from the following formula: Arterial surface area (cm^2) = arterial length × perimeter (cm). In each patient, the suprarenal and infrarenal aortic segments were

measured separately. In addition, the surface areas of the bilateral common iliac arteries and iliac-common femoral arteries were also measured. The suprarenal aortic segment was defined as the segment from the diaphragmatic level to the bifurcation of the renal artery, while the infrarenal aortic segment was defined as the segment from the renal artery bifurcation to the abdominal aorta bifurcation [Figure 1].

The total plaque surface in the above-mentioned vascular structures was estimated as follows: The width and length of the plaques were measured on coronal and sagittal sections on an abdominopelvic CT scan. We then calculated the plaque surface using the following formula: Plaque surface area (cm^2) = plaque width × plaque length (cm). The total plaque surface of the common iliac, external iliac, and common femoral arteries was calculated thereafter.

Statistical analysis

To assess the normality of the data, histogram and q-q plots were examined and a Shapiro–Wilk test was used. Levene's test was used to assess the variance in homogeneity. To compare the differences in continuous variables between the groups, a two-sided independent samples *t*-test or a Mann–Whitney U-test was performed. A Pearson's Chi-squared analysis or Fisher's exact test was used for the categorical variables. Quantitative data are expressed as frequencies and percentage; qualitative data are presented as a mean and standard deviation, geometric mean and 95% confidence interval, or median and interquartile range. We conducted a stratified analysis of covariance (ANCOVA) to evaluate the change in severity of the atheromatous plaques based on the presence of GD. The ANCOVA was applied after adjusting for age, BMI, LDL-C, DM, and smoking as covariates. Pearson correlations were used to examine the relationships between the severity of the atheromatous plaques and the clinical and laboratory variables of the patients. Patients were divided into two groups according to the median value of the atheromatous plaque ratios at the suprarenal and infrarenal aortic segments, bilateral common iliac arteries, and iliac-common femoral arteries. To distinguish the independent factors for the severity of atheromatous plaque, multivariate logistic regression analysis was performed, and backward elimination was conducted using the Wald statistic. Analyses were conducted using the SPSS version 15.0 (SPSS Inc.; Chicago, IL, USA) software. $P < 0.05$ was considered statistical significance.

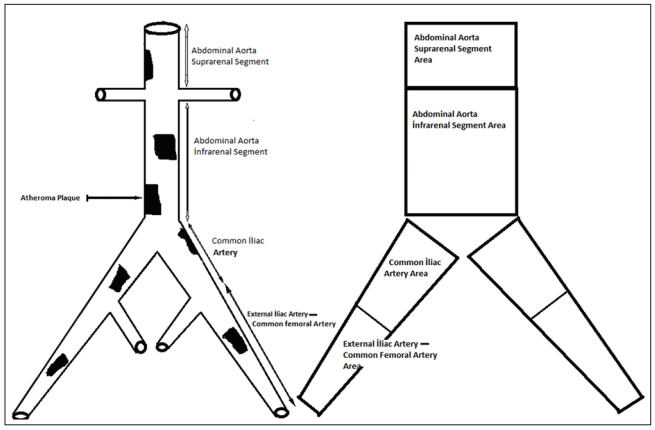

Figure 1: Artery fields that were measured for the study

RESULTS

The anthropometric, clinical, and laboratory data of the 136 patients with or without GD are provided in Table 1. The age and sex distribution of the two groups were similar. Patients with GD were more likely to have DM ($P < 0.05$). Smoking, alcohol consumption, and hypertension were all similar between the GD patients and controls. Individuals with GD had higher BMI ($P < 0.001$), cholesterol and LDL-C levels ($P < 0.05$) compared to the controls. No significant differences were found between the groups in terms of SBP, DBP, creatinine, alanine aminotransferase, aspartate aminotransferase, thyroglobulin (TG), and HDL between the controls and the GD group ($P > 0.05$).

