Original Research Paper

Volume - 16 | Issue - 01 | January - 2026 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

General Surgery

ASSOCIATION OF GALLSTONE DISEASE WITH METABOLIC SYNDROME

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ABSTRACT **Background:** Gallstone disease and metabolic syndrome are significant public health concerns with overlapping risk factors and shared pathophysiological mechanisms. Understanding their association is crucial for developing effective prevention and treatment strategies. Despite increasing prevalence in India, limited research has examined this relationship in the Indian context. **Methodology:** A hospital-based, cross-sectional, observational study was conducted at L.N. Medical College and J.K. Hospital, Bhopal, over 18 months. A total of 204 adult participants presenting with gallstone disease, metabolic syndrome or neither condition were enrolled. Participants underwent detailed clinical, anthropometric, biochemical and radiological evaluations using NCEP-ATP III criteria for metabolic syndrome diagnosis. Statistical analysis included chi-square tests and binary logistic regression. **Results:** Among 204 participants, 49% had gallstone disease and 47% had metabolic syndrome. Approximately 34% had both conditions simultaneously. Among those with gallstones, 72.92% had metabolic syndrome compared to 27.08% without gallstones ($p<0.0004$). Logistic regression revealed that individuals with metabolic syndrome were 6.98 times more likely to develop gallstone disease (OR=6.98, 95% CI: 3.7-12.9, p=0.001). Central obesity (OR=2.12, p=0.0021), high triglycerides (OR=2.81, p=0.002) and low HDL cholesterol (OR=1.579, p=0.041) were significantly associated with gallstone disease. Cholesterol stones were the most common type (62%), followed by mixed stones (31%) and pigment stones (7%). **Conclusion:** This study demonstrates a strong association between metabolic syndrome and gallstone disease in the Indian population. Metabolic syndrome components, particularly central obesity, elevated triglycerides and low HDL cholesterol, significantly increase gallstone risk. Early identification and management of metabolic syndrome may prevent gallstone disease and its complications.

KEYWORDS : Gallstone Disease, Metabolic Syndrome, Cholelithiasis, Central Obesity, Dyslipidemia, Insulin Resistance, NCEP-ATP III Criteria

INTRODUCTION

Gallstone disease involves the formation of solid particles in the gallbladder, which stores bile - a digestive fluid containing cholesterol, bile salts and bilirubin. These stones vary in size, composition and number, classified as cholesterol, pigment or mixed types (1). While they may remain asymptomatic, they can cause biliary colic, cholecystitis or biliary obstruction (2). Globally prevalent, gallstone disease affects 10% to 20% of Western populations, particularly older adults, women and obese individuals (3,4). Though historically less common in Asian populations including India (3,4), recent decades show sharply rising incidence due to dietary changes, sedentary lifestyles and increased obesity and metabolic syndrome (5,6). Improved ultrasonography diagnosis has contributed to apparent prevalence increases, with 10% to 25% of cases developing symptoms requiring intervention (2). Formation results from multifactorial influences including genetic, metabolic and environmental factors, primarily involving bile composition imbalance leading to cholesterol or bilirubin supersaturation (7). Risk increases with obesity, rapid weight loss, pregnancy and metabolic syndrome (7,8) with insulin resistance altering hepatic lipid metabolism and increasing bile cholesterol saturation (9,10).

Metabolic syndrome comprises interconnected metabolic disorders increasing cardiovascular disease, type 2 diabetes and stroke risk. Diagnosis requires at least three components (11): central obesity with population-specific increased waist circumference, elevated triglycerides ≥150 mg/dL, low HDL cholesterol (<40 mg/dL men, <50 mg/dL women), hypertension (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) and impaired fasting glucose (≥100 mg/dL). The National Cholesterol Education Program Adult Treatment Panel III and International Diabetes Federation provide diagnostic criteria with variations in thresholds (12,13). Central obesity associates with insulin resistance, systemic inflammation and lipid abnormalities contributing to other syndrome components (14,15). Prevalence has increased globally alongside rising obesity and sedentary lifestyles (16,17). Emerging Asian economies show steep rises from Westernized diets, reduced physical activity and aging populations (18). India faces alarming increases due to genetic predisposition to insulin resistance and urbanization-driven lifestyle changes, with 25% to 30% of urban adults and 10% to 15% of rural adults meeting metabolic syndrome criteria (18,19).

