Cross-sectional Study

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# Association between gallstone disease and carotid intima-media thickness: a prospective observational cross-sectional study in a tertiary care center

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**Background and objectives:** Gallstone disease (GD) is a prevalent health issue globally, particularly in developed nations, and has notable associations with cardiovascular disease (CVD). This prospective observational cross-sectional study aimed to investigate the association between gallstone disease and carotid intima-media thickness (CIMT), a marker of carotid atherosclerosis, in a tertiary care setting.

**Method:** Conducted at a tertiary care center, the study included 96 participants (48 with gallstone disease and 48 age and sex-matched controls). Data collection involved demographic information, BMI calculation, abdominal ultrasonography for gallstone detection, and carotid ultrasonography for CIMT measurement. Statistical analysis was performed using SPSS version 26.

**Results:** The study revealed higher CIMT values in GD patients compared to controls ($P < 0.001$). Additionally, a positive correlation was observed between CIMT and age ($r = 0.450$, $P < 0.001$) and BMI ($r = 0.550$, $P < 0.001$). The Cohen's d-test indicated a clinically significant difference in CIMT between GD patients and controls ($d = 1.47$).

**Conclusion:** This study revealed a significant association between gallstone disease and elevated CIMT, correlating with higher BMI indicating a potential link between gallstone disease and increased risk of carotid atherosclerosis. These findings highlight the importance of assessing cardiovascular risk in patients with gallstone disease, highlighting the potential utility of carotid ultrasonography as a non-invasive screening tool. Early intervention strategies may be warranted to mitigate cardiovascular risks associated with gallstone disease.

**Keywords:** cardiovascular disease, carotid intima-media thickness, cross-sectional study, gallstone disease

## Introduction

Gallstone disease (GD) persists as a significant contributor to abdominal morbidity and mortality worldwide[1]. In contemporary times, gallbladder disease has become a prevalent issue in developed nations, posing a substantial health burden[2]. Gallstones, primarily asymptomatic, are frequently incidentally detected during abdominal ultrasonography. The nexus between gallstone disease and cardiovascular disease (CVD) is notable, bearing significant economic implications[3].

Prevalence rates of GD vary across populations, with higher frequencies observed in Europe and the USA compared to certain African populations[1,4]. In Nepal, a multicenter ultrasonographic study conducted in 2007 revealed a prevalence of 4.87%, with a male-to-female ratio of 1:2.3[5]. While cholesterol stones prevail predominantly in Western nations, mixed stones are more common in regions like Nepal[6]. Notably, risk factors for GD overlap with those for atherosclerosis, suggesting a potential association between the two conditions[7,8].

Despite the asymptomatic nature of gallstones in the majority of cases, the prevalence of GD remains high, necessitating effective diagnostic methods[9]. Abdominal ultrasonography serves as a primary diagnostic tool, offering a non-invasive and cost-effective approach with high sensitivity (over 95%) and specificity for detecting gallbladder stones (> 1.5 mm diameter)[10].

### HIGHLIGHTS

- This prospective observational study examined the association between gallstone disease and carotid atherosclerosis, as indicated by carotid intima-media thickness (CIMT), in a population undergoing abdominal ultrasound.
- Results revealed significantly elevated CIMT in patients with gallstones compared to those without, suggesting a heightened risk of carotid atherosclerosis in individuals with gallstone disease.
- These findings highlight the importance of monitoring cardiovascular health in patients diagnosed with gallstones.

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CVD is the leading global cause of death, despite advances[11]. Prevention through risk factor modification is cost-effective and essential[12]. Given that CVD remains the leading cause of mortality globally, understanding and preventing its risk factors are imperative. Several observational studies have explored the relationship between GD and CVD, yielding varied results[13,14]. Furthermore, the impact of cholecystectomy on modifying CVD risk remains uncertain, with some studies suggesting a direct causal relationship between cholecystectomy and CVD[15]. Additional cohort studies investigating screen-detected GD and its relationship with CVD, along with the impact of cholecystectomy on CVD risk, have been conducted[16]. Carotid intima-media thickness (CIMT) measurement via ultrasound serves as a reliable screening approach for assessing cardiovascular risk. Therefore, evaluating the association between GD and CIMT can provide insights into the potential cardiovascular implications of gallstone disease[17].

