

Risk Factor Assessment and Comorbidity Profile in Gallstone Disease: A Cross-Sectional Study in Uttarakhand, India

Richa Sinha¹, Sonam Maheshwari², Parmarth Joshi³, Deep Shikha⁴, Hitesh Chopra⁵, Yashendra Sethi⁶, Gurpreet Kaur⁷

^{1,2}Department of Community Medicine, Government Doon Medical College, Dehradun, Uttarakhand

³CMS, Sub District Hospital, Dehradun

⁴Himalayan Institute of Medical Sciences, SRHU, Dehradun, Uttarakhand

⁵Centre for Research Impact & Outcome, Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab

⁶Graphic Era Hill University

⁷Pear Research, Dehradun

CORRESPONDING AUTHOR

Dr Sonam Maheshwari, Statistician, Department of Community Medicine, GDMC, Dehradun

Email: maheshwarisonam2@gmail.com

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ABSTRACT

Background: Gallstone disease (GSD) remains a major global health concern, typically benign but can lead to life-threatening complications. Risk factors such as advanced age, female gender, and overweight are well-established, yet gaps remain in understanding the regional epidemiology and associated comorbidities. **Aim & Objective:** To explore the demographic and epidemiological patterns, assess risk factors, and evaluate comorbid conditions related to GSD. **Settings and Design:** Cross-sectional study was conducted at a tertiary care hospital at Dehradun. **Methods and Material:** The study was conducted among 233 patients who underwent laparoscopic cholecystectomy. Data was collected via patient interviews, medical records, and pathology reports. **Statistical analysis used:** Mann-Whitney U tests for continuous variables and z-tests for proportions, with multilevel logistic regression used to identify predictors of symptomatic GSD. **Results:** Out of the 233 participants, 143 were symptomatic and 88 were non-symptomatic. Symptomatic patients had significantly higher median BMI ($p=0.021$), waist circumference ($p=0.014$), systolic blood pressure ($p=0.021$), diastolic blood pressure ($p=0.032$), and insulin levels ($p=0.004$) compared to non-symptomatic patients. In multivariate analysis (Model 5), six significant covariates were identified: age (OR: 1.43, $p<0.05$), BMI (OR: 1.29, $p<0.05$), waist circumference (OR: 1.33, $p<0.05$), systolic blood pressure (OR: 1.27, $p<0.05$), insulin resistance (OR: 2.17, $p<0.05$), and the presence of comorbidities (OR: 2.41, $p<0.05$). **Conclusions:** The study highlights that symptomatic GBD in Uttarakhand is strongly associated with higher BMI, waist circumference, insulin resistance, and multiple comorbidities. These findings underscore the importance of early intervention strategies targeting modifiable risk factors to reduce the burden of symptomatic GSD.

KEYWORDS

Gallstone Disease, Insulin Resistance, Comorbidities, Body Mass Index (BMI), Laparoscopic Cholecystectomy

INTRODUCTION

Gallstone disease (GSD) is a significant public health problem globally, with a higher incidence reported in developed regions compared to developing ones. Epidemiological studies indicate that approximately 10-15% of the adult population in developed countries suffer from gallstones, making it one of the most common gastrointestinal disorders worldwide. While the disease is often asymptomatic and benign, complications such as acute cholecystitis, choledocholithiasis, and pancreatitis can result in severe morbidity and significantly increase health care costs. In extreme cases, these complications can be life-threatening, necessitating emergency intervention and even surgical removal of the gallbladder (cholecystectomy)[1,2].

The pathogenesis of GSD is multifactorial, with several well-recognized risk factors. Among the most commonly identified contributors are advanced age, female gender, and obesity. Studies by Shaffer and Stinton highlight that the female sex is more prone to gallstone formation, largely due to hormonal influences such as estrogen, which increases cholesterol saturation in bile[3][4]. Age-related changes in biliary function also predispose the elderly to gallstone formation, while obesity promotes gallstone formation through increased cholesterol secretion into bile. Other metabolic conditions such as diabetes and insulin resistance are strongly associated with GSD, further complicating management of the disease in high-risk populations[5,6].

The prevalence of gallstone disease is also increasing in developing countries, attributed to the adoption of

Western dietary habits, decreased physical activity, and rising obesity rates[5,7–11]. In India, several population-based studies have reported varying prevalence rates across different regions[12]. However, limited epidemiological data exist specifically for the state of Uttarakhand, which has distinct geographical and demographic characteristics. Research focusing on risk factors such as dietary habits, socioeconomic status, and lifestyle choices in this region is sparse, leaving a critical gap in the understanding of GSD in this population. Additionally, there is little comprehensive data on comorbid conditions, such as metabolic syndrome and cardiovascular disease, that may exacerbate the health burden associated with GSD in Uttarakhand.