The relationship between gallstone disease and metabolic syndrome, first highlighted by Mendez-Sanchez et al. in 2005 (20), has been consistently confirmed by subsequent larger studies. Individuals with metabolic syndrome show higher gallstone likelihood than the general population, underscoring metabolic underpinnings of stone formation (9,21,22). Multiple overlapping mechanisms contribute to their coexistence. Insulin resistance affects hepatic lipid metabolism, increasing bile cholesterol secretion while reducing bile acid synthesis (9,10). Dyslipidemia elevated triglycerides and reduced HDL cholesterol critically links both conditions (23,24). High triglycerides associate with increased bile cholesterol saturation, while low HDL reduces cholesterol clearance from bile, promoting stone formation (23,24). Central obesity increases pro-inflammatory adipokine production while reducing anti-inflammatory adipokines, creating conditions favorable for gallstone development. Obesity also links to impaired gallbladder motility, predisposing to biliary stasis and stone formation (25,26).

METHODOLOGY

A single-center, hospital-based, cross-sectional, observational study evaluated the association between gallstone disease and metabolic syndrome at the Department of General Surgery and General Medicine, L.N. Medical College and J.K. Hospital and Medical Research Centre, Bhopal. The institution provided comprehensive diagnostic, clinical, biochemical and radiological facilities for accurate condition evaluation. Ethical clearance was obtained from the Institute's Ethical Committee via protocol no. 132 on 07/11/23. The study complied with the Declaration of Helsinki, protecting participants' rights, safety and well-being while adhering to ethical principles ensuring patient confidentiality, voluntary participation and informed consent.

Study Duration and Phases

The 18-month study comprised three phases. The planning phase (3 months) included protocol development, data collection forms and informed consent documents, Institutional Ethical Committee approval submission and pilot testing. The participant recruitment and data collection phase (12 months) involved screening patients with gallstone disease, applying inclusion and exclusion criteria, collecting clinical, biochemical and imaging data and monitoring data accuracy. The data analysis and report writing phase (3 months) included statistical analysis assessing the gallstone disease-metabolic syndrome association, result interpretation with literature comparison and final research report preparation.

Study Population and Sampling

Participants were adult patients (≥18 years) with suspected gallstone

disease who underwent clinical, biochemical and radiological evaluations for metabolic syndrome. Inclusion criteria comprised patients aged above 18 years presenting to LNMC Bhopal with gallstone disease and/or metabolic syndrome or its components and those willing to provide informed consent. Exclusion criteria included patients younger than 18 years, those not providing consent, patients with acalculous cholecystitis, gallbladder polyps without gallstones, congenital gallbladder abnormalities, history of repeated blood transfusion (hemolytic anemia) and gallbladder malignancy without gallstones. Hospital-based, cross-sectional sampling recruited participants from the Department of General Surgery and General Medicine at L.N. Medical College and Research Centre, Bhopal. All eligible patients aged above 18 years presenting with gallstone disease, metabolic syndrome, or metabolic syndrome components were screened. Consecutive sampling included all eligible individuals meeting criteria during the study period. The observational study sample size formula resulted in 204 enrolled participants.

Data Collection Procedures

Written informed consent was obtained before enrollment. The Principal Investigator explained the study's purpose, objectives, procedures, potential risks and benefits clearly. A bilingual consent form (Hindi and English) ensured full participant understanding. After consent, participants were screened for eligibility based on inclusion and exclusion criteria. Detailed clinical examination recorded anthropometric parameters including age, sex, demographic details (urban/rural residence, occupation, socioeconomic status), presenting complaints, symptom duration and past medical history. Anthropometric measurements included weight (calibrated digital weighing scale), height (stadiometer), Body Mass Index (weight kg/height m²) and waist circumference (flexible measuring tape at midpoint between lower rib and iliac crest). Blood pressure was measured using a sphygmomanometer with two readings in sitting position at 5-minute intervals, averaging the values.

Laboratory investigations assessed metabolic parameters from fasting blood samples collected after 8-12 hours fasting. Biochemical tests performed included fasting blood sugar (mg/dL, automated biochemical analyzer), lipid profile (serum triglycerides and HDL cholesterol in mg/dL) and liver function tests ruling out underlying liver disease. Trained phlebotomists collected samples, transported under controlled conditions to the laboratory and analyzed using standardized methods. Abdominal and pelvic ultrasonography confirmed gallstone presence, recording number and size of gallstones, gallbladder wall thickening or sludge presence and complication evidence such as cholecystitis or biliary obstruction. A qualified radiologist reviewed radiology reports and documented findings in the data collection proforma.