Against this backdrop, this study aims to investigate the association between gallstone disease and carotid intima-media thickness, shedding light on the cardiovascular risk profile of individuals with GD. By elucidating this relationship, we aim to contribute to the understanding of GD's broader health implications and inform preventive strategies for mitigating cardiovascular risk associated with gallstone disease.

### *Methodology*

This prospective observational cross-sectional study was conducted in the Department of Radiology and Imaging of a Tertiary Care Center from February 2021 to January 2022. Ethical approval for conducting the study was taken from the Institutional Review Board (IRB) (Approval number 650/2077/78). The study adhered to the Strengthening of the reporting of cohort, cross-sectional, and case-control studies in surgery (STROCSS) guidelines[18]. Additionally, the study was retrospectively registered in the research registry.

A sample size of 96 participants (48 patients with gallstone disease and 48 age- and sex-matched controls) was calculated based on a similar study by Jung *et al.*[19]

A consecutive sampling technique was applied. Adult patients aged 19 years and above undergoing abdominal ultrasound at the Department of Radiodiagnosis and Imaging with or without gallstone disease were included after obtaining informed consent. Exclusion criteria included age less than 19 years, history of cholecystectomy, common carotid artery surgery, myocardial infarction, stroke, and peripheral vascular disease (Fig. 1).

Detailed information was recorded using a pre-designed data collection sheet. Weight was measured using a standard digital weighing machine (Xiaomi Smart scale with 100 g precision), and height was measured using a height measuring scale/Stadiometer (Indosurgical-20015 with 20–210 cm measuring range and 1 mm graduation). The BMI was calculated by the following formula: BMI = weight [kg]/height [$m^2$]. The patients were divided into four BMI categories for both sexes: Category A: BMI less than 18.5, Category B: BMI 18.5–24.9, Category C: BMI 25–29.9, Category D: BMI greater than 30.

Abdominal ultrasonography was performed using a 3–5 MHz curved probe (Aloka F37; Hitachi) to detect gallstones. Gallstones were identified based on echo movements according to posture change with echogenic and posterior acoustic shadow[20].

