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Association between C-reactive protein to lymphocyte ratio and gallstones: a cross-sectional study

Xiaoyang Sun[1†], Jie Lin[1†], Zhenao Wang[1], Chenfang Zhang[1], Kai Zhao[1], Xuewen Zhang[1*] and Jiyao Sheng[1*]

Abstract

Background Inflammation plays a key role in the development of gallstones, and the C-reactive protein to lymphocyte ratio (CLR) has been introduced as a promising biomarker for evaluating inflammatory processes. Nonetheless, its correlation with gallstone prevalence remains ambiguous. This study aims to evaluate the potential link between CLR levels and gallstone prevalence.

Methods This study utilized data from the National Health and Nutrition Examination Survey, covering the periods from March 2017 to 2020 and 2021 to 2023. Multivariate logistic regression was employed to examine the association between CLR and gallstone prevalence. Furthermore, smoothed curve fitting, subgroup analysis, and interaction testing were performed to provide a comprehensive evaluation. We also employed receiver operating characteristic (ROC) curves to determine the predictive ability of the index for gallstones.

Results Among the 13,386 participants included in this study, 1,444 were diagnosed with gallstones. In a fully adjusted model, a small but statistically significant positive association between CLR and the prevalence of gallstones was observed (odds ratio [OR] = 1.07, 95% CI: 1.01–1.12). Compared to individuals in the lowest tertile of CLR (T1), those in the middle tertile (T2) showed a non-significant increase in gallstone prevalence (OR = 1.10, 95% CI: 0.94–1.29), while the highest tertile (T3) exhibited a statistically significant elevation (OR = 1.20, 95% CI: 1.03–1.41). Smoothed curve fitting further confirmed this positive relationship. Bonferroni-corrected subgroup analysis demonstrated a statistically significant association between CLR and gallstones in the "Married/Living with Partner" subgroup ($P < 0.0015$), while no significant associations were observed in the other subgroups. Additionally, Bonferroni-corrected interaction tests indicated no significant interactions between CLR and gallstones across all subgroups (P for interaction > 0.0038).

Conclusion Higher CLR was associated with higher gallstone prevalence. However, additional large-scale prospective studies are required to further investigate the role of CLR in the prevalence of gallstones.

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Keywords C-reactive protein to lymphocyte ratio, Gallstones, Cross-sectional study, Inflammation, NHANES

Introduction

Gallstone disease is a prevalent digestive condition characterized by the formation of solid crystalline material within the gallbladder or biliary tract [1]. This disorder is widespread globally, with particularly high prevalence rates in Western nations. Studies indicate that approximately 10–15% of American adults and up to 20% of European adults are affected by gallstones [2, 3]. These stones are primarily composed of cholesterol, bile pigments, or a combination of both, with stones composed of cholesterol being the most prevalent, especially in Western populations [2, 4]. Clinically, gallstones may present with a spectrum of symptoms, ranging from mild digestive discomfort to severe complications. In the early stages, most patients are asymptomatic, a condition termed "silent" or "occult gallstones." However, complications like acute cholecystitis, cholangitis, and pancreatitis can result in pronounced symptoms, including severe abdominal pain, fever, and jaundice, which may be life-threatening if untreated [5]. Moreover, gallstone disease poses a significant healthcare burden, contributing to increased healthcare costs and resource utilization. Complications often necessitate prolonged hospitalization and complex surgical interventions, exacerbating both individual and systemic healthcare expenses [6, 7].