Statistical Analysis

The study tested the hypothesis that there is no significant association between gallstone disease and metabolic syndrome (null hypothesis) versus a significant association exists (alternative hypothesis). Continuous variables (BMI, lipid levels, fasting glucose) were summarized as mean ± standard deviation or median (IQR) based on distribution, while categorical variables (metabolic syndrome presence) were presented as frequency and percentages. Inferential statistics included chi-square test comparing categorical variables (metabolic syndrome presence among gallstone patients), independent t-test or Mann-Whitney U test comparing continuous variables between groups based on normality and binary logistic regression analysis assessing the metabolic syndrome-gallstone disease association while adjusting for confounding variables. A p-value <0.05 was considered statistically significant. All statistical and graphical analysis used Stata software version 17.0.

RESULTS

The present hospital-based, cross-sectional, observational study was conducted to evaluate the association between gallstone disease and metabolic syndrome among adult patients. A total of 204 participants having either gallstone disease, metabolic syndrome, or neither condition were enrolled and each participant underwent detailed clinical, anthropometric, biochemical and radiological evaluation to determine the presence of metabolic syndrome, based on the NCEP-ATP III criteria.

Table 1: Demographic and Patient Characteristics

Characteristic	Category	n (%)
Age Distribution	18-20 years	4 (1.96%)
	21-30 years	16 (7.84%)
	31-40 years	44 (21.57%)
	41-50 years	61 (29.90%)
	51-60 years	55 (26.96%)
	61-70 years	24 (11.76%)
Gender	Female	146 (71.57%)
	Male	58 (28.43%)
BMI Category	Normal (<25 kg/m²)	85 (41.67%)
	Overweight (25-29 kg/m²)	75 (36.76%)
	Obese (≥30 kg/m²)	44 (21.57%)
Central Obesity	Absent	103 (50.49%)
	Present	101 (49.51%)

The majority of participants were in the 41-50 years age group, comprising 29.90% of the total, followed by 26.96% in the 51-60 years age group and 21.57% in the 31-40 years group. A female predominance was observed, with 71.57% of the participants being women, compared to 28.43% who were men. More than half of the participants (58.33%) were either overweight or obese, indicating a potential link between higher BMI and gallstone disease in this cohort. Central obesity was present in 49.51% of the participants.

Table 2: Metabolic Syndrome Components

Metabolic Component	Category	n (%)
High Blood Pressure	Normal (<140/90 mmHg)	83 (40.69%)
	Elevated (≥140/90 mmHg)	121 (59.31%)
Fasting Blood Sugar	Normal (<100 mg/dL)	106 (51.96%)
	Elevated (≥100 mg/dL)	98 (48.04%)
Triglycerides	Normal (<150 mg/dL)	118 (57.84%)
	Elevated (≥150 mg/dL)	86 (42.16%)
HDL Cholesterol	Normal	117 (57.35%)
	Low (<40/50 mg/dL)	87 (42.65%)

High blood pressure was recorded in 59.31% of participants, suggesting that hypertension was a frequent comorbidity in patients with gallstone disease. High fasting blood sugar was identified in 48.04% of participants. Elevated triglycerides (≥150 mg/dL or on treatment) were found in 42.16% of the study population, pointing towards a significant proportion of gallstone patients also presenting with dyslipidemia. Low HDL cholesterol was observed in 42.65% of participants.

Table 3: Risk Factors for Metabolic Syndrome

Number of Risk Factors	n (%)
No Risk Factor	16 (7.84%)
1 Risk Factor	51 (25.00%)
2 Risk Factors	40 (19.61%)
3 Risk Factors	40 (19.61%)
4 Risk Factors	43 (21.08%)
5 Risk Factors	13 (6.16%)
Metabolic Syndrome	
Absent (<3 risk factors)	108 (52.94%)
Present (≥3 risk factors)	96 (47.06%)

The distribution of metabolic syndrome risk factors revealed a progressive accumulation pattern, with only 7.84% of participants having no risk factors, while 92.16% had at least one component. Participants with 1-2 risk factors comprised 44.61%, indicating a substantial proportion at intermediate metabolic risk. Those meeting the diagnostic criteria for metabolic syndrome (≥3 risk factors) constituted 47.06%, with 19.61% having exactly three components, 21.08% having four, and 6.16% exhibiting all five risk factors. This distribution demonstrates a dose-response relationship between the number of metabolic abnormalities and disease burden, indicating that nearly half of the study population was affected by metabolic syndrome.

Table 4: Gallstone Characteristics

Gallstone Type	n (%)
Cholesterol Stone	62 (62.00%)
Pigment Stone	7 (7.00%)
Mixed Stone	31 (31.00%)
Total	100 (100.00%)

Among the 100 participants with confirmed gallstones, cholesterol stones were the predominant type, accounting for 62%, followed by mixed stones at 31%. Pigment stones were relatively uncommon, representing only 7% of cases. The preponderance of cholesterol

stones suggests that metabolic disturbances related to cholesterol metabolism, bile supersaturation and lipid abnormalities are the primary drivers of gallstone formation in this population.