Patients with GD had significantly higher rates of increased intima-media thickness, plaque formation, calcification, aneurysm, mural thrombosis, stenosis, and inflammation depending on the abdominal aortic segment ($P < 0.05$). When assessing the iliac artery segment, patients with GD were more likely to have increased intima-media thickness, plaque formation, calcification, aneurysm, mural thrombosis, stenosis, and inflammation ($P < 0.05$). At the femoral artery, patients with GD also had higher rates of increased intima-media thickness, plaque formation, calcification, mural thrombosis, stenosis, and inflammation ($P < 0.05$) but not aneurysm ($P > 0.05$) [Table 2]. While patients have a higher risk of cardiovascular problems at older ages, we also evaluated these vascular risk factors in patients over 50 years old according to gallstone status. In abdominal aorta, all GD patients over 50 years old have increased IMT and have significantly higher rates of calcification, aneurysm, mural thrombosis, stenosis, and inflammation were observed ($P < 0.05$). GD patients over 50 years old have significantly higher rates of plaque formation, calcification, aneurysm, mural thrombosis, stenosis, and inflammation at the iliac artery segment ($P < 0.05$). Higher rates of plaque formation, calcification, mural thrombosis, stenosis, and inflammation were also obtained at the femoral artery in patients with GD over 50 years old ($P < 0.05$).

GD patients had higher mean ratios of atheromatous plaque in all segments of the abdominal aorta, common iliac artery, external iliac artery, and CFA ($P < 0.001$). Table 3 shows the differences in the mean atheromatous plaque ratios

Table 1: Anthropometric, clinical, and laboratory data of patients with gallstone disease and controls

Variables	Patients without GD (*n*=88)	Patients with GD (*n*=48)	*P*
Age (years)	50.81±16.20	54.40±12.43	0.184
Gender (female)	40 (58.0)	48 (71.6)	0.109
BMI (kg/m^2)	29±3.48	32.14±2.51	<0.001
SBP (mmHg)	135.00 (120.00-153.75)	135.00 (120.00-140.00)	0.312
DBP (mmHg)	80.00 (75.00-90.00)	80.00 (71.25-85.00)	0.095
Creatinin	0.87 (0.76-1.15)	0.83 (0.73-0.93)	0.256
AST	24.50 (19.00-31.00)	23.50 (19.00-42.75)	0.329
ALT	22.50 (17.00-40.00)	29.50 (16.50-65.75)	0.075
Cholesterol	184.92±45.13	205.15±50.26	0.018
TG	148.00 (102.00-168.50)	147.50 (106.25-217.50)	0.085
LDL-C	121.00 (96.50-137.80)	131.00 (109.90-142.93)	0.029
HDL-C	42.00 (35.00-52.00)	42.00 (35.25-52.75)	0.960
Hypertension	10 (20.8)	30 (34.1)	0.119
DM	23 (26.1)	22 (45.8)	0.023
Smoking	26 (29.5)	13 (27.1)	0.844

Values are expressed as *n* (%), mean±SD or median (first to third quartiles). *P* = Raw *P* values; BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; DM = Diabetes mellitus; SD = Standard deviation; ALT = Alanine transaminase; AST = Aspartate transaminase; TG = Thyroglobulin; LDL-C = Low-density lipoprotein-cholesterol; HDL-C = High-density lipoprotein-cholesterol; GD = Gallstone disease

Table 2: Comparison of vascular risk factors of abdominal artery segments in patients

Variables	Patients without GD, *n*=88 (%)	Patients with GD, *n*=48 (%)	*P*
Abdominal aorta			
Intima-media thickness	66 (75.0)	47 (97.9)	0.001
Plaque formation	48 (54.5)	44 (91.7)	<0.001
Calcification	32 (36.4)	40 (83.3)	<0.001
Aneurysm	6 (6.8)	15 (31.3)	<0.001
Mural thrombosis	30 (34.1)	39 (81.3)	<0.001
Stenosis	1 (1.1)	10 (20.8)	<0.001
Inflammation	0 (0.0)	30 (22.1)	<0.001
Iliac artery			
Intima-media thickness	65 (73.9)	46 (95.8)	0.001
Plaque formation	42 (47.7)	43 (89.6)	<0.001
Calcification	30 (34.1)	39 (81.3)	<0.001
Aneurysm	4 (4.5)	11 (22.9)	0.002
Mural thrombosis	26 (29.5)	38 (79.2)	<0.001
Stenosis	0 (0.0)	10 (20.8)	<0.001
Inflammation	0 (0.0)	20 (41.7)	<0.001
Femoral artery			
Intima-media thickness	64 (72.7)	44 (91.7)	0.006
Plaque formation	22 (25.0)	42 (87.5)	<0.001
Calcification	17 (19.3)	40 (83.3)	<0.001
Aneurysm	1 (1.1)	4 (8.3)	0.052
Mural thrombosis	21 (23.9)	35 (72.9)	<0.001
Stenosis	0 (0.0)	8 (16.7)	<0.001
Inflammation	0 (0.0)	16 (33.3)	<0.001