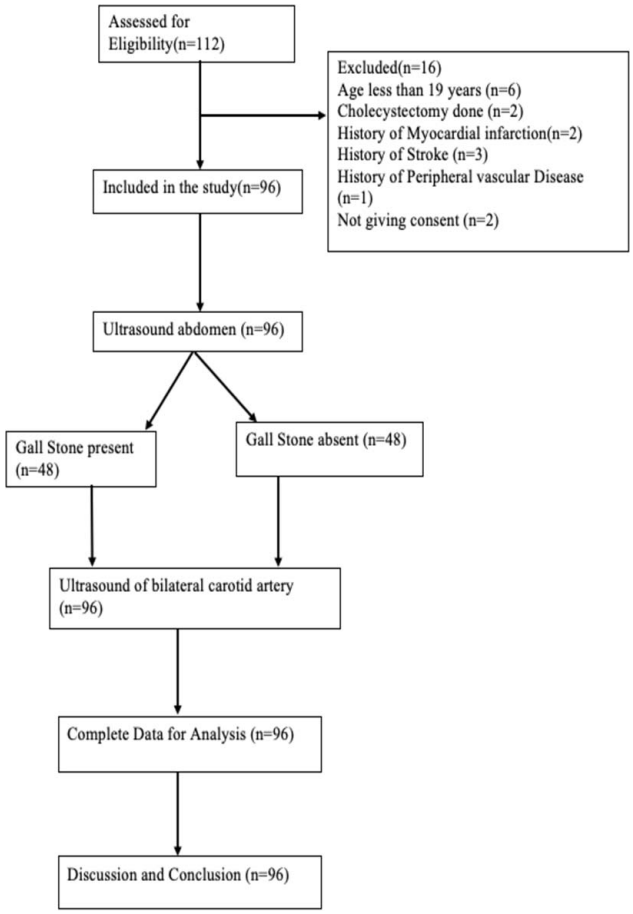


**Figure 1.** STROCS flow diagram of the participant.

Carotid ultrasonography was conducted to measure CIMT in all participants with or without gallstone disease after obtaining informed consent. A 5–12 MHz linear probe (Aloka F37; Hitachi) was used for B-mode imaging. CIMT was defined as the distance from the boundary of the lumen of the vessel and tunica intima to the boundary of tunica-media and tunica externa[21]. Measurements were taken at the proximal part of the far wall from the boundary that transitions the common carotid artery to the carotid bulb (Fig. 2). The value of the biggest IMT was obtained from both common carotid arteries. With the presence of atherosclerotic plaques, it was measured at the proximal part without atherosclerotic plaques. The atherosclerotic plaque was assumed when carotid IMT is 1.5 mm or greater and the presence of local thickness in the vessel[22].

The ultrasound devices used for carotid ultrasonography were selected based on their established reliability and validity in previous studies with sensitivity and specificity of 78% and 75%, respectively. Calibration procedures were followed to ensure accurate measurements[23].

Ultrasound examinations were performed by a consultant radiologist with significant experience, averaging 300 examinations performed annually, demonstrating proficiency and familiarity with the technique. To prevent bias, the radiologist performing carotid ultrasound was blinded to the abdominal ultrasound report, and vice versa.

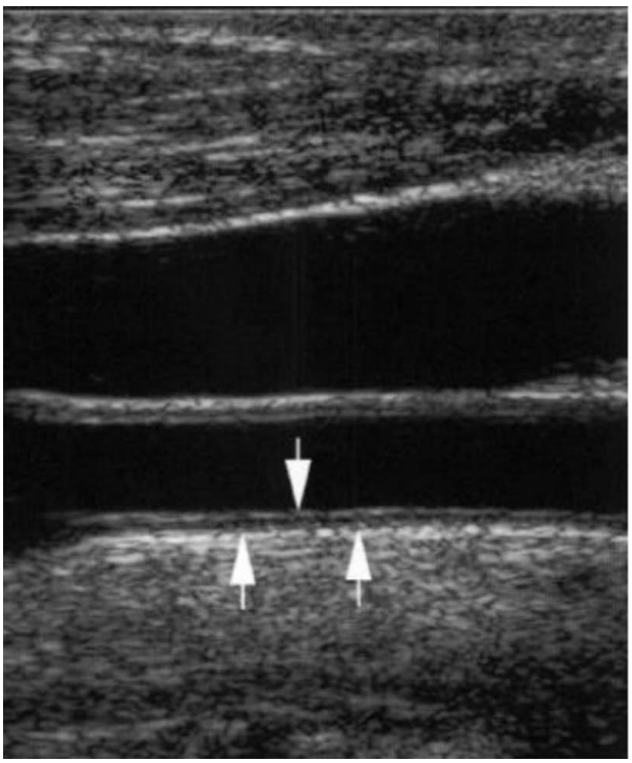

**Figure 2.** Ultrasound B-mode image showing intima-media complex (between the arrows).

The study involved patients and the public in research objectives, design, and outcome measures. They facilitated recruitment, provided feedback, and participated in meetings, dissemination, and knowledge translation activities.

Data were collected from the pre-structured proforma. Data obtained were entered into the Statistical Package for Social Science (SPSS) program version 26. Statistical analysis of obtained data was done by using relevant statistical tests. Pearson correlation and Cohen's d-test were utilized to assess the strength of association, with significance set at $P$ less than 0.05.

