ORIGINAL ARTICLE

From single risks to cumulative burden: Determinants of cholelithiasis in young adults

SAFRINA DWIYUNARTI[1], RINI R BACHTI[2], HIMAWAN SANUSI[3], SYAKIB BAKRI[4], SUDIRMAN KATU[5], ARIFIN SEWENG[6]

[1]Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia;[2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [3]Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [4]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [5]Division of Tropical Infections, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [6]Department of Public Health and Community Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

ABSTRACT

Background and aim: Cholelithiasis has traditionally been considered a disease of older adults; however, its incidence among young adults is increasing worldwide. Most previous studies have focused on isolated risk factors, despite growing evidence that gallstone formation is a multifactorial process involving the accumulation of multiple modest risk factors**.** This study aimed to evaluate the association between cumulative exposure to selected metabolic and demographic risk factors and the presence of cholelithiasis among young adults in a Southeast Asian population.

Methods: A hospital-based case–control study was conducted among adults aged 18–39 years at a tertiary referral center in Indonesia. A total of 141 participants were included (47 cases with cholelithiasis and 94 controls). Cholelithiasis was confirmed by abdominal ultrasonography or computed tomography. Independent variables included sex, body mass index (BMI), lipid profile, total bilirubin, physical activity, and a cumulative risk burden score constructed from multiple concurrent risk factors. Multivariable logistic regression analysis was performed.

Results: Female sex (adjusted OR 2.67; 95% CI 1.12–6.35) and obesity (adjusted OR 2.81; 95% CI 1.08–7.32) were independently associated with cholelithiasis. Individual metabolic parameters were not significant when analyzed separately. In contrast, participants with more than four concurrent risk factors had a substantially higher likelihood of cholelithiasis (adjusted OR 4.50; 95% CI 1.43–14.19), indicating a pattern of risk

Received: 27 December 2025 | Accepted: 27 January 2026

Correspondence: Safrina Dwiyunarti, MD / Department of Internal Medicine, Hasanuddin University Hospital A, Tamalanrea, Makassar, South Sulawesi, 90245, Indonesia / E-mail: safrina.dwiyunarti@yahoo.co.id
ORCID: 0009-0004-8020-8780

accumulation when multiple modest risk factors coexist rather than evidence of a biological threshold or synergistic effect.

Conclusions: Young-onset cholelithiasis appears to be associated with the cumulative burden of multiple modest risk factors rather than any single dominant determinant. Quantifying cumulative risk burden may offer an exploratory framework for early risk stratification and prevention in metabolically transitioning populations. (www.actabiomedica.it)

Key words: cholelithiasis; young adults; cumulative risk burden; obesity; metabolic risk

Introductions

Cholelithiasis has long been considered a disease predominantly affecting older adults; however, contemporary evidence indicates a clear epidemiological shift toward younger age groups. Global data have demonstrated that gallstone disease is increasingly diagnosed in individuals under 40 years of age, a phenomenon now referred to as young-onset cholelithiasis (1). This trend parallels the rising prevalence of obesity, sedentary lifestyles, and metabolic disturbances occurring at earlier stages of life, particularly in low- and middle-income regions undergoing rapid socioeconomic transitions. The clinical implications of cholelithiasis in young adults are substantial. Early-onset disease exposes individuals to a prolonged lifetime risk of biliary colic, acute cholecystitis, and recurrent hospital admissions, often culminating in surgical intervention at a relatively young age (2). Consequently, young-onset cholelithiasis represents not only a medical concern but also a long-term socioeconomic burden, affecting individuals during their most productive years. Despite extensive research on gallstone disease, most epidemiological studies continue to assess individual risk factors in isolation, such as female sex, obesity, or dyslipidemia. While these factors are well established, this reductionist approach may inadequately reflect the biological complexity of gallstone formation. Current pathophysiological evidence indicates that cholelithiasis is a multifactorial condition resulting from the coexistence of metabolic, hormonal, and lifestyle-related factors that collectively influence bile composition and gallbladder motility, rather than the effect of a single dominant abnormality (2,3). Emerging evidence suggests that the cumulative burden of multiple modest risk factors, rather than isolated exposures, may play a particularly important role in gallstone development among young adults, who may not yet exhibit advanced metabolic disease (4). However, studies explicitly examining the aggregation of risk factors in this age group remain limited, and age-specific data on cumulative risk patterns are still scarce. This knowledge gap is especially relevant in Southeast Asia, where rapid urbanization, dietary westernization, and increasing rates of overweight and obesity have substantially altered metabolic risk profiles in younger populations (5,6). Although gallstone disease is increasingly encountered in clinical practice across the region, existing studies largely focus on older adults or report prevalence estimates without addressing age-specific determinants or cumulative risk patterns. Therefore, the present study does not aim to introduce a novel conceptual framework, but rather to apply an established cumulative risk approach to young-onset cholelithiasis in a Southeast Asian population. This study aimed to explore whether the aggregation of multiple modest metabolic and demographic risk factors is associated with the presence of cholelithiasis among young adults, without implying causal, synergistic, or threshold mechanisms. By adopting this integrative but exploratory approach, the present study seeks to contribute region-specific evidence and to support earlier risk stratification strategies in younger populations.