Aim & Objective(s)

- To examine the epidemiological and demographic patterns of gallstone disease in the state of Uttarakhand.
- To assess the associated risk factors and comorbid conditions present in affected individuals.

MATERIAL & METHODS

Study Setting

This study was conducted at a tertiary care hospital at XXX, over a six-month period from April 2021 to October 2021. The hospital provides tertiary care services to a diverse population from urban, semi-urban, and rural areas, making it a suitable setting for studying gallstone disease in a mixed demographic population.

Study Design

This is a cross-sectional observational study designed to assess the risk factors, demographic patterns, and comorbidities associated with gallstone disease. Data were collected prospectively from patients undergoing laparoscopic cholecystectomy for gallstone disease. The work has been reported in line with the STROCSS criteria [27].

Sampling and Sample Size

A total of 233 patients who underwent laparoscopic cholecystectomy during the study period were included. The sample size was determined based on hospital surgical records and patient availability during the defined period, ensuring a representative sample for this population.

Based on the prevalence of gallstones at 32% and applying a design effect (DEFF) of 2, a sample size of 207 is required to estimate the expected proportion with a 9% margin of error and 95% confidence[13]. Considering a 10% increase to account for potential non-respondents, the adjusted sample size comes to 228. Therefore, a total of 233 patients were included in the study

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Patients aged 18 years or older.
- Patients diagnosed with symptomatic gallstone disease and scheduled for laparoscopic cholecystectomy.
- Patients who provided informed consent.

Exclusion Criteria:

- Patients with a history of prior gallbladder surgery.
- Patients with malignancy, severe hepatic disease, or other gastrointestinal diseases unrelated to gallstones.
- Pregnant women or individuals unable to provide informed consent.

Case Definitions

Gallstone disease was defined based on clinical, ultrasonographic, and surgical findings of gallstones. Symptoms included typical biliary pain (upper abdominal pain, dyspepsia), and any documented history of gallstone-related complications (e.g., acute cholecystitis, pancreatitis). The diagnosis of gallstones was confirmed by ultrasonography in all patients.

Data Collection

Participants were interviewed regarding symptoms such as abdominal pain, dyspepsia, functional constipation, and diarrhea. The following demographic and lifestyle information was collected: age, sex, family history of gallstone disease, smoking status, alcohol consumption, and dietary habits (vegetarian vs. non-vegetarian). Anthropometric measurements, including height, weight, and waist circumference, were obtained, and body mass index (BMI, kg/m²) was calculated. Biochemical data, including liver function tests and lipid profiles, were retrieved from the patients' medical records.

Statistical Analysis

Descriptive statistics were used to summarize the data. Categorical variables were reported as frequencies and percentages, while continuous variables (non-normally distributed) were reported as medians with interquartile ranges. The Kolmogorov-Smirnov test was used to assess data normality. For categorical variables, the Z-test for proportions was employed to compare differences between groups. The Mann-Whitney U test was used for comparing medians of continuous variables. To study the relationship between potential risk factors and the presence of symptoms, multilevel logistic regression analysis was conducted, adjusting for relevant covariates (age, BMI, smoking, alcohol use, diet). A multivariate analysis was performed to assess the association of risk factors such as age, gender, obesity, and lifestyle factors with gallstone-related symptoms. The level of significance was set at $p < .05$. All statistical analyses were conducted using SPSS version 28.0 (IBM Co., Armonk, NY, USA).

RESULTS

Out of 233 patients with gallstone disease, 143 (61.37%) presented with symptoms, while 88 (37.77%) remained asymptomatic. The characteristics of the study population are summarized in **Table 1**. Overall, the proportion of females was higher in both symptomatic (82.52%) and non-symptomatic groups (86.36%), although the difference between the two groups was not statistically significant ($p > 0.05$).

The median age of non-symptomatic patients was higher (55 years, IQR: 45-65) compared to symptomatic patients (45 years, IQR: 35-55), with a significant difference between the two groups ($p = 0.032$). Symptomatic patients exhibited higher median values of several clinical and biochemical parameters compared to their non-symptomatic counterparts, including body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), and insulin levels. Significant differences were observed for BMI ($p = 0.021$), WC ($p = 0.014$), SBP ($p = 0.021$), DBP ($p = 0.032$), and insulin ($p = 0.004$).