## Results

In this hospital-based cross-sectional study, 48 diagnosed gallstone cases along with 48 age and sex-matched control groups who did not have gallstones were taken based on US findings, and bilateral carotid intima-media thickness was measured in both groups (Table 1).

**Table 1**

**Demographic profile of patients with gallstone**

| S.N. | Age (years) | Male, *n* (%) | Female, *n* (%) | Total, *n* (%) |
|---|---|---|---|---|
| 1. | 30–40 | 8 (16.67) | 9 (18.75) | 17 (35.42) |
| 2. | 41–50 | 6 (12.5) | 11 (22.92) | 17 (35.42) |
| 3. | 51–60 | 3 (6.25) | 10 (20.83) | 13 (27.08) |
| 4. | 61–70 | 1 (2.08) | 0 | 1 (2.08) |
| | Total | 18 (37.5) | 30 (62.5) | 48 (100) |

**Table 2**

**Carotid intima-media thickness of right and left side**

| S.N. | Gallstone disease | No. patients | Minimum (mm) | Maximum (mm) | Mean IMT (mm) |
|---|---|---|---|---|---|
| Right carotid IMT | | | | | |
| 1. | Present | 48 | 0.4 | 1.3 | $0.763 \pm 0.18315$ |
| 2. | Absent | 48 | 0.31 | 0.81 | $0.4883 \pm 0.14607$ |
| | Total | 96 | | | $0.61234 \pm 0.20659$ |
| Left carotid IMT | | | | | |
| 1. | Present | 48 | 0.39 | 1.30 | $0.7558 \pm 0.19901$ |
| 2. | Absent | 48 | 0.32 | 0.82 | $0.4938 \pm 0.14757$ |
| | Total | | | | $0.6198 \pm 0.21546$ |

IMT, intima-media thickness.

Among the gallstone disease cases, the majority were females, comprising 30 (62.5%) of the participants. The age distribution of gallstone disease cases ranged from 30 to 70 years, with the highest prevalence observed in the 30–40 and 41–50 age groups. The age and sex distribution of the control group mirrored that of the gallstone disease group.

The overall minimum and maximum CIMT values were 0.31 and 1.3 mm, respectively. Comparing CIMT values between participants with gallstone disease and those without, it was noted that both the minimum and maximum CIMT values were higher in patients with gallstone disease. Specifically, the mean CIMT was higher on both sides among participants with gallstone disease compared to those without gallstone disease ($P < 0.001$) (Table 2).

Among all the cases of gallstone disease, most of them belonged to BMI category C (25–29.9 kg/m²). Similarly, in the control group without gallstone disease, most participants were categorized under BMI category C (Table 3).

The mean CIMT was highest on both sides in the BMI category C (25–29.9 kg/m$^2$) with $p$ value of less than 0.001 (Table 4).

The analysis reveals a robust positive correlation between the average carotid intima-media thickness and age ($r = 0.450$, $P < 0.001$). Similarly, a notable positive correlation is observed between BMI and average carotid intima-media thickness ($r = 0.550$, $P < 0.001$).

In our investigation, Cohen's d-test yielded a value of 1.47, with a mean difference of 0.25 in CIMT between patients with and without gallstones.

## Discussion

Recent cross-sectional, cohort, and prospective studies have elucidated a significant correlation between gallstone formation and

**Table 3**

**BMI group distribution in patients with or without gallstone disease**

| S.N. | BMI category | Gallstone present | Gallstone absent | Total |
|---|---|---|---|---|
| 1. | Category A (< 18.5 kg/m$^2$) | 0 | 0 | 0 |
| 2. | Category B (18.5–24.99 kg/m$^2$) | 8 | 20 | 28 |
| 3. | Category C (25–29.99 kg/m$^2$) | 27 | 24 | 51 |
| 4. | Category D (> 30 kg/m$^2$) | 13 | 4 | 17 |
| | | 48 | 48 | 96 |