Methods

This analytical observational study employed a hospital-based case control design to evaluate determinants of cholelithiasis among young adults. The study was conducted at a tertiary referral hospital in Indonesia between May 2025 and the time at which the required sample size was achieved. A case control approach was selected to efficiently assess multiple metabolic and lifestyle-related risk factors associated with a relatively uncommon clinical outcome in younger populations. The study population comprised adults aged 18–39 years who attended the gastrohepatology outpatient clinic or were admitted to the inpatient ward during the study period. This age range was chosen to specifically capture young-onset cholelithiasis and to examine risk patterns beyond the traditional age-centered framework associated with gallstone disease. Cases were defined as participants with cholelithiasis confirmed by abdominal ultrasonography or computed tomography. Controls were participants without evidence of cholelithiasis on imaging, who underwent abdominal imaging for non-biliary indications, such as nonspecific abdominal complaints or routine clinical evaluation. This approach was adopted to ensure that controls were derived from the same source population as cases. Participants were excluded if they had a history of gallstone-related complications (acute cholecystitis, cholangitis, choledocholithiasis, pancreatitis, or gallbladder malignancy), were pregnant, or had a history of current or prior use of medications known to influence bile composition or gallstone formation, including lipid-lowering agents or high-dose estrogen therapy. Sample size estimation for a case control study yielded a minimum requirement of 94 participants. To improve statistical precision and power, a total of 141 participants were ultimately included, consisting of 47 cases and 94 controls with a 1:2 case-to-control ratio. Participants were recruited using consecutive sampling, a pragmatic approach commonly applied in hospital-based observational studies. The dependent variable was the presence of cholelithiasis. Independent variables included sex, body mass index (BMI), lipid profile parameters, total bilirubin levels, physical activity, and cumulative risk burden. Body weight and height were measured using standardized instruments, and BMI was calculated as weight (kg) divided by height squared (m^2). Obesity was defined using Asia–Pacific criteria (BMI ≥25.0 kg/m^2), which have been shown to better reflect metabolic risk in Asian populations. Fasting blood samples were collected to assess high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and total bilirubin using enzymatic colorimetric methods. Dyslipidemia was defined as HDL cholesterol <40 mg/dL in men and <50 mg/dL in women, LDL cholesterol ≥130 mg/dL, or triglyceride levels ≥150 mg/dL, consistent with widely used clinical guidelines. Elevated total bilirubin was defined as a serum level >1.2 mg/dL. Physical activity was assessed using a standardized questionnaire and categorized according to metabolic equivalent task (MET)-minutes per week as light (<600 MET-min/week), moderate (600–2999 MET-min/week), or vigorous (≥3000 MET-min/week), in line with established physical activity classification frameworks. Cumulative risk burden was defined as the total number of concurrent metabolic and lifestyle-related risk factors present in each participant. The included risk factors were obesity, dyslipidemia, elevated total bilirubin levels, and low physical activity. Female sex was deliberately excluded from the cumulative risk score and was analyzed separately as an independent covariate to avoid conceptual overlap and collinearity. Each risk factor contributed one point to the cumulative score. Equal weighting was applied due to the exploratory nature of the study and the limited sample size, which precluded reliable derivation of weighted or interaction-based models. Participants were categorized into three groups: fewer than three risk factors, three to four risk factors, and more than four risk factors. This categorization was adopted solely to describe patterns of risk accumulation and does not imply the presence of biological thresholds or synergistic effects. Descriptive statistics were used to summarize participant characteristics. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized as mean ± standard deviation or median with interquartile range, as appropriate. Associations between cumulative risk burden and cholelithiasis were evaluated using chi-square tests and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Multivariable logistic regression

analysis using a backward stepwise approach was performed to identify independent determinants of cholelithiasis after adjustment for potential confounders. No formal interaction or non-linear analyses were conducted. A two-sided p-value <0.05 was considered statistically significant. Written informed consent was obtained from all participants prior to enrollment in the study.