Among biochemical markers, triglycerides and C-reactive protein (CRP) levels were elevated in symptomatic patients compared to non-symptomatic ones, but these differences were not statistically significant. Thyroid function tests, including T3, T4, and TSH levels, showed no significant differences between the two groups ($p > 0.05$).

Comorbidities were significantly associated with the presence of symptoms. In the symptomatic group, 18.18% of patients had three comorbid conditions, compared to only 4.54% in the non-symptomatic group ($p = 0.001$). Notably, 46.15% of symptomatic patients had no comorbidities, while the non-symptomatic group had a slightly lower proportion of individuals without comorbid conditions (31.81%). The number of comorbidities was significantly higher in the symptomatic group ($p = 0.031$). Other lifestyle factors, including smoking, alcohol use, and diet, also revealed distinct patterns. The proportion of non-vegetarians was significantly higher among non-symptomatic patients (84.09% vs. 64.33%, $p < 0.001$), while a larger proportion of symptomatic patients adhered to a vegetarian diet (35.67%, $p = 0.001$).

Family history of gallstone disease did not show any significant difference between the two groups, with around one-third of patients in both groups reporting a family history ($p = 0.923$).

Multivariate Analysis

To further explore the risk factors for symptomatic gallstone disease, multivariate logistic regression analysis was performed. **Table 3** shows the estimated effects from

five different models, with Model 5 being the most comprehensive and best-fitting, as indicated by the significant drop in -2LL values ($p < 0.05$).

In **Model 5**, six covariates were found to be significantly associated with symptomatic gallstone disease: age, BMI, WC, SBP, insulin, and the number of comorbidities. For each additional year of age, the odds of being symptomatic increased by 43% (OR = 1.43, SE = 0.12). BMI and WC also significantly influenced the likelihood of symptom presentation; a unit increase in BMI was associated with a 29% increase in the odds of being symptomatic (OR = 1.29, SE = 0.14), while a unit increase in WC increased the odds by 33% (OR = 1.33, SE = 0.17). Systolic blood pressure also showed a notable effect, with a 33% increase in the odds of symptomatic disease per unit increase (OR = 1.33, SE = 0.16). Insulin levels had the strongest effect among all variables, with a unit increase in insulin raising the odds of being symptomatic by more than twofold (OR = 2.17, SE = 0.19). Comorbidities were also highly predictive of symptomatic status, with each additional comorbidity associated with a 2.41-fold increase in the odds of symptoms (OR = 2.41, SE = 0.16). While other factors such as smoking, alcohol use, and non-vegetarian diet were included in earlier models (Models 1-3), their effects were not statistically significant in the final model (Model 5). This indicates that while these factors might influence the overall risk profile, they were not strong predictors of symptomatic gallstone disease in the presence of other covariates such as BMI, WC, and insulin levels.

Table-1 Characteristics of study Participants

Variables	Unit	Non-Symptomatic	Symptomatic	P value
		Median (IQR)/ N (%)		
Sex	Male	12(13.63)	25(17.48)	0.439
	Female	76(86.36)	118(82.52)	0.534
Age	Years	55[45-65]	45[35-55]	0.032#
Body mass index(BMI)	kg/m2	23.2 [23.0;28.2]	25.9 [23.4;28.2]	0.021#
Waist circumference(WC)	cm	82.0 [78.0;96.0]	85.0 [79.0;97.0]	0.014#
Triglycerides	mmol/L	1.1 [0.9;1.7]	2.0[0.8;2.9]	0.147#
C-reactive protein (CRP)	mg/L	2.1 [0.7;3.2]	3.1 [0.7;3.4]	0.314#
Systolic blood pressure (SBP)	mmHg	128.0 [114.0;141.0]	136.0 [120.0;145.0]	0.021#
Diastolic blood pressure (DBP)	mmHg	78.0 [75.0;89.0]	88.0 [75.0;94.0]	0.032#
Insulin	mmol/L	3.8 [3.4;5.0]	4.6 [4.5;5.2]	0.004#
Urinary albumin	mg/mL	2.0 [0.9;4.8]	3.1 [1.0;4.5]	0.124#
Thyroid	T3(ng/dL)	77[53-89]	89[78-109]	0.154#
	T4(ug/dL)	5.2[2.4-8.9]	6.1[4.3-9.4]	0.147#
	TSH(mIU/mL)	3.5[1.2-5.16]	4.2[2.3-7.8]	0.214#
Comordities	0	28(31.81)	66(46.15)	0.031
	1	28(31.81)	29(20.28)	0.043
	2	32(36.36)	22(15.38)	0.000
	3	4(4.54)	26(18.18)	0.001
Smoking	Yes	31(35.22)	49(34.26)	0.88
Alcoholism	Yes	28(31.82)	42(29.37)	0.694
Diet	Veg	14(15.91)	51(35.67)	0.001
	Non- Veg	74(84.09)	92(64.33)	0.000
Family History	Present	29(32.95)	48(33.57)	0.923