**Table 4**

**Study of CIMT in various BMI group.**

| BMI (kg/m$^2$) | Number (*N*) | Mean | Standard deviation | Standard error mean | Level of significance |
|---|---|---|---|---|---|
| CIMT right | | | | | |
| 18.5–24.9 kg/m$^2$ | 28 | 0.4814 | 0.16329 | 0.03086 | $P<0.001$ |
| 25–29.9 kg/m$^2$ | 51 | 0.6169 | 0.18935 | 0.02651 | |
| >30 | 17 | 0.8141 | 0.15182 | 0.03682 | |
| CIMT left | | | | | |
| 18.5–24.9 kg/m$^2$ | 28 | 0.4836 | 0.16067 | 0.03036 | |
| 25–29.9 kg/m$^2$ | 51 | 0.6233 | 0.19373 | 0.02713 | |
| >30 | 17 | 0.8335 | 0.18364 | 0.04454 | |

CIMT, carotid intima-media thickness.

various cardiovascular conditions. These include carotid atherosclerosis, ischemic heart disease, and overall cardiovascular morbidity and mortality[13,14,24]. For instance, Serin *et al.*[25] studied 136 patients, with 48 having GD, and Kim *et al.*[19] observed 330 male participants, 32 of whom had GD. Similarly, Méndez-Sánchez *et al.*[3] examined 191 subjects, finding 62 with GD; 53.2% of subjects with GD were male, and the rest were female. In our investigation, we enrolled 48 GD cases, comprising 18 males (37.5%) and 30 females (62.5%), along with age and sex-matched controls, ensuring comparability with prior studies.

The mean age of GD patients varied across investigations, with Kim *et al.*[19] reported 56.1 ± 10.1 years and Méndez-Sánchez *et al.*[3] noting 49.3 ± 12.3 years. In our study, the age range of GD patients was 30–70 years, with the highest prevalence observed in the 41–50 age group and a mean age of 45.5 ± 9.413 years, consistent with previous findings. The positive and significant correlation between carotid intima-media thickness and age observed in our study mirrors findings reported in a study conducted by Kim *et al.*[19]

Regarding CIMT, Méndez-Sánchez *et al.*[3] reported significant increases in GD patients compared to non-GD individuals, with CIMT values of 0.64 ± 0.17 mm and 0.63 ± 0.16 for the right and left sides, respectively. They noted a 0.1 mm increase in CIMT corresponded to a 1.25 times higher prevalence of GD (95% CI, 1.02–1.53; $P=0.027$). Similarly, Kim *et al.*[19] found a significantly higher mean CIMT in GD patients (0.99 ± 0.18 mm) compared to non-GD counterparts (0.85 ± 0.21 mm) ($P=0.002$). The elevated Cohen's d value (1.47)[26] in our study indicates a clinically significant disparity in CIMT between individuals with and without gallstones. This may suggest a notably heightened risk of carotid atherosclerosis in those with gallstone disease.

Our prospective cross-sectional study observed an overall mean CIMT of 0.6123 ± 0.20659 mm and 0.6198 ± 0.21546 mm on the right and left sides, respectively. Specifically, we found a mean CIMT of 0.7363 ± 0.18315 mm and 0.4883 ± 0.14607 mm on the right side for the gallstone disease (GD) and non-GD groups, respectively, while on the left side, these values were 0.7458 ± 0.19901 mm and 0.4938 ± 0.14757 mm for the GD and non-GD groups, respectively. Significant increases in CIMT were noted in both sides among GD cases compared to those without GD ($P<0.001$). Our findings regarding overall mean CIMT and CIMT in the GD and non-GD groups align with previous studies. The observed association could be due to shared risk factors such as obesity, diabetes, and metabolic syndrome, which may contribute to both conditions leading to systemic inflammation, endothelial dysfunction, and atherosclerosis. Additionally, bile acids and cholesterol may play a role in vascular inflammation and atherosclerotic plaque formation.