Table 5: Study Group Classification

Study Group	n (%)
Gallstone + Metabolic Syndrome	70 (34.31%)
Gallstone Only	30 (14.71%)
Metabolic Syndrome Only	26 (12.75%)
None	78 (38.24%)
Total	204 (100.00%)

Above table illustrates the distribution of participants based on their study group classification. A total of 34.31% of participants had both gallstone disease and metabolic syndrome (GS + MeTS), 14.71% had gallstone disease only, 12.75% had metabolic syndrome only and 38.24% had neither condition. This shows that a substantial proportion of participants suffered from the coexistence of both gallstone disease and metabolic syndrome.

Table 6: Association of Metabolic Syndrome with Gallstone

Gallstone	Metabolic Syndrome		
	Absent	Present	Total
Absent	78 (72.22%)	26 (27.08%)	104 (50.98%)
Present	30 (27.78%)	70 (72.92%)	100 (49.02%)
Total	108	96	204

Pearson Chi-square = 34.4, P-value = 0.0004

Among participants with gallstones, 72.92% had metabolic syndrome. The association between gallstone disease and metabolic syndrome was statistically significant (Pearson Chi-square = 34.4, p = 0.0004) suggesting a strong and significant relationship between the two conditions.

Table 7: Binary Logistic Regression of Gallstone and Metabolic Syndrome

Gallstone	Odds Ratio	Std. Error	p-value	95% CI
Metabolic Syndrome	6.98	2.201	0.001	3.7 - 12.9
No Metabolic Syndrome	1	-	-	-

The binary logistic regression analysis revealed that participants with metabolic syndrome had significantly higher odds of having gallstone disease, with an odds ratio of 6.98. The 95% confidence interval ranged from 3.779 to 12.965 and the association was highly statistically significant (p = 0.001). This indicates that individuals with metabolic syndrome were almost seven times more likely to have gallstones compared to those without metabolic syndrome.

Table 8: Multivariable Logistic Regression of Gallstone and Individual Components of Metabolic Syndrome

Risk Factor	Odds Ratio	Std. Error	p-value	95% CI
High Fasting Blood Sugar	1.37	0.46	0.342	0.713 - 2.65
Hypertension	1.45	0.464	0.238	0.78 - 2.71
Central Obesity	2.12	0.69	0.0021	1.12 - 4.01
High Triglycerides	2.81	0.924	0.002	1.48 - 5.35
Low HDL Cholesterol	1.579	0.489	0.041	1.16 - 2.89

Central obesity was found to significantly increase the risk of gallstones, with an odds ratio of 2.12 (p = 0.0021), indicating that individuals with central obesity were over twice as likely to have gallstones compared to those without. Similarly, high triglyceride levels were strongly associated with gallstone disease, with an OR of 2.81 (p = 0.002), suggesting nearly a threefold increased risk. Low HDL cholesterol was also significantly associated with gallstones, with an OR of 1.579 (p = 0.041). In contrast, high fasting blood sugar (OR = 1.37, p = 0.342) and high blood pressure (OR = 1.45, p = 0.238) did not show a statistically significant association with gallstone disease in this analysis.

DISCUSSION

This hospital-based cross-sectional study was conducted at the Department of General Surgery, L.N. Medical College and Research Centre, J.K. Hospital, Bhopal, involving adult patients diagnosed with either gallstone disease, metabolic syndrome, or neither condition. A total of 204 patients participated over an 18-month period. Each participant underwent comprehensive clinical, anthropometric, biochemical and radiological assessments. The primary objective of this study was to investigate the potential association between gallstone disease and metabolic syndrome, as well as to identify risk factors that might connect the two conditions. Both gallstone disease and metabolic syndrome are prevalent conditions, commonly observed in middle-aged adults and share several risk factors like central obesity, hypertension, hyperglycemia and dyslipidemia. Understanding this relationship is crucial as it could assist in identifying high-risk patients, thereby facilitating early screening and the implementation of lifestyle modifications to reduce the disease burden and improve patient outcomes.