Results

Participant characteristics

A total of 141 young adults aged 18–39 years were included in the analysis, consisting of 47 cases (33.3%) with cholelithiasis and 94 controls (66.7%) without cholelithiasis. The mean age was comparable between the two groups (cases: 31.02 ± 4.51 years; controls: 31.65 ± 5.97 years), indicating adequate age matching. Overall, the sex distribution was nearly equal; however, female participants were disproportionately represented in the cholelithiasis group. The mean body mass index (BMI) of the study population was 24.25 ± 3.93 kg/m², with a substantial proportion classified as overweight or obese. Metabolic profiling showed that more than half of participants had low HDL cholesterol, while nearly half exhibited elevated LDL levels. Elevated triglycerides and total bilirubin were less frequent. Most participants reported low levels of physical activity, reflecting a predominantly sedentary lifestyle.

Bivariate associations between individual risk factors and cholelithiasis

In bivariate analysis, female sex was significantly associated with cholelithiasis among young adults. Females had more than a fourfold higher odds of developing cholelithiasis compared with males (OR = 4.21; 95% CI: 1.96–9.03; $p < 0.001$). Similarly, obesity was strongly associated with cholelithiasis. Participants classified as obese had a 4.29-fold increased odds of cholelithiasis compared with non-obese individuals (OR = 4.29; 95% CI: 1.81–10.15; $p < 0.001$). In contrast, individual metabolic parameters, including HDL cholesterol, LDL cholesterol, triglyceride levels, total bilirubin, and physical activity level, were not independently associated with cholelithiasis ($p > 0.05$ for all). These findings indicate that no single metabolic abnormality alone was sufficient to substantially increase cholelithiasis risk in this young population.

Cumulative risk burden and cholelithiasis

When risk factors were evaluated cumulatively, a distinct pattern emerged. Among participants with fewer than three risk factors, cholelithiasis was uncommon, and most individuals belonged to the control group. Table 1 shows the association between the cumulative number of risk factors and cholelithiasis in young adults. Participants with three to four risk factors did not demonstrate a statistically significant increase in risk compared with the reference group (OR = 0.74; 95% CI: 0.23–1.60). In contrast, participants with more than four concurrent risk factors exhibited a markedly increased likelihood of cholelithiasis, with an 8.67-fold higher odds compared with those with fewer than three risk factors (95% CI: 2.62–21.8; $p < 0.001$). This increase in odds was observed in association with higher cumulative exposure to concurrent risk factors and should be interpreted as a descriptive pattern of risk accumulation rather than evidence of a biological threshold or synergistic effect.

Table 1. Association Between the Number of Risk Factors and Cholelithiasis in Young Adults

Cumulative Number of Risk Factors	Group		OR (CI95%)	p
	Case	Control		
<3 (Reference)	9 (23.1%)	30 (76.9%)	1.00	<0.001
3-4	12 (18.2%)	54 (81.8%)	0.74 (0.23-1.60)	
>4	26 (72.2%)	10 (27.8%)	8.67 (2.62-21.8)	

Multivariable logistic regression analysis

Multivariable logistic regression analysis using a backward stepwise approach was performed to identify independent determinants of cholelithiasis. The results of the multivariate logistic regression analysis are presented in Table 2. After adjustment, cumulative risk burden >4 emerged as the strongest independent determinant (OR = 4.50; 95% CI: 1.43–14.19; p = 0.010).

Female sex (OR = 2.67; 95% CI: 1.12–6.35; p = 0.027) and obesity (OR = 2.81; 95% CI: 1.08–7.32; p = 0.034) also remained independently associated with cholelithiasis after controlling for other variables.

The magnitude of the odds ratio associated with cumulative risk burden suggests that the aggregation of multiple modest risk factors may be descriptively more informative than individual risk factors alone in this population, although causal inference cannot be made.

Conclusions

This study indicates that cholelithiasis in young adults is more closely associated with the cumulative burden of multiple modest metabolic and demographic risk factors than with any single isolated determinant. Although female sex and obesity remained independently associated with cholelithiasis, individual metabolic parameters such as lipid fractions, total bilirubin levels, and physical activity were not sufficient, when evaluated separately, to substantially increase disease risk. This finding is consistent with contemporary evidence suggesting that gallstone disease reflects the combined influence of multiple metabolic disturbances rather than a single dominant abnormality (1-4). A pronounced increase in the odds of cholelithiasis was observed only among participants with a higher number of concurrent risk factors; however, this pattern should be interpreted as an associative and descriptive finding rather than evidence of a biological threshold or synergistic effect**.** Given the absence of formal interaction analyses and the limited sample size, the present results should be regarded as hypothesis-generating and interpreted with caution (4,7). These findings are particularly relevant in Southeast Asian populations undergoing rapid epidemiological and metabolic transitions, where clustering of modest risk factors in younger age groups is increasingly common. Previous studies have shown that obesity and early metabolic dysregulation play central roles in gallstone formation, while other metabolic abnormalities may act as amplifiers rather than independent drivers of disease (4,5,7). In summary, assessing cumulative risk burden may offer a more integrative, exploratory framework for understanding young-onset cholelithiasis in metabolically transitioning populations. Larger, population-based studies with more robust analytical designs are required to confirm these observations and to clarify the potential role of cumulative risk assessment in early prevention and risk stratification strategies (7-10).