Serin *et al.*[25] reported a mean BMI of (29 ± 3.48) kg/m² in patients without GD and (32.14 ± 2.51) kg/m² in patients with GD, showing a significant difference ($P<0.001$). Similarly, Méndez-Sánchez *et al.*[3] found a mean BMI of (26.4 ± 3.5) kg/m² in patients without GD and (28.1 ± 4.6) kg/m² in patients with GD, with a significant difference ($P=0.005$). In our study, the mean BMI was (28.03 ± 3.47) kg/m² in GD patients and (25.6 ± 2.63) kg/m² in non-GD patients, indicating a significant increase in BMI among GD patients ($P<0.001$), consistent with previous research. Our study reveals a robust correlation ($r=0.550$, $P<0.001$) between carotid intima-media thickness and BMI, notably among GD patients (28.03 ± 3.47 kg/m²) and non-GD patients (25.6 ± 2.63 kg/m²). Kim *et al.*'s[19] findings exhibit a lesser correlation ($r=0.115$, $P=0.036$), possibly influenced by sample heterogeneity, with BMI ranging differently.

Carotid artery intima-media thickness (CIMT) is a reliable and non-invasive method widely recognized as an indicator of cardiovascular risk for conditions such as myocardial infarction and stroke[21,27]. Studies have demonstrated that for each 0.15 mm increase in CIMT, the adjusted risk for myocardial infarction and stroke increases by a factor of 1.73[27]. Our investigation revealed that CIMT values were notably higher in individuals with gallstones compared to those without, implying an augmented cardiovascular risk among the former group. Notably, a CIMT threshold of 0.75 has been proposed as a diagnostic tool for assessing the risk of stroke, underscoring the clinical significance of CIMT measurements in predicting cardiovascular events[28].

The link between gallstone disease and cardiovascular risk is crucial, and clinicians should assess risk factors in patients with gallstone disease, especially those with obesity and diabetes. Early detection of increased CIMT can prompt interventions.

Our study is limited by its hospital-based, cross-sectional design with a relatively small sample size, potentially limiting generalizability. Additionally, missing data on hypertension, diabetes, exercise, smoking, and alcohol intake hindered a comprehensive evaluation. However, evidence supports gallstone disease as an independent risk factor for carotid atherosclerosis, and our sample included individuals clinically free of traditional cardiovascular risk factors, minimizing the impact of these limitations on the validity of our findings.

## Conclusion

This study provides evidence of an association between gallstone disease and increased carotid intima-media thickness correlating with higher BMI values, suggesting an elevated cardiovascular risk in individuals with gallstone disease. While further research is needed to elucidate the underlying mechanisms and establish causality, these findings highlight the importance of cardiovascular risk assessment in patients with gallstone disease and suggest the potential for targeted interventions to mitigate cardiovascular risk in this population.

## Ethical approval

We have conducted an ethical approval base on the Declaration of Helsinki with registration research at the Institutional Review Board (IRB) of the National Academy of Medical Sciences (NAMS), Nepal, Reference number: 650/2077/78.

## Consent

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-chief of this journal on request.

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Not applicable.

## Author contribution

L.T.: conceptualization, as mentor and reviewer for this original article and for data interpretation. S.K.: conceptualization, data analysis and reviewer for this case. B.R.T.: contributed in writing the paper and reviewer for this case. All authors have read and approved the manuscript.

## Conflicts of interest disclosure

All the authors declare no competing interest.

## Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry
2. Unique identifying number or registration ID: Researchregistry10092.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://researchregistry.knack.com/research-registry#home/registrationdetails/65f5d7aed9e7b6002a423a0c/

## Guarantor

Shailendra Katwal is the person in charge of the publication of our manuscript.

## Data availability statement

The materials datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

## Provinence and peer review

Not commissioned, externally peer-reviewed.

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