The formation of gallstones is influenced by various factors, with inflammation being a pivotal contributor [8]. C-reactive protein (CRP) is a well-established inflammatory marker that elevates in response to infection or inflammation. Research has demonstrated that CRP levels are significantly higher in patients with gallstones compared to healthy individuals, closely correlating with the onset and progression of inflammatory processes in the gallbladder [9]. Recent research has confirmed the important role of CRP-based inflammatory markers across various diseases, including diabetic nephropathy [10], thyroiditis [11], diabetic neuropathy [12], and hepatitis [13]. Lymphocytes are critical to the immune response, and alterations in lymphocyte count are also pertinent to inflammation associated with gallstones. Evidence suggests that gallstone formation involves not only disruptions in bile composition but is also intimately linked to changes in the immune microenvironment [14]. Recent studies have found that lymphocyte-based biomarkers are associated with a variety of diseases, including diabetes [15], Hashimoto's thyroiditis [16], irritable bowel syndrome [17], ICU mortality [18], and COVID-19 infection [19]. Therefore, the combination of C-reactive protein and lymphocytes can effectively capture the inflammatory response associated with gallstones, providing a foundation for further research and detection. CLR (C-reactive protein to lymphocyte ratio), as a novel inflammatory indicator, has gained widespread recognition in various disease contexts. In COVID-19 patients, admission levels of CLR have been shown to predict poor outcomes [20]. In the field of oncology, CLR values have been associated with poor prognosis in various cancers, including gastric cancer, colorectal liver metastases, and non-small cell lung cancer [21–23]. Furthermore, studies in cardiovascular diseases have shown that high CLR values are closely tied to an increased risk of cardiovascular events [24, 25]. However, no previous research has directly investigated the link between CLR and gallstone prevalence.

To address this gap, we performed a population-based cross-sectional analysis using data from the National Health and Nutrition Examination Survey (NHANES) to investigate the potential association between CLR and gallstone prevalence.

Methods

Study design and participants

Due to the impact of the COVID-19 pandemic, the NHANES project suspended field operations in March 2020, which resulted in incomplete data collection for the 2019–2020 cycle. To address this issue, the survey agency merged the data collected from 2019 through March 2020 with the data from the 2017–2018 cycle, thereby constructing a comprehensive dataset covering the period from 2017 to March 2020.

This study utilized data from the NHANES dataset covering the periods of March 2017–2020 and 2021–2023. Initially, 27,493 participants were considered. However, 10,495 were excluded due to missing gallstone information, 3,572 due to missing C-reactive protein information, and 40 due to missing lymphocyte information. After applying these criteria, a total of 13,386 participants were incorporated into the final study. Detailed participant selection is shown in Fig. 1. The research obtained authorization from the NCHS Ethical Review Committee, and all participants provided informed consent.

Assessment of the CLR and gallstones

CLR was defined as the ratio of high-sensitivity C-reactive protein (hs-CRP) to lymphocyte count (expressed per 1000 cells/μL). High-sensitivity C-reactive protein, measured via an ultrasensitive assay, serves as a more precise marker of inflammation, capable of detecting minor elevations in CRP even within the normal range. Complete blood counts, including hematocrit levels, were derived from participants' blood samples using the DxH800 analyzer (Beckman Coulter).

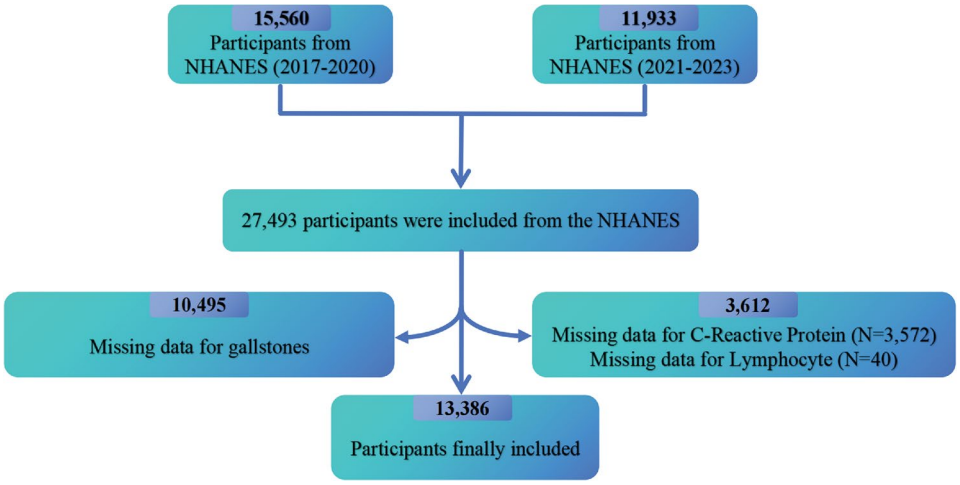

Fig. 1 Flow chart of participants selection. NHANES, National Health and Nutrition Examination Survey

Gallstones served as an outcome variable in this research. The existence of gallstones was assessed through participants' responses to the question, "Has a doctor or other healthcare professional ever diagnosed you with gallstones?" This self-reported measure captures a history of gallstone diagnosis, acknowledging that some participants may have already undergone cholecystectomy.