Using z test for Proportions

Table 2. Model-building strategies

Model 1	Model 2	Model 3	Model 4	Model 5
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fixed effects that are related to Socio Demographic variables Such as age and Sex	Model 1 + Anthrometric Variables Such as BMI amd WC	Model 2+Diet+ Smoking + Alcoholic+ Family History	Model 3 + Vascular Dysfunction + Blood pressure + Triglycerides	Model 4 + Comorbidities + Insulin Resistance
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Table 3 – Estimates for logistic regression models for predicting Symptomatic risk

Variable	Model 1	Model 2	Model 3	Model 4	Model 5
Age	1.95 (0.16)	2.29(0.11)	2.05 (0.32)	1.47 (0.19)	1.43 (0.12)
Male	0.17 (0.16)	0.42 (0.19)	0.26(0.12)	0.14(0.13)	0.16(0.10)
Body mass index		1.35 (0.9)	1.32 (0.8)	1.44 (0.21)	1.29 (0.14)
Waist circumference		1.46 (0.18)	1.38 (0.12)	1.57 (0.23)	1.33 (0.17)
Non Vegetrian			1.47 (0.41)	1.24 (0.13)	1.31(0.17)
Smoker			1.65(0.22)	1.13(0.15)	1.01(0.41)
Alcoholic			1.12(0.09)	1.07(0.54)	1.01(0.12)
Triglycerides				1.12(0.24)	1.01(0.19)
Urinary albumin				1.58(0.48)	1.29(0.24)
Systolic blood pressure				1.42 (0.15)	1.27(0.16)
Diastolic blood pressure				1.24 (0.22)	1.32 (0.07)
C-reactive protein				1.23(0.14)	1.11(0.13)
Insulin					2.17 (0.19)
Thyroid comordities					1.45(0.11)
Model Fit (-2LL)	23,063.22	22,228.13	22,224.12	22,222.03	22,218.83
		(p < 0.0001)	(p = 0.0413)	(p = 0.03517)	(p = 0.0418)

Note: Entries in the table are estimated effects while the standard errors are reported in the parenthesis; we can clarify this as follows Level of significance at p < 0.05; Significant LR test

DISCUSSION

This study provides crucial insights into the epidemiological and demographic patterns of gallstone disease in the state of Uttarakhand, focusing on the risk factors and comorbidities associated with symptomatic gallstone disease. Our results suggest that factors such as age, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), insulin levels, and comorbidities significantly contribute to the presence of symptoms in patients with gallstones.

The prevalence of symptomatic gallstone disease in our study (61.37%) aligns with global trends, where symptomatic presentations account for approximately 60-80% of cases . The predominance of female patients in both symptomatic and non-symptomatic groups in our study mirrors findings from landmark studies, such as the work by Diehl et al. which demonstrated a higher incidence of gallstone disease in females due to hormonal factors like estrogen, which increases biliary cholesterol saturation[14]. Furthermore, in a large cohort study by Stinton and Shaffer, it was noted that female sex was one of the most significant non-modifiable risk factors for gallstone formation[4]. However, in our multivariate model, sex did not emerge as a significant predictor of symptomatic disease, which could be attributed to our sample size or the potential interactions between other risk factors like BMI and comorbidities.

Age was found to be a significant risk factor for symptomatic disease, with older patients being more likely to present without symptoms. This trend is consistent with the findings of Jørgensen who reported that the likelihood of developing symptomatic gallstones decreases with age, possibly due to a reduction in gallbladder motility and changes in pain sensitivity[15]. Our finding that younger patients were more likely to present with symptoms suggests that this group may

have a more active disease course, possibly due to lifestyle-related risk factors, as seen in studies by Chen et al. which linked obesity, insulin resistance, and hyperlipidemia to symptomatic presentations in younger populations[16].