The results of the current study indicated that patients with metabolic syndrome had approximately seven times greater odds of developing gallstone disease compared to those without metabolic syndrome (Odds Ratio = 6.98, 95% Confidence Interval: 3.7-12.9, p = 0.001). This strong association suggests that metabolic syndrome may play a direct role in the formation of gallstones. These findings are consistent with the work of Chen et al. (2012), who conducted a similar cross-sectional study in China (27). Their study reported an age-adjusted odds ratio of 1.42 for gallstone disease in individuals with metabolic syndrome (95% CI: 1.23-1.64, p = 0.0001), with the risk increasing proportionally to the number of metabolic syndrome components present. In women, the odds ratio was as high as 1.68 (95% CI: 1.26-2.25, p = 0.0004). Kim et al. (2021) conducted a large longitudinal study in South Korea, involving 207,850 participants, which similarly demonstrated that the risk of cholelithiasis increased with the number of metabolic components. In this cohort, individuals with three metabolic components had an adjusted hazard ratio of 1.35 (95% CI: 1.17-1.57, p = 0.001), while those with four or more components exhibited a comparable risk (HR = 1.35, 95% CI: 1.15-1.57, p = 0.001). Their findings also identified low HDL cholesterol as the strongest individual predictor of gallstone disease (28). Similarly, Zhu et al. (2016) performed a six-year longitudinal cohort study in China involving 18,291 participants, revealing a significantly higher incidence of gallstones in individuals with metabolic syndrome (29). In men, the relative risk was 1.33 (p = 0.0020), with an incidence density of 10.27 per 1000 person-years in the metabolic syndrome group, compared to 5.79 in those without the syndrome. The risk increased with each additional metabolic component.

In a study conducted by Lin et al. (2014) in Taiwan, including 12,050 subjects, the association between metabolic syndrome and gallstone disease was statistically significant, with an odds ratio of 1.61 (p = 0.0001) (30). This study also highlighted central obesity and low HDL cholesterol as the most prominent risk factors (83). More recently, Zakeri Fardi et al. (2025), in their analysis based on the PERSIAN Guilan cohort, found that metabolic syndrome increased the odds of developing gallstone disease by 47% (adjusted OR=1.47, 95% CI: 1.10-1.97, p = 0.010) (31). They also observed a clear trend where the prevalence of gallstones rose with the number of metabolic components, from 0.56% in individuals with no metabolic components to 3.60% in those with all five (31). The present study demonstrated a significantly stronger association between metabolic syndrome and gallstone disease compared to previous reports. This may be attributed to differences in the study population, sample size, or the hospital-based nature of the study. Age also played a significant role in gallstone disease in the present study, with the highest prevalence observed in the age groups 41-50 years (29.90%) and 51-60 years (26.96%). This finding aligns with studies by Zhu et al. (2016)(29), Kim et al. (2021)(28), Chen et al. (2012)(27) and Lin et al. (2014)(30), all of which found that the incidence of gallstones increased with age, particularly after the age of 40. These age-related trends may be due to cumulative metabolic changes, hormonal shifts and alterations in bile composition that occur over time.

Study Limitations

This study has several limitations that should be considered. First, it was conducted at a single hospital, which may limit the generalizability of the findings. As such, the results may not be applicable to populations from different geographic regions or healthcare settings. Second, the study employed a cross-sectional design, which can identify associations but does not establish causality between gallstone disease and metabolic syndrome. Additionally, the study's inclusion criteria may have introduced selection bias, as it only involved patients who sought care at the hospital and were diagnosed with gallstone disease, metabolic syndrome, or neither. Consequently, individuals who were asymptomatic or had mild symptoms may not have been represented in the sample. Another potential limitation is measurement bias in clinical, biochemical, or radiological assessments. However, to reduce this risk, standardized protocols and

validated instruments were used for data collection and all biochemical tests were conducted in a single laboratory to ensure consistency. Despite these precautions, some degree of variability in individual assessments may still exist.

CONCLUSION

Most gallstone patients were middle-aged adults, predominantly female over half being overweight or obese and nearly half having central obesity highlighting strong links between body weight and gallstone formation. Hypertension, elevated fasting blood glucose, high triglycerides, and low HDL cholesterol were common, supporting the role of metabolic abnormalities in gallstone disease. About half of the patients met criteria for metabolic syndrome, and cholesterol stones were the most frequent type, suggesting metabolic factors drive cholesterol stone formation. The study found a strong, statistically significant association between metabolic syndrome and gallstone disease, with individuals having metabolic syndrome nearly seven times more likely to develop gallstones. Central obesity, high triglycerides, and low HDL were significant independent predictors, whereas high blood pressure and elevated fasting glucose were not. Overall, the findings emphasize that gallstone disease may serve as an indicator of underlying metabolic syndrome, underscoring the importance of early detection and management of metabolic risk factors to reduce gallstone risk and improve outcomes.

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