Covariables

Based on prior research, we identified several potential confounding variables to include in our analysis due to their possible impact on outcomes. These variables included age, ethnicity, sex, marital status, educational level, poverty-to-income ratio (PIR), body mass index (BMI), total cholesterol levels, direct high-density lipoprotein cholesterol (HDL-C), physical activity (duration of moderate-intensity activity), protein intake, carbohydrate intake, sugar intake, and fat intake. Additionally, data from questionnaires were collected on asthma, smoking history (defined as having smoked a minimum of 100 cigarettes in a lifetime), alcohol consumption (defined as consuming alcohol at least once per month in the preceding year), as well as the presence of hypertension, diabetes, and cancer.

Statistical analysis

Due to the skewed distribution of the CLR, a natural logarithm (LN) transformation was applied prior to data analysis. Additionally, multiple imputation was performed on covariates with missing data to maximize the sample size. The link between CLR and gallstones was explored using multivariate logistic regression. Covariates were not considered in Model 1; age, gender, and ethnicity were included in Model 2; and all covariates were accounted for in Model 3. It is important to note that the analyses were performed without applying NHANES sampling weights. To further investigate the relationship between CLR and gallstones, we utilized generalized additive modeling (GAM) and smoothed curve fitting (SCF) while adjusting for covariates. CLR was categorized into tertiles, and tertile 1 was used as the reference group. Stratified multivariate regression analyses were performed to examine the relationship between CLR and gallstones across different subpopulations, with interaction terms included to assess heterogeneity in subgroup associations. To address the increased risk of Type I errors resulting from multiple testing, we applied the Bonferroni correction to the results of both the subgroup analyses and the interaction tests. Specifically, the interaction tests involved 13 major subgroups, with a corrected significance level of $P^* < 0.0038$ ($\alpha = 0.05/13$). The subgroup analyses included 33 secondary subgroups, for which the corrected significance level was $P^* < 0.0015$ ($\alpha = 0.05/33$). Furthermore, receiver operating characteristic (ROC) curves were used to assess the predictive ability of CLR for gallstones. All statistical analyses were conducted using Empower Stats and R software version 4.2.3.

Results

Characteristics of the participants

A total of 13,386 participants met the inclusion criteria for this study. Table 1 provides an overview of the demographic characteristics and associated covariates of these participants. The mean age was 52.20 years with a standard deviation of 17.37 years, with 47.07% being male and 52.93% female. Participants were categorized into two groups according to gallstone status, consisting of 1,444 individuals with gallstones and 11,942 without. The prevalence of gallstones is 10.79%. Stone-formers were more likely to be older, have obesity (BMI ≥ 30 kg/