Values are expressed as *n* (%). *P* = Raw *P* values; GD = Gallstone disease

between the GD groups. According to gender, BMI, total cholesterol, and LDL-C groups, the ratio of atheromatous plaque was found to be higher in all abdominopelvic arterial segments with GD patients ($P < 0.001$). In GD patients, the age, BMI, SBP, and DBP parameters were all correlated with the severity of atheromatous plaque in all segments of the abdominal artery ($P < 0.05$). Conventional atherosclerotic risk factors such as age, gender, BMI, DM, hypertension, LDL-C, HDL-C, TG, and GD were included in multiple models. On multivariate analysis, age and GD were independently associated with the severity of atheromatous plaque in all segments of the abdominal artery ($P < 0.05$).

DISCUSSION

Among the various atherosclerotic risk factors, DM was more prevalent and higher BMI, cholesterol and LDL-C values were detected in patients with GD in our study. Patients with GD also had significantly higher rates of the vascular risk factors. In all groups stratified according to gender, BMI, total cholesterol, and LDL-C, the involvement ratio of atheromatous plaque was found to be higher in all abdominopelvic arterial segments with GD patients. The severity of atheromatous plaque was correlated with age, BMI, SBP, and DBP. Age and GD were independently associated with the severity of atheromatous plaque in all segments of the abdominal artery on multivariate analysis. To the best of our knowledge, this is the first study to investigate the direct relationship between GD and abdominopelvic atheromatous plaque.

Cholesterol accumulation is the main component in both atherosclerosis and GD. These disorders share common risk factors such as age, gender, obesity, and lipid and glucose metabolism disorders, which are also key components of metabolic syndrome (MS). MS is strongly related to coronary artery disease, and gallstones can be considered to be a biliary feature of this syndrome.[19] In patients with GD, the increased risk of CVD can be explained by the metabolic pathway of cholesterol. One of the main characteristics of MS is low HDL-C levels, with an increased risk of cardiovascular morbidity and mortality.[20,21] The

Table 3: The mean and standard error for atheroma plaque ratios between the gallstone disease status by analysis of covariance in abdominal artery segments

Variables	Abdominal artery segments								*P*
	Mean±SE								
	Suprarenal aorta		Infrarenal aorta		CIA		EIA-CFA		
	GD⁻	GD⁺	GD⁻	GD⁺	GD⁻	GD⁺	GD⁻	GD⁺	
Sex									
Male	12.12±9.1	22.99±9.9	12.21±9.1	22.10±12.3	12.47±9.4	24.02±13.2	12.50±9.5	24.45±13.5	<0.001
Female	13.17±8.7	25.47±13.8	12.88±8.9	25.94±14.0	13.03±8.9	26.31±13.7	13.36±9.1	27.47±10.5	
BMI (kg/m²)									
<30	8.72±7.9	14.97±10.8	8.74±8.1	13.01±12.1	8.99±8.5	13.81±13.1	9.09±8.7	13.51±12.5	
≥30	19.30±6.2	27.32±11.5	19.06±6.3	27.81±11.8	19.20±6.1	28.85±11.6	19.47±6.18	30.07±12.2	
Cholesterol (mg/dl)									
≤194	9.32±7.5	24.91±15.8	9.16±7.6	25.59±17.8	9.31±7.8	26.21±17.5	9.25±7.7	26.66±18.7	
>194	17.26±8.8	24.26±10.3	17.31±8.7	23.77±10.3	17.61±8.7	24.95±10.9	18.08±9.0	26.06±11.1	
LDL-C									
≤125.9	9.13±7.4	24.06±14.7	9.03±7.5	24.64±16.7	9.38±7.9	25.13±16.2	9.35±7.8	25.96±17.3	
>125.9	16.88±8.9	24.77±10.8	16.85±8.8	24.27±10.8	16.87±8.9	25.58±11.5	17.27±9.3	26.48±11.8	