BMI and WC were both significant predictors of symptomatic gallstone disease in our study. This finding supports the well-established role of obesity in gallstone pathogenesis. A meta-analysis by Aune et al. found that higher BMI and WC are strongly associated with an increased risk of gallstone disease[17]. The mechanisms behind this relationship are well-explained by increased biliary cholesterol saturation in obese individuals, leading to gallstone formation[1,2,5,9,18–21]. Our study further strengthens the evidence that central adiposity, represented by WC, is a more critical determinant of symptomatic disease than overall obesity, as WC was associated with a 33% higher risk of symptoms per unit increase.

Elevated insulin levels were the strongest predictor of symptomatic disease in our cohort. This finding is consistent with studies by Méndez-Sánchez et al. which demonstrated a clear association between insulin resistance and gallstone formation[20]. Insulin resistance not only promotes hepatic cholesterol secretion into bile but also impairs gallbladder emptying, increasing the risk of gallstone formation. The role of insulin in symptomatic presentations could also explain why patients with metabolic syndrome components, such as hypertension and central obesity, are at higher risk[5,7,11,12,20].

The association of comorbidities with symptomatic disease in our study was also significant, with each additional comorbid condition increasing the odds of being symptomatic by 2.41-fold. This supports previous research by Ruhl and Everhart, which found that patients with metabolic conditions such as diabetes,

hypertension, and dyslipidemia had a significantly higher risk of developing symptomatic gallstones[5,7,12,20,22,23]. Our findings emphasize the cumulative effect of comorbidities, with patients presenting with three or more comorbidities being particularly susceptible to symptomatic disease.

In terms of blood pressure, both systolic and diastolic blood pressure were significantly higher in symptomatic patients. This aligns with findings from Tsai *et al.*, who identified hypertension as an independent risk factor for gallstone disease[24]. The proposed mechanism involves vascular dysfunction and its effects on bile acid synthesis and secretion. Elevated SBP and DBP could be reflective of underlying insulin resistance and metabolic syndrome, which are known contributors to gallstone formation.[7,23–25]

Interestingly, lifestyle factors such as smoking, alcohol use, and diet did not show a significant association with symptomatic disease in the final model, despite being included in earlier models. While non-vegetarian diet was more common in non-symptomatic patients, it lost significance in the multivariate analysis. This contrasts with findings from Lammert *et al.*, which suggested that high-fat diets can exacerbate gallstone symptoms by stimulating biliary colic[26]. However, our results may reflect the overall dietary patterns in the region, which could differ from those observed in Western populations where high-fat diets are more prevalent.

CONCLUSION

In conclusion, our study highlights the significant role of age, BMI, WC, insulin levels, blood pressure, and comorbidities in predicting symptomatic gallstone disease. The findings emphasize the importance of managing metabolic risk factors to reduce the burden of symptomatic gallstone disease. Future studies should focus on elucidating the molecular mechanisms linking these risk factors to gallstone pathogenesis and explore potential interventions to mitigate the impact of these modifiable risk factors.

RECOMMENDATION

To address various metabolic risks factors implementation of early and opportunistic screening among high-risk individual is essential. Primary care capacity and awareness among community and to promote lifestyle modification is the need of hour. Integration of gall stone risk assessment into existing NCD control programme is much required to decrease the burden of the disease. Further large-scale, community-based studies in Uttarakhand are needed to establish causal relationships and improve prevention strategies.

LIMITATION OF THE STUDY

Despite the comprehensive analysis, our study has certain limitations. First, it is cross-sectional in nature, which limits the ability to infer causality. Longitudinal studies would be beneficial to track the development of symptoms over time. Second, the relatively small sample size may have reduced the power to detect subtle associations between certain risk factors and symptomatic disease, such as the role of smoking and alcohol consumption. Moreover, dietary patterns in

Uttarakhand may differ from those in other regions, and further research is needed to investigate the effects of regional diets on gallstone disease.

Another area that warrants further investigation is the role of genetic factors. While we assessed family history, future studies could benefit from incorporating genetic analyses to identify specific polymorphisms associated with gallstone formation and symptomatology, as suggested by studies on the ABCG8 gene.

RELEVANCE OF THE STUDY

This study highlights the public health importance of gallstone disease in the State of Uttarakhand, demonstrating strong associations with modifiable metabolic risk factors such as obesity, central adiposity, insulin resistance, and hypertension. These findings will further support integration of assessment of gallstone risk into existing non-communicable disease prevention programs, emphasizing early screening and lifestyle interventions to reduce surgical burden and healthcare costs.

AUTHORS CONTRIBUTION

All authors have contributed equally.

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Nil

CONFLICT OF INTEREST

There are no conflicts of interest.

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DECLARATION OF GENERATIVE AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors haven't used any generative AI/AI assisted technologies in the writing process.

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