Table 1 Baseline characteristics of participants

Characteristic	Non-stone formers	Stone formers	*P*-value
	N **= 11,942**	***N*** **= 1,444**	
Age (years)	51.33 ± 17.40	59.37 ± 15.35	< 0.001
Gender (%)			< 0.001
Male	5,896 (49.37)	405 (28.05)	
Female	6,046 (50.63)	1,039 (71.95)	
Race (%)			< 0.001
Mexican American	1,170 (9.80)	151 (10.46)	
Other Hispanic	1,231 (10.31)	163 (11.29)	
Non-Hispanic White	5,318 (44.53)	747 (51.73)	
Non-Hispanic Black	2,420 (20.26)	215 (14.89)	
Other Race	1,803 (15.10)	168 (11.63)	
Education level (%)			0.051
Less than high school	782 (6.55)	81 (5.61)	
High school	1138 (9.53)	163 (11.29)	
More than high school	10,022 (83.92)	1200 (83.10)	
Marital Status (%)			< 0.001
Married/Living with Partner	6,793 (56.88)	821 (56.86)	
Widowed/Divorced/Separated	2711 (22.70)	447 (30.96)	
Never married	2438 (20.42)	176 (12.19)	
PIR (%)			0.010
< 1	2209 (18.50)	265 (18.35)	
> =1, <4	6106 (51.13)	793 (54.92)	
> =4	3627 (30.37)	386 (26.73)	
BMI (kg/m ^{2}) (%)			< 0.001
< 25	3234 (27.08)	194 (13.43)	
> =25, < 30	3927 (32.88)	377 (26.11)	
> =30	4781 (40.04)	873 (60.46)	
Alcohol (%)			< 0.001
Yes	6426 (53.81)	591 (40.93)	
No	5516 (46.19)	853 (59.07)	
Smoked (%)			< 0.001
Yes	4893 (40.97)	660 (45.71)	
No	7049 (59.03)	784 (54.29)	
Hypertension (%)			< 0.001
Yes	4335 (36.30)	778 (53.88)	
No	7607 (63.70)	666 (46.12)	
Diabetes (%)			< 0.001
Yes	1993 (16.69)	427 (29.57)	
No	9949 (83.31)	1017 (70.43)	
Asthma (%)			< 0.001
Yes	1917 (16.05)	336 (23.27)	
No	10,025 (83.95)	1108 (76.73)	
Cancer (%)			< 0.001
Yes	1345 (11.26)	283 (19.60)	
No	10,597 (88.74)	1161 (80.40)	
HDL-cholesterol (mg/dL)	54.04 ± 15.63	53.09 ± 14.46	0.114
Total cholesterol (mg/dL)	186.92 ± 41.57	183.71 ± 42.62	0.002
Physical Activity (minutes)	125.54 ± 141.14	113.56 ± 115.44	0.008
Protein intake (g)	77.69 ± 34.27	69.17 ± 29.39	< 0.001
Carbohydrate intake (g)	232.62 ± 104.74	216.10 ± 93.89	< 0.001
Total sugar intake (g)	98.51 ± 62.36	96.59 ± 59.29	0.818

Table 1 (continued)

Characteristic	Non-stone formers	Stone formers	*P*-value
	N **= 11,942**	***N*** **= 1,444**	
Total fat intake (g)	84.17 ± 41.22	78.48 ± 36.22	< 0.001
Ln CLR	-0.05 ± 1.17	0.32 ± 1.15	< 0.001

Continuous variables: values are expressed as mean ± SD; Categorical variables: values are expressed as numbers (percentage); Abbreviation: PIR, poverty-to-income ratio; BMI, body mass index; CLR, C-reactive protein to lymphocyte ratio

Table 2 Association between CLR and the odds of gallstones

Characteristic	Model 1	Model 2	Model 3
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
ln CLR	1.29 (1.24, 1.36)	1.23 (1.18, 1.30)	1.07 (1.01, 1.12)
CLR Tertiles			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.55 (1.33, 1.79)	1.38 (1.18, 1.60)	1.10 (0.94, 1.29)
Tertile 3	2.13 (1.85, 2.45)	1.83 (1.58, 2.11)	1.20 (1.03, 1.41)
P for trend	< 0.0001	< 0.0001	0.0189

OR: odds ratio; 95%CI: 95% confidence interval; Model 1: no covariates were adjusted; Model 2: adjusted for gender, age, and race; Model 3: adjusted for gender, age, race, education level, marital status, PIR, BMI, alcohol, smoking status, asthma, cancer, hypertension, diabetes, HDL-cholesterol, total cholesterol, physical activity, protein, carbohydrate, sugar and fat

m^2), smoke, and have conditions such as hypertension, asthma, cancer, and diabetes mellitus compared to non-stone-formers ($P < 0.05$). Conversely, non-stone-formers exhibited higher dietary intake of protein, carbohydrates, and total fats, along with elevated total cholesterol levels ($P < 0.05$), and were more likely to consume alcohol.