Covariates included in the analysis of covariance were age, BMI, LDL, DM and smoking status. CIA = Common iliac artery; EIA = External iliac artery; CFA = Common femoral artery; GD = Gallstone disease; BMI = Body mass index; LDL-C = Low-density lipoprotein-cholesterol; SE = Standard error; DM = Diabetes mellitus

liver is the key organ that regulates the metabolism of cholesterol. In addition, it also regulates the concentration of cholesterol in plasma and bile.[22] Impaired cholesterol metabolism in patients with MS, DM, and fatty liver leads to either dyslipidemia or highly concentrated biliary cholesterol.[23,24] Several studies have shown the importance of HDL-C in the development of gallstones. HDL-C plays a role in the reverse transport of cholesterol and involves the transportation of cholesterol from peripheral tissues to the liver through a hepatic receptor, namely scavenger receptor B type 1 (SRB1).[25] It is thought that hepatic SRBI is increased in patients with GD, resulting in increased biliary cholesterol and the subsequent formation of gallstones.[26] Increasing age is a risk factor for GD and possibly explained by long-term exposure to other related environmental risk factors.[27] Moreover, an elevated fasting blood glucose level is another factor related to coronary artery disease as well as GD.[28] Elevated fasting blood glucose and DM can affect cholesterol and lipoprotein metabolism and cause defective gallbladder contractility. Studies indicate that obesity and MS are risk factors for GD.[29] The presence of three of the criteria for determining MS leads to a 7.89-fold increase in the risk of stone formation.[30] In conclusion, GD seems to be strongly related to MS and its components, as is the case for CVD.

Abdominal complex plaques are associated with myocardial infarction and complex coronary lesions.[31,32] In an autopsy series of abdominal aortic plaques, it was reported that plaques in the abdominal aorta were more severe in patients with cardiac injury compared to those without.[33] The presence and severity of plaques at the descending thoracic aorta were independently related to significant coronary artery disease detected by a coronary angiography CT.[34] Coronary calcification was found to be associated with carotid plaques.[35] Kälsch *et al*. reported that the aortic calcium score was associated with BMI, SBP, and pulse pressure.[36] A significant independent association between the total plaque score and MS was observed in males.[37] MS components are related to GD, and BMI and increased age are also related to GD.[9] The increased prevalence of MS components was observed in patients undergoing cholecystectomy.[7] As GD and plaque formation have common risk factors, we investigated the relationship between these frequent diseases. According to our study results, plaque formation in the abdominopelvic artery segments, accepted as a manifestation of atherosclerosis, is closely related to GD. We speculate that GD patients may have an increased risk of CVD. GD patients should, therefore, be evaluated according to CVDs.

The association between gallstones and cardiovascular disorders has been evaluated in many studies, with contradictory results. A 10-year follow-up study failed to find any relation between GD and CVD.[9] Another study mentioned the higher prevalence of MS components in patients undergoing cholecystectomy, but CVD was not increased in GD patients.[7] One study did not support any major association between ischemic heart disease and GD.[8] In a cross-sectional study on manual workers in Mexico, the likelihood of gallstones being detected on US was found to be three times higher in individuals diagnosed with cardiovascular disorder by a stress test.[38] In an 18-year follow-up study, it was shown that GD had a significant association with an increased risk of cardiovascular mortality.[11] In another study, it was found that the incidence of positive stress-induced myocardial ischemia, as assessed by the Bruce protocol, was higher in individuals with asymptomatic GD compared to those without GD after adjusting for age, gender, and BMI.[39] A population-based

case–control study from the UK demonstrated the likelihood of symptomatic GD to be increased by 30% after adjusting for confounding factors for ischemic heart disease. In a case-controlled GD and breast cancer study conducted in the USA, a strong association was incidentally found between GD and myocardial infarction.[39] In the 1980s, the Framingham study showed a prospective, independent association between GD and coronary heart disease. In that study, during 26 years of follow-up, the risk for a first coronary event was two times higher in patients who underwent cholecystectomy due to GD. However, this was only the case for men.[2]

Although an association was initially found between GD and coronary artery disease in another study, such an association was not observed when only those patients who underwent cholecystectomy were included in the analysis.[8] In our study, we evaluated for the first time the association between GD and abdominopelvic atheromatous plaque, a marker of atherosclerosis and showed that the risk of CVD was increased in patients with GD.

The limitations of this study include its cross-sectional design and relatively small sample size. In addition, we did not investigate the underlying pathogenetic mechanism, which may explain the relationship between gallstones and abdominopelvic atheromatous plaque.

CONCLUSION

We demonstrated the relationship between gallstones and abdominopelvic atheromatous plaque, which is a marker for increased cardiovascular risk. Patients with GD exhibit greater abdominopelvic atherosclerosis and therefore, have a higher risk of CVD.

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Nil.

Conflicts of interest
There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

- HIS contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work YKY contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- MC contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work EA contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- YT contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- MFE contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- AD contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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