Limitations

Several limitations of this study should be acknowledged. First, the hospital-based case–control design introduces the potential for selection bias, as both cases and controls were derived from individuals undergoing medical evaluation. Although control participants underwent abdominal imaging for non-biliary indications, their risk profile may not fully represent that of the general population. Second, the construction of the cumulative risk burden

Table 2. Multivariate Analysis of Risk Factors for Cholelithiasis

Step	Variabel	p	OR	95% C.I	
				Lower	Upper
Step 1	Sex	0.027	2.665	1.118	6.352
	BMI	0.034	2.813	1.081	7.318
	Cumulative Number of Risk Factors (3-4)	0.422	0.659	0.238	1.822
	Cumulative Number of Risk Factors (>4)	0.010	4.504	1.430	14.187

involved equal weighting of heterogeneous metabolic and lifestyle-related variables, which may oversimplify their relative biological contributions. This approach was adopted due to the exploratory nature of the study and the limited sample size, which precluded reliable derivation of weighted scores or formal interaction modeling. Third, the relatively small sample size resulted in wide confidence intervals and limited statistical power, restricting the ability to detect modest associations and precluding formal assessment of interaction, synergy, or non-linear effects among risk factors. Accordingly, the observed patterns of risk accumulation should be interpreted as descriptive and hypothesis-generating rather than confirmatory. Finally, the observational and cross-sectional nature of the data precludes causal inference, and residual confounding by unmeasured factors cannot be excluded.

Ethical approval: This study has been approved by the Research Ethics Committee of the Faculty of Medicine, Hasanuddin University through the publication of an ethical approval letter number 280/UN4.6.4.5.31/PP36/2025. The study adhered to the ethical principles, ensuring the protection of participants' rights and confidentiality.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Informed consent statement: Written informed consent was obtained from all participants involved in the study.

Author contributions: SD, RRB, and HS drafted the manuscript. RRB, HS, SB, and SK designed and concepted the study. SD and AS collected and analyzed and interpreted the data. HS, SB, and SK revised manuscript critically for important intellectual content. All authors participated in the final draft preparation, manuscript revision, and critical evaluation of the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work

Declaration on the use of AI: ChatGPT (OpenAI) was used to assist in language refinement, organization of the manuscript, and improvement of clarity. All scientific content, interpretation, and final decisions were made by the authors.

References

1. Lammert F, Gurusamy K, Ko CW, et al. Gallstones. Nat Rev Dis Primers. 2016;2:16024. doi: 10.1038/nrdp.2016.24
2. Portincasa P, Molina-Molina E, Garruti G, Wang DQ-H. Critical care aspects of gallstone disease. J Crit Care Med (Targu Mures). 2019;5(1):6–18. doi: 10.2478/jccm-2019-0003
3. Di Ciaula A, Wang DQ-H, Portincasa P. An update on the pathogenesis of cholesterol gallstone disease. Curr Opin Gastroenterol. 2021;37(2):99–105. doi: 10.1097/MOG.0000000000000423
4. Aune D, Norat T, Vatten LJ. Body mass index, abdominal fatness and the risk of gallbladder disease. Eur J Epidemiol. 2015;30(9):1009-1019. doi:10.1007/s10654-015-0081-y. PMID:26374741.
5. GBD 2021 Adult BMI Collaborators. Global, regional, and national prevalence of adult overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. *Lancet*. 2025;405:813-838. doi:10.1016/S0140-6736(25)00355-1.
6. Sarin SK, Kumar M, Eslam M, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2020. doi:10.1016/S2468-1253(19)30342-5.
7. Wang X, Yu W, Jiang G, et al. Global epidemiology of gallstones in the 21st century: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2024;22(2):1586–1595. doi: 10.1016/j.cgh.2024.01.051.
8. Gu LG, Zheng YM, Xu C, et al. Analysis of the pathogenesis and risk factors of gallstone disease. Zhonghua Wai Ke Za Zhi. 2023;61(5):389-394. doi:10.3760/cma.j.cn112139-20220927-00410. PMID:36987673.
9. Arida AU, Ruhl CE. Burden of gallstone disease in the United States population: prepandemic rates and trends. World J Gastrointest Surg. 2024;16(4):1130–1148. doi: 10.4240/wjgs.v16.i4.1130.
10. Gutt C, Schläfer S, Lammert F. The treatment of gallstone disease. Dtsch Arztebl Int. 2020;117(9):148–158. doi: 10.3238/arztebl.2020.0148.