The association between CLR and gallstones

Table 2 displays the outcomes of multivariate logistic regression analysis used to assess the relationship between CLR and gallstones. In the unadjusted model (Model 1), higher CLR levels correlated with a higher prevalence of gallstones (OR = 1.29, 95% CI: 1.24–1.36). In the fully adjusted model (Model 3), the positive association between CLR and gallstones remained statistically significant but with a modest effect size (OR = 1.07, 95% CI: 1.01–1.12). CLR was further categorized into tertiles for analysis. In Model 3, compared to the lowest tertile of CLR (T1), the odds of gallstones prevalence in the highest tertile (T3) increased by 20% (OR = 1.20, 95% CI: 1.03–1.41). Moreover, smoothed curve fitting further confirmed the positive association between CLR and gallstone prevalence, as depicted in Fig. 2. Furthermore, we compared the effect size of the C-reactive protein to lymphocyte ratio (CLR) with that of established risk factors for gallstones, such as obesity and diabetes. As demonstrated in Supplementary Tables 4 and 5, the odds ratio for obesity was 1.98 (95% CI: 1.75–2.24), whereas the odds ratio for diabetes was 1.35 (95% CI: 1.18–1.56). Although the effect size of CLR is relatively small, its potential role as an inflammatory marker in the pathogenesis of gallstones should not be underestimated.

Subgroup analysis and interaction tests

The findings of the subgroup analyses are presented in Table 3. Participants were stratified by gender, age, marital status, ethnicity, BMI, education level, and various health parameters, including alcohol consumption, smoking status, hypertension, diabetes, asthma, and cancer. We applied Bonferroni correction to the results of the interaction tests to minimize the impact of multiple testing. After correction, no significant interactions between CLR and gallstones were observed across all subgroups (P for interaction > 0.0038). Furthermore, applying Bonferroni correction to the results of the subgroup analyses revealed that the relationship between CLR and gallstones was statistically significant in the "Married/Living with Partner" subgroup ($P < 0.0015$), while no significant associations were found in the other subgroups.

ROC curve analysis

Supplementary Fig. 1 shows the results of the ROC curve analysis. The AUC value for CLR in predicting gallstones was 0.591, slightly lower than that of CRP (AUC = 0.595), but higher than that of the neutrophil to lymphocyte ratio (NLR) (AUC = 0.536) and the monocyte to lymphocyte ratio (MLR) (AUC = 0.506).

Incremental value of CLR over traditional inflammatory markers

We evaluated the incremental value of CLR compared to traditional inflammatory markers, including NLR, MLR, and CRP, in the diagnosis of gallstones. The analysis showed that CLR significantly improved the predictive performance of the NLR model, enhancing the AUC from 0.5356 to 0.5593 ($P < 0.0001$) (Supplementary Fig. 2, Supplementary Table 1). Similarly, incorporating CLR into the MLR model increased the AUC from 0.5058 to 0.5894 ($P < 0.0001$), demonstrating marked incremental value (Supplementary Fig. 3, Supplementary Table 2). In contrast, the addition of CLR to the CRP model did not provide additional incremental value, with the AUC decreasing slightly from 0.595 to 0.582 ($P = 0.0018$) (Supplementary Fig. 4, Supplementary Table 3). Overall, these findings indicate that CLR offers significant incremental value in enhancing the diagnostic accuracy of both the NLR and MLR models but does not improve the performance of the CRP model.

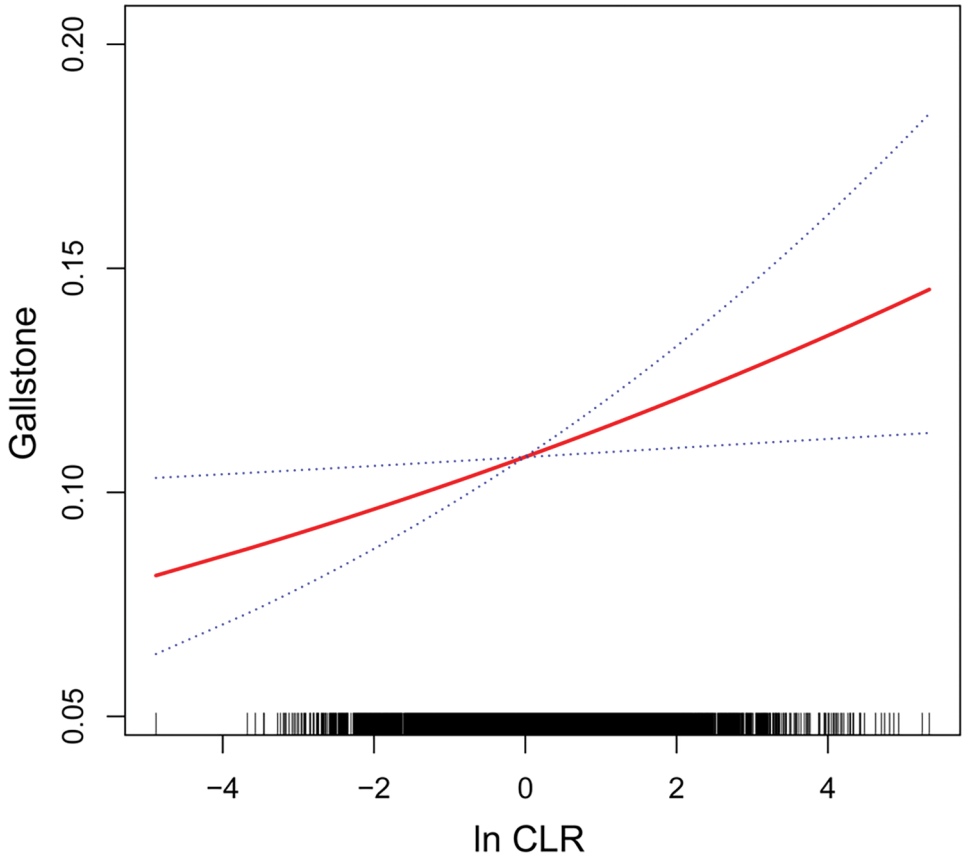

Fig. 2 The linear associations between CLR and gallstones. The solid red line illustrates the smooth curve fit between the variables. The blue bands represent the 95% confidence interval derived from the fit

Discussion

In this cross-sectional analysis of 13,386 participants from the NHANES database, we identified a positive correlation between CLR levels and the prevalence of gallstones. To further investigate this relationship, CLR values were categorized into tertiles. Participants in the highest tertile of CLR (T3) had 20% higher odds of having gallstones compared with those in the lowest tertile (T1) (OR = 1.20, 95% CI: 1.03–1.41).

This is the first study to explore the relationship between CLR and gallstone prevalence, indicating that higher CLR levels are associated with a greater prevalence of gallstones. Recently, CLR has gained recognition as a reliable marker for assessing adverse outcomes across various clinical settings. For instance, in a study of patients with acute pancreatitis, Chen et al. reported that CLR levels reflect the inflammatory status of patients, with higher CLR values correlating with poorer prognosis and a greater susceptibility to complications [26]. Hwang et al. similarly demonstrated that CLR is an independent predictor of survival in non-small cell lung cancer patients undergoing curative surgical resection, with higher levels of CLR significantly linked to lower survival rates [27]. Additionally, Wu et al. found that CLR is valuable for predicting post-surgical infection risk, particularly in patients undergoing high-risk surgeries, where higher CLR levels were linked to increased rates of postoperative infection [28]. This study expands the application of CLR, revealing a positive correlation between CLR levels and gallstone prevalence. This new finding aligns with previous research, highlighting the broad applicability of CLR as an inflammatory marker, and indicates the need for further prospective studies to validate the effectiveness of CLR in assessing gallstone risk.

A growing body of research has established a significant association between gallstone formation and both local and systemic inflammatory responses [29, 30]. Inflammation of the gallbladder wall has been identified as an early event in gallstone formation. Studies in animal models have shown that inflammatory markers, such as myeloperoxidase and interleukins, are markedly elevated in the gallbladder wall. This inflammatory response alters the absorptive and secretory functions of the gallbladder epithelium, ultimately influencing stone formation. Impaired absorption by the gallbladder weakens its natural defense mechanisms against gallstones, thereby promoting stone formation [31, 32].

Table 3 Subgroup analysis of the associations between the CLR and gallstones

Subgroup	OR (95%CI)	*P*-value	*P* for interaction
Age			0.198
< 40	1.15 (1.00, 1.32)	0.046	
>=40	1.04 (0.98, 1.10)	0.150	
Gender			0.357
Male	1.09 (1.00, 1.19)	0.052	
Female	1.04 (0.97, 1.11)	0.276	
Race			0.400
Mexican American	1.05 (0.88, 1.25)	0.598	
Other Hispanic	1.12 (0.94, 1.33)	0.198	
Non-Hispanic White	1.07 (1.00, 1.16)	0.066	
Non-Hispanic Black	1.12 (0.99, 1.28)	0.071	
Other Race	0.93 (0.80, 1.09)	0.369	
Education level			0.697
Less than high school	0.96 (0.76, 1.22)	0.747	
High school	1.08 (0.92, 1.25)	0.351	
More than high school	1.07 (1.01, 1.13)	0.030	
Marital Status			0.028
Married/Living with Partner	1.14 (1.06, 1.22)	0.001	
Widowed/Divorced/Separated	1.00 (0.91, 1.09)	0.941	
Never married	0.95 (0.83, 1.10)	0.531	
PIR			0.589
< 1	1.01 (0.90, 1.14)	0.863	
> =1, <4	1.08 (1.01, 1.16)	0.028	
> =4	1.08 (0.98, 1.21)	0.130	
BMI			0.437
< 25	1.02 (0.90, 1.16)	0.745	
> =25, < 30	1.00 (0.91, 1.11)	0.928	
> =30	1.08 (1.01, 1.17)	0.028	
Alcohol			0.046
Yes	1.00 (0.92, 1.09)	0.969	
No	1.11 (1.04, 1.19)	0.002	
Smoked			0.991
Yes	1.06 (0.99, 1.15)	0.111	
No	1.06 (0.99, 1.15)	0.093	
Asthma			0.123
Yes	1.15 (1.03, 1.29)	0.016	
No	1.04 (0.98, 1.10)	0.197	
Cancers			0.100
Yes	1.06 (0.95, 1.19)	0.297	
No	1.06 (1.00, 1.13)	0.040	
Hypertension			0.065
Yes	1.02 (0.94, 1.09)	0.681	
No	1.12 (1.04, 1.21)	0.004	
Diabetes			0.096
Yes	0.99 (0.90, 1.09)	0.843	
No	1.09 (1.03, 1.16)	0.006	

Gender, age, race, education level, marital status, PIR, BMI, alcohol, smoking status, asthma, cancer, hypertension, diabetes, HDL-cholesterol, total cholesterol, physical activity, protein, carbohydrate, sugar and fat were adjusted. Each subgroup analysis is adjusted for all other covariates except the stratifying variable

CRP is a key inflammatory biomarker utilized to assess the activity of inflammatory diseases, evaluate treatment efficacy, and predict disease risk [33, 34]. In a prospective cohort study, researchers found a significant association between elevated high-sensitivity CRP levels and the development of gallstone disease. Upon controlling for relevant confounders, individuals with elevated hs-CRP levels exhibited a greater risk of developing gallstones, indicating that CRP may act as an independent risk factor for gallstone disease [35]. Furthermore, immune cell

density (mast cells and T cells) in the gallbladder wall is significantly increased in patients with gallstones. Activation of these immune cells may lead to gallbladder dysfunction, exacerbating both inflammation and stone formation [36]. In particular, T cells are thought to play a crucial role in cholesterol stone formation [37]. Given these insights, we analyzed the correlation between CLR and gallstone prevalence using data from the NHANES database, revealing that higher CLR levels were associated with higher gallstone prevalence. These findings support a potential link between inflammation and gallstones, which could inform future prospective studies or risk stratification research.

In this study, although the effect size of CLR is relatively low, its potential role as an inflammatory marker in the pathogenesis of gallstones should not be overlooked. The inflammatory process is widely recognized as a significant pathological mechanism in the formation of gallstones, and CLR, as a composite indicator reflecting systemic inflammation and immune status, contributes to elucidating the relationship between inflammation and gallstones. Compared to traditional risk factors such as obesity (odds ratio of 1.98, 95% CI: 1.75–2.24) and diabetes (odds ratio of 1.35, 95% CI: 1.18–1.56), the effect of CLR, while comparatively limited, does not diminish its clinical value. Epidemiological studies emphasize that, for common diseases, even small effect sizes can have significant public health implications. Furthermore, the fully adjusted model used in this study has controlled for various confounding factors, including obesity and diabetes, indicating that the association between CLR and gallstone risk has a certain degree of independence. This suggests that CLR may complement traditional risk factors, enriching the multidimensional interpretation of gallstone risk assessment. These findings also contribute to a more comprehensive understanding of the risk characteristics associated with gallstones and may provide important reference for future large-scale prospective studies and more nuanced risk assessment targeting specific high-risk populations. We assert that even if the effect size is modest, recognizing and understanding this association is crucial for elucidating the complex etiological mechanisms of the disease.

When the association between CLR and gallstones is confirmed in prospective studies, CLR may help identify high-risk individuals in several ways. First, elevated CLR values may indicate an inflammatory state, allowing clinicians to effectively stratify gallstone risk and identify patients who require closer monitoring. Second, based on CLR assessment results, high-risk individuals can receive early interventions, such as lifestyle and dietary modifications, to reduce their likelihood of developing the disease. Additionally, the application of CLR can optimize healthcare resource allocation, enabling high-risk patients to receive prioritized diagnostic assessments and management, thereby enhancing overall treatment outcomes. Therefore, once the relationship between CLR and gallstones is validated in prospective research, it may play a significant role in the early identification and risk assessment of gallstone disease.

This study has several notable strengths. First, the subjects were drawn from the NHANES database, which provides rigorously controlled quality data with a large sample size, facilitating meaningful comparisons across different subgroups within the population. Second, we adjusted for various covariates to minimize potential biases. Third, we performed subgroup analyses and interaction tests to further explore differences among different population groups. However, there are several limitations to this study. Due to the focus of this study on the association between CLR levels and gallstone prevalence rather than on estimating national prevalence or its representativeness, no weighting of the data was conducted in the initial phase. This lack of weighting may impact the estimates of prevalence and effect size. Additionally, due to missing data, a large number of initially eligible NHANES participants had to be excluded (10,495 participants were removed due to missing gallstone data, and 3,612 participants were removed due to missing CLR data). These excluded participants may systematically differ from those included, which could introduce bias, and the final analytic sample may not fully represent all US adults. CRP is an acute-phase reactant that can be temporarily elevated due to acute infections or other transient conditions, which may not accurately reflect a patient's long-term or chronic inflammatory status. Therefore, a single measurement may be insufficient to comprehensively capture the entirety of inflammation. This limitation also justifies the need for longitudinal studies to examine the relationship between persistently high CLR and the development of gallstones. Despite adjusting for multiple covariates, we were unable to account for all potential confounding factors, such as hormonal status (estrogen exposure) and genetic predisposition. Future studies could further validate and expand our findings by incorporating variables related to hormonal status and genetic information. Additionally, gallstone diagnosis was based on self-reported questionnaires rather than precise imaging modalities, which may affect diagnostic accuracy. Future research is recommended to utilize imaging confirmation (such as ultrasound or CT scans) to enhance diagnostic accuracy and reduce potential bias. The design of this study is cross-sectional, which limits our ability to infer causal relationships. This means we cannot determine the causal relationship between CLR levels and gallstone formation, and the possibility of reverse causation exists. Therefore, future prospective cohort studies are necessary to clarify the temporal relationship between

CLR and gallstone formation, allowing for a better understanding of their interaction.

Conclusion

This study demonstrates that elevated CLR levels are associated with an increased prevalence of gallstones. This finding suggests a connection between inflammation and gallstones, which may inform future prospective studies or risk stratification research.

Abbreviations

CLR	C-reactive protein to lymphocyte ratio
NHANES	National Health and Nutrition Examination Survey
BMI	Body mass index
PIR	Poverty-to-income ratio
HDL-C	High-density lipoprotein cholesterol
NLR	Neutrophil to lymphocyte ratio
MLR	Monocyte to lymphocyte ratio
ROC	Receiver Operating Characteristic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-04000-z.

Supplementary Material 1

Supplementary Material 2

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Author contributions

XS and JL: Conceptualization, Formal Analysis, Methodology, Data curation, Validation, Writing– original draft, Writing– review & editing. ZW: Methodology, Data curation. CZ and KZ: Data curation. XZ: Supervision, Writing– review & editing. JS: Supervision, Writing– review & editing.

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Data availability

The data used in this study are publically available in the NHANES database(https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

Declarations

Ethics approval and consent to participate

The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and were approved by the National Center for Health Statistics Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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